





ORIGINAL RESEARCH

# Timing of Pubertal Development in Boys and Girls With Congenital Heart Defects: A Nationwide Cohort Study

Louise F. Udholm , MD; Anne Gaml-Sørensen , MHS; Linn H. Arendt, MD, PhD; Nis Brix, MD, PhD; Lea L. H. Lunddorf , MD; Andreas Ernst, MD, PhD; Ulla B. Knudsen, MD, PhD; Vibeke E. Hjortdal, MD, PhD, DMSc; Cecilia H. Ramlau-Hansen , MHS, PhD

**BACKGROUND:** Children with congenital heart defects (CHD) have an increased risk of developmental delay. It remains sparsely investigated if these patients also have a delayed pubertal development. In this nationwide cohort study, we evaluated if CHD was associated with timing of puberty using longitudinally collected data on pubertal milestones.

**METHODS AND RESULTS:** We used data from the Danish nationwide Puberty Cohort. Information on CHD was obtained from the Danish National Patient Register. Information on pubertal development was obtained from 15 780 children through questionnaires answered half-yearly from 11 years until 18 years or full maturity. Using a multivariable regression model for censored time-to-event data, mean difference in age at attaining each pubertal milestone was estimated, including a combined pubertal marker. Compared with children without CHD, analyses were performed for both CHD overall and subdivided into simple and complex CHD. In a subanalysis, analyses were repeated in children born at term. In total, 137 children (62 boys and 75 girls) had a CHD diagnosis. Overall, no difference in age at pubertal timing was observed for children with CHD compared with unaffected children. The average differences were small for both boys (1.6 [95% CI, -2.6 to 5.7] months) and girls (1.0 [95% CI, -2.5 to 4.4] months). The same differences were observed when subdividing into simple or complex CHD and when restricting to children born at term.

**CONCLUSIONS:** We found no association between CHD and pubertal timing. For the group of children with complex CHD, we were unable to exclude a later pubertal timing.

**Key Words:** congenital heart defects ■ menarche ■ puberty ■ sexual development ■ sexual maturation

The management of children with congenital heart defects (CHD) has improved substantially over the past decades.<sup>1-3</sup> The corresponding increase in long-term survival has shifted the research focus from mortality to morbidity, driving our attention to physical and cognitive development of the affected children.

Puberty is one of the fundamental periods of development during life. Its onset and progression are driven by a dynamic interplay between several factors, including genetics, nutritional status, and environmental exposures.<sup>4</sup> Both physical growth from

conception to early childhood and childhood body mass index (BMI) are highly associated with pubertal timing.<sup>5-9</sup> Although low birth weight is associated with earlier onset of puberty,<sup>5</sup> low childhood BMI may result in later pubertal onset.<sup>6,7,9</sup> Children with CHD are at risk of impaired fetal, neonatal, and early childhood growth.<sup>10-14</sup> With early detection and comprehensive and improved treatment, significant catch-up growth is observed in nearly all children with CHD.<sup>15-17</sup> The population of Danish children with CHD does, however, continue to have a slightly lower BMI and increased

Correspondence to: Louise F. Udholm, MD, Copenhagen University Hospital, Department of Cardiothoracic Surgery, Inge Lehmanns Vej 7, Copenhagen, N/A 2100, Denmark. Email: louise.fredsgaard.udholm@regionh.dk

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## CLINICAL PERSPECTIVE

### What Is New?

- With this nationwide cohort study, we are the first to evaluate whether children born with congenital heart defects had later pubertal onset compared with children born without congenital heart defects using longitudinally collected data every 6 months on several pubertal markers.
- We found normal age at pubertal onset in boys and girls with congenital heart defects compared with boys and girls without.
- This remained unchanged when evaluating simple and complex heart defect subgroups, though the complex group included a limited number of children.

### What Are the Clinical Implications?

- Our study adds to the very limited knowledge on pubertal development in children with congenital heart defects.
- Our findings for children with simple heart defects are reassuring information to patients and health care professionals, considering the markedly delayed puberty found in children with Fontan circulation.

## Nonstandard Abbreviations and Acronyms

<b>CHD</b>	congenital heart defects
<b>DNBC</b>	Danish National Birth Cohort

risk of underweight throughout childhood compared with the background population.<sup>18</sup> Children with CHD might therefore be at risk of a later pubertal timing. In children with univentricular heart defects, palliated with the Fontan circulation, a delay of 1.5 to 2.0 years has been found for breast, genital, and pubic hair development compared with national standard charts.<sup>19</sup> Further information on puberty in children with CHD is limited to studies on age at menarche including adult women with CHD, reporting higher recalled age at menarche in women with complex or cyanotic CHD such as women with Fontan circulation.<sup>20–25</sup> Thus, our knowledge on pubertal timing in children with CHD is limited and for children with more simple defects nonexistent. As late puberty has been associated with adverse health outcomes later in life,<sup>26–29</sup> including mental and psychosocial consequences,<sup>30</sup> further studies are needed to examine pubertal timing in children with CHD.

In this nationwide cohort study, we investigate whether children with CHD, including simple defects,

