Growth and Intellectual Abilities of Six-Year-Old Children with Congenital Heart Disease

Kristina Nadine Heye, MD[1,2,3], Valentin Rousson, PhD[3,4], Walter Knirsch, MD[2,3], Ingrid Beck, RN[1], Rabia Liamlahi, MD[1,3], Vera Bernet, MD[3,5], Hitendu Dave, MD[3,6], and Beatrice Latal, MD, MPH[1,3], for the Heart and Brain Research Group*

Objective To determine growth and its relationship to IQ in children with congenital heart disease (CHD) undergoing cardiopulmonary bypass surgery within the first year of life.

Study design Prospective single-center cohort study on 143 children (91 males) with different types of CHD (29 univentricular). Children with recognized genetic disorders were excluded. Growth (weight, height, and head circumference [HC]) was assessed at birth, before surgery, and at 1, 4, and 6 years and compared with Swiss growth charts. IQ was assessed at 6 years using standardized tests. Univariate and multivariable linear regressions were performed to determine predictors of HC and IQ at 6 years.

Results HC at birth was in the low average range (33rd percentile, $P = .03$), and weight (49th percentile, $P = .23$) and length (47th percentile, $P = .06$) were normal. All growth measures declined until the first surgery, with a catch-up growth until 6 years for height (44th percentile, $P = .07$) but not for weight (39th percentile, $P = .003$) or for HC (23rd percentile, $P < .001$). Children undergoing univentricular palliation showed poorer height growth than other types of CHD ($P = .01$). Median IQ at 6 years was 95 (range 50-135). Lower IQ at 6 years was independently predicted by lower HC at birth, lower socioeconomic status, older age at first bypass surgery, and longer length of intensive care unit stay.

Conclusions Smaller HC at birth and postnatal factors are predictive of impaired intellectual abilities at school age. Early identification should alert clinicians to provide early childhood interventions to optimize developmental potential. *(J Pediatr 2019;204:24-30).*

Children with congenital heart disease (CHD) are at risk of poor somatic growth,[1] particularly those with univentricular heart disease.[2] Many studies report growth for the first years of life, but fewer report long-term anthropometric outcome, and those most often report weight and height,[2-5] and less often head circumference (HC).[1,6,7] Determinants of growth retardation are multifactorial and include genetics[8] and hemodynamic factors related to the underlying CHD with altered cerebral and somatic blood perfusion.[5] Prenatal onset of poor growth may occur and has been linked to abnormal hemodynamic state.[9]

Small preoperative HC and poor postnatal head growth is related to impaired neurodevelopmental outcome from early childhood until adolescence in biventricular[10-14] and univentricular[6,15-18] types of CHD undergoing cardiopulmonary bypass (CPB) surgery. Results for weight and height are conflicting. Although some studies have not found any association,[15,19] others have demonstrated that birth weight[8] and low height trajectories were related to poorer neurodevelopmental outcome at 14 months.[20] However, the link between early growth and school-age outcome has not been determined for children with CHD.

Our aims were to describe growth trajectories from birth until 6 years of life and the relationship with IQ in children with CHD undergoing CPB surgery in infancy. We also sought to evaluate risk factors for lower HC and poorer IQ at 6 years of life.

Methods

The current study is an analysis of a prospective study evaluating neurodevelopmental outcome after open-heart surgery.[21,22] Between May 2004 and July 2009, 368 children

CHD	Congenital heart disease
CPB	Cardiopulmonary bypass
d-TGA	Dextro-transposition of great arteries
HC	Head circumference
ICU	Intensive care unit
SGA	Small for gestational age
SES	Socioeconomic status
TOF	Tetralogy of Fallot

From the [1]Child Development Center; [2]Pediatric Cardiology, Pediatric Heart Center; [3]Children's Research Center, University Children's Hospital, Zurich; [4]Division of Biostatistics, Institute of Social and Preventive Medicine, University Hospital of Lausanne, Lausanne; [5]Neonatology and Pediatric Intensive Care Unit; and [6]Congenital Cardiovascular Surgery, Pediatric Heart Center, University Children's Hospital Zurich, Zurich, Switzerland

*List of additional members of the Heart and Brain Research Group is available at www.jpeds.com (**Appendix**).

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with CHD undergoing CPB at the University Children's Hospital Zurich were preoperatively enrolled. They were subsequently examined at 1, 4, and 6 years of age. The exclusion criteria for this analysis were CPB before inclusion (n = 42), age older than 1 year at first CPB surgery (n = 58), a recognizable genetic or phenotypic syndrome (n = 80), gestational age less than $32^{0/7}$ weeks, and birth weight less than 2000 g (n = 7). Of the 181 remaining eligible patients, 14 died before the first examination and 2 between the 1-year and 4-year examinations. Six children moved away, and in 16 cases, the parents could not be reached or refused participation. Thus, information on growth and neurodevelopmental outcome at 6 years was available for 143 participants. Demographic, cardiac, and surgical characteristics did not differ between excluded and included children except for use of deep hypothermia during first CPB, which was used less often in the participants ($P = .03$, **Table I**; available at www.jpeds.com).

All demographic data were prospectively collected as described previously.[22] Socioeconomic status (SES) was determined based on maternal education and paternal occupation; each was scored from 1 to 6, resulting in a score ranging from 2 to 12.[23]

Cardiac diagnoses and severity of CHD were categorized as follows: univentricular and biventricular CHD, presence of cyanosis, and complexity of cardiac defect as proposed by Clancy et al (cardiac anatomy with presence of aortic arch obstruction, Class I-IV with increasing complexity).[24] The study was approved by the institutional review board (No.19/04), and parents or caregivers provided written consent.

Two cardiac surgeons performed CPB surgery in normothermia or mild hypothermia (rectal temperature >32°C).[22] Intensive care unit (ICU) management depended on the subsequent clinical course and complications, such as prolonged intubation, infections, sepsis, pneumothorax, chylothorax, renal insufficiency, peritoneal and hemodialysis, and seizures. Thirty-three patients (23%) were fed with a gastrointestinal tube at admission for cardiac surgery. At the 1-year examination, only 1 patient (1%) still needed a gastrointestinal tube.

Birth data were obtained retrospectively from birth records and hospital charts. Prospective measurements of weight, height, and HC were performed the day before surgery and at 1, 4, and 6 years by a trained study nurse. Data were transformed to SDS based on Swiss growth charts.[25] Growth restriction or microcephaly was defined by a SDS less than the third percentile and small for gestational age (SGA) as SDS weight and/or SDS length at birth less than the 10th percentile.

At the 6-year follow-up assessment, cognition was assessed with the third German version of the Wechsler Preschool and Primary Scale of Intelligence III.[26] Three children were tested with the German versions of the Snijders Oomen Non-verbal Test of Intelligence because they had a developmental and/or speech and language delay.[27] Another 3 children were tested in the Italian-speaking region of Switzerland and were examined with the third Italian version of the Wechsler Intelligence Scale for Children. To report overall cognitive function, we combined the IQs of all the tests applied.

Statistical Analyses

Data were analyzed with R (R Foundation for Statistical Computing, Vienna, Austria) and SPSS 24.0 0 (IBM Corp, Armonk, New York). Frequencies (percent) are given for categorical variables. Continuous variables are presented as median and range, and correlations were performed with Spearman rank correlation. Growth and growth trajectories were evaluated by converting the median SDS of children with CHD for height, weight, and HC measured at different ages into the corresponding quantile for normal children according to the Swiss growth charts.[25] Wilcoxon signed-rank tests were applied to determine whether the median SDS for children with CHD was significantly less than 0 and to compare the SDS of children with CHD at different ages. CHD subclasses were compared along the years in a linear mixed model. This model included a random child effect to take account of dependencies induced by multiple measurements on the same child. To explore the determinants of HC and IQ at 6 years, both univariate and multivariable linear regressions were performed, including SDS of height, weight, and HC at birth and before surgery, gestational age, SGA, SES, sex, cardiac class, age at surgery, use of deep hypothermic circulatory arrest, total extracorporeal circulation time (log2-transformed), length of ICU stay (log2-transformed), and length of hospital stay (log2-transformed). For the multivariable analysis, a stepwise backward regression was carried out including all predictors for which the P value was <0.2 in the univariate analysis. We found some high collinearity among early growth measures and among clinical variables (**Table II**; available at www.jpeds.com). Thus, in addition to the full models, a series of multivariable models was analyzed, each including a single growth variable. Hypothesis tests were 2-sided, and P values <.05 were considered statistically significant. For all regression analyses, SDS less than −4 or greater than 4 were set to −4 and 4, respectively, to reduce the effect of outliers.

