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ORIGINAL RESEARCH

Body Mass Index Trajectory and Outcome Post Fontan Procedure

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BACKGROUND: Patients with a single ventricle who experience early life growth failure suffer high morbidity and mortality in the perisurgical period. However, long-term implications of poor infant growth, as well as associations between body mass index (BMI) and outcome in adulthood, remain unclear. We aimed to model BMI trajectories of patients with a single ventricle undergoing a Fontan procedure to determine trajectory-based differences in baseline characteristics and long-term clinical outcomes.

METHODS AND RESULTS: We performed a retrospective analysis of medical records from patients in the Australia and New Zealand Fontan Registry receiving treatment at the Royal Children's Hospital, The Children's Hospital at Westmead, Royal Melbourne Hospital, and Royal Prince Alfred Hospital from 1981 to 2018. BMI trajectories were modeled in 496 patients using latent class growth analysis from 0 to 6 months, 6 to 60 months, and 5 to 16 years. Trajectories were compared regarding long-term incidence of severe Fontan failure (defined as mortality, heart transplantation, Fontan takedown, or New York Heart Association class III/IV heart failure). Three trajectories were found for male and female subjects at each age group—lower, middle, higher. Subjects in the lower trajectory at 0 to 6 months were more likely to have an atriopulmonary Fontan and experienced increased mortality long term. No association was found between higher BMI trajectory, current BMI, and long-term outcome.

CONCLUSIONS: Poor growth in early life correlates with increased long-term severe Fontan failure. Delineation of distinct BMI trajectories can be used in larger and older cohorts to find optimal BMI targets for patient outcome.

Key Words: body mass index ■ congenital heart disease ■ Fontan procedure ■ LCGA ■ single ventricle

Staged surgical palliation of patients born with a functional single ventricle (FSV) may culminate in a Fontan circulation.[1] In the Fontan circulation, systemic output is provided by the FSV and there is passive systemic venous return to the pulmonary arteries. Although survival for patients with a FSV has dramatically improved, patients with a Fontan circulation are still subject to significant early and late morbidity and mortality.[2,3]

Infants with an FSV commonly experience growth failure,[4–9] which may relate to increased baseline energy demands, reduced nutritional intake, and malabsorption, among other factors.[9–15] Growth failure in infancy has been shown to correlate with higher perioperative morbidity and mortality for some patients with a FSV.[10,12,14,15] However, the longer term impacts of early life growth failure for patients with a Fontan circulation remain unclear.

In contrast to early life growth failure in patients with a FSV, in older patients, some studies report high rates of overweight and obesity—documented as up to 40% of adult patients with Fontan.[16–21] Potential contributory factors to obesity in patients with a Fontan circulation

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CLINICAL PERSPECTIVE

What Is New?

- This is the first study to model distinct body mass index trajectories in patients with a single ventricle circulation.
- Patients with a single ventricle who grow poorly in the first 6 months of life experience greater mortality long term, many years following Fontan procedure.
- Although our study found high incidence of overweight and obesity, there was no association found between overweight status and incidence of severe Fontan failure—defined as mortality, heart transplant, takedown, or New York Heart Association grade III/IV heart failure.

What Are the Clinical Implications?

- The worldwide prevalence of children and adults with a Fontan circulation, including those achieving overweight and obese status, has been increasing over the past few decades.
- Our finding supports early hemodynamic and nutritional interventions in poorly growing infants with a single ventricle circulation in order to improve long-term outcome.
- Future research in this area should use body composition assessments to fully address the associations between body mass index trajectory, body composition, nutritional status, and clinical outcomes in patients with a single ventricle.

Nonstandard Abbreviations and Acronyms

ANZFR	Australia and New Zealand Fontan Registry
CDC	Centers for Disease Control and Prevention
FSV	functional single ventricle
NYHA	New York Heart Association

include disease-related activity restriction and intensive feeding regimes that aim to reverse early life growth failure.[10,12,15,22–24]

Both obesity and underweight status have been associated with adverse perioperative outcomes in patients with congenital heart disease.[14,25–28] Elevated adiposity in adults with a Fontan circulation, when measured by percentage of body fat, has been associated with adverse Fontan-related outcomes.[29–31] Some studies also suggest an association between higher body mass index (BMI) and poorer performance in surrogate physiological parameters.[32–36] However, it is still unclear if overweight and obesity are associated with late Fontan failure.

Distinct BMI trajectories have been identified across the life course in a number of large healthy cohort studies.[37–41] Persistently high BMI has been associated with an increased risk of cardiovascular disease and a higher prevalence of cardiovascular risk factors in adulthood.[37,40–42] Studies tracking BMI from childhood into adult life in patients with a FSV have been limited by small patient numbers, lack of BMI measurements before Fontan completion, and limited data on the association with late Fontan outcomes.[17,36] The effects of changing BMI trajectories on long-term Fontan outcomes are unknown.

Using data from the ANZFR (Australian and New Zealand Fontan Registry), the primary aims of this study were (1) to determine if discrete BMI trajectories across childhood can be modeled in patients with a FSV and a Fontan circulation and, if so, to evaluate patient characteristics associated with these different trajectories and (2) to examine if BMI trajectories are associated with adverse Fontan-related outcomes in adulthood. We hypothesized that the extremes of BMI trajectory—that is, persistently high and persistently low—may be associated with adverse Fontan outcomes.

METHODS

Study Population and Design

A retrospective analysis was performed of patients from the ANZFR who underwent Fontan completion at the Royal Children's Hospital, Melbourne or the Children's Hospital at Westmead, Sydney, over the period 1981 to 2018. Data for patients >16 years of age were collected from the ANZFR database and the adult congenital cardiology databases at Royal Prince Alfred Hospital, Sydney or Royal Melbourne Hospital, Melbourne. Only patients with a FSV who survived to Fontan completion are included in the ANZFR. Patients were excluded if the hospital clinical databases did not have sufficient anthropometric data—defined as fewer than 1 observation of height and weight—in any of the age groups: 0 to 6 months, 6 to 60 months, and 5 to 16 years. The project received ethics approval from the Royal Children's Hospital Melbourne Human Research Ethics Committee (Approval Number—36260), and project participants gave informed consent or consent by proxy. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Data Collection

Patient information was extracted from the ANZFR Redcap electronic research database, hosted by the Murdoch Children's Research Institute, on February 22, 2021. Data gathered included the primary cardiac morphological diagnosis, patient sex, pre-Fontan

clinical data (including number of procedures before Fontan completion), Fontan procedure data (including type of Fontan, conversion, and fenestration), and long-term outcome data. Participants were assumed to be alive if there was no date of death recorded in the REDCap database (updated annually) or at most recent follow-up in the hospital medical records (if more recent than the ANZFR update).

Individual paper and electronic patient medical records were used to gather anthropometric data—height and weight—for each patient from birth to 16 years, at which age patients begin to transition to adult care. Multiple height (or length) and weight data points were collected, where available, every month until 6 months of age, and every 6 months thereafter. The following information, relevant to BMI trajectories, was also ascertained: birthweight, gestational age, and major medical comorbidities. Of the potential 532 patients suitable to be included in the study, 496 had sufficient BMI data for analysis. BMI at most recent follow-up was calculated for all patients included in the analysis. For those patients who were ≥19 years of age at recent follow-up (n=138), BMI was categorized according to Centers for Disease Control and Prevention (CDC) adult BMI category—underweight (BMI <18.5 kg/m^2), normal weight (BMI=18.5–24.9 kg/m^2), overweight (BMI=25–29.9 kg/m^2), and obese (BMI ≥30 kg/m^2). For patients <19 years at most recent follow-up (n=358), CDC pediatric categories were used: normal weight (BMI <85th percentile), overweight (BMI ≥85th percentile and <95th percentile), and obese (BMI ≥95th percentile).[43]

BMI Trajectories and Clinical Outcome

Raw BMI derived from recorded values of height and weight—calculated as weight (kg)/height (m)^2—was used to determine trajectory instead of *Z* scores or percentiles, as raw BMI better maps within-child variability longitudinally and BMI results are more interpretable and more clinically useful.[44,45] Although BMI is not classically used for patients under 2 years of age,[46] we chose to use the same metric across all age groups for the purposes of interage group comparison.

