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Clinical Research Article

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Pubarche and Gonadarche Onset and Progression Are Differently Associated With Birth Weight and Infancy Growth Patterns

Christine Wohlfahrt-Veje,[1,2] Jeanette Tinggaard,[1,2] Anders Juul,[1,2] Jorma Toppari,[2,3] Niels E. Skakkebæk,[1,2] and Katharina M. Main[1,2]

[1]Department of Growth and Reproduction and EDMaRC, Copenhagen University Hospital–Rigshospitalet, DK-2100 Copenhagen, Denmark; [2]International Center for Research and Research Training in Endocrine Disruption of Male Reproduction and Child Health (EDMaRC), Rigshospitalet, University of Copenhagen, DK-2100 Copenhagen, Denmark; and [3]Institute of Biomedicine, Research Center of Integrative Physiology and Pharmacology, University of Turku, and Department of Pediatrics, Turku University Hospital, 20521 Turku, Finland

ORCiD numbers: 0000-0002-8920-950X (C. Wohlfahrt-Veje); 0000-0002-5317-1079 (J. Tinggaard); 0000-0002-0534-4350 (A. Juul); 0000-0003-2228-334X (J. Toppari); 0000-0001-7259-1039 (K. M. Main).

Abbreviations: AGA, appropriate for gestational age; B2, thelarche; BMI, body mass index; G2, gonardarche; HPG, hypothalamic-pituitary-gonadal; IGF-1, insulin-like growth factor 1; LGA, large for gestational age; OR, odds ratio; PH2, pubarche; SDS, SD score; SGA, small for gestational age; Tvol3+, testis size greater than 3 mL; WGA, weight for gestational age.

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Abstract

Context: Controversy exists regarding associations between early-life growth patterns and timing of puberty.

Objective: This work aims to investigate associations between birth anthropometry, early growth patterns, and onset/progression of pubertal milestones in boys and girls.

Methods: Among children examined at birth (1997-2003) and at age 36 months in a mother-child cohort, pubertal Tanner stages (B1-5, PH1-5, G1-5) and testicular volume were examined by trained physicians at 1 to 5 follow-up examinations during childhood and adolescence (672 girls and 846 boys, 2006-2013). With parametric survival models we analyzed associations between birth weight, changes in SD scores (SDS) from birth to 36 months (ΔSDS 0-36 > 0.67 SD defining catch-up growth), and age at pubertal onset/attainment of late pubertal stages/menarche.

Results: A 1-kg higher birth weight was associated with earlier onset of B2+ (thelarche): –3.9 months (CI, –6.7 to –1.1 months), G2+ (gonadarche): –2.7 months (–5.3 to –0.1 months), Tvol3+ (testis size > 3 mL): –2.8 months (CI, –4.9 to –0.7 months), but with later G4+ and PH4+ in boys, and a slower progression from B2 to menarche (5.3 months [CI, 1.2 to 9.4 months]) in girls. Catch-up growth was associated with earlier PH2+ (pubarche) in

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girls (–4.1 months [CI, –7.6 to –0.6 months]), earlier PH2+ in boys (–3.4 months [CI, –6.6 to –0.2 months]), faster progression from B2 to menarche in girls (–9.1 months [CI, 14.6 to 3.5 months]), and earlier G4+ and PH4+ in boys.

Conclusion: Associations between birthweight and infancy catch-up growth differed for gonadarche and pubarche, and for early and late pubertal markers, with similar patterns in both sexes.

Key Words: puberty, gonadarche, thelarche, menarche, catch-up growth

A large and poorly understood normal variation exists for the timing and progression of pubertal development. Some, but not all, of this variation seems to depend on genetics [1]. During recent decades trends toward earlier pubertal onset have been observed [2, 3].

Prenatal and postnatal growth patterns (birth weight and early catch-up growth) have been associated with timing of puberty [4, 5], but some of the epidemiological studies are conflicting. Some studies have shown associations between low birth weight and earlier menarche [6, 7]; a large study of more than 90 000 UK women showed that menarche occurred earlier in those born with low birth weight [8]. Other studies have found that being large at birth may also be associated with earlier pubertal development [9-11]. Similarly, studies have reported that being born preterm [12] or being small for gestational age (SGA) was associated with earlier pubertal development [13, 14], while a large Chinese study found that higher gestational age (as a continuous variable) was associated with earlier onset of thelarche in girls [15].

Pubertal maturation consists of 2 associated processes: adrenarche, the reappearance of adrenal androgen production in childhood, and gonadarche, the pubertal reactivation of the hypothalamic-pituitary-gonadal axis (HPG). In boys, a testis volume above 3 mL, or signs of androgenization (Tanner stage G2) are used as markers of gonadarche. In girls, the ovaries are not as easily examined as the gonads in boys, and the appearance of breast tissue development (thelarche) is used as a proxy of gonadarche. Pubarche, the appearance of pubic hair, is a pubertal manifestation that is linked to androgens and may be caused by gonadarche or adrenarche.

Many studies rely on questionnaire data on age of menarche (which is a late pubertal event), or self-reported pubertal status, which may introduce a bias [16]. Few studies have investigated associations between growth patterns and pubertal timing (eg, time at voice break) in boys [17, 18].

In our longitudinal birth cohort with children followed from birth to puberty, we have a unique opportunity to combine detailed information on infant growth with pubertal onset and progression. We aimed to investigate the associations between prenatal and early postnatal growth patterns and the timing of thelarche/gonadarche and pubarche as well as late pubertal markers both in boys and girls. We hypothesized that low and high birth weight could both be associated with the timing of pubertal development and that associations could differ for markers of gonadarche and pubarche as well as for early and late pubertal markers.

Materials and Methods

In a large, prospective mother-child cohort, Danish children (846 boys and 672 girls) born between 1997 and 2003 attended 1 to 5 annual pubertal evaluations between 2006 and 2013 (n = 4123, aged 4.5-14.9 years) (participation rate = 57.3%). Weight, length, and gestational age at birth were retrieved from birth records (missing data: birth weight n = 3, birth length = 9, gestational age n = 20). Height, weight, and skinfolds were measured at birth, and at 18 and 36 months (in 91.5% and 83.9% of children in the follow-up), and fat percentage was calculated from skinfolds as earlier described [19]. Height was measured lying down from birth to 18 months and thereafter standing height was used. Age- and sex-specific SD scores (SDS) for weight, height, body mass index (BMI), and fat percentage at all time points were calculated using reference data from Danish children [19, 20]. Changes in SDS (ΔSDS) over time were calculated by subtraction (eg, ΔSDS 0-36 = SDS36-SDS0). Catch-up growth was defined as ΔSDS greater than 0.67 SD according to earlier studies [21].