Results

Median gestational age at birth was 39.7 weeks (range, 32.2-42.0 weeks), of whom 11 (8%) patients were born between the 32nd and 37th week of gestation. Median age at CPB surgery was 1.2 months (range, 0.1-10.7 months). Median age at the follow-up assessments was 1 year (range, 0.9-1.7 years), 4.3 years (range, 3.9-4.7 years), and 6.3 years (range, 5.8-6.7 years). Selected patient characteristics are shown in **Table III**. The 143 patients (91 male) reflect a wide range of CHD, with dextrotransposition of great arteries (d-TGA) being the most frequent CHD (29%, n = 42). Seventy-one percent (101) had a cyanotic heart defect, of whom 29 (20% of whole sample) had a univentricular physiology.

Growth trajectories are presented in **Figure 1**, A-C, and the proportion of children with growth restriction (less than third percentile) for each time point is shown in **Figure 2**.

At birth, median weight (49th percentile, SDS −0.03, range −2.92 to 3.76) and height (47th percentile, SDS −0.08, range −3.84 to 4.22) were within the norm (weight $P = .23$, height $P = .06$), and the rate of growth restriction (SDS less than the

Table III. Demographic characteristics of patient population

Characteristics at baseline	n = 143
Male, n (%)	91 (63)
Birth weight, g	3300 (2060-5250)
Birth length, cm	49 (42-57)
HC at birth, cm	34 (30-38)
Gestational age, wk	39.7 (32.2-42.0)
SGA, n (%)	35 (24)
Apgar at 5 min	9 (1-10)
SES	8 (2-12)
Cardiac diagnosis	
Biventricular CHD, n (%)	114 (80)
d-TGA, n (%)	42 (29)
Other cyanotic, n (%)*	30 (21)
Other acyanotic, n (%)†	42 (29)
Univentricular CHD, n (%)	29 (20)
Cardiac diagnose classes	
Two ventricles, no arch obstruction (Class I), n (%)	100 (70)
Two ventricles, arch obstruction (Class II), n (%)	14 (10)
One ventricle, no arch obstruction (Class III), n (%)	14 (10)
One ventricle, arch obstruction (Class IV), n (%)	15 (10)

Values are expressed as n (%) or median (range).
*Cyanotic CHD despite d-TGA included biventricular repair in patients with TOF (n = 14), total anomalous pulmonary venous connection (n = 5), common arterial trunk (type I in n = 5, type II in n = 1), pulmonary atresia (with intact ventricular septum in n = 1, with ventricular septal defect in n = 2), Ebstein anomaly was associated with valvar pulmonary stenosis (n = 1), and hemitruncus arteriosus (n = 1).
†Other acyanotic CHD included isolated ventricular septal defect (n = 19), ventricular septal malalignment (n = 1), atrioventricular septal defect (complete in n = 5, partial in n = 1), ostium secundum atrial septal defect (n = 1), sinus venosus atrial septal defect (n = 1), coarctation of the aorta (n = 3), interrupted aortic arch (type A in = 1, type B in = 2), aortic valve stenosis (n = 3), valvular pulmonary stenosis (n = 2), Bland–White–Garland syndrome (n = 2), and left-position of great arteries (n = 1).

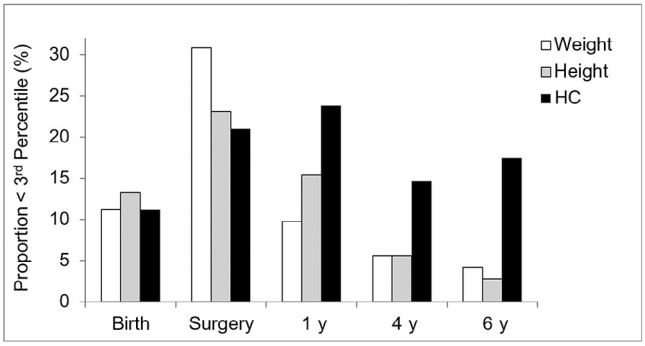

Figure 2. Proportion of children with growth less than the third percentile for each age. The proportion of children with growth indices less than the third percentile for each age is shown. *White bars* depict weight, *light gray bars* depict height, and *black bars* depict HC.

third percentile) was 11% for weight and 13% for height (both $P < .001$). The rate of children born SGA was 24%. We found median HC at birth in the low average range (33th percentile, SDS −0.43, range −4.89 to 2.86), which was significantly lower than the norm ($P = .03$). The prevalence of microcephaly (SDS less than third percentile) was 11% ($P < .001$).

Until the first CPB, all growth measures declined, most markedly for weight (**Figure 1**). All growth measures improved thereafter, and particularly within the first year of life. At 6 years, height (44th percentile, median SDS −0.16, range −2.46 to 1.90) was within the norm ($P = .07$), and weight (39th percentile, median SDS −0.29, range −4.07 to 3.11, p = 003) and especially HC (23th percentile, median SDS −0.75, range −4.43 to 2.11, $P < .001$) remained below the norm. Growth trajectories of children with CHD are presented in relation to normative growth curves in **Figure 3**, A-F (available at www.jpeds.com).

Growth trajectories of children with univentricular CHD and those with a d-TGA are presented in **Figure 4** (available at www.jpeds.com). Children with univentricular CHD showed poorer height growth until 6 years of age ($P = .01$), and weight ($P = .23$) and HC ($P = .59$) were similar to biventricular defects. Children with a d-TGA (n = 42, 29%) had better height ($P = .01$) and weight ($P = .04$) growth than children with other types of CHD, but HC trajectory did not differ ($P = .83$).

SES and growth measures at birth and surgery were related to HC at 6 years, as shown in the univariate analysis (**Table IV**). In the multivariable regression analysis, HC at birth and at first

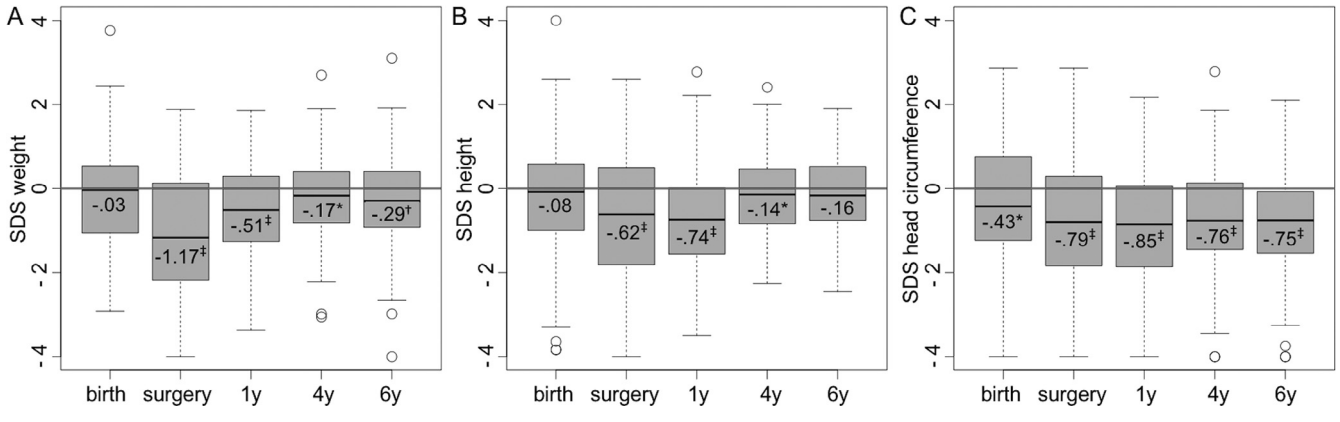

Figure 1. Median growth indices over time for 143 children with congenital heart defect for SDS of **A,** weight, **B,** height, and **C,** HC. *Horizontal lines* depict median and upper and lower boundary 75th and 25th percentile; *circles* represent outliers. *$P < .05$, †$P < .01$, ‡$P < .001$.

