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Pubertal Timing and Cardiometabolic Markers at Age 16 Years

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Objective To examine the association between pubertal timing and cardiometabolic markers among adolescents.

Study design We used data from Dutch adolescents participating in a birth cohort study. The study population for the current study consisted of 799 adolescents of whom data were available for at least 1 of the exposure variables (pubertal timing and/or age at menarche) and any of the cardiometabolic markers (waist circumference, cholesterol, blood pressure [BP], glycated hemoglobin) measured at age 16 years. Adolescents self-reported pubertal development at ages 11, 14, and 16 years. We categorized participants with early (84 girls, 88 boys), intermediate (240 girls, 211 boys), or late pubertal timing (89 girls, 85 boys). We estimated differences in cardiometabolic markers using linear regression analysis.

Results Girls with early pubertal timing had 1.54 cm larger waist circumference (95% CI .05; 3.03) and 3.98 mm Hg higher systolic BP (95% CI 1.69; 6.27) at age 16 years than girls with intermediate pubertal timing. The association with systolic BP remained after adjusting for childhood body mass index (BMI) (age 8 years) but attenuated after adjusting for BMI in adolescence (age 16 years). Boys with early pubertal timing had 0.79 mmol/mol lower glycated hemoglobin (95%CI -1.38; -0.20) than boys with intermediate pubertal timing.

Conclusions Girls with early pubertal timing had unfavorable BP levels at age 16 years, independent of BMI in childhood. Girls and boys with late pubertal timing had a tendency for lower waist circumference, but no differences in other cardiometabolic markers. Late pubertal timing does not appear to be a risk factor for unfavorable cardiometabolic markers in adolescence. (*J Pediatr* 2017;187:158-64).

Women with early menarche (<12 years) have an increased risk of overweight and cardiometabolic disorders such as hypertension, hypercholesterolemia, and coronary heart disease.¹⁻⁴ Childhood overweight is associated with earlier menarche^{5,6} and may therefore explain at least part of the association with later cardiometabolic disorders. However, studies in adults lack data on childhood adiposity and therefore have been unable to investigate the role of this potential confounder in the association between pubertal timing and adult cardiometabolic outcomes.¹ Prospective studies in younger populations have the advantage of assessments of childhood adiposity preceding puberty. The Bogalusa Heart Study and the Fels Longitudinal Study observed that girls with early menarche develop an unfavorable cardiometabolic profile independent of childhood adiposity, which appears to persist into early adulthood.^{7,8} In contrast, others have observed that early menarche follows increased childhood adiposity and stated that a strong independent effect of early menarche on adult cardiometabolic risk is unlikely.⁹

Two issues have remained largely unaddressed: cardiometabolic consequences of pubertal timing for boys and cardiometabolic consequences of late puberty in both boys and girls. The limited available evidence in men suggests associations with cardiometabolic outcomes in directions similar to those in women.^{1,4} Previous studies mainly investigated associations of pubertal timing with adult obesity and cardiometabolic risk. In the current study in Dutch boys and girls, we examined cardiometabolic markers already during adolescence to explore whether unfavorable differences related to pubertal timing are present from an early age or whether these unfavorable differences arise after puberty. We investigated the potential confounding role of adiposity in childhood and the potential mediating role of adiposity in adolescence. Because recent studies suggested a U-shaped association between menarcheal age and cardiovascular disease (CVD) risk,^{2,4,10} we separately considered early and late pubertal timing in relation to cardiometabolic markers.

BMI	Body mass index
BP	Blood pressure
CVD	Cardiovascular disease
HbA1c	Glycated hemoglobin
PIAMA	Prevention and Incidence of Asthma and Mite Allergy
PDS	Pubertal Development Scale
TC	Total cholesterol

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Methods

We used data from a population-based contemporary Dutch birth cohort, the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study, with prenatal inclusion of 3963 children in 1996 and 1997. A detailed description of the study design was published previously.¹¹ At age 16 years, 3263 children (82%) were still in the study. At age 16 years, a clinical assessment was performed within 3 of the 4 participating regional medical centers. A random subsample of the children still in the study at that time, excluding the Rotterdam area, was invited to the clinical assessment. Of the children invited to the clinical assessment at age 16 years ($n = 2159$; 54% of the population at baseline), 802 children participated (37%). The study population for the current study consisted of 799 adolescents (415 girls and 384 boys) for whom data were available for any of the cardiometabolic markers at age 16 years, and at least 1 of the exposure variables (pubertal timing and/or age at menarche). The 799 participants included in the current study had parents with a higher education and less frequently had a non-Western ethnicity than those not included in the current study population, but no differences were found in levels of puberty variables at age 11 and 14 years between those included and excluded in the current study. The study protocol was approved by the medical ethics committees of the participating institutes. All parents gave written informed consent for the general study and separately for the clinical assessment; in addition, participants themselves gave written informed consent for the clinical assessment.