Global BMI curves normally show rapidly increasing BMI from birth to ≈6 months, followed by a decrease to a nadir at ≈5 years, then a steady increase to young adulthood.[47] Because of this nonlinear pattern and to account for changes in BMI after the Fontan procedure, the BMI trajectories were estimated using a fragmented model with 3 time periods. The 3 time periods are bound by the mean age of the BMI trajectory milestones of infancy peak and subsequent adiposity rebound: birth to 6 months ($BMI_{0–6months}$), 6 months to 5 years ($BMI_{6months–5years}$), and 5 to 16 years ($BMI_{5–16years}$). This fragmented approach allowed for more accurate statistical modeling of trajectory patterns given the study sample size, as BMI patterns followed different, distinct shapes in each time period. To account for improved growth post-Fontan completion, in those where Fontan completion occurred between 4 and 5 years, we chose to include all post-Fontan BMI measurements to model the 5- to 16-year trajectory. If Fontan completion occurred between 5 and 6 years, then all BMI measurements up until Fontan completion were used in modeling 6-month to 5-year trajectory.

BMI trajectory plots were compared with sex- and age-specific BMI percentiles: World Health Organization reference criteria (for patients at 0 to 6 months and 6 to 60 months of age)[47] and CDC reference criteria (for when patients were 5 to 16 years).[43] Reference criteria were chosen by patient age according to CDC and National Health and Medical Research Council guidelines.[48] Using these reference criteria, patients were categorized by trajectory and compared regarding incidence of severe Fontan failure at any point, defined as the combined occurrence of mortality, heart transplantation, Fontan takedown, and New York Heart Association (NYHA) grade III/IV heart failure (dichotomous variable: NYHA III/IV [yes/no]). Association between BMI trajectory and components of severe Fontan failure were also assessed. Baseline characteristics were compared between the 3 trajectories for each age group.

Statistical Analysis

A latent class growth analysis model was used to estimate the trajectories via Mplus version 8.4 (Muthen & Muthen, Los Angeles, CA).[49,50] Latent class growth analysis modeling allows for identification of (latent) classes that are defined by their patterns of change over time. The latent class growth analysis estimates mean growth patterns for an age group, rather than estimating individual trajectories for each participant. Individuals are assigned a probability of belonging to each class and then assigned to the class for which they have the highest probability of membership. If a subject did not have any measurements in a specific time period, they were excluded from contributing to the estimation of the mean trajectory and not allocated a class for that age range. If a subject had 1 or more measurements in a specific time period, their information did contribute to the calculation of mean trajectories in that age range using full information maximum likelihood.[51]

To determine the optimum number of classes, we assessed model convergence and fit indices (Bayesian information criterion; Akaike's information criterion); entropy, class size, and interpretability.[52] The number of trajectories for each age group was determined by minimizing the Bayesian information criterion; the

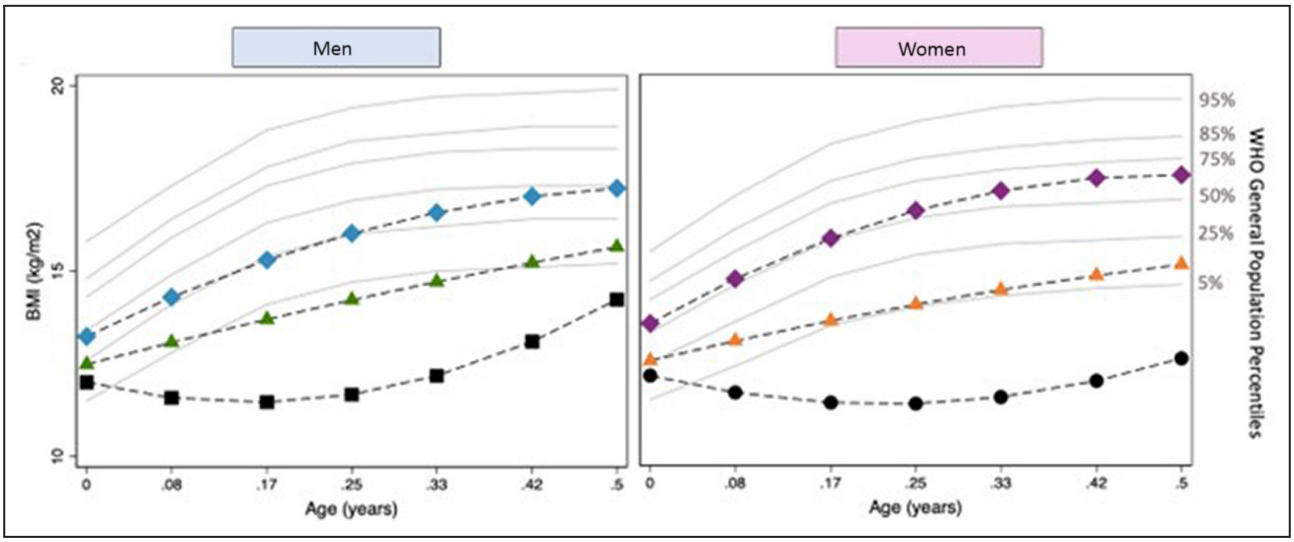

Figure 1. BMI trajectories for patients with a functional single ventricle (FSV) at 0–0.5-years of age.
Black=lower trajectory; green/orange=middle trajectory; blue/purple=higher trajectory; gray=World Health Organization (WHO) reference percentiles. BMI indicates body mass index.

groups were to be of a reasonable size for statistical analysis with minimal errors in the model—as determined by log-likelihood. Based on model fit statistics and visualization of expected mean plots, 3 BMI trajectory classes had the greatest discriminatory power at each time period for male and female participants. For all time periods, quadratic trajectories were estimated for each sex separately.

A sensitivity analysis was conducted, comparing the trajectories estimated with the full data set versus trajectories estimated from subjects with 5 or more measurements in each time period. The curves were very similar to those produced that included data from all participants. Therefore, the larger participant cohort was used for modeling and statistical analysis. Two male participants with BMI values far above the overweight population average were removed from trajectory computation for the purpose of classification quality. As 3 distinct trajectories (upper, middle, and lower) could be computed for both male and female subjects across each trajectory age group, the BMI trajectories were combined for male and female subjects in analyzing the association with Fontan-related outcomes.

Stata version 16.0 (StataCorp, College Station, TX, 2019) was used for all additional statistical analysis.[53] The zanthro package was used for CDC reference BMI percentiles. For comparing baseline characteristics between trajectories, Fisher's exact test and chi-square tests were used for categorical variables and ANOVA and Kruskal–Wallis tests were used for parametric and nonparametric continuous variables, respectively. Logistic regression was used to assess variables associated with severe Fontan failure. Cox proportional hazards and Kaplan–Meier survival curves were used to assess the risk of mortality associated with BMI trajectory. Years of follow-up were censored at 16 years to account for low participant numbers beyond this time. For association between BMI trajectory in infancy and adolescence, linear regression was used. Estimates are provided with corresponding 95% CI.