Prematurity was defined as a gestational age of less than 37 weeks. Weight for gestational age (WGA) was expressed as the deviation (%) from the expected mean WGA [22]. SGA was defined as birth weight deviation below –22% (–2 SD) and large for gestational age (LGA) above 22% (2 SD).

Pubertal stages in girls was evaluated as B1 to B5 and PH1 to PH5 by inspection according to Tanner [23] as well as palpation, thus minimizing misclassification of fat tissue as breast development. The girls were asked if they had started menstrual bleeding since the last examination. Onset of puberty greater than or equal to B2 or greater than or equal to PH2 was defined as thelarche (B2+) or pubarche (PH2+) [24, 25]. In boys, pubertal stages were evaluated by inspection as G1 to G5 and PH1 to PH5 [26] and

testicular volume was measured by Prader orchidometer (palpation). Onset of puberty in boys (gonadarche) was defined as testicular volume greater than 3 mL (tvol3+), genital stage greater than or equal to 2 (G2+), or pubarche, which was defined as pubic hair stage greater than or equal to 2 (PH2+) [27, 28]. If testicular volumes of the 2 testes were not equal, the larger testis measurement was used. Likewise, if a girl had a larger breast stage on one side, this stage was used. The physicians in the study participated in repetitive workshops to ensure and maintain standardization. Interobserver agreement was high [16], and sensitivity and specificity of thelarche was very high when evaluated toward glandular breast tissue by magnetic resonance imaging [29] in a small subgroup of girls.

In all children the longitudinal course was evaluated. If transient pubertal maturation was observed (eg, breast development appearing at one examination but not at the next) [30], we excluded this observation in the models until a consistent pubertal onset was observed (No. of excluded examinations: B2+: n = 33, Tvol3+: n = 1, PH2+: n = 8, G2+: n = 52).

Late pubertal markers were defined as: menarche, B4+, G4+, and PH4+. Progression time from onset to late pubertal markers were defined as time from B2+ to B4+, B2 to menarche, and G2+ to G4+ (ΔB2-menarche, ΔB2-B4 and ΔG2-G4).

When possible (in 41.2%), we assessed whether the children started with gonadarche/thelarche, pubarche, or both at the same examination (synchronous).

Statistics

We used parametric survival models (Proc Lifereg, Statistical Analysis Software Inc, version 9.3) to estimate the impact of birth anthropometry and growth parameters on pubertal timing. Owing to 1-year intervals between examinations, the precise age of a given pubertal milestone was not known. The last age when the child had not reached a given stage, and the ages at which he or she first did, were used as interval-censored data. Some of the children had signs of pubertal development already at the first examination (154 boys and 373 girls), and some children did not develop signs of puberty during the follow-up (388 boys and 158 girls). These data were included in models as left- and right-censored data, respectively. If a precise age of menarche could be obtained, this age was used as noncensored data. Associations with progression time were estimated using the lowest possible time interval and highest possible interval for censoring.

All estimates are given in months with 95% CI.

Because birth weight and postnatal weight catch-up growth were strongly inversely correlated, we also performed (mediation) analyses of birth weight adjusting for catch-up growth (ΔSDS weight 0-36 months > 0.67 SD: yes/no) and analyses of catch-up growth including birth weight (continuous variable).

Parental pubertal timing has earlier been shown to explain a large part of the variation within pubertal timing of the children in this cohort [1] and this was adjusted for in all analyses. Models for breast development and menarche were adjusted for maternal menarcheal age (as a continuous variable) and pubertal timing of the father (categorized as early, average, or late compared to peers). All other models were adjusted for paternal and maternal pubertal timing (categorized as early, average, or late compared to peers).

Group differences in birth and growth outcomes between children in the total birth cohort and children participating in the puberty follow-up, as well as between children starting with the pubarche and gonadarche pathway, were tested with *t* test for continuous variables and Fisher exact chi-square test for categorical variables.

Results

Birth and growth characteristics as well as estimated median ages at pubertal milestones and progression times between pubertal onset and late markers for children participating in the puberty follow-up are shown in Table 1. Birth and growth characteristics in participating children did not differ from children in the total birth cohort except for the proportion of SGA girls, which was slightly higher in the group who participated (7.6% compared to 6.0% in total cohort).

Associations Between Birth Weight and Pubertal Timing

In girls a higher birth weight was associated with earlier B2+ and a slower progression from B2 to B4 and B2 to menarche. Birth weight was not associated with PH2+ (Fig. 1A). Excluding SGA and LGA girls from the analyses gave similar results. Including only appropriate for gestational age (AGA) girls born at term, CIs increased and became insignificant for B2+.

Greater birth length was associated with earlier B2+ in girls, slower progression, and later menarche (Table 2). Associations were similar for BMI at birth and fat percentage at birth (although mostly nonsignificant) (see Table 2).

In boys a higher birth weight was associated with earlier G2+ and Tvol3, a later G4+ and PH4+, and a nonsignificant tendency to slower progression from G2+ to G4+. There was no association with PH2+ (Fig. 1B). Excluding SGA and LGA children from the analyses and including only AGA boys born at term gave similar associations. In boys, greater birth length was associated with earlier Tvol3+ and G2+ but later G4+ and PH4+ (Table 3). BMI and

fat percentage SDS at birth showed similar (mostly non-significant) associations (see Table 3).

Associations Between Being Born Preterm, Small for Gestational Age or Large for Gestational Age and Pubertal Timing

In girls, being born preterm was associated with later B2+, but earlier PH2+ (see Table 2). Gestational age as a continuous variable showed similar associations.

In boys, no significant effect of being born preterm was found, but lower gestational age was associated with earlier G4+ and PH4+ (see Table 3).

SGA and LGA girls both showed a tendency to earlier pubertal development, although this was significant for LGA only with B4+ (see Table 2).

In boys, being born SGA was associated with earlier PH4+, and being born LGA was associated with earlier G2+ and Tvol3+ (see Table 3).

