Pubertal Timing and Growth Influences Cardiometabolic Risk Factors in Adult Males and Females

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OBJECTIVE—Early pubertal onset in females is associated with increased risk for adult obesity and cardiovascular disease, but whether this relationship is independent of preceding childhood growth events is unclear. Furthermore, the association between male puberty and adult disease remains unknown. To clarify the link between puberty and adult health, we evaluated the relationship between pubertal timing and risk factors for type 2 diabetes and cardiovascular disease in both males and females from a large, prospective, and randomly ascertained birth cohort from Northern Finland.

RESEARCH DESIGN AND METHODS—Pubertal timing was estimated based on pubertal height growth in 5,058 subjects (2,417 males and 2,641 females), and the relationship between puberty and body weight, glucose and lipid homeostasis, and blood pressure at age 31 years was evaluated with linear regression modeling.

RESULTS—Earlier pubertal timing associated with higher adult BMI, fasting insulin, diastolic blood pressure, and decreased HDL cholesterol in both sexes ($P < 0.002$) and with higher total serum cholesterol, LDL cholesterol, and triglycerides in males. The association with BMI and diastolic blood pressure remained statistically significant in both sexes, as did the association with insulin levels and HDL cholesterol concentrations in males after adjusting for covariates reflecting both fetal and childhood growth including childhood BMI.

CONCLUSIONS—We demonstrate independent association between earlier pubertal timing and adult metabolic syndrome-related derangements both in males and females. The connection emphasizes that the mechanisms advancing puberty may also contribute to adult metabolic disorders.

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Accumulating evidence suggests an association between early timing of puberty and adverse health outcomes later in life. Typically evaluating females only, these studies show that early menarche is correlated with increased risk for several metabolic syndrome-associated disorders in adulthood [e.g., obesity, type 2 diabetes (1,2), and cardiovascular disease (3)]. The relationship between pubertal timing and BMI is particularly well-documented. Declining ages of pubertal onset associate with increased BMI in childhood (4–7). Likewise, studies addressing the link between pubertal timing and later risk for obesity show that pubertal onset is a negative predictor of adult BMI. Some studies claim that the link between puberty and adult BMI is a secondary consequence of a correlation between prepubertal BMI and puberty (6–8), but there are studies suggesting that the association between pubertal timing and adult BMI is independent of the degree of childhood obesity (9–12).

Data on the relationship between male pubertal timing and adult metabolic traits are scarce. Although abnormal levels of metabolic syndrome related-traits are more common in males than females, most studies exploring the relationship between pubertal timing and risk of adult disease have used age of menarche as the marker of puberty. One study showed that early pubertal timing may predict central adiposity in adult males (9). In addition, early puberty has been associated with elevated blood pressure in two reports, although the sample size was limited to only 135 males and 148 females in one of the studies (13,14). In contrast, early puberty was not associated with increased serum triglyceride levels in adult males, even if early puberty correlated with elevated triglycerides in adult females (12). Studies on the relationship between pubertal timing and adult glucose homeostasis in males appear to be lacking.

Because the risk for adult metabolic disease is shaped over the life course, detailed knowledge of the link with critical developmental events may highlight important pathogenic mechanisms. Therefore, to disentangle the relationship between puberty and cardiometabolic risk in both sexes, we studied 2,417 males and 2,641 females of a large, unique, and genetically homogenous birth cohort with data on longitudinal childhood growth and a wide spectrum of adult of cardiometabolic risk factors. Our study had the following specific aims: *1*) to assess the relationship

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between pubertal timing and adult body size, glucose, lipids, and blood pressure, both by evaluating the effect of pubertal timing alone and adjusting for patterns of prepubertal growth, and 2) to quantify the size of the pubertal timing effect on adult metabolic risk. Pubertal timing was assessed based on height growth during adolescence using a previously validated measurement, which allowed us to estimate the timing of puberty similarly in both sexes.