RESULTS

In the full cohort (n=496 total; n=390 at 0 to 6 months, n=463 at 6 to 60 months, and n=458 at 5–16 years), 64% were male, median age at Fontan completion was 4.68 years (interquartile range [IQR] 3.93–5.53), and median age at last follow-up was 13.57 years (IQR 8.79–18.92). At most recent follow-up, 358 were in the pediatric age group (≤18 years). Of these, 34 (9.5%) were underweight, 256 (71.5%) were normal weight, 34 (9.5%) were overweight, and 34 (9.5%) were obese. Median BMI percentile for the pediatric patients was 51.10 (IQR 24.30–78.71) (Table S1). In the 138 patients who were ≥19 years of age at last follow-up, 11 (8%) were underweight, 74 (53.6%) were normal weight, 37 (26.8%) were overweight, and 16 (11.6%) were obese. Median BMI for adults was 24.08 (IQR 21.39, 26.17) (Table S2).

Three distinct BMI trajectories for both sexes could be modeled for each age group ($BMI_{0–6months}$, $BMI_{6months–5years}$, and $BMI_{5–16years}$) classified as lower, middle, and upper (Figure 1 through 3). Subjects in the lower $BMI_{0–6months}$ trajectory had a lower birthweight, a higher number of procedures before Fontan completion, and were more likely to have an atriopulmonary Fontan (Table 1). The baseline characteristics by BMI

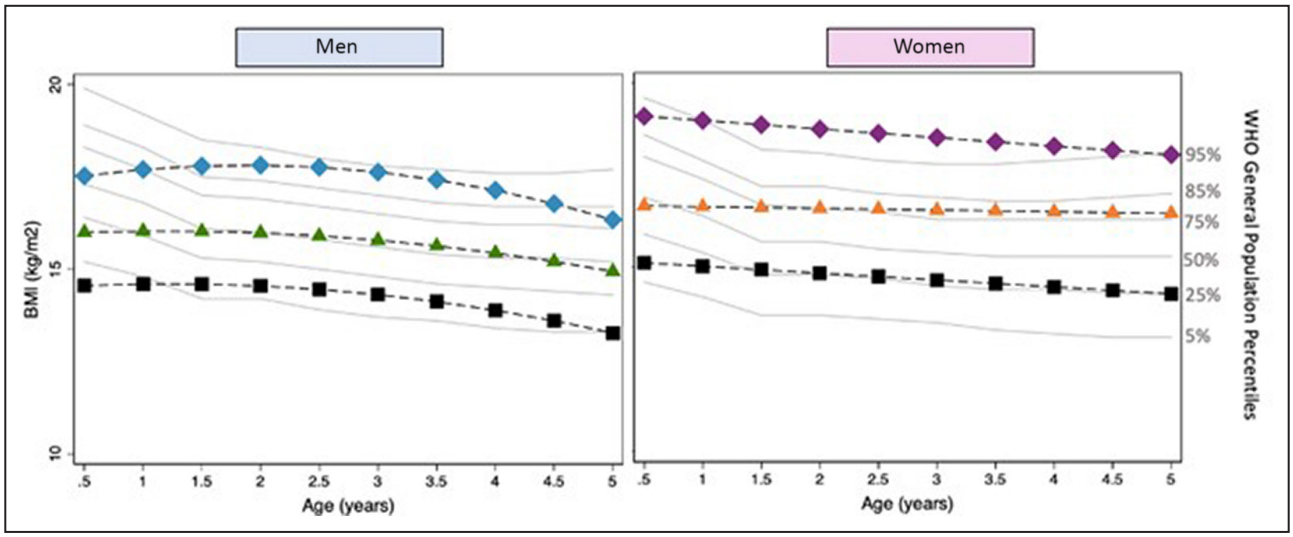

Figure 2. BMI trajectories for patients with a functional single ventricle (FSV) at 0.5–5-years of age.
Black=lower trajectory; green/orange=middle trajectory; blue/purple=higher trajectory; gray=World Health Organization (WHO) reference percentiles. BMI indicates body mass index.

trajectory group for $BMI_{6months–5years}$ and $BMI_{5–16years}$ are provided in Tables S3 and S4, respectively. For $BMI_{0–6months}$, the lower trajectory was below the fifth percentile using World Health Organization reference percentile data, whereas for $BMI_{5–16years}$, the upper trajectory was above the 95th percentile as per CDC reference percentiles.

A total of 46 patients experienced severe Fontan failure at a median age of 15 years (IQR 7–26 years) (Table 2). There were 24 deaths occurring at a median age of 21.5 years (IQR 13.5–30.5). Age at last follow-up was associated with increased risk of heart transplant (P=0.001), NYHA III/IV (P=0.001), and severe Fontan failure (P<0.001). BMI at last follow-up was not associated with any adverse clinical outcome (Table 3, Tables S1, S2). For the 211 patients with birthweights available, birthweight was not associated with any adverse clinical outcome (Table 3). Factors that were associated with increased incidence of severe Fontan failure include older age at last follow-up, an atriopulmonary type of Fontan, atrioventricular valve repair or replacement, and 0 to 1 versus ≥2 procedures before Fontan completion (Table 3). Age at last follow-up was the only variable associated with heart transplant on univariate regression (odds ratio [OR], 1.10, P=0.001). No variables demonstrated a significant association

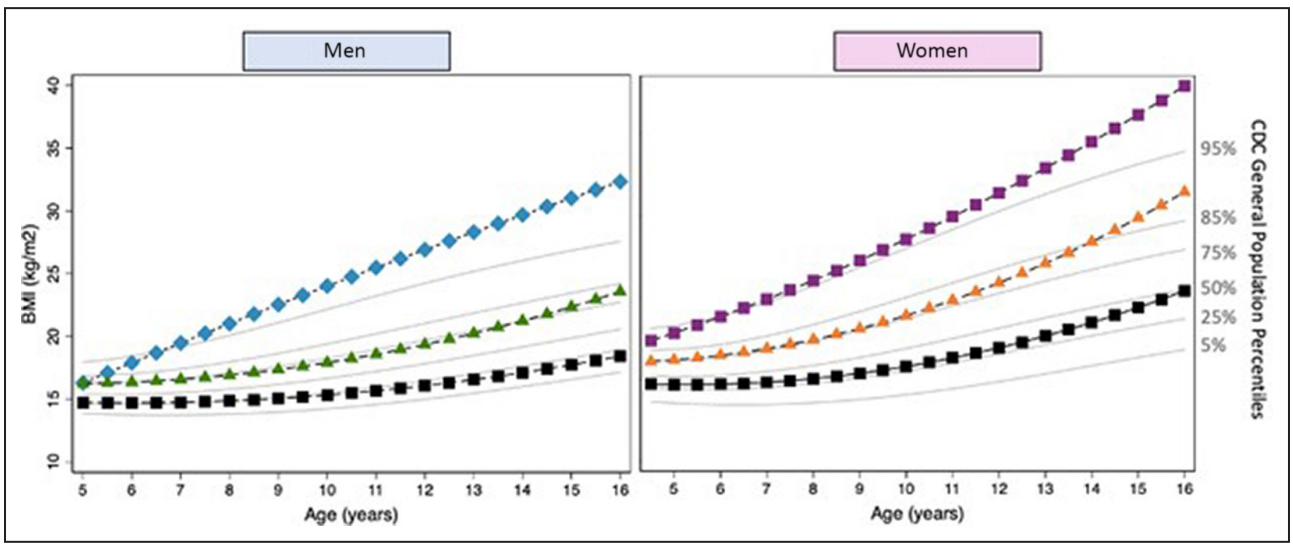

Figure 3. BMI trajectories for patients with a functional single ventricle (FSV) at 5–16-years of age.
Black=lower trajectory; green/orange=middle trajectory; blue/purple=higher trajectory; gray=Centers for Disease Control and Prevention (CDC) reference percentiles. BMI indicates body mass index.

