

**Delayed Puberty and Abnormal Anthropometry and its Associations with Quality of Life in Young Fontan Survivors: A Multicenter Cross-sectional Study**

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**Abbreviations:**

QoL: Quality of life

PedsQL: Pediatric Quality of Life inventory

BMI: Body mass index

PHN: Pediatric Heart Network

NYHA: New York Heart Association

BNP: B-type natriuretic peptide

HLHS: Hypoplastic left heart syndrome

NHANES: National Health and Nutrition Examination Survey

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**Abstract**

**Introduction:** We sought to evaluate the prevalence of delayed puberty and abnormal anthropometry and its association with quality of life (QoL) in young Fontan survivors.

**Methods:** This was a cross-sectional study at 11 Pediatric Heart Network centers. Demographic and clinical data, anthropometry and Tanner stage were collected. Anthropometric measurements and pubertal stage were compared to United States norms. QoL was assessed using Pediatric Quality of Life inventory (PedsQL). Mixed effects regression modeling adjusting for clustering by center was used to evaluate factors associated with abnormal anthropometry and delayed puberty, and associations with QoL.

**Results:** Of the 299 subjects, 42% were female. Median enrollment age was 13.9 years and median age at Fontan was 3 years. Fontan survivors had a higher prevalence of short stature relative to normative data (20% vs. 5%,  $p < 0.0001$ ) and an increased prevalence of abnormal BMI (16% vs. 10%,  $p < 0.0001$ ) [low (43%) and high (57%)]. Fontan subjects, both males (58%) and females (58%) had a delay of 1.5- 2 years in  $\geq 1$  Tanner stage parameter compared to normal population. There was no association between delayed puberty and QoL. Abnormal anthropometry was associated with lower overall ( $62.3 \pm 17.3$  vs.  $72.5 \pm 16.6$ ;  $p < 0.001$ ) and physical appearance scores ( $72.2 \pm 27.4$  vs.  $79.8 \pm 21.5$ ;  $p < 0.01$ ). Lower exercise capacity was associated with abnormal anthropometry and  $> 2$  surgeries before Fontan was associated with delayed puberty. Lower family income ( $< \$25,000$ ) and hypoplastic left heart syndrome were associated with lower QoL.

**Conclusion:** Compared to the normal population, Fontan survivors have high prevalence of short stature, abnormal BMI and delayed puberty. Abnormal anthropometry, but not delayed puberty, was associated with lower overall QoL and perceived physical appearance scores. Routine screening for abnormal anthropometry, especially in HLHS and in lower socioeconomic status families, should be considered to allow for interventions which might ameliorate the negative psychosocial impact.

**Background:**

Growth failure in infants and children with congenital heart disease, particularly in infants with single ventricle physiology, is a well-known phenomenon.<sup>1-3</sup> Patients with single ventricle physiology are a heterogeneous group who typically undergo a series of high-risk palliative cardiac surgeries culminating in the Fontan operation. Fontan physiology is inherently associated with a lifelong risk of multiple medical complications including ventricular dysfunction, arrhythmias, stroke, exercise intolerance, protein-losing enteropathy, plastic bronchitis, liver dysfunction and premature death.<sup>4-6</sup> These complications may predispose them at high risk for growth and pubertal aberrations. Abnormalities in height and weight have been reported in Fontan survivors<sup>7</sup> and abnormal anthropometry has been associated with lower functional health status scores.<sup>7</sup> Previous studies demonstrated long-term growth and cognitive aberrations secondary to growth failure in early life including higher prevalence of short stature, poor school performance, and higher incidence of behavioral and attention issues.<sup>8</sup> The same factors that predispose single ventricle patients to abnormal anthropometry have also been implicated in the delayed puberty. However, despite the high prevalence of these risk factors, the actual prevalence of delayed puberty in Fontan survivors is unknown. Furthermore, the effects of delayed puberty on quality of life (QoL) have not been studied in Fontan survivors.