RESEARCH DESIGN AND METHODS

—The Northern Finland Birth Cohort 1966 (NFBC1966) is a prospective cohort study conducted in the two northernmost provinces in Finland (5,15,16). The study enrolled mothers living in the district who had estimated dates of delivery in the year 1966, including 12,231 births representing 96% of all births in these provinces. Data on the mothers' height and prepregnancy weight were collected from standard pregnancy follow-up forms and maternity cards carried by all mothers. Growth data from the offspring were collected at ages 6 months and 1 year from child welfare centers and at age 14 years by self-report from questionnaires mailed to the adolescents. Data on age of menarche was retrospectively obtained by a postal questionnaire at age 31 years. Roughly 3,000 individuals had retrospectively obtained extended data on height and weight from 1–18 years, which had originally been collected by the primary health care service. A representative subsample of the study participants (at age 31 years) was invited for clinical examination, including measurements of height, weight, waist and hip circumference, blood pressure, and the drawing of fasting blood samples for the analyses of blood glucose, serum insulin, and blood lipids. The study design is shown in Fig. 1.

To validate the accuracy of the self-reported data, we compared self-reported height with the retrospectively obtained height measurements at age 14 years. Forty-nine percent of the study participants (1,229 males and 1,240 females) had both height estimates available. The agreement between the two assessments was quite good. Their relationship was linear, with a Pearson correlation coefficient of 0.95 vs. 0.96 in boys and girls, respectively (Supplementary Fig. 1). Previous studies have shown that adolescents often exaggerate their self-reported height and that males in the highest socioeconomic groups tend to overestimate their stature more often than males with lower socioeconomic status (17). As expected, self-reported height was slightly higher than measured height in our study (1.0 cm in boys and 1.1 cm in girls), However, we could not find any evidence that the error in self-reported height would correlate with social status (Supplementary Table 1).

Fasting glucose and insulin concentrations were used to calculate insulin resistance index according to homeostasis model assessment (HOMA-IR) (18). All study subjects gave their informed consent. The study protocol in accordance with the Declaration of Helsinki was approved by the ethical committees of University of Oulu and the Northern Ostrobothnia Hospital District.

Pubertal timing was assessed based on pubertal height growth using a previously evaluated quantitative estimate of the timing of the pubertal height growth spurt (19) (i.e., the change in relative height between a fixed age at puberty and adulthood); in our case, between ages 14 and 31 years. The reason for using the difference in relative height rather than the increase in absolute height is that the change in relative height is independent of final stature. Sex steroids are the main regulators of the pubertal spurt in height growth, the timing of which thus reflects full activation of the hypothalamic–pituitary–gonadal axis in both sexes (20). In practice, early-maturing individuals, whose growth spurt occurs before age 14 years, are expected to have larger relative height at age 14 years than they have as adults, whereas late-maturing individuals whose period of fast pubertal growth occurs at a higher age are expected to have shorter relative height at age 14 years than as adults. The exact age when the adolescent height and weight outcomes were obtained varied between ages 13.0 and 15.0 (mean 14.3) years. Individual estimates of height and weight at the 14th birthday were obtained from sex-specific regression analyses of the growth parameters and calendar age. Relative height (SD) at age 14 and 31 years was calculated based on the sex-specific population mean and standard deviation.

The current study was restricted to 5,058 study subjects with data on height both at age 14 and 31 years. Of all study subjects, 1,954 had complete data on all variables reflecting fetal and childhood growth. Subjects with missing data had similar adult anthropometric or metabolic trait values as individuals with complete information (Supplementary Table 2).

For descriptive purposes, means and SDs were calculated for tertiles of pubertal timing. The relationship between pubertal timing and adult, childhood, and maternal anthropometric in addition to adult metabolic parameters was evaluated with linear regression modeling using R (http://www.r-project.org/). The distributions of the mother's BMI, adult BMI, serum insulin, HOMA-IR, and serum triglycerides were normalized by logarithmic transformation.