Table 1. Baseline Characteristics of $BMI_{0-6months}$ Trajectory Groups (n=390)

	Total (n=390)	Lower (n=31)	Middle (n=255)	Upper (n=99)	*P* value
Sex					
Male	251 (64)	23 (78)	160 (62)	63 (64)	0.23
Female	139 (36)	8 (22)	95 (37.25)	36 (36)	
Birthweight (kg) (mean±SD)	3.27±0.62 (n=211)	2.82±0.64 (n=14)	3.16±0.56 (n=137)	3.64±0.56 (n=60)	<0.01
Ventricular morphology					
Left	185 (47)	17 (47)	125 (49)	43 (43)	0.58
Right	160 (41)	16 (44)	102 (40)	42 (42)	
Biventricular	30 (8)	1 (3)	19 (7)	10 (10)	
Indeterminate	10 (3)	1 (3)	5 (2)	4 (4)	
Isomerism/heterotaxy					
None	355 (91)	32 (89)	229 (90)	94 (95)	0.55
Left atrial isomerism	11 (3)	1 (3)	8 (3)	2 (2)	
Right atrial isomerism	21 (5)	2 (6)	16 (6)	3 (3)	
Cardiac position					
Normal	352 (90)	30 (83)	230 (90)	92 (93)	0.43
Dextrocardia/mesocardia	29 (7)	5 (14)	18 (7)	6 (6)	
Primary diagnosis					
Tricuspid atresia	63 (16)	3 (8)	39 (15)	21 (21)	0.15
Double outlet right ventricle	43 (11)	3 (8)	32 (13)	8 (8)	
Double inlet left ventricle	51 (13)	6 (17)	35 (14)	10 (10)	
Pulmonary atresia with ventricular septal defect	9 (2)	1 (3)	7 (3)	1 (1)	
Congenitally corrected transposition of the great arteries	24 (6)	1 (3)	15 (6)	8 (8)	
Ebstein's anomaly	5 (1)	0	3 (1)	2 (2)	
Unbalanced atrioventricular septal defect	38 (9)	5 (14)	28 (12)	5 (5)	
Pulmonary atresia with intact ventricular septum	28 (7)	2 (6)	22 (9)	4 (4)	
Hypoplastic left heart syndrome	88 (23)	7 (19)	50 (20)	31 (31)	
Other	39 (10)	7 (19)	23 (9)	9 (9)	
Number prior procedures					
0–1	65 (17)	5 (14)	39 (15)	21 (21)	<0.01
2	200 (51)	11 (31)	133 (52)	56 (57)	
3–6	125 (32)	20 (56)	83 (33)	22 (22)	
Type Fontan					
Atriopulmonary	27 (7)	6 (17)	20 (8)	1 (1)	0.01
Extracardiac conduit Fontan	327 (84)	29 (81)	208 (82)	90 (91)	
Lateral tunnel Fontan	32 (8)	1 (3)	25 (10)	6 (6)	
Not entered	4 (1)	0	2 (1)	2 (2)	
Conversion	11 (3)	1 (3)	8 (3)	2 (2)	0.90
Fenestration	142 (40)	12 (40)	81 (35)	49 (52)	0.02
Center					
Children's Hospital Westmead	202 (52)	17 (47)	143 (56)	42 (42)	0.15
Royal Children's Hospital, Melbourne	188 (48)	19 (53)	112 (44)	57 (58)	
Atrioventricular valve repair/ replacement	46 (12)	5 (14)	28 (11)	13 (13)	0.73
Date of Fontan (median [IQR])	2011 (2002–2015)	2008 (2000–2015)	2010 (2001–2014)	2012 (2006–2015)	0.18

(*Continued*)

Table 1. (Continued)

	Total (n=390)	Lower (n=31)	Middle (n=255)	Upper (n=99)	*P* value
Age at Fontan (median [IQR])	4.60 (3.98–5.38)	4.81 (4.02–5.46)	4.62 (3.89–5.45)	4.49 (4.00–5.23)	0.41
Age last follow-up (median [IQR])	12.71 (8.33–17.72)	14.63 (8.25–24.27)	12.95 (8.32–17.67)	11.91 (8.33–16.88)	0.52

Values are given as No. (%) unless otherwise indicated. *P* value X^2(2, n=390) indicates comparison between $BMI_{0–6months}$ trajectory groups. IQR indicates interquartile range.

with Fontan takedown and NYHA III/IV on univariate regression.

For $BMI_{0–6months}$, subjects in the lower trajectory had increased mortality after Fontan completion, adjusting for type of Fontan, number of prior procedures, and atrioventricular valve repair or replacement (Figure 4). This association remained after adjustment for birthweight (compared with lower trajectory—middle: 0.28 [95% CI, 0.10–0.85], *P*=0.03; higher: 0.17 [95% CI, 0.03–0.91], *P*=0.04). These deaths occurred at an earlier age in patients in the lowest $BMI_{0–6months}$ trajectory compared with the total population—16 (4–37) versus 20 (3–37) years of age. Different $BMI_{0–6months}$ trajectories were not associated with other outcome measures including severe Fontan failure (Table 4). For $BMI_{6months–5years}$ and $BMI_{5–16years}$, no significant differences were found in long-term outcomes based upon trajectory (Tables S5 and S6, respectively).

There was a positive correlation between trajectory at $BMI_{0–6months}$ and that at $BMI_{5–16years}$ (n=357, r_s=0.158, *P*=0.029) (Table S7). Compared with subjects who were in the middle trajectory at both $BMI_{0–6months}$ and $BMI_{5–16years}$ (n=74), those who went from middle/higher to lower (n=180), low to middle/higher (n=9), or low to low (n=24) trajectories did not have a significantly higher risk of mortality (Table 5). None of the patients who were in the highest trajectory at both periods experienced mortality over the study period (0/12 in high $BMI_{0–6months}$–high $BMI_{5–16years}$).

DISCUSSION

In this study, we have made several important findings about BMI and long-term Fontan-related outcomes. First, despite high rates of overweight and obesity, particularly in adult patients, we found no significant association between current BMI and Fontan failure. Second, we defined distinct BMI trajectories across childhood in patients with FSV using latent class growth analysis. Third, low BMI trajectory from 0 to 6 months was a risk factor for mortality after Fontan completion independent of birthweight and age at last follow-up. Fourth, higher BMI trajectories across childhood were not associated with adverse Fontan outcomes. Lastly, patients who changed BMI trajectory between infancy and later childhood—both from low to high, and high to low trajectories—were not at increased risk of mortality, though this finding may be underpowered owing to small sample size.

The strengths of the current study, using data from the ANZFR, include frequent anthropometric measures across childhood both before and after Fontan completion and good ascertainment of long-term outcomes in a relatively large patient population.