Associations Between Postnatal Growth and Pubertal Timing

In girls, having significant catch-up growth (Δweight SDS > 0.67 from birth to 36 months) was associated with earlier PH2+, PH4+, menarche, and faster progression from

Table 1. Characteristics of all girls and boys in the puberty follow-up, estimated mean ages at pubertal milestones, and progression time between pubertal onset and late puberty markers

	Girls	Boys
	N = 672	N = 846
Gestational age, mean (SD), d	277 (14)	278 (13)
Preterm < wk 37, n (%)	57 (8.7%)	64 (7.6%)
Birth wt, mean (SD), g	3387 (638)	3520 (609)
Birth length, mean (SD), cm	51.3 (3.0)	52.1 (2.9)
WGA %[a], mean (SD)	–1.8 (13.8)	–1.5 (13.0)
SGA (WGA < –22%), n (%)	50 (7.6%)	43 (5.1%)
LGA (WGA > 22%), n (%)	21 (3.2%)	24 (2.9%)
BMI at birth, mean (SD)	12.8 (1.5)	12.9 (1.4)
Fat % 0 mo, mean (SD)	9.5 (2.4)	9.5 (2.5)
Wt 18 mo, mean (SD), kg	11.0 (1.18)	11.7 (1.24)
Wt SDS[b] 18 mo, mean (SD)	–0.08 (1.00)	–0.09 (1.00)
Wt catch-up (ΔSDS 0-18 mo > 0.67), n (%)	180 (29.4%)	239 (30.8%)
Wt 36 mo, mean (SD), kg	14.5 (1.68)	14.9 (1.64)
Wt SDS[b] 36 mo, mean (SD)	–0.07 (1.05)	–0.08 (1.05)
Wt catch-up ΔSDS 0-36 mo, mean (SD)	0.06 (1.17)	0.09 (1.16)
Wt catch-up (ΔSDS 0-36 mo > 0.67), n (%)	165 (29.9%)	226 (31.4%)
Ht 18 mo, mean (SD), cm	81.8 (2.84)	83.5 (2.94)
Ht SDS[b] 18 mo, mean (SD)	–0.07 (0.99)	–0.08 (1.0)
Ht catch-up (ΔSDS 0-18 mo > 0.67), n (%)	159 (25.9%)	230(29.3%)
Ht 36 mo, mean (SD), cm	95.8 (3.66)	97.2 (3.62)
Ht SDS 36[b] mo, mean (SD)	–0.08 (1.0)	–0.07 (1.1)
Ht catch-up ΔSDS 0-36 mo, mean (SD)	0.01(1.24)	0.10 (1.13)
Ht catch-up (ΔSDS 0-36 mo > 0.67), n (%)	158(28.8%)	217 (30.7%)
Mean age (95% CI) at B2+, G2+/tvol3+, y	9.95 (9.82-10.09)	11.46 (11.34-11.58)/11.56 (11.46-11.66)
Mean age (95% CI) at B3+, G3, y	11.40 (11.29-11.51)	12.94 (12.82-13.05)
Mean age (95% CI) at B4+, G4+, y	12.75 (12.63-12.87)	13.67 (13.53-13.81)
Mean age (95% CI) at PH2+, y	10.99 (10.87-11.12)	11.89 (11.77-12.00)
Mean age (95% CI) at PH3+, y	12.00 (11.88-12.11)	13.23 (13.08-13.37)
Mean age (95% CI) at PH4+, y	12.93 (12.81-13.06)	13.99 (13.77-14.21)
Time (95% CI), B2-B4, G2-G4, y	3.02 (2.77-3.27)	2.17 (1.90-2.45)
Mean age (95% CI) at menarche, y	12.99 (12.86-13.12)	–
Time (95% CI) from B2 to menarche, y	3.3 (3.1-3.5)	–

Abbreviations: B2, thelarche; BMI, body mass index; G2, gonadarche; LGA, large for gestational age; PH2, pubarche; SDS, SD score; SGA, small for gestational age; WGA, weight for gestational age.

[a]WGA is expressed as the deviation (%) from the expected mean WGA [22].

[b]Age and sex-specific SDS for weight, height, BMI, and fat percentage were calculated using reference data from Danish children [19, 20].

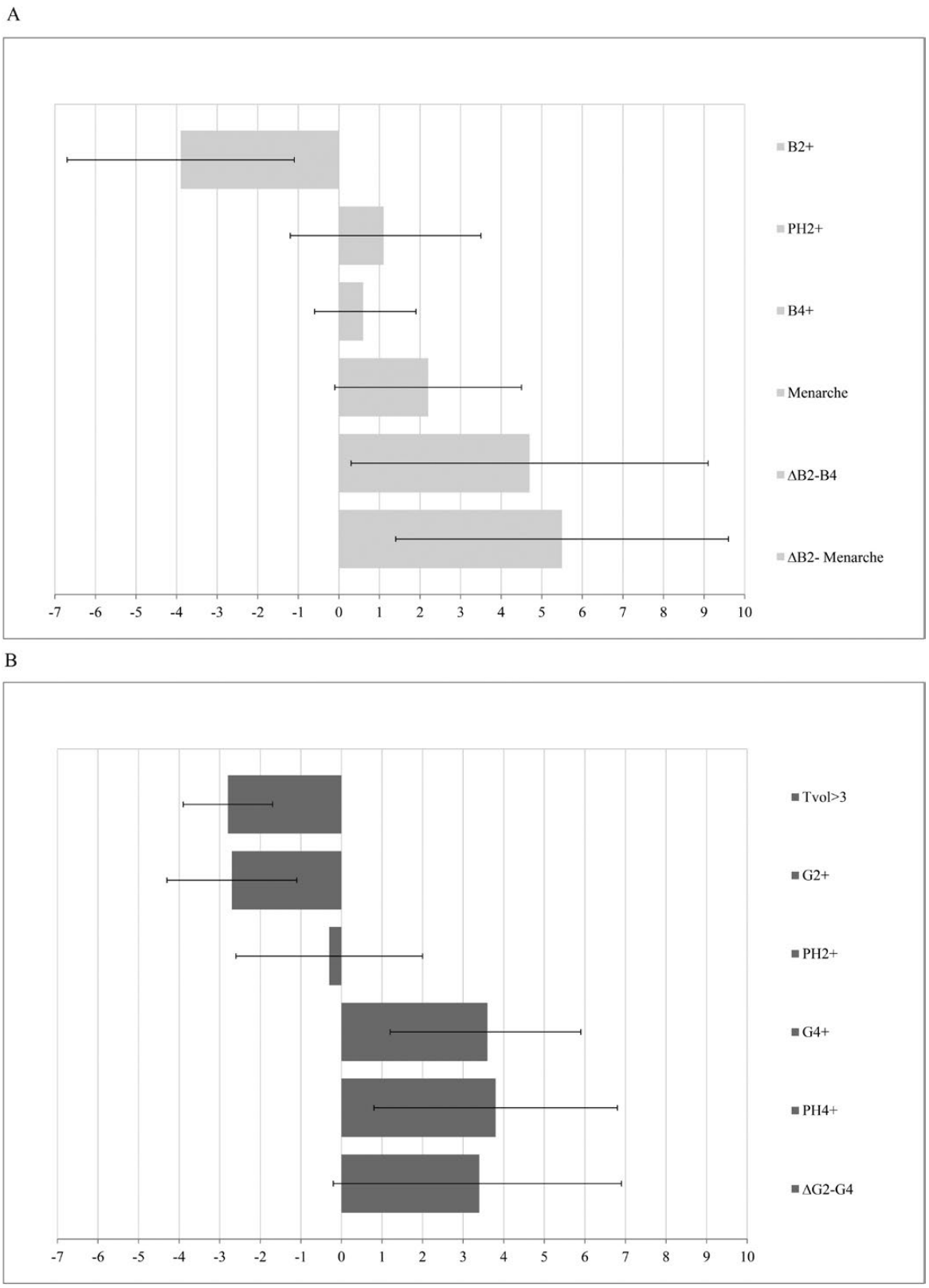

Figure 1. Effect estimates in A, light gray, girls, and B, dark gray boys, given in months with 95% CI (whiskers) for a 1-kg increase in birth weight on timing of pubertal markers and time between attainment of thelarche (B2) to B4, B2 to menarche, gonadarche (G2) to G4.

