WHAT’S KNOWN ON THIS SUBJECT: Children with congenital heart disease (CHD) are at increased risk for poor growth. Several factors may play a role in poor growth, including feeding difficulties, increased caloric requirements, and the effects of cardiac lesions on growth regulation.

WHAT THIS STUDY ADDS: In children with CHD, impaired growth as measured by weight, length, and head circumference occurs simultaneously rather than sequentially, supporting the theory that altered growth regulation likely plays an important role in the poor growth of children with CHD.
Congenital heart disease (CHD) is the most common congenital anomaly, affecting ∼8 in 1000 children. In addition to the management of the specific heart defect, practitioners are often challenged by issues related to the facilitation of normal growth and development in this population. Growth status in these vulnerable children may be associated with neurodevelopmental outcomes in addition to adult height and weight. Risk factors for poor growth are multifactorial and may include the increased metabolic demands of congestive heart failure, poor oral-motor skills, the physiologic impact of the primary cardiac defect, and associated genetic and noncardiac disease.

The timing of growth differences may provide insight into both the causes of poor growth and critical periods for possible intervention. Therefore, we sought to evaluate longitudinal growth in young children with CHD of variable severity compared with the growth of healthy peers.

METHODS

We performed a retrospective cohort study comparing attained growth in children with CHD to matched controls without CHD as well as published references. We used electronic medical record data from a large primary care network. The records included data from 33 practices in urban, suburban, and semirural locations in Pennsylvania, New Jersey, and Delaware. Practices in the network started using the electronic record between August 2001 and June 2006.

Patient Selection

We identified children born after January 1, 2000, and before January 31, 2009, with International Classification of Diseases, Ninth Revision (ICD-9) codes for structural CHD who had been seen in a primary care practice and had at least 2 weight measurements before age 3 years in the electronic record. Each chart was reviewed individually by at least 1 author to confirm a true diagnosis of CHD. Children born prematurely (before 37 weeks of gestation) and those with ICD-9 codes for noncardiac complex chronic conditions (as defined by Feudtner et al, including “malignancy, neuromuscular, respiratory, renal, gastrointestinal, immunodeficiency, and metabolic, genetic, and other congenital anomalies”), were excluded from the analysis.

Cases were categorized into 1 of 4 categories of CHD: single-ventricle (SV) physiology; 2-ventricle heart disease requiring complex repair (CR), defined as Risk Adjustment for Congenital Heart Surgery class 3 or higher; 2-ventricle heart disease requiring simple repair (SR), defined as Risk Adjustment for Congenital Heart Surgery class 1 or 2; and 2-ventricle heart disease requiring no repair (NR). Cases were classified on the basis of indicated or planned repair at the last evaluable visit rather than whether repair had occurred at the time of the last evaluated visit. Chart review was used to determine the age at repair.

Measures

All measurements for weight, length or height, and head circumference (HC) recorded before January 31, 2010, were obtained from the electronic medical record. Attained growth z scores for each parameter (as well as weight-for-length) were determined for the World Health Organization (WHO) 2006 growth standard by using data from the WHO Anthro macro.

Growth parameters that were determined likely to be nonrepresentative of actual growth based on the deviation of the recorded value from inverse distance-weighted means of the subject’s growth parameters were excluded from analysis; values that were extreme but consistent with a subjects’ other growth parameters were included.

Evaluation of growth parameters in a different cohort from the same primary care network indicated that the distribution of growth parameters in this regional population was not well-described by the WHO growth curves or by the Centers of Disease Control growth reference, as has been shown in other populations. To identify a population against which to compare growth, each case was matched to 10 control subjects in the primary care network database by year of birth (±1 year), gender, race, and primary care site. Site group (urban versus all others) was used to match when there were insufficient controls in a site. Some controls were excluded during analysis because of insufficient growth measurements at the evaluated ages.

