Mapping neurodevelopmental trajectories: A focus on autism with comparisons to psychosis

Sarah Ann Ashley

Division of Psychiatry, University College London

A thesis presented for the degree of Doctor of Philosophy (PhD)

April 2024

Declaration: I, Sarah Ashley, 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.

Thesis Summary

Both autism and schizophrenia are neurodevelopmental disorders. Autism is diagnosed early in childhood, whereas schizophrenia and psychotic disorders have a later onset in adolescence and early adulthood. A better understanding of the neurodevelopmental trajectories that underlie these disorders would provide insights into their underpinning biological mechanisms. Research indicates the neurodevelopmental abnormalities may also be present in participants with specific traits of autism or in participants with attenuated symptoms of schizophrenia. Autistic traits (e.g. social communication difficulties) can be measured psychometrically and are thought to lie on a continuum with normality. Psychotic experiences occur in 5-10% of the general population and are associated with an increased risk for developing schizophrenia.

The thesis comprises of 4 studies: (1) A meta-analysis of total brain volume trajectories in autism spectrum disorder (ASD); (2) An investigational study charting head circumference trajectories from birth to age 15 years in individuals with autism and elevated autistic traits relative to controls; (3) An investigational study charting head circumference trajectories in participants with psychotic disorder and psychotic experiences relative to controls; (4) An investigational study using magnetic resonance imaging (MRI) to explore grey matter brain alterations associated with autistic traits.

In chapter 2, I present a meta-analysis of longitudinal studies measuring total brain volume in ASD. I explore differences with controls at individual study timepoints as well as longitudinal changes over time. We find evidence of early brain overgrowth in ASD before the age of 5, but that changes in total brain volume over time were reduced, which is indicative of slowing or arrest of growth in ASD.

Chapter 3 presents original research using data from the Avon Longitudinal Study of Parents and Children (ALSPAC). Using linear mixed effects models, we charted head circumference trajectories from birth to 15 years in individuals (a) with and without ASD, (b) and elevated autistic traits. ASD was linked to larger head circumference from birth to adolescence compared to controls, with a clear difference emerging at 2 months of age. Enlarged head circumference was more pronounced in those with ASD and comorbid cognitive learning

needs. Children with autistic traits only, measured using the Social Communication Disorder Checklist (SCDC), had smaller head circumference compared to controls.

Chapter 4 presents novel findings of head circumference trajectories associated with psychotic experiences. Psychotic experiences measured using the semi structured PLIKS interview in ALSPAC at age 18 were associated with reduced head circumference trajectories in females but increased trajectories in males compared to controls. However, operationally defined 'psychotic disorder' was associated with reduced head circumference in both sexes. A subset of this sample also had neuroimaging at age 21 years, showing psychotic disorder to be associated with reduced total intracranial volume and total grey matter volume.

Finally, in chapter 5, we explore alterations in grey matter volume associated with autistic traits measured using the SCDC. We find that autistic traits are associated with grey matter volume alterations in frontal and parietal brain regions. These cortical regions are thought to contribute to deficits in higher-order cognitive functioning and atypical sensory processing. We did not find an association with total intracranial volume and total grey matter volume.

These findings provide important insights into the neurodevelopmental trajectories underlying ASD and psychotic disorder. Both conditions are associated with atypical growth, with increased total brain volume and head circumference in ASD, whereas head circumference and total brain volume was reduced in psychotic disorder. Neurodevelopmental trajectories differ between ASD and those with autistic traits, as autistic traits were associated with reduced head circumference, and no difference in total brain volume, although alterations in brain regional volumes were found.

When comparing psychotic disorder patients to participants with subthreshold psychotic experiences, females with psychotic experiences showed similar head circumference trajectories to those with psychotic disorder, whereas males with psychotic experiences showed larger head circumferences. Although reduced TIV and total grey matter volume was seen in psychotic disorder, no differences were found in participants with psychotic experiences compared to controls. In summary, more severe neurodevelopmental changes are present in ASD and psychotic disorder compared to those with sub-threshold traits.

Impact Statement

Academic impact

This thesis has strengthened our theoretical understanding of neurodevelopmental trajectories in individuals on the ASD and psychosis spectrums. Early brain overgrowth and increased head circumference in ASD are well cited in the literature, however it was unknown when this increase occurs, if it persists, and whether it manifests across the whole ASD spectrum. For psychosis related disorders such as schizophrenia, research has predominantly focused on birth (for measures of head circumference) and adulthood (for brain volumes). The neurodevelopmental trajectory between these ages has not been established. Furthermore, until now no research has explored head circumference trajectories in individuals with subthreshold psychotic experiences. This thesis addresses these gaps in the literature by utilising a variety of methodological approaches including a meta-analysis, and data from a UK-based population cohort to explore longitudinal head circumference measurements and cross-sectional volumetric neuroimaging data.

My thesis has shown that head circumference is atypical from birth in individuals with ASD and psychotic disorder, with increased trajectories in the former and reduced in the latter. We also add to the theoretical understanding of ASD as a continuum. Namely, we did not find evidence of a continuum between autistic traits and ASD, as individuals with elevated autistic traits had slightly reduced head circumference trajectories compared to controls. However, we did find evidence of a continuum when investigating regional differences in grey matter volume associated with elevated traits, as the regions correspond with those cited in clinical ASD cases. Our meta-analysis provided evidence that TBV is enlarged in early childhood while also highlighting the paucity of longitudinal data in adult ASD samples. Future work is needed to investigate brain changes across the full lifespan.

Clinical impact / impact outside of academia

This thesis provided evidence that small head circumference at birth can predict psychotic disorder, suggesting its potential use as a prognostic marker to guide diagnosis and intervention. This thesis also demonstrates the utility of head circumference as a proxy measure of brain development, and that collecting population measures of this variable

could be useful for public health. Furthermore, due to the low cost of head circumference as a measure, our findings are applicable to many settings including low-income countries.

Dissemination

Of the four analytical studies, two have been submitted to journals for review, and two are currently being drafted for journal submission. Work from all four studies has also been disseminated through posters and oral presentations at several conferences, including:

- UCL Faculty of Brain Sciences PGR Conference (UK, 2022)*
- European Society for Cognitive and Affective Neuroscience (Austria, 2022)
- Epidemiology & Social Psychiatry Conference (UK, 2022)
- International Society for Autism Research (Sweden, 2023)
- Schizophrenia International Research Society (Canada, 2023)
- British Neuropsychiatry Association (UK, 2024)*

I am grateful to have received awards for my presentations at two of the above conferences*. This highlights the importance of my findings to the wider academic community, particularly in improving our theoretical understanding of these conditions and opening discussions on the clinical utility of using head circumference as a diagnostic aid.

Acknowledgements

I would like to thank the following individuals for their support during my PhD.

Supervisors: I am *extremely* grateful to my supervisors Prof. Anthony David, Dr Kate Merritt, and Prof. Avi Reichenberg for their *invaluable* guidance and support throughout the entirety of my PhD. I have learned so much from their expertise and appreciate the time they have shared to help me develop as a researcher – I will forever be grateful.

Funders: I would like to say a *big* thank you for the generous financial support from the Beatrice & Samuel A Seaver Foundation who made this PhD research possible, as well as enabling me to visit Mount Sinai in New York and attend several conferences. I am also grateful for the funding and collaboration from my supervisors' MRC (MR/S003436/1) grant, which facilitated the neuroimaging analyses.

Collaborators: My thanks go to Dr Pedro Laguna and Dr Francesca Solmi, two key members of my thesis committee whom I am very grateful to have had as collaborators. I appreciate their support, particularly for the neuroimaging preprocessing/analyses and head circumference studies respectively. I would also like to thank collaborators and co-authors Pilar Letrondo, Matthew Kempton, Emily Hedges, Yanakan Logeswaran, Derek Jones, and David Linden.

Participants: This work would not have been possible without the young people and parents who participated in ALSPAC. I am grateful for their time and contribution.

Colleagues: Thank you to *all* my UCL and Mount Sinai colleagues that have been part of my PhD journey. I would especially like to thank Shivangi, Duaa, Pilar, Annie, Carlos, and Darci for their moral support, PhD/career advice, and for making my time at UCL so enjoyable. Thanks also go to Jehanita and Lina who both joined the lab during my final year, as well as to my mentor Dr Penny Rapaport and the PETAL team. Finally, thanks to the MSc and admin team, including Sarah Rowe, James Bisby, and Noorjaben Monowari for the opportunity to be a PGTA over the last three years.

Family and friends: I am beyond lucky to have had my mum and partner Chris support me all the way, to have their reassurance, and for helping me to always see the positive in things. I could not have done it without them. I am also grateful for my friends Amelia, Dana, Helena, Paige, and Veronica for sharing in this journey with me, and to my housemates Ellie and Carl for all the insightful discussions we have had about ASD and psychosis research.

Publications

UCL Research Paper Declaration Form 1
referencing the doctoral candidate's own published work(s)

Please use this form to declare if parts of your thesis are already available in another format, e.g. if data, text, or figures:

- *have been uploaded to a preprint server*
- *are in submission to a peer-reviewed publication*
- *have been published in a peer-reviewed publication, e.g. journal, textbook.*

This form should be completed as many times as necessary. For instance, if you have seven thesis chapters, two of which containing material that has already been published, you would complete this form twice.

1. **For a research manuscript prepared for publication but that has not yet been published**

   a) **What is the current title of the manuscript?**

   Meta-Analysis of Longitudinal Total Brain Volume Trajectories in Autism

   b) **Has the manuscript been uploaded to a preprint server?** (e.g. medRxiv; if 'Yes', please give a link or doi)

   No

   c) **Where is the work intended to be published?** (e.g. journal names)

   Review Journal of Autism and Developmental Disorders

   d) **List the manuscript's authors in the intended authorship order**

   Sarah A. Ashley, MSc[1], Kate Merritt, PhD[1], Pilar A. Letrondo, MSc[1], Pedro L. Laguna, PhD[2], Emily Hedges, PhD[3], Matthew J. Kempton, PhD[3], Abraham Reichenberg, PhD[4], Anthony S. David, MD[1]

   [1] Division of Psychiatry, University College London, UK

   [2] CUBRIC, Cardiff University, UK

   [3] Institute of Psychiatry, Psychology and Neuroscience, Kings College London, UK

   [4] Department of Psychiatry, Department of Environmental Medicine and Public Health, MINDICH Child and Health and Development Institute, and Seaver Center for Autism Research and Treatment, Icahn School of Medicine at Mount Sinai, USA

e) **Stage of publication** (e.g. in submission)

Prepared, awaiting submission to Journal for review.

2. **For multi-authored work, please give a statement of contribution covering all authors** (if single-author, please skip to section 4)

   SAA and PAL performed abstract and full-text screening, as well as assessing risk of bias. SAA, KM, PL, EH, MJK, AR, and ASD contributed to study methodology and analysis plan. All authors read and approved the final manuscript.

3. **In which chapter(s) of your thesis can this material be found?**

   Chapter 2

4. **e-Signatures confirming that the information above is accurate** (this form should be co-signed by the supervisor/ senior author unless this is not appropriate, e.g. if the paper was a single-author work)

   Candidate

   S.Ashley

   Date:

   29.04.24

   Supervisor/ Senior Author (where appropriate)

   Anthony David

   Date

   30/04/2024

UCL Research Paper Declaration Form 2
referencing the doctoral candidate's own published work(s)

Please use this form to declare if parts of your thesis are already available in another format, e.g. if data, text, or figures:

- *have been uploaded to a preprint server*
- *are in submission to a peer-reviewed publication*
- *have been published in a peer-reviewed publication, e.g. journal, textbook.*

This form should be completed as many times as necessary. For instance, if you have seven thesis chapters, two of which containing material that has already been published, you would complete this form twice.

5. For a research manuscript that has already been published

a) **What is the title of the manuscript?**

A Longitudinal Study of Head Circumference Trajectories in Autism and Autistic Traits

b) **Please include a link to or doi for the work**

https://doi.org/10.1007/s10803-024-06578-x

c) **Where was the work published?**

Journal of Autism and Developmental Disorders

d) **Who published the work?** (e.g. OUP)

Springer Nature

e) **When was the work published?**

12th October 2024

f) **List the manuscript's authors in the order they appear on the publication**

Sarah A. Ashley, Kate Merritt, Francesca Solmi, Pedro L. Laguna, Abraham Reichenberg & Anthony S. David

g) **Was the work peer reviewed?**

Yes

h) **Have you retained the copyright?**

Yes

i) **Was an earlier form of the manuscript uploaded to a preprint server?** (e.g. medRxiv). If 'Yes', please give a link or doi)

No

If ‘No’, please seek permission from the relevant publisher and check the box next to the below statement:

☒

*I acknowledge permission of the publisher named under **5d** to include in this thesis portions of the publication named as included in **5c**.*

6. For multi-authored work, please give a statement of contribution

SAA performed analyses and wrote manuscript. SAA, KM, PLL, FS, AR, and ASD contributed to study methodology and analysis plan. All authors read and approved the final manuscript.

7. **In which chapter(s) of your thesis can this material be found**

Chapter 3

e-Signatures confirming that the information above is accurate (this form should be co-signed by the supervisor/ senior author unless this is not appro priate, e.g. if the paper was a single-author work)

Candidate

S.Ashley

Date:

11.11.24

Supervisor/ Senior Author (where appropriate)

Anthony David

Date

11/11/2024

Abbreviations

ALSPAC: Avon Longitudinal Study of Parents and Children

ASD: Autism Spectrum Disorder

AQ: Autism Spectrum Quotient

M: Mean

N: Number of participants

OR: Odds Ratio

PE: Psychotic experiences

SCDC: Social Communication Disorder Checklist

SD: Standard Deviation

SRS: Social Responsiveness Scale

TBV: Total Brain Volume

TIV: Total Intracranial Volume

UK: United Kingdom

Table of Contents

Table of tables

Table of figures

Chapter 1: Background

1.1 Autism spectrum disorder

1.1.1 Introduction and diagnostic criteria

Autism spectrum disorder (ASD), as defined by the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5-TR),[1] is a neurodevelopmental disorder characterized by pervasive impairments in social interaction and communication, and the presence of restricted, repetitive patterns of behaviour. These symptoms emerge early in development and are typically recognised from 12 months of age but may be seen earlier if developmental delays are severe, or later if symptoms are more subtle.[2]

Severity is classified based on the level of support needed in social communication and restricted/repetitive behaviours. Examples of social communication impairments include deficits in social-emotional reciprocity, problems with initiating and maintaining conversation, and gaze avoidance. Conversely, restricted, repetitive behaviours include but are not limited to insistence on sameness, repetitive motor movements, intense or fixated interests, and hypo/hyper-sensitivities to sensory information. For a diagnosis of ASD to be made, these symptoms must cause clinically significant disruption to social, occupational, and daily functioning. Furthermore, the presence of co-occurring intellectual disability and/or language impairment may also be specified. Both verbal and nonverbal language is affected in ASD, with between 25-30% of individuals with ASD non- or minimally verbal.[3–5] Delayed language and communication problems are also one of the first reported areas of concern for parents of children later diagnosed with ASD, whereas concerns over repetitive behaviours are often reported later in development.[6]

The spectrum model of ASD highlights the heterogeneity in both symptom presentation and severity. Further support for a dimensional perspective to ASD comes from autistic trait literature in subclinical populations. For example, autistic traits have are shown to have a continuous distribution in the general population, and genetic studies report correlations between the same genetic susceptibilities in ASD as those with autistic traits.[7] Autistic traits are also more common in undiagnosed family members of individuals with ASD, suggesting a strong genetic influence.[8]

1.1.2 Epidemiology

Worldwide prevalence estimates suggest between 1-4% of individuals are diagnosed with ASD,[9,10] with an average age of diagnosis being 5 years.[11] Epidemiological studies report a male bias in prevalence rates of ASD, with an average ratio of 4:1 frequently cited.[12] Although, a recent meta-analysis of 53,712 individuals with ASD reports that the ratio may be closer to 3:1.[13] Other studies have shown disparate results when accounting for cognitive functioning, this can vary from 7:1 for high-functioning ASD to 2:1 for individuals with intellectual disability.[14]

This thesis will examine data from the Avon Longitudinal Study of Parents and Children (ALSPAC), a large population-based birth cohort study. Prevalence of ASD in the ALSPAC cohort is slightly reduced compared to worldwide estimates, at 0.51% (or 51.1 out of 10,000) using multi-professional diagnoses by age 11 years, and 0.62% (61.9 out of 10,000) if records from education were included.[15] Median age at diagnosis was 3.75 years for children with ASD, and 9.66 years for Asperger's, a milder subtype of autism before ASD was reclassified as a spectrum. Of the 86 cases of ASD identified (including Asperger's), 75 were males and 11 females, with a sex ratio of 6.8:1.

1.1.3 Aetiology / evidence for neurodevelopmental perspective

As a neurodevelopmental disorder, symptoms of ASD are thought to arise from perturbations to early brain development. Approximately 85% of ASD cases are idiopathic, which means the specific cause of these brain differences are unknown. However, several lines of research have implicated a complex blend of genetic and environmental risk factors. Among 69 of the most reported high-confidence ASD genes (i.e., genes that are believed to be strongly associated with increased risk for developing ASD), 94% are expressed prenatally and affect a wide range of processes in neural development, including the proliferation of cells, migration of cells to designated brain regions, and in the creation and functioning of synapses, which are the specialised connections between neurons that allow the transmission of signals across the brain (Figure 1 & Figure 2).[16,17] Evidence that ASD is a disorder of prenatal origin stems from postmortem and neuroimaging findings. An excess number of neurons is observed in the cerebral cortex in children with ASD.[18,19] The proliferation of cortical neurons takes place prenatally, between 4 and 24 weeks, and does

not occur postnatally, therefore an overabundance of neurons indicates that ASD may be strongly rooted in biological processes that take place early in foetal development.

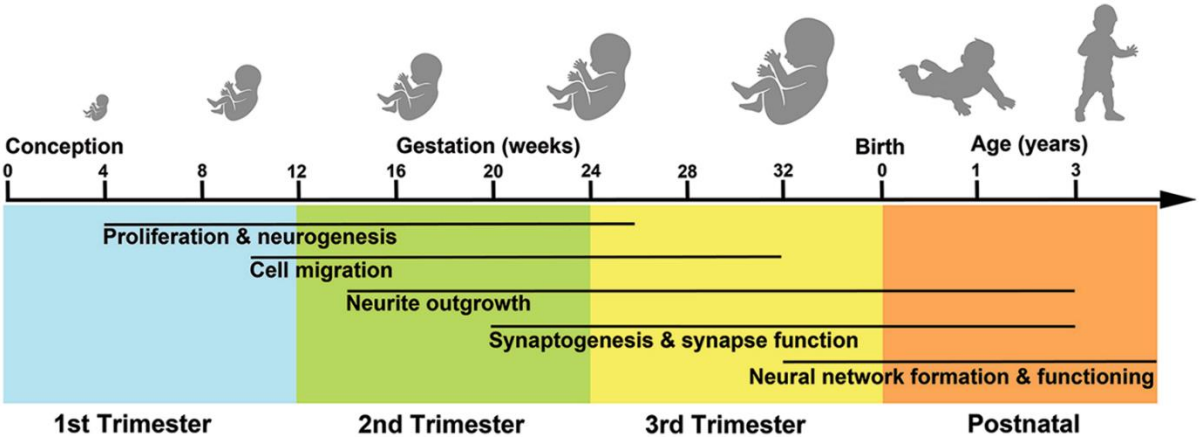


Figure 1. Developmental timeline of foetal and post-natal brain development. Figure retrieved from "The ASD Living Biology: from cell proliferation to clinical phenotype".[16]

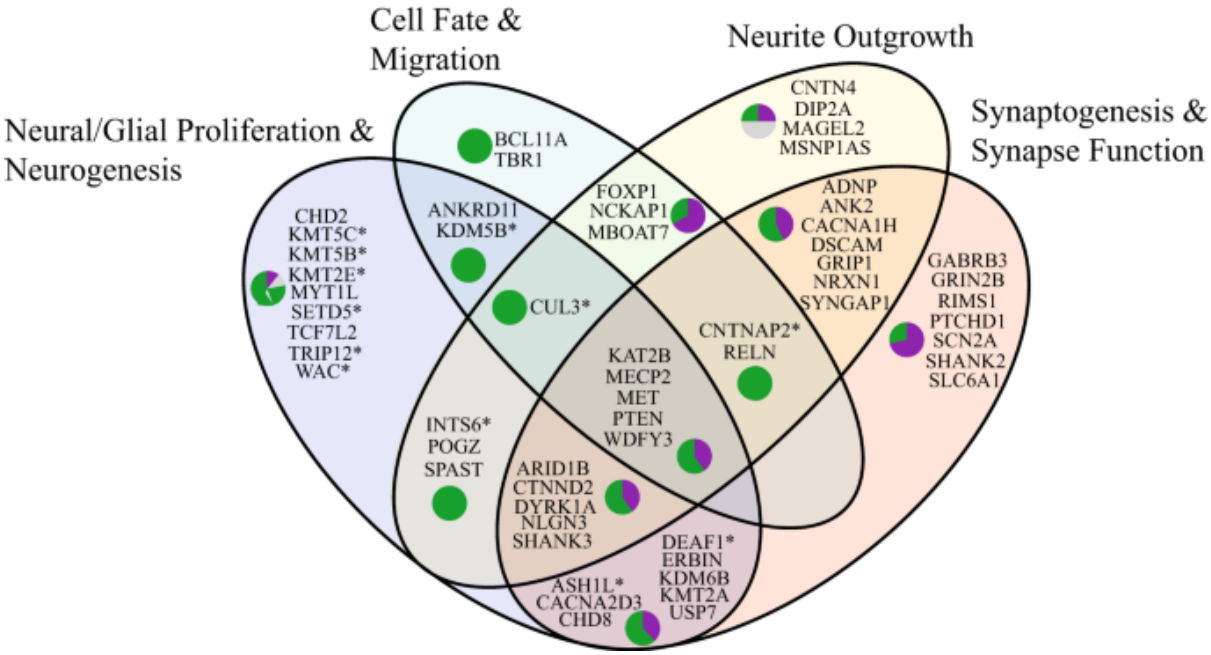


Figure 2. Distribution of 58 high confidence risk genes for ASD in neural development. Figure retrieved from *"The ASD Living Biology: from cell proliferation to clinical phenotype".*[16]

Substantial heterogeneity is observed in structural neuroimaging studies of ASD populations, both in terms of the implicated regions and the direction of the changes (i.e., volume increases or decreases).[20] Furthermore, age is another important factor with many brain regions demonstrating dynamic changes across the lifespan. Total brain volume (TBV) is the

sum of the brain's grey and white matter volume. In typical development, cortical grey matter volume increases rapidly after gestation before peaking at age 6-8 years and decreases from adolescence (Figure *3*).[21] Subcortical grey matter volume peaks during mid adolescence, while overall grey matter density continues to increase until early adulthood. In contrast, white matter - the fibrous connections comprising axons and their myelin covering between grey matter regions - develops much more gradually compared to grey matter, peaking at age 30 years.

While changes to brain development are observed across the lifetime, the time between birth and 2 years is often cited as one of the most critical periods of brain development as it is where the most rapid changes take place. At 3 weeks post-partum the brain is approximately 35% of its total adult size, reaching 80% by the age of 2 years.[22] During this period, the neural foundations for various cognitive, emotional, and social abilities are established. It is also believed to be a critical period of vulnerability for neurodevelopmental disorders. Indeed, numerous neuroimaging studies in infants with ASD provide evidence of atypical development of both grey and white matter volumes during this period,[23–25] which has led to the widely cited hypothesis of early brain overgrowth in ASD.[26] This phenomenon is characterised by (1) average TBV size at birth, (2) accelerated growth in early childhood, and (3) atypically slow or arrested growth between late childhood and adolescence. While there has been much support for the first two predictions, the third has proven controversial, with some studies reporting TBV to be persistently enlarged in ASD, [27,28] whilst others show a later period of arrested growth in adolescence followed by either normalization or reduction in adulthood.[20,29,30] Research that leverages longitudinal neuroimaging study designs may help elucidate these unanswered questions. Longitudinal research is superior to cross-sectional research due to its capacity to map brain development over time and allow cause-and-effect inferences, while also maintaining greater statistical power as it reduces variability from individual differences.

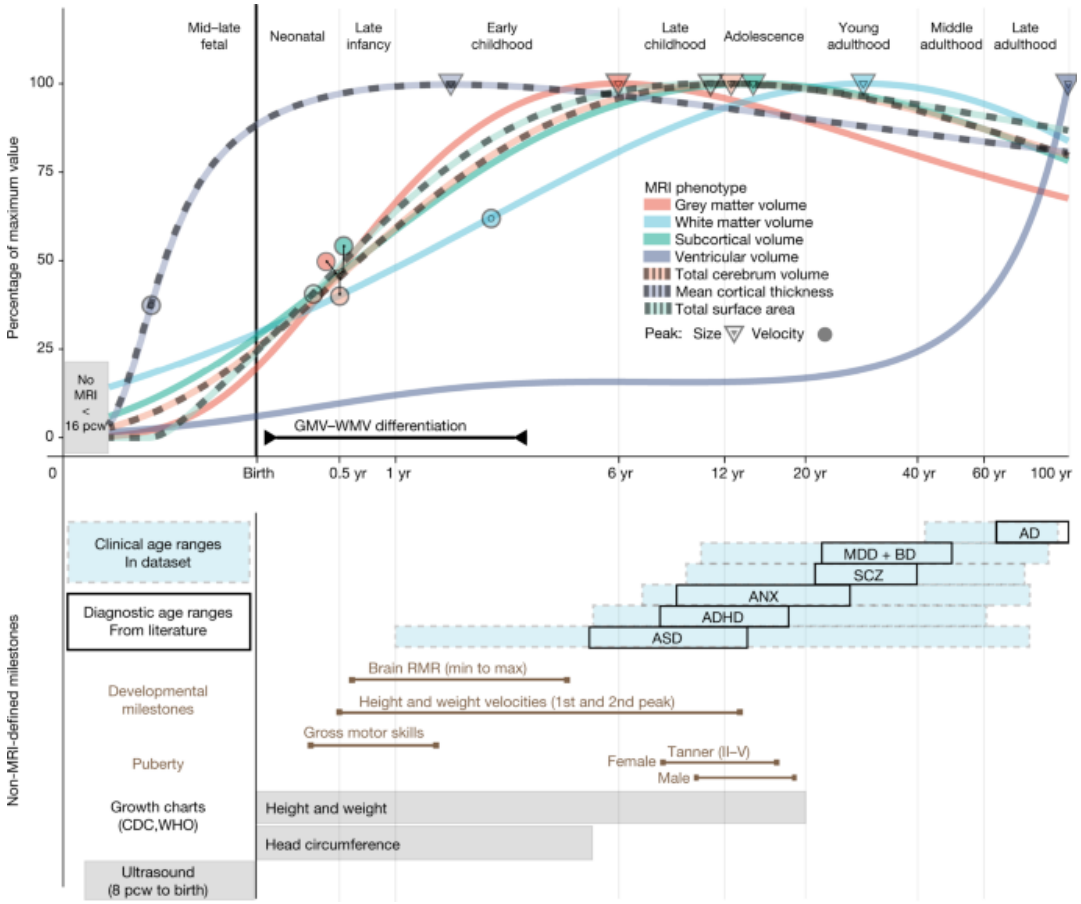


Figure 3. Normative trajectories of the median (50th centile) for each global MRI phenotype and diagnostic age ranges for clinical disorders. Figure retrieved from "Brain charts for the human lifespan"[21]

Head circumference has also been shown to strongly correlate with brain volume across childhood and adolescence, and some researchers propose it is a good proxy in adults. There are several advantages to using head circumference trajectories to monitor neurodevelopment, including that it is non-invasive and a highly feasible/cost-effective measure, as well as the fact that it is already a routinely collected measurement during childhood. Therefore, the combination of both neuroimaging and head circumference research should provide important insights into the elusive neurobiology of ASD.

ASD is highly heritable, with estimates of >90% for monozygotic twins, and 53% for dizygotic twins.[31,32] However, many genes associated with ASD are pleiotropic, which means that a singular gene can affect multiple phenotypic traits. This pleiotropy helps to explain the diversity in ASD symptoms. While genetic factors are theorised to play a crucial role in ASD aetiology, several environmental factors have also been linked to ASD risk. These include advanced parental age (possibly operating through genetic and non-genetic mechanisms),

birth complications such as hypoxia or birth injury, intrauterine infection, and maternal obesity. Population-based studies have shown increased risk for autism when infants were born either preterm or post term, regardless of whether size was congruent with age,[33] whilst another study reported that being preterm and small for gestational age is associated with increased autism risk, as does being large for gestational age when born at term.[34] Among factors associated with socioeconomic status, maternal education is the most strongly correlated with cognitive development in children. Low maternal education has been shown to correlate with autism risk and severity,[35–37] However some studies have shown the opposite, with a two-fold increase in autism diagnoses in children whose mothers were educated to A-level or above.[38] The latter finding alludes to possible inequalities in autism diagnosis, particularly in terms of service provision and ability to access information on health conditions for parents from lower education backgrounds.

In summary, while the exact aetiology of ASD remains unknown, several lines of research point to atypical neurodevelopment as well as joint genetic and environmental risk factors.

1.2 Psychotic experiences

1.2.1 Psychosis spectrum

Psychosis refers to a collection of symptoms and signs that affect a person's thoughts and perceptions and is often described as a loss of contact with reality. This might involve auditory or visual hallucinations, delusional thinking patterns such as paranoia and grandiosity, as well as thought interference or perceiving your own thoughts as someone else's. These symptoms reflect an excess or distortion of normal functioning and are referred to in psychosis literature as 'positive symptoms'. In contrast, negative symptoms refer to a reduction or absence of normal behaviours such as social withdrawal, anhedonia and blunted emotional responses.[39] Psychosis can complicate affective disorders usually in the form of mood-congruent hallucinations and delusions but the prototypical psychotic disorder is schizophrenia. Clinical psychotic disorders occur along a spectrum of symptom severity, ranging from schizoid personality disorder and brief psychotic disorder to schizophrenia. In schizophrenia, the average age of onset is between late adolescence to early 20s for men, and late 20s to early 30s for women, with a second peak onset occurring around the time of the menopause;[40] delusions and hallucinations may be mood-incongruent and their duration more persistent. Whilst age of onset is late compared to

other neurodevelopmental disorders such as ASD, there are premorbid changes to cognition that can be observed during infancy in individuals who later develop a psychotic disorder, further strengthening the current conceptualization of schizophrenia as a neurodevelopmental disorder. For example, a study in the ALSPAC cohort reported that progressive deficits in full-scale IQ and nonverbal IQ could be observed from 18 months through to 20 years in individuals who later develop psychotic disorder.[41] Developmental lags in processing speed, working memory, and attention were also reported, as were deficits in language abilities.

Hallucinations and delusions do not solely occur in clinical cases, as an estimated 5-10% of the general population have experienced some sort of psychotic experience.[42–44] Subclinical psychotic experiences are common in childhood and adolescence and are associated with a four-fold increased risk of developing psychotic disorder.[45] According to one meta-analysis, approximately 20% of individuals who report a PE go onto experience more persistent symptoms, and 7.4% develop psychotic disorder.[46] Transition is thought to be a result of a complex interplay between the environment and genetic liability, including exposure to trauma and environmental stressors, coping responses to initial psychotic experiences, and negative or depressed mental states.[47]

1.2.2 Epidemiology

Psychotic disorders affect 1-3% of the population.[48,49] The incidence of psychotic disorder and psychotic experiences have been examined within ALSPAC using the semi-structured Psychosis-like Symptoms Interview at ages 12, 18, and 24 (N = 7,900 with any data).[44] This measure is based on the principles of the Schedule for Clinical Assessment in Neuropsychiatry (SCAN), and consists of 6 questions on unusual experiences i.e., derealization, depersonalization, self-unfamiliarity, dysmorphophobia, and partial object perception, and a further 11 core questions on the primary symptoms of psychosis i.e., hallucinations, delusions and thought interference. Interviewers rated experiences as not present, suspected, definitely psychotic, and psychotic disorder, based on experiences since age 12 years.[50] For an individual to be classified as having a 'psychotic disorder', psychotic experiences must have occurred at least once per month over the previous 6 months and caused severe distress, negatively impact social or occupational functioning, or led to help-

seeking. Of 3,866 individuals interviewed at age 24, 313 (8.1%) had a definite psychotic experience and 109 (2.8%) met criteria for psychotic disorder. There was no difference in incidence rates between males and females, with incidence rates peaking at 18 years of age. Among individuals with psychotic disorder, 60% reported a PE at age 12, suggesting a continuum a pathology. The majority of those with psychotic disorder were help-seeking (70%), highlighting the burden of psychotic illnesses to the individual and health services. Risk of developing other disorders and adverse psychosocial outcomes is also increased in those with psychotic experiences.[51,52]

1.2.3 Aetiology / evidence for neurodevelopmental perspective

Psychosis was first formulated as a neurodevelopmental disorder based on three primary lines of evidence.[53] (1) Prenatal and perinatal risk factors such as obstetric complications, low birthweight, and maternal infection during pregnancy are linked to increased risk of schizophrenia; (2) evidence of delayed motor and social milestones and cognitive impairments that are present from infancy; and (3) atypical brain development, including reductions in grey matter volume, atypical white matter connections, and ventricular enlargement. Importantly, reductions in grey matter are not the result of neurodegenerative processes such as apoptosis or cell loss, but instead reduced dendritic- and synaptic density.[54]

Psychotic experiences share strong genetic correlations with psychotic disorders like schizophrenia.[55–57] The Longitudinal Experiences and Perceptions (LEAPS) study, drawing upon twin data, reports moderate heritability rates for psychotic experiences (15-59%). [58] However, in ALSPAC, while polygenic risk scores were higher in those with psychotic experiences at ages 12 and 18 years, it was not a significant risk factor.[59] Compared to ASD which has a strong basis on genetic factors, environmental factors are thought to play a greater role in the aetiology of psychotic experiences. A large twin study reported that as exposure to environmental factors increases, the contribution of genetic influences become less significant in psychosis.[60] This contrasts to the diathesis-stress perspective of psychosis, in which environmental risks are thought to trigger genetic susceptibility and therefore exert higher genetic heritability in the presence of environmental stressors.[61] Several environmental risk factors have been identified for psychotic experiences, including: urbanicity, poverty, cannabis usage, psychological and physical abuse, and environmental

toxins (e.g., lead exposure).[62–65] Within ALSPAC, greater population density at birth was associated with increased risk for psychotic experiences and positive symptoms at age 18 years (odds ratio [OR]: 1.77, 95% CI: 1.15-2.21],[66] whereas social fragmentation (i.e., poor community integration) was linked to negative symptoms. Recent work from ALSPAC finds that childhood psychological trauma and perinatal complications affect regional volumes within the 'salience network' in the brain, including the striatum and insula, indicating that environmental risk factors impact the same brain pathways that are altered in psychosis.[67]

Neuroanatomical abnormalities are well established in the psychosis literature, with a predominant theme of brain volume loss and ventricular enlargement, particularly in medial temporal regions. One longitudinal study over a 9-year period examining changes in TBV in adults with schizophrenia found the mean annualized rate of TBV change reduced by 0.69% in schizophrenia versus 0.49% in controls [68]. This suggests that there is progressive brain volume loss in schizophrenia patients. Given that brain volume is 90% developed by age 5,[69] it is possible that factors related to brain volume, even when detected in adults, might have developmental origins.

In order to study the neurodevelopmental origins of schizophrenia, it is necessary to study the psychosis prodrome. This can be approached by studying groups at high risk for psychosis to gain an understanding of how the disorder develops, whilst removing the confounds of medication effects. Neuroimaging studies in these groups also have the potential to identify biomarkers for psychosis-related conditions, which would allow early detection and facilitate the targeting of preventative interventions to vulnerable individuals to prevent transition to psychosis. Studies typically examine three types of high-risk cohorts: (1) clinical high risk (CHR) groups otherwise known as ultra-high risk, are help-seeking individuals who present with attenuated psychotic symptoms, (2) genetic high risk (GHR) groups refer to individuals with a family history of schizophrenia or psychotic disorder, and (3) PE groups who are not help-seeking but are found to have psychosis-like or subclinical psychotic symptoms. In the case of ALSPAC the group in question is drawn from an epidemiologically defined cohort and hence less obviously susceptible to selection bias. One review of longitudinal studies in high-risk groups reported accelerated grey matter loss in several brain regions, including temporal, frontal, cingulate and parietal cortices, regardless of the type of high-risk group [70]. Transition to psychosis was associated with greater grey

matter decline, whereas subjects whose symptoms remitted may demonstrate a normalization of grey matter trajectories. Grey matter loss in these regions is consistent with the findings in schizophrenia, emphasizing a continuum of neuropathology. Progression from clinical high-risk, recently diagnosed, to chronic schizophrenia appears to be associated with progression of cortical to subcortical involvement of brain structures.[71]

Within ALSPAC, grey matter reductions have been reported in individuals with psychotic experiences in the left supramarginal gyrus which forms part of the somatosensory cortex and is involved in language perception and processing among other roles.[72] This region may contribute to auditory hallucinations and difficulties in distinguishing self-generated speech from external stimuli. Additional regions of grey matter reductions include the left thalamus and right anterior and left posterior cingulate.[67] The anterior cingulate regulates higher-order cognitive an emotional processing, while the posterior cingulate is an important structure within the default mode network and supports internally directed cognition, retrieval of autobiographical information, focusing attention, and planning.[73] In contrast, the thalamus forms an important hub within the brain for the relaying of sensory information between cortical and subcortical regions. All three regions have been implicated in schizophrenia, providing support for a continuum view of psychosis pathophysiology.

The role of sex on head/brain growth in those with psychotic experiences and psychotic disorders is unclear. Some studies suggest that differences in relation to head size and brain volume may be more pronounced in females. For example, findings from a Finnish national birth cohort suggest that head growth during infancy is atypically accelerated in females but not males in those who later go on to develop schizophrenia. A retrospective study of 70 patients with schizophrenia reports more pronounced reductions in head circumference at birth in females compared to males.[74] These findings contrast to a study which reports greater differences in adult males than females with schizophrenia, specifically, head circumference was larger than expected in 14.9% of male patients (n = 67), with no difference in size between females patients (n = 33) and controls.[75] However, the majority of research in head circumference growth after birth is limited and requires replication in larger samples. Exploring interactions with age will also be important.

1.3 Autism and psychotic experiences: why study these conditions together?

Both ASD and schizophrenia are spectrum disorders with neurodevelopmental origins. Understanding their symptomatic and neurobiological trajectories may reveal critical periods or milestones associated with these conditions.

Several studies within the ALSPAC cohort have found an increased risk of psychotic experiences in those with autism/autistic traits. Sullivan et al., report that the odds of psychotic experiences during childhood are increased three times in conjunction with an autism diagnosis.[76] Furthermore, there is an 11% increase of risk with every 1 standard deviation (SD) increase in mean scores on the SCDC. With higher scores representing greater impairment. They also report an 11% increased risk associated with a 1 SD increase in scores on a repetitive behaviour measure, and 16% increase for coherence scores (i.e., ability to explain things pragmatically). Interestingly, increases in scores for social inhibition and semantic-pragmatic skills reduced the odds of psychotic experiences and therefore were resilient factors. Another study reported associations between the presence of autistic traits before the age of 3 and the development of psychotic experiences in later childhood, with 14% of children going on to develop psychotic experiences [77]. This figure increased to 17% when autistic traits persisted to age 7. Reports of suspected or definite psychotic experiences were associated with maternal concerns of speech problems and ritualistic behaviours at age 3, although social interaction problems appeared unrelated.

Phenotypically, autism and psychotic disorders share several similarities, including marked impairment in social interactions, paucity of gestures, deficits in interpreting mental and emotional states, processing speed, and working memory.[78–80] Early developmental delays are common in both conditions, although less marked and seldom remarked upon at the time in schizophrenia and psychotic conditions, and span cognitive, emotional, and motor domains.[81] While the two conditions exhibit similarities in relation to negative symptoms i.e., the absence of typical social behaviours; positive symptoms or the addition of atypical behaviours help to differentiate the two. For example, hallucinations and delusions are observed in individuals with schizophrenia but not in those with ASD, whereas stereotyped language and repetitive and restricted behaviours are typically associated with ASD.[82]

Due to the combination of both shared and unique symptomology, it is unsurprising that several neuroimaging studies report various similarities and differences within the brain.

Many studies suggest that ASD and schizophrenia are disorders of the 'social brain'. For example, around 80% of abnormalities in functional connectivity are shared between the two disorders, particularly in default mode, sensorimotor, and cognitive control circuits [83]. The default mode system refers to a network of brain structures, including the posterior cingulate cortex, medial prefrontal cortex, precuneus, temporoparietal junction and the hippocampus.[84] These brain regions have important social cognition functions, including the ability to infer mental states including thoughts and emotions, otherwise known as Theory of Mind.

However, overlap in shared regions of grey matter reductions was smaller, at 40.2%, with the primary overlaps observed in the middle occipital gyrus and cerebellum. Larger overlap was cited for grey matter density (89.8%), in the frontal gyrus, temporal gyrus, cerebellum, and insula among others. Unique disorder differences were cited in the temporal gyrus, frontal gyrus and cingulate gyrus, in which schizophrenia was associated with grey matter volume reductions and ASD with volume increases. It has also been proposed that ASD and schizophrenia exhibit contrasting patterns of grey and white matter volumes and may pose opposite extremes of a shared phenotypic spectrum. One study provided evidence that ASD is associated with greater-than-normal total grey matter and lower-than-normal white matter, whereas the opposite was found in patients with schizophrenia.[85] These patterns were observed at a whole-brain level as well as within individual lobes (frontal, parietal, temporal, occipital). Compared to controls, volume differences were more pronounced in those with schizophrenia as opposed to ASD.

A recent study has also revealed important insights into cross-disorder correlations in cortical thickness and genetics in 6 psychiatric disorders: autism, schizophrenia, ADHD, bipolar disorder, major depressive disorder, and OCD [86]. Autism and schizophrenia share the strongest correlation for cortical thickness ($r = 0.63$) alongside a small genetic correlation ($r = 0.21$), with bipolar and schizophrenia sharing the highest genetic correlation ($r = 0.68$). Another study reported genetic overlap of 15-25% in autism and schizophrenia, with approximately 130 genes that appear to be more common in both disorders [87].

While ASD is associated with increased TBV during childhood, less is known about early changes to TBV in patients who develop schizophrenia. Congruent with findings in adulthood, it is theorised that head circumference, and by association brain size, is reduced

in prodromal schizophrenia cases. However, upon closer examination of the literature, the story is much more complex and heterogenous. High quality research in this area is scarce and requires validation and replication. Difficulties are also presented when conducting prospective studies in schizophrenia due to the relatively low incidence rates in schizophrenia. Moreover, head circumference trajectories within individuals with psychotic experiences are yet to be explored in the literature, highlighting a significant gap in knowledge which warrants further investigation.

It is important for future research to parse out the cross-disorder similarities and differences so that a better picture of the two disorders can be established. The ALSPAC cohort offers a good opportunity to achieve this given the wealth of standardised cognitive, behavioural and psychopathology data gathered over key periods of development in a relatively large population-based sample.

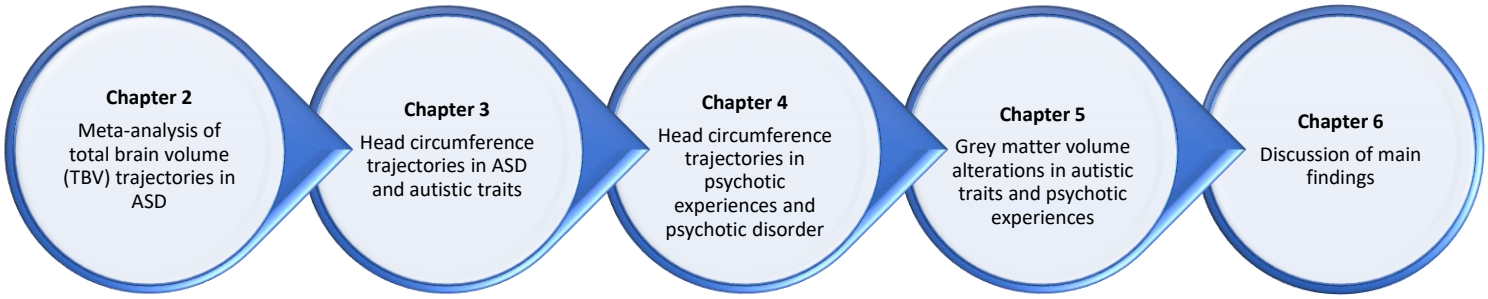
1.4 Thesis aims and outline

There are several clinical markers for ASD and psychotic disorders, but our knowledge of neurodevelopmental biomarkers is lacking. Although much research has examined brain and head circumference measures early in autism, there is a paucity of research in adults. On the other hand, in psychosis, much research has been conducted regarding differences in head circumference at birth and brain measures in adulthood, but less research is conducted after birth and in youth during the prodrome, due to the difficulty in conducting prospective studies in disorders with low incidence rates. Understanding the full picture of neurodevelopmental changes across the lifespan could reveal key pathophysiological processes in these two disorders and may reveal prognostic markers. Similarly, differences between males (in whom neurodevelopmental disorders are generally held to be more common) and females have seldom been explored in large samples. Lastly, much research has examined brain and head circumference measures in ASD, but fewer studies assess whether these alterations in biological measures are also present in those with high autistic traits, therefore it is not known whether neurodevelopmental changes associated with ASD lie on a continuum.