Table IV. Analysis of risk factors for HC and IQ at 6 years of age

		HC at 6 years			IQ at 6 years		
		Univariate		Multivariable $R^2 = 0.46$	Univariate		Multivariable $R^2 = 0.30$
n (%) or median (range)		β (CI)	R^2	β (CI)	β (CI)	R^2	β (CI)
Gestational age, wk	39.7 (32.2 – 42.0)	0.06 (–0.06 to 0.18)	0	–	**0.09 (0.002-0.17)***	**0.02**	–
SES	8 (2 – 12)	**0.10 (0.01- 0.19)***	**0.03**	**0.09 (0.02- 0.17)***	**0.14 (0.08-0.20)†**	**0.11**	**0.15 (0.09- 0.21)†**
Male sex, n (%)	91 (63)	0.09 (–0.33 to 0.51)	0	–	0.15 (–0.17 to 0.46)	0	–
Cardiac class	1 (1-4)	0.08 (–0.12 to 0.27)	0	–	–0.07 (–0.21 to 0.08)	0	–
Age at first CPB surgery, mo	1.2 (0.1-10.7)	–0.03 (–0.10 to 0.04)	0	–	**–0.04 (–0.09 to 0.02)**	**0.006**	**–0.08 (–0.14 to –0.02)‡**
Use of DHCA, n (%)	25 (17.5)	0.22 (–0.31 to 0.76)	0	–	**0.41 (0.02- 0.81)***	**0.02**	–
Cumulative ECC, min§	196 (40-818)	0.009 (–0.21 to 0.22)	0	–	–0.05 (–0.21 to 0.11)	0	–
ICU stay, d§	7 (1-227)	**–0.14 (–0.32 – 0.04)**	**0.01**	–	**–0.15 (–0.29 – –0.02)***	**0.03**	**–0.22 (–0.36 to –0.07)‡**
Hospital length of stay, d§	24 (7-232)	–0.13 (–0.34 to 0.08)	0.003	–	**–0.14 (–0.30 – 0.02)**	**0.01**	–
Weight at birth (SDS)	–0.03 (–2.9 to 3.8)	**0.38 (0.23 – 0.54)†**	**0.14**	–	**0.13 (0.004- 0.25)***	**0.02**	–
Weight at surgery (SDS)	–1.20 (–5.8 to 1.9)	**0.28 (0.16- 0.40)†**	**0.13**	–	0.04 (–0.05 to 0.14)	0	–
Height at birth (SDS)	–0.08 (–3.8 to 4.2)	**0.31 (0.17- 0.45)†**	**0.12**	–	0.11 (–0.002 to 0.22)	0.02	–
Height at surgery (SDS)	–0.62 (–6.4 to 2.6)	**0.22 (0.10- 0.33)†**	**0.09**	–	0.03 (–0.06 to 0.13)	0	–
SGA, n (%)	35 (24)	**–0.56 (–1.02 to –0.10)***	**0.03**	**0.53 (0.04- 1.01)***	**–0.38 (–0.72 to –0.03)***	**0.03**	–
HC at birth (SDS)	–0.43 (–4.9 to 2.9)	**0.46 (0.34- 0.58)†**	**0.31**	**0.31 (0.15- 0.46)†**	**0.20 (0.10 – 0.30)†**	**0.10**	**0.17 (0.08- 0.27)‡**
HC at surgery (SDS)	–0.80 (–4.8 to 2.9)	**0.45 (0.34 – 0.56)†**	**0.34**	**0.35 (0.20- 0.49)†**	0.09 (–0.01 to 0.19)	0.02	–

β, regression coefficient; R^2, adjusted coefficient of determination.
Numbers in bold represent factors included in the multivariable analysis.
*P <.05.
†P <.01.
‡P <.001.
§Due to non-normal distribution, the natural logarithm was used for the regression analysis.

CPB surgery, SGA, and SES contributed 46% of the variance in HC at 6 years. Cardiac diagnoses (presence of cyanosis, cardiac class), sex, and gestational age were not associated with HC at 6 years. If the multivariable models were run with only one growth variable included each together with SES and ICU stay, growth variables were retained in each of the models (**Table V**; available at www.jpeds.com).

Median IQ at 6 years was 95 (range, 50-135), with 7 patients (5%) performing at less than 70 (P compared with norm = 0.03, for details, see Limperopoulos et al[22]). Both patient and perioperative factors contributed to IQ at 6 years. This was significant for the following variables in the univariate analysis: GA, SES, use of deep hypothermic cardiac arrest, length of stay in the ICU, birth weight, born SGA, and HC at birth (**Table IV**). In the multivariable analysis, lower SES, smaller HC at birth, older age at first CPB surgery, and longer ICU stay were independent risk factors for a lower IQ at 6 years (**Table IV**), with an explained variance of 30%. If SES was excluded from the model, the explained variance decreased to 16%. If only 1 growth variable was included in the multivariable model together with the other covariables, the only difference was found for SGA at birth and height at birth: both were significantly associated with IQ at 6 years (**Table VI**; available at www.jpeds.com). Because patients with d-TGA were operated on during the neonatal period (<30 days) but only 1 of the patients with ventricular septal defect and none of the patients with Tetralogy of Fallot (TOF), we included cardiac diagnosis as a categorical factor in addition to age at operation in our model. The effect of age was not significant ($P = .67$), and the effect of diagnosis remained significant ($P = .036$) with lower IQ scores for children with TOF.

We also examined a variety of other potential risk factors (eg, gastrointestinal tube feeding, need for preoperative intubation, preoperative catecholamines, total number of cardiac CPB surgeries, lowest temperature during surgery, use of low-flow circulation, antegrade cerebral perfusion), none of which were significantly related to HC or IQ at 6 years of age (data not shown). These findings were independent of the underlying cardiac anatomy (single-ventricle vs biventricular CHD).

HC at 6 years correlated with IQ in biventricular CHD ($r = 0.32$, $P < .001$) but not in univentricular CHD ($r = 0.06$, $P = .78$), with an interaction term (HC at 6 years and type of CHD) that was borderline ($P = .06$).

Discussion

Our results expand those of previous studies, which demonstrated abnormal growth for all variables during the first few months of life in children with a similar spectrum of CHD diagnoses.[1,7] The etiology of poor weight and height growth is thought to be multifactorial. Factors that may contribute to this phenomenon include insufficient caloric intake, feeding difficulties, and non-nutritive factors such as the altered expression of growth factors in association with pulmonary hypertension.[28] As almost one-third of our population had a diagnosis of d-TGA and were operated within the first days of life, physiological postnatal weight loss may to some extent account for the marked decline in weight before CPB. In contrast, impaired HC growth reflects brain growth, which can be affected prenatally.[29]

Importantly, children with a univentricular CHD showed particularly poor height growth or stunting (**Figure 4**, B), a phenomenon that has been shown to persist after Fontan repair.[2,3,5] in contrast, children with d-TGA had normal growth except for HC. This long-lasting effect on HC in children with d-TGA is a new finding. Previous reports only showed poorer HC growth until 2 years of age.[30] The etiology remains elusive. However, limited fetal brain perfusion and redirected nutritional factors from the right ventricle to the descending aorta and to the lower part of the body in addition to preoperative hemodynamic stability seem to play a substantial role in later brain development.[31]

As HC remained below normal until the age of 6 years, we determined risk factors for poor HC: lower HC at birth and at first surgery, SGA status, and lower SES were the only risk factors for poorer HC at 6 years of age, explaining 46% of the variance. These findings are in agreement with previous studies[6,10,11] and demonstrate that cardiac and surgical variables appear to have less impact on brain growth, assuming head growth reflects brain growth, than was shown previously.[32]

We identified HC at birth, SES, length of ICU stay, and age at first surgery as independent predictors of IQ at 6 years. These risk factors have been consistently reported, and the latter 2 are potentially modifiable.[8,13,14,18] Older age at surgery was a risk factor for poorer IQ in our cohort, but only if we did not control for cardiac diagnosis. Although it is assumed that surgical intervention in neonates may be more harmful for the developing brain,[33] evidence is available that waiting for surgical repair is associated with poorer motor outcome and a greater frequency of brain injury due to persistent hypoperfusion.[10,34] Importantly, age at surgery was strongly confounded by the cardiac diagnosis: patients with d-TGA were operated on during the neonatal period, but only 1 of the patients with ventricular septal defect and none of the TOF patients. When we included the cardiac diagnosis as a categorical factor in the statistical model (TOF, TGA, ventricle septal defect, other), the effect of age was not significant anymore, suggesting that our effect of age could be due to a confounding effect of diagnosis.