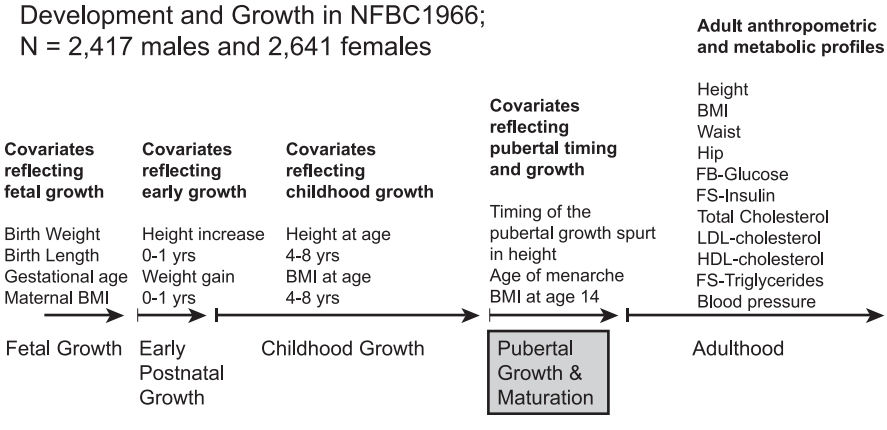

Figure 1—*Study design. The aim of the study is to evaluate the relationship between pubertal timing and adult anthropometric and metabolic profiles. The study subjects, all participants in the Northern Finland Birth Cohort Study 1966 (NFBC1966), have been prospectively followed from birth to adulthood and have data reflecting fetal, childhood, and pubertal growth, in addition to adult anthropometric and metabolic profiles. FB, fasting blood. FS, fasting serum. yrs, years.*

RESULTS—The descriptive analyses showed that individuals with earlier pubertal timing were both heavier and shorter as adults than individuals maturing later (Table 1). Earlier developing individuals also had more adverse lipid levels, glucose homeostasis, and blood pressure profiles. Because most of the quantified parameters were associated with pubertal timing in a

Table 1—*Mean (SD) of anthropometric and metabolic characteristics by timing of pubertal height growth in males and females*