This thesis aims to:

1. Synthesize and meta-analyse current longitudinal literature on TBV trajectories in ASD.
2. Compare trajectories of head circumference from birth through to adolescence in individuals with ASD and elevated autistic traits to controls.
3. Compare trajectories of head circumference from birth through to adolescence in individuals with psychotic experiences and psychotic disorder to controls.
4. Investigate grey matter volume alterations in young adults with autistic traits and make comparisons with previous ALSPAC research in individuals with psychotic experiences.

A summary of the thesis outline and chapters can be found below:



Chapter 2: Meta-analysis of longitudinal trajectories of total brain volume in autism

Early brain overgrowth is well-documented in autism spectrum disorder (ASD). However, longitudinal brain development in ASD, from infancy to adulthood has not been systematically charted. In this chapter, I present my meta-analysis of longitudinal total brain volume (TBV) trajectories in ASD.

This manuscript is being prepared for submission to the Review Journal of Autism and Developmental Disorders.

Title: Meta-Analysis of Longitudinal Total Brain Volume Trajectories in Autism

Intended journal: Review Journal of Autism and Developmental Disorders

Authors:

Sarah A. Ashley, MSc[1], Kate Merritt, PhD[1], Pilar A. Letrondo, MSc[1], Pedro L. Laguna, PhD[2], Emily Hedges, PhD[3], Matthew J. Kempton, PhD[3], Abraham Reichenberg, PhD[4], Anthony S. David, MD[1]

[1] Division of Psychiatry, University College London, UK

[2] CUBRIC, Cardiff University, UK

[3] Institute of Psychiatry, Psychology and Neuroscience, Kings College London, UK

[4] Department of Psychiatry, Department of Environmental Medicine and Public Health, MINDICH Child and Health and Development Institute, and Seaver Center for Autism Research and Treatment, Icahn School of Medicine at Mount Sinai, USA

2.1 Introduction

It is well established that autism spectrum disorder (ASD) is associated with early life brain overgrowth.[23,88–91] However, some studies report brain volume to be persistently enlarged in ASD, [27,28] whilst others show a later period of arrested growth in adolescence followed by either normalization or reduction in adulthood.[20,92–94] Reviews of brain development in ASD suggest an increased rate of growth in the first 3 to 4 years of life, followed by growth arrest or volume losses so that by adulthood, there is no difference in total brain volume (TBV) size

between autistic and neurotypical groups.[20,29,30] Consistent with this, a cross-sectional meta-analysis observed that while brain volume is 15% larger in ASD compared to neurotypical populations in early childhood, it was 2% larger by adolescence and just 1% larger in adulthood.[95] This is consistent with another meta-analysis finding increased volume in early childhood that attenuates with age, [96] although one meta-analysis reports increased TBV in ASD and did not find a relationship between age and TBV effect size. [97] These meta-analyses are limited to cross-sectional data, whereas the aggregation of longitudinal data would allow a more accurate analysis of brain growth trajectories in ASD. To date, longitudinal MRI studies of ASD TBV have not been summarised in a meta-analysis. There are several advantages to longitudinal research, including a better understanding of temporal sequences which may aid cause-and-effect inferences, as well as greater statistical power as it reduces variability from individual differences.

There are mixed findings regarding sex differences and brain overgrowth in ASD; one infant study reports macrocephaly in males with ASD, but not in females.[98] Another study observed overgrowth during infancy only in males with regressive ASD,[99] but not in autistic males without regression. Other studies report macrocephaly to be more common in females,[100] or no differences between sexes.[101] Trajectories of typical neurodevelopment differ between males and females,[102] so conflicting results regarding sex differences in ASD may depend on developmental stage. A study of 6-25 year olds found no significant age or sex interactions by diagnosis in TBV,[27] however the number of longitudinal studies examining sex-effects are limited,[93,103,104] and are typically conducted over short time periods. Therefore, aggregating longitudinal data by meta-analytic means may help parse out the timing of sex differences if they occur. Enlarged brain size has also been linked to lower intelligence quotient (IQ < 70) in ASD[96]. One longitudinal study reports fewer gains in IQ in males with ASD and brain overgrowth between the ages of 3-5 years compared to males with ASD and no overgrowth.[105] This research contrasts to that found in neurotypical populations, in which larger TBV is generally associated with higher IQ.[28,106–108]. Taken together, these findings suggest that while larger TBV may be positively associated with the development of cognitive abilities in neurotypical individuals, the same is not true for individuals with ASD. Aggregating longitudinal studies will help confirm the relationship between IQ and growth trajectories in ASD.

The aim of this meta-analysis was to compare differences in TBV in ASD and controls and to explore changes in TBV over time. We therefore present effect size differences for i) aggregated TBV measures across all ages and ii) changes in TBV over time. We hypothesised that TBV will be enlarged in ASD during early years, and will normalise with age. In accordance with this, we hypothesised there would be greater longitudinal change in TBV in the early years of ASD indicative of accelerated growth, which will be attenuated in later childhood/adolescence. Case-control meta-analyses will be complemented by meta-regressions with age, sex, and IQ. We further hypothesised that i) low IQ and ii) a greater proportion of males in a study sample will be associated with larger TBV in ASD compared to controls.

2.2 Methods

2.2.1 Search Strategy and Selection Criteria

We followed PRISMA guidelines and registered the study on PROSPERO (CRD42021239079). Systematic literature searches were conducted on four electronic databases from inception through June 2023: PubMed, PsycINFO, Embase (Embase Classic + Embase), and Web of Science (Core Collection). Search terms were based around three concepts: 1) ASD, 2) longitudinal design, and 3) structural neuroimaging (for full search strategy, see Supplementary Materials). To widen the search, total intracranial volume (TIV), whole brain volume (WBV), and total tissue volume (TTV) were also accepted as estimates of brain volume. While TBV is the sum of grey and white matter volumes, TIV is generally defined as the volume within the cranium, including the brain, meninges and cerebrospinal fluid.[109] Both measures share similar increases in volume during childhood, however from adolescence, TIV remains more stable with aging while TBV shows age-related decline.[110,111] Google Scholar was used to extract additional papers, and reference lists of selected studies and reviews were manually searched.

References were imported into Covidence Systematic Review Software[112] and independently rated at title, abstract and full text stages by two authors (S.A.A & P.A.L.). Studies were eligible providing they: 1) compared individuals with ASD to neurotypical controls; 2) reported longitudinal means and standard deviations (SD) for TBV. If overlapping samples were reported, only data from the study with the largest sample were included. Authors

were contacted for missing TBV values, if data were unable to be provided these studies were excluded.[93,113–120]

Studies were excluded if: 1) the clinical sample consisted only of those with secondary ASD (i.e., non-idiopathic conditions such as Rett syndrome, fragile X); 2) post-mortem, animal studies or studies using a genetic approach were used; 3) languages were other than English.

2.2.2 Data Extraction and Processing

The following data were extracted by author S.A.A: age, sex, IQ, medication use and ASD diagnosis assessments. Mean and SD values for TBV were extracted and converted into millilitres (ml). Two authors (S.A.A. & P.A.L.) assessed risk of bias using a quality assessment tool adapted from the Joanna Briggs Checklist for Cohort Studies (Supplementary Materials).[121] Studies were rated on a ten-point scale, with 0-3.5 indicating high, 4-6 moderate, and 6.5-10 low risk of bias.

If studies use a measure other than TBV (e.g., TIV), these studies will be assessed separately in the supplementary.

2.2.3 Analyses and Outcome Measures

Hedges' *g* was selected as the measure of effect size as it generates the standardised mean difference between clinical and control groups while also correcting for bias from small sample sizes. For each study's timepoints, we calculated a "cross-sectional" volumetric effect size by subtracting the mean TBV value for ASD by the mean reported value in the control group divided by the pooled SD across groups. Study effect size was weighted according to sample size.

For our "longitudinal" effect size, we assessed longitudinal change in TBV over time (i.e., Time 1 (T1) to T2, T2 to T3, etc) for each study. An optimal method to calculate effect sizes for repeated measures designs has been proposed by Morris and Deshon.[122,123] First, we performed Bartlett's test(cite) of homogeneity of variances across groups. As heterogeneity was observed, we used a corrected version of hedges' g which does not rely on the assumption of equal variances, in which separate effect size estimates are calculated for each group and subtracted from each other to generate an estimate for overall study effect size (equation 1). The precision of these estimates is accounted for by weighting studies by

the estimated sampling variance of the effect size (equation 2). Variances are estimated separately for each group and summed.

The sampling variance also requires an estimation of the correlation coefficient (rho) between timepoints, which was set at 0.8 and adjusted to 0.5 and 0.99 in sensitivity analyses. A rho of 0.5 is considered conservative,[124] while 0.99 was calculated based on one study that reported complete values for SD of change.[104] As a rho of 0.99 is regarded as a very strong correlation, we based the main analyses on the more conservative value of 0.8.

$$\text{Longitudinal effect size} = \frac{(M_{post,\ ASD} - M_{pre,\ ASD})}{(SD_{pre,\ ASD})} - \frac{(M_{post,\ Controls} - M_{pre,\ Controls})}{(SD_{pre,\ Controls})}$$

Equation 1. Longitudinal effect size estimated separately for each group by subtracting mean baseline (pre) total brain volume from mean follow-up (post) total brain volume and dividing by the standard deviation (SD) from baseline.

$$\text{Sampling variance} = \left[\frac{2\,(1-\rho)}{n}\right]\left(\frac{n-1}{n-3}\right)\left[1+\frac{n}{2\,(1-\rho)}\,\delta_{IG}^2\right]-\frac{\delta_{IG}^2}{[c(n-1)]^2}$$

Equation 2. *n is the number of paired observations in a single-group pretest-posttest design;* δ_{IG} *is the population effect size. C(df) is the bias function; p is the correlation coefficient (rho).*

For the meta-analyses, the individual study effect sizes (cross-sectional and longitudinal) were pooled separately using random effects models and between-study heterogeneity was assessed using the Cochran Q test the I^2 statistic. The jack-knife method was used to estimate bias by removing each study (and all its timepoints) one-by-one and observing changes to effect size. A further jack-knife analysis was applied to cross-sectional data by removing study timepoints showing heterogeneity in variance between comparison groups. This was not applicable to the longitudinal data because effect sizes calculations did not rely on the assumption of equal variances.[122,125]

Meta-regressions were conducted for age (combined ASD and controls), sex (percentage of male ASD participants) and IQ (ASD group). For the meta-regression analyses of longitudinal effect sizes, we used the median age between timepoints averaged across groups. Where some studies included multiple cognitive tests, the Full-Scale Intelligence Quotient (FSIQ) was used in analyses. We used the IQ at baseline if subsequent timepoints did not list this information. Meta-analyses were carried out in Microsoft Excel using meta-analytical equations taken from the Major Depressive Disorder Neuroimaging Database,[126] which are equivalent to the *metan* command in STATA. Regarding validation, previous meta-analyses have used this method in parallel with STATA and yielded the same results.[126,127] Meta-regressions and plots were conducted in STATA (v17) using the *metareg* command.

2.3 Results

2.3.1 Search Results and Study Characteristics

The literature search yielded 5,458 studies, with 4,002 remaining after deduplication. Of these studies, 7 were included in the meta-analysis (for Prisma Flow Diagram, see Supplement 2.6 Figure 9). Three studies examined overlapping samples. Of these, the studies with the smaller sample size were excluded,[128,129] including one study from the IBIS cohort.[103] The selected studies included data from 559 individuals with ASD and 3,635 controls. The number of MRI timepoints within a study ranged from two to five, with the mean age ranging from 6 months to 30 years (Figure 4), although one study recruited participants from a wider range of ages from 6-46 years. [130] All studies but one reported TBV, see Supplement for analyses that include the TIV dataset. [131132](see Supplement for analyses including this dataset). One selected study provided data split by sex; [104] to combine these samples we calculated the weighted average for TBV (means and standard deviations), age, and IQ. Table 1 summarises study characteristics, see supplement for TBV values and individual study effect sizes (Supplement 2.6 Table 2). All studies had low to moderate risk of bias and there was strong inter-rater agreement for quality assessments (IRR = 90%, see Supplementary Materials for risk of bias scores). There was moderate inter-rater reliability between raters for full-text screening, however all disputes were resolved. Egger's test for a regression intercept gave a p-value of < 0.05, indicating possible publication bias (Supplement 2.6 Figure 8).

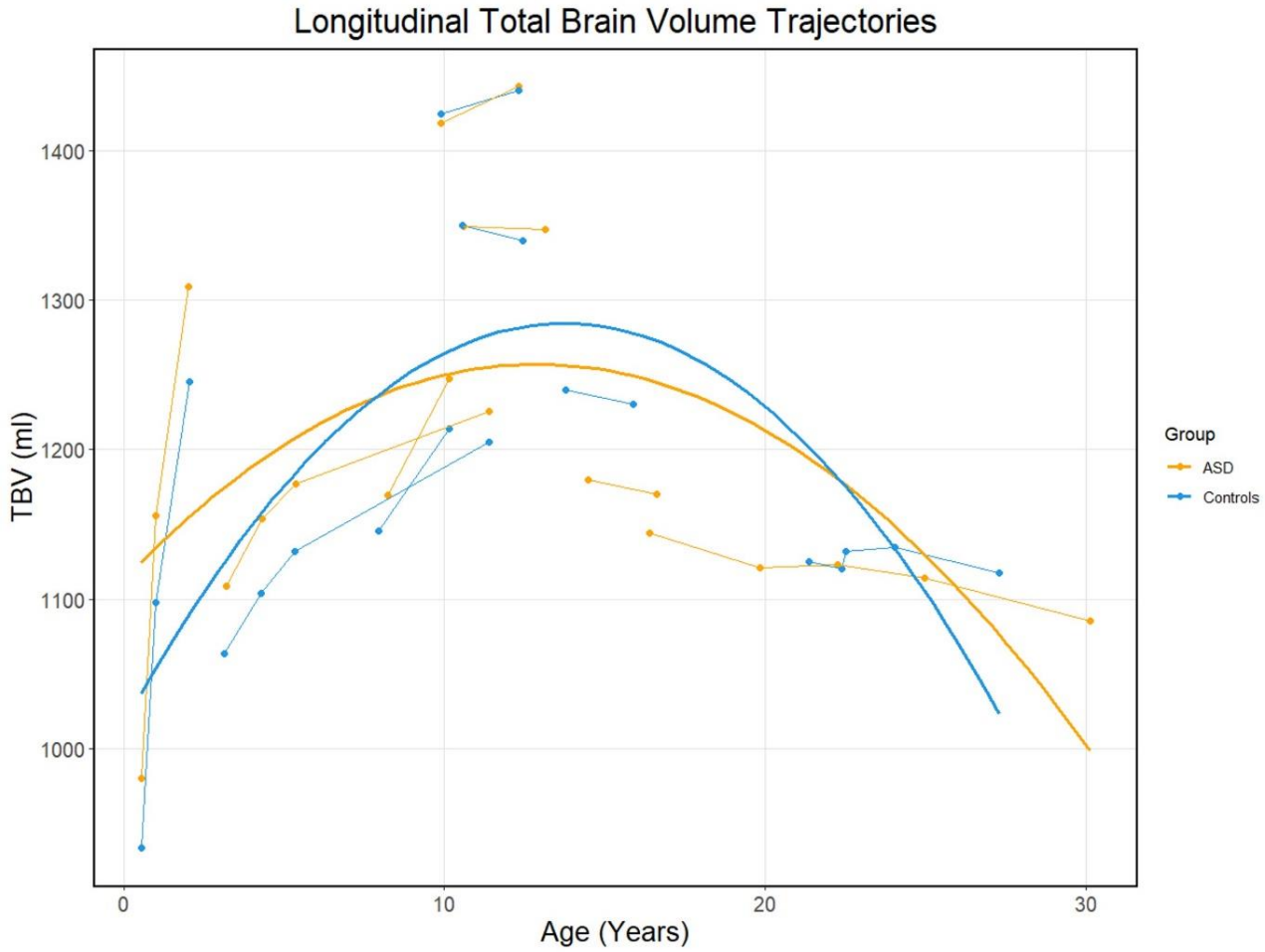


Figure 4. Visualization of longitudinal total brain volume (TBV) trajectories in individuals with autism spectrum disorder (ASD) in orange and controls in blue. The x-axis represents age in years, while the y-axis represents TBV in millilitres (ml). The scatterplot incorporates data from all seven studies identified in the meta-analysis, with each data point representing mean TBV per timepoint. Additionally, the timepoints from each study are connected to illustrate the overall trajectory. Owing to the non-linear fashion of brain development, two quadratic lines of best fit have also been drawn. The ASD group (orange) show initially larger brain volumes but fewer gains in growth compared to controls (blue).

Table 1. Study Characteristics and Descriptive Statistics (pooled ASD N = 559; controls = 3,635)

Author (Year)	ASD			Controls			ASD Diagnosis Tools (M score)	ASD IQ/Cognition (M Score)	Medication (%)
	Sample size	Age in years M (SD)	% Male	Sample size	Age in years M (SD)	% Male			
Li[133] (2023)	T1 = 29 T2 = 29 T3 = 29	T1 = 0.55 (0.05) T2 = 1.01 (0.03) T3 = 2.03 (0.06)	86%	T1 = 113 T2 = 113 T3 = 113	T1 = 0.55 (0.06) T2 = 1.01 (0.06) T3 = 2.04 (0.16)	67%	ADOS (NR)	NR	NR
Lee [104] (2021)	T1 = 286 T2 = 168 T3 = 120 T4 = 94	T1 = 3.21 (0.49) T2 = 4.30 (0.50) T3 = 5.35 (0.46) T4 = 11.38 (0.93)	T1 = 66.78% T2 = 69.64% T3% = 65% T4 = 78.72	T1 = 135 T2 = 97 T3 = 76 T4 = 66	T1 = 3.12 (0.55) T2 = 4.27 (0.54) T3 = 5.34 (0.57) T4 = 11.40 (0.72)	T1 = 54.81% T2 = 53.61% T3 = 55.26% T4 = 62.12%	ADI-R (NR) ADOS CSS (T1 = 7.50, T3 = 7.54, T4 = 7.8)	MSEL & DAS (T1 = 70.73, T2 = 74.13, T3 = 80.04, T4 = 81.80)	NR
Alemany[134] (2021)	T1 = 24 T2 = 34	T1 = 8.24 (1.14) T2 = 10.15 (0.73)	T1 = 83% T2 = 79%	T1 = 902 T2 = 3165	T1 = 7.94 (0.99) T2 = 10.14 (0.59)	T1 = 51.55% T2 = 49.42	Screening using SRS, CBCL, AND SCQ. Followed by review of medical records (NR)	SON (T1 = 97.57, T2 = 102.22)	NR
Langen[135] (2014)	T1 = 49 T2 = 49	T1 = 9.9 (-) T2 = 12.3 (-)	89%	T1 = 37 T2 = 37	T1* = 9.9 (-) T2* = 12.3 (-)	83.78%	ADI-R: Social deficits (18.34) Communication (14.55) Ritualistic/repetitive (4.83)	WASI/WISC IQ (107.47)	Neuropletic medication (21.6%)

Frazier[136] (2012)	T1 = 23 T2 = 19	T1 = 10.59 (1.00) T2 = 13.14 (1.50)	100%	T1 = 23 T2 = 19	T1 = 10.55 (1.5) T2 = 12.45 (1.75)	100%	ADI-R (51.35) ADOS = 15.52	FSIQ (94.61) VIQ (93.52) PIQ (96.48)	Psychotropic medications (39.13%)
Bieneck[13] [7] (2021)	T1 = 33 T2 = 33	T1 = 14.48 (2.51, 14.48) T2 = 16.61 (2.47)	81%	T1 = 37 T2 = 37	T1 = 13.76 (2.36) T2 = 15.89 (2.45)	81.08%	ADI-R Social Interaction (17.06) ADI-R Communication (13.06) ADI-R Repetitive Behaviors (4.76) ADOS CSS (T1 = 5.79, T2 = 5.95) RBS-R Total (T1 = 25.18, T2 = 22.48)	FSIQ (101.38)	NR
Prigge[130] (2021)	T1 = 105 T2 = 82 T3 = 70 T4 = 56 T5 = 36	T1 = 16. 40 (8.12) T2 = 19.84 (8.1) T3 = 22.25 (7.59) T4 = 24.94 (6.96) T5 = 30.01 (7.25)	100%	T1 = 125 T2 = 58 T3 = 41 T4 = 22 T5 = 12	T1 = 22.37 (8.66) T2 = 21.25 (8.95) T3 = 22.51 (8.59) T4 = 24.94 (6.49) T5 = 27.29 (6.36)	100%	ADOS-2 (NR)	FSIQ (103.7) NVIQ (104.8) VIQ (102.7)	Anti-depressants (45%), mood stabilizers (6%), anti-insomnia (5%), anticonvulsants (1%), multiple medications (30%)

Abbreviations: ADOS CSS = Autism Diagnostic Observation Schedule calibrated severity score; ADI-R = Autism Diagnostic Interview Revised; ASD=autism spectrum disorder; CBCL = Child Behavior Checklist; DAS = Differential Ability Scales; KBIT = Kaufman Brief Intelligence Test; MSEL = Mullen Scales of Early Learning; NR = not reported; RBS-R = Repetitive Behavior Scale Revised; SCQ = Social Communication Questionnaire; SRS = Social Responsiveness Scale; SON = Snijders-Oomen Nonverbal Intelligence Test; T =

timepoint (e.g., T1 = timepoint 1), WASI = Wechsler Abbreviated Scale of Intelligence; WISC = Wechsler Intelligence Scale for Children; FSIQ = Full scale IQ; NVIQ = Non-verbal IQ; VIQ =Verbal IQ.

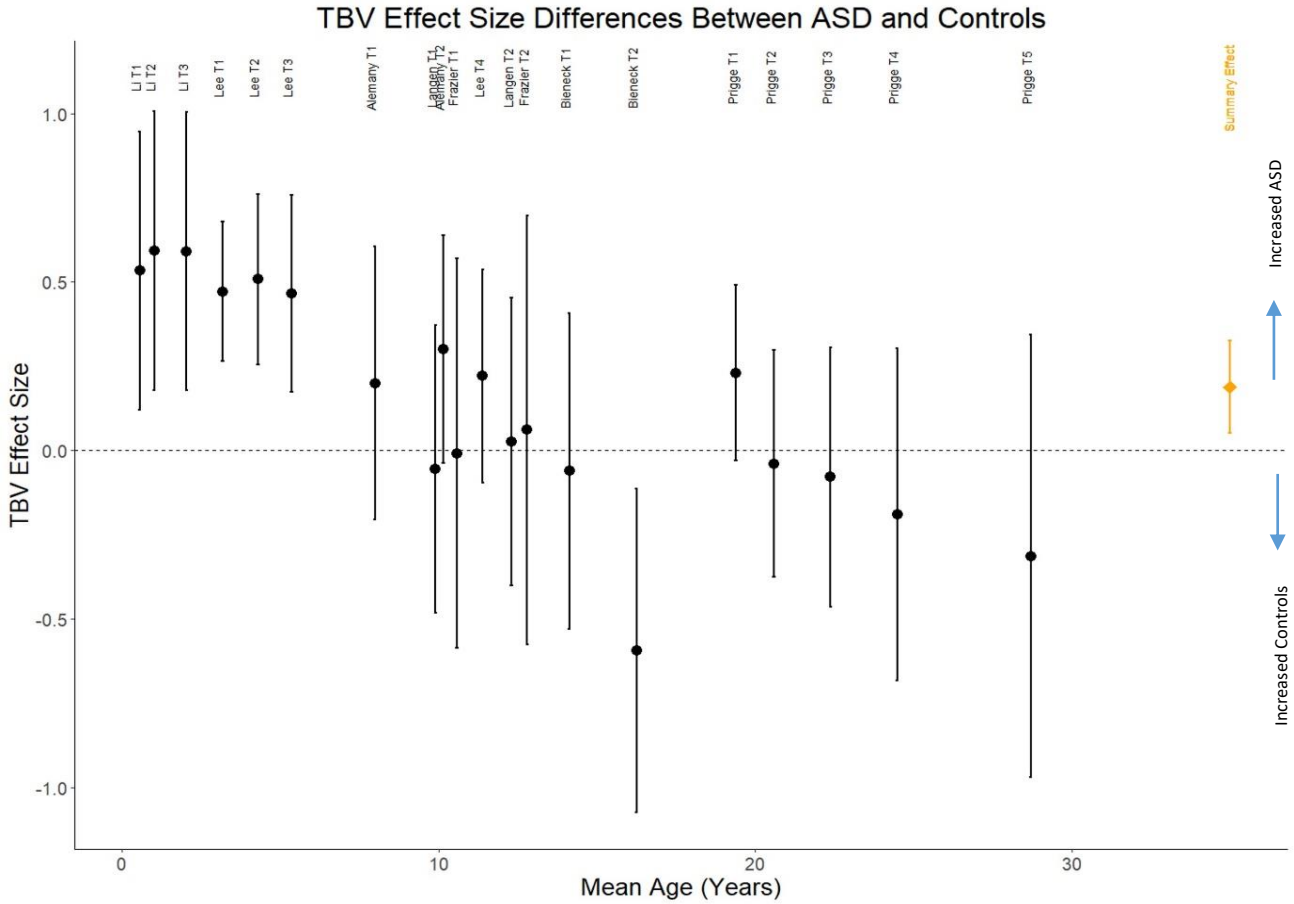


Figure 5. Forest plot of standardised mean differences (effect size) in total brain volume (TBV) between individuals with autism spectrum disorder (ASD) and controls. The x-axis represents mean age in years and the y-axis represents the magnitude of differences in TBV. Point estimates positioned above the line of null effect indicate that volume is increased in ASD compared to controls. Conversely, estimates below this line signify decreased volume in ASD. Study authors are listed systematically in order of mean age for each timepoint (T).

2.3.2 Differences in total brain volume in ASD vs Controls

We performed a cross-sectional meta-analysis to assess whether TBV across all ages differs between ASD and control groups. Overall, TBV was significantly larger in ASD compared to controls (Hedges' *g* = 0.19, 95% CI = 0.06 to 0.32, *p* < 0.01; Figure 5). Moderate heterogeneity was observed between studies (Q = 46.96, *df* = 19, I^2 = 59.54%, P < 0.001). Larger TBV in ASD was driven by two studies in early childhood (i.e., Li and Lee)[104,133] as jack-knife analyses were non-significant when these studies were excluded. Heterogeneity of variance was present between comparison groups for 2 studies; one in early childhood (i.e., Lee T1 and T2),[104] and another in adulthood (i.e., Prigge T1, T2, T3)[130]; removal of these timepoints resulted in a trend for larger TBV in ASD (Hedges' *g* = 0.16, 95% CI = -0.01 to 0.32, *p* = 0.068).

Meta-regressions revealed a significant relationship between TBV effect size and age (F(2, 18) = 35.38, b = -0.03, *p* <.001; Figure 6A), as younger age was associated with positive effect sizes (larger TBV in ASD), whereas adulthood was associated with negative effect sizes (smaller TBV in ASD). Lower IQ was associated with larger TBV in ASD relative to controls (F(2, 15) = 22.22, *b = -0.01, p* < .001; Figure 6B) and studies with a higher percentage of female participants were associated with larger TBV in ASD relative to controls (F(2, 18) = 10.62, *b = -0.01, p* = .01; Figure 6C). The correlation with larger TBV in ASD appears to be driven by females with low IQ. However, regressions with IQ (p = 0.76) and gender (p = 0.27) were no longer significant following the removal of Lee et al from analyses.[104]

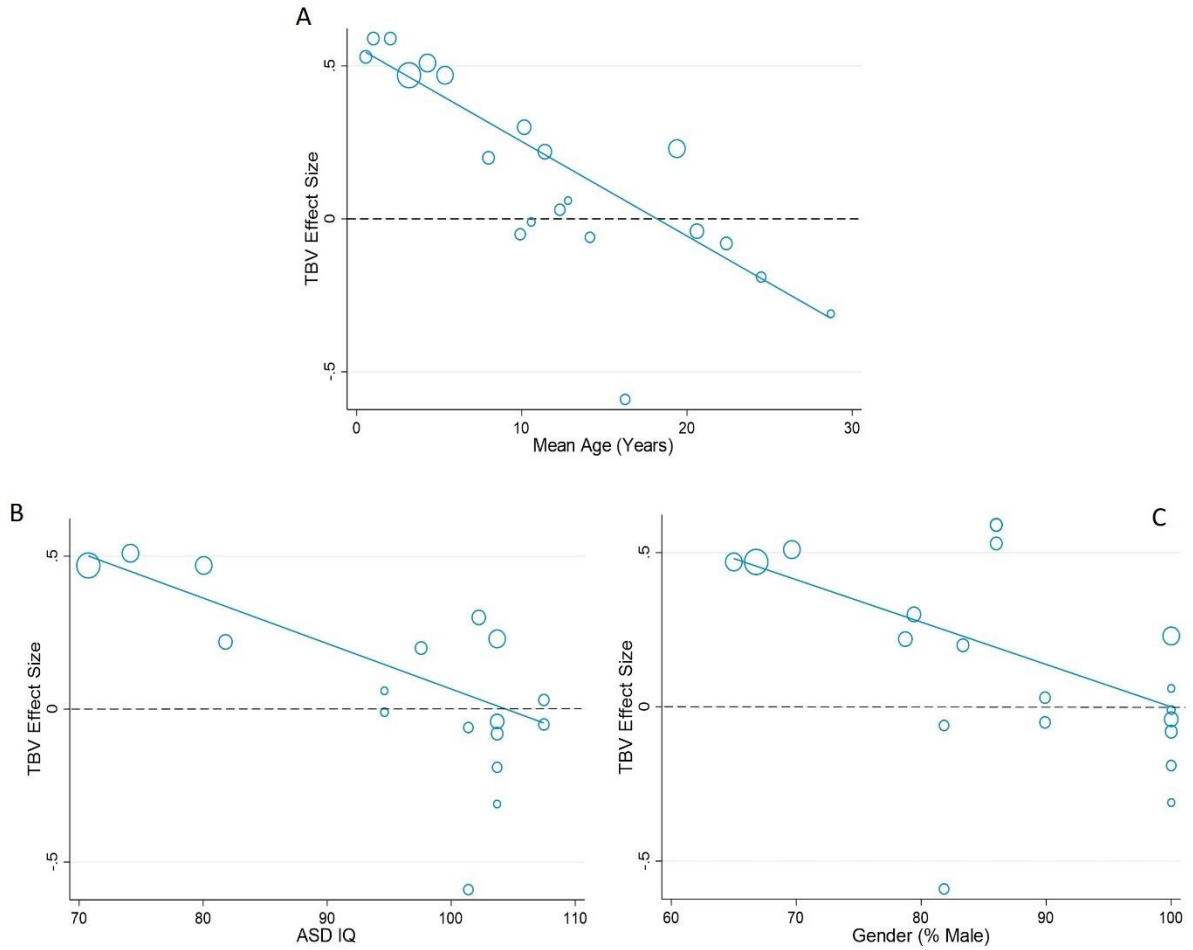


Figure 6. Meta-regressions examining the relationship between total brain volume (TBV) effect size and three demographic variables: age (plot A), IQ (plot B), and gender (plot C). Effect sizes were derived from calculating the standardised mean difference (SMD) for TBV between individuals with autism spectrum disorder (ASD) and controls at each study timepoint. Data above the dashed line indicate larger TBV in ASD compared to controls. As shown in all three plots, the blue line of best fit illustrates a negative relationship between TBV effect size and all demographic variables. The correlation with larger TBV in ASD appears to be driven by females with low IQ.

2.3.3 Changes in total brain volume over time

Longitudinally, TBV change over time was reduced in ASD compared to controls (g = -0.10, 95% CI = -0.18 to -0.01, p = 0.03; Figure 7). For sensitivity analyses, when rho was adjusted to 0.99 (g = -0.07, 95% CI = -0.15 to 0.00, p = 0.04) this result remained significant, but not at rho = 0.5 (g = -0.10, 95% CI = -0.23 to 0.03, p = 0.12). In jack-knife analyses, the results from the main analysis (rho = 0.8) were no longer significant following individual removal of two studies.[104,130] Meta-regressions found no association between change in TBV effect size and age ($F(2, 11) = 2.55$, p = 0.78), IQ ($F(2, 9) = 2.68$, p = 0.57), or gender ($F(2, 11) = 2.51$, p = 0.98).

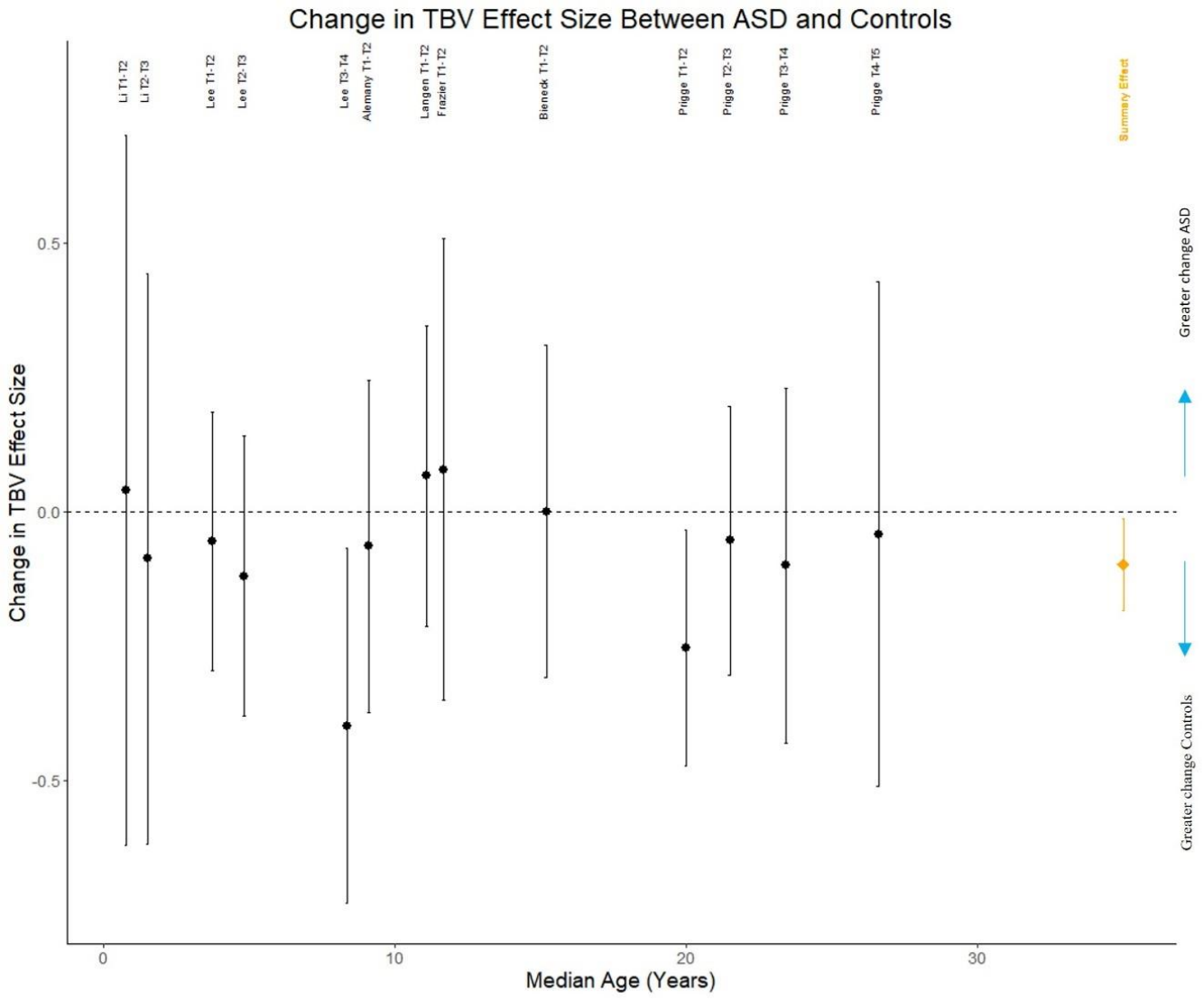


Figure 7. Forest plot of standardised mean differences (effect size) for change in total brain volume (TBV) over time in individuals with autism spectrum disorder (ASD) and controls (y axis) and median age between study timepoints (x axis). Point estimates below the line of null effect indicate greater change in TBV in controls. Study authors are listed in ascending order of median age between timepoints (T).

2.4 Discussion

This is the first meta-analysis of longitudinal brain growth in ASD. The results show that TBV is enlarged in ASD relative to controls, and meta-regressions with age show that this is not a static phenotype, as larger TBV in ASD is present in the first 10 years of life, in contrast to smaller or equal TBV during adulthood. These findings support previous cross-sectional meta-analyses indicating that brain overgrowth is largely restricted to early childhood.[95,96] Contrary to our hypothesis, accelerated rates of growth were not detected in this meta-

analysis, therefore rapid growth preceding enlarged TBV in childhood is likely to occur prior to the ages recorded in this meta-analysis i.e., 6 months. Further longitudinal studies measuring TBV with ultrasounds and MRI scans in utero and the first few months of life are needed to confirm this.

Case-control differences in TBV diminish over time,[95,96] and our longitudinal meta-analysis shows that this is due to a reduced rate of TBV change in ASD compared to controls. It is unclear whether the reduced rate of TBV change reflects arrested development or accelerated aging in ASD. However, due to the paucity of longitudinal MRI data in adulthood, caution is needed when interpreting findings beyond adolescence. As brain development is still ongoing during early adulthood, further work is needed to confirm whether TBV normalises with age in ASD or whether reductions persist, indicative of accelerated aging. The latter hypothesis is supported by a study of TBV changes from 1 to 50 years in ASD and controls which reports slowing or arrested growth during childhood, followed by accelerated volume reductions in adolescence through to middle age in ASD.[93]

Diverging trajectories of brain development may also be linked to functional outcomes, for example, one study reports that neuroanatomical deviation from control subjects in the left cerebral hemisphere was positively correlated with impairments in the social and communication domains of the ADI-R.[138] Furthermore, another study reports an association between higher self-reported autistic traits and an accelerated pace of physiological aging as well as increased vulnerability for poor physical and mental health outcomes.[139,140]

Previous work suggests that a sudden increase in head circumference, a strong predictor of brain size during childhood,[141] may begin as early as 2 months of age in infants later diagnosed with ASD.[142] Although our findings and previous work indicate larger TBV and head circumference in early ASD, studies also report increased variability in head circumference in ASD. In the first 3 months of life, those with ASD show disproportionate frequencies of extreme head circumference (both higher and lower than average) in comparison to neurotypical controls.[143] This may represent different pathophysiological mechanisms, for example, higher rates of megalencephaly are seen with developmental regression in ASD, [99] characterised by seemingly typical cognitive and social development which is then followed by a loss of language, diminished social interest, and essential

adaptive skills.[144] A better understanding of these trajectories, and whether they correspond to differences in functional outcomes is needed.

Extreme head circumference values during the first 3 months of life are seen in both males and females, however values tended to be more extreme in males, and divergence from the norm occurred at different times depending on sex.[143] For TBV, reports of sex differences in overgrowth during early infancy are mixed,[98–101] and often ASD studies do not have sufficient longitudinal data in females.[93] In the present meta-analysis, our findings on gender differences were inconclusive owing to the small proportion of females across studies (<40%). Whilst we reported some evidence that studies with a higher percentage of females were associated with larger TBV in ASD, this result appears to be an artefact from combining genders in the study by Lee et al. The authors examined sex differences separately and observed increased TBV in males across all timepoints, whereas there were no significant differences between females with and without ASD. Therefore, further studies are needed to confirm this finding and delineate neurodevelopmental trajectories in ASD females.

IQ of ASD participants was significantly associated with TBV, suggesting two distinct neurophenotypes; one group with enlarged TBV and below average IQ, and another with average IQ but normal-to-reduced TBV. This is consistent with previous ASD literature,[96] and contrasts to the positive correlation seen in neurotypical populations.[106–108] Volume reductions after initial enlargement may offer some sort of compensatory or even protective function over cognitive abilities, however the change in TBV over time was not associated with IQ in our analyses. Nearly all imaging studies in ASD focus exclusively on individuals with higher levels of functioning. This meta-analysis is no exception as only one study included those with below average IQ,[104] reporting that TBV was consistently increased in males with ASD and low IQ from age 3-12 years. More studies are needed to assess whether this trajectory persists into adulthood, or shows signs of convergence/decline as based on the findings from this meta-analysis.

Strengths of this meta-analysis include the use of longitudinal data to assess brain growth trajectories in a large ASD sample (*n* = 559). While prior meta-analyses have addressed cross-sectional neuroimaging findings in ASD,[95,96] this meta-analysis focuses specifically on longitudinally studies and provides a novel contribution to our understanding of brain development in ASD. Longitudinal studies are often considered as more powerful than their

cross-sectional counterparts and more accurately capture developmental trajectories. Uncertainty remains for brain growth in adulthood due to the paucity of data and potential confounding (e.g., from psychotropic medication use). The current meta-analysis was limited to examining changes in TBV up until the mean age of 30. In normal aging, TBV typically declines after the age of ~35 years,[21,132,145] with annual reductions of 0.2% in WBV after the age of 35, and 0.5% reductions by age 60.[132] Additional prospective studies of older ASD populations (>35 years) are needed to determine brain changes across the lifespan, and whether these link to functional outcomes.

Another limitation is the accuracy of age-related findings, as one study did not match ASD and controls for age, [130] as initial timepoints were acquired earlier in ASD participants, whereas ASD participants were older than controls at timepoints 4 to 5. However, cross-sectional results were unchanged when this study was excluded through jack-knife analysis. Differences in ASD diagnostic criteria among studies could confound our findings, as could the sampling bias of included studies which predominately exclude individuals with below average IQ. Another limitation is participant attrition, which could be overcome by future studies harmonizing MRI data from multiple sites to enable within-subject examination of neurodevelopmental trajectories.[146] There are also inconsistencies in the study that used TIV instead of TBV presented in the Supplement, as there was evidence of brain volume increases in participants over 50 years of age [131], which is inconsistent with the general finding of annual brain volume reductions during this age period.[132]

This meta-analysis identified only 7 studies which highlights the challenges of performing high-quality longitudinal studies of neurodevelopmental disorders. Despite the challenges posed, more longitudinal neuroimaging studies which encompass the full ASD spectrum are needed, particularly studies which recruit individuals with ASD and comorbid IQ difficulties.

2.5 Conclusion

Our findings indicate enlarged TBV in early life in ASD, followed by convergence with controls in late childhood, and possible reductions TBV in adulthood. Volume changes over time were reduced in ASD relative to controls, suggestive of slowed or arrested growth. Future MRI studies examining greater age ranges will help clarify trajectories of brain development over the life course in ASD, and whether ASD is associated with accelerated brain aging after 30 years of age. The analysis of divergent growth trajectories may enable early identification

and early implementation of clinical interventions. Based on our meta-analysis, these differences should be detectable as early as 6 months old or possibly earlier.

2.6 Supplement

2.6.1 Additional Analyses

2.6.2 Differences in TBV in ASD vs Controls

Data from Pagni[131] was excluded in the main analyses due to intracranial volume increases between T1 and T2 in participants over 50 years old for means of brain volumes, which is inconsistent with previous literature in this age group[147]. When including this study, brain volume remained increased in ASD compared to controls (Hedges' g = 0.24, 95% CI = 0.097 - 0.39, p = 0.001). Meta-regressions for age ($F(2, 20) = 9.87$, p = 0.027), sex($F(2, 20) = 13.13$, p = 0.006), and IQ ($F(2, 17) = 22.34$, p <.001) were also significant.