Our finding that HC at birth is an important predictor of IQ confirms previous studies that have demonstrated a relationship between poor fetal head growth[35] or small HC at birth and neurodevelopmental outcome in early childhood,[6,10,13,15,16,18] preschool age,[11,17] and adolescence.[14] There is consistent evidence that intrauterine brain growth is altered in children with complex CHD, starting at around 30 weeks of gestation,[29] resulting in smaller HC and smaller brain volumes at birth.[36,37] Etiologic factors include reduction of umbilical vein oxygen saturation, altered blood streaming, and reduced oxygen content in the ascending aorta.[38]

We found postoperative ICU stay to strongly predict IQ. This potentially modifiable risk factor has been identified by many studies[10,17,39] and may be a surrogate marker for surgical and postoperative complexity with negative impact on later neurodevelopmental outcome.[20]

A variety of other risk factors for poor IQ have been identified in other studies. For example, feeding problems have been associated with poorer growth trajectories and poorer neurodevelopmental outcome in infancy and early childhood.[13,15,16] We also examined this variable but did not find a significant association after controlling for other risk factors. This may be because we examined long-term outcome, during which early neurologic disturbances may be mitigated as children develop and other factors, such as SES, become more important. Further, stunting (low height z score trajectories) has been related to poor neurodevelopmental performance at early age.[15,20] We found a correlation of low birth weight and SGA with IQ only in the univariate analysis but not in the multivariable model. This is supported by the findings of Miller et al that growth asymmetry was not associated with early outcome.[6]

Six-year HC only correlated with IQ for children with a biventricular CHD but not for those with an univentricular CHD. A possible explanation might be that HC in univentricular CHD does not reflect brain volume. This has been shown in children undergoing Fontan repair, where HC at age 2-3 years was found within the normal range but brain volumes were smaller than in control children. One explanation for this discrepancy is that intracranial volume is determined not only by brain volume but also by cerebrospinal fluid volume, which was larger in this particular group, probably as a result of hemodynamic changes specific to the surgical repair in these children.[33]

Our study is limited by the heterogeneity of types of CHD, resulting in relatively small sample sizes for CHD subgroups. Some results may not be significant due to lack of power. Especially, the link between HC and IQ in univentricular CHD needs to be investigated in a larger cohort. Another limitation arises from inclusion of patients born late preterm, who are at risk for impaired neurocognitive outcome.[40] This limitation has been addressed by including gestational age as an independent variable in the statistical model. A methodologic limitation arises from the collinearity of some of our predictors (**Table II**). This possibly causes an issue for the interpretation of our selected model, because when 2 strong predictors are too strongly correlated, only one of them will be selected. Thus, the absence of a predictor in our selected model does not necessarily imply that this is a weak predictor, it could also be redundant with another predictor already in the model.

Further, we did not perform fetal or neonatal cerebral magnetic resonance imaging, which would allow us to relate HC to brain growth, volume, and cerebral lesions. Caloric intake was not measured continuously, and thus we could not assess the role of nutrition on growth. The growth curves we present come from a single-center, ethnically homogeneous sample; thus, growth trajectories in other centers may differ, depending on patient population characteristics and perioperative management. Anthropometric data at birth were collected retrospectively and may be of limited accuracy.

Children with CHD undergoing CPB may show persistent poor head growth until school age paralleled by poorer intellectual abilities. Weight and height growth show a decline before surgery, followed by near-complete catch-up growth for weight and complete catch-up growth for height. Other risk factors for poorer intellectual outcome include lower SES, older age at surgery, and longer ICU stay. Future research is needed for a better understanding of fetal factors causing altered brain development to allow for timely interventions and on improving postoperative management to shorten postoperative stay and thus improve long-term outcome for children with CHD. ■

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Reprint requests: Kristina Nadine Heye, MD, University Children's Hospital, Steinwiesstrasse 75, CH - 8032 Zurich, Switzerland. E-mail: kristina.heye@kispi.uzh.ch

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Appendix

Collaborators

The following Heart and Brain Research Group members are non-author contributors.

The Heart and Brain Research Group members from University Children's Hospital, Zurich, Children's Research Center; Child Development Center, Maria Feldmann; Pediatric Heart Center, Pediatric Cardiology, Oliver Kretschmar; Congenital Cardiac Surgery, Michael Hübler; Diagnostic Imaging/MR-Center, Christian Kellenberger, Raimund Kottke, Ruth O'Gorman Tuura; Anaesthesiology, Christoph Bürki; Pediatric Neurology, Annette Hackenberg; University Hospital Zurich, Neonatology Cornelia Hagmann.