We sought to determine the prevalence of abnormal anthropometry and delayed puberty in adolescent Fontan survivors and to define demographic and clinical factors associated with these abnormalities. We also explored the association between abnormal anthropometry and delayed puberty and QoL. We hypothesized that the prevalence of abnormal anthropometry and delayed puberty would be significantly higher in the study population compared to the normal population and these abnormalities would be associated with lower QoL scores.

**Methods**

This study was supported by a grant from the National Heart, Lung, and Blood Institute funded Pediatric Heart Network (PHN). The authors are solely responsible for the design and conduct of this study. All study analyses, the drafting and editing of the paper and its final contents were approved by all the authors.

## Study Population

This was a cross-sectional multicenter study of adolescent Fontan survivors between the ages of 8 and 18 years. All Fontan patients between the ages of 8 and 18 years who consented or whose parent/guardian consented to participate in the study from 11 PHN centers (02/2013-03/2015) were eligible to participate in the study. Patients or their parent/guardian who could not understand the QoL English forms were excluded. Patients with genetic syndrome were specifically excluded from the study. The study was approved by the Institutional Review Boards at all participating centers.

**Tanner staging:** Participants Tanner stage was determined by using a self-assessment pictorial Tanner stage questionnaire. Study subjects were given a previously validated standardized series of realistic color images with explanatory text to assess their own pubertal development<sup>9, 10</sup>. Compared with Tanner's original black and white pictures, self-assessment of the pubertal stage by using realistic color images is strongly associated with a clinician's objective assessment of Tanner stage<sup>9</sup>. Self-reported age of menarche was also recorded.

## Definitions

**Abnormal anthropometry:** Abnormal anthropometry was defined as presence of either short stature or abnormal BMI. Short stature was defined as height <5th percentile based on the CDC growth curves<sup>11</sup>. Abnormal BMI was defined as BMI <5th percentile or  $\geq$  95th percentile based on the NHANES III data.

**Delayed puberty:** Delayed puberty was clinically defined as failure to reach a Tanner stage at an age that is 2 standard deviation greater than the population mean for that specific Tanner stage obtained from the NHANES III data.<sup>12, 13</sup>

**Quality of Life (QoL):** QoL was assessed using a previously validated Pediatric Quality of Life Inventory (PedsQL) and Cardiac Module. We chose to use PedsQL for this study because it is shorter, easier to complete compared to other instruments and provides both the child's and the parent's perspectives across the entire study age range.<sup>14</sup> PedsQL was also a preferred instrument for QoL testing because its generic core scale has been obtained from a large normative database of ethnically diverse healthy children as well as children with chronic health conditions.<sup>14</sup> The 23-item PedsQL generic core scales

encompass physical functioning (8 items), emotional functioning (5 items), social functioning (5 items), and school functioning (5 items). The PedsQL 3.0 cardiac module has 5 scales related to symptoms, perceived physical appearance, treatment anxiety, cognitive problems, and communication for parent proxy report and children aged 8 to 18 years.

**Socioeconomic status:** Socioeconomic status was assessed using a parent-completed form that collected information regarding family income, race and ethnicity, education of the primary caregiver, family marital status and employment of the primary caregiver.

**Normative data:** Normative data for height were obtained from CDC growth curves. Normative data for BMI and Tanner stages were obtained from National Health and Nutrition Examination Survey (NHANES III). The NHANES surveys were designed to give national normative estimates of the health and nutritional status of the U.S. civilian, non-institutionalized population. NHANES III was conducted from 1988 through 1994 using a stratified, multistage probability design.

The medical record was reviewed for demographics, cardiac anatomic diagnosis, type of surgical palliation, details of Fontan and other surgical palliation including the timing, presence of ventricular dysfunction and atrioventricular valve regurgitation, medications, exercise stress test results, New York Heart Association (NYHA) Functional Classification and B-natriuretic peptide measurements (BNP). All data included in the study were collected within 6 months of study participation.