2.6.3 Changes in TBV over time

The effect size for longitudinal change remained significant after the inclusion of Pagni, with reduced change in ASD relative to controls (g = -0.09, 95% CI = -0.17 to -0.01, p = 0.04). Meta-regressions of age, gender, and IQ were all non-significant (p > 0.4).

2.6.4 Funnel Plot

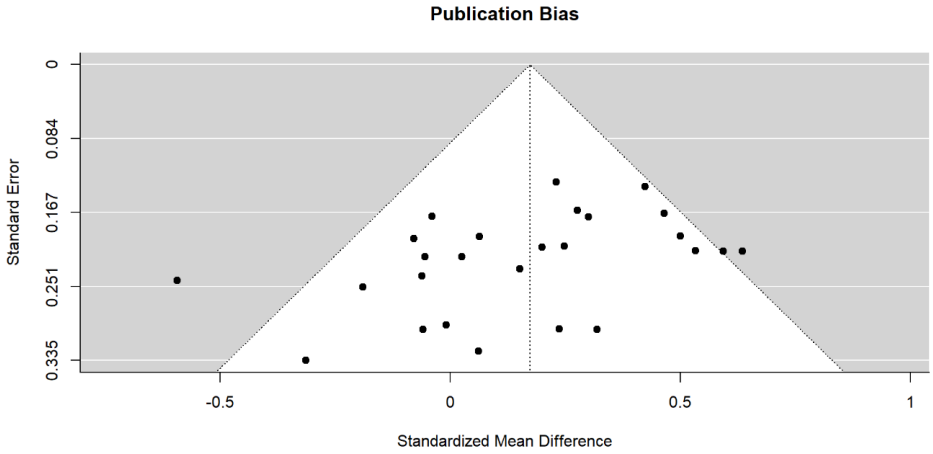


Figure 8. Funnel plot displaying standardized mean difference on the x axis and standard error on the y axis for all study timepoints (including Pagni 2022).

2.6.5 Study Characteristics – Effect Sizes and Raw Total Brain Volume Values

Table 2. Mean and SD for brain volume values (millimetres) at each timepoint. For some studies[130,131,133,134,148], authors were contacted to request mean and SD values.

Author (Year)	Volume Definition	Brain Volume Mean (SD)									
		T1		T2		T3		T4		T5	
		ASD	Controls	ASD	Controls	ASD	Controls	ASD	Controls	ASD	Controls
Li[133] (2023)	Total Brain Volume	979.79 (89.77)	933.32 (85.90)	1155.46 (103.98)	1097.96 (94.49)	1308.64 (114.79)	1245.51 (102.94)				
Lee[148] (2021)	Total Cerebral Volume (excluding brainstem and cerebellum)	1108.51 (100.95)	1063.69 (80.29)	1153.48 (105.56)	1103.87 (81.28)	1176.79 (103.69)	1131.62 (84.21)	1225.23 (94.98)	1204.76 (88.42)		
Alemany[134] (2021)	Total Brain Volume (including cerebellum, excluding brainstem)	1169.35 (152.39)	1145.25 (119.62)	1247.26 (108.27)	1214.13 (110.35)						
Langen[149] (2014)	Total Brain Volume	1418.65 (106.89)	1424.36 (98.90)	1442.97 (114.00)	1440.23 (96.93)						
Frazier[150] (2012)	Total Brain Volume (cerebrum, cerebellum, brainstem; excluding cerebrospinal fluid)	1349 (119.00)	1350 (103.00)	1347 (126.00)	1340 (97.00)						
Bieneck[137] (2021)	Total Brain Volume	1180 (1000.00)	1240 (940.00)	1170 (100.00)	1230 (100.00)						
Prigge[130] (2021)	Whole Brain Volume	1143.90 (116.70)	1120.25 (89.13)	1120.83 (125.22)	1125.30 (92.18)	1123.23 (124.84)	1132.01 (80.18)	1114.27 (113.15)	1134.34 (78.14)	1085.43 (105.26)	1117.74 (88.16)
Pagni[131] (2022)	Total Intracranial Volume	1222.88 (129.56)	1192.24 (124.22)	1236.83 (139.19)	1193.22 (129.35)						

Table 3. Cross-sectional effect size differences in total brain volume (TBV) between autism and controls per timepoint. Confidence intervals (95%) are also displayed.

Cross-sectional differences in TBV				
Author	Timepoint	Effect size	+95%	-95%
Li	1	0.53	0.94	0.12
Li	2	0.59	1.01	0.18
Li	3	0.59	1.01	0.18
Lee	1	0.47	0.68	0.26
Lee	2	0.51	0.76	0.25
Lee	3	0.47	0.76	0.17
Alemany	1	0.20	0.61	-0.21
Langen	1	-0.05	0.37	-0.48
Alemany	2	0.30	0.64	-0.04
Frazier	1	-0.01	0.57	-0.59
Lee	4	0.22	0.54	-0.10
Langen	2	0.03	0.45	-0.40
Frazier	2	0.06	0.70	-0.58
Bieneck	1	-0.06	0.41	-0.53
Bieneck	2	-0.59	-0.11	-1.07
Prigge	1	0.23	0.49	-0.03
Prigge	2	-0.04	0.30	-0.38
Prigge	3	-0.08	0.31	-0.46
Prigge	4	-0.19	0.30	-0.68
Prigge	5	-0.31	0.34	-0.97

Table 4. Effect sizes of changes in total brain volume (TBV) over time between autism and controls e.g., volume difference between timepoint 1-2, 2-3 etc.

Changes over time (longitudinal) in TBV				
Author	Timepoint	Effect size	+95%	-95%
Li	1-2	0.04	0.70	-0.62
Li	2-3	-0.09	0.45	-0.62
Lee	1-2	-0.05	0.19	-0.30
Lee	2-3	-0.12	0.14	-0.38
Lee	3-4	-0.40	-0.07	-0.73
Alemany	1-2	-0.06	0.25	-0.38
Langen	1-2	0.07	0.35	-0.22
Frazier	1-2	0.08	0.51	-0.35
Bieneck	1-2	0.00	0.31	-0.31
Prigge	1-2	-0.25	-0.03	-0.47
Prigge	2-3	-0.05	0.20	-0.30
Prigge	3-4	-0.10	0.23	-0.43
Prigge	4-5	-0.04	0.42	-0.51

2.6.2 PRISMA Flow Diagram

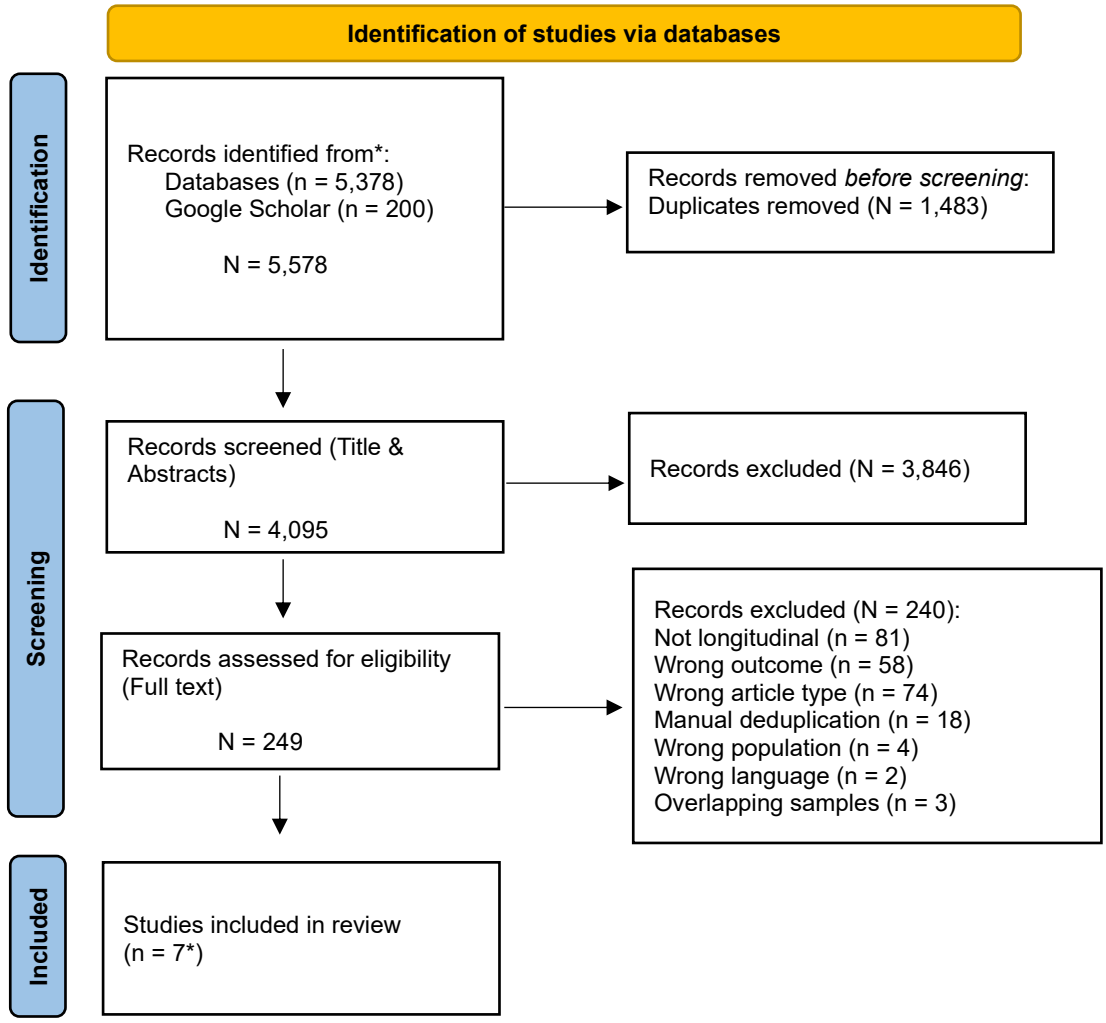


*Figure 9. Prisma Flow Diagram. The automated removal of duplicates in Covidence resulted in 4,002 studies for screening. *Following abstract and full-text screening, a total of seven studies were included in the meta-analyses, 8 including Pagni.*

2.6.3 Search Strategy

All databases were searched through 30th of June 2023

Pubmed

((((("autism spectrum disorder"[MeSH Terms] OR "autistic disorder"[MeSH Terms] OR "autis*"[Title/Abstract] OR asperger*[Title/Abstract] OR pervasive developmental disorder[Title/Abstract]) AND ("longitudinal studies"[MeSH Terms] OR "prospective studies"[MeSH Terms] OR "follow-up studies"[MeSH Terms] OR “cohort studies”[MeSH Terms] OR "longitudinal*"[Title/Abstract] OR prospective[Title/Abstract] OR follow*[Title/Abstract] OR cohort[Title/Abstract] OR trajector*[Title/Abstract] OR progressive[Title/Abstract])) AND ("magnetic resonance imaging"[MeSH Terms] OR "organ size"[MeSH Terms] OR "brain"[MeSH Terms] OR “structural magnetic resonance imaging”[Title/Abstract] OR "structural mri"[Title/Abstract] OR smri[Title/Abstract] OR “structural neuroimaging”[Title/Abstract] OR "volume"[Title/Abstract] OR "volumetric"[Title/Abstract] OR “brain size”[Title/Abstract] OR “brain development”[Title/Abstract]

OR "brain growth"[Title/Abstract] OR "early brain overgrowth"[Title/Abstract] OR "early brain enlargement"[Title/Abstract] OR "macrocephaly"[Title/Abstract] OR megalencephaly[Title/Abstract] OR "grey matter"[Title/Abstract] OR "gray matter"[Title/Abstract] OR "white matter"[Title/Abstract] OR "total brain volume"[All Fields] OR "whole brain volume"[All Fields] OR "total cerebral volume"[All Fields] OR "total cortical volume"[All Fields] OR "total tissue volume"[All Fields])) NOT ("animals"[MeSH Terms] NOT ("humans"[MeSH Terms] AND "animals"[MeSH Terms])) NOT ("electroencephalography"[MeSH Terms] OR "transcranial magnetic stimulation"[MeSH Terms] OR "spectroscopy, near infrared"[MeSH Terms])) AND ("english"[Language])

Web of Science

((autis* OR asperger* OR “pervasive developmental disorder”) AND (longitudinal* OR prospective OR follow* OR cohort OR trajector* OR progressive) AND (“structural magnetic resonance imaging” OR “structural mri” OR smri OR “structural neuroimaging” OR brain NEAR/10 (volume OR volumetric) OR "brain development" OR “brain size” OR "brain growth" OR "early brain overgrowth" OR "early brain enlargement" OR macrocephaly OR megalencephaly OR “grey matter” OR “gray matter” OR “white matter” OR "total brain volume" OR "whole brain volume" OR "total cerebral volume" OR "total cortical volume" OR "total tissue volume") NOT (electroencephalography OR "transcranial magnetic stimulation" OR “near infrared spectroscopy”))

Note: Structure search by Topic (i.e. searches title, abstract, author keywords, and keywords plus).

APA PsycInfo

1 exp autism spectrum disorders/

2 autis*.mp.

3 asperger*.mp.

4 pervasive developmental disorder.mp.

5 1 or 2 or 3 or 4

6 exp longitudinal studies/

7 exp Prospective Studies/

8 exp Cohort Analysis/

9 longitudinal.mp.

10 prospective.mp.

11 cohort.mp.

12 followup studies/

13 follow*.mp.

14 progressive.mp.

15 trajectory.mp.

16 or/6-15

17 structural magnetic resonance imaging.mp.

18 structural mri.mp.

19 smri.mp.

20 structural neuroimaging.mp.

21 brain development/

22 brain size/

23 (brain adj10 (volume or volumetric)).mp.

24 brain development.mp.

25 brain growth.mp.

26 early brain overgrowth.mp.

27 early brain enlargement.mp.

28 macrocephaly.mp.

29 megalencepaly.mp

30 white matter/

31 gray matter/

32 grey matter.mp.

33 whole brain volume.mp.

34 total cerebral volume.mp.

35 total tissue volume.mp.

36 total cortical volume.mp.

37 or/17-36

38 5 and 16 and 37

Embase Classic + Embase

1	exp autism/	83867
2	autis*.mp.	91469
3	asperger*.mp.	5835
4	pervasive developmental disorder.mp.	2642
5	exp longitudinal studies/	172199
6	exp prospective studies/	763353
7	exp cohort analysis/	832702
8	longitudinal.mp.	448057
9	prospective.mp.	1236830
10	cohort.mp.	1347050
11	follow up/	1869588
12	follow*.mp.	6215996

13 progressive.mp. 491354

14 trajectory.mp. 65159

15 structural magnetic resonance imaging.mp. 3630

16 structural mri.mp. 7159

17 exp brain development/ 50880

18 brain size/ 35299

19 brain development.mp. 58036

20 brain growth.mp. 3904

21 early brain overgrowth.mp. 36

22 early brain enlargement.mp. 4

23 macrocephaly.mp. 5898

24 megalencepaly.mp. 1

25 white matter/ 75904

26 gray matter/ 44134

27 grey matter.mp. 15710

28 whole brain volume.mp. 987

29 total cerebral volume.mp. 139

30 total tissue volume.mp. 201

31 total cortical volume.mp. 61

32 macrocephaly/ 4962

33 smri.mp. 805

34 structural neuroimaging.mp. 1637

35 or/1-4 97086

36 or/5-14 8182300

37 or/15-34 195340

38 35 and 36 and 37 1644

39 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.) 7610858

40 38 not 39 1478

Google Scholar

(autism OR autistic OR asperger OR “pervasive developmental disorder”) AND (longitudinal OR prospective OR follow-up OR cohort OR trajectory OR progressive) AND ("brain development" OR “brain size” OR "brain growth" OR "early brain overgrowth" OR "early brain enlargement" OR macrocephaly OR megalencephaly OR "total brain volume" OR "whole brain volume" OR "total cerebral volume" OR "total cortical volume" OR "total tissue volume")

Note: Sorted by relevance

2.6.4 Risk of Bias

Risk of bias scores were calculated for each study, questions were adapted from the Joanna Briggs Cohort Studies Risk of Bias tool. Each study was evaluated on ten questions, with the maximum score available of 10 (i.e., low risk of bias). See Table 5 for risk of bias summaries.

* Pagni 2022: cross-sectional data at baseline was available for >50 ASD cases, however for the purposes of this meta-analysis, we used the longitudinal sample from Pagni 2022 consisting of 23 participants at baseline and follow-up.

Table 5. Risk of Bias summaries for all studies.

Risk of Bias (Total out of 10)	Frazier 2012 (9 = low risk)	Langen 2014 (7 = low risk)	Li 2023 (4.5 = moderate risk)	Lee 2020 (7 = low risk)	Prigge 2021 (7 = low risk)	Alemany 2021 (4.5 = moderate risk)	Bieneck 2021 (8 = low risk)	Pagni 2022 (7.5 = moderate)
ASD baseline sample size ≥ 50								*
Were case-controls age matched								
Clear, detailed inclusion/exclusion criteria provided								
Was autism diagnosis measured in a valid and reliable way?								
Were confounding factors identified and adjusted for?								
Was follow-up complete, and if not, were the reasons to loss to follow-up described and explored?								
Were strategies to address incomplete follow-up utilized?		N/A	N/A	N/A			N/A	
Blinded or third-party raters at analysis stage								
Detailed reporting of neuroimaging acquisition i.e. device, sequence, type of space e.g. mni, slice thickness, pre-processing software								
Reporting of statistical thresholds and correction for multiple comparisons								

Key: Yes (1 point) Partial (.5 point) No (0 points) N/A (1 point)

Chapter 3: A prospective study of head circumference trajectories in autism

In Chapter 3, I use the ALSPAC dataset to explore head circumference trajectories in individuals (a) with and without ASD, and (b) with and without elevated autistic traits.

This study features as a manuscript published in the Journal of Autism and Developmental Disorders. See details below:

Title: A Longitudinal Study of Head Circumference Trajectories in Autism and Autistic Traits

DOI: https://doi.org/10.1007/s10803-024-06578-x

Publication date: 12th October 2024

Authors:

Sarah A. Ashley, MSc[1], Kate Merritt, PhD[1], Francesca Solmi, PhD[1], Pedro L. Laguna, PhD[2], Abraham Reichenberg, PhD[3], Anthony S. David, MD[1]

[1] Division of Psychiatry, University College London, UK

[2] CUBRIC, Cardiff University, UK

[3] Institute of Psychiatry, Psychology and Neuroscience, Kings College London, UK

[4] Department of Psychiatry, Department of Environmental Medicine and Public Health, MINDICH Child and Health and Development Institute, and Seaver Center for Autism Research and Treatment, Icahn School of Medicine at Mount Sinai, USA

3.1 Introduction

Head circumference strongly correlates with brain volume during childhood and remains a strong correlate of brain size during adolescence. [151,152] Large head circumference in children with ASD was first reported by Kanner in 1943,[153] and has been subsequently replicated in several systematic reviews and meta-analyses.[95,96,154] Importantly, this neurobiological abnormality can be detected early in life, before clinical signs and symptoms manifest.[142] Differences in HC between ASD and controls is largest in early childhood (10%) and reduces with age (1-2% greater in ASD in adolescence and adulthood).[95] However, it remains

unknown when altered head circumference in ASD begins; whether it is time-limited, and whether it reflects an ASD-specific process of brain pathology.

Some studies have detected increased head circumference in the first month of life,[155] while others report that any increases occur from 6 months or onwards.[88,142,156] Alternatively, some studies report no difference throughout early life.[157,158] Similarly, research examining whether head circumference overgrowth persists to adolescence shows mixed results.[92,93,104,159–161]

It is also unclear whether abnormal head circumference represents a brain-specific process, or a more generalized overgrowth.[162,163] In infancy (<2 years), one review reports that both head circumference and height are enlarged in infants with ASD compared to controls.[154] Studies across broader age ranges also report that height is a strong predictor of head circumference in ASD and should be included as a covariate.[96,163–165] In contrast, some studies suggest that head circumference is enlarged relative to height,[166,167] with one study spanning a large age range (3-47 years) citing no effect of age, sex or non-verbal IQ on HC in ASD.[166]

Previous studies have had several limitations: first, the majority are based on clinical ASD samples, which may not be representative of individuals in the general population; and obtained head circumference data retrospectively. Second, most studies are limited to investigating head circumference cross-sectionally or across limited timepoints. Third, studies did not consider potentially important confounding factors, which may lead to bias in estimating associations.

To address these limitations, we used general population data from the Avon Longitudinal Study of Parents and Children (ALSPAC) to investigate differences in head circumference trajectories from birth through to 15 years in children with ASD and controls, adjusting for important confounders. These analyses were repeated in children with elevated autistic traits to investigate whether differences in head circumference are observed across the full ASD spectrum.

3.2 Methods

3.2.1 Sample

ALSPAC recruited pregnant women resident in Avon, UK, with estimated delivery dates between 1st April 1991 and 31st December 1992.[168,169] The initial number of pregnancies enrolled was 14,541, with 14,062 live births and 13,988 children alive at 1 year of age. Additional families were recruited during a second period of enrolment when children were age 7 years and onwards, generating a total cohort size of 15,645 children.[170] As recommended for non-singleton births,[171] we excluded one individual from each set of twins to limit potential from biases arising from shared genetic and environmental effects.

This study included children who had at least one head circumference measurement, as well as complete data on diagnosis (ASD or autistic traits) and confounding variables.

Please note that the study website contains details of all the data available through a fully searchable data dictionary and variable search tool: http://www.bristol.ac.uk/alspac/researchers/our-data/. Ethical approval was granted by the ALSPAC Ethics and Law Committee (ALEC) and the Local Research Ethics Committees. Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALEC.

3.2.2 Outcome

The primary outcome measure was head circumference trajectories in individuals with autism, elevated autistic traits, and controls, and to investigate whether diagnosis status explains or predict changes in head circumference. Head circumference measurements were recorded for the whole ALSPAC cohort at birth to 1 year; age 7 and 15 years. The ALSPAC Children in Focus cohort recorded additional head circumference measures between ages 4 and 61 months in 10% of the-sample. Analyses only included timepoints in which head circumference measurements were available for at least 10 participants per group (ASD/autistic traits/controls). From an initial 100 timepoints, 19 met the criterion of 10 or more participants. This criterion was used in all analyses except for those involving ASD and CLN due to small sample sizes. From birth to age 12 months, head circumference and height data were available at the following age in months for individuals with ASD: birth, 1, 2, 3, 4, 8, 9, 12. All months were available from birth to 12 months in the autistic trait analyses. Head circumference data were collected by researchers and were supplemented by routine

measurements by nationally mandated local health services. If multiple head circumference measures were available for a specific month, the average head circumference value was calculated. Values were excluded if measurements differed by more than 3cm within a month. Outliers were identified using cut-offs from the WHO Child Growth Standards i.e., ± 5 SD from the mean for head circumference and ± 6 SD for height at each given age/timepoint, and ± 5 SD for weight at birth.[172,173]

3.2.3 Diagnosis status

3.2.3.1 ASD diagnosis

Participants with ASD were identified through parent-reports of whether their child had ever received a diagnosis of ASD, when the child was 9 years-old. Those who replied 'no' were classed as controls. This measure has strong sensitivity (95%) and specificity (99%) in identifying clinical ASD.[174,175]

Our main analyses used the case control definition above (ASD vs controls). However, we also investigated the influence of ASD comorbid for cognitive learning needs (CLN), defined as individuals with moderate, severe and profound learning difficulties, as well specific difficulties such as dyslexia or dyspraxia. The cognitive learning needs (CLN) variable is a measure of significant cognitive/learning impairment as noticed by the school. It is specific to cognition and learning educational needs and does not include other areas of SEN such as behaviour, emotional and social development needs / communication and interaction needs / sensory or physical needs which are classified as separate non-overlapping variables by ALSPAC. Records were retrieved from the National Pupil Leave Annual School Census for 2003/4. [176] In accordance with ALSPAC confidentiality guidelines, these data are aggregated across all cognitive levels. [177] Of the analytic sample (n = 6,482), 76.4% of participants (n = 4,952) also had data available on CLN. Those without CLN data either did not attend a state school in England, could not be matched (e.g., changes in personal information), or there were legal restrictions which prevented linkage.[178]

3.2.3.2 Autistic traits

Autistic traits were reported by parents using the Social and Communication Disorders Checklist (SCDC) when their child was approximately 7.5 years of age.[179] The SCDC is a 12-item questionnaire which measures social reciprocity and social communication difficulties. Scores range from 0-24, with 24 representing the highest level of impairment. In line with previous research, to derive a binary outcome measure, children scoring 8 or more were defined as having elevated autistic traits. The SCDC has excellent internal consistency (α = 0.93) and high test-retest reliability (*r* = 8.1, mean interval 2.7 years), as well as strong sensitivity and good specificity for ASD.[180]

	Not true	Quite or sometimes true	Very or often true
1. Not aware of other people's feelings	☐	☐	☐
2. Does not realise when others are upset or angry	☐	☐	☐
3. Does not notice the effect of his/her behaviour on other members of the family	☐	☐	☐
4. Behaviour often disrupts family life	☐	☐	☐
5. Very demanding of other people's time	☐	☐	☐
6. Difficult to reason with when upset	☐	☐	☐
7. Does not seem to understand social skills, e.g. persistently interrupts conversations	☐	☐	☐
8. Does not pick up on body language	☐	☐	☐
9. Does not appear to understand how to behave when out (e.g. in shops, or other people's homes)	☐	☐	☐
10. Does not realise if s/he offends people with her/his behaviour	☐	☐	☐
11. Does not respond when told to do something	☐	☐	☐
12. Cannot follow a command unless it is carefully worded	☐	☐	☐

Figure 10. List of items on the Social and Communication Disorders Checklist (SCDC)[179]

3.2.4 Confounders

We selected confounders based on previous literature which show associations with both head circumference and ASD.[164,181,182] These included: age, sex, maternal body mass index (BMI), gestational age, weight at birth and maternal highest level of education. To control for general growth, we added length/height as a time-varying covariate.

3.2.5 Data analysis

All analyses were conducted in Stata 17 (StataCorp, 2017).

We applied univariable and multivariable multilevel linear mixed regressions to model repeated time observations within participants, to compare head circumference trajectories in children with and without an ASD diagnosis and elevated autistic traits. We included a random intercept on child and a random slope on linear age. First, we fitted two unconditional models progressively including a mean centred indicator of child age in months (unconditional model 1) and age^2 (unconditional model 2) to assess the trajectory of head circumference over time. Model fit was assessed using Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). If there was evidence of a non-linear

association with age (i.e., $p < 0.05$) along with improved model fit (i.e., lower AIC and BIC values), we retained both the linear and squared age indicators in the final model. Output for unconditional models is listed in the supplement.

Next, we fitted a univariable model which included our clinical variable of interest (ASD diagnosis or elevated autistic traits; multivariable model 1) as well as the two age indicators. Subsequently, we fitted a series of multivariable models progressively adjusting for participant's sex (model 2); maternal education (model 3), maternal BMI (model 4), gestational age and birth weight (model 5). We also examined the following interactions with group in three separate models: i) age, ii) age and age squared, and iii) sex.

For comparisons between the analytic samples to the full ALSPAC cohort in terms of demographic characteristics and confounders, see supplement for percentage distributions, means and standard deviations (Table *14*).

3.2.6 Secondary analyses

In a secondary analysis we included height (model 6) to assess whether increased head circumference may constitute generalized growth as opposed to head/brain specific growth.

Due to limited statistical power, we selected univariable model 3 to examine the mean trajectory differences between ASD with and without CLN compared to controls (ASD with CLN n = 13; no ASD n = 4,906; total analytic sample N= 4,919). Additionally, we investigated the impact of removing those with CLN from the main ASD analyses, and explored within group differences by comparing ASD with CLN vs ASD without CLN.

To assess the time when group differences in head circumference emerge, we fitted post-hoc unadjusted two-sample t-tests between the ages of birth to 12 months, and also at age 15.5 years to see if differences persist (see supplement). To examine general growth effects, t-tests of height differences at these ages were also performed.

Sensitivity analyses

To improve comparability between groups, (1) we restricted analyses to participants who had complete data for both ASD and autistic traits. Finally, (2) to avoid biasing the results from the autistic traits group with individuals with ASD, we removed those with ASD from the autistic traits group (i.e., elevated autistic trait group consisted of individuals above the

cut-off for the SCDC but no ASD diagnosis) and compared those with controls below the SCDC cut-off.

3.3 Results

3.3.1 Sample

Of the 15,645 children within ALSPAC (n = 14,442 excluding twins), 7,695 had data on ASD, with 95 children reported to have a clinical diagnosis of ASD. All 95 children had at least one head circumference measure, and 78 also had complete data for confounding variables (controls = 6,404). The majority of ASD cases were male (78%), whereas controls were evenly split by sex (50% male). ASD and controls were comparable across demographic characteristics and confounders, although mean height at 15.5 years was higher in the ASD group compared to controls (Table 6). Per participant, the mean number of timepoints with available head circumference data were 4, with a median of 3 (SD = 3.22; range = 1-18). Compared to the full ALSPAC cohort, the demographic characteristics for the two analytic samples (ASD and autistic traits) shared comparable distributions. However, mean gestational age and birth weight were slightly lower in the full cohort compared to the analytic samples (Table 14).

There were 7,813 children with outcome data on autistic traits using the SCDC, 759 of which were classified as having elevated autistic traits. All but two of which had at least one head circumference measurement, and 639 had complete data for confounders (controls = 6,230). The majority of children with elevated autistic traits were male (64%), controls were evenly split by sex (50%). Within participants, the mean number of head circumference timepoints was 5, with a median of 4 (SD = 4.40; range 1-27). There were no significant differences in demographic characteristics for those with elevated autistic traits compared to controls (Table 6).

3.3.2 Trajectories of head circumference by ASD diagnosis

In the univariable model, participants with ASD had larger head circumference compared with controls (B = 0.69, 95% confidence interval [CI]: 0.28 – 1.09, p = 0.001; Figure 11A and Table 7). After adjusting for sex, there was still some evidence of an association between ASD and larger head circumference trajectory, although the magnitude of the association was reduced (B = 0.41, 95% CI: 0.02 - 0.80, p = 0.038). Results remained largely unchanged after adjustment for maternal education, maternal BMI, gestational age, and birth weight.

There was no evidence for effect modification by sex (p = 0.42), age (p = 0.87), or age squared (p = 0.58).

3.3.3 Secondary analyses (ASD)

After adjusting for height, there was no longer evidence of a difference in head circumference between ASD cases and controls (B = 0.06, 95% CI: -0.21 – 0.33, p = 0.66).

When investigating differences in trajectories of head circumference in children with comorbid ASD and CLN compared to controls (Figure 12), there was evidence of larger head circumference in the ASD CLN group (univariable model 3: B = 1.69, 95% CI: 0.75 – 2.63, p < 0.0001). The coefficient was approximately four times larger than when controls were compared to ASD without CLN (B = 0.45, CI: 0.03 – 0.87, p = 0.036). The previous analyses are based off complete data for the CLN variable. This analysis was repeated in the main analytic sample without complete data for CLN; when I removed those without CLN from the main analytic sample, the significant effect of group remained, with larger head circumference in ASD compared to controls (B = 0.47, CI: 0.01 – 0.90, p = 0.045). Finally, when investigating the differences in head circumference trajectories between the two ASD groups, there was evidence of differences between the groups, with larger head circumference in the ASD with CLN group compared to ASD without CLN (B = 1.70, 95% CI: 0.76 – 2.64, p < 0.0001).

When examining individual timepoints, group differences in head circumference were observed from 2 months (t[1772] = -2.69, p = 0.007; Figure 11B), differences in height occurred later (9 months; t[3115] = -2.43, p = 0.015; see Supplement 3.5 Table 9).

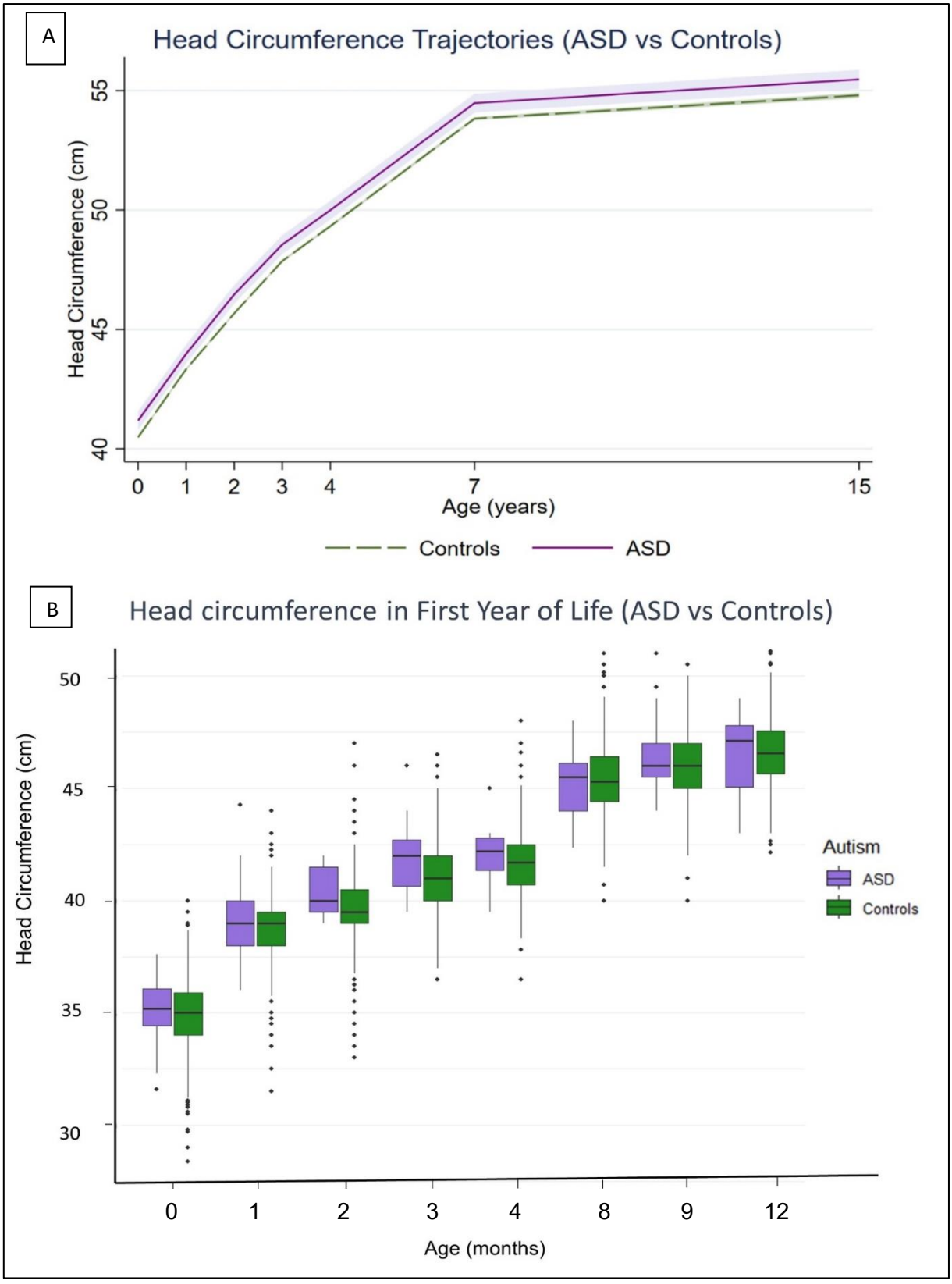


Figure 11. Head circumference trajectories (cm) in autism spectrum disorder (ASD) cases (purple) and controls (blue). Plot A shows modelled mean head circumference values (model 2, adjusted for sex) with 95% confidence intervals shown in lilac for ASD and light green for controls. (N = 6,482). Plot B is boxplot of head circumference measurements from birth to 12 months in ASD (purple) and controls (green). For clarity, integer numbers have been used in both plots to represent age in which head circumference measurements were collected.

Table 6. Characteristics of the analytical sample, overall and by case/control status. Sample based on participants with ASD **or** autistic traits and complete confounder data.

	ASD analytic sample	ASD absent	ASD present	Autistic traits analytic sample	Autistic traits absent	Autistic traits present
	N(%)	n(%)	n(%)	N(%)	n(%)	n(%)
Total	6,482 (100%)	6,404 (98.80%)	78 (1.20%)	6,869	6,230 (90.70%)	639 (9.30%)
Sex						
Male	3,239 (49.99%)	3,178 (98.12%)	61 (1.88%)	3,519	3,111 (88.41%)	408 (11.59%)
Female	3,243 (50.01%)	3,226 (99.48%)	17 (0.52%)	3,350	3,119 (93.10%)	231 (6.90%)
Ethnicity						
White	6,139 (94.72%)	6,062 (98.75)	77 (1.25)	6,507	5,900 (90.67%)	607 (9.33%)
Ethnic minority	228 (3.52%)	228 (100%)	0	240	219 (91.25%)	21 (8.75%)
Missing	115 (1.76%)					
Maternal highest educational attainment						
Compulsory	3,710	3,668 (98.87%)	42 (1.13%)	3,948	3,546 (89.82%)	402 (10.18%)
Non-compulsory	2,772	2,736 (98.70%)	36 (1.30%)	2,921	2,684 (91.89%)	237 (8.11%)
	Mean (SD)	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)
Gestational age (in weeks)	39.52 (1.73)	39.52 ()	39.49 (2.36)	39.51 (1.76)	39.51 (1.75)	39.47 (1.88)
Birth weight (grams)	3478.10 (518.25)	3446.02 (517.07)	3478.10 (608.52)	3438.76 (526.01)	3441.65 (523.48)	3410.76 (549.75)
Length at birth (cm)	50.89 (2.38)	50.89 (2.38)	51.03 (2.55)	50.88 (2.39)	50.90 (2.37)	50.70 (2.54)
Height at 15.5 years (cm)	169.37 (7.85)	169.34 (8.24)	172.91 (7.85)	169.40 (8.38)	169.37 (8.33)	169.69 (8.94)
Age in years at ASD/SCDC measurement	9.65 (1.52)	9.64 (1.23)	9.65 (1.52)	91.88 (1.69)	91.84 (1.64)	91.89 (1.58)
Maternal pre-pregnancy BMI	22.88 (3.68)	22.88 (3.68)	22.65 (3.67)	22.86 (3.67)	22.86 (3.66)	22.86 (3.77)
Average number of head circumference measurements	5 (3.25)	5 (3.24)	5(3.75)	6 (4.40)	6 (4.42)	6(4.14)

Note. BMI, body mass index; SCDC, Social and Communication Disorders Checklist; We collapsed maternal highest educational attainment into a binary variable due to small sample size and avoid possibility of participant identification. Analyses used the non-collapsed version consisting of 5 levels of educational attainment.

Table 7. Head circumference trajectories in ASD vs Controls showing increase in head circumference in ASD.

Univariable and multivariable linear mixed regressions assessing head circumference in ASD versus controls. Sample based on timepoints in which at least 10 people per group (ASD or controls) were present at each timepoint and complete data on the ASD measure. (Analytic sample N = 6,482, ASD = 78, Controls = 6,404)

	Head circumference trajectories in **ASD vs Controls**		
	Mean difference	95% Confidence intervals	*P*
Univariable model 1	0.69	0.28 – 1.09	0.001
Model 2: model 1 + child's sex	0.41	0.02 – 0.80	0.038
Model 3: model 2 + maternal education	0.41	0.02 – 0.80	0.039
Model 4: model 3 + maternal BMI	0.42	0.03 – 0.81	0.034
Model 5: model 4 + gestational age and birth weight	0.38	0.003 – 0.75	0.048
Model 6: model 5 + height	0.06	-0.21 – 0.33	0.66

Unconditional Model 1 (age) and Model 2 (mean centred age and age squared) are presented in supplemental material. For univariable model 1 onwards, we incorporated random effects of participant id and mean centred age. Univariable model 1 consisted of ASD and time variables. Interactions between ASD and age (p = 0.87), age squared (p = 0.58), and sex (p = 0.42) were non-significant and therefore the group coefficient was not included in this table.

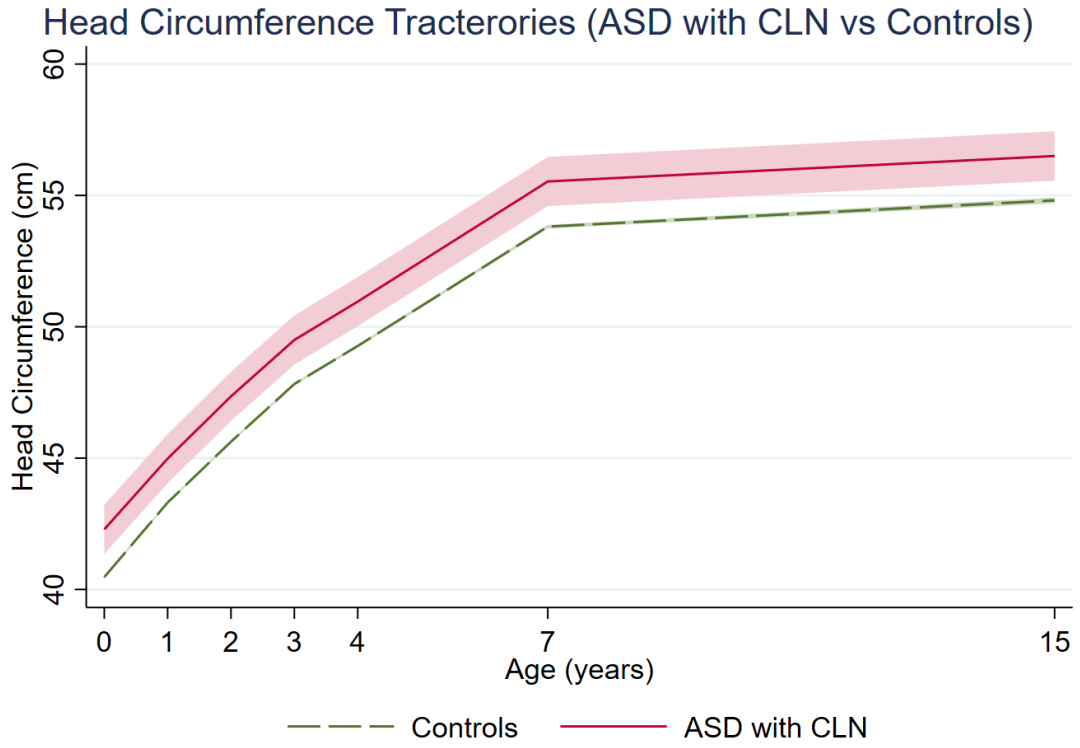


Figure 12. Head circumference trajectories in participants with ASD and CLN compared to controls (no ASD). Trajectories show modelled mean values when adjusting for sex (Model 2) with 95% confidence intervals in pink for ASD + CLN and green for controls. (N = 6,417)

3.3.4 Sensitivity analyses (ASD)

Sensitivity analyses showed similar results to the main analyses i.e., when participants had complete data for both diagnoses (ASD and autistic traits), i.e., there was evidence of larger head circumference trajectories in autism compared to controls. See Supplement 3.5 Table 11.

3.3.5 Trajectories of head circumference in elevated autistic traits

In the univariable analyses there was no evidence that mean head circumference differed between the autistic traits group and controls (B = -0.08, 95% CI: -0.22 – 0.06, p = 0.28, Table 12 and Figure 13). After adjusting for sex, the magnitude of the difference increased and there was weak evidence that participants with higher autistic traits had *lower* head circumference values compared to controls (B = -0.22, 95% CI: -0.36 – -0.09, p = 0.001). Results remained unchanged after adjusting for maternal education and maternal BMI, but the magnitude of effect was reduced after gestational age and birthweight were included in

the model (model 5: B = -0.16, CI: -0.28 – 0.03, p = 0.016). There was no evidence for interactions between autistic traits group and age (p = 0.54), age squared (p = 0.39) or sex (p = 0.20).

Table 8. Head circumference trajectories in Autistic Traits vs Controls showing decrease in head circumference in autistic traits.