Primary Analysis

The ages at which growth data were available for each patient varied widely. Therefore, we were unable to evaluate each case’s growth compared with its own controls at each age. Instead, we evaluated growth at the ages of typical preventive visits, comparing the mean attained z score for cases and controls for each of the four CHD classes separately. The birth age group consisted only of measurements on the first day of life, and the other age groups included visits at the ages at which children were most commonly seen for preventive visits in the network. We used a 1-week range of ages for the 1- and 2-week visits; a 2-week range for the 1-, 2-, and 4-month visits; a 1-month range for the 6-, 9-, 12-, 15-, and 18-month visits, and a 2-month range for the 24- and 36-month visits.

The analyses were limited to the first 36 months of life because of the relative scarcity of measurements after that age. When ≥1 value was available for a subject in an age group, 1 value per subject per age group was selected. Visits designated as preventive visits were retained preferentially, otherwise selection was random.
The primary endpoint was the difference in mean growth WHO z score for weight-for-age (WFAZ), length-for-age (LFAZ), weight-for-length (WFLZ), and HC-for-age (HCFAZ) between cases and controls in each group at each time point. We evaluated the statistical significance of the differences by using the Student’s t test with a threshold of $P = .05$. Differences between CHD categories were evaluated by using linear regression.

The proportion of subjects with a z score $\leq 1.88$ (corresponding to the third percentile) was also compared for cases and controls. For this analysis, the SV, CR, and SR groups were analyzed together as the repair-combined (R-C) group to have sufficient sample size. Statistical significance of the difference between cases and controls was evaluated by using Fisher’s exact test with a threshold of $P = .05$. Differences between CHD categories were evaluated by using logistic regression.

**Exploratory Analysis of Age and Repair Status**

Across CHD severity and growth parameters, the greatest difference between cases and controls was seen near 4 months of age. An exploratory post hoc analysis was designed to compare the association of improvement in WFAZ with age and with repair status in the R-C group. All available measurements, including those taken at ages not traditionally associated with preventive visits, were included in this analysis. Mixed effects models were designed by using the “xtmixed” command in Stata 11.2 to compare the change in slopes ($\Delta$z score/time in years) of WFAZ before and after a certain time point for cases and controls clustered at the level of subject nested within case group (a case and its matched controls). We compared the change in WFAZ slopes before and after 4 months of age for cases and controls and then compared the change in WFAZ slopes before and after the age at the cases’ second surgery (or first surgery if only 1 surgery was done). Cases with the first or second repair done after 365 days of life were excluded from this analysis.

All analyses were performed by using Stata 11.2. This project was approved by the Institutional Review Board at the Children’s Hospital of Philadelphia.

**RESULTS**

**Identified Cases**

There were 1862 potential cases initially identified based on ICD-9 codes for CHD (Fig 1). Three hundred twenty potential cases were excluded because the subject did not have CHD; in most of these cases, the ICD-9 code had been used to indicate potential CHD that was not confirmed with diagnostic testing. Ultimately, 64,116 visits from 856 cases and 7,674 controls were included in the primary analysis (Supplemental Table 3). Characteristics of included cases are described in Table 1 with primary diagnostic categories in Table 2.

During data cleaning, 0.8% of weight, 2.5% of length, and 1.2% of HC measurements were excluded because they were likely to be nonrepresentative of the subjects’ growth. A sensitivity analysis was performed including interpolated data to replace excluded values; results were almost identical to that of the primary analysis.

**Growth in Controls**

The means and SDs for WFAZ, LFAZ, LFAZ, and HCFAZ for controls were significantly different from zero ($P < .05$) at many ages for all 4 growth parameters (Fig 2). Z scores using Centers for Disease Control growth curves were also significantly different from zero at many ages. Therefore, our primary analysis was performed as planned by using the difference between case and control mean WHO z scores at the various time points as the primary endpoint.