Table 2. Associations between birth and growth parameters and age at Tanner stages B2+, B3+, B4+, PH2+, PH3+, PH4+, and menarche in girls

Girls	B2+[a]	PH2+[b]	B4+[a]	Menarche[a]	B2-B4[a]	B2-menarche[a]
Birth wt SDS (SD)	**–2.1 (–3.7 to –0.5)**[i]	0.5 (–0.8 to 1.8)	0.3 (–1.0 to 1.6)	1.2 (–0.1 to 2.5)	**2.6 (0.1 to 5.0)**[b]	**2.8 (0.4 to 5.2)**[b]
Birth wt (kg)[c]	**–5.0 (–8.4 to –1.7)**[i]	–1.1 (–4.1 to 1.8)	0.3 (–2.5 to 3.1)	1.0 (–1.7 to 3.8)	**5.7 (0.5 to 10.9)**[b]	4.5 (–0.3 to 9.3)
Birth length, cm	**–0.6 (–1.2 to –0.0)**[b]	0.2 (–0.3 to 0.7)	0.4 (–0.1 to 0.9)	**0.5 (0.1 to 1.0)**[b]	**1.0 (0.1 to 2.0)**[b]	**1.3 (0.4 to 2.3)**[i]
Birth length SDS (SD)	**–1.5 (–3.1 to 0.0)**[b]	0.4 (–0.9 to 1.8)	–0.2 (–1.4 to 1.1)	0.8 (–0.4 to 2.0)	2.1 (–0.3 to 4.5)	**3.2 (0.7 to 5.7)**[b]
Birth BMI SDS (SD)	–0.8 (–2.5 to 0.9)	1.2 (–0.2 to 2.6)	0.7 (–0.7 to 2.0)	**1.4 (0.0 to 2.7)**[b]	1.6 (–0.9 to 4.0)	2.0 (–0.4 to 4.4)
Fat % 0 mo SDS (SD)	–1.1 (–3.2 to 1.0)	1.2 (–0.4 to 2.9)	0.5 (–1.1 to 2.1)	0.5 (–1.1 to 2.0)	1.1 (–1.8 to 4.1)	**2.7 (0.1 to 5.3)**[b]
Gestational age, wk	**–1.2 (2.0 to –0.4)**[i]	0.7 (–0.0 to 1.5)	0.5 (–0.2 to 1.2)	0.6 (–0.1 to 1.3)	**2.2 (0.9 to 3.5)**[i]	**2.0 (0.8 to 3.3)**[b]
Preterm birth < 37 wk[d]	**6.3 (0.2 to 12.4)**[b]	**–6.2 (–11.6 to –0.8)**[b]	–2.9 (–8.1 to 2.4)	–3.1 (–8.1 to 1.8)	–6.2 (–16.6 to 4.3)	–8.0 (–17.1 to 1.1)
Preterm birth < 37 wk[c,d]	**7.0 (0.3 to 14.0)**[b]	–3.9 (–10.1 to 2.4)	–2.5 (–8.5 to 2.5)	–1.7 (7.5 to 4.1)	–5.7 (–17.3 to 5.9)	–4.8 (–14.9 to 5.3)
WGA (%)	**–0.13 (–0.3 to –0.0)**[b]	–0.0 (–0.1 to 0.1)	–0.0 (–0.1 to 0.1)	0.1 (–0.1 to 0.2)	–0.1 (–0.3 to 0.2)	0.1 (–0.1 to 0.3)
SGA[d]	2.7 (–3.9 to 9.2)	–2.5 (–8.7 to 3.7)	0.3 (–5.7 to 6.2)	–4.3 (–10.3 to 1.6)	1.7 (–9.6 to 12.9)	–4.5 (–15.1 to 6.0)
LGA[d]	–6.9 (–18.1 to 4.3)	–9.1 (–18.2 to 0.1)	**–8.3 (–16.5 to –0.1)**[b]	–2.9 (–12.3 to 6.5)	1.0 (–16.6 to 18.6)	–3.0 (–18.4 to 12.5)
Wt 36 mo SDS (SD)	–1.2 (–3.2 to 0.7)	**-2.0 (–4.0 to –0.4)**[b]	–0.9(–2.5 to 0.6)	–0.8 (–2.3 to 0.8)	0.9 (–2.2 to 3.9)	–0.8 (–3.7 to 2.1)
Ht 36 mo SDS (SD)	**–3.6 (–5.6 to –1.6)**[i]	**–1.8 (–3.5 to –0.1)**[b]	–1.2 (–2.7 to 0.3)	–0.8 (–2.3 to 0.8)	1.1 (–1.8 to 4.0)	0.6 (–2.1 to 3.3)
Ht catch-up > 0.67 SD[d,e]	–0.6 (–4.9 to 3.6)	–2.6 (–6.4 to 1.1)	**–5.7 (-9.0 to –2.3)**[i]	**–4.3 (–7.7 to –0.9)**[b]	**–7.6 (–14.2 to –1.1)**[b]	**–7.9 (–13.7 to –2.1)**[i]
Ht catch-up > 0.67 SD[d,f]	–1.9 (–6.2 to 2.5)	–2.4 (–6.2 to 1.4)	**–5.5 (–9.0 to –2.0)**[i]	**–4.3 (–7.8 to –0.8)**[b]	**–7.0 (–13.7 to –0.2)**[b]	**–6.8 (–12.9 to –0.7)**[b]
Wt catch-up > 0.67 SD[d,f,g]	–1.5 (–6.5 to 3.4)	**–6.0 (–10.3 to –1.7)**[b]	–1.5 (–5.4 to 2.4)	–3.8 (–7.4 to –0.2)	–0.3 (–7.9 to 7.1)	**–7.9 (–14.3 to –1.6)**[b]

Estimates are given as difference in months associated with a +1 increase in the parameters (parameter unit in parentheses).
Abbreviations: B2, thelarche; BMI, body mass index; LGA, large for gestational age; SGA, small for gestational age.
[a]Adjusted for maternal age at menarche and paternal pubertal timing (early, average, late).
[b]Adjusted for maternal and paternal pubertal timing (early, average, late).
[c]Adjusted also for ΔSDS weight 0 to 36 months greater than 0.67 SD: yes/no.
[d]Categorical yes/no.
[e]From birth to 18 months.
[f]From birth to 36 months.
[g]Adjusted also for birth weight.
[b]*P* less than or equal to .05.
[i]*P* less than .01.