Univariable and multivariable linear mixed regressions assessing head circumference in autistic traits versus controls. Sample based on timepoints with at least 10 participants per group, and those with complete data on the autistic traits measure. (Analytic sample N = 6,869, autistic traits = 639, controls = 6,230)

Head circumference trajectories in **Autistic Traits vs Controls**			
	Mean difference	95% Confidence intervals	*P*
Univariable model 1	-0.08	-0.22 – 0.06	0.28
Model 2: model 1 + child's sex	-0.22	-0.36 - -0.09	0.001
Model 3: model 2 + maternal education	-0.20	-0.33 - -0.08	0.003
Model 4: model 3 + maternal BMI	-0.20	-0.33 - -0.07	0.003
Model 5: model 4 + gestational age and birth weight	-0.16	-0.28 - -0.03	0.016
Model 6: model 5 + height	-0.10	-0.20 – 0.002	0.055

Unconditional Model 1 (age) and Model 2 (mean centred age and age squared) are presented in supplemental material. For univariable model 1 onwards, we incorporated random effects of participant id and mean centred age. Univariable model 1 consisted of ASD and time variables. Interactions between ASD and age (p = 0.54), age squared (p = 0.39), and sex (p = 0.20) were non-significant and therefore the group coefficient was not included in this table

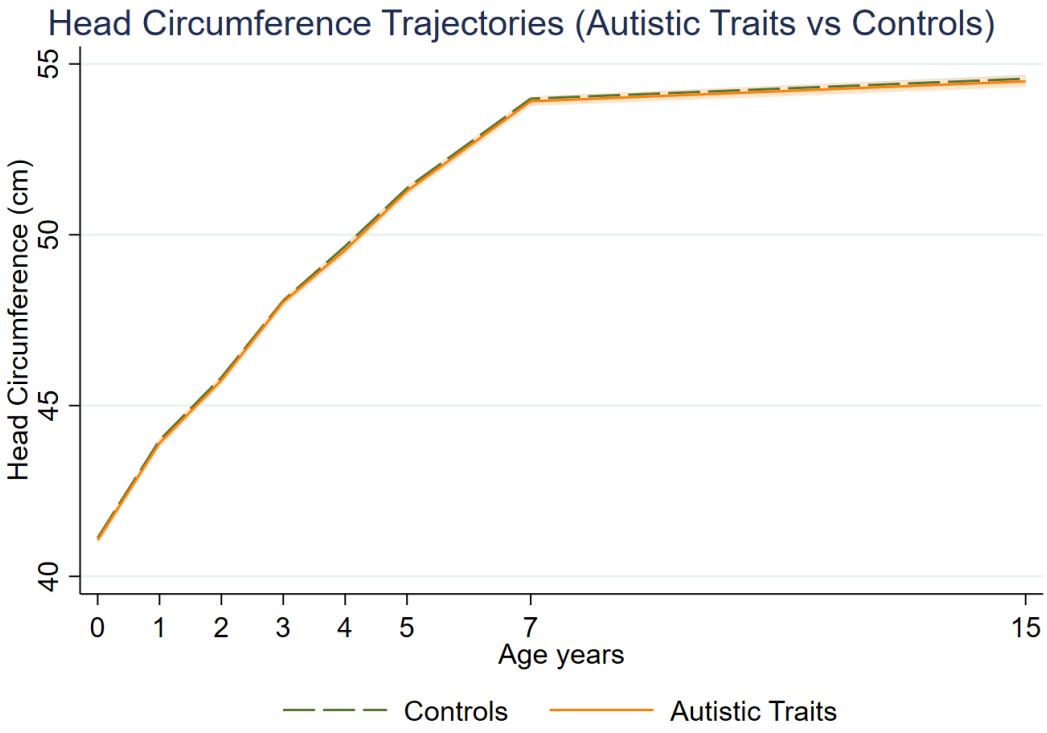


Figure 13. Head circumference trajectories in participants scoring high on the autistic traits measure (SCDC score of 8 or above) in comparison to controls. Trajectories show modelled mean values when adjusting for sex (Model 2) with 95% confidence intervals shown in orange for the autistic traits group and green for controls. Note that confidence intervals overlap between autistic traits and controls. (N = 6,869)

3.3.6 Secondary analyses (autistic traits)

When adjusting for height, the model showed weak evidence for an association (height model 6: MD = -0.10, CI: 0.20 – 0.001, p = 0.055). When examining individual timepoints, smaller head circumference in the elevated autistic traits group were observed at 6 months (t[269] = 2.01, p = 0.045) and 7 months (t[319] = 3.23, p = 0.001), whereas differences in height occurred at 3 months (t[942] = 2.15, p = 0.032; Supplement 3.5 Table 10).

3.3.7 Sensitivity analyses (autistic traits)

Sensitivity analyses showed similar results to the main analyses i.e., when participants had complete data for both diagnoses (ASD and autistic traits), i.e., there was evidence of smaller head circumference trajectories in those with elevated autistic traits compared to controls (Supplement 3.5 Table 12). Furthermore, similar results were observed when removing those with ASD from the autistic traits analyses (Supplement 3.5 Table 13).

3.4 Discussion

This study examined head circumference trajectories between birth and 15 years in young people with ASD and those with elevated autistic traits compared to controls. Children with ASD had significantly larger head circumference across this period, with this difference notable from 2 months of age. Conversely, children with elevated autistic traits had reduced head circumference compared to controls. These preliminary findings go against the idea of a pathophysiological continuum of autistic traits and ASD, highlighting potentially distinct aetiological differences that may separate clinical versus non-clinical cases.

Previous research on head circumference in ASD populations is typically restricted to the first 2-3 years of life,[157] and few studies prospectively chart head circumference beyond this period. Our study provides evidence that head circumference is consistently larger in ASD, as demonstrated by the lack of an age by group interaction, whilst also being robust against adjustment for multiple confounders. The timing of this increase has remained elusive in the literature, with some studies reporting the onset between 1 to 3 months of age[155,183] which is consistent with the findings from our study, whereas others report enlarged head circumference from 6 months onwards.[88,142,184] While the timing of onset may differ per study, our study provides evidence that these changes in head circumference are continuous and not time-limited to early development.

Previous literature has suggested that enlarged head circumference may only affect a subgroup of individuals with ASD. For example, one meta-analysis of children and adults reports macrocephaly (head circumference greater than 97th percentile) in 15.7% of individuals with ASD (versus 3% controls), and is more common in individuals with IQ scores below 70.[96] In our subgroup analyses, the largest effect size differences between ASD and controls were observed when participants with ASD had CLN, suggesting that there may be shared mechanisms that lead to larger head circumference and compromised intellectual functioning, or alternatively that cognitive impairments may be an important mediator in larger head circumference within ASD. Importantly, enlarged head circumference was observed in the ASD group regardless of additional CLN; however, the coefficient size was reduced when the CLN group were removed. CLN was included as a variable of interest in secondary analyses, as opposed to a confounding variable in all analytic models. Treating

this variable as a confounder would have restricted our ability to extract meaningful information on specific subgroups.

In the general population, head growth during infancy is a significant predictor of later intelligence quotient (IQ), with a 1 SD increase in growth with every 1.56 increase in full-scale IQ.[185] A birth cohort study found greater increases in HC and height during the first 5 years of life were associated with higher IQ in childhood, whereas greater weight gain after 1 year was not.[186] We used CLN as a proxy measure for low IQ, ideally we would have looked at IQ subgroups directly (e.g., ASD with IQ below 70 versus above 70). However, there was more data available for the CLN measure than the IQ measure in those with ASD. The CLN variable specifically measures significant cognitive/learning impairment as noticed by the school and does not measure other impairments such as behavioural or sensory needs.

Assuming that CLN is a proxy measure for IQ, our study suggests there may be an opposing effect of IQ on head growth in ASD samples, in which low IQ is associated with larger head size. One possible explanation for this paradox is that excess neural connections may limit efficiency and cognitive performance in ASD, and while the brain is larger, networks may be more disorganised, affecting the brains' ability to communicate and integrate information.[187] However, more research is needed to explore the different trajectories for individuals with ASD with high versus low IQ and to understand how brain size relates to underlying neural connections.

The question of whether large head circumference in ASD is related to a more general marker of dysregulated growth is debated in the literature. When controlling for height in our analyses, there were no longer group differences between ASD and controls in head circumference, which suggests that general growth, rather than brain growth specifically may be dysregulated in ASD. This is consistent with a review citing increased physical growth - including HC, height, weight and BMI - in children with ASD compared to typically developing individuals. The review also highlights that due to the paucity of longitudinal studies in adolescent and adulthood, it is unknown whether height and weight follow relative increased acceleration in childhood followed by deceleration in those with ASD as seen for HC and brain growth.[188] The timing of dysregulation may differ for height compared to head circumference, as increases to head circumference according to post-hoc t-tests occurred earlier (at 2 months) than height increases (at 9 months) in those with ASD. This

contrasts to one study which reports overgrowth in length/height earlier at 4 months, and increased head circumference at 8 months in ASD.[189] Some studies report that head circumference in ASD varies independently of height,[162,167] while others suggest that they covary and reflect a more generalised growth process.[163,164,190] Findings from the present study suggest that general growth, head circumference trajectories, and brain development are altered in ASD.

There are several possible reasons why autistic traits were associated with reduced head circumference. First, the aetiology of ASD may not be best explained through a continuum but instead by distinct symptom profiles. The SCDC which was used to measure autistic traits may pertain more to a measure of general psychopathology instead of being specific to ASD itself. Research has shown that the SCDC has strong specificity and sensitivity to detect ASD, although only 65% of the autistic traits group were diagnosed with ASD in our sample. The SCDC predominately captures deficits in social communication/reciprocity and does not include items on repetitive behaviours or restricted interests. Previous research has provided evidence of links between enlarged brain size during childhood in ASD and poor performance on repetitive behaviour scales, as well as with delayed language and skill regression.[99,142,166] It is therefore possible that the neurobiological mechanisms underlying enlarged head circumference show a greater association for certain clinical outcomes over others.

Research has shown that head circumference and brain size share a strong correlation,[151,152,191] and therefore can be used as a proxy measure of neurodevelopment.[37] Atypical cell proliferation and reductions in neuronal pruning are thought to underlie the growth differences in head circumference observed in ASD and cause an overabundance of cortical neurons, particularly in frontal and temporal brain networks which facilitate social and language processes.[16] There are several potential genes associated with ASD which affect brain size and general growth (e.g., mutations to chromodomain helicase DNA binding protein 8 (CHD8)). [192] [193]However, while larger head circumference may be a viable biomarker for ASD, it is also a biomarker for several other conditions, including Sotos, Cowden, and Costello syndromes.[194]

Several limitations should be considered when interpreting this study. As is common with longitudinal cohort studies, missing data reduced the sample size and representativeness of

the study. Replication in larger samples of participants with comorbid CLN is needed. The use of parent confirmation of a diagnosis of ASD may be less valid than formal diagnosis tools. However, the number of ASD cases was similar to that of previous ALSPAC studies which used multidisciplinary assessments from health and educational records.[15] We did not observe any sex by group interactions with head circumference, although we were likely underpowered to do so due to females representing only 21% (n = 15) of the ASD sample**.** Strengths of the study include the use of a representative birth cohort with multiple timepoints for head circumference measurements. Previous longitudinal studies typically consist of only 3-4 timepoints, often limited to early development.[88,155,195] Our analyses featured over 10 timepoints, allowing a more comprehensive overview of head circumference trajectories in ASD.

There are many clinical markers for ASD, but our knowledge of biomarkers is lacking. Findings from this study consolidate previous literature that large head circumference may be considered a biomarker for ASD and potentially complement behaviour assessments for diagnosis throughout childhood.[96,161,196] Importantly, differences were modelled from birth through infancy and beyond before behavioural traits can be used to diagnose ASD. Our findings suggest that head circumference enlargement is specific to those with clinical diagnoses as we do not find evidence of enlargement in our subclinical trait sample. It will be important for future studies to continue to monitor head circumference trajectories across a greater time period to see the full extent of the developmental trajectory.

3.5 Supplement

Model fit estimates for ASD analyses indicated that incorporating mean-centred age and quadratic terms i.e., mean centred age squared (AIC = 190958.5; BIC = 190984) yielded superior results (i.e., lower AIC and BIC values) and a significant p value (head circumference mean difference -0.0008 cm, 95% confidence interval [CI] -0.0008 - -0.0008, $p < 0.0001$) compared to model 1 with unadjusted age values (AIC = 210966.8; BIC = 211017.9; mean difference 0.10, 95% CI 0.098 – 0.099, $p < 0.0001$). Consequently, we incorporated the time variables from model 2 into all subsequent models. AIC and BIC values remained largely unchanged beyond this point in univariable and multivariable models.

3.5.1 Sensitivity analyses

To enable more comparability across groups by basing analyses from the same analytic sample, within our sensitivity analyses we only included participants with complete data on both outcome variables (ASD and autistic traits). A total of 5,636 had complete data on both clinical measures and confounders. From this sample, there were a total of 69 ASD cases and 487 participants in the autistic traits group.

In our sensitivity analyses we restricted the sample to those with complete data on both clinical outcomes and confounders. Across participants, the mean number of timepoints at which head circumference data was available was 5 (SD = 3.28, range: 1 - 18). 96.90% of participants were of white ethnicity, with 3.10% of non-white ethnicity. Within ASD cases, 100% of participants were of white ethnicity. In the high autistic traits group, 3.34% were of an ethnic minority. Length and weight at birth was on average larger in ASD, although only height at age 15.5 years was significantly larger in the ASD group compared to controls ($t(2907) = -2.65$, $p = 0.008$). There were no significant differences in the high autistic traits group compared to controls. Information on missing data can be found in the supplementary materials.

ASD sensitivity analyses showed similar results to the main analyses, i.e., when participants had complete data for both clinical outcomes (ASD and autistic traits), those with a diagnosis of ASD had higher head circumference values than controls (see Table S1). Likewise, reduced head circumference was observed in the autistic traits group (see Table S2). When we removed those with a diagnosis of ASD from trait analyses, more marked reductions in head circumference were observed see (Table S3).

Table 9. T-tests of head circumference values from birth to 12 months in ASD and controls. Head circumference at age 15.5 years is also reported

		Head Circumference in ASD vs Controls			Height in ASD vs Controls		
Age (months)	ASD / Controls N	ASD Mean (*SD*)	Controls Mean (*SD*)	T-Test	ASD Mean (*SD*)	Controls Mean (*SD*)	T-Test
0	61 / 4,948	35.18 (1.23)	34.92 (1.37)	T (5,007) = -1.48, p = 0.14	51.03 (2.55)	50.89 (2.38)	T (5007) = - 0.46, p = 0.65
1	48 / 4,215	39.10 (1.41)	38.76 (1.32)	T (4,261) = -1.75, p = 0.080	57.69 (2.89)	57.19 (2.51)	T (4,261) = - 1.36, p = 0.17
2	23 / 1,751	40.40 (1.08)	39.60 (1.43)	**T (1,772) = -2.69, p = 0.007**	59.83 (2.52)	58.83 (2.91)	T (1,772) = -1.63, p = 0.10
3	10 / 875	42.03 (1.97)	41.16 (1.38)	**T (883) = -1.97, p = 0.049**	63.45 (3.86)	62.06 (2.54)	T (883) = -1.71, p = 0.09
4	11 / 741	42.06 (1.50)	41.71 (1.44)	T (750) = -0.82, p = 0.42	62.35 (5.18)	62.96 (2.65)	T (750) = 0.74, p = 0.46
8	20 / 1,953	45.32 (1.51)	45.35 (1.48)	T (1,971) = 0.10, p = 0.92	71.10 (2.90)	71.09 (2.76)	T (1,971) = -0.02, p = 0.98
9	42 / 3,075	46.36 (1.54)	45.85 (1.40)	**T (3,115) = -2.35, p = 0.019**	73.37 (3.21)	72.28 (2.87)	**T (3,115) = -2.43, p = 0.015**
12	17 / 934	46.61 (1.79)	46.64 (1.44)	T (949) = 0.04, p = 0.97	76.07 (2.91)	75.74 (2.59)	T (949) = -0.53, p = 0.60
186 (15.5 years)	33 / 3,188	56.12 (1.82)	55.50 (1.73)	**T (3,219) = -2.02, p = 0.043**	172.91 (7.85)	169.34 (8.24)	**T (3,219) = -2.47, p = 0.013**

Table 10. T-tests of head circumference values from birth to 12 months in Autistic traits and controls. Head circumference at age 15.5 years is also reported.

		Head Circumference in Autistic Traits vs Controls			Height in Autistic Traits vs Controls		
Age (months)	Autistic Traits / Controls N	Autistic Traits Mean (*SD*)	Controls Mean (*SD*)	T-Test	Autistic Traits Mean (*SD*)	Controls Mean (*SD*)	T-Test
0	504 / 4,771	34.83 (1.45)	34.92 (1.37)	T (5,243) = 1.50, p = 0.13	50.70 (2.54)	50.90 (2.37)	T (5,273) = 1.73, p = 0.083
1	403 / 4,070	38.71 (1.34)	38.78 (1.31)	T (4,471) = 0.95, p = 0.34	57.24 (2.85)	57.20 (2.45)	T (4,471) = -0.29, p = 0.78
2	195 / 1,686	39.63 (1.61)	39.61 (1.40)	T (1,879) = -0.20, p = 0.84	58.76 (3.26)	58.85 (2.90)	T (1,879) = 0.40, p = 0.69
3	83 / 861	40.89 (1.63)	41.19 (1.38)	T (942) = 1.90, p = 0.058	61.46 (3.08)	62.12 (2.63)	**T (942) = 2.15, p = 0.032**
4	81 / 720	41.58 (1.68)	41.71 (1.44)	T (799) = 0.71, p = 0.48	62.81 (3.11)	62.95 (2.69)	T (799) = 0.46, p = 0.64
5	31 / 240	43.07 (1.56)	43.55 (1.46)	T (291) = 1.70, p = 0.09	66.48 (4.02)	67.12 (3.43)	T (291) = 0.96, p = 0.34
6	31 / 240	43.79 (269)	44.33 (1.40)	**T (269) = 2.01, p = 0.05**	67.97 (4.03)	68.42 (3.23)	T (269) = 0.72, p = 0.47
7	41 / 280	44.01 (1.87)	44.85 (1.50)	T (319) = 3.23, p = 0.001	68.97 (3.54)	70.15 (2.80)	**T (319) = 2.43, p = 0.016**
8	193 / 1,859	45.29 (1.65)	45.37 (1.47)	T (2,050) = 0.72, p = 0.47	70.91 (3.12)	71.10 (2.78)	T (2,050) = 0.91, p = 0.36

Age (months)	Autistic Traits / Controls N	Autistic Traits Mean (*SD*)	Controls Mean (*SD*)	T-Test	Autistic Traits Mean (*SD*)	Controls Mean (*SD*)	T-Test
9	317 / 3,012	45.78 (1.53)	45.86 (1.39)	T (3,327) = 1.05, p = 0.29	72.20 (2.98)	72.37 (2.91)	T (3,327) = 1.00, p = 0.32
10	70 / 605	46.51 (1.49)	46.31 (1.51)	T (673) = -1.08, p = 0.28	74.11 (3.32)	73.50 (3.05)	T (673) = -1.57, p = 0.12
11	35 / 300	46.40 (1.67)	46.86 (1.53)	T (333) = -1.68, p = 0.09	74.67 (3.78)	75.09 (3.12)	T (333) = 0.75, p = 0.46
12	97 / 918	46.47 (1.81)	46.66 (1.46)	T (1,013) = 1.20, p = 0.23	75.82 (2.99)	75.73 (2.70)	T (3,239) = -0.57, p = 0.57
186 (15.5 years)	261 / 2,980	55.41 (1.88)	55.52 (1.71)	T (3,239) = 1.02, p = 0.31	169.69 (8.94)	169.37 (8.33)	T (3,239) = -0.57, p = 0.57

Table 11. Output from ASD sensitivity analyses (1). Univariable and multivariable linear mixed regressions assessing head circumference in autism versus controls. Sample based on timepoints with at least 10 participants per group, and complete data for all clinical measures (ASD and autistic traits) and confounders. (N = 5,547, ASD = 68, Controls = 5,479)

Sensitivity: Head circumference trajectories in **ASD vs Controls**			
	Mean difference	95% Confidence intervals	*P*
Univariable model 1	0.78	0.36 – 1.20	<0.0001
Model 2: model 1 + child's sex	0.50	0.09 – 0.90	0.016
Model 3: model 2 + maternal education	0.50	0.09 – 0.90	0.017
Model 4: model 3 + maternal BMI	0.50	0.10 – 0.90	0.015
Model 5: model 4 + gestational age and birth weight	0.45	0.06 – 0.84	0.024
Model 6: model 5 + height	0.05	-0.24 – 0.33	0.75

Univariable model 1 consisted of ASD and time variables. Interactions between ASD and age (p = 0.93), age squared (p = 0.32), and sex (p = 0.59) were non-significant and therefore the group coefficient was not included in this table.

Table 12. Output from autistic traits sensitivity analyses (1). Univariable and multivariable linear mixed regressions assessing head circumference in autistic traits versus controls. Sample based on timepoints with at least 10 participants per group, and complete data for all clinical measures (ASD and autistic traits) and confounders. (N = 5,547, autistic traits = 478, controls = 5,069)

Sensitivity: Head circumference trajectories in **Autistic Traits Group vs Controls**			
	Mean difference	95% Confidence intervals	*P*
Univariable model 1	-0.05	-0.22 – 0.11	0.55
Model 2: model 1 + child's sex	-0.18	-0.34 - -0.02	0.026
Model 3: model 2 + maternal education	-0.17	-0.32 - -0.01	0.041
Model 4: model 3 + maternal BMI	-0.16	-0.32 - -0.005	0.043
Model 5: model 4 + gestational age and birth weight	-0.12	-0.27 – 0.03	0.12
Model 6: model 5 + height	-0.06	-0.17 – 0.05	0.29

Univariable model 1 consisted of autistic traits and time variables. Interactions between ASD and age (p = 0.63), age squared (p = 0.68) ,and sex (p = 0.09) were non-significant and therefore the group coefficient was not included in this table.

Table 13. Output from autistic traits sensitivity analyses (2). Univariable and multivariable linear mixed regressions assessing head circumference in autistic traits versus controls. We removed individuals with ASD so that we could assess mean differences in head circumference in a subclinical sample. Sample based on timepoints with at least 10 participants per group, and complete data for all clinical measures (ASD and autistic traits) and confounders. (N = 5,479; Autistic traits = 434, Controls = 5,045).

Sensitivity: Head circumference trajectories in **Autistic Traits Group vs Controls**			
	Mean difference	95% Confidence intervals	*P*
Univariable model 1	-0.15	-0.32 – 0.03	0.096
Model 2: model 1 + child's sex	-0.25	-0.42 - -0.09	0.003
Model 3: model 2 + maternal education	-0.24	-0.40 - -0.07	0.005
Model 4: model 3 + maternal BMI	-0.24	-0.40 - -0.07	0.005
Model 5: model 4 + gestational age and birth weight	-0.19	-0.35 - -0.03	0.017
Model 6: model 5 + height	-0.09	-0.20 - -0.03	0.15

For univariable models 2 onwards, we incorporated random effects of participant id and mean centred age. Univariable model 1 consisted of autistic traits and time variables. Interactions between ASD and age (p = 0.66), age squared (p = 0.83), and sex (p = 0.15) were non-significant and therefore the group coefficient was not included in this table.

3.5.2 Missing data

Based on the full ALSPAC sample (N = 15,645), a total of 6,482 participants (41.49%) had complete data for autism and covariates, and 6,869 participants (43.92%) had complete data on autistic traits and covariates (for sample flowcharts, see Figure 14, Figure 15, and Figure 16) Individuals with missing data on autism diagnosis had younger gestational age (M = 37.27 weeks vs M = 39.52), mothers with higher pre-pregnancy BMI (M = 23.00 vs M = 22.88) and mothers that were less educated (non-compulsory/higher education = 1,334 vs 2,772). Based on individuals with complete data on both clinical outcomes and covariates, there were 45 observations that were biologically implausible: head circumference (32

observations), height (6 observations) or birth weight (7 observations) values. This resulted in the removal of 2 participants from ASD analyses and 1 in autistic traits analyses (2 when participants had complete data on clinical outcomes). Additionally, we removed observations in which differences in head circumference or height if collected at the same timepoint were over 3 cm, this resulted in the removal of 45 observations for head circumference and 104 timepoints for height.

Table 14. Characteristics of the ASD and autistic traits analytic samples compared to the full ALSPAC cohort (excluding non-singleton births n = 203).

	Full ALSPAC cohort	Analytic sample (ASD analyses)	Analytic sample (autistic trait analyses)
	N (%)	n (%)	n (%)
Total	15,442 (100%)	6,482 (100%)	6,869 (100%)
Sex			
Male	7,583 (49.10%)	3,239 (49.99%)	3,519 (51.25%)
Female	7,262 (47.02%)	3,243 (50.01%)	3,350 (48.75%)
Missing	597 (3.87%)		
Ethnicity			
White	11,379 (73.62%)	6,139 (94.80%)	6,507 (94.73%)
Ethnic minority	604 (3.91%)	228 (3.52%)	240 (3.49%)
Missing	3,459 (22.46%)	343 (5.28%)	122 (1.78%)
Maternal highest education			
Compulsory/Vocational/None	7,975 (51.62%)	3,710 (57.29%)	3,948 (57.54%)
Non-compulsory	4,350 (28.12%)	2,772 (42.71%)	2,921 (42.46%)
Missing	3,117 (20.26%)		
	Mean (SD)	Mean (SD)	Mean (SD)
Gestational age (weeks)	38.41 (5.49)	39.52 (1.73)	39.51 (1.76)
Birth weight	3393.01 (570.72)	3478.10 (518.25)	3438.76 (526.01)
Length at birth	50.80 (2.69)	50.89 (2.38)	50.88 (2.39)
Height at age 15.5 years	169.23 (8.36)	169.37 (7.85)	169.40 (8.38)
Maternal pre-pregnancy BMI	22.93 (3.84)	22.88 (3.68)	22.86 (3.67)

3.5.3 Sample flowcharts

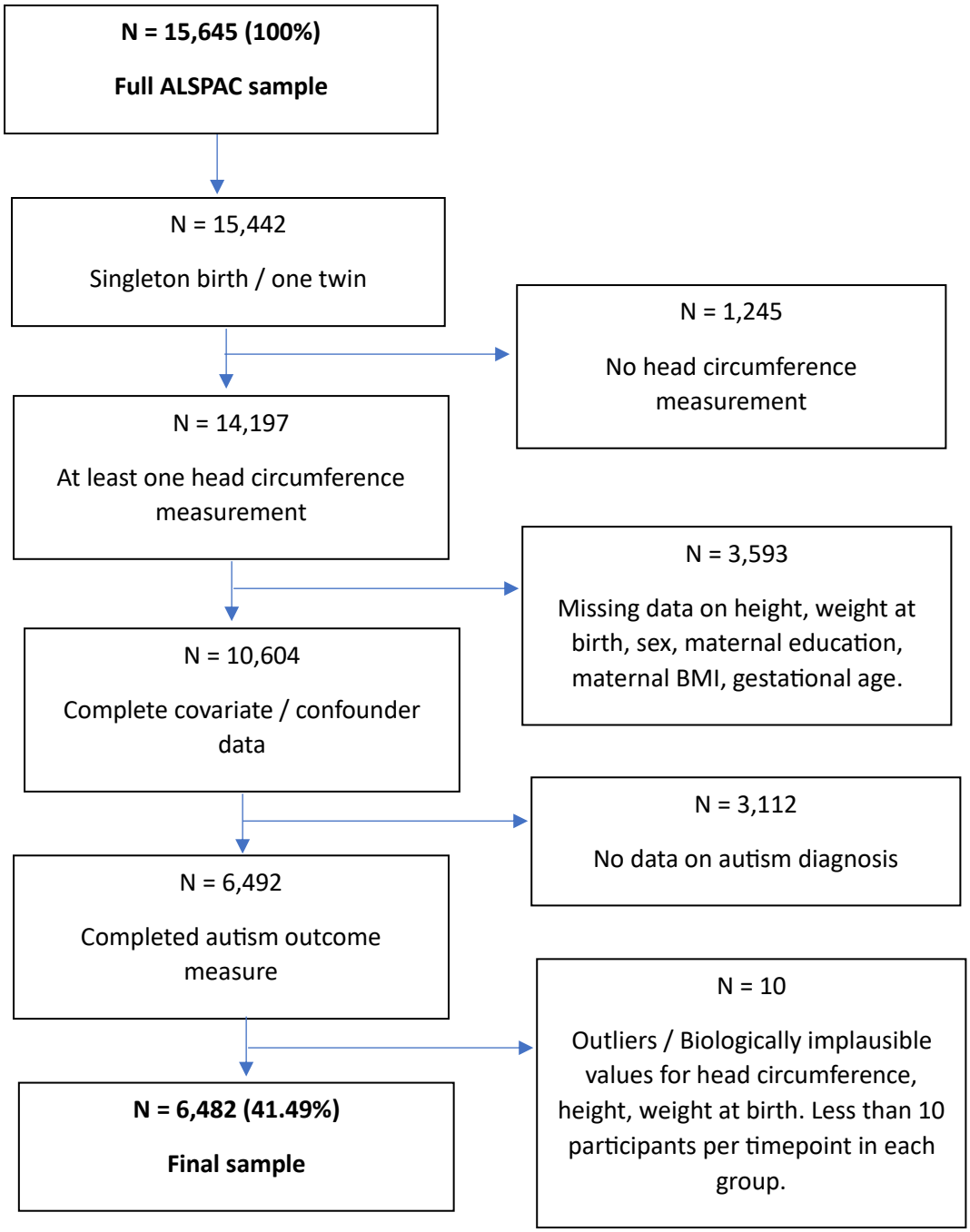


Figure 14. Flowchart of study participation (ASD analyses)

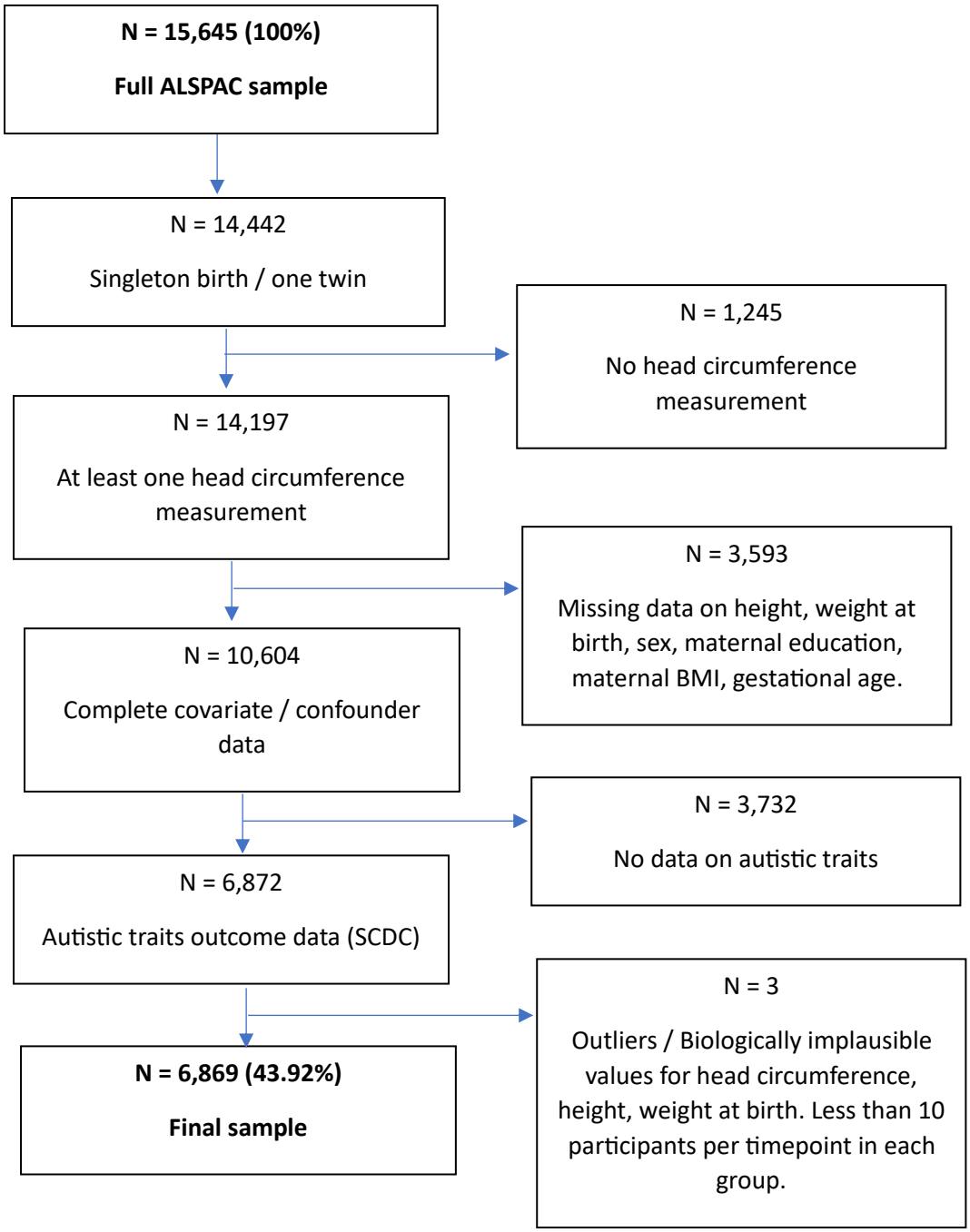


Figure 15. Flowchart of study participation (autistic traits analyses)

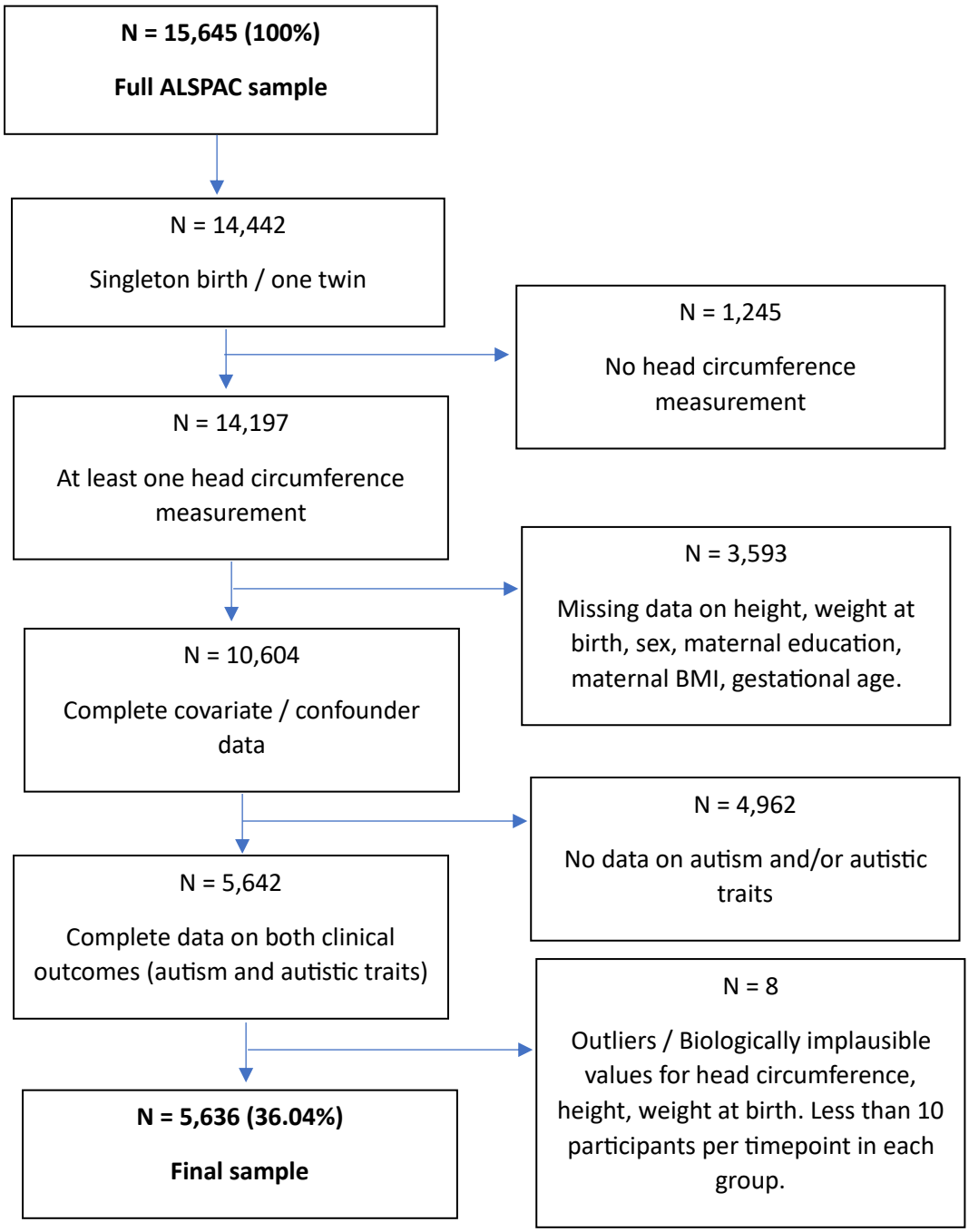


Figure 16. Flowchart of study participation (complete data on both clinical outcomes: autism and autistic traits).

Chapter 4: A prospective study of head circumference trajectories in psychotic experiences

In Chapter 4, I use the ALSPAC dataset to explore head circumference trajectories in individuals (a) with and without psychotic disorder, and (b) with and without psychotic experiences.

4.1 Introduction

Schizophrenia is associated with reduced total brain volume in adulthood;[197] however, the timing and trajectory of these volume changes are not well understood. Head circumference measurements accurately reflect brain size and offer valuable insights into how the brain is developing when studied longitudinally.[151,191] Despite interest in how the brain develops in psychotic conditions, the number of studies which assess head circumference are limited, often restricted to birth or early childhood.[74,198–200] Many studies also use retrospective data without a population-based control group.

Head circumference has been found to be atypical in at birth in those who go on to develop schizophrenia, with several studies reporting reductions in cases compared to controls.[74,198,200–202] However increased head circumference has also been reported,[203] as has no group difference.[199] Differences by sex are reported, with some studies suggesting largest effects are observed in females. One longitudinal study reported evidence of accelerated head growth from birth to 2 months in females but not in males who go on to develop schizophrenia.[204] Another birth cohort study showed that young female but not male adults with non-affective psychosis had larger head circumferences at birth than controls but no differences at 5 years old.[203] While these studies demonstrate evidence of atypical patterns of head growth associated with psychosis, no study has examined head circumference trajectories in childhood and adolescence. Longitudinal studies may be better powered to establish head circumference trajectories in psychosis, and the effect of sex.

Recruiting populations with psychotic experiences may help identify important biomarkers associated with the development of psychosis. Psychotic experiences are highly prevalent in the general population (5-10%)[44] and are associated with an increased risk of developing a clinical psychotic disorder. To our knowledge, no study has explored head circumference trajectories in individuals with psychotic experiences, highlighting an opportunity to provide novel insights into neurodevelopmental trajectories that precede psychosis onset.

This study aims to: (1) chart head circumference trajectories from birth to 15 years in young people with psychotic experiences and controls, using data from a population-representative longitudinal study (the Avon Longitudinal Study of Parents and Children [ALSPAC]). (2) Chart head circumference trajectories in a subset of participants with psychotic disorder. (3) To investigate whether head circumference findings are consistent with measures of adult total intracranial volume (TIV)] and total grey matter (GM) volume. Finally (4), we explore if head circumference at birth is predictive of psychotic experiences by looking at the relative risk for psychosis when head size is ranked in the top or bottom 10% in our sample.

4.2 Methods

Participants were drawn from ALSPAC, a UK based population study from the Southwest of England. Pregnant women with expected delivery dates between April 1991 to December 1992 were recruited (n = 14,541) and followed by a second wave of recruitment when children were age 7 and onwards, resulting in a total cohort of 15,645 children with adjustments for non-singleton births.

This study included children who had at least one head circumference measurement, as well as complete data on psychopathology and confounding variables. We also use data from a subset of individuals (n = 347) who have structural MRI scans. The study website contains details of available data: http://www.bristol.ac.uk/alspac/researchers/our-data/. Ethical approval was granted by the ALSPAC Ethics and Law Committee (ALEC) and the Local Research Ethics Committees. Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALEC.

4.2.1 Outcome

Head circumference was measured in the entire ALSPAC cohort at birth to 1 year, and at years 7 and 15. Additional measurements between ages 4-61 months were also collected from a subsample of this cohort (ALSPAC Children in Focus Cohort). We restricted timepoints to at least 10 participants per group to ensure each timepoint had sufficient data. From an initial 105 timepoints, 22 met criterion of 10 or more participants per group. Head circumference data were collected by researchers and supplemented by routine measurements by local health services. If multiple HC measures were available for a specific month, the average value was calculated. Values were excluded if measurements differed by

>3cm within a month. Outliers were identified using cut-offs from the WHO Child Growth Standards.[172,173]

4.2.2 MRI

Neuroimaging data was collected in a subpopulation of this sample when participants were aged ~20 years. [72,205] The MRI data were acquired on a 3-T MRI system (HDx; GE Medical Systems) using an eight-channel receive-only head RF coil. T1-weighted structural images were acquired with a 3D fast spoiled gradient echo (FSPGR) sequence (TR = 7.8 ms, TE = 3.0 ms, flip angle 20°, voxel size = 1 mm^3 isomorphic). T1-weighted structural images were skull stripped and grey matter segmented.[206,207] We extracted values for total intracranial volume (TIV) and volume to see whether values differ for psychotic experiences and psychotic disorder groups compared to controls.

4.2.3 Diagnosis

Psychotic experiences were assessed using the Psychosis-Like Symptom Interview,[44,50,208] a semi-structured interview comprising of 12 items relating to hallucinations (visual and auditory), delusions (spied on, persecution, grandiosity, thoughts read, reference, control, and other), and thought interference (broadcasting, insertion, and withdrawal). The interview was delivered by trained psychologists when the participant was aged 17/18 years. Participants were asked if they had ever had that experience since the age of 12, responding with either yes, no, or maybe. The interviewer followed up to determine if the experience met criteria for being psychotic, following definitions and guidelines from the Schedules for Clinical Assessment in Neuropsychiatry.[44,209] Interviewers rated psychotic experiences as either 'absent', 'suspected', or 'definitely present'. Unclear responses were "rated down".We also conducted separate analyses on those with 'psychotic disorder', defined as having had a 'definite psychotic experience' occurring at least once per month over the previous 6 months which also cause severe distress, impact social or occupational functioning, or led to help seeking which we designated 'psychotic disorder'.

4.2.4 Confounders

Confounders included: age, sex, maternal body mass index (BMI), gestational age, weight-at-birth and maternal highest-level-of-education. Height was added as a time-varying covariate.

4.2.5 Data analysis

All analyses were conducted in Stata 17 (StataCorp, 2017).

We charted head circumference trajectories in young people with and without psychotic experiences with linear mixed-effects models, incorporating a random intercept on child and a random slope on time. We began by assessing the trajectory of head circumference over time by running two unconditional models; the first using unadjusted age in months (unconditional model 1) and the second using mean centred indicator of child age in months and age squared (unconditional model 2). If there was evidence of a non-linear association with age, we retained it in the final model. We also ran model fit parameters Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC).

Next, we ran a univariable model (incorporating our clinical variable of interest: psychotic experiences or psychotic disorder; model 3) and several multivariable models that progressively adjusted for confounders while also incorporating the two age indicators (mean centred age and age squared). These included participant's sex (model 4); maternal education (model 5), maternal BMI (model 6), gestational age and birth weight (model 7). To determine whether atypical head circumference trajectories may reflect general growth differences, we included a model which used height as a time-varying covariate (model 8). Finally, we explored the following interactions with group in three separate models: i) age, ii) age and age squared, and iii) sex. If there was evidence of an interaction between group and sex, we present findings stratified by sex.

Group differences in TIV and GM volume were explored using independent t-tests. We ran Pearson correlation tests to ascertain whether head circumference correlates with TIV. Head circumference values at age 15 years were examined, as this was the closest age to when TIV was measured, as well as head circumference at birth and age 7. We also ran logistic regression odds ratios to calculate the risk for psychosis when scoring in the top or bottom 10% for head circumference at birth. Odds ratios were calculated for males and females combined, as well as separately.

4.3 Results

4.3.1 Sample

The complete ALSPAC sample consists of data from 15,645 children (N = 15,442 excluding twins), and 4,675 had data on psychotic experiences (PE = 428, Controls = 4,247). From this sample, 4,588 had at least one head circumference measurement and 3,866 also had complete confounder data. Therefore, our analyses comprised of 339 psychotic experience

cases (218 female) and 3,527 (1,959 female) controls. The total number of timepoints in which head circumference was collected was 22, with a mean of 6.5 timepoints across participants. This criterion was used in all analyses except for those involving participants with psychotic disorder due to small sample sizes. A total of 62 participants were classified as having psychotic disorder (49 females; 13 males). Out of the 22 timepoints, 11 timepoints had 10 or more participants with psychotic disorder.