### **Statistical analysis**

Continuous variables are described as mean  $\pm$  standard deviation or median (inter-quartile range). BMI and short stature were treated as categorical variables, based on the definition above. To evaluate the differences between subjects with abnormal measures (BMI and height) from the normal population, one-sample z-test was performed. For each of the Tanner stages, inverse variance weighting method to pool mean age difference across strata was used and then Z test was used to examine the statistical significance for the overall effect. Comparisons between self-reported and parent reports (proxy report) mean generic and domain scores and cardiac module domain score were performed using a paired T-test and Lin Index for concordance correlation coefficient. A mixed effects regression model adjusting for

clustering by center was performed to evaluate associations between demographic, anatomic and clinical factors and abnormal anthropometry and delayed puberty. A backwards elimination method was used for variable selection before performing the logistic regression. Similarly, to study the associations between delayed puberty and abnormal anthropometry and QoL, a mixed effects regression model adjusting for clustering by center was performed. In studies with multiple centers, we sometimes expect patient outcomes to differ according to center. This could be due to differences between patients who present to different centers, or because of differences between the centers themselves. To minimize the impact of any between-center differences on the study results, adjustment for clustering is performed to account for center-effects in the analysis model. This mixed effect model included basic demographic variables, family income, race, ethnicity, education of the primary caregiver, family marital status, and employment of the primary caregiver. All analyses were conducted using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

## Results

Of the 299 subjects enrolled in the study, 33% had hypoplastic left heart syndrome (HLHS). The median age of the study cohort was 13.9 years (IQR: 11.3, 16.1 years). Baseline characteristics of the study population are shown in Table 1.

### Abnormal anthropometry

**BMI:** Compared to a 10% prevalence of abnormal BMI in the normal US population, 16% of adolescent Fontan survivors had abnormal BMI ( $p < 0.0001$ ). Of the Fontan survivors who had an abnormal BMI, 43% had BMI  $< 5^{\text{th}}$  percentile and 57% had BMI  $> 95^{\text{th}}$  percentile.

**Short Stature:** The prevalence of short stature in adolescent Fontan survivors was higher relative to the normal population. In the study cohort, 20% of participants had short stature compared to 5% in the normal population ( $P < 0.0001$ ).

**Delayed Puberty:** More than half of the study population (males: 58%, females: 58%) had delay in at least one Tanner stage parameter. Pubic hair growth was delayed in 43% of males and 47% of females. Genitalia development was delayed in 54% of males and breast development was delayed in 47% of

females. A delay in both pubic hair growth and genitalia/breasts development was seen in 39% of males and 36% of females. On average, both in male and female Fontan survivors, there was a delay of 1.5-2 years in achievement of Tanner stages compared to the normal population (Figure 1).

**QoL:** There was moderate agreement between self-reported and proxy (parent reported) QoL scores (Figure 2). However, parent QoL scores were lower than the child/adolescent's scores (68.9 vs.72.6;  $p < 0.01$ ) for the majority of domains in generic core scale and cardiac module. In Fontan survivors, abnormal anthropometry was associated with lower QoL (generic core scale total score:  $62.3 \pm 17$  vs.  $72.5 \pm 16.6$ ;  $p < 0.001$ ) (Figure 2A and 2B) and lower cardiac module perceived physical appearance scores on proxy report ( $72.2 \pm 27.4$  vs.  $79.8 \pm 21.5$ ;  $p < 0.01$ ) (Figure 2D). Delayed puberty was not associated with lower QoL (generic core scale total score:  $68.3 \pm 17.4$  vs.  $70 \pm 17.5$ ;  $p = 0.4$ ) (Figure 2C).