The Long-Term Impact of Low Weight in Patients With an FSV

We have found that a low BMI trajectory from birth to 6 months is associated with increased mortality after Fontan completion. These deaths in the low trajectory group occurred at a median of 16 (4–37) years of age (as compared with 20 [3–37] years in the total population), many years after Fontan procedure.

Poor growth in early life has been considered a surrogate marker of a poorly functioning circulation.[10,12,14,15,23] Although previous reports have demonstrated higher morbidity and mortality in poorly growing patients with an FSV, these studies have been limited to the perioperative period.[10,12,14,15,22–24] Our findings demonstrate a mortality risk associated with poor infant growth that persists well into adulthood, independent

Table 2. Clinical End Points for Total Patient Population (n=496)

End point	No. of events, No. (%)	Age at event, y, median (IQR)	Years post-Fontan, median (IQR)
Death	24 (4.8)	21.5 (13.5–30.5)	15 (4.0–23.0)
Heart transplant	11 (2.2)	26 (13.5–31.5)	16 (3.5–26)
Takedown	3 (0.6)	4 (3.0–15.0)	0 (0)
New York Heart Association III/IV	18 (3.6)	11 (4.0–25.0)	4.95 (0.8–17.1)
Severe Fontan failure	46 (9.3)	15 (7.0–26.0)	8.1 (1.2–20.4)

IQR indicates interquartile range.

Table 3. Univariate Logistic Regression for Variables Associated with Mortality or Severe Fontan Failure in the Total Cohort (n=496)

	Mortality OR (95% CI)	*P* value	Severe Fontan failure OR (95% CI)	*P* value
Birthweight	1.62 (0.58–4.65)	0.35	1.35 (0.65–2.78)	0.42
Age last follow-up	1.03 (0.99–1.07)	0.20	1.06 (1.03–1.09)	<0.01
BMI percentile at last follow-up (pediatric)	1.00 (0.98–1.02)	0.90	1.00 (0.99–1.01)	0.85
BMI at last follow-up (adult)	1.23 (0.58–2.61)	0.59	1.11 (0.64–1.94)	0.70
Type of Fontan (relative to atriopulmonary)				
Extracardiac conduit Fontan	0.14 (0.05–0.37)	<0.01	0.15 (0.07–0.32)	<0.01
Lateral tunnel Fontan	0.37 (0.10–1.31)	0.12	0.27 (0.09–0.79)	0.02
Atrioventricular valve Repair/replacement	1.62 (0.53–4.91)	0.40	2.06 (0.97–4.38)	0.06
Number of procedures before Fontan (relative to 0–1 prior)				
2	0.22 (0.09–0.58)	<0.01	0.35 (0.17–0.73)	<0.01
3–6	0.27 (0.09–0.78)	0.02	0.49 (0.23–1.05)	0.07
Ventricular morphology*	0.87 (0.52–1.47)	0.61	1.45 (0.76–2.74)	0.25
Isomerism/heterotaxy	1.04 (0.50–2.19)	0.91	1.07 (0.62–1.84)	0.80
Cardiac position†	0.47 (0.06–3.59)	0.47	0.48 (0.11–2.06)	0.32
Surgical center	1.38 (0.60–3.14)	0.45	2.09 (0.11–3.92)	0.21

BMI indicates body mass index; and OR, odds ratio.
*Right compared with left.
†Normal versus dextrocardia/mesocardia.

of baseline differences in characteristics of the BMI trajectory groups including birthweight and type of Fontan. Whether poor infant growth is a cause for or marker of adverse long-term outcomes remains to be determined. The Pediatric Heart Network trial of enalapril in infants with FSV used weight-for-length *Z* score as a surrogate marker of hemodynamic insufficiency.[54] However, other factors affecting infant growth, such as

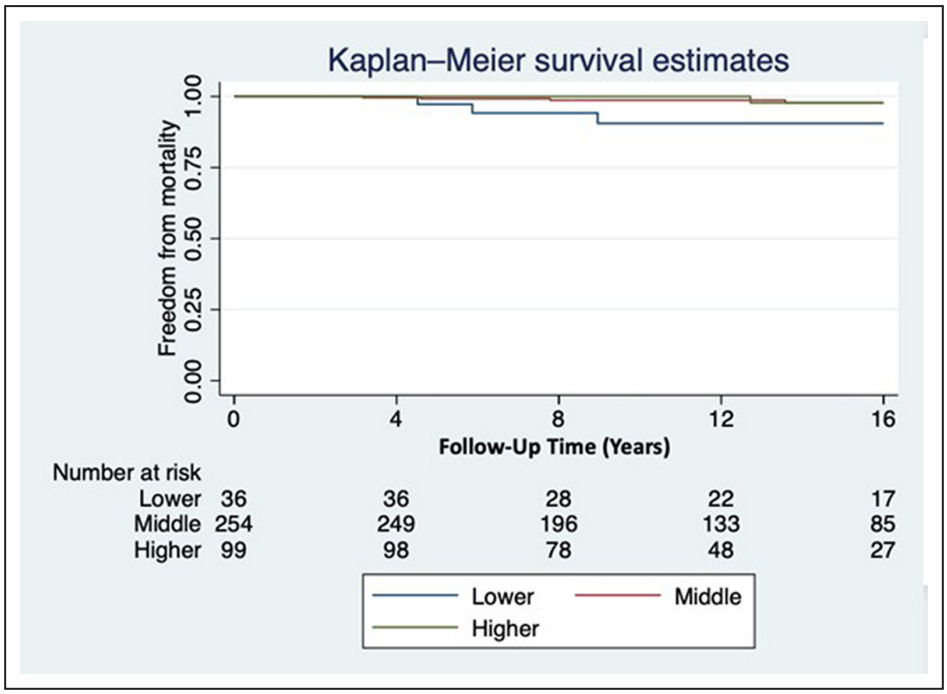

Figure 4. Kaplan–Meier freedom from mortality by $BMI_{0–6months}$ trajectory.
Hazard ratio (compared with lowest trajectory)—Middle: 0.28 (95% CI, 0.10–0.85); *P*=0.03. Higher: 0.17 (95% CI, 0.03–0.91); *P*=0.04 [adjusted for type of Fontan, atrioventricular valve repair/replacement, number of prior procedures]. Age at last follow-up censored at 16 years of age. BMI indicates body mass index.

Table 4. Long-Term Clinical Outcome by $BMI_{0–6months}$ Trajectory

	Total (n=390)	Lower (n=31)	Middle (n=255)	Upper (n=99)	*P* value
Severe Fontan failure	36 (9)	6 (17)	24 (9)	6 (6)	0.17
Deceased	18 (6)	6 (17)	10 (3.92)	2 (2)	<0.01
Age deceased, y (median [IQR])	20 (10–26)	16 (6–32)	24.5 (10–26)	17.5 (14–21)	0.90
Age at last follow-up/ censoring, y (median [IQR])	15 (8–16)	13 (8–16)	12 (8–16)	13 (8–16)	0.38
Heart transplant	8 (2)	1 (3)	6 (2)	1 (1)	0.69
Takedown	3 (1)	1 (3)	2 (1)	0	0.26
New York Heart Association III/IV	16 (4)	1 (3)	12 (5)	3 (3)	0.85
Ventricular failure					
None-mild	184 (91)	22 (96)	117 (89)	45 (94)	0.84
Moderate	16 (8)	1 (4)	12 (9)	3 (6)	
Severe	3 (1)	0	3 (2)	0	
Valvular regurgitation					
None-mild	164 (81)	19 (83)	106 (80)	39 (81)	0.87
Moderate	31 (15)	4 (17)	19 (14)	8 (17)	
Severe	8 (4)	0	7 (5)	1 (2)	
Venous thromboembolism	58 (15)	6 (17)	35 (13)	17 (17)	0.69

Values are given as No. (%) unless otherwise indicated. *P* value $X^2(2, N=390)$ indicates comparison between pediatric $BMI_{0–6months}$ trajectory groups. BMI indicates body mass index.

genetic disorders and lymphatic or gastrointestinal abnormalities, may also affect long-term outcomes after Fontan completion.[3,55–62] Nonetheless, our findings highlight the critical importance of tracking early life growth trajectory to predict and potentially later modify adverse Fontan outcomes.