	Timing of pubertal height growth in males			Timing of pubertal height growth in females		
Response variable	Early (n = 801, 33%)	Intermediate (n = 813, 34%)	Late (n = 803, 33%)	Early (n = 881, 34%)	Intermediate (n = 881, 34%)	Late (n = 879, 33%)
Change in relative height between age 14 years and adulthood (adult height SDS − 14 year height SDS)	−0.46 (0.89)	0.10 (0.93)	0.46 (0.95)	−0.23 (0.91)	0.00 (0.91)	0.35 (0.99)
Adult outcomes						
Height (cm)	175.3 (5.7)	178.9 (6.0)	181.2 (6.0)	163.2 (5.7)	164.7 (5.7)	166.9 (6.1)
BMI (kg/m^2)	26.1 (3.7)	25.4 (3.6)	24.1 (3.1)	25.5 (5.2)	23.9 (4.4)	22.9 (3.6)
Waist (cm)	90.0 (10.1)	89.6 (9.8)	87.0 (9.1)	81.1 (13.0)	78.6 (12.0)	76.6 (9.9)
Hip (cm)	97.5 (6.9)	97.9 (6.6)	97.2 (6.2)	99.2 (9.8)	96.6 (8.2)	95.8 (7.7)
FB-glucose (mmol/L)	5.2 (0.8)	5.2 (0.5)	5.2 (0.9)	5.0 (0.9)	4.9 (0.5)	4.9 (0.6)
FS-insulin (μU/mL)	9.5 (6.3)	8.9 (4.0)	8.0 (3.6)	8.8 (4.9)	8.2 (3.8)	8.1 (5.7)
HOMA-IR	2.3 (2.2)	2.1 (1.1)	1.9 (1.1)	2.0 (1.8)	1.8 (0.9)	1.8 (1.7)
Total cholesterol (mmol/L)	5.3 (1.0)	5.2 (1.0)	5.1 (1.0)	5.0 (1.0)	5.0 (1.0)	4.9 (1.0)
LDL cholesterol (mmol/L)	3.3 (0.9)	3.2 (0.9)	3.1 (0.9)	2.9 (0.8)	2.8 (0.8)	2.7 (0.8)
HDL cholesterol (mmol/L)	1.37 (0.94)	1.41 (0.33)	1.45 (0.32)	1.65 (0.39)	1.72 (0.38)	1.74 (0.39)
FS-triglycerides (mmol/L)	1.4 (0.9)	1.3 (0.9)	1.3 (0.7)	1.1 (0.6)	1.0 (0.5)	1.0 (0.6)
Systolic blood pressure (mmHg)	130.5 (13.3)	131.0 (12.7)	129.7 (12.0)	120.5 (12.7)	119.1 (11.7)	119.4 (11.7)
Diastolic blood pressure (mmHg)	81.3 (11.7)	80.9 (11.6)	78.6 (10.9)	75.3 (11.4)	74.0 (10.4)	74.2 (10.7)
Outcomes related to fetal and childhood growth						
Maternal BMI before pregnancy (kg/m^2)	23.5 (3.4)	23.4 (3.1)	23.0 (3.1)	23.4 (3.4)	23.1 (3.3)	23.0 (3.1)
Birth length (cm)	50.4 (2.0)	50.9 (2.2)	50.9 (2.3)	49.9 (2.0)	49.9 (2.0)	50.2 (2.0)
Birth weight (g)	3,479 (514)	3,589 (548)	3,617 (562)	3,408 (491)	3,419 (498)	3,502 (496)
Gestational age (weeks)	40.0 (1.9)	40.0 (1.8)	40.0 (2.0)	40.2 (1.9)	40.0 (2.0)	40.2 (1.8)
Height at age 1 year (cm)	76.3 (2.7)	76.7 (2.8)	76.9 (2.8)	75.1 (2.7)	75.1 (2.6)	75.1 (2.8)
Weight age 1 year (kg)	10.6 (1.2)	10.6 (1.1)	10.6 (1.2)	10.1 (1.2)	10.0 (1.1)	10.0 (1.2)
Mean relative height between age 4–8 years	0.01 (0.99)	0.04 (0.99)	0.02 (0.99)	0.12 (0.92)	0.01 (0.92)	−0.08 (1.01)
Mean relative BMI between age 4–8 years	0.24 (1.00)	−0.04 (0.93)	−0.17 (0.81)	0.24 (1.09)	−0.07 (0.91)	−0.15 (0.86)
BMI at age 14 years (kg/m^2)	19.9 (2.3)	19.2 (2.3)	18.2 (2.2)	20.0 (2.5)	19.3 (2.3)	18.3 (2.1)

FB, fasting blood; FS, fasting serum.

linear fashion, we tested the significance of the observed patterns with linear regression analysis. We observed strong association between adult height and pubertal timing, which in part might represent a spurious result of the formula used to estimate pubertal timing (i.e., the change in relative height between ages 14 and 31 years). Therefore, when testing the association between pubertal timing and all other adult outcomes, we adjusted the regression models with adult height. Almost all tested parameters measured at age 31 years showed significant association with pubertal timing in both sexes (Table 2). Only adult fasting blood glucose was not correlated with pubertal timing in males, whereas serum cholesterol and triglycerides did not correlate with pubertal timing in females.

A significant association between age at puberty and adult metabolic traits does not in itself prove a causal relationship. Prepubertal growth events also associate with adult metabolic outcomes. Therefore, part or most of the observed correlations might be explained by prepubertal growth associating both with timing of puberty and adult metabolic phenotypes. However, our follow-up analyses showed that pubertal timing indeed is an independent predictor of adult metabolic risk. Highly significant association between pubertal timing and BMI in addition to waist and hip circumference was obtained in both sexes using multivariate regression analyses, adjusting for variables reflecting fetal and childhood growth (Table 2). In addition, higher diastolic blood pressure was associated independently with earlier pubertal timing in both sexes ($P < 0.0006$). Higher levels of serum insulin and triglycerides and lower levels of HDL cholesterol were independently associated with earlier pubertal timing only in males ($P < 0.0002$).