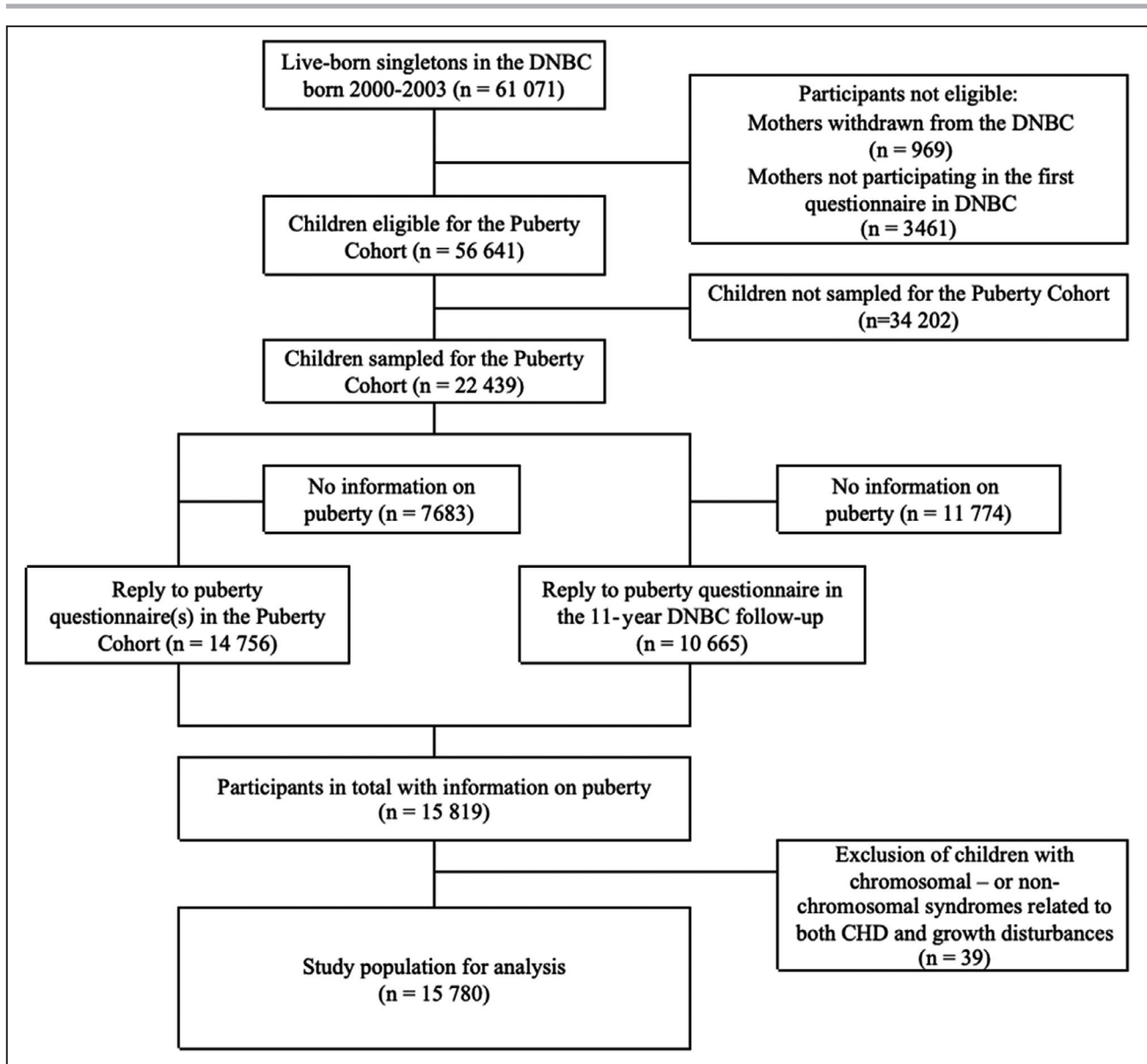
had later pubertal timing compared with children without CHD using longitudinally collected data.

## METHODS

The DNBC (Danish National Birth Cohort) operates an open access policy. Access to personalized data requires permission from both the Danish Data Protection Agency as well as from the DNBC Steering Committee. Please refer to <https://www.dnbc.dk/access-to-dnbc-data>.

### Study Population

This study used data from the Puberty Cohort, a subcohort of the DNBC, with more than 100 000 mother–child pairs.<sup>31</sup> Mothers were enrolled during early pregnancy from 1996 to 2002. Through computer-assisted telephone interviews, information on maternal lifestyle, health, and socioeconomic factors during pregnancy was obtained on average at gestational weeks 17 and 30. Follow-up of the children was performed at ages 7 and 11 years. Children eligible for being sampled for the Puberty Cohort were live-born singletons born between 2000 and 2003, whose mothers participated in the first computer-assisted telephone interview during pregnancy and had not withdrawn from the DNBC. In total, 22 439 of 56 641 eligible children were invited to participate in the Puberty Cohort. To increase the exposure contrast, the eligible children were sampled according to 15 different prenatal and perinatal exposures thought to be of relevance for pubertal development. Further, a random sample of 8000 of the 56 641 eligible children was added. From the age of 11.5 years, the participants in the Puberty Cohort were invited to give information on puberty every 6 months through web-based questionnaires until 18 years or full maturity. Full maturity was defined as Tanner stage 5 for genital and pubic hair development for boys and Tanner stage 5 for breast and pubic hair development for girls.<sup>32,33</sup> Additionally, the 11-year questionnaire in the DNBC also contained information on puberty. When combining the data from the 11-year questionnaire and the longitudinal data in the Puberty Cohort, information on pubertal development was available on 15 819 of the 22 439 children in the Puberty Cohort (participation rate 70%) (Figure 1). All children born with a chromosomal syndrome (*International Classification of Diseases, Tenth Revision [ICD-10]* codes DQ90–DQ99) or nonchromosomal syndrome (*ICD-10* codes DD82.1, DQ44.7B, DQ87.1D, DQ87.2A, DQ87.4, DQ87.8J, DQ93.8A) related to CHD and growth disturbances<sup>34</sup> were excluded from this study (n=39) yielding a final study population of 15 780.



**Figure 1.** Flow diagram on the inclusion of participants in the Puberty Cohort nested within the Danish National Birth Cohort (DNBC), Denmark, 2000 to 2018.

CHD indicates congenital heart disease.

The Committee for Biomedical Research Ethics in Denmark approved the collection of data in the DNBC ([KF]hn 01-471/94). The present study was approved by the steering committee of the DNBC (2020-04) and registered by the Danish Data Protection Agency (P-2020-728). When entering the cohort, mothers provided a written informed consent covering both themselves and their child.

### Assessment of Congenital Heart Defects

Information on CHD was obtained from the DNPR (Danish National Patient Register), which contains information on all hospital contacts in Denmark, dates of admission and discharge, surgical procedures, and

discharge diagnoses coded according to the *ICD*.<sup>35</sup> Children with CHD were identified using the *ICD-10* codes Q20-Q26 (except for Q26.5-Q26.6, not specific to CHD). Children with patent ductus arteriosus (DQ25.0) were included if born after gestational week 37. To increase the positive predictive value of the classification, we included only main (A) diagnoses registered at university hospitals in Denmark. We studied CHD overall, as well as subdivided into simple and complex CHD according to the classification presented by Larsen et al.<sup>3</sup> (Table S1). Children with more than 1 diagnosis were categorized according to the most severe main diagnosis obtained at a university hospital.<sup>36</sup>

