Cognitive, Language, and Psychosocial Outcomes in Children with Complex Congenital Heart Disease: A Longitudinal Cohort Study from Infancy to Early School Years.

Maneet Kaur Saini

UCL Great Ormond Street Institute of Child Health

Thesis submitted for the degree of

Doctor of Philosophy

March 2023
Declaration

I, Maneet Kaur Saini, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

31st March 2023
“I knew from months old that my son was different, but I was fobbed off by health visitors and community nurses, and told he would catch up. If it was established that congenital heart disease and developmental problems often occur together, then help could be offered sooner to benefit the child and support the parents.”

– Mother of 3 year-old with hypoplastic left heart syndrome
Abstract

Congenital heart disease (CHD) and its surgical treatment can expose neonates to episodes of hypoxia-ischaemia. Brain structures that have high oxygen requirements are susceptible to neurotoxic reactions potentially leading to hypoxic-ischaemic brain injury. Children with CHD may be at risk of adverse neurodevelopmental outcomes which can consequently impact their psychosocial functioning and quality of life. The aim of this research was to examine the emergence and longitudinal trajectories of cognition, language and motor function in the first three years of life, in a paediatric cohort with hypoplastic left heart syndrome (HLHS) (n=11), or d-transposition of the great arteries (TGA) (n=21), compared to a group of healthy controls (n=28). Speech, language, and pre-reading skills were then investigated at 4-5 years, coupled with an auditory event-related potential (ERP) study to explore neural correlates of speech sound processing. Parent-rated social-emotional, behavioural, and psychosocial functioning were also examined, including their role in overall quality of life.

A pattern was observed in children with TGA having scores similar to those of healthy controls in many domains, longitudinally. Children with HLHS showed impaired gross motor skills between 5-15 months, but by 3-4 years they scored within the normal range. At 4-5 years, the CHD groups displayed no impairments in expressive or receptive language, but some patients showed impaired phonological processing (31-60%), narrative skills (23-54%), and pragmatics (15-40%). ERP findings showed that children with CHD did not process phonemes differently to healthy controls and no significant associations were found between ERPs and behavioural measures of speech and language. Children with HLHS had poorer social-emotional, behavioural, executive functioning, and
psychosocial status and 71% had impaired quality of life, compared to other groups. A number of these outcomes were significantly associated with parental/maternal mental health and family functioning.

Overall, despite group scores in the normative range, a high proportion of children with complex CHD had impaired scores in one or more domains. This highlights the need for an individualised approach and regular neurodevelopmental surveillance, currently not routinely available in the UK.
Impact Statement

This research originated from parental concerns of children with congenital heart disease (CHD) during patient and public involvement work at Great Ormond Street Hospital for Children. Patients with CHD and their families have been at the forefront of this research, and research aims specifically addressed parental concerns relating to speech and language and behavioural outcomes in children with complex CHD.

The research presented in this thesis contributes to the field in four key ways. Firstly, the research provides previously unavailable evidence about the neurodevelopmental, language and psychosocial outcomes of children with complex CHD in the UK. Contrary to much existing literature, the study also looks at individual children as well as group differences, in a longitudinal design.

Secondly, it provides evidence of the efficacy of neuroimaging methodology, specifically electroencephalography, for studying functional speech processing in preschool and early school aged children with complex CHD. This thesis includes the first study to explore the neural responses underlying phoneme processing in children with CHD, using an auditory event-related potential (ERP) paradigm, to relate ERPs/functional measures of speech sound processing to behavioural measures of language. This will help to inform future research as this has the potential to contribute to the identification of early neural markers of atypical speech processing in complex CHD, which can help identify those children at high-risk for speech and language deficits and impairments. This is important for future research as much of the current literature has focussed on outcomes in a
range of domains in children with CHD, without consideration of the brain circuitry involved in specific delays/impairments.

Thirdly, these research findings can help to inform the development and effectiveness of targeted interventions. For example, phonological abilities, pragmatic language, and narrative skills were found to be specifically impaired, as opposed to expression or comprehension of language more widely. Future interventions need to consider this. Further, the high incidence of parent-rated social-emotional, behavioural, and psychosocial problems, and lower quality of life in children with CHD, was found to be associated with parental/maternal mental health and family functioning. Although causality cannot be determined, this relationship suggests that parent and family factors may play a key role in child outcomes. Again, future interventions need to focus on a family approach, rather than the child alone.

Overall, these findings are of high clinical relevance as early identification of delays/deficits is key in those children at high risk of compromised outcome. Identifying the extent and type of support children need is critical to avoid impairments becoming established. Not all children with complex CHD have poor outcomes or uncertain futures, and many have good quality of life, however, circumstances can change and many patients are known to grow into their deficits overtime. This ultimately means regular long-term neurodevelopmental surveillance is necessary in these children to allow for supported transition to school, adolescence, and eventually adulthood. Crucially, there are currently no follow-up neurodevelopmental programmes or routine monitoring of development in the UK for children born with CHD. This is something that needs to be prioritised in order to standardise the care for patients nationwide and globally.
The findings presented in this thesis have been disseminated within the wider scientific community through presentations at several academic meetings, and neuroscience symposiums.
Acknowledgements

First and foremost, I would like to express my deepest gratitude to my supervisors, Professor Faraneh Vargha-Khadem, Dr Jo Wray and Professor Michelle de Haan. Thank you for all the knowledge, expertise, and guidance you have given me over the past five years. Faraneh, thank you for giving me the incredible opportunity to work as your research assistant as part of the HI Baby Project, and trusting me to work independently with so many clinical patients. This ignited my passion for developmental cognitive neuroscience and I feel extremely privileged to have learnt so much from you over the years, including all the fascinating information and stories you have shared with me. Working with you introduced me to clinical research and congenital heart disease, and your encouragement helped me to apply for a PhD.

Jo, I am forever indebted for all your support. Thank you for believing in me, even when I did not believe in myself. I am incredibly fortunate to have met you through Kate Oulton which allowed me to apply for funding from the BRC to pursue my PhD. You have always gone above and beyond your duties as a supervisor and have always made time for me whenever I have needed it. Without your wealth of knowledge and expertise in congenital heart disease, I know I would not have produced the thesis I have today. Your involvement with CHD patients and projects such as The Heart of the Matter are truly inspiring, and I hope to continue to work with you in the future.
Michelle, thank you for all your guidance, wisdom and patience whilst I learnt about EEG. I have greatly benefited from all your expertise in infant ERP studies, and through that have become much more confident in my own abilities.

This research would not have been possible without the continued support of all the participating families and cohort of children involved, who were eager to support the project even during the pandemic. I have thoroughly enjoyed watching each of my participants grow, achieve their developmental milestones, and their personalities develop since my research began. Thank you all so much! I also wish to express my gratitude to the Great Ormond Street Hospital BRC and MRC for providing funding to support my PhD research.

To all my colleagues who have been a part of my PhD journey over the years and have provided continual support, help, and encouragement, thank you so much. A special thank you to Mariana Pereira for kindly and patiently sharing her expertise about EEG and the world of EEG Lab, Dr Rachael Elward for all your feedback and support over the years and especially recently for reviewing some of my chapters, and Gwyn Griffiths for all your IT wizardry and helping me format my thesis and bring everything together. Also, to the most supportive, caring, and kind personal tutor, Professor Claire Thorne, a massive thank you for being there for me every step of the way and for all the advice and meetings we have had since the beginning of my PhD journey. I’ve been so lucky to have had you.

To my amazing friends, Tajinder, Harjit, Christina, and Louis, to name but a few, thank you for always knowing the right things to say, for your endless messages,
calls and words of support and encouragement, for making me smile and giving me those much needed distractions and breaks during the writing of my thesis. Thank you for always being there.

To my incredible Mum and Dad who I owe my every success to, and brother, Harmeet, I cannot thank you enough for all your love, support and faith in me, and for being there for me always. And to my grandparents, who are all watching over me, I dedicate this PhD to all four of you. I hope you are proud that your granddaughter is finally a Dr – I only wish you were here to add another graduation photo to your cabinet.

And finally, to my husband, Ikki, thank you for being my rock, for believing in me always, for pushing me when I needed it most, and for being the most loving, patient, forgiving and supportive man I know. Without you, this whole process would not have been possible, especially since I have been juggling writing my thesis and teaching, and have had little time for anything else. Thank you endlessly for everything you have done for me, and for allowing me to put everything else on hold to complete my PhD. You are my world.
# List of Contents

Abstract ........................................................................................................................................ 7
Impact Statement .......................................................................................................................... 9
Acknowledgements ....................................................................................................................... 13
List of Contents ............................................................................................................................ 1
List of Figures ............................................................................................................................... 9
List of Tables .................................................................................................................................. 13
List of Abbreviations ..................................................................................................................... 17

Chapter 1: General Introduction ................................................................................................. 19
  1.1 Congenital Heart Disease ..................................................................................................... 21
  1.2 Cyanotic Heart Disease ......................................................................................................... 22
    1.2.1 Transposition of the Great Arteries (TGA) .................................................................... 23
    1.2.2 Hypoplastic Left Heart Syndrome (HLHS) ................................................................... 24
  1.3 The Heart and the Brain ....................................................................................................... 27
  1.4 Neurodevelopmental Outcomes in CHD ............................................................................. 30
  1.5 Social-Emotional and Behavioural Outcomes ................................................................... 34
    1.5.1 Outcomes in Children with TGA ............................................................................... 36
    1.5.2 Outcomes in Children with HLHS ............................................................................... 40
    1.5.3 Outcomes Across the Lifespan: Adolescence and Adulthood ................................... 44
    1.5.4 Management and Surveillance of Neurodevelopmental Outcomes ......................... 46
  1.6 Brain Abnormalities Associated with CHD ....................................................................... 47
    1.6.1 Functional Brain Abnormalities .................................................................................... 51
  1.7 Risk Factors for Adverse Neurodevelopmental Sequelae .................................................... 52
    1.7.1 Preoperative Factors .................................................................................................... 53
    1.7.2 Perioperative Factors .................................................................................................... 54
3.2 Methods .................................................................................. 122
  3.2.1 Participants ........................................................................ 123
  3.2.2 Procedure / Assessment ......................................................... 124
  3.2.3 Data analysis ........................................................................ 125
3.3 Results ...................................................................................... 127
  3.3.1 Bayley-3 Scores at 5-8 months .............................................. 127
  3.3.2 Bayley-3 Scores at 12-15 months .......................................... 129
  3.3.3 Bayley-3 Scores at 3-4 years ................................................ 131
  3.3.4 Time-point and Group Interaction ........................................ 135
  3.3.5 Longitudinal Bayley-3 Outcomes ......................................... 138
  3.3.6 Parent-Rated Behaviour ....................................................... 142
3.4 Discussion ............................................................................... 145
  3.4.1 Cognitive, Language, and Motor Development ....................... 145
  3.4.2 Time-point and Group Interaction ........................................ 148
  3.4.3 Longitudinal Bayley-3 Outcomes ......................................... 149
  3.4.4 Parent-Rated Behaviour ....................................................... 152
  3.4.5 Limitations ........................................................................... 154
  3.4.6 Conclusion and Future Research ........................................ 156

Chapter 4: Speech, Language, and Pre-Reading Skills in 4-5 year-old Children with Complex CHD .......................................................................... 159

4.1 Introduction ............................................................................. 161
  4.1.1 The Development of Language ............................................. 161
  4.1.2 Language Development in CHD ........................................... 163
  4.1.3 The Trajectory of Language Skills ...................................... 172
  4.1.4 Factors Affecting Language Outcomes ................................. 175
  4.1.5 Aims and Hypotheses ......................................................... 177
4.2 Methods ................................................................................. 178
4.2.1 Participants ........................................................................................................ 178
4.2.2 Procedure / Assessment .............................................................................. 178
4.2.3 Data Analysis ................................................................................................. 180
4.3 Results ................................................................................................................ 181
  4.3.1 Intellectual Function (IQ) ........................................................................... 181
  4.3.2 Speech and Language ............................................................................... 183
  4.3.3 Longitudinal Language Outcomes ............................................................ 186
  4.3.4 Parent-Rated Language ............................................................................ 192
4.4 Discussion ............................................................................................................ 198
  4.4.1 Speech and Language Outcomes ............................................................... 198
  4.4.2 Longitudinal Trajectory of Language ........................................................ 203
  4.4.3 Parent-Rated Language ............................................................................ 208
  4.4.4 Limitations of the Current Study ............................................................... 209
  4.4.5 Conclusion and Future Research ............................................................... 211

Chapter 5: Neural Markers of Speech Sound Processing ........................................ 213
5.1 Introduction ......................................................................................................... 215
  5.1.1 The Role of the Brain .............................................................................. 217
  5.1.2 Speech Sound Processing ....................................................................... 218
  5.1.3 ERPs and Brain Development .................................................................. 219
  5.1.4 The Auditory Oddball Paradigm ............................................................... 221
  5.1.5 Maturation of Auditory ERPs ................................................................. 230
  5.1.6 Aims and Hypotheses ............................................................................. 232
5.2 Methods .............................................................................................................. 233
  5.2.1 Participants ............................................................................................... 233
  5.2.2 EEG Auditory Oddball Task and Procedure .......................................... 235
  5.2.3 EEG Recording and Data Pre-Processing ............................................... 237
  5.2.4 ERP Data Analysis .................................................................................. 240
6.4 Discussion........................................................................................................310
6.4.1 Behavioural Outcomes ............................................................................311
6.4.2 The Role of Language ............................................................................318
6.4.3 Factors Associated with Psychosocial Status and HRQOL ............319
6.4.4 Longitudinal Outcomes ........................................................................322
6.4.5 Limitations ..............................................................................................324
6.4.6 Conclusion and Future Research .........................................................327

Chapter 7: Parent and Family Outcomes and Quality of Life ................331
7.1 Introduction ...............................................................................................333
7.1.1 Parent and Family Stress .................................................................333
7.1.2 Family Functioning and Parenting Style ...................................340
7.1.3 Factors Influencing Parent Adjustment, Stress and HRQOL ....343
7.1.4 Impact of Poor Outcomes in Parents ............................................344
7.1.5 Aims and Hypotheses ........................................................................348
7.2 Methods ....................................................................................................349
7.2.1 Participants .........................................................................................349
7.2.2 Procedure / Assessment .................................................................351
7.2.3 Data Analysis ...................................................................................351
7.3 Results ......................................................................................................353
7.3.1 Parent Self-Reported Outcomes ....................................................353
7.3.2 Correlational Analyses ....................................................................362
7.3.3 Relationship Between Parent and Child Outcomes .................365
7.4 Discussion ...............................................................................................368
7.4.1 Parent Self-Reported Outcomes ....................................................368
7.4.2 Associations Between Parent Outcomes ...................................373
7.4.3 Relationship Between Parent and Child Outcomes .................375
7.4.4 Limitations .........................................................................................378
Appendix 8. The tests/measures used directly with the child and parent-completed questionnaires at time-point 4 ................................................. 525

Appendix 9. Longitudinal trajectories for each individual participant who completed all three Bayley-3 time-points. Each graph per participant contains the longitudinal results for each subtest (i.e. Cognition, Receptive Language, Expressive Language, Fine Motor, and Gross Motor) at 5-8 months, 12-15 months, and 3-4 years. ........................................................................................................ 526

Appendix 10. Neural Markers of Speech Sound Processing (Chapter 5) ...... 539

Appendix 11. Parent and Family Outcomes and Quality of Life (Chapter 7)... 541

Appendix 12. Colour-coded longitudinal scores of each child in the longitudinal cohort at 4-5 years. ................................................................. 546
List of Figures

Figure 1.1 Schematic representation of the heart A) a normal healthy heart, B) TGA and C) HLHS, adapted from the British Heart Federation (2017a; 2017b) ........................................................................................................... 27

Figure 1.2 Foetal circulation in A) a normal healthy heart, and consequent disruption in circulation and blood flow in B) TGA and C) HLHS. Estimated blood oxygen saturation percentages are shown for each ventricle, where oxygen-rich blood is represented in red, and deoxygenated blood is blue-purple. In HLHS, the absent or underdeveloped left ventricle significantly limits or reverses blood flow, resulting in the mixing of desaturated and well-saturated/oxygenated blood in the right atrium and ventricle (edited from McQuillen et al., 2010) ................................................................. 28

Figure 1.3 A sequential model linking CHD-related heart abnormalities to abnormalities in the brain and consequent neurocognitive impairments across the lifespan, from perinatal brain development, through childhood, and into adulthood and the aging brain (Marelli et al., 2016) ........................................................................................................ 30

Figure 1.4 Factors affecting long-term neurodevelopmental outcome in children with CHD .................................................................................................................. 53

Figure 2.1 The PhD study structure, where green boxes indicate the stages where data collected have been used in this PhD .................. 66

Figure 2.2 The full PhD study timeline including neuropsychological tests used, electrophysiological (EEG) data collected, and parental questionnaires used at each assessment time-point. Data from each of these will be included in the chapters within this thesis. The timeline also highlights the time periods where CHD patients had their cardiac surgery/surgeries, which are shaded in grey ........................................................................................................... 67

Figure 2.3 The attrition of the longitudinal cohort in the study. The boxes shaded grey precede time-point 1 and are not relevant for the scope of this thesis, but are provided for context about attrition in the cohort. Green boxes indicate the time-points where data collected have been included in this PhD study ......................................... 71

Figure 2.4 An EEG recording during an auditory ERP experiment, where a cap with numerous electrodes is placed on the participant’s head, allowing electrical brain activity to be measured on the surface of the scalp. EEG is recorded and amplified while an auditory sound is presented. Adapted from Beres (2017) ................. 94

Figure 3.1. Longitudinal Bayley-3 outcomes for cognitive, receptive language, expressive language, fine motor, and gross motor subscales for each group at 5-8 months, 12-15 months, and 3-4 years .................................................................................................................................. 134
Figure 3.2 The interaction between Bayley-3 time-point and group type, for the Cognition subscale ........................................ 137
Figure 3.3 Longitudinal Bayley-3 trajectories for each individual participant per group at 5-8 months, 12-15 months, and 3-4 years .............. 139
Figure 4.1 The neural pathways and circuits underlying the development of language comprehension, adapted from Skeide and Friederici (2016) ................................................................................... 163
Figure 4.2 Boxplots for each group showing the longitudinal outcomes between time-points 3 (T3) and 4 (T4): A) Bayley-3 Cognition (3-4 years) and Full-Scale IQ (4-5 years), B) Bayley-3 Receptive Language and CELF-P2 Receptive Language, C) Bayley-3 Receptive Language and Receptive OWPVT score, D) Bayley-3 Expressive Language and CELF-P2 Expressive Language, and E) Bayley-3 Expressive Language and Expressive OWPVT score .......................................................... 188
Figure 4.3 Scatterplot showing significant moderate positive correlation between Bayley-3 cognitive scores and WPPSI-IV full scale IQ ... 191
Figure 4.4 Scatterplots showing significant moderate-to-strong positive correlations between Bayley-3 receptive and expressive language and CELF-P2 receptive and expressive language, and receptive and expressive OWPVT scores ................................................................. 192
Figure 4.5 Scatterplots showing the moderate positive significant correlations between the Coherence CCC-2 scale and each of the CELF-P2 scales: A) Core Language, B) Receptive Language, C) Expressive Language, D) Language Content, and E) Language Structure .................................................................................... 197
Figure 5.1 The dual-stream model of speech processing: a) Diagram of the dual-stream model which begins with the earliest stage of speech processing involving spectrotemporal analysis in the auditory cortices bilaterally. Subsequently, processing splits into the two streams: a left dominant dorsal pathway (in blue) and a ventral pathway (in pink); b) The anatomical locations of the dual-stream components (Hickok & Poeppel, 2007) .................. 219
Figure 5.2 Auditory oddball paradigm with frequent and infrequent speech sounds .................................................................................. 236
Figure 5.3 EEG data pre-processing pipeline ........................................ 239
Figure 5.4 Components identified by ICA as artifacts: A) heart rate and B) eye blinks, which were removed .................................. 239
Figure 5.5 EGI 128 channel Geodesic map displaying electrode selection for P50, N1 and P300 components using left (blue) and right (green) hemisphere clusters ....................................................... 241
Figure 5.6 EGI 256 channel Geodesic map displaying electrode selection for P50, N1 and P300 components using left (blue) and right (green) hemisphere clusters ....................................................... 243
Figure 5.7 ERP waveforms and the time windows of interest around each component, for each time-point, and the EEG net used ............ 246
Figure 5.8 Scatterplots showing the correlations between overall ERP and A) EOWPVT language scores, B) Rhyme Detection, and C) Letter Knowledge, at time-point 4, all of which were not significant..................................................................................................................252

Figure 6.1 The relationship between CHD and related morbidity factors impacting overall QoL, adapted from Marino et al. (2016) ............281

Figure 6.2 Scatterplots showing the moderate positive correlation between CCC-2 Nonverbal and A) ABAS Social and B) PedsQL Social Functioning, and the moderate negative correlation between CCC-2 Nonverbal and BRIEF-P C) Inhibit, D) Working Memory, E) Plan/Organise, and F) Flexibility.................................................................301

Figure 6.3 Scatterplots showing the strong negative correlation between PedsQL Psychosocial Health and A) CBCL Internalising Problems, B) CBCL Externalising Problems, C) CBCL Total Problems, and D) BRIEF-P Flexibility .................................................................304

Figure 6.4 Scatterplots showing the strong positive correlations between the two time-points for the CBCL summary and total scores: A) Internalising Problems, B) Externalising Problems, and C) Total Problems........................................................................................................310

Figure 7.1 Common psychosocial stressors during hospital stay in the intensive care unit experienced by parents, infants, and families affected by CHD (Kasparian et al., 2019)........................................................................................................335

Figure 7.2 The Impact of Parent Stress and Resilience in CHD Model adapted from Lisanti (2018) .........................................................................................................................347

Figure 7.3 Scatterplots showing the significant correlations between parent HRQOL and A) total impact of event score (i.e. CHD), B) family functioning, C) parent anxiety, D) parent depression, E) frequency of stress related to CHD, and F) difficulty of stress related to CHD. Lines on the x- and y-axis represent the respective means of the given measures..................................................................................364

Figure 7.4 Scatterplots showing the significant correlations between child HRQOL and A) parent HRQOL, B) family functioning, C) total family impact, D) parent anxiety, E) frequency of parent stress related to CHD, and F) difficulty of parent stress related to CHD. Lines on the x- and y-axis represent the respective means of the given measures..................................................................................367

Figure 7.5 The relationship between key parental and child outcome variables..................................................................................................................376

Figure 8.1 Case Study 1 ..................................................................................................................407

Figure 8.2 Case Study 2 ..................................................................................................................408

Figure 8.3 Case Study 3 ..................................................................................................................409

Figure 8.4 Proposed CHD healthcare pathway for young children in the UK..422

Figure 8.5 Multidisciplinary family-centred psychosocial care plan for children with CHD (Utens et al., 2018) .................................................................422
List of Tables

Table 2.1 Summary of the demographic characteristics of the cohort at time-point 4, including the level of deprivation ....................................78
Table 2.2 Proportion of English-speaking children in the cohort at time-point 4, at 4-5 years of age, detailing bilingualism and the other spoken languages alongside English ............................................80
Table 2.3 Summary of the key clinical variables of the (time-point 4) cohort ....81
Table 2.4 The subtests of the CELF-P2 and a description of what each subtest involves the child doing .................................................................89
Table 3.1 Mean scaled and composite scores on the Bayley-3 subtests for the UK and Ireland sample, with t-test and significance levels (sig) for comparison with expected values (10 for scaled, 100 for composite scores), weighted for disparity in levels of parental education (Bayley, 2010) .....................................................................111
Table 3.2 Patients with HLHS, TGA, and healthy controls who participated in the three longitudinal Bayley-3 assessments ................................124
Table 3.3 Bayley-3 outcomes in children with CHD and healthy controls at 5-8 months....................................................................................................................128
Table 3.4 The total number of participants with Bayley-3 scores 1-2 SD and ≥2 SDs below the mean at 5-8 months .............................129
Table 3.5 Bayley-3 outcomes in children with CHD and healthy controls at 12-15 months ........................................................................................................130
Table 3.6 The total number of participants with Bayley-3 scores 1-2 SD and ≥2 SDs below the mean at 12-15 months .........................131
Table 3.7 Bayley-3 outcomes in children with CHD and healthy controls at 3-4 years ................................................................................................................................132
Table 3.8 The total number of participants with Bayley-3 scores 1-2 SD and ≥2 SDs below the mean at 3-4 years .................................133
Table 3.9 Descriptive statistics displayed as mean (standard deviation) for each group, each Bayley-3 subscale, and each time-point for those children for whom data were collected at each time point ....135
Table 3.10 Repeated measures mixed ANOVA results for each Bayley-3 subscale, separately ...............................................................136
Table 3.11 Spearman’s correlation coefficients for each of the groups, between Bayley-3 subscale scores collected at each time-point ...141
Table 3.12 Bayley-3 parent-rated social-emotional and adaptive behaviour outcomes in children with HLHS, TGA, and healthy controls at each time-point ........................................................................142
Table 3.13 The total number and proportion of participants with Bayley-3 parent-rated social-emotional and adaptive behaviour scores 1-2 SD and ≥2 SDs below the normative range at each time point ...143
Table 3.14 Spearman’s correlation coefficients between parent-rated and directly measured Bayley-3 subscales, for all participants combined, at each time-point .................................................. 144

Table 4.1 Patients with HLHS, TGA, and healthy controls who participated in the 4-5 year assessments ................................................................. 178

Table 4.2 The Wechsler Preschool & Primary Scale of Intelligence (WPPSI-IV) outcomes in children with HLHS, TGA, and healthy controls at 4-5 years ................................................................. 182

Table 4.3 The total number and percentage of participants with WPPSI-IV scores 1-2 SD and ≥2 SDs below the mean ................................. 183

Table 4.4 Speech and language outcomes in children with HLHS, TGA, and healthy controls at 4-5 years ................................................................. 184

Table 4.5 The total number and percentage of participants with speech and language scores 1-2 SD and ≥2 SDs below the mean ................................. 185

Table 4.6 Repeated measures Wilcoxon signed-rank analyses of changes in cognition/IQ, and receptive and expressive language, between time-points 3 and 4 ................................................................. 186

Table 4.7 Spearman’s correlation coefficients between key language outcome measures including: Bayley-3 receptive and expressive language, CELF-P2 receptive and expressive language, and receptive and expressive OWPVT scores, as well as Bayley-3 cognitive scores and WPPSI-IV full scale IQ...... 189

Table 4.8 Children’s Communication Checklist (CCC-2) outcomes by subtest and overall GCC, in children with HLHS, TGA, and healthy controls at 4-5 years ................................................................. 193

Table 4.9 The total number and percentage of participants with CCC-2 subtest scores 1-2 SD and ≥2 SDs below the mean ................................. 194

Table 4.10 Spearman’s correlation coefficients between objectively measured CELF-P2 language scores and parent-rated CCC-2 scores (for the whole cohort together). ................................................................. 196

Table 5.1 The full cohort including patients with HLHS and TGA, and healthy controls who participated in the auditory oddball ERP study, longitudinally ................................................................. 235

Table 5.2 Summary of the main parameters for the quantitative ERP analysis, 128 channel net .................................................................................. 240

Table 5.3 Summary of the main parameters for the quantitative ERP analysis, 256 channel net .................................................................................. 242

Table 5.4 Mean amplitude median and interquartile range of each condition, component, and group .............................................................................. 248

Table 5.5 Spearman's correlation coefficients between key speech and language outcomes measured behaviourally and ERPs measured at time-points 3 and 4 ................................................................. 251

Table 5.6 Wilcoxon results for longitudinal speech sound ERPs, between time-points 3 and 4 (T3 and T4), by condition and component, within-groups ................................................................. 253
Table 6.1 Patients with HLHS, TGA, and healthy controls who participated in the behavioural and psychosocial outcomes study at 4-5 years (time-point 4) ................................................................. 284
Table 6.2 Child Behaviour Checklist (CBCL) outcomes by subtest in children with HLHS, TGA, and healthy controls at 4-5 years ........ 288
Table 6.3 The total number and percentage of participants with CBCL subtest scores in the borderline and clinical range ................... 290
Table 6.4 Strengths and Difficulties Questionnaire (SDQ) outcomes by subtest in children with HLHS, TGA, and healthy controls at 4-5 years ................................................................. 291
Table 6.5 The total number and percentage of participants with SDQ subtest scores in the high and very high range .................. 292
Table 6.6 Adaptive Behavior Assessment System (ABAS) outcomes by domain in children with HLHS, TGA, and healthy controls at 4-5 years ................................................................. 293
Table 6.7 The total number and percentage of participants with ABAS summary scores 1-2 SD and ≥2 SDs below the mean .......... 294
Table 6.8 Behavior Rating Inventory of Executive Function - Preschool (BRIEF-P) outcomes by subtest and index, in children with HLHS, TGA, and healthy controls at 4-5 years .................... 295
Table 6.9 The total number and percentage of participants with BRIEF-P subtest scores in the borderline and clinical range .......... 296
Table 6.10 Pediatric Quality of Life Inventory (PedsQL) outcomes by subtest, in children with HLHS, TGA, and healthy controls at 4-5 years ................................................................. 297
Table 6.11 The total number and percentage of participants with PedsQL subscale and summary scores 1-2 SD or ≥2 SDs below the mean ................................................................. 298
Table 6.12 Spearman’s correlation coefficients between objectively measured CELF-P2 Core Language and narrative scores from the Bus Story, and CCC-2 parent-rated pragmatic language, and parent-rated social skills and executive functioning (for the whole cohort together) .................... 300
Table 6.13 Spearman’s correlation coefficients between PedsQL Psychosocial Summary and PedsQL Total scores, and CBCL Internalising Problems, Externalising Problems, and Total Problems, SDQ Total Difficulties, ABAS General Adaptive Composite (GAC), and BRIEF-P Inhibit, Working Memory, and Flexibility scores (for the whole cohort together) ................. 303
Table 6.14 Spearman’s correlation coefficients between longitudinal Bayley-3 Social-emotional and Adaptive Behaviour scores (at each time-point), and CBCL internalising problems, externalising problems, and total problems, and ABAS GAC score ........................................................................ 305
Table 6.15 Wilcoxon results for longitudinal Child Behaviour Checklist (CBCL) outcomes between time-points 3 and 4 (T3 and T4) by subtests, within-groups ................................................................. 307

Table 6.16 Spearman’s correlation coefficients between all CBCL subscale scores at time-points 3 and 4 (for the whole cohort) .................. 309

Table 7.1 Parental demographic information including education and employment levels for the cohort of patients with HLHS, TGA, and healthy controls who participated in the behavioural and psychosocial outcomes study at 4-5 years (time-point 4) ............... 350

Table 7.2 PedsQL Family Impact Module outcomes by subtest in parents of children with HLHS, TGA, and healthy controls at 4-5 years .... 354

Table 7.3 The total number and percentage of parents with PedsQL Family Impact Module scores 1-2 SD or ≥2 SDs below the mean............................................................... 356

Table 7.4 The Hospital Anxiety and Depression Scale (HADS) outcomes by subtest in parents of children with HLHS, TGA, and healthy controls at 4-5 years .................................................. 357

Table 7.5 The total number and percentage of parents with HADs scores in the borderline (1-2 SD below the mean) and clinical (≥2 SDs) range.............................................................................. 358

Table 7.6 Paediatric Inventory for Parents (PIP) outcomes by subtest in parents of children with HLHS and TGA at 4-5 years ......... 359

Table 7.7 The total number and percentage of parents with PIP scores 1-2 SD or ≥2 SDs below the mean......................................................... 360

Table 7.8 Impact of Event Scale (IES) outcomes by subtest in parents of children with HLHS and TGA at 4-5 years ............................ 361

Table 7.9 The total number and percentage of parents with IES scores in the clinical relevant, PTSD diagnosis, and extremely severe range, according to the published cut-offs for these categories ..... 361

Table 7.10 Spearman’s correlation coefficients between some of the key parent outcome measures including HRQOL, family functioning, and overall scores from the HADS, PIP, and the total IES score ... 363

Table 7.11 Spearman’s correlation coefficients between key parent and child outcome measures including behavioural, psychosocial functioning and overall HRQOL in children, and parent HRQOL, family functioning, parent mental health, and stress ....................... 366

Table 8.1 Hypotheses addressed in each data chapter, and whether the results supported these.......................................................... 389
## List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABAS</td>
<td>Adaptive Behavior Assessment System</td>
</tr>
<tr>
<td>ADHD</td>
<td>Attention-deficit hyperactivity disorder</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>ASD</td>
<td>Autism spectrum disorders</td>
</tr>
<tr>
<td>ASQ</td>
<td>Ages and Stages Questionnaire</td>
</tr>
<tr>
<td>Bayley</td>
<td>Bayley Scales of Infant Development</td>
</tr>
<tr>
<td>BCAS</td>
<td>Boston Circulatory Arrest Study</td>
</tr>
<tr>
<td>BDA</td>
<td>Brief Developmental Assessment</td>
</tr>
<tr>
<td>BRIEF-P</td>
<td>Behavior Rating Inventory of Executive Function - Preschool</td>
</tr>
<tr>
<td>BV</td>
<td>Biventricular</td>
</tr>
<tr>
<td>CA</td>
<td>Circulatory arrest</td>
</tr>
<tr>
<td>CBCL</td>
<td>Child Behaviour Checklist</td>
</tr>
<tr>
<td>CCC</td>
<td>Children's Communication Checklist</td>
</tr>
<tr>
<td>CELF(-P)</td>
<td>Clinical Evaluation of Language Fundamentals (Preschool)</td>
</tr>
<tr>
<td>CHD</td>
<td>Congenital heart disease</td>
</tr>
<tr>
<td>DHCA</td>
<td>Deep hypothermic circulatory arrest</td>
</tr>
<tr>
<td>DQ</td>
<td>Development Quotients</td>
</tr>
<tr>
<td>DTI</td>
<td>Diffusion tensor imaging</td>
</tr>
<tr>
<td>ECMO</td>
<td>Extracorporeal membrane oxygenation</td>
</tr>
<tr>
<td>EEG</td>
<td>Electroencephalography</td>
</tr>
<tr>
<td>EF</td>
<td>Executive functions</td>
</tr>
<tr>
<td>EOWPVT</td>
<td>Expressive One-Word Picture Vocabulary Test</td>
</tr>
<tr>
<td>ERP</td>
<td>Event-related potentials</td>
</tr>
<tr>
<td>FA</td>
<td>Fractional anisotropy</td>
</tr>
<tr>
<td>FSIQ</td>
<td>Full Scale IQ</td>
</tr>
<tr>
<td>GAC</td>
<td>General Adaptive Composite</td>
</tr>
<tr>
<td>GCC</td>
<td>General Communication Composite</td>
</tr>
<tr>
<td>GOSH</td>
<td>Great Ormond Street Hospital</td>
</tr>
<tr>
<td>HADS</td>
<td>Hospital Anxiety and Depression Scale</td>
</tr>
<tr>
<td>HI</td>
<td>Hypoxia/Ischaemia</td>
</tr>
<tr>
<td>HLHS</td>
<td>Hypoplastic left heart syndrome</td>
</tr>
<tr>
<td>HRQOL</td>
<td>Health-related quality of life</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>ICA</td>
<td>Independent component analysis</td>
</tr>
<tr>
<td>ICH</td>
<td>Institute of Child Health</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive care unit</td>
</tr>
<tr>
<td>IES (-R)</td>
<td>Impact of Event Scale (-Revised)</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile ranges</td>
</tr>
<tr>
<td>LFCPB</td>
<td>Low-flow cardiopulmonary bypass</td>
</tr>
<tr>
<td>MBCDI</td>
<td>MacArthur-Bates Communicative Development Inventories</td>
</tr>
<tr>
<td>MMN</td>
<td>Mismatch negativity</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>MRS</td>
<td>Magnetic resonance spectroscopy</td>
</tr>
<tr>
<td>ms</td>
<td>Milliseconds</td>
</tr>
<tr>
<td>NEPSY</td>
<td>Developmental neuropsychological assessment</td>
</tr>
<tr>
<td>NIHR</td>
<td>National Institute for Health and Care Research</td>
</tr>
<tr>
<td>PAT</td>
<td>Phonological Abilities Test</td>
</tr>
<tr>
<td>PCQLI</td>
<td>Pediatric Cardiac Quality of Life Inventory</td>
</tr>
<tr>
<td>PedsQL</td>
<td>Paediatric Quality of Life Inventory</td>
</tr>
<tr>
<td>PIP</td>
<td>Paediatric Inventory for Parents</td>
</tr>
<tr>
<td>PPI</td>
<td>Patient and public involvement</td>
</tr>
<tr>
<td>PTSD</td>
<td>Post-traumatic stress disorder</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of Life</td>
</tr>
<tr>
<td>ROWPVT</td>
<td>Receptive One-Word Picture Vocabulary Test</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SDoH</td>
<td>Social determinants of health</td>
</tr>
<tr>
<td>SDQ</td>
<td>Strengths and Difficulties Questionnaire</td>
</tr>
<tr>
<td>SES</td>
<td>Socioeconomic status</td>
</tr>
<tr>
<td>SIDC</td>
<td>Social interaction deviance composite</td>
</tr>
<tr>
<td>SLI</td>
<td>Specific language impairment</td>
</tr>
<tr>
<td>SV</td>
<td>Single ventricle</td>
</tr>
<tr>
<td>SVRT</td>
<td>Single Ventricle Reconstruction Trial</td>
</tr>
<tr>
<td>TCPC</td>
<td>Total cavopulmonary connection</td>
</tr>
<tr>
<td>(d) TGA</td>
<td>(dextra) Transposition of the Great Arteries</td>
</tr>
<tr>
<td>WPPSI</td>
<td>Wechsler Preschool and Primary Scale of Intelligence</td>
</tr>
</tbody>
</table>
Chapter 1: General Introduction

This chapter provides an overview of the different types of congenital heart diseases and their treatments, beginning with an introduction to congenital heart disease and distinguishing cyanotic and complex heart disease before describing two specific types – transposition of the great arteries and hypoplastic left heart syndrome which are the focus of this research. The second part of the chapter will discuss neurodevelopmental outcomes in children following neonatal open-heart surgery. Next, brain abnormalities commonly associated with complex congenital heart disease are discussed as well as factors which affect brain injury and neurodevelopment, and potentially increase the risk of adverse outcomes. Finally, areas of research interest will be introduced within the CHD context, which form the basis of each of the following chapters in this thesis.
1.1 Congenital Heart Disease

Congenital heart disease (CHD) is the most common type of birth defect, affecting up to one in every 100 babies born in the UK (NHS, 2021). The term CHD refers to abnormalities in the heart’s structure or function that occur in many different forms and can be classified into two broad categories: biventricular (BV) and single ventricle (SV) heart disease (Bruneau, 2008). There is a broad spectrum of conditions ranging from low-risk simple defects such as ventricular or atrial septal defects, to more complex high-risk severe lesions such as pulmonary atresia and hypoplastic left heart syndrome which require multiple surgeries to improve the functioning of the heart (Brown et al., 2016; Buratto et al., 2016). Approximately, 20-30% of heart defects are considered severe and are life-threatening if left untreated or unpalliated within the first year of life (NICOR, 2022) with 50% of neonates with CHD requiring immediate surgical intervention in the first few days of life (Latal, 2016). When open-heart surgery for CHD was first started, it was uncommon for infants with complex CHD to survive into later childhood. However, over the last 40 years, medical and surgical advances have led to significantly increased survival rates with recent reports showing survival rates in the very short-term (30-day post-surgery) currently around 98% (NICOR, 2022). Attention is now shifting on other aspects of survival such as morbidity associated with CHD and its treatment and the impact on longer-term survival. Of note, currently reported long-term survival rates continue to improve and therefore may not be representative of children born with CHD today.

Currently in the UK, in approximately half of babies with CHD requiring an intervention, the heart defect is detected prenatally by ultrasound scans (NICOR, 2017). This rate increases to 80% in babies with more complex lesions such as
SV CHD as these are often easier to detect. Prenatal diagnosis is key in these conditions as it has numerous benefits including improved preoperative clinical status, shorter postoperative mechanical ventilator support, improved long-term neurological outcomes, and increased survival following initial surgery when compared with those diagnosed after birth (Liu et al., 2018). Early diagnosis also allows parents to be better prepared and informed and enables delivery at specialist hospitals and care centres that can provide optimal neonatal management for CHD.

The precise aetiology of cardiac malformations in CHD is not fully understood, with only 15% of CHD cases being attributable to a known cause (Wu et al., 2020). However, there are several factors which are known to increase the risk of CHD, including having parents or siblings with CHD; maternal illness and infections such as rubella during pregnancy; the use of certain medication; smoking or drinking alcohol during pregnancy; poorly controlled diabetes; and genetic and chromosome defects (NHS, 2022; R. Sun et al., 2015). Up to one-third of children with CHD are born with an underlying genetic disorder, most frequently Trisomy 21 (Down syndrome), 22q11 microdeletion (DiGeorge syndrome), and CHARGE syndrome (Bruneau, 2008; Latal, 2016).

1.2 Cyanotic Heart Disease

From the total population of infants born with CHD, around 15% are cyanotic and appear “blueish” at birth as a result of inadequate oxygenation of the blood (Hoffman and Kaplan, 2002). Deoxygenated blood is pumped to the body without passing through the lungs leading to the blue appearance of skin. Cyanotic CHD is a heterogenous group of abnormalities and all are considered to be severe.
Some can be ‘corrected’ by open-heart surgery such as tetralogy of Fallot and transposition of the great arteries, whereas others require multiple staged surgeries (which are palliative) such as hypoplastic right heart and hypoplastic left heart syndromes.

1.2.1 Transposition of the Great Arteries (TGA)

The incidence of TGA is 4.7 per 10,000 live births and it is one of the most common cyanotic heart diseases (Szymanski et al., 2021). It is a heart defect in which the two main blood vessels leaving the heart, the pulmonary artery and the aorta, are transposed so that the pulmonary artery connects to the left rather than the right ventricle and the aorta connects to the right rather than the left ventricle (Figure 1.1). Typically, the aorta is in front of the pulmonary artery towards the right of it (dextro) and this is commonly referred to as d-TGA in the literature (and TGA hereafter). Rarely, the aorta can be to the left of the pulmonary artery (levo or corrected transposition) (CDC, 2022). A range of other cardiac malformations can also occur in patients with TGA including atrial or ventricular septal defects. Neonates born with TGA who have insufficient mixing of oxygenated and deoxygenated blood in the atria and patent ductus arteriosus, and consequently have severe hypoxemia, require urgent intervention as part of their preoperative management to improve oxygenation. This involves a balloon atrial septostomy in the first few days of life to ensure adequate oxygen is circulating in their body while they wait for surgery. In this procedure a catheter with a small collapsed balloon at its end is placed into a vein at the top of the leg or the belly button, which is then guided up into the heart, the balloon is inflated making a hole in the septum to allow some oxygenated blood to circulate in the body before being deflated and removed (Patey et al., 2021; Villafañe et al., 2014).
Corrective open-heart surgery to swap the two main blood vessels to normal position and restore normal circulation is usually undertaken during the first two weeks of life, often referred to as the Arterial-Switch operation (Martins & Castela, 2008). Today, this is a relatively straightforward single surgery with reduced risk of future heart failure and further cyanosis. Commonly found genetic disorders in CHD are relatively rare with TGA (McQuillen and Miller, 2010). Generally, the prognosis for TGA following corrective surgery is excellent with systematic reviews reporting greater than 90% survival up to 20 years post-surgery (Morfaw et al., 2020).

1.2.2 Hypoplastic Left Heart Syndrome (HLHS)

The incidence of HLHS is approximately 2 per 10,000 live births (Siffel, et al., 2015). It affects several structures on the left side of the heart including the left ventricle, mitral valve and aorta, which are all underdeveloped and much smaller than normal (Figure 1.1), resulting in inadequate blood supply to the body (Tworetzky et al., 2001). Neonates born with HLHS require staged cardiac surgeries during the first five years of life, which are most commonly completed within the first 3-4 years (Barron et al., 2009). Surgeons cannot create optimal circulation in the neonatal period, so the staged surgery allows the patient’s body to adapt to the haemodynamic changes and reduces surgical morbidity and mortality (Fredenburg et al., 2011). It is important to note that the heart cannot be corrected, or made to function normally by restoring biventricular circulation. Instead, surgery is palliative and simply improves the functioning of the heart. The first stage of surgery (shortly after birth) is the Norwood procedure, which involves reconstruction of the aortic arch and connection of the aorta to the main
pulmonary artery via a shunt (either a Blalock-Taussig shunt or right ventricle–pulmonary artery conduit). This allows the right ventricle of the heart to pump blood into the aorta (i.e. become the main ventricle), and provide blood supply to the lungs (Barron et al., 2009; Feinstein et al., 2012). This complex procedure results in (right) univentricular circulation allowing adequate blood oxygen delivery whilst minimising volume overload of circulation. Approximately 4-6 months later, the Glenn operation is undertaken where a bidirectional Glenn shunt is used to replace the original shunt from stage one, connecting the right pulmonary artery to the superior vena cava. This allows deoxygenated blood back to the heart, allowing it to flow through the pulmonary artery to the lungs to be oxygenated, it also increases blood flow to the lungs and reduces the workload of the heart (Barron et al., 2009; Feinstein et al., 2012). However, deoxygenated blood is still able to mix with oxygenated blood in the left heart leaving the child mildly cyanotic. Therefore, a final operation known as the Fontan is required at approximately three years of age (but can be as early as 18 months) to improve the amount of oxygenated blood and exercise capacity. This involves a total cavopulmonary connection (TCPC) that connects both the superior and inferior vena cava to the right pulmonary artery, and allows all deoxygenated blood to flow passively through the lungs, bypassing the right ventricle (Fredenburg et al., 2011; Marino, 2002).

This is a severe and complex type of CHD and is associated with a higher risk for death within one year following hospital discharge or emergency readmission to intensive care (Brown et al., 2016). There is a high risk of mortality in patients with HLHS in the period between their staged surgeries, following the Norwood procedure and before the Fontan which is reported to be between 5-20%, although this risk has decreased in more recent years due to decreased time
between these staged surgeries (Kaplinski et al., 2020) and improved inter-stage monitoring. Open-heart surgery is required at each of these stages, which further increases risks of hypoxic-ischaemic brain injury, stroke, fluid around the lungs, and death. Currently, surgical mortality rate is historically low with the UK’s National CHD audit reporting 30 day post-operative survival for the Norwood, Glenn and Fontan procedures exceeding 90% (NICOR, 2022). However, these figures also include other forms of CHD that may require Fontan surgery which have a better outcome than HLHS. Further, long-term survival rates following the Fontan procedure are reported to vary. For example, some recent longitudinal studies and meta-analyses have reported 20 year post-Fontan survival rates of 74% and up to 82% (Downing et al., 2017; Poh and d’Udekem, 2018), whilst others report 6 month post-Fontan survival rates of only 67% (Liu et al., 2018). A small proportion (8-12%) of children with HLHS experience refractory cardiopulmonary failure after the Norwood procedure, and commonly require extracorporeal membrane oxygenation (ECMO). An ECMO machine is used as life support and similar to that used during open-heart surgery, but the reported survival rate to hospital discharge is poor and varies from 28-64% (Allan et al., 2007; Hoskote et al., 2006; Sherwin et al., 2012). Longer ventilation before cannulation, longer support duration, and ECMO complications are all linked to increased risk of mortality in neonates with HLHS.
The interdependent relationship between the heart and the brain begins early during foetal development as heart and brain organogenesis occurs simultaneously (McQuillen et al., 2010). As morphological development of both organs is completed, the brain continues to develop and significantly increases in size due to neuronal development and the beginning of myelination (Srivastava, 2006). Consequently, brain metabolism is increased which depends on the functioning of the heart in order to deliver adequate oxygen. In complex CHD, malformations of the heart can cause alterations in foetal blood flow which
then leads to decreased oxygen delivery to the brain. For example, in TGA, the aorta arises from the right ventricle and receives desaturated blood and subsequently delivers reduced oxygen to the brain, and in HLHS, the significantly underdeveloped or absent left ventricle increases pressure in the left atrium which limits blood flow, and leads to the mixing of deoxygenated and oxygenated blood in the right atrium and ventricle which impacts cerebral circulation (Figure 1.2) (McQuillen et al., 2010). In the latter condition, cerebral blood flow may also occur in a retrograde fashion from the patent ductus arteriosus.

![Figure 1.2 Foetal circulation in A) a normal healthy heart, and consequent disruption in circulation and blood flow in B) TGA and C) HLHS. Estimated blood oxygen saturation percentages are shown for each ventricle, where oxygen-rich blood is represented in red, and deoxygenated blood is blue-purple. In HLHS, the absent or underdeveloped left ventricle significantly limits or reverses blood flow, resulting in the mixing of desaturated and well-saturated/oxygenated blood in the right atrium and ventricle (edited from McQuillen et al., 2010)](image)

It is evident that there is a complex connection between blood circulation through the heart and to the brain during foetal and postnatal development, and deficient cerebral oxygen and blood flow (i.e. hypoxia/ischaemia) in complex CHD is
associated with abnormalities in brain development prior to neonatal cardiac surgery (Bonthrone et al. 2021; Marelli et al., 2016). Neonatal brains are extremely vulnerable to damage and several risk factors have been reported in neonates with cyanotic complex CHD. These include hypoxic-ischaemic injury, focal stroke, disturbances in cerebral oxidative metabolism, mild to moderate white matter injury, and delayed brain maturation (Licht et al., 2009; Miller et al., 2004). Each of these factors have different implications for neurodevelopmental outcomes. Previously, brain abnormalities had to be investigated using animal models or postnatal magnetic resonance imaging (MRI) in human babies. However, recent advances in foetal MRI allow brain abnormalities to be detected and assessed in utero, and this has revealed reduced cerebral oxygen delivery and consumption in utero are associated with reduced foetal brain size in CHD (L. Sun et al., 2015). Brain abnormalities associated with CHD are discussed in detail below in section 1.6.

Open-heart surgery procedures to treat cardiac defects in CHD are also associated with (further) risk of brain injury due to deep circulatory arrest and interference with oxygen and blood supply, leading to hypoxic and/or ischaemic events. The heart and the brain function interdependently, so it is not surprising that disruption in one organ will have significant impact on the other. It is clear that malformations in the structure and function of the heart can lead to impairments in the brain and neurodevelopment in various ways across the lifespan (Figure 1.3). Today, although the majority of children with CHD in the UK survive to adulthood (~80%), up to 70% of survivors experience neurodevelopmental delays and deficits across a wide spectrum of domains as they grow through childhood and adolescence (Donofrio & Massaro, 2010; Li et al., 2014). With increased survival rates, the focus of research has now shifted
from mortality towards long-term morbidity, neurodevelopmental outcomes, and quality of life in patients with CHD (Marino, 2002; Marino et al., 2016).

![Diagram showing the impact of CHD on brain development across the lifespan](image)

Figure 1.3 A sequential model linking CHD-related heart abnormalities to abnormalities in the brain and consequent neurocognitive impairments across the lifespan, from perinatal brain development, through childhood, and into adulthood and the aging brain (Marelli et al., 2016)

### 1.4 Neurodevelopmental Outcomes in CHD

Despite medical and surgical advances, survivors can suffer from morbidities as a result of their circulatory abnormalities and surgical therapies. Hence, children with CHD are at higher risk for neurodevelopmental problems compared to healthy children due to the impact of these morbidities and biological and environmental risk factors (Marino et al., 2012). The neurodevelopmental sequelae of CHD are often subtle in young infants and the extent of impairment
can be unrecognised until specific cognitive and higher order executive functions emerge with increasing age and experience, and teacher-based expectation at school age (Bhatt et al., 2015).

Extensive literature has reported on neurodevelopmental outcomes in children and adolescents with CHD. Severe global delays are generally uncommon; however, there is a distinctive pattern of mild or low severity cognitive impairment and/or combined disabilities in multiple domains. Wernovsky (2006) referred to this “high-prevalence, low severity” as the developmental “signature” in CHD, linking severity of the congenital cardiac defect to the severity of disability. Cognition/intelligence (IQ) scores reportedly fall within the low average range in children with CHD, while there are reports of impairments across several domains including attention, learning, executive function, communication and language skills, and motor and visual-spatial skills.

Preschool children with CHD who underwent open-heart surgery have been found to have lower scores in expressive language and logical reasoning when compared to non-operated children with CHD (Calderon et al., 2018). Although mean scores were within the normative range, 25% of the operated children had cognitive scores >1 standard deviation (SD) below test norms. Being small for gestational age was found to significantly increase the risk of cognitive impairment, after adjusting for maternal education, complexity of CHD, and perioperative variables. It is noteworthy that despite statistically significant differences between CHD patients and norms, scores within 1 SD are less clinically relevant as they are unlikely to represent delay, compared to scores >1, >2, or >3 SDs below the normative mean which are clinically significant and represent mild, moderate, and severe impairment, respectively (Johnson et al., 2014).
Brosig et al. (2017) examined pre-schoolers with CHD who were at risk of developmental delay. Scores on the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) did not differ based on cardiac anatomy (SV or BV condition), but both groups had scores lower than the normative population on fine motor and adaptive behaviour skills, though their scores were within 1 SD of the norms. The same group also reported that rates of delay for children with CHD changed over time; more children fell in the at-risk or delayed category at age 4, despite scores in the average range at age 2, on measures of both cognitive and fine motor skills (Brosig et al., 2018). This is in contrast to Gaudet et al. (2021) who found that the presence of earlier impairments was predictive of later impairments. Gaudet et al. (2021) found that 5 year-olds with CHD had scores significantly below the norms on most developmental domains including intelligence, expressive language, phonological awareness, and executive function. Despite the significant differences, most scores were within 1 SD of the norms. However, in their cohort there was an increased prevalence of impairments compared to the normative sample in cognitive and language domains. They also found evidence of impaired working memory, attention, and preacademic skills in 35-65% of children. Earlier language scores at 2 years of age predicted impaired language at 5 years.

Creighton et al. (2007) found that fewer children were delayed at 5 years than at 2 years-old. However, survival to age 5 in patients with TGA was 100% compared to only 54% for those with HLHS. Patients with TGA also had higher scores compared to those with HLHS on the Psychomotor Developmental Index (i.e. Bayley Scales of Infant and Toddler Development II – Bayley-2), Performance IQ (i.e. WPPSI), and Beery Visual Motor Integration test. Therefore, as well as lower survival rates in pre-schoolers with HLHS, these children also tend to have worse
neurodevelopmental outcomes compared to children with TGA. This is likely due to the increased severity of the heart defect, multiple open-heart surgeries within this time period, and the greater risk of morbidities associated with HLHS, which suggests that SV circulation has a greater adverse impact on brain development. Further, discrepancies between these studies may be explained by the fact that some apply specific exclusion criteria during recruitment such as the presence of any comorbid genetic syndromes known to impact neurodevelopment (e.g. Gaudet et al., 2021), whilst others do not or do not specifically specify this in their methodology.

There is clear evidence of the mild to low severity impairment pattern commonly found in CHD, but not all literature is in agreement. For example, McCusker et al. (2007) assessed five neuropsychological domains, namely attention, language, sensorimotor, visuospatial and memory skills, in 4-year-olds with CHD (including but not limited to HLHS and TGA). The cohort scored within the normal range for all domains with the exception of sensorimotor and visuospatial skills, for which they showed medium and high effect size deviations respectively from reference group norms. These results may be explained by several factors such as the type of heart defect included in the sample; the presence of comorbidities or genetic syndromes; surgical risk factors; and psychosocial and family influences. Though cognitive problems were not observed, they did find the cyanotic-corrected group (i.e. TGA) had fewer behavioural problems, whereas, the cyanotic-complex group (i.e. HLHS) had statistically higher behavioural scores, and higher frequency of clinically relevant scores. They concluded that although cyanosis is associated with poorer neuropsychological outcomes, it does not appear to be related per se to poorer behavioural outcomes. The same group later reported specific behavioural difficulties related to attention (i.e. inattention and hyperactivity),
social problems (i.e. peer relationships), and thought problems in severe CHD compared to healthy siblings (McCusker et al., 2013).

There are similar findings of the distinctive neurodevelopmental “signature” in older school-age children with CHD. For example, Derridj et al. (2021) found evidence that 8 year-old children with cyanotic CHD and heart failure (i.e. TGA and HLHS) had lower scores for IQ, receptive language and phonological encoding, memory (i.e. immediate and delayed word recall), auditory attention, and executive function (i.e. inhibition and flexibility) when compared to the control group (although they were within 1 SD).

1.5 Social-Emotional and Behavioural Outcomes

Multiple studies have identified an increased incidence of social-emotional and behavioural problems in school-age children and adolescents with CHD (Bellinger et al., 2003; Brosig et al., 2007; Casey et al., 1996; Dunbar-Masterson et al., 2001; Goldberg et al., 2000; Utens et al., 1993). Internalising socioemotional problems appear to be more common in older children with CHD, including social withdrawal, anxiety, somatic complaints, and depressive symptoms, (Dahlawi et al., 2020; Marino et al., 2012). Externalising behavioural problems have also been identified. For example, there is a high prevalence of inattention and hyperactive behaviours in the school age population with CHD (Hövels-Gürich et al., 2007; Kirshbom et al., 2005; Mahle et al., 2000). Shillingford et al. (2008) found that 5-10 year-olds with CHD were receiving clinically significant ratings for inattention and hyperactivity, with 30% of their parents reporting high-risk scores for inattention and 29% for hyperactivity. Recent reviews have also reported a high prevalence of low-severity socioemotional and
behavioural dysregulation, and concluded that children with severe CHD or comorbid conditions experience greater impairment, with higher rates of externalising behaviour problems, although internalising behaviour problems were also evident (Clancy et al., 2020; Dahlawi et al., 2020). These socioemotional and behavioural impairments are also detectable in very early infancy, unlike some of the neurodevelopmental outcomes discussed previously. However, not all impairments can be detected early (e.g. executive dysfunction) as they appear to be ‘hidden’ until later in development when greater cognitive demands are placed on the child and academic performance is affected. This presents the idea of children with CHD ‘growing into their deficits’, which has also been seen in other clinical populations including children born with chronic hydrocephalus (de Beer and Scheltens, 2016) and extremely preterm (O’Reilly et al., 2020). Further, cognitive development itself is not all or none; different components emerge at different time-points throughout development, influenced by both biological and environmental factors. Some deficits could also be compensated for to a certain extent by the developing brain, as they are seen to improve overtime (e.g. motoric function) (Ferentzi et al., 2017). This reinforces the need for long-term surveillance of children with CHD. Congenital heart disease has a multifactorial impact on neurodevelopment which can change with age; while cross-sectional studies are important to better understand the delays and/or impairments in children with CHD, more longitudinal research is needed to build a complete and reliable picture.
1.5.1 Outcomes in Children with TGA

1.5.1.1 Longitudinal Studies

One of the most studied types of CHD is TGA and there are a number of longitudinal studies as well as cross-sectional studies. The landmark Boston Circulatory Arrest Study (BCAS) (Bellinger et al., 1991; 1995; 1999; 2003; 2011; Rappaport et al., 1998) followed 171 children with d-TGA longitudinally following heart surgery in infancy. Patients were randomly split into two treatment groups: deep hypothermia with total circulatory arrest (CA) or low-flow cardiopulmonary bypass (LFCPB). At 1 year of age, infants in the CA group had lower scores on the Psychomotor Development Index of the Bayley-1 with a higher proportion having scores ≥2 SDs below the normative mean compared to those in the LFCPB group. Psychomotor scores were inversely related to the duration of CA (Bellinger et al., 1995). Infants with post-operative seizures were also more likely to have worse neurodevelopmental outcomes at 1 and 2.5 years as well as neurological and MRI abnormalities at 1 year of age (Rappaport et al., 1998). At 4 years, the CA group scored lower on tests of motor function and had more severe speech abnormalities. All patients performed below expectations in IQ, expressive language, visual-motor integration, motor function, and oromotor control. By 8 years, the CA group was still performing worse compared to the LFCPB group on tests of motor and cognitive function including manual dexterity, apraxia of speech, visual-motor tracking, and phonological awareness (Bellinger et al., 2003). There were no differences in IQ score, academic achievement, memory, problem solving, and visual-motor integration between the treatment groups. The LFCPB group tended to be more impulsive, and had worse behaviour as rated by teachers, compared to the CA group. By 16 years of age, few significant treatment group differences were observed. Both CA and LFCBP
groups scored lower than normative populations, with 26-54% scoring ≥1 SDs below the expected mean, across all domains. Despite the adolescent cohort scoring within the average range, 65% were receiving remedial academic or behavioural services (Bellinger et al., 2011).

At the 4 and 8 year follow-up of the BCAS, Bellinger (2008) also reported deficits in social cognition and particularly in theory of mind. Theory of mind is a key component of social cognition, referring to the ability to make inferences about other people’s mental state and using these to interpret others’ goal-directed behaviour. Bellinger (2008; 2010) found that speech and language deficits in the TGA cohort were not limited to motor-speech programming problems, but also included pragmatic language skills (e.g. storytelling, pretend play) which were moderately severe and persistent. These skills are essential for engagement in complex social interactions and have reportedly been linked to immature executive functioning (i.e. cognitive and behavioural inhibition) in 7 year-old children with TGA (Calderon et al., 2010). These results suggest that CHD may affect the brain structures and circuits responsible for social cognition and affective processing. Moreover, it is widely assumed that certain brain areas are particularly susceptible to hypoxic/ischaemic injury, and this includes the prefrontal cortex and striate body assumed to be associated with the executive control network of attention (Hövels-Gürich et al., 2007).

Hövels-Gürich et al.’s (2002) longitudinal study followed 60 children with TGA through school age and reported that at 10 years of age overall IQ scores were not significantly different than population norms. They did however find gross and fine motor dysfunction (>20%), reduced expressive and receptive language (~20%), and speech abnormalities (40%). Neurodevelopmental impairment in one or more domains was found in 55% of children with TGA at 10 years,
compared to 26% at 5 years of age. They also concluded that longer bypass duration predicted neurological (e.g. head shape and growth, cranial nerves, motor dyspraxia, seizures) and speech dysfunction, while peri and postoperative cardiocirculatory insufficiency predicted neurological and motor dysfunction. This indicates further brain regions responsible for speech and motoric function being susceptible to hypoxic/ischaemic injury in CHD. McGrath et al. (2004) investigated the predictability of IQ and academic achievement at 8 years from neurodevelopmental status at 1 year in children with TGA. They found patterns to suggest that scores from the Bayley at 1 year had poor sensitivity and poor positive predictive value, and concluded that more than 50% of children with low scores at 8 years had scores in the normal range at 1 year. Therefore, school-aged children who are at risk for poor outcomes may not be identified from earlier assessment scores.

1.5.1.2 Cross-Sectional Studies

Cross-sectional studies also provide evidence of neurodevelopmental delays in children with TGA. It is important to note, however, that studies focussing on neurodevelopmental outcomes in infants with TGA have mixed results. For example, Andropoulos et al. (2012) and Lim et al. (2019) respectively found that 12 and 18 month-olds had cognitive, language, and motor scores measured with the Bayley-3 which were all within the normal range. Similar results have been observed in 18-24 month-olds investigated using the Bayley-2 (Freed et al., 2006). This is in contrast with longitudinal studies such as those mentioned above which have used Bayley-2 to evaluate neurodevelopment at 1 year and found 9% of the cohort had Mental Development Index scores and 21% had Psychomotor
Development Index scores >1 SD below the normative mean (McGrath et al., 2004).

Ramanan et al. (2021) followed up 61 3-5 year-olds with TGA. Neurological abnormalities were reported in 31%, of which 28% had neurodevelopmental disorder; 16% had speech and language impairment; 3% had attention-deficit hyperactivity disorder (ADHD); and 7% had neuromotor impairment. They concluded that increasing time to lactate normalisation and low socioeconomic status were associated with developmental delay, following corrective surgery. Executive function components such as inhibition and cognitive flexibility have also been found to be significantly delayed in 5-7 year-olds with TGA, as well as first and second level theory of mind, despite normal working memory and IQ (Calderon et al., 2010; 2014). Further, Dunbar-Masterson et al. (2001) reported 8 year-olds with TGA had significantly more problems with attention, learning, and speech, and greater frequency of developmental delay, compared with normative samples.

Recent reviews also summarise the typical neurodevelopmental and behavioural phenotype associated with children with TGA who have IQ scores in the normal range but display impairments in visual-spatial and fine-motor abilities, executive functioning, processing speed, attention, working memory, higher-order language skills, and social cognition (Kasmi et al., 2017; Kordopati-Zilou et al., 2022). It is important to acknowledge that some of these impairments, such as processing speed and working memory, contribute to the IQ score in intelligence tests, so they are not independent. As these children age, they face increasing challenges including deteriorating higher order cognitive skills, problems in psychosocial adjustment, and increased risk of psychiatric disorders such as ADHD, depression, and anxiety (Kasmi et al., 2017; Kordopati-Zilou et al., 2022).
1.5.2 Outcomes in Children with HLHS

1.5.2.1 Longitudinal Studies

The Single Ventricle Reconstruction Trial (SVRT) represents the largest cohort of surviving children with HLHS (Ohye et al., 2008) who have been longitudinally studied following their Norwood procedure. Neurodevelopmental outcome was first assessed at 14 months using the Bayley-2. The Psychomotor Development Index score (74±19) and Mental Development Index score (89±18) of 321 children were significantly lower than normative means (Newburger et al., 2012). The surviving SVRT cohort were assessed again at 3 years (Goldberg et al., 2014). Scores from all domains on the parent-completed Ages and Stages Questionnaire (ASQ) were significantly lower than the normative population suggesting impaired neurodevelopment. The percentage of children with scores >2 SDs below the mean was 20% for Communication, 30% for Gross Motor, 35% for Fine Motor, 24% for Problem Solving and 17% for the Personal-Social Scale. Lower Bayley-2 scores at 14 months only modestly predicted lower ASQ scores at 3 years, emphasising the need for longitudinal follow-up of children with HLHS. Importantly, Bayley-2 is administered directly with the child whereas the ASQ is parent-completed. By 4 years of age, only 38% of the cohort reported using no early intervention services; the remainder of the cohort were accessing speech and language, physical, and occupational therapy, with a small proportion receiving cognitive disorder interventions (Mussatto et al., 2018). At 6 years, the majority of the cohort had motor skills scores within 1 SD of population norms, with 11% scoring below this range. Overall, the cohort showed difficulty in adaptive behaviour, behavioural symptoms, quality of life, and functional status (Goldberg et al., 2019; Sananes et al., 2021). A greater proportion of the cohort
had scores outside the normal range than would be expected for the general population. Neurodevelopment is currently being studied in the surviving SVRT cohort at 10-12 years of age.

1.5.2.2 Cross-Sectional Studies

The SVRT findings from infancy are consistent with earlier research by Tabbutt et al. (2008) who reported similar mean scores, and found that 48% of 1 year-olds had Psychomotor Development Index scores >2 SDs below the general population mean, and 11% for Mental Development Index scores. Brosig et al. (2013) found that average neurodevelopmental performance and IQ scores of 4-6 year-olds with HLHS did not differ significantly from test norms. However, the cohort performed significantly worse than norms on measures of visual-motor integration, fine motor skills, memory, and the word structure subtest of the Clinical Evaluation of Language Fundamentals (CELF) - Preschool. On parent and teacher completed questionnaires, they were also rated higher on attention problems compared to the test norms, where higher scores indicate greater difficulties. More recently, Atallah et al. (2020) reported 4-5 year-olds with HLHS had mean full-scale, performance, and verbal IQ within 1 SD of population norms. However, 13%, 15%, and 12%, respectively, had IQ scores >2 SDs below norms, and visual-motor integration scores were >1 SD below the mean. These findings are clinically relevant as they reflect moderate-to-severe impairments. Importantly, only 58% of children survived post-Fontan surgery to undergo neurodevelopmental assessment, which provides support for the fact that children with HLHS have worse survival rates and neurodevelopmental outcomes compared to children with TGA.
Among some of the first survivors of staged reconstruction, Mahle et al. (2000) found that the majority of school-aged children (6-13 years) with HLHS had IQ scores within the normal range. However, the mean performance for this cohort was lower than the general population, as were their language scores on the CELF-Revised. Sixty-nine percent had evidence of attention deficit disorder, one-third were receiving special education services, and 18% had mental restrictions (IQ <70). In contrast, Oberhuber et al. (2017) reported that the average IQ of older school-age children (i.e. 6-16 years) with HLHS was 84.5 which is significantly lower than the test norms. Average cognitive development of the cohort was below normal: 25.5% were in the ‘far below average’ range, 27.9% were in the ‘below average’ range, and the remaining were in the ‘average’ range. Again, discrepancies between these studies may be explained by the fact that some (e.g. Brosig et al., 2013) have excluded participants with known genetic syndromes, whereas others have not specified this, making it difficult to know if genetic abnormalities were known to the researchers and/or if these patients were included in their cohorts. This is particularly problematic when comparing research findings in the literature, as genetic abnormalities and syndromes are widely known to affect neurodevelopmental outcomes, but these are not always controlled for, making it challenging to decipher if neurodevelopmental outcomes are a result of the CHD or a combination of CHD and genetic abnormalities.

Across studies from early infancy to school-age, while reports vary, they generally suggest that children with CHD are at increased risk of neurodevelopmental delay or impairment. Some findings suggest that HLHS patients in particular have the worst neurodevelopmental outcomes (e.g. Baum et al., 2004; Donofrio & Massaro, 2010; Mussatto et al., 2018; Reich et al.; 2017), whilst others have found no differences between TGA and HLHS patients (e.g. Brosig et al., 2017).
The latter is surprising given that it is widely accepted that severity of CHD is linked to the severity of disability and neurodevelopmental impairment (Wernovsky, 2006), and mortality and morbidity rates in HLHS are much higher than those in TGA. Consequently, it is plausible to assume that individuals with HLHS would have worse neurodevelopmental outcomes, compared to those with other types of CHD. In a recent review, Burns et al. (2021) identified that patients with single ventricle CHD (e.g. HLHS) are at increased risk of impairments in motor function, speech and language, cognitive development, and behavioural problems and reduced quality of life. These neurodevelopmental delays can be evident in infancy, but are more common in later childhood so long-term follow-up is imperative.

A pattern is emerging in the literature of normal to low-average IQ which is distinct from some aspects of sensorimotor function and speech and language which appear to be more vulnerable to compromise in complex CHD. Overall, CHD patients tend to score below test norms or healthy controls, even if that is generally within the average range. This high prevalence but mild severity of deficits is the developmental signature of many CHD patients. Although severe abnormalities and disability are uncommon, many of the studies discussed have provided evidence for moderate to severe impairments (i.e. 1-2 SD and ≥2 SDs below norms) which are clinically relevant in a range of functions, especially in HLHS patients. Consequently, it is apparent that there are multiple factors affecting neurodevelopmental outcomes in CHD, besides cardiac morphology. Understanding which factors lead to poorer outcomes in select CHD patients is of utmost importance, and these are discussed below in section 1.7.
1.5.3 Outcomes Across the Lifespan: Adolescence and Adulthood

Given the increasing number of children with severe and complex CHD surviving into adolescence and especially adulthood (NICOR, 2017), recent research has begun to explore lifespan outcomes in these individuals. The extent to which neurodevelopmental delay and disability continue into adolescence and adulthood currently remains unclear, but understanding the long-term trajectory and manifestation of early impairments has important clinical implications for advances in effective interventions and management. Recent systematic reviews and studies have reported that adolescents with CHD have poorer neurodevelopmental outcomes in a range of domains including full-scale IQ, processing speed, perceptual reasoning, working memory, attention, visual perception, visuomotor integration, motor functioning, reading, mathematics, and aspects of executive functioning such as cognitive flexibility, problem solving, and inhibition (Huisenga et al., 2020; Verrall et al., 2019). This suggests that the increased risk of impairments in many of these domains in childhood are persistent and continue into adolescence. Adolescents with SV defects have also been reported to be at increased risk of lifetime psychiatric diagnoses, ADHD, and self-reported anxiety (Huisenga et al., 2020). MRI studies in adolescents have also revealed that brain abnormalities such as reduced total brain volume are related to poorer intelligence, memory, visual-spatial skills and executive functioning (Aleksonis and King, 2022; Bellinger et al., 2011) which implicates global impairment. However, other studies have reported more selective reductions in brain volume. For example, reduced hippocampal volumes have been specifically related to long-term memory deficits, in the absence of impaired IQ (Muñoz-López et al, 2017). Many of these brain abnormalities are likely to be acquired as a consequence of CHD and its surgical treatment, rather than being
developmental. This provides further support for the idea that certain brain regions and circuits are more susceptible to hypoxic/ischaemic insults during infancy and childhood, and the impact of this damage continues throughout the lifespan.

Research in young adults is more limited but many of the poorer outcomes described in adolescence persist in adulthood, these include reduced abilities and/or impairments in executive functioning, social cognition, information processing speed, working memory, overall and divided attention, psychomotor speed and reaction time, fine motor function, and visuospatial skills (Ilardi et al., 2017; Klouda et al., 2017; Tyagi et al., 2017). Again, adults with more complex CHD (i.e. SV morphology) are more notably affected and have poorer outcomes compared to adults with other types of CHD. They also have been reported to have increased neurological comorbidities, such as stroke and seizures, comorbid psychiatric disorders such as anxiety and depression, greater risk of dementia, are more likely to be unemployed (18–50%), have pragmatic language impairment, and have reduced overall quality of life compared to healthy populations (Bagge et al., 2018; Hunter and Swan, 2016; Verrall et al., 2019). Marelli et al. (2016) put forward the idea that impaired neurocognitive development becomes neurocognitive decline in adults with CHD, hence, emphasising the importance of a lifespan perspective of neurocognitive functioning in CHD which includes a better understanding of early foetal haemodynamics and their role in lesion-specific alterations in the brain, which continue to have lifelong implications for optimal functioning.
1.5.4 Management and Surveillance of Neurodevelopmental Outcomes

Neurodevelopmental delays and/or impairments can be substantial and persist throughout life, which places an increased burden upon families, health care systems and educational facilities. Hence, developmental surveillance of children with complex CHD is recommended. Early referral, support and access to intervention services are key for the most vulnerable children in order to avoid morbidities becoming entrenched. This could prevent later academic, social, and behavioural problems, and provide a basis for the development of early targeted interventions, where required, as well as improving overall quality of life. A statement from the American Heart Association puts forward a CHD algorithm aimed at medical professionals for the periodic surveillance, screening, evaluation, and re-evaluation of children in order to enhance the identification of potential developmental delays and/or disorders (Marino et al., 2012). This is especially relevant for those patients at high risk with complex CHD, including those with TGA and HLHS. More recently, the Cardiac Neurodevelopmental Outcome Collaborative has put forward specific guidelines for the neurodevelopmental evaluation of children with CHD from birth through to 5 years of age for use in clinical and research applications. They have designed an assessment battery including a neurological assessment at 6 months, and long-term neurodevelopmental assessments at 18, 36, and 60 months to assess a range of developmental domains including cognition, language, motor, adaptive behaviour, executive functions, school readiness, and primary caregiver mental health (Ware et al., 2020).

However, there are currently no healthcare guidelines or formalised neurodevelopmental screening or surveillance pathway for the evaluation and
management of children with CHD in the UK, above that offered to healthy children. Consequently, much of the literature discussed above has been focussed on outcomes in North America, Europe, Japan and Brazil, with limited research coming from the UK. To try and address the challenges of follow-up for children with CHD in the UK, the Brief Developmental Assessment (BDA) was developed and validated as an early recognition tool for identifying children with CHD up to the age of 5 years at possible risk of developmental delay (Brown et al., 2018; Hoskote et al., 2020; Wray et al. 2018). The BDA is recommended as a screening tool and it is based on domains covered in existing assessment measures used in the UK, including fine and gross motor skills, daily living, communication, socialisation and general understanding. A traffic light scoring system allows for the easy interpretation of results and identification of children with possible delays. If a child with CHD is flagged as amber (equivocal) or red (delayed) during screening using the BDA, they can then be appropriately referred for support and interventions. A recent consensus study identified a referral pathway for children with CHD who were flagged using the BDA: children with delayed development (red) should be referred immediately and put under the care of a paediatrician with expertise in cardiology, those suspected (amber) should be re-assessed within 1-2 months before referral to community paediatricians (Hoskote et al., 2020). If used widely, the BDA has the potential to aid early, targeted referral and intervention in at-risk children with CHD.

1.6 Brain Abnormalities Associated with CHD

Studies involving MRI taken in the preoperative period have revealed structural abnormalities in a high proportion of children with CHD. These abnormalities
include congenital brain malformations, altered brain development, metabolic
dysfunction, and acquired ischaemic and haemorrhagic injury (Peyvandi et al.,
2019; Sethi et al., 2022). The anomalous foetal circulation in CHD is considered
to be a contributing factor to age-adjusted low brain volume and immaturity.
Limperopoulos et al. (2010) were the first to identify reduced brain volume in
foetuses with CHD, and other MRI studies have replicated these findings in both
HLHS and TGA (e.g. Rollins et al., 2021). Bonthrone et al. (2021) reviewed the
literature and summarised that smaller brain volumes compared to healthy
controls are evident in foetuses with CHD at approximately 30 weeks gestation,
as well as increased extracerebral cerebrospinal fluid. Reduced cerebral oxygen
delivery in utero, longer time to surgery, and prolonged hospital stay were
identified as risk factors for impaired brain growth, which persists throughout
childhood into adolescence. Licht et al. (2009) also investigated brain maturation
(i.e. evaluating myelination, cortical folding, involution of glial cell migration
bands, and germinal matrix tissue) and reported delays in both neonates with
HLHS and TGA. Mean head circumference was reported as 1 SD below normal,
and mean total brain maturation was also significantly below normative data. This
reflected a 1 month delay in structural brain development.

White matter injury (particularly in HLHS) and stroke (particularly in TGA) are
common in the pre and postoperative period, and brain immaturity also increases
the vulnerability for preoperative brain injury (Morton et al., 2017). Preoperative
and postoperative white matter injury have been identified in 25% and 36%, and
arterial ischaemic stroke in 6% and 14%, of neonates with complex CHD
(including but not limited to HLHS and TGA), respectively (Stegeman et al.,
2021). The third trimester is an important period for white matter development,
when oligodendrocytes have high metabolic activity and are highly susceptible to
hypoxia. Diffusion tensor imaging (DTI) provides unique information about white matter microstructures, maturation, and injury by measuring fractional anisotropy (FA). Preoperative DTI studies indicate key white matter structures which are underdeveloped in infants and adolescents with CHD. Mulkey et al. (2014) reported reduced FA in the splenium of the corpus callosum, posterior limb of the internal capsule, corticospinal tracts, and the optic radiation in infants with CHD and preoperative brain injury. However, this did not persist and FA significantly increased post-operatively with increasing brain maturity. Reduced FA in the splenium of neonates with CHD pre and postoperatively is consistently reported in the literature, and Hagmann et al. (2016) concluded that this is comparable to findings in preterm neonates with psychomotor delay. It is not yet clear if and how these brain abnormalities impact brain function, and whether the effect of early injury is global leading to multi-system functional deficits, or more local/regional leading to more focal impairments in vulnerable circuits.

The influence of neonatal brain injury on later neurodevelopmental outcome is not well understood in complex CHD. Some studies suggest that neonatal white matter injury in associated with impaired outcomes, but this becomes more apparent after 3 years of age when skills are more developed and easier to measure (Sethi et al., 2022). Claessens et al. (2018) found that cognitive scores at 2 years-old and full-scale IQ at 6 years-old were lower in children with CHD with neonatal white matter injury. They were also significantly more likely to have attentional problems, while those with injury to the posterior limb of the internal capsule showed significantly more motor problems. Children with below-average IQ had significantly smaller basal ganglia and brain stem volumes. In a recent review, Schiller et al. (2018) highlighted that survivors of preterm birth, CHD (especially HLHS), and those treated with ECMO all share an increased risk of
long-term memory deficits associated with hippocampal alterations. This may point to a common neurodevelopmental pathway following neonatal critical illness due to shared vulnerabilities such as hypoxia, neuroinflammation, or exposure to anaesthesia, as opposed to diagnosis per se. Damage to the hippocampus is plausible given that it is a structure highly susceptible to hypoxic/ischaemic injury. Cooper et al. (2015) reported reduced hippocampal volumes which were predictive of the degree of memory impairment in patients who experienced a hypoxic/ischaemic episode early in life, many of whom were treated with ECMO. Similar long-term memory deficits have also been reported in 8-16 year-olds with TGA who underwent the arterial switch operation, but they had relatively normal intelligence, academic attainment, and verbal fluency (Muñoz-López et al., 2017). Further, Jakab et al. (2019) found evidence of a strong correlation between the growth rate of the left planum temporale and posterior operculum of the left frontal lobe, and language score in 12 month-olds with CHD. More longitudinal research is needed to understand and evaluate the impact of early neurological abnormalities on later neurodevelopmental outcome.

Perioperative variables such as CPB and DHCA can also result in (further) brain injury. More than 50% of newborns with CHD have been found to have ischaemic lesions postoperatively, whilst 24% had preoperative ischaemic lesions (Mahle et al., 2002). Reduced hippocampal volumes have been observed in adolescents who underwent CHD surgery using CPB (Latal et al., 2016). Skotting et al. (2021) analysed postoperative MRI scans of infants with CHD and found that they had smaller brains, cerebrums, and cerebral grey matter than infants without CHD. These differences in brain volume observed in the weeks after birth and following cardiac surgery confirm that CHD and its surgical treatment have an impact on the brain structurally. What is unclear is whether this damage occurs during foetal
development or as a result of surgery. It is reasonable to assume that multiple staged surgeries can increase the risk of further brain injury, in addition to multiple postoperative factors. Consequently, we may expect the degree of neurological impairment in these children to be higher which in turn may increase the risk of adverse neurodevelopmental outcomes.

1.6.1 Functional Brain Abnormalities

The brain abnormalities discussed above refer specifically to brain structure. Much less literature is available on functional brain abnormalities, particularly in children, as the use of MRI is particularly challenging in this population especially in the early preschool years due to movement and apprehension about the scanner environment (Cusack et al., 2018). One particularly useful functional measure in developing populations is event-related potentials (ERPs) which provide accurate temporal measures of processing in the brain, allowing neural correlates of different aspects of cognitive functioning to be investigated. Specific components can be identified and investigated in ERP waveforms and abnormality of such components may reflect abnormal processing in the brain of a given cognitive process (Luck et al., 2011). However, studies using ERPs to investigate early functional brain abnormalities in CHD and correlating these with neurodevelopmental outcome are limited. ERPs in other clinical developmental populations such as children born preterm have revealed atypical auditory ERPs within the first year of life which may indicate an increased risk for cognitive dysfunction (Fellman et al., 2004). Similarly, abnormalities in auditory processing have also been reported in 12 month-old infants at risk of ASD and language impairment, and these early ERP responses correlated with later expressive language at 20 months (Riva et al., 2018).
The use of ERPs has been successfully applied to relate brain circuit responses to various aspects of cognitive processing including language (Bishop et al., 2007a) and memory (Reynolds & Richards, 2005; Pfister et al., 2016) from infancy to childhood/adolescence in both healthy and clinical cohorts. Importantly, the relationship between brain abnormalities and function are correlative, not causative; there is often no information on premorbid status; functions emerge over time; and functional abnormalities can be global or focal depending on the measure and/or the type of function. These are important considerations when evaluating the literature.

1.7 Risk Factors for Adverse Neurodevelopmental Sequelae

It is widely accepted that a myriad of factors affect neurodevelopmental and behavioural outcomes in children with CHD, particularly those with complex cardiac anomalies. These factors can be split into preoperative, perioperative and postoperative clinical factors, and family and environmental factors, in the absence of any genetic comorbidity (Figure 1.4). Depending on the number of factors, the incidence of abnormalities may range from rare to multiple. Many of these factors are also linked to the extent of brain abnormalities commonly reported in CHD patients, discussed above (section 1.6).
Figure 1.4 Factors affecting long-term neurodevelopmental outcome in children with CHD

1.7.1 Preoperative Factors

Several preoperative factors are important for long-term outcomes in CHD patients including pre versus postnatal diagnosis of CHD, type of cardiac anatomy/disease, and gestational age. Advancements in foetal echocardiography enable CHD diagnosis and a precise understanding of cardiac anatomy and physiology, which allows for accurate prediction of critical and severe CHD in utero (Sethi et al., 2022). A delivery care plan can be made where there has been a prenatal diagnosis of CHD, which can lead to more stable cardiorespiratory status and timely CHD-specific care. This can reduce the risk of cerebral injury and preoperative death in neonates. Neonates with complex
CHD require immediate hospitalisation after birth in order to receive medical interventions prior to open-heart surgery. These can include intubation, mechanical ventilation, invasive interventions such as balloon atrial septostomy, and intravenous prostaglandin infusion (Wernovsky, 2006). All of these carry risks to the central nervous system. Patients also have low saturations of oxygen, which can potentially compromise both the delivery of oxygen and blood flow to the brain (Licht et al., 2004; Peyvandi et al., 2019). This poses the initial risk of hypoxic/ischaemic injury prior to surgery. Gestational age <39 weeks and low birthweight are associated with worse neurodevelopmental outcomes following cardiac surgery, and present an increased risk for hospital mortality, increased postoperative length of stay in hospital and other complications (Costello et al., 2014; Gaynor et al., 2007). Microcephaly (small head circumference despite normal birth weight) has also been observed in 30% of newborns with CHD, and neurobehavioural abnormalities such as hypotonia, hypertonia, jitteriness, and absent suck have been observed in more than 50% of newborns prior to surgery (Limperopoulus et al., 2000). More recent studies suggest that certain types of CHD such as HLHS are associated with smaller head circumference, but only in TGA is it smaller relative to birth weight (Matthiesen et al., 2016).

1.7.2 Perioperative Factors

Perioperative risk factors are particularly important as these can cause brain injury leading to worse long-term neurodevelopment, and remain the prime area of focus in CHD research. The processes used during cardiac surgery introduce multiple risk factors. These include the use of cardiopulmonary bypass (CPB) during open-heart surgery, air or particulate emboli, rate and depth of core cooling, duration of aortic cross-clamp, deep hypothermic circulatory arrest
(DHCA), reperfusion injury and inflammation, rate of core rewarming/hyperthermia, hyperglycaemia, hyperoxia, and pH and haematocrit management during cardiopulmonary bypass (Wernovsky & Licht, 2016). Two techniques, namely DHCA and CPB, have been widely used to provide optimal operating conditions while providing cerebral protection. Using DCHA induces hypothermia to preserve organ function whilst circulation is ceased during surgery. Most patients can tolerate 30 minutes of circulatory arrest at 18°C without significant neurological adverse events (Conolly et al., 2010; Fuller et al., 2010). Low-flow CPB provides selective perfusion to the brain and limits or completely avoids the use of circulatory arrest. Prolonged CPB and DHCA duration can lead to detrimental outcomes in patients with CHD due to increased risk of cerebral hypoxia/ischaemia (Hoffman et al., 2016). Recently, research has begun to explore the use of normothermic CPB (35-37°C) as opposed to hypothermia (28°C) during cardiac surgery for CHD, but long-term surveillance data of neurodevelopmental outcomes are currently unavailable (Howell et al., 2019). The duration of aortic cross-clamping has also been identified as a risk factor in neurodevelopmental outcomes. For example, Hövels-Gürich et al. (2007) reported prolonged duration was related to reduced attentional functions, specifically, orientation to and selection of stimuli.

The management of blood gas during deep hypothermia using either alpha-stat (temperature-uncorrected blood-gas management) or pH-stat (temperature-corrected blood-gas management), and haemodilution (removing red blood cells) are also important perioperative factors. The pH-stat method is known to improve brain recovery time and reduce postoperative morbidity, but neurodevelopmental outcomes are not known to differ (Bellinger et al., 2001; Howell et al., 2019). Excessive haemodilution can also lead to organ ischaemia; maintaining
haematocrit above 24% has a protective effect (Howell et al., 2019; Newburger et al., 2008).