**Factors associated with abnormal anthropometry and delayed puberty:** NYHA Class III and IV and lower oxygen consumption on exercise stress test were independently associated with higher risk of abnormal anthropometry (Table 2). More than two cardiac surgeries before Fontan procedure was the only factor associated with higher risk of delayed puberty. Importantly, ventricle morphology, weight-for-age z-score, age at any surgical palliation procedure, cardiac diagnoses, atrioventricular valve regurgitation, use of digoxin therapy, use of pulmonary vasodilator therapy, BNP level, and number of Fontan complications were not associated with either abnormal anthropometry or delayed puberty.

**Association between abnormal anthropometry and delayed puberty and QoL:** On multivariable mixed effects modeling controlling for clustering among centers, delayed puberty was not associated with lower QoL. Factors independently associated with lower overall QoL score were abnormal anthropometry, family income  $< \$25000$ , and HLHS. Female sex and lower family income were independently associated with lower perceived physical appearance scores (Table 2).

## Discussion

This is the first study to evaluate the prevalence of delayed puberty and its impact on QoL in young Fontan survivors. More than half of the Fontan survivors had delay in one of the Tanner stage parameters and in both sexes, there was a delay of 1.5-2 years between Fontan survivors and the normal population



in achievement of earlier Tanner stages. Even though pubertal attainment was noted to be slower in children with Fontan than in healthy controls, it was not associated with lower overall QOL. Instead, abnormal anthropometry was associated with lower overall QOL and perceived physical appearance scores.

### **Delayed puberty**

Many chronic diseases are known to be associated with delayed puberty.<sup>15</sup> In chronic diseases, delayed puberty is usually accompanied by a delay in physical growth and the pubertal growth spurt.<sup>15</sup> The etiology of delayed puberty in Fontan survivors is likely to be multifactorial and may include chronic low cardiac output state and cyanosis, multiple cardiopulmonary bypass, endocrine abnormalities and Fontan associated complications like Fontan associated liver disease and protein losing enteropathy.<sup>4-6</sup> More than two cardiac surgeries before Fontan palliation was the only factor independently associated with delayed puberty in this study. We speculate that multiple cardiopulmonary bypass surgeries early in childhood may result in hypothalamic-pituitary gonadal axis malfunction. Although cardiopulmonary bypass associated hypothalamic-pituitary-adrenal axis malfunction is a known phenomenon, the effects of cardiac bypass surgery on gonadal function has not been evaluated.<sup>16</sup> Future studies should evaluate the effects of multiple cardiopulmonary bypass surgeries on adolescent gonadal function and integrity of hypothalamic-pituitary-adrenal axis.

In this study we did not find an association between delayed puberty and QoL scores. A possible explanation for this finding is that Fontan survivors have significantly lower QoL compared to peers secondary to a multitude of health issues and delayed puberty may not be perceived by them as a significant concern. An alternate explanation for the lack of association between delayed puberty and QoL may be secondary to the fact that even though the onset of puberty was delayed, older participants achieved complete pubertal development (Tanner stage 5). Since delayed puberty was not associated with worse QoL scores in Fontan survivors, the rationale for evaluation and management of delayed puberty and hypogonadism in this population may be improving fertility and bone mineralization and achievement of height potential. Although, at present, majority of women with Fontan are advised against pregnancy, with improvement in their management could change this recommendation in the future.

### **Abnormal anthropometry**

Short stature: Compared to the normal population, Fontan survivors have a 4-fold increase in the prevalence of short stature and nearly 2-fold higher abnormality in their BMI. These findings are similar to previous reports of abnormal BMI and short stature in Fontan survivors.<sup>7, 17, 18</sup> Short stature was seen in 20% of young Fontan survivors in this study which is similar to previous report of a quarter of young Fontan survivors with short stature.<sup>7</sup> Similar to the possible etiologies for delayed puberty, short stature in Fontan patients may be secondary to the multisystem abnormalities. In other chronic diseases, a slowing of growth velocity and a delayed pubertal growth spurt observed in early adolescence may lead to short adult height.<sup>15, 19</sup>