Our analyses showed that pubertal timing influences adult metabolic outcomes both through unique mechanisms and mechanisms shared with preceding events of childhood growth (Table 3). In multivariate regression analyses, fetal, childhood, and pubertal growth together explained a considerable proportion of the variation of adult anthropometric traits (30–40% of adult BMI, 25–35% of waist and hip circumference, and ~10% of adult waist-to-hip ratio) in both sexes. They explain less of the variation of adult metabolic phenotypes (~5% of the variation in serum insulin, 1–4% of blood pressure, and 1–1.5% of blood lipid variation). When analyzed alone, prepubertal growth events explained 19–25% of the adult BMI variation, whereas pubertal timing accounted for 6 to 7%. When

pubertal timing was added to the regression model including prepubertal growth variables, the proportion of explained adult BMI variance increased only by 2 to 3%. This suggests that even if part of the correlation between pubertal timing and adult BMI is uniquely due to puberty, at least half of the pubertal effect is shared with prepubertal growth events. Quite expectedly, BMI during puberty showed strong correlation with adult BMI. The addition of BMI at age 14 years to the regression analysis, including prepubertal growth and pubertal timing, increased the proportion of adult BMI variance explained with more than 10%. Pubertal BMI also had a strong influence on adult serum insulin levels.

Thus, early life-course events account for a significant proportion of the adult metabolic trait variation. For most of the analyzed adult traits, prepubertal growth explained a much greater proportion than pubertal timing. For some variables (i.e., blood lipids and blood pressure), pubertal timing appeared to play a greater role. In males, total cholesterol, HDL and LDL cholesterol, and diastolic blood pressure were influenced almost exclusively by the timing of the pubertal growth spurt and not by prepubertal growth.

To explore whether choosing a different indicator of pubertal timing would alter the observed relationships between puberty and adult anthropometric and metabolic profiles, we reran the regression analyses substituting pubertal height growth in females with age of menarche. Age at menarche, which is indicative of almost complete sexual maturation, is a much later event in the process of female pubertal development than the acceleration of pubertal growth. The correlation between the two manifestations of puberty is 0.52 (21). Nonetheless, indexing pubertal timing based on menarcheal age yielded remarkably similar, highly significant associations with most of the adult anthropometric and metabolic traits as did pubertal height growth (Supplementary Tables 3 and 4).

CONCLUSIONS—Our longitudinal population-based study provides detailed information on factors associated with cardiovascular risk in >5,000 children from the genetically and environmentally homogenous population of Northern Finland. The results highlight that pubertal timing and growth are associated with the propensity to gain weight and adverse metabolic profiles in adulthood both in

Table 2—*The relationship between pubertal timing and adult anthropometric and metabolic outcomes*