Age-Related Rise in Prevalence of Overweight and Obesity in Patients With a Fontan Circulation

In patients with a Fontan circulation, there was a higher prevalence in adults than children of both overweight (30% versus 10%) and obesity (14% versus 9%). From age 5 to 16 years, the upper BMI trajectory passed from a normal weight percentile to overweight/obesity. This substantial age-dependent rise in prevalence of overweight/obesity in patients with Fontan, as in the general population, has been previously reported.[17,55]

Table 5. Mortality According to Change in BMI Trajectory From $BMI_{0–6months}$ to $BMI_{5–700\ 16years}$

	Number	HR	95% CI	*P* value
Lower–lower	24	1.75	0.32–9.58	0.52
Lower–middle/ higher	9	4.97	0.47–52.08	0.18
Middle/ high–low	180	0.28	0.06–1.40	0.12

P value indicates comparison between trajectory change groups compared with middle trajectory at both 0–6-months and 5–16-years. BMI indicates body mass index; and HR, hazard ratio.

As in populations with noncongenital heart disease, potential modifiable risk factors contributing to this late rise in obesity include reduced physical activity and continued high caloric intake, which may be a legacy from the period pre-Fontan completion where excess calories are provided in the face of an incompletely palliated circulation.[18,21,42,56] The specific factors contributing to overweight/obesity in patients with a Fontan circulation requires further investigation.

The Association of BMI With Adverse Fontan Outcomes

Various cardiovascular risk factors found to coexist with overweight/obesity—such as hypertension, reduced lung compliance, and diastolic dysfunction—may have a greater effect on the Fontan than the normal biventricular circulation. However, the long-term impact of overweight and obesity on the Fontan circulation remains uncertain. In an adult population with Fontan (n=79, median age 29.5 years), Martinez et al. (2016) reported a higher incidence of heart failure and increased diuretic requirement in patients who were overweight and obese.[58] These authors also found an increased risk of mortality, heart transplant, or hospice care with increasing BMI (hazard ratio [HR], 3.206 [95% CI, 1.096–9.379] per 1 kg/m^2 unit increase in BMI). Decreased transplant-free survival was also reported in a cohort (n=139, median age=23.2 years) undergoing Fontan conversion.[56] A study by Byrne et al. (2021) (n=104, median

age not provided) found that increasing weight gain post-Fontan—independent of overweight category—was associated with a combined end point of mortality, heart transplant, protein-losing enteropathy, VO2<50%, and new use of a loop diuretic (HR, 1.36 [95% CI, 1.07–1.73]; *P*=0.011).[55] By contrast, in a study of 395 adults and children with a Fontan circulation, Chung et al. (2016) found that there was no difference in rates of heart failure comparing the children who had normal weight and children who were overweight/obese. However, adults who were overweight/obese demonstrated lower rates of heart failure than those who were normal and underweight (8% versus 19%; *P*=0.03).[17] These authors suggested that excess weight gain may be a marker of positive nutritional balance, improved cardiac health, or less severe disease. In our study, we were not able to find an association between current BMI and adverse Fontan-related outcomes.

BMI as a Measure of Adiposity After Fontan Completion

BMI is an easily derived surrogate measure of body adiposity that incorporates mass differences related to height. However, BMI does not differentiate between lean and fat mass, and several recent studies have observed moderate to severe skeletal muscle mass deficit in patients with a FSV circulation.[29,31,44,45] Thus, in the setting of Fontan-associated sarcopenia, BMI may underestimate true patient adipose mass. Studies, including ours, using BMI alone may thus misclassify adiposity and its impact after Fontan completion. For example, in a study of adult patients with a Fontan circulation (n=144, age=23±8 years), Cao et al. (2021) found that a 1% increase in percentage of body fat, as measured by dual-energy X-ray absorptiometry, was associated with an increased risk of reaching a composite clinical end point of death, heart transplantation, NYHA III/IV heart failure, protein-losing enteropathy, and/or plastic bronchitis (HR, 1.10 [95% CI, 1.01–1.19]; *P*=0.03).[29]

The Utility of BMI Trajectories in Patients With an FSV Circulation

Modeling of BMI trajectories can capture age of onset, intensity, and duration of exposure to a particular BMI group. In otherwise healthy populations, a high BMI trajectory across childhood has been associated with increased prevalence of adverse cardiometabolic risk factors in young adulthood.[37,41] Examination of baseline determinants of BMI trajectories may assist in identification of individuals at increased risk of adverse health outcomes related to either high or low BMI over time.[37]

To date, very few studies have examined serial changes of BMI in patients with a FSV reaching Fontan completion. Lambert et al. (2020) studied serial BMIs of 362 patients who were post-Fontan over a 10-year period (mean age 21±3.5 years at last follow-up).[36] For those who were over 20-years of age, a positive change in BMI was associated with decreased maximal exercise capacity (VO_{2max}) (slope=–1.25, *P*<0.001).

Chung et al. (2016) reported on 68 patients with serial BMI measurements across childhood.[17] Of the 14/68 overweight/obese adolescents, 8/14 of those were already overweight/obese at ages 2 to 5 years. The low patient numbers and paucity of serial anthropometry allowed neither for modeling of BMI trajectories nor assessment of associations with Fontan outcomes.

Change in BMI Trajectory From Infancy to Later Childhood

We found a correlation between infant and post-Fontan BMI trajectory. This is in keeping with other studies in congenital heart disease and the general population, showing persistence of growth patterns between childhood and later life.[3,8,37,41,58] Early BMI patterns are likely to predict those in later childhood and may be useful for identification of patients who are at increased risk of later excessive weight gain. The number of subjects who changed their BMI trajectory class between infancy and the post-Fontan period was small, limiting our ability to assess the impact of changes in growth trajectory across time on long-term Fontan outcomes.

Limitations and Future Research

In this study, the median age at recent follow-up was 13.6 years with a range of 1 to 47 years. This duration may have been insufficient to have detected other important differences in Fontan outcome based upon BMI or BMI trajectory. Consistent with this was the low number of cases of severe Fontan failure (n=46/496). This cohort and others should be evaluated for late time-related adverse outcomes. The data examining baseline determinants of BMI trajectories did not incorporate factors beyond those related to the cardiac diagnosis. For example, maternal prepregnancy BMI or diabetes, ethnicity, prematurity, genetic diagnoses, markers of nutritional status, infant feeding practices, physical activity levels, and socioeconomic status, among other factors, were not able to be ascertained.[63,64] Prospective birth cohorts of patients with FSV are required to evaluate the late impacts of these factors. As discussed, the use of BMI rather than other measures of body composition may have misclassified body fat status. Future research should incorporate additional metrics of

body composition—such as percentage of body fat and skeletal muscle mass—in order to completely assess the adverse implications of excess adiposity in patients with a Fontan circulation.