**Comparison of Means**

At birth, WFA and LFA z scores for cases in the SV, CR, and SR groups were all lower than control z scores at birth, but differences were relatively small and were statistically significant ($P < .05$) only for LFA in the SR group (Fig 2 and Fig 3). For children with CHD requiring repair, larger and statistically significant
TABLE 1 Characteristics of Cases

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SV</th>
<th>CR</th>
<th>SR</th>
<th>NR</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (cases)</td>
<td>37</td>
<td>52</td>
<td>159</td>
<td>608</td>
</tr>
<tr>
<td>n (controls)</td>
<td>344</td>
<td>464</td>
<td>1377</td>
<td>5489</td>
</tr>
<tr>
<td>Median age (d) at first repair</td>
<td>4</td>
<td>5</td>
<td>126</td>
<td>NA</td>
</tr>
<tr>
<td>Male</td>
<td>23 (62%)</td>
<td>31 (60%)</td>
<td>85 (53%)</td>
<td>260 (43%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>0 (0%)</td>
<td>2 (4%)</td>
<td>12 (8%)</td>
<td>15 (2%)</td>
</tr>
<tr>
<td>Black/African American</td>
<td>12 (32%)</td>
<td>11 (21%)</td>
<td>43 (27%)</td>
<td>150 (25%)</td>
</tr>
<tr>
<td>Native American</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (1%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>White</td>
<td>24 (65%)</td>
<td>32 (62%)</td>
<td>92 (58%)</td>
<td>367 (60%)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (3%)</td>
<td>7 (13%)</td>
<td>10 (6%)</td>
<td>75 (12%)</td>
</tr>
</tbody>
</table>

TABLE 2 Diagnostic Categories of Cases with CHD by Repair Category

<table>
<thead>
<tr>
<th>CHD Diagnostic Categories</th>
<th>SV</th>
<th>CR</th>
<th>SR</th>
<th>NR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoplastic left heart syndrome</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tricuspid atresia</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unspecified single ventricle abnormality</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Double-outlet right ventricle</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary valve abnormalities</td>
<td>4</td>
<td>2</td>
<td>13</td>
<td>84</td>
</tr>
<tr>
<td>Transposition of the great arteries</td>
<td>21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Truncus arteriosus</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrioventricular canal</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary abnormalities</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>5</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total anomalous pulmonary venous return</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial anomalous pulmonary venous return</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic abnormalities</td>
<td>19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic valve abnormalities</td>
<td>6</td>
<td>75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonic artery abnormalities</td>
<td>2</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>23</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial septal defect (including patent foramen ovale)</td>
<td>17</td>
<td>54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>40</td>
<td>360</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular ring</td>
<td>8</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitral or tricuspid valve abnormalities</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>37</td>
<td>52</td>
<td>159</td>
<td>608</td>
</tr>
</tbody>
</table>

Because gender and race were used as matching criteria, the proportions are the same in controls as for cases. NA, not applicable.

differences appeared by 1 week of age. Peak differences for WFAZ occurred at 4 months of age in each category: −1.6 (SV), −1.5 (CR), −0.6 (SR), −0.2 (NR). Peak differences for LFAZ were −1.4 at 4 months (SV), −1.3 at 2 months (CR), −0.6 at 2 months (SR), and −0.3 at 0.5 months (NR). Differences in growth were smaller after 4 months of age but persisted through age 36 months, except WFAZ in the SR group. The decreases in mean WFAZ between cases in the NR group and matched controls were small compared with the decreases for children requiring repair but were significant between 2 and 18 months.

There were substantial differences between controls and cases requiring repair in length as well as weight. Accordingly, decreases in WFLZ were generally smaller than for WFAZ.

Few HC measurements were available at birth and 36 months in the electronic record, so only measurements between 1 week and 24 months were evaluated. Even at those ages, HC was measured less often than weight and length. Between 2 weeks and 24 months, the pattern of differences in HCFAZ between cases and controls was generally similar to the pattern seen for weight and length with a few important exceptions. There was no difference in mean HCFAZ between cases and controls in the SR group. There were also no differences in HCFAZ between cases and controls in the SV group at 9 months and older, but a substantial decrease in HCFAZ persisted for cases in the CR and SR groups.