	Males		Females	
Response variable	Pubertal timing in simple regression analysis	Pubertal timing in multivariate regression analysis	Pubertal timing in simple regression analysis	Pubertal timing in multivariate regression analysis
Height (cm)	2.83 (0.12), $P < 2e\text{-}16$, $n = 2,417$	2.67 (0.11), $P < 2e\text{-}16$, $n = 993$	1.51 (0.11), $P < 2e\text{-}16$, $n = 2,641$	1.82 (1.22), $P < 2e\text{-}16$, $n = 961$
BMI (kg/m^2)*	−0.018 (0.001), $P < 2e\text{-}16$, $n = 2,416$	−0.014 (0.002), $P = 5.6e\text{-}13$, $n = 993$	−0.017 (0.001), $P < 2e\text{-}16$, $n = 2,626$	−0.016 (0.002), $P = 3.5e\text{-}14$, $n = 956$
Waist (cm)	−2.54 (0.21), $P < 2e\text{-}16$, $n = 2,393$	−2.17 (0.34), $P = 2.1e\text{-}10$, $n = 983$	−2.25 (0.24), $P < 2e\text{-}16$, $n = 2,472$	−2.25 (0.38), $P = 3.3e\text{-}09$, $n = 898$
Hip (cm)	−1.37 (0.14), $P < 2e\text{-}16$, $n = 2,392$	−1.08 (0.22), $P = 1.2e\text{-}06$, $n = 983$	−1.90 (0.18), $P < 2e\text{-}16$, $n = 2,471$	−1.77 (0.26), $P = 3.2e\text{-}11$, $n = 898$
WHR	−0.013 (0.001), $P < 2e\text{-}16$, $n = 2,392$	−0.012 (0.002), $P = 24.7e\text{-}08$, $n = 983$	−0.006 (0.002), $P = 7.9e\text{-}05$, $n = 2,469$	−0.008 (0.003), $P = 0.002$, $n = 898$
FB-glucose (mmol/L)	−0.01 (0.02), $P = 0.61$, $n = 2,361$	−0.02 (0.03), $P = 0.58$, $n = 983$	−0.03 (0.01), $P = 8.5e\text{-}03$, $n = 2,587$	−0.01 (0.03), $P = 0.77$, $n = 953$
FS-insulin (μU/mL)*	−0.029 (0.004), $P = 1.6e\text{-}13$, $n = 2,345$	−0.027 (0.007), $P = 6.4e\text{-}05$, $n = 976$	−0.011 (0.003), $P = 0.001$, $n = 2,580$	−0.008 (0.006), $P = 0.16$, $n = 949$
HOMA-IR*	−0.029 (0.004), $P = 6.2e\text{-}12$, $n = 2,340$	−0.028 (0.008), $P = 2.1e\text{-}04$, $n = 974$	−0.013 (0.004), $P = 8.7e\text{-}4$, $n = 2,569$	−0.008 (0.007), $P = 0.22$, $n = 945$
Total cholesterol (mmol/L)	−0.09 (0.02), $P = 1.1e\text{-}04$, $n = 2,380$	−0.08 (0.04), $P = 0.04$, $n = 991$	−0.00 (0.02), $P = 0.92$, $n = 2,607$	−0.01 (0.04), $P = 0.81$, $n = 960$
LDL cholesterol (mmol/L)	−0.09 (0.02), $P = 9.1e\text{-}06$, $n = 2,371$	−0.07 (0.04), $P = 0.04$, $n = 987$	−0.04 (0.02), $P = 0.03$, $n = 2,603$	−0.04 (0.03), $P = 0.17$, $n = 956$
HDL cholesterol (mmol/L)	0.049 (0.007), $P = 1.4e\text{-}11$, $n = 2,380$	0.046 (0.012), $P = 2.2e\text{-}04$, $n = 991$	0.031 (0.008), $P = 6.0e\text{-}05$, $n = 2,607$	0.028 (0.014), $P = 0.04$, $n = 958$
FS-triglycerides (mmol/L)*	−0.032 (0.005), $P = 2.9e\text{-}10$, $n = 2,379$	−0.033 (0.009), $P = 2.1e\text{-}04$, $n = 990$	−0.004 (0.004), $P = 0.29$, $n = 2,607$	−0.005 (0.007), $P = 0.52$, $n = 958$
Systolic BP (mmHg)	−0.87 (0.29), $P = 0.003$, $n = 2,398$	−1.06 (0.51), $P = 0.04$, $n = 987$	−0.58 (0.24), $P = 0.02$, $n = 2,621$	−0.98 (0.44), $P = 0.03$, $n = 953$
Diastolic BP (mmHg)	−1.81 (0.26), $P = 3.6e\text{-}12$, $n = 2,397$	−1.93 (0.46), $P = 3.2e\text{-}05$, $n = 986$	−0.68 (0.22), $P = 0.002$, $n = 2,615$	−1.37 (0.40), $P = 6.0e\text{-}04$, $n = 952$

Data are β (SE) unless otherwise indicated. The simple analysis included pubertal timing (i.e., the change in relative between age 14 years and adulthood) as the only effect variable. The multivariate analysis includes birth length, birth weight, gestational age, maternal BMI before pregnancy, height and weight increase between age 0 and 1 year, mean relative height and BMI at age 4–8 years, and the residual variation of BMI at age 14 years after adjusting for pubertal timing. Relative height and BMI between ages 4 and 8 years were calculated as follows: in case an individual had a height or BMI measurement within ±0.5 years of a specific birthday, the exact height or BMI at that birthday was evaluated with sex-specific linear regression. The sex-specific relative height or BMI was then calculated at ages 4, 6, 7, and 8 years. If a study subject had height or BMI measurements available at multiple birthdays, the mean of all available measurements was used in the regression analysis. All regression models are adjusted for adult stature, except when the response variable equals height. BP, blood pressure; FB, fasting blood; FS, fasting serum; WHR, waist-to-hip ratio. *The variable has been logarithm-transformed prior to the regression analysis.

