TITLE: Influence of sex, ethnicity and deprivation on survival and completion of the Fontan pathway for children with functionally single ventricle heart disease

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SHORT TITLE: Influence of social factors on Fontan-type surgery

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The influence of key social determinants of health (sex, race and ethnicity and local area deprivation) on childhood mortality and timing of completion of palliative stage 3 Fontan-type surgery were investigated for a nationally representative cohort of children with functionally single ventricle hearts (f-SV). The UK National Health Service provides universal free healthcare; therefore, ability to pay should not directly influence service access. Nevertheless, socio-cultural factors and lifestyle factors may lead to outcome disparities.

The study included children born 2000 to 2018 who underwent palliative procedures for f-SV recorded in the mandatory National Congenital Heart Disease Audit.[1] Primary and secondary outcomes were childhood survival and completion of Fontan-type surgery. Five-year survival was 72.1%. IRB approval was obtained from National Health Service Research Ethics Committee (approval 18/LO/1688) alongside Confidentiality Advisory Group support to waive consent (waiver 17/CAG/0071). Data supporting this study are available from the National Institute for Cardiac Outcomes Research (www.nicor.org.uk/researchers).

Participants were classified based on biologic sex at birth. Race and ethnicity was recorded using National Health Service coding, which emphasizes self-reporting, and grouped using nationally recognized categories (White, Black, Asian, mixed ethncity, or other). Residential postal code was converted into Index of Multiple Deprivation scores for English children and grouped into quintiles from 1 (most deprived) to 5 (least deprived). Children were classified into 8 f-SV subgroups (Table).[1]

Univariable and multivariable Cox proportional hazards models were developed to explore relationships between childhood survival and sex, race and ethnicity and area deprivation, adjusting for prespecified clinical factors. Children who survived

transplantation were included as survivors. Comparisons between risk factors and likelihood of achieving Fontan-type surgery used one-way ANOVA with Bonferroni correction. The association between risk factors (Table) and completing Fontan-type surgery was investigated using multivariable Fine-Gray regression; competing events were death and cardiac transplantation. The National Congenital Heart Disease Audit is a procedure-based data set; therefore, it excludes patients who did not undergo procedures, and cannot capture differences in survival prior to intervention or because of pregnancy termination. Moreover, it lacks information to investigate geographic factors, including distance to specialist care.

Of 3292 children (Table), 1362 (41.4%) were girls, 195 (5.9%) were preterm, and f-SV was diagnosed antenatally in 2449 (74.4%). Girls were more likely to have f-SV isomerism and additional cardiac risk factors than boys. Most children were White (68.6%) or Asian (15.7%). Asian children were more likely to have f-SV isomerism and congenital noncardiac comorbidities, acquired comorbidity or more severe illness at first procedure. Children from more deprived areas were more likely to have noncardiac congenital comorbidities.

No evidence of differences in survival to 18 years by sex, race and ethnicity, or area deprivation was found after adjusting for clinical factors (Table). In multivariable competing risk models, adjusted for prespecified clinical and time-varying factors (Table), female sex was associated with lower likelihood of completing Fontan-type surgery (adjusted subhazard ratio, 0.88 [95% CI 0.80, 0.97]). Children from the most deprived quintile were significantly less likely to complete Fontan-type surgery than those in the least deprived quintile (adjusted subhazard ratio, 0.81 [0.68, 0.96]). Asian children were less likely to complete Fontan-type surgery than White children (adjusted subhazard ratio, 0.85 [95% CI 0.74, 0.98]); this was partly explained by

higher preoperative mortality (adjusted subhazard ratio,: 1.24 [95% CI 1.02, 1.52]).

For 1582 (48.1%) children who completed Fontan-type surgery, median age at completion was 4.52 (interquartile range, 3.68, 5.60) years and median weight 16.0 kg (interquarttile range, 14.3, 18.4). Completion rates varied by f-SV subgroup. At all ages, girls were less likely to complete Fontan-type surgery than boys, and Asian or Black children were less likely to complete Fontan-type surgery than White children. Girls and Asian children underwent Fontan-type surgery at higher median ages compared with boys and White children, and children in the most deprived quintile were operated at older median age than those in the least deprived quintile (P<0.05 1-way ANOVA and post hoc Bonferroni tests).