**Comparison of Proportion Below the Third Percentile**

There was no difference in the proportion of cases and controls with growth parameters below the third percentile (z score = 1.88) at birth in either the R-C or NR categories (Fig 4). In the combined repair group, cases were significantly more likely than controls to be less than the third percentile for all growth parameters starting at 1 month of age and persisting through 24 months (WFAZ), 36 months (LFAZ), and 9 months (HCFAZ). In the NR group, differences in proportions for cases and controls were statistically significant at fewer ages. For WFAZ, differences in the R-C group were significantly larger than for the NR group at 1, 2, and 6 months. The odds ratios for being less than the third percentile for cases versus controls were generally large in the postnatal period. At 2 months, the odds ratios for the R-C group were 12.1 (WFAZ), 3.8 (LFAZ), and 20.9 (HCFAZ) and for the NR group were 3.9 (WFAZ), 2.1 (LFAZ), and 2.5 (HCFAZ).

**Exploratory Analysis of Age and Repair Status**

There were 25,973 visits from 180 cases and 1,643 controls included in the following analyses. The median age at second repair (or first if only 1 was performed) was 130 days (interquartile range 46–213). Among cases in the R-C group, increasing z scores were, temporally, more strongly associated with age than with repair status. There was a large, significant increase in slopes (Δz score/time in years) for WHO weight z score before and after 4 months (β = 4.2, 95% confidence interval 3.6–4.9). The difference in slopes before and after repair was smaller (β = 2.1, 95% confidence interval 1.7–2.5). This overall pattern of findings was robust to sensitivity analyses excluding data from the first month after surgery and using the age at first surgery rather than second surgery when >1 was performed.

**DISCUSSION**

Within weeks of birth, children with CHD show large, early, statistically significant deficits in weight, length, and HC trajectory compared with matched controls without CHD from the same
primary care network. The largest differences in weight occurred at 4 months of age. Full catch-up growth was not seen by 36 months for children with CHD requiring repair. Children with CHD requiring repair were much more likely to be below the third percentile for weight, length, and HC in early infancy. The magnitude and timing of differences for WFAZ and LFAZ for cases in the SV group were similar to those published by Williams et al in 2011, and the magnitude of differences in WFAZ at 1 year for cases in the CR and SR groups was similar to those described by Knirsch et al.19,20

A small increase in the risk of poor growth is seen even in the population of patients with CHD that does not require surgery (NR group). The majority of subjects in this group had ventricular septal defects, which may be hemodynamically significant early in life even if they later self-resolve.

The strengths of our study include comparison of growth of cases with a control population rather than solely with published references, the relatively large sample size, and the confirmation of diagnoses with chart review rather than reliance solely on billing codes. Analysis of cases using z scores without comparison with peers would have mischaracterized the differences between these children with CHD and healthy children. For example, at 6 months of age, 5.8% of cases, and 0.5% of controls in the C-R group had microcephaly (HC less than third percentile). Therefore, cases were 11.6 times as likely as controls to have microcephaly. If we had compared them only to the WHO standards, the expected proportion of underweight would have been 3%, and it would have appeared that cases were only 1.9 times as likely as healthy children to have microcephaly, dramatically underestimating the difference between children with CHD and healthy children from the same population. Extensive efforts were also made to identify

FIGURE 2
Means and 95% confidence intervals at typical ages for preventive visits for WHO z scores for cases and controls. Means are plotted when data were available for at least 6 cases. Statistically significant differences (P < .05 using Student’s t test) are marked with a small plus.