CONCLUSIONS

We have shown adverse long-term post-Fontan outcomes in poorly growing compared with normally growing infants with a FSV circulation. This finding supports early hemodynamic and nutritional intervention in poorly growing infants with a FSV circulation in order to improve long-term outcome. Distinct BMI trajectories can be modeled using latent class growth analysis. However, neither high BMI nor high BMI trajectory were associated with adverse Fontan outcomes over the duration of our study. Future research in this area should uses body composition assessments to fully address the associations between BMI, body composition, nutritional status, and clinical outcomes in patients with a FSV.

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Disclosures

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Supplemental Material

Tables S1–S7

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Supplemental Material

Table S1. Frequency of clinical outcome by BMI category at most recent follow-up in paediatric patients.

	Total N=358 (N (%))	**Underweight N=34 (N (%))**	**Normal N=256 (N (%))**	**Overweight N=34 (N (%))**	**Obese N=34 (N (%))**	***P*-Value**
Deceased	13 (4)	1 (3)	9 (4)	2 (6)	1 (3)	0.95
Age Deceased (Years) (Median (IQR))	14 (6, 19)	19 (19, 19)	10 (5, 14)	25 (25, 25)	13 (13, 13)	0.24
Transplant	2 (1)	0	2 (1)	0	0	1.00
Takedown	2 (1)	0	2 (1)	0	0	1.00
NYHA III/IV	9 (3)	2 (6)	5 (2)	2 (6)	0	0.19
Severe Fontan Failure	23 (6)	3 (9)	15 (6)	4 (12)	1 (3)	0.39
Age Severe Fontan Failure (Years) (Median (IQR))	7 (4, 14)	9.5 (5, 16)	6 (4, 14)	16 (5.5, 25)	13 (13, 13)	0.65

P-value indicates comparison between paediatric BMI groups.

Table S2. Frequency of clinical outcome by BMI at most recent follow-up in adult patients.

	Total N=138 (N (%))	**Underweight N=11 (N (%))**	**Normal N=74 (N (%))**	**Overweight N=37 (N (%))**	**Obese N=16 (N (%))**	***P*-Value**
Deceased	11 (8)	1 (9)	5 (7)	3 (8)	2 (13)	0.7
Age Deceased (Years) (Median (IQR))	30 (22, 32)	31 (31, 31)	22 (21, 32)	30 (24, 35)	31.5 (26, 37)	0.61
Transplant	9 (7)	0	5 (7)	4 (11)	0	0.51
Takedown	1 (1)	1 (9)	0	0	0	0.08
NYHA III/IV	9 (7)	0	6 (8)	2 (5)	1 (6)	0.95
Venous Thromboembolism	36 (31)	3 (43)	21 (34)	8 (24)	4 (27)	0.65
Severe Fontan Failure	23 (17)	2 (18)	11 (15)	7 (19)	3 (19)	0.87
Age Severe Fontan Failure (Years) (Median (IQR))	26 (19, 31)	23 (15, 31)	25 (19, 27)	26 (14, 34)	37 (26, 39)	0.25

P-value indicates comparison between adult BMI groups.

Table S3. Baseline characteristics of patients by $BMI_{6-60month}$ trajectory.

		Total N=463 (N (%))	Lower N=154 (N (%))	Middle N=234 (N (%))	Upper N=75 (N (%))	*P*-Value
Sex	Male	295 (64)	51 (33)	181 (77)	63 (84)	< 0.01
	Female	168 (36)	103 (67)	53 (23)	12 (16)	
Birthweight (kg) (Mean ± SD)		3.26 ± 0.61	3.13 ± 0.59	3.32 ± 0.61	3.33 ± 0.62	0.13
Ventricular Morphology	Left	231 (50)	80 (52)	114 (49)	37 (49)	0.78
	Right	174 (38)	53 (34)	19 (8)	27 (36)	
	Biventricular	38 (8)	12 (8)	19 (8)	7 (9)	
	Indeterminate	14 (3)	7 (5)	5 (2)	2 (3)	
Isomerism/ Heterotaxy	None	422 (91)	136 (88)	215 (92)	71 (85)	0.37
	Left Atrial Isomerism	13 (3)	7 (4)	5 (2)	1 (1)	
	Right Atrial Isomerism	25 (5)	11 (7)	12 (5)	2 (3)	
Cardiac Position	Normal	414 (89)	134 (87)	212 (91)	68 (91)	0.02
	Dextrocardia/ Mesocardia	39 (8)	20 (13)	14 (6)	5 (7)	
Primary Diagnosis	Tricuspid Atresia	78 (17)	23 (15)	37 (16)	18 (24)	0.32
	DORV	50 (11)	18 (12)	22 (9)	10 (13)	
	DILV	68 (15)	25 (16)	37 (16)	6 (8)	
	Pulmonary Atresia with VSD	14 (3)	6 (4)	8 (3)	0	
	ccTGA (VA discordance and AV discordance)	28 (6)	7 (5)	15 (6)	6 (8)	
	Ebstein's Anomaly	5 (1)	0	3 (1)	2 (3)	
	Atrioventricular Canal or AVSD (aka unbalanced AVSD or common AV valve)	47 (10)	20 (13)	20 (9)	7 (9)	
	Pulmonary Atresia with	33 (7)	11 (7)	20 (9)	2 (3)	

	Intact Ventricular Septum					
	HLHS	91 (20)	25 (16)	48 (21)	18 (24)	
	Other	46 (10)	17 (11)	23 (10)	6 (8)	
Number Prior Procedures	0–1	85 (18)	35 (23)	30 (17)	10 (13)	0.06
	2	233 (50)	64 (42)	123 (53)	46 (61)	
	3–6	145 (31)	55 (36)	71 (30)	19 (25)	
Type Fontan	AP	34 (7)	13 (8)	17 (7)	4 (5)	0.01
	ECC	383 (83)	116 (75)	197 (84)	70 (93)	
	LT	42 (9)	24 (16)	17 (7)	1 (1)	
	Not Entered	4 (1)	1 (1)	3 (1)	0	
Conversion		13 (3)	5 (3)	7 (3)	1 (1)	0.86
Fenestration		159 (38)	53 (38)	80 (38)	26 (37)	0.96
Centre	Children's Hospital Westmead	246 (53)	82 (53)	128 (55)	40 (53)	0.61
	Royal Children's Hospital, Melbourne	213 (46)	72 (47)	106 (45)	35 (47)	
AV Valve Repair/Replacement		53 (11)	19 (12)	27 (12)	7 (9)	0.83
Date of Fontan (Median (IQR))		2010 (2000–2014)	2008 (1998–2014)	2010 (2001–2014)	2012 (2006–2014)	0.03
Age at Fontan (Median (IQR))		4.67 (3.96, 5.48)	4.86 (4.11, 5.61)	4.60 (3.87, 5.39)	4.47 (3.93, 5.08)	0.47
Age Last Follow-Up (Median (IQR))		13.30 (8.75, 18.14)	14.47 (9.09, 21.36)	12.84 (8.49, 17.72)	11.88 (8.10, 15.73)	0.46

P-value indicates comparison between paediatric $BMI_{6–60month}$ trajectory groups.

Table S4. Baseline characteristics of patients by $BMI_{5\text{-}16year}$ trajectory.