Most participants in the analytic sample were of white ethnicity (95.92%). Both length and weight at birth were comparable between female controls and females with psychotic experiences, as well as between male controls and males with psychotic experiences (Table *15*).

From our analytic sample, 347 participants (PE = 114; 78 female) had additional neuroimaging data for TIV and GM. Within this sample, 31 (24 female) were also classified as having psychotic disorder.

Demographic characteristics did not differ substantially between the psychotic experiences analytic sample and full ALSPAC cohort, although the analytic sample had gestational age that was 1 week later than the full cohort (Supplement 4.4 Table 19).

Table 15. Characteristics of the analytical sample, overall and by case/control status for psychotic experiences in females and males.

	Female analytic sample	PE absent	PE present	Male analytic sample	PE absent	PE present
	N(%)	n(%)	n(%)	N(%)	n(%)	n(%)
Total	2,177	1,959 (89.99%)	218 (10.01%)	1,689	1,568 (%)	121 (%)
Ethnicity						
White	2,057 (96.08%)	1,857 (%)	200 (%)	1,596	1,487 (%)	109 (%)
Ethnic minority	84 (3.92%)	75 (%)	9 (%)	72	64 (%)	8 (%)
Missing	36			21		
Maternal highest educational attainment						
CSE/None	260	216	44	164	152	12
Vocational	148	136	12	121	111	10
O level	781	685	96	546	504	42
A level	574	533	41	506	484	22
Degree	414	389	25	352	317	35
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Gestational age (weeks)	39.60 (1.65)	39.61 (1.66)	39.57 (1.59)	39.37 (1.86)	39.37 (1.87)	39.38 (1.74)
Birth weight (grams)	3393.34 (483.52)	3392.79 (478.30)	3398.35 (529.27)	3484.18 (572.31)	3488.74 (576.18)	3425.18 (518.17)
Length at birth (cm)	50.51 (2.24)	50.51 (2.19)	50.51 (2.66)	51.20 (2.51)	51.21 (2.51)	51.05 (2.58)
Height at 15.5 years (cm)	164.73 (6.02)	164.77 (5.97)	164.33 (6.46)	174.43 (7.54)	174.44 (7.48)	174.24 (8.29)
Age in years at PE assessment				?		
Maternal pre-pregnancy BMI	22.78 (3.68)	22.76 (3.67)	22.97 (3.84)	22.90 (3.76)	22.88 (3.73)	23.18 (4.21)
Average number of head circumference measurements	6.4	6.4	5.9	6.7	6.6	6.8

Note. PE = psychotic experiences

4.3.2 Head circumference trajectories in females with psychotic experiences

As there was evidence of a group by sex interaction, we examined head circumference trajectories findings for psychotic experiences stratified by sex. Using univariable and multivariable models, we found evidence of reduced head circumference in females with psychotic experiences compared to female controls across childhood and adolescence (univariable model: B = -0.27, 95% CI: -0.49 - -0.05, p = 0.016; fully adjusted multivariable model: B = -0.25, 95% CI: -0.46 to -0.04, p = 0.022; Table 16 and Figure 17, for boxplot visualisation, see Supplement 4.4 Figure 20). The coefficient remained similar when adjusting models for confounders. When covarying for height, group differences in head circumference were no longer statistically significant at p < 0.05 (B = -0.12, 95% CI: -0.29 to 0.05, p = 0.16).

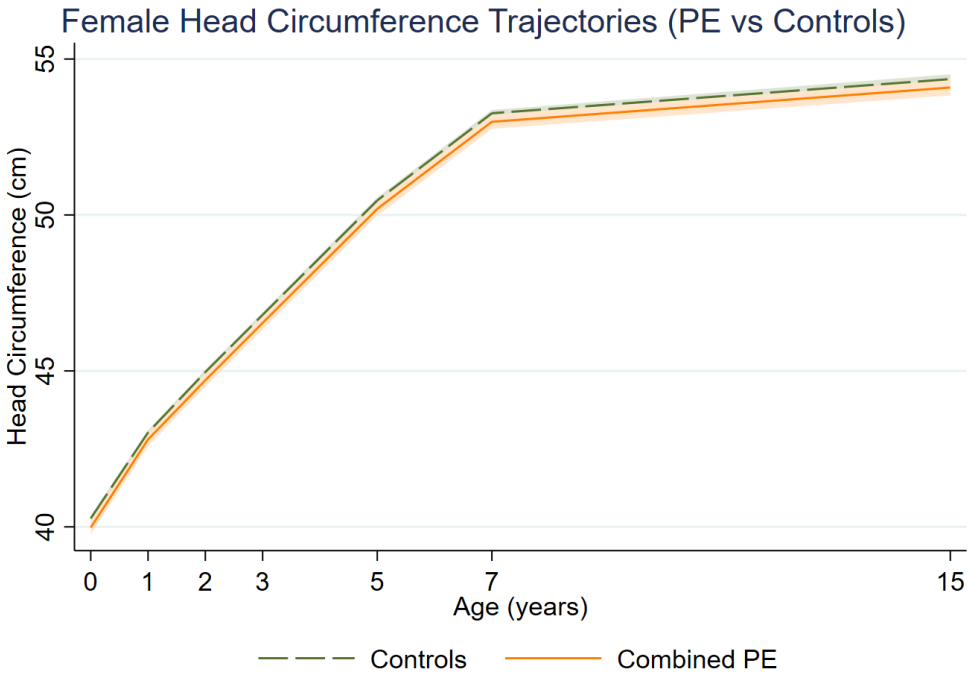


Figure 17. Head circumference trajectories (cm) in females with and without psychotic experiences (PE). Head circumference is modelled with 95% confidence intervals. We present age in years using integer values (N = 2,177).

4.3.3 Head circumference trajectories in males with psychotic experiences

In contrast to the reduced head circumference trajectories observed in females, males with psychotic experiences had increased head circumference across childhood and adolescence compared to male controls (univariable model: B = 0.35, 95% CI: 0.05 – 0.65, *p* = 0.023; fully adjusted multivariable model: 0.40, 95% CI: 0.12 – 0.69, p = 0.006; Table 17 and Figure 18, for boxplot visualisation see Supplement 4.4 Figure 21). The effect of group (psychotic experiences vs controls) remained after adding height as a covariate (B = 0.36, 95% CIL: 0.13 – 0.58, *p* = 0.002).

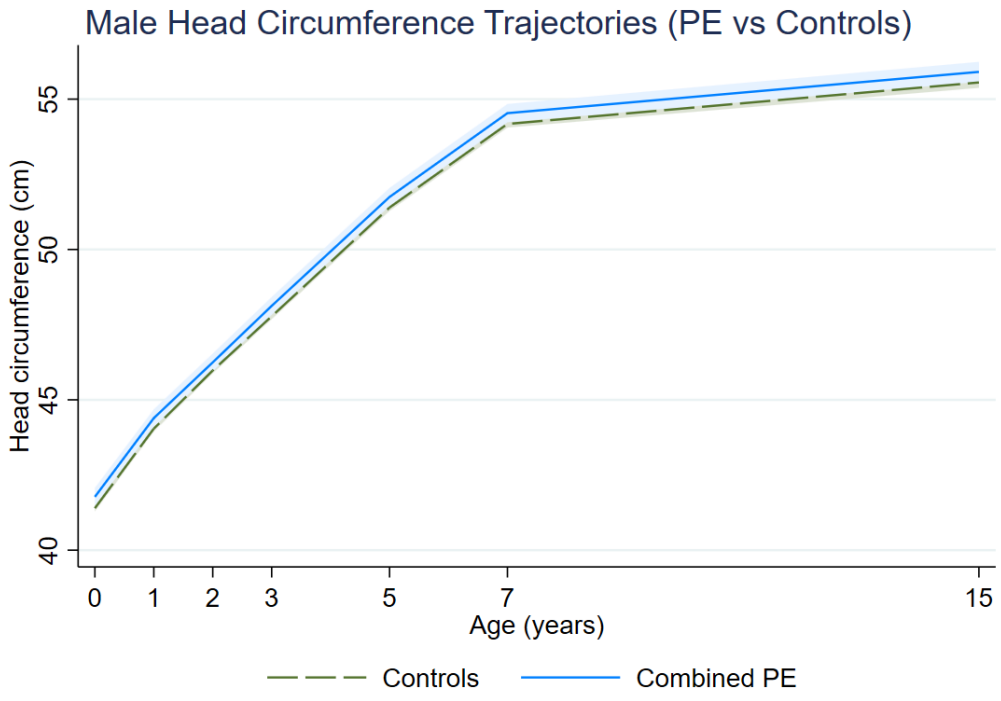


Figure 18. Head circumference trajectories (cm) in males with and without psychotic experiences (PE). Head circumference is modelled with 95% confidence intervals. We present age in years using integer values (N = 1,689).

Table 16. Head circumference trajectories in females with psychotic experiences (PE) vs female Controls, showing reduction in head circumference in PE.

Univariable and multivariable linear mixed regressions assessing head circumference in PE versus controls. Sample based on timepoints in which at least 10 people per group were present at each timepoint (Analytic sample N = 2,177, PE = 218, Controls = 1,959).

Female head circumference trajectories in **PE vs Controls**			
	Mean difference	95% Confidence intervals	*P*
Univariable model 1	-0.27	-0.49 - -0.05	0.016
Model 2: model 1 + maternal education	-0.23	-0.45 - -0.006	0.044
Model 3: model 2 + maternal BMI	-0.22	-0.44 - -0.004	0.046
Model 4: model 3 + gestational age and birth weight	-0.25	-0.46 - -0.04	0.022
Model 5: model 4 + height	-0.12	-0.29 – 0.05	0.16

Unconditional Model 1 (age) and Model 2 (mean centred age and age squared) are presented in supplemental material. For univariable model 1 onwards, we incorporated random effects of participant id and mean centred age. Univariable model 1 consisted of PE and time variables. Interactions between PE and age (p = 0.995), age squared (p = 0.80) were non-significant and therefore the group coefficient was not included in this table.

Table 17. Head circumference trajectories in males with psychotic experiences (PE) vs male controls, showing larger head circumference in those with PE.

Univariable and multivariable linear mixed regressions assessing head circumference in PE versus controls. Sample based on timepoints in which at least 10 people per group were present at each timepoint (Analytic sample N = 1,689, PE = 121, Controls = 1,568).

Male head circumference trajectories in **PE vs Controls**			
	Mean difference	95% Confidence intervals	*P*
Univariable model 1	0.35	0.05 – 0.65	0.023
Model 2: model 1 + maternal education	0.34	0.04 – 0.65	0.025
Model 3: model 2 + maternal BMI	0.33	0.03 – 0.64	0.029
Model 4: model 3 + gestational age and birth weight	0.40	0.12 – 0.69	0.006
Model 5: model 4 + height	0.36	0.13 – 0.58	0.002

Unconditional Model 1 (age) and Model 2 (mean centred age and age squared) are presented in supplemental material. For univariable model 1 onwards, we incorporated random effects of participant id and mean centred age. Univariable model 1 consisted of PE and time variables. Interactions between PE and age (p = 0.58), age squared (p = 0.93) were non-significant and therefore the group coefficient was not included in this table.

4.3.4 Head circumference trajectories in psychotic disorder

In the univariable model there was evidence of smaller head circumference in those with psychotic disorder compared to controls (B = -0.26, 95% CI: -0.47 - -0.04, *p* = 0.02; Figure 19 and Table 18). There was no evidence of an interaction with sex (*p* = 0.10), therefore we did not stratify results based on sex. When excluding sex as a confounder, results remained significant when incorporating multivariable models incorporating maternal education (B = -0.23, 95% CI: -0.45 - -0.02, *p* = 0.035) and BMI (B = -0.23, 95% CIL -0.44 - -0.02, *p* = 0.035), with slightly weaker evidence for reduced head circumference when gestational age and weight at birth were included (B = -0.20, 95% CI: -0.41 – 0.003, *p* = 0.054). When covarying for height, group differences in head circumference were no longer statistically significant (-0.05, 95% CI: -0.21 – 0.11, *p* = 0.52). Similarly, when multivariable analyses included sex as a confounder, there was no evidence of differences in head circumference trajectories in each model (*p* > 0.23).

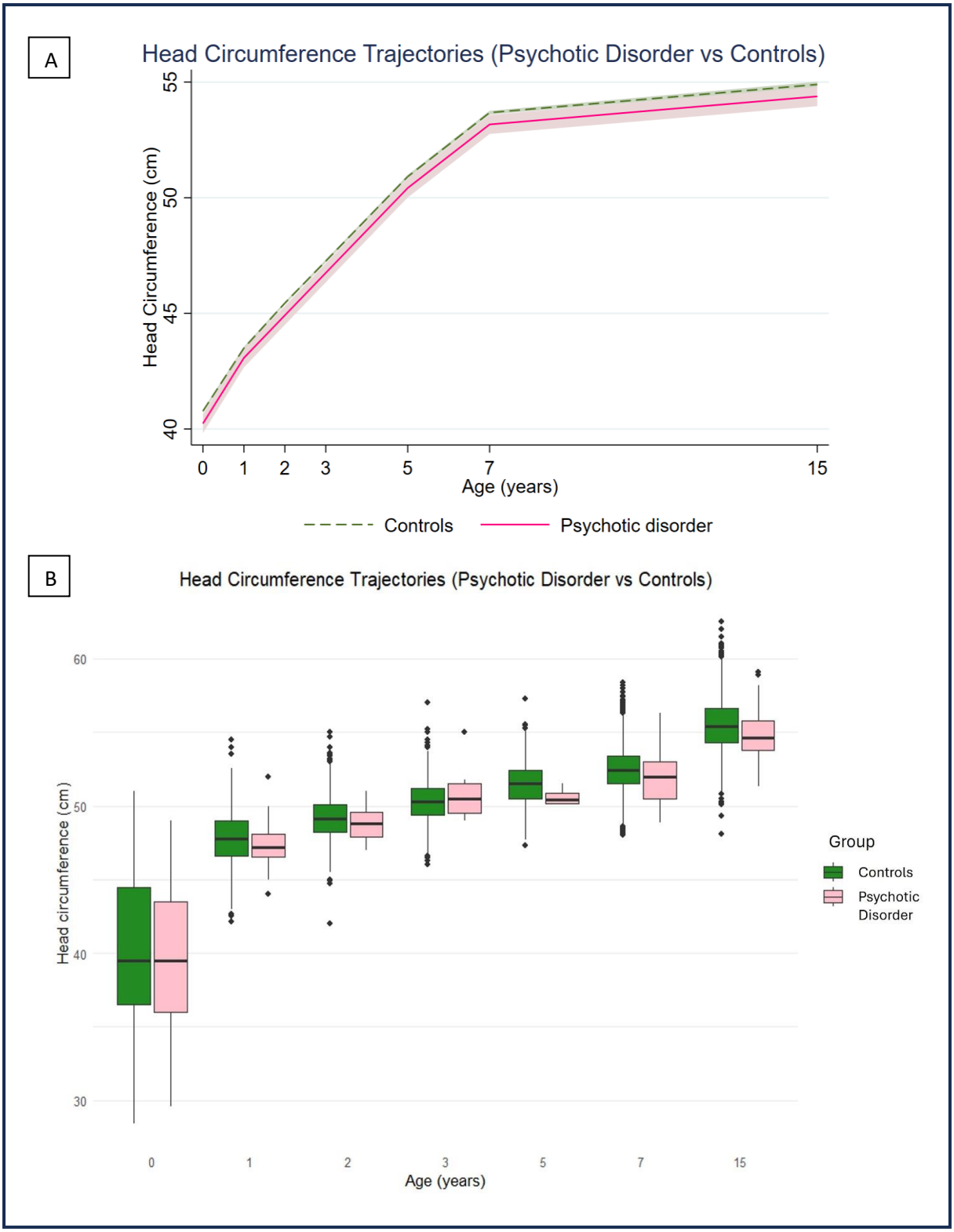


Figure 19. Head circumference trajectories (cm) in participants with and without psychotic disorder. As there was no interaction with sex, we present data for both males and females combined. Plot A shows results from fitting multivariable model 2 controlling for sex. Plot B charts head circumference data using boxplots. Both plots are modelled using 95% confidence intervals. We present age in years using integer values (N =3,589).

Table 18. Head circumference trajectories in participants with Psychotic Disorder vs Controls showing reduction in head circumference in Psychotic Disorder.

Univariable and multivariable linear mixed regressions assessing head circumference in psychotic disorder versus controls. We present results for multivariable analyses including and excluding sex as a confounder (Analytic sample N = 3,589, Psychotic Disorder = 62, Controls = 3,527)

Head circumference trajectories in **Psychotic Disorder vs Controls (not controlling for sex)**				Head circumference trajectories in **Psychotic Disorder vs Controls (controlling for sex)**			
	Beta coefficient	95% Confidence intervals	*P*		Beta coefficient	95% Confidence intervals	*P*
Univariable model 1	- 0.26	-0.47 - -0.04	0.02	Univariable model 1	- 0.26	-0.47 - -0.04	0.02
				Model 2: model 1 + sex	-0.13	-0.33 – 0.08	0.21
Model 2: model 1 + maternal education	-0.23	-0.45 - -0.02	0.035	Model 3: model 2+ maternal education	-0.11	-0.31 – 0.099	0.31
Model 3: model 2 + maternal BMI	-0.23	-0.44 - -0.02	0.035	Model 4: model 3 + maternal BMI	-0.10	-0.31 – 0.10	0.31
Model 4: model 3 + gestational age and birth weight	-0.20	-0.41 - -0.003	0.054	Model 5: model 4 + gestational age and birth weight	-0.09	-0.29 – 0.11	0.36
Model 5: model 4 + height	-0.05	-0.21 – 0.11	0.52	Model 6: model 5 + height	-0.03	-0.13 – 0.18	0.73

Unconditional Model 1 (mean centred age) and Model 2 (model 1 + age squared) are presented in supplemental material. For univariable model 1 onwards, we incorporated random effects of participant id and mean centred age. Univariable model 1 consisted of PE and time variables. Interactions between PE with age ($p > 0.5$) and age squared ($p = 0.85$) were non-significant and therefore the group coefficient was not included in this table.

4.3.5 MRI measures (TIV and GM volume)

Across participants, there was a moderate correlation between head circumference at birth and TIV at age 20 years (r = 0.45, p < 0.0001), and a stronger correlation between head circumference at ages 7 years (r = 0.77, p <0.0001) and 15 years (r = 0.77, p <0.0001) with TIV.

There was weak evidence males with psychotic disorder had larger TIV (*M* = 1591.25, SD = 121.03 vs *M* = 1551.25, *SD* = 110.44; *t* = -0.92, *p* = 0.36). However, females with psychotic disorder (*M* = 1330.46ml, *SD* = 101.02) had significantly smaller TIV compared to female controls (*M* = 1385.15ml, *SD* = 102.98; *t* = 2.40, *p* = 0.02). For psychotic experiences, there was weak evidence that males with psychotic experiences (1573.43ml, *SD* = 120.17) had larger TIV compared to male controls (*M* = 1551.25ml, *SD* = 110.43; *t* = -1.02, *p* = 0.31), whereas females had smaller TIV than female controls (*M* = 1385.15ml, *SD* = 102.98; t = 1.28, *p* = 0.20).

Grey matter volumes did not differ substantially between male participants with psychotic experiences (*M* = 747.24, SD = 55.05; *t* = -1.42, *p* = 0.16) or psychotic disorder *(M* = 767.62ml, SD = 49.02; *t* = -1.72, *p* = 0.089) to controls (*M* = 732.72ml, *SD* = 52.25). No evidence of grey matter differences was observed for females with psychotic experiences compared to female controls (*M* = 654.23ml, *SD* = 58.09 vs *M* = 661.26, *SD* = 47.85), however females with psychotic disorder (*M* = 637.62ml, *SD* = 42.44) displayed significantly smaller grey matter volumes compared to female controls (*M* = 661.26ml, SD = 47.85; *t* = 2.26*, p* = 0.025).

4.3.6 Odds ratios

Head circumference was a significant predictor of psychosis; scoring in the smallest 10% for head size was associated with an elevated risk for psychotic experiences in the combined sex group (OR = 1.51, 95% CI: 1.04 – 2.18, *p* = 0.026) and in females separately (OR = 1.82, 95% CI: 1.21 – 2.77, *p* = 0.005), but not in males (OR: 0.72, 95% CI: 0.34 – 1.53, *p* = 0.40). In contrast, scoring in the largest 10% was not associated with elevated risk (p = 0.99). Larger odds ratios were observed when looking specifically at psychotic disorder cases, with increased risk in the combined sex group (OR = 2.56, 95% CI: 1.29 – 5.06, *p* = 0.007) and in females (OR = 3.16, 95% CI: 1.54 – 6.49, *p* = 0.002) for small head circumference. No males with psychotic disorder were classed as having head circumference in the smallest 10%.

4.4 Discussion

Using data from a large population birth cohort, we present the first comprehensive exploration of head circumference trajectories from birth through to age 15 years in individuals with psychotic experiences. Our findings suggest that even at a subclinical level, head growth is atypical in individuals with psychotic symptoms. Smaller head circumference trajectories were observed in female with psychotic experiences relative to female controls, whereas males displayed a tendency for larger head circumference relative to male controls. Nevertheless, our findings support the neurodevelopmental model of psychosis, as smaller head circumference was observed during childhood and adolescence which was also linked with smaller TIV and GM volumes in adulthood. We also provide evidence that smaller, and not larger head circumference is associated with increased risk for both psychotic experiences and psychotic disorder.

Small head circumference at birth in individuals who go on to develop schizophrenia has been reported in several studies,[74,198,200–202] however the longitudinal trajectory of head circumference is unclear. Moreover, not all studies find reduced head circumference in neonates and during infancy, with some studies reporting larger head circumference and/or increased growth.[203,204] In adulthood, schizophrenia is associated with reduced total brain volume,[197] and one might hypothesise that differences in head circumference may emerge early during development. Our study provides evidence that head circumference is significantly reduced in those with psychotic disorder, as well as in females with psychotic experiences. This reduction is present from birth through to adolescence, as noted by the lack of an age by group interaction. In contrast, there was no evidence of reduced head circumference in males with psychotic experiences, which is congruent with findings at time of birth from two retrospective studies in individuals who go on to develop schizophrenia[74] or schizo-affective disorder/unspecified functional psychosis.[198] Furthermore, at least two studies in adulthood report increased head circumference in males with schizophrenia, [75,210] which corresponds with our finding of increased head circumference for male youth with psychotic experiences.

Head circumference shares a strong correlation with TIV (r = >0.70) and can be used as a proxy for brain development across the lifespan.[191] However, one meta-analysis of total brain volume (27 studies), intracranial volume (18 studies) and extracranial/head

circumference (8 studies) in adults with schizophrenia reports small but statistically significant reduction in brain and intracranial size, whereas differences in head circumference were inconclusive.[211] [75,210]. [99],[76,77]The incongruent findings between the two may be a result of the various tissues and spaces e.g., the skull, sinus, muscle, subcutaneous fat, meninges, and epidermal layers, which contribute towards head circumference and not brain volume.[212] [211]Furthermore, the present study collected data on children and adolescents, whereas the meta-analysis was based on adult data with a specific schizophrenia diagnosis. This meta-analysis was published in 1996, more up-to-date research is required to explore the relationships between the psychosis spectrum and head size across the lifespan.

The lack of research in this area limits our understanding of potential meaningful clinical subgroups which may or may not be linked to distinct head circumference trajectories. A subset of individuals with psychotic experiences also have a comorbid diagnosis of ASD, although this represents a small percentage (6%). It could be hypothesised that these individuals may share a common neurobiology with those with ASD. Given that psychosis was associated with smaller head circumference compared to controls, while ASD was linked to enlarged head circumference, it would be interesting to explore whether individuals comorbid for ASD and psychosis present with intermediate head circumference, or could be further sub-grouped into larger or smaller head circumference categories. If the latter, this distinction could provide insight into symptom profiles of these complex cases and might help inform future treatment strategies. However, this study was underpowered to examine whether the comorbid group showed distinct head circumference trajectories, due to the small number of participants who had both ASD and psychosis.

Despite reporting increased head circumference in males with psychotic experiences, scoring in the largest 10% of head size was not associated with increased risk for psychotic experiences or psychotic disorder. Small head circumference at birth was a better predictor of psychosis risk and could serve as a potential biomarker to aid identification of individuals at risk for psychosis. The mechanisms for reduced head circumference in psychosis are complex and likely multifaceted. Perinatal insults such as maternal infection, nutritional deficiencies, and complications during childbirth such as hypoxia are all linked to increased

risk of psychotic disorders and reduced head circumference.[199,213] Further reductions in GM volume may occur just before or at the onset of clinical disorder.[214]

There are several limitations to consider. As with most longitudinal studies, attrition and missing data reduced the sample size and representativeness of the study. We attempted to minimise the potential for selection bias by including participants with at least one head circumference measurement instead of requiring complete data on this measure. The number meeting our operational case definition of psychotic disorder was small and did not entail independent diagnosis by a healthcare provider. There were few males with psychotic disorder in this sample (n = 13), so the findings based on these individuals must be treated with caution. We adjusted for the main but not all confounders that have been implicated both in risk for psychosis and in head circumference, to avoid complicating the models so it is possible that we missed other factors that may have altered our results. Despite these limitations, this study makes a unique contribution to the investigation of head circumference within populations at risk for psychosis and improves our understanding of the neurodevelopmental trajectories within this group.

This study provides novel evidence for atypical head circumference trajectories that persist from birth to adolescence in young people with psychotic experiences, and compliments observations of brain volume in adults with psychosis. As measures of head circumference provide a useful proxy of brain development, our findings highlight that deviations in brain development are present at an early age across the psychosis spectrum.

4.4 Supplement

Model fit estimates for analyses in *females with psychotic experiences* indicated that incorporating mean-centred age and quadratic terms i.e., mean centred age squared (AIC = 705514.39; BIC = 70567.13) yielded superior results (i.e., lower AIC and BIC values) and a significant p value (head circumference B = -0.0008 cm, 95% confidence interval [CI] -0.0008 - -0.0008, $p < 0.0001$) compared to model 1 with unadjusted age values (AIC = 78560.03; BIC = 78605.24; B = 0.09, 95% CI 0.09 – 0.09, $p < 0.0001$). Consequently, we incorporated the time variables from model 2 into all subsequent models. AIC and BIC values remained largely unchanged beyond this point in univariable and multivariable models.

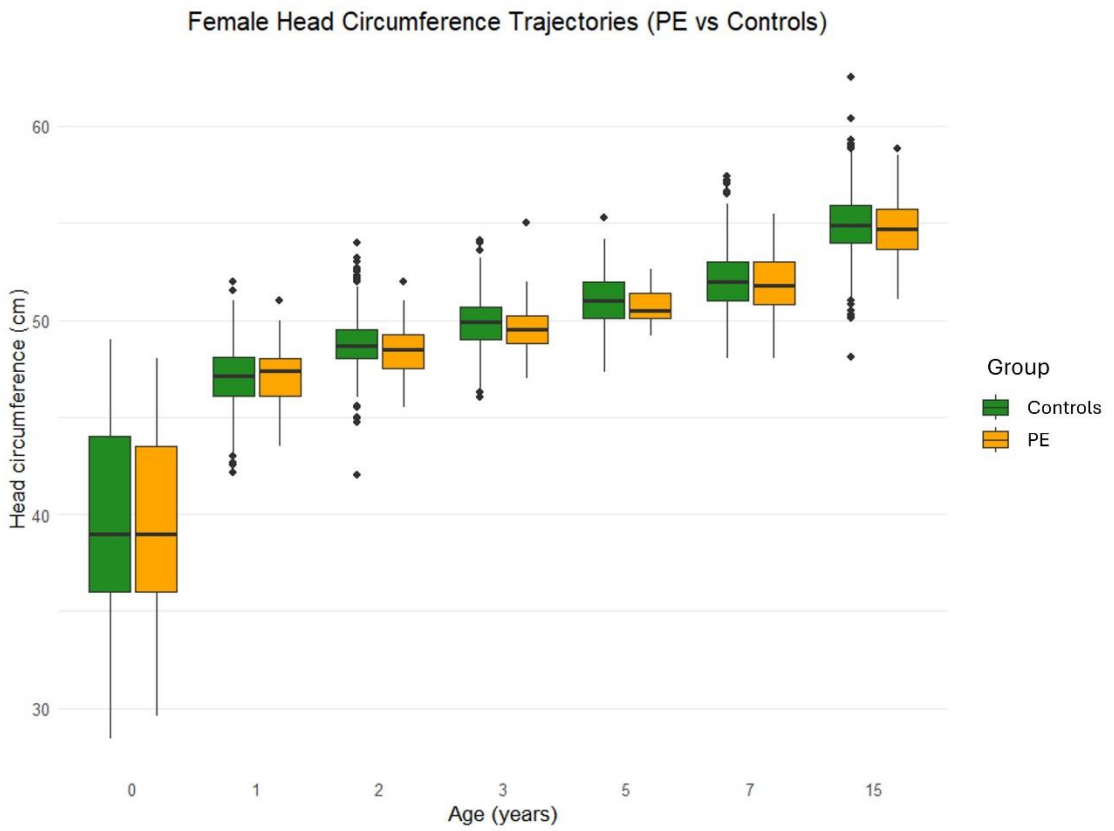


Figure 20. Boxplot of head circumference trajectories from birth to 15 years in females with psychotic experiences (PE).

Model fit estimates for analyses in *males with psychotic experiences* indicated that incorporating mean-centred age and quadratic terms i.e., mean centred age squared (AIC = 58624.74, BIC = 58676.03) yielded superior results (i.e., lower AIC and BIC values) and a significant p value (head circumference B = -0.0008 cm, 95% confidence interval [CI] -0.0008 - -0.0008, $p < 0.0001$) compared to model 1 with unadjusted age values (AIC = 64277.08, BIC = 64321.04; B = 0.09, 95% CI 0.09 – 0.09, $p < 0.0001$). Consequently, we incorporated the time variables from model 2 into all subsequent models. AIC and BIC values remained largely unchanged beyond this point in univariable and multivariable models.

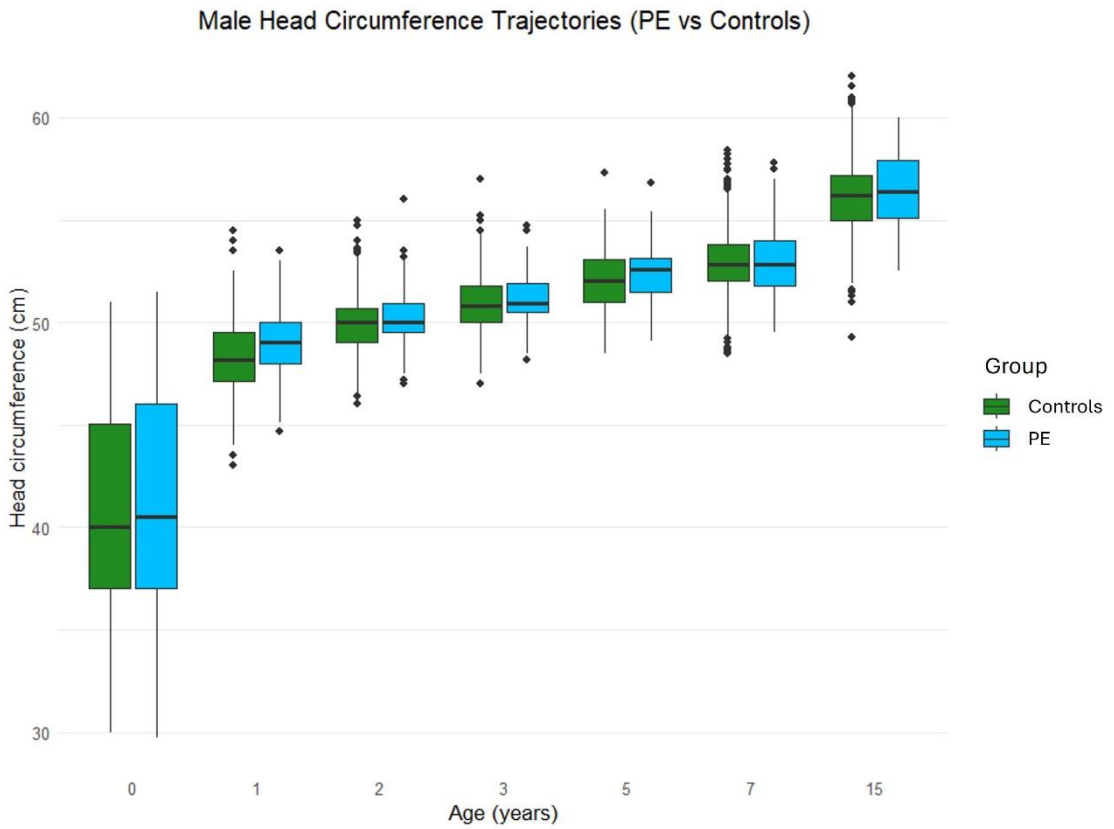


Figure 21. Boxplot of head circumference trajectories from birth to 15 years in males with psychotic experiences (PE).

Model fit estimates for analyses in *individuals with psychotic disorder* indicated that incorporating mean-centred age and quadratic terms i.e., mean centred age squared (AIC = 120473.5, BIC = 120529.9) yielded superior results (i.e., lower AIC and BIC values) and a significant p value (head circumference B = -0.0008 cm, 95% confidence interval [CI] -0.0008 - -0.0008, $p < 0.0001$) compared to model 1 with unadjusted age values (AIC = 133144.6, BIC = 133192.9; B = 0.09, 95% CI 0.09 – 0.09, $p < 0.0001$). Consequently, we incorporated the time variables from model 2 into all subsequent models. AIC and BIC values remained largely unchanged beyond this point in univariable and multivariable models.

Table 19. Characteristics of the full ALSPAC Cohort (N = 15,442).

	Full ALSPAC cohort
	N (%)
Total	15,442 (100%)
Sex	
Male	7,583 (49.10%)
Female	7,262 (47.02%)
Missing	597 (3.87%)
Ethnicity	
White	11,379 (73.62%)
Ethnic minority	604 (3.91%)
Missing	3,459 (22.46%)
Maternal highest education	
Compulsory/Vocational/None	7,975 (51.62%)
Non-compulsory	4,350 (28.12%)
Missing	3,117 (20.26%)
	Mean (SD)
Gestational age (weeks)	38.41 (5.49)
Birth weight	3393.01 (570.72)
Length at birth	50.80 (2.69)
Height at age 15.5 years	169.23 (8.36)
Maternal pre-pregnancy BMI	22.93 (3.84)

Chapter 5: Volumetric brain characteristics associated with autistic traits and psychotic experiences

Chapters 3 and 4 examine head circumference and total intracranial volume (TIV) in both ASD and psychosis. This chapter will examine differences in grey matter volume in individuals with high autistic traits, using the ALSPAC dataset.

5.1 Introduction

Growing evidence suggests that autistic traits lie on a continuum, with autism spectrum disorder (ASD) representing the extreme end of the distribution. ASD and autistic traits are aetiologically linked, with similarities in affected brain regions and reports of a linear relationship between severity of autistic traits and neuroanatomical changes.[215,216] Despite this current conceptualisation, most neuroimaging studies use case-control designs,[217] which may not accurately reflect the complex and dimensional nature of this condition.

Within ASD, findings relating to brain morphology are heterogenous, with widespread regions implicated and possible age-varying effects. For example, a 2015 meta-analysis of high-functioning ASD cases versus controls cited positive correlations between age and GM volumes in frontal and anterior-temporal regions, and negative correlations for parietal and inferior temporal regions in ASD.[218] Subcortical volume differences have been explored in the ENIGMA ASD working group,[217] the largest case-control mega-analysis to date, combining neuroimaging data from 49 cohorts (ASD N = 1,571, Controls = 1,651, age range: 2-64 years). ASD was linked with significantly smaller volumes in the basal ganglia and amygdala, while the lateral ventricles, TIV, and total grey matter volume were larger in ASD compared to controls. No interaction effects between diagnosis and age on subcortical volume were observed, indicating similar neurodevelopmental trajectories. However, a more recent meta-analysis reported no regions of GM increase or decrease in ASD, even when age was accounted for,[219] while our own meta-analysis of longitudinal imaging studies found increased total brain volume limited to childhood (see chapter 2). These meta- and mega-analyses highlight the complex and challenging nature of attempts to understand ASD and its neurobiological underpinnings. Using a dimensional rather than a categorical approach offers a broader and more inclusive avenue for investigating underlying neurobiology of ASD and better reflects the current nosological perspective.

Few studies have assessed grey matter differences associated with autistic traits, especially in adolescents and adults. Within neuroimaging samples, dimensional approaches have generally employed the Autism Spectrum Quotient (AQ)[220] or the Social Responsiveness Scale (SRS).[221] The AQ is a self-administered questionnaire designed to measure autistic traits in the general population. It comprises 50 questions assessing the concepts of social skills, attention switching, attention to detail, communication, and imagination. The SRS is a 65-item questionnaire measuring communication, interpersonal behaviours, and repetitive or stereotyped behaviours. Several neuroimaging studies in adolescents and adults report positive correlations between scores on these measures and GM volume in mainly cortical and some subcortical regions, [222–228] although the same studies also report instances of negative correlations. These regions are widespread, incorporating frontal, parietal and temporal cortices. While most studies using the AQ have found an association with brain morphology, one study found no significant associations between AQ scores and GM volume.[229]

The Social Communication Disorders Checklist (SCDC) is a brief 12-item population screening tool for autistic traits based on parental- rather than self-report. ASD is a highly heritable disorder, with heritability estimates of 0.8-0.9.[230] Heritability of the SCDC is 0.76, whereas estimates for the AQ (0.63) and SRS (0.48) are less impressive.[179,231] One might hypothesise that the scale's greater heritability might also yield disorder-relevant neuroanatomical correlations. Until now, no neuroimaging study has investigated the association between SCDC scores and grey matter volume. We hypothesised that higher scores on the SCDC would be associated with grey matter differences in young adults across predominately cortical brain areas associated with higher order language and cognition, i.e., left temporal, frontal, and parietal regions, with instances of both regional increases and decreases in grey matter volume, as found with other measures.

5.2 Methods

Sample

Neuroimaging data were acquired from two different sub-studies in the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort.[205,232–236] The ALPSAC Psychotic Experiences (PE) study recruited participants who were assessed for psychotic experiences at ages 17-18 years using the PLIKSi, selecting individuals with (n = 126) and without (n = 126) such

experiences.[235] The ALSPAC Schizophrenia-by-Genotype study recruited participants with high (n = 98) and low (n = 98) genetic risk for schizophrenia, scanning ages 21-24 years.[236] To maximise the number of scans, the samples of these two studies were combined, with unique structural MRI data were available for 434 participants (mean age 21 years). From this group, 359 participants also had complete data on the SCDC. The SCDC is a parent-report 12-item scale completed when the child was aged 7.5 years and assesses autism-like behaviours such as difficulties with social reciprocity and social communication.[237] Scores range from 0-24, with 24 representing the highest level of impairment. This continuous/dimensional scale was maintained in our analyses in lieu of using a cut-off of >=8. This approach facilitated greater sampling power and hence sensitivity, as a categorical approach would have resulted in only 25 participants with SCDC scores >= 8.

Written informed consent was obtained prior to scanning and participants received modest financial compensation. Approval was granted by Cardiff University, the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Bristol.[238] REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies. The study website contains details of all the data that is available through a fully searchable data dictionary and variable search tool http://www.bristol.ac.uk/alspac/researchers/our-data/.

MRI Acquisition

MRI data were acquired at Cardiff University Brain Research Imaging Centre (CUBRIC) on a 3T scanner (Signa HDx;GE Medical Systems) using an 8-channel head coil for radiofrequency reception. A high-resolution, 3D fast spoiled gradient-echo (FSPGR) T1-weighted isotropic image was oriented to the AC–PC line (TR= 7.8 ms, TE=3ms, inversion time=450ms, flip angle=20°, field of view=256mm× 256mm× 192mm, 1mm isotropic resolution) to assess grey matter volume.

Voxel-based morphometry (VBM)

The standard automated approach for measuring grey matter (GM) volume is with voxel-based morphometry (VBM).[239] This technique involves spatially normalising each T1-weighted brain scan into a standardised anatomical template and segmenting grey matter from white matter and cerebrospinal fluid. The Computational Anatomy Toolbox (CAT12,

http:// dbm.neuro.uni-jena.de/cat12/) for Statistical Parametric Mapping (SPM 12) was used to preprocess the brain scans. 'Modulated' images corrected for non-linear deformations were used for analyses. Spatial smoothing used a Gaussian kernel of 8mm full width at half maximum using SPM 12 standard routines. Voxel-wise comparison of modulated T1-segmented grey matter images was performed using a general linear model, examining the effect of SCDC scores (continuous from 0-24) on grey matter volume. Age, sex and TIV were included as covariates. Thresholds were set at $p < 0.001$ uncorrected at the voxel level, using family-wise error correction for multiple comparisons at *p*FWE <0.05 at the cluster level. We also report results using *p*FDR (<0.05) correction threshold, which is slightly less stringent than *p*FWE. After extracting TIV and total grey matter volume, we performed Kendall correlations in R (version 4.3.0) to investigate the association between these variables and SCDC scores.

5.3 Results

5.3.1 Descriptive statistics

Analyses included data from 359 participants (211 female) with SCDC and MRI data (Table 20). Age at scan ranged from 19 – 25 years, with a mean of 21.26 years. The average score on the SCDC was 2.57 (SD = 3.38), with a range of 0-21. Mean scores were similar to those observed in the whole ALSPAC sample (N = 7,813, M = 2.81, SD = 3.74, range: 0-24). Figure 22 shows the half-normal distribution of SCDC scores with neuroimaging data. Most participants exhibited minimal autistic traits, with the frequency of elevated autistic traits progressively decreasing.

Table 20. Demographic characteristics of MRI analytic sample (N = 359) compared to full ALSPAC sample (N = 15,442)

	Analytic Sample N (%)	Full ALSPAC Sample N(%)
Total	359 (100%)	15,442 (100%)
Sex		
Male	148 (41.23%)	7,583 (49.10%)
Female	211 (58.77%)	7,262 (47.02%)
Missing	0	597 (3.87%)
Ethnicity		
White	341 (95.01%)	11,379 (73.62%)
Ethnic minority	8 (2.22%)	604 (3.91%)
Missing	10 (2.77%)	3,459 (22.46%)
Maternal highest educational attainment		
Compulsory/Vocational/None	168 (46.80%)	7,975 (51.62%)
Non-compulsory	185 (51.53%)	4,350 (28.12%)
Missing	6 (1.67%)	3,117 (20.26%)
Mean IQ (SD)	110.9 (15.15)	104.1 (16.53)
Mean SCDC score (SD)	2.57 (3.38)	2.81 (3.74)
ASD Diagnosis Present (age 9 years)	2 (0.56%)	95
Psychotic Experiences Present (age 18 years)	149 (41.54%)	432

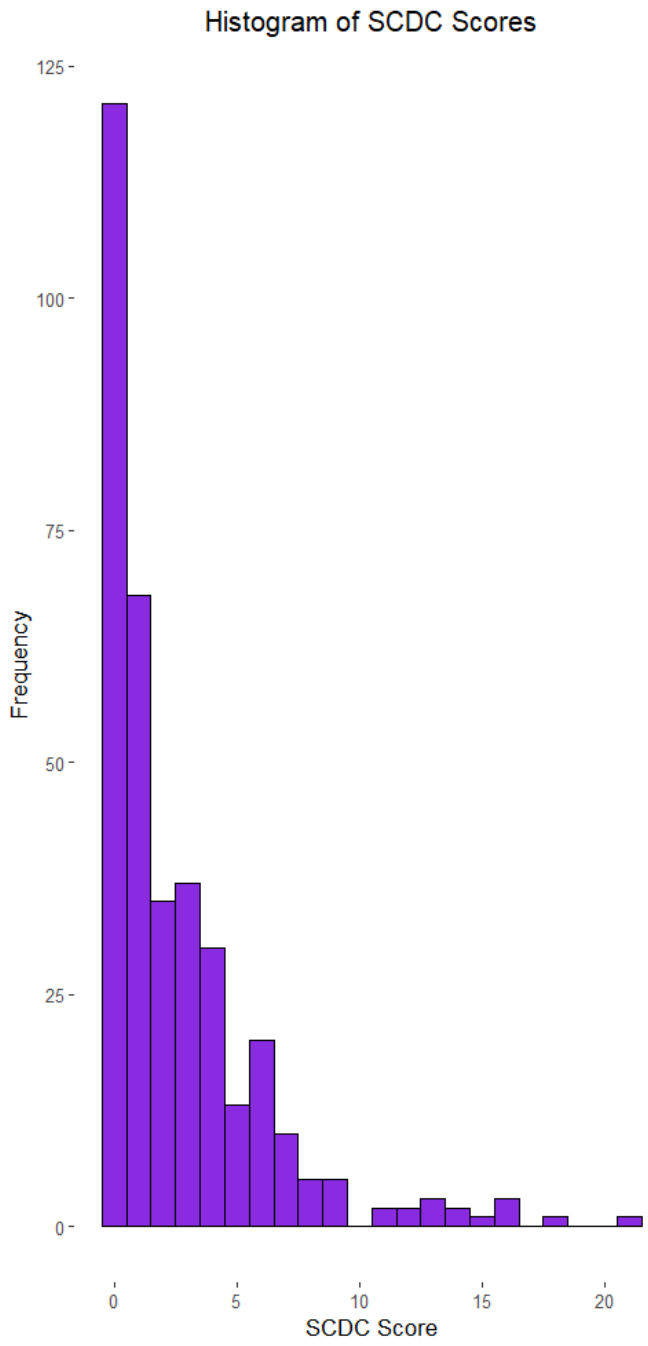


Figure 22. Histogram displaying frequencies of SCDC scores across the neuroimaging sample (N = 359).