Surgical procedures for complex CHD can require a prolonged duration of anaesthesia for several hours or even days (if needed during recovery post-surgery), on multiple occasions, due to staged-surgeries in the first few years of life (Howell et al., 2019; Morton et al., 2017). The effects of exposure to anaesthesia on early brain development are controversial, but some studies have demonstrated a strong link between increased exposure and poorer neurodevelopmental outcomes (e.g. lower full-scale and verbal IQ) in 4-5 year-olds with HLHS (Diaz et al., 2016).

1.7.3 Postoperative Factors

The management and care of children with CHD in the postoperative period is critical. Postoperative temperature control is crucial as hypothermia can have detrimental effects on the brain in the presence of hypoxic/ischaemic injury, and can exacerbate structural and functional injury (Massaro et al., 2008). Seizures may occur in the immediate postoperative period in one-fifth of neonates, but it remains unclear if they are simply a marker of brain injury, or a predictor of outcome. In the Boston Circulatory Arrest Study, seizures were associated with worse scores in the Bayley-2 at 1 years-old, and lower IQ at 4 years of age (Bellinger, 1999); more recently however, Gaynor et al. (2006) did not find this to be the case. Cardiac arrest can also occur in up to 20% of newborns with complex CHD (Wernovsky & Litcht, 2016). This can result in significant brain injury as a result of hypoxia to structures that are especially sensitive to oxygen deprivation and may result in the need for mechanical ventilation or ECMO, which is itself
associated with high mortality and higher rates of disability. For example, Hamrick et al. (2003) found that of the patients with CHD supported with ECMO postoperatively, only 13% survived completely intact, 50% had abnormal cognitive outcome, and 28% had abnormal neuromotor outcome.

Infants and children remain vulnerable even after open-heart surgery and several factors continue to be a potential threat to their long-term neurodevelopment. These postoperative morbidities include length of stay in the intensive care unit (ICU); cardiac arrest; acute neurological events (e.g. seizures); the need for further open-heart surgeries/reintervention; use of ECMO post-surgery; feeding strategy (e.g. oral versus supplemental tube), renal replacement therapy, infection, and pleural effusion (Soto et al., 2011; Pagel et al., 2017). Prolonged stay in hospital, particularly within the ICU, may indicate more severe CHD or complicated medical course, and has been linked to gross and fine motor delays, lower full-scale and verbal IQ, and overall, adverse neurological and neurodevelopmental outcomes (Newburger et al., 2012). This is not surprising given that a longer hospital stay often requires sedation and long periods of immobilisation, which significantly inhibit an infant’s opportunity to engage, play, explore, and develop key skills, and adversely impact infants’ motor and cognitive development.

Other risk factors can impact neurodevelopment beyond the immediate postoperative period. Low cardiac output and low blood pressure are known to correlate with postoperative brain injury which is a known risk for developmental delays (Howell et al., 2019). Low mean blood pressure has been found to be associated with newly acquired (white matter) brain injury during the first postoperative day, and hypoxic/ischaemic injury in the following weeks in neonates who underwent CPB during surgery (Morton et al., 2017). Low cardiac
output which is found in approximately 25% of children with CHD (Chandler and Kirsch, 2016), has also been shown to be associated with more complicated hospital course and worse health-related quality of life at 4 years (Garcia Guerra et al., 2013). These risk factors can lead to prolonged hospital stay and possible mechanical ventilation, which too are risks for neurodevelopmental impairments and delays. Further postoperative risk factors are feeding dysfunction and malnutrition which can lead to failure in reaching growth milestones. This may require supplemental gastrostomy tube placement. A recent review reported an overall pooled prevalence of 42.9% for feeding and swallowing difficulties in infants with CHD, and these are associated with significant morbidity, including respiratory disease, poor weight gain, longer duration in ICU and overall hospital stay, and increased caregiver stress (Norman et al., 2022). Feeding dysfunction has profound implications for quality of life, neurodevelopmental outcomes, sensory regulation, and social-emotional bonding with parents and other caregivers (Jones et al., 2021). Some of these postoperative factors are potentially modifiable, but without intervention can make children more susceptible to worse neurodevelopmental outcomes.

1.7.4 Family and Environmental Factors

Several family and environmental factors can affect long-term outcomes in patients with CHD including socioeconomic status (SES), maternal mental health and stress, social support, parenting style and family functioning which may all be aetiologically more important than disease and surgical factors (McCusker et al., 2007). The impact of SES has been widely researched for its pivotal role in child development. It encompasses parental education, income, and environmental stimulation (Morton et al., 2017). Lower SES has been associated
with neurological outcome, a range of neurodevelopmental deficits following surgery for CHD, and can also negatively impact a family’s ability to access healthcare, therapies and interventions. In older children and adolescents with HLHS who have undergone the Fontan procedure, SES explained one-sixth of the variability in IQ scores, whereas, surgical variables only explained 6% (Dunbar-Masterson et al., 2001). Many of these factors are also influenced by social determinants of health (SDoH) such as race/ethnicity, poverty/deprivation, housing status, parental educational, immigration status, and transportation barriers (Davey et al., 2021). These SDoH have a bidirectional relationship with CHD, impacting both aetiology and outcomes, and being impacted by living with CHD (Wong et al., 2018). Recent systematic reviews have reported that SDoH are significantly associated with lower likelihood of antenatal CHD diagnosis, higher incidence and prevalence of CHD, increased infant mortality, adverse post-surgical outcomes, decreased healthcare access, impaired neurodevelopmental outcomes, and reduced quality of life (Davey et al., 2021). More specifically, they have found that Black patients with non-critical and critical CHD have increased mortality within the first year of life, as do socioeconomically-deprived patients and patients with critical CHD born to mothers younger than 18 years of age who have less than 12 years of education (Tran et al., 2022). Further, a recent statement from the American Heart Association addressed SDoH across the lifespan in CHD and highlighted that longstanding systemic inequities, disparities in SDoH, and the inability to obtain quality lifelong care contribute to poorer outcomes, and a more complicated course (Lopez et al., 2022).

Several factors discussed above, the potentially traumatic experience following the diagnosis of complex CHD, and uncertainty of survival can all lead to
increased parental stress, feelings of helplessness, anxiety, postpartum depression, and abnormal parent-child relationships (Wernovsky & Litcht, 2016). McCusker et al. (2012) investigated maternal worry and mental health, and found that they accounted for almost 28% of variability in child behaviour adjustment in the first year of school. This explained 5-10 times more of the variance than any perioperative factors discussed. Research has also found that 30% of parents have symptoms consistent with post-traumatic stress disorder (PTSD), 25-50% reported clinically elevated symptoms of depression and/or anxiety, and 30-80% reported experiencing severe psychological distress, particularly in the weeks and months following their child’s cardiac surgery (Woolf-King et al., 2017). It has been suggested that parents of children with more complex conditions such as SV CHD have poorer psychological outcomes compared to parents of children with other types of heart defects such as BV CHD, including several years after surgery (Wray et al., 2018). It is important to note that SDoH also impact parents and this can lead to poorer outcomes and access to healthcare and support for parents, which is subsequently likely to impact outcomes in children with CHD. Indeed, parental, and especially maternal, mental health have been shown to strongly predict child behavioural adjustment and development, particularly in children with complex CHD (Ryan et al., 2019). It is therefore plausible to assume that poorer psychosocial adjustment in parents and reduced quality of life are likely to be associated with poorer psychosocial outcomes in children with complex CHD. This is discussed in more detail in Chapter 7.
1.8 Summary

Overall, it is evident that a plethora of factors can impact neurodevelopmental outcomes in children with CHD. Many studies have provided evidence for the developmental signature in CHD which includes high prevalence low severity impairments. There are also numerous studies indicating delays and/or impairments across several domains including communication and language, motor skills, attention, executive function, and socioemotional and behavioural functioning. These are known to impact overall psychosocial functioning and quality of life in both children with CHD, and their parents. However, many of these studies are cross-sectional which makes it difficult to document the trajectory of delays, and investigate whether early delays are overcome, or whether they are chronic impairments. There are relatively few longitudinal cohort studies focusing on the early school age period or studies combining neuropsychological measures with neuroimaging techniques to directly measure functional brain activity, detailed language assessment, or studies investigating neurodevelopmental outcomes alongside psychosocial functioning and quality of life in children with complex CHD.

1.9 The Current Research

Building on the published evidence, patient and public involvement work was conducted as part of the preparation for this project in order to guide the formulation and design. This work is described in detail in the following chapter. The approach in this thesis is to examine the emergence of cognition, language and motor function in the first three years of life, and subsequently focus on the language domain in relation to a measure of brain function at 4-5 years of age.
Socioemotional, behavioural, and psychosocial functioning will also be explored, including their role in overall quality of life in children with CHD, and finally, psychosocial outcomes and quality of life of parents of children with CHD will also be presented.

The current research project is divided into five main parts, and each of these are presented as separate data chapters:

- Chapter 3 – Longitudinal early neurodevelopmental outcomes in preschoolers with CHD (i.e. cognitive, language and motor skills at 5-8 months, 12-15 months, and 3-4 years).

- Chapter 4 – Speech and language outcomes in early school-aged (4-5 years) children with CHD.

- Chapter 5 – The neural correlates of speech sound processing (i.e. auditory ERP paradigm at 3-4 years and 4-5 years).

- Chapter 6 – Parent-rated socioemotional, behavioural, and psychosocial functioning in 4-5 year-old children with CHD, and their overall quality of life.

- Chapter 7 – Psychosocial functioning and quality of life of parents of children with CHD.

In each data chapter the relevant aims and hypotheses are presented. The next chapter (Chapter 2) will describe the methods used in this project.
Chapter 2: General Methods

This chapter describes the general methodological approach of this thesis and provides details of the population under investigation, the participant recruitment process, the longitudinal study timeline, a brief description of the tasks and neuropsychological assessments administered, and the statistical approaches for all analyses reported in the results chapters. The specific detailed methods for task administration will be included in the relevant chapters hereafter.
2.1 Context of the Current Investigation

A rare opportunity became available to study a cohort of preschool children with CHD who had been longitudinally investigated (since birth) as part of a larger programme grant referred to as “The Hypoxia/Ischaemia (HI) Study”. The HI Study focussed on the incidence of memory impairment, but a range of neurodevelopmental measures were used to track development throughout infancy and in the preschool years across three longitudinal assessment time-points: 5-8 months, 12-15 months, and 3-4 years. The cohort of participants in the current thesis was therefore inherited from this previous longitudinal HI Study. Initial recruitment and the inclusion/exclusion criteria for the participants as well as brief details of this previous research are described in Appendix 1. This thesis is based on the data obtained at a new follow-up assessment at 4-5 years of age. However, it utilises and reports on the data collected at three previous time-points (i.e. 5-8 months, 12-15 months, and 3-4 years) in order to track longitudinal aspects of performance and investigate early correlates of cognitive and language outcomes at early school age (i.e. 4-5 years). The structure of the PhD study is presented in Figure 2.1, which also highlights the previous research time-points where data were utilised in this thesis. A detailed timeline of the PhD study including assessment time-points and the data collected at each time-point, including the parental questionnaires used, is presented in Figure 2.2.
Figure 2.1 The PhD study structure, where green boxes indicate the stages where data collected have been used in this PhD.
Figure 2.2 The full PhD study timeline including neuropsychological tests used, electrophysiological (EEG) data collected, and parental questionnaires used at each assessment time-point. Data from each of these will be included in the chapters within this thesis. The timeline also highlights the time periods where CHD patients had their cardiac surgery/surgeries, which are shaded in grey.

Neuropsychological tests: Bayley-3 = Bayley Scales of Infant and Toddler Development (3rd edition) including parental questionnaire; WPPSI-IV = Wechsler Preschool & Primary Scale of Intelligence (4th edition); CELF-P2 = Clinical Evaluation of Language Fundamentals Preschool (2nd edition); ROWPVT & EOWPVT = Receptive and Expressive One-Word Picture Vocabulary Tests; PAT = Phonological Abilities Test.

Parental questionnaires: CCC-2 = Children’s Communication Checklist (2nd edition); CBCL = Child Behaviour Checklist; SDQ = Strengths and Difficulties Questionnaire; ABAS-2 = Adaptive Behavior Assessment System (2nd edition); BRIEF-P = Behavior Rating Inventory of Executive Function (preschool version); PedsQL = Paediatric Quality of Life Inventory; Family Impact = PedsQL Family Impact Module; HADS = Hospital Anxiety and Depression Scale; PIP = Paediatric Inventory for Parents; IES = Impact of Event Scale (revised version).
2.2 Participant Recruitment

Before children and their families from the longitudinal cohort could be contacted for recruitment for time-point 4, the researcher had to check all CHD patients’ records at Great Ormond Street Hospital (GOSH) in order to check their survival status and whether or not they were currently hospitalised or there was any other reason why they should not be contacted. Once patient status was confirmed, the child’s GP surgery was contacted by telephone to cross-reference and ensure that there had been no recent adverse medical events that may have been unknown since the previous assessment time-point. Following GP confirmation of health status of all CHD patients, all participants were screened for eligibility. There was an inclusion criterion to ensure that if a child had participated in time-point 3 (3-4 years of age), there was at least a one year gap between that previous assessment and the current one at 4-5 years. This was to allow sufficient time for development between assessments. However, participation at time-point 3 was not an essential criterion given the nature of longitudinal cohort research. Parents of eligible CHD patients and healthy controls were contacted via email or telephone for recruitment. Parents were given information about the new time-point and told what participation would involve. If parents were happy to participate, assessments were arranged at a time that was convenient for the child and their family. From the participants who were identified as being eligible, a total of 28 participants participated in the current research at 4-5 years of age (time-point 4). This included five children with HLHS, 13 with TGA, and 10 healthy controls.
2.2.1 Attrition

There was significant attrition in participant numbers in the PhD follow-up study at time-point 4. This was predominantly due to the COVID-19 pandemic which meant that data-collection was stopped and face-to-face assessments could not be conducted. Consequently, of a potential 48 children who were screened for eligibility for participation, nine (19%) could not be assessed due to the pandemic despite being interested in participating, a further nine (19%) were too young to be assessed pre-pandemic as a year had not passed since the previous assessment time-point, one (2%) healthy control child withdrew from the study, and one (2%) child with HLHS had died since participation in time-point 3, leaving 28 (58%) participants.

Given that nine participants could not be assessed in person at time-point 4 due to the pandemic, parents of these children were asked to complete a range of parental questionnaires. This was to maximise data collection given the small sample size, and to allow those families who wanted to participate an opportunity to do so remotely via questionnaires sent by email. Details of these questionnaires are discussed in the relevant chapters. Of the nine participants, parents of four returned completed questionnaires by email, this includes one healthy control, two children with HLHS, and one child with TGA. Therefore, in addition to the 28 participants described above, a further four participants were included in the cohort for whom only parent-rated data were available. Of the 32 participants with parent-rated questionnaire data, seven children had HLHS (mean age = 5.09 ± 0.45 years), 14 had TGA (mean age = 5.28 ± 0.27 years), and 11 were healthy controls (mean age = 5.23 ± 0.43 years). Appendix 2 contains a table showing the longitudinal data each participant has across time-points 1-4.
Due to the longitudinal nature of the cohort study, a number of children who were originally recruited in the HI Study did not complete all assessment time-points, and others were recruited after the first time-point. Chapter 3 describes data obtained at time-points 1, 2, and 3 and so attrition across all these time-points is important to note. Figure 2.3 highlights the attrition in participant numbers over the duration of the longitudinal study, relevant to this thesis, including the PhD study at time-point 4. Pre-pandemic, the main reasons for attrition between time-points 1, 2, and 3 were due to parents withdrawing from the study, moving away from London, changes in contact details making the families uncontactable, and ‘no-shows' where families did not attend scheduled assessments. A proportion of children did not withdraw from the study but were unable to attend specific assessment time-points due to illness, prior commitments or other family circumstances.
Figure 2.3 The attrition of the longitudinal cohort in the study. The boxes shaded grey precede time-point 1 and are not relevant for the scope of this thesis, but are provided for context about attrition in the cohort. Green boxes indicate the time-points where data collected have been included in this PhD study.
2.3 Ethical Approval

This PhD study which formed the final time-point 4 assessment was approved by the London Hampstead NHS Research Ethics Committee (reference number 12/LO/1425) and was registered with the Joint Research and Development Office of GOSH and UCL GOS Institute of Child Health (ICH) (R&D number: 17BT29). The study required a major amendment (dated 15/03/2018) to the original ethical approval of the HI Study to extend the age limit of the participants from 36 months to 5 years, and a minor amendment (dated 12/03/2018) to extend the end date of the longitudinal project given the new time-point 4 assessment. An ICH risk assessment was also completed before research commenced, as per the approval conditions. Appendix 3 contains the approval letters for both these amendments, as well as the R&D approval confirmation for the current study (time-point 4). It should be noted that the title of the study has changed slightly in this thesis compared to the R&D project title but the numbers are consistent.

2.4 Patient and Public Involvement (PPI)

Patient and Public Involvement (PPI) is defined as a partnership or co-production of research between patients, carers, and members of the public with researchers, to ensure that research is carried out ‘with’ patients as opposed to conducting research ‘on’, ‘about’, or ‘for’ them (National Institute for Health and Care Research, 2021). It is a key element in healthcare to enable patient-centred research which can improve the relevance and quality of research by ensuring it focusses on issues and unanswered questions which are important to the patients themselves (Brett et al., 2014; Staniszewska et al., 2017). Patients and members of the public can be involved in multiple phases throughout the research
process such as designing research questions and protocols, recruitment, and dissemination of findings, and greater involvement enhances the quality and relevance of the research (Price et al., 2022).

Funding from the National Institute for Health and Care Research (NIHR) GOSH Biomedical Research Centre allowed for PPI work to be conducted in preparation for this PhD research. PPI in the form of engagement with parents of children with CHD was conducted in two stages and has played a significant role in the development of this project. In the first stage, parents helped to identify research priorities and questions by enabling researchers to understand key areas of concern to them about their child’s development, which could be studied at 4-5 years of age. For this initial PPI work, a questionnaire about child development and parental concerns was posted on the Little Hearts Matter Facebook page. This is a charity specifically supporting children with single ventricle conditions and their families (https://www.lhm.org.uk/). Children with HLHS are known to be at risk for neurodevelopmental delays and impairments so it was important to focus on this group for the PPI work. Appendix 4.1 details the specific questions which were posted. A total of 16 parents completed the online questionnaire and their responses were recorded.

Parents indicated the areas of greatest concern in their child’s development, the most common of which were behavioural problems (63% said anger, aggression, disruptive behaviours), speech and language/communication (44%), social and emotional development (38%), and physical and motor skills (19%). Other concerns parents described included attention, impulsivity, learning difficulties, anxiety, attention-deficit hyperactivity disorder (ADHD), autism spectrum disorders (ASD) and eating and sleeping problems. Parents described how important it was to adequately prepare and support children with CHD for school
entry, noting if they require further support, and identifying if there are risks or indicators of early impairments. Currently, there is no long-term routine neurodevelopmental surveillance of children with CHD in the UK, and this leaves many parents confused, uninformed, unsupported and unprepared for their child’s future, despite many parents having a “gut feeling” or “mother’s instinct” that “something wasn’t quite right” with their child. Consequently, parents want more research to be available as it is clinically relevant, and 63% of parents said this research study was important/very important. Based on the outcome of this PPI, research protocols were selected based on concerns about speech and language development and appropriate parental questionnaires were selected to capture problems in communication, behaviour, social and emotional development, and executive function. Interestingly, three parents specifically mentioned noticing a change in their child’s behaviour/development after the Fontan procedure which is the final staged-surgery in HLHS. This period of time precedes the time-point 4 assessment which allowed any changes in development to be captured by the current protocols.

In the second PPI stage, parents of children with CHD were informally interviewed at the GOSH outpatient clinic where they were attending a cardiac appointment for their child. These interviews were conducted over a period of three months, where a total of 6 clinic visits were made by the researcher and 33 parents/families were interviewed. In instances where both parents attended the clinic, they were interviewed together as a family, but otherwise parents were interviewed individually as they attended, rather than as a group. The interviews allowed parents to directly speak to the researcher and raise their concerns and views, and notes were made based on parental responses. Appendix 4.2 details the dialogue used by the researcher to approach parents, and the questions
which were discussed during informal interviews. Questions aimed to probe parental concerns about development, but also to address the logistics of a typical day of assessment. Responses were collated based on the notes made during each interview. Consistent with earlier responses from the first PPI stage, parents commonly reported speech and language, behaviour, and emotional problems in their children. Some also mentioned gross motor skills and being able to physically keep up with peers in the playground, as well as learning delays and keeping up academically in the classroom. Three school-aged children with CHD had also been diagnosed with ADHD and this was also a particular concern to parents.

The primary aim of this second PPI stage was to help make the logistical decisions regarding the assessments by speaking to parents of patients with CHD who would have similar experiences and life commitments as the parents of the participants in this research. The assessments were predicted to take up to 4 hours, but this depended on the individual child on the day. The majority of parents/families (88%) indicated that if they were to participate in a study like this, the assessment should begin late morning, incorporating lunchtime, but end in the early afternoon as this is when their child would be most alert and compliant. All parents wanted to avoid rush hour traffic at the beginning and end of the day. Some (27%) thought assessments should coincide with GOSH clinic visits as they were travelling from further away outside London, or be split over two days if they lived closer (15%), whilst the majority preferred to avoid this and wanted a separate single-day assessment. Parents also indicated that their child would benefit from regular short breaks/snack time, at the expense of a longer lunch, so would prefer the assessment to be broken down into shorter periods. Some children might not need as many breaks, and others might still need a longer
lunch break to allow them to “go outside and have a little run around”. Therefore, based on the PPI, assessments were tailored to individual preferences, as much as possible.

PPI work has helped to ensure that this research is parent-driven throughout, and based on articulated parental concerns and preferences. PPI is beginning to grow internationally and is a formal requirement for some types of research in the USA, and is also widely used in Canada, but it is used much less frequently in the UK and Europe, and is reported even less frequently within the CHD literature. Recently, however, the James Lind Alliance (2021) set up the Congenital Heart Disease Priority Setting Partnership in order to identify the unanswered questions about CHD in children and adults, from patient, carer (primarily parents) and clinical perspectives, and then to prioritise the areas that by consensus are agreed to be the most important for research to address. Therefore, the present research is unique as to the best of the researcher’s knowledge, this is one of the few studies in the UK which is CHD patient-centred and parent-driven throughout.

The findings from James Lind Alliance (2022) have been published since data collection for the current project was completed, and two of the ten national priorities for research in child/antenatal CHD are particularly relevant: “What are the effects of CHD, low oxygen saturations and interventions on brain development and behavioural outcomes, and how can these be improved?” and “What is the impact of living with CHD on quality of life in children and how can this be improved?".
2.5 Demographic Data

At the final time-point at 4-5 years, parents of both CHD patients and healthy controls were asked to complete a demographics questionnaire to obtain information about the child’s and family’s background (Appendix 5). This included details about when the child was diagnosed with CHD (patients only), the birth, siblings, ethnicity, education, primary spoken language at home and school, concerns about development, postcode and the parents’ socioeconomic status (educational background and employment status). Table 2.1 summarises the demographic characteristics of the whole cohort at time-point 4, including the level of deprivation.

Deprivation was calculated using the child’s postcode, Lower-Layer Super Output Area (LSOA) name, and Local Authority District code. In England, LSOAs are a standard statistical geography and were produced by the Office for National Statistics for the reporting of small area statistics (Government of the United Kingdom, 2019). Two key scores of deprivation were calculated for the cohort: the index of multiple deprivation and the index of income deprivation affecting children. These scores are given as deciles in Table 2.1 which represent the range from the most deprived 10% of neighbourhoods to the least deprived 10%.
Table 2.1 Summary of the demographic characteristics of the cohort at time-point 4, including the level of deprivation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total N = 32</th>
<th>HLHS N = 7</th>
<th>TGA N = 14</th>
<th>Healthy Controls N = 11</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Premature birth, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1 (3)</td>
<td>0</td>
<td>1 (7)</td>
<td>0</td>
</tr>
<tr>
<td>No</td>
<td>31 (97)</td>
<td>7 (100)</td>
<td>13 (93)</td>
<td>11 (100)</td>
</tr>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>22 (69)</td>
<td>4 (57)</td>
<td>9 (64)</td>
<td>9 (82)</td>
</tr>
<tr>
<td>Female</td>
<td>10 (31)</td>
<td>3 (43)</td>
<td>5 (36)</td>
<td>2 (18)</td>
</tr>
<tr>
<td><strong>Ethnicity, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>5 (16)</td>
<td>0</td>
<td>3 (21)</td>
<td>2 (18)</td>
</tr>
<tr>
<td>Black</td>
<td>3 (9)</td>
<td>1 (14)</td>
<td>2 (14)</td>
<td>0</td>
</tr>
<tr>
<td>White</td>
<td>18 (56)</td>
<td>6 (86)</td>
<td>7 (50)</td>
<td>5 (46)</td>
</tr>
<tr>
<td>Other/Mixed</td>
<td>3 (9)</td>
<td>0</td>
<td>1 (7)</td>
<td>2 (18)</td>
</tr>
<tr>
<td><strong>Education, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nursery</td>
<td>1 (3)</td>
<td>1 (14)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mainstream school</td>
<td>29 (91)</td>
<td>5 (72)</td>
<td>14 (100)</td>
<td>10 (91)</td>
</tr>
<tr>
<td>Mainstream with learning support</td>
<td>1 (3)</td>
<td>1 (14)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>1 (3)</td>
<td>0</td>
<td>0</td>
<td>1 (9)</td>
</tr>
<tr>
<td><strong>School Attendance, mean</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days per week</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Hours per day</td>
<td>6.79</td>
<td>7</td>
<td>6.54</td>
<td>7</td>
</tr>
<tr>
<td><strong>Socioeconomic factors (at time-point 4)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest maternal education level, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCSE/O-levels/equivalent</td>
<td>4 (13)</td>
<td>2 (29)</td>
<td>2 (14)</td>
<td>0</td>
</tr>
<tr>
<td>A-levels/equivalent</td>
<td>6 (19)</td>
<td>2 (29)</td>
<td>4 (29)</td>
<td>0</td>
</tr>
<tr>
<td>University graduate</td>
<td>9 (28)</td>
<td>0</td>
<td>4 (29)</td>
<td>5 (46)</td>
</tr>
<tr>
<td>Postgraduate</td>
<td>12 (38)</td>
<td>2 (29)</td>
<td>4 (29)</td>
<td>6 (55)</td>
</tr>
<tr>
<td>Maternal employment, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed full-time</td>
<td>5 (16)</td>
<td>0</td>
<td>2 (14)</td>
<td>3</td>
</tr>
<tr>
<td>Employed part-time</td>
<td>15 (47)</td>
<td>2 (29)</td>
<td>7 (50)</td>
<td>6 (55)</td>
</tr>
<tr>
<td>Self-employed</td>
<td>6 (19)</td>
<td>3 (43)</td>
<td>1 (7)</td>
<td>2 (18)</td>
</tr>
<tr>
<td>Unemployed/stay at home mum</td>
<td>4 (13)</td>
<td>0</td>
<td>4 (29)</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>1 (3)</td>
<td>1 (14)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Highest paternal education level, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCSE/O-levels/equivalent</td>
<td>5 (16)</td>
<td>2 (29)</td>
<td>2 (14)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>A-levels/equivalent</td>
<td>4 (13)</td>
<td>1 (14)</td>
<td>2 (14)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>University graduate</td>
<td>14 (44)</td>
<td>3 (43)</td>
<td>6 (43)</td>
<td>5 (46)</td>
</tr>
<tr>
<td>Variable</td>
<td>Total N = 32</td>
<td>HLHS N = 7</td>
<td>TGA N = 14</td>
<td>Healthy Controls N = 11</td>
</tr>
<tr>
<td>----------</td>
<td>-------------</td>
<td>------------</td>
<td>------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Postgraduate</td>
<td>5 (16)</td>
<td>0</td>
<td>1 (7)</td>
<td>4 (36)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (3)</td>
<td>0</td>
<td>1 (7)</td>
<td>0</td>
</tr>
</tbody>
</table>

**Paternal employment, n (%)**

<table>
<thead>
<tr>
<th>Employment Status</th>
<th>Total N = 32</th>
<th>HLHS N = 7</th>
<th>TGA N = 14</th>
<th>Healthy Controls N = 11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Employed full-time</td>
<td>23 (72)</td>
<td>4 (57)</td>
<td>11 (79)</td>
<td>8 (73)</td>
</tr>
<tr>
<td>Employed part-time</td>
<td>2 (6)</td>
<td>0</td>
<td>0</td>
<td>2 (18)</td>
</tr>
<tr>
<td>Self-employed</td>
<td>4 (13)</td>
<td>1 (14)</td>
<td>2 (14)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Index of multiple deprivation**

decile (where 1 is most deprived 10% of LSOAs)\(^{a}\)

<table>
<thead>
<tr>
<th>Decile</th>
<th>Total N = 32</th>
<th>HLHS N = 7</th>
<th>TGA N = 14</th>
<th>Healthy Controls N = 11</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.69</td>
<td>5.29</td>
<td>5.36</td>
<td>6.36</td>
<td></td>
</tr>
</tbody>
</table>

**Income deprivation affecting children**

decile (where 1 is most deprived 10% of LSOAs)\(^{b}\)

<table>
<thead>
<tr>
<th>Decile</th>
<th>Total N = 32</th>
<th>HLHS N = 7</th>
<th>TGA N = 14</th>
<th>Healthy Controls N = 11</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.41</td>
<td>5.29</td>
<td>5.14</td>
<td>5.82</td>
<td></td>
</tr>
</tbody>
</table>

**Parental concerns about child’s development, n (%)**

<table>
<thead>
<tr>
<th>Concern</th>
<th>Total N = 32</th>
<th>HLHS N = 7</th>
<th>TGA N = 14</th>
<th>Healthy Controls N = 11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>7 (22)</td>
<td>4 (57)</td>
<td>3 (21)</td>
<td>0</td>
</tr>
<tr>
<td>No</td>
<td>25 (78)</td>
<td>3 (43)</td>
<td>11 (79)</td>
<td>11 (100)</td>
</tr>
</tbody>
</table>

---

\(^{a}\) Premature birth: one TGA child born at 35 (-4) weeks

\(^{b}\) Asian ethnicity: 5 children were either Indian, Pakistani, Bangladeshi, or Filipino/Mauritian

\(^{c}\) Other/mixed ethnicity: 3 children were either White and Asian, White and Jewish, or White and Caribbean

\(^{d}\) Other education: 1 child attended private school

\(^{e}\) Other paternal education level: one father had a higher national diploma (HND)

\(^{ab}\) Deprivation is calculated using child’s postcode, Lower-Layer Super Output Area (LSOA) name, and Local Authority District code. Index of multiple deprivation combines 7 domains of deprivation: income, employment, education, health, crime, barriers to housing and services, and living environment. Income deprivation affecting children index measures the proportion of all children aged 0-15 years living in income deprived families (Government of the United Kingdom, 2019).

\(^{f}\) Parental concerns about child’s development – reasons for yes included: academically behind at school, severely delayed speech and language skills, problems with reading, trouble with handwriting/weak muscles/fine motor skills, squints eyes, gets out of breath/can’t keep up physically, school has reported behavioural problems, poor sleep, poor physical balance, and spastic bladder.

### 2.6 Primary Language of Cohort

During initial recruitment, the study was explained in English, all information sheets at each time-point were printed in English, and consent was given and taken in English. Families needed to be fluent in English in order to participate, but it did not need to be the mother tongue or primary language spoken at home. Some children were bilingual and spoke English at school and their given mother tongue whilst at home. Throughout the study, all communication and
assessments with children were completed in English. Given that the final assessment at 4-5 years was focussed on speech and language, the level of understanding of the child was key. Hence, this is when the predominant language spoken within the home was recorded as well as the child’s knowledge of English. The proportion of children who spoke English within the home is detailed in Table 2.2. At this age, all children had started formal schooling (nursery or primary school) five days a week, and so all had a good level of understanding and spoke English. In instances where the mother tongue was not English and the child displayed signs of misinterpretation of task instructions, the parent was asked to give their child an exact translation in their mother tongue, during any given task.

Table 2.2 Proportion of English-speaking children in the cohort at time-point 4, at 4-5 years of age, detailing bilingualism and the other spoken languages alongside English

<table>
<thead>
<tr>
<th>Only English</th>
<th>Bilingual (other language)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Total (N = 32)</td>
<td>21 (66)</td>
</tr>
<tr>
<td>HLHS (N = 7)</td>
<td>4 (57)</td>
</tr>
<tr>
<td>TGA (N = 14)</td>
<td>7 (50)</td>
</tr>
<tr>
<td>Healthy Controls (N = 11)</td>
<td>10 (91)</td>
</tr>
</tbody>
</table>

Other spoken languages

| Afrikaans       | 1 (3) |
| Bengali         | 1 (3) |
| French          | 1 (3) |
| Ghanian         | 1 (3) |
| Igbo (Nigerian) | 1 (3) |
| Polish          | 2 (6) |
| Portuguese      | 1 (3) |
| Punjabi         | 2 (6) |
| Russian         | 1 (3) |
2.7 Clinical Variables

As discussed in Chapter 1, section 1.7, there are a myriad of risk factors which are associated with adverse neurodevelopmental and behavioural outcomes in children with complex CHD. These include preoperative, perioperative and postoperative factors, some of which are routinely recorded in the medical notes at the time of the cardiac surgery at GOSH. These clinical/medical variables include: birthweight, time of diagnosis, surgery variables such as cardiopulmonary bypass time, and length of stay in hospital, summarised in Table 2.3.

Table 2.3 Summary of the key clinical variables of the (time-point 4) cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>HLHS N = 7</th>
<th>TGA N = 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational Age, mean weeks (SD)</td>
<td>38.14 (0.69)</td>
<td>37.64 (1.15)</td>
</tr>
<tr>
<td>Birthweight, mean kg (SD)</td>
<td>2.93 (0.38)</td>
<td>3.08 (0.37)</td>
</tr>
<tr>
<td>Diagnosis, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antenatal</td>
<td>7 (100)</td>
<td>7 (50)</td>
</tr>
<tr>
<td>Postnatal</td>
<td>0</td>
<td>7 (50)</td>
</tr>
<tr>
<td>Age at 1st Surgery, mean days (SD)</td>
<td>4.43 (1.99)</td>
<td>15.03 (17.59)</td>
</tr>
<tr>
<td>Operative Variables, mean minutes (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiopulmonary bypass time</td>
<td>111.00 (15.48)</td>
<td>136.14 (14.45)</td>
</tr>
<tr>
<td>Aortic cross-clamp time</td>
<td>45.86 (8.21)</td>
<td>87.29 (12.71)</td>
</tr>
<tr>
<td>Hospital Stay, mean days (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of stay in CICU</td>
<td>14.43 (6.35)</td>
<td>8.79 (4.73)</td>
</tr>
<tr>
<td>Total hospital stay</td>
<td>48.29 (51.74)</td>
<td>15.36 (6.65)</td>
</tr>
<tr>
<td>Age at 2nd Surgery, mean days (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glenn procedure</td>
<td>127.20 (48.75)</td>
<td>N/A</td>
</tr>
<tr>
<td>Hospital Stay, mean days (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of stay in CICU</td>
<td>21.75 (22.95)</td>
<td>N/A</td>
</tr>
<tr>
<td>Total hospital stay</td>
<td>43.75 (36.09)</td>
<td>N/A</td>
</tr>
<tr>
<td>Variable</td>
<td>HLHS N = 7</td>
<td>TGA N = 14</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>------------</td>
<td>------------</td>
</tr>
<tr>
<td>Age at 3rd Surgery, mean years (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCPC procedure</td>
<td>3.63 (0.40)</td>
<td>N/A</td>
</tr>
<tr>
<td>Hospital Stay, mean days (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of stay in CICU</td>
<td>3.25 (1.50)</td>
<td>N/A</td>
</tr>
<tr>
<td>Total hospital stay</td>
<td>21.75 (12.01)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

2.8 Neuropsychological Assessments

Testing took place in the UCL ICH Wolfson Centre in laboratories designed for research with infants and children. Assessments were completed on one day, where possible, but were split across two visits if this was necessary or preferred by the families. In these cases, the two visits were arranged in close proximity to one another to ensure the child’s age remained within the same starting point on the given neuropsychological test. Written informed consent was obtained before beginning the assessment, and parents were given a copy of the information sheet as well as an information sheet about general data protection regulation (Appendix 6). Parents were allowed to accompany their child in the testing laboratory if they wished but were asked to remain silent and not interfere with the assessment unless requested to do so. During the assessment of their child, parents were asked to complete a number of parental questionnaires (detailed below in section 2.9.2.4) including a demographics questionnaire.

Assessments at time-point 4 were expected to last 3-4 hours but this depended on the temperament of the child on the day and time of testing. Children were given regular breaks throughout the assessments, as required. At each time-point, children were given a certificate, stickers, and a £10 gift voucher as a ‘thank you’ for participating in the study. Families of the children were reimbursed for
any expenses related to the study, including travel and food. Parents were also sent a neuropsychological report outlining how their child had performed at the assessment. A copy of the report template can be found in Appendix 7.

2.9 Summary of Study Protocols and Assessment Methodology

As highlighted in Figure 2.1, the following chapters of this thesis are based on data collected at four assessment time-points: time-point 1 (5-8 months), time-point 2 (12-15 months), time-point 3 (3-4 years), and time-point 4 (4-5 years). The results of time-points 1-3 will be reported and presented together in Chapter 3. This part of the study aimed to longitudinally assess the development of early cognitive, language, and motor skills in pre-schoolers with HLHS and TGA, compared to healthy controls, to identify the emergence of neurodevelopmental delays in children with CHD. The results from time-point 4 will then be divided into four separate chapters. This final assessment aimed to comprehensively assess speech, language and pre-reading skills in school-aged children with HLHS and TGA, compared to healthy controls (Chapter 4), as well as utilising auditory event-related potentials to explore differences in neural correlates between children with CHD and healthy controls during speech sound processing (Chapter 5). Parent-reported behavioural and socioemotional outcomes, adaptive and executive functioning, and psychosocial health and quality of life outcomes are reported (Chapter 6), as well as parent self-reported mental health, family functioning, and quality of life (Chapter 7). The table in Appendix 8 shows all the tests and questionnaires used at time-point 4 and how long each took.
The sections below describe the details of each of the assessments and the tests and protocols used, including parental questionnaires. Within each relevant chapter the literature will be reviewed, and full methodologies relating to procedures and apparatus required will be defined in the methods section.

2.9.1 Early Neurodevelopment (Time-points 1-3)

2.9.1.1 Cognitive, Language and Motor Development

The Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-3) at the time of the study was widely considered to be one of the most comprehensive tools and the gold standard for assessment of early child development. Bayley-3 allows infants and children aged between one and 42 months to be individually examined in five key developmental domains: cognition, language, motor, social-emotional, and adaptive behaviour (Bayley, 2006). Assessment of the cognitive, language, and motor domains involves administering structured items to the child, and occasionally engaging the primary caregiver to support the child’s responses where appropriate. The language and motor domains are each split into two subtests: receptive and expressive communication, and fine and gross motor, respectively. The social-emotional and adaptive behaviour domains are administered via caregiver questionnaires which allow them to score the child’s abilities based on their own observations.

Bayley-3 and its predecessors have been widely used by clinicians and researchers to identify potential developmental delay in high-risk children such as those with prenatal and neonatal complications, congenital disorders, or neurodevelopmental disorders (Del Rosario et al., 2021). The scores and abilities of these children are compared to a normative age-matched sample of children.
Scaled scores from individual subtests have a normative mean of 10 and a standard deviation (SD) of 3, these scores can also be converted into composite (standard) scores which have a mean of 100 and SD of 15. Significant neurodevelopmental impairments are detected by scores 2 SD below the mean, which can be predictive of later impairments (Del Rosario et al., 2021).

The Bayley-3 was used to measure cognitive, language and motor development of the cohort longitudinally, at 5-8 months, 12-15 months, and 3-4 years of age.

2.9.1.2 Behaviour

The Bayley-3 parent questionnaire was also used to assess parent-rated social-emotional development and adaptive behaviour of the cohort longitudinally, at all three time-points.

The Child Behaviour Checklist (CBCL) is a norm-referenced parental questionnaire used to detect behavioural and socioemotional problems in children aged 1.5-5 years-old (Achenbach & Rescorla, 2001). The checklist consists of 99 ‘problem’ items that describe children, and parents rate them on a scale of 0 (not true), 1 (sometimes true), and 2 (often true). For example, item 21 asks the parent if their child is disturbed by any change in routine. These item scores are used to produce overall scores for seven syndrome scales: Emotionally Reactive, Anxious/Depressed, Somatic Complaints, Withdrawn, Sleep Problems, Attention Problems, and Aggressive Behaviour. These scales also group into two higher-order factors: Internalising Problems and Externalising Problems, which combine to produce a Total Problems score. There are also five further DSM-oriented scales consistent with DSM diagnostic categories: Depressive Problems, Anxiety Problems, ASD Problems, ADHD Problems, and
Oppositional Defiant Problems. Raw scores for each scale are converted into norm-referenced T-scores (mean = 50, SD = 10), with separate norms provided for each gender, as well as a percentile rank score. Clinically significant elevations are indicated by T-scores ≥70, and borderline scores are between 64-69.

An important feature of the CBCL preschool checklist is the inclusion of the Language Development Survey developed by Dr Leslie Rescorla, which assesses children’s word combinations, expressive vocabulary (based on 310 word items), and risk factors for language delays in children aged 18-35 months. Two overall scores are produced for average length of phrases and a total vocabulary score, where scores below 20th percentile suggest delayed phrase development and scores below 15th percentile suggest delayed vocabulary development, respectively.

The CBCL was used to assess behavioural and socioemotional outcomes longitudinally at time-points 3 and 4.

2.9.2 Neurodevelopment at School Age (Time-point 4)

2.9.2.1 Intelligence

The Wechsler Preschool & Primary Scale of Intelligence, Fourth Edition (WPPSI-IV) is used to measure cognitive development in preschool and young children between 2 years 6 months to 7 years 7 months (Wechsler, 2012). Young school-aged children (4 years to 7 years 7 months) are assessed using a total of 15 subtests, 10 of which form the core battery. The 10 core subtests measure ability across five key areas of cognitive functioning: Verbal Comprehension, Visual Spatial, Fluid Reasoning, Working Memory, and Processing Speed. The scores
from six of these core subtests combine to form the Full Scale IQ (FSIQ), which is considered to be the most representative indicator of global intellectual functioning. Raw scores are calculated for each subtest which are then converted into scaled scores before being summed to obtain a total standard score for each of the five key areas as well as FSIQ. These scores are then also converted in to percentile ranks.

The WPPSI-IV is a reliable measure used widely by psychologists and neuropsychologists working in schools, clinics, and hospitals to document children’s cognitive status and evaluate any delays and learning difficulties for referral to specialist services. The subtests are easy to administer and each takes between 5-10 minutes on average (60 minutes total), and many are game-like which are especially engaging for younger children. This edition incorporates several revisions including an extended age range, updated UK norms, new subtests, and significant changes to score terminology. There is strong evidence of test-retest stability and convergent concurrent validity between scores on the WPPSI-IV and scores on multiple other measures of cognitive ability, including the WPPSI predecessor and Bayley-3 (Thorndike, 2014).

2.9.2.2 Language

A battery of tests was used to comprehensively assess speech, language and pre-reading skills in the cohort of children with HLHS and TGA, and healthy controls.
2.9.2.2.1 Clinical Evaluation of Language Fundamentals Preschool, Second Edition (CELF-P2)

The CELF-P2 is used to measure a broad range of expressive and receptive language skills in children aged three years to 6 years 11 months (Wiig et al., 2004). The child is assessed individually and is expected to respond appropriately to instructions given by the examiner, through spoken or unspoken communication. There are seven subtests: Sentence Structure, Word Structure, Expressive Vocabulary, Concepts and Following Directions, Recalling Sentences, Basic Concepts, and Word Classes. Table 2.4 summarises each of these subtests and gives a brief description of what each task involves. Raw scores are calculated for each subtest which are then converted into scaled scores. The scaled scores from each of these subtests combine in various ways to give overall summed scaled scores for five key components of language: Core Language, Receptive Language, Expressive Language, Language Content, and Language Structure. These scores are then converted into standard/composite scores and percentile ranks.

The CELF-P2 evaluates all four aspects of language: morphology and syntax, semantics, pragmatics, and phonology. The Core Language score is considered to be the most representative measure of language skills, and it encompass the first three subtests: Sentence Structure, Word Structure, and Expressive Vocabulary. Language Content focusses on semantic knowledge, and Language Structure probes understanding and production of syntactical structures and morphology.

The CELF-P2 is a practical and efficient clinical tool that can be used to identify a language disorder, describe the nature of the disorder, determine eligibility for
services, and identify strengths and weaknesses/needs of the child (Wiig et al., 2004).

Table 2.4 The subtests of the CELF-P2 and a description of what each subtest involves the child doing

<table>
<thead>
<tr>
<th>Subtest</th>
<th>Description of task</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sentence Structure</td>
<td>Point to pictures in response to oral directions (e.g. which one smells nice?)</td>
</tr>
<tr>
<td>Word Structure</td>
<td>Complete a sentence with the correct form of a word (e.g. tenses, plurals, word endings)</td>
</tr>
<tr>
<td>Expressive Vocabulary</td>
<td>Identify an object, person, or activity shown in a given picture</td>
</tr>
<tr>
<td>Concepts and Following Directions</td>
<td>Point to a series of pictures, often in a particular order, in response to oral directions (e.g. first point to the giraffe, then point to the monkey)</td>
</tr>
<tr>
<td>Recalling Sentences</td>
<td>Repeat sentences spoken and presented by the examiner, which increase in length and complexity</td>
</tr>
<tr>
<td>Basic Concepts</td>
<td>Point to a picture that illustrates the targeted concept instructed by the examiner (e.g. point to the one which is cold)</td>
</tr>
<tr>
<td>Word Classes</td>
<td>Choose two words from a given multiple choice that are related, and describe the relationship (e.g. which of these items go together (crayon, pencil, strawberry)? How do the words crayon and pencil go together (you draw with them)?</td>
</tr>
</tbody>
</table>

2.9.2.2.2 Receptive and Expressive One-Word Picture Vocabulary Tests, Fourth Edition (ROWPVT and EOWPVT)

The ROWPVT and EOWPVT are individually administered to each child, and are co-normed tests which allow for the accurate comparison of a child’s receptive and expressive vocabulary skills (Martin & Brownell, 2010; 2011). Both tests take 15-25 minutes to administer and can be used with children aged 2 years through to adulthood. The ROWPVT tests an individual’s ability to match a given spoken
Both tests measure the total acquired vocabulary of a child, rather than language proficiency. Despite using subtests from other assessment tools and tests which also measure expressive and receptive language, the ROWPVT and EOWPVT are more comprehensive as they each contain approximately 190 test items. Total raw scores are calculated separately for the ROWPVT and EOWPVT, and these are directly converted into standard scores, percentile ranks, and an age-equivalent range. Standard scores for the two tests can then be compared by finding the difference between them, using the age of the child at the time of testing, and the manual to identify if this difference is statistically significant.

These tests can be used to screen for early language delay, assess reading skills and vocabulary development, and evaluate intervention programmes. It is important to note that these tests do not have UK specific norms, and are standardised on English-speaking individuals in the US.

2.9.2.2.3 Phonological Abilities Test (PAT)

The PAT was used to specifically measure pre-reading skills in the cohort. The test measures phonological awareness using a range of subtests which are known to predict reading ability and outcome (Muter et al., 1997). Reports vary with regard to which measures of phonological awareness predict reading. Some argue that segmentation over rhyming better predicts literacy (Muter et al., 2004), whilst others have found a strong causal link between rhyming skills and reading (Goswami, 2015). Children with weak phonological skills and low sensitivity to
rhyme awareness are at risk of dyslexia. Letter knowledge competence is widely believed to be a significant precursor and predictor of word recognition and reading, and it has recently been suggested that the link between rhyme perception and letter-sound knowledge is mediated through phonological awareness (Ozernov-Palchik et al., 2018).

Two subtests were selected based on the literature as being highly predictive of later reading skills: Rhyme Detection and Letter Knowledge. Rhyme Detection involves the child selecting which of three words (e.g. fish, gun, hat) rhyme with a target word (e.g. cat); there are a total of ten test items, each presented as pictures and read out by the examiner. In the Letter Knowledge subtest, the child must say the name or sound of each of the 26 letters of the alphabet, presented in lower case, in a random order, individually on flashcards. The total raw scores for each subtest and the age of the child being tested are then used to obtain the centile equivalents. Centile scores allow the score of a child on a given subtest to be related to the standardised sample. Scores falling at the 50th centile are normal for the age, whilst scores falling below the 10th centile are considered impaired.

The PAT can be used as a screening test to identify children at risk of reading delays or difficulties, or as a diagnostic test to assess the extent and nature of possible phonological difficulties, where reading problems have been identified (Muter et al., 1997).

2.9.2.2.4 Renfrew Bus Story

The Bus Story is part of the Renfrew Language Scales, and is a test of narrative speech used with children aged 3-8 years (Renfrew, 1991). The test involves a
colourful picture book being shown to the child whilst they listen to the examiner
telling them a story about a ‘naughty’ bus, after which the child must retell the
story from their memory, using only the picture book to help guide them. The story
recall is audio recorded and then carefully transcribed, before being re-written in
separate sentences following guidelines on which the norms are based. The
transcription is then scored for information content and average sentence length
(i.e. the mean number of words in the five longest sentences). Points are awarded
for accurate information, using the correct referent (e.g. the bus ran away), and
in the correct order of events. Age-equivalent scores can then be calculated
accordingly, from UK norms.

The test can be used as a screening tool but should be used alongside other
assessment tools to further guide specific areas of diagnostic testing. Performance on the Bus Story has been found to be a predictor of reading
comprehension (Haynes and Naidoo, 1991).

2.9.2.3 Electrophysiological Measures

Chapter 5 focusses on the longitudinal electrophysiological data collected from
both time-points 3 and 4. The aim of the study was to investigate the neural
correlates of speech sound processing by employing electroencephalography
(EEG) to measure electrical brain activity on the surface of the skull, using
electrodes placed on the scalp. Event-related potentials (ERPs) are parts of the
continuous EEG recording, reflecting time-locked electrical activity in response to
a specific sensory stimulus. This neuroimaging technique is non-
invasive and has high temporal resolution, allowing it to capture neural markers
of sensory-cognitive processes even in passive tasks where overt responses are
not required (de Haan, 2007; Luck, 2014). Consequently, it is a very effective way to investigate the relationship between brain and behaviour in the early years.

ERPs can be elicited by a wide range of sensory, cognitive, or motor events. They reflect the summed activity of postsynaptic potentials when a large number of neurons fire in synchrony during information processing (Peterson et al., 1995). ERP waveforms are commonly split into two categories: early waves or components and later. Components are given specific labels which refer to their polarity and position within the waveform. Classically, early components which peak within the first 100 milliseconds (ms) following stimulus presentation, are considered to be ‘sensory’ or ‘exogenous’ as they depend on physical parameters of the stimulus. In contrast, later components are ‘cognitive’ or ‘endogenous’ as they reflect how the stimulus is evaluated, and examine information processing (Luck, 2014; Sur & Sinha, 2009).

ERPs cannot be typically seen within the raw EEG recording due to their very small amplitude relative to the background EEG, so they need to be singled out from the continuous recording by averaging activity time-locked to repeated stimulus presentations (Beres, 2017). This allows EEG fluctuations unrelated to the given stimuli to be averaged out, leaving only the activity persistently related to the given stimuli. Single-trial waveforms are averaged together to create averaged ERP waveforms for each stimulus type. An example of an EEG experimental recording is presented in Figure 2.4.
Figure 2.4 An EEG recording during an auditory ERP experiment, where a cap with numerous electrodes is placed on the participant’s head, allowing electrical brain activity to be measured on the surface of the scalp. EEG is recorded and amplified while an auditory sound is presented. Adapted from Beres (2017)

ERP waveforms contain a series of positive and negative peaks which are otherwise known as ‘components’, labelled according to their polarity (P for positive and N for negative) and approximate latency in milliseconds. Specific components can be distinguished in the ERP waveform depending on the eliciting stimulus and the experimental paradigm, and these are related to different processing stages. For example, the N100 is a negative peak around 100ms after stimulus presentation. ERP components are commonly described according to mean or peak amplitude and/or onset or peak latency. Amplitude refers to the amount of neural activity during processing of a given stimulus, and latency reflects the speed of that processing. The peak is commonly measured at the maximum amplitude. Details of the components for the current study will be described in Chapter 5.
2.9.2.4 Parental Questionnaires

2.9.2.4.1 Parent-Rated Child Outcomes

A battery of parent-completed questionnaires was used to evaluate language, behaviour, executive function, and quality of life in children with CHD and healthy controls. Each questionnaire was scored to obtain subscale scores and overall total scores as relevant for each given questionnaire. Based on normative data or available published cut-offs, the proportion of children scoring within the borderline or clinical range was calculated based on those scoring 1-2 SD or ≥2 SDs below the normative mean, respectively, unless specific clinical cut-offs were described in the manual or published for any given questionnaire.

2.9.2.4.1.1 Language

In addition to the language assessments undertaken directly with the child, language was also assessed using parental ratings on the Children’s Communication Checklist, second edition (CCC-2) (Bishop, 2003). The CCC-2 is a checklist used to assess communication in children aged 4-16 years. There are a total of 70 items divided into 10 subscales: Speech, Syntax, Semantics, Coherence, Inappropriate Initiation, Stereotyped Language, Use of Context, Nonverbal Communication, Social Relations, and Interests. The first four subscales measure aspects of language structure, vocabulary, and discourse. The following four subscales evaluate aspects of communication (i.e. pragmatics) which are otherwise difficult to assess using conventional language assessments. The final two subscales assess behaviours that are usually impaired in cases with ASD.
For each subscale, there are seven items, five describing difficulties and two describing strengths. Each item is scored by the parent with a rating reflecting the frequency with which a behaviour is observed (0 = less than once a week/never, 1 = at least once a week, but not daily, 2 = once or twice a day, and 3 = several times a day/always). Raw scores from each subscale are converted into scaled scores, and percentile ranks, and the sum of the first eight subscale scores combine to give a General Communication Composite (GCC) score. The GCC score is useful for identifying communication difficulties and few affected children obtain a GCC above the 10th percentile (Bishop, 2003). The Social Interaction Deviance Composite (SIDC) is useful for identifying children with an uneven communicative profile, and disproportionate impairment in pragmatic communication compared to structural language skills. This score has good reliability and is sensitive to ASD. According to Bishop (2003), “a negative SIDC score in combination with GCC below 55 indicates a communicative profile suggestive of ASD, a SIDC of -15 or below is abnormal, even in a child with a normal GCC score, and a SIDC of 9 or more in a child with GCC below 55 indicates a communicative profile characteristic of specific language impairment”.

The CCC-2 is useful for quantifying pragmatic language impairments in children, screening children at risk of language impairment or communication disorders, and to help identify children who may require a referral for further assessment for ASD.
2.9.2.4.1.2 Behaviour

Multiple parent-completed questionnaires assessing child behaviour were used, including the CBCL (detailed in section 2.9.1.2) which assesses socioemotional behaviour.

2.9.2.4.1.2.1 Strengths and Difficulties Questionnaire (SDQ)

The SDQ is a screening questionnaire which contains 25 items designed to assess behaviours, emotions and relationships over the last six months in children and young people aged 4-17 years (Goodman, 1997). There are various versions available including those designed for pre-schoolers, educators, as well as self-report versions for older children and adults. The 25 items are divided between 5 subscales: Emotional Symptoms, Conduct Problems, Hyperactivity, Peer Problems and Prosocial Behaviour. Parents record their responses using a 3-point Likert scale (0 = ‘Not True’, 1 = ‘Somewhat True’, and 2 = ‘Certainly True’).

The questionnaire measures both negative and positive attributes. For example, in the emotion subscale “many worries, often seems worried”, in the conduct subscale “generally obedient, usually does what adult requests”, and in the hyperactivity subscale “restless, overactive, cannot stay still for long”.

Raw scores are totalled for each subscale, and a Total Difficulties score can be calculated by summing all the subscales scores except Prosocial Behaviour. The conduct and hyperactivity subscales can also be summed to obtain an overall Externalising score, and the emotional and peer problems subscales can be summed to produce an Internalising score. These scores can be categorised based on the UK sample for normative scores. There is a fourfold classification which categorises scores as being ‘close to average’, ‘slightly raised’, ‘high’, and
'very high'. For the Prosocial subscale, the latter categories change to 'low' and 'very low'. The normative categories reflect the proportion of children scoring in each category: 80%, 10%, 5%, and 5%, respectively. The SDQ identifies the risk of a child developing socioemotional problems.

2.9.2.4.1.2.2 Adaptive Behavior Assessment System, Second Edition (ABAS-2)

The ABAS-2 is a comprehensive assessment of adaptive and daily functional skills of individuals aged from birth to 89 years (Harrison & Oakland, 2003). There are various forms available for pre-schoolers, teachers, and self-report adult forms. It evaluates function across multiple environments and is particularly valuable for identifying individuals experiencing difficulties with daily functioning, which can impact their quality of life. This is done by measuring performance (as rated by parents in this case) in ten skills areas: Communication, Functional (Pre) Academics, Self-Direction, Leisure, Social, Community Use, Home/School Living, Self-Care, Health and Safety, Motor/Work (depending on the age of the individual). Examples of behavioural skills include: “asks to go to a park, or other favourite community place” (for Community Use), “sings the alphabet song” (for Functional Academics), “tells an adult if he/she has a stomach ache or other illness” (for Health and Safety), and “holds and drinks from a sipping cup” (for Self-Care). These skills areas are grouped into three broad domains: Conceptual (first three subscales), Social (following two subscales), and Practical (the latter five subscales).

Parents indicate if their child is able to perform a given activity independently, and if so, the frequency with which it is done, by circling the relevant answer (0 = is not able, 1 = never when needed, 2 = sometimes when needed, and 3 = always
when needed). Raw scores are calculated for each subscale and then are converted into scaled scores. These scores are summed to provide totals for each of the three domains, and then converted into composite scores and percentile ranks. The General Adaptive Composite (GAC) can also be calculated which is the sum of all the subscale scores.

The ABAS-2 can be used as a diagnostic assessment to identify developmental delays and disabilities, including intellectual disability, alongside the assessment of intelligence. Strengths and weaknesses of an individual can be identified which allows for an appropriate intervention plan to be developed and implemented. It can also be useful to document and monitor the performance of an individual over time.

2.9.2.4.1.3 Executive Function

The Behavior Rating Inventory of Executive Function, preschool version (BRIEF-P) is a questionnaire that assesses executive function behaviours within the home and (pre) school environments, in children aged 2-5 years (Gioia et al., 2003). According to the manual, executive functions refer to interrelated processes that are responsible for directing and managing cognitive, emotional, and behavioural functions. The BRIEF-P form contains 63 items that measure various aspects of executive functioning that divide into five scales: Inhibit, Shift, Emotional Control, Working Memory, and Plan/Organize. The scales form three broad indexes (Inhibitory Self-Control, Flexibility, and Emergent Metacognition) and one composite score (Global Executive Composite). The Inhibitory Self-Control Index represents the child’s ability to modulate actions, responses, emotions, and behaviour through appropriate inhibitory control. The Flexibility
Index is the child’s ability to move flexibly between actions, responses, emotions, and behaviour. The Emergent Metacognition Index reflects the child’s ability to sustain ideas and activities in working memory and to plan and organise problem-solving approaches. The Global Executive Composite is a summary score which incorporates all the BRIEF-P scales.

Parents score each item by circling the correct response for the frequency with which a given behaviour is performed: never, sometimes, and often. These ratings are then converted into numerical scores of either 1, 2, or 3, respectively, in order to calculate raw score totals for each scale. Raw scores are then converted into T-scores (mean = 50 and SD = 10) using the normative conversion tables. T-scores ≤ 59 are typical and normal, 60-64 are mildly elevated, and ≥ 65 are clinically elevated.

The BRIEF-P has clinical utility in the diagnosis and assessment of children with a range of medical, acquired neurological and developmental conditions/disorders, emerging learning disabilities, attentional and language disorders, and traumatic brain injuries (Greene et al., 2019). It does not, however, have UK specific norms, and is standardised on ratings of children from the US, but does reflect the 1999 UK census estimates for age, gender, ethnicity, and socio-economic status, although this is now very dated.

2.9.2.4.1.4 Quality of Life (QoL)

Children with CHD suffer from morbidities which significantly impact neurodevelopmental, psychosocial, and physical functioning; which subsequently reduces their overall QoL (Kharitonova & Marino, 2016; Marino et al., 2016). The Paediatric Quality of Life Inventory (PedsQL) 4.0 Generic Core
Scales were designed to measure health-related QoL (HRQOL) in children and young people aged 2-18 years (Varni et al., 1999). There are various forms available for the different age bands, but two were used in this study based on the age of the current cohort: PedsQL 4.0 2-4 years and 5-7 years. There are a total of 23 items which encompass: Physical Functioning (8 items), Emotional Functioning (5 items), Social Functioning (5 items), and School Functioning (5 items, but only 3 items for the 2-4 years form). Examples of items the child may have had problems with include: “participating in sports activities or exercise” (for Physical Functioning), “feeling afraid or scared” (for Emotional Functioning), “not being able to do things that other children his/her age can do” (for Social Functioning), and “missing school to go to the doctor/hospital” (for School Functioning).

The form asks parents to rate how much of a problem each activity has posed for their child during the past one month. A 5-point response scale is used where, 0 = never a problem; 1 = almost never a problem; 2 = sometimes a problem; 3 = often a problem; and 4 = almost always a problem. Items are reverse-scored and linearly transformed to a 0-100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0), so that higher scores indicate better HRQOL. Mean scores are computed for each of the four scales, as well as a combined Psychosocial Health Summary score (mean of the Emotional, Social and School Functioning scales), and a Total Score (mean of all the items). The PedsQL has been used in a wide range of clinical populations and age-appropriate normative scores from a very large healthy population are also available for children aged 2-16 years (Varni et al., 2007).
2.9.2.4.2 Parent Self-Rated Outcomes

Parental questionnaires were also used to measure psychosocial and QoL outcomes and mental health of parents. Many of these questionnaires have been used in populations suffering from chronic illnesses including CHD, and this research and other information will be provided in the relevant chapters (6 and 7).

2.9.2.4.2.1 Family Impact

The PedsQL Family Impact Module was developed to measure the impact paediatric chronic health conditions have on the parents and family (Varni et al. 2004). The questionnaire contains 36 items which encompass six scales measuring parent self-reported functioning: Physical Functioning (6 items), Emotional Functioning (5 items), Social Functioning (4 items), Cognitive Functioning (5 items), Communication (3 items), Worry (5 items), and two scales measuring parent-reported family functioning: Daily Activities (3 items) and Family Relationships (5 items). Examples of items parents and families may have had problems with include: “I feel too tired to do the things I like to do” (for Physical Functioning), “It is hard for me to talk about my child’s health with others” (for Communication), “I worry about my child’s future” (for Worry), and “Stress or tension between family members” (for Family Relationships).

As with the PedsQL 4.0, parents are asked to rate how much of a problem each item has been for them and their family (last two scales) during the past month. The same 5-point response scale is used, and the form is scored in the same way. Mean scores are computed for each of the eight scales, as well as a combined Parent HRQOL Summary Score (mean of the Physical, Emotional,
Social, and Cognitive Functioning scales), Family Functioning Summary Score (mean of the Daily Activities and Family Relationships scales), and a Total Score (mean of all the items). The PedsQL Family Impact Module has been used in a wide range of paediatric clinical populations and normative scores from a large healthy population are also available for families of children aged 2-17 years (Medrano et al., 2013).

2.9.2.4.2.2 The Hospital Anxiety and Depression Scale (HADS)

Based on the severity of complex CHD and the stress a paediatric chronic illness can have not only on the individual but on the family too, together with what is known about the impact of maternal mental health on child development, it was considered important to measure anxiety and depression (which often coexist) in parents (Woolf-King et al., 2017; Wray et al., 2018). The HADS is a standardised self-rated questionnaire that detects and indicates the severity of anxiety and depression simultaneously, in non-psychiatric patients in a hospital setting (Zigmond & Snaith, 1983). It is short, simple and easy to complete and enables mild degrees of mood disorders in adults to be detected.

The questionnaire comprises seven questions each for anxiety and depression. Caregivers are asked to rate items based on their feelings in the last two weeks, without overthinking too much. Responses are given using a Likert scale ranging from 1 to 4, where 1 = definitely/most of the time and 4 = not at all. Examples of anxiety items include: “I feel tense or wound up”, “I get a sort of frightened feeling as if something awful is about to happen”, or “I get sudden feelings of panic”. Examples of depression items include: “I can laugh and see the funny side of things”, “I feel as if I am slowed down”, or “I have lost interest in my appearance”.

103
A separate score for anxiety and depression is calculated, where scores ≤7 are considered normal, those in the range 8-10 are borderline, ≥11 is clinically relevant, and ≥15 is severe (Zigmond & Snaith, 1983).

2.9.2.4.2.3 Paediatric Inventory for Parents (PIP)

The PIP measures levels of stress suffered by parents caring for a child with a chronic disease, and was consequently given to parents of CHD patients only (Streisand et al., 2001). The questionnaire includes 42 items, grouped into four subscales: Communication, Medical Care, Emotional Distress, and Role Function. Parents provide two responses for each item for the frequency and difficulty of each, using a five-point Likert scale, ranging from 1 (“never/not at all”) to 5 (“very often/extremely”). For example, an item in the Communication subscale is “arguing with family member(s)”, and the parent must rate the frequency/how often this happens, and the level of difficulty. Other examples include: “being with my child during medical procedures” (for Medical Care), “feeling helpless over my child’s condition” (for Emotional Distress), and “being far away from family and/or friends” (for Role Function).

Total scores are calculated for each subscale as well as an overall Frequency score and Difficulty score. Scores can range from 42-210, where higher scores indicate higher levels of stress. The PIP has been used in a wide range of clinical populations including CHD patients. Consequently, scores from CHD cohorts in the literature (e.g. Kaugars et al., 2018; Wray et al., 2018) were used to compare scores with the current cohort of CHD patients.
2.9.2.4.2.4 Impact of Event Scale - Revised (IES-R)

The IES-R assesses subjective distress caused by traumatic events, and was therefore given to parents of CHD patients only. The self-report questionnaire contains 22 items which measure Avoidance, Intrusion, and Hyperarousal (Weiss & Marmar, 1996). Parents provided responses by identifying a specific stressful life event, in this case related to their child’s CHD, and then indicated how distressed they were by this event during the past seven days. Each "difficulty" item is rated on a 5-point scale ranging from 0 ("not at all") to 4 ("extremely"). For example, an item in the Avoidance subscale is “I avoided letting myself get upset when I thought about it or was reminded of it”. Other examples include: “pictures about it popped into my mind” (for Intrusion), and “reminders of it caused me to have physical reactions, such as sweating, trouble breathing, nausea, or a pounding heart.” (for Hyperarousal).

The IES-R yields total scores for each subscale, and an overall IES score which combines all the subscale scores (ranging from 0 to 88). Scores that exceed 24 are clinically meaningful and indicate post-traumatic stress disorder (PTSD) is a concern, scores of 33 represent the best cut-off for diagnosis of PTSD, and scores exceeding 37 are believed to be “high enough to suppress the immune system’s functioning” (Weiss & Marmar, 1996).

2.10 Statistical Analyses

All statistical analyses were performed using IBM SPSS Statistics Version 28 for Windows. Data were analysed following a set procedure, detailed below.

Data were first examined for normality using histograms and the Shapiro-Wilk test of normality which is appropriate for small sample sizes. If data were not
normally distributed a transformation (i.e. log and square root transformation) was applied to try and achieve normality. If normality could not be reached, non-parametric statistical tests were used. For all non-parametric analyses, medians and interquartile ranges (IQR) are reported, and for any parametric analyses, means and standard deviation (SD) are reported.

Following this exploration of the data, descriptive statistics were used to characterise the sample. Appropriate statistical tests were then selected to examine group differences, this depended on whether three groups were compared (i.e. HLHS, TGA, and healthy controls) or two (i.e. CHD patients and healthy controls, or HLHS and TGA CHD patient groups). The specific statistical tests used are reported in the methods and results sections of each of the data chapters.

Post-hoc analyses with uncorrected p-values were used to uncover the pairwise differences, and calculate effect size using Cohen’s $r$, as suggested by Fritz et al. (2012). Effect sizes were defined as small (0.1-0.2), medium (0.3-0.4), or large ($\geq 0.5$) (Field, 2009). Statistical advice was sought from the Senior Research Fellow in Biostatistics (Deborah Ridout) and UCL ICH, and as a result uncorrected p-values were used with non-parametric analyses due to the reduced power of these analyses. The post-hoc tests used are reported in each data chapter accordingly.

Correlational analyses were also conducted to explore the relationship between key variables of interest, and explore the longitudinal trajectories within each group across different domains, details of which are provided in the relevant data chapters.
This chapter focusses on the early longitudinal neurodevelopmental outcomes in a cohort of children with complex CHD. This cohort is split into two groups: children with HLHS and children with TGA. The Bayley Scales of Infant and Toddler Development, third edition (Bayley-3) were used to assess cognitive, language, and motor skills at three assessment time-points throughout the first four years of life. Outcomes in children with HLHS and TGA are discussed in relation to a group of healthy controls, and the longitudinal trajectories in each group are investigated. Bayley-3 parent-reported social-emotional and adaptive behaviour skills are also compared to scores of direct observation of the child in order to explore whether parental ratings were consistent with the child’s performance.
3.1 Introduction

Children with complex CHD have an increased risk of developmental delay or disabilities. Developmental surveillance is important in these children throughout childhood to enable early identification of deficits, thereby allowing appropriate interventions to be implemented, to reduce the likelihood of such impairments becoming entrenched and impacting academic, behavioural, psychosocial, and adaptive functioning. Marino et al. (2012) put forward a statement on behalf of the American Heart Association outlining the need for periodic developmental investigation, screening, and evaluation of children with CHD. For toddlers up to the age of 3.5 years, they recommended the use of Bayley-3, or alternatively, the Mullen Scales of Early Learning.

3.1.1 The Bayley Scales

The Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-3) are widely considered to be one of the most comprehensive tools and the gold standard for assessment of early child development (Bayley, 2006). Bayley-3 has been widely used by clinicians and researchers to identify potential developmental delays in a range of high-risk developmental populations. Details of Bayley-3 have been previously described in Chapter 2, section 2.9.1.1.

The original Bayley Scales were first developed and published by Nancy Bayley in 1969 and measured mental and motor development in infants aged 3-28 months-old (Bayley 1969). They have since been updated multiple times in order to update the normative sample means, increase assessment sensitivity and accuracy, and to remain relevant with the current times. For example, Bayley-2 extended the testing age range to 1-42 months and included the Mental
Developmental Index which measured cognitive and language development, the Psychomotor Developmental Index, and a behavioural rating scale (Bayley, 1993). The most recent update is Bayley-4 (Bayley, 2019) which is currently available in the US, and soon to be available in the UK following the completion of the validation study to produce UK specific norms.

3.1.2 Bayley-3 UK Validation

The Bayley-3 UK and Ireland Supplement reports the results from the UK and Ireland validation study (Bayley, 2010) which included a representative sample of 221 children aged between 12-24 months, taking into consideration geographic region, gender, age, ethnicity, and parental education. The validation study was conducted to achieve a valid normative reference for the use of Bayley-3 in the UK and Ireland. Data from the validation study were scored according to the US norm tables provided in the Bayley-3 Administration Manual. These scores were then adjusted for sampling bias by applying weightings for parental education level to create UK and Ireland specific norms. There were no statistically significant differences between scores from the UK and Ireland sample so it was concluded that the same norm table could be used for both. T-tests were used to compare the mean scaled and composite scores from each subtest between the US and UK norms. This revealed some statistically significant differences (Table 3.1), for example, UK and Irish children under-perform in the Gross Motor subtest, and over-perform in the Fine Motor subtest when compared with the US sample. The reason for this is unknown but it is important to consider this when assessing healthy control children in the UK in comparison to a clinical sample (Bayley, 2010).
Table 3.1 Mean scaled and composite scores on the Bayley-3 subtests for the UK and Ireland sample, with t-test and significance levels (sig) for comparison with expected values (10 for scaled, 100 for composite scores), weighted for disparity in levels of parental education (Bayley, 2010)

<table>
<thead>
<tr>
<th>Subtest</th>
<th>Mean</th>
<th>t</th>
<th>sig</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scaled Scores</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive</td>
<td>10.25</td>
<td>1.23</td>
<td>n.s.</td>
</tr>
<tr>
<td>Language: Receptive Communication</td>
<td>9.75</td>
<td>1.16</td>
<td>n.s.</td>
</tr>
<tr>
<td>Language: Expressive Communication</td>
<td>10.03</td>
<td>0.14</td>
<td>n.s.</td>
</tr>
<tr>
<td>Motor: Fine Motor</td>
<td>10.72</td>
<td>4.78</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Motor: Gross Motor</td>
<td>9.12</td>
<td>4.21</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td><strong>Composite Scores</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive</td>
<td>101.23</td>
<td>1.23</td>
<td>n.s.</td>
</tr>
<tr>
<td>Language</td>
<td>99.24</td>
<td>0.61</td>
<td>n.s.</td>
</tr>
<tr>
<td>Motor</td>
<td>100.04</td>
<td>0.04</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

*Note.* n.s. = not significant

### 3.1.3 The Flynn Effect

The Flynn effect refers to the natural increase in standardised test scores of IQ or Development Quotients (DQ) over time (Flynn, 1999). It is more robust in older children and adults, but with each updated edition of the Bayley Scales, the Flynn effect is expected. There is an average increase of 19 points which is a gain of approximately 3.7 DQ points per decade, and similar gains of approximately 3.9 IQ points per decade have been present in preschool children aged 4-6 years (Lynn, 2009). Comparable gains in IQ have been observed in school-aged children and adults on intelligence tests which suggests that the same factor is responsible for these gains (Trahan et al., 2014). Various hypotheses have been proposed for the cause of the Flynn effect, including genetic and environmental factors, improvements in education, and increased test sophistication. However,
it has been commonly suggested that the most probable cause is improvements in prenatal and early postnatal nutrition (Lynn, 2009; Trahan et al., 2014).

The Flynn effect can result in norms becoming obsolete, so regular updates of increasing sensitivity and country specific norms are imperative. With each new edition of the Bayley Scales, discrepancies have been reported in the scores which has led some to question which edition is most accurate. Apart from the Flynn effect, variations between different versions of Bayley Scales have been attributed to over and underestimation of normative data, differing base and ceiling criteria, and changes in formats (Aylward & Zhu, 2019).

3.1.4 Problems with Bayley-3

Bayley-3 scores are known to be considerably higher than those of its predecessor, which has led to the edition being criticised for suspected inflation of normative scores. For example, Anderson et al. (2010) found evidence that Bayley-3 significantly underestimates developmental delay in 2 year-old Australian children who were born extremely premature and those born with extremely low birth weight. They also reported that Bayley-3 cognitive and language composite scores were elevated by more than 0.5 SD, and more than 1 SD on the motor composite, in healthy full-term controls relative to the normative mean. Similar results have also been reported in the UK in the EPICure-2 cohort (Moore et al., 2012) and in Brazil (Silveira et al., 2012).

When directly comparing Bayley-3 with Bayley-2, the mean cognitive and language scores were significantly higher in Bayley-3, and the rate of impairment also dropped from 25% with Bayley-2 to only 14% with Bayley-3 (Moore et al., 2012). Therefore, it appears that Bayley-3 may not identify all children with
developmental delay and may be a poor predictor of later impairments (Anderson and Burnett, 2017). Similar findings have been reported in many at-risk populations such as children born preterm (Moore et al., 2012), but also in children with CHD (Acton et al., 2015). Johnson et al. (2014) suggested that conventional cut-offs may not be appropriate for Bayley-3. They identified that Bayley-3 cognitive and language composite scores <85 had 99% agreement with the Mental Developmental Index <70 on Bayley-2, and underestimated delay by 1.1%. Consequently, scores <85 on Bayley-3 are most reflective of moderate to severe neurodevelopmental delay, for comparison with the Mental Developmental Index <70 on Bayley-2.

Further problems with the Bayley-3 as well as other similar neurodevelopmental assessments relate to the variability corresponding to the differential developmental rates of very young children. This often means that the age at which individual children achieve various developmental milestones varies, even with typically developing children. Therefore, normative age bands are often used in assessments such as the Bayley-3. However, the sequence of milestones can also vary considerably between children; Vereijken (2010) suggested that infants can often “skip” developmental stages or go back and forth between them, they can achieve more advanced milestones ahead of less advanced ones, and sometimes, an advanced milestone can be briefly sampled before being consistently achieved several days or even weeks later. Standardised assessments such as Bayley-3 assume that children develop skills in a fixed order or similar sequence, and test items are ordered based on their level of difficulty, determined by scores of mostly typically developing children in the standardisation sample (Visser et al., 2017).
Many longitudinal studies in the literature suggest that developmental assessments before the age of two years poorly predict later skills, including cognitive, language and motor skills (Petrill et al., 2004). Bayley-3 has been found to result in highly unstable delay classifications, low sensitivities, and poor positive predictive values across the first two years of life, in a range of typically developing populations worldwide (Kvestad et al., 2022), and in a range of clinical populations including high-risk preterm infants (Lobo et al., 2014). This low predictability may reflect poor stability of early cognitive development, the influence of environmental factors, or possibly the psychometric limitations of the assessment tool (Schneider et al., 2014). For example, it has been suggested that Bayley-3 measures more perceptual and motor skills than those specifically targeted by IQ tests, such as reasoning, and verbal and nonverbal problem-solving (Krogh and Væver, 2019; Peyre et al., 2017). Test-retest stability of the Bayley-3 has been investigated with an average six day interval between testing time-points and average stability was found to be acceptable, but higher in older children (Anderson and Burnett, 2017; Bayley, 2006). Cognitive skills have been found to be more progressively correlated with later measures of skills and are strongly correlated from five years of age onwards (Schneider et al., 2014).

The predictive validity of Bayley-3 over time has been investigated in longitudinal studies but these are limited in the literature, in comparison to studies exploring the predictability of Bayley-3 scores in the preschool years with later intelligence measures at school age. Krogh and Væver (2019) examined the predictive validity of all the Bayley-3 subtests in a sample of 55 healthy controls who were assessed at six time-points between 4-36 months (i.e. 4, 7, 10, 13, 24, and 36 months). They found significant correlations ranging from weak-to-strong for all ages and subtests, but the three main domains of Cognition, Language and Motor
differed with respect to predictive validity. The Cognitive Scale was predictive and significant correlations were found between 7-10, 7-13 and 10-13 months, suggesting that cognitive development is relatively stable during this period, but it was not from 13 months onwards. The Language Scale was predictive from 10 months onwards, and the Motor Scale was predictive at all ages, but only with respect to adjacent assessment time-points, not distant ones. The authors also suggested that the Cognitive Scale is to some extent dependent on fine motor skills, as these subscales correlated significantly in five out of six ages. Further, they suggest that earlier language assessments may not have been significantly correlated as Bayley-3 focusses more on behaviours which are expected to be prerequisites for language development rather than language per se (e.g. does the child react to voices or sounds).

3.1.5 U-Shaped Curve in Typical Development

The lack of stability and poor predictability in longitudinal Bayley-3 scores may be explained by the phenomenon of a characteristic U-shaped curve in typical childhood development. A U-shaped curve in a cognitive-developmental trajectory refers to a three-step process: good performance at the first step, followed by a drop in performance relative to the latter, followed by good performance once again at the third step (Carlucci and Case, 2013; Pauls et al., 2013). This is said to reflect a temporary regression before a newly acquired ability is able to consolidate, and is likely to be followed by a rapid acceleration which marks a developmental transition (Blijd-Hoogewys and van Geert, 2017). This U-shaped pattern in typical development seems to contradict the idea that development is linear with performance improving with age, and that learning is a monotonic, cumulative process of improvement (Carlucci and Case, 2013).
With respect to the Bayley Scales, which are age-normed, this suggests that the developmental trajectory of certain skills may appear to ‘dip’ or reduce with age, before increasing again at a later point in time. Consequently, this may explain the instability, low predictability and lack of moderate or strong significant associations between different Bayley-3 assessment time-points. However, it raises questions regarding the interpretation of results, and makes possible comparisons between longitudinal assessments challenging, beyond just the varying sequence or achievability of milestones between children as Vereijken (2010) suggested.

Siegler (2004) presented three main reasons for the declining performance within U-shaped functions in childhood. Firstly, the acquisition of systematic processing might result in reduced performance on specific tasks. Therefore, a U-shaped course of development is characterised by initial correct performances based on a lack of knowledge, followed by consistently incorrect performances as a result of incomplete knowledge. These are later superseded by correct performances based on advanced knowledge and experience. Secondly, U-shaped functions could explain the adoption of novel processing strategies which initially involve a cognitive overload and temporary losses of processing efficiency. Once novel processing strategies have been completely adopted, they lead to a more efficient cognitive processing. Finally, the unequal rates of change in certain monotonically improving processes may cause a U-shaped course of development.

The U-shaped pattern has been debated in the literature but it has been commonly reported with respect to language acquisition and motor development. For example, in the English language it has been observed that in early acquisition of past tense verbs, children learn correct syntactic forms (e.g.
call/called), then undergo a period of over-regularisation in which they attach regular verb endings such as “ed” to the present tense forms (e.g. break/breaked, speak/speaked), and then eventually reach a final phase in which they correctly handle both regular past-tense formation and the exceptions of irregular verbs (Carlucci and Case, 2013). Another well-known U-shaped curve that has been observed is the regression of newborn stepping movement (Gershkoff-Stowe and Thelen, 2004). When newborn infants are held upright, with their feet on a surface, they make step-like movements, with alternating leg flexions and extensions. This occurs in typically developing infants around 3 months of age, then disappears, before reappearing at approximately 8 months, before cruising and walking. This U-shaped pattern needs to be considered when interpreting longitudinal developmental trajectories, including those obtained using Bayley-3, especially when development of CHD patients is being compared to typically developing controls.

3.1.6 Bayley-3 and CHD

The Bayley Scales have been frequently used with children with CHD to evaluate early neurodevelopmental milestones and outcomes. As discussed in Chapter 1 section 1.4, there is commonly a distinctive pattern of mild or low severity impairments in children with CHD, with cognitive/intelligence scores falling within the average to low-average range. When children with CHD are compared to healthy controls or normative scores, they tend to score within 1 SD, with a small proportion usually scoring in the clinically impaired range (≥2 SD). It is important to consider the tendency for Bayley-3 to inflate scores when interpreting the CHD literature and possible neurodevelopmental impairment.
Acton et al. (2015) compared Bayley-3 scores from 21 month-old children with different types of CHD and reported that HLHS patients had the lowest scores and TGA patients had the highest scores, overall. There were significant differences in mean composite scores for the language and motor subtests, when comparing these two groups. Impairments in language were considerably higher compared to the other domains, and 27.3% of children with HLHS had language impairment. They also directly compared Bayley-3 scores to Bayley-2 and found an average increase of 10 points in mean cognitive composite score, 1.4 in language, and 6.9 in motor. Similarly, Hicks et al. (2016) found that 2 year-olds with TGA had Bayley-3 scores comparable to the normative sample, with the exception of the language subscale. Language delay was found in 29% of the cohort and maternal education and cross-clamp duration were identified as predictive risk factors. Children with TGA were 4.7 times and 1.8 times more likely to have a composite language score <70, and <85, respectively, compared to the normative sample. It is noteworthy that in both these studies, patients were excluded if they had any known genetic or chromosomal abnormalities, or if they required extracorporeal membrane oxygenation or heart transplantation, both of which are known to be associated with poorer neurodevelopmental outcomes.

Several factors have been identified as being associated with lower Bayley-3 scores. In children with TGA, age at repair and days of open chest are also significantly associated with lower composite language scores, whilst length of stay in hospital is significantly associated with lower composite cognitive scores (Lim et al., 2019). In children with HLHS, higher lactate levels were associated with lower cognitive scores; longer stay in ICU and longer overall hospital stay, as well as more complications following stage 2 surgery, were associated with lower motor scores; lower weight was associated with lower language and
cognitive scores (Khalid and Harrison, 2019). Beyond surgical and clinical variables, Meuwly et al. (2019) investigated brain abnormalities associated with neurodevelopmental outcomes at one year in children with complex CHD. They reported that infants with CHD had smaller pre- and post-operative total and regional brain volumes, and significantly poorer Bayley-3 cognitive and motor outcomes (with a trend towards lower language scores), compared to healthy controls. It was concluded that reduced cerebral volume in neonates with CHD may serve as a biomarker for impaired neurodevelopmental outcome.

The predictive value of early Bayley-3 scores in later neurodevelopment has also been explored in the literature. There is conflicting evidence about whether early neurodevelopmental outcomes can accurately predict later outcomes at preschool and school age. Brosig et al. (2018) found that earlier cognitive and motor scores from Bayley-3 at 2 years of age were significantly correlated with later IQ and motor scores at 4 years. Agreement for score categories was 79% and 61% for cognitive and fine motor scores, respectively. Despite this, more children with CHD had at-risk or delayed scores at 4 years, than at 2 years. This again suggests that Bayley-3 may underestimate delays. In contrast, Gaudet et al. (2021) explored the stability of neurodevelopmental outcomes in CHD by investigating whether Bayley-3 scores at 2 years of age were predictive of later impairments at 5 years of age. They found that Bayley-3 language scores did accurately identify children with impaired language at 5 years. The developmental trajectory between 1 and 5 years was different for cognitive and language domains, with a decline in cognitive functioning with age, stable expressive language, and improved receptive language. Fairbairn et al. (2018) reported that although Bayley-3 outcomes at one year of age in Australian children with CHD were statistically significantly associated with outcomes at 3 years in all domains,
they were weak predictors of outcomes at 3 years in all domains. There was good specificity for cognitive, receptive communication, and fine motor outcomes at 3 years, but sensitivity was poor for cognitive, expressive and receptive communication, and fine motor outcomes. They concluded that it is difficult to predict later performance in the Bayley-3, using earlier assessment scores in these children. Comparably, literature has also found that cognitive assessments in the preschool years in healthy control children are an insufficient predictor of later intelligence as ability is so variable, but scores stabilise and become more reliable in the later school years (Mansson et al., 2019).

Sprong et al. (2022) focussed specifically on motor developmental outcomes in different types of CHD, including TGA and single ventricle physiology. Bayley-3 was used to assess motor skills at 3, 9, and 18 months of age, and at each time-point, the mean motor composite score fell within the average range. Motor scores were consistent over time, with gross motor deficits being observed more than fine motor deficits. A small proportion of children with CHD (3%) also had abnormal fine motor scores. Impaired gross motor scores increased with age, and children with single-ventricle physiology performed significantly worse at 9 and 18 months for both fine and gross motor skills, compared to children with other types of CHD, with 32.2% having a clinically abnormal score. The authors suggest that this is likely due to the fact that children with single-ventricle CHD require more surgeries, have longer stays in hospital and have long-term oxygen saturation levels below 85%. Their final surgery is also unlikely to have taken place by 18 months of age which may result in reduced energy and activity levels, and increased risk of white-matter injury.

In a recent study, Goldstone et al. (2020) compared Bayley-3 and Bayley-2 scores in a large group of children with various types of CHD including children
with HLHS, TGA, tetralogy of Fallot, and ventricular septal defect. Their results support earlier findings in the CHD literature as well as preterm literature. Bayley-3 generated significantly higher scores than Bayley-2, and classified fewer children with CHD as severely or mild-to-moderately impaired, particularly within the motor domain. This suggests the scale may underestimate neurodevelopmental disability following cardiac surgery. At-risk children with CHD who may have been flagged for early neurodevelopmental delay and/or impairment may not be identified using Bayley-3, and therefore may not be given appropriate intervention or support. Consequently, the updated cut-off scores (<85) suggested by Johnson et al. (2014) should be considered when evaluating and interpreting moderate to severe neurodevelopmental delay using Bayley-3.