Table 3. Associations between birth parameters and age at testis size greater than 3 mL and Tanner stages G2+, G3+, G4+, PH2+, PH3+, and PH4+ in boys

Boys	Tvol > 3 mL	G2+	PH2+	G4+	PH4+	G2-G4
Birth wt SDS (SD)	**–1.6 (–2.7 to –0.5)**[g]	**–1.6 (–3.0 to –0.2)**[f]	–0.3 (–1.6 to 0.9)	**2.0 (0.7 to 3.2)**[g]	**2.0 (0.4 to 3.7)**[f]	1.8 (–0.1 to 3.7)
Birth wt, kg[a]	**–3.9 (–6.3 to –1.5)**[g]	**–3.9 (–6.9 to –0.9)**[f]	–1.5 (–4.1 to 1.1)	2.7 (–0.1 to 5.4)	1.9 (–1.5 to 5.3)	3.5 (–0.4 to 7.4)
Birth length, cm	**–0.8 (–1.2 to –0.3)**[g]	**–0.6 (–1.2 to –0.1)**[f]	0.0 (–0.5 to 0.5)	**0.8 (0.3 to 1.3)**[g]	**0.9 (0.2 to 1.5)**[f]	**1.0 (0.3 to 1.7)**[g]
Birth length (SD)	**–2.2 (–3.3 to –1.0)**[g]	**–1.8 (–3.2 to –0.3)**[f]	–0.3 (–1.5 to 1.0)	**2.2 (0.9 to 3.5)**[g]	**2.3 (0.6 to 4.1)**[g]	**3.0 (0.9 to 5.1)**[g]
BMI 0 mo (SD)	–0.4 (–1.6 to 0.8)	–0.7 (–2.2 to 0.8)	0.0 (–1.3 to 1.4)	1.3 (–0.0 to 2.7)	1.4 (–0.3 to 3.1)	0.4 (–1.1 to 1.9)
Fat % 0 mo SDS (SD)	–0.5 (–1.7 to 0.7)	0.0 (–1.5 to 1.6)	0.3 (–1.1 to 1.7)	**1.7 (0.4 to 3.0)**[f]	1.7 (–0.0 to 3.3)	–0.6 (–2.6 to 1.5)
Gestational age, wk	–0.1 (–0.8 to 0.6)	–0.5 (–1.3 to 0.3)	0.5 (–0.3 to 1.2)	**0.9 (0.1 to 1.6)**[f]	**1.3 (0.4 to 2.3)**[g]	0.6 (–0.7 to 1.9)
Preterm birth < 37 wk[b]	0.3 (–4.6 to 5.2)	2.3 (–3.8 to 8.5)	–3.8 (–9.1 to 1.5)	–3.6 (–8.6 to 1.5)	–5.9 (–12.1 to 0.3)	13.9 (–173.2 to 201.0)
Preterm birth < 37 wk[a,b]	–0.12 (–3.2 to 2.9)	3.6 (–3.1 to 10.4)	–0.8 (–6.8 to 4.9)	0.6 (–5.7 to 6.8)	–3.3 (–10.1 to 3.6)	14.3 (–139.5 to 168.2)
WGA %	**–0.16 (–0.3 to –0.06)**[f]	–0.1 (–0.2 to 0.1)	–0.1 (–0.2 to 0.0)	0.1 (–0.0 to 0.2)	0.1 (–0.1 to 0.2)	0.1 (–0.0 to 0.3)
SGA([a])	–1.0 (–6.8 to 4.7)	–1.8 (–9.0 to 5.4)	–3.7 (–10.0 to 2.6)	–5.6 (–11.3 to 0.1)	**–7.2 (–14.3 to –0.2)**[f]	–4.3 (–13.3 to 4.7)
LGA[a]	**–8.4 (–15.2 to –1.6)**[f]	**–8.6 (–17.2 to –0.1)**[f]	–3.1 (–10.9 to 4.6)	0.2 (–7.6 to 8.0)	–1.9 (–11.7 to 7.9)	2.3 (–7.2 to 11.8)
Wt SDS 36 mo (SD)	**–2.1 (–3.4 to –0.9)**[g]	**–2.6 (–4.2 to 1.1)**[g]	**–2.3 (–3.7 to –0.9)**[g]	–0.2 (–1.8 to 1.3)	–1.6 (-3.6 to 0.3)	1.4 (–0.9 to 3.6)
Ht SDS 36 mo (SD)	**–2.7 (–4.0 to –1.4)**[g]	**–2.9 (–4.5 to –1.2)**[g]	**–2.0 (–3.5 to –0.6)**[g]	–0.1 (–1.6 to 1.7)	–1.3 (–3.4 to 0.7)	0.8 (–1.5 to 3.1)
Ht catch-up > 0.67 SD[b,c]	0.9 (–2.0 to 3.7)	–1.1 (–4.8 to 2.5)	–2.5 (–5.7 to 0.8)	**–4.7 (–7.9 to –1.4)**[g]	**–7.8 (–11.8 to –3.7)**[g]	**–4.6 (–9.0 to -0.3)**[f]
Ht catch-up > 0.67 SD[b,d]	0.3 (–2.7 to 3.2)	0.2 (–3.5 to 3.9)	–2.0 (–5.2 to 1.3)	**–5.7 (–9.0 to -2.4)**[g]	**–7.7 (–11.7 to –3.7)**[g]	**–5.3 (–9.3 to –1.2)**[f]
Wt catch-up > 0.67 SD[b,d,e]	–1.6 (–4.5 to 1.3)	–3.2 (–6.9 to 0.5)	–3.2 (–6.8 to 0.4)	–2.7 (–6.4 to 1.0)	**–4.6 (–8.2 to –0.9)**[f]	1.5 (–3.8 to 6.9)

Estimates are given as difference in months associated with a +1 increase in the parameters (parameter unit in parentheses) (all adjusted for maternal and paternal pubertal timing (early, average, late).
Abbreviations: BMI, body mass index; G2, gonadarche; LGA, large for gestational age; PH2+, pubarche; SDS, SD score; SGA, small for gestational age; Tvol3+, testis size greater than 3 mL.
[a]Adjusted also for ΔSDS weight 0 to 36 months greater than 0.67 SD: yes/no.
[b]Categorical yes/no.
[c]From birth to 18 months.
[d]From birth to 36 months.
[e]Adjusted also for birth weight.
[f]*P* less than or equal to .05.
[g]*P* less than .01.