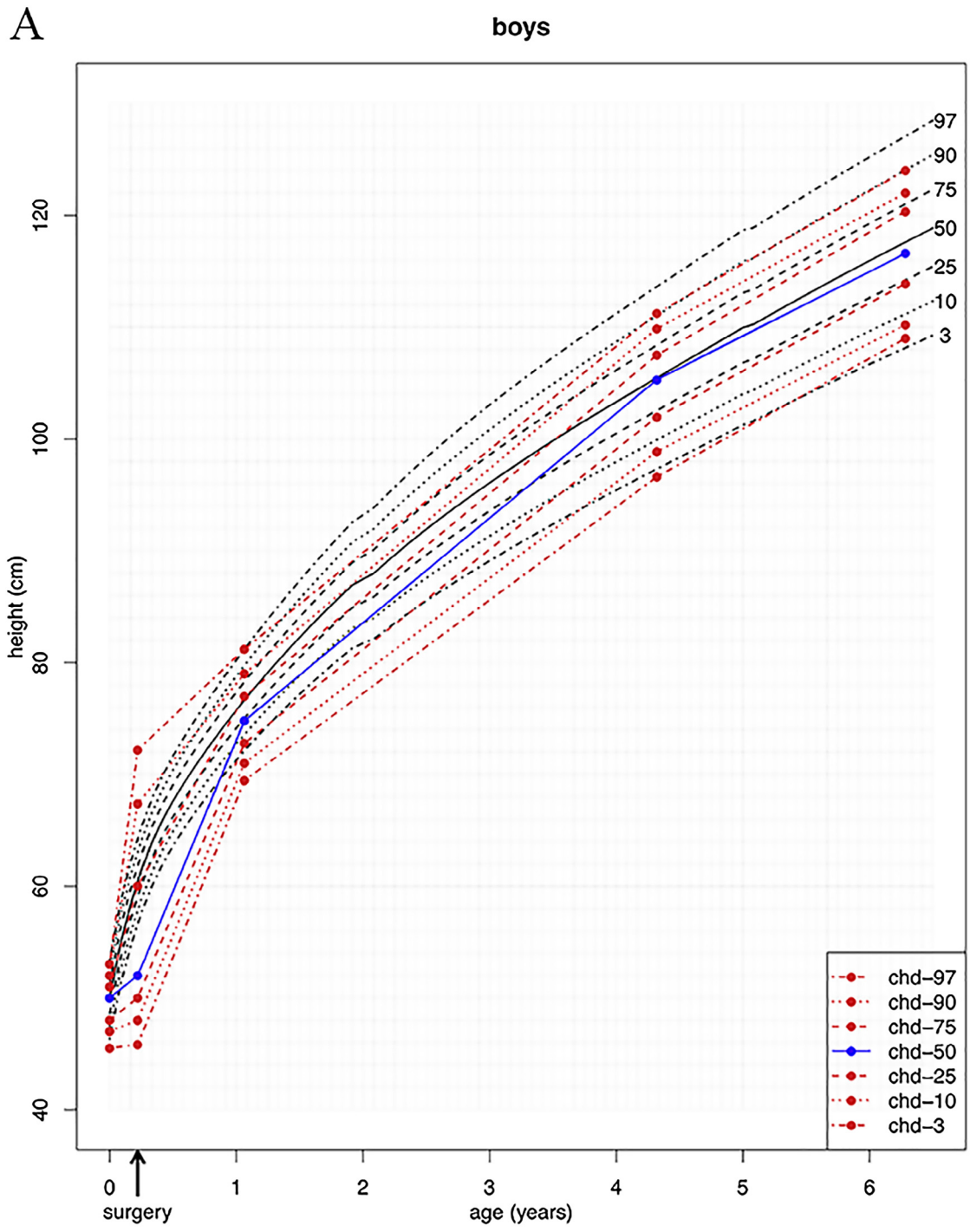
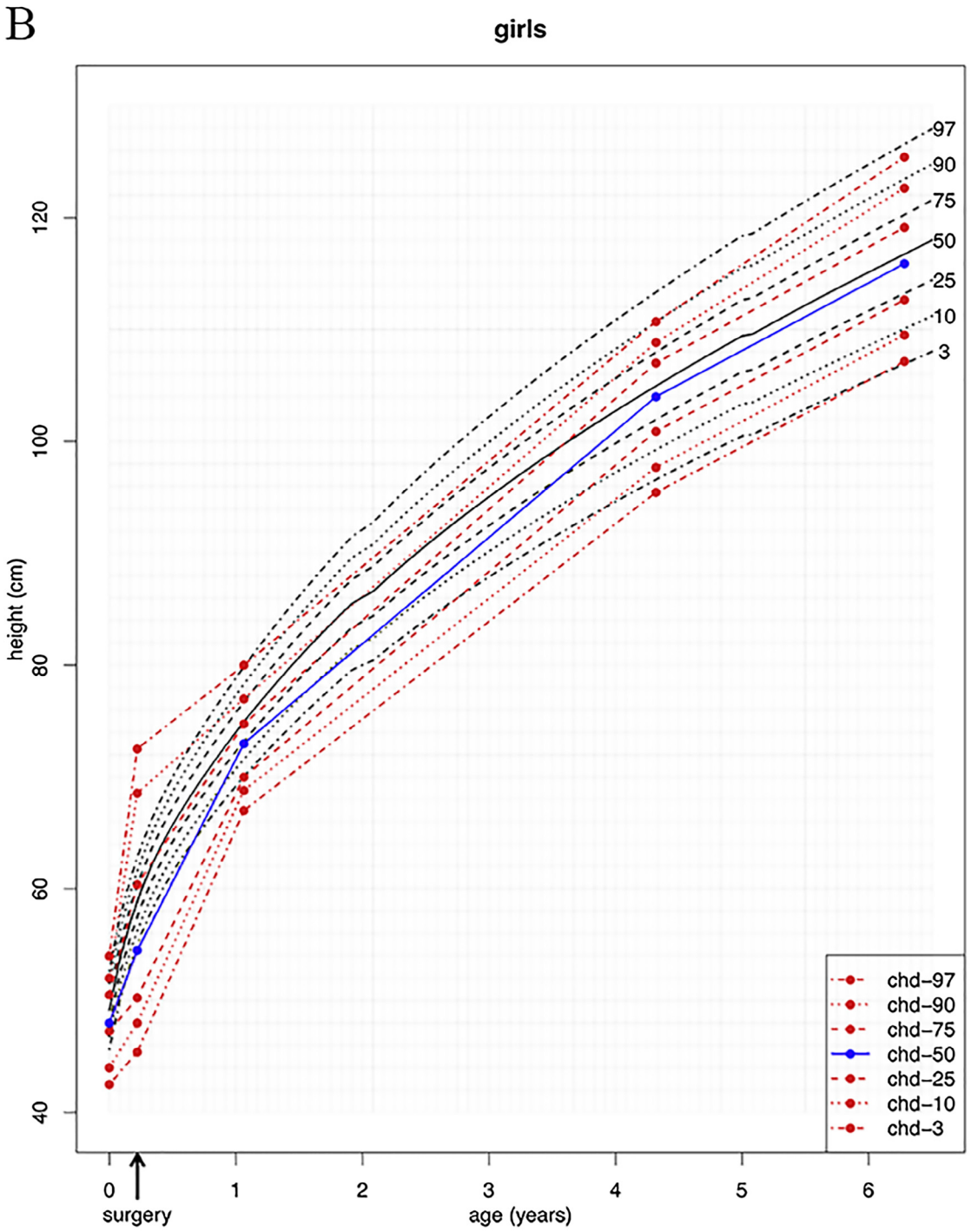


Figure 3. **A-F,** Growth trajectories of children with CHD in relation to Swiss normative growth curves. (*Continues*)



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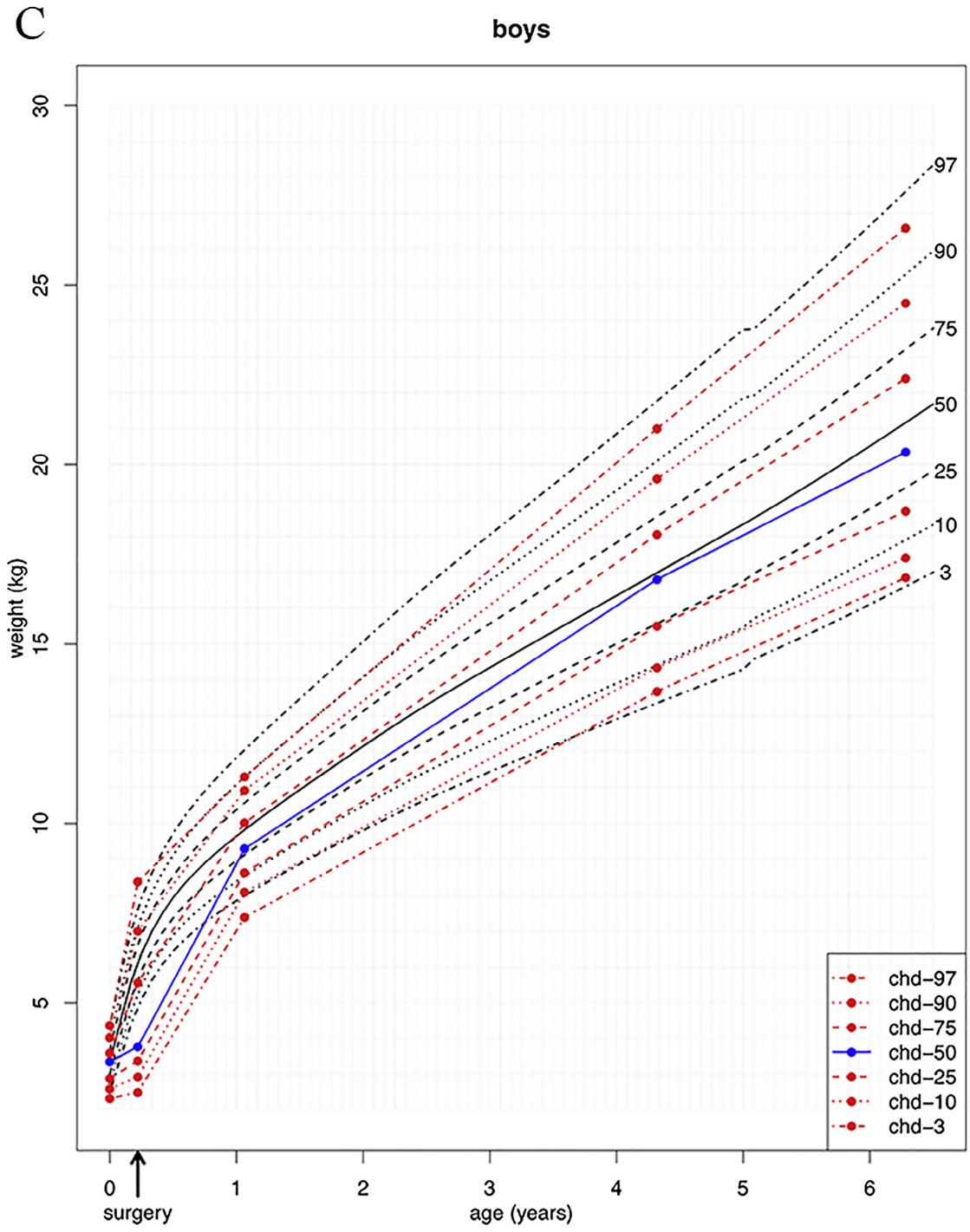