3.1.7 Aims and Hypotheses

The primary aim of this study was to investigate the development of early cognitive, expressive language, receptive language, fine motor and gross motor skills, and parent-rated socioemotional and adaptive behavioural development in pre-schoolers with HLHS and TGA, compared to healthy controls, at 5-8 months, 12-15 months, and 3-4 years of age. Through longitudinal assessments the aim was to identify any emerging neurodevelopmental delays in these two subgroups of children with CHD. A secondary aim was to explore the link between parent-rated outcomes and direct measures of the child’s skills.

The following hypotheses draw on a priori literature as well as addressing a gap in the literature with regards to longitudinal development in the same cohort. It was hypothesised that:
• Preschool children with CHD, particularly those with HLHS, will have lower Bayley-3 scores in cognition, language and motor skills, compared to the healthy controls.
• A higher proportion of pre-schoolers with complex CHD will have neurodevelopmental delays, particularly in language and motor skills, compared with healthy controls.
• Children with HLHS will have different longitudinal developmental trajectories compared to healthy controls and children with TGA.
• In the healthy controls, but not children with CHD, earlier Bayley-3 scores will be associated with later Bayley-3 scores.
• Preschool children with complex CHD, and in particular those with HLHS, will have an increased incidence of early social-emotional and adaptive behavioural problems compared with healthy children.
• Parental ratings of socio-emotional and adaptive behaviour will be associated with objective measures of the child’s performance.

3.2 Methods

Researchers received training for the administration of Bayley-3 from Dr Betty Hutchon, a Consultant Neurodevelopmental Therapist at University College London Hospital and an international Bayley Scales Trainer since 1994. The interactive training involved video cases and live demonstrations in order to learn how to administer each item as well as learning how to score each scale and interpret the results. Strict administration practices were applied to each assessment in order to ensure consistency across the two subgroups of patients with CHD and healthy controls.

The Bayley-3 provides seven raw scores for each of the seven subscales: cognition, receptive and expressive communication, fine and gross motor, social-emotional, and adaptive behaviour. Raw scores were converted into scaled scores using the Bayley-3 Administration Manual. Scaled scores take into
consideration the age of the child at the time of testing and have a mean of 10 and SD of 3. The two subscales for language and motor domains can be combined to provide an overall language and motor score, respectively. Scaled scores were then also converted into composite (standard) scores which have a normative mean of 100 and SD of 15. These composite scores are calculated based on a comparison of the child being tested to a normative age-matched sample (e.g. the UK validation study sample). A total of five composite scores are obtained on the Bayley-3, one for each of the five domains. Composite scores are interpreted based on their deviation from the normative mean. Therefore, a composite score of <85 (1 SD below the mean) indicated mild impairment or a child at risk of developmental delay, and a score of <70 (2 SD below the mean) indicated moderate/severe impairment requiring early intervention (Del Rosario et al., 2020). Given what is known about the tendency for Bayley-3 to underestimate neurodevelopmental delay, more suitable cut-off composite scores of <85 were used to identify children with CHD at possible risk of delay. Johnson et al. (2014) recommended this as being most reflective of moderate to severe neurodevelopmental delay.

### 3.2.1 Participants

The cohort described in Chapter 2 section 2.2 and depicted in Figure 2.3 was invited to take part at each stage of neurodevelopmental assessment, involving administration of Bayley-3 at three different stages: time-point 1 where the cohort was assessed at 5-8 months, time-point 2 at 12-15 months, and time-point 3 at 3-4 years of age. Sixty-one children participated in the first assessment, 1 healthy control was excluded from the dataset due to a later diagnosis of ASD during the
study, leaving a total sample of 60 infants at time-point 1. At the time-point 2 assessment, 4 children (i.e. 3 healthy controls and 1 TGA patient) had withdrawn from the study, leaving 56 children who continued with the second assessment. Additionally, three new CHD patients (2 HLHS and 1 TGA) were recruited at this time-point giving a total sample of 59 children at time-point 2. At the final time-point 3 assessment, 10 further children had withdrawn (2 HLHS, 5 TGA, and 3 healthy controls), and 3 TGA patients could not be assessed due to the COVID-19 pandemic during which data collection was ceased. This left a total sample of 46 children at time-point 3. The full sample at each time-point is summarised in Table 3.2.

<table>
<thead>
<tr>
<th>Bayley-3</th>
<th>HLHS</th>
<th>TGA</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time-point 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>11</td>
<td>21</td>
<td>28</td>
</tr>
<tr>
<td>Age (months), Mean (SD)</td>
<td>6.55 (0.93)</td>
<td>6.29 (1.23)</td>
<td>5.36 (1.89)</td>
</tr>
<tr>
<td>Gender (M:F)</td>
<td>4:7</td>
<td>13:8</td>
<td>17:11</td>
</tr>
<tr>
<td><strong>Time-point 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>13</td>
<td>21</td>
<td>25</td>
</tr>
<tr>
<td>Age (months), Mean (SD)</td>
<td>12.85 (1.28)</td>
<td>12.67 (1.28)</td>
<td>13.00 (0.96)</td>
</tr>
<tr>
<td>Gender (M:F)</td>
<td>6:7</td>
<td>13:8</td>
<td>14:11</td>
</tr>
<tr>
<td><strong>Time-point 3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>11</td>
<td>14</td>
<td>21</td>
</tr>
<tr>
<td>Age (months), Mean (SD)</td>
<td>38.91 (2.88)</td>
<td>41.29 (4.55)</td>
<td>39.14 (5.51)</td>
</tr>
<tr>
<td>Gender (M:F)</td>
<td>6:5</td>
<td>9:5</td>
<td>12:9</td>
</tr>
</tbody>
</table>

### 3.2.2 Procedure / Assessment

The Bayley-3 assessment took place at the UCL Wolfson Centre, and typically lasted between 30-90 minutes depending on the age of the child, their temperament on the day of testing, and the capabilities of the child. CHD patients
can often need longer or more frequent breaks throughout testing so these accommodations were made during each assessment. The cognitive subscale was typically administered first as this involves more testing materials and the child should be seated at a table. This was followed by the language subscale, and finally the motor subscale was assessed last as this allowed children to sit, walk, run or move around the lab at a time when they would naturally tire and would struggle to remain seated.

At time-points 1 and 2, infants were sat on the lap of their primary caregiver during the assessment to complete the cognitive, language, and fine motor scales, and then were sat or lay prone or supine on the floor for the gross motor scale as necessary. At time-point 3, the child was seated at the table on their own chair. Primary caregivers, most often mothers, were given the parental questionnaire containing the social-emotional and adaptive behaviour scales. This was completed on the day of the assessment at their convenience. Breaks were given to the child when required, between subscales.

3.2.3 Data analysis

All Bayley-3 scaled scores were converted into composite/standard scores using psychometric conversion tables.

Descriptive statistics were first used to characterise the sample, and data were tested for normality and homogeneity of variance. Given the small and unequal sample sizes of all three groups and a violation of the homogeneity of variance assumption and non-normally distributed data, log and square root transformations were applied independently to try and achieve normality of the data. Data from 4 control participants were identified as outliers as their scores
were >2 SDs above the mean, and these were removed to try to achieve normality. However, both transformation attempts and removal of outliers were unsuccessful and normality could not be reached as identified using the Shapiro-Wilk test. Consequently, non-parametric Kruskal-Wallis analyses were conducted to compare Bayley-3 scores at each time-point between the three groups. For the post-hoc analyses, Mann-Whitney U tests with uncorrected p-values were used to uncover the pairwise differences, and calculate effect size (\(r\)). For non-parametric analyses, medians and interquartile ranges (IQR) are reported.

Despite the issues of normality and homogeneity of variance with the data, an exploratory two-way repeated measures mixed analysis of variance (ANOVA) was conducted in order to specifically explore the interaction between time-point and group, as there is no non-parametric alternative to test this interaction. For the repeated measures ANOVA, time-point was used as the within subjects factor and group as the between subjects factor. The interaction between these two variables was explored for each Bayley-3 subscale separately. Effect size was calculated using eta squared (\(\eta^2\)) where 0.01 indicates a small effect; 0.06 indicates a medium effect; and 0.14 indicates a large effect size (Field, 2009). For parametric analyses, means and standard deviations are reported.

Non-parametric Spearman’s rank-order correlations were conducted to explore the relationship between each respective Bayley-3 subscale longitudinally to investigate possible associations between earlier and later assessment scores (i.e. between time-points 1 and 2; time-points 1 and 3; and time-points 2 and 3).

Further correlational analyses were used to explore the relationship between the longitudinal parental Bayley-3 scores, and between parent-rated social-emotional and adaptive behaviour scores and directly measured Bayley-3 scores of cognition, language and motor skills.
3.3 Results

To address the first hypothesis and investigate differences in Bayley-3 subscale scores between the groups, Kruskal-Wallis analyses were conducted. To address the second hypothesis that pre-schoolers with complex CHD will have neurodevelopmental delays, particularly in language and motor skills, the proportions of pre-schoolers with scores 1-2 SD and ≥2 SDs below the mean were calculated for each group.

3.3.1 Bayley-3 Scores at 5-8 months

Eleven children with HLHS, 21 with TGA, and 28 healthy controls completed the Bayley-3 assessment at 5-8 months-old. Significant group differences were observed in Cognition, Expressive Language, and Fine and Gross Motor subscales, but not Receptive Language. Post-hoc Mann Whitney tests revealed the HLHS group had significantly lower scores compared to the Control group in all these subscales. The TGA group also had lower scores than the Control group in Fine and Gross Motor subscales. These results are summarised in Table 3.3. The median Gross Motor composite score for the HLHS group was 75.00 which is 1-2 SD below the normative mean, compared to the TGA and healthy control groups who scored within the normal range.
Table 3.3 Bayley-3 outcomes in children with CHD and healthy controls at 5-8 months

<table>
<thead>
<tr>
<th></th>
<th>HLHS</th>
<th>TGA</th>
<th>Controls</th>
<th>H</th>
<th>p</th>
<th>Post-hoc</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cognition</strong> (5-8 months Bayley-3 (median composite score (IQR)))</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognition</td>
<td>95.00 (35)</td>
<td>100.00 (28)</td>
<td>115.00 (19)</td>
<td>6.51</td>
<td>.04*</td>
<td>HLHS &lt; C: U = 76.50, z = -2.44, p = 0.01, r = -0.39</td>
</tr>
<tr>
<td>Receptive Language</td>
<td>100.00 (35)</td>
<td>95.00 (23)</td>
<td>105.00 (18)</td>
<td>4.08</td>
<td>.13</td>
<td>-</td>
</tr>
<tr>
<td>Expressive Language</td>
<td>90.00 (15)</td>
<td>100.00 (15)</td>
<td>105.00 (20)</td>
<td>8.90</td>
<td>.01*</td>
<td>HLHS &lt; C: U = 67.50, z = -2.73, p = 0.01, r = -0.44</td>
</tr>
<tr>
<td>Fine Motor</td>
<td>95.00 (20)</td>
<td>100.00 (20)</td>
<td>112.50 (24)</td>
<td>7.84</td>
<td>.02*</td>
<td>TGA &lt; C: U = 191.50, z = -2.09, p = 0.04, r = -0.30</td>
</tr>
<tr>
<td>Gross Motor</td>
<td>75.00 (25)</td>
<td>90.00 (20)</td>
<td>105.00 (20)</td>
<td>24.05</td>
<td>***</td>
<td>HLHS &lt; C: U = 23.50, z = -4.09, p &lt; 0.001, r = -0.65</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TGA &lt; C: U = 111.50, z = -3.71, p &lt; 0.001, r = -0.53</td>
</tr>
</tbody>
</table>

*Note. Data are presented as group median (interquartile range), Kruskal-Wallis H and p-value, where statistically significant differences between groups denoted as *p<0.05, **p<0.01, and ***p<0.001, and post-hoc pairwise group differences: Mann-Whitney U, z, p-value, and effect size r (where healthy controls are denoted as C). Despite there being significant differences between the groups on many of the Bayley-3 subscales at 5-8 months, the majority of the CHD patients scored within the normative range. However, a proportion of HLHS and TGA patients had particularly impaired Gross Motor scores (a total of 63% and 38%, respectively). Table 3.4 summarises the proportion of children in each group with standard scores <85 (1-2 SD below the mean) or <70 (≥2 SDs below the mean) scores at 5-8 months.
Table 3.4 The total number of participants with Bayley-3 scores 1-2 SD and ≥2 SDs below the mean at 5-8 months

<table>
<thead>
<tr>
<th>5-8 months Bayley-3 (N (%))</th>
<th>HLHS (N=11)</th>
<th>TGA (N=21)</th>
<th>Controls (N=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 SD</td>
<td>1 (9)</td>
<td>1 (5)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>≥2 SD</td>
<td>2 (18)</td>
<td>0</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Receptive Language</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 SD</td>
<td>0</td>
<td>2 (10)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>≥2 SD</td>
<td>1 (9)</td>
<td>1 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Expressive Language</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 SD</td>
<td>2 (18)</td>
<td>3 (14)</td>
<td>0</td>
</tr>
<tr>
<td>≥2 SD</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fine Motor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 SD</td>
<td>1 (9)</td>
<td>1 (5)</td>
<td>0</td>
</tr>
<tr>
<td>≥2 SD</td>
<td>2 (18)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gross Motor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 SD</td>
<td>4 (36)</td>
<td>7 (33)</td>
<td>0</td>
</tr>
<tr>
<td>≥2 SD</td>
<td>3 (27)</td>
<td>1 (5)</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

3.3.2 Bayley-3 Scores at 12-15 months

Thirteen children with HLHS, 21 with TGA, and 25 healthy controls completed the Bayley-3 assessment at 12-15 months-old. Significant group differences were observed in Cognition, Expressive Language, and Fine and Gross Motor subscales. The HLHS group had significantly lower scores compared to the Control group in Cognition, and Fine and Gross Motor subscales. The TGA group also had lower scores than the Control group in Cognition, Expressive Language, and Fine Motor subscales. There was no main effect of group in Receptive Language scores. These results are summarised in Table 3.5. The median Gross Motor composite score for the HLHS group was 85.00 which is 1 SD below the normative mean, compared to the TGA and healthy control groups who scored within the normal range.
### Table 3.5 Bayley-3 outcomes in children with CHD and healthy controls at 12-15 months

<table>
<thead>
<tr>
<th></th>
<th>HLHS</th>
<th>TGA</th>
<th>Controls</th>
<th>H</th>
<th>p</th>
<th>Post-hoc</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>12-15 months Bayley-3</strong> (median composite score (IQR))</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cognition</strong></td>
<td>95.00 (10)</td>
<td>100.00 (18)</td>
<td>110.00 (13)</td>
<td>17.18</td>
<td>***</td>
<td></td>
</tr>
<tr>
<td><strong>Receptive Language</strong></td>
<td>90.00 (15)</td>
<td>95.00 (20)</td>
<td>95.00 (23)</td>
<td>2.29</td>
<td>.32</td>
<td></td>
</tr>
<tr>
<td><strong>Expressive Language</strong></td>
<td>95.00 (15)</td>
<td>95.00 (10)</td>
<td>100.00 (13)</td>
<td>8.09</td>
<td>.02*</td>
<td>TGA &lt; C: U = 140.00, z = -2.76, p = 0.01, r = -0.41</td>
</tr>
<tr>
<td><strong>Fine Motor</strong></td>
<td>95.00 (15)</td>
<td>95.00 (18)</td>
<td>105.00 (20)</td>
<td>12.74</td>
<td>.002**</td>
<td>HLHS &lt; C: U = 77.50, z = -2.64, p = 0.01, r = -0.43</td>
</tr>
<tr>
<td><strong>Gross Motor</strong></td>
<td>85.00 (15)</td>
<td>90.00 (30)</td>
<td>100.00 (18)</td>
<td>9.79</td>
<td>.01*</td>
<td>TGA &lt; C: U = 118.00, z = -3.21, p = 0.001, r = -0.47</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HLHS &lt; C: U = 56.50, z = -3.29, p &lt; 0.001, r = -0.53</td>
</tr>
</tbody>
</table>

**Note.** Data are presented as group median (interquartile range), Kruskal-Wallis H and p-value, where statistically significant differences between groups denoted as *p<0.05, **p<0.01, and ***p<0.001, and post-hoc pairwise group differences: Mann-Whitney U, z, p-value, and effect size r (where healthy controls are denoted as C).

Again, despite there being significant differences between the groups on many of the Bayley-3 subscales at 12-15 months, the majority of the CHD patients scored within the normative range. However, a total of 39% of HLHS and TGA patients had impaired Gross Motor scores. Table 3.6 summarises the proportion of children in each group with standard scores 1-2 SD or ≥2 SDs below the mean at 12-15 months.
Table 3.6 The total number of participants with Bayley-3 scores 1-2 SD and ≥2 SDs below the mean at 12-15 months

<table>
<thead>
<tr>
<th></th>
<th>HLHS (N=13)</th>
<th>TGA (N=21)</th>
<th>Controls (N=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cognition</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 SD</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>≥2 SD</td>
<td>0</td>
<td>1 (5)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Receptive Language</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 SD</td>
<td>2 (15)</td>
<td>2 (10)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>≥2 SD</td>
<td>0</td>
<td>2 (10)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Expressive Language</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 SD</td>
<td>0</td>
<td>1 (5)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>≥2 SD</td>
<td>1 (8)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Fine Motor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 SD</td>
<td>0</td>
<td>1 (5)</td>
<td>0</td>
</tr>
<tr>
<td>≥2 SD</td>
<td>0</td>
<td>1 (5)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Gross Motor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 SD</td>
<td>5 (39)</td>
<td>6 (29)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>≥2 SD</td>
<td>0</td>
<td>2 (10)</td>
<td>0</td>
</tr>
</tbody>
</table>

3.3.3 Bayley-3 Scores at 3-4 years

Eleven children with HLHS, 14 with TGA, and 21 healthy controls completed the Bayley-3 assessment at 3-4 years-old. Significant group differences were observed in Receptive and Expressive Language, and Fine and Gross Motor subscales. The HLHS group had significantly lower scores compared to the Control group in all these subscales. They also had scores significantly lower than the TGA group in all these subscales, except Expressive Language. There was no main effect of group in Cognition. Table 3.7 summarises these results. Children with HLHS had the lowest scores across all subtests, but these were all within the normative range at this time-point.
Table 3.7 Bayley-3 outcomes in children with CHD and healthy controls at 3-4 years

<table>
<thead>
<tr>
<th></th>
<th>HLHS</th>
<th>TGA</th>
<th>Controls</th>
<th>H</th>
<th>p</th>
<th>Post-hoc</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3-4 years Bayley-3</strong></td>
<td>(median composite score (IQR))</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognition</td>
<td>105.00 (10)</td>
<td>105.00 (16)</td>
<td>105.00 (10)</td>
<td>4.92</td>
<td>.09</td>
<td>-</td>
</tr>
<tr>
<td>Receptive Language</td>
<td>105.00 (10)</td>
<td>112.50 (11)</td>
<td>115.00 (8)</td>
<td>12.05</td>
<td>.002**</td>
<td>HLHS &lt; C: U = 31.50, z = -3.40, p &lt; 0.001, r = -0.60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HLHS &lt; TGA: U = 39.00, z = -2.13, p = 0.04, r = -0.43</td>
</tr>
<tr>
<td>Expressive Language</td>
<td>100.00 (15)</td>
<td>105.00 (10)</td>
<td>110.00 (10)</td>
<td>7.63</td>
<td>.02*</td>
<td>HLHS &lt; C: U = 46.50, z = -2.78, p = 0.01, r = -0.49</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fine Motor</td>
<td>100.00 (15)</td>
<td>112.50 (15)</td>
<td>120.00 (20)</td>
<td>11.03</td>
<td>.004**</td>
<td>HLHS &lt; C: U = 38.00, z = -3.11, p = 0.001, r = -0.55</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HLHS &lt; TGA: U = 36.00, z = -2.27, p = 0.03, r = -0.45</td>
</tr>
<tr>
<td>Gross Motor</td>
<td>95.00 (10)</td>
<td>105.00 (19)</td>
<td>115.00 (25)</td>
<td>7.48</td>
<td>.02*</td>
<td>HLHS &lt; C: U = 52.50, z = -2.54, p = 0.01, r = -0.45</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HLHS &lt; TGA: U = 35.50, z = -2.33, p = 0.02, r = -0.47</td>
</tr>
</tbody>
</table>

**Note.** Data are presented as group median (interquartile range), Kruskal-Wallis H and p-value, where statistically significant differences between groups denoted as *p<0.05, **p<0.01, and ***p<0.001, and post-hoc pairwise group differences: Mann-Whitney U, z, p-value, and effect size r (where healthy controls are denoted as C).

The majority of the CHD patients scored within the normative range at the final assessment time-point. Table 3.8 summarises the proportion of children in each group with standard scores 1-2 SD or ≥2 SDs below the mean at 3-4 years. Figure 3.1 shows the longitudinal Bayley-3 outcomes for each group at 5-8 months, 12-15 months, and 3-4 years, split by subscale.
Table 3.8 The total number of participants with Bayley-3 scores 1-2 SD and ≥2 SDs below the mean at 3-4 years

<table>
<thead>
<tr>
<th>3-4 years Bayley-3 (N (%))</th>
<th>HLHS (N=11)</th>
<th>TGA (N=14)</th>
<th>Controls (N=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cognition</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 SD</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>≥2 SD</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Receptive Language</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 SD</td>
<td>1 (9)</td>
<td>1 (7)</td>
<td>0</td>
</tr>
<tr>
<td>≥2 SD</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Expressive Language</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 SD</td>
<td>0</td>
<td>1 (7)</td>
<td>0</td>
</tr>
<tr>
<td>≥2 SD</td>
<td>1 (9)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Fine Motor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 SD</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>≥2 SD</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Gross Motor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 SD</td>
<td>1 (9)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>≥2 SD</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Figure 3.1. Longitudinal Bayley-3 outcomes for cognitive, receptive language, expressive language, fine motor, and gross motor subscales for each group at 5-8 months, 12-15 months, and 3-4 years

Note. The solid line represents the normative mean composite score of 100, and the dashed line represents a composite score of 85 which is 1 SD below, and the scale begins with a composite score of 60 which is >2 SD below the mean.
3.3.4 Time-point and Group Interaction

A 3x3 repeated measures mixed ANOVA was conducted using ‘time-point’ as the within subjects factor, and ‘group’ as the between-subjects factor, to investigate the interaction between these two variables. This was done separately for each Bayley-3 subscale: Cognition, Receptive Language, Expressive Language, Fine Motor, and Gross Motor. Nine children with HLHS, 14 with TGA, and 21 healthy controls completed the Bayley-3 assessments at all three time-points. Data from 4 healthy controls were removed as outliers as they were >2 SDs above the mean. This left a total longitudinal sample of 9 HLHS patients, 14 TGA patients, and 17 healthy controls. Table 3.9 shows the descriptive statistics, and Table 3.10 outlines the results of all the main effects of the ANOVAs, but the interaction effects are discussed below.

Table 3.9 Descriptive statistics displayed as mean (standard deviation) for each group, each Bayley-3 subscale, and each time-point for those children for whom data were collected at each time point

<table>
<thead>
<tr>
<th>Bayley-3 (composite score)</th>
<th>HLHS</th>
<th>TGA</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time-point 1 (5-8 months), mean (SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognition</td>
<td>89.44 (21.86)</td>
<td>103.21 (13.39)</td>
<td>113.24 (10.89)</td>
</tr>
<tr>
<td>Receptive Language</td>
<td>103.89 (21.91)</td>
<td>97.50 (9.76)</td>
<td>109.41 (16.95)</td>
</tr>
<tr>
<td>Expressive Language</td>
<td>93.33 (14.36)</td>
<td>101.79 (13.10)</td>
<td>109.71 (11.66)</td>
</tr>
<tr>
<td>Fine Motor</td>
<td>89.44 (21.57)</td>
<td>101.07 (9.03)</td>
<td>114.41 (15.20)</td>
</tr>
<tr>
<td>Gross Motor</td>
<td>76.67 (12.75)</td>
<td>90.36 (12.48)</td>
<td>102.06 (15.01)</td>
</tr>
<tr>
<td><strong>Time-point 2 (12-15 months), mean (SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognition</td>
<td>96.11 (7.41)</td>
<td>99.29 (12.54)</td>
<td>111.76 (9.99)</td>
</tr>
<tr>
<td>Receptive Language</td>
<td>90.56 (10.74)</td>
<td>93.21 (14.76)</td>
<td>101.76 (12.24)</td>
</tr>
<tr>
<td>Expressive Language</td>
<td>93.33 (12.50)</td>
<td>96.43 (5.69)</td>
<td>103.53 (11.01)</td>
</tr>
<tr>
<td>Fine Motor</td>
<td>93.89 (7.41)</td>
<td>95.36 (12.48)</td>
<td>111.76 (10.89)</td>
</tr>
<tr>
<td>Gross Motor</td>
<td>84.44 (6.82)</td>
<td>90.00 (19.32)</td>
<td>98.24 (11.17)</td>
</tr>
</tbody>
</table>
Bayley-3 (composite score) | HLHS | TGA | Controls
--- | --- | --- | ---
### Time-point 3 (3-4 years), mean (SD)
| Cognition | 100.00 (7.50) | 106.79 (11.87) | 105.29 (5.15) |
| Receptive Language | 102.22 (9.39) | 107.86 (11.39) | 113.24 (7.28) |
| Expressive Language | 99.44 (13.33) | 106.79 (12.03) | 111.18 (8.01) |
| Fine Motor | 101.11 (9.28) | 111.43 (10.64) | 116.47 (13.32) |
| Gross Motor | 95.00 (10.31) | 110.36 (15.87) | 109.71 (13.97) |

**Table 3.10 Repeated measures mixed ANOVA results for each Bayley-3 subscale, separately**

<table>
<thead>
<tr>
<th>Source</th>
<th>df</th>
<th>MS</th>
<th>F</th>
<th>p</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cognitive Subscale</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bayley Time-point</td>
<td>2</td>
<td>44.24</td>
<td>0.40</td>
<td>0.67</td>
<td>-</td>
</tr>
<tr>
<td>Group</td>
<td>2</td>
<td>2009.29</td>
<td>11.30</td>
<td>&lt;0.001***</td>
<td>0.38</td>
</tr>
<tr>
<td>Time-point x Group</td>
<td>4</td>
<td>375.55</td>
<td>3.37</td>
<td>0.01*</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>Receptive Language Subscale</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bayley Time-point</td>
<td>2</td>
<td>1534.56</td>
<td>8.84</td>
<td>&lt;0.001***</td>
<td>0.19</td>
</tr>
<tr>
<td>Group</td>
<td>2</td>
<td>1154.81</td>
<td>6.89</td>
<td>0.003**</td>
<td>0.27</td>
</tr>
<tr>
<td>Time-point x Group</td>
<td>4</td>
<td>113.45</td>
<td>0.65</td>
<td>0.63</td>
<td>-</td>
</tr>
<tr>
<td><strong>Expressive Language Subscale</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bayley Time-point</td>
<td>2</td>
<td>602.74</td>
<td>5.38</td>
<td>0.01*</td>
<td>0.13</td>
</tr>
<tr>
<td>Group</td>
<td>2</td>
<td>1496.17</td>
<td>9.72</td>
<td>&lt;0.001***</td>
<td>0.34</td>
</tr>
<tr>
<td>Time-point x Group</td>
<td>4</td>
<td>42.52</td>
<td>0.38</td>
<td>0.82</td>
<td>-</td>
</tr>
<tr>
<td><strong>Fine Motor Subscale</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bayley Time-point</td>
<td>2</td>
<td>952.43</td>
<td>5.91</td>
<td>0.004**</td>
<td>0.14</td>
</tr>
<tr>
<td>Group</td>
<td>2</td>
<td>22.86</td>
<td>22.86</td>
<td>&lt;0.001***</td>
<td>0.55</td>
</tr>
<tr>
<td>Time-point x Group</td>
<td>4</td>
<td>198.43</td>
<td>1.23</td>
<td>0.31</td>
<td>-</td>
</tr>
<tr>
<td><strong>Gross Motor Subscale</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bayley Time-point</td>
<td>2</td>
<td>2709.25</td>
<td>15.00</td>
<td>&lt;0.001***</td>
<td>0.29</td>
</tr>
<tr>
<td>Group</td>
<td>2</td>
<td>2848.77</td>
<td>13.13</td>
<td>&lt;0.001***</td>
<td>0.42</td>
</tr>
<tr>
<td>Time-point x Group</td>
<td>4</td>
<td>243.66</td>
<td>1.35</td>
<td>0.26</td>
<td>-</td>
</tr>
</tbody>
</table>

*Note.* df = degrees of freedom, MS = Mean squares, statistically significant differences are denoted *p<0.05, **p<0.01, and ***p<0.001, and effect size = η².
Cognition

There was a statistically significant interaction effect between Bayley-3 time-point and group type, \( F(4, 74) = 3.37, \ p = 0.01, \ \eta^2 = 0.15 \). Figure 3.2 shows this interaction. This effect suggests that cognitive scores differ at the three time-points and in the three groups. Pairwise comparisons were conducted to further investigate where the significant interactions lay. At time-point 1, HLHS patients had significantly lower cognitive scores (mean = 89.44, SD = 21.86) compared to healthy controls (mean = 113.24, SD = 10.89), \( p = 0.001 \). At time-point 2, HLHS patients had significantly lower cognitive scores (mean = 96.11, SD = 7.41) compared to healthy controls (mean = 111.76, SD = 9.99), \( p = 0.003 \) and TGA patients also had significantly lower cognitive scores (mean = 99.29, SD = 12.54) compared to healthy controls, \( p = 0.01 \). At time-point 3, there were no significant differences between any of the groups.

![Figure 3.2 The interaction between Bayley-3 time-point and group type, for the Cognition subscale](image-url)
Language and Motor

There were no significant interactions between time-point and group on any of the language or motor subscales (Receptive Language, $F(4, 74) = 0.65, p = 0.63$; Expressive Language, $F(4, 74) = 0.38, p = 0.82$; Fine Motor, $F(4, 74) = 1.23, p = 0.31$; Gross Motor, $F(4, 74) = 1.35, p = 0.26$).

3.3.5 Longitudinal Bayley-3 Outcomes

To address the third hypothesis regarding different developmental trajectories in CHD patients, especially HLHS patients, compared to healthy controls, graphs were plotted to visualise the longitudinal trajectories of each participant in each group, per Bayley-3 subscale. These participants included 9 children with HLHS, 14 with TGA and 17 healthy controls (4 were removed as outliers) who completed the Bayley-3 assessment at all three time-points. Figure 3.3 shows the longitudinal trajectories for each participant and each Bayley-3 subscale, split by group. Appendix 9 contains graphs for the longitudinal trajectories for each individual participant who completed all three Bayley-3 time-points, where each graph per participant contains the longitudinal results for each subtest at 5-8 months, 12-15 months, and 3-4 years.
Figure 3.3 Longitudinal Bayley-3 trajectories for each individual participant per group at 5-8 months, 12-15 months, and 3-4 years

*Note.* Each row of graphs represents each subscale: cognitive, receptive language, expressive language, fine motor, and gross motor. The solid line represents the normative mean of 10/100, and the dashed line represents 1 SD below (i.e. scaled score of 7/composite of 85).
To address the fourth hypothesis and explore the relationship between each Bayley-3 assessment, correlations were conducted for those participants who had data for all 3 time-points, to investigate possible associations between earlier and later assessment scores. Table 3.11 shows the results of the Spearman’s correlations between subscale scores at time-points 1 and 2; time-points 1 and 3; and time-points 2 and 3. Overall, there were no significant correlations between subscale scores at each of the time-points, with the exception of two. There was a strong significant positive relationship between expressive language scores in the HLHS group at time-points 2 and 3, $r = 0.89$, $p < 0.01$. There was also a moderate-to-strong significant positive relationship between cognitive scores in the TGA group at time-points 1 and 3, $r = 0.74$, $p < 0.01$. 
Table 3.11 Spearman’s correlation coefficients for each of the groups, between Bayley-3 subscale scores collected at each time-point

<table>
<thead>
<tr>
<th>Spearman’s correlation coefficient, ( r_s )</th>
<th>HLHS</th>
<th>TGA</th>
<th>Healthy Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C T2</td>
<td></td>
<td>C T2</td>
</tr>
<tr>
<td></td>
<td>RL T2</td>
<td></td>
<td>RL T2</td>
</tr>
<tr>
<td></td>
<td>EL T2</td>
<td></td>
<td>EL T2</td>
</tr>
<tr>
<td></td>
<td>FM T2</td>
<td></td>
<td>FM T2</td>
</tr>
<tr>
<td></td>
<td>GM T2</td>
<td></td>
<td>GM T2</td>
</tr>
<tr>
<td></td>
<td>C T3</td>
<td></td>
<td>C T3</td>
</tr>
<tr>
<td></td>
<td>RL T3</td>
<td></td>
<td>RL T3</td>
</tr>
<tr>
<td></td>
<td>EL T3</td>
<td></td>
<td>EL T3</td>
</tr>
<tr>
<td></td>
<td>FM T3</td>
<td></td>
<td>FM T3</td>
</tr>
<tr>
<td></td>
<td>GM T3</td>
<td></td>
<td>GM T3</td>
</tr>
<tr>
<td>HLHS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C T2</td>
<td>0.29</td>
<td></td>
<td>0.18</td>
</tr>
<tr>
<td>RL T2</td>
<td>-0.40</td>
<td></td>
<td>-0.02</td>
</tr>
<tr>
<td>EL T2</td>
<td>0.17</td>
<td></td>
<td>-0.04</td>
</tr>
<tr>
<td>FM T2</td>
<td>0.45</td>
<td></td>
<td>0.18</td>
</tr>
<tr>
<td>GM T2</td>
<td>0.08</td>
<td></td>
<td>0.45</td>
</tr>
<tr>
<td>C T3</td>
<td>0.27</td>
<td></td>
<td>0.74**</td>
</tr>
<tr>
<td>RL T3</td>
<td>0.01</td>
<td></td>
<td>-0.05</td>
</tr>
<tr>
<td>EL T3</td>
<td>0.14</td>
<td></td>
<td>0.21</td>
</tr>
<tr>
<td>FM T3</td>
<td>0.14</td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>GM T3</td>
<td>0.26</td>
<td></td>
<td>-0.19</td>
</tr>
<tr>
<td>TGA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C T2</td>
<td>0.11</td>
<td></td>
<td>0.11</td>
</tr>
<tr>
<td>RL T2</td>
<td>0.33</td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>EL T2</td>
<td>0.89**</td>
<td></td>
<td>0.33</td>
</tr>
<tr>
<td>FM T3</td>
<td>0.07</td>
<td></td>
<td>0.10</td>
</tr>
<tr>
<td>GM T3</td>
<td>0.40</td>
<td></td>
<td>-0.20</td>
</tr>
<tr>
<td>Healthy Controls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C T2</td>
<td>-0.03</td>
<td></td>
<td>0.24</td>
</tr>
<tr>
<td>RL T2</td>
<td>0.47</td>
<td></td>
<td>-0.38</td>
</tr>
<tr>
<td>EL T2</td>
<td>-0.14</td>
<td></td>
<td>-0.10</td>
</tr>
<tr>
<td>FM T2</td>
<td>-0.40</td>
<td></td>
<td>0.00</td>
</tr>
<tr>
<td>GM T2</td>
<td>0.34</td>
<td></td>
<td>-0.13</td>
</tr>
</tbody>
</table>

Note. C = Cognitive scale, EL = Expressive Language, FM = Fine Motor, GM = Gross Motor at time-point 1 (T1) (5-8 months); time-point 2 (T2) (12-15 months);
and time-point 3 (T3) (3-4 years), respectively. Statistically significant correlations denoted as *p<0.05, **p<0.01, and ***p<0.001.

3.3.6 Parent-Rated Behaviour

To address the fifth hypothesis of increased incidence of parent-rated early social-emotional and adaptive behavioural problems in children with CHD, group differences were explored at each time-point. Overall, no significant group differences were observed in social-emotional skills at any of the three longitudinal time-points. There was a significant main effect of group in adaptive behaviour scores at time-point 1 (5-8 months). Post-hoc tests indicated that the HLHS group had significantly lower scores compared to the Control group. No other significant differences were observed in adaptive skills at time-points 2 and 3. Table 3.12 summarises the Bayley-3 parental questionnaire results.

Table 3.12 Bayley-3 parent-rated social-emotional and adaptive behaviour outcomes in children with HLHS, TGA, and healthy controls at each time-point

<table>
<thead>
<tr>
<th></th>
<th>HLHS (median composite score (IQR))</th>
<th>TGA (N = 19)</th>
<th>Controls (N = 26)</th>
<th>H</th>
<th>p</th>
<th>Post-hoc</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bayley-3 Parent Questionnaire</strong></td>
<td>(median composite score (IQR))</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T1</strong></td>
<td>(N = 8) (N = 19) (N = 26)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social-emotional</td>
<td>100 (29) 100 (25) 100 (13)</td>
<td>100 (25)</td>
<td>100 (13)</td>
<td>0.20</td>
<td>.91</td>
<td>-</td>
</tr>
<tr>
<td>Adaptive Behaviour</td>
<td>95 (20) 103 (29) 112 (20)</td>
<td>103 (29)</td>
<td>112 (20)</td>
<td>7.86</td>
<td>.02*</td>
<td>HLHS &lt; C: U = 48.00, z = -2.61, p = 0.008, r = -0.44</td>
</tr>
<tr>
<td><strong>T2</strong></td>
<td>(N = 12) (N = 19) (N = 23)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social-emotional</td>
<td>105 (18) 100 (10) 105 (15)</td>
<td>100 (10)</td>
<td>105 (15)</td>
<td>2.92</td>
<td>.23</td>
<td>-</td>
</tr>
<tr>
<td>Adaptive Behaviour</td>
<td>94 (24) 95.50 (25) 100.50 (12)</td>
<td>95.50 (25)</td>
<td>100.50 (12)</td>
<td>1.63</td>
<td>.44</td>
<td>-</td>
</tr>
<tr>
<td><strong>T3</strong></td>
<td>(N = 10) (N = 10) (N = 21)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social-emotional</td>
<td>112.50 (24) 115 (16) 112.50 (29)</td>
<td>115 (16)</td>
<td>112.50 (29)</td>
<td>0.81</td>
<td>.67</td>
<td>-</td>
</tr>
<tr>
<td>Adaptive Behaviour</td>
<td>99 (26) 97 (13) 103 (15)</td>
<td>97 (13)</td>
<td>103 (15)</td>
<td>3.58</td>
<td>.17</td>
<td>-</td>
</tr>
</tbody>
</table>
Note. T1, T2, and T3 = time-points 1-3. Data are presented as group median (interquartile range (IQR)), Kruskal-Wallis H and p-value, where statistically significant differences between groups denoted as *p<0.05, **p<0.01, and ***p<0.001, and post-hoc group differences: Mann-Whitney U, z, p-value, and effect size r (where healthy controls are denoted as C).

Despite group median scores being in the normative range, a proportion of CHD patients and healthy controls had scores which were in the mildly and severely impaired range (1-2 SD and ≥2 SDs below the mean). Table 3.13 summarises the proportion of children with impaired parent Bayley-3 scores, across the three time-points.

Table 3.13 The total number and proportion of participants with Bayley-3 parent-rated social-emotional and adaptive behaviour scores 1-2 SD and ≥2 SDs below the normative range at each time point

<table>
<thead>
<tr>
<th>Bayley-3 Parent Questionnaire</th>
<th>HLHS</th>
<th>TGA</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T1 (N (%))</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social-emotional</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 SD</td>
<td>3 (38)</td>
<td>4 (21)</td>
<td>6 (23)</td>
</tr>
<tr>
<td>≥2 SD</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Adaptive Behaviour</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 SD</td>
<td>2 (25)</td>
<td>5 (26)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>≥2 SD</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>T2 (N (%))</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social-emotional</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 SD</td>
<td>1 (8)</td>
<td>2 (11)</td>
<td>2 (9)</td>
</tr>
<tr>
<td>≥2 SD</td>
<td>0</td>
<td>1 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Adaptive Behaviour</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 SD</td>
<td>2 (17)</td>
<td>3 (16)</td>
<td>0</td>
</tr>
<tr>
<td>≥2 SD</td>
<td>1 (8)</td>
<td>1 (5)</td>
<td>0</td>
</tr>
<tr>
<td><strong>T3 (N (%))</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social-emotional</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 SD</td>
<td>1 (10)</td>
<td>1 (10)</td>
<td>0</td>
</tr>
<tr>
<td>≥2 SD</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Adaptive Behaviour</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 SD</td>
<td>3 (30)</td>
<td>0</td>
<td>1 (5)</td>
</tr>
<tr>
<td>≥2 SD</td>
<td>1 (10)</td>
<td>2 (20)</td>
<td>0</td>
</tr>
</tbody>
</table>
To address the final hypothesis, the relationship between parental scores and directly measured Bayley-3 scores were explored, longitudinally. Table 3.14 shows the results of the Spearman's correlations for all participants (CHD patients and healthy controls), at each time-point. Overall, there were no significant correlations between parent-rated social-emotional scores and any of the Bayley-3 objectively measured scores. There were some weak significant positive correlations between parent-rated adaptive behaviour scores and Bayley-3 objectively measured scores, including Gross Motor at time-point 1 \( (r = 0.31, p = 0.02) \), Expressive Language \( (r = 0.31, p = 0.01) \) and Fine Motor \( (r = 0.31, p = 0.03) \) at time-point 2, and Expressive Language at time-point 3 \( (r = 0.31, p = 0.02) \).

Table 3.14 Spearman’s correlation coefficients between parent-rated and directly measured Bayley-3 subscales, for all participants combined, at each time-point

<table>
<thead>
<tr>
<th>Time</th>
<th>Scales</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Directly measured Bayley-3 Scales</td>
</tr>
<tr>
<td></td>
<td>C</td>
</tr>
<tr>
<td><strong>T1</strong></td>
<td>Parent-rated Scales</td>
</tr>
<tr>
<td>Social-emotional</td>
<td>0.18</td>
</tr>
<tr>
<td>Adaptive Behaviour</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>T2</strong></td>
<td>Social-emotional</td>
</tr>
<tr>
<td>Adaptive Behaviour</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>T3</strong></td>
<td>Social-emotional</td>
</tr>
<tr>
<td>Adaptive Behaviour</td>
<td>0.17</td>
</tr>
</tbody>
</table>

*Note.* C = Cognitive score, RL = Receptive Language, EL = Expressive Language, FM = Fine Motor skills, GM = Gross Motor. Statistically significant correlations denoted as *\( p<0.05 \), **\( p<0.01 \), and ***\( p<0.001 \).
3.4 Discussion

The primary goal of this longitudinal study was to investigate and track the development of early cognitive, language, and motor skills in pre-schoolers with HLHS and TGA in order to identify the emergence of neurodevelopmental delays. Clinically, it is important to identify CHD patients who are especially vulnerable and at risk for developing delays and/or impairments as early as possible, before such problems become rooted and seriously interfere with other aspects of their lives.

3.4.1 Cognitive, Language, and Motor Development

It was hypothesised that the children with CHD, but particularly those with HLHS, would have lower cognitive, language, and motor scores, compared to the healthy controls. This is due to the severity and complex nature of their CHD. The results of the current investigation support this hypothesis and provide evidence that severity of CHD is linked to the severity of delay because children with HLHS had significantly lower scores compared to the healthy controls on many of the Bayley-3 subtests, across the three assessment time-points. A consistent pattern was also observed in children with HLHS obtaining lower scores than children with TGA although these differences were not significant, except for the receptive language, and fine and gross motor scores at 3-4 years. This suggests that differences in the HLHS patients become more apparent with age, when they begin to diverge not only from healthy controls, but also from the TGA patients. As the literature suggests, this is likely due to the multiple staged surgeries that children with HLHS undergo as well as their more complex physiology and nature of their heart defect.
Despite there being a significant main effect of group at all three time-points, the majority of the CHD patients scored within the normative range, and group medians fell within 1 SD of the normative range. However, there were some CHD patients who had impaired scores for each of the subtests, particularly at the first two time-points. Gross motor skills appeared to be particularly affected in children with CHD and to a greater extent in children with HLHS. At 5-8 months of age, 63% of children with HLHS, and 38% of children with TGA had gross motor scores either 1-2 SD or ≥2 SDs below the normative range. By 12-15 months of age, this reduced to 39% of children with HLHS but remained as 39% of children with TGA. By 3-4 years of age, these scores fell within the normative range for both patient groups, and only 9% of children with HLHS had gross motor scores in the borderline range. Therefore, although a significant proportion of patients had impaired scores in the earlier assessments in infancy, these scores appeared to improve over time, and by 3-4 years they fell within the normal range. One explanation for this may be their early start in life in hospital, with time spent in the ICU where they were medicated, and prolonged periods of time spent recovering from heart surgery. This would have prevented them being exposed to normal life and being allowed to explore their environment which is key in early development. Consequently, there may be an initial early delay in gross motor skills in these children with parents being reluctant or extra protective with their children during this period. At the 5-8 months assessment parents of patients were often cautious with items involving their child lying prone and commented that their child disliked ‘tummy time’ due to the surgery scar on their chest. However, these skills then began to improve as the child recovered. These findings provide some support for the second hypothesis that pre-schoolers with CHD will have neurodevelopmental delays in motor skills, but fine motor skills
were impacted to a much lesser extent. Similarly, only a small proportion of CHD patients had borderline and clinical scores for receptive and/or expressive language skills, longitudinally, which does not support the hypothesis.

The pattern for scores to fall within the normative range for the majority of children with CHD, with a small proportion scoring in the impaired range, is distinctive and similar to findings in the CHD literature. Acton et al. (2015) found that 21 month-old children with HLHS had the lowest Bayley-3 scores compared to those with TGA. Group means for the HLHS group were within the normative range for all subscales except Expressive Language and Gross Motor which were both ≥2 SDs below the mean. However, they observed that impairments in language were considerably higher compared to the other domains, with 27% of children with HLHS having impaired scores, compared to 4.5% for motor skills. Similarly, Hicks et al. (2016) reported that 2 year-olds with TGA had Bayley-3 scores comparable to the normative sample, but language delay was found in 29% of the cohort. At 5-8 months, the current investigation found 18% of children with HLHS and 14% with TGA had expressive language scores 1-2 SD below the normative mean. However, by 3 years, only 9% of children with HLHS and 7% with TGA had expressive language delay. In the present study, expressive language delay was less pronounced compared to gross motor delay at both 5-8 and 12-15 months, in both children with HLHS and TGA. However, these findings combined do support the hypothesis that a higher proportion of children with complex CHD will have delayed language and motor skills compared to healthy controls.

The results of this study resonate with those of Sprong et al. (2022) who also found evidence of longitudinal motor deficits in children with CHD, despite mean motor composite scores falling within the average range. In their study, gross motor skills were particularly affected and the proportion of impaired scores
increased with age at 3, 9, and 18 months of age. They also found that children with single-ventricle physiology (e.g. HLHS) performed significantly worse at 9 and 18 months, compared to children with other types of CHD. In the present study, impaired gross motor scores were consistently observed at 5-8 and 12-15 months in the HLHS patients, but the proportion of patients with these scores did not increase with age, as Sprong et al. (2022) observed. Instead, the proportion reduced over time and gross motor scores seemed to improve longitudinally. This is somewhat surprising given that HLHS patients require multiple staged surgeries and Sprong et al. (2022) suggested that this was an explanation for the increasing impaired results with age in their study. However, the majority of HLHS patients in the present study had not completed their final Fontan surgery prior to being assessed at the final time-point, which may explain why only a small proportion had abnormal scores at 3-4 years of age. Alternatively, it may be the case that early gross motor delays in infancy were present in the current cohort due to the prolonged early hospital stays following surgery, but that these skills eventually “catch-up” within the normative range at 3-4 years. This highlights the early vulnerability of the motor system specifically during infancy in complex CHD.

### 3.4.2 Time-point and Group Interaction

A repeated measures mixed ANOVA was conducted to investigate a possible interaction between time-point and group. A significant interaction was found between these two variables in the Cognition subscale, specifically, HLHS patients had significantly lower cognitive scores compared to the healthy controls at both time-points 1 and 2, and the TGA patients also had significantly lower cognitive scores compared to healthy controls at time-point 2, but there were no significant differences between any of the groups at time-point 3. No other
significant interactions were observed for the other Bayley-3 subscales. These results are interpreted with caution given this was an exploratory analysis due to issues regarding the data and normality and homogeneity of variance violations.

3.4.3 Longitudinal Bayley-3 Outcomes

It was hypothesised that children with HLHS would have different longitudinal developmental trajectories compared to healthy controls and children with TGA. The results provide support for this hypothesis. Graphs of longitudinal Bayley-3 outcomes at 5-8 months, 12-15 months, and 3-4 years for each group and each subscale (Figures 3.1 and 3.3) revealed some interesting patterns. The healthy controls appeared to show a U-shaped curve in the development of receptive language and fine and gross motor skills. This is the pattern argued to show a period of temporary regression in learning described by Blijd-Hoogewys and van Geert (2017) and Carlucci and Case (2013) which is evident at the second time-point (12-15 months), and is then followed by a rapid acceleration as evidenced by the increase in median scores by 3-4 years in each of these subscales. This U-shaped pattern was not seen in cognitive skills where median scores appeared to be stable in the first two time-points but then declined at the final time-point, or expressive language skills which remained relatively stable over time. The TGA patients also showed a similar U-shaped pattern in the same subscales, but the curve appears to be less robust compared to the controls. The HLHS patients, however, do not show this U-shaped pattern of development in any of the subscales, except receptive language. In all other subscales, the scores improve with age albeit gradually, with the exception of gross motor skills, for which there is a much more progressive improvement from 5-8 months. Again, an explanation for this pattern in the HLHS group, specifically in gross motor skills, may be due
to the lengthy periods of time these patients spend in the hospital for the first few months of their life following their first Norwood procedure. This would explain their significantly impaired scores at the first two time-points where the group median fell within the clinical and borderline range, respectively.

It was also hypothesised that earlier Bayley-3 scores will be associated with later Bayley-3 scores in the healthy controls, but not in the CHD patients. However, the findings of the present study do not support this hypothesis. No significant correlations were observed in healthy controls who completed all three assessments for any of the subscales between scores at any time-points (i.e. 1 and 2; 1 and 3; or 2 and 3).

The literature varies with respect to whether Bayley-3 scores are predictive of later skills in the early school years, but longitudinal studies using the Bayley-3 to track development in healthy controls are limited. Therefore, it is currently unclear whether earlier scores would be expected to be significantly correlated with later scores. Given that the healthy controls in the current study did not experience any adverse health experiences, it seems plausible to assume that this group would have stable scores between time-points. Krogh and Væver (2019) investigated Bayley-3 correlations between six time-points from 4-36 months in healthy controls and found evidence of significant correlations between many of the time-points but these differed for each of the subscales. For example, correlations between early time-points suggested stability in the development of cognitive skills between 7-13 months of age only, compared to 10 months onwards for language skills, and motor skills were correlated at all ages, but only with respect to adjacent assessment time-points, not distant ones. However, despite having some similar assessment time-points, the results of the present study do not support Krogh and Væver’s (2019) findings. The lack of longitudinal
correlations in the current healthy controls may reflect the U-shaped curve noted in the development of receptive language and fine and gross motor skills. This may indicate the ‘temporary regression’ of these skills as suggested by Blijd-Hoogewys and van Geert (2017), at 12-15 months. However, given the lack of the U-shaped pattern in expressive language skills which remained relatively stable overtime, a significant correlation may have been anticipated in this subscale.

When looking at children with CHD who had completed all three assessments, few longitudinal correlations were observed, supporting the hypothesis. Only two correlations were significant: between expressive language scores at time-points 2 and 3, in children with HLHS, where a strong positive relationship was found; and between cognitive scores at time-points 1 and 3, in children with TGA, where again, a strong positive relationship was observed. Longitudinal scores for the CHD patients were expected to be less stable, as has been found. Although correlation does not imply causation, these positive relationships in the CHD patients suggest that expressive language and cognitive scores are consistent over time, but the pattern of stability is different in children with HLHS and TGA. The absence of significant correlations in the CHD patients may indicate that some children with CHD have improved scores over time, whilst others have decreased scores. This is evident in the longitudinal trajectories for individual children (Appendix 9), which differ across the different developmental domains. The reason for this is unknown without further investigation but it does suggest that earlier scores are poor predictors of later neurodevelopment. This also emphasises the need for regular, longitudinal neurodevelopmental follow-up in children with complex CHD, as it is evident that individual children have different development trajectories for different domains/skills.
The predictive value of early Bayley-3 scores in later neurodevelopment has been explored in the CHD literature, but this tends to be between early preschool and later school-aged developmental scores. Again, there is conflicting evidence about whether early neurodevelopmental outcomes can accurately predict later outcomes at school age. For example, Gaudet et al. (2021) suggested that early Bayley-3 scores can successfully identify children with impaired language at 5 years. However, McGrath et al. (2004) investigated the predictability of IQ and academic achievement at 8 years from neurodevelopmental status at 1 year in children with TGA. They found patterns to suggest that scores from the Bayley-3 had poor sensitivity and poor positive predictive value and concluded that more than 50% of children with low scores at 8 years had scores in the normal range at 1 year. These results are similar to those of Brosig et al. (2018) who found that although cognitive and motor scores from Bayley-3 at 2 years of age were significantly correlated with later IQ and motor scores at 4 years, more children with CHD had at-risk or delayed scores at 4 years than 2 years. Therefore, school-aged children who are at risk for poor outcomes may not be identified from earlier Bayley-3 assessment scores, which also highlights that Bayley-3 may underestimate delays. Alternatively, it is important to consider that many deficits only present later in life when they become more evident given that children with CHD are known to grow into their deficits (Ijsselstijn et al., 2021).

3.4.4 Parent-Rated Behaviour

It was hypothesised that children with complex CHD and in particular those with HLHS, would have more early social-emotional and adaptive behavioural problems than healthy children. The findings of the present study did not support this hypothesis as no significant group differences were observed for Bayley-3
social-emotional and adaptive behavioural skills at time-points 1-3. The only exception was adaptive behaviour scores at time-point 1 where children with HLHS had significantly lower scores compared to healthy controls. It is noteworthy that despite this difference, all groups had scores within the normative range, and only a small proportion of CHD patients had scores ≥2 SDs below the mean, compared to none of the healthy controls.

It is challenging to compare the present findings with those in the CHD literature. This is due to the fact that parent-rated outcomes in Bayley-3 are rarely reported, particularly in the CHD literature. Given that the ABAS can be used to measure adaptive behaviour from birth and the CBCL can measure socioemotional and behavioural outcomes as early as one year, researchers have tended to use these measures over Bayley-3. It has been reported that socioemotional and behavioural difficulties are present in infants and toddlers with complex CHD (Bonthrone et al., 2022; Cassidy et al., 2018), but despite this, the present study was not able to replicate these findings using the Bayley-3 parental questionnaires.

Parent-rated Bayley-3 outcomes were also compared with direct measures of child performance using Bayley-3, and it was hypothesised that these scores would be associated. The findings provide some support for this hypothesis as adaptive behaviour scores were significantly positively correlated with three directly measured subscale scores: expressive language, and fine and gross motor scores, differentially across time-points 1-3. This is important as it suggest that parental reporting is consistent with directly measured speech and motor abilities of the child. However, parent-rated social-emotional and adaptive behaviour scores were not correlated with cognitive or receptive language scores, at any of the time-points. Again, given the lack of published parent Bayley-3
outcomes in CHD, comparisons with the literature are challenging. Nagy and Kenyhercz (2021) correlated parent-rated and objective Bayley-3 scales in 2 year-old preterm children. They found that both social-emotional and adaptive behaviour scores were moderately correlated with cognitive, language, and motor scores, with the language scale being the more strongly correlated scale with both parental scales. Importantly, the authors combined both language and motor subscale scores so it is not possible to decipher whether one, and if so which, or both subscale scores were correlated with parent scales.

3.4.5 Limitations

There are several limitations of the present study. First, the overall sample size was very small, particularly for the HLHS group, and the group sizes were unequal. This impacted data analyses and has important implications regarding extrapolating findings and increased likelihood of type two errors. However, this limitation impacts all data in this thesis and will therefore be discussed in detail in the General Discussion (Chapter 8). Another limitation of the study is the higher than average achieving healthy control group who consistently achieved scores above the normative mean. This is an important consideration for interpreting many of the significant group differences observed between the healthy control and CHD groups. However, the scores of the children with CHD were also compared to the normative mean in order to identify the proportion of HLHS and TGA patients who had Bayley-3 scores in the borderline and clinical range (i.e. 1 and 2 SDs below the normative mean).

There are also issues with the use of Bayley-3 despite it being internationally recognised as the gold standard assessment tool. Previous literature has
emphasised the tendency for Bayley-3 to inflate scores and minimise possible neurodevelopmental impairment in CHD. Several researchers have directly compared Bayley-3 scores to Bayley-2 in various clinical populations and found increases of approximately 7-10 points in all subtests (Acton et al., 2015; Anderson and Burnett, 2017; Aylward & Zhu, 2019; Johnson et al., 2014). This would mean that children with CHD who are at risk of delay may not be detected using the Bayley-3. It is therefore important to consider the conclusions made by Johnson et al. (2014) who suggested using a more suitable cut-off composite score of <85, as opposed to <70, to reflect moderate to severe neurodevelopmental delay in clinical patients.

Further, it may have been better to avoid such a large age gap in assessments between time-points 2 and 3. There were at least 2 years between these time-points during which key developmental milestones would have been achieved. An age gap of one year would have been preferrable in order to better track longitudinal trajectories in this cohort of children. This would have meant a time-point at 24-27 months, and then possibly the final time-point at 3-4 years, but ensuring this was after the final Fontan procedure in order to be able to assess outcomes following all three staged surgeries in the HLHS group. It is likely that scores would change following the final surgery in this group, and this would allow that to be tracked. The timing of assessments is important as The Cardiac Neurodevelopmental Outcome Collaborative have recommended investigating motor development from six months and cognitive and language development from 18 months of age (Ware et al., 2020). This is to allow for reliable assessment of early development, at critical developmental time-points.
3.4.6 Conclusion and Future Research

The current study documented the early developmental trajectories of cognition, language, and motor skills from infancy to the preschool years in children with HLHS, TGA, and healthy controls. In line with previous studies, children with HLHS were found to have lower Bayley-3 scores longitudinally, compared to healthy controls. They also had lower scores compared to children with TGA, but only at time-point 3. Children with TGA had scores lower than healthy controls too but only at time-points 1 and 2. Early gross motor skills are particularly affected in this cohort of CHD patients, but scores seem to improve by 3-4 years. Children with TGA tended to have similar scores to the healthy controls. However, despite scores within the normative range for both HLHS and TGA patients, a proportion of these children do have impaired scores across all three time-points, although the proportion decreases with age. Overall, there does appear to be a different developmental trajectory for children with HLHS, as they do not have the U-shaped pattern in longitudinal Bayley-3 scores observed in the healthy controls, and to a lesser extent in the children with TGA, across many of the subscales.

What is clear is that there are a proportion of children with HLHS and TGA who have neurodevelopmental delay, despite group averages reflecting otherwise. These are the children that need to be flagged for longitudinal neurodevelopmental surveillance which is currently not routinely provided in the UK, unlike in parts of the US where neurodevelopmental programmes are specifically designed to capture these at-risk children with complex CHD (Marino et al., 2012).

It is clearly important to track development in the preschool years in order to detect delays and/or impairment as early as possible, even if early evaluations
do not identify any significant delays or concerns. This holds promise for the identification of specific preschool skills that could potentially be targeted in early interventions, in order to support children with complex CHD and their families, and to reduce educational challenges and the burden associated with complex CHD. In light of the present findings, and considering previous literature, it may be better to focus on neurodevelopmental trajectories from two years onwards, when scores in cognitive assessments are known to stabilise and there is better predictive validity for future abilities and attainment. Further research is required to investigate whether longitudinal Bayley-3 scores are correlated across time-points and are predictive of later scores, in healthy controls, before being able to properly investigate whether a similar pattern is observed or should be expected in patients with CHD.
Chapter 4:  Speech, Language, and Pre-Reading Skills in 4-5 year-old Children with Complex CHD

This chapter focuses on language outcomes in a longitudinal cohort of children with complex CHD. It begins by explaining normal language development, before describing language outcomes in children with CHD, in detail. Patient and public involvement work conducted in preparation for this project played an important role in the development of this research. Speech and language were key areas of concern identified by parents of children with complex CHD. Consequently, these skills, along with phonological abilities which are known to be important pre-reading skills, are examined in depth in this cohort of patients with HLHS and TGA. Early longitudinal language outcomes discussed in the previous Chapter 3 are compared to current language outcomes at 4-5 years. Parent-reported language scores are also compared with direct measures of the child’s language skills in order to explore whether parental ratings are consistent with the child’s performance.
4.1 Introduction

4.1.1 The Development of Language

Prior to examining language outcomes in children with complex CHD, it is important to consider the acquisition and development of language in healthy ‘normal’ development in order to understand the key pathways in the brain which are important for the domains of speech and language. Language acquisition appears to be effortless and develops as the brain matures with age, and as children are exposed to speech in their natural environments. Milestones in normal language development include phonemes perception (speech sound detection and acquisition at 6-8 months of age), speech (first few words at 10-12 months), and word comprehension (emerging a few weeks earlier), and by the end of the pre-school stage (3-4 years), most children have mastered the basic morphological and syntactic structures of their language (Conti-Ramsden & Durkin, 2012; Friederici, 2006; Kuhl, 2004). Language is a complex ability which involves the processing of multiple types of information.

The neural ‘blueprint’ of language has been split into two developmental stages: the first developing over the first three years of life, involving rapid acquisition of bottom-up processes (i.e. low-level mental representations), and the second emerging in the third year and continuing into adolescence, involving top-down processes (i.e. complex higher-order mental representations) which emerge gradually (Friederici, 2012; Skeide & Friederici, 2016). Bottom-up processes are responsible for early language development: this begins with phonological awareness, and leads to morphosyntactic categorisation or word arrangement (syntax), lexical-semantic categorisation or word meaning (semantics), lexical access and retrieval, phrase structure, and prosodic processing (speech) (Figure
4.1). Top-down processes involve the integration of syntactic and semantic information, which refine gradually, and it is only after the age of ten that there is efficient processing of complex syntax (due to maturity of Brodmann area 44). These processes are generally split across two key pathways in the brain: the earlier developing dorsal pathway and the later maturing ventral pathway. The dorsal pathway is involved in early phonology-based learning and allows auditory-to-motor mapping, from the temporal cortex to the premotor cortex, whereas the ventral pathway maps acoustic speech input onto conceptual and semantic representations (Friederici, 2012; Hickok and Poeppel, 2007). An additional dorsal pathway connects the temporal cortex to Broca’s area which is present in adults but not myelinated in infants.

If early bottom-up skills are impaired or delayed in pre-schoolers, this can potentially be detected through use of tests tapping the functions of these selective aspects of language. Identifying problems in a child’s acquisition of speech, language, and communication skills is essential as language skills are strongly associated with literacy levels and both are predictive of educational attainment. For example, phonological skills, letter knowledge, grammatical skills, and vocabulary knowledge are predictors of word recognition, reading comprehension, and spelling (Muter et al., 2004; Fraser & Conti-Ramsden, 2008). It is also important to distinguish between language problems that are reflective of IQ and parental education, versus those reflecting a specific impairment. For example, distinguishing a child who has an average nonverbal IQ with a strong parental education background, but specifically impaired aspects of language, compared to a child with impaired language skills among a more general global impairment. Auditory ERPs can be used to investigate language processing in the brain, to identify if there is atypical processing in children. This early functional
measure can then be used to explore associations with later speech and language competence.

4.1.2 Language Development in CHD

Children with complex CHD have an increased risk of a plethora of neurodevelopmental delays or deficits across a wide spectrum of domains, including speech and language. Despite this, the majority of literature focusses on cognition and motor skills specifically. If language skills are examined this is usually as part of a wider standardised assessment tool for cognitive development such as Bayley-3, as opposed to detailed examination of language skills, such as grammar, semantics, and pragmatics. However, language plays a critical role in child development, social interactions, play, daily functioning, and
academic performance, so it is somewhat surprising that, to date, there has been notably less attention on the receptive (comprehension of language) and expressive (communication of language) language outcomes of children with complex CHD.

Infants who have undergone cardiac surgery are at increased risk for delays in reaching early speech and language milestones (Andropoulos et al., 2014; Mussatto et al., 2015). Reduced verbal skills, such as poor oral motor coordination or speech articulation, are known to characterise these children early in life and they persist over time (Bellinger et al., 2003; 1999). More specifically, children with CHD requiring open-heart surgery have been found to perform worse than healthy children on tasks assessing phonological awareness, sentence production, word generation, and pragmatic skills (Bellinger et al., 2003; Brosig et al., 2017; Miatton et al., 2007). Many of these children are also known to require speech or language therapy, but rates vary depending on the severity of the heart defect (Fourdain et al., 2019; Hövels-Gürich et al., 2008).

### 4.1.2.1 Language Outcomes in Preschool Children

A recent systematic review by Turner et al. (2022) is the first to synthesise the literature on language abilities in preschool children aged 5 years and below with critical CHD (including but not limited to HLHS and TGA). They included 13 studies which examined language outcomes in children aged 2-5 years, using a range of measures including the Bayley-3, Receptive and Expressive One-Word Picture Vocabulary Tests, and Clinical Evaluation of Language Fundamentals – Preschool. Their results revealed statistically significant deficits in overall expressive and receptive language, compared to normative data, but scores were
within 1 SD of normative means. Specifically, 31% of studies reported significantly lower expressive language scores (Bellinger et al., 1999; Brosig et al., 2013; Fourdain et al., 2019; Yoshida et al., 2020), 23% reported significantly lower receptive language scores (Bellinger et al., 1999; Fourdain et al., 2019; Yoshida et al., 2020), and 22% reported a significantly lower overall language score (Bonthrone et al., 2020; Gunn et al., 2016; Yoshida et al., 2020). Children with single ventricle (SV) physiology had lower language scores than children with biventricular (BV) physiology, with one study suggesting significantly worse expressive language (Brosig et al., 2007), and two studies suggesting worse receptive language in SV CHD, compared to BV CHD (Brosig et al., 2007; Yoshida et al., 2020).

In the preschool years, much of the literature has investigated language skills as part of a wider standardised assessment tool such as the Bayley-3. Many of these studies have reported mean language scores in the Bayley-3 within the average to low-average range for children with various types of CHD, but despite this, a significant proportion of children have borderline or severely impaired language skills. For example, in 2 year-olds with CHD (including but not limited to HLHS and TGA), between 17-29% have been reported to have borderline language impairment (at least 1 SD below the normative mean), and 2-10% had severe language impairment (more than 2 SDs below the mean) (Gunn et al., 2016; Hick et al., 2016; Reich et al., 2017). Similar rates of prevalence (19% and 9%, respectively) were reported in 3 year-olds with CHD by Yoshida et al. (2020). These rates are significantly higher than the normative population, and again, the lowest scores were in infants and children born with SV physiology. Some studies have also reported that these impairments in language are specific as rates of cognitive impairments remain within the normal range (i.e. <2.3%) (Fourdain et
al., 2019). However, the type of CHD physiology and diagnosis in these patients varies in each of the studies, and consequently the severity of the CHD varies, but these studies did all exclude patients with known and suspected chromosomal abnormalities and/or genetic comorbidities. Risk factors for poorer language outcomes included reduced gestational age, cross-clamp time ≥70 min, prolonged mechanical ventilation, postoperative lactate elevation, longer days of hospital stay, more reinterventions, and <12 years of maternal education (Gunn et al., 2016; Hick et al., 2016; Reich et al., 2017).

Further, Ramanan et al. (2021) investigated language development among other aspects of development in 3-5 year-olds with TGA and other types of biventricular CHD requiring neonatal cardiac surgery in South India. They assessed speech and language using the Receptive-Expressive Emergent Language Scale which is a standardised parent-rated test used to screen for emergent receptive and/or expressive language problems, and the Malayalam Diagnostic Articulation Test which involves picture naming. Speech and language problems were identified as the most common affected domain of development with 8% of their cohort having receptive language delay and 16% with expressive language delay. From the overall cohort, 13% had isolated language delay compared to 7% with global developmental delay. The authors did state that the growth and nutritional status of some patients was extremely low, but both low weight- and height-for-age were not significantly associated with developmental delay. They also found that a higher first postoperative lactate value and increased time to lactate normalisation were associated with language delay, similar to the findings of Gunn et al. (2016).

Ovadia et al. (2000) investigated language development through play habits in 4 year-old children with TGA. These children were compared to typically developing healthy children on basic language measures (i.e. the Expressive One-Word
Picture Vocabulary Test (EOWPVT) and on the proportions of symbolic and non-symbolic talk during play with parents. Symbolic talk includes conversation about play characters, their imagined actions, speech, and states. The children with TGA had weaker vocabulary skills overall and more non-symbolic talk during play, focusing more on concrete “here-and-now” talk and less symbolic talk than healthy children, and only a third were able to produce story episodes. This suggests that pre-schoolers with TGA may have immature participation in joint pretence which may be due to difficulties coordinating more complex social intentions with appropriate language forms.

4.1.2.2 Language Outcomes in School-Age Children

Limited studies have focused on language skills in school-age children with complex CHD. An early study by Hövels-Gürich et al. (2002) measured language and speech in 7-14 year-olds with TGA, using the Kaufman Assessment Battery for Children and the Oral and Speech Motor Control test and the children’s battery of the Mayo Tests of Speech and Oral Apraxia. They reported reduced language skills in children with TGA compared to the general population, and frequent speech impairments in 40% of their cohort. They also found that speech dysfunction was associated with longer bypass duration as well as lower motor quotient and IQ, poorer outcomes for acquired abilities (i.e. learning and academic knowledge), and expressive and receptive language. The same group of researchers also assessed the long-term outcome of speech and language in 5-10 year-old children with CHD (but not HLHS or TGA) (Hövels-Gürich et al., 2018). They reported that oral and speech motor control functions and oral and speech apraxia were significantly reduced in the cyanotic group compared to the acyanotic group, but no differences were found for auditory word recognition and
phonological awareness. They concluded that children with preoperative hypoxemia due to cyanotic CHD in infancy are at increased risk for speech and language dysfunction. Age at testing, socioeconomic status, and duration of bypass influenced test results.

Miatton et al. (2007) used the Developmental Neuropsychological Assessment battery (NEPSY) to assess language skills among many other domains. They showed that 8 year-old children with CHD scored significantly lower than healthy peers in tasks assessing phonological processing, lexical access, and syntactic comprehension. This suggests that language remains an area of concern in school-age children particularly in the ability to manage and manipulate phonemes and to attach meaning to sounds in spoken language, word access, use and recognition, and the ability to understand the relationship between words and the meaning of sentences. It is noteworthy that the CHD group included a range of physiologies and both cyanotic and acyanotic heart disease, but they did not have any noncardiac malformations or genetic abnormalities.

Similarly, Sarrechia et al. (2015) reported poor expressive and receptive language skills in 9 year-old children with acyanotic corrected CHD. Specifically, they performed worse on tasks assessing phonological encoding, word productivity, and receptive language. More recently, Sommariva et al. (2020) conducted a pilot study to characterise language development in 9 year-old children with CHD (this included TGA but not HLHS), without intellectual disability. Language skills were assessed using a standardised Italian battery that assesses oral language (e.g. phonological skills, lexical processing and repertoire, and grammatical processing). Many of the tasks used were selected on the basis of them assessing language functions subserved by the dorsal and ventral pathways in the brain which have been found to be altered in CHD. They
found that children with CHD scored significantly below healthy controls on tasks of lexical and grammatical processing as well as the episodic buffer component of working memory, but the two groups did not differ in terms of their lexical repertoire and phonological discrimination abilities. Within the CHD group, children scored at least 1.5 SDs below the normative mean in four linguistic tasks: lexical comprehension, syntactic comprehension, sentence completion, and sentence repetition, with fewer having impaired scores for phonological discrimination, naming, and semantic fluency.

These studies clearly indicate an increased incidence of speech and language problems in school-age children with CHD. However, findings are less consistent with regards to which children are most at-risk or vulnerable to experiencing delays and deficits. For example, some studies suggest increased risk of speech and language problems, particularly phonological awareness, whereas other do not find evidence of this in their cohort. Sommariva et al. (2020) did not include children with HLHS and neither did Hövels-Gürich et al. (2008), the latter group also did not include children with TGA. This would perhaps suggest that the children with more severe CHD may be the ones who experience problems with phonology, and those with less severe cyanotic heart disease do not. However, both Sarrechia et al. (2015) and Miatton et al. (2007) did not specify the type of CHD but did include acyanotic CHD, which is usually less severe than cyanotic CHD, and both reported problems with phonological awareness. This then contradicts the idea that more severe types of CHD may impact the type of speech and language problems children experience, and the degree to which problems are manifested. One consistency among all these studies is the exclusion of children with any chromosome or genetic abnormalities. However, the age range of cohorts in each of these studies varies which makes
comparisons more challenging. Further, there is still a gap or period of time which is relatively under-researched and that is the early school-age years from 4/5 years onwards. Language skills also develop exponentially in the preschool and early school years so some variability is expected, but more longitudinal research is needed in this period of development to fully evaluate language skills.

Importantly, these studies do not distinguish between problems with speech articulation as opposed to language processing. For example, phonological problems are related to language but not speech per se. This distinction is important as it relates speech to fine motor control, and language to higher levels of cognitive and verbal processing.

4.1.2.3 Speech and Language Status Across the Ages

Much of the literature discussed thus far focusses on a specific time period or age of children with CHD. However, it is also necessary to explore how language skills develop overtime and whether early delays or impairments reduce with age. Kharitonova & Marino (2016) summarised and evaluated speech and language phenotypes in complex CHD survivors across ages. They concluded that infants with CHD did not differ from population norms but as language is in its very early stages, this is not unexpected. Toddlers (i.e. 1-3.5 year-olds) show deficits in early communication and have 2-4 months delay in expressive language development on Bayley-2, and pre-schoolers (i.e. 3.5-5 year-olds) have verbal and performance IQ scores below typically developing children, more concrete and less symbolic speech patterns, and produced fewer narrative components. By school-age (i.e. 5-12 years-old), language function is relatively well preserved as children with CHD have scores in the low average range for both expressive
and receptive language, but a significant proportion (25%) score in the “at risk” range for both. Deficiencies have also been observed in oral and speech motor control, though these seem to improve with age. The incidence of speech problems is more prevalent in children with severe CHD, with up to 34-50% reported to receive speech therapy or be seeing a speech pathologist. It is important to note, however, that much of the literature Kharitonova & Marino (2016) reviewed for school-aged children with CHD focussed on children aged 7 years and above.

A more recent systematic review by Huisenga et al. (2020) also evaluated language outcomes in children with complex CHD from infancy to adolescence. Language outcome of infants with SV CHD was inferior to those with BV CHD, and those with SVs were at greater risk of language impairment, especially expressive language. They also found that speech disorders such as apraxia or abnormalities of volitional oral movements emerged during preschool age and persisted in primary school age. However, it was not clear whether children with CHD outgrow these impairments because speech and language were not assessed specifically in adolescence.

Evidently, there is a broad pattern of speech and language delays and incidence of impairments throughout the ages of childhood. However, it is expressive language skills in particular that appear to be especially vulnerable in children with CHD, and receptive language to a lesser extent. Ultimately, although these studies help to review the literature across the ages in CHD, they involve combining findings from individual cross-sectional studies. This means that the same cohort has not been longitudinally followed-up and variations in individual cohorts make it more problematic to determine cause-and-effect relationships and a developmental effect cannot be established. Longitudinal cohort studies...
are needed to evaluate language skills in children with complex CHD across the ages, and to determine the relationship between risk factors and language delays and impairments, as well as determining the outcomes of interventions over time.

4.1.3 The Trajectory of Language Skills

Longitudinal research investigating the trajectory of language skills in specific cohorts is limited. Much of the literature has instead focussed on a wide range of neurodevelopmental outcomes over time of which language is one, such as those studies which have used the Bayley-3 to investigate cognitive, language, and motor outcomes over multiple time-points across infancy and toddler age. These longitudinal studies are further limited by lack of language specific assessment tools used to measure language skills beyond the preschool years.

The Boston Circulatory Arrest Study originally compared the developmental outcomes of 171 children with TGA who underwent the arterial switch operation using deep hypothermia with either total circulatory arrest (CA) or continuous low-flow cardiopulmonary bypass (LFCBP) as the predominant method of vital organ support. This research group has reported the language status of this original cohort at 4 and 8 years of age (Bellinger et al., 1999; 2003). At 4 years, the CA group had more severe speech abnormalities and both groups had expressive language scores below normative expectations. By 8 years the CA group still had worse performance including in tests of apraxia of speech and phonological awareness. Both groups had significantly lower scores for formulating sentences compared to norms, and letter fluency was below the 20th percentile for age. Interestingly, the groups did not differ in terms of reading skills, despite the CA group having worse phonological awareness which is considered to be an
important pre-reading skill. Reading scores of both groups were significantly below normative expectations as well as lower than expected based on full-scale IQ.

The Single Ventricle Reconstruction Trial was conducted to compare outcomes in HLHS patients using two different types of shunts in the Norwood procedure: the traditional modified Blalock-Taussig shunt, or substituting a shunt from the right ventricle to the pulmonary artery (Rosenthal, 2014). The original cohort has been longitudinally followed-up to explore neurodevelopmental outcomes. Language outcomes were first reported at 3 years where 20% of the cohort had impaired communication skills (scores >2 SDs below the mean), and 28% were receiving speech and language therapy (Goldberg et al., 2014). By 4 years of age, the majority of the cohort were accessing early interventional services, including 23% receiving speech and language therapy, slightly lower than the previous year (Mussatto et al., 2018). However, language outcomes were not reported at the latest assessment at 6 years.

In both of these landmark longitudinal studies, however, the trajectory of language skills has not been discussed and it is unclear whether early competence or delay is stable overtime, or if there are specific periods of increased risk to language skills. A recent longitudinal study aimed to describe the trajectory of language development in infants with CHD. Fourdain et al. (2019) conducted developmental assessments using the Bayley-3 and the MacArthur-Bates Communicative Development Inventories (MBCDI) at 12, 18 and 24 months. Compared to normative populations, infants with CHD showed significantly lower mean scores in both receptive and expressive language scales of the Bayley-3 and the MBCDI at 12 months, whereas at 18 and 24 months only expressive language scores were reduced. Communicative gestures measured
with MBCDI and Bayley-3 expressive language at 12 months were predictive of language skills at 24 months. These findings suggest that there is a specific vulnerability of language outcome, especially in expressive skills, and that communicative gestures can be used as an early marker of language development in order to better detect at-risk infants with CHD.

A further recent study by Gaudet et al. (2021) is among the first to characterise the neuropsychological profile of children with CHD, elucidate the developmental patterns of cognitive and language abilities between 1-5 years, and identify early markers predictive of cognitive and language impairments at preschool age. Gaudet et al. (2021) used Bayley-3 to evaluate cognitive and language skills at 1 and 2 years, and the WPPSI-IV and CELF-4 for later assessment at 5 years. At 5 years, their cohort obtained scores significantly below the norms on several language subtests including: receptive, expressive, global/core language, phonological awareness, and the verbal comprehension index from the WPPSI-IV. The prevalence of impairments (i.e. ≥1 SD below norms) in the CHD group ranged from 15-45% across all of these subtests. Developmental trajectories were different for cognitive and language domains, with a decline with age for cognitive functioning, stable results for expressive language, and an improvement in receptive language skills. They found several significant positive correlations between global language scale scores at 2 years and intelligence, receptive, expressive, and core language functioning at 5 years. Similar but weaker correlations were also found between receptive and expressive language scores at 2 years and almost all these domains at age 5 years. This suggests that Bayley-3 language scores at 2 years had predictive value for identifying children with impaired language at 5 years of age.
4.1.4 Factors Affecting Language Outcomes

Given that the profile of speech and language skills varies across the lifespan as well as across different physiologies in CHD, many researchers have focussed on investigating causes and predictors of language and neurodevelopmental outcomes more widely. Hypoxia is common in CHD and refers to a lack of oxygen in tissue such as the brain which can result in white matter abnormalities (Kinney et al., 2005). There are specific structures in the brain which are particularly vulnerable to hypoxic injury such as the dorsal and ventral pathways of language processing. Damage to these regions including both the duration and severity of hypoxic injury can lead to specific impairments. For example, white matter abnormalities in the dorsal and ventral neural pathways of language processing have been observed in neonates with CHD using advanced diffusion imaging (Karmacharya et al., 2018). The dorsal pathway is responsible for phonological processing, whereas the ventral pathway is involved in speech recognition, representation of lexical concepts and semantic processing of language (Chang et al., 2015). With increasing evidence of language delay and dysfunction in individuals with CHD, these neuroimaging results observed in the language pathways, with strong evidence of abnormalities in the left hemisphere (Hickok and Poeppel, 2007; Karmacharya et al., 2018), provide evidence of the possible factors contributing to these impairments. Aberrant white matter development in CHD and particularly in HLHS has been widely reported in other regions of the brain too, including the corpus callosum which enables interhemispheric communication essential for higher-order cognitive function (Morton et al., 2017). Foetal brain volume has also been found to be predictive of neurodevelopmental outcomes including language. Sadhwani et al. (2022) found that children with CHD had lower Bayley-3 scores including the language domain compared to
healthy controls, but in the CHD group only, larger total foetal brain volume correlated with higher Bayley-3 scores. Similarly, intraoperative regional cerebral oxygen saturation has also been identified as a potential contributor to neurodevelopmental outcomes in children with CHD and no chromosomal abnormalities. Sood et al. (2013) reported that 23% of patients were delayed in receptive communication and 18% were delayed in expressive communication at 2 years of age. They found that intraoperative decrease from baseline cerebral oxygen saturation was associated with receptive communication, and reported the threshold for predicting receptive communication delay was 52% intraoperative decrease.

Other factors which have been relatively understudied but may influence neurodevelopmental outcomes include feeding and nutritional problems which are common in children with CHD, and the possible effects of any resulting anaemia on cerebral blood flow (Wray, 2006). Further, hearing loss is common in children with CHD and specifically HLHS with a prevalence ranging from 22-29% in pre-schoolers (Grasty et al., 2018; Robertson et al., 2012). Younger gestational age, longer postoperative length of stay in hospital, low arterial oxygen, a confirmed genetic anomaly (e.g. 22q11 deletion syndrome), and ECMO are known to be associated with increased risk of hearing loss, which itself is known to be linked to impaired language development and worse language skills in CHD, as well as behavioural problems (Marino et al., 2012). Further, previous studies have also shown that children from lower socioeconomic backgrounds and those with low maternal education are at increased risk of speech and language problems as well as lower school achievement, cognitive attainment, problem solving skills, and adaptive behaviours (Bucholz et al., 2021; Hick et al., 2016).
4.1.5 Aims and Hypotheses

The primary aim of this study was to examine language skills in depth using a range of measures in children with HLHS and TGA in the early school years, and compare these to healthy controls. Secondary aims were to explore the longitudinal trajectory of early cognition and language skills in the same cohort, and the relationship between parent-rated and directly measured language skills of the child.

The following hypotheses draw on a priori literature, particularly Turner et al. (2022), as well as addressing a gap in the literature with regards to longitudinal development of language skills in the same cohort, and consistency between parent-rated language skills and direct measures of language. It was hypothesised that:

- Children with complex CHD, and in particular those with HLHS, will have lower language scores and especially lower expressive language, compared to healthy control children.
- Children with CHD will have language impairments, particularly in expressive language and phonological abilities (which is an indicator of pre-reading skills), compared to healthy controls.
- The longitudinal trajectory of language skills will differ in children with CHD compared to healthy controls, and those children with early language delays will have later delays at early school age.
- Children with complex CHD, and in particular those with HLHS, will have lower parent-rated language scores, compared to healthy control children.
- Parent-rated language scores will be associated with direct measures of language performance.
4.2 Methods

4.2.1 Participants

The longitudinal cohort described in Chapter 3 was invited to take part at the fourth and most recent assessment time-point at 4-5 years of age. A total of 48 children were eligible to participate, one HLHS patient had died since the previous assessment, one healthy control child withdrew from the study, nine children were too young to be tested at this time-point, and a further nine children could not be assessed due to the COVID-19 pandemic during which data collection was stopped. This left a total sample of 28 children who participated in the 4-5 year assessment at time-point 4. The full sample is summarised in Table 4.1.

Table 4.1 Patients with HLHS, TGA, and healthy controls who participated in the 4-5 year assessments

<table>
<thead>
<tr>
<th>Time-point 4</th>
<th>HLHS</th>
<th>TGA</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>5</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Age (years), Mean (SD)</td>
<td>4.88 (0.33)</td>
<td>5.22 (0.19)</td>
<td>5.21 (0.45)</td>
</tr>
<tr>
<td>Gender (M:F)</td>
<td>3:2</td>
<td>8:5</td>
<td>8:2</td>
</tr>
</tbody>
</table>

4.2.2 Procedure / Assessment

The assessment took place at the UCL Wolfson Centre, and typically lasted between 3-4 hours depending on the age of the child, their temperament on the day of testing, the capabilities of the child, and how often they needed breaks. As testing time was long for 4-5 year-olds, breaks were given frequently between tests as well as a longer break for lunch. Parents were also offered the option of splitting the assessment over two days if this was more suitable for the family.
A battery of speech and language tests were administered to all children, as well as a test of intellectual function. During testing, the child was seated at a table, opposite the researcher, and parents had the option to sit beside their child or in the waiting room. Each test was completed in order of priority. The Wechsler Preschool and Primary Scale of Intelligence (WPPSI IV) was given first in order to have a measure of IQ, followed by the Clinical Evaluation of Language Fundamentals – Preschool (CELF-P2), the Receptive and Expressive One-Word Picture Vocabulary Tests (ROWPVT-4 and EOWPVT-4), the Phonological Abilities Test (PAT), and the Renfrew Bus Story. Parents were also asked to complete the Children's Communication Checklist (CCC-2) in order to assess parent-rated language skills in children. These speech and language tests were used in order to assess language skills in their entirety, including: receptive and expressive vocabulary, sentence structure and length, recalling sentences, word structure and classes, letter knowledge, rhyming, oral narrative skills, and grammatical complexity. Details of each of these tests are provided in Chapter 2, Section 2.9.2.

All the tests administered provide raw scores which are then converted into subtest scaled scores (mean of 10 and SD of 3), or composite/standard scores (mean of 100 and SD of 15). Scaled and composite scores are calculated based on a comparison of the child’s score being evaluated relative to a normative age-matched sample. As in Chapter 3, these scores are interpreted based on their deviation from the normative mean. Therefore, a composite score of 71-85 (1-2 SD below the mean) indicates borderline or mild impairment, and a score of ≤70 (≥2 SDs below the mean) indicates moderate to severe impairment. In tests where only scaled scores were available, these were converted into composite scores using psychometric conversion tables. The PAT and Bus Story are the
only tests for which raw scores are used as scaled or composite scores were not available.

4.2.3 Data Analysis

Descriptive statistics were used to explore the data and to characterise the sample. Data were also explored for normality using histograms and tested using the Shapiro Wilk test of normality (for small sample size). As there was a violation of the homogeneity of variance assumption and non-normally distributed data, log and square root transformations were applied independently to try and achieve normality of the data. However, both transformation attempts were unsuccessful and normality could not be reached. Consequently, non-parametric Kruskal-Wallis analyses were conducted to compare test scores between the three groups. For the post-hoc analyses, Mann-Whitney U tests with uncorrected p-values were used to uncover the pairwise differences, and calculate effect size ($r$). For non-parametric analyses, medians and interquartile ranges (IQR) are reported.

Non-parametric repeated measures analyses were also conducted using the Wilcoxon signed-rank test to investigate age-related changes in language outcomes over time, and to explore the longitudinal trajectory of language within each group.

Non-parametric Spearman’s rank-order correlations were conducted to measure the strength and direction of association between longitudinal language variables including earlier Bayley-3 receptive and expressive language scores at 3-4 years and those collected in the current study at 4-5 years of age in the same participants. Further correlational analyses were used to explore the relationship
between parent-rated CCC-2 scores and directly measured Core Language scores from the CELF-P.