B2 to menarche, and a nonsignificant tendency to later B2+ (Fig. 2A). Results were similar for height and for Δheight SDS greater than 0.67 from birth to 18 months (see Table 2).

In boys, catch-up growth (Δweight SDS > 0.67) was associated with earlier G4+ and PH4+, but not with G2+ and Tvol3+ (Fig. 2B). Results were similar for height and for Δ height SDS greater than 0.67 from birth to 18 months (see Table 3).

Children (boys and girls) who were taller at 3 years experienced earlier pubertal onset (B2+, G2+, Tvol3, and PH2+). Results were similar for weight SDS (see Tables 2 and 3).

Association Between Birth Weight and Postnatal Catch-up/Mediation Analyses

The degree of catch-up growth in weight between birth and 36 months (ΔSDS weight 0-36 months) was inversely associated with birth weight SDS (β = –0.57; 95% CI, –0.61 to –0.52).

When adjusting associations between birth weight and pubertal timing for postnatal catch-up growth (ΔSDS weight 0-36 months > 0.67 SD: yes/no), estimates were largely unchanged for B2+, ΔB2 to B4, and ΔB2 to menarche in girls (see Table 2) as well as for Tvol3+, G2+, PH4+, and G4+ (see Table 3).

The association between being preterm and timing of PH2+ in girls became insignificant when adjusting for catch-up weight (see Table 2).

Adjusting for the association between catch-up growth and puberty timing for birth weight gave unchanged associations in girls for PH2+, menarche, and B2+ to menarche.

In boys, adjusting for birth weight gave unchanged associations for G4+ and PH4+. For G2+ and Tvol3+ associations were altered from no associations toward a tendency to earlier attainment.

Differences in Growth Parameters Between Children With Different Pubertal-Onset Pathways

Table 4 displays characteristics for the children in whom the first sign of puberty could be determined (40.5% of girls and 42.4% of boys). Most girls (77.5% of eligible) started puberty with breast development (thelarche). Girls starting with pubarche (11%) or with thelarche and pubarche synchronously (11.4%) differed from girls starting with thelarche in several ways. They had lower birth weight/length/BMI and fat percentage SDS, were born at a lower gestational age, and had a higher weight and BMI catch-up between birth and 36 months. They did not differ in age at menarche, but progression time from B2+ to menarche was longer. Among boys, the majority started with gonadarche (63.7%), but also a large proportion (22.9%) started with pubarche and gonadarche synchronously. Boys starting with pubarche or synchronously differed from boys starting with gonadarche only in a higher catch-up growth for weight. For some of the other parameters, there were nonsignificant tendencies in the same direction as in the girls. When pooling boys and girls, we found significant differences between onset pathway (thelarche/gonadarche vs pubarche or synchronous) for birth weight SDS, birth length SDS, birth BMI SDS, fat percentage SDS at 0 months, weight ΔSDS 0 to 36 months, height ΔSDS 0 to 36 months, BMI ΔSDS 0 to 36 months, and fat percentage ΔSDS 0 to 36 months (data shown only for weight ΔSDS 0-36 months, Fig. 3).

Children in whom a starting pathway could not be determined did not significantly differ from the other children (data not shown).

Discussion

We investigated associations between size at birth and infancy growth with onset and progression of thelarche/gonadarche and pubarche in a large group of girls and boys using longitudinal data from repetitive physical examinations. Our study revealed diverging associations related to markers of gonadarche (thelarche/B2+ and Tvol3+/G2+) compared to markers of pubarche and to late pubertal markers. These differential associations were seen both in girls and boys. Birth weight was inversely associated with age at thelarche in girls and gonadarche in boys. The associations persisted after exclusion of SGA/LGA children as well as after adjustment for postnatal catch-up growth. The fact that associations were similar for birth length, but not significant for BMI and body fat percentage, indicates that it was the absolute size rather than the degree of fatness that was mostly linked to pubertal onset.

We found that catch-up growth in infancy was associated with early timing of pubarche and with earlier menarche, in accordance with many prior studies [4, 8, 18, 31-33].

Because the degree of postnatal catch-up growth was inversely associated with birth weight, we performed mediation analyses, which supported that birth weight and postnatal growth play independent roles.

Our finding of differential associations between birth weight, infancy growth pattern, and pubertal milestones related to different pubertal pathways may explain previous apparent discrepancies in epidemiological findings. Our findings are in line with a US study using data from the National Health and Nutrition Examination Survey (NHANES) III physical examinations [11]. The authors reported that in girls a high birth weight (≥ 4000 g, compared