## Assessment of Pubertal Development

Information on pubertal development was collected through web-based questionnaires at 11 years of age in the DNBC and from 11.5 years of age and every 6 months in the Puberty Cohort. Boys were asked to report their current Tanner stage of genital development (G1–G5), Tanner stage of pubic hair development (PH1–PH5), as well as axillary hair (yes or no), acne (yes or no), voice break (yes or no), and first ejaculation of semen (yes or no; if yes: years and months). Girls were asked to report their Tanner stage of breast development (B1–B5), pubic hair development (PH1–PH5), axillary hair (yes or no), acne (yes or no), and age at menarche (years and months). The questionnaires included illustrations and a short description of each Tanner stage.<sup>37</sup>

## Covariates

Information on maternal lifestyle and health during pregnancy was available from the interviews conducted in the DNBC. Mothers were also asked to report their own age at menarche. Information on childhood BMI was available from the 7-year questionnaire in the DNBC. Further, from the Danish Medical Birth Register, information on maternal age at delivery, parity, gestational age, birth weight, and head circumference was obtained.<sup>38</sup> Birth weight and head circumference were both converted into Z scores using reference material by Marsal et al.,<sup>39</sup> Olsen et al.,<sup>40</sup> and World Health Organization standard head circumference curves.<sup>41,42</sup> Z scores express the number of SDs the birth weight deviates from the expected birth weight based on sex and gestational age. The same applied for head circumference. Lastly, information on pregestational diabetes was available from the DNPR,<sup>35</sup> and information on highest social class of parents was obtained from Statistics Denmark, defined by level of education and occupation according to the International Standard Classification of Occupation and Education codes. Covariates were categorized or kept continuous as shown in Table 1.

Based on reviews of the current literature, potential confounders were identified using directed acyclic graphs,<sup>43</sup> and we included highest social class of parents, maternal smoking in first trimester, prepregnancy BMI, and maternal age at menarche.

## Statistical Analysis

As the children in the Puberty Cohort were asked to report their pubertal stage every 6 months, the data on age at achieving the pubertal milestones were either left, interval, or right censored.<sup>44</sup> Data were left censored if the pubertal stage was attained before first completed questionnaire, interval censored if the pubertal stage was attained between 2 questionnaires,

or right censored if not attained by the last questionnaire. Data were analyzed using a multivariable regression model for censored time-to-event data fitted by maximum likelihood estimation (STATA's `-intreg-` package). This model assumes normally distributed residuals. This was assessed by plotting the residuals from each of the regression models in R (x64 3.3.1) as the cumulative incidence function, based on the Turnbull estimator, against the normal distribution. Data were compatible with the assumption (data not shown).

In the main analyses, we estimated the mean monthly difference in age at attaining each pubertal milestone for boys and girls with CHD compared with those born without CHD. All pubertal milestones were also combined into 1 estimate for each sex using Huber-White robust variance estimation. This approach reduces the risk of type 1 errors due to multiple testing of correlated outcomes.<sup>45,46</sup> Furthermore, the main analyses were repeated with CHD subdivided into simple and complex CHD. Lastly, we performed a subanalysis restricting our study population to boys and girls born at term because gestational age may be related to pubertal timing.

To account for the oversampling of children exposed to potential risk factors of altered pubertal onset, sampling weights were used in the Puberty Cohort as described in detail elsewhere.<sup>44</sup> Furthermore, selection weights were applied to account for potential selection bias due to nonparticipation.<sup>47</sup> Selection weights were estimated as the inverse probability of participation using a logistic regression model on participation (yes/no), including CHD and all potential confounders included as explanatory variables. This was done separately for boys and girls. The estimates for the participating 15 819 children should be representative for all 22 439 invited. Further information about the derivation of selection weights, including tables with coefficients, standard errors, and intercept, is presented in Data S1 through S3 and Tables S2 through S5. The sampling and selection weights were then multiplied and included in all analyses. Lastly, all models were fitted with robust standard errors to account for the weights and clustering of siblings. All analyses were conducted in STATA 16.1 MP software (Statacorp, College Station, TX).

## RESULTS

Of the 15 780 children included, 137 (0.9%) had a CHD diagnosis (62 boys and 75 girls). When dividing into subtypes, 111 (81.0%) children had a simple defect (50 boys and 61 girls) and 26 (19.0%) were diagnosed with a complex defect (12 boys and 14 girls) (Table 1). The most frequent simple cardiac diagnoses were ventricular and atrial septal defect, whereas atrioventricular septal defect was most common in the complex group

**Table 1. Background Characteristics According to CHDs for 15 780 Children in the Puberty Cohort, Denmark, 2000 to 2018**

	No CHD	CHD
	n=15 643 (99.1%)	n=137 (0.9%)
Child's characteristics		
Subtype of CHD, n (%)		
Simple CHD		111 (81.0)
Complex CHD		26 (19.0)
Mean birth weight Z score (SD)*	0.0 (1.2)	-0.3 (1.3)
Mean head circumference Z score (SD)*	1.2 (1.7)	1.0 (1.9)
Birth before gestation wk 37, n (%)*		
No	14 470 (92.9)	119 (86.9)
Yes	1098 (7.1)	18 (13.1)
BMI at 7 y, mean (SD)†	15.6 (1.7)	15.6 (1.7)
Maternal characteristics		
Prepregnancy BMI, mean (SD)*	23.8 (4.6)	24.3 (4.5)
Maternal age at delivery in years, mean (SD)*	30.6 (4.4)	30.1 (4.6)
Smoking during first trimester, n (%)*		
No	11 224 (72.0)	96 (70.1)
Yes	4366 (28.0)	41 (29.9)
Maternal age of menarche, n (%)*		
Earlier than peers	3964 (25.5)	34 (25.2)
Same time as peers	8894 (57.3)	<77 (<56.2)‡
Later than peers	2665 (17.2)	>26 (>19.0)‡
Highest social class of parents, n (%)*		
High/low grade professional	8791 (56.3)	>71 (>51.8)‡
Skilled/unskilled worker	6426 (41.2)	<59 (<43.0)‡
Student/economically inactive	396 (2.5)	7 (5.1)
Pregestational diabetes, n (%)		
No	15 245 (97.5)	130 (94.9)
Yes	398 (2.5)	7 (5.1)

BMI indicates body mass index; and CHD, congenital heart defects.

\*<10% of data were missing.

†≈30% of data were missing.

‡Owing to local data regulations, it is not allowed to report smaller numbers than 5, including missing data on smaller than 5. The numbers have therefore been changed to mask these instances.