4.3 Results

To address the first hypothesis and investigate group differences in language skills, Kruskal-Wallis analyses were conducted. To address the second hypothesis that children with CHD will have language impairments, particularly in expressive language and phonological abilities, the proportion of children with scores 1-2 SD and ≥2 SDs below the mean were calculated for each group.

Five children with HLHS, 13 with TGA, and 10 healthy controls completed the intelligence and speech and language assessment at 4-5 years-old. There were 2 HLHS and 4 TGA patients who were unable to complete the Bus Story, due to either being too nervous, anxious, or simply said they did not remember the story when asked to recall i. Therefore, a total of 3 HLHS and 9 TGA patients, and 10 healthy controls completed the Bus Story test.

4.3.1 Intellectual Function (IQ)

There was a significant main effect of group in only one scale of the WPPSI-IV which was Verbal Comprehension. Post-hoc Mann Whitney tests revealed that both the HLHS and TGA groups had significantly lower scores compared to the Control group. There were no other significant group differences observed on the other subscales: Fluid Reasoning, Working Memory, Processing Speed, and Full Scale IQ. Table 4.2 summarises these results.
The majority of children scored within the normative range for all subscales, however, a proportion of CHD patients and healthy controls did have impaired WPPSI-IV scores. Table 4.3 summarises the proportion of children in each group with scores 1-2 SD or ≥2 SDs below the mean. The TGA group had the largest proportion of children with impaired scores including 3 (23%) for Processing Speed.

Table 4.2 The Wechsler Preschool & Primary Scale of Intelligence (WPPSI-IV) outcomes in children with HLHS, TGA, and healthy controls at 4-5 years

<table>
<thead>
<tr>
<th>WPPSI-IV (median composite score (IQR))</th>
<th>HLHS</th>
<th>TGA</th>
<th>Controls</th>
<th>H</th>
<th>p</th>
<th>Post-hoc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal Comprehension</td>
<td>98.00(18)</td>
<td>102.00(18)</td>
<td>111.00(11)</td>
<td>8.93</td>
<td>.01*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual Spatial</td>
<td>94.00(34)</td>
<td>97.00(23)</td>
<td>112.00(11)</td>
<td>5.25</td>
<td>.07</td>
<td></td>
</tr>
<tr>
<td>Fluid Reasoning</td>
<td>104.00(17)</td>
<td>101.00(16)</td>
<td>97.00(35)</td>
<td>0.87</td>
<td>.65</td>
<td></td>
</tr>
<tr>
<td>Working Memory</td>
<td>109.00(31)</td>
<td>112.00(23)</td>
<td>106.00(9)</td>
<td>1.21</td>
<td>.55</td>
<td></td>
</tr>
<tr>
<td>Processing Speed</td>
<td>94.00(22)</td>
<td>100.00(20)</td>
<td>98.50(18)</td>
<td>1.24</td>
<td>.54</td>
<td></td>
</tr>
<tr>
<td>Full Scale IQ</td>
<td>98.00(27)</td>
<td>103.00(17)</td>
<td>107.50(10)</td>
<td>1.84</td>
<td>.40</td>
<td></td>
</tr>
</tbody>
</table>

Note. Data are presented as median (interquartile range (IQR)), Kruskal-Wallis H and p-value, where statistically significant differences between groups denoted as *p<0.05, **p<0.01, and ***p<0.001, and post-hoc pairwise group differences: Mann-Whitney U, z, p-value, and effect size r (where healthy controls are denoted as C).
Table 4.3 The total number and percentage of participants with WPPSI-IV scores 1-2 SD and ≥2 SDs below the mean

<table>
<thead>
<tr>
<th>WPPSI-IV (N (%))</th>
<th>HLHS (N=5)</th>
<th>TGA (N=13)</th>
<th>Controls (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Verbal Comprehension</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 SD</td>
<td>1 (20)</td>
<td>1 (8)</td>
<td>0</td>
</tr>
<tr>
<td>≥2 SD</td>
<td>0</td>
<td>1 (8)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Visual Spatial</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 SD</td>
<td>1 (20)</td>
<td>2 (15)</td>
<td>0</td>
</tr>
<tr>
<td>≥2 SD</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Fluid Reasoning</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 SD</td>
<td>1 (20)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>≥2 SD</td>
<td>0</td>
<td>0</td>
<td>2 (20)</td>
</tr>
<tr>
<td><strong>Working Memory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 SD</td>
<td>0</td>
<td>1 (8)</td>
<td>0</td>
</tr>
<tr>
<td>≥2 SD</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Processing Speed</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 SD</td>
<td>0</td>
<td>3 (23)</td>
<td>0</td>
</tr>
<tr>
<td>≥2 SD</td>
<td>1 (20)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Full Scale IQ</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 SD</td>
<td>1 (20)</td>
<td>2 (15)</td>
<td>0</td>
</tr>
<tr>
<td>≥2 SD</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

4.3.2 Speech and Language

There was no significant main effect of group in any of the CELF-P2 scales: Core Language, Receptive Language, Expressive Language, Language Content, and Language Structure.

No significant group differences were observed in receptive vocabulary scores from the ROWPVT, but there was a trend towards significance in expressive vocabulary scores from the EOWPVT.

A similar trend was observed in the Rhyme Detection subtest of the PAT, but there was no main effect of group in Letter Knowledge.

In the Bus Story test, again, there was a trend towards significance in both the Information and Utterance Length scores. These results are summarised in Table 4.4.
Table 4.4 Speech and language outcomes in children with HLHS, TGA, and healthy controls at 4-5 years

<table>
<thead>
<tr>
<th></th>
<th>HLHS</th>
<th>TGA</th>
<th>Controls</th>
<th>H</th>
<th>p</th>
<th>Post-hoc</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CELF-P2</strong> (median composite score (IQR))</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Core Language</td>
<td>92.00 (19)</td>
<td>102.00 (39)</td>
<td>103.00 (16)</td>
<td>1.19</td>
<td>.55</td>
<td>-</td>
</tr>
<tr>
<td>Receptive Language</td>
<td>94.00 (18)</td>
<td>95.00 (30)</td>
<td>105.00 (27)</td>
<td>0.66</td>
<td>.72</td>
<td>-</td>
</tr>
<tr>
<td>Expressive Language</td>
<td>91.00 (17)</td>
<td>100.00 (36)</td>
<td>104.50 (14)</td>
<td>2.84</td>
<td>.24</td>
<td>-</td>
</tr>
<tr>
<td>Language Content</td>
<td>93.00 (10)</td>
<td>95.00 (29)</td>
<td>102.50 (21)</td>
<td>2.04</td>
<td>.36</td>
<td>-</td>
</tr>
<tr>
<td>Language Structure</td>
<td>96.00 (23)</td>
<td>100.00 (45)</td>
<td>105.00 (18)</td>
<td>1.65</td>
<td>.44</td>
<td>-</td>
</tr>
<tr>
<td><strong>ROWPVT</strong> (median composite score (IQR))</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Receptive Vocabulary</td>
<td>99.00 (12)</td>
<td>103.00 (15)</td>
<td>108.00 (12)</td>
<td>3.54</td>
<td>.17</td>
<td>-</td>
</tr>
<tr>
<td><strong>EOWPVT</strong> (median composite score (IQR))</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expressive Vocabulary</td>
<td>103.00 (25)</td>
<td>106.00 (30)</td>
<td>117.50 (19)</td>
<td>4.72</td>
<td>.09†</td>
<td>-</td>
</tr>
<tr>
<td><strong>PAT</strong> (median raw score (IQR))</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhyme Detection</td>
<td>1.00 (7)</td>
<td>7.00 (5)</td>
<td>8.00 (4)</td>
<td>4.70</td>
<td>.08†</td>
<td>-</td>
</tr>
<tr>
<td>Letter Knowledge</td>
<td>23.00 (9)</td>
<td>25.00 (5)</td>
<td>25.00 (3)</td>
<td>1.20</td>
<td>.55</td>
<td>-</td>
</tr>
<tr>
<td><strong>Bus Story</strong> (median raw score (IQR))</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Information</td>
<td>12.00 (3)</td>
<td>18.00 (10)</td>
<td>24.00 (10)</td>
<td>5.07</td>
<td>.08†</td>
<td>-</td>
</tr>
<tr>
<td>Utterance Length</td>
<td>6.00 (2)</td>
<td>10.00 (4)</td>
<td>13.00 (6)</td>
<td>5.11</td>
<td>.08†</td>
<td>-</td>
</tr>
</tbody>
</table>

Note. CELF-P2 = The Clinical Evaluation of Language Fundamentals – Preschool, ROWPVT and EOWPVT = Receptive and Expressive One-Word Picture Vocabulary Tests, and PAT = Phonological Abilities Test. Data are presented as median (interquartile range (IQR)), Kruskal-Wallis H and p-value, where statistically significant differences between groups denoted as *p<0.05, **p<0.01, ***p<0.001, and a trend towards significance is denoted as †, and post-hoc pairwise group differences: Mann-Whitney U, z, p-value, and effect size r (where healthy controls are denoted as C).

Table 4.5 summarises the proportion of children in each group with scores 1-2 SD or ≥2 SDs below the mean. There were several domains of language across the assessment battery in which children with CHD had impaired scores. For
example, in the CELF-P2, 3 (23%) children with TGA had scores 1-2 SD below
the mean for Receptive Language, and 2 (15%) had scores ≥2 SDs below the
mean for Core Language, Expressive Language, and Language Structure. In the
PAT, 3 out of 5 children (60%) with HLHS and 4 (31%) with TGA had Rhyme
Detection scores equal to or below the 10th percentile. In the Bus Story, 2 out of
5 children (40%) with HLHS and 7 (54%) with TGA had an Information score
below age-equivalent norms, as did 2 out of 5 (40%) with HLHS and 3 (23%) with
TGA for mean length of utterance.

Table 4.5 The total number and percentage of participants with speech and
language scores 1-2 SD and ≥2 SDs below the mean

<table>
<thead>
<tr>
<th>CELF-P2 (N (%))</th>
<th>HLHS (N=5)</th>
<th>TGA (N=13)</th>
<th>Controls (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core Language</td>
<td>1-2 SD</td>
<td>1 (20)</td>
<td>2 (15)</td>
</tr>
<tr>
<td></td>
<td>≥2 SD</td>
<td>0</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Receptive</td>
<td>1-2 SD</td>
<td>1 (20)</td>
<td>3 (23)</td>
</tr>
<tr>
<td>Language</td>
<td>≥2 SD</td>
<td>0</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Expressive</td>
<td>1-2 SD</td>
<td>1 (20)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Language</td>
<td>≥2 SD</td>
<td>0</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Language</td>
<td>1-2 SD</td>
<td>1 (20)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Content</td>
<td>≥2 SD</td>
<td>0</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Language</td>
<td>1-2 SD</td>
<td>1 (20)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Structure</td>
<td>≥2 SD</td>
<td>0</td>
<td>2 (15)</td>
</tr>
<tr>
<td>OWPVT (N (%))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Receptive</td>
<td>1-2 SD</td>
<td>0</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Vocabulary</td>
<td>≥2 SD</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Expressive</td>
<td>1-2 SD</td>
<td>1 (20)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Vocabulary</td>
<td>≥2 SD</td>
<td>0</td>
<td>1 (8)</td>
</tr>
<tr>
<td>PAT (N (%))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhyme Detection</td>
<td>≤10%ile</td>
<td>3 (60)</td>
<td>4 (31)</td>
</tr>
<tr>
<td>Letter Knowledge</td>
<td>≤10%ile</td>
<td>1 (20)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Bus Story (N (%))</td>
<td>(N=3)</td>
<td>(N=9)</td>
<td>(N=10)</td>
</tr>
</tbody>
</table>
4.3.3 Longitudinal Language Outcomes

To address the third hypothesis and explore the longitudinal trajectory of language skills and whether there were changes in language scores overtime, repeated measures analyses were conducted for all participants who had earlier language scores measured by the Bayley-3 at 3-4 years, and current language scores approximately a year later at 4-5 years of age. There were a total of 27 children: 5 with HLHS, 12 with TGA, and 10 healthy controls. The Wilcoxon signed rank test was used to compare earlier Bayley-3 cognitive, receptive and expressive language scores with current full-scale IQ (FSIQ) and receptive and expressive language scores measured using the WPPSI-IV, CELF-P2, and ROWPVT and EOWPVT. Table 4.6 shows the results of the repeated measures Wilcoxon analyses. Figure 4.2 shows the boxplots for the longitudinal cognitive and language outcomes for each group.

<table>
<thead>
<tr>
<th></th>
<th>HLHS</th>
<th>TGA</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bayley-3 Cognition / WPPSI-IV FSIQ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bayley-3 Cognition &gt; FSIQ</td>
<td>-0.67</td>
<td>0.50</td>
<td>-0.21</td>
</tr>
<tr>
<td>Bayley-3 Cognition &gt; FSIQ</td>
<td>-2.09</td>
<td>0.04*</td>
<td>-0.43</td>
</tr>
<tr>
<td>Bayley-3 Cognition &gt; FSIQ</td>
<td>-1.48</td>
<td>0.14</td>
<td>-0.33</td>
</tr>
</tbody>
</table>
A similar pattern was seen in all three groups of children; Bayley-3 scores from 12 months previously were higher than current scores at 4-5 years of age, across all the domains of cognition/IQ, receptive language, and expressive language. The only exception was when comparing Bayley-3 expressive language and current EOWPVT scores, where the latter was found to be higher in all three groups, although this difference was not statistically significant.

The statistical significance of many of these differences between the time-points differed between each of the three groups. It was only for the comparison

### Table

<table>
<thead>
<tr>
<th></th>
<th>HLHS</th>
<th>TGA</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bayley-3 / CELF-P2 Receptive Language</td>
<td>-2.02 0.04* -0.64</td>
<td>-2.24 0.03* -0.46</td>
<td>-2.14 0.03* -0.48</td>
</tr>
<tr>
<td></td>
<td>Bayley-3 &gt; CELF-P2</td>
<td>Bayley-3 &gt; CELF-P2</td>
<td>Bayley-3 &gt; CELF-P2</td>
</tr>
<tr>
<td>Bayley-3 / ROWPVT Receptive Language</td>
<td>-2.03 0.04* -0.64</td>
<td>-2.24 0.03* -0.46</td>
<td>-1.80 0.07 -0.40</td>
</tr>
<tr>
<td></td>
<td>Bayley-3 &gt; ROWPVT</td>
<td>Bayley-3 &gt; ROWPVT</td>
<td>Bayley-3 &gt; ROWPVT</td>
</tr>
<tr>
<td>Bayley-3 / CELF-P2 Expressive Language</td>
<td>-1.76 0.08 -0.56</td>
<td>-2.40 0.02* -0.49</td>
<td>-2.25 0.03* -0.50</td>
</tr>
<tr>
<td></td>
<td>Bayley-3 &gt; CELF-P2</td>
<td>Bayley-3 &gt; CELF-P2</td>
<td>Bayley-3 &gt; CELF-P2</td>
</tr>
<tr>
<td>Bayley-3 Expressive Language / EOWPVT</td>
<td>0 1.00 0</td>
<td>0.80 0.42 -0.16</td>
<td>-1.31 0.19 -0.29</td>
</tr>
<tr>
<td></td>
<td>Bayley-3 &lt; EOWPVT</td>
<td>Bayley-3 &lt; EOWPVT</td>
<td>Bayley-3 &lt; EOWPVT</td>
</tr>
</tbody>
</table>

*Note. WPPSI-IV = Wechsler Preschool & Primary Scale of Intelligence and FSIQ = full-scale IQ, CELF-P2 = Clinical Evaluation of Language Fundamentals Preschool, ROWPVT and EOWPVT = Receptive and Expressive One-Word Picture Vocabulary Tests.*
between the Bayley-3 receptive language scores and CELF-P2 receptive language scores that the Bayley-3 scores were higher in all three groups.

Figure 4.2 Boxplots for each group showing the longitudinal outcomes between time-points 3 (T3) and 4 (T4): A) Bayley-3 Cognition (3-4 years) and Full-Scale IQ (4-5 years), B) Bayley-3 Receptive Language and CELF-P2 Receptive Language, C) Bayley-3 Receptive Language and Receptive OWPVT score, D) Bayley-3 Expressive Language and CELF-P2 Expressive Language, and E) Bayley-3 Expressive Language and Expressive OWPVT score
Note. WPPSI-IV = The Wechsler Preschool & Primary Scale of Intelligence, CELF-P2 = The Clinical Evaluation of Language Fundamentals – Preschool, ROWPVT and EOWPVT = Receptive and Expressive One-Word Picture Vocabulary Tests.

To further explore the relationship between earlier cognitive and language scores measured at 3-4 years of age and current IQ and language scores measured at 4-5 years of age, non-parametric correlations were conducted. This included correlations between Bayley-3 cognitive, receptive and expressive language scores and current IQ and receptive and expressive language scores measured using the WPPSI-IV, CELF-P2, and ROWPVT and EOWPVT. Table 4.7 shows the results of the Spearman’s correlations for all these key cognitive and language variables.

Table 4.7 Spearman’s correlation coefficients between key language outcome measures including: Bayley-3 receptive and expressive language, CELF-P2 receptive and expressive language, and receptive and expressive OWPVT scores, as well as Bayley-3 cognitive scores and WPPSI-IV full scale IQ.

<table>
<thead>
<tr>
<th></th>
<th>Cognitive</th>
<th>Receptive</th>
<th>Expressive</th>
</tr>
</thead>
<tbody>
<tr>
<td>WPPSI-IV Full Scale IQ</td>
<td>0.42*</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CELF-P2 Receptive</td>
<td>-</td>
<td>0.43*</td>
<td>-</td>
</tr>
<tr>
<td>CELF-P2 Expressive</td>
<td>-</td>
<td>-</td>
<td>0.56**</td>
</tr>
<tr>
<td>Receptive OWPVT</td>
<td>-</td>
<td>0.65***</td>
<td>-</td>
</tr>
<tr>
<td>Expressive OWPVT</td>
<td>-</td>
<td>-</td>
<td>0.69***</td>
</tr>
</tbody>
</table>
There were significant moderate positive correlations between many of the variables including: Bayley-3 cognitive scores and WPPSI-IV full scale IQ \((r = 0.42, p = 0.03)\); Bayley-3 receptive language and CELF-P2 receptive language \((r = 0.43, p = 0.03)\); and Bayley-3 receptive and receptive OWPVT scores \((r = 0.56, p < 0.01)\).

There were also significant moderate-to-strong positive correlations between some of the variables including: Bayley-3 expressive language and CELF-P2 expressive language \((r = 0.65, p < 0.001)\); and Bayley-3 expressive language and expressive OWPVT \((r = 0.69, p < 0.001)\). Figures 4.3 and 4.4 show scatterplots for these correlations. From these scatterplots it appears that children with TGA are doing worse than those with HLHS, as they have the lowest longitudinal scores in cognition/IQ, and receptive and expressive language.
Figure 4.3 Scatterplot showing significant moderate positive correlation between Bayley-3 cognitive scores and WPPSI-IV full scale IQ.

*Note.* Lines on the x and y axis denote the mean of 100.
Figure 4.4 Scatterplots showing significant moderate-to-strong positive correlations between Bayley-3 receptive and expressive language and CELF-P2 receptive and expressive language, and receptive and expressive OWPVT scores.

*Note.* Lines on the x and y axis denote the mean of 100.

### 4.3.4 Parent-Rated Language

There was no significant main effect of group in any of the CCC-2 subscales: Speech, Syntax, Semantic, Coherence, Inappropriate Initiation, Stereotyped, Use of Context, Nonverbal, Social, Interests, or the combined General Communication Composite (GCC). Table 4.8 summarises results for the CCC-2.
Table 4.8 Children’s Communication Checklist (CCC-2) outcomes by subtest and overall GCC, in children with HLHS, TGA, and healthy controls at 4-5 years.

<table>
<thead>
<tr>
<th>CCC-2 Scale (median composite score (IQR))</th>
<th>HLHS</th>
<th>TGA</th>
<th>Controls</th>
<th>H</th>
<th>p</th>
<th>Post-hoc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speech</td>
<td>87.50 (36.25)</td>
<td>87.50 (40.00)</td>
<td>85.00 (45.00)</td>
<td>0.47</td>
<td>0.79</td>
<td>-</td>
</tr>
<tr>
<td>Syntax</td>
<td>85.00 (27.50)</td>
<td>82.50 (40.00)</td>
<td>90.00 (35.00)</td>
<td>1.63</td>
<td>0.44</td>
<td>-</td>
</tr>
<tr>
<td>Semantic</td>
<td>92.50 (30.00)</td>
<td>85.00 (16.25)</td>
<td>85.00 (20.00)</td>
<td>0.85</td>
<td>0.65</td>
<td>-</td>
</tr>
<tr>
<td>Coherence</td>
<td>87.50 (32.50)</td>
<td>90.00 (17.50)</td>
<td>90.00 (10.00)</td>
<td>1.42</td>
<td>0.49</td>
<td>-</td>
</tr>
<tr>
<td>Inappropriate Initiation</td>
<td>97.50 (26.25)</td>
<td>90.00 (20.00)</td>
<td>95.00 (15.00)</td>
<td>0.56</td>
<td>0.76</td>
<td>-</td>
</tr>
<tr>
<td>Stereotyped</td>
<td>85.00 (40.00)</td>
<td>95.00 (22.50)</td>
<td>95.00 (20.00)</td>
<td>0.29</td>
<td>0.86</td>
<td>-</td>
</tr>
<tr>
<td>Use of Context</td>
<td>87.50 (37.50)</td>
<td>90.00 (16.25)</td>
<td>90.00 (30.00)</td>
<td>0.57</td>
<td>0.75</td>
<td>-</td>
</tr>
<tr>
<td>Nonverbal</td>
<td>97.50 (41.25)</td>
<td>82.50 (27.50)</td>
<td>95.00 (35.00)</td>
<td>2.71</td>
<td>0.26</td>
<td>-</td>
</tr>
<tr>
<td>Social</td>
<td>75.00 (17.50)</td>
<td>92.50 (45)</td>
<td>90.00 (45.00)</td>
<td>3.27</td>
<td>0.20</td>
<td>-</td>
</tr>
<tr>
<td>Interests</td>
<td>85.00 (18.75)</td>
<td>90.00 (20.00)</td>
<td>95.00 (15.00)</td>
<td>0.27</td>
<td>0.87</td>
<td>-</td>
</tr>
<tr>
<td>General Communication Composite (GCC)</td>
<td>64.00 (45.25)</td>
<td>59.00 (44.25)</td>
<td>72.00 (30.00)</td>
<td>1.32</td>
<td>0.52</td>
<td>-</td>
</tr>
</tbody>
</table>

*Note.* The General Communication Composite (GCC) is a norm-referenced standard score of the sum of the first eight subtests (Speech – Nonverbal) scaled scores. Data are presented as group median (interquartile range (IQR)), Kruskal-Wallis H and p-value, where statistically significant differences between groups denoted as *p<0.05, **p<0.01, and ***p<0.001.

Table 4.9 summarises the proportion of children in each group with scores 1-2 SD or ≥2 SDs below the mean. Two out of 5 (40%) children with HLHS had scores ≥2 SDs below the mean for Nonverbal skills and 4 out of 5 (80%) had scores 1-2 SD below the mean for Social skills; 3 (23%) and 5 (39%) children with TGA had...
scores ≥2 SDs below the mean for Speech and Syntax respectively. The CCC-2 also identified further scores of clinical relevance: 1 (20%) patient with HLHS, 2 (15%) with TGA, and 1 (10%) healthy control had a GCC and Social Interaction Deviance Composite (SIDC) indicative of specific language impairment (SLI), and one further patient with HLHS had a GCC and SIDC suggestive of autism spectrum disorder (ASD).

Table 4.9 The total number and percentage of participants with CCC-2 subtest scores 1-2 SD and ≥2 SDs below the mean

<table>
<thead>
<tr>
<th>CCC-2 Scale (N (%))</th>
<th>HLHS (N=5)</th>
<th>TGA (N=13)</th>
<th>Controls (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speech</td>
<td>1-2 SD</td>
<td>1 (20)</td>
<td>2 (15)</td>
</tr>
<tr>
<td></td>
<td>≥2 SD</td>
<td>1 (20)</td>
<td>3 (23)</td>
</tr>
<tr>
<td>Syntax</td>
<td>1-2 SD</td>
<td>1 (20)</td>
<td>1 (8)</td>
</tr>
<tr>
<td></td>
<td>≥2 SD</td>
<td>1 (20)</td>
<td>5 (39)</td>
</tr>
<tr>
<td>Semantic</td>
<td>1-2 SD</td>
<td>0</td>
<td>3 (23)</td>
</tr>
<tr>
<td></td>
<td>≥2 SD</td>
<td>1 (20)</td>
<td>0</td>
</tr>
<tr>
<td>Coherence</td>
<td>1-2 SD</td>
<td>1 (20)</td>
<td>1 (8)</td>
</tr>
<tr>
<td></td>
<td>≥2 SD</td>
<td>0</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Inappropriate Initiation</td>
<td>1-2 SD</td>
<td>1 (20)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>≥2 SD</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stereotyped</td>
<td>1-2 SD</td>
<td>1 (20)</td>
<td>1 (8)</td>
</tr>
<tr>
<td></td>
<td>≥2 SD</td>
<td>1 (20)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Use of Context</td>
<td>1-2 SD</td>
<td>2 (40)</td>
<td>1 (8)</td>
</tr>
<tr>
<td></td>
<td>≥2 SD</td>
<td>0</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Nonverbal</td>
<td>1-2 SD</td>
<td>0</td>
<td>4 (31)</td>
</tr>
<tr>
<td></td>
<td>≥2 SD</td>
<td>2 (40)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Social</td>
<td>1-2 SD</td>
<td>4 (80)</td>
<td>2 (15)</td>
</tr>
<tr>
<td></td>
<td>≥2 SD</td>
<td>0</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Interests</td>
<td>1-2 SD</td>
<td>1 (20)</td>
<td>3 (23)</td>
</tr>
<tr>
<td></td>
<td>≥2 SD</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>General Communication Composite (GCC) (N (%))</td>
<td>&lt;55</td>
<td>2 (40)</td>
<td>7 (54)</td>
</tr>
<tr>
<td>Social Interaction Deviance Composite (SIDC) (N (%))</td>
<td>≤ -15</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>≥9</td>
<td>2 (40)</td>
<td>4 (31)</td>
</tr>
</tbody>
</table>

194
<table>
<thead>
<tr>
<th>CCC-2 Scale (N (%))</th>
<th>HLHS (N=5)</th>
<th>TGA (N=13)</th>
<th>Controls (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCC &amp; SIDC (N (%))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASD</td>
<td>1 (20)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SLI</td>
<td>1 (20)</td>
<td>2 (15)</td>
<td>1 (10)</td>
</tr>
</tbody>
</table>

Note. A GCC composite score <55 is considered abnormal, SIDC composite score ≤-15 or ≥9 is considered abnormal, and a combination of a negative SIDC and GCC <55 indicates a communicative profile suggestive of autism spectrum disorder, and a combination of a SIDC of ≥9 and GCC <55 indicates a communicative profile characteristic of specific language impairment.

To address the final hypothesis, the relationship between parent-rated and direct measures of child language was explored. Table 4.10 shows the results of the Spearman’s correlations for all participants (CHD groups and healthy controls). Overall, there were significant correlations between many of the variables. Speech, Coherence and Use of Context scales from the CCC-2 were moderately significantly positively correlated with all five scales of the CELF-P2. Figure 4.5 shows the correlations between the Coherence CCC-2 scale and each of the CELF-P2 scales. There were no significant correlations between the Syntax and Nonverbal scales of the CCC-2 and any of the CELF-P2 scales.
Table 4.10 Spearman’s correlation coefficients between objectively measured CELF-P2 language scores and parent-rated CCC-2 scores (for the whole cohort together).

<table>
<thead>
<tr>
<th>(N = 28)</th>
<th>Core Language</th>
<th>Receptive Language</th>
<th>Expressive Language</th>
<th>Language Content</th>
<th>Language Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCC-2 Scale</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Speech</td>
<td>0.44*</td>
<td>0.44*</td>
<td>0.49*</td>
<td>0.46*</td>
<td>0.49*</td>
</tr>
<tr>
<td>Syntax</td>
<td>0.25</td>
<td>0.21</td>
<td>0.33</td>
<td>0.22</td>
<td>0.33</td>
</tr>
<tr>
<td>Semantic</td>
<td>0.34</td>
<td>0.47*</td>
<td>0.38</td>
<td>0.43*</td>
<td>0.40*</td>
</tr>
<tr>
<td>Coherence</td>
<td>0.54**</td>
<td>0.58**</td>
<td>0.57**</td>
<td>0.56**</td>
<td>0.62***</td>
</tr>
<tr>
<td>Use of Context</td>
<td>0.46*</td>
<td>0.42*</td>
<td>0.41*</td>
<td>0.40*</td>
<td>0.48*</td>
</tr>
<tr>
<td>Nonverbal</td>
<td>0.20</td>
<td>0.23</td>
<td>0.25</td>
<td>0.18</td>
<td>0.34</td>
</tr>
</tbody>
</table>

**Note.** CELF-P2 = Clinical Evaluation of Language Fundamentals Preschool and CCC-2 = Children’s Communication Checklist. Statistically significant correlations denoted as *p<0.05, **p<0.01, and ***p<0.001.
Figure 4.5 Scatterplots showing the moderate positive significant correlations between the Coherence CCC-2 scale and each of the CELF-P2 scales: A) Core Language, B) Receptive Language, C) Expressive Language, D) Language Content, and E) Language Structure

Note. Lines on the x and y axes represent the standardised mean of 100.
4.4 Discussion

The primary goal of this study was to conduct an in-depth examination of speech and language skills in children with HLHS and TGA in the early school years, and compare these scores to healthy controls. Through PPI work done in preparation for this study, it was clear that parents of children with complex CHD were concerned with speech and language development in their children and felt that it was important for this to be further investigated.

4.4.1 Speech and Language Outcomes

It was hypothesised that firstly, children with complex CHD, and in particular those with HLHS, would have lower language scores and especially lower expressive language scores, compared to healthy controls; and secondly that when comparing children with CHD, those with HLHS would have worse language outcomes compared to children with TGA. However, the findings of this study do not support this hypothesis. No significant group differences were observed in any of the speech and language tests including CELF-P2, Receptive and Expressive OWPVTs, PAT, and the Bus Story. The HLHS group did have the lowest scores in all these tests compared to both the TGA and healthy control groups, but these differences were not statistically significant. There was a trend towards significance between the groups in Expressive OWPVT, Rhyme Detection in the PAT, and both Information and mean length of utterance scores in the Bus Story.

Intellectual functioning was also examined in these children in order to identify whether any language impairments or delays were specific or driven by potential delays/impairments in cognition. Again, there was no significant main effect of
group in full-scale IQ or the other scales of the WPPSI-IV, except Verbal Comprehension where both children with HLHS and TGA had significantly lower scores compared to the healthy controls. There was a trend towards significance in Visual Spatial skills, with both CHD groups scoring below the healthy controls. These results are surprising and somewhat unexpected given the literature which strongly suggests language delays and deficits in children with complex CHD. For example, Turner et al. (2022) reviewed the literature on language abilities and reported significant deficits in overall, expressive, and receptive language in 2-5 year-olds with critical CHD, compared to normative data. They also concluded that SV patients such as those with HLHS had worse language outcomes compared to BV CHD patients such as those with TGA. The lack of significant group differences in speech and language abilities in the current cohort may be explained by the relatively ‘clean’ sample of CHD patients in terms of comorbidities, which makes them less representative of the wider CHD population, and the sample size was also small. These points are discussed in further detail in Chapter 8.

It was also hypothesised that children with complex CHD would have language impairments, particularly in expressive language and phonological abilities, compared to healthy controls. The findings here provide some support for this hypothesis. Overall, it is children with TGA who have a higher proportion of expressive language impairments defined as a score ≥2 SDs below the normative mean (15%), compared to those with HLHS (0%). However, impairments in phonological abilities were much higher with 20-60% of the HLHS cohort and 8-31% of the TGA cohort having impaired phonology skills measured in the PAT. Story narrative skills measured in the Bus Story were also impaired in the CHD groups. This suggests that phonological abilities and narrative skills in particular
may be more vulnerable to delays and impairments than wider measures of speech and language.

Ramanan et al. (2021) identified that speech and language were the most commonly affected domains of delay in 3-5 year-olds with TGA. They reported that 8% of their cohort had receptive language delay, and 16% had expressive language delay. In the present study, 8% and 15% of TGA patients had scores ≥2 SDs below the normative mean for receptive and expressive language in the CELF-P2, respectively, suggesting language delay/impairment. This prevalence of delay is similar to that of Ramanan et al. (2021), despite both CHD groups having language scores within the normal range. This suggests that group analyses and averages may be minimising the presence of language delay in children with complex CHD, given that a proportion have abnormal scores within the impaired range.

It is important to note, however, that much of the literature focusses on language development in pre-schoolers, or older school-age children with CHD. Fewer studies focus on early school-age children of a similar age to the current cohort, which makes comparisons challenging. Gaudet et al. (2021) found that 5 year-olds with CHD obtained scores significantly below the norms on language subtests of the CELF-4, and the Verbal Comprehension index from the WPPSI-IV. Although group means for language subtests were in the normal range for CHD patients, a proportion had impairments (which they defined as ≥1 SD below norms) in: receptive language (15-39%), expressive language (25-45%), core language (27%), phonological awareness (35%), and WPPSI-IV verbal comprehension (31%). Similar prevalence was also observed in the current cohort of 4-5 year-olds with complex CHD including: receptive language (20-
31%), expressive language (20-30%), core language (20-30%), and WPPSI-IV verbal comprehension (16-20%).

In the present study, a variety of tests and standardised assessments were used to measure and evaluate language skills. Therefore, there are multiple scores for the same domains such as receptive and expressive language. An important distinction to make is that the prevalence of impairment differs depending on which test was used. For example, 16% of TGA patients had scores at least 1 SD below the norms for expressive language measured by the EOWPVT. However, there is a discrepancy between the rate of prevalence in the CELF-P2 (30%) which is most likely due to the fact that both the receptive and expressive OWPTs assess a child’s understanding/comprehension of language and spoken language based on their repertoire of vocabulary (i.e. single words). In contrast, the CELF-P2 measures a broader range of skills such as Sentence Structure, Word Structure, Recalling Sentences, and Word Classes, which are comparatively more difficult and require a deeper comprehension and greater competence of skills, beyond one-word responses.

Further, in the PAT two subtests were specifically selected for assessing phonological awareness due to being the strongest early predictors of later reading skills (Bradley & Bryant, 1983; Bryant & Goswami, 1987; Muter et al., 2004), these were Rhyme Detection and Letter Knowledge. In the current cohort, 3 out of 5 and 1 out of 5 (60% and 20%) of HLHS patients and 31% and 8% of TGA patients had scores below the 10th percentile for these two subtests, respectively. Although this test is different to that used by Gaudet et al. (2021) to measure phonological awareness, the prevalence of impairment is very similar to that reported. Multiple previous studies have also reported specific delays and impairments in phonological processing in school-age children with CHD (Mlatton
et al., 2007; Sarrechia et al., 2015). However, the literature appears to be divided as some researchers (Hövels-Gührich et al., 2008; Sommariva et al., 2020) have found that children with CHD have phonological awareness skills similar to those of healthy controls. However it should be noted that they may not include CHD patients with the same physiology as those in the current study which may explain the difference in results between their studies and those in the present study.

The Bus Story was used to assess oral narrative skills based on story recall using a picture book to guide the child. This was the last language test in the battery, and six children with CHD (2 HLHS and 4 TGA) were unable to compete it and said they did not remember the story when asked to recall. It is likely that these patients were tired as this was near the end of testing, or they may not have been able to do it. Although no group differences were observed between children with CHD and healthy controls for information and mean length of utterance scores, there was a trend towards significance with both CHD groups having lower scores. A significant proportion of children with CHD (23-54%) also had scores below age-equivalent norms suggesting that a deficit was common in this cohort.

Reduced length of utterance has been reported in the CHD literature in preschoolers (Fourdain et al., 2019; Ovadia et al., 2000), as well as deficits in both oral and written narrative discourse (Hemphill et al., 2002). Narrative recall has also been assessed in terms of verbal working memory, which has been reported to be poorer in SV CHD (Sarrechia et al., 2016). Immediate and delayed verbal memory has also been associated with reduced hippocampal volume as a result of neonatal hypoxia in children with TGA (Muñoz-López et al., 2017). Deficits in narrative discourse reflect pragmatic language difficulties (Bellinger and Newburger, 2010), which are strongly linked to social skills, and these along with working memory in the current cohort will be discussed in Chapter 6.
4.4.2 Longitudinal Trajectory of Language

A secondary aim of this study was to explore the longitudinal trajectory of early cognition and language skills in those children who had participated in the current and previous investigations and had longitudinal data. It was hypothesised that the longitudinal trajectory of language skills would differ in children with CHD compared to healthy controls, and those children with early language delays would have later delays at early school age. Within-group repeated measures analyses were conducted to explore the stability of scores overtime between those assessed at 3-4 years using Bayley-3 and scores of the same domain measured a year later. The results revealed that earlier Bayley-3 cognitive scores and FSIQ measured using the WPPSI-IV a year later were not significantly different in children with HLHS and healthy controls. This suggests that their scores are consistent overtime, whereas those with TGA had significantly lower FSIQ compared to their earlier cognitive score, but this was within the normal range. This may be because children with HLHS consistently have lower scores overtime, whereas those with TGA may be growing into their deficits overtime, which is a common finding in the CHD literature.

However, with regards to receptive language scores, children with HLHS and TGA both had significantly lower scores in the CELF-P2 and ROWPVT compared to earlier Bayley-3, which suggests that receptive language scores are not consistent overtime and instead appear to reduce in this cohort. A similar significant pattern was also observed for healthy controls, but only when comparing Bayley-3 receptive language with CELF-P2 scores, and not the ROWPVT.
With respect to expressive language scores, children with TGA and healthy controls both had significantly lower scores on the CELF-P2 compared to earlier Bayley-3, which suggests that expressive language scores are also not consistent over time and instead appear to reduce in the current cohort. A similar pattern was observed in the HLHS group, but this was not significant. Similarly, there were no significant differences between earlier Bayley-3 and later EOWPVT scores in any of the three groups. Again, an explanation for this may be that the EOWPVT is similar to the Bayley-3 expressive language subtest in that it is based on single words, rather than more complex sentence structures, which is why CELF-P2 scores may be reduced in comparison.

These results suggest that the developmental trajectories are different for cognitive and language domains, with stable results for cognitive functioning, and a decline with age for both receptive and expressive language skills. Contrary to what was hypothesised, the longitudinal trajectory of language skills does not appear to differ in children with CHD compared to healthy controls. All three groups show lower scores at 4-5 years compared to scores a year earlier. There are differences in the rate of decline with age, particularly in the HLHS and TGA groups, and the HLHS group has the lowest cognitive and language scores overall over time. Despite this, when looking at the longitudinal scatterplots there are three children with TGA who have the poorest performance in all measures of cognitive and language functioning. On closer inspection of the data, these were the same three children. This is not what would be expected, given that children with HLHS are known to have worse outcomes than those with TGA. These results emphasise the need for an individual approach to patient care and follow-up, and highlight that group averages often mask the performance of individual children who are doing especially poorly.
Bayley-3 items for both receptive and expressive communication are very similar to the receptive and expressive OWPVTs given their reliance on one-word communication and language skills. The CELF-P2, in contrast, is more complex and assesses language across multiple domains and goes beyond single word responses; it is also more difficult for the child than the Bayley-3 assessment which requires less from participants. This is supported by the findings from correlational analyses in the present study. Moderate-to-strong significant positive correlations were observed between Bayley-3 receptive language and ROWPVT scores as well as Bayley-3 expressive language and EOWPVT scores. Weaker moderate correlations were found between Bayley-3 language scores and later CELF-P2 language scores. It was hypothesised that children with early language delays would have persistent delays at early school age too. Given the significant positive correlations observed, it does appear that earlier performance is associated with later performance in these children, but it is important to emphasise that more children with CHD were identified as having impaired language skills at 4-5 years than in the same cohort at 3-4 years.

It is widely accepted that Bayley-3 scores are inflated and consequently the measure significantly underestimates developmental delay in children, including those with CHD (Acton et al., 2011). Johnson et al. (2014) suggested that an updated cut-off of scores more than 1 SD below the mean (as opposed to 2 SD) should be used when evaluating and interpreting moderate to severe impairment using Bayley-3. Therefore, given the earlier Bayley-3 language scores in this cohort and the proportion of children with abnormal scores reflecting early impairment, it was plausible to assume that a similar, if not higher, proportion would also have abnormal scores in the investigation of language at 4-5 years of age. Only 2 children with CHD (1 with HLHS and 1 with TGA) had scores in the
impaired range for receptive and expressive language in the Bayley-3 at 3 years. In contrast, a larger proportion of the same cohort had impaired scores measured by the CELF-P2, suggesting that early Bayley-3 language scores may not be good predictors of later language impairment, again, emphasising that Bayley-3 may underestimate delays. Previous literature has also found this to be the case and concluded that Bayley-3 sensitivity is poor for all subtests including cognition, and receptive and expressive communication (Brosig et al., 2018; Fairbairn et al., 2018).

In contrast to what has been said above, Bayley-3 scores are known to be correlated with scores from various measures used with school-age children including later IQ measured using the WPPSI-IV, as well as early language scores and later language scores measured using the CELF-P2 (Anderson & Burnett, 2017; Aylward & Zhu, 2019). One of the few longitudinal studies to investigate correlations between early Bayley-3 and later assessment scores in early school-age children with complex CHD using similar measures to the present study was conducted by Gaudet et al. (2021). They reported several significant moderate positive correlations between scores at 2 and 5 years, including: global Bayley-3 language score and FSIQ measured using the WPPSI-IV, and receptive, expressive and core language measured using the CELF-4. When Bayley-3 global language scores were split into receptive and expressive communication, similar significant correlations were found, but these were weaker. Their findings also suggested that there are different developmental patterns for cognitive and language domains, with a decline with age for cognitive functioning, stable results for expressive language, and an improvement in receptive language skills. These patterns differ to those observed in the present study, but this may be due to the younger age of their cohort in the earlier
assessment, and/or the physiology of their cohort. They reported that 87% of their cohort had BV CHD, compared to 71% of the current cohort. They also mention the remaining cohort had SV CHD but it is not clear whether this included patients with HLHS specifically. As discussed previously, this group is known to have worse outcomes among others with SV CHD which may explain the divergent patterns.

The results of the present study may also be explained by the characteristics of the CHD cohort. This cohort of HLHS and TGA are considered to be a relatively ‘clean’ sample and are unlikely to have many of the comorbidities which are known to be common in CHD. Consequently, the current cohort is not necessarily representative of the wider CHD population. However, even in studies where there are significant group differences and children with CHD have lower scores compared to healthy controls or normative means, they do predominantly have scores within the average to low average range. What is important is the prevalence of delays and impairments in children with complex CHD. The present study clearly shows that despite the lack of group differences in speech and language skills, and in the absence of multiple comorbidities in this cohort, a significant proportion of children with CHD still have impaired language skills including reception, expression, core language, phonological awareness, and narrative skills. This impairment also appears to be specific to language because FSIQ appears to be in the average to low average range, and no patients have scores within the clinically impaired range.
4.4.3 Parent-Rated Language

It was hypothesised that children with complex CHD, and in particular those with HLHS, would have lower parent-rated language and communication scores, compared to healthy control children. The findings did not support this hypothesis as no significant group differences were observed in any of the CCC-2 scales. Again, this was somewhat surprising given the language outcomes in the CHD literature discussed at length, but an explanation for these language outcomes has been discussed above. However, these parent-rated findings do appear to be consistent with the directly measured language outcomes in the current cohort which is important when interpreting the present findings. The CCC-2 identified some children as having communication or language impairments, including one HLHS patient for ASD, another for SLI, two TGA patients for SLI as well as one healthy control. Despite this not being a significantly higher proportion of children with CHD, compared to healthy controls, it would be important to monitor these children longitudinally given the sensitivity of the CCC-2 in identifying children with ASD and SLI, especially given that these are common in CHD (Huisenga et al., 2020; Kovacs and Bellinger, 2021; Norbury et al., 2004).

Another secondary aim of this element of the study was to explore the links between parent-rated and direct measures of the child’s language skills. It was hypothesised that parental scores would be associated with direct measures of language performance. The findings support this hypothesis. All parent-rated CCC-2 language scales, except Syntax and Nonverbal scales, were moderately significantly positively correlated with all five scales of the CELF-P2 (i.e. Core, Receptive and Expressive Language, and Language Content and Structure). This suggests that language outcomes are consistent across direct objectively measured speech and language tests and parent-rated questionnaires. This is
an important finding given that parent-rated outcomes can sometimes be inaccurate and susceptible to bias (Goldberg et al., 2019). Research has indicated that CCC-2 parental scores are consistent with formal direct assessments in children with a range of communication disorders including Developmental Language Disorder (Andres-Roqueta et al., 2021).

4.4.4 Limitations of the Current Study

There are some key limitations to the current study, primarily related to the methodology. Firstly, despite trying to keep a tight age range between children across all three groups, overall, children with HLHS were younger than those with TGA and healthy controls. Although there were no significant differences between the groups in terms of their age, the younger age of the HLHS group is noteworthy given that language skills can still be quite variable at this age. It could therefore be argued that the youngest children with HLHS may have less mature language competence compared to the other two groups. It is also noteworthy that not all children had English as the only language spoken at home. Eleven children (34%) were bilingual and had other first languages, although they were able to speak and comprehend English. This could have impacted their performance in the current assessment and their speech and language development.

Another limitation is one which is commonly seen in longitudinal research, and that is the incidence of missing data due to children having missed some of the assessment time points, which accounts in part for the small sample size. Assessment of the current cohort was particularly affected by the COVID-19 pandemic as in-person evaluation could not be completed. This meant the overall
sample size was reduced by nine participants who would have most likely completed the assessments otherwise.

A further methodological limitation relates to the use of the Bayley-3. Despite being considered the gold-standard for neurodevelopment assessment in preschool children, it is now understood to be a less sensitive measure of language, since higher scores are acquired as soon as a few words are listed or become known to the child (Fourdain et al., 2019). Bayley-3 is also known to overestimate abilities (Johnson et al., 2014), including in children with CHD, leading to a potential under-identification of developmental delays. The impact of this is discussed in more detail in the previous Chapter 3.

In hindsight the Phonological Awareness subtest of the CELF-P2, a supplementary test which can evaluate compound words, syllable blending, sentence and syllable segmentation, rhyme detection, and production might have been a better test to use rather than the PAT. This would also have allowed direct comparisons to be made with more recent previous studies which have also used the CELF to measure phonological skills. However, the PAT was chosen due to it specifically and solely assessing phonology, and the two subtests of Rhyme Detection and Letter Knowledge were chosen based on the fact that rhyming ability and letter knowledge (significant precursors of reading) are known to be the strongest early predictors of reading acquisition and ability (Bryant & Goswami, 1987; Grofčíková & Máčajová, 2021; Muter et al., 2004). This also helped to reduce the burden on children of being assessed for prolonged periods of time.

Similarly, it would perhaps be more useful to use parental questionnaires with similar domains to those measured in the assessments to allow for comparisons to be made between parent-rated language skills and researcher observations of
language skills in children. Currently, this is not possible as the CCC-2 is comprised of different subtests compared to the measures used to assess language by the researcher – e.g. the CCC-2 provides a parent-rated score for syntax, but to assess for syntax in the CELF-P2 a supplementary test needs to be used which was not conducted in the present study.

4.4.5 Conclusion and Future Research

This is one of the few studies to investigate speech and language skills in depth in the early school years, using multiple measures to examine the full extent of language competence, and then to compare these scores to those collected one year earlier using the Bayley-3. This allowed for the exploration of longitudinal trajectories of language development in children with CHD, compared to healthy controls. The findings reveal that children with complex CHD in the current cohort do not display any impairments in language when they are examined as a group. However, there are individual children with HLHS or TGA who do show clear language impairments at 4-5 years of age. Many of these children were not flagged as having impaired or delayed language scores a year earlier using the Bayley-3. However, those that did have low scores at 3 years tended to have lower scores a year later, suggesting some stability and persistency in language impairments over time.

Further work is needed to look at the longitudinal trajectory of speech and language development and ability, throughout the preschool years, the early school years, and beyond. The majority of literature currently available comes from across the world including North America, Australia, Switzerland, and Japan, but the UK appears to be underrepresented, which may reflect the lack of
neurodevelopmental follow-up in children with complex CHD in the UK. Future research needs to adopt similar strategies to those proposed by the Cardiac Neurodevelopmental Outcome Collaborative who recommended the use of specific standardised assessments such as the Bayley-3, WPPSI-IV, Wechsler Intelligence Scale for Children, and the CELF to measure cognition and language from infancy throughout the school years, to ensure appropriate neurodevelopmental follow-up of CHD patients (Marino et al., 2012). Using the same measures as other researchers would also allow for better comparisons to be made and also ensure consistency among research studies.

Given the crucial role language plays in human behaviour, it is not surprising that language delays or impairments are a risk factor for associated difficulties in other aspects of children’s lives such as the acquisition of literacy skills, and the development of memory skills throughout childhood, adolescence and beyond. More broadly, language deficits can also impact social interactions, and make children more vulnerable for academic failure, social exclusion, behavioural and emotional difficulties, and to being bullied (Conti-Ramsden et al., 2009; Conti-Ramsden & Durkin, 2012). Surveillance is imperative in these children throughout childhood to enable early identification of speech and language deficits/impairments, allowing for appropriate interventions to reduce the likelihood of these impairments becoming worse with age, and impacting other areas of development and life including academic attainment, behavioural, psychosocial, and adaptive functioning, and quality of life.
Chapter 5: Neural Markers of Speech Sound Processing

Children with complex CHD are known to be at increased risk of delays and impairments in speech and language. These skills were investigated in detail in Chapter 4 where it was revealed that the current cohort do not display any impairments in language when they are examined as a group. However, a proportion of individuals with CHD, particularly HLHS, and fewer with TGA, showed clear language impairments at 4-5 years of age: they had scores ≥1 SDs below the normative means. This included a range of language domains including receptive and expressive language, language structure, rhyme detection, and narrative skills. This chapter will further investigate language in this cohort of CHD patients, specifically looking at speech sound processing using an auditory event-related potential (ERP) study to examine neural markers of speech processing. ERPs will be linked to behavioural measures of speech and language discussed in Chapter 4, in order to investigate if they are associated with one another.
5.1 Introduction

Children with complex CHD are at increased risk of delays and impairments in a wide range of domains including speech and language skills (Bellinger et al., 2003; Brosig et al., 2017; Miatton et al., 2007). Many of these delays and impairments in infancy have been found to continue into adolescence and adulthood. Literature investigating speech and language skills in pre-schoolers and school aged children with CHD report problems in receptive and expressive language, global language, and more specifically, phonological awareness, verbal comprehension, sentence production, word generation, and pragmatic skills, in school-aged children with CHD (Bellinger et al., 2003; Gaudet et al., 2021; Kharitonova & Marino, 2016; Miatton et al., 2007).

In Chapter 4 speech and language skills were investigated in-depth based on behavioural measures of these skills (i.e. standardised competence tests). In contrast to what was hypothesised, children with complex CHD (both HLHS and TGA) did not have lower language scores compared to healthy controls at 4-5 years of age, with the exception of verbal comprehension measured in the WPPSI-IV. There were also no differences observed between the two CHD patients groups, which was unexpected given the poorer expected outcomes for children with HLHS, compared to TGA. However, despite the lack of group differences, there was a high prevalence of poor language scores (i.e. borderline or clinically impaired) including receptive language (28%), expressive language (28%), core language (28%), verbal comprehension (31%), and two subtests of phonological abilities: rhyme detection (39%) and letter knowledge (11%). The prevalence of these delays/impairments are similar to those reported in the
literature (Gaudet et al., 2021; Ramanan et al., 2021), despite both CHD groups having language scores within the normal range.

Phonological skills are a critical part of speech and language development and are considered to be significant precursors of reading ability (Grofčíková & Máčajová, 2021; Muter et al., 2004). Phonology refers to the patterns of sounds within a language, and the smallest unit is called a phoneme, which is the individual speech sound of a single letter or occasionally two letters (e.g. /m/ for the letter m and /sh/ for the letters s and h) (Henry, 2014). As language competence improves, and sounds and rules are mastered, these can be combined to create words in the language that children are predominantly exposed to. Phonological processing is necessary for both comprehension (receptive) and production (expressive) of speech and language, as well as being a critically strong predictor of later reading and spelling abilities (Bryant & Goswami, 1987; Muter et al., 2004). Literature reporting phonological outcomes in children with CHD is divergent. Some researchers have reported specific delays and impairments in phonological processing in older school-age children (8 and 9 year-olds) with CHD (Bellinger et al., 2003; Miatton et al., 2007; Sarrechia et al., 2015), whilst others have found that children with CHD have phonological awareness skills similar to those of healthy controls (Hövels-Gürich et al., 2018; Sommariva et al., 2020). What is unclear in these studies, however, is the role the brain and any associated abnormalities play in the development of speech and language skills in children with complex CHD.
5.1.1 The Role of the Brain

Neuroimaging studies in young children with CHD are extremely limited due to the practical implications involved. However, Rollins et al. (2017) found that infants with biventricular CHD showed reductions in total brain volume at 1 year of age, including reduced white matter and brainstem volumes. These structural MRI findings were also positively correlated with language development measured using the MacArthur-Bates Communicative Development Inventory, but not broader developmental indices measured using Bayley-2. Further, MRI studies in older children and adolescents with CHD have found altered white matter microstructure and resulting differences in network processes which may underlie cognitive impairments (Marelli et al., 2016). These results suggest that the brain networks associated with speech and language development such as the dorsal and ventral pathways [including posterior and anterior superior temporal gyrus and sulcus, primary auditory cortex (i.e. Brodmann area 41 and 42), frontal opercular cortex, and the inferior frontal gyrus (Brodmann area 47) which includes Broca’s area (Brodmann area 44 and 45) (Skeide and Friederici, 2016)], may be adversely affected in CHD, as a result of various preoperative, perioperative, and postoperative factors (all discussed in Chapter 1). These abnormalities refer to the structure of the brain, however research investigating functional brain abnormalities in children with CHD is even more limited.

Auditory ERPs are a particularly useful technique used in developmental populations (discussed in Chapter 2 section 2.9.2.3). They can be used to investigate functional speech processing in the brain, and to identify if there is atypical processing in children with CHD. This can then be used to explore concurrent associations with speech and language competence measured via behavioural assessment and, longitudinally, in order to establish whether auditory
ERPs can be successfully used as neural markers of early speech and language impairments in children with CHD.

5.1.2 Speech Sound Processing

Before attempting to identify abnormalities in speech and language processing using ERPs, it is important to understand the neural pathway associated with auditory information. A dual-stream model of speech processing has been outlined (Figure 5.1) which includes a ventral stream involved in processing speech signals for comprehension, and a dorsal stream which maps these speech signals to frontal lobe articulation networks (Hickok & Poeppel, 2000; 2004; 2007; Skeide & Friederici, 2016). The ventral stream is bilaterally organised with a weak left hemisphere bias, whilst the dorsal stream is strongly left dominant. The dominant pathway for processing auditory information runs contralaterally from the ear of stimulation (Scott & Wise, 2004). The information is passed between the two hemispheres via the corpus callosum (Bamiou et al., 2007). For verbal stimuli, a right ear/left hemisphere advantage is extensively attributed to language specialisation (Kimura, 1967), and this lateralisation/specialisation is typical in the normative population. Research in developmental clinical populations has revealed that reversed or atypical hemispheric lateralisation in response to speech stimuli and language is associated with language impairments including in autism spectrum disorder (ASD), specific language impairment (SLI), and children born very preterm (de Guibert et al., 2011; Finch et al., 2017; Seery et al., 2013; Stipdonk et al., 2022).
Figure 5.1 The dual-stream model of speech processing: a) Diagram of the dual-stream model which begins with the earliest stage of speech processing involving spectrotemporal analysis in the auditory cortices bilaterally. Subsequently, processing splits into the two streams: a left dominant dorsal pathway (in blue) and a ventral pathway (in pink); b) The anatomical locations of the dual-stream components (Hickok & Poeppel, 2007)

5.1.3 ERPs and Brain Development

ERPs recorded on the scalp are dependent on brain development. Given that the human brain continues to develop into adulthood, these developmental changes should be reflected in ERPs. Electrophysiological responses are known to change over time from infancy to adulthood. As the brain matures and becomes tuned to the experienced world, transmission speeds up as pathways become efficient (for example, due to the increase in myelination), which translates into latency changes, whilst changes in the amplitude of ERP components are more influenced by changes in synaptic density (de Haan, 2007; 2008). For example, there are large differences between children, adolescents and adults in late
auditory ERPs (e.g. P300), so brain maturity may be assessed through analysis of waveform shape (Bishop et al., 2007a).

Studies have linked cognitive development and behavioural skills to myelination and maturation of white matter (Luna et al., 2001; Nagy et al., 2004). Given the increased incidence of delayed brain maturation and white matter injury in CHD, particularly in children with HLHS, it is plausible to assume that such brain abnormalities may be reflected in the latency of ERP components in these children. In contrast to white matter impairments, comparatively little is known about synaptogenesis in the brain but there is a general pattern of early overproduction, decrease due to pruning, and plateau (Luck & Kappenman, 2012). This pattern is thought to vary among cortical regions. Impaired perinatal cortical maturation has been reported in CHD. For example, foetuses with HLHS have been found to have reduced cortical and subcortical grey matter volume (Clouchoux et al., 2013; Leonetti et al., 2019).

Studies using ERPs to investigate early brain abnormalities in CHD and correlate these with neurodevelopmental outcome are extremely limited in humans. Animal models have revealed that periods of hypoxia and/or ischaemia can substantially alter the amplitude and latency of electrophysiological responses, and this is linked to the underlying brain abnormalities (Alvarez et al., 2015; Branston et al., 1984). Specifically, in humans, the alterations reported include increased latencies and decreased amplitude as a result of induced hypothermia in CHD (Rodriguez et al., 1995). Limperopoulos et al. (1999) also found abnormalities in perioperative somatosensory evoked potentials, including increased latency and decreased amplitude in newborns with CHD, and this was linked to abnormal neurological examination and developmental deficits in several domains one year post-surgery including motor performance, daily living, and socialisation skills. It
is important to distinguish these more global electrophysiological responses which are useful for clinical neurological monitoring from quantitative assessment of auditory ERPs, where early evoked potentials may represent neural markers of later delays and impairments, and could be a useful prognostic tool for neonates with CHD following open-heart surgery procedures.

5.1.4 The Auditory Oddball Paradigm

ERPs are particularly suitable for studying auditory processing in preverbal and developmental populations (Bell & Cuevas, 2012) and those with a limited attention span. Auditory ERP “holds promise as an index of the brain’s responses to auditory stimuli in real-time” (Bishop et al., 2007b p. 565). For example, in a classic oddball paradigm, discriminating the infrequent target from the more frequently occurring standard produces robust ERP components which are known to have larger amplitudes for infrequent compared to frequent stimuli (Luck et al., 2011). As ERPs are sensitive to novelty detection in such paradigms, they may be useful biomarkers of brain integrity and maturation. Further, if specific language stimuli are used, such as speech sounds, then ERPs can be used to help identify early abnormalities such as delayed/altered processing in various clinical populations including CHD. That is, if a given ERP component measures the operation of a given sensory-cognitive process (e.g. processing of speech sounds), then an abnormality of this component may reflect abnormal processing in the brain of this given cognitive process (Luck et al., 2011). Despite this, ERP literature on auditory processing within the CHD population is extremely limited.
A series of peaks occur during an auditory ERP. The earlier components after the onset of the stimulus seem to reflect more perceptive and stimuli-driven processing (Luck, 2014). One of these components is P50, a positive peak around 50ms after the auditory stimulus, produced in primary and secondary auditory cortices. It is generally measured around F3/F4 and C3/C4, frontal and central areas over the left (i.e. 3) and right (i.e. 4) hemispheres respectively, where P50 amplitude is largest. The auditory P50 seems to reflect “sensory gating” which refers to the inhibition of irrelevant, repetitive or distracting stimuli at an early sensory stage of processing (Green et al. 2015; Ross et al. 2013). This allows individuals to selectively attend salient stimuli and protects the brain from information overload. P50 amplitudes are higher in response to infrequent stimuli, reflecting the system’s recognition of novel stimuli, compared to frequent stimuli (Boutros et al., 1995). This is useful when studying children with various neuropsychiatric disorders as it provides a window into the developmental time course of attentional deficits. Durukan et al. (2011) found significant differences in P50 test latency, amplitude, and P50 ratio values in a group of 9-14-year-olds diagnosed with attention-deficit hyperactivity disorder (ADHD) compared to a group of healthy controls. In an oddball task involving speech sounds, Maurer et al. (2003) found that children at familial risk of dyslexia, differed from healthy controls in their processing of phonemes/consonant changes in a passive oddball paradigm, and had attenuated responses.

Another component that seems to reflect auditory processing is the N1, a negative deflection peaking around 100ms after the stimulus onset, generated in the supratemporal auditory cortex. The N1 is maximally recorded at frontocentral sites (e.g. Fz, F3, F4, Cz, C3, C4; with odd numbers reflecting the left hemisphere, even numbers the right hemisphere, and ‘z’ midline recording sites).
but also consists of temporal components. It is elicited by any discernible auditory stimulus, and the amplitude is influenced by several factors, including interstimulus interval, stimulus intensity, arousal level, and participants’ attention (Wang et al., 2005). It reflects an orienting response or “matching process” whereby a presented stimulus is matched with the previous one, and consequently is significantly affected by attentional focus of the listener (Sur & Singha, 2009; Trainor, 2007). Age-related changes in the latency and amplitude of the N1 have been previously reported, demonstrating a general maturational development of the auditory ERPs and also a specific maturational process for temporal encoding of information in the auditory cortex. Bruneau and Gomot (1998) described left lateralised negativity (in T3) in children around 70 to 180ms, in response to stimuli (i.e. tone bursts with two different intensities) presented at random to left and right ears. Reversed laterality was also described in response to speech sounds in children with language impairment, which is thought to reflect overactivation of the right hemisphere which may interfere with normal language processing. McArthur and Bishop (2005) reported poor auditory processing in SLI, measured in early sensory components including the N1.

More endogenous components appear later on, after 250ms (Luck, 2014). One of the most well studied endogenous ERPs in auditory and attentional tasks is the P300. It manifests as a larger positivity around 300ms after stimulus onset. The P300 is an important ERP component for evaluating cognitive functions in humans and is commonly largest at parietal and central electrode locations (Triantafyllou et al., 1992). The oddball paradigm commonly elicits P300 which reflects inadvertent capture of attention. This paradigm involves the detection of the target salient (i.e. infrequent) stimuli in a stream of frequent stimuli. The temporoparietal P300 (or P3b) reflects the extent of resources
allocated to processing an unexpected stimulus. Here, the amplitude of P300 increases with greater attention and demand on memory updating, whereas, the frontal P300 (or P3a) represents the cortical orienting response to trial unique categories, and the amplitude increases with perceptual discrimination difficulties (Winterer et al., 2003). This frontal response is often elicited in a 3-stimulus oddball, rather than 2-stimulus, which has been the focus of discussion in this chapter. Further, it has been established that P300 amplitude derived from auditory stimuli remains the same from 5 years of age throughout adulthood (Luck & Kappenman, 2012). The P300 has also been implicated in SLI. Ors et al. (2002) found normal early sensory ERP components (N1/P2) in children with SLI but abnormalities in later-stage auditory perceptual processing indexed by the P300 that reflects broad recognition and memory-updating processes. Children with SLI had larger P300 amplitude for target/infrequent stimuli but, overall, had reduced amplitude for speech sounds which the authors describe as representing less efficient context updating in working memory.

The components described above do not show the same topography. Each component is recorded from different scalp locations which leads to the possibility that the measured activity is from different functional cognitive processes. For example, in the case of the P3b component, a larger amplitude from electrodes placed in temporoparietal regions (T3, T4, T5, T6, P3, P4, P5, and P6) reflects increased attention to given auditory stimuli. In contrast, larger amplitude from frontal regions (F3, F4) represents the P3a cortical orienting response, whereby the amplitude increases with perceptual discrimination difficulties, in response to the exact same stimuli (Winterer et al., 2003). There are further differences in age groups, as well as healthy versus clinical samples. The P50, N1, and P300 components have been widely investigated as biomarkers of early abnormalities
in a range of clinical populations including schizophrenia and Alzheimer’s disease, and various developmental populations such as children born very preterm, and those with ASD and ADHD. In these latter populations, research has revealed atypical auditory ERPs within the first year of life which may indicate an increased risk for cognitive dysfunction (Fellman et al., 2004; Riva et al., 2018).

However, there are very few studies exploring these components using an auditory oddball paradigm in children with CHD. Guan et al. (2011) investigated the P3b in older school-aged children with CHD (specifically ventricular septal defect, but not HLHS or TGA) using an auditory oddball paradigm with tones. The auditory stimuli were presented binaurally with target tones presented 20% of the time and standard tones 80% of the time. Participants were required to respond to the target by pressing a button but to ignore the standard stimuli. They found that children with CHD had longer P300 peak latencies and lower P300 amplitude in Fz and Cz (but not Pz), in response to target tones, compared to healthy controls, which the authors interpreted as poorer information processing (i.e. stimulus evaluation, alertness, and memory updating). They also concluded that this poorer cognitive function may be linked to duration of cardiopulmonary bypass and aortic clamping. It is important to note that ventricular septal defect is not considered to be a complex or severe type of CHD, but given these findings, it is plausible to assume that atypical auditory ERPs are perhaps more likely to be observed in children with HLHS and TGA. Moreover, given the link that Guan et al. (2011) made between cognitive functioning at 6-13 years of age and early peri-operative factors during surgery in the preschool years, it is important to consider when abnormalities may be able to be detected at the earliest opportunity. For example, longitudinal ERP studies investigating different
components with different latencies and amplitudes are necessary in the preschool and early school years to help decipher the stage and age at which processing atypicality occurs in children with complex CHD.

The auditory ERP components discussed above have been reported to be lateralised. For example, the N1 has long been considered to have larger amplitude in the auditory cortex contralateral to ear stimulation (Näätänen & Picton, 1987), but reports vary on the degree of P300 hemispheric lateralisation. Gilmore et al. (2009) found N1 contralateral bias during an auditory oddball paradigm, but right hemisphere sources were activated regardless of ear stimulation. During N1 through to P300 duration, temporal-parietal and frontal areas were more activated in the right hemisphere, compared to the left, regardless of ear stimulation. P300 amplitudes were influenced by ear stimulation, but there was stronger activity in the right hemisphere. These results suggest that the right hemisphere plays a prominent role in sustained attention, stimulus evaluation, target detection and context updating. In contrast, the left hemisphere has a dominant role in language specialisation and auditory speech processing. Tervaniemi and Hugdahl (2003) reviewed the literature on lateralisation of auditory cortex functions and concluded that speech stimuli produce a reliable left hemisphere asymmetry advantage. Processing of right ear stimuli is a measure of left-temporal lobe processing superiority for phonological stimuli. This right-ear advantage is likely caused by the fact that although auditory input is transmitted to both auditory cortices in the temporal lobes, the contralateral projections are stronger and may consequently block the processing of the ipsilateral projections.
5.1.4.1 Discriminating Speech Sounds

ERPs are widely used to study speech and language processing in infants and children. They can elucidate the underlying neural mechanisms of language, and particularly speech processing. In the first studies to use ERPs as predictive variables of later language skills, Molfese and Molfese (1985; 1997) showed that responses to speech sounds (i.e. consonant-vowel syllables) at birth were predictive of language skills at the ages of 3 and 5 years. Auditory sensory discrimination of speech sounds has been widely investigated in different clinical populations including children born preterm, SLI, dyslexia, and ADHD. For example, Jansson-Verkasalo et al. (2003) measured mismatch negativity (MMN) amplitudes (i.e. subtracting the standard stimuli ERP from the deviant stimuli) in 4 year-old preterm children with very low birthweight. They found preterm children had smaller MMN amplitudes compared to controls and these amplitudes also varied as a function of the child’s performance on language tasks.

In SLI there is a delay in oral language skills compared with nonverbal cognitive abilities. Bishop et al. (2007a) investigated atypical auditory ERP in 5-10 year-olds with SLI compared to age-matched healthy controls. They used an auditory oddball paradigm involving tones and consonant-vowel speech sounds (e.g. /da/). Intraclass correlation was used to compare individual SLI participants’ auditory ERP waveforms in the range of 100-228ms (i.e. N1) with the grand average waveform from the healthy control group. They found that waveforms of children with receptive SLI differed from the normative waveform (based on the control grand average), reflecting atypical lateralisation (i.e. right-sided electrodes) of brain responses to both tones and speech sounds in SLI. They concluded that despite a large proportion of children with SLI having normal age-appropriate N1 waveforms, the proportion of those with atypical findings is higher
than that in healthy controls. It has also been suggested that children with SLI take longer time to perceive and discriminate between either tonal or speech auditory stimuli than children with typical speech and language development (Munivrana et al., 2011).

Kujala and Leminen (2017) reviewed studies investigating auditory discrimination dysfunction in SLI and concluded that children with SLI have smaller amplitudes and longer latencies for both speech and non-speech sound discrimination, compared to typically developing children. This suggests impaired auditory discrimination and shortened sensory memory duration in SLI. Associations have also been observed between ERP measures and scores on language tests. Consequently, ERPs can shed light on the neural basis of potential auditory impairments, and these are likely to influence speech perception as well as being associated with potential language impairments. Further, Uwer et al. (2002) studied frequency and duration discrimination in 5-10 year-olds with SLI using both tone and consonant-vowel syllables, and found that they had attenuated MMN amplitudes to speech stimuli, but not tones. These children also made more errors in behavioural discrimination tasks, but these did not correlate with the MMN amplitudes. They concluded that this processing deficit in SLI is specific to speech. Overall, the SLI literature varies with respect to whether early sensory components including P50 and N1 are implicated (Korpilahti & Lang, 1994; Uwer et al., 2002) or whether later components are attenuated, delayed, or absent (Tonnquist-Uhlen et al., 1996; McArthur & Bishop, 2005).

Comparable findings have also been observed in children with dyslexia. Leppänen et al. (2011) observed an overall atypical right hemispheric dominance in response to speech sounds (e.g. /ba/, /da/, and /ga/) in dyslexic children. Early ERPs from infancy were also related to poorer receptive language at 2.5 years,
and were correlated with later phonological processing at 3.5 years and letter-naming skills at 5 years, as well as phoneme duration perception, reading, and writing skills at school age (6-7 years). These findings suggest that the neural networks sub-serving auditory and speech perception differ in children with dyslexia, which influence later reading abilities. These results are consistent in the dyslexia literature and have been reported by many others including recent meta-analyses (e.g. Gu and Bi, 2020; Moll et al., 2016). Further, Hämäläinen et al. (2013) reported atypical ERP responses to both speech and non-speech stimuli at 6 years were correlated with later reading problems at 9 years. Similarly, Maurer et al. (2009) showed that 6 year-olds at familial risk for dyslexia had differing ERP responses to speech sounds presented in a passive oddball paradigm, compared to control children. Specifically, in the later 457-636ms time window, the at-risk children showed attenuated responses to both speech and non-speech sounds and a more bilateral response to the phoneme change, whereas control children showed left lateralisation. These differences were also found to significantly predict reading skills at school age. Therefore, atypical auditory and speech processing may serve as a neural-level risk factor for future reading problems, and may help to identify those children at risk of dyslexia before reading problems become apparent at school.

Auditory ERPs have also been used to investigate speech and non-speech processing in typically developing children. For example, left-lateralised ERP components such as the P100 have been found to be associated with better phonological and prereading skills; larger P100 amplitude to nonspeech than speech stimuli is linked to poorer verbal reasoning performance in pre-schoolers (Kuuluvainen et al., 2016). These findings suggest that children’s ERPs reflect neural markers of sound processing, as well as lexical access, but also indicate
that speech and nonspeech sounds are processed by at least partially distinct neural substrates.

It is important to note that the majority of these ERP studies investigating speech and language processing in children, using the oddball paradigm, predominantly tend to measure MMN, as opposed to individual ERP components such as the P50, N1, or P300. However, a problem with this is that it is difficult to know whether the mismatch is being driven by the standard/frequent stimuli or deviant/infrequent stimuli. Day (2017) used an auditory oddball paradigm to explore processing of speech sounds in 30-month-old infants born very preterm, with a focus on N1 and P300 components. For standard speech sounds, in the N1 component, term born controls displayed larger responses to left ear sounds in both hemispheres, compared to the preterm infants. In the P300, sounds to the left ear elicited greater mean amplitude in the contralateral hemisphere of the term controls, compared to the preterm infants who had larger ipsilateral responses. For deviant sounds, in the N1 component, there was a greater response in the contralateral hemisphere when sounds were presented to the right ear, in both groups. However, in the P300, no significant main effects were observed.

5.1.5 Maturation of Auditory ERPs

Age-related maturation is known to occur in the classic auditory oddball paradigm. For example, children tend to show relatively greater peak amplitudes than adults at temporal sites (Bruneau and Gomot, 1998). However, reports vary in the literature regarding the differential maturation of each ERP component. Brinkman and Stauder (2007) found that children aged 5-7 years had smaller P50
amplitudes and therefore, showed less sensory gating compared to older children, whilst 10-12 year-olds had larger amplitudes compared to adults. In line with this, Friedman (2012) outlined that the P50 and N1 amplitudes to standard stimuli have been found to be enhanced in older adults, which may reflect inefficient inhibition of irrelevant information.

With regards to the N1 component, there is conflicting evidence as to whether amplitude increases with age. Some studies have reported no significant age-related increases in N1 amplitude after 6 years of age (Anderer et al., 1996; Sharma et al., 1997). Johnstone et al. (1996) found this was specifically the case with standard stimuli, but for target stimuli, N1 amplitude showed a linear decrease with age. However, others have shown increases in N1 amplitude with age from childhood to adolescence and adulthood (Bruneau et al., 1997; McArthur and Bishop, 2002; Tsai et al., 2012). The N1 is known to be one of the components that changes most with maturation, and it can be recorded from around three years of age (Čeponiene et al., 2002).

The literature for the P300 is somewhat mixed, but reports are considerably more consistent. For example, van Dinteren et al. (2014) showed auditory P300 amplitude increases with age-related maturation. They found P300 amplitude increases during childhood until its maximum is reached at 16 years, at which point it begins to decrease gradually. This supports the earlier findings of both Polich et al. (1990) and Tsai et al. (2012).

Overall, ERPs can provide biomarkers of auditory and speech sound processing in a range of relevant clinical populations. Prior studies have shown that impaired auditory processing or speech sound discrimination is predictive of language and reading skills in preschool and school-aged children (Jansson-Verkasalo et al., 2003; Leppänen et al., 2011; Maurer et al., 2009). However, auditory ERP
literature focussing on speech sound discrimination in children with CHD is extremely limited. Given what we know about non-speech sound discrimination and processing in children with CHD (Guan et al., 2011) and the language, behavioural and attentional deficits commonly reported in CHD, it seems plausible to assume that speech sound processing may also be affected in this population. Such impairments can be reflected in ERP responses, which can be used as biomarkers to predict later more sophisticated language development and to highlight those children with CHD who experience pre-reading and early language delays and/or deficits. To the authors’ knowledge, there are no current longitudinal ERP studies exploring speech sound processing in children with CHD. Therefore, the present study aims to explore the neural markers of speech sound processing in a cohort of children with complex CHD. The approach was to use an auditory oddball paradigm involving phonemes adapted from Day (2017), with stimuli presented to the left and right ears separately to help evaluate lateralisation of response.

5.1.6 Aims and Hypotheses

The primary aim is to use an auditory oddball ERP task to examine the brain network supporting speech sound processing, in order to investigate whether there are biomarkers of delays and/or impairments in early language skills, mainly targeting changes in amplitude of the P50, N1, and P300 components. These electrophysiological markers of speech sound processing are then related to the behavioural measures of speech and language, specifically, phonological awareness skills and expressive language. A secondary aim is to study the age-related maturation of this network, by assessing changes in amplitudes between time-points longitudinally. This will determine whether delays are relative to
chronological age, or due to a selective deficit in the language network caused by early hypoxic-ischaemic episodes.

To address a gap in the CHD literature and considering the standard ERP waveform for an auditory oddball paradigm, the meaning of each ERP component (i.e. P50, N1, and P300), and how potential hypoxic/ischaemic injury in CHD could affect the brain network supporting language and early reading skills, the main hypotheses are:

- There will be significant group differences in the mean amplitudes for frequent and infrequent speech sounds, in the P50, N1, and P300, reflecting atypical speech sound processing.
- Within groups, both TGA and HLHS patients will show a reduced classic oddball effect of higher mean amplitudes of the P50, N1, and P300 for the infrequent stimuli compared to the frequent stimuli. In comparison, the healthy controls will show larger mean amplitudes in these components for the infrequent stimuli.
- Speech sound ERPs will be associated with scores of phonological abilities (i.e. rhyme detection and letter knowledge) and expressive language.
- Children with CHD will show different developmental profiles/age-related maturation of the brain network supporting speech sound processing, compared to healthy controls who will show increases in P50, N1, and P300 amplitude over time.

### 5.2 Methods

#### 5.2.1 Participants

The cohort participated in the auditory ERP study twice, with a minimum of a year in between the two assessments. The longitudinal cohort who participated in the time-point 3 assessment at 3-4 years of age described in Chapter 3 and the same cohort who participated in the final time-point 4 assessment at 4-5 years of age
described in Chapter 4, were invited to take part in the ERP study at both assessment time-points. A total of 31 children (7 HLHS patients, 11 TGA patients, and 13 healthy controls) completed the auditory ERP paradigm at time-point 3, and a total of 24 children (4 HLHS patients, 13 TGA patients, and 7 healthy controls) completed the auditory ERP paradigm at time-point 4 (the sample is summarised in Table 5.1).

There was some attrition in participant numbers between the two assessment time-points, and the reasons for this were described previously in Chapter 4. However, a smaller proportion of the cohort participated in the ERP study, compared to the other behaviourally measured tests due to apprehension over the EEG cap. Given the nature of the experiment and the requirements involved such as being still and not being able to communicate during the task, some children were not able to complete the ERP experiments as they were highly distressed and upset during the placement of the cap on their head. This was the primary cause for the significant attrition in the ERP study, which was particularly evident in the healthy controls, compared to the CHD patient groups. A total of 15 children (4 HLHS, 3 TGA, and 8 healthy controls) were unable to complete the ERP study at time-point 3, and 4 children (1 HLHS and 3 healthy controls) at time-point 4.

Consequently, to maximise the sample size per group, data were collapsed together from time-points 3 and 4. In cases where participants had data from both time-points, one was chosen at random ensuring an equal sampling from each time-point across all groups where possible, whilst maintaining a similar and tight age gap between the groups. A total of 8 HLHS patients, 15 TGA, and 16 healthy controls were included in the auditory ERP analysis to explore sound processing at a mean age of 4 years (Table 5.1).
Table 5.1 The full cohort including patients with HLHS and TGA, and healthy controls who participated in the auditory oddball ERP study, longitudinally

<table>
<thead>
<tr>
<th>Time-point 3</th>
<th>N</th>
<th>HLHS</th>
<th>TGA</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (SD)</td>
<td>3.24 (0.27)</td>
<td>3.60 (0.33)</td>
<td>3.48 (0.32)</td>
<td></td>
</tr>
<tr>
<td>Gender (M:F)</td>
<td>5:2</td>
<td>7:4</td>
<td>5:8</td>
<td></td>
</tr>
<tr>
<td>Time-point 4</td>
<td>N</td>
<td>HLHS</td>
<td>TGA</td>
<td>Controls</td>
</tr>
<tr>
<td>Age in years (SD)</td>
<td>4.94 (0.34)</td>
<td>5.22 (0.19)</td>
<td>5.13 (0.29)</td>
<td></td>
</tr>
<tr>
<td>Gender (M:F)</td>
<td>3:1</td>
<td>8:5</td>
<td>5:2</td>
<td></td>
</tr>
<tr>
<td>Time-points 3 &amp; 4 randomly combined</td>
<td>N</td>
<td>8</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>Age in years (SD)</td>
<td>4.12 (0.93)</td>
<td>4.54 (0.88)</td>
<td>4.13 (0.96)</td>
<td></td>
</tr>
<tr>
<td>Gender (M:F)</td>
<td>6:2</td>
<td>10:5</td>
<td>7:9</td>
<td></td>
</tr>
<tr>
<td>Time-point (3:4)</td>
<td>4:4</td>
<td>6:9</td>
<td>9:7</td>
<td></td>
</tr>
<tr>
<td>Longitudinal data (both time-points)</td>
<td>N</td>
<td>3</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Gender (M:F)</td>
<td>2:1</td>
<td>5:4</td>
<td>3:1</td>
<td></td>
</tr>
</tbody>
</table>

5.2.2 EEG Auditory Oddball Task and Procedure

The EEG apparatus was prepared approximately fifteen minutes before the task to allow the net to soak in a saline solution of 1000ml of lukewarm water, 5ml of baby shampoo, and 10g of potassium chloride for at least 5 minutes. The child’s head circumference was measured to determine the size of the net to be used. The child sat comfortably on a chair and the EEG net was positioned by the researcher on the child’s head, ensuring Cz was in the centre of the head. The impedances were measured and any electrodes with impedance above 50kOhm were adjusted or treated using more saline solution until they were below 50kOhm. Lightweight children’s headphones were then placed on top of the net for the auditory stimulation. To reduce movement artefacts, the child was allowed to watch a cartoon or video of their choice on a handheld device such as a mobile
phone, with the volume muted so not to interfere with the task. Once the child was comfortable and still, the task began. Neither the researcher nor the parents spoke to the child throughout the experiment unless it was absolutely necessary, for example if the child became distressed. The paradigm was presented as an auditory oddball design in MATLAB (2017, The Mathworks, Inc., Massachusetts, USA). It comprised two computer-synthesised consonant-vowel speech sounds (/da/-/ga/ continuum), presented monaurally in an oddball design. The frequency of the two 100ms phoneme variants was presented in a 70:30 ratio. /da/ was presented as the deviant (infrequent) sound and /ga/ as the standard (frequent). There was a total of 400 trials with a random silent inter-stimulus interval of between 0.8 and 1.8 seconds (Figure 5.2); the task lasted a total of 12 minutes. Each block alternated between the left and right ear presentation, with the first ear of presentation counterbalanced between subjects. The stimuli were selected and used in a previous study with preterm children (Day, 2017).

Figure 5.2 Auditory oddball paradigm with frequent and infrequent speech sounds
5.2.3 EEG Recording and Data Pre-Processing

EEG data were acquired at a digitising rate of 250Hz using either a 128- or 256-channel EEG Hydrocel Geodesic Sensor Net (2008, EGI, Electrical Geodesics, Inc., Eugene, OR, USA). Netstation version 4.5.1 was used to record the data. The signal was referenced online to the vertex (Cz). During time-point 3 data collection, two different EEG caps were used (i.e. 128- or 256- channel) due to head circumference differences between participants, and at time-point 4, only the 256-channel net was used. Consequently, data were pre-processed separately for each cap, before being combined for final analyses.

Figure 5.3 outlines the steps of EEG data pre-processing. Post-recording, raw EEG data were imported and analysed using EEGLab version 14.1.1 (Delorme & Makeig, 2004), a MATLAB toolbox. Channel location was imported (depending on the net) and channel data were visually inspected. In the 256-channel net, some electrodes were identified as possibly damaged as electrical activity appeared as a flatline throughout the experiment during visual inspection. These electrodes were noted in each participant and those which were damaged in the majority (i.e. more than or equal to half) of participants were permanently removed from the analysis to avoid additional noise. These electrodes were mirrored so that symmetrical electrodes in the opposite hemisphere were also removed to ensure equal distribution of electrodes across both hemispheres. Facial electrodes were also permanently removed as these were consistently noisy in all participants due to either eye movements, lack of contact, or being repeatedly probed by the child as a result of discomfort during the experiment. Figure 5.5 highlights all the electrodes which were permanently removed from analysis. A total of 116 electrodes remained following permanently channel removal and these were taken forward for analysis. It is important to note that
due to permanent removal of more than half the channels in the 256 net, the remaining surviving electrodes were not evenly distributed across the scalp, as they would initially have been prior to removal. In a standard net the electrodes are equally distributed across the scalp with equal spacing between them, to ensure that electrical activity is representative of the whole brain, or specific region of interest.

The data were then band-pass filtered (i.e. high and low pass filtering at 0.1-30Hz). Channels with bad data, presenting flatline, drifts, or excessive noise, were removed. The signal was then submitted to an Independent Component Analysis (ICA) to identify and correct artefacts such as eyeblinks, saccades, and heart rate. Removal of components was not an automated process; components which were identified by ICA based on their location and spectral behaviours were visually inspected. Those components which appeared to be artefacts, eyeblinks, saccades or heart rate from the topographical maps, spectral distribution and activation patterns, were removed manually. Figure 5.4 shows examples of such artifacts which were removed following ICA. This was followed by the interpolation of the previously removed bad channels, and the signal was referenced to Cz. Finally, epochs of 1000ms (-200ms pre-stimulus baseline and 800ms post-stimulus) were extracted for each trial, and visually inspected. The epochs were then manually inspected to ensure all artefacts had been removed. Some epochs were identified as having remaining artefacts following ICA which may have been missed, and those containing artefacts were rejected prior to averaging. The remaining epochs were then baseline-corrected and averages for each electrode and each condition were created for each individual child. Grand average waveforms were then created for the three groups: HLHS, TGA and healthy controls. The waveforms for each condition were compared within and
between groups. Mean amplitudes were calculated for each component within the waveforms (i.e. P50, N1, and P300).

Figure 5.3 EEG data pre-processing pipeline

Figure 5.4 Components identified by ICA as artifacts: A) heart rate and B) eye blinks, which were removed

*Note.* A combination of topography, spectral distribution, and activation pattern were manually inspected to correctly detect all types of artifacts accurately and remove them as necessary. A) includes an image of the topographical map and activation pattern of heart rate, and B) includes the topographical map and spectral distribution of eye blinks.
5.2.4 ERP Data Analysis

A series of peaks are known to occur during an auditory oddball paradigm. Based on previous literature three main components of interest were identified: a positive peak around 50ms (termed P50); a negative peak around 100ms (termed N1); and a later positive peak around 300ms (termed P300) (Day, 2017; Luck, 2014). Time windows for each component are summarised in Tables 5.2 and 5.3. Temporal clusters in the left and right hemispheres were selected including T3 and T5, and T4 and T6, respectively, and these clusters are shown in Figures 5.5 and 5.6. Due to the two different EEG nets used, electrodes which were common in both nets were selected (i.e. T3, T4, T5, and T6). However, the clusters around these electrodes of interest differed in the two caps due to the distribution of electrodes in each cap, and the removal of damaged electrodes (Figure 5.6).