Despite marked improvements in childhood survival with f-SV, disparities related to social determinants have been reported.[2,3] Disadvantaged populations can experience multiple barriers to accessing high-quality care, including inequitable provision, structural racism, and geography. Within the UK context of universal free access to healthcare, no association was found between childhood survival and sex, race and ethnicity, or deprivation. Importantly, a recent US analysis suggested that enhanced health insurance coverage improved access to care and reduced racial and ethnic disparities in mortality rates.[4]

The optimal age for stage 3 Fontan-type surgery depends on multiple clinical factors. In this study, female sex, Asian race, and area deprivation were associated with lower likelihood of completing Fontan-type surgery after adjustment for f-SV subtype and comorbidities. In these subgroups, Fontan-type surgery was performed at a higher median age and lower weight z score. Evidence that growth in f-SV patients is modifiable suggests that additional effort could be focused on optimising interstage growth.[5] Whether the observed disparities are also associated with adult mortality,

exercise performance or neurodevelopment merits further investigation.

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DISCLOSURES

KB and RF sit on the steering committee of National Congenital Heart Disease Audit.

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Table – Primary (All-Cause Mortality) and Secondary (Fontan-Type Surgery Completion) Outcomes in Children With Functionally Single-Ventricle Disease by Risk Factor

	Outcome 1: Mortality (all-cause)		Outcome 2: Fontan-type surgery completion †	
Risk factor, by total number of included patients *n*=3292	**Adjusted Cox proportional hazard ratio (95%CI)**	***P* value**	**Adjusted subdistribution hazards ratio (95%CI)**	***P* value**
Sex (Ref: Male, 1930)				
Female, 1362 (41.4%)	1.13 (0.99, 1.29)	0.06	0.88 (0.80, 0.97)	0.01[a]
Race and ethnicity ** (Ref: White, 2257)				
Black, 189 (5.7%)	1.13 (0.86, 1.49)	0.38	0.97 (0.79, 1.20)	0.78
Asian, 517 (15.7%)	1.20 (0.99, 1.44)	0.06	0.85 (0.74, 0.98)	0.03[a]
Mixed/Other, 166 (5.0%)	1.07 (0.79, 1.46)	0.65	0.87 (0.68, 1.12)	0.28
Missing, 163 (5.0%)	2.52 (1.90, 3.33)	<0.001[a]	0.16 (0.08, 0.33)	<0.001[a]
IMD score (Ref: Quintile 5 least deprived, 329)				
Quintile 4, 387 (11.7%)	0.98 (0.73, 1.30)	0.87	0.96 (0.78, 1.19)	0.72
Quintile 3, 510 (15.5%)	0.91 (0.69, 1.19)	0.49	0.92 (0.75, 1.12)	0.40
Quintile 2, 713 (21.7%)	1.10 (0.85, 1.41)	0.48	0.85 (0.71, 1.03)	0.09
Quintile 1 most deprived, 1090 (33.1%)	1.05 (0.82, 1.34)	0.69	0.81 (0.68, 0.96)	0.02[a]
Missing, 263 (8.0%) #	0.93 (0.68, 1.29)	0.68	0.89 (0.72, 1.10)	0.27
Recent birth (ref: born before April 2009, 1595) §				
born in/after April 2009, 1697 (51.5%)	0.86 (0.74, 1.00)	0.05[a]	3.70 (2.60, 5.27)	<0.001[a]
born in/after April 2009*follow up time	*not significant*		0.73 (0.68, 0.79)	<0.001[a]
Antenatal diagnosis (Ref: postnatal diagnosis, 683 (20.8%)				
Antenatal diagnosis, 2449 (74.4%)	1.49 (1.23, 1.80)	<0.001[a]	1.74 (1.22, 2.46)	<0.01[a]
Antenatal*follow up time	*not significant*		0.90 (0.85, 0.96)	<0.01[a]
Missing, 160 (4.8%)	3.07 (2.22, 4.24)	<0.001[a]	7.24 (0.92, 56.81)	0.06
Missing*follow up time	*not significant*		0.54 (0.33, 0.89)	0.02[a]
Preterm birth (Ref: Born ≥37 weeks gestation, 3097)				
Born <37 weeks, 195 (5.9%)	0.89 (0.68, 1.16)	0.39	1.03 (0.81, 1.32)	0.79
Diagnostic subgroup (Ref: HLHS, 1276)				
f-SV isomerism, 238 (7.2%)	0.54 (0.40, 0.73)	<0.001[a]	0.16 (0.08, 0.35)	<0.001[a]
f-SV isomerism*follow up time	1.24 (1.13, 1.37)	<0.001[a]	1.43 (1.25, 1.63)	<0.001[a]
DILV, 322 (9.8%)	0.17 (0.11, 0.26)	<0.01[a]	0.34 (0.20, 0.57)	<0.001[a]
DILV*follow up time	1.23 (1.09, 1.39)	<0.01[a]	1.42 (1.28, 1.57)	<0.001[a]
Tricuspid atresia, 440 (13.4%)	0.39 (0.30, 0.52)	<0.001[a]	0.29 (0.18, 0.47)	<0.001[a]
Tricuspid atresia*follow up time	0.93 (0.77, 1.11)	0.40	1.43 (1.30, 1.58)	<0.001[a]
Mitral atresia, 110 (3.3%)	0.35 (0.22, 0.56)	<0.001[a]	0.30 (0.13, 0.69)	<0.01[a]
Mitral atresia*follow up time	1.17 (1.00, 1.37)	0.04[a]	1.38 (1.18, 1.62)	<0.001[a]
Unbalanced AVSD, 227 (6.9%)	0.93 (0.72, 1.19)	0.55	0.27 (0.14, 0.49)	<0.001[a]