Abnormal BMI: Similar to findings of this study increased prevalence of abnormal BMI in Fontan patients has been reported previously.<sup>17, 18</sup> The abnormal BMI were almost equally split between low BMI (43%) and high BMI (57%). Not surprisingly, reduced exercise performance (NYHA grade 3 and 4 and lower maximal oxygen uptake) was associated with abnormal anthropometry. This finding suggests a possible role of reduced cardiac output state as an etiology for anthropometric abnormalities in Fontan patients. It is widely believed that short children can suffer from physical, social, and psychological problems.<sup>20, 21</sup> Our findings are similar to those reported by previous studies in that the Fontan survivors with shorter stature and high BMI have poorer functional health status.<sup>17</sup> We also noted that abnormal anthropometry was associated with lower self-reported QoL. Association of abnormal anthropometry with lower parent reported physical appearance domain score (cardiac module) but not with self-reported score is an interesting and new finding and further points to the differences in health perceptions between children and their parents.

It's not surprising that Fontan survivors in this study have significantly lower QoL compared to their peers.<sup>5, 13, 22-24</sup> Multiple prior reports have shown reduced QoL in patients with significant congenital heart diseases including patients with single ventricle physiology and Fontan.<sup>23</sup> Our study finding of worse parent's perceptions of QoL status of their children compared to the children's perceptions after the Fontan procedure has been reported before.<sup>24</sup> Lower family income was associated with lower health-related QoL in Fontan survivors. In fact a family income of < \$25,000 was associated with a greater

reduction in QoL compared to abnormal anthropometry. Other reports have shown positive correlations between income and health-related quality of life (QoL).<sup>25</sup> In this study HLHS was associated with lower QoL compared to non-HLHS patients and this could be related to the higher mortality and morbidity associated with HLHS. This finding is in contrast to a previous study that reported no difference in QoL between HLHS and non-HLHS Fontan survivors.<sup>22</sup>

**Limitations:** There is potentially a selection bias with a healthier population of Fontan survivors more likely consenting to study participation. However, the prevalence of Fontan associated complications in this study cohort is similar to contemporary reports indicating that the study population is a representative sample of the contemporary Fontan cohort. The consent rate at most centers was more than 90% minimizing the selection bias. The study population was primarily Caucasian and generalizability of pubertal findings that are influenced by race/ethnicities to other groups is unknown.

### **Conclusion**

Compared to the normal population, Fontan survivors have a 4-fold higher prevalence of short stature and nearly 2-fold higher prevalence of abnormal BMI. Delayed puberty is common among Fontan survivors of both genders. More than half of the Fontan survivors (58%) had delay in one of the Tanner stage parameters and on an average both in males and females, there was a delay of 1.5-2 years in achievement of earlier Tanner stages compared to the normal population. Abnormal anthropometry, but not delayed puberty, was associated with lower overall QoL and perceived physical appearance scores. Routine screening for abnormal anthropometry, especially in HLHS and in lower socioeconomic status families, should be considered to allow for interventions that might ameliorate the negative psychosocial impact.

**Brief description of each author's contribution**

Shaji C. Menon MD: Research design, acquisition, analysis or interpretation of data; drafting the paper; revising it critically; approval of the submitted and final versions.

Ragheed Al-Dulaimi MD, MPH; Research design, acquisition, analysis or interpretation of data; drafting the paper; revising it critically; approval of the submitted and final versions.

Brian W. McCrindle MD, MPH: Research design, acquisition, analysis or interpretation of data; drafting the paper; revising it critically; approval of the submitted and final versions.

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Tiffany Johnson MD: Research design, acquisition, analysis or interpretation of data; drafting the paper; revising it critically; approval of the submitted and final versions.