(Table S1). Children with CHD were more often born preterm compared with children born without CHD. Compared with mothers of unaffected children, mothers of children with CHD had more often pregestational diabetes and were of lower socioeconomic status. Birth weight Z score, head circumference Z score and childhood BMI did not differ between the 2 groups (Table 1).

Overall, no differences in mean age at achieving the pubertal milestones were observed in boys and girls with CHD (Figure 2 and Table 2). For the combined estimate, we observed a 1.5 (95% CI, -2.6 to 5.7) months difference among boys and a 1.0 (95% CI, -2.5 to 4.4) month difference among girls. The same pattern was observed when subdividing CHD into simple and complex CHD (Figure 3 and Table 3). Results remained

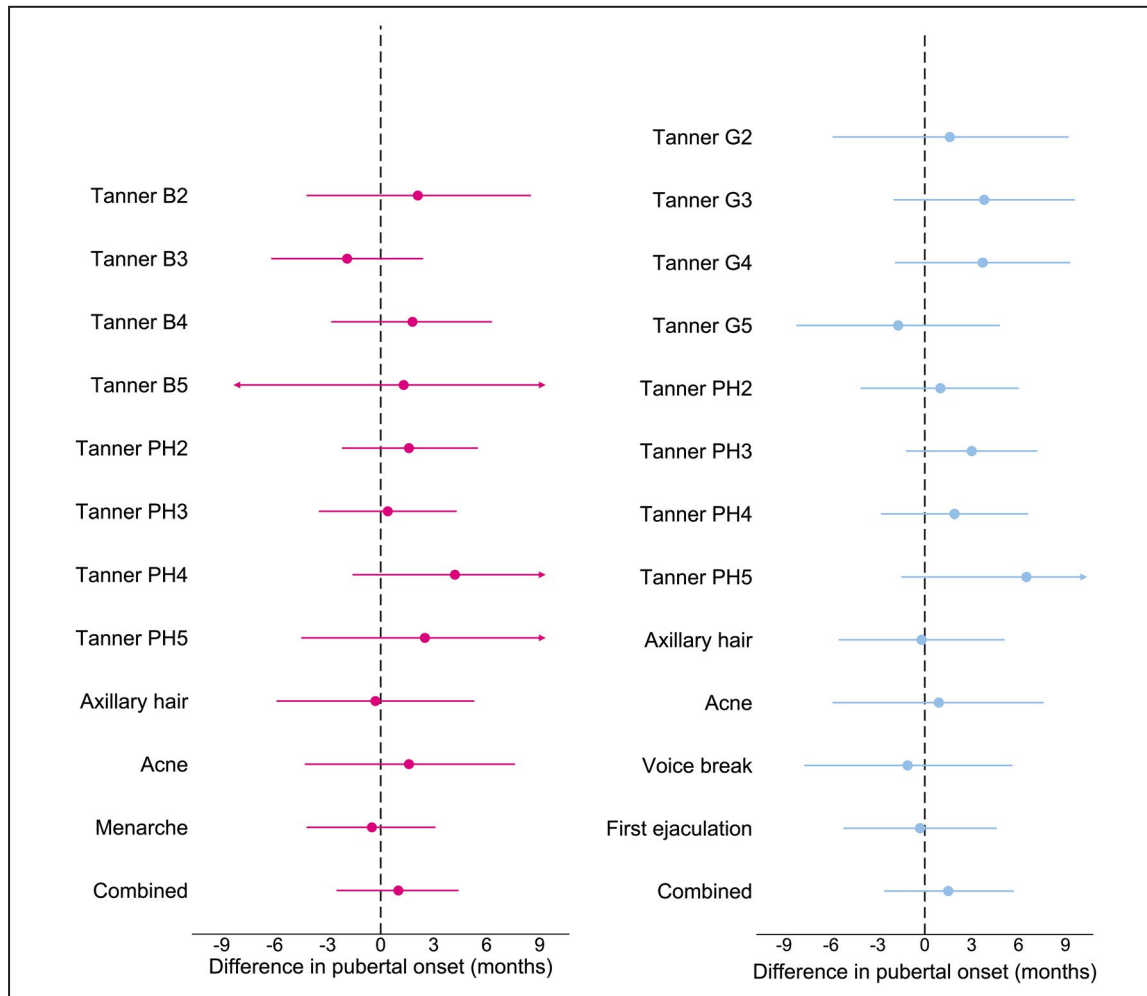
unchanged when we restricted the study population to children born at term (Table S6).

## DISCUSSION

This is the first nationwide cohort study evaluating pubertal timing in boys and girls with CHD in comparison with children without CHD. Children with CHD reached puberty at an age comparable with those born without CHD, both overall and when subdividing into simple and complex CHD. For the complex CHD group, however, we were not able to rule out a later pubertal development because of the few cases included. Results were consistent when evaluating pubertal timing in boys and girls born at term.

With the present study, we are the first to provide knowledge on pubertal development in children with





**Figure 2.** Adjusted mean differences in age at attaining different pubertal milestones in boys and girls according to congenital heart defects among 15 780 children in the Puberty Cohort, Denmark, 2012 to 2018. B1–B5 indicates Tanner stages of breast development; G1–G5, Tanner stages of genital development; and PH1–PH5, Tanner stages of pubic hair development.

simple CHD. Our findings are reassuring considering the increasing amount of literature suggesting that patients with simple CHD may not be as healthy as previously expected.<sup>48–55</sup> Despite ventricular and atrial septal defects traditionally being considered minor heart defects, growth impairment is described in fetal and neonatal life<sup>10–12</sup> and early childhood until closure.<sup>13,14</sup> Further, a Danish nationwide study evaluating BMI in 2679 children with CHD aged 1 to 15 years found an increased risk of underweight in children with simple defects, although less pronounced than children with severe defects. Although rapid catch-up growth in infancy has been associated with earlier onset of puberty,<sup>5</sup> the potentially continued growth impairment throughout early childhood may affect later physical growth.<sup>6,8</sup> Therefore, a pubertal delay might have been anticipated in children with simple heart defects. However, our findings of normal pubertal timing in this subgroup indicates that the prevalence, magnitude, or

duration of growth impairment in early life may not be significant enough to affect pubertal development. In children with complex CHD, we were unable to detect a pubertal delay. This may be explained by the low number of children in the group, as well as participation of, presumably, the healthiest children with complex CHD. As such, our group of children with complex defects is most likely not representative of all children with severe heart defects. In addition, our CHD group included no children with hypoplastic left heart syndrome, which generally has major impacts on growth.