Unbalanced AVSD*follow up time	1.11 (0.99, 1.24)	0.07	1.29 (1.14, 1.45)	<0.001[a]
Pulmonary atresia, 138 (4.2%)	0.14 (0.07, 0.26)	<0.001[a]	0.50 (0.25, 1.00)	0.05
Pulmonary atresia*follow up time	1.25 (1.06, 1.49)	0.01[a]	1.25 (1.09, 1.45)	<0.01[a]
All other f-SV, 541 (16.4%)	0.21 (0.16, 0.29)	<0.001[a]	0.29 (0.18, 0.46)	<0.001[a]
All other f-SV*follow up time	1.26 (1.15, 1.38)	<0.001[a]	1.39 (1.27, 1.53)	<0.001[a]
Congenital noncardiac comorbidity (Ref: no comorbidity, 2744)				
Comorbidity, 548 (16.6%)	0.93 (0.77, 1.13)	0.46	0.47 (0.32, 0.68)	<0.001[a]
Comorbidity*follow up time	1.10 (1.04, 1.17)	<0.01[a]	1.12 (1.04, 1.19)	<0.01[a]
Index procedure acquired comorbidity (Ref: no comorbidity, 3133)				
Comorbidity, 159 (4.8%)	1.85 (1.44, 2.37)	<0.001[a]	0.54 (0.39, 0.75)	<0.001[a]
Index procedure increased severity of illness (Ref: no increased severity, 2908)				
Increased severity, 384 (11.7%)	1.45 (1.19, 1.76)	<0.001[a]	0.66 (0.53, 0.81)	<0.001[a]
Additional cardiac risk factor (Ref: no additional, 3058)				
Additional, 234 (7.1%)	0.96 (0.74, 1.24)	0.74	0.66 (0.52, 0.83)	<0.001[a]
Additional*follow up time	1.14 (1.05, 1.23)	<0.01[a]	*not significant*	
Weight z-score (first cardiac procedure)				
per 1SD increase	0.85 (0.81, 0.89)	<0.001[a]	1.08 (1.04, 1.12)	<0.001[a]
Age at first cardiac procedure (years)				
Per year increase	0.33 (0.21, 0.53)	<0.001[a]	0.69 (0.62, 0.77)	<0.001[a]
Per year increase*follow up time	1.08 (1.04, 1.12)	<0.001[a]	1.03 (1.02, 1.05)	<0.001[a]

The proportional hazards assumption was checked for each factor in turn using statistical tests based on the Schoenfeld residuals. The assumption was checked graphically using log-log plots and observed versus predicted survival curves. Time*covariate interaction terms were considered if the proportional-hazards assumption was not met. AVSD indicates atrioventricular septal defect; DILV, double inlet left ventricle; f-SV, functionally single ventricle; HLHS, hypoplastic left heart syndrome; IMD, Index of Multiple Deprivation (relative local area deprivation); IQR, interquartile range; NS, not significant; and Ref, reference category.

† For the second outcome (completion of Fontan-type surgery), patients who underwent competing events, such as death or heart transplant before Fontan-type surgery, were censored. There were 48 children who had transplants; 5 of these transplants occurred before Fontan-type surgery and were therefore treated as competing events.

[a] Risk factors which are independently associated with the outcome after adjustment for all other variables included in the model.

** Race and ethnicity categories comprised British Asian/Asian (Indian, Pakistani, Bangladeshi, Chinese, Other Asian), Black British/Black (African, African Caribbean, Other Black), White (British, Irish, European, Other White), Mixed (Mixed White and Asian, Mixed White and Black, Other Mixed), Other (Any other ethnic group, including travelers) and missing (not stated or unknown).

Although the audit includes children in England and Wales, IMD score was only available for children in England, therefore all children from Wales are in the group with missing IMD.

§ Externally validated national capture of all cardiac procedures for National Audit in England and Wales occurred from the year 2000, but procedures for capture of noncardiac variables were improved from 2009; hence, an era variable (born after versus born before 2009) was added to the models.

***follow up time** denotes time from birth, i.e. age in years. These factors were the time-varying factors included in the model. All other variables were fixed.