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**Figure legends:**

**Figure 1:** Shown in this forest plot are the mean differences in years between the Fontan study cohort and the normal population (NHANES III) in achieving various Tanner stages. The mean age at which the normal population achieves a specific Tanner stage is shown in the last column.

**Figure 2:** Box and whisker plot in panel A and B depict the total generic QoL scores for subjects with normal versus abnormal anthropometry stratified by 2 age groups. The dotted redline indicates the mean score for normal children in the same age group. Panel C shows the total generic QoL scores for normal subjects versus those with delayed puberty for the entire study cohort. Panel D depicts the difference in perceived physical appearance score (cardiac module) for subjects with normal versus abnormal anthropometry. \* represent statistically significant difference with p value <0.05.

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**Table 1: Baseline characteristics of study cohort (n=299)**

|  |                    |
|--|--------------------|
| Females  | 125 (42%)          |
| Age groups (years)                                 | 41%                |
| 8-12   | 33%                |
| 13-15  | 26%                |
| ≥16  |                    |
| Race   |                    |
| White  | 224 (75%)          |
| Black  | 35 (12%)           |
| Others   | 40 (13%)           |
| Ethnicity  |                    |
| Hispanic   | 43 (14%)           |
| Non-Hispanic                                       | 255 (86%)          |
| Hypoplastic left heart syndrome N (%)              | 98 (33%)           |
| Heterotaxy N (%)                                   | 24 (8%)            |
| <b>Ventricular morphology</b>                      |                    |
| Left ventricle dominant                            | 152(50%)           |
| Right ventricle dominant                           | 136 (46%)          |
| Mixed ventricular morphology                       | 11 (4%)            |
| Median age at enrollment (years) (IQR)             | 13.9 (11.3, 16.1)  |
| Median age at Fontan (years) (IQR)                 | 3 (2,4)            |
| Median age at Glenn (months) (IQR)                 | 4 (3,5)            |
| Median weight at Fontan in Kg (IQR)                | 13.7 (11.9, 15.3)  |
| Mean height at Fontan in cm (SD)                   | 93.3 (±15.2)       |
| Median number of surgeries before Fontan (range)   | 2 (1-3)            |
| >2 cardiac surgeries                               | 96 (32%)           |
| <b>Type of Fontan</b>                              |                    |
| Extra/intra-cardiac conduit                        | 199 (67%)          |
| Lateral tunnel                                     | 85(29%)            |
| Hemi-Fontan  | 56 (19%)           |
| Kawashima  | 6 (2%)             |
| Other Fontan type                                  | 9 (4%)             |
| <b>Post-Fontan Complications</b>                   |                    |
| Pacemaker  | 45 (15%)           |
| Stroke   | 33 (11%)           |
| PLE  | 15 (5%)            |
| Cirrhosis  | 3 (1%)             |
| Arrhythmia   | 39 (13%)           |
| Thrombosis   | 20 (7%)            |
| Seizure  | 10 (3%)            |
| <b>Severity of ventricular dysfunction (N=270)</b> |                    |
| Mild   | 17 (6%)            |
| Moderate   | 5 (2%)             |
| Severe   | 7 (2%)             |
| <b>Severity of AV valve regurgitation (N=268)</b>  |                    |
| Mild   | 118 (39%)          |
| Moderate   | 34 (11%)           |
| Severe   | 3 (1%)             |
| NYHA grade 3 and 4                                 | 30 (10%)           |
| % Predicted Peak VO <sub>2</sub> max (N=102)       | 67.5±15.4          |
| B-Natriuretic Peptide (BNP) pg/ml (N=39)           | 29.1 (15.9, 139.2) |
| Pulmonary vasodilators                             | 15 (5%)            |

|   |                    |
|---|--------------------|
| Coumadin                                  | 32 (11%)           |
| Digoxin                                   | 30 (10%)           |
| ACE inhibitors                            | 156 (52%)          |
| Beta blockers                             | 34 (11%)           |
| Diuretics                                 | 48 (16%)           |
| Mean age at menarche in years (SD) (N=76) | 12.5 ( $\pm$ 1.7)  |
| Mean Height Z-score                       | -0.7 ( $\pm$ 1.6)  |
| BMI Z-score                               | -0.01 ( $\pm$ 1.9) |

PLE: protein losing enteropathy; AV: atrioventricular; NYHA: New York Heart Association; ACE: Angiotensin converting enzyme; BMI: Body mass index. For missing values, we have added number of subjects in column 1.