Our knowledge on pubertal development in children with CHD is sparse. The available literature is limited to 9 studies, of which 8 reported only recalled age at menarche among adult women with CHD. In the Puberty Cohort, girls with CHD had their menarche at a mean age of 12.7 years, comparable with girls without CHD. Similar age at menarche was found by Opic et al., who included 136 Dutch women operated for

**Table 2. Mean Age and Adjusted Mean Monthly Differences in Age at Attaining Pubertal Milestones in Boys and Girls According to CHDs, Puberty Cohort, Denmark, 2012 to 2018**

Pubertal milestones	No CHD (ref.)	CHD	
	Mean age (y)*	Mean age (y)†	Adjusted mean monthly age difference from ref. (95% CI)‡
Boys <sup>§</sup>			
Tanner genital stage 2	10.9	11.1	0.7 (–8.2 to 9.5)
Tanner genital stage 3	12.5	12.8	3.1 (–3.6 to 9.3)
Tanner genital stage 4	13.7	14.0	3.3 (–2.9 to 9.5)
Tanner genital stage 5	15.8	15.8	–1.6 (–8.6 to 5.6)
Tanner pubic hair stage 2	11.3	11.4	1.0 (–4.4 to 6.5)
Tanner pubic hair stage 3	12.7	13.0	2.1 (–2.5 to 6.7)
Tanner pubic hair stage 4	13.5	13.7	1.6 (–3.6 to 6.8)
Tanner pubic hair stage 5	14.8	15.2	6.4 (–2.4 to 15.2)
Axillary hair	13.3	13.5	–1.2 (–6.9 to 4.5)
Acne	12.2	12.3	0.3 (–7.4 to 7.9)
Voice break	13.0	13.0	–1.3 (–8.8 to 6.2)
First ejaculation	13.3	13.3	–1.1 (–6.0 to 3.9)
Combined estimate	13.1	13.3	1.1 (–3.5 to 5.6)
Girls <sup>  </sup>			
Tanner breast stage 2	9.8	10.0	2.4 (–4.0 to 8.7)
Tanner breast stage 3	11.6	11.5	–2.0 (–6.5 to 2.4)
Tanner breast stage 4	13.0	13.1	1.7 (–3.0 to 6.4)
Tanner breast stage 5	16.0	16.1	0.9 (–8.9 to 10.6)
Tanner pubic hair stage 2	11.2	11.3	1.6 (–2.3 to 5.5)
Tanner pubic hair stage 3	12.5	12.4	0.0 (–4.0 to 4.0)
Tanner pubic hair stage 4	13.5	13.6	4.0 (–1.9 to 9.9)
Tanner pubic hair stage 5	15.5	15.4	2.2 (–4.5 to 9.6)
Axillary hair	11.9	11.8	–0.8 (–6.6 to 5.0)
Acne	11.4	11.7	1.1 (–5.1 to 7.2)
Menarche	13.0	13.0	–0.6 (–4.3 to 3.1)
Combined estimate	12.6	12.6	0.8 (–2.7 to 4.4)

CHD indicates congenital heart defects; and ref., reference cohort.

\*Crude mean age at pubertal milestones in boys and girls not exposed to CHD (reference group).

†Crude mean age at pubertal milestones in boys and girls exposed to CHD.

‡Adjusted for maternal age at menarche, maternal smoking during pregnancy, maternal body mass index before pregnancy, and socioeconomic status.

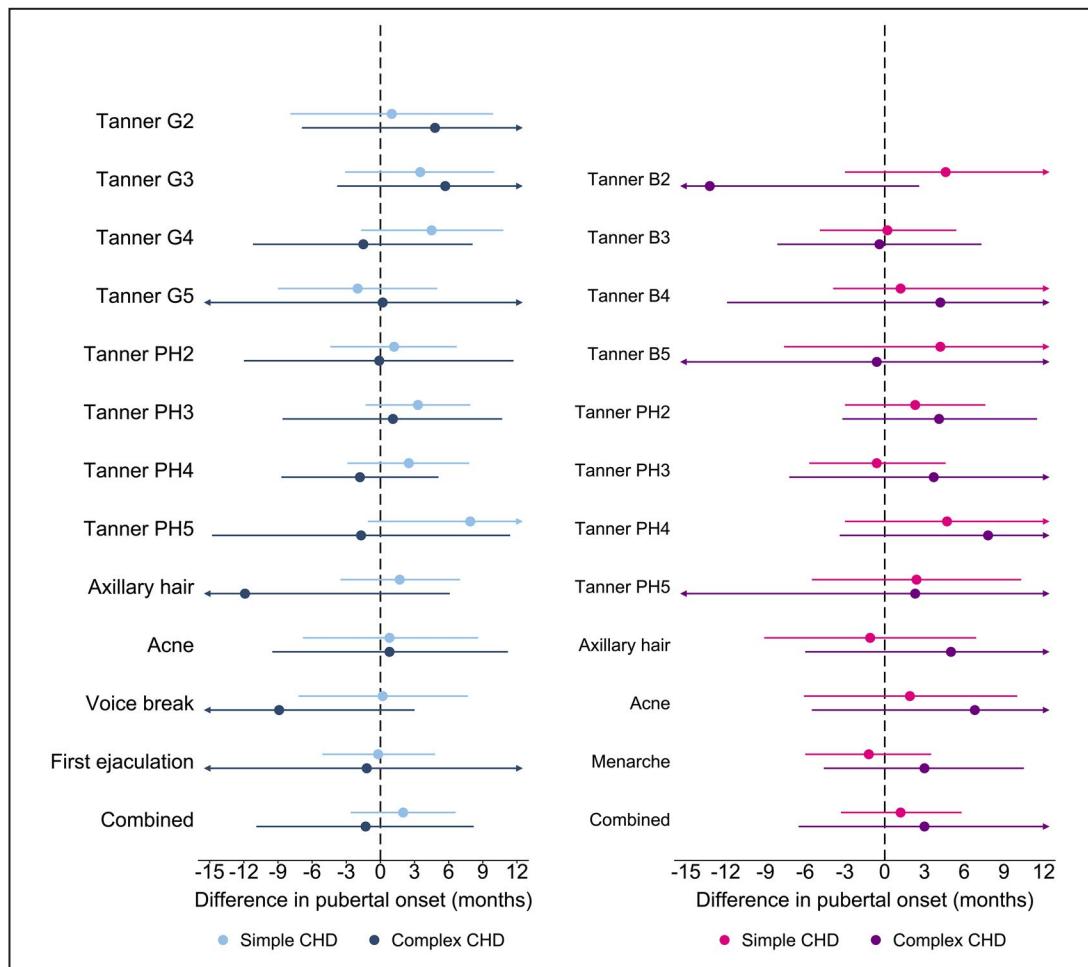
<sup>§</sup>n=7685.