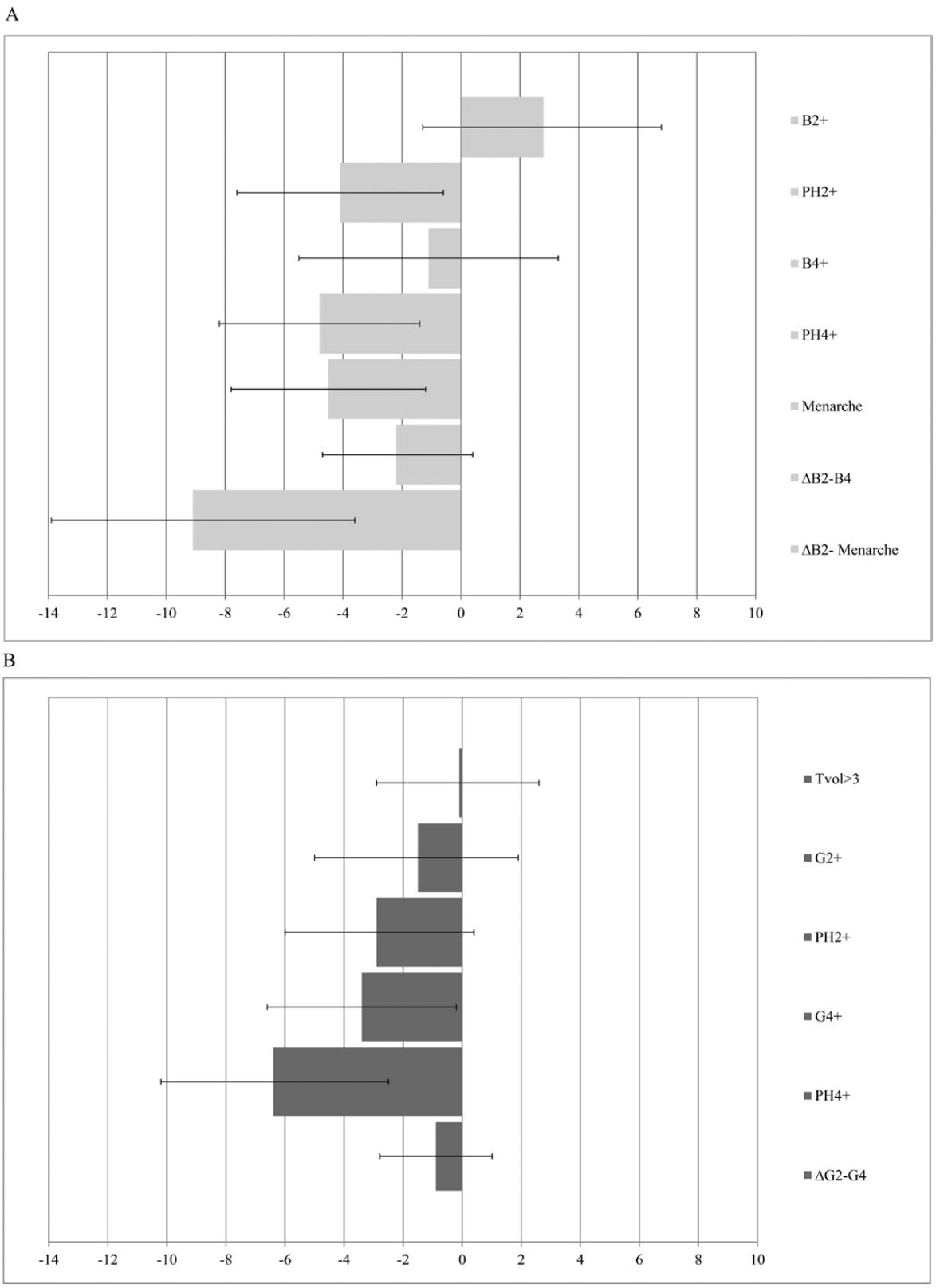

Figure 2. Effect estimates in A, light gray, girls, and B, dark gray boys, given in months with 95% CI (whiskers) for a greater than 0.67 increase in ΔSD score weight 0 to 36 months on timing of pubertal markers and time between attainment of (B2) to B4, B2 to menarche, gonadarche (G2) to G4.

to normal birth weight of 3000-3500 g) was associated with a higher odds ratio (OR) of breast stage B3+, whereas low birth weight was associated with a higher OR for PH3+. In boys low and high birth weight both were associated with a higher OR of Tanner stage 2 (either PH2 or G2). Our findings differ from the findings of Maisonet et al [34], who

Table 4. Growth parameters and timing of pubertal onset in girls and boys separated by pubertal starting pathway[a]

Means (SD) or n (%)	Girls			Boys		
	Thelarche N = 211 (72.6%)	Synchronous N = 31 (11.4%)	Pubarche N = 30 (11.0%)	Gonadarche N = 225 (63.7%)	Synchronous N = 81 (22.9%)	Pubarche N = 47 (13.3%)
Gestational age, d	279 (13)[b]	274 (12)	272 (17)	279 (13)	275 (14)	277 (17)
Preterm (< 37 wk)	10 (4.8%)[b]	2 (6.5%)	6 (20%)	10 (4.4%)	9 (11.1%)	3 (6.4%)
Birth wt, g	3472 (574)[b]	3230 (506)	2989 (674)	3560 (592)	3481 (605)	3486 (776)
Birth length, cm	51.5 (2.8)[b]	50.6 (1.9)	50.3 (2.9)	52.3 (2.8)	52.0 (2.6)	51.7 (3.5)
WGA, %	–0.6 (12.8)[b]	–3.5 (13.6)	–9.7 (13.2)	–1.5 (12.3)	–0.5(13.2)	–2.8 (14.0)
SGA, WGA < –22%	12 (5.7%)	3 (9.7%)	5 (16.7%)	11 (4.9%)	4 (4.9%)	4 (8.5%)
LGA, WGA > 22%	5 (2.4%)	0 (0%)	0 (0%)	7 (3.1%)	3 (3.7%)	1 (2.1%)
BMI birth	13.0 (1.4)[b]	12.6 (1.6)	11.8 (1.6)	12.9 (1.3)	12.8 (1.4)	12.8(1.6)
Fat % 0 mo	9.9 (2.3)[b]	9.1 (3.1)	8.6 (2.7)	9.4 (2.5)	9.3 (2.2)	9.2 (2.2)
Wt SDS 36 mo	–0.19 (0.98)	–0.23 (1.08)	–0.55 (0.95)	–0.11 (1.06)	–0.06 (0.99)	0.03 (1.14)
Wt ΔSDS 0-36 mo	–0.19 (1.21)[b]	–0.09 (1.03)	0.30 (1.23)	–0.02 (1.07)[b]	0.23 (1.13)	0.30 (1.24)
Ht ΔSDS 0-36 mo	–0.05 (1.25)	0.05 (0.75)	0.10 (1.41)	0.04 (1.17)	0.22 (1.07)	0.14 (1.30)
BMI ΔSDS 0-36 mo	–0.18 (1.27)[b]	0.19 (1.41)	0.56 (1.15)	–0.02 (1.24)	0.09 (1.34)	0.52 (1.29)
Mean age at B2+/G2+	9.22 (8.99-9.45)	11.14 (10.82-11.45)	11.39 (10.91-11.86)	10.95 (10.73-11.17)	11.44 (11.20-11.68)	12.38 (12.04-12.73)
Mean age at PH2+	11.84 (11.69-11.99)	11.14 (10.82-11.45)	9.21 (8.62-9.81)	12.56 (12.40-12.73)	11.36 (11.13-11.58)	10.10 (9.73-10.47)
Mean age at menarche	13.3 (13.0-13.5)	14.33 (12.88-15.77)	14.0 (12.6-15.33)			
Time from B2 to menarche	4.3 (3.8-4.7)[b]	1.6 (1.1-2.1)	2.0 (1.2-2.8)			

Abbreviations: B2, thelarche; BMI, body mass index; G2, gonadarche; LGA, large for gestational age; PH2+, pubarche; SDS, SD score; SGA, small for gestational age; WGA, weight for gestational age.

[a]Determination of pubertal pathway possible in 625 of 1518 equals 41.2% of children.

[b]Difference thelarche/gonadarche vs pubarche + synchronous *P* less than .05, differences tested with *t* test (continuous variables) and Fisher exact test (categorical variables).