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Table 2: Results of multivariable mixed effect regression analysis accounting for clustering showing factors associated with abnormal anthropometry, delayed puberty and QoL scores.

|  | Adjusted OR | 95% CI |       | P-Value |
|--|-------------|--------|-------|---------|
| <b>Factors associated with abnormal anthropometry [AIC=115.3]</b>                |             |        |       |         |
| NYHA grade 3 and 4 vs. lower   | 10.9        | 1.8    | 124.3 | 0.046   |
| Oxygen consumption   | 0.9         | 0.88   | 0.98  | 0.04    |
| <b>Factors associated with delayed puberty [AIC=230.5]</b>                       |             |        |       |         |
| Cardiac surgeries before Fontan >2 vs ≤2   | 2.98        | 1.45   | 6.5   | 0.02    |
| <b>Factors associated with PedsQL scores</b>                                     |             |        |       |         |
|  | Estimate    | 95% CI |       | P-Value |
| <b>Self-report (total score) [R<sup>2</sup>= 0.132]</b>                          |             |        |       |         |
| Abnormal anthropometry   | -7.4        | -11.3  | -3.6  | <0.001  |
| Family income < \$25,000 (ref: ≥\$75,000)  | -9.1        | -16.4  | -1.7  | .01     |
| HLHS vs. others  | -4.5        | -8.3   | -0.6  | .02     |
| <b>Proxy report (total score) [R<sup>2</sup>= 0.157]</b>                         |             |        |       |         |
| Abnormal anthropometry   | -9.2        | -13.5  | -4.9  | <0.001  |
| Family income < \$25,000   | -10.0       | -18.3  | -1.8  | .01     |
| HLHS vs. others  | -4.2        | -8.5   | .03   | .05     |
| <b>Self-report (cardiac domain 3:physical appearance) [R<sup>2</sup>= 0.079]</b> |             |        |       |         |
| Male vs. female  | 8.2         | 2.2    | 14.2  | 0.007   |
| Abnormal anthropometry   | -5.3        | -11.5  | 0.98  | 0.1     |
| Family income \$25,000 - \$49,999  | -11.2       | -21.5  | -0.98 | 0.03    |
| Family income < \$25,000   | -12.4       | -24.4  | -0.3  | 0.04    |
| <b>Proxy report (cardiac domain 3:physical appearance) [R<sup>2</sup>=0.138]</b> |             |        |       |         |
| Abnormal anthropometry   | -12.6       | -18.8  | -6.4  | < 0.001 |
| Family income- \$50,000 - 74,999   | -16.5       | -26.5  | -6.4  | 0.001   |
| Family income- \$25,000 - \$74,999   | -14.2       | -24.6  | -3.8  | 0.007   |
| Family income < \$25,000   | -19.4       | -31.6  | -7.2  | 0.002   |

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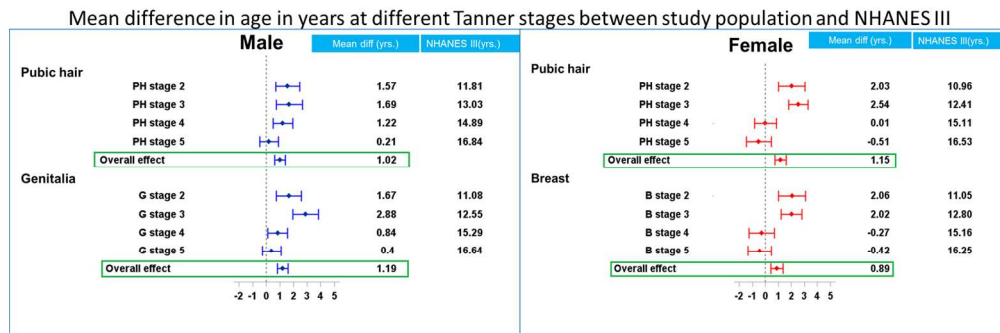