<sup>||</sup>n=8095.

CHD.<sup>56</sup> In contrast, Drenthen et al. published a case-series of more than 1500 Dutch and Belgian women with CHD, reporting a slightly later age at menarche (13.3 years) in comparison with the general population (13.15 years).<sup>20</sup> The highest age at menarche was found in women with pulmonary hypertension including Eisenmenger (13.8 years), and complex CHD (14.1 years). These subgroups also had increased risk of primary amenorrhea (absence of menarche by 15 years of age) when compared with simple CHD women (odds ratio, 2.08; 95% CI, 1.25–3.47). Other studies also found later menarche in complex and cyanotic subgroups.<sup>22,57,58</sup> In women with Fontan circulation, representing those with highest grade of severity, 3 studies found later age at menarche when compared

with the general population.<sup>23–25</sup> To our knowledge, the Fontan population is the only CHD subgroup with previous assessment of Tanner stages. Using self-reported questionnaires, Menon et al. evaluated 299 American boys and girls with single ventricle physiology and found an average pubertal delay of 1.5 to 2.0 years compared with background population.<sup>19</sup>

Several limitations must be noted in the aforementioned studies. With the exception of Canobbio et al.,<sup>21</sup> all studies were case series with no comparison groups. The study populations mainly consisted of adult women, who retrospectively reported their age at menarche, which increased the risk of recall bias, and none of the studies adjusted for potential confounders. Nevertheless, higher severity of a heart defect may be associated with



**Figure 3. Adjusted mean differences in age at attaining different pubertal milestones in boys and girls according to subgroups of congenital heart defects, Puberty Cohort, Denmark, 2012 to 2018.**

B1–B5 indicates Tanner stages of breast development; CHD, congenital heart disease; G1–G5, Tanner stages of genital development; and PH1–PH5 Tanner stages of pubic hair development.

an increased risk of later onset of menarche, and, potentially, other pubertal milestones as well.

### Methodological Considerations

The main strength of this cohort study was the longitudinal design with information on several pubertal milestones collected every 6 months throughout puberty. This approach reduced the risk of recall bias. With detailed information on several maternal demographic, health, and lifestyle factors obtained during pregnancy, we had the ability to adjust for important potential confounders.

As gestational age may be related to pubertal timing, we performed a subanalysis restricting the study population to children born at term and found similar results to the main analyses. However, interpretation must be done with caution as gestational age may act as an intermediate factor in the path between CHD and puberty. In addition, conditioning on gestational age poses a risk of collider stratification bias, that

is, introducing bias in case of unmeasured common causes of the intermediate and puberty.<sup>59</sup>

The Puberty Cohort had a participation rate of 70%.<sup>60</sup> The prevalence of CHD in the Puberty Cohort is comparable with the prevalence worldwide,<sup>61,62</sup> and participation in the Puberty Cohort was found to be independent of pubertal timing in an earlier study.<sup>63</sup> As such, the risk of selection bias is considered limited. Selection weights were applied to further reduce potential selection bias. As recruitment into the cohort were performed by email or letter, the group of CHD children might only represent the healthier CHD population with mental resources to participate in such a cohort. The finding of normal childhood BMI in the group of CHD children support these speculations. In addition to the risk of live-birth bias, caution is therefore needed when extrapolating our results to the general CHD population.

We identified patients with CHD using the DNPR, and to improve the positive predictive value of the information used, only patients diagnosed at a university



**Table 3. Mean Age and Adjusted Mean Monthly Differences in Age at Attaining Pubertal Milestones in Boys and Girls According to Simple or Complex CHDs, Puberty Cohort, Denmark, 2012 to 2018**

Pubertal milestones	No CHD (ref.)	Simple CHD		Complex CHD	
	Mean age (y)*	Mean age (y)†	Adjusted mean monthly age difference from ref. (95% CI)‡	Mean age (y)†	Adjusted mean monthly age difference from ref. (95% CI)‡
<b>Boys<sup>§</sup></b>					
Tanner genital stage 2	10.9	11.0	1.0 (−7.9 to 9.9)	11.5	4.8 (−6.9 to 16.5)
Tanner genital stage 3	12.5	12.9	3.5 (−3.1 to 10.0)	13.1	5.7 (−3.8 to 15.2)
Tanner genital stage 4	13.7	14.1	4.5 (−1.7 to 10.0)	13.7	−1.5 (−11.2 to 8.1)
Tanner genital stage 5	15.8	15.8	−2.0 (−9.0 to 5.0)	15.7	0.2 (−17.7 to 18.1)
Tanner pubic hair stage 2	11.3	11.4	1.2 (−4.4 to 6.7)	11.5	−0.1 (−12.0 to 11.7)
Tanner pubic hair stage 3	12.7	13.2	3.3 (−1.3 to 7.9)	13.0	1.1 (−8.6 to 10.7)
Tanner pubic hair stage 4	13.5	13.8	2.5 (−2.9 to 7.8)	13.4	−1.8 (−8.7 to 5.1)
Tanner pubic hair stage 5	14.8	15.4	7.9 (−1.1 to 16.9)	14.6	−1.7 (−14.8 to 11.4)
Axillary hair	13.3	13.7	1.7 (−3.5 to 7.0)	13.1	−11.9 (−29.8 to 6.1)
Acne	12.2	12.4	0.8 (−6.8 to 8.6)	12.3	0.8 (−9.5 to 11.2)
Voice break	13.0	13.1	0.2 (−7.2 to 7.7)	12.7	−8.9 (−20.9 to 3.0)
First ejaculation	13.3	13.4	−0.2 (−5.1 to 4.8)	13.6	−1.2 (−19.6 to 17.2)
Combined estimate	13.1	13.4	2.0 (−2.6 to 6.6)	13.2	−1.3 (−10.9 to 8.2)
<b>Girls<sup>  </sup></b>					
Tanner breast stage 2	9.8	10.0	4.6 (−3.0 to 12.2)	9.3	−13.2 (−29.0 to 2.6)
Tanner breast stage 3	11.6	11.4	0.2 (−4.9 to 5.4)	11.7	−0.4 (−8.1 to 7.3)
Tanner breast stage 4	13.0	13.0	1.2 (−3.9 to 20.3)	13.5	4.2 (−11.9 to 20.3)
Tanner breast stage 5	16.0	16.0	4.2 (−7.6 to 16.0)	13.7	−0.6 (−23.4 to 22.4)
Tanner pubic hair stage 2	11.2	11.2	2.3 (−3.0 to 7.6)	11.4	4.1 (−3.2 to 11.5)
Tanner pubic hair stage 3	12.5	12.3	−0.6 (−5.7 to 4.6)	12.9	3.7 (−7.2 to 14.7)
Tanner pubic hair stage 4	13.5	13.5	4.7 (−3.0 to 12.4)	14.2	7.8 (−3.4 to 19.0)
Tanner pubic hair stage 5	15.5	15.3	2.4 (−5.5 to 10.3)	15.8	2.3 (−16.0 to 20.5)
Axillary hair	11.9	11.6	−1.1 (−9.1 to 6.9)	12.5	5.0 (−6.0 to 16.1)
Acne	11.4	11.6	1.9 (−6.1 to 10.0)	12.1	6.8 (−5.5 to 19.1)
Menarche	13.0	12.7	−1.2 (−6.0 to 3.5)	13.7	3.0 (−4.6 to 10.5)
Combined estimate	12.6	12.5	1.2 (−3.3 to 5.8)	13.2	3.0 (−6.5 to 12.5)