5.3.2 Regional grey matter volume

Higher scores on the SCDC (i.e., >= 8) were associated with *increased* grey matter volume in the left paracentral lobule extending into the medial surface of the superior frontal gyrus (*p*FWE = 0.033; -2, -16, 74, *Z* = 4.10, 313 voxels; Figure 23). Using false discovery rate (FDR), the left precuneus also showed *increased* grey matter volume associated with autistic traits (*p*FDR = 0.037; -21 -48 10; Z = 3.71, voxels = 122; Figure 24). *Reductions* in grey matter were

observed in the left supramarginal gyrus extending into the inferior postcentral gyrus (somatosensory cortex) (*p*FWE < 0.001; -66, -27, 33, *Z* = 4.02, 664 voxels; Figure 25).

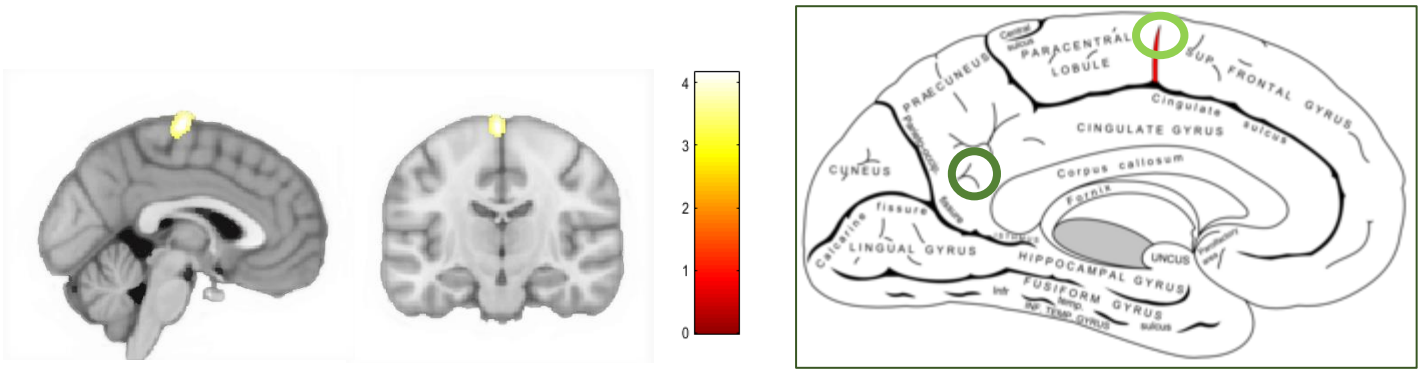


Figure 23. Autistic traits were associated with *increased* grey matter volume in the left paracentral lobule and superior frontal gyrus at FWE correction. This cluster has been circled in light green on the medial brain schematic. Schematic taken from Wikimedia Commons.

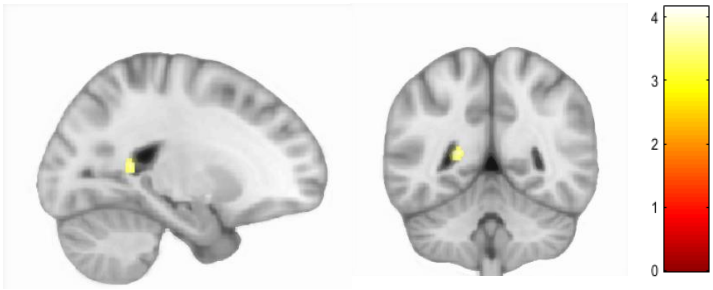


Figure 24. Using FDR correction, autistic traits were associated with *increased* grey matter volume in the precuneus. See medial brain schematic above with the precuneus circled in dark green.

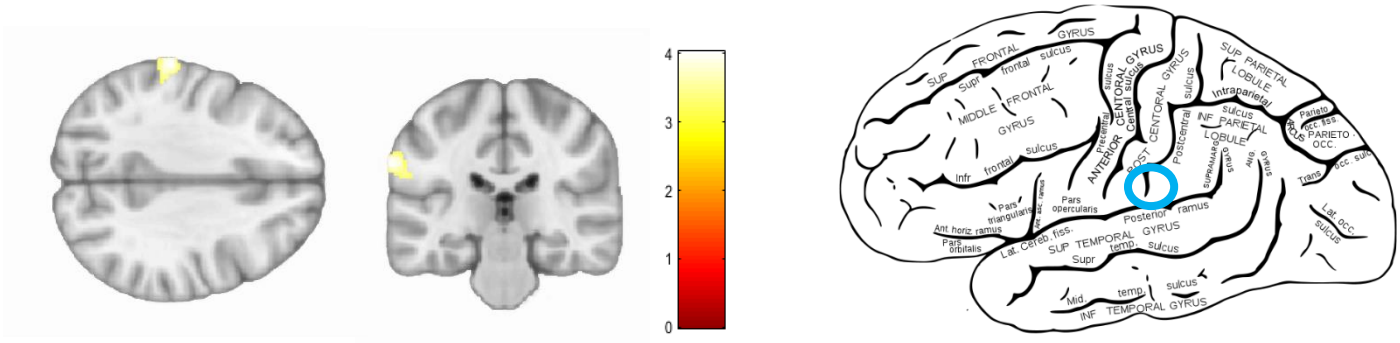


Figure 25. Autistic traits were associated with *reductions* in grey matter volume in the left supramarginal gyrus extending into the inferior postcentral gyrus (primary somatosensory cortex). This cluster has been highlighted in blue on the cortical surface brain schematic. Schematic by Henry Carter, Wikimedia Commons.

5.3.3 Total intracranial volume (TIV) and total grey matter volume

There was no evidence of a significant correlation between SCDC scores and TIV (tau [357] = 0.01, p = 0.76; Figure 26) or total grey matter volume (tau [357]= 0.02, p = 0.62; Figure 27).

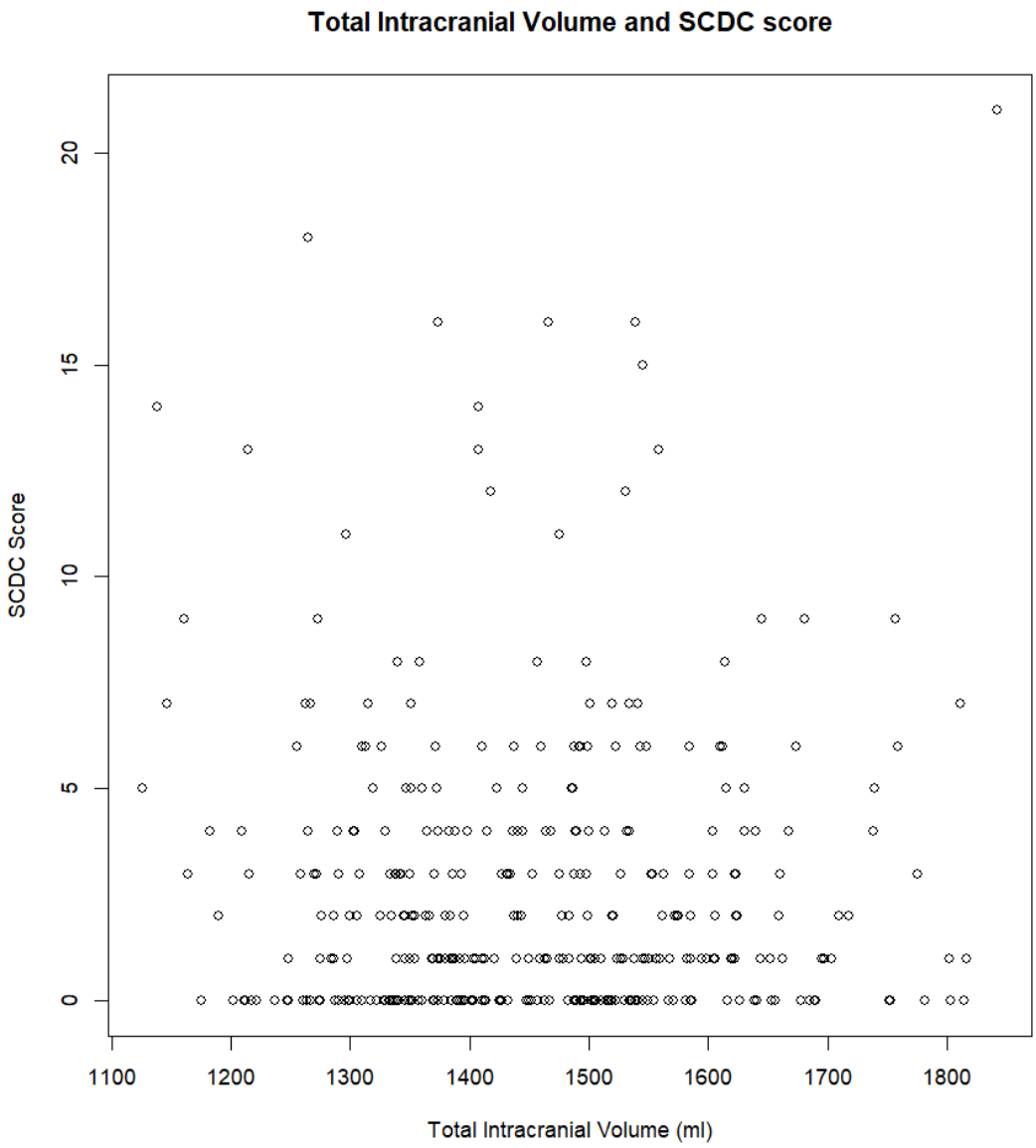


Figure 26. No signification correlation between scores on the social communication disorder checklist (SCDC) and total intracranial volume (ml).

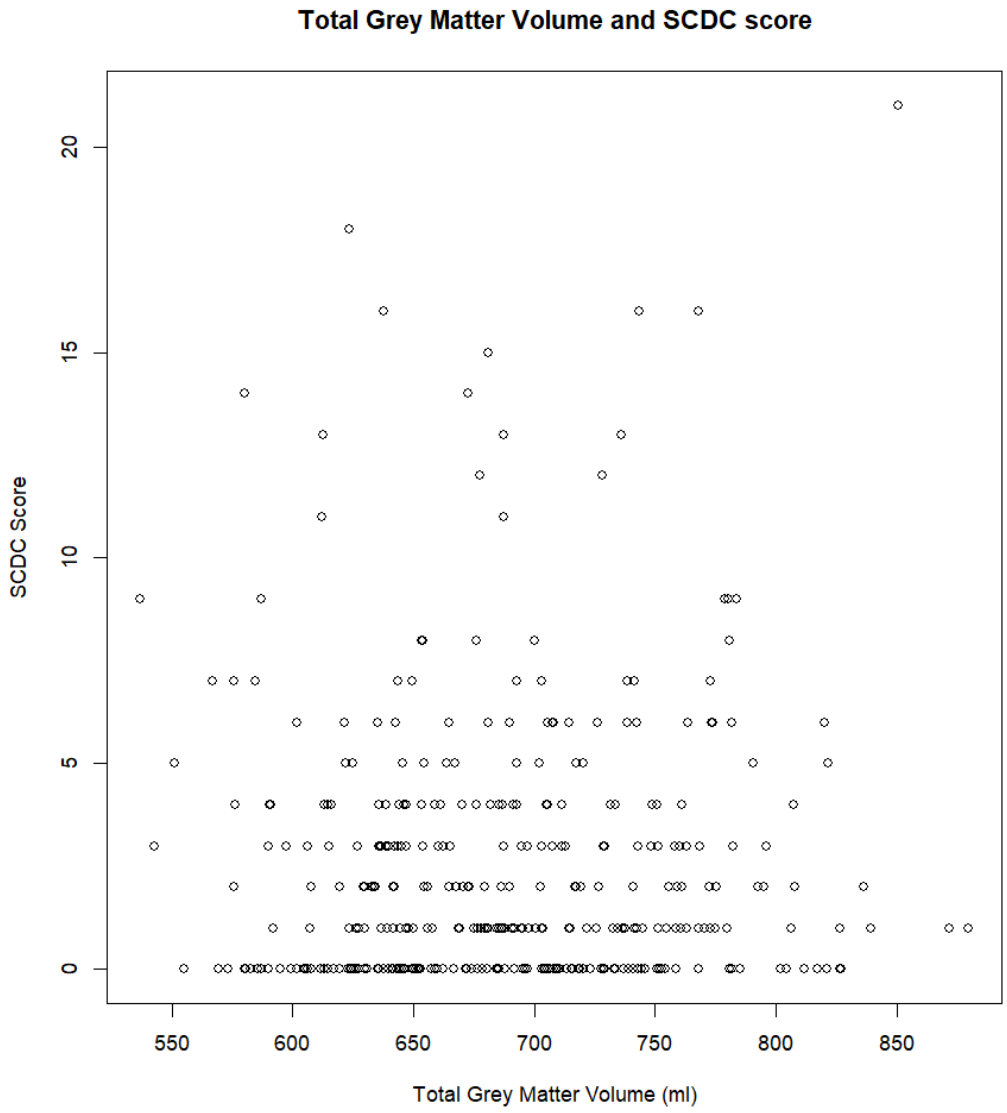


Figure 27. No significant correlation between scores on the social communication disorder checklist (SCDC) and total grey matter volume (ml).

5.4 Discussion

In the current study, we investigated associations between grey matter volume and autistic traits (measured by the SCDC). Consistent with our hypotheses, autistic traits were associated with grey matter alterations in cortical brain regions, with no subcortical regions identified. Differential effects were observed depending on brain region, with both increased grey matter volume (superior frontal/paracentral and precuneus) and reduced grey matter volume reported (somatosensory cortex). Our findings suggest alterations in regions responsible for processing sensory signals from the body (postcentral, supramarginal, and paracentral gyrus), as well as top-down processing in frontal and parietal regions (superior

frontal and precuneus). We found no association between autistic traits and TIV or total grey matter volume in our sample.

Our finding of increased grey matter volume in the left superior frontal gyrus is consistent with studies of adolescents and adults with high-functioning ASD,[240,241] as well as a meta-analysis spanning ages 7-44 years.[242] Functionally, this region has been linked to theory of mind (i.e., attribution of mental states to the self and others), self-reflection, working memory, and the mediation of cognitive control during social-emotional appraisal.[243,244] In studies examining autistic traits, no alterations were reported in this region, but instead increased volume was found in an adjacent region, in the left middle frontal gyrus.[225] The middle frontal gyrus contributes to literacy development and conversational pragmatics,[245,246] with lesions to this area resulting in individuals using simple sentence structure and fixation of thought patterns.[247,248] The functions of the superior and middle frontal gyrus both have clear implications in ASD symptomatology, the fact that both regions were not simultaneously identified in our study might be a reflection of trait heterogeneity across the spectrum, with some individuals affected by one or the other, or possibly alterations in both regions, as shown in research from the ENIGMA consortium.[249]

The precuneus, another region associated with theory of mind and self-awareness, showed increased volume with ASD traits in our study, consistent with findings from two case-control meta-analysis.[242,250] Greater impairment on the autism diagnostic observation schedule (ADOS) communication and social subscales, a gold standard assessment tool for ASD, has been shown to correlate with weakened connectivity of the middle temporal gyrus with the superior frontal gyrus, precuneus and paracentral lobule.[251] The paracentral lobule and the precuneus are thought to operate together to produce a sense of self and body/spatial representation. Increased volume in the paracentral lobule, alongside increased volume in the precuneus as found in our study, and knowledge of its functional connections with other regions suggests that ASD comprises of deficits in intrapersonal and interpersonal domains which may affect how theory of mind develops.

A number of significant clusters within our study overlap with regions responsible for processing sensory signals from the body, including the postcentral, supramarginal, and paracentral gyrus. The postcentral gyrus is the location of the primary somatosensory cortex within the parietal lobe. The somatosensory cortex processes sensory information from the

body and is topographically arranged into where each part of the body is processed (i.e., homunculus). Atypical sensory processing is common in ASD, affecting 82%-97% of cases, and documented for all sensory modalities.[252,253] Our findings of reduced grey matter volume in the left inferior postcentral gyrus may correspond with sensory processing of the face and mouth as this is represented in the inferior region of the homunculus.[254] The postcentral gyrus has also been shown to influence emotional processing, including the identification, generation, and regulation of emotional states.[255] Individuals with ASD are often reported to have atypical or diminished emotional expression in the face and voice, as well as difficulty with identifying and understanding their own emotions.[256] This finding is supported by the multicentre study EU-AIMS LEAP (age range 6-30 years) in which ASD was associated with reduced grey matter of the postcentral gyrus compared to controls,[257] and in another meta-analysis in adults with ASD.[250] A meta-analysis of functional imaging studies also reported reduced activation in this area in adults with ASD compared to controls.[258]

Extending from the postcentral gyrus, we also found reductions in grey matter volume in the left supramarginal gyrus associated with elevated SCDC scores. This region forms part of the somatosensory association cortex, which receives input from the primary somatosensory cortex, occipital and temporal lobes, and projects to supplementary motor and premotor cortices.[259] The left supramarginal gyrus has been linked to phonological processing and verbal working memory,[260,261] as well as gesture planning and comprehension.[262,263] Previous research has shown evidence of impaired speech-and-gesture integration in ASD,[264] as well as generally using less gestures during social interactions.[265] Another phenotypic characteristic of ASD is cognitive inflexibility and insistence on sameness. One study in autistic youths ages 10-23 years reported grey matter reductions in the left supramarginal gyrus in those classified as high insistence on sameness compared to the low insistence group.[266] Finally, increased volume was found in the left paracentral lobule, which is the medial continuation of the precentral and postcentral gyri (moving deeper within the brain). The left paracentral lobule controls motor and sensory innervations of the right lower extremity (leg, foot, genitals) as well as body and spatial representation.

The superior frontal gyrus and precuneus play a critical role in higher order cognition and top-down processing, in which schemas built on prior knowledge and expectations guide perceptions of incoming sensory information. Top-down processing is important to navigate

complex behaviours, such as social interactions, and allows for predictions to be made about a stimulus e.g., expected facial expressions in different contexts. Several studies have demonstrated that top-down processing is atypical in individuals with ASD,[267] with a bottom-up detail driven approach being the more dominant cognitive style. The imbalance between the use of top-down versus bottom-up approaches may result in poor social adaptation and difficulties understanding the broader context. [268]

While the regions identified in this study correspond to affected regions in ASD cases, we only found one region which overlapped with previous findings examining autistic traits, [225] namely the left postcentral gyrus. Scores on the SRS and AQ were associated with grey matter alterations in both cortical and subcortical regions, [222–228] whereas SCDC scores were specifically associated with cortical volumes. Several overlapping regions were identified between the SRS and AQ, including the right orbitofrontal cortex, left middle temporal gyrus, and parahippocampal gyrus. The putamen also showed overlap between measures, however volumes were reduced using the SRS in an adolescent sample, but increased when using the AQ in an adult sample. Additionally, the cerebellum was larger in the SRS adolescent sample, but smaller using the AQ in an adult female sample. There does, however, appear to be a predominance of cortical regions affected across measures, with over double the number of cortical regions (n = 17) than subcortical (n = 7) when combining findings across studies using the AQ and SRS. [222–228] This suggests that autistic traits within the general population are predominantly an impairment of higher order cognition as opposed to lower-level emotional processing in limbic regions in the subcortex. This is reasonable when considering the complex nature of human social communication and the need for integration across visual, auditory, somatosensory and frontal regions for decision-making and inferences.

The general lack of overlapping regions between the SCDC with the SRS and AQ may reflect that fact these scales capture different aspects of autistic traits. For example, the SCDC may better capture social and communication impairments that are characteristic of ASD, whereas the AQ and SRS may capture autistic traits more broadly as they include additional questions on repetitive behaviours, restricted interests, and need for routine. It also highlights how brain related findings remain highly heterogenous across the ASD spectrum. Moreover, there are differences in administration of these scales, as the SRS and AQ are self-administered questionnaires, with the SRS also having options for teacher/parent

completion in younger ages, whereas the SCDC is based on parent report and has not been validated in adult samples. Indeed, two of the studies cited using the SRS were based on parent-report in adolescents aged 14-17 years,[227] and 14-22 years.[228] All of the studies using the AQ were based on adult self-report, with the majority based on young adults (ages 18-29 years),[222,223,225] but some were based on older cohorts (>38 years).[224,226] One of the AQ studies used the 28-item short version,[223] whereas the others used the full length 50-item questionnaire.[222,224–226] The present study assessed SCDC at age 7.5 and was parent-reported. Therefore, our study is at a younger age than the studies using the SRS and AQ. Discrepancies between the age of cohorts, length/version of the questionnaire, and whether the measure was self-report or parent-report may have contributed to the lack of agreement between studies.

In clinical samples, sensitivities for ASD screening are higher using the SCDC (0.85 – 0.90) compared to the SRS (0.74 – 0.80), whereas specificities were higher for the SRS (0.69 – 1.00) than the SCDC (0.28 – 0.82).[269] The SCDC may therefore be superior to the SRS for screening more general social-communicative psychopathology, including autism, whereas the SRS may be more suitable for autism specific diagnoses in clinical settings. Within ALSPAC, a cut-off score of 8 or more yielded sensitivities of 0.75 – 0.94 and specificity of 0.90 – 0.91 in relation to independently diagnosed cases of ASD in the general population.[270] In sum, the brevity (12 items) and strong sensitivity of the SCDC for social and communication deficits makes this measure well-suited to population-based studies, whereby enhanced sensitivities are also noted.

One of the most consistently reported brain findings in ASD is that of early brain overgrowth.[95,96,271] Whether this overgrowth persists has been questioned in the literature, however our own findings in study 1 of this thesis (chapter 2) suggest that overgrowth is restricted to the first few years of life, and normalises with age. In the current study, autistic traits were not associated with increased TIV in adulthood. This might reflect normalisation of brain volumes akin to findings from study 1, although earlier MRI data is not available in this study. One population-based cohort (Generation R) which scanned individuals at 10 years of age reported that autistic traits, as measured using the SRS, were negatively correlated with total brain volume and cortical grey matter volume.[272] The Adolescent Brain Cognitive Development Study also reported lower ICV associated with elevated scores on

the SRS in children aged 9-10 years.[273] It is possible that while we found regional differences in frontal/parietal brain regions, these differences are not found globally for total brain volume. This suggests TIV and total brain volume may be altered in childhood and adolescence in ASD and ASD traits, but are only seen in adulthood in more severe ASD cases and not at a trait level.

This study combines data from two neuroimaging cohorts within ALSPAC initially recruited based on assessments for psychotic experiences and genetic risk for schizophrenia. As such, sampling bias is present within this study, with 40% of the sample also reporting a history of psychotic experiences. Subgroup analyses were considered in which those with comorbid elevated autistic traits and psychotic experiences could be compared to those with elevated autistic traits alone, however due to the low sampling power (N = 9) these analyses were not undertaken.

Previous research in the ALSPAC cohort has demonstrated a link between autistic traits and psychotic experiences. One study which measured autistic traits using the SCDC at 7.5 years and psychotic experiences at age 12 years reported an 11% increase in odds for every 1 SD increase in SCDC scores.[76] A separate study using the SCDC reported larger odds ratios when psychotic experiences were distressing and/or frequent until age 24 years (adjusted OR: 1.54, 95% CI: 0.97 – 2.45, p = 0.07).[274] Within the ALSPAC cohort, grey matter alterations in those with psychotic experiences (n = 138, controls = 275) have already been investigated with the use of VBM analyses. Volumes were reduced in three regions, the left anterior cingulate, posterior cingulate, and the thalamus, all of which have been implicated in those with clinical diagnoses of schizophrenia.[67] No regions overlapped with the findings identified in this study, however another study in a slightly smaller subset of this cohort reports reduced grey matter in the left supramarginal gyrus was associated with psychotic experiences (n = 125, controls = 125), matching the results with ASD traits in our study, suggesting this may be a region of shared psychopathology. A meta-analysis of VBM studies in individuals at clinical-high risk for schizophrenia, recently diagnosed and chronic schizophrenia patients showed disorder-related cortical to subcortical, left to right progression of grey matter reductions.[71] It is possible that like the psychosis spectrum, the ASD spectrum may follow a similar pattern of brain alterations, as only left lateralised cortical regions were affected in this study. Typically developing individuals generally have

slight asymmetry between left and right hemispheres,[275] favouring left lateralization in language regions. In contrast, ASD has been shown to be associated with atypical left-to-right lateralization, with reduced grey matter volume and connections between language regions and the default mode network in the left hemisphere.[276–278]

There are several strengths and limitations to consider. This is the first VBM study of autistic traits using the SCDC. By using a continuous approach, we avoid artificial cutoffs and can study brain differences more naturally based on how traits may appear in the population. However, our sample was initially recruited for a case-control study of psychotic experiences, based on the psychosis-Like symptoms semi-structured interview, and as a result the brain regions identified may not fully be representative of autistic trait related changes but also confounded by psychotic experiences. Nevertheless, the design included controls without such experiences and with low genetic risk for psychosis, [72,236] and we also identified novel brain regions associated with social and communication difficulties that were not observed in previous psychotic experience papers within ALSPAC. Second, the current study focused on young adults hence developmental changes prior to this age will have been missed; future work is needed to examine grey matter alterations associated with SCDC scores in younger samples.

In conclusion, elevated autistic traits measured using the SCDC were associated with significant increases in grey matter volume in the left paracentral lobule, superior frontal gyrus, and precuneus, with reductions in the left supramarginal gyrus and postcentral gyrus. These regions have also been identified as areas of difference in case control studies of people with ASD, although not in MRI studies examining the SRS and AQ, highlighting the heterogeneity of autistic traits and ASD.

Chapter 6: General discussion

In this chapter, I summarise the main findings from my thesis and contextualize these findings based on the existing literature. I explore the strengths and limitations of my research, including threats to validity such as bias and confounding. The theoretical and clinical implications of my findings are discussed along with suggestions for future research. Finally, I provide overall conclusions to this thesis.

6.1 Summary of main findings

Our knowledge of biomarkers for ASD and psychotic experiences are limited, and it is not clear how neurodevelopmental trajectories might differ between the two. This thesis had four main aims:

1. To understand the longitudinal trajectories of TBV in ASD by synthesizing the current literature through a meta-analysis.
2. To explore head circumference trajectories from birth through to adolescence in individuals with and without ASD and elevated autistic traits.
3. To explore head circumference trajectories in individuals with psychotic experiences and psychotic disorder.
4. To examine changes in grey matter volume associated with autistic traits in young adults, and to compare findings to those with psychotic experiences within the same cohort.

In the first study of my thesis (chapter 2), I synthesized data from 7 longitudinal neuroimaging studies comparing TBV in individuals with ASD (n = 559) to controls (n = 3,645). I began with a cross-sectional analysis in which I explored differences in TBV across all available studies and their timepoints, with an overall finding that TBV was larger in ASD compared to controls. However, a meta-regression with age revealed that brain overgrowth appeared to be specific to early childhood (6 months-5 years), with a trend for reduced TBV in adulthood. For longitudinal changes in TBV over time, ASD showed reduced rate of TBV growth over time compared to controls. Meta-regressions indicated that lower IQ was associated with larger TBV in ASD. This is the first neuroimaging meta-analysis to focus exclusively on longitudinal studies in individuals with ASD, providing novel findings relating to changes in neurodevelopment over time.

The remaining chapters of this thesis use data from the population-based cohort ALSPAC. In chapter 3, longitudinal head circumference trajectories are charted from birth through to 15 years in young people, (a) with and without ASD and (b) elevated autistic traits. There was evidence of increased head circumference trajectories in ASD which persisted across this time period. Severity of ASD was shown to impact trajectories, with largest head circumference observed in individuals with ASD and comorbid cognitive learning needs (CLN). However, scoring in the top 10% for largest head circumference at birth was not associated with later ASD risk, indicating that differences in head circumference may be subtle initially. Contrary to our hypothesis that elevated autistic traits would be associated with intermediary trajectories between ASD and controls, our results show significantly smaller head circumference in the autistic trait group compared to controls. These findings highlight the distinct trajectories for subclinical traits compared to clinical ASD cases.

Chapter 4 explored head circumference trajectories in those with and without psychotic experiences. Females with psychotic experiences had smaller head circumference trajectories compared to female controls, whereas the opposite was observed in males with psychotic experiences. Those with a more severe classification of psychotic disorder had smaller head circumference trajectories with no interaction effect with sex. Head circumference in the lowest 10% at birth was associated with increased odds for developing both psychotic experiences and psychotic disorder. Based on a subset of this sample, we also reported that head circumference at birth, 7, and 15 years positively correlated with TIV at 21 years, with coefficients ranging from 0.45 at birth to 0.77 at 7 and 15 years. Therefore, head circumference is a strong proxy measure for later brain volume, and consistent with this, we found that females with psychotic disorder had smaller TIV and total grey matter volume at 21 years compared to female controls. Despite larger head circumference in males with psychotic experiences, there were no differences in TIV at age 21 in this group, and males with psychotic disorder also showed no differences in TIV.

Finally, in chapter 5 we investigated differences in TIV and regional grey matter volumes in individuals according to levels of autistic traits as measured using the SCDC. There was a positive association between SCDC scores and grey matter volume in the left paracentral lobule, superior frontal gyrus, and precuneus, and negative association in the left supramarginal gyrus and inferior postcentral gyrus. These regions are all located within the

cortex and are typically involved in higher-order cognition and sensory processing. Despite these regional differences in brain volume, there was no significant correlation between SCDC scores with TIV and total grey matter volume. While autistic traits were associated with increases and decreases in cortical brain regions, previous ALSPAC research on individuals with psychotic experiences indicate alterations in limbic subcortical structures. One brain region was associated with both autistic traits and PE and that was the left supramarginal gyrus, an important region linked to language processes, which showed reduced grey matter volume.

6.2 Findings in context

Our finding of increased TBV in ASD during early childhood corresponds with two meta-analyses of cross-sectional MRI data which cite initial brain overgrowth followed by normalisation of volumes with age.[95,96] The timing of brain enlargement is of importance, as the early years of life are critical in establishing the foundational neural architecture of the brain while also having implications for future cognitive, social, and behavioural outcomes.[22] These early alterations to the developing brain in ASD occur prior to the emergence of ASD diagnostic behaviours,[279,280] with the average age of diagnosis 5 years.[281] The discrepancy between the timing of brain-based changes and ASD diagnosis highlights an opportunity for early detection and intervention which may help to improve developmental trajectories. Our meta-analysis did not reveal an accelerated rate of change in ASD, suggesting that rapid growth must have occurred prior to 6 months of age (the earliest neuroimaging timepoint). One retrospective study of perinatal head size provides evidence of subtle yet atypical prenatal trajectories in children with ASD, with overgrowth present from the second trimester (22nd week of pregnancy) though to the third trimester.[282] The authors also report no significant between-group differences in head circumference at birth, however overgrowth was present at 12 and 24 months, suggesting that both pre- and post-natal head growth trajectories are affected in ASD. However, another study which combined data from two longitudinal cohorts (Generation R and Raine) reported no differences in prenatal head growth across the three trimesters between individuals with ASD and controls.[283] Our research suggests that head circumference is subtly increased from birth but becomes more notably increased from 2 months of age, consistent with findings from two studies which report overgrowth at 2-3 months.[155,159] In contrast, a population-based study found no

difference in mean head growth from birth to 12 months in boys with ASD compared to boys without ASD,[284] and another study found no difference until 36 months, where head circumference was again larger in boys with ASD.[285]

While the majority of studies are underpowered to assess sex differences, two studies reported smaller head circumference in girls with ASD compared to girls without ASD between birth and 17 months.[143,284] Moreover, research shows that the frequency of extreme head size (1 standard deviation above or below the average) is greater in boys and girls with ASD compared to typically developing children, and that boys with ASD in particular are more likely to have either extremely large or small head circumference.[143] In contrast, our study found no significant sex effects on head size across groups. However, out of 78 individuals with ASD, only 17 were female. Therefore, we may have been underpowered to observe any effects of sex.

While the autistic brain may undergo atypically accelerated growth in prenatal and early postnatal life, the neurotypical brain may have a greater and more protracted period of refinement for neural organisation and connectivity during the first years of life. In ASD, excess neurons are observed mostly in the frontal and temporal cortices, with minimal changes to the occipital lobe.[93] This expansion of postnatal brain volumes is likely due to a combination of disorganised cortical layers and atypical neural migration during prenatal development, as well as atypical gene expression that affects postnatal neurite outgrowth and synaptogenesis.[17,286] However, our meta-analysis also revealed "normalisation" of brain volumes with age. It is not clear whether this normalisation is protective or perhaps a second phase of atypical neurodevelopment. One study using a cohort sequential design spanning participant ages 6-35 years reports similar trajectories as our meta-analysis, however the additional datapoints in adulthood reveals that instead of TBV normalising with age, it continues to decrease into adulthood beyond that of neurotypical controls.[128] There is some evidence that ASD is associated with atypical activation of apoptotic (cell death) pathways, with deficient apoptosis in the developing infant brain resulting in excess neurons/overgrowth, and excessive apoptosis in later childhood and adolescence.[287] If these findings are correct, capturing group differences in brain volume using cross-sectional analyses may potentially lead to incorrect assumptions about brain development being "typical" in ASD, particularly in adolescents and early adulthood where no group differences

are often cited. Conversely, some cross-sectional studies in adults report larger head circumference in those with ASD compared to controls,[92,161] suggesting that for some individuals or subgroups, the head/brain may remain enlarged across development relative to neurotypical individuals. Longitudinal approaches, while being more time-consuming and costly for researchers, are much more adept at establishing the temporal dynamics of neurodevelopment and highlighting elements of brain growth which may be atypical in ASD.

Only one out of the seven studies in our meta-analysis included individuals with ASD and IQ scores of 70 or below, therefore it is difficult to make conclusions about the association between TBV and IQ based on this study alone. However, the direction of results from our meta-regression, i.e., lower IQ associated with larger TBV in ASD, is consistent with findings from another meta-analysis.[96] Previous research suggests that enlarged TBV occurs only in a subset of individuals (5-37%).[23] In addition to lower IQ being associated with larger TBV, regressive autism has been linked to larger TBV. Regression in ASD refers to the loss of previously acquired skills in language and social cognition, normally occurring between 2-3 years following a period of seemingly typical development.[288] One study of 114 children with autism with and without regression reported atypically enlarged TBV only in boys with regressive ASD, whereas boys without regression did not differ from controls and there were no differences in females with and without regression.[99] However, the current meta-analysis highlights the clear lack of longitudinal studies that involve individuals with ASD and low cognitive abilities. This is often due to studies using IQ matched samples, and there may be challenges in cooperation, particularly in younger children, with laying still for extended periods in the MRI scanner, following instructions, and difficulties tolerating scanner noise. Together, this suggests that neuroimaging studies may be underestimating the prevalence of larger TBV in ASD as they often exclude important subgroups with lower cognitive abilities.

Complementing these findings on the relationship between low IQ and TBV, we also explored head circumference trajectories in those with ASD, including subset analyses of individuals with comorbid ASD and cognitive learning needs (CLN). We found that those with ASD and comorbid CLN had the largest increase in head circumference trajectories compared to controls. However, we also found that head circumference trajectories in ASD remained enlarged compared to controls even when this CLN group were removed, suggesting that autism in general is associated with atypically increased head circumference

trajectories. Importantly, we did not observe any interactions between group and age, suggesting that trajectories are consistently increased in those with ASD from birth to 15 years within our sample.

Compared to research in ASD samples, very little research has investigated head circumference trajectories associated with elevated autistic traits, especially in population-based cohorts. In chapter 3, we analysed head circumference data from a large birth cohort and found autistic traits, as measured using the SCDC, to be associated with reduced head circumference trajectories. This goes against the idea of neuropathological changes occurring along a continuum, as one might expect trajectories to be intermediary between controls and ASD. However, our findings are consistent with those from the Generation R cohort, albeit during pregnancy, where they reported higher scores on the SRS at age 20 years to be associated with smaller head circumference during late pregnancy. [283] When these results were pooled together with findings from the Raine study (pooled n = 3,820), which assessed autistic traits at age 20 years using the AQ, no overall differences in prenatal head circumference were found. It is possible that the differences in trait measures and age at measurement may have impacted the findings and be a possible source of confounding. However, the authors did note that convergent validity is strong between the two measures, as well as autistic traits being relatively stable across the lifespan. In contrast to these findings, another study assessing autistic traits (AQ scores) in adults born to term compared to pre-term with very low birthweight (>1500g) cited faster growth in head circumference from birth to term to be associated with reduced autistic traits.[289] These findings suggest that extreme growth, both larger and smaller than expected, are associated with altered cognitive outcomes and may influence the severity of autistic traits. Some research suggests that increased head circumference in ASD may be related to a pattern of general increased growth throughout the body, incorporating height and weight, and that head circumference may not be uniquely altered compared to the rest of the body.[154,163,164,190] While ASD has been linked to faster growth across all three measurements,[154] neuroimaging findings support the idea that there are indeed uniquely altered volumetric changes within the brain in those with ASD compared to controls, even when TIV is controlled for.[240,290,291] This goes to highlight that although some head circumference variance is attributed to overall growth, some variance must also be related to unique changes in brain development in ASD.

Our two investigational studies on head circumference revealed divergent trajectories for individuals with ASD compared to psychotic disorder. Namely, head circumference was increased in ASD but decreased in psychotic disorder. Atypical head circumference at birth in those who go on to develop schizophrenia is relatively well documented, with a recent meta-analysis reporting reduced head circumference at birth in schizophrenia, although narrowly missing formal statistical thresholds (p = 0.057).[213] Our findings suggested that scoring in the smallest 10% for head circumference at birth was significantly associated with increased risk for psychotic disorder, with head circumference consistently decreased from birth through to adolescence. Although, a study of neonates with genetic risk for schizophrenia reports the opposite with no significant group differences in head circumference,[292] consistent with findings from a population-based cohort.[293] There is a lack of studies investigating head circumference during childhood and adolescence in this clinical group. Therefore, the findings from our study have addressed a significant gap in the literature regarding how head circumference develops across these developmental ages. The most recent meta-analysis of adult schizophrenic patients dates back to 1996 and reports no significant difference compared to controls.[211] Since then, limited research has been conducted in this area, with one study reporting smaller head circumference in adult patients (n = 190) compared to controls (p = 0.056),[294] which conflicts with two studies reporting larger head circumference in males with schizophrenia.[75,295] The heterogeneity of results indicates that more research is needed to fully understand the developmental trajectory from birth to adulthood, and the possibility of subgroups with either increased or reduced head circumference trajectories.

We also found evidence of reduced TIV and total grey matter volume in individuals with psychotic disorder scanned at age 21 years, corresponding with the findings from another meta-analysis in over 18,000 patients. [197] The same meta-analysis also compares the differences in brain size in medicated versus antipsychotic-naïve patients, reporting reductions of 1.7% to 2% in TIV and TBV respectively in the naïve patients, whereas reductions were greater in medicated patients at 2% - 2.6%.[197] Research from a Finnish longitudinal birth cohort also reveals expedited rates of brain volume loss in schizophrenia, with average TBV reductions of 0.69% in schizophrenia compared to reductions of 0.49% in controls between the ages of 33-44 years.[68] These findings contrast to what we observed in

ASD, in which our meta-analysis showed generally increased TBV and reduced/slower rate of volume change, suggesting that the brain may stay larger for longer while growth in neurotypical individuals catches-up and has more protracted change over time. However, it is important to note that these studies differ in terms of the age-range of individuals studied, with our meta-analysis based on childhood to early adulthood whereas the schizophrenia paper is based on early-to-middle adulthood.

Our examination of regional brain volumes in those with elevated autistic traits compared to those with psychotic experiences/disorder revealed marked differences between groups. Autistic traits were associated with both volume increases and decreases in cortical regions responsible for somatosensory processing and higher-order functions, whereas another study in the ALSPAC sample found that psychotic experiences were associated with reduced volume in limbic and subcortical areas deeper in the brain.[67] The paracentral lobule, superior frontal gyrus, precuneus, and postcentral gyrus were all associated with elevated autistic traits, and the only overlapping brain region that was also associated with psychotic experiences/disorder was the supramarginal gyrus. The general lack of overlap in affected regions further supports the idea that these two conditions follow distinct as opposed to converging trajectories, albeit at a trait level. Future research is needed to understand the overlap or divergence of brain changes at the disorder level. The supramarginal gyrus, the region found to be affected in both disorders, is linked to phonological word processing. Therefore, grey matter loss in this area may contribute to auditory hallucinations in schizophrenia, as it is significantly associated with the severity of auditory hallucinations in schizophrenia,[296] whereas for both psychosis and autism, alterations in this region may contribute to alexithymia or deficits in emotional self-awareness.[297] There is currently no literature on how head circumference is affected in individuals with subclinical psychotic experiences, highlighting an important literature gap that might inform on neurodevelopmental trajectories that underlie the prodrome. Our study of head circumference trajectories in those with psychotic experiences revealed sex-related differences, with smaller head circumference trajectories in females with psychotic experiences and larger trajectories in males with psychotic experiences. Furthermore, while we did not find significant differences in TIV and total grey matter volume between those with and without psychotic experiences, the direction of changes was the same as that

observed for head circumference, as mean TIV and total grey matter volume were larger in males and smaller in females. This corroborates the strong relationship between head circumference and brain volume and that the former can be used as a proxy measure. A study of head circumference in individuals at genetic high risk for schizophrenia (two first/second degree relatives, with or without attenuated symptoms), however report no association with head circumference.

Overall, our results suggest that changes in head circumference and brain structure are subtle in those with psychotic experiences compared to psychotic disorder, but that they appear to lie on a continuum, whereas autistic traits do not seem to be on the same continuum with ASD as we find opposing head circumference trajectories. Furthermore, we reported no significant differences in ICV for those with autistic traits compared to controls, whereas we did observe significant differences in TBV for clinical ASD cases compared to controls in our meta-analysis. However, more research examining TBV in adulthood in autism is needed, as TBV may normalise or reduce following this age. Therefore, using these measures alone, it is hard to accurately say whether autistic traits lie on a continuum with ASD.

While there was no striking evidence for a continuum between autistic traits and ASD based on more global measurements such as overall head size and TBV, our investigation of regional brain volumes did provide some evidence of a continuum. All regions that we found to be associated with autistic traits have also been reported in previous ASD studies, [29,298] highlighting that frontal and parietal regions are impacted both at a trait level and in clinical ASD cases. The paracentral lobule and inferior post-central gyrus were identified as regions of altered grey matter volume in those with elevated autistic traits. Combined, these regions are documented to affect sensory processing across the whole body, from the face to the lower extremities. Other regions identified included the superior frontal gyrus and precuneus. These regions have been linked to theory of mind and the ability to make inferences based on previous conceptual knowledge (top-down processing), both of which are reported to be atypical in ASD.[251,299,300] Although brain findings in those with ASD traits were consistent with findings in ASD disorder, our findings were less consistent with studies examining other measures of autistic traits, as only the left post-central gyrus was identified in studies using the SRS and AQ questionnaires, suggesting that the specific scale that

researchers use may have a significant impact on neuroimaging results, despite all measures being strong predictors of clinical ASD. It should be acknowledged that the imaging data reported here are exploratory rather than *a priori* predictions, hence the findings require replication before they can be considered secure.