		Total N=458 (N (%))	Lower N=273 (N (%))	Middle N=155 (N (%))	Higher N=30 (N (%))	*P*-Value
Sex	Male	291 (64)	165 (60)	109 (70)	17 (57)	0.08
	Female	167 (36)	108 (40)	46 (30)	13 (43)	
Birthweight (kg) (Mean ± SD)		3.27 ± 0.62	3.18 ± 0.61	3.33 ± 0.61	3.62 ± 0.68	0.03
Ventricular Morphology	Left	232 (51)	126 (46)	90 (58)	16 (53)	0.20
	Right	166 (36)	102 (37)	53 (34)	11 (37)	
	Biventricular	39 (9)	28 (10)	8 (5)	3 (10)	
	Indeterminate	15 (3)	13 (5)	2 (1)	0	
Isomerism/ Heterotaxy	None	418 (91)	241 (88)	150 (97)	27 (90)	0.01
	Left Atrial Isomerism	11 (2)	9 (3)	2 (1)	0	
	Right Atrial Isomerism	25 (5)	21 (8)	1 (1)	3 (10)	
Cardiac Position	Normal	411 (90)	242 (89)	139 (90)	30 (100)	0.07
	Dextrocardia/ Mesocardia	38 (8)	28 (10)	10 (6)	0	
Primary Diagnosis	Tricuspid Atresia	77 (17)	39 (14)	32 (21)	6 (20)	0.53
	DORV	52 (11)	31 (11)	17 (11)	4 (13)	
	DILV	72 (16)	41 (15)	28 (18)	3 (10)	
	Pulmonary Atresia with VSD	15 (3)	11 (4)	4 (3)	0	
	ccTGA (VA discordance and AV discordance)	26 (6)	17 (6)	9 (6)	0	
	Ebstein's Anomaly	5 (1)	2 (1)	3 (2)	0	
	Atrioventricular Canal or AVSD (aka unbalanced AVSD or	47 (10)	35 (13)	9 (6)	3 (10)	

	common AV valve)					
	Pulmonary Atresia with Intact Ventricular Septum	31 (7)	17 (6)	12 (8)	2 (7)	
	HLHS	85 (19)	50 (18)	29 (19)	6 (20)	
	Other	45 (10)	28 (10)	11 (7)	6 (20)	
Number Prior Procedures	0–1	97 (21)	60 (22)	32 (21)	5 (17)	0.16
	2	225 (49)	126 (46)	78 (50)	21 (70)	
	3–6	136 (30)	87 (32)	45 (29)	4 (13)	
Type Fontan	APP	43 (9)	26 (10)	15 (10)	2 (7)	0.76
	ECC	354 (79)	213 (78)	124 (80)	27 (9)	
	LT	49 (11)	33 (12)	15 (10)	1 (3)	
	Not Entered	2 (0)	1 (0)	1 (1)	0	
Conversion		14 (3)	9 (3)	5 (3)	0	0.91
Fenestration		159 (39)	97 (40)	51 (37)	11 (39)	0.88
Centre	Children's Hospital Westmead	140 (52)	143 (52)	83 (54)	14 (47)	0.93
	Royal Children's Hospital, Melbourne	218 (48)	130 (48)	72 (46)	16 (53)	
AV Valve Repair/Replacement		54 (12)	32 (12)	19 (12)	3 (10)	0.97
Date of Fontan		2009 (1999–2012)	2009 (1999–2014)	2010 (1999–2014)	2010 (2003–2012)	0.58
Age at Fontan (Median (IQR))		4.70 (3.97, 5.52)	4.87 (4.13, 5.90)	4.45 (3.78, 5.14)	4.26 (3.35, 4.97)	0.36
Age Last Follow-Up (Median (IQR))		13.83 (9.36, 18.88)	14.38 (9.45, 20.09)	13.14 (8.99, 17.67)	13.54 (10.58, 17.25)	0.50

P-value indicates comparison between paediatric $BMI_{5\text{-}16year}$ trajectory groups.

Table S5. Frequency of long-term clinical outcome by $BMI_{6–60month}$ trajectory group.

		Total N=463 (N (%))	**Lower N=154 (N (%))**	**Middle N=234 (N (%))**	**Higher N=75 (N (%))**	***P*-Value**
Severe Fontan Failure		39 (8)	17 (11)	15 (6)	7 (9)	0.25
Time to Severe Fontan Failure (Years) (Median (IQR)		8.05 (2.51, 22.15)	3.51 (2.07, 18.80)	17.08 (4.78, 22.16)	5.53 (1.10, 6.82)	0.30
Deceased		20 (4)	10 (6)	7 (3)	3 (4)	0.26
Age Deceased (Years) (Median (IQR))		20.5 (11.5–29)	20.5 (6–25)	32 (19–35)	13 (5–15)	**0.05**
Transplant		8 (2)	3 (2)	3 (1)	2 (3)	0.64
Takedown		3 (1)	3 (2)	0	0	0.07
NYHA III/IV		18 (4)	7 (5)	8 (3)	3 (4)	0.81
Ventricular Function	None-Mild	220 (90)	76 (89)	114 (91)	30 (88)	0.89
	Moderate	21 (9)	8 (9)	9 (7)	4 (12)	
	Severe	3 (1)	1 (1)	2 (2)	0	
Valvular Regurgitation	Mild	198 (81)	7 (82)	99 (79)	29 (85)	0.85
	Moderate	37 (15)	11 (13)	22 (18)	4 (12)	
	Severe	9 (4)	4 (5)	4 (3)	1 (3)	

P-value indicates comparison between paediatric $BMI_{6–60month}$ trajectory groups.

Table S6. Frequency of long-term clinical outcome by $BMI_{5–16year}$ trajectory.

		Total N=458 (N (%))	Lower N=273 (N (%))	Middle N=155 (N (%))	Higher N=30 (N (%))	*P*-Value
Severe Fontan Failure		41 (9)	21 (8)	18 (12)	2 (7)	0.36
Time to Severe Fontan Failure (Years) (Median (IQR))		8.94 (3.92, 8.93)	12.71 (3.92, 22.15)	15.75 (6.82, 22.16)	4.31 (0.80, 8.93)	0.40
Deceased		20 (4)	10 (4)	8 (5)	2 (7)	0.45
Age Decease (Years) (Median (IQR))		23 (14.5–30.5)	20.5 (14–32)	22.5 (14.5–27.5)	25.5 (25–26)	0.74
Transplant		11 (2)	5 (2)	6 (4)	0	0.33
Takedown		1 (0)	0	1 (1)	0	0.40
NYHA III/IV		18 (4)	10 (4)	8 (5)	0	0.45
Ventricular Dysfunction	Mild/None	220 (90)	126 (88)	76 (94)	18 (95)	0.57
	Moderate	22 (9)	16 (11)	5 (6)	1 (5)	
	Severe	2 (1)	2 (1)	0	0	
Valvular Regurgitation	Mild/None	198 (81)	113 (78)	71 (88)	14 (74)	0.24
	Moderate	38 (16)	24 (17)	9 (11)	5 (26)	
	Severe	8 (3)	7 (5)	1 (1)	0	

P-value indicates comparison between paediatric $BMI_{5–16year}$ trajectory groups.

Table S7. $BMI_{5–16years}$ trajectory according to $BMI_{0–6months}$ trajectory (n=357 with data at both 0–6-months and 5–16-years).

Change in BMI Trajectory		$BMI_{5–16years}$			
		Lower (n=204) N (%)	Middle (n=128) N (%)	Higher (n=25) N (%)	Total (n=357) N (%)
$BMI_{0–6months}$	Lower	24 (12)	8 (6)	1 (4)	33 (9)
	Middle	141 (69)	74 (58)	12 (48)	227 (64)
	Higher	39 (19)	46 (36)	12 (48)	97 (27)