Figure 1: Shown in this forest plot are the mean differences in years between the Fontan study cohort and the normal population (NHANES III) in achieving various Tanner stages. The mean age at which the normal population achieves a specific Tanner stage is shown in the last column.

292x99mm (150 x 150 DPI)

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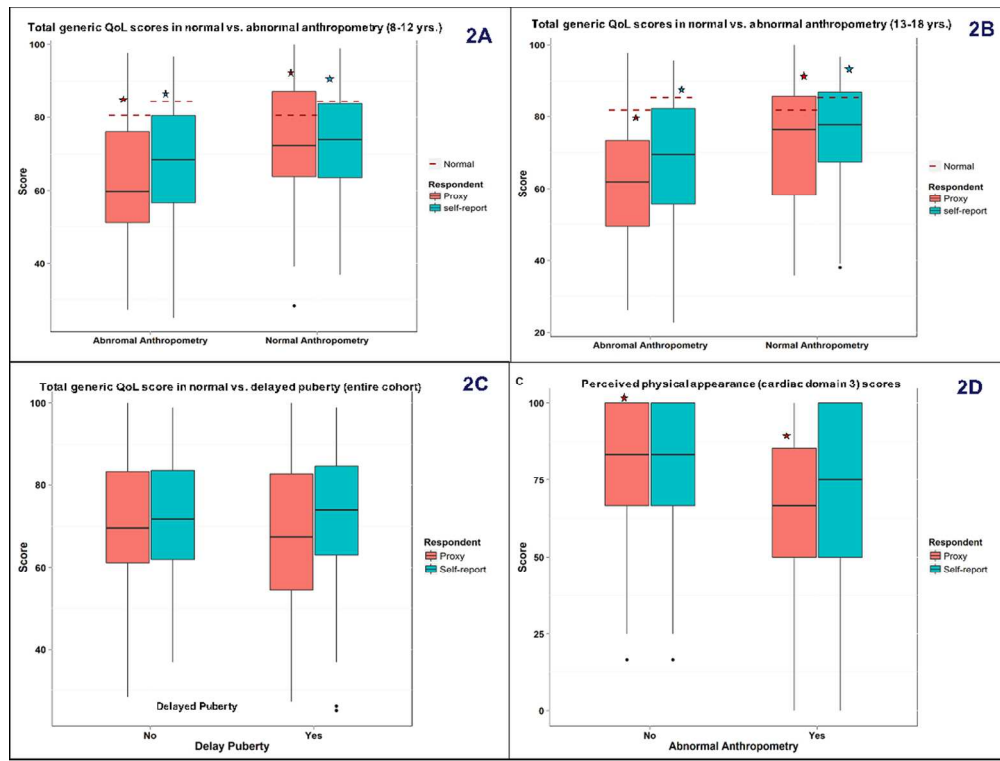


Figure 2: Box and whisker plot in panel A and B depict the total generic QoL scores for subjects with normal versus abnormal anthropometry stratified by 2 age groups. The dotted redline indicates the mean score for normal children in the same age group. Panel C shows the total generic QoL scores for normal subjects versus those with delayed puberty for the entire study cohort. Panel D depicts the difference in perceived physical appearance score (cardiac module) for subjects with normal versus abnormal anthropometry. \* represent statistically significant difference with p value <0.05.

317x238mm (96 x 96 DPI)

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