One of the key differences between ASD and schizophrenia is the timing of disorder onset i.e., early childhood versus young adulthood. Aberrations in neurodevelopment must therefore occur early in ASD, whereas schizophrenia may result from alterations taking place across a longer period, spanning pre-natal development through to adulthood. Prenatal risk factors such as maternal infection, stress, nutrition, and hypoxia disrupt neurodevelopment and confer vulnerability to schizophrenia.[213] However, exposure to risk factors during adolescence and adulthood such as cannabis use, migration, urbanicity, social adversity, and stressful life events are also linked to schizophrenia risk.[301] Therefore, the time window of vulnerability for schizophrenia may be larger than that of ASD and may impact age of onset. One conceptual model suggests that the initial prenatal risk factor is enough for schizophrenia to develop in later life, alternatively the "2-hit model" proposes that the prenatal exposure is "buffered" until a second post-adolescent insult occurs and the buffering is no longer adequate.[302] However, adolescence is also a period of substantial reorganisation of cortical connections, with some regions pruned by 50% and other regions with very little change.[303] There is evidence of atypical synaptic pruning in schizophrenia. One hypothesis is that certain genetic variants heighten the vulnerability for synapses to be pruned, and environmental risk factors such as stress in adolescence may induce additional atypical glial-mediated pruning.[304] This excessive pruning results in imbalanced cortical excitation and inhibition, leading to changes to cognition and contributing to negative symptoms. Imbalanced signals from the cortex are thought to project to the subcortex and cause dopaminergic dysregulation, impairing predictive learning and sensory processing, ultimately causing psychosis. Finally, stress from psychotic symptoms may then also feed into the model and further disrupt pruning processes. Based on these findings, there is evidence that both schizophrenia and ASD are associated with aberrant changes to synapses, although the specific genetic variants, timing of pruning and location of these changes may play an important role in disorder-related symptomology and onset.

Ultimately, ASD and schizophrenia are separate disorders with neurodevelopmental origins. While there are some shared symptoms and biological mechanisms that underlie the two, we also show that there are distinct differences. This is best highlighted by our findings of increased head circumference trajectories and TBV in ASD whereas we saw the opposite associated with psychotic disorder.

6.3 Strengths and limitations

This thesis provides novel findings on the neurodevelopmental trajectories relating to both ASD and psychosis spectra and is strengthened by the longitudinal approaches used in three of the four studies. A major strength of this work is the use of a large representative population sample (ALSPAC), which facilitated analyses across a wide-age range and extensive number of timepoints for head circumference measurements. Most longitudinal head circumference studies in ASD focus on a restricted time window between birth to 5 years, therefore we provide new data on how trajectories develop across late childhood and adolescence. This thesis also provides the first study to investigate head circumference differences in individuals with a history of psychotic experiences. Using this at-risk subclinical group helps to expand our knowledge of neurodevelopmental trajectories in the prodrome, as well as aiding our theoretical understanding of when developmental disorder related changes emerge.

As is common with longitudinal cohort studies, missing data due to attrition reduced the sample size and representativeness of the study. However, we did not find any substantial differences in demographic or clinical factors between the complete and analytic sample, and therefore our sample is generalisable to the complete sample. We examined the impact of missing data by performing sensitivity analyses on those with and without complete data for both the ASD and autistic trait measures, in which we observed no differences in results. We were likely underpowered to explore head circumference differences in those with ASD and cognitive learning needs (n = 15), and for males with psychotic disorder (n = 13), therefore caution is advised when interpreting these results as the regression models may be overfitting the data. Larger samples are needed to confirm these findings, and greater clinical profiling of the ASD and autistic traits group beyond CLN subgroups would be useful. For example, exploring whether those with elevated repetitive behaviours or sensory

sensitivities display different growth trajectories to those with more social deficits, as well as the impact of common comorbid diagnoses such as ADHD.

For confidentiality reasons, the CLN variable consisted of aggregated data on the level of cognitive impairment experienced (i.e., specific, moderate, severe, profound learning difficulties). A limitation of this broad classification is the loss of detailed information about the specific IQ levels of participants. While less precise, the CLN variable was selected as it offered more comprehensive data coverage compared to IQ measures and therefore reduces the risk of bias associated with missing data. Future research should aim to recruit larger and more diverse range of participants across different IQ levels, enabling improved insights into how cognition affects outcomes in ASD populations.

Furthermore, we were unable to perform neuroimaging analyses on clinical ASD cases as only one individual was included in this sample. Within our head circumference analyses, the sample could have also been boosted through multiple imputation of missing data on confounding variables, however the linear mixed model included subjects in the analysis as long as they contributed head circumference data for at least one timepoint, minimising data loss.

Another potential limitation stems from the concept of psychopathological continua. People with autistic traits and/or psychotic experiences appear to be vulnerable to a range of psychopathological and behavioural outcomes so their links to ASD and schizophrenia respectively are not direct and wholly predictable. This means that the association between such traits and experiences with biomarkers is correspondingly weaker such that a signal may be hard to detect within the statistical noise.

One disadvantage of our neuroimaging analysis is that the sample was preselected for an earlier study concerned with psychosis, based on responses to a measure of psychotic experiences as opposed to autistic traits. This sampling bias led to a substantial proportion of individuals with a history of psychotic experiences, which may confound our findings. This was clearly acknowledged in the chapter and is reiterated here. Previous research has already highlighted the heightened prevalence of psychotic experiences in those with elevated autistic traits and ASD, therefore it may be hard to remove this bias. It could even

be argued that this particular sampling strategy suited the aims of our analysis namely to explore whether or not there are changes in focal brain areas common to both disorders.

To ascertain ASD diagnoses, we used parent-report as opposed to data from general practitioner or healthcare data. This measure was selected as it is a quick and simple measure and has been used as a diagnosis measure for ASD in ALSPAC and internationally.[174,175] The number of cases identified is similar, although slightly overestimated, compared to that of previous ALSPAC studies using multidisciplinary health and educational records.[15] However, we acknowledge that generally multiple sources of diagnosis are preferred to ensure that diagnoses are accurate and representative of the full sample.

Finally, while we controlled for several confounding variables, there is a likelihood that some important confounders may have also been missed. For example, genetic ancestry, maternal smoking/drinking, parity, and maternal age at delivery have been considered as confounders in previous studies.[154] However, it is not possible to measure all potential confounders for practical reasons for both the researcher and the participant, as well as the added model complexity when samples may already be small. Ethnicity is an important covariate to consider in head circumference research, however the majority of our analytic sample (94%) were of white ethnicity, our findings therefore have limited generalizability to other ethnic groups. We included height as a covariate in a separate model to enable comparisons with the current literature base, as there is conflicting research regarding the role of height in head circumference.[164] Our results indicate that changes to head circumference are confounded by changes to height, and therefore that growth in general is atypical in ASD. Social economic status was first considered as a confounder in our analyses, however we opted to use maternal education as a proxy for this as there were fewer missing data for this variable, there is strong evidence that maternal education predicts family resources and child development, and it is more likely to remain stable compared to other measures such as income or occupation.[305]

6.4 Implications

The main conclusion of this thesis is that both ASD and psychotic disorder are associated with atypical growth. This has important implications for both theory and practice.

Knowledge of the growth differences can help with the identification of genetic and environmental risk factors and take a step forward towards earlier detection and intervention, especially as changes to head circumference were seen prior to behavioural/diagnosis onset.

Head size at birth within the smallest 10th percentile was a significant predictor of psychotic experiences and psychotic disorder, suggesting that it could be explored as a prognostic marker to predict psychosis. Moreover, head circumference trajectories were atypically decreased from birth through to age 15 years. This finding addresses a clear gap in existing literature, as previous research has primarily concentrated on birth or adulthood, often overlooking childhood and adolescence. We also show that head circumference during childhood and adolescence strongly correlated with TIV in young adulthood, therefore highlighting that neurodevelopmental changes occurring within the brain can be studied with the use of head circumference measurements, a cheaper, more feasible and highly accessible method.

While ASD was associated with increased head circumference from birth and particularly from 2 months of age, head size within the largest 10th percentile was not associated with increased risk for ASD. This means that while head circumference is atypical, it may not be as accurate a prognostic marker compared to small head circumference for psychosis. However, we did find a link between enlarged TBV and head circumference with lower IQ in ASD, suggesting that atypical trajectories are more pronounced in this group and perhaps easier to detect on a prognostic level, but larger sample sizes will be needed to consolidate this finding.

Our research also has important theoretical implications for these conditions being classified as part of a continuum. Through head circumference and brain measurements, we have shown that psychotic experiences lie on a continuum with psychotic disorder, evidenced by the similar head circumference trajectories in subclinical and clinical groups, as well as TIV and total grey matter volume at trend level. In contrast, autistic traits were associated with opposing trajectories compared to ASD. It is possible that this may reflect possible greater heterogeneity of the ASD/trait spectrum compared to the psychosis spectrum. It is also important to factor in that our measurement of autistic traits did not reflect the full ASD symptom profile, as the SCDC does not assess repetitive behaviours, restricted interests, or

sensory sensitivities. It may be that greater similarities for head circumference trajectories would be observed when these additional symptoms are accounted for. That said, previous research within the ALSPAC cohort shows that the SCDC at 7.5 years is one of four best individual predictors of ASD based on an assessment of 93 measures relating to autistic traits.[306]

6.5 Future directions

Our meta-analysis revealed the sparse number of longitudinal neuroimaging studies that recruit individuals with ASD and low IQ, and therefore current research is not entirely representative of the full ASD spectrum. While recruiting individuals with IQ difficulties poses unique challenges, it will be important for future research to accommodate the needs of individuals with ASD and low IQ to improve our theoretical understanding, and perhaps inform clinical guidance as to whether these individuals may form part of a separate subgroup which may respond differently to intervention.

A recent review of research in older adults with ASD reveals the striking lack of studies in this age group, with only 0.4% of published ASD studies over the last decade pertaining to older adults.[307] Within the meta-analysis, only one of the studies included participants over the age of 18, therefore our understanding of whether changes in neurodevelopment over time are protective or degenerative is incredibly limited. It will be important for current and new longitudinal cohorts to track development across larger age periods to see the full extent of the neurodevelopmental trajectory. Furthermore, although our head circumference measurements spanned ages birth through 15 years, we need to chart beyond this age to delineate if increased head circumference trajectories persist.

While clinical markers of ASD and psychosis are abundant, there are currently no validated biological markers. Our research finds evidence of atypical head circumference in ASD and psychotic disorder, it will be important for future research to see if these findings replicate in larger samples and explore the clinical utility of using head growth as a diagnostic aid.

This study used cross-sectional neuroimaging data to study volumetric differences in those with elevated autistic traits. ALSPAC has recently finished collecting a second wave of neuroimaging data at age 30 years, offering an exciting opportunity to explore trait and disorder-related brain changes over time. Upcoming research will explore whether factors

like transience versus persistence of psychotic experiences may be related to differences within the brain, which may have important theoretical implications. Moreover, only a small number of participants in our neuroimaging analyses were comorbid for elevated autistic traits and psychotic experiences (n = 9). It would be interesting for future research to see whether comorbidity is associated with any unique structural differences, or whether regions overlap with those identified in individual cases of ASD/traits or psychotic disorders.

6.6 Conclusions

Our findings provide important insights into the neurodevelopmental trajectories of ASD and psychotic disorder. Both conditions are associated with atypical growth, with increased TBV and head circumference in ASD; whereas reductions in head circumference trajectories and TIV were seen in those with psychotic disorder. On a trait level, autistic traits were not associated with increased head circumference trajectories or TIV, however, we did find evidence of structural grey matter changes in the trait group in regions which correspond to previous literature in ASD samples. Evidence of a continuum was clearer when exploring head circumference trajectories and TIV in those with psychotic experiences compared to psychotic disorder, at least in females. Our research provides important information in relation to the developmental timing of atypical head growth, with both ASD and psychotic disorder associated with changes from birth. It is crucial to acknowledge the limitations of these studies when interpreting the findings. A key limitation was the small sample size in specific groups, particularly among individuals with ASD and comorbid cognitive learning needs, as well as for males with psychotic disorder. Furthermore, we could not examine head circumference trajectories in those with intellectual disability (IQ <70) groups directly, and instead used CLN as a proxy measure. Future research should aim to replicate these analyses in larger, more diverse samples to validate the results. Additionally, further investigation is needed to evaluate the reliability of using brain growth and head circumference trajectories as prognostic markers for these conditions.

References

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5-TR*. 5th ed., text rev. American Psychiatric Association Publishing; 2022.

2. Ozonoff S, Iosif AM, Baguio F, et al. A Prospective Study of the Emergence of Early Behavioral Signs of Autism. *J Am Acad Child Adolesc Psychiatry*. 2010;49(3):256-266.e2. doi:10.1016/J.JAAC.2009.11.009

3. Tager-Flusberg H, Kasari C. Minimally verbal school-aged children with autism spectrum disorder: The neglected end of the spectrum. *Autism Research*. 2013;6(6):468-478. doi:10.1002/aur.1329

4. Anderson DK, Lord C, Risi S, et al. Patterns of Growth in Verbal Abilities Among Children With Autism Spectrum Disorder. *J Consult Clin Psychol*. 2007;75(4):594-604. doi:10.1037/0022-006X.75.4.594

5. Norrelgen F, Fernell E, Eriksson M, et al. Children with autism spectrum disorders who do not develop phrase speech in the preschool years. *Autism*. 2015;19(8):934-943. doi:10.1177/1362361314556782

6. Herlihy L, Knoch K, Vibert B, Fein D. Parents' first concerns about toddlers with autism spectrum disorder: Effect of sibling status. *Autism*. 2015;19(1):20. doi:10.1177/1362361313509731

7. Lundström S, Chang Z, Råstam M, et al. Autism Spectrum Disorders and Autisticlike Traits: Similar Etiology in the Extreme End and the Normal Variation. *Arch Gen Psychiatry*. 2012;69(1):46-52. doi:10.1001/ARCHGENPSYCHIATRY.2011.144

8. Gerdts J, Bernier R. The Broader Autism Phenotype and Its Implications on the Etiology and Treatment of Autism Spectrum Disorders. *Autism Res Treat*. 2011;2011:1-19. doi:10.1155/2011/545901

9. Zeidan J, Fombonne E, Scorah J, et al. Global prevalence of autism: A systematic review update. *Autism Research*. 2022;15(5):778-790. doi:10.1002/aur.2696

10. Olusanya BO, Davis AC, Wertlieb D, et al. Developmental disabilities among children younger than 5 years in 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Glob Health*. 2018;6(10):e1100-e1121. doi:10.1016/S2214-109X(18)30309-7

11. van 't Hof M, Tisseur C, van Berckelear-Onnes I, et al. Age at autism spectrum disorder diagnosis: A systematic review and meta-analysis from 2012 to 2019. *Autism*. 2021;25(4):862-873. doi:10.1177/1362361320971107

12. Ferri SL, Abel T, Brodkin ES. Sex Differences in Autism Spectrum Disorder: A Review. *Curr Psychiatry Rep*. 2018;20(2):9. doi:10.1007/S11920-018-0874-2

13. Loomes R, Hull L, Mandy WPL. What Is the Male-to-Female Ratio in Autism Spectrum Disorder? A Systematic Review and Meta-Analysis. *J Am Acad Child Adolesc Psychiatry*. 2017;56(6):466-474. doi:10.1016/J.JAAC.2017.03.013

14. Napolitano A, Schiavi S, La Rosa P, et al. Sex Differences in Autism Spectrum Disorder: Diagnostic, Neurobiological, and Behavioral Features. *Front Psychiatry*. 2022;13. doi:10.3389/fpsyt.2022.889636

15. Williams E, Thomas K, Sidebotham H, Emond A. Prevalence and characteristics of autistic spectrum disorders in the ALSPAC cohort. *Dev Med Child Neurol*. 2008;50(9):672-677. doi:10.1111/j.1469-8749.2008.03042.x

16. Courchesne E, Pramparo T, Gazestani VH, Lombardo M V., Pierce K, Lewis NE. The ASD Living Biology: from cell proliferation to clinical phenotype. *Molecular Psychiatry 2018 24:1*. 2018;24(1):88-107. doi:10.1038/s41380-018-0056-y

17. Courchesne E, Gazestani VH, Lewis NE. PRENATAL ORIGINS OF ASD: THE WHEN, WHAT AND HOW OF ASD DEVELOPMENT. *Trends Neurosci*. 2020;43(5):326. doi:10.1016/J.TINS.2020.03.005

18. Courchesne E, Mouton PR, Calhoun ME, et al. Neuron Number and Size in Prefrontal Cortex of Children With Autism. *JAMA*. 2011;306(18):2001-2010. doi:10.1001/JAMA.2011.1638

19. Courchesne E, Pierce K. Brain overgrowth in autism during a critical time in development: implications for frontal pyramidal neuron and interneuron development and connectivity. *Int J Dev Neurosci*. 2005;23(2-3):153-170. doi:10.1016/J.IJDEVNEU.2005.01.003

20. Ismail MMT, Keynton RS, Mostapha MMMO, et al. Studying autism spectrum disorder with structural and diffusion magnetic resonance imaging: A survey. *Front Hum Neurosci*. 2016;10(MAY2016):211. doi:10.3389/FNHUM.2016.00211/BIBTEX

21. Bethlehem RAI, Seidlitz J, White SR, et al. Brain charts for the human lifespan. *Nature*. 2022;604(7906):525-533. doi:10.1038/s41586-022-04554-y

22. Gilmore JH, Knickmeyer RC, Gao W. Imaging structural and functional brain development in early childhood. *Nature Publishing Group*. 2018;19. doi:10.1038/nrn.2018.1

23. Courchesne E, Karns CM, Davis HR, et al. Unusual brain growth patterns in early life in patients with autistic disorder. *Neurology*. 2001;57(2):245-254. doi:10.1212/WNL.57.2.245

24. Godel M, Andrews DS, Amaral DG, et al. Altered Gray-White Matter Boundary Contrast in Toddlers at Risk for Autism Relates to Later Diagnosis of Autism Spectrum Disorder. *Front Neurosci*. 2021;15. doi:10.3389/fnins.2021.669194

25. Wolff JJ, Gu H, Gerig G, et al. Differences in white matter fiber tract development present from 6 to 24 months in infants with autism. *American Journal of Psychiatry*. 2012;169(6):589-600. doi:10.1176/appi.ajp.2011.11091447

26. Courchesne E. Brain development in autism: Early overgrowth followed by premature arrest of growth. *Ment Retard Dev Disabil Res Rev*. 2004;10(2):106-111. doi:10.1002/mrdd.20020

27. Yankowitz LD, Herrington JD, Yerys BE, Pereira JA, Pandey J, Schultz RT. Evidence against the "normalization" prediction of the early brain overgrowth hypothesis of autism. Published online 2020. doi:10.1186/s13229-020-00353-2

28. Freitag CM, Luders E, Hulst HE, et al. Total Brain Volume and Corpus Callosum Size in Medication-Naïve Adolescents and Young Adults with Autism Spectrum Disorder. *Biol Psychiatry*. 2009;66(4):316. doi:10.1016/J.BIOPSYCH.2009.03.011

29. Ha S, Sohn IJ, Kim N, Sim HJ, Cheon KA. Characteristics of Brains in Autism Spectrum Disorder: Structure, Function and Connectivity across the Lifespan. *Exp Neurobiol*. 2015;24(4):273-284. doi:10.5607/en.2015.24.4.273

30. Baribeau DA, Anagnostou E. A Comparison of Neuroimaging Findings in Childhood Onset Schizophrenia and Autism Spectrum Disorder: A Review of the Literature. *Front Psychiatry*. 2013;4(DEC). doi:10.3389/FPSYT.2013.00175

31. Freitag CM. The genetics of autistic disorders and its clinical relevance: a review of the literature. *Molecular Psychiatry 2007 12:1*. 2006;12(1):2-22. doi:10.1038/sj.mp.4001896

32. Genovese A, Butler MG. The Autism Spectrum: Behavioral, Psychiatric and Genetic Associations. *Genes (Basel)*. 2023;14(3). doi:10.3390/GENES14030677

33. Persson M, Opdahl S, Risnes K, et al. Gestational age and the risk of autism spectrum disorder in Sweden, Finland, and Norway: A cohort study. *PLoS Med*. 2020;17(9):e1003207. doi:10.1371/JOURNAL.PMED.1003207

34. Moore GS, Kneitel AW, Walker CK, Gilbert WM, Xing G. Autism risk in small- and large-for-gestational-age infants. *Am J Obstet Gynecol*. 2012;206(4):314.e1. doi:10.1016/J.AJOG.2012.01.044

35. Dong HY, Feng JY, Li HH, Yue XJ, Jia FY. Non-parental caregivers, low maternal education, gastrointestinal problems and high blood lead level: predictors related to the severity of autism spectrum disorder in Northeast China. *BMC Pediatr*. 2022;22(1):1-8. doi:10.1186/S12887-021-03086-0/TABLES/3

36. Jackson MI, Kiernan K, McLanahan S. Maternal Education, Changing Family Circumstances, and Children's Skill Development in the United States and UK. *Ann Am Acad Pol Soc Sci*. 2017;674(1):59. doi:10.1177/0002716217729471

37. Delobel-Ayoub M, Ehlinger V, Klapouszczak D, et al. Socioeconomic Disparities and Prevalence of Autism Spectrum Disorders and Intellectual Disability. *PLoS One*. 2015;10(11). doi:10.1371/JOURNAL.PONE.0141964

38. Kelly B, Williams S, Collins S, et al. The association between socioeconomic status and autism diagnosis in the United Kingdom for children aged 5–8 years of age: Findings from the Born in Bradford cohort. *Autism*. 2019;23(1):131-140. doi:10.1177/1362361317733182/ASSET/IMAGES/LARGE/10.1177_1362361317733182-FIG2.JPEG

39. Correll CU, Schooler NR. Negative symptoms in schizophrenia: A review and clinical guide for recognition, assessment, and treatment. *Neuropsychiatr Dis Treat*. 2020;16:519-534. doi:10.2147/NDT.S225643

40. Riecher-Rössler A, Butler S, Kulkarni J. Sex and gender differences in schizophrenic psychoses—a critical review. *Arch Womens Ment Health*. 2018;21(6):627-648. doi:10.1007/s00737-018-0847-9

41. Mollon J, David AS, Zammit S, Lewis G, Reichenberg A. Course of cognitive development from infancy to early adulthood in the psychosis spectrum. *JAMA Psychiatry*. 2018;75(3):270-279. doi:10.1001/jamapsychiatry.2017.4327

42. McGrath JJ, Saha S, Al-Hamzawi A, et al. Psychotic experiences in the general population: A cross-national analysis based on 31 261 respondents from 18 countries. *JAMA Psychiatry*. 2015;72(7):697-705. doi:10.1001/jamapsychiatry.2015.0575

43. Van Os J, Linscott RJ, Myin-Germeys I, Delespaul P, Krabbendam L. A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. *Psychol Med*. 2009;39(2):179-195. doi:10.1017/S0033291708003814

44. Sullivan SA, Kounali D, Cannon M, et al. A population-based cohort study examining the incidence and impact of psychotic experiences from childhood to adulthood, and prediction of psychotic disorder. *American Journal of Psychiatry*. 2020;177(4):308-317. doi:10.1176/appi.ajp.2019.19060654

45. Healy C, Brannigan R, Dooley N, et al. Childhood and adolescent psychotic experiences and risk of mental disorder: a systematic review and meta-analysis. *Psychol Med*. 2019;49(10):1589-1599. doi:10.1017/S0033291719000485

46. Linscott RJ, Van Os J. An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: on the pathway from proneness to persistence to dimensional expression across mental disorders. *Psychol Med*. 2013;43(6):1133-1149. doi:10.1017/S0033291712001626

47. Krabbendam L, Myin-Germeys I, Bak M, Os J Van. Explaining Transitions Over the Hypothesized Psychosis Continuum. *http://dx.doi.org/101080/j1440-1614200501541.x*. 2005;39(3):180-186. doi:10.1080/J.1440-1614.2005.01541.X

48. Bebbington PE, McManus S. Revisiting the one in four: The prevalence of psychiatric disorder in the population of England 2000-2014. *British Journal of Psychiatry*. 2020;216(1):55-57. doi:10.1192/bjp.2019.196

49. Perälä J, Suvisaari J, Samuli ;, et al. *Lifetime Prevalence of Psychotic and Bipolar I Disorders in a General Population*. Vol 64.; 2007.

50. Zammit S, Kounali D, Cannon M, et al. Psychotic experiences and psychotic disorders at age 18 in relation to psychotic experiences at age 12 in a longitudinal population-based cohort study. *American Journal of Psychiatry*. 2013;170(7):742-750. doi:10.1176/APPI.AJP.2013.12060768/ASSET/IMAGES/LARGE/742F2.JPEG

51. Healy C, Brannigan R, Dooley N, et al. Childhood and adolescent psychotic experiences and risk of mental disorder: A systematic review and meta-analysis. *Psychol Med*. 2019;49(10):1589-1599. doi:10.1017/S0033291719000485

52. Knight C, Russo D, Stochl J, et al. Prevalence of and recovery from common mental disorder including psychotic experiences in the UK Primary Care Improving Access to Psychological Therapies (IAPT) Programme. *J Affect Disord*. 2020;272:84-90. doi:10.1016/j.jad.2020.04.015

53. Howes OD, Murray RM. Schizophrenia: an integrated sociodevelopmental-cognitive model. *The Lancet*. 2014;383(9929):1677-1687. doi:10.1016/S0140-6736(13)62036-X

54. Glantz LA, Lewis DA. Decreased Dendritic Spine Density on Prefrontal Cortical Pyramidal Neurons in Schizophrenia. *Arch Gen Psychiatry*. 2000;57(1):65-73. doi:10.1001/ARCHPSYC.57.1.65

55. Tavares V, Vassos E, Marquand A, et al. Prediction of transition to psychosis from an at-risk mental state using structural neuroimaging, genetic, and environmental data. *Front Psychiatry*. 2023;13. doi:10.3389/FPSYT.2022.1086038/FULL

56. Legge SE, Jones HJ, Kendall KM, et al. Association of Genetic Liability to Psychotic Experiences With Neuropsychotic Disorders and Traits. *JAMA Psychiatry*. 2019;76(12):1256-1265. doi:10.1001/JAMAPSYCHIATRY.2019.2508

57. Barkhuizen W, Pain O, Dudbridge F, Ronald A. Genetic overlap between psychotic experiences in the community across age and with psychiatric disorders. *Translational Psychiatry 2020 10:1*. 2020;10(1):1-12. doi:10.1038/s41398-020-0765-2

58. Zavos HMS, Freeman D, Haworth CMA, et al. Consistent Etiology of Severe, Frequent Psychotic Experiences and Milder, Less Frequent Manifestations: A Twin Study of Specific Psychotic Experiences in Adolescence. *JAMA Psychiatry*. 2014;71(9):1049-1057. doi:10.1001/JAMAPSYCHIATRY.2014.994

59. Zammit S, Hamshere M, Dwyer S, et al. A Population-Based Study of Genetic Variation and Psychotic Experiences in Adolescents. *Schizophr Bull*. 2014;40(6):1254-1262. doi:10.1093/schbul/sbt146

60. Taylor MJ, Freeman D, Lundström S, Larsson H, Ronald A. Heritability of Psychotic Experiences in Adolescents and Interaction With Environmental Risk. *JAMA Psychiatry*. 2022;79(9):889-897. doi:10.1001/JAMAPSYCHIATRY.2022.1947

61. Murray RM, Bhavsar V, Tripoli G, Howes O. 30 Years on: How the Neurodevelopmental Hypothesis of Schizophrenia Morphed Into the Developmental Risk Factor Model of Psychosis. *Schizophr Bull*. 2017;43(6):1190-1196. doi:10.1093/SCHBUL/SBX121

62. Catone G, Marwaha S, Lennox B, Broome MR. Bullying victimisation and psychosis: The interdependence and independence of risk trajectories. *BJPsych Adv*. 2017;23(6):397-406. doi:10.1192/APT.BP.116.016584

63. Wainberg M, Jacobs GR, di Forti M, Tripathy SJ. Cannabis, schizophrenia genetic risk, and psychotic experiences: a cross-sectional study of 109,308 participants from the UK Biobank. *Translational Psychiatry 2021 11:1*. 2021;11(1):1-9. doi:10.1038/s41398-021-01330-w

64. Cosgrave J, Purple RJ, Haines R, et al. Do environmental risk factors for the development of psychosis distribute differently across dimensionally assessed psychotic experiences? *Translational Psychiatry 2021 11:1*. 2021;11(1):1-13. doi:10.1038/s41398-021-01265-2

65. Karcher NR, Schiffman J, Barch DM. Environmental Risk Factors and Psychotic-like Experiences in Children Aged 9–10. *J Am Acad Child Adolesc Psychiatry*. 2021;60(4):490-500. doi:10.1016/J.JAAC.2020.07.003

66. Solmi F, Lewis G, Zammit S, Kirkbride JB. Neighborhood Characteristics at Birth and Positive and Negative Psychotic Symptoms in Adolescence: Findings From the ALSPAC Birth Cohort. *Schizophr Bull*. 2020;46(3):581-591. doi:10.1093/SCHBUL/SBZ049

67. Merritt K, Luque Laguna P, Sethi A, et al. The impact of cumulative obstetric complications and childhood trauma on brain volume in young people with psychotic experiences. *Mol Psychiatry*. 2023;28(9):3688-3697. doi:10.1038/s41380-023-02295-6

68. Veijola J, Guo JY, Moilanen JS, et al. Longitudinal changes in total brain volume in schizophrenia: Relation to symptom severity, cognition and antipsychotic medication. *PLoS One*. 2014;9(7):101689. doi:10.1371/journal.pone.0101689

69. Lenroot RK, Giedd JN. Brain development in children and adolescents: Insights from anatomical magnetic resonance imaging. *Neurosci Biobehav Rev*. 2006;30:718-729. doi:10.1016/j.neubiorev.2006.06.001

70. Merritt K, Luque Laguna P, Irfan A, David AS. Longitudinal Structural MRI Findings in Individuals at Genetic and Clinical High Risk for Psychosis: A Systematic Review. *Front Psychiatry*. 2021;12:49. doi:10.3389/FPSYT.2021.620401/BIBTEX

71. Liloia D, Brasso C, Cauda F, et al. Updating and characterizing neuroanatomical markers in high-risk subjects, recently diagnosed and chronic patients with schizophrenia: A revised coordinate-based meta-analysis. *Neurosci Biobehav Rev*. 2021;123:83-103. doi:10.1016/j.neubiorev.2021.01.010

72. Drakesmith M, Dutt A, Fonville L, et al. Volumetric, relaxometric and diffusometric correlates of psychotic experiences in a non-clinical sample of young adults. *Neuroimage Clin*. 2016;12:550-558. doi:10.1016/j.nicl.2016.09.002

73. Leech R, Sharp DJ. The role of the posterior cingulate cortex in cognition and disease. *Brain*. 2014;137(1):12. doi:10.1093/BRAIN/AWT162

74. McNeil TF, Cantor-Graae E, Nordstrom LG, Rosenlund T. Head circumference in "preschizophrenic" and control neonates. *British Journal of Psychiatry*. 1993;162(APR.):517-523. doi:10.1192/bjp.162.4.517

75. Bassett AS, Chow EWC, Bury A, et al. Increased head circumference in schizophrenia. *Biol Psychiatry*. 1996;40(11):1173-1175. doi:10.1016/S0006-3223(96)00288-0

76. Sullivan S, Rai D, Golding J, Zammit S, Steer C. The association between autism spectrum disorder and psychotic experiences in the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort. *J Am Acad Child Adolesc Psychiatry*. 2013;52(8):806-814. doi:10.1016/J.JAAC.2013.05.010

77. Bevan Jones R, Thapar A, Lewis G, Zammit S. The association between early autistic traits and psychotic experiences in adolescence. *Schizophr Res*. 2012;135(1-3):164-169. doi:10.1016/J.SCHRES.2011.11.037

78. Harrington L, Siegert R, Mcclure J, Siegert RJ. Cognitive Neuropsychiatry Theory of mind in schizophrenia: A critical review Theory of mind in schizophrenia: A critical review. Published online 2010. doi:10.1080/13546800444000056

79. Marinopoulou M, Lugnegård T, Hallerbäck MU, Gillberg C, Billstedt E. Asperger Syndrome and Schizophrenia: A Comparative Neuropsychological Study. *J Autism Dev Disord*. 2016;46(7):2292-2304. doi:10.1007/S10803-016-2758-9/TABLES/5

80. Jutla A, Foss-Feig J, Veenstra-Vanderweele J. Autism spectrum disorder and schizophrenia: An updated conceptual review. Published online 2021. doi:10.1002/aur.2659

81. Sørensen HJ, Mortensen EL, Schiffman J, Reinisch JM, Maeda J, Mednick SA. Early developmental milestones and risk of schizophrenia. A 45-year follow-up of the Copenhagen Perinatal Cohort. *Schizophr Res*. 2010;118(0):41. doi:10.1016/J.SCHRES.2010.01.029

82. Trevisan DA, Foss-Feig JH, Naples AJ, et al. Autism Spectrum Disorder and Schizophrenia Are Better Differentiated by Positive Symptoms Than Negative Symptoms. *Article*. 2020;11:1. doi:10.3389/fpsyt.2020.00548

83. Du Y, Fu Z, Xing Y, et al. Evidence of shared and distinct functional and structural brain signatures in schizophrenia and autism spectrum disorder. *Commun Biol*. 2021;4. doi:10.1038/s42003-021-02592-2

84. Utevsky A V, Smith D V, Huettel SA. Precuneus Is a Functional Core of the Default-Mode Network. Published online 2014. doi:10.1523/JNEUROSCI.4227-13.2014

85. Mitelman SA, Bralet MC, Haznedar MM, et al. Diametrical relationship between gray and white matter volumes in autism spectrum disorder and schizophrenia. *Brain Imaging Behav*. 2017;11(6):1823-1835. doi:10.1007/S11682-016-9648-9/FIGURES/4

86. Paus T. Virtual Histology of Cortical Thickness and Shared Neurobiology in 6 Psychiatric Disorders Writing Committee for the Attention-Deficit/Hyperactivity Disorder; Autism Spectrum Disorder; Bipolar Disorder; Major Depressive Disorder; Obsessive-Compulsive Disorder; and Schizophrenia ENIGMA Working Groups Supplemental content. *JAMA Psychiatry*. 2021;78(1):47-63. doi:10.1001/jamapsychiatry.2020.2694

87. Vorstman JAS, Peter J, Burbach H. Autism and Schizophrenia: Genetic and Phenotypic Relationships. *Comprehensive Guide to Autism, Springer*. Published online 2014. doi:10.1007/978-1-4614-4788-7_96

88. Hazlett HC, Poe M, Gerig G, et al. Magnetic Resonance Imaging and Head Circumference Study of Brain Size in Autism: Birth Through Age 2 Years. *Arch Gen Psychiatry*. 2005;62(12):1366-1376. doi:10.1001/ARCHPSYC.62.12.1366

89. Lucibello S, Verdolotti T, Giordano FM, et al. Brain Morphometry of Preschool Age Children Affected by Autism Spectrum Disorder: Correlation with Clinical Findings. *Clinical Anatomy*. 2019;32:143-150. doi:10.1002/ca.23252

90. Piven J, Arndt S, Bailey J, Andreasen N. Regional brain enlargement in autism: a magnetic resonance imaging study. *J Am Acad Child Adolesc Psychiatry*. 1996;35(4):530-536. doi:10.1097/00004583-199604000-00020

91. Sparks BF, Friedman SD, Shaw DW, et al. Brain structural abnormalities in young children with autism spectrum disorder. *Neurology*. 2002;59(2):184-192. doi:10.1212/WNL.59.2.184

92. Aylward EH, Minshew NJ, Field K, Sparks BF, Singh N. Effects of age on brain volume and head circumference in autism. *Neurology*. 2002;59(2):175-183. doi:10.1212/WNL.59.2.175

93. Courchesne E, Campbell K, Solso S. Brain growth across the life span in autism: Age-specific changes in anatomical pathology. *Brain Res*. 2011;1380:138-145. doi:10.1016/j.brainres.2010.09.101

94. Hallahan B, Daly EM, McAlonan G, et al. Brain morphometry volume in autistic spectrum disorder: a magnetic resonance imaging study of adults. *Psychol Med*. 2009;39(2):337-346. doi:10.1017/S0033291708003383

95. Redcay E, Courchesne E. When is the brain enlarged in autism? A meta-analysis of all brain size reports. *Biol Psychiatry*. 2005;58(1):1-9. doi:10.1016/j.biopsych.2005.03.026

96. Sacco R, Gabriele S, Persico AM. Head circumference and brain size in autism spectrum disorder: A systematic review and meta-analysis. *Psychiatry Res Neuroimaging*. 2015;234(2):239-251. doi:10.1016/j.pscychresns.2015.08.016

97. Stanfield AC, McIntosh AM, Spencer MD, Philip R, Gaur S, Lawrie SM. Towards a neuroanatomy of autism: A systematic review and meta-analysis of structural magnetic resonance imaging studies. *European Psychiatry*. 2008;23(4):289-299. doi:10.1016/J.EURPSY.2007.05.006

98. Campbell DJ, Chang J, Chawarska K. Early Generalized Overgrowth in Autism Spectrum Disorder: Prevalence Rates, Gender Effects, and Clinical Outcomes Dr. *J Am Acad Child Adolesc Psychiatry*. 2014;53(10):1063-1073. doi:10.1038/nature08365.Reconstructing

99. Nordahl CW, Lange N, Li DD, et al. Brain enlargement is associated with regression in preschool-age boys with autism spectrum disorders. *Proceedings of the National Academy of Sciences*. 2011;108(50):20195-20200. doi:10.1073/pnas.1107560108

100. Lainhart JE, Piven J, Wzorek M, et al. *Macrocephaly in Children and Adults With Autism*. Vol 36.; 1997. doi:10.1097/00004583-199702000-00019

101. Ben-Itzchak E, Ben-Shachar S, Zachor DA. Specific Neurological Phenotypes in Autism Spectrum Disorders Are Associated with.pdf. Published online 2013:461-659.

102. Lenroot RK, Giedd JN. Sex differences in the adolescent brain. *Brain Cogn*. 2010;72(1):46-55. doi:10.1016/j.bandc.2009.10.008

103. Hazlett HC, Gu H, Munsell BC, et al. Early brain development in infants at high risk for autism spectrum disorder. *Nature Publishing Group*. Published online 2017. doi:10.1038/nature21369

104. Lee JK, Andrews DS, Ozonoff S, et al. Longitudinal Evaluation of Cerebral Growth Across Childhood in Boys and Girls With Autism Spectrum Disorder. *Biol Psychiatry*. 2021;90(5):286-294. doi:10.1016/j.biopsych.2020.10.014

105. Amaral DG, Li D, Libero L, et al. In pursuit of neurophenotypes: The consequences of having autism and a big brain. *Autism Research*. 2017;10(5):711-722. doi:10.1002/aur.1755

106. Emily Kilroy, Lirong Yan, Danny J.J. Wang, et al. Relationships between Cerebral Blood Flow and IQ in Typically Developing Children and Adolescents. *J Cogn Sci (Seoul)*. 2011;12(2):151-170. doi:10.17791/jcs.2011.12.2.151

107. Pietschnig J, Penke L, Wicherts JM, Zeiler M, Voracek M. Meta-analysis of associations between human brain volume and intelligence differences: How strong are they and what do they mean? *Neurosci Biobehav Rev*. 2015;57:411-432. doi:10.1016/j.neubiorev.2015.09.017

108. McDaniel MA. Big-brained people are smarter: A meta-analysis of the relationship between in vivo brain volume and intelligence. *Intelligence*. 2005;33(4):337-346. doi:10.1016/J.INTELL.2004.11.005

109. Malone IB, Leung KK, Clegg S, et al. Accurate automatic estimation of total intracranial volume: A nuisance variable with less nuisance. Published online 2014. doi:10.1016/j.neuroimage.2014.09.034

110. Royle NA, Booth T, Valdés Hernández MC, et al. Estimated maximal and current brain volume predict cognitive ability in old age. *Neurobiol Aging*. 2013;34(12):2726-2733. doi:10.1016/J.NEUROBIOLAGING.2013.05.015

111. Courchesne E, Chisum HJ, Townsend J, et al. Normal brain development and aging: Quantitative analysis at in vivo MR imaging in healthy volunteers. *Radiology*. 2000;216(3):672-682. doi:10.1148/RADIOLOGY.216.3.R00AU37672/ASSET/IMAGES/LARGE/R00AU37L4B.JPEG

112. Covidence. Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org. https://support.covidence.org/help/how-can-i-cite-covidence

113. Mensen VT, Wierenga LM, van Dijk S, et al. Development of cortical thickness and surface area in autism spectrum disorder. *Neuroimage Clin*. 2017;13:215. doi:10.1016/J.NICL.2016.12.003

114. Barnea-Goraly N, Frazier TW, Piacenza L, et al. A preliminary longitudinal volumetric MRI study of amygdala and hippocampal volumes in autism. *Prog Neuropsychopharmacol Biol Psychiatry*. 2014;48:124-128. doi:10.1016/j.pnpbp.2013.09.010

115. Shen MD, Ph D, Kim SH, et al. Increased Extra-axial Cerebrospinal Fluid in High-Risk Infants who Later Develop Autism. 2018;82(3):186-193. doi:10.1016/j.biopsych.2017.02.1095.Increased

116. Smith E, Thurm A, Greenstein D, et al. Cortical thickness change in autism during early childhood. *Hum Brain Mapp*. 2016;37(7):2616-2629. doi:10.1002/hbm.23195

117. Jou RJ, Frazier TW, Keshavan MS, Minshew NJ, Hardan AY. A two-year longitudinal pilot MRI study of the brainstem in autism. *Behavioural Brain Research*. 2013;251:163-167. doi:10.1016/j.bbr.2013.04.021

118. Shen MD, Nordahl CW, Young GS, et al. Early brain enlargement and elevated extra-axial fluid in infants who develop autism spectrum disorder. *Brain*. 2013;136(9):2825-2835. doi:10.1093/brain/awt166

119. Schumann CM, Bloss CS, Barnes CC, et al. Longitudinal magnetic resonance imaging study of cortical development through early childhood in autism. *Journal of Neuroscience*. 2010;30(12):4419-4427. doi:10.1523/JNEUROSCI.5714-09.2010

120. Hazlett HC, Poe MD, Lightbody AA, et al. Trajectories of early brain volume development in fragile X syndrome and autism. *J Am Acad Child Adolesc Psychiatry*. 2012;51(9):921-933. doi:10.1016/j.jaac.2012.07.003

121. Joanna Briggs Institute Critical Appraisal Checklist. *Checklist for Cohort Studies Available from https://jbi.global/critical-appraisal-tools*.

122. Morris SB, DeShon RP. Combining effect size estimates in meta-analysis with repeated measures and independent-groups designs. *Psychol Methods*. 2002;7(1):105-125. doi:10.1037/1082-989X.7.1.105

123. Morris SB. Estimating effect sizes from pretest-posttest-control group designs. *Organ Res Methods*. 2008;11(2):364-386. doi:10.1177/1094428106291059

124. Pearson MJ, Smart NA. Reported methods for handling missing change standard deviations in meta-analyses of exercise therapy interventions in patients with heart failure: A systematic review. *PLoS One*. 2018;13(10):1-14. doi:10.1371/journal.pone.0205952

125. Hedges EP, See C, Si S, McGuire P, Dickson H, Kempton MJ. Meta-Analysis of longitudinal neurocognitive performance in people at clinical high-risk for psychosis. *Psychol Med*. 2022;52(11):2009-2016. doi:10.1017/S0033291722001830

126. Kempton MJ, Salvador Z, Munafò MR, et al. *Structural Neuroimaging Studies in Major Depressive Disorder Meta-Analysis and Comparison With Bipolar Disorder*. Vol 68.; 2011.