FIGURE 3
Median weight for cases requiring CR and matched controls plotted on WHO growth curve. Values for male and female subjects are combined by converting female z scores to the equivalent weight for male subjects and plotting on the male growth curve. All time points demonstrated statistically significant (P < .05) differences between case and control groups at $>=1$ month.
erroneous values without eliminating values from subjects with growth at the extremes of the distribution. The limitations of our study include its reliance on a single network, its retrospective nature, the lack of HC data at birth and in the neonatal period, lower case numbers for specific categories of disease complexity, and the variability in timing of growth measurements. We also did not have sufficient information to determine whether some patients were cyanotic before repair, which likely has a large impact on growth.7,21

A postnatal decrease in HC growth velocity in children with CHD would indicate a restriction of brain growth during the critical developmental period of infancy and may have lifelong effects on neurodevelopment.2,3 It is important to determine whether this decrease in HC growth in children with CHD is confirmed in other studies and whether it is modifiable by nutritional or other treatments. The lack of HC values at birth and our subsequent inability to determine more precisely the time point at which differences in HC become apparent, particularly in the SV and CR groups, is a significant limitation to our study. Review of 3 published studies evaluating HC at birth in children with CHD does not reveal a consistent answer.22–25 One previous study found no association between prerepair weight <10th percentile and neurodevelopmental outcomes among children with CHD. However, the sample size of 101 subjects may not have been sufficient to identify an association if one were present, and the study did not formally assess HC.20

It is important to identify the etiology of poor growth in CHD in order to guide attempts to improve growth. Inadequate caloric intake certainly plays a role in poor growth for at least some children with CHD.19 Children with CHD frequently have feeding difficulties,6 and many have increased metabolic demands as a result of their cardiac defect.26 These higher demands are often most profound in the first 6 months of life as pulmonary vascular resistance decreases. However, decreased growth in children with CHD may also be related to other factors, such as genetic abnormalities, decreased growth factors, and hormonal changes. When caloric intake is inadequate to meet demands, effects are generally seen in weight before length and finally HC. In this population, no lag was seen between the decreased growth trajectory for cases in WFAZ, LFAZ, and HCFAZ. This simultaneous change in trajectory supports the idea that impaired growth in children with CHD requiring repair is mediated at least in part by factors unrelated to nutrition.

Dinleyici et al identified decreases in insulin-like growth factor 1 (IGF-1), an important anabolic hormone affecting childhood growth, in children with CHD, particularly those who are cyanotic.21 Another recent study identified increases in IGF-1 and its carrier protein insulin-like growth factor binding protein-3 after surgical repair in children with acyanotic CHD.27 Although the authors postulate that these increases are related to improved postoperative nutrition, the increase in growth factors may be more directly related to the repair, which often results in resolution of congestive heart failure with improved cardiovascular physiology. However, our exploratory analysis of time at repair did not suggest a strong independent association between repair and growth velocity in the overall population. Rather, a consistent improvement of growth velocity at ∼4 months was seen. Prospective evaluation will be crucial to confirm this finding and to determine if it is related to diet, such as the addition of solid foods at ∼4 months of age, or primarily mediated by growth factors or other physiologic changes.

CONCLUSIONS

Children with complex CHD have large, early, and sustained decreases in growth trajectory compared with their peers. The simultaneous change in all 3 parameters seen in this analysis...
supports the role of factors beyond calorie balance in the growth of children with CHD. However, the extent to which the poor growth seen in children with CHD is caused by potentially modifiable factors, such as the amount and type of nutrition support, medical treatment of CHD, and timing of surgical repair, is unclear. Additional observational studies would provide information to allow appropriate design of randomized controlled trials. Such studies would ideally be prospective evaluations of populations in other centers and include longitudinal evaluations of body growth, head growth, and neurodevelopment. Study designs involving data on nutritional support, metabolic rate and demands, CHD treatment, degree of CHF and cyanosis, as well as biochemical markers associated with growth, including hormones and inflammatory markers, would add greatly to our understanding of the growth and development of children with CHD.

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Carrie Daymont, Ashley Neal, Aaron Prosnitz and Meryl S. Cohen
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