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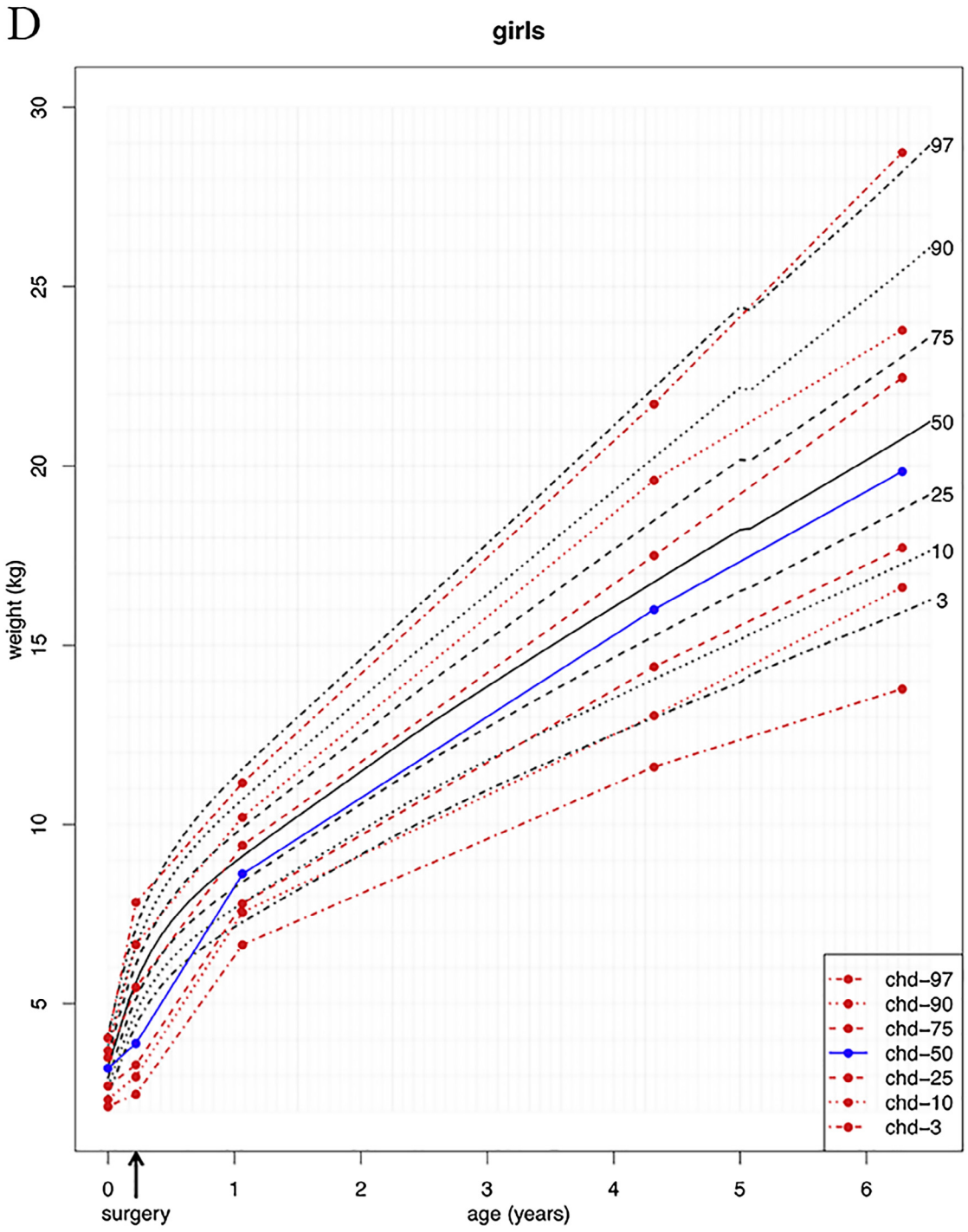

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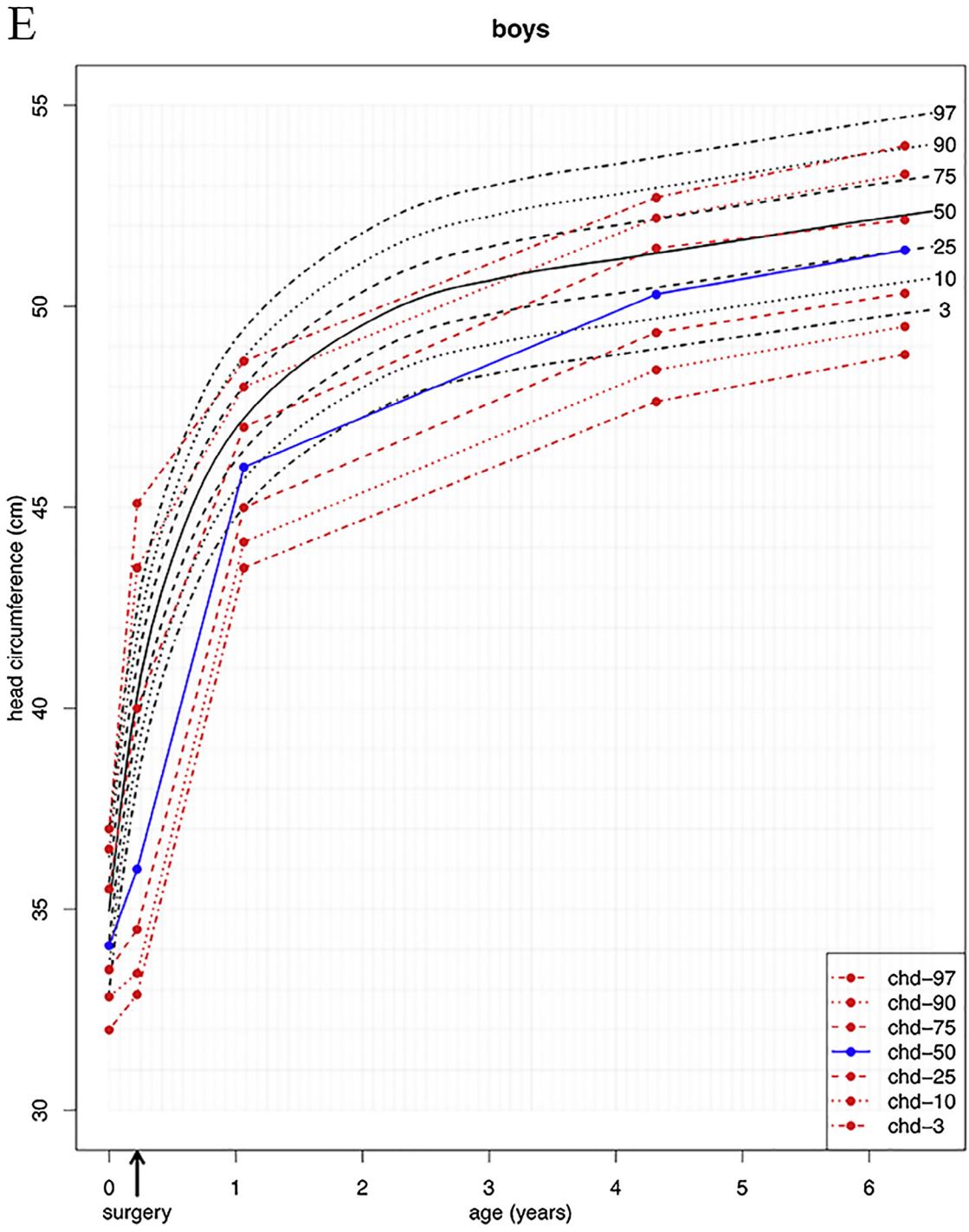