127. Bromis K, Calem M, Reinders AATS, Williams SCR, Kempton MJ. Meta-Analysis of 89 Structural MRI studies in posttraumatic stress disorder and comparison with major depressive disorder. *American Journal of Psychiatry*. 2018;175(10):989-998. doi:10.1176/appi.ajp.2018.17111199

128. Lange N, Travers BG, Bigler ED, et al. Longitudinal Volumetric Brain Changes in Autism Spectrum Disorder Ages 6–35 Years. *Autism Research*. 2015;8(1):82-93. doi:10.1002/aur.1427

129. Reinhardt VP, Iosif AM, Libero L, et al. Understanding Hippocampal Development in Young Children With Autism Spectrum Disorder. In: *Journal of the American Academy of Child and Adolescent Psychiatry*. Vol 59. Elsevier Inc.; 2020:1069-1079. doi:10.1016/j.jaac.2019.08.008

130. Prigge MBD, Lange N, Bigler ED, et al. A 16-year study of longitudinal volumetric brain development in males with autism. *Neuroimage*. 2021;236:118067. doi:10.1016/J.NEUROIMAGE.2021.118067

131. Pagni BA, Walsh MJM, Ofori E, et al. Effects of age on the hippocampus and verbal memory in adults with autism spectrum disorder: Longitudinal versus cross-sectional findings. *Autism Research*. 2022;15(10):1810-1823. doi:10.1002/AUR.2797

132. Hedman AM, Haren NEM van, Schnack HG, Kahn RS, Pol HEH. Human brain changes across the life span: A review of 56 longitudinal magnetic resonance imaging studies. *Hum Brain Mapp*. 2012;33(8):1987. doi:10.1002/HBM.21334

133. Li G, Chen MH, Li G, et al. Volumetric Analysis of Amygdala and Hippocampal Subfields for Infants with Autism. *J Autism Dev Disord*. 2023;53:2475-2489. doi:10.1007/s10803-022-05535-w

134. Alemany S, Blok E, Jansen PR, Muetzel RL, White T. Brain morphology, autistic traits, and polygenic risk for autism: A population-based neuroimaging study. *Autism Research*. 2021;14(10):2085-2099. doi:10.1002/AUR.2576

135. Langen M, Bos D, Noordermeer SDS, Nederveen H, Van Engeland H, Durston S. Changes in the development of striatum are involved in repetitive behavior in autism. *Biol Psychiatry*. 2014;76(5):405-411. doi:10.1016/j.biopsych.2013.08.013

136. Frazier TW, Keshavan MS, Minshew NJ, Hardan AY. A two-year longitudinal MRI study of the corpus callosum in autism. *J Autism Dev Disord*. 2012;42(11):2312-2322. doi:10.1007/s10803-012-1478-z

137. Bieneck V, Bletsch A, Mann C, et al. Longitudinal Changes in Cortical Thickness in Adolescents with Autism Spectrum Disorder and Their Association with Restricted and Repetitive Behaviors. Published online 2021. doi:10.3390/genes12122024

138. Ecker C, Marquand A, Mourão-Miranda J, et al. Neurobiology of Disease Describing the Brain in Autism in Five Dimensions-Magnetic Resonance Imaging-Assisted Diagnosis of Autism Spectrum Disorder Using a Multiparameter Classification Approach. Published online 2010. doi:10.1523/JNEUROSCI.5413-09.2010

139. Buckley E, Pellicano E, Remington A. Higher levels of autistic traits associated with lower levels of self-efficacy and wellbeing for performing arts professionals. *PLoS One*. 2021;16(2 Febuary). doi:10.1371/journal.pone.0246423

140. Mason D, Ronald A, Ambler A, et al. Autistic traits are associated with faster pace of aging: Evidence from the Dunedin study at age 45. *Autism Research*. 2021;14(8):1684-1694. doi:10.1002/AUR.2534

141. Bartholomeusz HH, Courchesne E, Karns CM. Relationship between head circumference and brain volume in healthy normal toddlers, children, and adults. *Neuropediatrics*. 2002;33(5):239-241. doi:10.1055/s-2002-36735

142. Courchesne E, Carper R, Akshoomoff N. Evidence of Brain Overgrowth in the First Year of Life in Autism. *J Am Med Assoc*. 2003;290(3):337-344. doi:10.1001/jama.290.3.337

143. Crucitti J, Hyde C, Enticott PG, Stokes MA. Head circumference trends in autism between 0 and 100 months. *Autism*. 2020;24(7):1726-1739. doi:10.1177/1362361320921037

144. Backer NB Al. Developmental regression in autism spectrum disorder. *Sudan J Paediatr*. 2015;15(1):21. Accessed March 20, 2022. /pmc/articles/PMC4949854/

145. Peters R. Ageing and the brain. *Postgrad Med J*. 2006;82(964):84-88. doi:10.1136/pgmj.2005.036665

146. Martinez-Murcia FJ, Lai MC, Górriz JM, et al. On the brain structure heterogeneity of autism: Parsing out acquisition site effects with significance-weighted principal component analysis. *Hum Brain Mapp*. 2017;38(3):1208-1223. doi:10.1002/hbm.23449

147. Caspi Y, Brouwer RM, Schnack HG, et al. Changes in the intracranial volume from early adulthood to the sixth decade of life: A longitudinal study. *Neuroimage*. 2020;220. doi:10.1016/j.neuroimage.2020.116842

148. Lee JK, Andrews DS, Ozonoff S, et al. Longitudinal Evaluation of Cerebral Growth Across Childhood in Boys and Girls With Autism Spectrum Disorder. *Biol Psychiatry*. Published online November 3, 2020. doi:10.1016/j.biopsych.2020.10.014

149. Langen M, Bos D, Noordermeer SDS, Nederveen H, Van Engeland H, Durston S. Changes in the development of striatum are involved in repetitive behavior in autism. *Biol Psychiatry*. 2014;76(5):405-411. doi:10.1016/j.biopsych.2013.08.013

150. Frazier TW, Keshavan MS, Minshew NJ, Hardan AY. A two-year longitudinal MRI study of the corpus callosum in autism. *J Autism Dev Disord*. 2012;42(11):2312-2322. doi:10.1007/s10803-012-1478-z

151. Bartholomeusz HH, Courchesne E, Karns CM. Relationship between head circumference and brain volume in healthy normal toddlers, children, and adults. *Neuropediatrics*. 2002;33(5):239-241. doi:10.1055/s-2002-36735

152. Piven J, Arndt S, Bailey J, Andreasen N. Regional Brain Enlargement in Autism: A Magnetic Resonance Imaging Study. *J Am Acad Child Adolesc Psychiatry*. 1996;35(4):530-536. doi:10.1097/00004583-199604000-00020

153. Kanner L. Autistic disturbances of affective contact. *Nervous child*. 1943;2:217-250. Accessed August 25, 2023. http://www.th-hoffmann.eu/archiv/kanner/kanner.1943.pdf

154. Molani-Gol R, Alizadeh M, Kheirouri S, Hamedi-Kalajahi F. The early life growth of head circumference, weight, and height in infants with autism spectrum disorders: a systematic review. *BMC Pediatr*. 2023;23(1). doi:10.1186/s12887-023-04445-9

155. Fukumoto A, Hashimoto T, Ito H, et al. Growth of head circumference in autistic infants during the first year of life. *J Autism Dev Disord*. 2008;38(3):411-418. doi:10.1007/S10803-007-0405-1/FIGURES/2

156. Jane Webb S, Nalty T, Munson J, Brock C, Abbott R, Dawson G. Rate of Head Circumference Growth as a Function of Autism Diagnosis and History of Autistic Regression. *J Child Neurol*. 2007;22(10):1182-1190. doi:10.1177/0883073807306263

157. Constantino JN, Majmudar P, Bottini A, et al. Infant head growth in male siblings of children with and without autism spectrum disorders. *J Neurodev Disord*. 2010;2(1):39-46. doi:10.1007/s11689-009-9036-5

158. Surén P, Stoltenberg C, Bresnahan M, et al. EARLY GROWTH PATTERNS IN CHILDREN WITH AUTISM. doi:10.1097/EDE.0b013e31829e1d45

159. McKeague IW, Brown AS, Bao Y, Hinkka-Yli-Salomäki S, Huttunen J, Sourander A. Autism with intellectual disability related to dynamics of head circumference growth during early infancy. *Biol Psychiatry*. 2015;77(9):833-840. doi:10.1016/j.biopsych.2014.08.008

160. Libero LE, Nordahl CW, Li DD, Ferrer E, Rogers SJ, Amaral DG. Persistence of megalencephaly in a subgroup of young boys with autism spectrum disorder. *Autism Research*. 2016;9(11):1169-1182. doi:10.1002/aur.1643

161. Denier N, Steinberg G, van Elst LT, Bracht T. The role of head circumference and cerebral volumes to phenotype male adults with autism spectrum disorder. *Brain Behav*. 2022;12(3). doi:10.1002/brb3.2460

162. Dawson G, Munson J, Webb SJ, Nalty T, Abbott R, Toth K. Rate of Head Growth Decelerates and Symptoms Worsen in the Second Year of Life in Autism. *Biol Psychiatry*. 2007;61(4):458-464. doi:10.1016/j.biopsych.2006.07.016

163. Chawarska K, Campbell D, Chen L, Shic F, Klin A, Chang J. Early Generalized Overgrowth in Boys With Autism. *Arch Gen Psychiatry*. 2011;68(10).

164. Chaste P, Klei L, Sanders SJ, et al. Adjusting Head Circumference for Covariates in Autism: Clinical Correlates of a Highly Heritable Continuous Trait. *Biol Psychiatry*. Published online 2013. doi:10.1016/j.biopsych.2013.04.018

165. Mraz KD, Green J, Dumont-Mathieu T, Makin S, Fein D. Correlates of head circumference growth in infants later diagnosed with Autism spectrum disorders. *J Child Neurol*. 2007;22(6):700-713. doi:10.1177/0883073807304005

166. Lainhart JE, Bigler ED, Bocian M, et al. Head Circumference and Height in Autism: A Study by the Collaborative Program of Excellence in Autism. *Am J Med Genet A*. 2006;140:2257-2274. doi:10.1002/ajmg.a.31465

167. Miles JH, Hadden LL, Takahashi TN, Hillman RE. Head Circumference Is an Independent Clinical Finding Associated With Autism. *J Med Genet*. 2000;95:339-350. doi:10.1002/1096-8628(20001211)95:4<339::AID-AJMG9>3.0.CO;2-B

168. Fraser A, Macdonald-wallis C, Tilling K, et al. Cohort Profile: the Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. *Int J Epidemiol*. 2013;42(1):97-110. doi:10.1093/IJE/DYS066

169. Boyd A, Golding J, Macleod J, et al. Cohort Profile: The 'Children of the 90s'-the index offspring of the Avon Longitudinal Study of Parents and Children. doi:10.1093/ije/dys064

170. Northstone K, Lewcock M, Groom A, et al. The Avon Longitudinal Study of Parents and Children (ALSPAC): an update on the enrolled sample of index children in 2019 [version 1; peer review: 2 approved]. *Wellcome Open Res*. 2019;4. doi:10.12688/wellcomeopenres.15132.1

171. Solmi F, Bentivegna F, Bould H, et al. Trajectories of autistic social traits in childhood and adolescence and disordered eating behaviours at age 14 years: A UK general population cohort study. *J Child Psychol Psychiatry*. Published online 2020. doi:10.1111/jcpp.13255

172. Shi J, Korsiak J, Roth DE. New approach for the identification of implausible values and outliers in longitudinal childhood anthropometric data. Published online 2018. doi:10.1016/j.annepidem.2018.01.007

173. De Onis M. WHO Child Growth Standards based on length/height, weight and age. *Acta Paediatrica, International Journal of Paediatrics*. 2006;95(SUPPL. 450):76-85. doi:10.1080/08035320500495548

174. Russell G, Collishaw S, Golding J, Kelly SE, Ford T. Changes in diagnosis rates and behavioural traits of autism spectrum disorder over time. *BJPsych Open*. 2015;1(2):110-115. doi:10.1192/bjpo.bp.115.000976

175. Hall A, Maw R, Iles-Caven Y, Gregory S, Rai D, Golding J. Associations between autistic traits and early ear and upper respiratory signs: a prospective observational study of the Avon Longitudinal Study of Parents and Children (ALSPAC) geographically defined childhood population. *BMJ Open*. 2023;13(3). doi:10.1136/bmjopen-2022-067682

176. Department for Education and Skills. *Data Collection by Type of Special Educational Need (DfES-1889-2005)*.; 2005.

177. Golding G, Pembrey P, Jones J. ALSPAC–The Avon Longitudinal Study of Parents and Children. *Paediatr Perinat Epidemiol*. 2001;15(1):74-87. doi:10.1046/j.1365-3016.2001.00325.x

178. Madley-Dowd P, Thomas R, Boyd A, Zammit S, Heron J, Rai D. Intellectual disability in the children of the Avon Longitudinal Study of Parents and Children (ALSPAC). *Wellcome Open Res*. 2022;7. doi:10.12688/WELLCOMEOPENRES.17803.2

179. Skuse DH, Mandy WPL, Scourfield J. Measuring autistic traits: heritability, reliability and validity of the Social and Communication Disorders Checklist. *Br J Psychiatry*. 2005;187(DEC.):568-572. doi:10.1192/BJP.187.6.568

180. Skuse DH, Mandy WPL, Scourfield J. Measuring autistic traits: Heritability, reliability and validity of the Social and Communication Disorders Checklist. *British Journal of Psychiatry*. 2005;187(DEC.):568-572. doi:10.1192/bjp.187.6.568

181. Zwaigenbaum L, Young GS, Stone WL, et al. Early head growth in infants at risk of autism: a baby siblings research consortium study. *J Am Acad Child Adolesc Psychiatry*. 2014;53(10):1053-1062. doi:10.1016/J.JAAC.2014.07.007

182. Modabbernia A, Velthorst E, Reichenberg A. Environmental risk factors for autism: an evidence-based review of systematic reviews and meta-analyses. *Mol Autism*. 2017;8(1):1-16. doi:10.1186/s13229-017-0121-4

183. McKeague IW, Brown AS, Bao Y, Hinkka-Yli-Salomäki S, Huttunen J, Sourander A. Autism with intellectual disability related to dynamics of head circumference growth during early infancy. *Biol Psychiatry*. 2015;77(9):833-840. doi:10.1016/j.biopsych.2014.08.008

184. Webb JS, Nalty T, Munson J, Brock C, Abbott R, Dawson G. Rate of head circumference growth as a function of autism diagnosis and history of autistic regression. *J Child Neurol*. 2007;22(10):1182-1190. doi:10.1177/0883073807306263

185. Gale CR, O'Callaghan FJ, Bredow M, Martyn CN. The Influence of Head Growth in Fetal Life, Infancy, and Childhood on Intelligence at the Ages of 4 and 8 Years. *Pediatrics*. 2006;118(4):1486-1492. doi:10.1542/PEDS.2005-2629

186. Kirkegaard H, Möller S, Wu C, et al. Associations of birth size, infancy, and childhood growth with intelligence quotient at 5 years of age: a Danish cohort study. *Am J Clin Nutr*. 2020;112(1):96-105. doi:10.1093/AJCN/NQAA051

187. Supekar K, Uddin LQ, Khouzam A, et al. Brain Hyperconnectivity in Children with Autism and its Links to Social Deficits. *Cell Rep*. 2013;5(3):738-747. doi:10.1016/j.celrep.2013.10.001

188. Green C, Dissanayake C, Loesch D. A review of physical growth in children and adolescents with Autism Spectrum Disorder. *Developmental Review*. 2015;36:156-178. doi:10.1016/j.dr.2015.02.001

189. Campbell DJ, Chang J, Chawarska K. Early Generalized Overgrowth in Autism Spectrum Disorder: Prevalence Rates, Gender Effects, and Clinical Outcomes. *J Am Acad Child Adolesc Psychiatry*. 2014;53(10):1063-1073. doi:10.1016/j.jaac

190. Dissanayake C, Bui QM, Huggins R, Loesch DZ. Growth in stature and head circumference in high-functioning autism and Asperger disorder during the first 3 years of life. *Dev Psychopathol*. 2006;18(2):381-393. doi:10.1017/S0954579406060202

191. Hshieh TT, Fox ML, Kosar CM, et al. Head circumference as a useful surrogate for intracranial volume in older adults. *Int Psychogeriatr*. 2016;28(1):157-162. doi:10.1017/S104161021500037X

192. Sugathan A, Biagioli M, Golzio C, et al. CHD8 regulates neurodevelopmental pathways associated with autism spectrum disorder in neural progenitors. *Proc Natl Acad Sci U S A*. 2014;111(42):E4468-E4477. doi:10.1073/pnas.1405266111

193. Adam MP, Feldman J, Mirzaa GM. *CHD8-Related Neurodevelopmental Disorder with Overgrowth*.; 2022.

194. McCaffery P, Deutsch CK. Macrocephaly and the control of brain growth in autistic disorders. *Prog Neurobiol*. 2005;77(1-2):38-56. doi:10.1016/j.pneurobio.2005.10.005

195. Dissanayake C, Bui QM, Huggins R, Loesch DZ. Growth in stature and head circumference in high-functioning autism and Asperger disorder during the first 3 years of life. Published online 2006. doi:10.1017/S0954579406060202

196. Muratori F, Calderoni S, Apicella F, et al. Tracing back to the onset of abnormal head circumference growth in Italian children with autism spectrum disorder. *Res Autism Spectr Disord*. 2012;6(1):442-449. doi:10.1016/j.rasd.2011.07.004

197. Haijma S V, Haren N Van, Cahn W, et al. Brain Volumes in Schizophrenia: A Meta-Analysis in Over 18 000 Subjects. *Schizophr Bull*. 2013;39(5):1129-1138. doi:10.1093/schbul/sbs118

198. McNeil TF, Cantor-Graae E, Nordström LG, Rosenlund T. Are reduced head circumference at birth and increased obstetric complications associated only with schizophrenic psychosis? A comparison with schizo-affective and unspecified functional psychoses. *Schizophr Res*. 1996;22(1):41-47. doi:10.1016/0920-9964(96)00045-X

199. Hultman CM, Sparén P, Takei N, Murray RM, Cnattingius S. Prenatal and perinatal and perinatal risk factors for early onset schizophrenia, affective psychosis, and reactive psychosis. *BMJ*. 1999;318(7181):426.

200. Kunugi H, Takei N, Murray RM, Saito K, Nanko S. Small head circumference at birth in schizophrenia. *Schizophr Res*. 1996;20(1-2):165-170. doi:10.1016/0920-9964(96)00007-2

201. Cannon M, Jones PB, Murray RM. Obstetric complications and schizophrenia: Historical and meta-analytic review. *American Journal of Psychiatry*. 2002;159(7):1080-1092. doi:10.1176/appi.ajp.159.7.1080

202. Nilsson E, Stålberg G, Lichtenstein P, Cnattingius S, Olausson PO, Hultman CM. Fetal growth restriction and schizophrenia: A Swedish twin study. *Twin Research and Human Genetics*. 2005;8(4):402-408. doi:10.1375/1832427054936727

203. Welham J, Scott J, Williams G, Najman J, Callaghan MO, Mcgrath J. Growth in Young Adults Who Screen Positive for Non-Affective Psychosis: Birth Cohort Study. 2009;(July 2008).

204. Brown AS, Gyllenberg D, Hinkka-Yli-Salomäki S, Sourander A, McKeague IW. Altered growth trajectory of head circumference during infancy and schizophrenia in a National Birth Cohort. *Schizophr Res*. 2017;182:115-119. doi:10.1016/j.schres.2016.10.032

205. Drakesmith M, Dutt A, Fonville L, et al. Mediation of developmental risk factors for psychosis by white matter microstructure in young adults with psychotic experiences. *JAMA Psychiatry*. 2016;73(4):396-406. doi:10.1001/jamapsychiatry.2015.3375

206. Smith SM. Fast robust automated brain extraction. *Hum Brain Mapp*. 2002;17(3):143. doi:10.1002/HBM.10062

207. Zhang Y, Brady M, Smith S. Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. *IEEE Trans Med Imaging*. 2001;20(1):45-57. doi:10.1109/42.906424

208. Niarchou M, Zammit S, Lewis G. The Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort as a resource for studying psychopathology in childhood and

adolescence: a summary of findings for depression and psychosis. *Soc Psychiatry Psychiatr Epidemiol*. 2015;50(7):1017-1027. doi:10.1007/S00127-015-1072-8

209. World Health Organization (WHO). *Schedules for Clinical Assessment in Neuropsychiatry*. American Psychiatric Press (on behalf of WHO); 1994.

210. Weinberger DR, Berman KF, Iadarola M, Driesen N, Karson C, Coppola R. Hat Size in Schizophrenia. *Arch Gen Psychiatry*. 1987;44(7):672-672. doi:10.1001/ARCHPSYC.1987.01800190092014

211. Ward KE, Friedman L, Wise A, Charles Schulz S. Meta-analysis of brain and cranial size in schizophrenia. *Schizophr Res*. 1996;22:213.

212. Friedman L, Wiechers IR, Cerny CA, Schulz SC, Buckley P. If patients with schizophrenia have small brains, why don't they have small heads? *Schizophr Res*. 2000;42(1):1-6. doi:10.1016/S0920-9964(99)00098-5

213. Davies C, Segre G, Estradé A, et al. Prenatal and perinatal risk and protective factors for psychosis: a systematic review and meta-analysis. *Lancet Psychiatry*. 2020;7(5):399-410. doi:10.1016/S2215-0366(20)30057-2

214. Cannon TD, Chung Y, He G, et al. Progressive Reduction in Cortical Thickness as Psychosis Develops: A Multisite Longitudinal Neuroimaging Study of Youth at Elevated Clinical Risk. *Biol Psychiatry*. 2015;77(2):147. doi:10.1016/J.BIOPSYCH.2014.05.023

215. Blanken LME, Mous SE, Ghassabian A, et al. Cortical morphology in 6- to 10-year old children with autistic traits: A population-based neuroimaging study. *American Journal of Psychiatry*. 2015;172(5):479-486. doi:10.1176/APPI.AJP.2014.14040482/ASSET/IMAGES/LARGE/APPI.AJP.2014.14040482F1.JPEG

216. Bralten J, Van Hulzen KJ, Martens MB, et al. Autism spectrum disorders and autistic traits share genetics and biology. *Molecular Psychiatry 2018 23:5*. 2017;23(5):1205-1212. doi:10.1038/mp.2017.98

217. Van Rooij D, Anagnostou E, Arango C, et al. Cortical and subcortical brain morphometry differences between patients with autism spectrum disorder and healthy individuals across the lifespan: Results from the ENIGMA ASD working group. *American Journal of Psychiatry*. 2018;175(4):359-369. doi:10.1176/APPI.AJP.2017.17010100/ASSET/IMAGES/LARGE/APPI.AJP.2017.17010100F3.JPEG

218. Deramus TP, Kana RK. Anatomical likelihood estimation meta-analysis of grey and white matter anomalies in autism spectrum disorders. *Neuroimage Clin*. 2015;7:525-536. doi:10.1016/J.NICL.2014.11.004

219. Sader M, Williams JHG, Waiter GD. A meta-analytic investigation of grey matter differences in anorexia nervosa and autism spectrum disorder. *European Eating Disorders Review*. 2022;30(5):560-579. doi:10.1002/ERV.2915

220. Baron-Cohen S, Wheelwright S, Skinner R, Martin J, Clubley E. The Autism-Spectrum Quotient (AQ): Evidence from Asperger Syndrome/High-Functioning Autism, Males and Females,

Scientists and Mathematicians. *J Autism Dev Disord*. 2001;31(1):5-17. doi:10.1023/A:1005653411471/METRICS

221. Constantino JN, Todd RD. Autistic Traits in the General Population: A Twin Study. *Arch Gen Psychiatry*. 2003;60(5):524-530. doi:10.1001/ARCHPSYC.60.5.524

222. Yaxu Y, Ren Z, Ward J, Jiang Q. Atypical Brain Structures as a Function of Gray Matter Volume (GMV) and Gray Matter Density (GMD) in Young Adults Relating to Autism Spectrum Traits. *Front Psychol*. 2020;11. doi:10.3389/FPSYG.2020.00523/FULL

223. Koolschijn PCMP, Geurts HM, van der Leij AR, Scholte HS. Are Autistic Traits in the General Population Related to Global and Regional Brain Differences? *J Autism Dev Disord*. 2015;45(9):2779-2791. doi:10.1007/S10803-015-2441-6

224. An K min, Ikeda T, Hirosawa T, et al. Decreased grey matter volumes in unaffected mothers of individuals with autism spectrum disorder reflect the broader autism endophenotype. *Sci Rep*. 2021;11(1):10001. doi:10.1038/s41598-021-89393-z

225. Geurts HM, Ridderinkhof KR, Scholte HS. The relationship between grey-matter and ASD and ADHD traits in typical adults. *J Autism Dev Disord*. 2013;43(7):1630-1641. doi:10.1007/S10803-012-1708-4/FIGURES/3

226. Chandran VA, Pliatsikas C, Neufeld J, et al. Brain structural correlates of autistic traits across the diagnostic divide: A grey matter and white matter microstructure study. Published online 2021. doi:10.1016/j.nicl.2021.102897

227. Nees F, Banaschewski T, Bokde ALW, et al. Global and Regional Structural Differences and Prediction of Autistic Traits during Adolescence. *Brain Sciences 2022, Vol 12, Page 1187*. 2022;12(9):1187. doi:10.3390/BRAINSCI12091187

228. Gros G, Miranda Marcos R, Latrille A, et al. Whole-brain gray matter maturation trajectories associated with autistic traits from adolescence to early adulthood. *Brain Struct Funct*. 2024;229(1):15-29. doi:10.1007/S00429-023-02710-2

229. Koolschijn PCMP, Geurts HM, van der Leij AR, Scholte HS. Are Autistic Traits in the General Population Related to Global and Regional Brain Differences? *J Autism Dev Disord*. 2015;45(9):2779. doi:10.1007/S10803-015-2441-6

230. Sandin S, Lichtenstein P, Kuja-Halkola R, Hultman C, Larsson H, Reichenberg A. The Heritability of Autism Spectrum Disorder. *JAMA*. 2017;318(12):1182-1184. doi:10.1001/JAMA.2017.12141

231. Taylor SC, Steeman S, Gehringer BN, et al. Heritability of quantitative autism spectrum traits in adults: A family-based study. *Autism Res*. 2021;14(8):1543. doi:10.1002/AUR.2571

232. Sharp TH, McBride NS, Howell AE, et al. Population neuroimaging: generation of a comprehensive data resource within the ALSPAC pregnancy and birth cohort. *Wellcome Open Res*. 2020;5. doi:10.12688/WELLCOMEOPENRES.16060.1

233. Drakesmith M, Caeyenberghs K, Dutt A, et al. Schizophrenia-like topological changes in the structural connectome of individuals with subclinical psychotic experiences. *Hum Brain Mapp*. 2015;36(7):2629-2643. doi:10.1002/hbm.22796

234. Fonville L, Kadosh KC, Drakesmith M, et al. Psychotic experiences, working memory, and the developing brain: A multimodal neuroimaging study. *Cerebral Cortex*. 2015;25(12):4828-4838. doi:10.1093/cercor/bhv181

235. Fonville L, Drakesmith M, Zammit S, Lewis G, Jones DK, David AS. MRI indices of cortical development in young people with psychotic experiences: Influence of genetic risk and persistence of symptoms. *Schizophr Bull*. 2019;45(1):169-179. doi:10.1093/schbul/sbx195

236. Lancaster TM, Dimitriadis SL, Tansey KE, et al. Structural and Functional Neuroimaging of Polygenic Risk for Schizophrenia: A Recall-by-Genotype-Based Approach. *Schizophr Bull*. 2019;45(2):405-414. doi:10.1093/schbul/sby037

237. Robinson EB, Munir K, Munaf MR, Hughes M, McCormick MC, Koenen KC. The stability of autistic traits in the general population: further evidence for a continuum of impairment. *J Am Acad Child Adolesc Psychiatry*. 2011;50(4):376. doi:10.1016/J.JAAC.2011.01.005

238. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)-A metadata-driven methodology and workflow process for providing translational research informatics support. Published online 2008. doi:10.1016/j.jbi.2008.08.010

239. Zhou X, Wu R, Zeng Y, et al. Choice of Voxel-based Morphometry processing pipeline drives variability in the location of neuroanatomical brain markers. *Communications Biology 2022 5:1*. 2022;5(1):1-12. doi:10.1038/s42003-022-03880-1

240. Zhao X, Zhu S, Cao Y, et al. Abnormalities of Gray Matter Volume and Its Correlation with Clinical Symptoms in Adolescents with High-Functioning Autism Spectrum Disorder. *Neuropsychiatr Dis Treat*. 2022;18:717. doi:10.2147/NDT.S349247

241. Eilam-Stock T, Wu T, Spagna A, Egan LJ, Fan J. Neuroanatomical alterations in high-functioning adults with autism spectrum disorder. *Front Neurosci*. 2016;10(JUN):1-10. doi:10.3389/fnins.2016.00237

242. Cauda F, Geda E, Sacco K, et al. Grey matter abnormality in autism spectrum disorder: an activation likelihood estimation meta-analysis study. *J Neurol Neurosurg Psychiatry*. 2011;82(12):1304-1313. doi:10.1136/JNNP.2010.239111

243. Koush Y, Pichon S, Eickhoff SB, Van De Ville D, Vuilleumier P, Scharnowski F. Brain networks for engaging oneself in positive-social emotion regulation. *Neuroimage*. 2019;189:106-115. doi:10.1016/J.NEUROIMAGE.2018.12.049

244. Li W, Qin W, Liu H, et al. Subregions of the human superior frontal gyrus and their connections. *Neuroimage*. 2013;78:46-58. doi:10.1016/J.NEUROIMAGE.2013.04.011

245. Martín-Luengo B, Vorobiova AN, Feurra M, Myachykov A, Shtyrov Y. Transcranial magnetic stimulation of the left middle frontal gyrus modulates the information people communicate in different social contexts. *Sci Rep*. 2023;13(1):1-10. doi:10.1038/s41598-023-36192-3

246. Koyama MS, O'Connor D, Shehzad Z, Milham MP. Differential contributions of the middle frontal gyrus functional connectivity to literacy and numeracy. *Sci Rep*. 2017;7(1):1-13. doi:10.1038/s41598-017-17702-6

247. Chen J, Wei Z, Liang C, et al. Dysfunction of the Auditory Brainstem as a Neurophysiology Subtype of Autism Spectrum Disorder. *Front Neurosci*. 2021;15(March):1-11. doi:10.3389/fnins.2021.637079

248. Coelho C, Lĉ K, Mozeiko J, Krueger F, Grafman J. Discourse production following injury to the dorsolateral prefrontal cortex. *Neuropsychologia*. 2012;50(14):3564-3572. doi:10.1016/j.neuropsychologia.2012.09.005

249. Sha Z, van Rooij D, Anagnostou E, et al. Subtly altered topological asymmetry of brain structural covariance networks in autism spectrum disorder across 43 datasets from the ENIGMA consortium. *Mol Psychiatry*. 2022;27(4):2114-2125. doi:10.1038/s41380-022-01452-7

250. Guo Z, Tang X, Xiao S, et al. Systematic review and meta-analysis: multimodal functional and anatomical neural alterations in autism spectrum disorder. *Mol Autism*. 2024;15(1):1-13. doi:10.1186/s13229-024-00593-6

251. Cheng W, Rolls ET, Gu H, Zhang J, Feng J. Autism: reduced connectivity between cortical areas involved in face expression, theory of mind, and the sense of self. *Brain*. 2015;138(5):1382-1393. doi:10.1093/BRAIN/AWV051

252. Dellapiazza F. Links between sensory processing, adaptive behaviours, and attention in children with autism spectrum disorder: A systematic review. *Psychiatry Res*. 2018;270:78-88. doi:10.1016/J.PSYCHRES.2018.09.023

253. Thye MD, Bednarz HM, Herringshaw AJ, Sartin EB, Kana RK. The impact of atypical sensory processing on social impairments in autism spectrum disorder. *Dev Cogn Neurosci*. 2018;29:151-167. doi:10.1016/J.DCN.2017.04.010

254. Moseley RL, Pulvermüller F. What can autism teach us about the role of sensorimotor systems in higher cognition? New clues from studies on language, action semantics, and abstract emotional concept processing. *Cortex*. 2018;100:149-190. doi:10.1016/J.CORTEX.2017.11.019

255. Kropf E, Syan SK, Minuzzi L, Frey BN. From anatomy to function: the role of the somatosensory cortex in emotional regulation. *Brazilian Journal of Psychiatry*. 2018;41(3):261-269. doi:10.1590/1516-4446-2018-0183

256. Moseley RL, Pulvermüller F. What can autism teach us about the role of sensorimotor systems in higher cognition? New clues from studies on language, action semantics, and abstract emotional concept processing. *Cortex*. 2018;100:149-190. doi:10.1016/J.CORTEX.2017.11.019

257. Mei T, Forde NJ, Floris DL, et al. Autism Is Associated With Interindividual Variations of Gray and White Matter Morphology. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2023;8(11):1084-1093. doi:10.1016/J.BPSC.2022.08.011

258. Dickstein DP, Pescosolido MF, Reidy BL, et al. Developmental Meta-Analysis of the Functional Neural Correlates of Autism Spectrum Disorders. *J Am Acad Child Adolesc Psychiatry*. 2013;52(3):279-289.e16. doi:10.1016/J.JAAC.2012.12.012

259. Borich MR, Brodie SM, Gray WA, Ionta S, Boyd LA. Understanding the role of the primary somatosensory cortex: Opportunities for rehabilitation. *Neuropsychologia*. 2015;79(Pt B):246. doi:10.1016/J.NEUROPSYCHOLOGIA.2015.07.007

260. Deschamps I, Baum SR, Gracco VL. On the role of the supramarginal gyrus in phonological processing and verbal working memory: Evidence from rTMS studies. *Neuropsychologia*. 2014;53(1):39-46. doi:10.1016/J.NEUROPSYCHOLOGIA.2013.10.015

261. Li X, Jiang M, Zhao L, et al. Relationship between autism and brain cortex surface area: genetic correlation and a two-sample Mendelian randomization study. *BMC Psychiatry*. 2024;24(1). doi:10.1186/S12888-024-05514-8

262. Yang J, Andric M, Mathew MM. The neural basis of hand gesture comprehension: A meta-analysis of functional magnetic resonance imaging studies. *Neurosci Biobehav Rev*. 2015;57:88-104. doi:10.1016/J.NEUBIOREV.2015.08.006

263. Króliczak G, Piper BJ, Frey SH. Specialization of the left supramarginal gyrus for hand-independent praxis representation is not related to hand dominance. *Neuropsychologia*. 2016;93:501-512. doi:10.1016/J.NEUROPSYCHOLOGIA.2016.03.023

264. Silverman LB, Bennetto L, Campana E, Tanenhaus MK. Speech-and-gesture integration in high functioning autism. *Cognition*. 2010;115(3):380-393. doi:10.1016/J.COGNITION.2010.01.002

265. Ye QY, Liu LR, Lv SL, et al. The Gestures in 2–4-Year-Old Children With Autism Spectrum Disorder. *Front Psychol*. 2021;12:604542. doi:10.3389/FPSYG.2021.604542/BIBTEX

266. Seng GJ, Lai MC, Goh JOS, Tseng WYI, Gau SSF. Gray matter volume alteration is associated with insistence on sameness and cognitive flexibility in autistic youth. *Autism Research*. 2022;15(7):1209-1221. doi:10.1002/aur.2732

267. Cook J, Barbalat G, Blakemore SJ, Frith C, Hamilton A. Top-down modulation of the perception of other people in schizophrenia and autism HUMAN NEUROSCIENCE. *Article*. 2012;6(1). doi:10.3389/fnhum.2012.00175

268. Ursino M, Serra M, Tarasi L, Ricci G, Magosso E, Romei V. Bottom-up vs. top-down connectivity imbalance in individuals with high-autistic traits: An electroencephalographic study. *Front Syst Neurosci*. 2022;16. doi:10.3389/fnsys.2022.932128

269. Bölte S, Westerwald E, Holtmann M, Freitag C, Poustka F. Autistic Traits and Autism Spectrum Disorders: The Clinical Validity of Two Measures Presuming a Continuum of Social Communication Skills. Published online 2010. doi:10.1007/s10803-010-1024-9

270. Skuse DH, Mandy W, Clin D, et al. Social Communication Competence and Functional Adaptation in a General Population of Children: Preliminary Evidence for Sex-by-Verbal IQ Differential Risk. doi:10.1097/CHI.0b013e31819176b8

271. Courchesne E, Pierce K. Brain overgrowth in autism during a critical time in development: Implications for frontal pyramidal neuron and interneuron development and connectivity. *International Journal of Developmental Neuroscience*. 2005;23(2-3 SPEC. ISS.):153-170. doi:10.1016/j.ijdevneu.2005.01.003

272. Alemany S, Blok E, Jansen PR, Muetzel RL, White T. Brain morphology, autistic traits, and polygenic risk for autism: A population-based neuroimaging study. *Autism Research*. 2021;14(10):2085-2099. doi:10.1002/AUR.2576

273. Sharp TH, Elsabbagh M, Pickles A, Bedford R. The subcortical correlates of autistic traits in school-age children: a population-based neuroimaging study. *Mol Autism*. 2023;14(1):1-12. doi:10.1186/S13229-023-00538-5/FIGURES/3

274. Dardani C, Schalbroeck R, Madley-Dowd P, et al. Childhood Trauma As a Mediator of the Association Between Autistic Traits and Psychotic Experiences: Evidence From the Avon

Longitudinal Study of Parents and Children Cohort. *Schizophr Bull*. 2023;49(2):364-374. doi:10.1093/schbul/sbac167

275. Sha Z, Schijven D, Carrion-Castillo A, et al. The genetic architecture of structural left–right asymmetry of the human brain. *Nat Hum Behav*. 2021;5(9):1226-1239. doi:10.1038/s41562-021-01069-w

276. Postema MC. Altered structural brain asymmetry in autism spectrum disorder in a study of 54 datasets. *Nat Commun*. 2019;10(1):1-12.

277. Floris DL, Lai MC, Auer T, et al. Atypically rightward cerebral asymmetry in male adults with autism stratifies individuals with and without language delay. *Hum Brain Mapp*. 2016;37(1):230-253. doi:10.1002/hbm.23023

278. Nielsen JA, Zielinski BA, Fletcher PT, et al. Abnormal lateralization of functional connectivity between language and default mode regions in autism. *Mol Autism*. 2014;5(1):1-11. doi:10.1186/2040-2392-5-8

279. Shen MD, Piven J. *Brain and Behavior Development in Autism from Birth through Infancy*.; 2017. www.dialogues-cns.org

280. Freeman. The emergence of autism spectrum disorder (ASD): Insights gained from studies of brain and behaviour in high-risk infants. *Physiol Behav*. 2018;176(1):139-148. doi:10.1117/12.2549369.Hyperspectral

281. van 't Hof M, Tisseur C, van Berckelear-Onnes I, et al. Age at autism spectrum disorder diagnosis: A systematic review and meta-analysis from 2012 to 2019. *Autism*. 2021;25(4):862-873. doi:10.1177/1362361320971107

282. Bonnet-Brilhault F, Rajerison TA, Paillet C, et al. Autism is a prenatal disorder: Evidence from late gestation brain overgrowth. *Autism Research*. 2018;11(12):1635-1642. doi:10.1002/AUR.2036

283. Blanken LME, Dass A, Alvares G, et al. A prospective study of fetal head growth, autistic traits and autism spectrum disorder. *Autism Research*. 2018;11(4):602-612. doi:10.1002/aur.1921

284. Surén P, Stoltenberg C, Bresnahan M, et al. Early growth patterns in children with autism. *Epidemiology*. 2013;24(5):660-670. doi:10.1097/EDE.0b013e31829e1d45

285. Libero L. Persistence of Megalencephaly in a Subgroup of Young Boys With Autism Spectrum Disorder. *Physiol Behav*. 2017;176(5):139-148. doi:10.1016/j.physbeh.2017.03.040

286. Beopoulos A, Géa M, Fasano A, Iris F. Autism spectrum disorders pathogenesis: Toward a comprehensive model based on neuroanatomic and neurodevelopment considerations. *Front Neurosci*. 2022;16. doi:10.3389/FNINS.2022.988735

287. Wei H, Alberts I, Li X. The apoptotic perspective of autism. *International Journal of Developmental Neuroscience*. 2014;36(1):13-18. doi:10.1016/J.IJDEVNEU.2014.04.004

288. Backer NB Al. Developmental regression in autism spectrum disorder. *Sudan J Paediatr*. 2015;15(1):21. Accessed April 24, 2024. /pmc/articles/PMC4949854/

289. Pyhälä R, Hovi P, Lahti M, et al. Very Low Birth Weight, Infant Growth, and Autism-Spectrum Traits in Adulthood. *Pediatrics*. 2014;134(6):1075-1083. doi:10.1542/PEDS.2014-1097

290. Guo X, Duan X, Suckling J, et al. Mapping Progressive Gray Matter Alterations in Early Childhood Autistic Brain. *Cerebral Cortex*. 2021;31(3):1500-1510. doi:10.1093/cercor/bhaa304

291. Arutiunian V, Gomozova M, Minnigulova A, et al. Structural brain abnormalities and their association with language impairment in school-aged children with Autism Spectrum Disorder. *Sci Rep*. 2023;13(1). doi:10.1038/s41598-023-28463-w

292. Gilmore JH, Kang C, Evans DD, et al. Prenatal and neonatal brain structure and white matter maturation in children at high risk for schizophrenia. *American Journal of Psychiatry*. 2010;167(9):1083-1091. doi:10.1176/APPI.AJP.2010.09101492/SUPPL_FILE/AJP_167_09_1083_01.PDF

293. Wahlbeck K, Forsén T, Osmond C, Barker DJP, Eriksson JG. Association of Schizophrenia With Low Maternal Body Mass Index, Small Size at Birth, and Thinness During Childhood. *Arch Gen Psychiatry*. 2001;58(1):48-52. doi:10.1001/ARCHPSYC.58.1.48

294. Tsehay B, Seyoum G. The neurodevelopmental basis of schizophrenia: clinical clues from craniofacial dysmorphology in northwest Ethiopia, 2020. *BMC Neurosci*. 2021;22(59). doi:10.1186/s12868-021-00663-y

295. Lawrie SM, Byrne M, Miller P, et al. Neurodevelopmental indices and the development of psychotic symptoms in subjects at high risk of schizophrenia. *British Journal of Psychiatry*. 2001;178(JUNE):524-530. doi:10.1192/bjp.178.6.524

296. Gaser C, Nenadic I, Volz HP, Büchel C, Sauer H. Neuroanatomy of "Hearing Voices": A Frontotemporal Brain Structural Abnormality Associated with Auditory Hallucinations in Schizophrenia. *Cerebral Cortex*. 2004;14(1):91-96. doi:10.1093/cercor/bhg107

297. Kubota M, Miyata J, Hirao K, et al. Alexithymia and regional gray matter alterations in schizophrenia. *Neurosci Res*. 2011;70(2):206-213. doi:10.1016/j.neures.2011.01.019

298. Sun F, Chen Y, Huang Y, Yan J, Chen Y. Relationship between gray matter structure and age in children and adolescents with high-functioning autism spectrum disorder. *Front Hum Neurosci*. 2022;16:1039590. doi:10.3389/FNHUM.2022.1039590

299. Xiao Y, Wen TH, Kupis L, et al. Atypical functional connectivity of temporal cortex with precuneus and visual regions may be an early-age signature of ASD. *Mol Autism*. 2023;14(1). doi:10.1186/s13229-023-00543-8

300. Liu J, Yao L, Zhang W, et al. Gray matter abnormalities in pediatric autism spectrum disorder: a meta-analysis with signed differential mapping. *Eur Child Adolesc Psychiatry*. 2017;26(8):933-945. doi:10.1007/s00787-017-0964-4

301. Stilo SA, Murray RM. Non-Genetic Factors in Schizophrenia. *Curr Psychiatry Rep*. 2019;21(10). doi:10.1007/s11920-019-1091-3

302. Eyles DW. How do established developmental risk-factors for schizophrenia change the way the brain develops? *Translational Psychiatry 2021 11:1*. 2021;11(1):1-15. doi:10.1038/s41398-021-01273-2

303. Spear LP. Adolescent Neurodevelopment. *J Adolesc Health*. 2013;52(2 0 2):S7. doi:10.1016/J.JADOHEALTH.2012.05.006

304. Howes OD, Onwordi EC. The synaptic hypothesis of schizophrenia version III: a master mechanism. *Mol Psychiatry*. 2023;28(5):1843. doi:10.1038/S41380-023-02043-W

305. Jackson MI, Kiernan K, McLanahan S. Maternal Education, Changing Family Circumstances, and Children's Skill Development in the United States and UK. *Annals of the American Academy of Political and Social Science*. 2017;674(1):59-84. doi:10.1177/0002716217729471

306. Steer CD, Golding J, Bolton PF. Traits contributing to the autistic spectrum. *PLoS One*. 2010;5(9):1-13. doi:10.1371/journal.pone.0012633

307. Mason D, Stewart GR, Capp SJ, Happé F. Older Age Autism Research: A Rapidly Growing Field, but Still a Long Way to Go. *Autism Adulthood*. 2022;4(2):164. doi:10.1089/AUT.2021.0041