Table 5.2 Summary of the main parameters for the quantitative ERP analysis, 128 channel net

<table>
<thead>
<tr>
<th>Component</th>
<th>Hemisphere</th>
<th>Equivalent 10-20 region (approx.)</th>
<th>Latency window</th>
<th>Amplitude measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>P50</td>
<td>Left</td>
<td>T3 &amp; T5 (E39, E40, E45, E46, E50, E51, E52, E58, E59, E64)</td>
<td>[30-70] ms</td>
<td>Mean</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>T4 &amp; T6 (E91, E92, E95, E96, E97, E101, E102, E108, E109, E115)</td>
<td>[30-70] ms</td>
<td>Mean</td>
</tr>
<tr>
<td>N1</td>
<td>Left</td>
<td>T3 &amp; T5 (E39, E40, E45, E46, E50, E51, E52, E58, E59, E64)</td>
<td>[80-200] ms</td>
<td>Mean</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>T4 &amp; T6 (E91, E92, E95, E96, E97, E101, E102, E108, E109, E115)</td>
<td>[80-200] ms</td>
<td>Mean</td>
</tr>
<tr>
<td>P300</td>
<td>Left</td>
<td>T3 &amp; T5 (E39, E40, E45, E46, E50, E51, E52, E58, E59, E64)</td>
<td>[240-450] ms</td>
<td>Mean</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>T4 &amp; T6 (E91, E92, E95, E96, E97, E101, E102, E108, E109, E115)</td>
<td>[240-450] ms</td>
<td>Mean</td>
</tr>
</tbody>
</table>
Figure 5.5 EGI 128 channel Geodesic map displaying electrode selection for P50, N1 and P300 components using left (blue) and right (green) hemisphere clusters

Note. Darker blue and green electrodes highlight T3, T4, T5, and T6, around which the temporal clusters were created.
Table 5.3 Summary of the main parameters for the quantitative ERP analysis, 256 channel net

<table>
<thead>
<tr>
<th>Component</th>
<th>Hemisphere</th>
<th>Equivalent 10-20 region (approx.)</th>
<th>Latency window</th>
<th>Amplitude measure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P50</strong></td>
<td>Left</td>
<td>T3 &amp; T5 (E62, E68, E69, E70, E74, E75, E85, E95, E97, E106)</td>
<td>[30-70] ms</td>
<td>Mean</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>T4 &amp; T6 (E161, E169, E171, E178, E180, E192, E193, E202, E210, E211)</td>
<td>[30-70] ms</td>
<td>Mean</td>
</tr>
<tr>
<td><strong>N1</strong></td>
<td>Left</td>
<td>T3 &amp; T5 (E62, E68, E69, E70, E74, E75, E85, E95, E97, E106)</td>
<td>[80-200] ms</td>
<td>Mean</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>T4 &amp; T6 (E161, E169, E171, E178, E180, E192, E193, E202, E210, E211)</td>
<td>[80-200] ms</td>
<td>Mean</td>
</tr>
<tr>
<td><strong>P300</strong></td>
<td>Left</td>
<td>T3 &amp; T5 (E62, E68, E69, E70, E74, E75, E85, E95, E97, E106)</td>
<td>[240-450] ms</td>
<td>Mean</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>T4 &amp; T6 (E161, E169, E171, E178, E180, E192, E193, E202, E210, E211)</td>
<td>[240-450] ms</td>
<td>Mean</td>
</tr>
</tbody>
</table>
Figure 5.6 EGI 256 channel Geodesic map displaying electrode selection for P50, N1 and P300 components using left (blue) and right (green) hemisphere clusters

*Note.* Darker blue and green electrodes highlight T3, T4, T5, and T6, around which the temporal clusters were created. Grey electrodes have been permanently removed due to possible damage, mirrored so symmetrical electrodes have also been removed, and facial electrodes due to excessive and constant noise in the signal. A total of 116 electrodes remained.

The oddball paradigm produced responses to frequent and infrequent phonemes. Responses were investigated according to ear stimulation (speech sounds presented to the left or right ear), and hemispheric cluster (left or right), for each ERP component independently. The number of frequent and infrequent phoneme trials included in the analysis were matched for each participant individually as there were fewer number of trials for infrequent sounds. This was done by
randomly selecting trials from the frequent condition to match the number of trials from the infrequent condition, in each participant individually. This ensured that trials were not unnecessarily removed for some participants who had a larger number of infrequent trials. Appendix 10.1 shows the mean number of frequent and infrequent trials per group. There were no significant differences between the groups in terms of the number of surviving trials.

Descriptive statistics were used to explore the data. Data were also explored for normality using histograms and tested using the Shapiro Wilk test of normality (for small sample size). Given a violation of the homogeneity of variance assumption, non-normally distributed data, and small and unequal sample sizes of all three groups, non-parametric statistics were computed in order to discover group or condition effects on the ERP mean amplitudes. For this purpose, Kruskal-Wallis analyses were conducted. For the post-hoc analyses, Mann-Whitney U tests with uncorrected p-values were used to uncover the pairwise differences, and calculate effect size ($r$). For the non-parametric analyses, medians and interquartile ranges (IQR) are reported.

Wilcoxon analyses were also conducted to explore differences in mean amplitudes for frequent versus infrequent responses within-groups, as well as for analysing longitudinal data investigating age-related maturation of each ERP component.

Finally, non-parametric Spearman’s rank-order correlations were conducted to measure the strength and direction of association between key speech and language scores measured behaviourally at time-point 4, and ERP mean amplitudes measured at both time-points 3 and 4, separately.
5.3 Results

Following separate pre-processing of the data from the two EEG nets, final ERPs were combined for the following analyses. Figure 5.7 shows the ERP waveforms for all conditions and groups combined, and the time windows of interest around each component, for each time-point, and the two nets/caps used.
Figure 5.7 ERP waveforms and the time windows of interest around each component, for each time-point, and the EEG net used

Note. A) time-point 3 using the 128 channel cap, B) time-point 3 using the 256 channel cap, and C) time-point 4 using the 256 channel cap. The waveforms are shown from the pre-stimulus (-200ms) to post-stimulus (800ms) time window. Grey boxes represent the time windows of interest around each component, where P50 = 30-70ms, N1 = 80-200ms, and P300 = 240-450ms. One HLHS patient had to be removed as an extreme outlier from each waveform A, B, and C, and a low-pass filter of 12Hz was applied for visualisation purposes for this figure only, to remove excessive noise from the waveforms.
5.3.1 Group Effects in Frequent vs Infrequent Phonemes

To address the first hypothesis, group differences were explored in mean amplitudes for frequent and infrequent speech sounds/phonemes (averaged across all electrodes in both hemispheres), in the P50, N1, and P300. In the analysis of mean amplitude of the P50 component for the oddball response, the main effect of group was not significant for frequent phonemes, $H(2) = 1.12, p = 0.57$, or infrequent phonemes, $H(2) = 0.01, p = 0.99$. The P50 did not appear to significantly differ between healthy controls and HLHS and TGA patients for either of the two conditions when exploring mean amplitude. Table 5.4 outlines the frequent and infrequent P50 mean amplitude median and interquartile range (IQR) for each group.

For the N1 component, there was no significant main effect of group for frequent phonemes, $H(2) = 1.00, p = 0.6$, or infrequent phonemes, $H(2) = 1.77, p = 0.41$. The N1 mean amplitude also did not appear to significantly differ between healthy controls and HLHS and TGA patients for either of the two conditions. Table 5.4 outlines the frequent and infrequent N1 mean amplitude median and IQR for each group.

For the P300 component, there was also no significant main effect of group for frequent phonemes, $H(2) = 2.90, p = 0.23$, or infrequent phonemes, $H(2) = 0.44, p = 0.80$. The P300 did not appear to significantly differ between healthy controls, and HLHS and TGA patients for either of the two conditions. The P300 mean amplitude median and IQR for each group can be found in Table 5.4.
Table 5.4 Mean amplitude median and interquartile range of each condition, component, and group

<table>
<thead>
<tr>
<th>Group</th>
<th>Component</th>
<th>Condition</th>
<th>Median (mean) Amplitude (µV)</th>
<th>IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy Controls (N = 16)</td>
<td>P50</td>
<td>Frequent</td>
<td>0.07</td>
<td>1.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infrequent</td>
<td>0.16</td>
<td>1.14</td>
</tr>
<tr>
<td></td>
<td>N1</td>
<td>Frequent</td>
<td>-0.13</td>
<td>3.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infrequent</td>
<td>-0.52</td>
<td>1.90</td>
</tr>
<tr>
<td></td>
<td>P300</td>
<td>Frequent</td>
<td>1.47</td>
<td>2.94</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infrequent</td>
<td>2.46</td>
<td>4.43</td>
</tr>
<tr>
<td>HLHS Patients (N = 8)</td>
<td>P50</td>
<td>Frequent</td>
<td>0.26</td>
<td>2.71</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infrequent</td>
<td>0.37</td>
<td>1.75</td>
</tr>
<tr>
<td></td>
<td>N1</td>
<td>Frequent</td>
<td>0.37</td>
<td>4.52</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infrequent</td>
<td>0.83</td>
<td>3.22</td>
</tr>
<tr>
<td></td>
<td>P300</td>
<td>Frequent</td>
<td>1.33</td>
<td>6.66</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infrequent</td>
<td>1.97</td>
<td>7.42</td>
</tr>
<tr>
<td>TGA Patients (N = 15)</td>
<td>P50</td>
<td>Frequent</td>
<td>0.28</td>
<td>1.74</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infrequent</td>
<td>0.65</td>
<td>1.66</td>
</tr>
<tr>
<td></td>
<td>N1</td>
<td>Frequent</td>
<td>-0.12</td>
<td>1.41</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infrequent</td>
<td>-0.29</td>
<td>1.76</td>
</tr>
<tr>
<td></td>
<td>P300</td>
<td>Frequent</td>
<td>0.66</td>
<td>1.96</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infrequent</td>
<td>1.76</td>
<td>3.73</td>
</tr>
</tbody>
</table>

Note. Median values are provided here, but these are group medians of the individual mean amplitudes of each participant, which is the ERP measure of interest here, hence, median (mean) amplitude.

5.3.2 Within-group Oddball Effect

To address the second hypothesis, within-group Wilcoxon analyses were conducted to explore the classic oddball effect (i.e. higher mean amplitudes of the P50, N1, and P300 for the infrequent compared to frequent stimuli) in each group, for each component. In the healthy control group, the main effect of condition was not significant for the P50 component ($T = 101$, $z = -1.71$, $p = 0.09$, $r = -0.43$), the N1 component ($T = 79$, $z = -0.57$, $p = 0.57$, $r = -0.14$), or the P300
component \((T = 77, z = -0.47, p = 0.64, r = -0.12)\). The healthy controls did not have higher mean amplitudes for the infrequent compared to the frequent phonemes in any of the components of interest.

For the oddball effect in the HLHS group, the main effect of condition was not significant for the P50 component \((T = 14, z = -0.56, p = 0.58, r = -0.20)\), the N1 component \((T = 18, z = 0, p = 1.00), r = 0\), or the P300 component \((T = 18, z = 0, p = 1.00, r = 0)\).

For the oddball effect in the TGA group, the main effect of condition was not significant for the P50 component \((T = 60, z = 0, p = 1.00, r = 0)\), the N1 component \((T = 50, z = -0.57, p = 0.57, r = -0.15)\), or the P300 component \((T = 88, z = -1.59, p = 0.11, r = -0.41)\). Therefore, both the CHD patient groups also did not have higher mean amplitudes for the infrequent compared to the frequent phonemes in any of the components of interest. Appendix 10.2 contains the auditory oddball ERP waveforms for each group and each condition.

### 5.3.3 Phoneme ERPs and Language Abilities

To address the third hypothesis, the relationship between ERPs for speech sounds/phonemes and behavioural measures of speech and language was explored. Due to the wide variety of speech and language measures used behaviourally (discussed in Chapter 4), as well as different combinations of mean amplitude ERPs, specific variables were selected to minimise the number of correlations performed. Rhyme Detection and Letter Knowledge scores from the Phonological Abilities Test (PAT) were selected based on the key role they play in pre-reading skills and given that the ERP oddball task involved phonemes. The Expressive One-Word Picture Vocabulary Test (EOWPVT) score and the
Expressive Language score from the CELF-P2 were also selected given that they assess speech and spoken language. However, these two latter scores were strongly significantly positively correlated \( r = 0.83, p < 0.001 \), so the EOWPVT was taken forward for analyses given that it focuses on one-word expression.

For the ERPs, an average mean amplitude was calculated for all components, and conditions combined, for each participant, to create a general overall ERP response to phonemes. Based on left-hemisphere lateralisation of language, average mean amplitudes were also calculated for each component, combining both the frequent and infrequent conditions measured in the left hemisphere clusters. This was to obtain a left hemisphere specific ERP response to phonemes.

Spearman’s correlations were conducted to explore the relationship between these four ERP measures (i.e. overall ERP response and left hemisphere ERP response, measured at time-points 3 and 4, separately) and Rhyme Detection, Letter Knowledge, and EOWPVT language scores. Table 5.5 shows the results of the Spearman’s correlations for all participants (CHD patients and healthy controls), for the two time-points. Overall, there were no significant correlations between any of the variables, at either time-point. Mean amplitude ERPs for phonemes were not associated with scores of phonological ability or one-word expressive language. Figure 5.8 shows the correlations between overall ERP and Rhyme Detection, Letter Knowledge, and EOWPVT language scores, at time-point 4.
Table 5.5 Spearman’s correlation coefficients between key speech and language outcomes measured behaviourally and ERPs measured at time-points 3 and 4

<table>
<thead>
<tr>
<th></th>
<th>EOWPVT</th>
<th>PAT Rhyme Detection</th>
<th>PAT Letter Knowledge</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time-point 3 ERPs</strong> (N = 16)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall ERP</td>
<td>-0.35</td>
<td>0.11</td>
<td>0.10</td>
</tr>
<tr>
<td>P50 Left Hemisphere</td>
<td>0.19</td>
<td>0.27</td>
<td>-0.19</td>
</tr>
<tr>
<td>N1 Left Hemisphere</td>
<td>-0.46</td>
<td>-0.27</td>
<td>-0.29</td>
</tr>
<tr>
<td>P300 Left Hemisphere</td>
<td>-0.40</td>
<td>0.12</td>
<td>-0.02</td>
</tr>
<tr>
<td><strong>Time-point 4 ERPs</strong> (N = 24)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall ERP</td>
<td>-0.04</td>
<td>-0.09</td>
<td>0.01</td>
</tr>
<tr>
<td>P50 Left Hemisphere</td>
<td>-0.11</td>
<td>-0.26</td>
<td>-0.11</td>
</tr>
<tr>
<td>N1 Left Hemisphere</td>
<td>-0.10</td>
<td>-0.27</td>
<td>-0.27</td>
</tr>
<tr>
<td>P300 Left Hemisphere</td>
<td>-0.02</td>
<td>-0.14</td>
<td>-0.11</td>
</tr>
</tbody>
</table>

*Note.* EOWPVT = Expressive One-Word Picture Vocabulary Test, PAT = Phonological Abilities Test, overall ERP = average mean amplitude of all components and conditions combined, and left hemisphere = average mean amplitude of left hemisphere cluster, combining frequent and infrequent conditions.
5.3.4 Longitudinal Analysis

To address the final hypothesis, age-related maturation of the oddball response was explored in each component between the two time-points, separately for each group. In the healthy control group, the main effect of time-point was not significant for any of the components (i.e. P50, N1, or P300), in the infrequent or frequent phoneme conditions. There were also no significant main effects for either condition in the HLHS and TGA patients.

There was no age-related maturation in the groups, for any of the components. Mean amplitudes for each component did not increase for infrequent or frequent
phonemes in the later time-point, compared to the earlier time-point. Table 5.6 shows the results of the Wilcoxon longitudinal analyses, and the mean amplitude median and IQR of each condition and component, at each time-point.

Table 5.6 Wilcoxon results for longitudinal speech sound ERPs, between time-points 3 and 4 (T3 and T4), by condition and component, within-groups

<table>
<thead>
<tr>
<th>Component</th>
<th>HLHS (N = 3)</th>
<th>TGA (N = 9)</th>
<th>Controls (N = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P50 Component</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequent</td>
<td>T3 = 0.36 (4.84)</td>
<td>T3 = 0.40 (2.02)</td>
<td>T3 = 1.28 (0.84)</td>
</tr>
<tr>
<td></td>
<td>T4 = 1.69 (1.08)</td>
<td>T4 = -0.11 (1.78)</td>
<td>T4 = -0.05 (0.69)</td>
</tr>
<tr>
<td>z</td>
<td>= -0.54</td>
<td>= -0.53</td>
<td>= -1.83</td>
</tr>
<tr>
<td>p</td>
<td>= 0.59</td>
<td>= 0.59</td>
<td>= 0.07</td>
</tr>
<tr>
<td>Infrequent</td>
<td>T3 = 2.60 (4.02)</td>
<td>T3 = 0.14 (1.66)</td>
<td>T3 = 1.41 (3.79)</td>
</tr>
<tr>
<td></td>
<td>T4 = 0.08 (0.36)</td>
<td>T4 = 0.65 (1.56)</td>
<td>T4 = 0.08 (2.25)</td>
</tr>
<tr>
<td>z</td>
<td>= -1.60</td>
<td>= -0.42</td>
<td>= -1.46</td>
</tr>
<tr>
<td>p</td>
<td>= 0.11</td>
<td>= 0.68</td>
<td>= 0.14</td>
</tr>
<tr>
<td>N1 Component</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequent</td>
<td>T3 = 2.72 (6.67)</td>
<td>T3 = -0.23 (1.40)</td>
<td>T3 = -1.14 (5.01)</td>
</tr>
<tr>
<td></td>
<td>T4 = 0.42 (1.75)</td>
<td>T4 = 0.01 (2.42)</td>
<td>T4 = 0.88 (4.00)</td>
</tr>
<tr>
<td>z</td>
<td>= -0.54</td>
<td>= -0.65</td>
<td>= -0.37</td>
</tr>
<tr>
<td>p</td>
<td>= 0.59</td>
<td>= 0.52</td>
<td>= 0.72</td>
</tr>
<tr>
<td>Infrequent</td>
<td>T3 = 2.84 (5.39)</td>
<td>T3 = -0.04 (2.52)</td>
<td>T3 = 1.35 (5.05)</td>
</tr>
<tr>
<td></td>
<td>T4 = 0.54 (1.14)</td>
<td>T4 = -0.34 (1.89)</td>
<td>T4 = -0.39 (3.26)</td>
</tr>
<tr>
<td>z</td>
<td>= -1.60</td>
<td>= -0.65</td>
<td>= -1.46</td>
</tr>
<tr>
<td>p</td>
<td>= 0.11</td>
<td>= 0.52</td>
<td>= 0.14</td>
</tr>
<tr>
<td>P300 Component</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequent</td>
<td>T3 = 2.78 (13.64)</td>
<td>T3 = 1.21 (2.77)</td>
<td>T3 = 1.68 (6.38)</td>
</tr>
<tr>
<td></td>
<td>T4 = 1.81 (4.32)</td>
<td>T4 = 0.47 (4.37)</td>
<td>T4 = 2.90 (10.37)</td>
</tr>
<tr>
<td>z</td>
<td>= -0.54</td>
<td>= -0.54</td>
<td>= 0</td>
</tr>
<tr>
<td>p</td>
<td>= 0.59</td>
<td>= 0.59</td>
<td>= 1.00</td>
</tr>
<tr>
<td>Infrequent</td>
<td>T3 = 4.52 (12.55)</td>
<td>T3 = 1.76 (2.66)</td>
<td>T3 = 4.69 (4.87)</td>
</tr>
<tr>
<td></td>
<td>T4 = 0.24 (2.82)</td>
<td>T4 = 1.92 (3.03)</td>
<td>T4 = 2.94 (8.89)</td>
</tr>
<tr>
<td>z</td>
<td>= -0.54</td>
<td>= -1.01</td>
<td>= -0.37</td>
</tr>
<tr>
<td>p</td>
<td>= 0.59</td>
<td>= 0.31</td>
<td>= 0.72</td>
</tr>
</tbody>
</table>

Note. Statistically significant differences between the time-points are denoted as *p<0.05, **p<0.01, and ***p<0.001.
5.3.5 Exploratory Analyses - Hemispheric Speech Sound Processing

Exploratory analyses were conducted to further explore the ERP data, specifically looking at hemispheric differences and ear stimulation effects.

To explore hemispheric and ear stimulation differences in speech sound processing, all frequent and infrequent sounds were collapsed together to create overall speech sound mean amplitudes for each component separately. There was a significant main effect of group in the P50 component for phonemes presented to the left ear and measured in the left (ipsilateral) hemisphere cluster, $H(2) = 6.63, p = 0.04$. Post-hoc Mann Whitney tests were used to examine significant interactions between groups. The healthy controls had lower mean amplitude (median = -0.57 and IQR = 1.23) compared to the HLHS group (median = 1.00 and IQR = 2.73), this difference was statistically significant, $U = 29, z = -2.14, p = 0.03, r = -0.44$. The TGA group also had lower mean amplitude (median = -0.32 and IQR = 2.00) than the HLHS group (median = 1.00 and IQR = 2.73), this difference was statistically significant, $U = 21, z = -2.52, p = 0.01, r = -0.52$.

There were no other significant main effects or interactions in the N1 or P300 components.

5.4 Discussion

The primary aim of this chapter was to examine the brain network supporting speech sound processing in children with CHD. The approach was to investigate whether there are predictive biomarkers of delays and/or impairments in early
language skills, mainly targeting changes in amplitude of the P50, N1, and P300 components.

It was hypothesised that there would be significant group differences in the mean amplitudes for frequent and infrequent speech sounds in the P50, N1, and P300, reflecting atypical speech sound processing in the CHD patients. The results did not support this hypothesis. All of the main components of interest showed no statistically significant group differences in mean amplitude between the frequent and infrequent conditions. This suggests that patients with CHD do not process speech sounds differently to the healthy controls, in terms of mean amplitude.

This finding differs from that of Guan et al. (2011) who reported that children aged 6-13 years with CHD had lower P300 amplitude in Fz and Cz, in response to an auditory oddball task involving tones, compared to healthy controls, which they interpreted as poorer information processing. This is one of the only other studies to investigate auditory processing in children with CHD using ERPs. Importantly, there are several differences between the current study and Guan et al.’s (2011) study which may explain the differing results. Firstly, their participants were older than the current cohort; secondly, they measured P300 in medial electrodes including Cz, whereas the current study used Cz as the reference electrode; and finally they used tones as opposed to phonemes.

Based on previous literature from other clinically relevant groups (e.g. preterm children, SLI, and dyslexia), it was plausible to assume that both HLHS and TGA patient groups would have smaller mean amplitudes of the P50, N1, and P300 for the infrequent stimuli compared to the frequent stimuli. Smaller mean amplitudes reflected as less negativity in the N1 or less positive P50 and P300 for the infrequent stimuli may have reflected impaired or atypical speech processing, but the results here do not provide evidence for this. It is noteworthy
that this was the first study of its kind to explore neural markers of speech sound processing in children with complex CHD, using ERPs.

5.4.1 Within-Group Oddball Effect

The auditory oddball effect or novelty detection was also investigated within groups in order to identify if each group was showing the classic oddball evoked response. It was hypothesised that the healthy controls would show higher amplitudes of the P50, N1, and P300 for the infrequent stimuli compared to frequent stimuli. This is in contrast to the CHD patients who it was anticipated would show a reduced or different oddball effect. However, the results have not confirmed this hypothesis as there were no significant differences between the two conditions (i.e. frequent and infrequent) in any of the components. This is especially surprising in the control group as it demonstrates that they did not have the anticipated classic oddball response. Group medians of mean amplitudes were visually inspected to identify patterns suggestive of the oddball effect, despite differences not being statistically significant. Visual patterns do emerge from the median (mean) amplitudes in Table 5.4. Firstly, in the P50, all three groups had higher mean amplitude for the infrequent speech sounds compared to the frequent speech sounds, despite this not being statistically significant. Importantly, in the healthy controls, there was a medium to large effect size, suggesting that there may be differences between the frequent and infrequent conditions, but the sample may not be large enough for this to be significant. The P50 reflects “sensory gating” which is the brain’s ability to detect novel stimuli whilst inhibiting processing of repetitive, non-informative sensory stimuli. Given that all three groups have larger evoked responses for infrequent stimuli, there does appear to be some “gating” of the irrelevant frequent stimuli, which reflects
novelty detection (Boutros et al., 1995). However, given that these differences were not statistically significant they are interpreted with caution.

Similar patterns are observed in the N1 component where all three groups have larger evoked responses for infrequent compared to frequent stimuli. The N1 peak signals the detection of abrupt changes in sensory input and processing of potentially informative (unexpected) events (Luck, 2014). However, given that differences between the two conditions were not significant and the effect size was small in each group, this is interpreted with caution. Importantly, N1 is a downward deflection from the previous component, and is anticipated to have greater negativity in response to infrequent stimuli. In the HLHS group, the N1 had a positive rather than negative peak which may be due to a more positive P50 amplitude which prevents N1 negativity, or because mean amplitude is measured relative to the baseline. Future studies should dissociate the effect of the previous component on the N1 with a peak-to-peak analysis.

Again, in the P300 component, all three groups had larger evoked responses (i.e. greater positivity) for infrequent speech sounds, compared to frequent speech sounds. Larger P300 amplitude reflects increased attention to a task, and the context-updating hypothesis suggests that working memory and active awareness also play a role in updating target (i.e. infrequent) stimulus probability (Luck, 2014). Although the main effect of group was not significant, there is substantial literature focussing on increased attentional problems in children with HLHS which may explain the smaller difference between the two conditions and the greater variability in P300 evoked responses (i.e. IQR) in this group. Several authors have reported increased incidence of inattention, hyperactivity, and ADHD in children with HLHS (Brosig et al., 2013; Hovels-Gurich et al., 2007;
Mahle et al.; 2000; McCusker et al., 2013). This is also discussed in the current cohort in Chapter 6.

The absence of significant differences between conditions may be explained by the muted cartoon participants watched to avoid movement artefacts during EEG recording. Consequently, the current oddball paradigm was a passive rather than active task which is likely to have reduced evoked responses to infrequent stimuli. This is especially relevant for the temporoparietal P300 as it reflects the extent of resources allocated to processing an unexpected stimulus (Winterer et al., 2003). The P300 is also commonly largest at parietal and central electrode locations (Triantafyllou et al., 1992), but in the present study it was measured from temporal clusters due to the auditory speech stimuli used, and the replication of the methodology used by Day (2017) in preterm children.

5.4.2 Phoneme ERPs and Language Abilities

The relationship between ERPs for phonemes and behavioural measures of speech and language was explored. It was hypothesised that speech sound ERPs would be associated with scores of phonological abilities (i.e. rhyme detection and letter knowledge) and expressive language. The present findings do not support this hypothesis. Despite carefully selected scores of phonological abilities and one-word expression given that the ERP oddball task involved phonemes, no significant correlations were observed between ERPs and behavioural measures of language skills. ERPs from time-points 3 and 4 were correlated separately with the behavioural measures of speech, in order to investigate whether earlier ERPs would be associated with later speech skills, and therefore, hold some predictive value; and then whether concurrent ERPs
and speech skills were associated with one another. However, no ERPs from either time-point were significantly correlated with any of the behavioural language scores. This is somewhat surprising given that the ERP task involved phonemes, and the language scores selected involved phonological awareness. However, this lack of association may be explained by the fact the ERP task was passive so participants were not actively processing or attending to the phonemes they were listening to. There is no previous literature exploring this in children with CHD, and more research is needed to further investigate this. Findings from typically developing children and those with SLI have shown there are ERP indicators of phonological awareness, including latencies and amplitudes, using different ERP components to reflect phonological awareness, such as the MMN, N400 and an earlier N240 (Bishop et al., 2007a; Hämäläinen et al., 2018). However, recent reviews and studies have indicated that there are no clear correlations between behavioural and neural measures for phonological processing, which highlights the importance of including neurocognitive methods when investigating language and pre-reading skills (Coch, 2021; Stekić et al., 2023). This provides some support for the lack of correlations found in the present study.

5.4.3 Longitudinal Analysis

A secondary aim of the current ERP study was to investigate age-related maturation of the network which supports speech sound processing, by assessing changes in mean amplitude between time-points longitudinally. It was hypothesised that healthy controls would show normal age-related maturation with increases in P50, N1, and P300 amplitude over time, compared to children with CHD. The results revealed no statistically significant differences in mean
amplitude of any of the components of interest between the two time-points, in each of the groups. Therefore, this hypothesis is not supported.

Based on the participants being aged between 3-5 years-old between the two time-points, literature has suggested that mean amplitudes should increase relative to age in all the components (Brinkman and Stauder, 2007; Bruneau et al., 1997; McArthur and Bishop, 2002; van Dinteren et al., 2014; Tsai et al., 2012). However, this pattern of age-related maturation was not observed between the two time-points in the current cohort. An explanation for these findings may be that the difference of age was not large enough between the time-points to observe any significant maturation. Perhaps the gap between longitudinal testing needs to be larger than a year, as it was in the current study, to allow for maturational effects to be observed. For example, Brinkman and Stauder (2007) found that children aged 5-7 years had smaller P50 amplitudes and therefore showed less sensory gating compared to older children aged between 8-9 years and 10-12 years. However, given the other results from the current study and the extremely small longitudinal sample, these results are again interpreted with caution. It is noteworthy that, to the authors knowledge, this was the first study to explore age-related maturation of these components in relation to speech sound processing in patients with CHD.

5.4.4 Exploratory Analyses

Based on the lack of significant results throughout this study, some exploratory analyses were conducted post-hoc in order to further examine the data. Consequently, there were no a-priori hypotheses for these analyses. Instead, analyses specifically aimed to explore hemispheric lateralisation and ear of
stimulation, regardless of frequent or infrequent phonemes. There was a significant main effect of group in the P50 component for phonemes presented to the left ear and measured in the left (ipsilateral) hemisphere. Both healthy controls and TGA patients had significantly lower mean amplitude compared to the HLHS patients. There were no other significant main effects or interactions in the N1 or P300 components. These findings suggest that in the P50, children with TGA appear to process phonemes in a similar way to healthy controls in that they have smaller responses in the hemisphere ipsilateral to ear stimulation compared to children with HLHS. Again, these results are interpreted with caution given the limitations of the current study. There is no previous research within the CHD literature with which to compare these findings. However, Day (2017) used the same ERP auditory paradigm in children born very preterm and reported that in the P300, frequent sounds presented to the left ear elicited greater mean amplitude in the ipsilateral hemisphere of the preterm infants compared to the controls who had larger contralateral responses. Day (2017) did not look at the P50 component, so it is unknown whether a similar pattern would have been observed in that component in the preterm infants.

5.4.5 Limitations

There are several limitations of the present study and hence the data are interpreted with caution. The first and most obvious limitation is the small sample size, particularly for the longitudinal analyses. This factor is discussed in detail in the General Discussion (Chapter 8) as it is relevant to all chapters within this thesis. However, it is worth mentioning that the sample size for the ERP study was smaller than that of the other studies, given that a smaller proportion of the whole cohort was able to overcome apprehension over the EEG cap, and other
requirements including remaining still and not being able to communicate for the duration of the 12 minute experiment. The lack of significant results may be explained by the extremely limited sample size, which also restricted the analyses which could be conducted, and was the main reason for combining data from time-points 3 (3-4 years) and 4 (4-5 years) to maximise the sample; this may itself have created extra noise and variation in the data.

Secondly, children were allowed to watch a silent cartoon during the ERP experiment, making it a passive task. This is likely to have resulted in smaller responses in each component and reduced difference between frequent and infrequent conditions. However, an active ERP task was not used due to methodological limitations such as the requirement for only using correct responses, increased movement artefacts due to a response such as a button-press, and the known motor impairments commonly experienced by children with CHD. These factors could have potentially reduced data further and increased variability.

Thirdly, the P300 is maximally recorded in fronto-central electrodes, but in the current study it was measured in temporal clusters. Therefore, it is plausible to assume that the response may have been more subtle in response to infrequent sounds, and potentially lost due to the current topography of the P300 component. This may explain why no significant differences were observed between P300 mean amplitude for frequent and infrequent phonemes, within-groups.

ERP data were also potentially compromised due to the number of damaged electrodes/channels in the 256 net which had to be permanently removed. Therefore, the selected temporal clusters did not always include all the electrodes neighbouring T3, T4, T5, and T6, as they had been removed. This also meant
that the distribution of surviving electrodes was not even across the scalp, and
the average reference could not be used. As a result, Cz was used but this is
problematic too as some components have larger peaks at the vertex. For
example, N1 is maximally recorded at frontocentral sites including midline
electrodes such as Cz. This may explain the lack of significant findings in this
study as task-related activity was expected in the Cz, but this was used as the
reference electrode and it would be preferable to use a more neutral reference
electrode such as mastoids.

Another major limitation is the lack of non-speech sounds in the oddball
paradigm. This would serve as a comparison and enable a distinction to be made
between speech-specific ERP responses, compared to non-speech sounds such
as tones. The ERP literature has widely reported the use of tones and speech
sounds in oddball paradigms, but it would be useful to include both as two
separate paradigms in order to know whether ERP responses differ for speech
sounds compared to tones in CHD. This may be challenging to do given the
current cohort and their age, as the current paradigm was already 12 minutes
long and many children were unable to complete the task.

Finally, given that the ERP task involved listening to speech sounds, it would
have been helpful to specifically ask parents about hearing problems as this may
affect task performance. All children were asked if they could hear the speech
sounds at the beginning of the task and the volume in the headphones was
adjusted accordingly. However, a formal note was not made about hearing
problems prior to the ERP study and some parents did mention in parental
questionnaires which were only seen post-assessment that their child had glue
ear when they were younger. Hearing problems are common in the CHD
literature, specifically in children with HLHS where the prevalence of hearing loss ranges from 22-29% in pre-schoolers (Grasty et al., 2018; Robertson et al., 2012).

5.4.6 Conclusion and Future Research

To the authors knowledge, this was the first study to explore speech sound processing in children with CHD, to relate ERPs/functional measures of speech sound processing to behavioural measures of language, and to study this longitudinally to allow exploration of age-related maturation of the brain network supporting speech sound processing in patients with CHD. The findings revealed that children with complex CHD do not process phonemes presented in an oddball paradigm differently to healthy controls. Surprisingly, the classic oddball response of higher mean amplitude for infrequent compared to frequent sounds was not observed in any of the children, including the healthy controls. This puts into question the reliability of this specific task and the results presented here, in spite of the fact that it has previously been used successfully. The present study also did not find a significant association between ERPs and behavioural measures of speech and language, as well as not finding evidence of age-related maturation in the brain network supporting speech sound processing i.e. increased mean amplitude between two longitudinal time-points.

It is noteworthy that the oddball task was passive, the sample size was limited and further work is needed to improve the exploration of speech processing in children with CHD using ERPs. Future research should focus on increasing the number of trials and/or decrease the number of infrequent stimuli to increase the novelty detection response. Research has suggested that a higher infrequent to frequent phoneme ratio results in larger ERP responses, as well as binaural
presentation of stimuli (Näätänen and Winkler, 1999). It would also be beneficial to include non-speech sounds such as tones to investigate whether there is differential processing for speech sounds compared to tones in children with CHD. Further investigation into hemispheric lateralisation and ear stimulation is also needed, and latency measures are necessary for this (as opposed to mean amplitude) in order to explore interhemispheric transfer during speech sound processing. This would be particularly important given the literature and what is known about white matter damage in CHD, including the corpus callosum which is key to hemispheric transfer. Finally, it would be interesting to investigate ERP markers of speech sound processing and then relate them to behavioural measures of attention and executive function. This is important given the oddball paradigm involves attentional processing, and the fact that attentional problems and executive dysfunction are common in children with CHD (which will be discussed in Chapter 6). These problems are likely to influence speech sound processing in an oddball paradigm.
Chapter 6: Parent-Reported Child Behavioural, Psychosocial and Quality of Life Status

This chapter focusses on parent-reported outcomes measures of child behaviour including social-emotional development and adaptive behaviour, executive functioning, psychosocial outcomes, and quality of life. The status of these skills are examined in children with CHD compared to healthy controls. Some of these measures have been used longitudinally in the preschool years (e.g. time-point 3), whilst others were only used in the early school years at time-point 4, and data are presented accordingly.
6.1 Introduction

Advances in surgical techniques and postoperative medical treatment have led to prolonged life expectancy of children with complex CHD. Despite this, children with CHD suffer from morbidities which significantly affect neurodevelopmental, psychosocial, and physical functioning, subsequently impacting their overall quality of life (QoL) (Kharitonova & Marino, 2016). Psychosocial outcomes encompass a range of domains such as emotions, feelings, behaviour, social interactions, relationships, self-esteem, and social cognition (including theory of mind) (Abda et al., 2019; Goldman, 2012). These are all important aspects of personal development in childhood and adolescence. QoL is difficult to define given that it is a subjective concept based on an individual’s perception of their own or others’ physical, social, emotional and cognitive functioning (Latal et al., 2009). Traditionally, QoL in CHD was based on objective measures of health outcomes such as cardiopulmonary exercise capacity, exercise tolerance, breathlessness, and common physical disorders such as leg cramps (Casey et al., 1994). However, more recently, it has been recognised as being a multidimensional construct which includes three crucial domains: physical health status and physical functioning; psychological status; and social functioning (Marino et al., 2016; Verrall et al., 2019). With respect to health, QoL refers to the influence of a specific illness, medical therapy, and/or health service on a patient’s ability to function and derive personal satisfaction from physical, psychological, and social life contexts (Marino et al., 2016). This will be referred to as health-related QoL (HRQOL) hereafter, with respect to CHD.
6.1.1 Psychosocial Profile in CHD

A multitude of outcome studies and recent systematic reviews have highlighted psychosocial vulnerabilities and adjustment difficulties in individuals with CHD across the lifespan. PPI work (detailed in Chapter 2, section 2.4) conducted in preparation for this study indicated that key areas of parental concern included behavioural problems, social and emotional development, and increased risk of attention-deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) in children with complex CHD.

6.1.1.1 Emotional and Behavioural Status

Psychological challenges commonly experienced by children with CHD include internalising (e.g. depression, anxiety, and withdrawal) and externalising (e.g. aggression, disruption, hyperactivity, and inattention) behaviours (Jilek et al., 2021). Psychological concerns have been reported in early childhood and predictors of behavioural and emotional problems have been identified. The Child Behaviour Checklist (CBCL) has frequently been used in research to evaluate behavioural and emotional outcomes in children. Bonthrone et al. (2022) studied 43 toddlers in the UK with severe CHD and found that 28% had elevated internalising or externalising problems scores in the borderline or clinical range using the CBCL. They also identified significant associations between reduced frontal-limbic structural connectivity and integration of the right inferior frontal gyrus pre-surgery, and elevated externalising symptoms at 22 months. However, internalising symptoms were associated with earlier surgery in the neonatal period or the final palliative surgery (in the case of HLHS patients), but not brain connectivity. In their study conducted in Wisconsin, Jilek et al. (2021) found that
the incidence of internalising problems was higher in children aged 2-3 years with CHD compared to the general population. Lower Bayley-3 language composite scores at 12 months significantly predicted clinical CBCL internalising, externalising, and total problems scores at 24-36 months. Lower maternal education level also significantly predicted these CBCL scores. These findings suggest that children with CHD are at increased risk of emotional and behavioural regulation impairments, even from early childhood. That said, relatively little is known about the onset and trajectory of emotional and behavioural development in children with CHD. It is also noteworthy that both these studies include mixed CHD diagnoses, including but not limited to HLHS and TGA. Further, Jilek et al. (2021) did not exclude children with genetic conditions or chromosomal abnormalities, in contrast to Bonthrone et al. (2022), which makes comparison difficult.

A meta-analysis of 16 studies examining psychosocial outcomes in 916 children and adolescents (aged 6-18 years) with severe CHD concluded that 25% of participants had internalising behavioural problems, and 15% had externalising behaviour difficulties (Abda et al., 2019). Younger participants also had significantly more difficulty understanding the mental state of others. This suggests that internalising and externalising behavioural problems may persist throughout early childhood and adolescence. Recent reviews of the literature conclude that in addition to internalising and externalising behavioural problems, withdrawal, depression, anxiety, somatic, social, and attention problems have also been widely reported by parents of children with complex CHD (Dahlawi et al. 2020; Huisenga et al., 2020). Teacher-rated CBCL forms further reveal problematic adaptive functioning, social relationships, and school performance. However, when older children self-report, similar problems have not been
observed. In their systematic review, Huisenga et al. (2020) also found that ADHD was reported to be three to four times higher at school age than in the general population, based on parent and teacher ratings, as well as psychiatrists' diagnoses. They concluded that school-age children with complex CHD have similar problems to children with other chronic diseases, and there is similarity with children born very preterm. Shillingford et al. (2008) specifically investigated inattention and hyperactivity using the Behaviour Assessment System for Children, in 5-10 year-olds with complex CHD. They found that 30% had parent-reported scores of clinical significance for inattention, and 29% for hyperactivity. From the total sample of 109 children, 49% were receiving remedial academic services and 15% were placed in a special education classroom.

The Strengths and Difficulties Questionnaire (SDQ) is another questionnaire used to assess behaviours, emotions and relationships in children and young people. Unlike the studies discussed above, Werninger et al. (2020) found that 10 year-olds with CHD showed no significant general behavioural difficulties as measured by the parent- and teacher-reported SDQ, compared to healthy controls. They did, however, have increased ADHD-related symptoms and social interaction problems, with 23% having a combination of both. It is important to note that the SDQ is a brief screening questionnaire unlike the CBCL. Goodman and Scott (1999) compared the two questionnaires and found that scores were highly correlated, but the SDQ was significantly better than the CBCL at detecting inattention and hyperactivity, and equally as good at detecting internalising and externalising problems. In contrast, Warnick et al. (2008) concluded there were no significant differences between CBCL and SDQ scores within any of the domains evaluated, but for total problem scores the SDQ had better specificity and the CBCL had better sensitivity. Recently, Mansolf et al. (2022) confirmed
that scores from the two measures are highly correlated and attempted to create conversion tables to allow for easier comparison of scores between the two measures. Despite this, different findings within the literature using different measures highlights the challenges of selecting appropriate measures. It is important to understand the purpose of a given measure, as well as potential participant burden when selecting measures for use in children with CHD. For example, it may be better to use the SDQ as a screening tool in the first instance, and then use the CBCL if required for further more detailed evaluation.

The frequency and severity of neurodevelopmental and behavioural difficulties tend to increase with age, especially during middle and later primary school years. Kovacs and Bellinger (2021) suggest that this is most likely due to increasing demands for self-regulation and other executive skills, especially in the school setting. Problems that might emerge include time management, planning and organising, seeing the ‘big picture’ without getting lost in details, cognitive flexibility (e.g. multitasking), working memory, impulse control and anticipating future consequences. Parental ratings of behavioural problems in children with CHD also increase with age, and these concerns are more likely to be identified. However, it is unclear whether this is due to changes in child behaviours or the parents’ perceptions of the child behaviours (Bellinger and Newburger, 2010).

Many of the neurodevelopmental, psychosocial, and behavioural deficits first detected in childhood are unsurprisingly also present in adolescence and adulthood, often becoming more pronounced. In a recent systematic review, Ryan et al. (2019) outlined the psychosocial phenotype across the lifespan in complex CHD. During toddlerhood, children begin to exhibit internalising and externalising behavioural symptoms, and by school-age they have problems with
emotional comprehension, inattention, hyperactivity, and impulsivity. Then by adolescence and young adulthood, this develops further into impaired social interaction and social cognition, psychosocial maladjustment, internalising and externalising behaviours, increased incidence of psychiatric disorders (e.g. anxiety, depression, post-traumatic stress disorder), and decreased HRQOL. This provides support for the idea that children with CHD often grow into their deficits, many of which do not present until later in life. They also identified three specific modifiable risk factors impacting neurodevelopmental and psychosocial outcomes: environmental exposure to stress in early infancy, parental stress, and lack of standardised long-term follow-up and support for children and their families.

Research has previously suggested that children with cyanotic lesions have more behavioural and attention problems than children with acyanotic lesions (Dunbar-Masterson et al., 2001; Kirshbom et al., 2005). However, more recent research argues that it is children who have undergone palliative interventions or who have more severe CHD who are at increased risk for poor behavioural outcomes and psychosocial maladjustment (Howell et al., 2019; Latal et al., 2009; McCusker et al., 2007). Clancy et al. (2020) concluded that children with severe CHD or comorbid conditions experience greater impairment, with higher rates of externalising behaviour problems, although internalising behaviour problems were also evident. Further, Kovacs and Bellinger (2021) found that among adolescents with single-ventricle CHD, the frequency of any psychiatric disorder may be as high as 65%. This suggests that individuals with severe and complex CHD, such as those with HLHS, may be at high risk of psychosocial maladjustment, with those with other comorbidities being at the highest risk.
6.1.1.2 Adaptive Behaviour

Adaptive functioning or behaviour refers to comprehensive functional abilities that involve the practical skills necessary for daily living and environmental demands, including caring for oneself and interpersonal abilities (Harrison & Oakland, 2015). The Adaptive Behaviour Assessment System (ABAS), is a widely used questionnaire which assesses adaptive functioning (described in detail in Chapter 2 section 2.9.2.4.1.2.2) (Harrison & Oakland, 2003). It comprises questions examining ten adaptive skill areas including: Communication, Functional Academics, and Self-Care, and is particularly valuable for identifying individuals experiencing difficulties with daily functioning, which can impact their quality of life. Sananes et al. (2021) followed up 244 children from the original Single Ventricle Reconstruction Trial (SVRT, described in section 1.5.2) cohort at 6 years, and reported that 29% had adaptive skills scores in the at-risk or impaired range. These impairments at 6 years were poorly predicted by earlier assessments, and the developmental trajectory revealed worsening scores with age.

Tan et al. (2022) investigated adaptive functioning in 109 adolescents with complex CHD (including but not limited to HLHS and TGA), and their results revealed delayed functional skills which are integral for transition into adulthood. They found that 33-39% of the sample had scores ≥1 SD lower than the mean, and 16-23% had scores ≥2 SD below the mean. These clinically relevant impairments were found in six of the nine adaptive skills subtests: Community Use, Functional Academics (e.g. application of literacy in everyday life), Self-Care, Self-Direction (e.g. responsibility), and Social Skills. Lower adaptive skills were associated with biventricular CHD, increased use of services, lower intellectual and academic abilities, and developmental diagnoses. Overall, lower
adaptive functioning has been associated with lower QoL in children with severe CHD, particularly those with SV CHD such as HLHS (Goldberg et al., 2019).

### 6.1.1.3 Social Cognition

Social interactions require the use of social cognitive skills (e.g. affect recognition and theory of mind) which enables social competence (Gaudet et al., 2022). Possessing appropriate social skills is essential for developing and sustaining meaningful relationships, which in turn impact psychological well-being and QoL, and in children social functioning is associated with school readiness. Kovacs and Bellinger (2021) described higher rates of ASD and poorer social cognition skills in individuals with CHD compared to their healthy peers. They also highlighted the interaction between neurocognitive and psychosocial functioning. A recent review also found twice as many children with complex CHD had a diagnosis of ASD compared with the general population (Huisenga et al., 2020).

Gaudet et al. (2022) characterised the sociocognitive profile and assessed the contribution of language, executive functions (EF), and social cognition to social competence in 55 5 year-olds with CHD. They used a variety of standardised measures to assess these domains including the CELF-4 (language) and Developmental Neuropsychological Assessment (NEPSY-II) (EF) and social competence was assessed using the Paediatric Evaluation of Emotions, Relationships, and Socialisation Questionnaire. Children with CHD performed significantly worse than norms in language and theory of mind skills (i.e. social cognition), whereas EF and social competence were generally preserved. They concluded that children with CHD have a specific vulnerability in social cognition.
and language skills but not in social competence more generally, and that a combination of social cognition, language, and EF contribute to social outcomes.

6.1.1.4 Executive Dysfunction

Executive functioning (EF) encompasses three core components: inhibitory control, working memory, and cognitive flexibility, which serve as the foundation for higher-order EF including reasoning, planning, organisation, and problem-solving. (Cassidy, 2020). Various studies have reported deficits in EF in individuals with CHD, although to varying degrees of severity and with heterogeneity across investigations. The age at which executive dysfunction becomes observable is also a source of differing views in the literature. Some researchers have suggested executive dysfunction is observable in children with CHD from the preschool period onwards (Hovels-Gurich, 2007; Sanz et al., 2018), whilst others have argued that executive dysfunction becomes more prevalent and problematic during adolescence (Cassidy et al., 2021). A recent systematic review of 28 studies and 7789 individuals with CHD over the age of three years reported significant moderate deficits in EFs including cognitive flexibility, inhibition, working memory, planning/problem solving, and summary EF scores, compared to 8187 healthy controls (Jackson et al., 2021). This suggests that executive dysfunction is observable from preschool age onwards, throughout the lifespan. Executive dysfunction is also a strong predictor of academic achievement, psychosocial adjustment and HRQOL in children with complex CHD (Sanz et al., 2018), which can affect competence in adaptive skills and may further compromise the transition to adulthood.
Calderon et al. (2014) described significant delays in inhibition and cognitive flexibility, but normal working memory, in 5-7 year-olds with TGA, whereas Sanz et al. (2017) reported executive dysfunction in school-aged children with CHD aged 6-17 years, particularly for working memory and flexibility. The latter group also found that male gender, premature birth, and CHD with aortic obstruction were predictive of executive dysfunction. The discrepancy in results between these studies may be due to multiple reasons such as the heterogeneity of the CHD population studied including diagnosis and surgical procedure, and the use of different assessment measures. For example, Calderon et al. (2014) used separate specific measures for each component of EF such as the Day and Night task for cognitive inhibition and the Dimensional Change Card Sorting Test for cognitive flexibility, whereas, Sanz et al. (2017) used the parent- or primary caregiver-rated Behaviour Rating Inventory of Executive Function (BRIEF) for all EF components. This may explain their different findings as each of these measures and tasks may have different levels of sensitivity, in addition to differences between direct testing with the child and parent completed measures. Similarly, the study by Gaudet et al. (2022) described above used a single task from the NEPSY-II to measure EF which is known to be less clinically sensitive (McCormack & Atance, 2011) and also does not measure individual components of EF, which may explain why they failed to identify any problems in EFs.

### 6.1.1.5 The Role of Language

Language skills and social cognition are closely linked as social cognition is required for children to be able to acquire language, and once acquired, language becomes a useful tool for social cognition (Fitch et al., 2010). Hence, there appears to be an interdependent relationship between the two. Moreover,
pragmatic language and social skills are linked to capabilities of building peer relationships and difficulties in each of these are known to be prevalent in ASD, across a range of verbal and cognitive abilities (Sturrock et al., 2020). The Children’s Communication Checklist (CCC) was designed to enable the systematic assessment of pragmatic communication based on parental report, given that it is challenging to measure objectively, and pragmatic difficulties are often missed in other standardised language assessments (Bishop and Baird, 2001). The second edition (CCC-2) allows for the identification of children with pragmatic difficulties which are distinguishable from others with more typical language structure problems, as is the case in SLI, and the checklist also assesses behaviours which are characteristic of ASD (Bishop, 2003; Bishop, 2015). There are not many reports of CCC-2 outcomes in children with CHD, but in other clinical patients where CHD is also common such as Noonan and Williams Syndromes, children have been found to have pragmatic language difficulties and high rates of impairment (Mervis and Velleman, 2011; Selas and Helland, 2016).

Executive dysfunction has been reported in higher-order language skills such as narrative and pragmatic language tasks in children with CHD. In their review, Calderon and Bellinger (2015) reported that children with TGA fail to organise a given set of data, and fail to plan, structure, and modify appropriately based on feedback when given tasks involving the correct assembly of elements in a complex design, including story elements. They tended to get lost in the details and could not see how the elements combined to make a whole. Deficits in narrative discourse specifically reflect difficulties in pragmatic language skills which involve using language in the correct context, considering the listener’s needs, and following the conventions of conversation and story-telling (Bellinger
and Newburger, 2010). These skills are strongly linked to social skills. This provides support for the fact that language skills, social cognition, and EF are all linked as Gaudet and colleagues (2022) suggested, and together these may influence psychosocial adjustment and HRQOL in children with CHD.

6.1.2 Quality of Life

Children with CHD are at increased risk of impairments in emotional and behavioural outcomes, adaptive behaviour, social cognition, and executive dysfunction which can impact their overall HRQOL. Multiple studies have shown psychosocial adjustment problems and reduced HRQOL in children and adolescents with CHD (including those with TGA and HLHS) compared to the healthy population. Heart disease complexity is also associated with lower psychosocial HRQOL (Marino et al., 2010; Wray et al., 2014; 2018).

The Pediatric Quality of Life (PedsQL) is a generic measure of HRQOL (Varni et al., 1999) which has been used in many studies of healthy children and those with acute or chronic conditions, including CHD. Higher scores indicate better HRQOL, and scores 1SD below the normative mean indicate an ‘at-risk’ status for impaired HRQOL (Varni et al., 2003). Denniss et al. (2019) found that 60% of children (aged 1-5 years) with single ventricle CHD (i.e. HLHS) and 25% with biventricular repair (e.g. TGA among other types) had total PedsQL scores within the at-risk range. They concluded that lower HRQOL was significantly and strongly associated with single ventricle physiology, physical comorbidity, feeding difficulties, and greater maternal psychological stress, which accounted for 52% of the variance in HRQOL. Many of these predictors are potentially modifiable which offers plausible pathways for early intervention and prevention.
Dempster et al. (2018) and Goldberg et al. (2019) have also found evidence of significantly reduced overall HRQOL in children and adolescents with HLHS compared to healthy controls and those with other acute chronic illnesses. Predictors of worse psychosocial and QoL outcomes included sociodemographic factors, morbidities, CHD complexity, and the presence of neurological complications (e.g. stroke and seizures). Reich et al. (2017) investigated HRQOL in children with HLHS prior to their (final) Fontan procedure and unlike recent studies, they found that parents reported good QoL for their children. However, they did conclude that a complicated postoperative course requiring prolonged hospital stay and reinterventions are risk factors for impaired neurodevelopmental and QoL outcomes. The discrepancy in findings between these studies may be explained by the fact that patients had not had their final staged surgery in Reich and colleagues’ study, but 90-100% of the participants had in the other two more recent studies.

HRQOL has also been examined in children with TGA, and despite better outcomes compared to children with HLHS, the incidence of poorer HRQOL in this population is higher than would be expected in the general population. Robson et al. (2019) conducted the 16 year follow-up of the original Boston Circulatory Arrest Study cohort. They reported that patients with TGA had lower psychosocial and physical health as well as lower overall HRQOL compared to healthy controls. Attention problems at 8 years predicted worse psychosocial scores at 16 years.

It is clear that CHD severity and palliative interventions as well as a multitude of other factors can impact psychosocial outcomes, which subsequently influence overall HRQOL. A number of factors need to be considered when evaluating and discussing the psychosocial and HRQOL profile in children with CHD. These
include repeat hospitalisations, multiple heart surgeries, the need for invasive and non-invasive investigations, separation from caregivers and the family, and disruption to daily routines, which can all have a traumatic impact on the child (Wray, 2010). Therefore, a comprehensive approach is required in order to provide effective early interventions and adequate support for children with CHD. Evaluating long-term outcomes in children with CHD should include the assessment of HRQOL alongside neurodevelopmental outcomes, as these are likely to influence and impact one another (Denniss et al., 2019; Marino et al., 2016). Given that heart disease complexity and a combination of medical/clinical and demographic risk factors can influence a child’s neuropsychological outcomes (Costello et al., 2014; Marelli et al., 2016; McCusker et al., 2013; Wernovsky & Licht, 2016), it is possible that these risk factors impact physical and psychosocial outcomes too, which then subsequently influence overall HRQOL in CHD (Figure 6.1).

![Figure 6.1 The relationship between CHD and related morbidity factors impacting overall QoL, adapted from Marino et al. (2016)](image)
As discussed, a combination of factors including behavioural regulation, adaptive skills, social-emotional functioning, attention, EF, and higher-order language skills are all known to impact an individual’s psychosocial functioning and overall HRQOL. Despite increasing numbers of studies investigating psychosocial and QoL outcomes in older children, adolescents and young adults, research focusing on younger school-aged children is still limited. Based on the findings reported in the literature in relation to each of these factors and their impact on HRQOL in CHD, a number of hypotheses were tested in the current study.

6.1.3 Aims and Hypotheses

There were two main aims of the current study: firstly, to investigate social-emotional and adaptive behavioural skills and EF status, as well as HRQOL, and the association between these domains in 4-5 year-olds with CHD; and secondly, to identify whether early preschool scores are associated with later scores in the early school years. Secondary aims were to explore the role of language skills in behavioural outcomes.

The following hypotheses draw on a priori literature regarding HRQOL and address a gap in the literature between preschoolers and older school aged children with CHD with regards to social-emotional and adaptive behavioural skills and EF status, as well as examining the development of these skills longitudinally. It was hypothesised that:

- Children with complex CHD, particularly those with HLHS, will have an increased incidence of socioemotional and behavioural problems, and poorer adaptive behaviour and executive functioning, compared to healthy controls.
- Children with complex CHD, and particularly those with HLHS, will have poorer HRQOL scores, compared to healthy controls.
• Children with HLHS will have worse psychosocial profiles and scores and reduced overall HRQOL, compared to children with TGA.

• Core language, pragmatic language and narrative skills will be associated with parent-rated social skills and EF scores.

• CHD physiology, behavioural problems, adaptive behavioural skills, and executive dysfunction will be associated with poorer psychosocial functioning and reduced overall HRQOL.

Longitudinally:

• Earlier socioemotional, behavioural, and adaptive skills scores will be associated with later scores at 4-5 years of age.

6.2 Methods

6.2.1 Participants

The longitudinal cohort described in Chapter 4 were invited to take part in this study which was part of the fourth and most recent assessment time-point at 4-5 years of age. A total of 48 children were eligible to participate, one HLHS patient had died, one healthy control child withdrew from the study, and nine children were too young to be tested at this time-point so were not eligible. A further nine children could not be assessed in-person due to the COVID-19 pandemic during which data collection was stopped. However, parents of these nine children were sent the parental questionnaires to complete and return via email, at the beginning of the pandemic. Of these, four parents completed the questionnaires (including 2 parents of children with HLHS, one with TGA, and one healthy control), and five did not. This left a total sample of 32 children who participated in this part of the study at time-point 4. The full sample is summarised in Table 6.1.
Table 6.1 Patients with HLHS, TGA, and healthy controls who participated in the behavioural and psychosocial outcomes study at 4-5 years (time-point 4)

<table>
<thead>
<tr>
<th>Time-point 4</th>
<th>HLHS</th>
<th>TGA</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>7</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Age (years), Mean (SD)</td>
<td>5.09 (0.45)</td>
<td>5.28 (0.27)</td>
<td>5.23 (0.43)</td>
</tr>
<tr>
<td>Gender (M:F)</td>
<td>4:3</td>
<td>9:5</td>
<td>9:2</td>
</tr>
</tbody>
</table>

6.2.1.1 Longitudinal Participants

This chapter also includes data collected at previous time-points in order to examine the longitudinal trajectory of social-emotional and behavioural skills. This includes the parental Bayley-3 Social-Emotional and Adaptive Behaviour Questionnaire described in Chapter 3, and the Child Behaviour Checklist (CBCL). The CBCL was first given to parents when children were aged between 3-4 years (i.e. time-point 3), as described in Chapter 2, section 2.9.1.2, and more recently at the current time-point 4. Therefore, longitudinal data are available for some children using these measures of behavioural and socioemotional outcomes. Parents of 33 children (6 HLHS patients, 9 TGA patients, and 18 healthy controls) completed the Bayley-3 parent questionnaire at all time-points 1-3, and these are the children for whom longitudinal data are available. Parents of 27 children (6 HLHS patients, 11 TGA patients, and 10 healthy controls) completed the CBCL at both time-points 3 and 4, and these are the children for whom longitudinal CBCL data are available.
6.2.2 Procedure / Assessment

All assessments with children took place at the UCL Wolfson Centre, as detailed in Chapter 4. For this study, parents (most often mothers) were asked to complete a battery of questionnaires to evaluate their child’s behaviour, executive function, psychosocial development and HRQOL. They did this at the same time that their child was being assessed by the researcher. Parents were taken to the waiting room at the Wolfson Centre, or sat quietly in the testing lab where they were asked to complete each of the questionnaires. The questionnaire pack included the Child Behaviour Checklist (CBCL), Strengths and Difficulties Questionnaire (SDQ), Adaptive Behavior Assessment System (ABAS-2), Behavior Rating Inventory of Executive Function, preschool version (BRIEF-P), and the Pediatric Quality of Life Inventory (PedsQL) 4.0 Generic Core Scales (all detailed sequentially in Chapter 2 section 2.9.2.4.1). The time it took to complete all the questionnaires was estimated to be 1-1.5 hours, but this often varied depending on whether parents needed to support their child during testing, or if breaks were taken by the child or parent.

If parents were unable to complete all questionnaires during the assessment visit, they were given a freepost envelope to return any questionnaires completed at home. The researcher stressed the importance of completing all questionnaires as close in time to the assessment as possible.

6.2.3 Data Analysis

Descriptive statistics were used to characterise the sample, and data were tested for homogeneity of variance and distribution. Given the small and unequal sample sizes of all three groups and a violation of the homogeneity of variance
assumption and non-normally distributed data, non-parametric Kruskal-Wallis analyses were conducted to compare questionnaire scores between the three groups. For the post-hoc analyses, Mann-Whitney U tests with uncorrected p-values were used to uncover the pairwise differences and calculate effect size \( r \). For non-parametric analyses, medians and interquartile ranges (IQR) are reported.

Non-parametric Spearman’s rank-order correlations were conducted to measure the strength and direction of association between two ranked variables. Based on the previous literature reviewed, specific subtests across the parental questionnaires were selected to investigate the relationship between HRQOL and social-emotional and behavioural outcomes, and EFs. These included the PedsQL Psychosocial Summary and PedsQL Total scores, and CBCL Internalising Problems, Externalising Problems, and Total Problems, SDQ Total Difficulties, ABAS General Adaptive Composite (GAC), and BRIEF-P Inhibit, Working Memory, and Flexibility scores. Also, based on the literature, the relationships between Core Language scores from the CELF-P2, narrative recall scores from the Bus Story, and pragmatic language scores from the CCC-2 (i.e. Inappropriate Initiation, Stereotyped, Use of Context, and Nonverbal) (all discussed in Chapter 4), and the Social domain of the ABAS, PedsQL Psychosocial Summary, and BRIEF-P Inhibit, Working Memory, and Flexibility scores were also explored.

Correlational analyses were conducted to explore the relationships between the longitudinal parental Bayley-3 subscales scores and CBCL summary scores from time-points 3 and 4 to investigate possible associations between earlier and later assessment scores.
Finally, for the longitudinal CBCL data, non-parametric Wilcoxon Signed Ranks analyses were conducted to explore differences in CBCL subtest scores between time-points 3 and 4 within-groups.

6.3 Results

Parents of 32 children completed the questionnaires at the current time-point 4. This included 7 children with HLHS, 14 with TGA, and 11 healthy controls. To address the first three hypotheses, group differences in socioemotional and behavioural problems, adaptive behaviour, executive functioning, psychosocial functioning, and HRQOL were analysed. The median scores and interquartile range for each test/domain, and between-group results are presented separately for each measure/questionnaire below. Overall, at 4-5 years of age, children with HLHS had scores indicating poorer functioning on many of the tests/domains, compared to children with TGA and healthy controls.

The majority of group differences were observed between HLHS patients and healthy controls, and some between HLHS and TGA patients. Overall, between 14-71% of HLHS patients had scores within the clinical range (≥2 SDs below the mean) across the measures. Despite TGA patients scoring within the normal range on many of the tests as a group, several patients and a small proportion of healthy controls had scores within the borderline or clinical range. These results are also summarised below in separate tables to highlight the proportion of participants with scores 1-2 SD (i.e. borderline) and ≥2 SDs (i.e. clinical) below the normative range.
6.3.1 Behavioural Outcomes

6.3.1.1 CBCL

Significant group differences were observed in many subtests and summary scores of the CBCL, including Emotionally Reactive, Sleep Problems, Aggressive Behaviour, Externalising Problems, Total Problems, Depressive Problems, and Oppositional Defiant. Post-hoc Mann Whitney tests indicated that across many of the subtests, the HLHS group had significantly higher T-scores (indicating higher symptomology) compared to the Control group, and/or the TGA group. No significant group differences were observed in eight domains of the CBCL: Anxious/Depressed, Somatic Complaints, Withdrawn, Attention Problems, Internalising Problems, Anxiety Problems, ASD problems, and ADHD Problems.

Table 6.2 summarises the results for the CBCL. Table 6.3 summarises the proportion of children in each group with borderline or clinical CBCL scores. There were some CBCL subtests in which both patients with HLHS and TGA had scores within the clinical range, these included: internalising problems (3 out of 7 (43%) of HLHS patients and 14% of TGA patients) and ASD problems.

Table 6.2 Child Behaviour Checklist (CBCL) outcomes by subtest in children with HLHS, TGA, and healthy controls at 4-5 years

<table>
<thead>
<tr>
<th>CBCL Scale (median T-score (IQR))</th>
<th>HLHS</th>
<th>TGA</th>
<th>Controls</th>
<th>H</th>
<th>p</th>
<th>Post-hoc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syndrome Scales</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotionally Reactive</td>
<td>62 (18)</td>
<td>50 (6)</td>
<td>50 (1)</td>
<td>7.35</td>
<td>.03*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HLHS &gt; C: U = 14.00, z = -2.38, p = 0.03, r = -0.56</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HLHS &gt; TGA: U = 20.00, z = -2.30, p = 0.03, r = -0.50</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxious Depressed</td>
<td>66 (16)</td>
<td>50.50 (6)</td>
<td>50 (2)</td>
<td>3.03</td>
<td>.22</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 6.3 summarises the proportion of children in each group with borderline or clinical CBCL scores.
<table>
<thead>
<tr>
<th></th>
<th>HLHS</th>
<th>TGA</th>
<th>Controls</th>
<th>H</th>
<th>p</th>
<th>Post-hoc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatic Complaints</td>
<td>53 (8)</td>
<td>50 (8)</td>
<td>50 (3)</td>
<td>2.92</td>
<td>.23</td>
<td>-</td>
</tr>
<tr>
<td>Withdrawn</td>
<td>50 (13)</td>
<td>51 (10)</td>
<td>51 (13)</td>
<td>0.29</td>
<td>.87</td>
<td>-</td>
</tr>
<tr>
<td>Sleep Problems</td>
<td>62 (17)</td>
<td>50.50 (14)</td>
<td>50 (1)</td>
<td>6.93</td>
<td>.03*</td>
<td>HLHS &gt; C: U = 14.50, z = -2.39, p = 0.03, r = -0.56</td>
</tr>
<tr>
<td>Attention Problems</td>
<td>57 (9)</td>
<td>50.50 (7)</td>
<td>53 (3)</td>
<td>5.51</td>
<td>.06</td>
<td>-</td>
</tr>
<tr>
<td>Aggressive Behaviour</td>
<td>53 (13)</td>
<td>50 (0)</td>
<td>50 (1)</td>
<td>6.07</td>
<td>.05</td>
<td>HLHS &gt; TGA: U = 21.50, z = -2.35, p = 0.04, r = -0.51</td>
</tr>
<tr>
<td>Internalising Problems</td>
<td>61 (14)</td>
<td>46 (24)</td>
<td>41 (20)</td>
<td>4.77</td>
<td>.09</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>54 (18)</td>
<td>43 (14)</td>
<td>44 (16)</td>
<td>6.71</td>
<td>.04*</td>
<td>HLHS &gt; C: U = 16.50, z = -2.00, p = 0.04, r = -0.47</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HLHS &gt; TGA: U = 16.00, z = -2.47, p = 0.01, r = -0.54</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HLHS &gt; C: U = 13.50, z = -2.27, p = 0.02, r = -0.53</td>
</tr>
<tr>
<td>Total Problems</td>
<td>58 (18)</td>
<td>42.50 (17)</td>
<td>41 (20)</td>
<td>6.04</td>
<td>.05</td>
<td>HLHS &gt; TGA: U = 20.50, z = -2.13, p = 0.03, r = -0.46</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DSM-Oriented Scales</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressive Problems</td>
<td>60 (11)</td>
<td>51 (2)</td>
<td>51 (2)</td>
<td>12.42</td>
<td>.002**</td>
<td>HLHS &gt; C: U = 4.00, z = -3.22, p &lt; 0.001, r = -0.76</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HLHS &gt; TGA: U = 8.50, z = -3.08, p = 0.001, r = -0.67</td>
</tr>
<tr>
<td>Anxiety Problems</td>
<td>60 (25)</td>
<td>50.50 (5)</td>
<td>50 (1)</td>
<td>3.73</td>
<td>.16</td>
<td>-</td>
</tr>
<tr>
<td>ASD Problems</td>
<td>58 (18)</td>
<td>51 (4)</td>
<td>50 (8)</td>
<td>2.42</td>
<td>.30</td>
<td>-</td>
</tr>
<tr>
<td>ADHD Problems</td>
<td>52 (2)</td>
<td>50 (3)</td>
<td>50 (4)</td>
<td>3.32</td>
<td>.19</td>
<td>-</td>
</tr>
<tr>
<td>Oppositional Defiant</td>
<td>59 (17)</td>
<td>50 (1)</td>
<td>51 (2)</td>
<td>5.87</td>
<td>.05</td>
<td>HLHS &gt; TGA: U = 22.00, z = -2.24, p = 0.05, r = -0.49</td>
</tr>
</tbody>
</table>

**Note.** Data are presented as group median (interquartile range (IQR)), Kruskal-Wallis H and p-value, where statistically significant differences between groups denoted as *p<0.05, **p<0.01, and ***p<0.001, and post-hoc pairwise group differences: Mann-Whitney U, z, p-value, and effect size r (where healthy controls are denoted as C).
Table 6.3 The total number and percentage of participants with CBCL subtest scores in the borderline and clinical range

<table>
<thead>
<tr>
<th>CBCL Scale</th>
<th>HLHS (N=7)</th>
<th>TGA (N=14)</th>
<th>Controls (N=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Syndrome Scales (N (%))</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotionally Reactive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>borderline</td>
<td>2 (29)</td>
<td>1 (7)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>clinical</td>
<td>1 (14)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anxious Depressed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>borderline</td>
<td>3 (43)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>clinical</td>
<td>1 (14)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Somatic Complaints</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>borderline</td>
<td>0</td>
<td>1 (7)</td>
<td>0</td>
</tr>
<tr>
<td>clinical</td>
<td>1 (14)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Withdrawn</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>borderline</td>
<td>0</td>
<td>1 (7)</td>
<td>0</td>
</tr>
<tr>
<td>clinical</td>
<td>0</td>
<td>1 (7)</td>
<td>0</td>
</tr>
<tr>
<td>Sleep Problems</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>borderline</td>
<td>2 (29)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>clinical</td>
<td>1 (14)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Attention Problems</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>borderline</td>
<td>1 (14)</td>
<td>1 (7)</td>
<td>0</td>
</tr>
<tr>
<td>clinical</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Aggressive Behaviour</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>borderline</td>
<td>1 (14)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>clinical</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Internalising Problems</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>borderline</td>
<td>1 (14)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>clinical</td>
<td>3 (43)</td>
<td>2 (14)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Externalising Problems</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>borderline</td>
<td>0</td>
<td>1 (7)</td>
<td>0</td>
</tr>
<tr>
<td>clinical</td>
<td>2 (29)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total Problems</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>borderline</td>
<td>1 (14)</td>
<td>1 (7)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>clinical</td>
<td>2 (29)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>DSM-Oriented Scales (N (%))</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressive Problems</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>borderline</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>clinical</td>
<td>1 (14)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anxiety Problems</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>borderline</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>clinical</td>
<td>3 (43)</td>
<td>0</td>
<td>1 (9)</td>
</tr>
<tr>
<td>ASD Problems</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>borderline</td>
<td>1 (14)</td>
<td>0</td>
<td>1 (9)</td>
</tr>
<tr>
<td>clinical</td>
<td>1 (14)</td>
<td>1 (7)</td>
<td>0</td>
</tr>
<tr>
<td>ADHD Problems</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>borderline</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>clinical</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Oppositional Defiant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>borderline</td>
<td>1 (14)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>clinical</td>
<td>1 (14)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
6.3.1.2 SDQ

Significant group differences were observed in Total Difficulties and the Peer Problems subscale. Post-hoc tests revealed the HLHS group had significantly higher raw scores compared to the Control group and/or the TGA group. No significant group differences were observed in four subtests of the SDQ: Emotional Symptoms, Conduct Problems, Hyperactivity and Prosocial Behaviour.

Table 6.4 summarises the results for the SDQ. Table 6.5 summarises the proportion of children in each group with borderline (i.e. high) or clinical (i.e. very high) SDQ scores. Peer Problems was the subtest of particular concern with 3 out of 7 (43%) of HLHS patients and 29% of TGA patients having very high scores.

<table>
<thead>
<tr>
<th>SDQ Scale (median raw score (IQR))</th>
<th>HLHS</th>
<th>TGA</th>
<th>Controls</th>
<th>H</th>
<th>p</th>
<th>Post-hoc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Difficulties</td>
<td>12 (13)</td>
<td>12 (6)</td>
<td>9 (3)</td>
<td>6.52</td>
<td>.04*</td>
<td></td>
</tr>
<tr>
<td>Emotional Symptoms</td>
<td>3 (6)</td>
<td>1 (2)</td>
<td>0 (1)</td>
<td>5.29</td>
<td>.07</td>
<td></td>
</tr>
<tr>
<td>Conduct Problems</td>
<td>2 (4)</td>
<td>2 (0)</td>
<td>1 (1)</td>
<td>5.57</td>
<td>.06</td>
<td></td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>5 (3)</td>
<td>4 (3)</td>
<td>4 (2)</td>
<td>0.74</td>
<td>.69</td>
<td></td>
</tr>
<tr>
<td>Peer Problems</td>
<td>5 (1)</td>
<td>4 (1)</td>
<td>3 (4)</td>
<td>9.34</td>
<td>.01*</td>
<td></td>
</tr>
<tr>
<td>Prosocial Behaviour</td>
<td>9 (3)</td>
<td>9 (2)</td>
<td>9 (4)</td>
<td>0.39</td>
<td>.82</td>
<td></td>
</tr>
</tbody>
</table>
Note. Data are presented as group median (interquartile range (IQR)), Kruskal-Wallis H and p-value, where statistically significant differences between groups denoted as *p<0.05, **p<0.01, and ***p<0.001, and post-hoc pairwise group differences: Mann-Whitney U, z, p-value, and effect size r (where healthy controls are denoted as C).

Table 6.5 The total number and percentage of participants with SDQ subtest scores in the high and very high range

<table>
<thead>
<tr>
<th>SDQ Scale (N (%))</th>
<th>HLHS (N=7)</th>
<th>TGA (N=14)</th>
<th>Controls (N=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Difficulties</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>high</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>very high</td>
<td>3 (43)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Emotional Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>high</td>
<td>2 (29)</td>
<td>0</td>
<td>1 (9)</td>
</tr>
<tr>
<td>very high</td>
<td>1 (14)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Conduct Problems</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>high</td>
<td>1 (14)</td>
<td>1 (7)</td>
<td>0</td>
</tr>
<tr>
<td>very high</td>
<td>1 (14)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>high</td>
<td>1 (14)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>very high</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Peer Problems</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>high</td>
<td>3 (43)</td>
<td>10 (71)</td>
<td>4 (36)</td>
</tr>
<tr>
<td>very high</td>
<td>3 (43)</td>
<td>4 (29)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Prosocial Behaviour</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>high</td>
<td>1 (14)</td>
<td>0</td>
<td>1 (9)</td>
</tr>
<tr>
<td>very high</td>
<td>1 (14)</td>
<td>2 (14)</td>
<td>1 (9)</td>
</tr>
</tbody>
</table>

6.3.1.3 ABAS

There was a significant main effect of group in the overall general adaptive composite (GAC), but not in any of the other domains including Conceptual, Social, and Practical. Post-hoc tests revealed the HLHS group had significantly lower (indicating worse functioning) composite scores compared to both the Control and TGA groups. Table 6.6 summarises the results for the ABAS. Table 6.7 summarises the proportion of children in each group with borderline (1-2 SD)
or clinical (≥2 SDs below the mean) ABAS scores. Practical skills was the area of particular concern in the HLHS patients, with 7 out of 7 (100%) scoring either 1-2 SD or ≥2 SDs below the mean.

Table 6.6 Adaptive Behavior Assessment System (ABAS) outcomes by domain in children with HLHS, TGA, and healthy controls at 4-5 years

<table>
<thead>
<tr>
<th>ABAS Scale (median composite score (IQR))</th>
<th>HLHS</th>
<th>TGA</th>
<th>Controls</th>
<th>H</th>
<th>p</th>
<th>Post-hoc</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAC</td>
<td>86 (16)</td>
<td>98 (13)</td>
<td>97 (7)</td>
<td>7.38</td>
<td>.03*</td>
<td>HLHS &lt; C: U = 11.50, z = -2.45, p = 0.01, r = -0.58</td>
</tr>
<tr>
<td>Conceptual</td>
<td>97 (13)</td>
<td>102 (17)</td>
<td>99 (8)</td>
<td>2.15</td>
<td>.34</td>
<td>-</td>
</tr>
<tr>
<td>Practical</td>
<td>79 (16)</td>
<td>87.50 (19)</td>
<td>84 (21)</td>
<td>5.57</td>
<td>.06</td>
<td>-</td>
</tr>
</tbody>
</table>

Note. GAC = the general adaptive composite, which is the sum of all the subscales scores. Data are presented as group median (interquartile range (IQR)), Kruskal-Wallis H and p-value, where statistically significant differences between groups denoted as *p<0.05, **p<0.01, and ***p<0.001, and post-hoc pairwise group differences: Mann-Whitney U, z, p-value, and effect size r (where healthy controls are denoted as C).
Table 6.7 The total number and percentage of participants with ABAS summary scores 1-2 SD and ≥2 SDs below the mean

<table>
<thead>
<tr>
<th>ABAS Scale (N (%))</th>
<th>HLHS (N=7)</th>
<th>TGA (N=14)</th>
<th>Controls (N=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GAC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 SD</td>
<td>2 (29)</td>
<td>1 (7)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>≥2 SD</td>
<td>1 (14)</td>
<td>1 (7)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Conceptual</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 SD</td>
<td>0</td>
<td>1 (7)</td>
<td>0</td>
</tr>
<tr>
<td>≥2 SD</td>
<td>1 (14)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Social</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 SD</td>
<td>1 (14)</td>
<td>1 (7)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>≥2 SD</td>
<td>1 (14)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Practical</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 SD</td>
<td>5 (71)</td>
<td>3 (21)</td>
<td>4 (36)</td>
</tr>
<tr>
<td>≥2 SD</td>
<td>2 (29)</td>
<td>1 (7)</td>
<td>2 (18)</td>
</tr>
</tbody>
</table>

6.3.1.4 Executive Function

Significant group differences were observed in some subtests and indexes of the BRIEF-P, including Shift, Emotional Control, Working Memory, and Flexibility Index (FI). Post-hoc Mann-Whitney tests revealed that the HLHS group had significantly higher (worse) T-scores compared to the Control group, and/or the TGA group. No significant group differences were observed in five subtests/indexes of the BRIEF-P: Inhibit, Plan/Organise, inhibitory self-control (ISCI), emergent metacognition (EMI), and the global executive composite (GEC). Table 6.8 summarises results for the BRIEF-P. Table 6.9 summarises the proportion of children with HLHS or TGA, and healthy controls with borderline or clinical BRIEF-P scores. There were some subtests/indexes in which both patients with HLHS and TGA had scores within the clinical range, these included Working Memory (3 out of 7 (43%) of HLHS patients and 21% of TGA patients) and EMI (3 out of 7 (43%) of HLHS patients and 7% of TGA patients).
Table 6.8 Behavior Rating Inventory of Executive Function - Preschool (BRIEF-P) outcomes by subtest and index, in children with HLHS, TGA, and healthy controls at 4-5 years

<table>
<thead>
<tr>
<th>BRIEF-P Scale (median T-score (IQR))</th>
<th>HLHS</th>
<th>TGA</th>
<th>Controls</th>
<th>$H$</th>
<th>$p$</th>
<th>Post-hoc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibit</td>
<td>60 (24)</td>
<td>48.50 (12)</td>
<td>45 (9)</td>
<td>3.89</td>
<td>.14</td>
<td>-</td>
</tr>
<tr>
<td>Shift</td>
<td>59 (21)</td>
<td>47 (0)</td>
<td>42 (5)</td>
<td>6.09</td>
<td>.05</td>
<td>-</td>
</tr>
<tr>
<td><strong>Emotional Control</strong></td>
<td>61 (22)</td>
<td>41.50 (19)</td>
<td>48 (9)</td>
<td>6.23</td>
<td>.04*</td>
<td>-</td>
</tr>
<tr>
<td>Working Memory</td>
<td>60 (28)</td>
<td>56 (19)</td>
<td>44 (16)</td>
<td>6.48</td>
<td>.04*</td>
<td>-</td>
</tr>
<tr>
<td>Plan/Organise</td>
<td>54 (23)</td>
<td>51 (21)</td>
<td>41 (10)</td>
<td>2.55</td>
<td>.28</td>
<td>-</td>
</tr>
<tr>
<td>ISCI</td>
<td>63 (22)</td>
<td>48 (18)</td>
<td>44 (13)</td>
<td>4.50</td>
<td>.11</td>
<td>-</td>
</tr>
<tr>
<td>FI</td>
<td>63 (15)</td>
<td>42.50 (16)</td>
<td>43 (8)</td>
<td>6.74</td>
<td>.03*</td>
<td>-</td>
</tr>
<tr>
<td>EMI</td>
<td>60 (28)</td>
<td>55.50 (21)</td>
<td>42 (15)</td>
<td>5.18</td>
<td>.08</td>
<td>-</td>
</tr>
<tr>
<td>GEC</td>
<td>57 (20)</td>
<td>52.50 (19)</td>
<td>44 (12)</td>
<td>5.09</td>
<td>.08</td>
<td>-</td>
</tr>
</tbody>
</table>

*Note.* The subscales form three broad indexes: inhibitory self-control (ISCI), flexibility (FI), and emergent metacognition (EMI), and one composite score global executive composite (GEC). Data are presented as group median (interquartile range (IQR)), Kruskal-Wallis H and p-value, where statistically significant differences between groups denoted as *$p<0.05$, **$p<0.01$, and ***$p<0.001$, and post-hoc pairwise group differences: Mann-Whitney U, z, p-value, and effect size r (where healthy controls are denoted as C).
### Table 6.9 The total number and percentage of participants with BRIEF-P subtest scores in the borderline and clinical range

<table>
<thead>
<tr>
<th>BRIEF-P Scale (N (%)</th>
<th>HLHS (N=7)</th>
<th>TGA (N=14)</th>
<th>Controls (N=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>borderline</td>
<td>2 (29)</td>
<td>1 (7)</td>
<td>0</td>
</tr>
<tr>
<td>clinical</td>
<td>2 (29)</td>
<td>1 (7)</td>
<td>0</td>
</tr>
<tr>
<td>Shift</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>borderline</td>
<td>1 (14)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>clinical</td>
<td>2 (29)</td>
<td>0</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Emotional Control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>borderline</td>
<td>2 (29)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>clinical</td>
<td>2 (29)</td>
<td>1 (7)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Working Memory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>borderline</td>
<td>1 (14)</td>
<td>3 (21)</td>
<td>0</td>
</tr>
<tr>
<td>clinical</td>
<td>3 (43)</td>
<td>3 (21)</td>
<td>0</td>
</tr>
<tr>
<td>Plan/Organise</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>borderline</td>
<td>2 (29)</td>
<td>3 (21)</td>
<td>0</td>
</tr>
<tr>
<td>clinical</td>
<td>1 (14)</td>
<td>1 (7)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>ISCI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>borderline</td>
<td>1 (14)</td>
<td>1 (7)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>clinical</td>
<td>3 (43)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>FI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>borderline</td>
<td>1 (14)</td>
<td>1 (7)</td>
<td>0</td>
</tr>
<tr>
<td>clinical</td>
<td>3 (43)</td>
<td>0</td>
<td>1 (9)</td>
</tr>
<tr>
<td>EMI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>borderline</td>
<td>1 (14)</td>
<td>2 (14)</td>
<td>0</td>
</tr>
<tr>
<td>clinical</td>
<td>3 (43)</td>
<td>1 (7)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>GEC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>borderline</td>
<td>0</td>
<td>1 (7)</td>
<td>0</td>
</tr>
<tr>
<td>clinical</td>
<td>3 (43)</td>
<td>0</td>
<td>1 (9)</td>
</tr>
</tbody>
</table>

### 6.3.1.5 Quality of Life

Significant group differences were observed in some subtests and summary scores of the PedsQL including: Physical Functioning, Emotional Functioning, Social Functioning, and Psychosocial Functioning. Post-hoc tests revealed the HLHS group had significantly lower scores compared to the Control group, and/or the TGA group, indicating reduced HRQOL. No significant group differences were observed in the School Functioning subtest and the overall Total Score. Table 6.10 summarises the results for the PedsQL. Table 6.11 summarises the proportion of children with HLHS, TGA, and healthy controls with PedsQL scores.
1-2 SD and ≥2 SDs below the mean. Overall, children with HLHS had poorer HRQOL outcomes on the PedsQL compared with children with TGA and healthy controls, with 4 out of 7 (57%) having physical, social, and total PedsQL scores ≥2 SD below the normative mean and 5 out of 7 (71%) having psychosocial health summary scores ≥2 SD below the normative mean.

Table 6.10 Pediatric Quality of Life Inventory (PedsQL) outcomes by subtest, in children with HLHS, TGA, and healthy controls at 4-5 years

<table>
<thead>
<tr>
<th>PedsQL Scale (median transformed score (IQR))</th>
<th>HLHS</th>
<th>TGA</th>
<th>Controls</th>
<th>H</th>
<th>p</th>
<th>Post-hoc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Functioning</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Summary Score</td>
<td>46.88 (50.00)</td>
<td>90.63 (21.88)</td>
<td>90.63 (31.25)</td>
<td>6.01</td>
<td>.05</td>
<td></td>
</tr>
<tr>
<td>Psychosocial Functioning</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional Functioning</td>
<td>55.00 (40.00)</td>
<td>82.50 (36.25)</td>
<td>65.00 (30.00)</td>
<td>6.21</td>
<td>.05</td>
<td></td>
</tr>
<tr>
<td>Social Functioning</td>
<td>43.75 (55.00)</td>
<td>100.00 (26.25)</td>
<td>95.00 (20.00)</td>
<td>8.45</td>
<td>.02*</td>
<td></td>
</tr>
<tr>
<td>School Functioning</td>
<td>55.00 (50.00)</td>
<td>90.00 (32.05)</td>
<td>90.00 (20.00)</td>
<td>5.39</td>
<td>.07</td>
<td></td>
</tr>
<tr>
<td>Psychosocial Functioning Summary Score</td>
<td>45.00 (46.66)</td>
<td>86.67 (26.93)</td>
<td>80.00 (20.00)</td>
<td>8.34</td>
<td>.02*</td>
<td></td>
</tr>
<tr>
<td>Total Score (all items)</td>
<td>51.19 (41.66)</td>
<td>89.68 (21.91)</td>
<td>86.96 (23.91)</td>
<td>5.71</td>
<td>.06</td>
<td></td>
</tr>
</tbody>
</table>

Note. Data are presented as group median (interquartile range (IQR)), Kruskal-Wallis H and p-value, where statistically significant differences between groups denoted as *p<0.05, **p<0.01, and ***p<0.001, and post-hoc pairwise group
differences: Mann-Whitney U, z, p-value, and effect size r (where healthy controls are denoted as C).

<table>
<thead>
<tr>
<th>PedsQL Scale (N (%))</th>
<th>HLHS (N=7)</th>
<th>TGA (N=14)</th>
<th>Controls (N=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Functioning</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 SD</td>
<td>1 (14)</td>
<td>2 (14)</td>
<td>0</td>
</tr>
<tr>
<td>≥2 SD</td>
<td>4 (57)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Psychosocial Functioning (N (%))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional Functioning</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 SD</td>
<td>2 (29)</td>
<td>2 (14)</td>
<td>5 (46)</td>
</tr>
<tr>
<td>≥2 SD</td>
<td>3 (43)</td>
<td>1 (7)</td>
<td>0</td>
</tr>
<tr>
<td>Social Functioning</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 SD</td>
<td>1 (14)</td>
<td>0</td>
<td>1 (9)</td>
</tr>
<tr>
<td>≥2 SD</td>
<td>4 (57)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>School Functioning</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 SD</td>
<td>2 (29)</td>
<td>2 (14)</td>
<td>2 (18)</td>
</tr>
<tr>
<td>≥2 SD</td>
<td>3 (43)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Psychosocial Functioning</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 SD</td>
<td>0</td>
<td>3 (22)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>≥2 SD</td>
<td>5 (71)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total Score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 SD</td>
<td>1 (14)</td>
<td>2 (14)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>≥2 SD</td>
<td>4 (57)</td>
<td>0</td>
<td>1 (9)</td>
</tr>
</tbody>
</table>

6.3.2 Correlational Analyses

Given the association between executive dysfunction, narrative and pragmatic language skills, and social skills in the CHD literature, the relationships between Core Language (from the CELF-P2), pragmatic language (i.e. Inappropriate Initiation, Stereotyped, Use of Context, and Nonverbal) (from the CCC-2), narrative skills (from the Bus Story), Social skills (from the ABAS), Social Functioning (from the PedsQL), and EF (from the BRIEF-P) were also explored to address hypothesis four. Table 6.12 shows the results of the Spearman’s correlations for all participants (CHD groups and healthy controls). Significant weak-to-moderate positive correlations were observed between three pragmatic
language scales and social skills, the only exception was Inappropriate Initiation which was not significantly correlated. Significant moderate negative correlations were also observed between all four pragmatic language scales and EF domains, with the exception of the Plan/Organise domain which was not significantly correlated with two pragmatic language scales: Stereotyped and Use of Context. Overall, the Nonverbal pragmatic scale was the most strongly correlated with each of the other scales/domains (Figure 6.3).