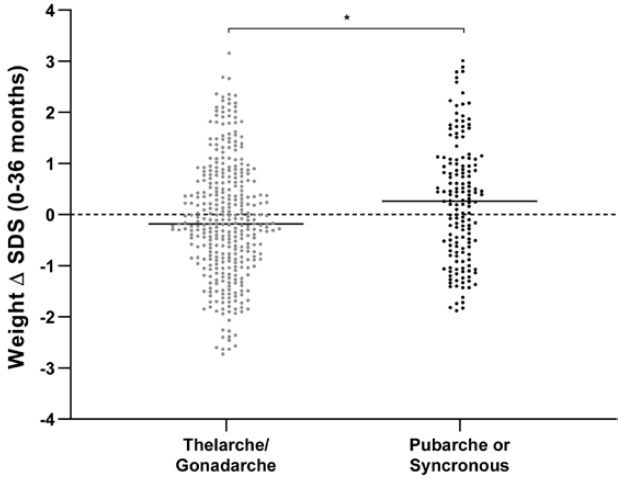

Figure 3. Δ Weight SD score 0 to 36 months (in boys and girls together) separated by pubertal onset pathway. **P* less than .05 in *t* test.

found no significant associations between birth weight and pubertal development, but that change in weight SDS between birth and 20 months was associated both with earlier pubarche and thelarche in girls. A possible explanation for these differences could be that their study did not include preterm girls and was based on self-assessed pubertal development, which may introduce bias [16].

In girls, being preterm was associated with earlier pubarche and later thelarche. The latter finding was consistent with the previously cited Chinese study [15]. In the same investigation, the authors also did not find associations between prematurity and gonadarche in boys. The Chinese study did not investigate associations with pubarche. However, our findings are in line with the observation of premature adrenarche in prematurely born children who display higher serum testosterone and dehydroepiandrosterone sulfate levels in infancy than children born at term [35].

In boys, being LGA was associated with earlier pubertal onset, whereas SGA was associated with earlier attainment of late pubertal stages compared to AGA boys. In girls we found similar tendencies in accordance with earlier findings that low and high birth weight both were (nonsignificantly) associated with earlier menarche [10]. Our findings of differential associations of early growth patterns with pubertal markers are in line with a recent Danish study based on questionnaire data that reported that children born SGA in general reached pubertal markers earlier, but not earlier B2 and G2 [14].

Most girls in our cohort started with thelarche and only a few with pubarche, which is in accordance with another contemporary Danish study with 6-month examination intervals [36]. Our findings of differences in early growth parameters between children starting with gonadarche/pubarche respectively are to our knowledge novel.

Some growth parameters were similarly associated with early and late pubertal stages. This was seen for weight at 36 months, which was associated with earlier age at thelarche, gonadarche, pubarche, and earlier attainment of late puberty markers, in accordance with previous findings [9, 18]. However, we found that birth weight was negatively associated with age at early markers, but positively with age at late markers. This is in line with the finding of a differential impact of genetic loci on age of thelarche and menarche [37]. It may also indicate that early infancy growth patterns affect the pubertal progression. We investigated this further and found that higher birth weight was associated with slower progression. Conversely, catch-up growth was associated with faster progression from B2 to menarche. The latter is in accordance with findings from a Finnish study of children with premature adrenarche. They observed that girls with premature adrenarche had accelerated infant growth [38] as well as earlier menarche compared to controls and that low birth length was a predictor of this [39]. Another study reported that high prepubertal BMI and fat mass were associated with a shorter time between age at the start of the pubertal growth spurt and age at peak height velocity [40]. This is in line with our findings that duration of puberty may be affected by growth in infancy. Another study found that girls with the synchronous pathway had the fastest progression through puberty [41]. It is furthermore a clinical experience that some girls with early breast development progress slowly to later stages of puberty [42]. This slowly progressing variant of early pubertal onset can be left untreated as opposed to central precocious puberty [43], and the incidence seems to be increasing [44]. Thelarche may therefore not always be synonymous with activation of the HPG axis. Possible clinical implications of this could be to take birth weight and early growth patterns into account when evaluating children with early puberty. Girls with a high birth weight who develop breasts early (without simultaneous pubic hair development) may not progress as fast as low birth weight, SGA, or preterm girls with catch-up growth. This hypothesis will need to be tested in a clinical population.

A possible explanation for our findings of differing associations between growth patterns and pubertal markers could be that pubarche represents also adrenarche, as opposed to gonadarche/thelarche representing activation of the HPG axis. Postnatal catch-up growth may be more associated with insulin resistance and exaggerated adrenarche rather than activation of the HPG axis [45]. Adrenarche appears to be a phenomenon limited to humans and higher primates [46], and the timing of activation of the HPG axis and timing of the maturation of the zona reticularis in the adrenal cortex may be differently regulated by adipokines such as leptin and adiponectin [47]. Also, the occurrence

of adrenarche in patients with HPG axis disorders also indicates that the regulatory mechanisms responsible for adrenarche and gonadarche differ [48].

As it is well-known that the growth hormone insulin-like growth factor 1 (IGF-1) axis plays a role in the development of the reproductive system and IGF-1 receptors are widely distributed in the reproductive organs of both sexes [49], IGF-1 could possibly be a mediator of the association between growth and pubertal markers.

Our study supports the hypothesis of a link between prenatal and postnatal growth and pubertal development, but it cannot prove causality. Other factors may affect both prenatal and postnatal growth and pubertal development, and it may not be the growth per se that has an influence on pubertal onset. In countries like Denmark and China, where secular trends of earlier pubertal maturation have been reported [2, 3, 50], there has also been an increase in size at birth [51, 52]. However, given the effect estimates of our models, this increase in birth weight alone cannot account for the trends, and other factors likely play a role.

The most important strength of this study is that the children were followed longitudinally from birth to puberty by standardized clinical examinations. Another major strength of our study is that pubertal onset was examined by trained physicians, which, compared to self-assessment, probably limited misclassification (eg, between pseudomammae and true development of breast tissue).

We performed multiple tests according the guidelines of the American Society of Statistics [53]; we did not correct for this. The biological questions behind the analyses were interrelated and thus elucidate our hypothesis from different angles, including mediation analyses to differentiate between parameters showing colinearity.

A limitation of our study was the dropout rate of participants over time, which is an inherent problem of population-based longitudinal surveys. Furthermore, we examined the children only once a year. This, as well as the reduced overall number of observations in late puberty, may have decreased statistical power and our ability to detect associations. We cannot exclude that the dropout introduced a bias not detected by the group comparison between participants and nonparticipants. Furthermore, findings in a White, Nordic population may not be applicable to populations with other ethnicities that may have different growth trajectories and patterns of pubertal development.

Conclusions

Higher birth weight and length were associated with earlier onset of gonadarche/thelarche and slower progression from B2+ to menarche. Infant catch-up growth was associated with earlier pubarche, menarche, and G4+ as well as with a faster progression from B2+ to menarche. Our findings suggest that the early and late milestones of puberty as well as pubarche/gonadarche pathways are differently affected by prenatal and postnatal growth both in boys and girls.

Additional Information

Correspondence: Christine Wohlfahrt-Veje, MD, PhD, Department of Growth and Reproduction, Section 5064, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark. Email: christine.veje@regionh.dk.

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Data availability: Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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