Table 3—*The proportion of variability (adjusted r^2) of adult anthropometric and metabolic traits that is explained by prepubertal growth, pubertal timing, and BMI*

	Males				Females			
Response variable	Prepuberty*	Prepuberty and pubertal timing†	Prepuberty, pubertal timing, and BMI‡	Pubertal timing alone	Prepuberty*	Prepuberty and pubertal timing†	Prepuberty, pubertal timing, and BMI‡	Pubertal timing alone
Height (cm)	0.563	0.724	0.722	0.194	0.560	0.636	0.644	0.063
BMI (kg/m^2)§	0.191	0.216	0.324	0.071	0.247	0.269	0.432	0.057
Waist (cm)	0.156	0.178	0.242	0.085	0.159	0.167	0.292	0.039
Hip (cm)	0.208	0.253	0.316	0.156	0.202	0.220	0.365	0.073
WHR	0.050	0.073	0.097	0.044	0.046	0.047	0.080	0.007
FB-glucose (mmol/L)	0.004	0.003	−0.003	−0.001	0.001	0.005	0.005	0.004
FS-insulin (μU/mL)§	0.024	0.032	0.048	0.023	0.020	0.020	0.051	0.004
HOMA-IR§	0.025	0.030	0.043	0.019	0.019	0.021	0.048	0.005
Total cholesterol (mmol/L)	0.001	0.004	0.004	0.006	0.005	0.004	0.007	0.003
LDL cholesterol (mmol/L)	0.001	0.006	0.005	0.009	0.013	0.016	0.019	0.010
HDL cholesterol (mmol/L)	0.003	0.013	0.017	0.018	0.012	0.017	0.019	0.011
FS-triglycerides (mmol/L)§	0.015	0.025	0.030	0.016	0.009	0.008	0.013	0.002
Systolic blood pressure (mmHg)	0.014	0.017	0.022	0.006	0.024	0.029	0.052	0.004
Diastolic blood pressure (mmHg)	0.002	0.016	0.019	0.024	0.010	0.012	0.045	0.004

The models Prepuberty and pubertal timing; Prepuberty, pubertal timing, and BMI; and Pubertal timing alone have been adjusted for adult stature except when the response variable equals height. FB, fasting blood; FS, fasting serum; WHR, waist-to-hip ratio. *Model 1: the model includes the following prepubertal predictor variables: birth length, birth weight, gestational age, maternal BMI before pregnancy, height and weight increase between age 0 and 1 year, and height and BMI between age 4 and 8 years. †Model 2: the model includes all prepubertal predictor variables of Model 1 and the change in relative height between age 14 years and adulthood as a measure of pubertal timing. ‡Model 3: the model includes all predictor variables of Model 2 and BMI at age 14 years. §The variable has been logarithm-transformed prior to the analyses.

males and females. More specifically, whereas the observed correlations in part are mediated through preceding childhood growth events, part of the correlation is due to a unique pubertal timing-related effect.

In contrast to our findings, some reports have challenged that pubertal timing correlates with adult BMI independently of childhood BMI (6–8). Because these studies have measured age of menarche in females, the discrepancy may imply that childhood obesity more strongly influences menarcheal age than the timing of the pubertal growth spurt. In contrast, the previous studies adjusted their analyses for BMI between ages 9 and 12 years (6–8) (i.e., during early to midpuberty), whereas we adjusted for prepubertal BMI. Thus, the discrepancy may be explained because the BMI measurements in the previous studies likely reflect weight changes that are associated with sexual maturation rather than with prepubertal growth. In support of the latter hypothesis, our follow-up analyses of menarcheal age indeed showed significant evidence for association between age of menarche and adult BMI even if prepubertal BMI was adjusted. Similar results have been obtained from a British Birth Cohort study (12) assessing pubertal timing based on menarcheal age and adjusting for childhood BMI at age 7 years. Furthermore, a Swedish study showed that the timing of the pubertal growth spurt independently predicts young adult BMI and central fat mass in males (9). Thus, the accumulating data together suggest that pubertal timing indeed has an independent influence on adult body weight.