There were no significant correlations between objectively measured language and narrative scores and parent-rated social skills and EF, with the exception of the CELF-P2 Core Language scale and the PedsQL Social Functioning score which were weakly positively correlated ($r = 0.38$, $p = 0.05$).
Table 6.12 Spearman’s correlation coefficients between objectively measured CELF-P2 Core Language and narrative scores from the Bus Story, and CCC-2 parent-rated pragmatic language, and parent-rated social skills and executive functioning (for the whole cohort together)

<table>
<thead>
<tr>
<th>Parent-rated Behaviour</th>
<th>Core Language</th>
<th>Bus Story Information</th>
<th>Bus Story Mean Utterance</th>
<th>Inappropriate Initiation</th>
<th>Stereotyped</th>
<th>Use of Context</th>
<th>Nonverbal</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABAS Social</td>
<td>-0.02</td>
<td>0.08</td>
<td>-0.06</td>
<td>0.31</td>
<td>0.37*</td>
<td>0.49*</td>
<td>0.51**</td>
</tr>
<tr>
<td>PedsQL Social Functioning</td>
<td>0.38†</td>
<td>-0.04</td>
<td>0.07</td>
<td>0.30</td>
<td>0.47*</td>
<td>0.38*</td>
<td>0.40*</td>
</tr>
<tr>
<td>BRIEF-P Inhibit</td>
<td>-0.10</td>
<td>-0.06</td>
<td>-0.13</td>
<td>-0.46*</td>
<td>-0.45*</td>
<td>-0.47*</td>
<td>-0.59***</td>
</tr>
<tr>
<td>BRIEF-P Working Memory</td>
<td>-0.30</td>
<td>-0.24</td>
<td>-0.41</td>
<td>-0.43*</td>
<td>-0.43*</td>
<td>-0.44*</td>
<td>-0.62***</td>
</tr>
<tr>
<td>BRIEF-P Plan/Organise</td>
<td>-0.06</td>
<td>-0.08</td>
<td>-0.25</td>
<td>-0.50**</td>
<td>-0.25</td>
<td>-0.24</td>
<td>-0.51**</td>
</tr>
<tr>
<td>BRIEF-P Flexibility</td>
<td>-0.30</td>
<td>-0.05</td>
<td>-0.22</td>
<td>-0.40*</td>
<td>-0.41*</td>
<td>-0.44*</td>
<td>-0.46*</td>
</tr>
</tbody>
</table>

Note. CCC-2 = Children’s Communication Checklist, ABAS = Adaptive Behavior Assessment System, PedsQL = Paediatric Quality of Life Inventory, and BRIEF-P = The Behavior Rating Inventory of Executive Function. Statistically significant correlations denoted as †p = 0.05, *p<0.05, **p<0.01, and ***p<0.001.
Figure 6.2 Scatterplots showing the moderate positive correlation between CCC-2 Nonverbal and A) ABAS Social and B) PedsQL Social Functioning, and the moderate negative correlation between CCC-2 Nonverbal and BRIEF-P C) Inhibit, D) Working Memory, E) Plan/Organise, and F) Flexibility

Note. The solid line on the x-axes represents the normative mean of 100 for the CCC-2 Nonverbal scale. The y-axis line in A also represents the normative mean of 100 for the ABAS, in B the solid y-axis line represents the mean of 81.03 and the dashed line represents 1 SD below the mean. In C-F, the solid y-axes lines...
represent a BRIEF-P T-score of 60 which is considered mildly elevated, whilst scores ≥65 are considered clinically elevated.

To address the fifth hypothesis, the relationships between key behavioural, adaptive functioning and EF factors and psychosocial functioning, and overall HRQOL, were explored. Table 6.13 shows the results of the Spearman’s correlations for all participants (CHD groups and healthy controls). Overall, there were significant correlations between almost all of the variables. Strong significant negative correlations were found between PedsQL Psychosocial Health Summary and CBCL Internalising Problems \( (r = -0.70, \ p < 0.001) \), CBCL Externalising Problems \( (r = -0.66, \ p < 0.001) \), CBCL Total Problems \( (r = -0.68, \ p < 0.001) \), and BRIEF-P Flexibility \( (r = -0.68, \ p < 0.001) \) (Figure 6.4). Moderate significant negative correlations were also observed between PedsQL Total Score and CBCL Internalising Problems \( (r = -0.64, \ p < 0.001) \), CBCL Total Problems \( (r = -0.60, \ p < 0.001) \), and BRIEF-P Flexibility \( (r = -0.67, \ p < 0.001) \).

There was a significant but weak negative association between SDQ Total Difficulties and both PedsQL Psychosocial Health \( (r = -0.39, \ p = 0.03) \) and PedsQL Total Score \( (r = -0.44, \ p = 0.01) \). No significant correlation was observed between PedsQL Total Score and the ABAS General Adaptive Composite (GAC) \( (r = 0.26, \ p = 0.15) \).
Table 6.13 Spearman’s correlation coefficients between PedsQL Psychosocial Summary and PedsQL Total scores, and CBCL Internalising Problems, Externalising Problems, and Total Problems, SDQ Total Difficulties, ABAS General Adaptive Composite (GAC), and BRIEF-P Inhibit, Working Memory, and Flexibility scores (for the whole cohort together)

<table>
<thead>
<tr>
<th>(N = 32)</th>
<th>PedsQL Psychosocial Health Summary</th>
<th>PedsQL Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBCL Internalising</td>
<td>-0.70***</td>
<td>-0.64***</td>
</tr>
<tr>
<td>CBCL Externalising</td>
<td>-0.66***</td>
<td>-0.53**</td>
</tr>
<tr>
<td>CBCL Total Problems</td>
<td>-0.68***</td>
<td>-0.60***</td>
</tr>
<tr>
<td>SDQ Total Difficulties</td>
<td>-0.39*</td>
<td>-0.44*</td>
</tr>
<tr>
<td>ABAS GAC</td>
<td>0.36*</td>
<td>0.26</td>
</tr>
<tr>
<td>BRIEF-P Inhibit</td>
<td>-0.59***</td>
<td>-0.56***</td>
</tr>
<tr>
<td>BRIEF-P Working Memory</td>
<td>-0.59***</td>
<td>-0.58***</td>
</tr>
<tr>
<td>BRIEF-P Flexibility</td>
<td>-0.68***</td>
<td>-0.67***</td>
</tr>
</tbody>
</table>

Note. CBCL = Child Behaviour Checklist, SDQ = Strengths and Difficulties Questionnaire, ABAS = Adaptive Behavior Assessment System, BRIEF-P = The Behavior Rating Inventory of Executive Function, and PedsQL = Paediatric Quality of Life Inventory. Statistically significant correlations denoted as *p<0.05, **p<0.01, and ***p<0.001.
Figure 6.3 Scatterplots showing the strong negative correlation between PedsQL Psychosocial Health and A) CBCL Internalising Problems, B) CBCL Externalising Problems, C) CBCL Total Problems, and D) BRIEF-P Flexibility.

Note. The solid line on the x-axes represents the normative mean of 79.87, and the dashed line represents <1 SD. In A-C, the y-axis line represents a CBCL T-score of 64 which is considered borderline whilst score ≥70 are considered clinically relevant, and in D, a BRIEF-P T-score of 60 which is considered mildly elevated whilst scores ≥65 are considered clinically elevated.

6.3.3 Longitudinal Outcomes

To address the final hypothesis and investigate whether early socioemotional, behavioural, and adaptive skills scores were associated with later scores at 4-5 years of age, several analyses were conducted. Firstly, early infancy and
 preschool scores of social-emotional development and adaptive behaviour from parent-rated Bayley-3 were correlated with later measures of social-emotional and adaptive behaviour at 4-5 years using the CBCL and ABAS, respectively. Parents of 33 children including 6 with HLHS, 9 TGA, and 18 healthy controls completed the Bayley-3 parental questionnaire at all time-points 1-3. Of these children, 22 (3 with HLHS, 8 TGA, and 11 healthy controls) also had parent-completed CBCL and ABAS scores at time-point 4. These 22 children had full longitudinal data and were included in the analyses.

Table 6.14 shows the results of the Spearman’s correlations for all participants (CHD groups and healthy controls). Overall, there were no significant correlations between any of the variables, except for Bayley-3 adaptive behaviour scores at time-point 1 and overall ABAS GAC scores at time-point 4, which were moderately positively correlated ($r = 0.62, p < 0.01$).

Table 6.14 Spearman’s correlation coefficients between longitudinal Bayley-3 Social-emotional and Adaptive Behaviour scores (at each time-point), and CBCL internalising problems, externalising problems, and total problems, and ABAS GAC score

<table>
<thead>
<tr>
<th>Spearman’s correlation coefficient, $r_s$ (N = 22)</th>
<th>Parental Bayley-3 Scores (Time-point 1)</th>
<th>Parental Bayley-3 Scores (Time-point 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parental Bayley-3 (Social-Emotional)</td>
<td>[CBCL Internalising: -0.17]</td>
<td>[CBCL Internalising: 0.13]</td>
</tr>
<tr>
<td></td>
<td>[CBCL Externalising: -0.12]</td>
<td>[CBCL Externalising: 0.13]</td>
</tr>
<tr>
<td></td>
<td>[CBCL Total Problems: -0.10]</td>
<td>[CBCL Total Problems: 0.11]</td>
</tr>
<tr>
<td></td>
<td>ABAS GAC: 0.62**</td>
<td>ABAS GAC: 0.24</td>
</tr>
</tbody>
</table>
Parental Bayley-3 Scores (Time-point 3)

<table>
<thead>
<tr>
<th></th>
<th>Social-Emotional</th>
<th>Adaptive Behaviour</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBCL Internalising</td>
<td>-0.29</td>
<td></td>
</tr>
<tr>
<td>CBCL Externalising</td>
<td>-0.17</td>
<td></td>
</tr>
<tr>
<td>CBCL Total Problems</td>
<td>-0.18</td>
<td></td>
</tr>
<tr>
<td>ABAS GAC</td>
<td></td>
<td>0.38</td>
</tr>
</tbody>
</table>

Note. CBCL = Child Behaviour Checklist, ABAS = Adaptive Behavior Assessment System, and GAC = general adaptive composite. Statistically significant correlations denoted as *p<0.05, **p<0.01, and ***p<0.001.

To explore within-group differences in the longitudinal CBCL data, non-parametric Wilcoxon Signed Ranks analyses were conducted. Significant within-group differences were observed between scores at time-points 3 and 4 in several subtests of the CBCL, in the healthy control and TGA groups. These subtests included: Aggressive Behaviour, Externalising Problems, Total Problems, ADHD Problems, and Oppositional Defiant. However, no significant differences were observed between the two longitudinal time-points in the HLHS group. Table 6.15 summarises the results for the longitudinal CBCL data, within each group.
Table 6.15 Wilcoxon results for longitudinal Child Behaviour Checklist (CBCL) outcomes between time-points 3 and 4 (T3 and T4) by subtests, within-groups

<table>
<thead>
<tr>
<th>CBCL Scale</th>
<th>HLHS</th>
<th>TGA</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Wilcoxon, z; significance, p; time-point 3 median (IQR); time-point 4 median (IQR))</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Syndrome Scales</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Emotionally Reactive</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3 = 65.50 (19)</td>
<td>T3 = 50.00 (9)</td>
<td>T3 = 50.00 (4)</td>
<td></td>
</tr>
<tr>
<td>T4 = 61.50 (13)</td>
<td>T4 = 55.00 (7)</td>
<td>T4 = 51.50 (6)</td>
<td></td>
</tr>
<tr>
<td>z = -1.63</td>
<td>z = -1.49</td>
<td>z = -0.32</td>
<td></td>
</tr>
<tr>
<td>p = 0.10</td>
<td>p = 0.14</td>
<td>p = 0.75</td>
<td></td>
</tr>
<tr>
<td><strong>Anxious Depressed</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3 = 58.00 (16)</td>
<td>T3 = 51.00 (6)</td>
<td>T3 = 50.00 (2)</td>
<td></td>
</tr>
<tr>
<td>T4 = 54.50 (11)</td>
<td>T4 = 52.00 (12)</td>
<td>T4 = 51.00 (2)</td>
<td></td>
</tr>
<tr>
<td>z = -0.11</td>
<td>z = -2.32</td>
<td>z = -0.95</td>
<td></td>
</tr>
<tr>
<td>p = 0.92</td>
<td>p = 0.02*</td>
<td>p = 0.34</td>
<td></td>
</tr>
<tr>
<td><strong>Somatic Complaints</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3 = 53.00 (14)</td>
<td>T3 = 53.00 (8)</td>
<td>T3 = 50.00 (3)</td>
<td></td>
</tr>
<tr>
<td>T4 = 59.50 (8)</td>
<td>T4 = 57.00 (14)</td>
<td>T4 = 53.00 (7)</td>
<td></td>
</tr>
<tr>
<td>z = -0.95</td>
<td>z = -1.25</td>
<td>z = -1.57</td>
<td></td>
</tr>
<tr>
<td>p = 0.34</td>
<td>p = 0.21</td>
<td>p = 0.12</td>
<td></td>
</tr>
<tr>
<td><strong>Withdrawn</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3 = 55.00 (13)</td>
<td>T3 = 51.00 (10)</td>
<td>T3 = 51.00 (13)</td>
<td></td>
</tr>
<tr>
<td>T4 = 52.50 (7)</td>
<td>T4 = 56.00 (11)</td>
<td>T4 = 50.50 (3)</td>
<td></td>
</tr>
<tr>
<td>z = -0.41</td>
<td>z = -0.07</td>
<td>z = -1.52</td>
<td></td>
</tr>
<tr>
<td>p = 0.68</td>
<td>p = 0.94</td>
<td>p = 0.13</td>
<td></td>
</tr>
<tr>
<td><strong>Sleep Problems</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3 = 64.50 (19)</td>
<td>T3 = 51.00 (3)</td>
<td>T3 = 50.00 (1)</td>
<td></td>
</tr>
<tr>
<td>T4 = 61.00 (13)</td>
<td>T4 = 51.00 (6)</td>
<td>T4 = 50.00 (2)</td>
<td></td>
</tr>
<tr>
<td>z = -0.84</td>
<td>z = -0.93</td>
<td>z = -0.56</td>
<td></td>
</tr>
<tr>
<td>p = 0.40</td>
<td>p = 0.35</td>
<td>p = 0.58</td>
<td></td>
</tr>
<tr>
<td><strong>Attention Problems</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3 = 57.00 (8)</td>
<td>T3 = 51.00 (7)</td>
<td>T3 = 52.00 (3)</td>
<td></td>
</tr>
<tr>
<td>T4 = 57.00 (6)</td>
<td>T4 = 53.00 (6)</td>
<td>T4 = 52.50 (5)</td>
<td></td>
</tr>
<tr>
<td>z = -1.29</td>
<td>z = -0.46</td>
<td>z = -1.00</td>
<td></td>
</tr>
<tr>
<td>p = 0.20</td>
<td>p = 0.64</td>
<td>p = 0.32</td>
<td></td>
</tr>
<tr>
<td><strong>Aggressive Behaviour</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3 = 52.00 (14)</td>
<td>T3 = 50.00 (0)</td>
<td>T3 = 50.00 (2)</td>
<td></td>
</tr>
<tr>
<td>T4 = 59.00 (7)</td>
<td>T4 = 56.00 (11)</td>
<td>T4 = 56.00 (7)</td>
<td></td>
</tr>
<tr>
<td>z = -1.13</td>
<td>z = -2.53</td>
<td>z = -2.38</td>
<td></td>
</tr>
<tr>
<td>p = 0.26</td>
<td>p = 0.01*</td>
<td>p = 0.02*</td>
<td></td>
</tr>
<tr>
<td><strong>Internalising Problems</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3 = 58.50 (21)</td>
<td>T3 = 47.00 (17)</td>
<td>T3 = 42.00 (21)</td>
<td></td>
</tr>
<tr>
<td>T4 = 57.00 (15)</td>
<td>T4 = 52.00 (16)</td>
<td>T4 = 50.00 (8)</td>
<td></td>
</tr>
<tr>
<td>z = -0.11</td>
<td>z = -1.73</td>
<td>z = -1.72</td>
<td></td>
</tr>
<tr>
<td>p = 0.92</td>
<td>p = 0.08</td>
<td>p = 0.09</td>
<td></td>
</tr>
<tr>
<td><strong>Externalising Problems</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3 = 53.50 (20)</td>
<td>T3 = 43.00 (12)</td>
<td>T3 = 44.00 (18)</td>
<td></td>
</tr>
<tr>
<td>T4 = 59.00 (10)</td>
<td>T4 = 55.00 (14)</td>
<td>T4 = 54.50 (14)</td>
<td></td>
</tr>
<tr>
<td>z = -1.16</td>
<td>z = -2.94</td>
<td>z = -2.19</td>
<td></td>
</tr>
<tr>
<td>p = 0.25</td>
<td>p = 0.003**</td>
<td>p = 0.03*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HLHS</td>
<td>TGA</td>
<td>Controls</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------------------</td>
<td>----------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td><strong>Total Problems</strong></td>
<td>T3 = 58.00 (24)</td>
<td>T3 = 44.00 (14)</td>
<td>T3 = 41.50 (20)</td>
</tr>
<tr>
<td></td>
<td>T4 = 61.00 (13)</td>
<td>T4 = 61.00 (18)</td>
<td>T4 = 51.00 (1)</td>
</tr>
<tr>
<td>z</td>
<td>-0.63</td>
<td>z = -2.94</td>
<td>z = 2.20</td>
</tr>
<tr>
<td>p</td>
<td>0.53</td>
<td>0.003**</td>
<td>0.03*</td>
</tr>
</tbody>
</table>

**DSM-Oriented Scales**

|                  | T3 = 58.00 (16)       | T3 = 51.00 (1)       | T3 = 51.00 (2)        |
| Depressive Problems | T4 = 58.00 (9)       | T4 = 54.00 (11)      | T4 = 50.00 (6)        |
| z                | -0.11                 | z = -1.61            | z = 0.07              |
| p                | 0.92                  | 0.11                 | 0.94                 |

|                  | T3 = 61.50 (27)       | T3 = 51.00 (4)       | T3 = 50.00 (1)        |
| Anxiety Problems  | T4 = 61.00 (18)       | T4 = 54.00 (18)      | T4 = 55.50 (8)        |
| z                | -0.41                 | z = -2.52            | z = -1.19             |
| p                | 0.68                  | 0.01*                | 0.24                 |

|                  | T3 = 54.50 (19)       | T3 = 51.00 (4)       | T3 = 50.00 (10)       |
| ASD Problems      | T4 = 54.00 (11)       | T4 = 54.00 (15)      | T4 = 51.00 (3)        |
| z                | -0.68                 | z = -1.52            | z = -1.27             |
| p                | 0.50                  | 0.13                 | 0.20                 |

|                  | T3 = 52.00 (4)        | T3 = 50.00 (2)       | T3 = 50.50 (4)        |
| ADHD Problems     | T4 = 56.50 (6)        | T4 = 54.00 (12)      | T4 = 54.00 (7)        |
| z                | -0.95                 | z = -2.53            | z = -2.21             |
| p                | 0.34                  | 0.01*                | 0.03*                |

|                  | T3 = 55.00 (18)       | T3 = 50.00 (1)       | T3 = 51.00 (3)        |
| Oppositional Defiant Problems | T4 = 58.00 (9)    | T4 = 56.00 (11)      | T4 = 57.50 (9)        |
| z                | -0.37                 | z = -2.53            | z = -2.13             |
| p                | 0.72                  | 0.01*                | 0.03*                |

*Note.* Statistically significant differences between the two time-points are denoted as *p<0.05, **p<0.01, and ***p<0.001.

Finally, to explore the relationship between the CBCL subtest scores from the two longitudinal time-points (T3 and T4), non-parametric correlations were conducted. Table 6.16 shows the results of the Spearman’s correlations for all participants (CHD groups and healthy controls). Overall, there were significant correlations between all of the CBCL subscale scores between the two time-points, except for Somatic Complaints. There were strong significant positive correlations between the two time-points for Attention Problems, Internalising Problems, Externalising Problems, and Total Problems (Figure 6.5). Moderate
significant positive correlations were also observed between the time-points for Emotionally Reactive, Anxious Depressed, Withdrawn, Sleep Problems, Aggressive Behaviour, Depressive Problems, Anxiety Problems, ASD Problems, ADHD Problems, and Oppositional Defiant.

Table 6.16 Spearman’s correlation coefficients between all CBCL subscale scores at time-points 3 and 4 (for the whole cohort)

<table>
<thead>
<tr>
<th>Syndrome Scales</th>
<th>Spearman’s correlation coefficient, $r_s$</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N = 27) T3</td>
<td>T4</td>
</tr>
<tr>
<td><strong>Emotionally Reactive</strong></td>
<td>$0.63^{***}$</td>
</tr>
<tr>
<td><strong>Anxious Depressed</strong></td>
<td>$0.60^{**}$</td>
</tr>
<tr>
<td><strong>Somatic Complaints</strong></td>
<td>$0.33$</td>
</tr>
<tr>
<td><strong>Withdrawn</strong></td>
<td>$0.52^*$</td>
</tr>
<tr>
<td><strong>Sleep Problems</strong></td>
<td>$0.44^*$</td>
</tr>
<tr>
<td><strong>Attention Problems</strong></td>
<td>$0.76^{***}$</td>
</tr>
<tr>
<td><strong>Aggressive Behaviour</strong></td>
<td>$0.52^*$</td>
</tr>
<tr>
<td><strong>Internalising Problems</strong></td>
<td>$0.73^{***}$</td>
</tr>
<tr>
<td><strong>Externalising Problems</strong></td>
<td>$0.70^{***}$</td>
</tr>
<tr>
<td><strong>Total Problems</strong></td>
<td>$0.69^{***}$</td>
</tr>
<tr>
<td><strong>DSM-Oriented Scales</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Depressive Problems</strong></td>
<td>$0.58^{**}$</td>
</tr>
<tr>
<td><strong>Anxiety Problems</strong></td>
<td>$0.64^{***}$</td>
</tr>
<tr>
<td><strong>ASD Problems</strong></td>
<td>$0.62^{***}$</td>
</tr>
<tr>
<td><strong>ADHD Problems</strong></td>
<td>$0.67^{***}$</td>
</tr>
<tr>
<td><strong>Oppositional Defiant</strong></td>
<td>$0.54^{**}$</td>
</tr>
</tbody>
</table>

*Note.* Statistically significant correlations denoted as *$p<0.05$, **$p<0.01$, and ***$p<0.001$.
Figure 6.4 Scatterplots showing the strong positive correlations between the two time-points for the CBCL summary and total scores: A) Internalising Problems, B) Externalising Problems, and C) Total Problems

Note. Lines on the x and y axes represent a T-score of 64 which is considered a borderline score, whilst score ≥70 are considered clinically relevant.

6.4 Discussion

This chapter has focussed on socioemotional, behaviourial, adaptive behaviour and EF outcomes and their association with psychosocial functioning and overall HRQOL in children with CHD, compared to healthy controls. A child’s
psychosocial profile encompasses behavioural outcomes, adaptive behaviour, EF and social cognition and combined, these factors can significantly affect HRQOL. This was investigated using a battery of parent-completed questionnaires. Parent-reported outcome measures have been widely used to evaluate psychosocial and QoL outcomes in children with CHD.

**6.4.1 Behavioural Outcomes**

Previous literature has found that type of CHD physiology and related morbidity factors impact overall HRQOL (Marino et al., 2016). The current investigation found evidence to support this with a clear pattern emerging in children with HLHS having poorer outcomes compared to those with TGA and healthy controls. Significant group differences were observed across a wide range of behavioural, psychosocial, and QoL domains, including externalising behaviour problems, depressive problems, oppositional defiant behaviour, overall adaptive behavioural functioning, emotional control, working memory, physical and social functioning, and overall psychosocial functioning. This supports the hypotheses that children with HLHS in particular will have worse outcomes compared to children with TGA, and also compared to healthy controls. Compared to children with TGA and healthy controls, a significant proportion (43-100%) of children with HLHS exhibited borderline and clinical behaviours in a wide range of domains, including: anxious/depressed symptoms, internalising problems, peer problems, practical adaptive skills, inhibition, emotional control, working memory and social communication skills. Five out of 7 (71%) also had reduced scores in all domains of the PedsQL. Given that in a normal population 85% of scores are expected to fall within the normal range and 15% would be expected to fall within the
abnormal range, the proportion of children with HLHS with abnormal scores is noticeably higher in the present study.

It was hypothesised that children with complex CHD, including those with TGA, would have worse socioemotional, behaviour, EF and HRQOL outcomes compared to healthy controls, but this was not supported. Children with TGA generally had outcome scores similar to those of healthy controls, with the exception of Total Difficulties and Peer Problems measured on the SDQ in which they had higher scores (i.e. worse outcomes) compared to controls, similar to those with HLHS. Despite having higher median scores, no children with TGA had scores within the clinical range for Total Difficulties, but all had high or very high scores for Peer Problems. The domains in which a higher proportion of children with TGA had borderline or clinical scores were peer problems, practical adaptive skills, working memory, and planning and organising skills. The proportions were higher than would be expected in a normal healthy population.

The prevalence of borderline/clinical scores in each of these domains in children with TGA is important, given that overall, group means suggest that they have scores similar to healthy controls as opposed to other children with CHD.

These findings are similar to those reported in the CHD literature. McCusker et al. (2007) reported that it is only children with complex conditions and palliative interventions that seem at increased risk of poor behavioural outcomes. They found that those with complete repair, such as TGA, showed favourable behavioural outcomes similar to controls, with only 5% having Total Problem scores on the CBCL within the clinical range, compared to 33% of those with HLHS. These figures are similar to those of the current study, where 2 out of 7 (29%) of children with HLHS had clinical scores for Total Problems, compared to none with TGA. Additionally, Brosig et al. (2007) found that children with HLHS
also had higher rates of attention and externalising behaviour problems than children with TGA. They reported 15% of 3-6 year-olds with HLHS and 10% with TGA had externalising problems scores in the clinical range, and 23% of the HLHS group compared to none of the TGA group showed attention problems in the clinical range. Importantly, these group differences were not statistically significant. However, in the current cohort, 2 out of 7 (29%) of children with HLHS had clinical scores for externalising problems, compared to none of those with TGA, and this difference was statistically significant. This suggests that externalising problems are particularly evident in the HLHS cohort.

In contrast to previous studies (Huisenga et al., 2020; Shillingford et al., 2008; Tsao et al., 2017; Werninger et al., 2020), the present study did not indicate an increased incidence of inattention or hyperactivity. In fact, no child with CHD had scores in the borderline/clinical range for either inattention or hyperactivity, and only one child with HLHS and one with TGA had scores for ASD problems in the clinical range. This may be because the current cohort is considerably younger in age compared to others investigated in the literature (Shillingford et al., 2008; Tsao et al., 2017; Werninger et al., 2020), and these problems may not yet manifest at 4-5 years of age. Another possible reason for the discrepancy in results may be due to the fact that different measures have been used and these may have different levels of sensitivity and specificity. For example, Werninger et al. (2020) used the Conners-3 questionnaire to measure ADHD-related symptoms and common comorbidities. Further, the Behaviour Assessment System for Children has been found to be better at accurately distinguishing children with ADHD compared to non-ADHD, but the CBCL is superior for predicting primarily inattentive children (Ostrander et al., 1998; Shillingford et al., 2008).
Recent reviews of the literature have also concluded that in addition to the problems discussed above, withdrawal, depression, anxiety, and somatic problems are also widely reported by parents of children with complex CHD (Dahlawi et al. 2020; Huisenga et al., 2020). The present investigation found that over half of the children with HLHS had elevated levels of anxious/depressed symptoms and just under half had anxiety problems. Children with TGA did not have similar elevations in these domains, and although 14% had increased withdrawal scores, the prevalence is similar to that expected in the normal population. This suggests that although recent reviews indicate that these symptoms are likely to be reported in complex CHD, it is those with the more severe types of CHD with more complex morphology who are likely to experience problems with depression, anxiety, withdrawal etc.

Further impairments have also been described in adaptive functioning which incorporates practical skills required for daily life. Goldberg et al. (2019) and Sananes et al. (2021) examined behavioural, adaptive functioning, and QoL outcomes in 6 year-olds with HLHS, who were part of the original SVRT. They found that 71% of the cohort demonstrated age-appropriate adaptive skills, but 22% were at risk, and 7% were impaired. In comparison, in the current HLHS cohort, the figures were somewhat higher in the overall GAC of the ABAS, but the current cohort is significantly smaller in size compared to that of both Goldberg et al. (2019) and Sananes et al. (2021), so this difference is considered with caution. Children with HLHS tended to have poorer practical adaptive skills (i.e. Community Use, Home Living, Health and Safety, and Self-Care) compared to the other domains, with all of them obtaining scores in the at-risk or impaired range. Similarly, Tan et al. (2022) found that adolescents with high-risk CHD (single and biventricular CHD) had adaptive functioning skills below age
expectations across six of the nine adaptive skill areas: Community Use, Functional Academics, Home Living, Self-Care, Self-Direction, and Social Skills. Many of these areas overlap with those which were found to be particular weaknesses at 4-5 years of age in the present study. However, Tan et al. (2022) found that poorer adaptive skills were associated with biventricular rather than single-ventricle CHD. This was unexpected and they suggested that socio-economic status including parental education did not relate to adaptive functioning in their cohort which may have otherwise explained their results. This finding was not replicated in the current study, in which the TGA (biventricular CHD) cohort had higher scores in all of the adaptive behaviour domains of the ABAS, and only 7% were at risk and 7% were impaired. It is noteworthy that the participants in Tan et al.’s (2022) study were older school-aged children compared to the current cohort. It is plausible to assume that adaptive behaviour problems are more prevalent in older children, similar to EFs which are known to get worse as increased cognitive demands are placed on older children. This provides support for the idea that children with CHD often grow into their deficits, and these are not always observable in the early school age or preschool years.

It has been suggested that poorer adaptive functioning is associated with poorer EF in children with CHD (Ilardi et al., 2020). However, literature focussing on EF differs with respect to the level of executive dysfunction severity and prevalence across the lifespan. Some have suggested that EFs are generally preserved in 5 year-olds with CHD (Gaudet et al., 2022), whilst others have described significant delays in inhibition and cognitive flexibility, but normal working memory in 5-7 year-olds with TGA (Calderon et al., 2014). Sanz et al. (2017) reported high rates of executive dysfunction for working memory and flexibility in 7-10 year-olds with CHD. They also concluded that children with single ventricle defects were not
more likely to experience executive dysfunction, as has been previously suggested. In fact, children with biventricular CHD were more likely to have problems with emotional control and planning/organising. In contrast, findings from the current study found higher rates of executive dysfunction in children with HLHS compared to those with TGA and healthy controls, with 4 out of 7 (57%) having at-risk or impaired inhibition, emotional control, working memory, and flexibility. Twenty-nine percent of children with TGA had problems with planning and organising but not with emotional control. Approximately half of both CHD groups were found to have at-risk or impaired working memory, in contrast to the findings of Calderon et al. (2014). These findings suggest that children with HLHS and TGA may have different types of executive dysfunction, affecting different components of EF, rather than just varying degrees of dysfunction alone. Again, different measures have been used across the studies which may also explain the conflicting findings. This emphasises the need for standardised measures to be used in research, ideally following recently published guidelines and recommendations from the Cardiac Neurodevelopmental Outcome Collaborative who have set out neurodevelopmental evaluation strategies for behaviour regulation, adaptive skills, social-emotional functioning, attention, behaviour and EF (Ware et al., 2020). A more cohesive approach to instrument selection would allow comparisons to be made between studies more easily.

Recent systematic reviews (Clancy et al., 2020; Howell et al., 2019; Ryan et al., 2019) have concluded that children with CHD are at increased risk for psychosocial and emotional challenges, but again, those with cardiac conditions exacerbated by complex palliative status (e.g. HLHS) were found to be more at risk for poor outcomes than children diagnosed with other cardiac conditions. They also recognised that symptoms of psychosocial impairment are detectable
in early infancy, though they may initially present as internalising and externalising behavioural symptoms and social-emotional problems, but evolve to include problems with emotional comprehension, inattention, hyperactivity, impulsivity and problems with mental health. Despite this, our understanding about the onset and trajectory of early social, emotional and behavioural problems in infants and young children with CHD is limited as much of the literature has focussed on older school-aged children. The frequency and severity of behavioural and psychosocial difficulties tend to increase with age, especially during middle and later primary school years when there are greater academic demands on the child (Kovacs and Bellinger, 2021). This again emphasises that children with CHD grow into their deficits with age, and many of these may present differently in the early years or evolve to include deficits in other domains which were not previously apparent.

Impairments in emotional and behavioural outcomes, adaptive behaviour, social cognition, and EF can all impact overall HRQOL. An increasing number of studies have shown psychosocial maladjustment and reduced HRQOL in children and adolescents with CHD. For example, Dempster et al. (2018) evaluated HRQOL in 2-18 year-olds with HLHS using the PedsQL and found that they had significantly lower overall QoL compared to healthy children and those with other acute or chronic illnesses. Group averages in the present study are consistent with those reported by Dempster and colleagues. In each domain almost half to three quarters of children with HLHS had QoL scores ≥2 SD below the normative mean. These figures are somewhat different to those reported by Goldberg et al. (2019), where scores ranged from 2-10.5%. In contrast, Denniss et al. (2019) found that 60% of children with single ventricle CHD and 25% with biventricular repair had total QoL scores ≥2 SD below the mean, supporting the current
findings for HLHS but not TGA, where a smaller proportion of children had scores ≥2 SD below the mean. This suggests that, overall, children with TGA have better outcomes and HRQOL than children with HLHS, with scores comparable to healthy controls.

6.4.2 The Role of Language

Pragmatic language plays a key role in social cognition and based on the literature emphasising the link between these domains and narrative skills and EF, the association between all of these was explored. It was hypothesised that core language, pragmatics and narrative skills would be associated with parent-rated social skills and EF scores. The findings provide some support for this hypothesis. Core Language scores were significantly weakly positively correlated with Social Functioning scores from the PedsQL. However, no other significant correlations were observed between Core Language from the CELF-P2 and narrative skills from the Bus Story, and any of the EF domains from BRIEF-P or Social skills from the ABAS. In contrast, almost all of the parent-rated measures of pragmatic language in the CCC-2 were significantly correlated with parent-rated social skills and EF. Correlations ranged from weak-to-moderate, and were positive for social skills, and negative for EF. BRIEF-P Inhibition, Working Memory and Flexibility were significantly negatively correlated with all pragmatic language scales of the CCC-2. These results suggest that higher BRIEF-P scores, representing executive dysfunction, are associated with poorer pragmatic language scores. The scatterplots also reveal that it is consistently children with CHD that have clinically elevated EF scores suggestive of dysfunction, and these children are the ones who also have lower pragmatic language (i.e. 1-2 SD or ≥2 SDs below the normative mean).
In their review article, Calderon and Bellinger (2015) reported that children with TGA show executive dysfunction in narrative and pragmatic language tasks, and suggested that deficits in narrative discourse are associated with poorer pragmatic skills. However, the results of the present study did not find that narrative skills were significantly associated with EF scores, despite finding that executive dysfunction was associated with poorer pragmatic language. This may be explained by the task involved in narrative discourse, which in the present study involved narrative recall specifically, and children were scored for accuracy of recall information and mean length of utterance. This task is quite different to that described by Calderon and Bellinger (2015) which involved story elements being put into the correct order. Further, in the current cohort, six CHD patients were unable to complete the Bus Story task with most saying they did not remember the story when asked to recall it. Therefore, there were fewer participants with these data compared to the parent-rated scores and other scores of language which may have impacted the results.

6.4.3 Factors Associated with Psychosocial Status and HRQOL

It was hypothesised that CHD physiology, behavioural problems, adaptive behavioural skills and executive dysfunction would all be associated with psychosocial adjustment and reduced overall HRQOL. The findings of the present study revealed several significant associations between behavioural problems and executive dysfunction, and psychosocial health and HRQOL outcomes. Specifically, a moderate-to-strong correlation was observed between Psychosocial Health and Internalising Problems, as well as moderate associations between Psychosocial Health and Externalising Problems, Total Problems, Inhibition, Working Memory, and Cognitive Flexibility. Similar
moderate associations were also found between each of these factors and overall HRQOL. In contrast to what was hypothesised, weak correlations were found between adaptive behaviour skills and both psychosocial health and HRQOL. Interestingly, Total Difficulties as measured by the SDQ was weakly associated with both psychosocial health and HRQOL, compared to Total Problems in the CBCL, suggesting that the SDQ is distinct to the CBCL. This conflicts with previous findings that both the CBCL and SDQ are highly correlated and there are no significant differences between their scores in any of the domains (Goodman and Scott, 1999; Warnick et al., 2008).

Previous literature has emphasised lower QoL in children with more complex heart lesions such as HLHS (e.g. Denniss et al., 2019), but studies focussing on children with single ventricle anatomy only have reported that few cardiac-specific factors are related to QoL (Latal et al., 2009). Various psychosocial factors have been found to be associated with lower QoL in children with severe CHD, including behavioural problems (Majnemer et al., 2006), lower adaptive functioning (Goldberg et al., 2019), poor attention (Robson et al., 2019), executive dysfunction (White et al., 2019), and higher illness-related parental stress particularly maternal stress, post-traumatic stress, anxiety and depression (Marino et al., 2010; Wray et al., 2014; 2018). The findings of the present study support many of these findings, as the children with HLHS have the lowest scores for psychosocial health and overall HRQOL, compared to both children with TGA and healthy controls and it is these same children who also have the highest scores for behavioural problems and executive dysfunction.

Majnemer et al. (2006) reported a significant weak-to-moderate negative relationship between internalising, externalising, and total behavioural problems measured by the CBCL and psychosocial functioning, in children with CHD. The
current study has found evidence to support these findings given the significant moderate-to-strong correlations observed between psychosocial health and internalising, externalising, and total problems. Although correlation does not imply causation, there is some evidence here to suggest that higher parent-reported behavioural problems in CHD are associated with lower psychosocial functioning, and overall HRQOL. However, of note, shared method variance may be a contributing factor, as all these domains are parent-rated so any bias would impact both measures equally. Lower adaptive functioning has also been associated with lower HRQOL in children with severe CHD, and especially in children with HLHS (Goldberg et al., 2019). However, no correlations were observed between adaptive functioning measured by the ABAS and either psychosocial functioning or HRQOL in the current cohort of children with CHD.

Reports regarding executive dysfunction in CHD vary considerably in the literature. Inhibition or inhibitory control, working memory, and cognitive flexibility are all fundamental to EF (Cassidy, 2020). Sanz et al. (2018) described that executive dysfunction is a strong predictor of academic achievement, psychosocial adjustment and HRQOL in children with complex CHD. They also concluded that single-ventricle CHD did not significantly predict executive dysfunction or HRQOL. The current investigation found significant moderate negative correlations between all three core components of EF (inhibition, working memory, and cognitive flexibility) and both psychosocial health and HRQOL. This suggests that a higher degree of executive dysfunction is associated with lower psychosocial functioning and HRQOL. It was cognitive flexibility, which reflects a child’s ability to move flexibly among actions, responses, emotions and behaviour, and is an important component of behavioural regulation, that was most strongly associated with psychosocial
health and HRQOL. Further, it was children with HLHS who also consistently had the highest scores of executive dysfunction and these were associated with lower psychosocial health and HRQOL scores.

The absence of adaptive functioning problems in the current cohort of CHD patients may be explained by the fact that these impairments are most frequently reported in older children and adolescents with CHD (Tan et al., 2022). EF impairments in childhood have long-term consequences for development and adaptive functioning and can increase the risk of psychiatric disorders in adolescents with CHD (Calderon et al., 2016). Executive dysfunction is known to become more prevalent and problematic during adolescence (Cassidy et al., 2021). Long-term executive dysfunction may subsequently affect adaptive functioning as increasing everyday demands are placed on the child and they find themselves unable to keep up with healthy peers, compromising their transition into adolescence and adulthood and reducing their overall HRQOL.

As the literature reports, maternal stress, anxiety and depression, as well as family functioning are all associated with psychosocial and HRQOL outcomes in children. These will be discussed in detail in Chapter 7. It is noteworthy that many of these predictors or factors which are known to be correlated with psychosocial and HRQOL outcomes are potentially modifiable which offers plausible pathways for early intervention and prevention.

6.4.4 Longitudinal Outcomes

Finally, it was hypothesised that earlier socioemotional, behavioural, and adaptive skills scores would be associated with later scores at 4-5 years of age. The results of the present investigation found some support for this. When looking
at earlier social-emotional scores from Bayley-3 during infancy and the preschool years, no significant correlations were observed between this scale at time-points 1-3 and Internalising, Externalising, and Total Problems scores measured using the CBCL at 4-5 years. Similar results were observed for adaptive behaviour scores from Bayley-3 and overall adaptive behaviour (GAC) from the ABAS at 4-5 years, with the exception of time-point 1, where Bayley-3 adaptive behaviour scores correlated with later ABAS GAC scores. These results are somewhat surprising, given that the current cohort of HLHS patients had scores in the abnormal range for many socioemotional and behavioural domains at 4-5 years, as discussed above. Further, as some researchers have found that socioemotional and behavioural difficulties are present in the early years (Bonthrone et al., 2022; Cassidy et al., 2018), it was reasonable to assume that they would have been detected in the current cohort too. However, it may be the case that these deficits do not present themselves until later. These results may also indicate that the Bayley-3 does not measure the same components of socioemotional and adaptive behaviour skills as the ABAS and CBCL, and may not be as sensitive as these measures overall.

This longitudinal hypothesis is further supported by the results of the longitudinal CBCL data collected at both time-points 3 and 4. Within-groups analyses revealed that scores did not significantly differ between these two time-points, in each of the groups, in most of the CBCL scales. There were some exceptions in the TGA and healthy control groups for some scales including Anxious Depressed, Aggressive Behaviour, Externalising Problems, Total Problems, ADHD problems and Oppositional Defiant, where scores increased overtime but remained within the normative range. In contrast, children with HLHS had consistent scores over these two assessments for all CBCL scales. Correlational
analyses also revealed significant positive correlations ranging from moderate-to-strong in all the CBCL scales longitudinally, except Somatic Complaints. This suggests that behaviours were stable over time, apart from somatic behaviours. These longitudinal CBCL findings provide support for the final hypothesis suggesting that earlier scores are associated with later scores, and that they remain stable between 3-5 years of age, especially in children with HLHS.

6.4.5 Limitations

There is one important limitation of the current study. Due to the age of the participants, their limited communication abilities, and lack of knowledge about the impact of their CHD, parents were asked to provide insights about their child. Therefore, this study is heavily reliant on parent-reported outcome measures for all the domains which have been investigated. There are inherent problems with parental questionnaires, particularly with regards to accuracy, subjectivity and potential bias (Goldberg et al., 2019; Visconti et al., 2002). This is particularly problematic in parents of children with health conditions as they may be hesitant to score and flag certain behaviours they have observed in their child. There is also a tendency for parents to underestimate internalising symptoms in children and they can be biased by their own traumatic experiences, guilt, or misconceptions that their child is “too young” to be affected (Clancy et al., 2020). Parents may consciously or subconsciously give socially desirable responses, either to improve perceptions of their parenting skills or because they perceive their child is a ‘survivor’ of CHD (Gaynor et al., 2009). The impact of the child’s CHD on their well-being may have also been taken into account when parents completed the questionnaires, so behaviours may not have been rated as aberrant, reflecting a response shift in some parents of children with CHD,
particularly those with more severe CHD. This also links to the problem of shared method variance, as parents have provided ratings of their child’s behaviour across a range of measures, and consequently, their perceptions are likely to have impacted all these measures equally. Hence, any bias in scores is likely to be seen in all measures used, including overall HRQOL, which may also influence the likelihood of these measures being significantly correlated.

A further limitation concerns the use of the CBCL within CHD populations. The CBCL has been widely used in research to evaluate child behaviour and assess psychological adjustment, and while it has been validated for psychiatric populations, its suitability for use in children with chronic disease is unclear. It has previously been suggested that there may be bias in interpreting data regarding physical symptoms, when ideally an assessment scale should allow for clear distinction between symptoms associated with the disease and those associated with consequences of the disease, validated for the target population (Latal et al., 2009). For example, somatic symptoms may reflect physical symptoms of CHD such as breathlessness or fatigue which are common in complex CHD, rather than physiological behavioural symptoms as they are interpreted in the CBCL. Despite this, research has documented good convergence between CBCL clinical scales and clinical diagnoses, particularly ADHD, oppositional defiant disorder, and ASD (Biederman et al., 2020). The CBCL has also been extensively reported in the CHD literature which makes comparisons between datasets and cohorts relatively easy and reliable, in the absence of validation in specific CHD populations.

The Cardiac Neurodevelopmental Outcome Collaborative (Ilardi et al., 2020; Marino et al., 2012; Ware et al., 2020) have recommended the use of parental questionnaires to evaluate attention, emotional and behavioural outcomes,
adaptive functioning, social competence, and QoL. However, it may be beneficial
to use these alongside other direct observational methods and standardised
assessments. Age-appropriate self-report measures can also be used but this
would only be possible in older children. Some questionnaires which have been
used in the current investigation have been found to be particularly powerful such
as the BRIEF-P for the assessment of EF which is unique from traditional paper-
pencil measures (Sanz et al., 2017).

Another limitation is the lack of a disease-specific QoL measure more suitable for
use in children with CHD. Given that HRQOL is defined as the impact of a specific
given illness, disorder, or medical treatment on an individual’s QoL, a measure of
CHD-related QoL should ideally be taking into account cardiac specific problems
relating to physical symptoms, psychological functioning and social functioning
(Wray et al., 2013). This would allow the measure to be more sensitive and
accurate when evaluating HRQOL in CHD. Three parental questionnaires are
esspecially relevant for CHD patients: the PedsQL enhanced Cardiac Module
(Uzark et al., 2003), the Pediatric Cardiac Quality of Life Inventory (PCQLI)
(Marino et al., 2008) which is for children aged 8 years and above, as well as the
preschool version of the PCQLI (Niemitz et al., 2013). However, as these would
not be appropriate for use with healthy controls, it would not have been possible
to explore group differences in the cohort by comparing HLHS and TGA patients
with healthy controls. Wray et al. (2013) recommended that the gold standard for
evaluating HRQOL is to use both a generic and a disease-specific measure, such
as the PedsQL and PCQLI together. Differences have been reported between
the two measures which indicates that they are evaluating different factors, so it
would be beneficial to use both. The PedsQL would allow for comparisons with
both healthy children and children with CHD or other illnesses, and a disease-
specific measure is more likely to detect differences between CHD subgroups, as well as smaller clinically significant changes in HRQOL longitudinally.

6.4.6 Conclusion and Future Research

In line with previous studies, this study has found evidence of poorer emotional and behavioural outcomes, adaptive functioning, EF and psychosocial and HRQOL outcomes in children with HLHS, compared to those with TGA and healthy controls. A substantial proportion of 4-5 year-olds with HLHS had clinically relevant scores in each domain, and 71% had reduced scores in all PedsQL domains, including total HRQOL. Overall, children with TGA had outcome scores similar to those of healthy controls, including HRQOL, with the exception of peer problems and working memory. Moderate-to-strong negative associations were also found between internalising, externalising and total behavioural problems and executive dysfunction, and both psychosocial functioning and overall HRQOL. It is clear that assessment and surveillance of emotional and behavioural regulation and social development needs to be routinely conducted from infancy to enable identification of problems and early intervention.

Future research needs to focus on the early developmental precursors of psychosocial maladjustment identified in later childhood, the way in which such difficulties develop and manifest in early childhood, and the clinical and socio-environmental factors that put children with CHD at later risk. Studies need to avoid solely relying on parent reported outcome measures and should incorporate direct observations and standardised assessments to evaluate behaviours and outcomes in children with CHD. For example, using tests of EF
such as the Shape School or Preschool Trail Making Test (Epsy, 1997; Epsy & Cwik, 2004) alongside the parent-reported BRIEF-P, or using an assessment battery such as the NEPSY-2 (Korkman et al., 2007) to assess EF/attention, memory/learning, sensorimotor functioning, and social perception. There is a surprising limitation in the lack of standardised objective measures of emotional and behavioural functioning in young children. In this instance, researchers could consider using multiple informants (e.g. using teacher-reported outcome measures) to measure skills and behaviours across different settings (e.g. home versus school and social environments). This would allow for more reliable assessment of psychosocial outcomes, as comparisons could be made between informants to establish if there is consistency among them. Research would also benefit from the inclusion of more objective measures of social skills, peer functioning and school performance, for example academic grades, participation in after-school clubs and activities and days missed of school. Finally, future research needs to utilise disease-specific measures of QoL in CHD in order to comprehensively evaluate HRQOL in CHD subgroups, and to track subtle changes in outcomes longitudinally.

It is important to note that a considerable proportion of studies in the literature group complex or severe CHD patients together rather than evaluating their outcomes individually depending on cardiac physiology. This can make it challenging to compare outcomes between children with HLHS and TGA, as they are often combined and compared to those with less severe types of CHD. Overall, despite increasing numbers of studies investigating psychosocial and QoL outcomes in older children and adolescents with CHD in recent years, research focussing on younger school-aged children is still limited. Research is further limited by lack of longitudinal cohort studies which allow us to be better
informed about long-term psychosocial and QoL outcomes and trajectories in CHD. Longitudinal surveillance and screening of pre-schoolers and young children with complex CHD is especially necessary as this can serve in the early identification of the symptoms associated with common learning and behaviour disorders seen during school age.
Chapter 7: Parent and Family Outcomes and Quality of Life

This chapter will focus on parent self-reported outcomes including family functioning, parent HRQOL, parent mental health, and the impact of CHD on the family. This is a vast topic in the CHD literature and although the research in this thesis is focussed on outcomes in children with complex CHD, it is important to look at the impact of CHD on the parents and family too. Caring for and living with a child with complex heart disease can be challenging and in some cases is associated with high levels of stress and vulnerability in parents. This can impact their mental wellbeing and their overall HRQOL, which in turn impacts their child’s development and HRQOL too. Importantly, all these parental outcomes may also impact how parents interact with their children and report on their child’s behaviour/performance. Consequently, this chapter also examines the relationship between parent-rated child outcomes and HRQOL and parent self-rated mental health and HRQOL.
7.1 Introduction

Multiple factors increase the risk of psychosocial challenges for children with CHD, leading to reduced HRQOL, including parental and family factors such as parental stress, parenting style, and family functioning. Many of these factors have been found to be stronger predictors of poorer psychosocial functioning and HRQOL in children with CHD than cardiac-specific or medical factors (Latal et al., 2009; Ryan et al., 2019; Werninger et al., 2020). Over a decade ago, Bellinger and Newburger (2010) reviewed the literature and concluded that a relatively neglected area of investigation is the impact of having a child with CHD on parents’ psychosocial morbidity and family dynamics. Recent research since then has emphasised the importance of parent psychopathology and family functioning which impact the whole family and their ability to cope with the challenges of having a child with complex CHD. More recently, the Cardiac Neurodevelopmental Outcome Collaborative has recognised that caring for a child with complex CHD places significant demands on parents who are vulnerable to high levels of both acute and persistent psychological stress (Sood et al., 2021). Given that parents and the family environment exert a significant influence on child neurodevelopment and behaviour, parent mental health can exacerbate or mitigate the effects of medical CHD experiences on child outcomes (Sood et al., 2021; Wray et al., 2021).

7.1.1 Parent and Family Stress

A recent systematic review by Kasparian et al. (2019) summarised that CHD-related parental stress often begins prenatally when a substantial proportion of babies with complex CHD are diagnosed. This can be a time of intense fear,
anxiety, and sadness for parents which endures throughout pregnancy and beyond hospital discharge. There are also multiple psychosocial stressors for parents during their child’s stay in the hospital intensive care unit, including intense fear of their child dying, witnessing painful procedures and traumatic events, periods of separation from their child which can affect bonding and attachment, depression and post-traumatic stress disorder (PTSD) (Figure 7.1) (Bishop et al., 2020; Brosig et al., 2007b; Hearps et al., 2014; Kasparian et al., 2016; 2019; Sood et al., 2021; Woolf-King et al., 2017). Woolf-King et al. (2018) conducted a qualitative study of mental health among parents of children with critical CHD. Parents as well as healthcare providers (in paediatric cardiology) provided evidence of psychological morbidity among families of children with critical CHD. One provider stated: “…when you’re in the ICU for so much time there’s a child and the warning bells going off all the time it is just incredibly stressful...and there is no acknowledgement of what this does to people” (pg. 2789). Post-operative recovery for children with complex CHD is non-linear, and the need for future open-heart surgeries particularly in those with HLHS, as well as the presence of comorbidities and unexpected complications, can all further exacerbate parental stress (Sood et al., 2021). Therefore, it is not surprising that repeated exposure to traumatic events, prolonged heightened emotions, worrying about their child’s prognosis, and uncertainty about the future can lead to psychological adjustment difficulties in parents.
Earlier reports of CHD-related parental stress provided conflicting findings, and despite many reporting elevated levels of parental stress, anxiety, and depression following neonatal surgery, some researchers (Spijkerboer et al., 2007) found normal psychological functioning, comparable to parents of healthy controls. Spijkerboer et al. (2007) did not, however, include the most complex patients, such as those with HLHS, in their sample, but did include those with TGA and other forms of CHD. Hearps et al. (2014) described that the majority of parents can adapt to acute stress following children’s surgery, but they did identify 38.5% of parents with persisting high psychological risk associated with substantial
emotional distress. Similar levels of psychological distress have been reported by Woolf-King et al. (2017) who reviewed 30 studies of parental mental health. They found that 30% of parents had symptoms consistent with a diagnosis of PTSD, over 80% had clinically significant symptoms of trauma, 25-50% reported clinically elevated symptoms of depression and/or anxiety, and 30-80% reported experiencing severe psychological distress, particularly in the weeks and months following cardiac surgery. Stress in parents of children with CHD has also been found to be elevated at preschool age (Majnemer et al., 2006; Soulvie et al. 2012). Longitudinal research is limited, but researchers have shown that parental stress is persistent overtime. For example, Lawoko and Soares (2002) reported persistent psychological problems in parents with scores within/above psychiatric outpatient levels, and prevalence rates above those of the general population for depression (18%), anxiety (15%), somatisation (32%), and hopelessness (13%). This is compared to rates of 10%, 7%, 21%, and 5%, respectively in the normative group. Mothers also had higher scores than fathers and were also more pessimistic about the future; CHD severity only accounted for 1-3% of the variation in psychological distress and hopelessness. Similarly, Mussatto et al. (2021) investigated parent/family outcomes over time, when children were approximately 8 weeks, 6 months and 16 months of age. They found QoL and well-being in parents of children with CHD were significantly lower than adult norms, and QoL scores declined over time, whereas self-reported well-being improved. Scores from mothers were worse than fathers on most measures and at most time-points.

Recent studies have also focussed on PTSD and post-traumatic stress symptoms more specifically in parents of children with CHD. For example, Golfenshtein et al. (2022) found that from 158 parent-infant dyads, 9% of mothers met the criteria
for PTSD at the time of hospital discharge, and this increased to 14% four months later, with a large proportion of mothers also experiencing moderate stress symptoms at both time-points. They also found that parenting stress, education level, and amount of infant's medication were linked to the severity of PTSD symptomatology at discharge, and tube-assisted feeding predicted PTSD. At four months, parenting stress, ethnicity, number of visits to the emergency department and/or cardiologist visits predicted the severity and number of symptoms, whilst parenting stress, single ventricle physiology, and number of children predicted PTSD. The symptoms of PTSD are split into four clusters: intrusion, avoidance of trauma reminders, negative alterations in thoughts/feelings and altered physiological arousal/reactivity, and McWhorter et al. (2022) reported that 18% of parents of children with critical CHD met the criteria for PTSD and 70% met the criteria in one or more clusters. They also found that post-traumatic stress symptoms were positively associated with overprotective parenting and total child emotional/behavioural problems. The prevalence of PTSD has also been reported to be higher in studies focusing on parents of children with HLHS. Cantwell-Bartl and Tibballs (2013) investigated PTSD in 18 parents whose infants were diagnosed with HLHS either in utero or post-birth. They found that 89% of mothers and 67% of fathers whose infant was diagnosed in utero had PTSD, compared to 86% of mothers and 50% of fathers who had acute stress disorder, and one mother and father who had PTSD, following diagnosis post-birth. They suggested that traumatic stress in parents was related to the multiple stressors they experienced, including the HLHS diagnosis received after birth (for 50% of parents), the life-threatening nature of HLHS, the ICU environment, and associated cardiac surgery.
Further research has also differentiated between stress in parents of children with different types of CHD physiology. Wray et al. (2018) described the psychological functioning of parents of 8-18 year-old children with various types of CHD or acquired heart disease. Data were collected at a later time point than in many of the other studies, which focussed on parent outcomes within a year of cardiac surgery. They assessed parental mental health, coping, and family functioning and reported that parents of children with complex single ventricle conditions and cardiomyopathy had significantly higher levels of anxiety and depression than reported in published norms. They concluded that there are two different pathways for the long-term psychological well-being of parents of children with heart disease, and these depend on the complexity and nature of the heart disease. In one pathway, more complex heart disease is associated with poorer long-term psychosocial outcomes, whereas in the second pathway, better more optimistic psychosocial outcomes are predicted for both children and parents based on less complex heart conditions. In their study, parents of children with more complex conditions had poorer psychological outcomes compared to parents of children from other cardiac groups such as biventricular CHD. These findings support those of others who also found that parents of school-aged children who had undergone repair of less complex heart lesions reported lower levels of distress and similar coping styles to parents of typically developing controls (Spijkerboer et al., 2007). Golfenshtein et al. (2019) also explored parenting stress in biventricular (BV) compared to single-ventricle (SV) complex CHD during infancy. They found that parents of infants with SV conditions experienced a decrease in total stress over time, specifically the stress resulting from attachment issues, parental role restriction, and infant temperamental characteristics, whereas, parents of infants with BV heart conditions experienced
a decrease in attachment-related stress, and an increase in stress related to infant temperament over time (i.e. mood and distractibility). The authors do not offer a clear explanation for this finding but suggest that this difference in the parents of the BV group may be attributable to temperamental changes in children with CHD, given that those with more complex conditions often experience irritability and moodiness in the early years which can be increasingly stressful for parents. This explanation, however, does not explain why parents of the SV children do not experience similar increases in stress related to temperament given that their children have increased heart disease complexity, compared to BV children. An alternative explanation may be that there is a response shift in parents impacted by SV CHD, as they have learned to adapt and possibly lower their expectations of their child’s functioning and so do not report an increase in difficult or challenging behaviour overtime.

It is noteworthy that children with complex CHD such as SV conditions commonly undergo multiple open-heart surgeries, have frequent hospitalisations which may require lengthier stays, require more frequent medical follow-up and have less certain futures compared to those with less severe CHD. All these factors cause a considerable amount of stress and anxiety for parents, as well as pain and discomfort for the child, which may further exacerbate the stress parents experience and overwhelm them. It is likely that this consequently places a greater burden on parents and families which can impact their own psychological adjustment, coping and mental health (Woolf-King et al., 2017). These high-stress situations over prolonged periods of time may lead to emotional and behavioural regulatory difficulties and psychosocial impairment in parents of children with more complex and severe CHD (Clancy et al., 2020).
7.1.2 Family Functioning and Parenting Style

Family functioning encompasses many facets of the family environment including relationships between family members, parent-child attachment, and levels of conflict, cohesion, adaptation, communication quality and organisation (Sood et al., 2021). The impact of having a child with CHD is known to influence family relationships, especially those between parent and child, marital/partners, and siblings. Mothers are particularly affected with many reporting that cardiac surgery affected their relationship with their baby and up to 23% experienced bonding difficulties (Jordan et al., 2014). A recent review of 22 studies involving parental-report measures and observational results found that difficulties in parent-child interaction on one or more affective or behavioural domains (e.g. lower maternal sensitivity, or lower infant responsiveness) was commonly reported in the majority of studies (Tesson et al. 2022). However, research on parental-foetal bonding, father-child relationships, and child attachment behaviour was limited.

Many mothers have also reported marital problems, decreasing relationship satisfaction from 18 months after delivery up to 36 months after delivery, and divorce, regardless of CHD severity (Biber et al., 2019; Dale et al., 2013). Further, parents have reported feelings of decreased competence, isolation, and problems in social functioning and communication which are affected by lack of others’ understanding of the family’s situation, parents’ difficulty talking about their child’s health condition, and the need to have effective conversations with health professionals (Gregory et al., 2018). Parents of children with CHD have also reported difficulties maintaining a work-life balance with increased need for workplace support and leisure activities, and fathers specifically stated that providing emotional support for their partner was the most time-consuming and
difficult task. Siblings of children with CHD can also be impacted as family members, whilst also being additional sources of stress for their parents. Parker et al.'s (2020) review suggested that siblings experience adverse life changes which lead to negative impacts in several domains including: emotional and behavioural functioning, school functioning, QoL and health, despite being otherwise healthy. Siblings are often given greater responsibilities but have their social activities restricted, and their parents’ resources are split and are often focussed on their sibling with CHD.

The Resiliency Model of Family Stress, Adjustment, and Adaptation developed by McCubbin et al. (1996) describes how families of chronically ill children cope based on available resources such as the cohesiveness of the family, social and community support, and inherent abilities of the individual family members. This enables them to achieve long-term adaptation which itself is either positive or negative, depending on how successful they are. The model takes into consideration many factors which can influence parents’ wellbeing and the experience of caring for a child with a chronic condition such as CHD, apart from the severity of the condition itself. These factors include the family’s prior experience with stress, state and trait anxiety, available social support, socioeconomic status, problem-solving, and communication skills (Dale et al., 2013). Tak and McCubbin (2002) investigated family stress, perceived social support and coping following a CHD diagnosis. They found that perceived social support functioned as a resiliency factor between family stress and parental/family coping. The presence of social support may moderate the impact of stress and explain why some individuals experience higher life stresses but do not show a high level of distress. Child and family characteristics were also important predictors of perceived social support and parental coping. Jackson et
al. (2015) conducted a systematic review of 25 qualitative studies focussing on family impact and coping in CHD families. They found support for the finding that families who have fewer psychosocial resources and lower levels of support may be at risk of higher psychological distress and lower well-being over time, for both parent and the child. Again, factors such as family cohesiveness and adaptive parental coping strategies were necessary for successful parental adaptation to CHD in their child.

Further support for this model comes from Wray et al. (2018) who observed that family cohesion was higher and levels of conflict were lower in parents of children with CHD and acquired heart disease, compared to published norms. This suggests that resilience (i.e. effective functioning and adjustment to stress) and positive adaptation is possible in CHD families depending on available internal and external resources such as the family unit and strength, and social support and the community. They also found higher levels of organisation and control in these CHD families, suggesting that planning and rules are incorporated into family life. Significant positive correlations have been identified between family cohesion, organisation, and lack of conflict and children’s psychological health, social competence, and behaviour across a range of chronic illnesses, including CHD (Landolt et al., 2008). Recently, Mussatto et al. (2021) investigated family functioning and QoL in parents of children with HLHS. Given previous findings in children with HLHS and their families, it is somewhat surprising that they found parents reported better family functioning compared to published norms, but 26% did experience family dysfunction, parents reported somewhat worse family function over time, and parent QoL and wellbeing were significantly below adult norms. The authors suggest a possible explanation for this unexpected finding may be due to changes in social support networks which are readily available.
early in the course of an infant’s illness, but then dissipate over time, which also explains the worse family function scores in later time-points of the study. In their study, predictors of better family function included greater family hardiness and resources (e.g. support, communication, financial stability), as well as being married or living with a partner. Being a single parent was a risk factor for poorer family function, but not for lower individual parent QoL or wellbeing.

Parent stress is also known to impact parenting style which then consequently impacts both parent and child HRQOL. Parenting style refers to the beliefs, behaviours and attitudes parents hold, including responsiveness and regulation, which influences their effectiveness in child behaviour management and adjustment (Luyckx et al., 2011; McCusker et al., 2007). Brosig et al. (2007) found that parents of children with HLHS reported more negative impact of the heart disease on the family, and more parenting stress than parents of children with TGA. However, parents of both groups of children were more permissive in their parenting style than parents of healthy controls. Parental stress was significantly positively correlated with overall impact of the disease on the family, and the HLHS group showed higher scores on child demandingness, which made parenting more difficult. Findings on parenting styles in CHD are conflicting, with some reporting more permissive parenting styles compared to healthy controls, and others showing nurturing and discipline patterns similar to healthy controls (Jackson et al., 2015).

7.1.3 Factors Influencing Parent Adjustment, Stress and HRQOL

The role of social support and available resources in families affected by CHD have been discussed, but there are many other factors which are also known to
influence parent adjustment to CHD and associated stress. A number of medical and psychological factors have been identified as correlates of parental adjustment including: time since cardiac surgery, the number of cardiac operations, family cohesion, and family conflict (Wray et al., 2018). Others have also suggested that parent education level, household income, family structure, country of birth and language may also influence parent mental health following diagnosis of CHD in their children (Franck et al., 2010; Lisanti, 2018). Many of these factors are considered measures of socioeconomic status (SES) of which education status is widely used as a proxy, followed by income and occupation. These SES measures have been shown to influence parental stress and mental health in a range of clinical paediatric populations including CHD. For example, lower education level, family income, and poverty have all been significantly associated with increased risk for parental stress and mental health problems, including PTSD (Franck et al., 2010; Lisanti, 2018; Roberts et al., 2021; Spijkerboer et al., 2007). These findings highlight the need for greater attention and support to be given to parents from socially and economically disadvantaged backgrounds.

7.1.4 Impact of Poor Outcomes in Parents

It is clear that a myriad of factors can impact parental stress, these include parental and more specifically maternal mental health, family functioning, and coping and adaptation to CHD. These also subsequently impact behaviour, adaptation, psychosocial functioning and HRQOL in children with CHD, but the relationship between parent and child outcomes has been less frequently investigated, until recently. Denniss et al. (2019) investigated HRQOL in families of 1-5 year-old children with either SV or BV CHD, and reported that lower child
HRQOL was associated with SV morphology, physical morbidity, feeding difficulties, and greater maternal psychological stress. They also found that lower maternal HRQOL was significantly and strongly associated with poorer family functioning, greater maternal psychological stress, child physical comorbidity, and a ‘difficult’ child temperament, which accounted for 73% of the variance in maternal HRQOL. Maternal mental health measured when a child is a pre-schooler has been found to be predictive of behavioural outcomes, social interaction, and ADHD-related symptoms in 10 year-old children, whilst cardiac and medical risk factors were not predictive of later outcomes (Werninger et al., 2020). Therefore, the psychological status of mothers in the early years of their child’s life can continue to have an impact on the child’s behavioural and psychosocial functioning long-term. Further support for the role of parental stress in child outcomes comes from Chang et al. (2020) who found that 2-17 year-olds with complex cyanotic CHD had increased levels of internalising behavioural problems, and this was mediated by level of parenting stress. Children with HLHS are known to have poorer outcomes compared to those with other types of CHD, but family factors are more important than disease factors in predicting negative behavioural outcomes in these children. These family factors include: high maternal worry and anxiety, general family mental health issues, parenting style and control, and single parent status (Howell et al., 2019; McCusker et al., 2007).

Despite some clear associations between parent mental health and child neurodevelopment, psychosocial functioning and HRQOL outcomes, there is currently no research which investigates the experience of stress for parents of children with CHD and its full impact on the family across the child’s life span. Lisanti (2018) created the Parental Stress and Resilience in CHD Model which is the first comprehensive framework to describe the impact of parental stress
specifically within CHD. This was developed to help address health disparity variables which are known to influence parental stress as well as impacting children with CHD, and inform the development of targeted interventions to better support families affected by CHD. Figure 7.2 outlines Lisanti’s model and depicts the longitudinal cumulative impact of the stress/coping/response cycle and the process of resilience which influences parental outcomes, and then ultimately influences children’s mental and physical health, neurodevelopment, behaviour, and HRQOL. Overall, more longitudinal research is needed in order to examine the long-term impact of early psychological adjustment problems in parents of children with CHD.
Figure 7.2 The Impact of Parent Stress and Resilience in CHD Model adapted from Lisanti (2018)
There are multiple psychosocial stressors for parents throughout their child’s life, and although certain factors such as available social support, coping, and resilience can mediate the impact of these stressors, and help parents adapt to living with their child’s CHD, intense parental fears, anxiety, and sadness can endure and persist long-term many years after the initial diagnosis and surgery (Kasparian et al., 2019; Lawoko and Soares, 2002; Majnemer et al., 2006). Consequently, there is a high prevalence of parental mental health problems including PTSD, stress symptoms and distress, feelings of hopelessness, and anxiety and depression (Golfenshtein et al., 2022; McWhorter et al., 2022; Woolf-King et al., 2017). Given that HLHS and other SV conditions are more severe and complex types of CHD requiring multiple surgeries, and are associated with non-linear postoperative recovery and multiple comorbidities, it is not surprising that parents of children with these conditions have been found to have worse psychosocial outcomes and HRQOL, compared to parents of those with other types of CHD (Wray et al., 2018). However, literature has suggested that parent, and particularly, maternal mental health is known to significantly impact child outcomes, more so than heart disease severity and other clinical/medical factors (Chang et al., 2020; Denniss et al., 2019; McCusker et al., 2013; Werninger et al., 2020).

7.1.5 Aims and Hypotheses

The primary aim of this study is to investigate family functioning, the impact of CHD on the family, parent HRQOL and mental health outcomes using parent self-reported measures. A secondary aim is to examine the relationship between parent-rated child behavioural, psychosocial and HRQOL outcomes, and parent mental health and HRQOL.
The following hypotheses draw on a priori literature regarding HRQOL and mental health in parents, especially mothers of children with CHD and address a gap in the literature in terms of investigating these outcomes 4-5 years after initial diagnoses and open-heart surgery. It is hypothesised that:

- Parents of children with CHD and particularly HLHS, will have higher levels of anxiety and depression, and poorer family functioning and HRQOL, compared with parents of healthy controls.
- Higher illness-related parental stress and mental health problems, poorer family functioning and greater severity of CHD (i.e. HLHS) will be negatively associated with overall parental HRQOL.
- Elevated behavioural problems and executive dysfunction in children with CHD will be positively correlated with parental mental health problems, and negatively correlated with family functioning and parent HRQOL.
- Poor parental HRQOL will be associated with psychosocial problems and reduced overall HRQOL in children with CHD, particularly those with HLHS.

7.2 Methods

7.2.1 Participants

The parents of the longitudinal cohort described in Chapter 6 participated in this element of the study, which was part of the final time-point at 4-5 years of age. A total of 32 parents (31 mothers and 1 father) of 32 children participated. The full sample and parental demographics are summarised in Table 7.1.
Table 7.1 Parental demographic information including education and employment levels for the cohort of patients with HLHS, TGA, and healthy controls who participated in the behavioural and psychosocial outcomes study at 4-5 years (time-point 4)

<table>
<thead>
<tr>
<th>Time-point 4</th>
<th>HLHS</th>
<th>TGA</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (N)</td>
<td>7</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Child's Age (years), mean (SD)</td>
<td>5.09 (0.45)</td>
<td>5.28 (0.27)</td>
<td>5.23 (0.43)</td>
</tr>
<tr>
<td>Child's Gender (M:F)</td>
<td>4:3</td>
<td>9:5</td>
<td>9:2</td>
</tr>
</tbody>
</table>

**Parent Information**

<table>
<thead>
<tr>
<th></th>
<th>HLHS</th>
<th>TGA</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent, N (mothers : fathers)</td>
<td>7:0</td>
<td>14:0</td>
<td>10:1</td>
</tr>
<tr>
<td>Mother's Age, mean (SD)</td>
<td>34.83 (5.12)</td>
<td>34.14 (4.02)</td>
<td>38.55 (4.25)</td>
</tr>
<tr>
<td>Father's Age, mean (SD)</td>
<td>36.80 (2.28)</td>
<td>36.86 (6.74)</td>
<td>39.30 (2.75)</td>
</tr>
</tbody>
</table>

**Highest maternal education level, N (%)**

<table>
<thead>
<tr>
<th></th>
<th>HLHS</th>
<th>TGA</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCSE/O-levels/equivalent</td>
<td>2 (28.57)</td>
<td>2 (14.29)</td>
<td>0</td>
</tr>
<tr>
<td>A-levels/equivalent</td>
<td>2 (28.57)</td>
<td>4 (28.57)</td>
<td>0</td>
</tr>
<tr>
<td>University graduate</td>
<td>0</td>
<td>4 (28.57)</td>
<td>5 (45.45)</td>
</tr>
<tr>
<td>Postgraduate</td>
<td>2 (28.57)</td>
<td>4 (28.57)</td>
<td>6 (54.55)</td>
</tr>
</tbody>
</table>

**Maternal employment, N (%)**

<table>
<thead>
<tr>
<th></th>
<th>HLHS</th>
<th>TGA</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Employed full-time</td>
<td>0</td>
<td>2 (14.29)</td>
<td>3</td>
</tr>
<tr>
<td>Employed part-time</td>
<td>2 (28.57)</td>
<td>7 (50)</td>
<td>6 (54.55)</td>
</tr>
<tr>
<td>Self-employed</td>
<td>3 (42.86)</td>
<td>1 (7.14)</td>
<td>2 (18.18)</td>
</tr>
<tr>
<td>Unemployed/stay at home mum</td>
<td>0</td>
<td>4 (28.57)</td>
<td>0</td>
</tr>
<tr>
<td>Student</td>
<td>1 (14.29)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Highest paternal education level, N (%)**

<table>
<thead>
<tr>
<th></th>
<th>HLHS</th>
<th>TGA</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCSE/O-levels/equivalent</td>
<td>2 (28.57)</td>
<td>2 (14.29)</td>
<td>1 (9.09)</td>
</tr>
<tr>
<td>A-levels/equivalent</td>
<td>1 (14.29)</td>
<td>2 (14.29)</td>
<td>1 (9.09)</td>
</tr>
<tr>
<td>University graduate</td>
<td>3 (42.86)</td>
<td>6 (42.86)</td>
<td>5 (45.45)</td>
</tr>
<tr>
<td>Postgraduate</td>
<td>0</td>
<td>1 (7.14)</td>
<td>4 (36.36)</td>
</tr>
<tr>
<td>Other (higher national diploma)</td>
<td>0</td>
<td>1 (7.14)</td>
<td>0</td>
</tr>
</tbody>
</table>

**Paternal employment, N (%)**

<table>
<thead>
<tr>
<th></th>
<th>HLHS</th>
<th>TGA</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Employed full-time</td>
<td>4 (57.14)</td>
<td>11 (78.57)</td>
<td>8 (72.73)</td>
</tr>
<tr>
<td>Employed part-time</td>
<td>0</td>
<td>0</td>
<td>2 (18.18)</td>
</tr>
<tr>
<td>Self-employed</td>
<td>1 (14.29)</td>
<td>2 (14.29)</td>
<td>1 (9.09)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
7.2.2 Procedure / Assessment

The assessment at the UCL Wolfson Centre followed the same procedure described in Chapter 6. Parents were reminded about what the assessment involved, and were given a copy of the study information sheet, before they were asked to sign a consent form. Parents were asked to complete a battery of parental questionnaires which included a demographics questionnaire, the PedsQL Family Impact Module, and The Hospital Anxiety and Depression Scale (HADS). Parents of children with CHD only were also asked to complete the Paediatric Inventory for Parents (PIP) and the Impact of Event Scale - Revised (IES-R) as these were relevant to their child having a serious illness and the stress likely caused by this (all detailed in Chapter 2 section 2.9.2.4.2). These questionnaires were completed by the parents, most often by the mothers, whilst their child was being tested by the researcher. All the parent/family focussed questionnaires took approximately 40 minutes to complete, not including those that were focussed on child outcomes described in Chapter 6.

If parents were unable to complete all questionnaires during the assessment visit, they were given a freepost envelope to return any questionnaires completed at home. Researchers stressed the importance of completing all questionnaires as close in time to the assessment as possible.

7.2.3 Data Analysis

Descriptive statistics were first used to characterise the sample, and data were tested for homogeneity of variance and distribution. Given the small and unequal sample sizes of all three groups and a violation of the homogeneity of variance assumption and non-normally distributed data, non-parametric Kruskal-Wallis
analyses were conducted to compare parental questionnaire scores between the three groups. For the post-hoc analyses, Mann-Whitney U tests with uncorrected p-values were used to uncover the pairwise differences and calculate effect size. For non-parametric analyses, medians and interquartile ranges (IQR) are reported.

For analysis of the PIP and IES which were only completed by parents of patients with CHD, and not healthy controls, Mann-Whitney U tests with uncorrected p-values were used to compare questionnaire scores between HLHS and TGA patients. Effect sizes were also calculated for significant results only.

In order to calculate the proportion of parents scoring in the borderline (i.e. 1-2 SD below the mean/cut-off) and clinical (i.e. ≥2 SDs) range for each questionnaire and subscale, specific cut-offs were used based on published norms by the authors of the measures, or available data in the normative population or the CHD literature where appropriate. More specifically, for the PedsQL Family Impact Module, Medrano et al.’s (2013) subscale means and SD were used from a community sample; for the HADS, Zigmond and Snaith’s (1983) original published cut-offs were used; for the PIP, Kaugars et al.’s (2018) total CHD cohort cut-offs were used; and for the IES, Weiss and Marmar’s (1996) original published cut-offs were used.

Non-parametric Spearman’s rank-order correlations were conducted to measure the strength and direction of association between two ranked variables. Based on the literature reviewed above, specific subtests of the parental questionnaires were selected to investigate the relationship between parent HRQOL, family functioning, parent mental health, CHD-related stress and the total impact of CHD on the family. Correlational analyses were also used to look at the relationship between child and parent outcomes, including psychosocial health and HRQOL.
7.3 Results

Parents of a total of 32 children completed the questionnaires. This included parents of 7 children with HLHS, 14 with TGA, and 11 healthy controls. One parent of a child with TGA did not complete the HADS questionnaire so there were a total of 31 parent responses for the two subtests of the HADS. The median scores and IQR for each subtest in each group and between-group results are presented separately for each measure/questionnaire below. Parents of children with HLHS had the highest scores indicating increased symptomology on many of the subtests, with the exception of the PedsQL Family Impact scores where they had the lowest scores indicating worse outcomes, compared to parents of children with TGA and healthy controls.

7.3.1 Parent Self-Reported Outcomes

7.3.1.1 PedsQL Family Impact Module

Significant group differences were observed in almost all subtests of the PedsQL Family Impact, including: Physical Functioning, Emotional Functioning, Social Functioning, Cognitive Functioning, Communication, Worry, Daily Activities, as well as Total Score, Parent HRQOL and Family Functioning summary scores. Post-hoc tests showed that across many of the subtests, parents of the HLHS group had significantly lower scores compared to parents of both the Control and TGA groups. No significant group differences were observed in the Family Relationships subtest. Table 7.2 summarises results for the PedsQL Family Impact Module.

Table 7.3 summarises the proportion of parents with children with HLHS, TGA and healthy controls with PedsQL Family Impact Module scores 1-2 SD and ≥2
SDs below the mean. There were some subtests in which parents of both patients with HLHS and TGA had scores ≥2 SDs below the mean, these included: Social Functioning, Communication, and Worry. Overall, a greater proportion of parents of the HLHS group had scores either 1-2 SD or ≥2 SDs below the mean, compared to the TGA and healthy control groups.

Table 7.2 PedsQL Family Impact Module outcomes by subtest in parents of children with HLHS, TGA, and healthy controls at 4-5 years

<table>
<thead>
<tr>
<th></th>
<th>HLHS</th>
<th>TGA</th>
<th>Controls</th>
<th>H</th>
<th>p</th>
<th>Post-hoc</th>
</tr>
</thead>
</table>
| **PedsQL Family Impact** (median transformed score (IQR))
<p>| Parent Functioning   |      |     |          |     |       |          |
| Physical Functioning | 45.83| 87.50| 87.50    | 7.74| .02*  |          |
|                      | (37.50) | (37.50) | (33.33) |     |       |          |
|                      |       |       |          |     |       |          |
| Emotional Functioning| 50.00| 80.00| 85.00    | 8.96| .01*  |          |
|                      | (25.00) | (35.00) | (40.00) |     |       |          |
|                      |       |       |          |     |       |          |
| Social Functioning   | 43.75| 100.00| 81.25    | 11.80| .003**|          |
|                      | (25.00) | (37.50) | (37.50) |     |       |          |
|                      |       |       |          |     |       |          |
| Cognitive Functioning| 55.00| 80.00| 77.50    | 11.15| .004**|          |
|                      | (25.00) | (22.50) | (22.50) |     |       |          |</p>
<table>
<thead>
<tr>
<th></th>
<th>HLHS</th>
<th>TGA</th>
<th>Controls</th>
<th>H</th>
<th>p</th>
<th>Post-hoc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Communication</td>
<td>50.00 (58.33)</td>
<td>75.00 (45.84)</td>
<td>100.00 (16.67)</td>
<td>11.69</td>
<td>.003**</td>
<td>HLHS &lt; C: U = 3.50, z = -3.27, p &lt; 0.001, r = -0.77</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TGA &lt; C: U = 41.50, z = -2.04, p = 0.05, r = -0.41</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HLHS &lt; C: U = 4.00, z = -3.19, p &lt; 0.001, r = -0.75</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HLHS &lt; TGA: U = 17.00, z = -2.40, p = 0.02, r = -0.52</td>
</tr>
<tr>
<td>Worry</td>
<td>40.00 (25.00)</td>
<td>85.00 (36.50)</td>
<td>100.00 (10.00)</td>
<td>12.35</td>
<td>.002**</td>
<td></td>
</tr>
<tr>
<td>Family Functioning</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HLHS &lt; C: U = 7.00, z = -2.89, p = 0.003, r = -0.68</td>
</tr>
<tr>
<td>Daily Activities</td>
<td>33.33 (50.00)</td>
<td>100.00 (41.67)</td>
<td>91.67 (25.00)</td>
<td>10.05</td>
<td>.01*</td>
<td>HLHS &lt; TGA: U = 13.50, z = -2.73, p = 0.01, r = -0.60</td>
</tr>
<tr>
<td>Family Relationships</td>
<td>65.00 (55.00)</td>
<td>100.00 (30.00)</td>
<td>100.00 (30.00)</td>
<td>2.81</td>
<td>.25</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HLHS &lt; C: U = 3.00, z = -3.22, p &lt; 0.001, r = -0.76</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HLHS &lt; TGA: U = 9.00, z = -2.99, p = 0.002, r = -0.65</td>
</tr>
<tr>
<td>Total Score</td>
<td>49.31 (19.16)</td>
<td>84.03 (32.63)</td>
<td>87.50 (25.00)</td>
<td>12.09</td>
<td>.002**</td>
<td>HLHS &lt; C: U = 8.50, z = -2.72, p = 0.004, r = -0.64</td>
</tr>
<tr>
<td>(all items)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HLHS &lt; TGA: U = 12.00, z = -2.78, p = 0.004, r = -0.61</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HLHS &lt; C: U = 13.50, z = -2.29, p = 0.02, r = -0.54</td>
</tr>
<tr>
<td>Parent HRQOL</td>
<td>55.00 (27.50)</td>
<td>91.25 (34.38)</td>
<td>93.75 (30.00)</td>
<td>9.46</td>
<td>.01*</td>
<td></td>
</tr>
<tr>
<td>Summary Score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HLHS &lt; TGA: U = 17.00, z = -2.44, p = 0.02, r = -0.53</td>
</tr>
<tr>
<td>Family Functioning</td>
<td>62.50 (37.50)</td>
<td>100.00 (34.37)</td>
<td>96.88 (34.37)</td>
<td>7.15</td>
<td>.03*</td>
<td></td>
</tr>
</tbody>
</table>

Note. Data are presented as group median (IQR), Kruskal-Wallis H and p-value, where statistically significant differences between groups denoted as *p<0.05, **p<0.01, and ***p<0.001, post-hoc pairwise group differences: Mann-Whitney U, z, p-value, and effect size r (where healthy controls are denoted as C).
Table 7.3 The total number and percentage of parents with PedsQL Family Impact Module scores 1-2 SD or ≥2 SDs below the mean

<table>
<thead>
<tr>
<th>PedsQL Family Impact (N (%))</th>
<th>HLHS (N=7)</th>
<th>TGA (N=14)</th>
<th>Controls (N=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Functioning</td>
<td>1-2 SD</td>
<td>4 (57)</td>
<td>1 (7)</td>
</tr>
<tr>
<td></td>
<td>≥2 SD</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Emotional Functioning</td>
<td>1-2 SD</td>
<td>2 (29)</td>
<td>2 (14)</td>
</tr>
<tr>
<td></td>
<td>≥2 SD</td>
<td>1 (14)</td>
<td>0</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>1-2 SD</td>
<td>3 (43)</td>
<td>1 (7)</td>
</tr>
<tr>
<td></td>
<td>≥2 SD</td>
<td>2 (29)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Cognitive Functioning</td>
<td>1-2 SD</td>
<td>2 (29)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>≥2 SD</td>
<td>1 (14)</td>
<td>0</td>
</tr>
<tr>
<td>Communication</td>
<td>1-2 SD</td>
<td>1 (14)</td>
<td>3 (21)</td>
</tr>
<tr>
<td></td>
<td>≥2 SD</td>
<td>3 (43)</td>
<td>2 (14)</td>
</tr>
<tr>
<td>Worry</td>
<td>1-2 SD</td>
<td>3 (43)</td>
<td>2 (14)</td>
</tr>
<tr>
<td></td>
<td>≥2 SD</td>
<td>2 (29)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Daily Activities</td>
<td>1-2 SD</td>
<td>3 (43)</td>
<td>2 (14)</td>
</tr>
<tr>
<td></td>
<td>≥2 SD</td>
<td>2 (29)</td>
<td>0</td>
</tr>
<tr>
<td>Family Relationships</td>
<td>1-2 SD</td>
<td>1 (14)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>≥2 SD</td>
<td>1 (14)</td>
<td>0</td>
</tr>
<tr>
<td>Total Score</td>
<td>1-2 SD</td>
<td>3 (43)</td>
<td>2 (14)</td>
</tr>
<tr>
<td></td>
<td>≥2 SD</td>
<td>1 (14)</td>
<td>0</td>
</tr>
<tr>
<td>Parent HRQOL</td>
<td>1-2 SD</td>
<td>3 (43)</td>
<td>2 (14)</td>
</tr>
<tr>
<td></td>
<td>≥2 SD</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Family Functioning</td>
<td>1-2 SD</td>
<td>2 (29)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>≥2 SD</td>
<td>1 (14)</td>
<td>0</td>
</tr>
</tbody>
</table>

7.3.1.2 Hospital Anxiety and Depression Scale

Significant group differences were observed in both the Anxiety and Depression subtests of the HADS. Post-hoc Mann Whitney tests showed that in both the subtests, parents of the HLHS group had significantly higher scores compared to parents of both the Control and TGA groups. Table 7.4 summarises results for
the HADS. Table 7.5 summarises the proportion of parents with children with HLHS, TGA, and healthy controls with borderline and clinical HADS scores. For Anxiety, both parents of patients with HLHS and TGA had scores within the clinical range (4 out of 7 (57%) of parents of HLHS patients and 8% of TGA patients), but neither group of parents had clinical Depression scores. Overall, a greater proportion of parents of the HLHS group had scores in the borderline and clinical range, compared to the TGA and healthy control groups.