CHD indicates congenital heart defects; and ref., reference cohort.

\*Crude mean age at pubertal milestones in boys and girls not exposed to CHD (reference group).

†Crude mean age at pubertal milestones in boys and girls exposed to CHD.

‡Adjusted for maternal age at menarche, maternal smoking during pregnancy, maternal body mass index before pregnancy, and socioeconomic status.

§n=7685.

||n=8095.

hospital were included. Based on a previous validation study on the DNPR, this strategy reduces the risk of misclassification of simple CHD diagnoses in particular, although some of the milder cases may be excluded.<sup>64</sup> Any potential misclassification is expected to be independent of future pubertal development. Information on pubertal milestones was obtained from self-reported questionnaires. A study within the Puberty Cohort compared the self-assessed Tanner stages with clinical examination and found fair to moderate agreement for most pubertal milestones with no systematic under- or overestimation.<sup>65,66</sup>

Although the Puberty Cohort is one of the largest of its kind worldwide, only 137 children diagnosed with CHD were included. We consequently lacked power to differentiate into smaller subgroups of CHD and to investigate the potential effect of surgical repair. Unfortunately, we did not have the possibility to assess participants' medical records. Thus, we were therefore unable to obtain information on New York Heart Association Functional Classification, ventricular function, B-natriuretic peptide levels, and heart-related complications. The Puberty Cohort primarily consist of White people, reflecting the Danish population, and

ethnicity-based differences were therefore not evaluated in the present study.

## CONCLUSIONS

This is the first nationwide cohort study to investigate pubertal development in children with CHD, including simple defects and various pubertal milestones. Overall, we found no difference in pubertal timing between children born with CHD and children born without. For the complex CHD, we were not able to rule out a later pubertal development. However, the findings for children with simple CHD are encouraging information to patients and their parents. Although such findings need to be explored in larger longitudinal studies, it adds to the limited knowledge on pubertal development in children with CHD.

## ARTICLE INFORMATION

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### Affiliations

Department of Cardiothoracic Surgery, Copenhagen University Hospital, Copenhagen, Denmark (L.F.U., V.E.H.); Department of Clinical Medicine, Copenhagen University, Copenhagen, Denmark (L.F.U., V.E.H.); Department of Public Health, Research Unit for Epidemiology, Aarhus University, Aarhus, Denmark (L.F.U., A.G., L.H.A., N.B., L.L.L., A.E., C.H.R.); Department of Obstetrics and Gynaecology, Horsens Regional Hospital, Horsens, Denmark (L.H.A., U.B.K.); Department of Clinical Genetics, Aarhus University Hospital, Aarhus, Denmark (N.B.); and Department of Clinical Medicine, Aarhus University, Aarhus, Denmark (U.B.K.).

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### Disclosures

None.

### Supplemental Material

Data S1–S3  
Tables S1–S6

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# **Supplemental Material**

## **Data S1.**

### **Information on the derivation of selection weights.**

Despite a participation rate of 70% of the 22,439 children invited for participation in the Puberty Cohort, selection weights were used to account for potential underlying selective mechanisms (47). Weights were derived using a logistic regression model predicting the individuals' probability for participation. This was done for each sex separately. The models included the primary exposure variable (congenital heart defect: yes, no) and the potential confounding factors as explanatory variables for participation. These factors were highest social status of parents, maternal pre-pregnancy BMI (as second-order polynomial), maternal age at menarche, maternal age at delivery (as second-order polynomial), maternal smoking in first trimester, maternal pregestational diabetes, preterm birth, and birthweight. The probability for participation were transformed into selection weights by taking the inverse of the probability. By reweighting the 15,819 participating children, the resulting pseudopopulation was representative of the 22,439 invited children, if our assumptions of the potential selective mechanisms were correct.

## **Data S2.**

### **The logistic regression model used for the derivation of selections weight for boys in the Puberty Cohort:**

```
Logit participation_boys i. SES c.pre_BMI#pre_BMI i.mat_AAM i.birth_before_week37  
c.mat_age#mat_age i.smoking_1trim c.weight#weight i.preges_diabetes i.CHD if sex==1
```

## **Data S3.**

### **The logistic regression model used for the derivation of selections weight for girls in the Puberty Cohort:**

```
Logit participation_girls i. SES c.pre_BMI#pre_BMI i.mat_AAM i.birth_before_week37  
c.mat_age#mat_age i.smoking_1trim c.weight#weight i.preges_diabetes i.CHD if sex==2
```



**Table S1. Categorization of congenital heart defects (CHD) into simple and complex subgroups, 11 subtypes, diagnostic ICD-10 codes, and the number of individuals included.**