The current study is unique in that it provides comprehensive information on the relationship between pubertal timing and multiple adult metabolic traits both in females and males. A limited number of studies have addressed the relationship between pubertal timing and metabolic outcomes in males, and previous studies of females and males have mostly addressed rather few adult traits in addition to providing slightly divergent correlation patterns (12–14). The divergent results likely reflect the heterogeneity of the metabolic phenotypes, the varying methods used for assessing puberty, and the varying ages at which the relationship with puberty has been assessed. Provided a significant correlation between pubertal timing and adult metabolic profiles exists, it is tempting to speculate that the increase in adult body size, insulin, and lipoprotein levels associated with early puberty would affect cardiovascular morbidity

and risk for metabolic disease. Data in females suggest that this indeed might be the case. Increased cardiovascular morbidity and mortality (1–3), in addition to increased incidence of type 2 diabetes, have been reported in women with early puberty. Our study provides strong evidence that early pubertal timing is associated with multiple adult metabolic derangements both in females and in males and consequently implies that the puberty-associated disease risk also applies in males.

Our study has several strengths. It is a prospective birth cohort study of large sample size, representing a genetically homogenous population (22). The study design offers the possibility of detecting subtle differences between the groups with varying pubertal timing. Furthermore, basing the analysis on the timing of the pubertal spurt in height growth allowed us to estimate the timing of central onset of puberty similarly in both sexes. However, the study has limitations. Even though the pubertal spurt in height growth is a characteristic of puberty in both sexes, the current study is limited by the fact that the growth spurt measurement described in this article is not directly comparable between the sexes. Puberty begins on average 2 years later in boys than in girls. Because the age of fastest pubertal growth occurs at age 12 years in girls and age 14 years in boys, the change in relative height between ages 14 and 31 years provides a rather good estimate of the timing of height growth in males. Nonetheless, the measurement is bound to be less informative in girls, especially its resolution to distinguish very early puberty. However, the similar association patterns between puberty and adult traits obtained with menarcheal age and pubertal growth suggest that our used growth measurement, despite its limited resolution, still quite accurately reflects the variation in pubertal timing in girls. Nevertheless, caution is warranted when interpreting possible differences in pubertal timing-related outcomes between sexes in this study.

Another limitation of the current study is that height at age 14 years is based on self-report. Thus, we might have underestimated the degree of pubertal delay in some males, as short boys may exaggerate their self-reported heights (23). In addition, the error of self-reported height might be systematically correlated with potential confounders such as socioeconomic status (17). Nonetheless, our verification analyses show that the self-reported data are quite accurate. As assessed in 49% of the study participants, there was a very close correlation between measured and reported height (Supplementary Fig. 1). Furthermore, social status as assessed by the occupation of the father did not have an impact on the accuracy of self-reported height, and including social status in the multivariate regression analyses did not change the association between pubertal timing and adult anthropometric and metabolic traits (Supplementary Tables 3 and 5). Thus, the potential impreciseness introduced by using self-reported height data at age 14 years most likely is random, therefore causing a dilution rather than an inflation of the observed associations.

Multiple factors contribute to the lifetime risk for complex, common, noncommunicable disorders, such as obesity, type 2 diabetes, and cardiovascular disease. Our results pinpoint pubertal timing as one such risk factor, which independently influences several metabolic disease-related traits, including the degree of obesity, serum lipids, and insulin, both in adult females and males. The observed connection between pubertal timing and adult metabolic outcomes implies that mechanisms advancing puberty also may contribute to adult metabolic disorders. The link furthermore implies that the detailed characterization of these mechanisms potentially might help promoting the development of more specific individual prevention strategies.

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