Table 7.4 The Hospital Anxiety and Depression Scale (HADS) outcomes by subtest in parents of children with HLHS, TGA, and healthy controls at 4-5 years

<table>
<thead>
<tr>
<th></th>
<th>HLHS</th>
<th>TGA</th>
<th>Controls</th>
<th>H</th>
<th>p</th>
<th>Post-hoc</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HADS (median raw score (IQR))</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>11.00 (5.00)</td>
<td>4.00 (6.00)</td>
<td>4.00 (10.00)</td>
<td>7.83</td>
<td>.02*</td>
<td>HLHS &gt; C: U = 10.50, z = -2.55, p = 0.01, r = -0.60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HLHS &gt; TGA: U = 15.50, z = -2.39, p = 0.01, r = -0.53</td>
</tr>
<tr>
<td>Depression</td>
<td>7.00 (2.00)</td>
<td>4.00 (4.00)</td>
<td>2.00 (5.00)</td>
<td>6.86</td>
<td>.03*</td>
<td>HLHS &gt; C: U = 13.50, z = -2.28, p = 0.02, r = -0.54</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HLHS &gt; TGA: U = 17.50, z = -2.24, p = 0.02, r = -0.50</td>
</tr>
</tbody>
</table>

*Note.* Data are presented as group median (IQR), Kruskal-Wallis H and p-value, where statistically significant differences between groups denoted as *p<0.05, **p<0.01, and ***p<0.001, and post-hoc pairwise group differences: Mann-Whitney U, z, p-value, and effect size r (where healthy controls are denoted as C).
Table 7.5 The total number and percentage of parents with HADs scores in the borderline (1-2 SD below the mean) and clinical (≥2 SDs) range

<table>
<thead>
<tr>
<th>HADS</th>
<th>HLHS (N=7)</th>
<th>TGA (N=13)</th>
<th>Controls (N=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety (N (%))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>borderline</td>
<td>2 (29)</td>
<td>3 (23)</td>
<td>2 (18)</td>
</tr>
<tr>
<td>clinical</td>
<td>4 (57)</td>
<td>1 (8)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Depression (N (%))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>borderline</td>
<td>3 (43)</td>
<td>1 (8)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>clinical</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

7.3.1.3 Paediatric Inventory for Parents

Each item of the PIP is scored for both frequency and difficulty. A significant main effect of group was observed in all subtests scored for frequency: Communication, Medical Care, Emotional Distance, Role Function, and Total Frequency. There was also a significant main effect of group in all the same subtests scored for difficulty, except Medical Care Difficulty. Parents of the HLHS group had significantly higher scores on all subtests compared to parents of the TGA group. Table 7.6 summarises results for the PIP. Table 7.7 summarises the proportion of parents of children with HLHS and TGA, with borderline and clinical PIP scores. Overall, a greater proportion of parents of the HLHS group had scores in the borderline and clinical range, compared to the TGA groups, who had no borderline scores, and only one parent had a score in the clinical range for Total Frequency and Total Difficulty.
Table 7.6 Paediatric Inventory for Parents (PIP) outcomes by subtest in parents of children with HLHS and TGA at 4-5 years

<table>
<thead>
<tr>
<th></th>
<th>HLHS</th>
<th>TGA</th>
<th>p</th>
<th>Mann-Whitney U</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PIP (median raw score (IQR))</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Communication</td>
<td>26.00 (14.00)</td>
<td>13.50 (7.00)</td>
<td>.03*</td>
<td>HLHS &gt; TGA: U = 19.00, z = -2.25, r = -0.49</td>
</tr>
<tr>
<td>Medical Care</td>
<td>24.00 (21.00)</td>
<td>14.00 (11.00)</td>
<td>.05</td>
<td>HLHS &gt; TGA: U = 22.50, z = -1.98, r = -0.43</td>
</tr>
<tr>
<td>Emotional Distance</td>
<td>48.00 (20.00)</td>
<td>26.50 (17.00)</td>
<td>.02*</td>
<td>HLHS &gt; TGA: U = 17.50, z = -2.36, r = -0.51</td>
</tr>
<tr>
<td>Role Function</td>
<td>30.00 (17.00)</td>
<td>15.50 (9.00)</td>
<td>.003**</td>
<td>HLHS &gt; TGA: U = 11.00, z = -2.84, r = -0.62</td>
</tr>
<tr>
<td><strong>Total Frequency</strong></td>
<td>138.00 (68.00)</td>
<td>74.50 (39.00)</td>
<td>.01*</td>
<td>HLHS &gt; TGA: U = 16.00, z = -2.47, r = -0.54</td>
</tr>
<tr>
<td><strong>Difficulty</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Communication</td>
<td>23.00 (24.00)</td>
<td>13.50 (8.00)</td>
<td>.05</td>
<td>HLHS &gt; TGA: U = 22.50, z = -1.98, r = -0.43</td>
</tr>
<tr>
<td>Medical Care</td>
<td>23.00 (19.00)</td>
<td>13.50 (11.00)</td>
<td>.07</td>
<td>HLHS &gt; TGA: U = 24.50, z = -1.84</td>
</tr>
<tr>
<td>Emotional Distance</td>
<td>48.00 (23.00)</td>
<td>29.00 (19.00)</td>
<td>.02*</td>
<td>HLHS &gt; TGA: U = 18.50, z = -2.28, r = -0.50</td>
</tr>
<tr>
<td>Role Function</td>
<td>27.00 (17.00)</td>
<td>13.50 (10.00)</td>
<td>.02*</td>
<td>HLHS &gt; TGA: U = 18.00, z = -2.32, r = -0.51</td>
</tr>
<tr>
<td><strong>Total Difficulty</strong></td>
<td>119.00 (76.00)</td>
<td>74.50 (43.00)</td>
<td>.02*</td>
<td>HLHS &gt; TGA: U = 18.00, z = -2.31, r = -0.50</td>
</tr>
</tbody>
</table>

*Note.* Data are presented as group median (IQR), group difference p-value, where statistically significant differences between groups denoted as *p<0.05, **p<0.01, and ***p<0.001, and Mann-Whitney U, z, p-value, and effect size r (for significant results only).
Table 7.7 The total number and percentage of parents with PIP scores 1-2 SD or ≥2 SDs below the mean

<table>
<thead>
<tr>
<th>PIP</th>
<th>HLHS (N=7)</th>
<th>TGA (N=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Frequency (N (%))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 SD</td>
<td>2 (29)</td>
<td>0</td>
</tr>
<tr>
<td>≥2 SD</td>
<td>3 (43)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Total Difficulty (N (%))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 SD</td>
<td>1 (14)</td>
<td>0</td>
</tr>
<tr>
<td>≥2 SD</td>
<td>3 (43)</td>
<td>1 (8)</td>
</tr>
</tbody>
</table>

7.3.1.4 Impact of Event Scale

Significant group differences were observed in the Intrusion and Hyperarousal subtests of the IES and the Total Impact of Event Score, but there were no differences in the Avoidance subtest scores. Parents of the HLHS group had significantly higher scores on all subtests compared to parents of the TGA group.

Table 7.8 summarises results for the IES. Table 7.9 summarises the proportion of parents of children with HLHS and TGA, with clinically relevant IES scores, as well as those with scores meeting the criteria for PTSD, and extremely severe scores. Overall, the proportion of parents with these scores is different in the two CHD patient groups for clinically relevant scores (2 out of 7 (29%) of parents of HLHS patients and no parents of TGA patients), PTSD (no parents of HLHS patients and 8% of TGA patients), and severe scores (1 out of 7 (14%) of parents of HLHS patients and 8% of TGA patients).
Table 7.8 Impact of Event Scale (IES) outcomes by subtest in parents of children with HLHS and TGA at 4-5 years

<table>
<thead>
<tr>
<th></th>
<th>HLHS</th>
<th>TGA</th>
<th>p</th>
<th>Mann-Whitney U</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IES (median raw score (IQR))</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avoidance</td>
<td>3.00 (10.00)</td>
<td>1.00 (5.00)</td>
<td>.26</td>
<td>HLHS &gt; TGA: U = 33.00, z = -1.23</td>
</tr>
<tr>
<td>Intrusion</td>
<td>8.00 (9.00)</td>
<td>3.50 (5.00)</td>
<td>.03*</td>
<td>HLHS &gt; TGA: U = 19.50, z = -2.21, r = -0.48</td>
</tr>
<tr>
<td>Hyperarousal</td>
<td>4.00 (7.00)</td>
<td>1.00 (3.00)</td>
<td>.03*</td>
<td>HLHS &gt; TGA: U = 20.50, z = -2.19, r = -0.48</td>
</tr>
<tr>
<td>Total Impact Score</td>
<td>2.35 (3.00)</td>
<td>0.87 (2.00)</td>
<td>.04*</td>
<td>HLHS &gt; TGA: U = 21.50, z = -2.06, r = -0.44</td>
</tr>
</tbody>
</table>

*Note.* Data are presented as group median (IQR), group difference p-value, where statistically significant differences between groups denoted as *p<0.05, **p<0.01, and ***p<0.001, and Mann-Whitney U, z, p-value, and effect size r (for significant results only).

Table 7.9 The total number and percentage of parents with IES scores in the clinical relevant, PTSD diagnosis, and extremely severe range, according to the published cut-offs for these categories

<table>
<thead>
<tr>
<th>IES</th>
<th>HLHS (N=7)</th>
<th>TGA (N=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>clinical</td>
<td>PTSD</td>
</tr>
<tr>
<td>Total Impact Score (N (%))</td>
<td>2 (29)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 (8)</td>
</tr>
</tbody>
</table>

Overall, a significant proportion of parents of HLHS patients had scores within the borderline and clinical range and parents of TGA patients had scores which were similar to parents of healthy controls. The pattern of these results is similar to the parent-reported outcome measures for children reported in Chapter 6. A very small proportion of parents of TGA patients also had scores within the borderline
and clinical range, but this was usually only one parent, with the exception of some subtests in the PedsQL Family Impact Module, and the Anxiety subtest measured by the HADS where 23% (n=3) of parents of children with TGA had borderline scores.

### 7.3.2 Correlational Analyses

To explore the relationships between key parent self-reported outcome measures, particularly parent HRQOL, family functioning, parent mental health, CHD-related stress and the total impact of CHD on the family, non-parametric correlations were conducted. Table 7.10 shows the results of the Spearman’s correlations for all parents (including parents of both CHD patients and healthy controls). There were moderate-to-strong significant positive correlations between many of the parent outcome variables particularly in relation to the frequency and difficulty scores on the PIP and the HADS and IES scores.

There were also moderate significant negative correlations between both parent HRQOL and family functioning, and measures of mood and stress. Figure 7.3 shows scatterplots for the correlations between parent HRQOL and the other parental outcomes. Other scatterplots are provided in Appendix 11.1.
Table 7.10 Spearman’s correlation coefficients between some of the key parent outcome measures including HRQOL, family functioning, and overall scores from the HADS, PIP, and the total IES score

<table>
<thead>
<tr>
<th></th>
<th>Parent HRQOL (N = 32)</th>
<th>Family Functioning (N = 32)</th>
<th>HADS Anxiety (N = 20)</th>
<th>HADS Depression (N = 20)</th>
<th>PIP Frequency (N = 21)</th>
<th>PIP Difficulty (N = 21)</th>
<th>Impact of Event Total (N = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent HRQOL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family Functioning</td>
<td>0.73***</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HADS Anxiety</td>
<td>-0.68***</td>
<td>-0.68***</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HADS Depression</td>
<td>-0.63***</td>
<td>-0.63***</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIP Frequency</td>
<td>-0.61**</td>
<td>-0.60**</td>
<td>0.68***</td>
<td>0.60**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIP Difficulty</td>
<td>-0.57**</td>
<td>-0.61**</td>
<td>0.68**</td>
<td>0.69***</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impact of Event Total</td>
<td>-0.52*</td>
<td>-0.67***</td>
<td>0.42</td>
<td>0.65**</td>
<td>0.57**</td>
<td>0.61**</td>
<td></td>
</tr>
</tbody>
</table>

Note. Statistically significant correlations denoted as *p<0.05, **p<0.01, and ***p<0.001.
Figure 7.3 Scatterplots showing the significant correlations between parent HRQOL and A) total impact of event score (i.e. CHD), B) family functioning, C) parent anxiety, D) parent depression, E) frequency of stress related to CHD, and F) difficulty of stress related to CHD. Lines on the x- and y-axis represent the respective means of the given measures.
7.3.3 Relationship Between Parent and Child Outcomes

Further correlations were conducted to explore the relationship between key parent outcome measures and behavioural, psychosocial functioning and overall HRQOL in children. Table 7.11 shows the results of the Spearman's correlations for all parents (including parents of both CHD patients and healthy controls). There were weak-to-moderate significant positive correlations between many of the child and parent outcome variables, particularly between child and parent HRQOL, family functioning and total family impact, as well as parental stress scores on the PIP and child behaviour on the CBCL.

There were also moderate-to-strong significant negative correlations between many of the other child and parent outcome variables, including parent anxiety and stress scores on the HADS and PIP and child psychosocial functioning and HRQOL, and child behaviour on the CBCL and parent HRQOL, family functioning, and total family impact. Parent depression measured by the HADS was not significantly correlated with any of child outcome measures, except working memory from the BRIEF-P. Figure 7.4 shows scatterplots for the correlations between child HRQOL (i.e. PedsQL Total score) and parent HRQOL and family functioning outcomes (from the PedsQL Family Impact Module).
Table 7.11 Spearman’s correlation coefficients between key parent and child outcome measures including behavioural, psychosocial functioning and overall HRQOL in children, and parent HRQOL, family functioning, parent mental health, and stress

<table>
<thead>
<tr>
<th></th>
<th>Parent HRQOL</th>
<th>Family Functioning</th>
<th>Family Impact Total</th>
<th>HADS Anxiety</th>
<th>HADS Depression</th>
<th>PIP Frequency</th>
<th>PIP Difficulty</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N = 32)</td>
<td>(N = 32)</td>
<td>(N = 32)</td>
<td>(N = 31)</td>
<td>(N = 31)</td>
<td>(N = 21)</td>
<td>(N = 21)</td>
<td></td>
</tr>
<tr>
<td>PedsQL Psychosocial Functioning</td>
<td>0.35</td>
<td>0.41*</td>
<td>0.50**</td>
<td>-0.44*</td>
<td>-0.30</td>
<td>-0.70***</td>
<td>-0.65**</td>
</tr>
<tr>
<td>PedsQL Total</td>
<td>0.37*</td>
<td>0.39*</td>
<td>0.50**</td>
<td>-0.40*</td>
<td>-0.30</td>
<td>-0.69***</td>
<td>-0.65**</td>
</tr>
<tr>
<td>CBCL Internalising</td>
<td>-0.40*</td>
<td>-0.52**</td>
<td>-0.54**</td>
<td>0.46**</td>
<td>0.27</td>
<td>0.62**</td>
<td>0.57*</td>
</tr>
<tr>
<td>CBCL Externalising</td>
<td>-0.41*</td>
<td>-0.43*</td>
<td>-0.48**</td>
<td>0.52**</td>
<td>0.18</td>
<td>0.49*</td>
<td>0.42</td>
</tr>
<tr>
<td>BRIEF-P Inhibit</td>
<td></td>
<td></td>
<td></td>
<td>0.46**</td>
<td>0.21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRIEF-P Working Memory</td>
<td></td>
<td></td>
<td></td>
<td>0.42*</td>
<td>0.44*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRIEF-P Flexibility</td>
<td></td>
<td></td>
<td></td>
<td>0.40*</td>
<td>0.34</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note. Statistically significant correlations denoted as *p<0.05, **p<0.01, and ***p<0.001.*
Figure 7.4 Scatterplots showing the significant correlations between child HRQOL and A) parent HRQOL, B) family functioning, C) total family impact, D) parent anxiety, E) frequency of parent stress related to CHD, and F) difficulty of parent stress related to CHD. Lines on the x- and y-axis represent the respective means of the given measures.
7.4 Discussion

7.4.1 Parent Self-Reported Outcomes

Parent self-reported outcome measures were used to investigate the impact of CHD on parent mental health and the family. This was investigated in parents of children with complex CHD, 4-5 years after their child’s initial CHD diagnosis, and following the completion of all necessary open-heart surgeries (i.e. the third and final Fontan procedure in HLHS patients). Parents were asked to complete a battery of parental questionnaires measuring the impact of their child’s CHD on the family, their own stress and mental health, and HRQOL in order to describe parental functioning and to explore the associations between parental and family functioning and psychosocial outcomes and HRQOL in parents of children with complex CHD.

As hypothesised, parents of children with HLHS had scores indicative of worse outcomes on all measures compared to parents of children with TGA and healthy controls. Significant group differences were observed in all parental mental health and family functioning subtests, except Family Relationships measured by the Family Impact Module, Medical Care Difficulty measured by the PIP, and Avoidance measured by the IES. Parents of children with HLHS exhibited the greatest proportion of scores 1-2 SD and ≥2 SDs below the mean, ranging between 43-86% in all the measures. Two parents (29%) of HLHS patients had total impact of CHD scores (i.e. IES) in the clinical range for PTSD concern, and another parent (14%) had a score severe enough to suppress the functioning of the immune system (Weiss & Marmar, 1996), even 4-5 years after the initial diagnosis of CHD.
Parents of children with TGA generally had outcome scores similar to those of parents of healthy controls, but a small proportion (0-36%) did have scores 1-2 SD and ≥2 SDs below the mean in a number of measures including Emotional and Social Functioning, Communication, and Anxiety. Fewer parents compared to those of children with HLHS had low HRQOL and none had abnormal family functioning scores. One parent (8%) of a TGA patient also had a total impact of CHD score reflecting probable diagnosis of PTSD, and another parent (8%) had a score severe enough to suppress the functioning of the immune system, despite TGA being a less severe type of CHD.

The findings of the present study support those in the CHD literature. For example, Woolf-King et al. (2017) reported 30% of parents had symptoms consistent with a diagnosis of PTSD, and 25-50% reported clinically elevated symptoms of depression and/or anxiety. Although their sample combined populations of parents of children with different critical CHD lesions, the ranges of their results were similar to those reported in the current study, where 8-29% of parents scored in the clinically relevant range for PTSD. Further, in the current study, 4 out of 7 (57%) of parents of HLHS patients had clinically elevated scores for anxiety and up to 31% of parents of TGA patients had borderline or clinical scores for anxiety. Again, the prevalence of anxiety among parents of children with complex CHD is similar to that reported by Woolf-King et al. (2017). These rates however, are higher than Roberts et al. (2021) who found that 25% and 20% of parents of children with CHD reported moderate/severe levels of anxiety and depression, respectively. In the current cohort of parents, however, there were no clinically elevated scores for depression in either CHD group. This discrepancy between the results may be explained by two reasons: firstly, the cohort in Roberts et al.’s study was aged between three months to three years,
and given the different stages of CHD treatment involved, some children may have been still going through or waiting for surgery. This may have caused parents to experience differing levels of anxiety and depression accordingly. Secondly, the authors stated that a large number of parents declined participation in their study due to feeling overwhelmed and lacking the time to commit, which they suggested may mean their sample underrepresents the level of stress parents experience as they care for a child diagnosed with CHD.

Mussatto et al. (2021) found QoL and well-being in parents of children with CHD were significantly lower than adult norms, and QoL scores declined over time, up to 16 months after CHD diagnosis and surgery. Responses from mothers and fathers showed different trends, with mothers having worse scores on most measures and at most time-points. Their parent HRQOL findings are consistent with the current cohort of parents of HLHS patients which were significantly worse than healthy adult norms, but parents of TGA patients and healthy controls had similar HRQOL scores. The present study did not compare ratings from mothers and fathers given that only two fathers attended the assessments, of which only one completed the questionnaires. It is also important to note that responses from parents came 4-5 years after initial CHD diagnosis and surgery, which differs to the time frame in Mussatto et al.'s (2021) study.

Although parental outcome results from the current study are from a single time-point, it was 4-5 years after initial CHD diagnosis and surgery. Much of the literature focuses on parental outcomes in the immediate months and year following diagnosis, but outcomes can change over time and CHD is a lifelong condition, so it is important to review longitudinal research. For example, Lawoko and Soares (2002) reported persistent psychological problems in parents of children with CHD up to 20 years-old. Despite the difference in age range
compared with the current cohort, these findings provide evidence for the persistent nature of adverse parental outcomes in CHD, several years after the initial impact of the diagnosis of the disease. Although the prevalence of clinical scores in parents may reduce over time, a significant proportion of parents continue to experience long-term psychological dysfunction, as observed by Lawoko and Soares (2002).

It is noteworthy that many studies in the literature group CHD patients together and do not always specify the type of CHD physiology in their cohort. This makes comparisons with the literature challenging as it is widely accepted that HLHS is a more severe type of heart disease compared to TGA and other milder diseases. The absence of particular groups of patients such as those with HLHS can significantly impact overall group means, which emphasises the need to be cautious when making comparisons and conclusions. For example, Spijkerboer et al. (2007) found psychological functioning, including stress, anxiety and depression, in parents of children with CHD was comparable to functioning of parents of healthy controls. They did not, however, include HLHS patients in their sample, but did include those with TGA and other forms of CHD.

Some research studies have differentiated between stress in parents of children with different types of CHD physiology. Appendix 11.2 details these studies and compares scores from these with those in the present study. Wray et al. (2018) reported that parents of children with complex SV conditions and cardiomyopathy had significantly higher levels of anxiety and depression than healthy norms. These parents also had poorer psychological outcomes compared to parents of children with other forms of CHD such as BV CHD. More specifically, they found group differences in the proportion of mothers’ ratings on the HADS in the borderline or clinical range for anxiety (46% BV and 63% SV) and depression
(14% BV and 25% SV). When measuring the total frequency and difficulty of stressors rated by mothers using the PIP, they also found that mothers of children with SV CHD had higher scores indicating greater symptomology compared to BV CHD. The PIP subscale scores in the TGA group of the present study are similar to those reported by Wray et al. (2018) (Appendix 11.2), but overall, the current HLHS group had considerably higher scores for all subscales, indicating increased frequency and difficulty of stressors related to CHD in these parents. Similarly, the prevalence of anxiety and depression in parents of children with TGA in the current study are comparable to the BV group reported by Wray et al., but again, parents of children with HLHS reported noticeably higher rates of anxiety and depression (86% and 43%, respectively) in the current study, compared to their cohort. Notably though, the results in Wray et al.’s (2018) study came from parents of 8-18 year-old children with CHD, which is older than the current CHD cohort and also later in time than other studies which focused on parent outcomes within a year of cardiac surgery.

Similar patterns of results from the PIP can be seen in Kaugars et al.’s (2018) study, where parents of children with SV CHD had higher total frequency and difficulty of stress scores than parents of children with BV CHD (Appendix 11.2). They also investigated the impact of CHD on the family using the PedsQL Family Impact Module. However, unlike the present study, they reported no statistically significant differences between SV and BV groups for parent HRQOL, Total Family Functioning, and Total impact score. Further, the scores from the current TGA group for these subscales are higher than the BV group of Kaugars et al., whilst the scores for the HLHS group were lower, indicating worse outcomes, compared to the SV group of Kaugars and colleagues. Eagleson et al. (2013) explored CHD family impact in parents of 2-4 year-olds with HLHS and a milder
type of CHD. They reported worse parental HRQOL, Total Family Functioning, and Total impact in HLHS compared to milder CHD, with scores similar to those of the SV group in the study of Kaugars et al. (2018), but again the HLHS group in the current study had lower scores. This suggests that disease severity significantly impacts parental HRQOL and family functioning of children with CHD. Children with HLHS undergo more surgical interventions, have extended and intensive treatment, and are at greater risk of neurological, neurodevelopmental and behavioural problems. This may place significant burden on parents caring for these children, which consequently impacts their own psychological functioning, and may be the cause of persistent stress and worry in some parents. These results clearly reflect the impact of CHD severity on parents and families. More recently, Mussatto et al. (2021) found that 26% of parents of children with HLHS experienced family dysfunction, parents reported somewhat worse family function over time, and parent HRQOL was significantly below adult norms.

7.4.2 Associations Between Parent Outcomes

Correlations were conducted in order to investigate associations between key parental outcome measures. It was hypothesised that higher parental stress and mental health problems, poorer family functioning and greater severity of CHD would be negatively associated with overall parental HRQOL. Several significant moderate-to-strong negative correlations were found between both parent HRQOL and overall family functioning and anxiety, depression, frequency and difficulty of stress-related symptoms, and overall impact of event/CHD on the family. This indicates that higher mental health and stress symptomology, as well as greater impact of CHD on parents, is associated with lower parent HRQOL
and family functioning. Significant moderate positive correlations were also observed between both frequency and difficulty of stress-related symptoms (as measured by the PIP) and anxiety and depression in parents of children with CHD (both HLHS and TGA). This suggests that higher frequency and greater difficulty of CHD-related stress was associated with higher anxiety and depression symptoms in parents. However, it was parents of HLHS patients who had worse outcomes throughout, compared to parents of TGA patients.

These associations between parental outcome measures replicate those observed in previous studies. For example, Kaugars et al. (2018) found strong significant negative correlations between measures of parental stress (including total PIP scores) and parent HRQOL, Family Impact Total Score, and Family Functioning indicating that higher parental stress is associated with lower parental and family HRQOL and poorer family functioning. Interestingly, they found no significant associations between parental stress, parental HRQOL, and objective medical variables. Moreover, Medrano et al. (2013) found that lower parental HRQOL and family functioning were significantly associated with higher reported parental anxiety and depression (measured by the HADS). Comparable but stronger correlations have been found between these parental outcomes measured in the present study, suggesting that parental mental health is related to HRQOL and family functioning. However, the current study design does not enable confirmation of causality. Further, Roberts et al. (2021) found that higher parental stress was associated with higher levels of anxiety and depression, more severe types of CHD, older child age, and lower child cognitive scores. This provides support for the association between the increased frequency and difficulty of stress symptoms and anxiety and depression observed in parents in
the present study, particularly those parents of children with HLHS who tended to have higher scores indicating increased symptomology.

7.4.3 Relationship Between Parent and Child Outcomes

The literature has reported that maternal stress, anxiety and depression, and family functioning, are predictors of child psychosocial and QoL outcomes (Latal et al., 2009; Ryan et al., 2019; Werninger et al., 2020). Correlations were also used to explore the relationship between key parent and child outcomes, particularly HRQOL, parental mental health, child behavioural outcomes and psychosocial functioning. It was hypothesised that more behavioural problems and executive dysfunction would be positively correlated with parental mental health problems (measured by the HADS), and negatively correlated with family functioning and parent HRQOL. The results of the current study provide support for this hypothesis. Specifically, significant moderate positive correlations were observed between parental anxiety and internalising and externalising behavioural problems and executive dysfunction in children with CHD, summarised in Figure 7.5. Interestingly, parental depression was not significantly correlated with any of these child outcome measures, except working memory which was moderately positively correlated. Internalising and externalising behaviours were also both significantly moderately negatively correlated with total family impact score and parental HRQOL. Similar significant correlations were observed between parental anxiety and child psychosocial outcomes and HRQOL. Parental stress scores in the PIP were significantly moderate-to-strongly negatively correlated with child psychosocial functioning and HRQOL (Figure 7.5).
It was also hypothesised that parental HRQOL would be associated with reduced psychosocial functioning and HRQOL in children with CHD. The findings only partially support this hypothesis as parent HRQOL was only weakly significantly positively correlated with child HRQOL and was not significantly correlated with child psychosocial functioning. This is somewhat surprising because worse parental mental health and stress were associated with lower parental HRQOL,
so it was reasonable to expect that lower parental HRQOL would subsequently impact child HRQOL. The literature has also reported that lower parental HRQOL and family functioning are significantly associated with lower child HRQOL (Medrano et al., 2013). However, the findings here suggest that there are other factors also associated with child HRQOL apart from parent HRQOL, such as parental anxiety, and in parents of CHD patients specifically, the frequency of illness related stressors was strongly associated with child HRQOL. This may reflect the parents’ perceptions of their child’s HRQOL because of the number of things the child is experiencing, or it may be that it is actually because of those things their child is experiencing that is having a real impact on the parent. Importantly, all these measures are parent-rated which again, brings the problem of shared method variance. There is also no objective measure or assessment by any other person, such as the father.

Denniss et al. (2019) found that lower HRQOL in children with HLHS was strongly associated with greater maternal anxiety and depression, which accounted for 52% of the variance in child HRQOL. Likewise, in this study, increased parental anxiety was moderately associated with lower HRQOL in children with CHD, but depression was not significantly associated. Majnemer et al. (2006) found that parents perceived their child’s HRQOL as good, five years post-surgery. Despite this, many parents experienced persistent stress and were defensive about their child’s development and HRQOL, especially if they exhibited behavioural difficulties. High parental stress was associated with having a child with increased behavioural problems. Elevated scores for internalising and externalising behaviours in children were moderately associated with elevated parental stress. They also found that higher parental stress was moderately associated with lower psychosocial wellbeing of the children. Similarly, the present study found strong
correlations between increased frequency and difficulty of stress symptoms in parents and lower psychosocial functioning in children. Further, internalising and externalising child behavioural problems were moderate-to-strongly positively correlated with frequency and difficulty of stress symptoms in parents.

Overall, it is evident that numerous factors are associated with both parental and child HRQOL in complex CHD. This includes parental and family factors such as coping and resilience, stress, mental health, and family functioning, and child outcomes such as behavioural problems, adaptive functioning, and executive dysfunction. The relationship between these factors is often mutual and impacts both parents and children simultaneously. Ultimately, many of the parental outcome factors discussed here are potentially modifiable which offers plausible pathways for early intervention and prevention. The health and wellbeing of parents of children with CHD cannot be overlooked and long-term surveillance is necessary in order to screen parents and enable appropriate referral to psychosocial services to address their needs and enhance their ability to cope with the myriad of stressors they encounter.

7.4.4 Limitations

There are some important limitations to the current study, primarily related to the methodology. Firstly, parent self-reported outcomes measures are often criticised because of the risk of parents providing socially desirable responses whereby parents of children with CHD may answer questions in a favourable manner based on what they believe researchers are expecting. There was no way to assess for social desirability bias in this study, but it may have contributed to the higher/lower scores reported reflecting better outcomes/decreased
symptomology in parents of children with TGA, particularly when they were higher/lower compared to parents of healthy controls. Secondly, parents were not questioned about their marital or relationship status in the demographics questionnaire, which would have been an important factor to explore. However, the focus of the overall research was on child outcomes, so it was not possible to investigate all parental outcomes and the factors which may impact them. Parental information such as education level and employment was obtained, but the questionnaire did not specifically focus on the relationship between the child’s parents so it was not possible to investigate whether this is associated with any variables impacting parent outcomes, as Mussatto et al. (2021) explored in their study. Thirdly, fathers are notably underrepresented in this research, similar to other findings in the literature (Shudy et al., 2006; Sood et al., 2018). This is because child assessments were most frequently attended by only one parent who accompanied the child, and this was predominantly mothers. Only two fathers accompanied their child in this study and one of these fathers attended with the child’s mother, therefore only one father completed the parental questionnaires reflecting his own viewpoint instead of the mother’s. As the literature has clearly concluded, parental self-report scores vary considerably when mothers’ and fathers’ scores are compared (Cantwell-Bartl and Tibballs, 2013; Lawoko and Soares, 2002; Mussatto et al., 2021). Therefore, it would be ideal to obtain self-report parental scores from both parents to gain a more complete picture and understanding of the impact of CHD on the whole family, rather than the mother alone. It is also important to note that parental responses in the current study were grouped together for the analysis which means that the one/two response(s) from fathers were combined with those of mothers (94%).
Numbers were too small to evaluate the impact of their child’s CHD on mothers and fathers separately.

Additionally, the choice of measures used meant that normative data did not exist for all measures. The HADS has published norms for anxiety and depression, as does the IES for abnormal levels of stress and PTSD following the impact of a significant event. However, the PIP does not have any published norm data as it is not used in normal populations. Therefore scores from parents in the current study had to be compared to those in the CHD literature, of which there are few. Kaugars et al.’s (2018) results from their CHD sample were used for cut-offs to compare results in the current study, but importantly their sample was heterogeneous and included other diagnoses besides HLHS and TGA. Despite this, the scores from the current study for parents of children with TGA were comparable to both Kaugars et al. (2018) and Wray et al. (2018), but parents of children with HLHS in this study reported much higher scores compared with scores in these two studies. Similarly, the PedsQL Family Impact Module is also used in a variety of clinical and healthy populations, with limited studies using it with parents affected by CHD, making comparisons difficult with the present findings. Medrano et al.’s (2013) results from a non-clinical community sample were used for cut-offs to compare results in the current study. However, parents of healthy controls had higher scores throughout which suggests better outcomes compared to Medrano et al.’s (2013) sample. Upon further inspection of their data it became clear that overall their sample had very low means for each subscale in the Family Impact Module. This may be due to the fact that despite this being a community sample, 41% of parents (mostly mothers), reported that their child had at least one chronic condition such as feeding and nutritional problems, ADHD, ear infections, sleep problems, bedwetting, etc. This is a relatively high
proportion of children and needs to be taken into consideration. Again, given the limited data available from CHD populations using the Family Impact Module, comparisons of the current cohort with similar studies has been challenging.

Further, the current study did not focus on mental health diagnoses in parents but instead relied on mental health symptoms and/or general indicators of psychological distress. Thus the full extent of psychological morbidity among these parents is unknown and inferences can only be drawn from the self-reported symptoms of these parents, mainly mothers, and their openness to discuss their experiences. Parents were not asked if they had been formally diagnosed with any mental health conditions, but were able to give information or notes they felt may be relevant. One mother described having high anxiety alongside problems with addiction, and another mother reported that she had a serious chronic health condition herself and that her child needed close surveillance for further heart surgery; all of which may have impacted these mothers’ scores.

7.4.5 Conclusion and Future Research

Literature has explored parental mental health, family functioning and HRQOL in the periods shortly after CHD diagnosis and surgery, but not necessarily longitudinally or several years after their child’s final surgery. This is one of the few studies to look at parental outcome measures when children are 4-5 years old. The findings reveal that parents of children with HLHS have poorer outcomes and exhibit a higher proportion of borderline and clinical scores compared to parents of TGA patients. Parents of children with TGA generally have outcomes similar to parents of healthy controls, but despite this almost a third have
borderline or clinical scores for anxiety and a sixth for HRQOL. This suggests that CHD physiology does have a significant impact on parent and family functioning, mental health, and overall QoL.

Parental mental health problems and psychological distress were significantly associated with parent QoL and family functioning. Total family impact, and parental anxiety and stress were also significantly and strongly associated with child internalising and externalising behaviours, psychosocial functioning and HRQOL. Children with CHD undergo invasive and serious medical procedures and treatments, which require hospital admissions and cause considerable stress, pain and discomfort. More severe CHD, such as HLHS, requires multiple surgeries and prolonged hospital admissions in the first few years of life. Experiencing these highly traumatic events can overwhelm parents' capacity to regulate the associated stress leading to psychological adjustment problems, and emotional and behavioural regulatory difficulties and psychosocial impairment in children. These maladjustments and impairments can be long-lasting and persist many years after initial CHD diagnosis, and beyond final staged surgery in HLHS patients.

Further work is needed to look at the longitudinal trajectory of parental outcomes overtime, in the same cohort of patients in order to determine if there is a period of time when outcomes improve, or if parental status remains constant across the child's lifespan. This would also help to identify whether there is a critical period of increased risk, which could be the target for future interventions to better support parents and families. Future studies should also focus on the impact of CHD on fathers' stress levels and mental health, by asking both parents to complete questionnaires and comparing responses between them. Additional measures should also be considered for a more comprehensive understanding
of parental outcomes following child CHD diagnosis and treatment. These may include observational measures to quantify parent behaviours and reduce the bias of social desirability in self-report. Alternatively, qualitative interviews could be used to gain a better understanding of subtle differences in parenting or detailed information about coping, adjustment, and potential reasons for resilience in some parents of children with complex CHD which is not possible with quantitative questionnaires. Results from qualitative research can also allow for a more individualised approach to treatment and interventions in parents as opposed to a “one size fits all” approach. Finally, future research also needs to identify factors other than disease severity which might explain poorer (or better) functioning in some parents of children with more complex CHD.
Chapter 8: General Discussion

This final chapter will start by summarising the main findings reported in this thesis. Some case studies will then be presented to highlight the individuality of children with complex CHD and the difficulty of assessing and evaluating neurodevelopmental outcomes in these children. This will illustrate how specific children failed to meet developmental milestones and had clear delays and/or impairments in a range of the domains assessed, despite overall group averages indicating ‘normal’ performance in children with HLHS and TGA. Strengths and limitations of the present research will be discussed, as well as the clinical implications of these findings for patients with CHD currently living in the UK. Finally, this chapter closes with some suggestions for future further research and final conclusions.
8.1 Summary of Findings

Congenital heart disease (CHD) is the most common birth defect and covers a spectrum of severity and complexity from very minor to life-threatening. Hypoplastic left heart syndrome (HLHS) and transposition of the great arteries (TGA) are two types of CHD which are considered to be complex, with HLHS being more severe due to the specific anatomy and requirement for staged cardiac surgeries in the first few years of life. The heart and brain have an interdependent relationship, and heart malformations in CHD requiring open-heart surgery can cause alterations in foetal blood flow resulting in decreased oxygen delivery to the brain. Neurodevelopmental delays and impairments in a range of domains including attention, executive function, communication and language, and motor and visual-spatial skills, are common in CHD. These are characterised by a high-prevalence but low severity developmental signature (Wernovsky, 2006). Several risk factors (genetic, preoperative, perioperative, postoperative, family and environmental) can lead to adverse neurodevelopmental sequelae, and consequently impact the child’s overall health-related quality of life (HRQOL) as well as parental mental health and HRQOL.

The findings reported in this thesis arose from parental concerns highlighted in patient and public involvement (PPI) work conducted in preparation for this research. Parents of early school-aged children with CHD indicated that the areas of greatest concern in their child’s development included behavioural problems, speech and language/communication, and social and emotional development.

The aims of this research were therefore to: 1) longitudinally assess the development of early cognitive, language, and motor skills in pre-schoolers with
HLHS and TGA, compared to healthy controls, to identify the emergence of neurodevelopmental delays in children with CHD (Chapter 3); 2) comprehensively assess speech, language and pre-reading skills in school-aged children aged 4-5 years with HLHS and TGA, compared to healthy controls (Chapter 4); 3) utilise auditory event-related potentials (ERPs) to examine the brain network supporting speech sound processing, in order to investigate whether there are biomarkers of delays and/or impairments in early language skills, mainly targeting changes in amplitude of the P50, N1, and P300 components (Chapter 5); 4) investigate parent-reported behavioural, social-emotional, adaptive behavioural, executive functioning, and language outcomes, as well as psychosocial health and HRQOL, in children with HLHS and TGA, compared to healthy controls (Chapter 6); and 5) investigate parent self-reported mental health, family functioning, and QoL, and to relate these parental outcomes to child psychosocial health and HRQOL (Chapter 7).

This first section will be presented according to the data chapters described previously. Table 8.1 summarises the hypotheses addressed in each of these chapters, and whether these were supported, partially supported or not supported.
<table>
<thead>
<tr>
<th>Chapter</th>
<th>Hypothesis</th>
<th>Hypothesis Supported?</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Preschool children with CHD, particularly those with HLHS, will have lower Bayley-3 scores in cognition, language and motor skills, compared to the healthy controls.</td>
<td>Supported</td>
</tr>
<tr>
<td></td>
<td>A higher proportion of pre-schoolers with complex CHD will have neurodevelopmental delays, particularly in language and motor skills, compared with healthy controls.</td>
<td>Partially supported</td>
</tr>
<tr>
<td></td>
<td>Children with HLHS will have different longitudinal developmental trajectories compared to healthy controls and children with TGA.</td>
<td>Supported</td>
</tr>
<tr>
<td></td>
<td>In the healthy controls, but not children with CHD, earlier Bayley-3 scores will be associated with later Bayley-3 scores.</td>
<td>Not supported</td>
</tr>
<tr>
<td></td>
<td>Preschool children with complex CHD, and in particular those with HLHS, will have an increased incidence of early social-emotional and adaptive behavioural problems compared with healthy children.</td>
<td>Partially supported</td>
</tr>
<tr>
<td></td>
<td>Parental ratings of socio-emotional and adaptive behaviour will be associated with objective measures of the child’s performance.</td>
<td>Partially supported</td>
</tr>
<tr>
<td>4</td>
<td>Children with complex CHD, and in particular those with HLHS, will have lower language scores and especially lower expressive language, compared to healthy control children.</td>
<td>Not supported</td>
</tr>
<tr>
<td></td>
<td>Children with CHD will have language impairments, particularly in expressive language and phonological abilities (which is an indicator of pre-reading skills), compared to healthy controls.</td>
<td>Partially supported</td>
</tr>
<tr>
<td></td>
<td>The longitudinal trajectory of language skills will differ in children with CHD compared to healthy controls, and those children with early language delays will have later delays at early school age.</td>
<td>Partially supported</td>
</tr>
<tr>
<td></td>
<td>Children with complex CHD, and in particular those with HLHS, will have lower parent-rated language scores, compared to healthy control children.</td>
<td>Not supported</td>
</tr>
<tr>
<td></td>
<td>Parent-rated language scores will be associated with direct measures of language performance.</td>
<td>Supported</td>
</tr>
<tr>
<td>5</td>
<td>There will be significant group differences in the mean amplitudes for frequent and infrequent speech sounds, in the P50, N1, and P300, reflecting atypical speech sound processing.</td>
<td>Not supported</td>
</tr>
<tr>
<td></td>
<td>Within groups, both TGA and HLHS patients will show a reduced classic oddball effect of higher mean amplitudes of the P50, N1, and P300 for the infrequent stimuli compared to the frequent stimuli. In comparison, the healthy controls will show larger mean amplitudes in these components for the infrequent stimuli.</td>
<td>Not supported</td>
</tr>
<tr>
<td></td>
<td>Speech sound ERPs will be associated with scores of phonological abilities (i.e. rhyme detection and letter knowledge) and expressive language.</td>
<td>Not supported</td>
</tr>
<tr>
<td></td>
<td>Children with CHD will show different developmental profiles/age-related maturation of the brain network supporting speech sound processing, compared to healthy controls who will show increases in P50, N1, and P300 amplitude over time.</td>
<td>Not supported</td>
</tr>
<tr>
<td>Chapter</td>
<td>Hypothesis</td>
<td>Hypothesis Supported?</td>
</tr>
<tr>
<td>---------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>6</td>
<td>Children with complex CHD, and in particular those with HLHS, will have an increased incidence of social-emotional and behavioural problems, and poorer adaptive behaviour and executive functioning, compared to healthy controls.</td>
<td>Supported</td>
</tr>
<tr>
<td></td>
<td>Children with complex CHD, and particularly those with HLHS, will have poorer overall QoL scores, compared to healthy controls.</td>
<td>Partially supported</td>
</tr>
<tr>
<td></td>
<td>Children with HLHS will have worse psychosocial profiles and scores and reduced overall HRQOL, compared to children with TGA.</td>
<td>Supported</td>
</tr>
<tr>
<td></td>
<td>Core language, pragmatic language and narrative skills will be associated with parent-rated social skills and EF scores.</td>
<td>Partially supported</td>
</tr>
<tr>
<td></td>
<td>CHD physiology, behavioural problems, adaptive behavioural skills, and executive dysfunction will all be associated with poorer psychosocial functioning and reduced overall HRQOL.</td>
<td>Partially supported</td>
</tr>
<tr>
<td></td>
<td>Earlier social-emotional, behavioural, and adaptive skills scores will be associated with later scores at 4-5 years of age.</td>
<td>Supported</td>
</tr>
<tr>
<td>7</td>
<td>Parents of children with CHD and particularly HLHS, will have higher levels of anxiety and depression, and poorer family functioning and HRQOL, compared with healthy controls.</td>
<td>Partially supported</td>
</tr>
<tr>
<td></td>
<td>Higher illness-related parental stress and mental health problems, poorer family functioning and greater severity of CHD (i.e. HLHS) will be negatively associated with overall parental HRQOL.</td>
<td>Supported</td>
</tr>
<tr>
<td></td>
<td>Elevated behavioural problems and executive dysfunction in children with CHD will be positively correlated with parental mental health problems, and negatively correlated with family functioning and parent HRQOL.</td>
<td>Supported</td>
</tr>
<tr>
<td></td>
<td>Poor parental HRQOL will be associated with psychosocial problems and reduced overall HRQOL in children with CHD, particularly those with HLHS.</td>
<td>Partially supported</td>
</tr>
</tbody>
</table>

8.1.1 Early Longitudinal Neurodevelopmental Outcomes

Clinically, it is important to identify children who are vulnerable and at risk for developing delays and/or impairments as early as possible, before such problems become established and begin to interfere with academic attainment and other aspects of their lives. Global delays/impairments are uncommon but preschoolers with CHD have been reported to have specific delays/impairments in early language and motor skills measured using Bayley-3 (Acton et al., 2015; Hicks et al., 2016; Sprong et al., 2022). Poorer neurodevelopmental outcomes in
a range of domains have also been widely reported in older school-aged children with complex CHD, compared to healthy controls and published norms (Derridj et al., 2021; Gaudet et al., 2021). Longitudinal cohort studies tracking the emergence of neurodevelopmental delays and their trajectories are limited within the CHD literature.

In the current investigation, a pattern was observed in children with HLHS consistently scoring below healthy controls and children with TGA. The latter two groups were found to have comparable scores in a range of domains, across the time-points. Using the Bayley-3, both CHD groups were found to have cognitive, receptive and expressive language, and fine motor scores within the normative range at all three longitudinal time-points from 5 months to 3-4 years-old. This is despite significant group differences being observed between HLHS patients and healthy controls, which may in part be explained by the observation that the healthy controls were high achieving and often scored above the normative range. Of note, the HLHS patients had impaired gross motor skills at both earlier time-points (5-8 and 12-15 months) with the group scoring 1-2 SDs below the normative mean, supporting previous findings (Acton et al., 2015; Sprong et al., 2022). This impairment may be explained in part by the first two staged surgeries they experienced and the consequent prolonged stays in hospital and recovery time required. During this period these patients are unable to interact with and explore their environment as other healthy children would. They experience periods of sedation and spend time recovering in bed laying on their back. As a result of their surgeries and the sternotomy wounds on their chest, many of these children do not enjoy or spend much time lying prone. Parents are also often reluctant or worried to engage in ‘tummy time’. These factors are likely to have impacted gross motor performance during Bayley-3 assessments at time-points
1 and 2. However, gross motor skills were improved and within the normative range by 3-4 years, suggesting that these children may ‘catch-up’ following early delays.

Children with TGA tended to have scores similar to those of healthy controls, with the exception of fine and gross motor scores at 5-8 months and cognitive, expressive language, and fine motor scores and 12-15 months where they had significantly lower scores. However, their scores were within 1 SD of the normative range, suggesting that the higher-achieving control group may explain this difference. By 3-4 years, there were no differences between these groups, but the disparity between the CHD patient groups did become apparent at this final stage, indicating that with increasing age HLHS patients begin to diverge from both healthy controls and TGA patients. Previous literature has also found that children with TGA have scores similar to healthy controls or within the normative range in all domains of the Bayley-3 except language (Hicks et al., 2016; Hövels-Gürich et al., 2002). Importantly, despite group scores being within the normative range for all subscales (except gross motor), a significant proportion of CHD patients, particularly those with HLHS, had scores in the mildly and severely impaired range (i.e. 1-2 SD and ≥2 SDs below the normative mean), across all subscales at time-points 1 and 2, compared to the healthy controls. In contrast to previous literature, the present investigation found gross motor delay to be particularly pronounced compared to language delay/impairment (Acton et al., 2015; Hicks et al., 2016).

The longitudinal group trajectories of each subscale revealed some further patterns. A U-shaped curve was observed in the development of receptive language and fine and gross motor skills in healthy controls. This curve is thought to represent temporary regression in learning (Blijd-Hoogewys and van Geert,
which can be seen at time-point 2, and is followed by rapid acceleration as evidenced by the increase in scores by time-point 3, in each of these subscales. The TGA patients show a similar U-shaped trajectory in the same subscales, but the curve appears to be less robust compared to the healthy controls. The HLHS patients showed evidence of a different developmental trajectory as their scores very gradually increased over time, with the exception of gross motor skills which rapidly incline from the first time-point.

The literature presents mixed findings as to whether early Bayley-3 scores are predictive of later abilities at school age but studies are more limited with regards to longitudinal Bayley-3 development. Krogh and Væver (2019) reported significant correlations between many of their six time-points from 4-36 months in healthy controls, but these differed for each of the subscales. Given that there had been no health adversity in the healthy controls in the current study, it was anticipated that earlier Bayley-3 scores would remain stable and be associated with later scores. However, the present findings failed to find evidence of this. This may in part be due to the U-shaped curve observed in some subscales, but no correlations were found in the other subscales for which this pattern was not seen. This leads one to question the reliability of early Bayley-3 assessments, and their predictive or associated value for later assessments. In the HLHS and TGA patients, longitudinal Bayley-3 scores were also not associated with one another, with the exception of expressive language at time-points 2 and 3, and cognitive scores at time-points 1 and 3 in the HLHS and TGA groups, respectively. This suggests that earlier scores are not significantly associated with later scores, in contrast to previous studies indicating good predictive value (Gaudet et al., 2021; Creighton et al., 2007). The exception may be expressive
language and cognitive scores which are stable, but these trajectories differ in the two domains and between CHD groups.

Parent-rated Bayley-3 questionnaires were also used to examine social-emotional development and adaptive behaviour, and there was no evidence of early problems in the present cohort of CHD patients, compared to healthy controls. This is in contrast to other researchers who have reported socioemotional and behavioural difficulties in infants and toddlers with complex CHD (Bonthrone et al., 2022; Cassidy et al., 2018). The relationship between directly measured Bayley-3 scores and parent-rated social-emotional and adaptive behaviour scores was also investigated. Although these parental questionnaires assessed different domains often encompassing cognition, language and motor abilities, it was important to investigate whether there was an association between parental ratings and skills scored by the researcher via direct assessment of the child. No significant correlations were observed between parent-rated social-emotional development and any of the objective Bayley-3 domains, but expressive language and fine and gross motor scores (from direct assessment) were positively correlated with parent-reported adaptive behaviour across some of the time-points. This is important as it suggests there is some consistency between parent-rated behaviour and actual performance of the child, especially when considering speech and motor abilities. Although the parental ratings are measuring different behaviours to those assessed directly, these correlations indicate that adaptive behavioural skills are associated with expressive language and motor skills. The correlations between these variables are likely driven by the fact that parent-rated adaptive behaviour skills encompass communication, social, and motor skills.
8.1.2 Speech, Language, and Pre-Reading Skills at 4-5 Years

Speech and language problems are known to affect infants and children with complex CHD. Many studies assess these skills using tools measuring development more widely such as Bayley-3, or simply investigate receptive and expressive language only. Given that language plays such a crucial role across development in a range of other areas such as social skills and interactions, play, theory of mind, daily functioning, and academic performance, in-depth language investigations are clearly important but they are limited in the literature. Poorer speech articulation, phonological awareness, sentence production and pragmatic skills, and increased non-symbolic talk have been reported in complex CHD (Bellinger et al., 2003; Brosig et al., 2017; Miatton et al., 2007; Ovadia et al., 2000). Many of these children require speech and/or language therapy, and impairments vary depending on the severity of the heart defect (Fourdain et al., 2019; Hövels-Gürich et al., 2008). Overall, expressive language skills are particularly vulnerable in children with CHD, and receptive language to a lesser extent.

One of the main aims of the present research was to comprehensively assess speech, language and pre-reading skills in 4-5 year-olds with HLHS and TGA. Surprisingly, this cohort of CHD patients did not have impairments at the group level. A similar pattern to that seen with the early neurodevelopmental assessments was observed, whereby the HLHS patients had the lowest scores across tests of intellectual functioning and speech and language, compared to TGA patients and healthy controls. However, many of these differences were not significant, and all group scores were within the normative range. The main effect of group was only observed in the Verbal Comprehension subtest of the WPPSI-IV, but in none of the many measures of speech and language. There was a trend
towards significance in the Expressive One-Word Picture Vocabulary Test (OWPVT), Rhyme Detection in the PAT, and narrative skills (i.e. Information and Utterance Length) from the Bus Story test. These results were not anticipated given previous findings and recent reviews indicating significant deficits in language abilities in children with complex CHD, and particularly in those children with single-ventricle CHD such as HLHS (Turner et al., 2022). However, the present findings may be explained by the small and relatively ‘clean’ sample of CHD patients with respect to comorbidities, making them less representative of the wider CHD population. This is discussed in more detail below in section 8.4.1.

As identified previously, a proportion of individual children with CHD had impaired speech and language scores, despite group scores suggesting otherwise. Contrary to expectations and previous reviews (Huisenga et al., 2020), a higher proportion of children with TGA had expressive language impairments, compared to those with HLHS. It was anticipated that children with HLHS would have a higher proportion of impaired speech and language scores due to the severity of their heart defect and the multiple staged surgeries they undergo, together with the often prolonged and repeated hospitalisations, and the impact this is known to have on neurodevelopmental outcomes. Overall, in both HLHS and TGA patients, there were greater impairments in Rhyme Detection from the PAT and narrative skills from the Bus Story, where the prevalence of impairment was higher than would be expected in the normative population. This suggests that higher-order language skills and pre-reading skills may be particularly susceptible to delays and impairments in children with complex CHD than wider measures of speech and language, likely due to a range of inter-related factors.

Given the longitudinal nature of the study, it was important to compare earlier cognitive and language scores from Bayley-3 with later scores from the WPPSI-
IV, CELF-P2 and receptive and expressive OWPVTs, within groups. However, given the inconsistency of Bayley-3 scores over time, this investigation was focussed on the final Bayley-3 assessment at 3-4 years. Repeated measures analyses revealed that healthy controls had inconsistent Bayley-3 and CELF-P2 receptive and expressive language scores, whilst cognition remained stable over time. Surprisingly, HLHS patients also had stable cognitive/IQ scores and expressive language scores, but receptive language scores were significantly higher at the earlier time-point. In contrast, the TGA patients had inconsistent scores across all cognitive and language measures, with the exception of expressive language from Bayley-3 and later EOWPVT which indicated stability. These results suggest that the developmental trajectories differ for CHD patients and cognitive and language domains, with stable results for cognitive functioning in HLHS patients, and inconsistencies with receptive and expressive language skills. The idea of unique developmental trajectories in different domains supports some previous findings (Fourdain et al., 2019), but contradicts others which suggest a decline in cognitive functioning with age, stability in expressive language, and an improvement in receptive language skills (Gaudet et al., 2021). These discrepancies in findings may be due to the differences in diagnostic groups across the studies.

When all groups were combined, there were significant moderate-to-strong positive correlations between earlier and later scores of cognition/IQ, and receptive and expressive language. This further suggests that earlier scores are likely to be associated with later scores in these specific domains, and children with early impairments are likely to have later impairments, particularly children with TGA, although importantly, this is not always the case as can be seen in the table in Appendix 12. Overall, Bayley-3 scores at 3-4 years were higher than later
IQ, receptive, and expressive language scores at 4-5 years, except for EOWPVT which was higher than Bayley-3 expressive language one year earlier. Children with CHD show different rates of delay over time, and there are different explanations for this including: the testing instruments/measures used, the emergence of specific delays/deficits, and the increasingly acknowledged view that children with CHD grow into their deficits. Previous studies have reported higher rates of at-risk or delayed children at 4 years despite scores in the average range at 2 years using Bayley-3 (Brosig et al., 2018). This finding may be attributable, at least in part, to the fact that Bayley-3 scores are widely accepted to be inflated compared to its predecessor and are reported to underestimate developmental delay (Anderson et al., 2010; Johnson et al., 2014; Moore et al., 2012). Earlier studies using Bayley-2 have reported 2-4 months delay in expressive language skills in toddlers with CHD (Kharitonova & Marino, 2016), and studies directly comparing both Bayley-2 and -3 have found that the latter, on average, increases scores by 1.4-10 points depending on the specific domain being assessed (Acton et al., 2015).

Directly measured language skills were also compared to parent-rated communication skills in the CCC-2 to explore consistency between parent perceptions of their child’s language and direct observation of the child’s language. Significant correlations were observed between four of the six CCC-2 language domains and all five scales of the CELF-P2. This indicates consistency between parent-rated communication skills and actual speech and language ability in this cohort of children. The CCC-2 also flagged three CHD patients (2 TGA and 1 HLHS) for specific language impairment and one HLHS patient for autism spectrum disorder. This questionnaire is a widely used screening tool, but
further in-depth assessment would be necessary to follow-up these patients to explore the likelihood of these diagnoses.

8.1.3 Neural Markers of Speech Sound Processing

Auditory event-related potentials (ERPs) can provide functional measures of language processing, and thus help to identify neural markers of atypical processing. Research has shown reversed or atypical hemispheric lateralisation as well as attenuated responses in specific ERP components such as N1, in response to speech stimuli/phonemes in an auditory oddball paradigm (de Guibert et al., 2011; Finch et al., 2017; Maurer et al., 2003; McArthur and Bishop, 2005; Seery et al., 2013; Stipdonk et al., 2022). Phonological awareness is critical to speech and language development and is considered to be a significant precursor and predictor of reading ability (Bryant & Goswami, 1987; Grofčíková & Máčajová, 2021; Muter et al., 2004). Studies have reported specific delays/impairments in phonological processing in older school-age children with CHD (Bellinger et al., 2003; Miatton et al., 2007; Sarrechia et al., 2015). However, it is unclear what role the brain and any functional abnormalities play in the development of speech and language skills in children with complex CHD.

To the researcher’s knowledge, this was the first study to employ ERPs to explore functional speech sound processing in children with CHD, to relate speech sound ERPs to behavioural measures of language, and to study this longitudinally to allow exploration of age-related maturation of the brain network supporting speech sound processing in patients with CHD. The results revealed that children with HLHS and TGA had similar responses to phonemes in a passive auditory oddball task as healthy controls as no group differences were identified. Contrary
to what was expected, although the healthy controls did show a pattern resembling the classic oddball response of higher mean amplitude for infrequent phonemes compared to frequent phonemes, in the components of interest, this difference was not significant. This complicates the interpretation of findings given that the oddball response is robust and has been widely reported in the literature. The lack of significant results in the present investigation may have been due to the numerous methodological limitations in the ERP study discussed previously in Chapter 5 section 5.4.5.

Further, electrophysiological markers of speech sound processing measured at 3-4 years of age and 4-5 years of age, were not associated with behavioural measures of phonological awareness and expressive language at 4-5 years. This brings into question the reliability of using auditory ERPs as neural markers of early speech and language impairments in this cohort of children with CHD. Despite not finding language impairments at the group level in this cohort of CHD patients, more than a third had scores for Rhyme Detection below the 10th percentile. Given that this is a key phonological skill important for later reading competence, it was plausible to assume that this behavioural measure of phonological awareness would be associated with ERPs for phonemes. Again, this lack of finding may be attributed to the specific methodology such as the type of stimuli used, or the actual paradigm.

There was also no evidence of age-related maturation of the brain network supporting speech sound processing; no longitudinal increases in P50, N1, and P300 amplitude were observed. Exploratory analyses suggested that children with HLHS had greater sensory gating reflecting inhibition of irrelevant stimuli to allow selective attention to salient stimuli, in the ipsilateral hemisphere to the ear of stimulation. In comparison, children with TGA and healthy controls who had
attenuated P50 responses to phonemes in the ipsilateral hemisphere. These ERP findings need to be interpreted with caution given several methodological limitations of the ERP study discussed in Chapter 5, and due to the limited sample size. More ERP research is needed in children with complex CHD to further explore functional speech processing and the brain network supporting this, and to investigate whether ERPs can successfully be used as early neural markers of atypical speech and language development. Given that the current ERP paradigm has previously been used successfully in a cohort of children born very preterm (Day, 2017), it was plausible to assume this would be successful for use with children with complex CHD too.

8.1.4 Parent Reported Child Behavioural, Psychosocial and HRQOL Outcomes

CHD and its related morbidities not only impact neurodevelopmental outcomes but also overall HRQOL, which encompasses physical, psychological, and social functioning (Marino et al., 2016). To directly address parental concerns identified during PPI work, social-emotional, behavioural, psychosocial and HRQOL outcomes were investigated. Contrary to expectations, children with TGA had similar outcomes to healthy controls but, as anticipated, children with HLHS had poorer functioning and outcomes across all domains assessed. More than half of the HLHS cohort had borderline or clinical internalising problems scores, and just less than half had total problem scores in the borderline or clinical range. Other impairments included practical adaptive skills, many domains of EF including inhibition, emotional control, and working memory, and almost three quarters of the HLHS cohort had reduced HRQOL in all domains. This suggests that greater heart disease complexity is associated with poorer behavioural, psychosocial,
and HRQOL outcomes. McCusker et al. (2007) reported that only children with complex and palliative CHD were at increased risk of poorer behavioural outcomes, whilst those with complete repair, such as TGA, showed favourable behavioural outcomes similar to controls. The present findings are comparable with the literature suggesting increased prevalence of internalising and to a lesser extent externalising behavioural problems in complex CHD (Abda et al., 2019; Bonthrone et al., 2022; Jilek et al., 2021), impaired adaptive behavioural skills (Sananes et al., 2021; Tan et al., 2022), executive dysfunction (Calderon et al., 2014; Sanz et al., 2017), and reduced HRQOL (Dempster et al., 2018; Goldberg et al., 2019) in complex CHD, and to a greater degree in children with HLHS (Wray et al., 2014; 2018).

Social functioning/cognition is known to be influenced by higher-order language skills such as pragmatic and narrative language, and executive functions (EF) (Calderon and Bellinger, 2015; Gaudet et al., 2022). In the current cohort, parent-rated pragmatic language, social skills, and EF were all significantly associated. Greater executive dysfunction was associated with poorer pragmatic language, whilst better social skills were associated with higher pragmatic language scores. Further, correlations suggested that increased behavioural problems and executive dysfunction were associated with lower psychosocial functioning and overall HRQOL.

Importantly, as discussed, early social-emotional and adaptive behaviour development from Bayley-3 measured longitudinally between 5 months and 3-4 years of age did not indicate any early impairments in this cohort, and these earlier scores were also not associated with later social-emotional and adaptive behaviour at 4-5 years. Some researchers have found that social-emotional and behavioural difficulties are present in the early years (Bonthrone et al., 2022;
Cassidy et al., 2018), so it was reasonable to assume that this would be the case in the current cohort too. However, it may be that these deficits do not present themselves until later as children with CHD grow into their deficits (Ijsselstijn et al., 2021; Ryan et al., 2019). Longitudinal social-emotional scores from the CBCL obtained one year apart were found to be consistent as all syndrome and DSM-oriented scales were longitudinally correlated, except for Somatic Complaints. Within groups, children with HLHS had consistent longitudinal scores suggesting that their social-emotional status was stable between 3-5 years. Children with TGA and healthy controls had some variations including in Externalising, Total, and ADHD Problems, which increased with age but remained within the normative range. Scatterplots including all children further showed that socioemotional behaviour was generally stable overtime from the preschool to early school-age period. Consequently, children who had scores in the clinical range a year earlier were likely to have them a year later, and upon further inspection of the data, these tended to be those with HLHS. This was despite instability in early infancy, measured by the parental Bayley-3 questionnaire. This suggests that social-emotional behaviour may be measured differently in Bayley-3 compared to the CBCL, given the lack of association between these two measures.

8.1.5 Parent and Family Outcomes and Quality of Life

Parents and families are likely to be significantly impacted by the initial diagnosis and caring for a child with complex CHD, making them vulnerable to high levels of both acute and persistent psychological stress (Sood et al., 2021), which can impact their own overall HRQOL. Anxiety, depression, and post-traumatic stress disorder (PTSD) are reported in parents in the weeks and months following their
child’s cardiac diagnosis and surgery (Woolf-King et al., 2017). Given that children with HLHS require multiple staged surgeries over the first few years of life, it is likely that these symptoms could persist long-term. Parents and the family environment are highly influential in child development and consequently, parental mental health can intensify or moderate the effects of medical CHD experiences on child outcomes (Wray et al., 2021).

The findings in the current study revealed that predominantly mothers of children with HLHS had the worst outcomes, and exhibited the greatest proportion of borderline and clinical scores in a range of domains including social functioning, worry, daily activities, anxiety, frequency of stress and family functioning. Furthermore, some mothers were flagged for PTSD 4-5 years after their child’s initial diagnosis of CHD. Overall, parents of children with TGA had outcomes similar to those of parents of healthy children. Higher mental health and stress symptomatology and greater impact of CHD on parents was associated with lower parent HRQOL and family functioning. Moreover, higher parental CHD-related stress was associated with higher anxiety and depression symptoms in parents. These findings support those of previous studies (Kaugars et al., 2018; Medrano et al., 2013).

Further, elevated behavioural problems and executive dysfunction in children with CHD described in Chapter 6, were found to be positively correlated with parental mental health problems, and negatively correlated with family functioning and parent HRQOL. Therefore, in a family with a child with complex CHD displaying increased behavioural problems and executive dysfunction, parents were more likely to have increased mental health problems, and poorer family functioning and HRQOL. Finally, poor parental HRQOL was associated with psychosocial maladjustment and reduced overall HRQOL in children with
CHD, particularly those with HLHS. Of note, these associations between parent and child outcomes may be due, at least in part, to shared method variance as all measures used were parent-completed. Consequently, a stressed and highly anxious parent who rated their own psychosocial functioning and HRQOL as poor may also be more likely to rate their child’s behaviour and HRQOL as low too. Alternatively, these associations may be due to the interdependent relationship between child and parental functioning. For example, a child with increased behavioural problems may cause a higher degree of mental health problems in the parent, or a highly stressed, worried and anxious parent may struggle to manage their child’s behaviour which further exacerbates problems. What is unclear from this research is which preceded what, as causality cannot be determined from correlational analyses, based on this cross-sectional element of the study. Longitudinal data are needed in order to examine this further in the current cohort of children with complex CHD.

Overall, the findings suggest that parents and the wider family environment may exert a significant influence on the development and outcomes of children with complex CHD, particularly with regards to their social-emotional and behavioural outcomes, and that complex CHD in a child is likely to impact parents and the family. Consequently, it is recommended that parent mental health screening and assessment are undertaken following CHD diagnosis, alongside the surveillance of children with CHD throughout the lifespan (Sood et al., 2021). This would allow effective and timely interventions to be implemented to support parents’ and families’ wellbeing and promote psychosocial adaptation to achieve the best outcomes for children with CHD.
8.2 Case Studies

Published studies generally report group data but this removes the ability to look at individual cases in detail. This is especially important when children have not followed the expected or group trend. There is a clear pattern evident of CHD group averages being in the normative range, albeit often at the lower end, for given skills, but a significant proportion of individual children having impaired scores. Whilst some of these children could be considered as ‘outliers’, when the proportion of abnormal scores is greater than would be expected in the normative population, it is important to consider that these individual children are key to comprehensively understanding outcomes in CHD. This is especially true in cases where scores are consistently impaired longitudinally. However, given that the phenomenon of growing into deficits appears to be common in CHD, it may be even more important to avoid classifying children as outliers, as this may be part of the deficits associated with CHD which present later in life. For an insight into each individual child’s course of development over the four time-points from 5-8 months to 4-5 years, a traffic-light coded database of key neurodevelopmental, behavioural, and HRQOL scores can be found in Appendix 12.

Three case studies will be presented to highlight the complexities of evaluating neurodevelopmental outcomes in children with complex CHD, especially given that the current cohort was considered a relatively ‘clean’ sample with no known comorbidities. These case studies also help to synthesise the findings and provide a better insight into the ‘bigger picture’ of neurodevelopmental, behavioural, and HRQOL outcomes in individual children with CHD. Reported parental concerns are from the assessment at 4-5 years. The first case study is
a child with TGA for whom most early neurodevelopmental scores were in the normative range, and later problems presented at 4-5 years (Figure 8.1).

Figure 8.1 Case Study 1

Note. Colour-coding represents the range of outcomes, where: green = good/normal expectation, orange = borderline (1-2 SD below norms), red = poor (≥2 SDs below norms), and grey = data not available/completed.
The second case study is a child with HLHS with many consistently poor and impaired neurodevelopmental scores, longitudinally (Figure 8.2).

**Case Study 2: HLHS 6**

Female patient born cyanotic (no respiratory effort), Uneventful Norwood operation at 7 days-old, Glenn at 6 months, and TCPC at 3 years.

Mother concerned about her development as she is very behind at school compared to peers, low confidence and needs assistance when working for constant reassurance and struggles to understand things.

Not attending school at final assessment (4-5 years) due to health concerns and awaiting confirmation for further surgical intervention.

Inconsistent cognitive/IQ and speech and language scores longitudinally, IQ in the normative range at 4-5 years, but speech and language skills 1-2 SDs below. Patient flagged for SLI in parent completed communication screening questionnaire. Poor phonology skills (≥2 SD below norms) and unable to complete story narrative task due to apprehension and lack of concentration and tiredness. Borderline social/emotional and adaptive behaviour, but poor executive functioning and overall child HRQOL. Difficult assessment with evident low mood, very easily tired and needed frequent breaks, was apprehensive to do tasks, and needed a lot of encouragement. Tended to scratch temples when task was difficult, and she did not/could not do something.

**Note.** Colour-coding represents the range of outcomes, where: green = good/normal expectation, orange = borderline (1-2 SD below norms), red = poor (≥2 SDs below norms), and grey = data not available/completed. TCPC = total cavopulmonary connection, the final HLHS staged surgery.
The third case study is a child with HLHS who had almost all longitudinal scores across the tested domains in the normative range, with the exception of phonological awareness and narrative skills, despite some significant clinical/medical events which would classify this patient as high-risk (Figure 8.3).

**Figure 8.3 Case Study 3**

*Note.* Colour-coding represents the range of outcomes, where: green = good/normal expectation, orange = borderline (1-2 SD below norms), red = poor (≥2 SDs below norms), and grey = data not available/completed. TCPC = total cavopulmonary connection, the final HLHS staged surgery.
These case studies help to highlight that some individual CHD patients do very well, despite being high-risk and having palliative HLHS. This is an important, clinically relevant finding as it provides parents with hope that not all children with complex CHD have poor outcomes. Conversely, a child with no significant negative medical or clinical events can still go on to experience impairments at school-age. These impairments may also impact the family and especially the mothers who concurrently often have high level of stress, anxiety/depression and poorer HRQOL outcomes. These findings support studies which indicate that other factors such as the family and environment are more influential in neurodevelopmental outcomes in children with CHD, than clinical or medical variables alone (Chang et al., 2020; Denniss et al., 2019; McCusker et al., 2013; Werninger et al., 2020). Further, they illustrate the key role parents and especially mothers play in their child’s development as highly anxious and stressed mothers are likely to parent and engage with their child differently. This is then likely to impact their child’s development and overall HRQOL. This work also highlights the individual nature of responses and the pitfalls of making assumptions based on published group means/scores. Consequently, an individualised approach is necessary in the care of patients with complex CHD.

It is important to identify the key parent mental health and family factors which have the strongest influence on child outcomes, in order to better understand how to support children with complex CHD and their families, and provide appropriate interventions. Sood et al. (2021) outlined that parent mental health, parenting style and behaviours and the wider family environment exert a powerful influence on child neurodevelopment, behaviour and psychosocial functioning, and can either exacerbate or mitigate the effects of CHD-related medical experiences on
child outcomes. Given the repeated exposure to traumatic events many parents have to experience as a result of their child’s complex and severe CHD, it is not surprising that the mental health of many of these parents is substantially affected long-term, many years after the initial diagnosis and surgeries for CHD (Denniss et al., 2019; McCusker et al., 2013). Further investigations are needed to explore maternal stress biomarkers in complex CHD, in order to develop interventions which can be implemented from the time of diagnosis. A recent review by Kasparian et al. (2019) indicated a positive impact on maternal coping, mother-infant attachment, parenting confidence, as well as infant mental development at 6 months using Bayley-2, from early mental health interventions for parents in the neonatal and infancy period (van der Mheen et al., 2019; McCusker et al., 2010; 2012; 2013), and the findings from the current study highlight the importance of an individualised approach when implementing interventions, to ensure optimal outcomes for children with CHD and their families.

8.3 Strengths

There are some key strengths of the present research. Firstly, detailed longitudinal investigations have enabled the assessment of several domains including cognition/IQ, language abilities in their entirety, and social-emotional and behavioural skills, in individual children with complex CHD over the first five years of their life. Secondly, these patients did not have any known genetic or chromosomal abnormalities which could have impacted neurodevelopmental, psychosocial and HRQOL outcomes. Thirdly, the same researcher completed the majority of the longitudinal assessments between time-points 1-3, and all assessments at time-point 4. Consequently, researcher variation has been
minimised, and any researcher bias is likely to have remained consistent across the data collection longitudinally. Linked to this, participants were able to build a rapport with the same researcher over time which helped to make them feel comfortable during assessments. All assessments were also conducted in research labs at the UCL Wolfson Centre and were arranged outside of the patients’ hospital visits and in a child-friendly environment.

Further, this research adds to the limited CHD literature from the UK, compared to that from North America, Australia, Japan, and other parts of Europe. The UK is underrepresented in this field, which may reflect the lack of neurodevelopmental follow-up in children with complex CHD in the UK. Many of the standardised measures used in this research have been recommended by the American Heart Association, and Cardiac Neurodevelopmental Outcome Collaborative as appropriate measures for the neurodevelopmental follow-up of CHD patients (Marino et al., 2012; Ware et al., 2020). Using the same measures across countries and research sites allows for consistency, thereby enabling easier and better comparisons to be made between studies.

This was also the first study to examine functional speech sound processing using ERPs in children with CHD, and then to relate these to behavioural measures of language. Finally, many previous studies focus on either child or parental outcomes in isolation. However, this research has assessed these outcomes concurrently and highlighted the interdependent relationship between parental and child outcomes in complex CHD, using both parent-rated measures and behavioural assessments.
8.4 Limitations

The limitations relevant to each individual component/study of this research have been discussed in the relevant data chapters for each study. Here, limitations applicable to the entire thesis are discussed.

8.4.1 Sample Selection and Size

As outlined in Appendix 1, the current cohort of CHD patients was initially recruited for a study investigating neuropathology associated with memory impairment. Consequently, a relatively ‘clean’ sample of CHD patients was recruited to ensure there were no confounding outcomes as a result of comorbidities. Some of these comorbidities are widely reported in the CHD literature such as prematurity, low birthweight, cardiac arrest, and genetic or chromosomal abnormalities/syndromes. As a result of this selection process it is evident that the current cohort of CHD patients, recruited from a single centre, is not representative of the wider CHD population. Initial recruitment of neonatal patients, particularly those with HLHS, was especially challenging; some parents declined to participate, most likely due to the severity of their child’s condition and the strain families were under and some children died following cardiac surgery whilst still at GOSH. Some TGA neonates were also discharged before parents could be approached for recruitment. Other challenges which affected recruitment included change of clinical fellows at GOSH which meant that no referrals were made for six months, and changes within the research team which meant that there was not an appropriate member of staff to liaise with the clinical team at GOSH for recruitment of patients.
These recruitment difficulties impacted the initial sample size of the CHD cohort, which then experienced attrition at each time-point, a common finding in longitudinal studies. Attrition in CHD patients may have led to bias in that the children who were sicker may have been more likely to drop-out and withdraw from the study, and/or had poorer performance and may have been more likely not to complete all the tasks, despite attending the assessment. This led to an overall small sample size which was further restricted by having unequal samples of HLHS and TGA patients, and healthy controls.

Healthy controls were predominantly recruited from London (e.g. University College London Hospital, The Royal Free Hospital, local GP practices, health centres, nurseries, and UCL Institute of Child Health) and, consequently, may not be demographically representative of the general population. Parental education and socioeconomic status (SES) information were collected and all mothers of healthy controls were either university graduates or postgraduates, compared to only 29% of mothers of children with either HLHS or TGA who were postgraduates. A similar proportion of fathers were university graduates across all three groups, but again, a higher proportion of fathers of healthy controls were postgraduates. However, levels of deprivation, including the Index of Multiple Deprivation and income deprivation affecting children, were similar across all three groups. During recruitment, groups were not individually matched for age and gender. The age range in each group was not significantly different, and although the proportion of males and females differed in each group, there was no statistically significant association between group and gender. Gender distribution may have impacted the data given the gender differences known to be present, particularly in behavioural outcomes and language development and associated disorders (Adani and Cepanec, 2019; Van der Sluis et al., 2017).
Consequently, the higher proportion of males in the healthy control group may have masked some of the group differences in the domains investigated where males are known to do worse, but this is difficult to determine given the small sample size.

These sample size limitations ultimately restricted the statistical analyses which could be conducted (e.g. regression analyses) as well as conclusions which could be drawn from the data presented in this thesis. Some factors which are known to impact neurodevelopmental outcomes in CHD could not be assessed in this research given the restrictions of sample size. These included the influence of clinical/medical variables at the time of cardiac surgery, and parental/maternal education and SES.

8.4.2 COVID-19 Impact

The COVID-19 pandemic impacted this research in a number of ways. Firstly, data collection had to be stopped during lockdown and could not be completed. This is reflected in participant numbers at the later time points as children could not be invited to complete in-person assessments. Consequently, a decision was made to try and maximise the data that could be collected. Parental questionnaires were sent to those parents who could not attend in-person assessments, at the beginning of the pandemic, who were keen to participate. The impact of the pandemic is likely to have influenced parents’ responses, which may have compromised the data. Parents were home-schooling during this period, and many may have been very stressed. Although this is likely to have been true for all groups, for those whose children had CHD their stress may have been exacerbated by their child’s CHD if care had been impacted during this time.
and through worry about the possible impact of COVID-19 on their child’s health. Given that some questionnaires examined parental mental health, this needs to be taken into consideration, as the pandemic may have negatively impacted these outcomes. The impact of lockdown and isolation on child development is also unknown, so this needs to be borne in mind. However, there is also some evidence that children with chronic health conditions benefitted from lockdown and being socially isolated, in terms of experiencing fewer infections and periods of illness. The wider impact of the pandemic on children, and those with chronic health conditions in particular, is not likely to be fully realised for many years, if at all. It is therefore important to view the findings from the final time-point of this thesis in the context of the COVID-19 pandemic.

8.4.3 Methodological Considerations

There are several methodological limitations which may have impacted the research and data in this thesis. Firstly, the researcher collecting longitudinal data was not blind to the CHD patient groups due firstly to the ethical guidelines in place to check patients’ medical records and contact their GP prior to each assessment to ensure that children with CHD had not experienced any adverse medical events; and secondly due to the different information sheets given to the parents at the time of testing.

Secondly, it is preferrable to have behavioural measures of certain domains alongside parental questionnaires, such as the direct assessment of EF and attention. This not only enables a more thorough examination of these skills, but also allows for comparisons to be made between directly measured and parent-rated skills. However, this would have increased the time of testing and the
duration of the overall assessment at the final time-point 4 was already extensive for a 4-5 year-old. Therefore, to minimise burden on parents, and particularly on children with CHD, tests/tasks were kept to a minimum as much as possible. Linked to this, given that assessment days were long, it is possible that children and especially those with CHD may have been tired nearer the end of the assessment battery, which may have affected their performance. Also, it is difficult to ascertain whether the child was having a ‘bad day’ or on the contrary a ‘good day’ which may also have affected their performance and scores on the day.

It would also have been preferrable to have multiple informants of child behaviour and skills, rather than focussing on one parent’s rating alone. For example, some previous studies have also included teacher ratings for an independent evaluation of the child’s performance (Bellinger et al., 2003; Brosig et al., 2013). This is possible with many of the questionnaires used in this research such as the CBCL, SDQ, ABAS, and CCC-2 for which teacher versions are available. However, logistical challenges meant this was not possible in the present research and these challenges were made worse during the pandemic. Teacher ratings, together with those from parents, would have enabled a more reliable measure of skills. Further, it is important to consider the role of fathers which was not possible in the present research given that the majority of assessments were attended by mothers only and only they rated their child’s behaviour/skills. Fathers are notably underrepresented in previous research, which is problematic given that self-reported measures from mothers and fathers show different trends, with mothers having worse outcomes related to well-being, mental health, and HRQOL (Cantwell-Bartl and Tibballs, 2013; Lawoko and Soares, 2002; Mussatto et al., 2021; Wray et al., 2018). It would also be interesting to see how
mothers’ and fathers’ ratings of their child’s performance differ from one another. If mothers are known to have poorer outcomes, then it is reasonable to assume that mothers experiencing psychological adjustment difficulties and poor HRQOL may rate their child’s behaviour/performance more negatively.

Finally, the timing of longitudinal assessments was not always optimal. Time-point 1 at approximately six months of age coincides with teething milestones which often impacts the assessment of neurodevelopmental skills. Further, there was a large gap between time-points 2 and 3 which is particularly problematic given the accelerating rate and extent of variation between children at which skills are learnt and mastered during early years of development. It would have been preferable to assess the cohort at approximately two years, to keep follow-up consistent and regular, particularly given that neurodevelopmental skills are known to begin to stabilise at this age (Kvestad et al., 2022; Petrill et al., 2004), and prior to this are widely reported to be poor predictors of later performance. The timing of assessments is even more crucial in children with HLHS who have three staged surgeries over the first few years of their lives. Ideally, assessments would take place after each surgery to determine whether subsequent open-heart surgeries lead to poorer outcomes or increased delays and/or impairments.

8.5 Clinical Implications

The findings presented in this thesis have important implications for clinical practice in the UK and the care of young children with complex CHD. In line with previous research, these findings confirm that early neurodevelopmental assessments in infancy and the preschool years are not always indicative or predictive of later abilities at school-age. Children with CHD with impaired scores
at 4-5 years of age were not always flagged in earlier assessments for having impairments. This highlights the need for longitudinal investigations in children with complex CHD. There are currently no follow-up neurodevelopmental programmes or routine monitoring of development in the UK for children born with CHD, compared to those available across North America. This means that outside of regular out-patient clinic visits with a paediatric cardiologist and any standardised follow-up with health visitors, children are not assessed for any neurodevelopmental, behavioural, or psychosocial delays/impairments, unless there are obvious impairments or known comorbidities which may impact the child's development. This is particularly concerning for those children who present with subtle difficulties and mild impairments, who may otherwise get missed if longitudinal surveillance and assessment are not conducted. Children with CHD are also known to grow into their deficits, and these often become more pronounced as the child gets older and they experience greater cognitive demands and their difficulties begin to affect school performance and attainment which is brought to their teachers’ attention.

Whilst efforts are being made to develop specific guidelines for monitoring children with CHD in Europe and the UK, currently cardiac care in the UK focusses on immediate care and treatment, and involves cardiac follow-up with a paediatric cardiologist and the opportunity for possible specialist referrals to a psychologist or speech and language therapist etc, if any delays/impairments are evident. However, this is usually when the child is older and thus delays recognition and the possibility for early intervention. There is no focus on long-term neurodevelopmental follow-up, although there are opportunities to improve this. GOSH is part of the One Heart CHD Network, developed to streamline the pathway and improve the delivery of joined-up cardiac care in London and East
England to people with CHD across the age-span. Similarly, recognising the challenges in the UK of providing neurodevelopmental follow-up to all children with CHD, early screening tools have been developed and tested, such as the Brief Developmental Assessment (BDA) (Brown et al., 2018; Wray et al., 2018), to improve the ability to identify children with CHD known to be at risk of developmental delays/impairments as early as possible, before such problems become established.

Currently in the UK, only one research group (in Belfast) have undertaken a randomised control trial with children with CHD and implemented interventions in a research paradigm (McCusker et al., 2010; 2012; 2013). These interventions have focused on improving mother-infant interactions and promoting psychosocial adjustment in infants and 4-5 year-old children with CHD and their families. Results have shown positive effects in measures of feeding practices, appraisal of the mother’s/family’s situation, maternal mental health and family functioning, and although there were no significant differences in child behavioural outcomes, maternal mental health and worry were found to be important predictors of child outcomes (McCusker et al., 2010; 2012). This research was extended and a sibling-controlled study at 7 years (McCusker et al., 2013) found that disease and surgical factors, and neurodevelopmental functioning were not related to behavioural problems in children with complex CHD. The latter were mediated by maternal mental health and family factors, from infancy. Also, the sub-group who had previously participated in the early intervention programme maintained limited gains from this intervention in infancy, suggesting that follow-up sessions may have been necessary. This research group is currently trying to set up a neurodevelopmental clinic in Belfast involving a multidisciplinary team. However, these strategies need to be adopted across
the UK and Europe to ensure a similar level of care is given to all CHD patients, and the necessary emphasis is placed on long-term regular surveillance and implementation of appropriate interventions.

In PPI work undertaken for this research, parents described how important it was to adequately prepare and support children with CHD for school entry, noting if they require further support, and identifying if there are risks or indicators of early impairments. Without long-term neurodevelopmental surveillance of children with CHD, which is part of the care plan, parents are often left feeling confused, uninformed, unsupported and unprepared for their child’s future, despite many parents having a “gut feeling” or “mother’s instinct” that “something wasn’t quite right” with their child. Thus, a UK public health framework for CHD is necessary, similar to that recommended by the American Heart Association for the appropriate neurodevelopmental follow-up of CHD patients (Marino et al., 2012; Ware et al., 2020). This is crucial given that more children with CHD are now living into adulthood and they need to be supported in the early years in order to have better prognosis through the lifespan. Figure 8.4 outlines a proposed cardiac care pathway for children with CHD; although it is unlikely to be a linear process, the pathway includes regular screening, and if indicated, further assessment to be conducted. Utens et al. (2018) proposed recommendations for multidisciplinary family-centred care for patients with CHD in Europe (Figure 8.5). They suggest that parents are supported at every step of their child’s care, from initial antenatal screening, during hospitalisation for cardiac surgeries, to bereavement support following the death of a child. Concurrently, children should be followed-up from infancy through to adolescence using standardised measures of neurodevelopment, psychological functioning, social-emotional and
behavioural functioning, and HRQOL, alongside usual outpatient care and examinations, leading to a more supported transition into adulthood.

Figure 8.4 Proposed CHD healthcare pathway for young children in the UK

Figure 8.5 Multidisciplinary family-centred psychosocial care plan for children with CHD (Utens et al., 2018)
8.6 Directions for Future Research

Having established a cohort of children with CHD who have been followed longitudinally, it would be beneficial to continue with further follow-up investigations, but it may be necessary to include a cross-sectional cohort to mitigate the present limitations of sample size. Firstly, the ERP study was the first of its kind in CHD, and has provided the initial steps necessary to examine the brain network involved in functional speech processing. The oddball paradigm could be adapted to include more age-appropriate speech and language processing, during active rather than passive processing. It would also be necessary to include non-speech sounds in order to ascertain whether neural responses are specific to language, and consequently change for tones. Secondly, selective subtests of phonological awareness were chosen based on their predictive value of later reading skills. However, future research should focus on all aspects of phonology to gain a better insight into early pre-reading skills. Thirdly, the assessment battery could be refined to include fewer measures and subtests given the correlations observed between many of the measures in the current investigation. Fourthly, behavioural measures of certain domains are necessary to corroborate parent-rated outcomes, particularly in EF, attention, and behaviour, as these are known to be worse in older school-aged children with CHD. Given that CHD patients grow into their deficits and the fact that developmental scores are known to stabilise at school-age, it would be important to continue longitudinal follow-ups of this cohort. Ideally, any further follow-up should include neuroimaging such as MRI brain scans which would allow neurodevelopmental outcomes to be linked with structural and functional brain findings.
More generally, longitudinal multi-centre research is needed in the UK in a cohort which is representative of the wider CHD population, following the neurodevelopmental guidelines previously suggested. Given that more children with CHD survive into adulthood, it is important to track how outcomes develop over the life-span. It is evident from the literature that there is a high incidence of neurodevelopmental delays/impairments in CHD, but the focus now needs to turn to the management of known problems and novel early interventions to better support children. For example, Calderon et al. (2020) reported on the outcome of a randomised control trial in adolescents with CHD, and found that although Cogmed Working Memory Training did not improve working memory in the cohort, it did demonstrate benefits in executive function and attention three months post-intervention. The development and implementation of novel interventions involves working with key stakeholders such as schools, local communities, families, and healthcare providers, to ensure a multidisciplinary approach is used.