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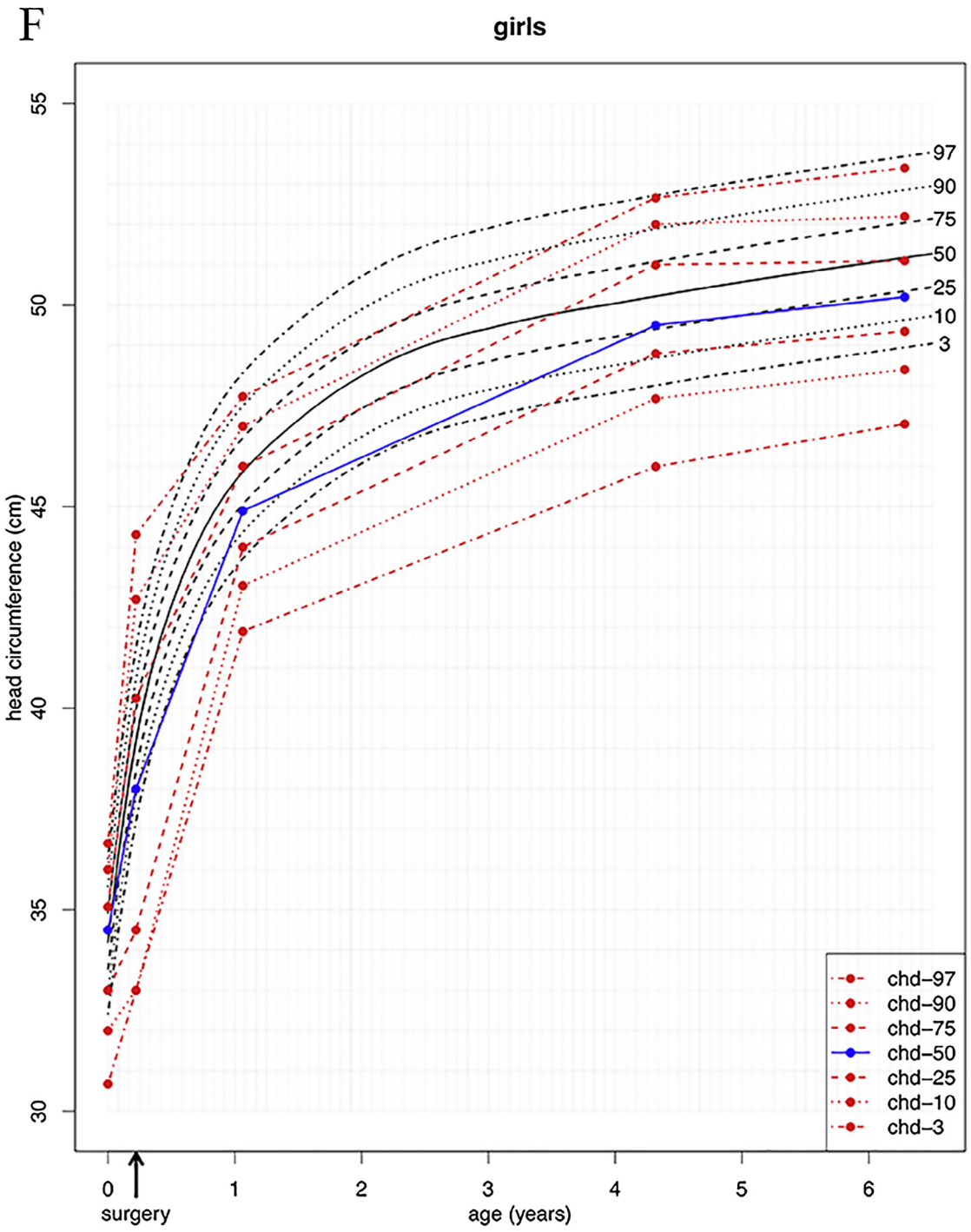

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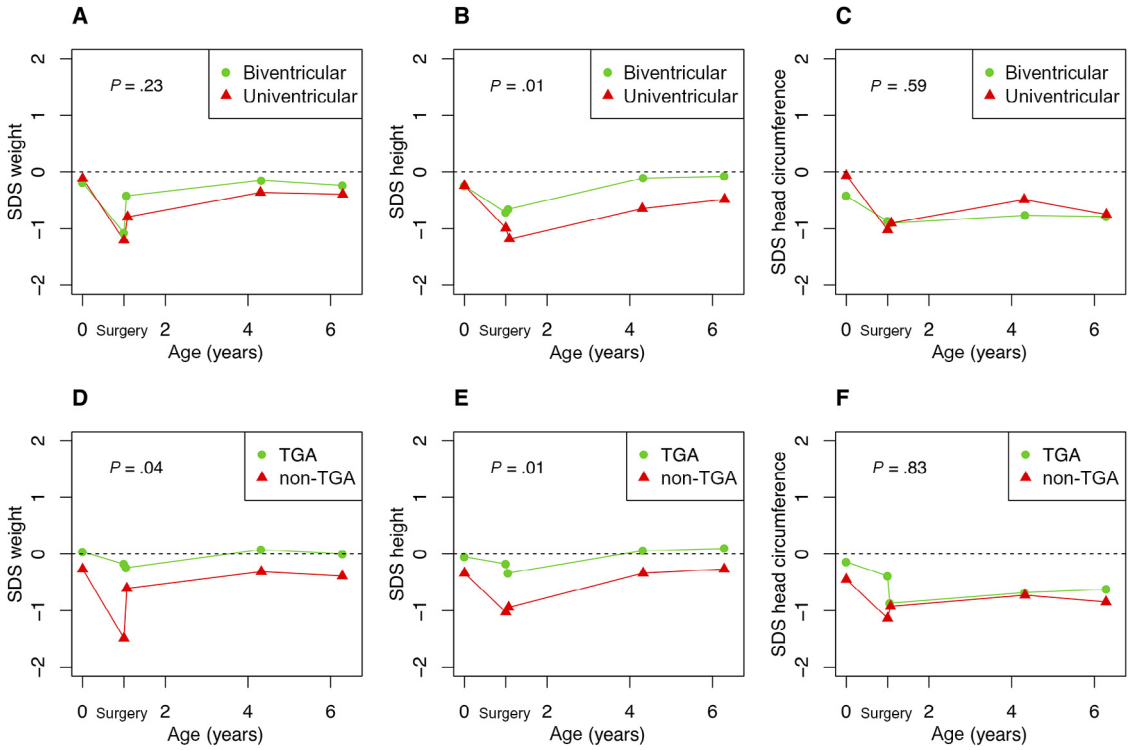

Figure 4. **A-F,** Growth trajectories for univentricular CHD and d-TGA. Mean of growth trajectories for SDS of **A** and **D**, weight; **B** and **E**, height; and **C** and **F**, head circumference for children with univentricular CHD and d-TGA compared with the sample.

Table I. Characteristics of included and excluded patients

Characteristics at baseline	Included (n = 143)	Excluded (n = 38)	*P* value
Male	91 (63)	22 (58)	.52
Gestational age, wk	39.7 (32.2-42.0)	39.7 (34.4-41.2)	.36
SGA	35 (24)	9 (24)	.92
Apgar at 5 min	9 (1-10)	9 (5-10)	.55
SES	8 (2-12)	8 (3-12)	.93
Cardiac diagnosis			
Univentricular CHD	29 (20)	11 (29)	.25
Cyanotic CHD	101 (71)	28 (74)	.71
Age at first CPB surgery, mo	1.2 (0.1-10.7)	0.47 (0.1-9.0)	.12
Use of DHCA	25 (18)	13 (34)	.03
Cumulative ECC, min	196 (40-818)	228 (70-715)	.053
ICU stay, d	7 (1-232)	10 (3-156)	.06
Weight at birth (SDS)	−0.03 (−2.9 to 3.8)	−0.36 (3.2 to 3.6)	.78
Weight at surgery (SDS)	−1.20 (−5.8 to 1.9)	−0.76 (−6.9 to 2.6)	.49
Height at birth (SDS)	−0.08 (−3.8 to 4.2)	−0.54 (−2.8 to 2.2)	.78
Height at surgery (SDS)	−0.62 (−6.4 to 2.6)	−0.76 (−7.3 to 2.1)	.82
HC at birth (SDS)	−0.43 (−4.9 to 2.9)	−0.89 (−4.2 to 3.8)	.30
HC at surgery (SDS)	−0.80 (−4.8 to 2.9)	−1.06 (−11.4 to 1.9)	.81

DHCA, deep hypothermic cardiac arrest; *ECC*, extracorporeal circulation.