<b>Severity</b>	<b>Subtypes</b>	<b>ICD-10 codes</b>	<b>n =</b>
Simple CHD	Ventricular septal defect	Q21.0	30
	Atrial septal defect	Q21.1	24
	Coarctatio of the aorta	Q25.1	5
	Pulmonary valve disease	Q22.1, Q25.6	7
	Aortic valve disease	Q23.0, Q23.1, Q23.1A	11
	Mitral valve disease	Q23.3, Q23.8	8
	Patent ductus arteriosus*	Q25.0	11
	Simple miscellaneous	Q21.9, Q24.8, Q24.9, Q26.4	15
Complex CHD	TGA, TOF, and PA	Q20.1, Q20.3, Q21.3, Q22.0	10
	Atrioventricular septal defect	Q21.2	5
	Complex miscellaneous	Q20.0, Q20.8, Q20.9, Q25.2, Q25.4, Q25.5, Q25.9, Q26.2, Q26.8	11

ICD-10 = International Classification of Diseases, Tenth Revision, CHD = congenital heart defect, TGA = transposition of the great arteries, TOF = Tetralogy of Fallot, PA = pulmonary atresia

\*Only included if born after gestational week 37

**Table S2. Output from the logistic regression model for boys.**

<b>Boys:</b>	Coefficient	Standard error	95% Conf. Interval
SES			
	2 -0.41	0.04	-0.50; -0.33
	3 -0.66	0.12	-0.89; -0.43
pre_BMI^2	-4.60e-04	8.05e-05	-6.18e-04; -3.02e-04
mat_AAM			
Same time as peers	0.02	0.05	-0.07; 0.12
Later than peers	0.10	0.07	-0.03; 0.23
birth_bef_week37	0.17	0.09	0.00; 0.34
mat_age	2.33e-04	7.85e-05	7.96e-05; 3.87e-04
smoking	-0.37	0.04	-0.45; -0.28
birthweight^2	1.76e-08	5.45e-09	6.88e-09; 2.83e-08
pregest_diabetes	0.02	0.13	-0.22; 0.27
CHD	-0.45	0.19	-0.82; -0.07
_cons	0.85	0.12	0.61; 1.09

**Table S3. Predicted probability of participation among boys.**

Variable	Obs	Mean	Std. Dev.
participation_boys	7,436	0.684	0.077

Based on this model, the predicted probability of participation in the Puberty Cohort among all boys invited was 68.4 %.

**Table S4. Output from the logistic regression model for girls.**

<b>Girls:</b>	Coefficient	Standard error	95% Conf. Interval
SES			
	2 -0.41	0.05	-0.50; -0.31
	3 -.4374545	.1288801	-0.69; -0.18
pre_BMI^2	-4.88e-04	8.55e-05	-6.55e-04; -3.20e-04
mat_AAM			
Same time as peers	0.04	.05	-0.06; 0.15
Later than peers	0.00	0.07	-0.14; 0.14
birth_bef_week37	-0.05	0.09	-0.23; 0.14
mat_age^2	2.90e-04	8.52e-05	1.23e-04; 4.60e-04
smoking	-0.37	0.05	-0.46; -0.27
birth weight^2	2.48e-08	6.56e-09	1.20e-08; 3.77e-08
pregest_diabetes	-0.30	0.13	-0.43; 0.43
CHD	0.00	0.22	-0.41; 0.45
_cons	1.09	0.14	0.83; 1.36

**Table S5. Predicted probability of participation among girls.**

<u>Variable</u>	<u>Obs</u>	<u>Mean</u>	<u>Std. Dev.</u>
participation_girls	7,857	0.748	0.070

Based on this model, the predicted probability of participation in the Puberty Cohort among all girls invited was 74.8 %.



**Table S6. Mean age and adjusted mean monthly differences in age at attaining pubertal milestones in boys and girls born at term according to congenital heart defects, Puberty Cohort, Denmark, 2012-2018.**

Pubertal Milestones	No CHD (ref.)	CHD	
	Mean age (years)*	Mean age (years)†	Adjusted mean monthly age difference from ref. (95% CI)‡
<b>Boys§</b>			
Tanner genital stage 2	10.9	11.1	0.7 (-8.2; 9.5)
Tanner genital stage 3	12.5	12.8	3.1 (-3.6; 9.3)
Tanner genital stage 4	13.7	14.0	3.3 (-2.9; 9.5)
Tanner genital stage 5	15.8	15.8	-1.6 (-8.6; 5.6)
Tanner pubic hair stage 2	11.3	11.4	1.0 (-4.4; 6.5)
Tanner pubic hair stage 3	12.7	13.0	2.1 (-2.5; 6.7)
Tanner pubic hair stage 4	13.5	13.7	1.6 (-3.6; 6.8)
Tanner pubic hair stage 5	14.8	15.2	6.4 (-2.4; 15.2)
Axillary hair	13.3	13.5	-1.2 (-6.9; 4.5)
Acne	12.2	12.3	0.3 (-7.4; 7.9)
Voice break	13.0	13.0	-1.3 (-8.8; 6.2)
First ejaculation	13.3	13.3	-1.1 (-6.0; 3.9)
Combined estimate	13.1	13.3	1.1 (-3.5; 5.6)
<b>Girls  </b>			
Tanner breast stage 2	9.8	10.0	2.4 (-4.0; 8.7)
Tanner breast stage 3	11.6	11.5	-2.0 (-6.5; 2.4)
Tanner breast stage 4	13.0	13.1	1.7 (-3.0; 6.4)
Tanner breast stage 5	16.0	16.1	0.9 (-8.9; 10.6)
Tanner pubic hair stage 2	11.2	11.3	1.6 (-2.3; 5.5)
Tanner pubic hair stage 3	12.5	12.4	0.0 (-4.0; 4.0)
Tanner pubic hair stage 4	13.5	13.6	4.0 (-1.9; 9.9)
Tanner pubic hair stage 5	15.5	15.4	2.2 (-4.5; 9.6)
Axillary hair	11.9	11.8	-0.8 (-6.6; 5.0)
Acne	11.4	11.7	1.1 (-5.1; 7.2)
Menarche	13.0	13.0	-0.6 (-4.3; 3.1)
Combined estimate	12.6	12.6	0.8 (-2.7; 4.4)

CHD = congenital heart defects, ref. = reference cohort, CI = confidence interval

\*Crude mean age at pubertal milestones in boys and girls not exposed to congenital heart defects (reference group)

†Crude mean age at pubertal milestones in boys and girls exposed to congenital heart defects

‡Adjusted for maternal age at menarche, maternal smoking during pregnancy, maternal body mass index before pregnancy, and socioeconomic status

§n = 7,038

||n = 7,551