From the literature reviewed, the theoretical framework guiding the majority of published investigations is unclear. Many studies are concerned with global functioning and report the outcomes of neurodevelopmental testing suggesting impairments in a wide range of domains. However, they do not propose mechanisms for their findings, and do not consider what brain circuitry is implicated. Some MRI studies have indicated that white matter injury and resulting differences in network processes are implicated in cognitive impairments such as executive functioning which relies on prefrontal white matter pathways (Marelli et al., 2016). However, there are very limited studies which combine structural brain findings with functional and behavioural outcomes in children with complex CHD. This needs to be addressed in future research.
Finally, the role of social determinants of health and health inequalities for longer term outcomes is gaining increasing focus. These should be incorporated into future multi-centre research studies with larger and more diverse populations so as to be able to inform truly holistic care and the implementation of targeted interventions for children and their families.

8.7 Final Conclusions

More children with complex CHD are surviving into adulthood than ever before. Many of these are high-risk and are susceptible to delays and impairments across a range of domains including speech and language, social-emotional and behavioural skills, executive function, and adaptive behaviour. These impairments can impact their psychosocial development and overall HRQOL. The investigations in this thesis have provided detailed longitudinal observations of the developmental trajectories of cognition, speech and language, social-emotional, and behavioural skills in a cohort of children with complex CHD (i.e. HLHS and TGA), across the first five years of life. The brain network supporting speech processing was also examined longitudinally using a passive ERP auditory oddball paradigm. This was the first investigation of its kind exploring functional language processing in children with CHD, and relating this to behavioural measures of speech and language (i.e. phonological awareness and one-word expressive language). Pre-reading and narrative skills, adaptive behaviour, executive function and HRQOL were also explored in this cohort at 4-5 years of age. Concurrently, family functioning, parental and particularly maternal mental health and HRQOL, and the overall impact of CHD on parents/mothers was also investigated.
Overall, children with HLHS consistently have poorer outcomes compared to those with TGA across all the domains assessed in this project. This is likely due to the increased severity of the heart defect, multiple open-heart surgeries required, and the greater risk of morbidities associated with HLHS, which suggests that single ventricle circulation is likely to have a greater adverse impact on brain development. However, there are some children at high-risk of neurodevelopmental delays/impairments who have relatively positive outcomes, similar to normative expectations and healthy controls. The longitudinal trajectories and outcomes in individual children can vary substantially and the specific causes for this are unknown. It is likely that a combination of many factors impact outcomes, including medical/clinical factors, family and environmental factors, and continued care and long-term surveillance. Importantly, early neurodevelopment is not always predictive or indicative of later impairments and problems. Consequently, the findings presented in this thesis highlight the need for detailed longitudinal investigations and long-term follow-up in children with complex CHD. The lack of follow-up neurodevelopmental programmes or routine monitoring in the UK for children with CHD, which would allow for early screening of delays/impairments and implementation of early targeted interventions, leading to a supported transition to school and eventually adulthood, needs to be addressed and the findings from this research provide previously unavailable evidence from England to support this.
References


Neurodevelopmental Outcome Collaborative. *Cardiology in the Young, 31*(6), 888–899. https://doi.org/10.1017/S1047951121002158


after cardiac surgery in infancy: an unintended consequence of life-saving care. 
https://doi.org/10.1016/j.jpeds.2017.09.049


https://doi.org/10.1097/JCN.0000000000000466


https://doi.org/10.1177/0883073815591214

https://doi.org/10.1080/87565641.2012.718817

443


Marino, B. S., Lipkin, P. H., Newburger, J. W., Peacock, G., Gerdes, M., Gaynor, J. W., Mussatto, K. A., Uzark, K., Goldberg, C. S., Johnson, W. H., Jr., Li, J., Smith, S. E., Bellinger, D. C., Mahle, W. T., on behalf of the American Heart Association Congenital Heart Defects Committee of the Council on


coping, in parents of children and adolescents who underwent invasive treatment for congenital cardiac disease. *Cardiology in the Young*, 17(6), 638–645. https://doi.org/10.1017/S1047951107001333


Sun, L., Macgowan, C. K., Sled, J. G., Yoo, S. J., Manlhiot, C., Porayette, P., Grosse-Wortmann, L., Jaeggi, E., McCrindle, B. W., Kingdom, J., Hickey, E.,


Appendices
Appendix 1. The Hypoxia/Ischaemia Study

To provide context to the current thesis, it is important to note that all children (CHD patients and healthy controls) had previously participated in longitudinal investigations which were part of a large MRC programme grant. This prospective cohort study was titled ‘Hypoxia/ischaemia and patterns of neuropathology associated with memory impairment in infancy’. This is referred to as “The Hypoxia/Ischaemia (HI) Study” hereafter. The HI Study focussed on the incidence of memory impairment associated with hypoxic/ischaemic damage to brain networks that are particularly vulnerable to the adverse effects of oxygen deprivation. The study was approved by the London Hampstead NHS Research Ethics Committee (reference number 12/LO/1425) and was registered with the Joint Research and Development Office of GOSH and UCL GOS ICH (R&D number 12CN02). The study recruited patients with HLHS and TGA who underwent cardiac surgery at Great Ormond Street Hospital (GOSH) for Children as well as a group of healthy controls, from birth until four years of age. Early neurodevelopment was tracked throughout the first few years of life over three neurodevelopmental testing time-points: 5-8 months, 12-15 months, and the pre-schooler stage (3-4 years). These assessments focussed on cognitive and behavioural development, memory, and electroencephalography protocols assessing visual and auditory attention.

1.1 Participant Recruitment

1.1.1 CHD Patient Inclusion Criteria

Neonates with HLHS and TGA who had undergone cardiac surgery (Norwood Procedure or Arterial Switch operation, respectively) at GOSH shortly after birth were identified by a clinical fellow or research nurse according to the inclusion criteria in Table 1. Strict inclusion criteria were applied when recruiting CHD patients. This was to ensure there were no comorbidities present pursuant to cardiac surgery which could lead to confounding outcomes.
Table 1. MRC project patient recruitment inclusion/exclusion criteria.

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prematurity</td>
<td>Gestational age &lt;36 weeks</td>
</tr>
<tr>
<td>No neonatal depression</td>
<td>5 min Apgar score of &lt;5 or cord pH &lt;7.0</td>
</tr>
<tr>
<td>Not small for gestational age</td>
<td>Birthweight &lt;2kg</td>
</tr>
<tr>
<td>No perinatal seizures</td>
<td>-</td>
</tr>
<tr>
<td>No cardiac arrest requiring chest compression</td>
<td>-</td>
</tr>
<tr>
<td>No significant intracerebral haemorrhage</td>
<td>Intracerebral haemorrhage grade 3/4</td>
</tr>
<tr>
<td>No overt neurological impairment</td>
<td>-</td>
</tr>
<tr>
<td>No genetic or phenotype syndromes (except</td>
<td>-</td>
</tr>
<tr>
<td>chromosome 22q11 microdeletions)</td>
<td></td>
</tr>
<tr>
<td>English speaking parents (if bilingual, a good</td>
<td></td>
</tr>
<tr>
<td>understanding of written and spoken English</td>
<td></td>
</tr>
<tr>
<td>is necessary)</td>
<td></td>
</tr>
</tbody>
</table>

In the first instance, the clinical team made contact with families of children with CHD who met the inclusion criteria. All CHD patients were recruited on the cardiac Bear Ward at GOSH, following discharge from the intensive care unit. A member of the clinical team spoke to families to see if they were interested in participating in the study. If families agreed, their details were taken and passed onto the research team. Members of the research team then approached the families and gave them written information about the study and explained what participation would involve which was not part of their child’s routine medical follow-up. Parents were often left with the information sheet to read over it and have time to decide if they were interested. Researchers returned to the ward to speak with parents a few days later or when agreed and if parents were happy to proceed, informed consent was gained from them by the research team. Copies of consent forms and study documents were also included in the patients’ medical files. Parent contact details were obtained in order for the research team to organise follow-up assessments.

1.1.2 Healthy Controls Inclusion Criteria

For recruitment of healthy control infants, pregnant women were recruited predominantly through maternity clinics at both University College London
Hospital and The Royal Free Hospital. Midwives identified pregnant woman and introduced those who were interested in the study to members of the research team. A member of the research team then spoke to mothers/parents about the study and what their baby’s participation would involve. Parents who registered interest were given an information leaflet about the longitudinal study, and gave the researcher their contact details to be contacted after their child was born. Some controls were recruited through fliers at local GP practices, health centres, nurseries, cafes, and at the Institute of Child Health (ICH), as well as emails sent through mailing-lists at UCL. All parents who agreed to be contacted or registered interest were contacted by a member of the research team after their child’s due date and completed a questionnaire over the phone in order to assess the eligibility of their child for participation in the study. Table 2 outlines the inclusion criteria for healthy controls.

### Table 2. MRC project healthy controls recruitment inclusion criteria.

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Born full term</td>
</tr>
<tr>
<td>Normal birthweight</td>
</tr>
<tr>
<td>No history of medical illness</td>
</tr>
<tr>
<td>No complications during birth</td>
</tr>
<tr>
<td>No genetic conditions (medical or neurological)</td>
</tr>
<tr>
<td>Normal vision and hearing (if this has been tested)</td>
</tr>
<tr>
<td>English speaking parents (if bilingual, a good understanding of written and spoken English is necessary)</td>
</tr>
</tbody>
</table>

Parents of recruited healthy infants were reminded about the details of the longitudinal study, and were asked whether they wanted to be emailed a copy of the information sheet. Written consent was obtained from parents by the research team during the first visit of the study when the child and family came to ICH to participate. Another copy of the information sheet was also given to parents at this time. Healthy controls were age-matched as best as possible to the patient groups.
1.2 Statement of Contribution

The author of this thesis was employed on the MRC programme grant as a research assistant from January 2015 until January 2020. This role involved recruitment of HLHS and TGA patients, and healthy controls, conducting neuropsychological and electrophysiological assessments of almost all of the participants across all time-points, as well as contributing towards ethical amendments, and data analysis. Early neurodevelopmental data (i.e. cognitive, language and motor skills) collected as part of the MRC project formed the contents of the first part of this thesis (Chapter 3). The structure of the whole MRC study is presented in Figure 1, which also highlights the stages where data were used in this thesis.
Appendix 2. Longitudinal data each participant has across time-points 1-4, including all measures/tests used.

*Note.* Light green box with tick = child obtained data, box with cross = child did not obtain data, and a grey box with N/A = the measure was not applicable for healthy control children.
WPPSI-IV

CELF-P

ROWPVT

EOWPVT

Bus Story

PAT

EEG

CCC-2

CBCL

SDQ

ABAS

BRIEF-P

PedsQL

PedsQL Family Impact

x
x
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
x
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
x
✓
✓
✓

x
x
✓
✓
✓
✓
✓
✓
✓
✓
x
✓
✓
✓
x
✓
✓
✓
✓
✓
✓
x
x
x
✓
✓
✓
✓
x
✓
✓
✓
✓
✓
✓
✓
✓
✓
x
✓
✓
✓
✓
x
✓
x
✓
x
✓
✓
✓
✓
✓
✓
✓
✓
x
✓
✓
x
x
x
x

x
x
✓
x
✓
✓
✓
x
x
x
x
x
x
x
x
✓
✓
✓
✓
✓
✓
x
x
x
✓
✓
✓
x
x
x
✓
x
x
✓
✓
✓
x
✓
x
✓
✓
✓
✓
x
✓
x
✓
x
✓
✓
x
✓
✓
x
✓
✓
x
x
✓
x
x
x
x

x
x
✓
✓
✓
✓
✓
✓
✓
✓
x
✓
✓
✓
x
✓
✓
✓
✓
✓
✓
x
x
x
✓
✓
✓
✓
x
✓
✓
✓
✓
✓
✓
✓
✓
✓
x
✓
✓
✓
✓
x
✓
x
✓
x
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
x
x
x
x

x
x
✓
✓
x
✓
✓
✓
✓
✓
x
✓
✓
x
x
x
x
x
x
✓
x
x
x
x
x
x
x
x
x
x
✓
✓
✓
x
✓
x
x
x
x
✓
x
x
✓
x
✓
x
✓
x
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
x
x
x
x
x

x
x
✓
✓
x
✓
✓
✓
✓
✓
x
✓
✓
x
x
x
x
x
x
✓
x
x
x
x
x
x
x
x
x
x
✓
✓
✓
x
✓
x
x
x
x
✓
x
x
✓
x
✓
x
✓
x
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
x
x
x
x
x

x
x
✓
✓
x
✓
✓
✓
✓
✓
x
✓
✓
x
x
x
x
x
x
✓
x
x
x
x
x
x
x
x
x
x
✓
✓
✓
x
✓
x
x
x
x
✓
x
x
✓
x
✓
x
✓
x
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
x
x
x
x
x

x
x
✓
✓
x
✓
✓
✓
✓
✓
x
✓
✓
x
x
x
x
x
x
✓
x
x
x
x
x
x
x
x
x
x
✓
✓
✓
x
✓
x
x
x
x
✓
x
x
✓
x
✓
x
✓
x
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
x
x
x
x
x

x
x
✓
✓
x
x
✓
✓
✓
✓
x
✓
✓
x
x
x
x
x
x
✓
x
x
x
x
x
x
x
x
x
x
✓
x
x
x
✓
x
x
x
x
✓
x
x
✓
x
x
x
x
x
x
✓
x
✓
✓
✓
✓
✓
✓
✓
x
x
x
x
x

x
x
✓
✓
x
✓
✓
✓
✓
✓
x
✓
✓
x
x
x
x
x
x
✓
x
x
x
x
x
x
x
x
x
x
✓
✓
✓
x
✓
x
x
x
x
✓
x
x
✓
x
✓
x
✓
x
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
x
x
x
x
x

x
x
✓
x
x
✓
✓
x
✓
✓
x
x
✓
x
x
x
x
x
x
✓
x
x
x
x
x
x
x
x
x
x
✓
x
✓
x
✓
x
x
x
x
✓
x
x
✓
x
✓
x
✓
x
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
x
x
x
x
x

x
x
✓
✓
x
✓
✓
✓
✓
✓
x
✓
✓
✓
x
x
x
x
x
✓
x
x
x
x
x
x
x
x
x
x
✓
✓
✓
x
✓
x
✓
✓
x
✓
x
x
✓
x
✓
x
✓
x
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
x
x
x
x

x
x
✓
✓
x
✓
✓
✓
✓
✓
x
✓
✓
✓
x
x
x
x
x
✓
x
x
x
x
x
x
x
x
x
x
✓
✓
✓
x
✓
x
✓
✓
x
✓
x
x
✓
x
✓
x
✓
x
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
x
x
x
x

x
x
✓
✓
x
✓
✓
✓
✓
✓
x
✓
✓
✓
x
x
x
x
x
✓
x
x
x
x
x
x
x
x
x
x
✓
✓
✓
x
✓
x
✓
✓
x
✓
x
x
✓
x
✓
x
✓
x
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
x
x
x
x

x
x
✓
✓
x
✓
✓
✓
✓
✓
x
✓
✓
✓
x
x
x
x
x
✓
x
x
x
x
x
x
x
x
x
x
✓
✓
✓
x
✓
x
✓
✓
x
✓
x
x
✓
x
✓
x
✓
x
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
x
x
x
x

x
x
✓
✓
x
✓
✓
✓
✓
✓
x
✓
✓
✓
x
x
x
x
x
✓
x
x
x
x
x
x
x
x
x
x
✓
✓
✓
x
✓
x
✓
✓
x
✓
x
x
✓
x
✓
x
✓
x
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
x
x
x
x

x
x
✓
✓
x
✓
✓
✓
✓
✓
x
✓
✓
✓
x
x
x
x
x
✓
x
x
x
x
x
x
x
x
x
x
✓
✓
✓
x
✓
x
✓
✓
x
✓
x
x
✓
x
✓
x
✓
x
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
x
x
x
x

x
x
✓
✓
x
✓
✓
✓
✓
✓
x
✓
✓
✓
x
x
x
x
x
✓
x
x
x
x
x
x
x
x
x
x
✓
✓
✓
x
✓
x
✓
✓
x
✓
x
x
✓
x
✓
x
✓
x
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
x
x
x
x

480

Impact of Event

CBCL

✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
x
✓
✓
✓
✓
✓
✓
✓
✓
x
✓
✓
✓
✓
✓
x
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓

PIP

EEG

Control 1
Control 2
Control 3
Control 4
Control 5
Control 7
Control 8
Control 9
Control 10
Control 11
Control 12
Control 14
Control 16
Control 18
Control 19
Control 20
Control 21
Control 22
Control 23
Control 25
Control 26
Control 27
Control 28
Control 29
Control 30
Control 31
Control 32
Control 33
HLHS 1
HLHS 3
HLHS 5
HLHS 6
HLHS 8
HLHS 9
HLHS 10
HLHS 11
HLHS 13
HLHS 14
HLHS 15
HLHS 16
HLHS 19
TGA 1
TGA 2
TGA 3
TGA 4
TGA 5
TGA 7
TGA 8
TGA 9
TGA 10
TGA 11
TGA 12
TGA 13
TGA 14
TGA 15
TGA 16
TGA 17
TGA 21
TGA 22
TGA 24
TGA 29
TGA 31
TGA 32

HAD

Participant

Bayley-3

Time-point 2

Time-point 4 - Parental questionnaires

Bayley-3

Time-point 1

Time-point 4 - Direct child measures

Bayley-3

Time-point 3

x
x
✓
✓
x
✓
✓
✓
✓
✓
x
✓
✓
✓
x
x
x
x
x
✓
x
x
x
x
x
x
x
x
x
x
✓
✓
✓
x
✓
x
✓
✓
x
✓
x
x
✓
x
✓
x
✓
x
✓
✓
✓
✓
✓
x
✓
✓
✓
✓
✓
x
x
x
x

N/A
N/A
N/A
N/A
N/A
N/A
N/A
N/A
N/A
N/A
N/A
N/A
N/A
N/A
N/A
N/A
N/A
N/A
N/A
N/A
N/A
N/A
N/A
N/A
N/A
N/A
N/A
N/A

N/A
N/A
N/A
N/A
N/A
N/A
N/A
N/A
N/A
N/A
N/A
N/A
N/A
N/A
N/A
N/A
N/A
N/A
N/A
N/A
N/A
N/A
N/A
N/A
N/A
N/A
N/A
N/A

x
x
✓
✓
✓
x
✓
x
✓
✓
x
✓
x
x
✓
x
✓
x
✓
x
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
x
x
x
x

x
x
✓
✓
✓
x
✓
x
✓
✓
x
✓
x
x
✓
x
✓
x
✓
x
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
✓
x
x
x
x


Appendix 3. Ethical Approval

3.1 Approval of Major Amendment

20 April 2018

Professor Faraneh Vargha-Khadem
Head of Unit, and Professor of Developmental Cognitive Neuroscience
UCL Institute of Child Health/Great Ormond Street Hospital NHS Trust
30 Guilford Street
London
WC1N 1EH

Dear Professor Vargha-Khadem

Study title: Hypoxia/ischaemia and Patterns of Neuropathology Associated with Memory Impairment in Infancy
Rec reference: 12/LO/1425
Amendment number: Amendment 4
Amendment date: 15 March 2018
IRAS project ID: 109008

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

Approval was sought for a request to extend the upper age limit of the participants for the final stage of the assessment from 36 months (3 years) to 5 years.

There were no ethical issues raised.

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.
Approved documents

The documents reviewed and approved at the meeting were:

<table>
<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Notice of Substantial Amendment (non-CTIMP)</td>
<td>Amendment 4</td>
<td>15 March 2018</td>
</tr>
<tr>
<td>Participant consent form</td>
<td>3</td>
<td>15 March 2018</td>
</tr>
<tr>
<td>Participant information sheet (PIS) [Parents - controls]</td>
<td>4</td>
<td>15 March 2018</td>
</tr>
<tr>
<td>Participant information sheet (PIS) [parents - patients]</td>
<td>4</td>
<td>15 March 2018</td>
</tr>
<tr>
<td>Participant information sheet (PIS) [Parents - patients TGA-ECMO]</td>
<td>4</td>
<td>15 March 2018</td>
</tr>
<tr>
<td>Research protocol or project proposal</td>
<td>5</td>
<td>15 March 2018</td>
</tr>
</tbody>
</table>

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

Working with NHS Care Organisations

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our Research Ethics Committee members' training days – see details at [http://www.hra.nhs.uk/hra-training/](http://www.hra.nhs.uk/hra-training/)

| 12/LO/1425: | Please quote this number on all correspondence |

Yours sincerely

On behalf of
Miss Stephanie Ellis, BEM
Chair

E-mail: nrescommittee.london-hampstead@nhs.net

Enclosures: List of names and professions of members who took part in the review

Copy to: Marice Lunny,
Great Ormond Street Hospital for Children NHS Foundation Trust
and UCL-Institute of Child Health
London - Hampstead Research Ethics Committee

Attendance at Sub-Committee of the REC meeting

Committee Members:

<table>
<thead>
<tr>
<th>Name</th>
<th>Profession</th>
<th>Present</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Rahul Chodhari</td>
<td>Consultant Paediatrician</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Miss Stephanie Ellis, BEM Chair</td>
<td>Former Civil Servant</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

Also in attendance:

<table>
<thead>
<tr>
<th>Name</th>
<th>Position (or reason for attending)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miss Ewa Grzegorska</td>
<td>Acting REC Manager</td>
</tr>
<tr>
<td>Miss Nafeesa Khanam</td>
<td>REC Assistant</td>
</tr>
</tbody>
</table>
3.2 Approval of Minor Amendment

Thomas Lewis

From: AMENDMENTS, Hra (HEALTH RESEARCH AUTHORITY) <hra.amendments@nhs.net>
Sent: 29 March 2018 09:44
To: fvargha-khadem@ucl.ac.uk; marice.lunny@gosh.nhs.uk
Subject: IRAS 109008. Amendment categorisation and implementation information

Amendment Categorisation and Implementation Information

Dear Professor Vargha-Khadem,

<table>
<thead>
<tr>
<th>IRAS Project ID:</th>
<th>109008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short Study Title:</td>
<td>Hypoxia/ischaemia and Memory Impairment in Infancy</td>
</tr>
<tr>
<td>Date complete amendment submission received:</td>
<td>14/03/2018</td>
</tr>
<tr>
<td>Amendment No/ Sponsor Ref:</td>
<td>Minor Amendment 4 - Extension of study</td>
</tr>
<tr>
<td>Amendment Date:</td>
<td>12 March 2018</td>
</tr>
<tr>
<td>Amendment Type:</td>
<td>Non-substantial</td>
</tr>
<tr>
<td>Outcome of HRA Assessment</td>
<td>This email also constitutes HRA Approval for the amendment, and you should not expect anything further from the HRA.</td>
</tr>
<tr>
<td>Implementation date in NHS organisations in England</td>
<td>35 days from date amendment information together with this email, is supplied to participating organisations (providing conditions are met)</td>
</tr>
<tr>
<td>Amendment Category</td>
<td>A</td>
</tr>
</tbody>
</table>

For NHS/HSC R&D Office information

Thank you for submitting an amendment to your project. We have now categorised your amendment and please find this, as well as other relevant information, in the table above.

What should I do next?

Please read the information in IRAS, which provides you with information on how and when you can implement your amendment at NHS/HSC sites in each nation, and what actions you should take now.

If you have participating NHS/HSC organisations in any other UK nations please note that we will forward the amendment submission to the relevant national coordinating function(s).

If not already provided, please email to us any regulatory approvals (where applicable) once available.

When can I implement this amendment?

You may implement this amendment in line with the information in IRAS. Please note that you may only implement changes described in the amendment notice.

Who should I contact if I have further questions about this amendment?

If you have any questions about this amendment please contact the relevant national coordinating centre for advice:

1
• England – hra.amendments@nhs.net
• Northern Ireland – research.gateway@hsoni.net
• Scotland – nhsg.NRSPCC@nhs.net
• Wales – research-permissions@wales.nhs.uk

Additional information on the management of amendments can be found in the IRAS guidance.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: [http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance](http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance).

Please do not hesitate to contact me if you require further information.

Kind regards

Miss Jade Robinson
Amendment Coordinator
Health Research Authority
Ground Floor | Skipton House | 80 London Road | London | SE1 6LH
E: hra.amendments@nhs.net
W: www.hra.nhs.uk

Sign up to receive our newsletter [HRA Latest](http://www.hra.nhs.uk).
3.3 R&D Study Approval

1/05/2018

Dear Professor Faraneh Varga-Khadem,

Project Title: Effects of neonatal hypoxia/ischaemia on language and phonological abilities in pre-schoolers with complex congenital heart disease

R&D Number: 17BT29

Protocol version/date: As per 12CN02

Funder: GOSH Biomedical Research Centre (GOSH BRC)

This project has been granted Management Approval by the Joint Research & Development Office.

Approval Conditions:
- An ICH Risk Assessment must be submitted to Kate Thornton, kate.thornton@ucl.ac.uk for approval within 30 days of the date of this letter. Please contact Kate for advice.
- You must submit an annual report which will be sent to you by the Joint R&D Office when it is due.
- The PI must inform the Joint R&D Office of any changes to the start and end dates of the project, or if there are any changes to the protocol or personnel. At the end of the study the PI will be sent a final report form to complete and return to the Joint R&D Office.

Please be aware that although you have been granted R&D approval you will not be authorised to spend against your award unless there is a signed contract with the research funder/lead site.

Please contact the Joint R&D Office if you require any further guidance or information on any matter mentioned above. We wish you every success in your research.

Yours sincerely,

Dr Thomas Lewis
Research Management and Governance Officer
Joint Research and Development Office

cc: ICH Finance - ich-costing@ucl.ac.uk
Kate Thornton - kate.thornton@ucl.ac.uk
Appendix 4. PPI Work

Appendix 4.1 Questions for Little Hearts Matter Facebook Page

1. How old is your child with congenital heart disease?

2. Do you have any concerns about your child's development or behaviour? If so, please could you tell us what they are specifically?

3. Which areas of development and/or behaviour do you think it is important for us to focus on when we see children aged 4-5 years-old?

4. How important do you think it is for us to conduct research into children's development and behaviour?

5. Are there any other comments you would like to make?

4.2 Dialogue Transcript and Questions for Parents at GOSH Outpatient Clinic

Greet Parent!

Introduce myself – research assistant at the Institute of Child Health, UCL. Working on a research study with congenital heart disease patients. I am proposing a new project for my PhD investigating development in CHD patients.

Ask for a moment of their time (to ask you a few questions that will help me shape my project so that it is driven by parents and families with them in mind, rather than research on them).

This will only take a couple minutes, and you will not be asked to participate.
Previously, parents/families told us their key concerns about their child with CHD, these included: language and speech problems/delays, behavioural problems, and motor related problems.

Is there anything else you would add to that based on your experience? If so, what?

These parents also said that a research study investigating the effects of early cardiac surgery on pre-schoolers’ speech and language would be very relevant/something they were interested in. Therefore, being the parent of a child who has had cardiac surgery, I would like to ask you some logistical questions regarding your preferences for this type of study.

Multiple standardised assessments would be conducted which would involve a range of activities investigating language, communication, telling stories using pictures, playing interactive games, and EEG (briefly explain this to them), these are usually quite fun and children enjoy them.

Firstly, would a research study such as this interest you and/or would you take part?

Yes / No

Logistical research questions:

1) Overall, assessments are likely to last a good few hours (up to 4 hours, though this ultimately depends on the child) so would you prefer all the assessments to be done on a single day, or spread over two days/visits? (*mention that we pay for travel and lunch expenses)
2) If a single day/visit, then would you prefer to have assessments earlier in the morning, late afternoon, or midday and then including a lunch break?

3) Would it benefit you to have the assessment on the same day as a clinic appointment at GOSH, or separate?

4) Do you think your child would benefit from regular short breaks during the assessments, or one large break such as lunchtime?

5) Would you give us permission to video and record your child’s voice as part of an assessment? (e.g. record them engaging in an activity, playing, or telling a story)

Is there anything else you would like to add or want us to consider?

Thank parents for their time!
# Appendix 5. Demographics Questionnaire for Parents

<table>
<thead>
<tr>
<th>INFORMATION ABOUT THE CHILD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child’s Date of Birth: ______________________</td>
</tr>
<tr>
<td>Today’s Date: ______________________</td>
</tr>
<tr>
<td>Child’s Gender: ☐ Male ☐ Female</td>
</tr>
<tr>
<td>Was your child premature at birth? (Defined as less than 37 weeks gestation) ☐ Yes ☐ No</td>
</tr>
<tr>
<td>If premature, how many weeks early was your baby born: ___________ Weeks</td>
</tr>
<tr>
<td>Birth Weight: ___________ Kg</td>
</tr>
<tr>
<td>Was your child a multiple birth? ☐ Yes ☐ No</td>
</tr>
<tr>
<td>Does the child have any siblings? Please specify (e.g. younger sister, older brother): ______________________</td>
</tr>
<tr>
<td>If so, ages of other siblings: ______________________</td>
</tr>
<tr>
<td>When was your child diagnosed with heart disease: ☐ Antenatal ☐ Postnatal before discharge home</td>
</tr>
<tr>
<td>☐ Post discharge to 29 days of life ☐ 30 days of life to 1 year</td>
</tr>
<tr>
<td>What is the postcode of child’s main address: ______________________</td>
</tr>
<tr>
<td>Child’s Ethnicity: ☐ White British ☐ Black British</td>
</tr>
<tr>
<td>☐ White Irish ☐ Black Caribbean</td>
</tr>
<tr>
<td>☐ White and Caribbean ☐ Black African</td>
</tr>
<tr>
<td>☐ White and African ☐ Black: Other ______________________</td>
</tr>
<tr>
<td>☐ White: Other ______________________</td>
</tr>
<tr>
<td>☐ Other (please specify): ______________________</td>
</tr>
<tr>
<td>☐ Unknown/Not Reported</td>
</tr>
<tr>
<td>Child’s Education: ☐ Mainstream School ☐ Mainstream School with Learning Support ☐ Nursery</td>
</tr>
<tr>
<td>☐ School for Children with Learning Difficulties ☐ Too Young/N/A</td>
</tr>
<tr>
<td>Child’s School, Address, and Teacher’s name: ______________________</td>
</tr>
<tr>
<td>Are you happy for us to contact your child’s teacher for him/her to complete a questionnaire? ☐ Yes ☐ No</td>
</tr>
<tr>
<td>How often does your child attend school/nursery per week, and for how long? _________ Days a week</td>
</tr>
<tr>
<td>_________ Hours per day</td>
</tr>
</tbody>
</table>
Do you have any concerns about how your child is getting on at nursery/school?  
☐ Yes  ☐ No

If so, please specify: ____________________________________________________________

____________________________________________________

____________________________________________________

What languages does the child speak both at home and school, please specify?  
___________________________________________________________________________

____________________________________________________

Does anyone in the child’s family have a language impairment?  
☐ Yes  ☐ No

If so, please specify: ____________________________________________________________

<table>
<thead>
<tr>
<th>PARENTAL INFORMATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother’s Age: _______ Years</td>
</tr>
<tr>
<td>Mother’s Education:</td>
</tr>
<tr>
<td>☐ School, College or Training up to, or equivalent to GCSEs</td>
</tr>
<tr>
<td>☐ School, College or Training up to, or equivalent to 6th Form/A-Levels</td>
</tr>
<tr>
<td>☐ University Graduate</td>
</tr>
<tr>
<td>☐ Postgraduate</td>
</tr>
<tr>
<td>☐ Other (please specify): ___________________________</td>
</tr>
</tbody>
</table>
| Mother’s Employment (please be specific, if self-employed, state as what?):  
___________________________________________________________________________ |
| ☐ Full Time  ☐ Part Time |
| Father’s Age: _______ Years |
| Father’s Education:  |
| ☐ School, College or Training up to, or equivalent to GCSEs |
| ☐ School, College or Training up to, or equivalent to 6th Form/A-Levels |
| ☐ University Graduate |
| ☐ Postgraduate |
| ☐ Other (please specify): ___________________________ |
| Father’s Employment (please be specific, if self-employed, state as what?):  
___________________________________________________________________________ |
| ☐ Full Time  ☐ Part Time |
Appendix 6. Consenting Information

Consent forms and all information sheets from the HI Study were amended (i.e. to reflect the new time-point 4 assessment at 4-5 years of age) for use in this PhD project as per the ethical approval for this study.

6.1 Consent Form

6.2 Information Sheet for HLHS patients

6.3 Information Sheet for TGA patients

6.4 Information Sheet for Healthy Controls

6.5 General Data Protection Regulation for CHD Patients

6.6 General Data Protection Regulation for Healthy Controls
CONSENT FORM

Project Title: Hypoxia/ischaemia and patterns of neuropathology associated with memory impairment in infancy

Researchers' Names: Faraneh Vargha-Khadem, Rachael Elward, Maneet Kaur Saini

Name of participant (child):

For parent(s) to fill in:

<table>
<thead>
<tr>
<th>Please initial</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I confirm that I have read and understood the information sheet dated 15.03.2018, for the above study and have had the opportunity to ask questions.</td>
</tr>
<tr>
<td></td>
<td>I give my permission for the research team to inform my child's GP that s/he has participated in this study.</td>
</tr>
<tr>
<td></td>
<td>I agree for the use of audio/visual recording devices.</td>
</tr>
<tr>
<td></td>
<td>I understand that my child’s participation is voluntary, and that my child and I are free to withdraw from the study at any time, even after signing this form, without giving any reason, without our legal rights being affected, and that this will not affect any present or future medical treatment that I or my child receive.</td>
</tr>
<tr>
<td></td>
<td>I agree for my child’s personal information being retained for over 3 years after the completion of the study so that I can be contacted for future research studies.</td>
</tr>
<tr>
<td></td>
<td>I understand that relevant sections of my child’s medical notes and/or data will be looked at by individuals from UCL-ICH, Regulatory Authorities or by researchers from Great Ormond Street Hospital Foundation Trust where it is relevant to my child’s taking part. I agree for them to have access to this information.</td>
</tr>
<tr>
<td></td>
<td>I give my permission for my child to participate in the above study.</td>
</tr>
</tbody>
</table>

Cognitive Neuroscience & Neuropsychiatry Section
Developmental Neurosciences Programme
UCL Institute of Child Health
30 Guilford Street, London, WC1N 1EH
Tel: +44 (0)20 7905 2746 Fax: +44 (0)20 7905 2616

UCL Institute of Child Health in partnership with Great Ormond Street Hospital for Children NHS Foundation Trust
The child first and always

REC Reference No. 12/LO/1425, Consent form for parents of controls and patients, Version 3, 15th March 2018
Parent’s Name

Parent’s Signature

Date

Relationship to child (mother/father/guardian)


Researcher’s Name

Researcher’s Signature

Date

When completed: 1 copy for participant; 1 copy for researcher site file; 1 (original) copy to be kept in medical notes.
6.2 Information Sheet for HLHS patients

**Great Ormond Street Hospital for Children**

**UCL INSTITUTE OF CHILD HEALTH**

**DEVELOPMENTAL NEUROSCIENCES PROGRAMME**

**INFORMATION SHEET FOR PARENTS/GUARDIANS**

**Project Title:** Hypoxia/ischaemia and patterns of neuropathology associated with memory impairment in infancy – led by Professor Faraneh Vargha-Khadem

We would like to ask you to consider enrolling your child in a research project. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read this carefully and discuss it with others if you wish.

**Why have you been invited?**

We are inviting you and your baby to take part in a new research study that aims to investigate the course of development of infants and toddlers who have experienced a period of lack of oxygen to the brain when they were first born or shortly thereafter. We are inviting you and your child to participate as part of this study, because he/she has had surgery for Hypoplastic Left Heart Syndrome (HLHS).

**What is the purpose of the study?**

This research study aims to investigate the cognitive development of babies who suffered some form of lack of oxygen (hypoxia) when they were first born or shortly after. We are particularly interested in the effects of low oxygen levels on the development of specific abilities, especially memory and motor function. This detailed investigation includes:

1. Brain scans using magnetic resonance imaging (MRI), in order to assess areas that may have been affected during your baby’s hypoxic episode.
2. Observing your baby’s behaviour while she or he looks at pictures, listens to sounds and plays with toys.
3. Measuring brain activity using electroencephalography (EEG) while your baby watches pictures or listens to sounds.
4. Using state-of-the-art cameras and sensors to assess your baby’s movements.

*None of the tests are painful or prone risks or side effects.*

---

Cognitive Neurosciences & Neuropsychiatry Section
Developmental Neurosciences Programme
UCL Institute of Child Health
30 Guilford Street, London, WC1N 1EH
Tel: +44 (0)20 7905 2746  Fax: +44 (0)20 7905 2816

REC Reference No. 12/L0/1425, Information sheet for parent (patient-HLHS), Version 4, 15th March 2018
Do I have to take part?

You and your child are free to decline to take part, or withdraw from the study at any time. If you decide not to take part, this will not have any effect on the treatment you receive from your GP or on any present or future treatment you receive at Great Ormond Street Hospital for Children NHS Foundation Trust or University College London Hospital.

What will happen if my child takes part?

Because this study aims to understand the developmental trajectory of babies exposed to low oxygen levels early in life, we would ask you and your child to participate twice during your baby’s development. By giving us the opportunity to assess your child at multiple stages during development (i.e. when they are between 16-24 weeks, 10-14 months and 18-36 months), you are helping us understand how lack of oxygen early in life can affect the way in which your baby’s brain develops and changes. The details of each study phase are given below.

*Early infancy (16-24 weeks)*

Once your child reaches the age of 16-24 weeks and is selected to participate in this research, you will be invited to the UCL Institute of Child Health (this is very near to Great Ormond Street Hospital) for your child to be assessed on a variety of neuropsychological, as well as memory specific, tests. We will also do an MRI brain scan, which will help us evaluate if any brain areas are damaged and how such damage may be contributing to potential memory or motor impairments.

Your baby will be assessed using neuropsychological tests, relating to general thinking and communication skills, as well as special tests designed to measure memory functioning. The tests will examine how your baby is developing by observing how she/he responds to things they see and hear, and how they interact with people and objects. The specific things we look at will depend on the age and abilities of the baby, but overall we aim to evaluate motor skills (e.g., Can they roll over? Can the baby follow a moving object with their eyes?), early language skills (e.g., Does the baby turn the head when they hear a sound?) These tasks will take about half an hour.

Next, your baby’s fine motor coordination will be assessed while they move their limbs using sensors placed on the body; this takes about half an hour including time to set up.
We will also examine your baby’s memory skills by showing pictures. Some pictures will repeat, and some will be new and we will measure how your baby looks at the pictures by tracking their eye movements with a special camera. At the same time, we will measure your baby’s brain activity by recording their EEG. We record the brain activity using a special hat, which has sensors wrapped in sponges, all held together with stretchy elastic. This is not painful, and children need only wear the hat for about 45 minutes to take these measurements.

Finally, there will be an MRI scan, so that we can get a picture of your baby’s brain. MRI scans are safe and use a magnetic field to generate an image. The MRI scan will be done under general anaesthesia as part of your baby’s routine cardiac scan. This procedure is not painful or harmful in any way, and will last an extra 35 minutes in addition to the cardiac clinical scan.

The whole investigation will take about 4 hours, including breaks as needed, as well as time for questions.

**Mid Infancy (10-14 months)**

When your child is about 10-14 months old, we will ask you to come back to participate in the next stage of the study. We will use similar tests as before, but we will be performing more tests as your child is older and has a larger range of behaviours and abilities.

Your child will be assessed on a set of neuropsychological tests, just as before, but because your child has developed greatly in thinking, communication and motor skills, the test will take a bit longer, around 1.5 hours.

Next, your baby’s fine motor coordination will be assessed while they move around and play, using sensors placed on the body; this takes about 45 min including time to set up.

We will again examine your baby’s memory skills by showing pictures and recording brain activity (EEG). This assessment will take about 45 minutes.

This visit will take about 4 hours, again allowing time for breaks as needed and time for questions.
**Early Childhood (18 months – 5 years)**

When your child is about 1½ - 5 years old, we will ask you to come back to participate in Stage IV of the study. We will use similar tests as before, but we will be performing more tests as your child is older and has a larger range of behaviours and abilities.

Your child will be assessed on a set of neuropsychological tests, just as before, but because your child has developed greatly in thinking, communication and motor skills, the test will take a bit longer, around 1.5 hours.

Next, your baby’s fine motor coordination will be assessed while they move around and play, using sensors placed on the body; this takes about 45 min including time to set up.

We will again examine your baby’s memory skills by showing pictures and recording brain activity (EEG). This assessment will take about 45 minutes.

Finally, there will be an MRI scan again which, as before, will be done under general anaesthesia as part of your baby’s routine cardiac scan. This procedure is not painful or harmful in any way, and will last about 35 minutes in addition to the cardiac clinical scan.

This last visit will take about 5 hours, again allowing time for breaks as needed and time for questions.

**What happens after these assessments?**

Each child’s details and records will be stored securely and confidentially by the research team. We will then analyse this information and draw conclusions about the status of your child’s development in the domains assessed. The results of the study will then be shared at the end of the project with you as parents.

The GP of your child will be informed of his/her participation in the study, but only if you consent to this in writing.

**What are the risks and discomforts?**

There are no foreseeable risks from the tests themselves. The MRI scan is painless and has no side effects. The behavioural assessment will not result in any discomfort to your child. It is possible that during the EEG testing or kinematic assessment, your child may
not like the placement of the sensors on the skin, in which case this test will be
discontinued for your child.

You are free to stop the study, immediately, at any moment.

**What are the benefits of taking part?**

If any obvious changes in your infant’s brain is identified on the scan, this will be
communicated to you via your GP, and we will indicate the implications of these changes
in terms of your baby’s development and possible learning needs and support in the
future.

The study will also provide you with an opportunity to further your understanding of your
infant’s functioning and development.

Lastly, in the long-term, we hope that this research will provide further information
regarding the long-term outcome of infants who are likely to develop memory and/or
coordination difficulties, with the view to set up support for the affected children as early in
life as possible.

**Who will have access to the case/research records?**

The information we collect about you and your child will be anonymised, and only the
researchers involved in the study will have access to your/your child’s personal
information.

Individuals from the Regulatory Authorities and Great Ormond Street Hospital may require
access to your child’s medical notes and data as part of routine monitoring of the research.

The use of some types of personal information is safeguarded by the Data Protection Act
1998 (DPA). The DPA places an obligation on those who record or use personal
information, but also gives rights to people about whom information is held. Your rights
include being allowed to find out what information is being held about you and your child
and asking not to store information if it is distressing to you. If you have any questions
about data protection and/or the information that is being stored about you and your child,
please ask the researcher involved in the study or, contact the Data Protection Officer on
020 7679 0166.

**What are the arrangements for compensation?**
This project has been approved by an independent Research Ethics Committee which believes that it is of minimal risk to you. However, research can carry unforeseen risks and we want you to be informed of your rights in the unlikely event that any harm should occur as a result of taking part in this study.

It is unlikely that you or your child are harmed as a result of taking part, however if you feel that you have been harmed you have the right to claim damages in a court of law but may need to cover the legal costs. This would require you to prove fault on the part of UCL-Institute of Child Health and Great Ormond Street Hospital NHS Foundation Trust.

If you decide to participate, we will cover your travel and other expenses, and compensate you for your time.

Who do I speak to if problems arise?

If you have any complaints about the way in which this research project is or has been conducted, please, in the first instance discuss them with the researcher. If the problems are not resolved, or you wish to comment in any other way, please contact the Principal Investigator, Professor Faraneh Vargha-Khadem. Additionally, you may contact GOSH PALS, a free and confidential service which helps patients, parents and carers with any information, concerns, or problems that they have about their NHS care/service.

Who has reviewed the study?

This research has been approved by the London- Hampstead Research Ethics Committee.

Who is organising and funding the research?

This study is sponsored by the Great Ormond Street Hospital for Children NHS Foundation Trust, and the research is funded by the Medical Research Council.

Further Information

All members of the research team have undergone Child Protection Training at Great Ormond Street Hospital for Children NHS Foundation Trust.

Details of how to contact the researchers:

Cognitive Neuroscience & Neuropsychiatry Section
Developmental Neurosciences Programme
UCL Institute of Child Health
30 Guilford Street, London, WC1N 1EH
Tel: +44 (0)20 7905 2746 Fax: +44 (0)20 7905 2616

REC Reference No. 12/L0/1425, Information sheet for parent (patient-HLHS), Version 4, 15th March 2018
6.3 Information Sheet for TGA patients

Great Ormond Street Hospital for Children

UCL Institute of Child Health
Developmental Neurosciences Programme

INFORMATION SHEET FOR PARENTS/GUARDIANS

Project Title: Hypoxia/schaemia and patterns of neuropathology associated with memory impairment in infancy – led by Professor Faranbeh Vargha-Khadem

We would like to ask you to consider enrolling your child in a research project. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read this carefully and discuss it with others if you wish.

Why have you been invited?

We are inviting you and your baby to take part in a new research study that aims to investigate the course of development of infants and toddlers who have experienced a period of lack of oxygen to the brain when they were first born or shortly thereafter. We are inviting you and your child to participate as part of this study, because he/she has had surgery for Transposition of the Great Arteries (TGA), or has had Extracorporeal Membrane Oxygenation (ECMO) treatment, shortly after birth.

What is the purpose of the study?

This research study aims to investigate the cognitive development of babies who suffered some form of lack of oxygen (hypoxia) when they were first born or shortly after. We are particularly interested in the effects of low oxygen levels on the development of specific abilities, especially memory and motor function. This detailed investigation includes:

1. Brain scans using magnetic resonance imaging (MRI), in order to assess areas that may have been affected during your baby’s hypoxic episode.

2. Observing your baby’s behaviour while she or he looks at pictures, listens to sounds and plays with toys.

3. Measuring brain activity using electroencephalography (EEG) while your baby watches pictures or listens to sounds.

Cognitive Neuroscience & Neuropsychiatry Section
Developmental Neurosciences Programme
UCL Institute of Child Health
30 Guilford Street, London, WC1N 1EH
Tel. +44 (0)20 7905 2748 Fax: +44 (0)20 7905 2816

REC Reference No. 12/L0/1425, Information sheet for parent (TGA/ECMO), Version 4. 15th March 2018

UCL Institute of Child Health in partnership with Great Ormond Street Hospital for Children NHS Trust
The child first and always

503
4. Using state-of-the-art cameras and sensors to assess your baby’s movements.

None of the tests are painful or prone risks or side effects.

Do I have to take part?

You and your child are free to decline to take part, or withdraw from the study at any time. If you decide not to take part, this will not have any effect on the treatment you receive from your GP or on any present or future treatment you receive at Great Ormond Street Hospital for Children NHS Foundation Trust or University College London Hospital.

What will happen if my child takes part?

Because this study aims to understand the developmental trajectory of babies exposed to low oxygen levels early in life, we would ask you and your child to participate twice during your baby’s development. By giving us the opportunity to assess your child at multiple stages during development (i.e., when they are between 4-12 weeks, 16-24 weeks, 10-14 months and 18-36 months), you are helping us understand how lack of oxygen early in life can affect the way in which your baby’s brain develops and changes. The details of each study phase are given below.

Stage I - Early MRI scan (4-12 weeks)

When your baby is around 2 months of age there will be an MRI scan, so that we can get a picture of your baby’s brain. MRI scans are safe and use a magnetic field to generate an image. For this, we will ask you to feed your baby, and then we will wait until they fall asleep and then lay them in the scanner. If your child wakes up at any point during the scan, we will remove them from the scanner, and if possible, attempt to resume the scan once they have fallen asleep once again. This procedure is not painful or harmful, and will last about 40 minutes.

Before you come for this visit, we will send you a CD in the mail. This will have ambient sounds and lullaby music, which we ask that you play for your baby around naptime. We will then play this same music while they are in the MRI scanner, in order to make them feel more at ease and sleepy.
Stage II - Early infancy (16-24 weeks)

Once your child reaches the age of 16-24 weeks and is selected to participate in this research, you will be invited to the UCL Institute of Child Health (this is very near to Great Ormond Street Hospital) for your child to be assessed on a variety of neuropsychological, as well as memory specific, tests. Using the MRI brain scan from Stage I, will help us evaluate if any brain areas are damaged and how such damage may be contributing to potential memory or motor impairments.

Your baby will be assessed using neuropsychological tests, relating to general thinking and communication skills, as well as special tests designed to measure memory functioning. The tests will examine how your baby is developing by observing how she/he responds to things they see and hear, and how they interact with people and objects. The specific things we look at will depend on the age and abilities of the baby, but overall we aim to evaluate motor skills (e.g., Can they roll over? Can the baby follow a moving object with their eyes?), early language skills (e.g., Does the baby turn the head when they hear a sound?) These tasks will take about half an hour.

Next, your baby’s fine motor coordination will be assessed while they move their limbs using sensors placed on the body; this takes about half an hour including time to set up.

We will also examine your baby’s memory skills by showing pictures. Some pictures will repeat, and some will be new and we will measure how your baby looks at the pictures by tracking their eye movements with a special camera. At the same time, we will measure your baby’s brain activity by recording their EEG. We record the brain activity using a special hat, which has sensors wrapped in sponges, all held together with stretchy elastic. This is not painful, and children need only wear the hat for about 45 minutes to take these measurements.

The whole investigation will take about 3 hours, including breaks as needed, as well as time for questions.

Stage III - Mid Infancy (10-14 months)

When your child is about 10-14 months old, we will ask you to come back to participate in the next stage of the study. We will use similar tests as before, but we will be performing more tests as your child is older and has a larger range of behaviours and abilities.
Your child will be assessed on a set of neuropsychological tests, just as before, but because your child has developed greatly in thinking, communication and motor skills, the test will take a bit longer, around 1.5 hours.

Next, your baby’s fine motor coordination will be assessed while they move around and play, using sensors placed on the body; this takes about 45 min including time to set up.

We will again examine your baby’s memory skills by showing pictures and recording brain activity (EEG). This assessment will take about 45 minutes.

This visit will take about 4 hours, again allowing time for breaks as needed and time for questions.

Stage IV – Early Childhood (18 months – 5 years)

When your child is about 1½ - 5 years old, we will ask you to come back to participate in Stage IV of the study. We will use similar tests as before, but we will be performing more tests as your child is older and has a larger range of behaviours and abilities.

Your child will be assessed on a set of neuropsychological tests, just as before, but because your child has developed greatly in thinking, communication and motor skills, the test will take a bit longer, around 1.5 hours.

Next, your baby’s fine motor coordination will be assessed while they move around and play, using sensors placed on the body; this takes about 45 min including time to set up.

Lastly, we will again examine your baby’s memory skills by showing pictures and recording brain activity (EEG). This assessment will take about 45 minutes.

This last visit will take about 4 hours, again allowing time for breaks as needed and time for questions.

What happens after these assessments?

Each child’s details and records will be stored securely and confidentially by the research team. We will then analyse this information and draw conclusions about the status of your child’s development in the domains assessed. The results of the study will then be shared at the end of the project with you as parents.
The GP of your child will be informed of his/her participation in the study, but only if you consent to this in writing.

What are the risks and discomforts?

There are no foreseeable risks from the tests themselves. The MRI scan is painless and has no side effects. The behavioural assessment will not result in any discomfort to your child. It is possible that during the EEG testing or kinematic assessment, your child may not like the placement of the sensors on the skin, in which case this test will be discontinued for your child.

You are free to stop the study, immediately, at any moment.

What are the benefits of taking part?

If any obvious changes in your infant’s brain are identified on the MRI scan, this will be communicated to you via your GP, and we will indicate the implications of these changes in terms of your baby’s development and possible learning needs and support in the future.

The study will also provide you with an opportunity to further your understanding of your infant’s functioning and development.

Lastly, in the long-term, we hope that this research will provide further information regarding the outcome of infants who are likely to develop memory and/or coordination difficulties, with the view to set up support for the affected children as early in life as possible.

Who will have access to the case/research records?

The information we collect about you and your child will be anonymised, and only the researchers involved in the study will have access to your/your child’s personal information.

Individuals from the Regulatory Authorities and Great Ormond Street Hospital may require access to your child’s medical notes and data as part of routine monitoring of the research.

The use of some types of personal information is safeguarded by the Data Protection Act 1998 (DPA). The DPA places an obligation on those who record or use personal information, but also gives rights to people about whom information is held. Your rights include being allowed to find out what information is being held about you and your child and asking not to store information if it is distressing to you. If you have any questions about data protection and/or the information that is being stored about you and your child, please ask the researcher involved in the study or, contact the Data Protection Officer on 020 7679 0166.
What are the arrangements for compensation?

This project has been approved by an independent Research Ethics Committee which believes that it is of minimal risk to you. However, research can carry unforeseen risks and we want you to be informed of your rights in the unlikely event that any harm should occur as a result of taking part in this study.

It is unlikely that you or your child are harmed as a result of taking part, however if you feel that you have been harmed you have the right to claim damages in a court of law but may need to cover the legal costs. This would require you to prove fault on the part of UCL-Institute of Child Health and Great Ormond Street Hospital NHS Foundation Trust.

If you decide to participate, we will cover your travel and other expenses, and compensate you for your time.

Who do I speak to if problems arise?

If you have any complaints about the way in which this research project is or has been conducted, please, in the first instance discuss them with the researcher. If the problems are not resolved, or you wish to comment in any other way, please contact the Principal Investigator, Professor Faranbahz Vargha-Khadem. Additionally, you may contact GOSH PALS, a free and confidential service which helps patients, parents and carers with any information, concerns, or problems that they have about their NHS care/service.

Who has reviewed the study?

This research has been approved by the London- Hampstead Research Ethics Committee.

Who is organising and funding the research?

This study is sponsored by the Great Ormond Street Hospital for Children NHS Foundation Trust, and the research is funded by the Medical Research Council.

Further Information

All members of the research team have undergone Child Protection Training at Great Ormond Street Hospital for Children NHS Foundation Trust.
Details of how to contact the researchers:

Professor Faraneh Vargha-Khadem
Email: f.vargha-khadem@ucl.ac.uk
Tel: 020 7905 2746

Dr Rachael Elward
Email: r.elward@ucl.ac.uk
Tel: 020 7905 2730

Maneet Kaur Saini (Research Assistant)
Email: m.saini@ucl.ac.uk
Tel: 020 7905 2607

Address:
Cognitive Neuroscience & Neuropsychiatry Section
Developmental Neurosciences Programme
UCL Institute of Child Health
30 Guilford Street
London, WC1N 1EH
6.4 Information Sheet for Healthy Controls

Great Ormond Street Hospital for Children NHS Foundation Trust

UCL INSTITUTE OF CHILD HEALTH
DEVELOPMENTAL NEUROSCIENCES PROGRAMME

INFORMATION SHEET FOR PARENTS/GUARDIANS

Project Title: Hypoxia/ischaemia and patterns of neuropathology associated with memory impairment in infancy – led by Professor Faraneh Vargha-Khadem

We would like to ask you to consider enrolling your child in a research project. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read this carefully and discuss it with others if you wish.

Why have you been invited?
We are inviting you and your baby to take part in a new research study that aims to investigate the course of development of infants and toddlers who have experienced a period of lack of oxygen to the brain when they were first born or shortly thereafter. In order to find out if these infants and young children are affected by the period of oxygen deprivation, we need to study a comparison group of healthy children. We are inviting you and your child to participate in our research study as part of this comparison group.

What is the purpose of the study?
We aim to study healthy babies as part of a research project that tracks the emergence and early development of memory and movement coordination. Our aim is to assess the development of these functions in relation to brain activity as measured by EEG, and brain structure and function as measured by MRI. Information obtained from the group of healthy babies will then be compared with those from babies with heart/lung disease who may have had brain injury as neonates due to lack of oxygen to the brain. By comparing the standard of development of healthy babies to those of patients with heart/lung disease, we will find out if the young patients are developing differently from normal. Participation of your healthy baby will enable us to make this comparison to benefit the diagnosis of early problems in the young patients, and hopefully lead, in due course, to provision of appropriate help and support for them.
The aim of the study

We are particularly interested in the effects of low oxygen levels on the development of specific abilities, especially memory and movement. This detailed investigation includes:

1. Completion of a questionnaire on the phone with a member of our team.
2. Observing your baby’s behaviour while she or he looks at pictures, listens to sounds and plays with toys.
3. Measuring brain activity using electroencephalography (EEG) while your baby watches pictures or listens to sounds.
4. Using state-of-the-art cameras and sensors to assess your baby’s movements.
5. Brain scans using magnetic resonance imaging (MRI) to obtain pictures of the brain of your baby.

None of the tests are harmful or cause discomfort for your baby.

Do I have to take part?

You and your child are free to decline to take part, or withdraw from the study at any time. If you decide not to take part, this will not have any effect on the treatment you receive from your GP or on any present or future treatment you receive at Great Ormond Street Hospital for Children NHS Foundation Trust or University College London Hospital.

What will happen if my child takes part?

The study consists of four stages: one around two months of age involving only an MRI scan, the next around four months of age (between 16-24 weeks) and another two further sessions, when your child is older, between 10-14 months, and again at 18-36 months. Once you have agreed to participate in our study, a member of our team will help you fill out a questionnaire over the telephone relating to your child’s development.

Stage I - Early MRI scan (4-12 weeks)

When your baby is around 2 months of age there will be an MRI scan, so that we can get a picture of your baby’s brain. MRI scans are safe and use a magnetic field to generate an image. For this, we will ask you to feed your baby, and then we will wait until they fall asleep and then lay them in the scanner. If your child wakes up at any point during the scan, we will remove them from the scanner, and if possible, attempt to resume the scan.
once they have fallen asleep once again. This procedure is not painful or harmful, and will
last about 40 minutes.

Before you come for this visit, we will send you a CD in the mail. This will have ambient
sounds and lullaby music, which we ask that you play for your baby around naptime. We
will then play this same music while they are in the MRI scanner, in order to make them
feel more at ease and sleepy.

**Stage II - Early infancy (16-24 weeks)**

Once your child reaches the age of 16-24 weeks, you and your baby will be invited to the
UCL Institute of Child Health for your child to be assessed on a variety of
neuropsychological, as well as memory specific, tests.

Your baby will be assessed using neuropsychological tests, relating to general thinking
and communication skills, as well as special tests designed to measure memory
functioning. The tests will examine how your baby is developing by observing how she/he
responds to things they see and hear, and how they interact with people and objects. The
specific things we look at will depend on the age and abilities of the baby, but overall we
aim to evaluate motor skills (e.g., Can they roll over? Can the baby follow a moving object
with their eyes?), early language skills (e.g., Does the baby turn the head when they hear
a sound?). These tasks will take about half an hour.

Next, your baby’s fine motor coordination will be assessed while they move their limbs
using sensors placed on the body; this takes about half an hour including time to set up.

We will also examine your baby’s memory skills by showing pictures. Some pictures will
repeat, and some will be new and we will measure how your baby looks at the pictures by
tracking their eye movements with a special camera. At the same time, we will measure
your baby’s brain activity by recording their EEG. We record the brain activity using a
special hat, which has sensors wrapped in sponges, all held together with stretchy elastic.
This is not painful, and children need only wear the hat for about 45 minutes to take these
measurements.

Like faces, brains come in all shapes and sizes, so there are many normal variations of
what the scan shows. There is a very small chance that your child’s scan may show an
abnormality of which you are unaware. In such circumstances, we will consult with one of
our neuroradiologist colleagues and will contact you, as well as your child’s GP, for referral to the appropriate specialist services.

The whole visit should take about 3 hours, including breaks as needed and time for questions.

**Stage III - Mid Infancy (10-14 months)**

When your child is about 10-14 months old, we will ask you to come back to participate in the next stage of the study. We will use similar tests as before, but we will be performing more tests as your child is older and has a larger range of behaviours and abilities.

Your child will be assessed on a set of neuropsychological tests, just as before, but because your child has developed greatly in thinking, communication and motor skills, the test will take a bit longer, around 1.5 hours.

Next, your baby’s fine motor coordination will be assessed while they move around and play, using sensors placed on the body; this takes about 45 min including time to set up.

We will again examine your baby’s memory skills by showing pictures and recording brain activity (EEG). This assessment will take about 45 minutes.

This visit will take about 4 hours, again allowing time for breaks as needed and time for questions.

**Stage IV – Early Childhood (18 months – 5 years)**

When your child is about 18 months - 5 years old, we will ask you to come back to participate in Stage IV of the study. We will use similar tests as before, but we will be performing more tests as your child is older and has a larger range of behaviours and abilities.

Your child will be assessed on a set of neuropsychological tests, just as before, but because your child has developed greatly in thinking, communication and motor skills, the test will take a bit longer, around 1.5 hours.

Next, your baby’s fine motor coordination will be assessed while they move around and play, using sensors placed on the body; this takes about 45 min including time to set up.
Lastly, we will again examine your baby’s memory skills by showing pictures and recording brain activity (EEG). This assessment will take about 45 minutes. This last visit will take about 4 hours, again allowing time for breaks as needed and time for questions.

**What happens after these assessments?**

Each child’s details and records will be stored securely and confidentially by the research team. We will then analyse this information and draw conclusions about the status of your child’s development in the domains assessed. The results of the study will then be shared at the end of the project with you as parents.

The GP of your child will be informed of his/her participation in the study, but only if you consent to this in writing.

**What are the risks and discomforts?**

There are no foreseeable risks from the tests themselves. The MRI scan is painless and has no side effects. The behavioural assessment will not result in any discomfort to your child. It is possible that during the EEG testing or kinematic assessment, your child may not like the placement of the sensors on the skin, in which case this test will be discontinued for your child.

You are free to stop the study, immediately, at any moment.

**What are the benefits of taking part?**

The study will provide you with an opportunity to further your understanding of your infant’s functioning and development.

Also, in the long-term, we hope that this research will provide further information regarding the outcome of infants who are likely to develop memory and/or coordination difficulties, with the view to set up support for the affected children as early in life as possible.

**Who will have access to the case/research records?**

Cognitive Neuroscience & Neuropsychiatry Section  
Developmental Neurosciences Programme  
UCL Institute of Child Health  
30 Guilford Street, London, WC1N 1EH  
Tel: +44 (0)20 7905 2746 Fax: +44 (0)20 7905 2616

UCL Institute of Child Health in partnership with Great Ormond Street Hospital for Children NHB Foundation Trust

The child first and always

REC Reference No. 12/LO/1425, Information sheet for parent (control), Version 4, 15th March 2018
The information we collect about you and your child will be anonymised, and only the researchers involved in the study will have access to your/your child’s personal information.

Individuals from the Regulatory Authorities and Great Ormond Street Hospital may require access to your child’s medical notes and data as part of routine monitoring of the research. The use of some types of personal information is safeguarded by the Data Protection Act 1998 (DPA). The DPA places an obligation on those who record or use personal information, but also gives rights to people about whom information is held. Your rights include being allowed to find out what information is being held about you and your child and asking not to store information if it is distressing to you. If you have any questions about data protection and/or the information that is being stored about you and your child, please ask the researcher involved in the study or, contact the Data Protection Officer on 020 7679 0166.

What are the arrangements for compensation?

This project has been approved by an independent Research Ethics Committee which believes that it is of minimal risk to you. However, research can carry unforeseen risks and we want you to be informed of your rights in the unlikely event that any harm should occur as a result of taking part in this study.

It is unlikely that you or your child are harmed as a result of taking part, however if you feel that you have been harmed you have the right to claim damages in a court of law but may need to cover the legal costs. This would require you to prove fault on the part of UCL-Institute of Child Health and Great Ormond Street Hospital NHS Foundation Trust.

If you decide to participate, we will cover your travel and other expenses, and compensate you for your time.

Who do I speak to if problems arise?

If you have any complaints about the way in which this research project is or has been conducted, please, in the first instance discuss them with the researcher. If the problems are not resolved, or you wish to comment in any other way, please contact the Principal Investigator, Professor Faraneh Vargha-Khadem.

Who has reviewed the study?

This research has been approved by the London- Hampstead Research Ethics Committee.
Who is organising and funding the research?

This study is sponsored by the Great Ormond Street Hospital for Children NHS Foundation Trust, and the research is funded by the Medical Research Council.

Further information

All members of the research team have undergone Child Protection Training at Great Ormond Street Hospital for Children NHS Foundation Trust.

Details of how to contact the researchers:

Professor Faraneh Vargha-Khadem
Email: f.vargha-khadem@ucl.ac.uk
Tel: 020 7905 2746

Dr Rachael Elward
Email: r.elward@ucl.ac.uk
Tel: 020 7905 2730

Maneet Kaur Saini (Research Assistant)
Email: m.saini@ucl.ac.uk
Tel: 020 7905 2607

Address:
Cognitive Neuroscience & Neuropsychiatry Section
Developmental Neurosciences Programme
UCL Institute of Child Health
30 Guilford Street
London, WC1N 1EH

Cognitive Neuroscience & Neuropsychiatry Section
Developmental Neurosciences Programme
UCL Institute of Child Health
30 Guilford Street, London, WC1N 1EH
Tel: +44 (0)20 7905 2746 Fax: +44 (0)20 7905 2616

REC Reference No. 12/LC/1425, Information sheet for parent (control), Version 4, 15th March 2018
6.5. General Data Protection Regulation (GDPR) for CHD Patients

The Hypoxia/Ischaemia Study and your personal data:
patient information sheet

Study name: Hypoxia/Ischaemia and patterns of neuropathology associated with memory impairment

Introduction
From the 25th May 2018 new rules have been introduced about personal data (General Data Protection Regulation — GDPR). We are giving you this information sheet now so that you know what personal data are shared when you agreed to being involved in the Hypoxia/Ischaemia study and your rights are under the law.

Sponsor Information
Great Ormond Street Hospital for Children NHS Foundation Trust is the sponsor for this study based in the United Kingdom. We have used information from you and/or your child as appropriate (name, NHS number, information about your child’s medical condition) in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after this information and using it properly. Our study is longitudinal and we will need to gather information about you, or your child as she/he develops. Great Ormond Street Hospital for Children NHS Foundation Trust will keep identifiable information about you and/or your child for 7 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible. Our Data Protection Officer is Anna Ferrant and you can contact her at your.data@gosh.nhs.uk

At your Great Ormond Street Hospital

Great Ormond Street Hospital for Children NHS Foundation Trust have collected information from you and/or from your child’s medical records for this research study in accordance with
our instructions. Great Ormond Street Hospital for Children NHS Foundation Trust have
passed these details to the research team at the UCL Institute for Child Health.

Great Ormond Street Hospital for Children NHS Foundation Trust have used you or your
child’s name, and NHS number to contact you about the research study, and to make sure
that relevant information about the study is recorded. Individuals from Great Ormond Street
Hospital for Children NHS Trust, and regulatory organisations, may look at your child’s
medical and research records to check the accuracy of the research study, if you consented to
participate.

With your consent, the people who analyze the information will be able to identify you and/or
your child including having access to names, contact details and NHS numbers.

As described in the participant information sheet, any published reports of analyzed data will
only contain anonymous information. This means it would not be possible to identify either
you or your child from any such report.

Great Ormond Street Hospital for Children NHS Foundation Trust and the researchers at UCL
institute of Child Health will keep identifiable information from this longitudinal study for 7
years after the study has finished.

What to do if you wish to make a complaint about how we have looked after your
data
If you wish to raise a complaint on how we have handled your personal data, you can contact
our Data Protection Officer who will investigate the matter. If you are not satisfied with our
response or believe we are processing your personal data in a way that is not lawful you can
complain to the Information Commissioner’s Office (ICO) https://ico.org.uk
The Hypoxia/Ischaemia Study and your personal data: information sheet

Study name: Hypoxia/Ischaemia and patterns of neuropathology associated with memory impairment

Introduction
From the 25th May 2018 new rules have been introduced about personal data (General Data Protection Regulation — GDPR). We are giving you this information sheet now so that you know what personal data are shared when you agreed to being involved in the Hypoxia/Ischaemia study and your rights are under the law.

Sponsor Information
Great Ormond Street Hospital for Children NHS Foundation Trust is the sponsor for this study based in the United Kingdom. We have used information from you and/or your child as appropriate (name, date of birth, address) in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after this information and using it properly. Our study is longitudinal and we will need to gather information about you, or your child as she/he develops. Great Ormond Street Hospital for Children NHS Foundation Trust will keep identifiable information about you and/or your child for 7 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible. Our Data Protection Officer is Anna Ferrant and you can contact her at your.data@gosh.nhs.uk

At your Great Ormond Street Hospital

Great Ormond Street Hospital for Children NHS Foundation Trust have collected information from you for this research study in accordance with our instructions. Great Ormond Street
Hospital for Children NHS Foundation Trust have passed these details to the research team at the UCL Institute for Child Health.

Great Ormond Street Hospital for Children NHS Foundation Trust have used you or your child’s name and address to contact you about the research study, and to make sure that relevant information about the study is recorded. Individuals from Great Ormond Street Hospital for Children NHS Trust, and regulatory organisations, may look at your child’s medical and research records to check the accuracy of the research study, if you consented to participate.

With your consent, the people who analyse the information will be able to identify you and/or your child including having access to names, contact details and NHS numbers.

As described in the participant information sheet, any published reports of analysed data will only contain anonymous information. This means it would not be possible to identify either you or your child from any such report.

Great Ormond Street Hospital for Children NHS Foundation Trust and the researchers at UCL institute of Child Health will keep identifiable information from this longitudinal study for 7 years after the study has finished.

**What to do if you wish to make a complaint about how we have looked after your data**

If you wish to raise a complaint on how we have handled your personal data, you can contact our Data Protection Officer who will investigate the matter. If you are not satisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner’s Office (ICO) [https://ico.org.uk](https://ico.org.uk).
Appendix 7. Template of Time-point 4 Neuropsychological Report for Parents

Developmental Assessment Report

Research Project: ‘Hypoxia-ischaemia in infants: Patterns of neuropathology and associated memory impairment’ and ‘Effects of neonatal hypoxia/ischaemia on language abilities in children with congenital heart disease’

Ethical Approval: NHS Research Ethics Committee – Approval code: 12/LO/1425

<table>
<thead>
<tr>
<th>Surname</th>
<th>Forename</th>
<th>Date of Birth</th>
<th>Sex</th>
<th>Date of assessment</th>
<th>Age at assessment</th>
</tr>
</thead>
</table>

Our research aims to study healthy children as part of a research project that tracks the emergence and early development of memory, movement coordination, and speech and language in children who may have experienced a lack of oxygen to the brain when they were first born or shortly thereafter. As you know, you have been part of this longitudinal study for some years now, and at [child’s name] most recent visit we were looking at her language development in more detail. The main aim of this project is to identify speech and language problems, and pre-cursors of difficulties with literacy skills in children with congenital heart disease. Early identification of children at risk is essential. Please note that the following tests are used for research purposes only and were not conducted for clinical purposes.

Wechsler Preschool and Primary Scale of Intelligence – Fourth Edition (WPPSI-IV)

[child’s name] was administered subtests from the Wechsler Preschool and Primary Scale of Intelligence – Fourth Edition (WPPSI-IV). This assessment measures ability across five areas of cognitive functioning and produces scores that show how [child’s name] performed in these areas, as well as producing a composite score that represents his/her overall intellectual ability (Full Scale IQ).

<table>
<thead>
<tr>
<th>Developmental subtest</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal comprehension</td>
<td></td>
</tr>
<tr>
<td>Visual Spatial</td>
<td></td>
</tr>
</tbody>
</table>

Cognitive Neuroscience & Neuropsychiatry Section
Developmental Neurosciences Programme
UCL Institute of Child Health
30 Guilford Street, London, WC1N 1EH
Fluid reasoning
Working memory
Processing speed
Full scale IQ

**Clinical Evaluation of Language Fundamentals – Preschool 2 (CELF-P2)**

The Clinical Evaluation of Language Fundamentals – Preschool 2 (CELF-P2) was administered to assess a broad range of expressive and receptive language abilities. The CELF-P2 includes a variety of subtests that assess aspects of language necessary for preschool children to transition to the classroom.

<table>
<thead>
<tr>
<th>Developmental subtest</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core language</td>
<td></td>
</tr>
<tr>
<td>Receptive language</td>
<td></td>
</tr>
<tr>
<td>Expressive language</td>
<td></td>
</tr>
<tr>
<td>Language content</td>
<td></td>
</tr>
<tr>
<td>Language structure</td>
<td></td>
</tr>
</tbody>
</table>

**Phonological Abilities Test (PAT)**

The Phonological Abilities Test was administered to assess early reading progress – ‘rhyme detection’ and ‘letter knowledge’ are widely considered to be early identifiers of reading competency. For both of these language tests [child’s name] scored within the X percentile, which is much lower/higher/in line with than peers his/her age.

**Children’s Communication Checklist (CCC-2)**

[parent’s name] completed the Children’s Communication Checklist which is a questionnaire that screens for communication problems in children.

<table>
<thead>
<tr>
<th>Developmental subtest</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speech</td>
<td></td>
</tr>
<tr>
<td>Syntax</td>
<td></td>
</tr>
<tr>
<td>Semantic</td>
<td></td>
</tr>
<tr>
<td>Coherence</td>
<td></td>
</tr>
<tr>
<td>Inappropriate initiation</td>
<td></td>
</tr>
<tr>
<td>Stereotyped language</td>
<td></td>
</tr>
<tr>
<td>Use of context</td>
<td></td>
</tr>
<tr>
<td>Nonverbal communication</td>
<td></td>
</tr>
<tr>
<td>Social relations</td>
<td></td>
</tr>
<tr>
<td>Interests</td>
<td></td>
</tr>
</tbody>
</table>
Strengths and Difficulties Questionnaire (SDQ)
This brief behavioural screening questionnaire was also completed by [parent’s name] which asks about 25 attributes, some positive and others negative. These 25 items are divided between 5 scales, and [child’s name] scores for these are as follows:

<table>
<thead>
<tr>
<th>Developmental subtest</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emotional problems</td>
<td></td>
</tr>
<tr>
<td>Conduct problems</td>
<td></td>
</tr>
<tr>
<td>Hyperactivity/inattention</td>
<td></td>
</tr>
<tr>
<td>Peer relationships</td>
<td></td>
</tr>
<tr>
<td>Prosocial behaviour</td>
<td></td>
</tr>
</tbody>
</table>

Adaptive Behaviour Assessment System (ABAS-2)
[parent’s name] completed this questionnaire which is used to evaluate levels of adaptive functioning/skills. It is the first test that comprehensively assesses all 10 areas of adaptive behaviours as specified by DSM-IV in relation to learning difficulties. The scores from these 10 areas are then grouped into three broad domains: conceptual, social, and practical. An overall score is also given for the General Adaptive Composite (GAC). [child’s name] scores are as follows:

<table>
<thead>
<tr>
<th>Developmental subtest</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Communication</td>
<td></td>
</tr>
<tr>
<td>Community Use</td>
<td></td>
</tr>
<tr>
<td>Functional Academics</td>
<td></td>
</tr>
<tr>
<td>Home Living</td>
<td></td>
</tr>
<tr>
<td>Health and Safety</td>
<td></td>
</tr>
<tr>
<td>Leisure</td>
<td></td>
</tr>
<tr>
<td>Self-Care</td>
<td></td>
</tr>
<tr>
<td>Self-Direction</td>
<td></td>
</tr>
<tr>
<td>Social</td>
<td></td>
</tr>
<tr>
<td>Motor</td>
<td></td>
</tr>
<tr>
<td>Conceptual</td>
<td></td>
</tr>
<tr>
<td>Social</td>
<td></td>
</tr>
<tr>
<td>Practical</td>
<td></td>
</tr>
<tr>
<td>General Adaptive Composite (GAC)</td>
<td></td>
</tr>
</tbody>
</table>
All of [child’s name] results above indicate that overall, he/she is developing above/on par/slightly behind other children his/her age.

[Describe some of the results in a some detail]

These two areas (behaviour and language development) have often been highlighted as problem areas by other parents of children with congenital heart disease. We hope that once this research is completed, we will be able to highlight this so parents can be better supported.

I also like to remind parents that these assessments are undertaken purely for the purpose of research, they are not detailed diagnostic assessments, and they have not been reviewed by an expert clinician, therefore, we cannot make any strong statements about your child’s development on the basis of these results. They may be of clinical relevance though, so we suggest having a follow-up wherever possible, and using these scores as a guide.

Thank you again for your time and commitment to our research project.

Yours sincerely,

Maneet Kaur Saini (PhD student)
Appendix 8. The tests/measures used directly with the child and parent-completed questionnaires at time-point 4

<table>
<thead>
<tr>
<th>Domain</th>
<th>Assessment name</th>
<th>What is measured</th>
<th>Total duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intellectual function</td>
<td>Wechsler Preschool and Primary Scale of Intelligence - Fourth Edition (WPPSI IV)</td>
<td>Verbal comprehension, visual spatial skills, working memory, fluid reasoning, processing speed, vocabulary acquisition, nonverbal skills, general ability, and cognitive proficiency</td>
<td>45-60 mins (age-dependent)</td>
</tr>
<tr>
<td>Language &amp; speech</td>
<td>Clinical Evaluation of Language Fundamentals - Preschool - 2 (CELF-P2)</td>
<td>Concepts and following directions, word structure, expressive vocabulary, recalling sentences, sentence structure, basic concepts, recalling sentences in context, word classes</td>
<td>30-45 mins</td>
</tr>
<tr>
<td></td>
<td>Renfrew Bus Story (RBS)</td>
<td>Oral narrative skills, grammatical complexity, information load and sentence length</td>
<td>5 mins</td>
</tr>
<tr>
<td></td>
<td>Phonological Abilities Test (PAT)</td>
<td>Rhyme detection and letter-knowledge subtests used only</td>
<td>10-15 mins</td>
</tr>
<tr>
<td>Parental Questionnaires</td>
<td>ASEBA Child Behaviour Checklist Ages 1.5 - 5 (CBCL)</td>
<td>Specific behavioural and emotional problems (includes language development)</td>
<td>15-20 mins</td>
</tr>
<tr>
<td></td>
<td>Adaptive Behaviour Assessment System - Second Edition (ABAS II)</td>
<td>Adaptive skills functioning</td>
<td>15 mins</td>
</tr>
<tr>
<td></td>
<td>The Strengths and Difficulties Questionnaire (SDQ)</td>
<td>Behavioural screening questionnaire</td>
<td>5-10 mins</td>
</tr>
<tr>
<td></td>
<td>Children's Communication Checklist (CCC-2)</td>
<td>Screens for communication problems (including ASD)</td>
<td>5-15 mins</td>
</tr>
<tr>
<td></td>
<td>Demographic Information</td>
<td>Information about child and parents</td>
<td>5 mins</td>
</tr>
<tr>
<td></td>
<td>Behaviour Rating Inventory of Executive Function - Preschool (BRIEF-P)</td>
<td>Measures executive functioning: inhibit, shift, emotional control, working memory, and plan/organise</td>
<td>10-15 mins</td>
</tr>
<tr>
<td></td>
<td>Paediatric Quality of Life Inventory (PedsQL; 2-4 and 5-7)</td>
<td>Measures health-related quality of life in children</td>
<td>2-5 mins</td>
</tr>
<tr>
<td></td>
<td>Hospital Anxiety and Depression Scale (HADS)</td>
<td>A reliable self-rating scale that measures anxiety and depression (in the parent)</td>
<td>2-5 mins</td>
</tr>
<tr>
<td></td>
<td>Pediatric Inventory for Parents (PIP)</td>
<td>Childhood illness-related parenting stress</td>
<td>10 mins</td>
</tr>
<tr>
<td></td>
<td>Impact of Event Scale</td>
<td>Parental stress caused by traumatic events</td>
<td>2-5 mins</td>
</tr>
<tr>
<td></td>
<td>Family Impact (PedsQL module)</td>
<td>Impact of paediatric acute/chronic health conditions on parents and the family</td>
<td>5-10 mins</td>
</tr>
</tbody>
</table>
Appendix 9. Longitudinal trajectories for each individual participant who completed all three Bayley-3 time-points. Each graph per participant contains the longitudinal results for each subtest (i.e. Cognition, Receptive Language, Expressive Language, Fine Motor, and Gross Motor) at 5-8 months, 12-15 months, and 3-4 years.

Healthy Controls:
Hypoplastic Left Heart Syndrome Patients
Transposition of the Great Arteries Patients
Appendix 10. Neural Markers of Speech Sound Processing
(Chapter 5)

10.1 Mean number of frequent and infrequent matched oddball trials per group, and statistical analysis showing no significant main effect of group.

<table>
<thead>
<tr>
<th></th>
<th>HLHS</th>
<th>TGA</th>
<th>Controls</th>
<th>Kruskal-Wallis Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infrequent Oddball Trials (Mean (SD))</td>
<td>64.13 (11.69)</td>
<td>68.93 (19.65)</td>
<td>65.75 (15.25)</td>
<td>$H = 1.48, p = 0.48$</td>
</tr>
</tbody>
</table>

*Note.* The number of frequent trials was matched to the number of infrequent trials, in each child, separately, and consequently, the numbers above are the same for frequent trials.

10.2 Figure of the auditory oddball ERP waveforms for each group and each condition, for A) time-point 3 using the 128 channel cap, B) time-point 3 using the 256 channel cap, and C) time-point 4 using the 256 channel cap.
Note. The waveforms are shown from the pre-stimulus (-200ms) to the post-stimulus (800ms) time window. One HLHS patient had to be removed as an extreme outlier from each of the figures A, B, and C, and a low-pass filter of 12Hz was applied for visualisation purposes for this figure only, to remove excessive noise from the waveforms.
Appendix 11. Parent and Family Outcomes and Quality of Life
(Chapter 7)

11.1 Scatterplots for the correlations between different parent outcome measures, including: family functioning and A) parent anxiety, B) parent depression, C) frequency of stress related to CHD, D) difficulty of stress related to CHD, and E) total impact of CHD; parent anxiety and F) frequency of stress related to CHD, G) difficulty of stress related to CHD, and H) total impact of CHD; parent depression and I) frequency of stress related to CHD, J) difficulty of stress related to CHD, and K) total impact of CHD; frequency of stress related to CHD and L) total impact of CHD; difficulty of stress related to CHD and M) total impact of CHD.
Note. Lines on the x- and y-axis represent the respective means of the given measures.
11.2 A comparison of key parental outcome scores from the PIP and PedsQL Family Impact Module in the present study, and other studies in the CHD literature.

<table>
<thead>
<tr>
<th>Research Author</th>
<th>Test</th>
<th>N (BV:SV)</th>
<th>Subscale</th>
<th>BV Mean</th>
<th>SV Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Study</td>
<td>PIP</td>
<td>14:7</td>
<td>Total Frequency</td>
<td>79.00</td>
<td>123.29</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total Difficulty</td>
<td>78.57</td>
<td>124.57</td>
</tr>
<tr>
<td></td>
<td>PedsQL Family Impact</td>
<td>14:7</td>
<td>Parent HRQOL</td>
<td>83.65</td>
<td>55.96</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Family Functioning</td>
<td>84.86</td>
<td>56.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total Impact</td>
<td>79.94</td>
<td>49.56</td>
</tr>
<tr>
<td>Wray et al.</td>
<td>PIP</td>
<td>544:130</td>
<td>Total Frequency</td>
<td>78.7</td>
<td>94.3</td>
</tr>
<tr>
<td>(2018)</td>
<td></td>
<td></td>
<td>Total Difficulty</td>
<td>77.7</td>
<td>89.8</td>
</tr>
<tr>
<td>Kaugars et al.</td>
<td>PIP</td>
<td>22:32</td>
<td>Total Frequency</td>
<td>78.31</td>
<td>99.00</td>
</tr>
<tr>
<td>(2018)</td>
<td></td>
<td></td>
<td>Total Difficulty</td>
<td>68.13</td>
<td>95.36</td>
</tr>
<tr>
<td></td>
<td>PedsQL Family Impact</td>
<td>22:32</td>
<td>Parent HRQOL</td>
<td>76.63</td>
<td>69.18</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Family Functioning</td>
<td>73.36</td>
<td>70.80</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total Impact</td>
<td>75.51</td>
<td>69.18</td>
</tr>
<tr>
<td>Eagleson et al.</td>
<td>PedsQL Family Impact</td>
<td>n/a :31</td>
<td>Parent HRQOL</td>
<td>-</td>
<td>65.9</td>
</tr>
<tr>
<td>(2013)</td>
<td></td>
<td></td>
<td>Family Functioning</td>
<td>-</td>
<td>62.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total Impact</td>
<td>-</td>
<td>63.4</td>
</tr>
</tbody>
</table>

*Note:* N = total number of participants in the study, split by CHD type (BV:SV), where BV = biventricular CHD, and SV = single ventricle CHD. BV patients include those with TGA, and SV patients include those with HLHS.
Appendix 12. Colour-coded longitudinal scores of each child in the longitudinal cohort at 4-5 years.

Note. Green = score within normative range, Amber = score 1-2 SD below mean, Red = ≥2 SDs below mean, and x = no data available/test not completed.
<table>
<thead>
<tr>
<th>Participant</th>
<th>Time-point 1</th>
<th>Time-point 2</th>
<th>Time-point 3</th>
<th>Time-point 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bayley-3 Time-point 1</td>
<td>Bayley-3 Time-point 2</td>
<td>Bayley-3 Time-point 3</td>
<td>CBCL</td>
<td>WPPSI-IV</td>
</tr>
<tr>
<td>Control 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control 7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control 8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control 9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control 10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control 11</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control 14</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control 16</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control 18</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control 25</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLHS 5</td>
<td>x x x x x x</td>
<td>x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLHS 6</td>
<td>x x x x x x</td>
<td>x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLHS 8</td>
<td>x x x x x x</td>
<td>x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLHS 10</td>
<td>x x x x x x</td>
<td>x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLHS 13</td>
<td>x x x x x x</td>
<td>x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLHS 14</td>
<td>x x x x x x</td>
<td>x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLHS 16</td>
<td>x x x x x x</td>
<td>x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGA 2</td>
<td>x x x x x x</td>
<td>x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGA 4</td>
<td>x x x x x x</td>
<td>x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGA 7</td>
<td>x x x x x x</td>
<td>x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGA 9</td>
<td>x x x x x x</td>
<td>x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGA 10</td>
<td>x x x x x x</td>
<td>x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGA 11</td>
<td>x x x x x x</td>
<td>x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGA 12</td>
<td>x x x x x x</td>
<td>x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGA 13</td>
<td>x x x x x x</td>
<td>x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGA 14</td>
<td>x x x x x x</td>
<td>x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGA 15</td>
<td>x x x x x x</td>
<td>x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGA 16</td>
<td>x x x x x x</td>
<td>x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGA 17</td>
<td>x x x x x x</td>
<td>x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGA 21</td>
<td>x x x x x x</td>
<td>x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGA 22</td>
<td>x x x x x x</td>
<td>x x x x x x</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

547
### Parental Questionnaires (Time-point 4)

<table>
<thead>
<tr>
<th>Participant</th>
<th>CCC-2</th>
<th>CBCL</th>
<th>SDQ</th>
<th>ABAS</th>
<th>BRIEF-P</th>
<th>PedsQL</th>
<th>PedsQL Family Impact</th>
<th>Family Functioning Summary</th>
<th>Parent HRQL Summary</th>
<th>Total</th>
<th>Anxiety</th>
<th>Depression</th>
<th>Difficulty</th>
<th>Total Difficulties</th>
<th>Impact of Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Control 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Control 7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Control 8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Control 9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Control 10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Control 11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Control 14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Control 16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Control 18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Control 21</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>HLHS 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>HLHS 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>HLHS 8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>HLHS 10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>HLHS 13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>HLHS 14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>HLHS 16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>TGA 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>TGA 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>TGA 7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>TGA 9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>TGA 10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>TGA 11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>TGA 12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>TGA 13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>TGA 14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>TGA 15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>TGA 16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>TGA 17</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>TGA 21</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>TGA 22</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
</tbody>
</table>