Table II. Collinearity among risk factors for HC and IQ at 6 years of age

Patient and clinical factors	GA	SES	Male sex	Cardiac class	Age at surgery	Use of DHCA	Cum. ECC	ICU stay	Hospital stay	Weight at birth	Weight at surgery	Height at birth	Height at surgery	SGA	HC at birth	HC at surgery
Gestational age		0.128	0.048	–0.100	0.015	0.014	–0.04	–0.037	0.010	0.478*	0.162	0.336*	0.174†	–0.465*	0.329‡	0.263‡
SES	0.128		–0.114	–0.037	0.017	0.045	0.095	0.028	0.010	0.150	0.023	0.016	–0.049	–0.012	0.053	0.074
Male sex	0.048	–0.114		–0.027	–0.159	0.003	–0.029	0.071	0.001	0.021	0.184†	0.094	0.093	–0.009	–0.107	0.060
Cardiac class	–0.100	–0.037	–0.027		–0.035	0.316*	0.567*	0.278‡	0.249‡	0.051	0.021	0.044	–0.025	–0.041	0.081	0.007
Age at surgery	0.015	0.017	–0.159	–0.035		–0.385*	–0.187†	–0.397*	–0.381*	–0.132	–0.444*	–0.121	–0.212†	0.108	–0.123	–0.273‡
Use of DHCA	0.014	0.045	0.003	0.316*	–0.385*		0.341*	0.303*	0.299*	–0.007	0.157	–0.021	0.078	–0.005	–0.035	0.107
Cum. ECC	–0.040	0.095	–0.029	0.567*	–0.187†	0.341*		0.521*	0.535*	0.109	0.135	0.108	0.057	–0.075	0.065	0.061
ICU stay	–0.037	0.028	0.071	0.278†	–0.397*	0.303*	0.521*		0.755*	–0.040	0.085	–0.016	–0.042	0.035	–0.174†	–0.051
Hospital stay	0.025	0.010	0.001	0.249‡	–0.381*	0.299*	0.535*	0.755*		–0.075	–0.066	–0.095	–0.202†	0.048	–0.142	–0.123
Weight at birth	0.478*	0.150	0.021	0.051	–0.132	–0.007	0.109	–0.040	–0.075		0.598*	0.757*	0.568*	–0.711*	0.665*	0.577*
Weight at surgery	0.162	0.023	0.184†	0.021	–0.444*	0.157	0.135	0.085	–0.066	0.598*		0.582*	0.840*	–0.491*	0.401*	0.718*
Height at birth	0.336*	0.016	0.094	0.044	–0.121	–0.021	0.108	–0.016	–0.095	0.757*	0.582*		0.719*	–0.705*	0.555*	0.543*
Height at surgery	0.174†	–0.049	0.093	–0.025	–0.212†	0.078	0.057	–0.042	–0.202†	.0568*	0.840*	0.719*		–0.523*	0.427*	0.672*
SGA	–0.465*	–0.012	–0.009	–0.041	0.108	–0.005	–0.074	0.048	0.035	–0.711*	–0.491*	–0.705*	–0.523*		–0.471*	–.0452*
HC at birth	0.329*	0.053	–0.107	0.081	–0.123	–0.035	0.065	–0.174†	–0.142	0.665*	0.401*	0.555*	0.427*	–0.471*		0.695*
HC at surgery	0.263‡	0.074	0.060	0.007	–0.273‡	0.107	0.061	–0.051	–0.123	0.577*	0.718*	0.543*	0.672*	–0.452*	0.695*	

cum ECC, cumulative extracorporeal circulation time.
Values are Spearman correlations between patient characteristics and medical variables.
*$P < .05$.
†$P < .01$.
‡$P < .001$.

Table V. Multivariable analysis of risk factors for HC at 6 years of age

Patient and clinical factors	Multivariable $R^2 = 0.17$ β (CI)	Multivariable $R^2 = 0.21$ β (CI)	Multivariable $R^2 = 0.17$ β (CI)	Multivariable $R^2 = 0.12$ β (CI)	Multivariable $R^2 = 0.07$ β (CI)	Multivariable $R^2 = 0.35$ β (CI)	Multivariable $R^2 = 0.39$ β (CI)
SES	NS	0.104 (0.02-0.19)*	0.104 (0.01-0.20)*	0.119 (0.03-0.21)*	0.047 (0.00-0.20)*	0.087 (0.01-0.17)*	0.101 (0.02-0.18)*
ICU stay, d§	NS	–0.209 (–0.39 to –0.03)*	–0.196 (–0.38 to –0.01)*	NS	NS	NS	NS
Weight at birth (SDS)	0.416 (0.24-0.59)†	–	–	–	–	–	–
Weight at surgery (SDS)	–	0.324 (0.19-0.46)†	–	–	–	–	–
Height at birth (SDS)	–	–	0.307 (0.16-0.46)†	–	–	–	–
Height at surgery (SDS)	–	–	-	0.236 (0.12-0.36)‡	-	–	–
SGA	–	–	–	–	–0.690 (–1.21 to –0.17)*	–	–
HC at birth (SDS)	–	–	–	–	–	0.463 (0.34-0.59)†	–
HC at surgery (SDS)	–	–	–	–	–	–	0.468 (0.35–0.58)†

–, not included in the model; *NS*, included in the model but not significant.
*$P < .05$.
†$P < .01$.
‡$P < .001$.
§Due to non-normal distribution, the natural logarithm was used for the regression analysis.

Table VI. Multivariable analysis of risk factors for IQ at 6 years of age

	Multivariable $R^2 = 0.22$	Multivariable $R^2 = 0.22$	Multivariable $R^2 = 0.27$	Multivariable $R^2 = 0.22$	Multivariable $R^2 = 0.26$	Multivariable $R^2 = 0.30$	Multivariable $R^2 = 0.22$
Patient and clinical factors	**β (CI)**	**β (CI)**	**β (CI)**	**β (CI)**	**β (CI)**	**β (CI)**	**β (CI)**
Gestational age, wk	NS	NS	NS	NS	NS	NS	NS
SES	0.154 (0.09- 0.22)*	0.154 (0.09- 0.22)*	0.152 (0.09- 0.22)*	0.154 (0.09- 0.22)*	0.156 (0.09- 0.22)*	0.150 (0.09- 0.21)*	0.154 (0.09- 0.22)*
Age at first CPB surgery, mo	–0.087 (–0.15 to –0.03)†	–0.087 (–0.15 to –0.03)†	–0.067 (–0.13 to –0.01)*	–0.087 (–0.15 to –0.03)*	–0.077 (–0.14 to –0.02)*	–0.079 (–0.14 to –0.02)†	–0.09 (–0.15 to –0.03)†
Use of DHCA, n (%)	NS	NS	0.426 (0.02- 0.84)*	NS	NS	NS	NS
ICU stay, d§	–0.255 (–0.40 to –0.11)†	–0.255 (–0.40 to –0.11)†	–0.264 (–0.41 to –0.12)*	–0.255 (–0.40 to –0.11)†	–0.223 (–0.37 to –0.08)†	–0.216 (–0.36 to –0.07)†	–0.255 (–0.40 to –0.11)‡
Hospital length of stay, d§	NS	NS	NS	NS	NS	NS	NS
Weight at birth (SDS)	NS	–	–	–	–	–	–
Weight at surgery (SDS)	–	NS	–	–	–	–	–
Height at birth (SDS)	–	–	0.139 (0.03 – 0.25)‡	–	–	–	–
Height at surgery (SDS)	–	–	–	NS	-	–	–
SGA	–	–	–	–	–0.457 (–0.81 - –0.10)‡	–	–
HC at birth (SDS)	–	–	–	–	–	0.174 (0.08-0.27)†	–
HC at surgery (SDS)	–	–	–	–	–	–	NS

*$P < .05$.
†$P < .01$.
‡$P < .001$.
§Due to non-normal distribution, the natural logarithm was used for the regression analysis.