Pubertal stage was assessed with the Pubertal Development Scale (PDS).¹² Participants rated their pubertal development on a 4-point scale for 5 items: growth spurt, pubic hair, skin changes, and additionally menarche and breast development (girls) and voice change and facial hair (boys). The total PDS scores for the 5 items were averaged to maintain the original metric (range 1 to 4). The PDS was reported during 3 waves of follow-up, around age 11, 14, and 16 years. Correction for the influence of variation in age at each wave of follow-up on the PDS was achieved by standardizing the PDS values, using the residuals obtained when regressing the PDS on the participant's age.

Based on the age-standardized and sex-specific PDS at age 11 and 16 years (girls) or age 14 and 16 years (boys), we categorized participants as early, intermediate, or late pubertal timing. Early pubertal timing was defined as a PDS >75th percentile at age 11 years (girls) or 14 years (boys) and late pubertal timing was defined as a PDS <25th percentile at age 16 years. Boys and girls not categorized as either early or late were categorized as intermediate pubertal timing. Corresponding cut-off values and n were early pubertal timing (girls: PDS age 11 years >2.3 $n = 84$, boys PDS age 14 years >3.4 $n = 88$); late pubertal timing (girls: PDS age 16 years ≤ 3.2 $n = 89$, boys: PDS age 16 years <2.8 $n = 85$); intermediate pubertal timing (all others, girls: $n = 240$, boys: $n = 211$). The percentile cut-off values were based on the PDS scores of the total PIAMA popu-

lation at age 11 years and at age 14 years, and were based on the PDS scores in the subsample used for this study at age 16 years. According to this categorization, 13 girls and no boys had both early and late pubertal timing. We categorized these girls as having intermediate pubertal timing. For 49 participants (28 girls and 21 boys), the PDS was available at 1 age only. We retained these participants in the analyses and categorized them according to their single PDS value. Power calculations indicated that with the current group sizes for early, intermediate, and late pubertal timing, and a fixed 80% power (0.8) at a significance level (α) of .05, a clinically relevant difference¹³ of 2.4 cm waist circumference could be detected in boys and girls.

Additionally to groups of pubertal timing, we assessed early, intermediate, and late menarche for comparison with studies in the adult population. During 3 waves of follow-up, around ages 11, 14, and 16 years, girls reported whether menstrual periods had begun and, if so, the age at initiation, in years and months. Regarding reliability of self-reported menarcheal age, age reported during the first (at age 11 years) and second wave (at age 14 years) or first (at age 11 years) and third (at age 16 years) wave differed by ≤ 1 year among 86% of the girls, and among 82%, respectively. Mean difference in recalled age at menarche between any 2 waves (at age 11, 14, and 16 years) was <0.3 years (SD 0.7). Bland-Altman plots¹⁴ did not provide evidence for systematic variation of differences with age. We used age reported during the first available wave to reduce potential misclassification because errors in recalling age at menarche are likely to increase with time. If a participant reported years of age at menarche but not months, the month was imputed as 6 months later than the reported integer age at menarche ($n = 3$). We categorized girls as having early (≤ 11 years, $n = 43$), intermediate (12-14 years, $n = 319$), or late (≥ 15 years, $n = 49$) menarche. Those who had not yet reached menarche by the age of 16 years were included in the late menarche group.

Clinical assessments at age 16 years (range 15.9-17.5 years) were performed by trained staff at visits to medical centers according to standardized protocols. Systolic and diastolic blood pressure (BP) was measured according to the recommendations of the American Heart Association Council on High Blood Pressure Research.¹⁵ BP readings were obtained from the nondominant upper arm using an Omron M6 monitor (Omron Healthcare Europe, Hoofddorp, The Netherlands) while the child was seated. The first measurement was taken after ≥ 5 minutes of rest, without talking. Depending on arm circumference, 17- to 22-cm or 22- to 42-cm cuffs were used. BP was measured at least twice with 5-minute intervals. If 2 consecutive measures differed by >5 mm Hg, a third measurement was taken. The means of (2 or 3) systolic and diastolic measurements were used in analyses. Blood was drawn for measurement of cholesterol and glycated hemoglobin (HbA1c). Serum total and high-density lipoprotein (HDL) cholesterol were determined enzymatically using Roche automated clinical chemistry analyzers (Roche Diagnostics, Indianapolis, Indiana). The ratio between total and HDL cholesterol was calculated [total cholesterol (TC)/HDL cholesterol ratio]. For analysis of HbA1c, erythrocytes from blood samples were stored,

a 5- μ L cell mass was lysated and HbA1c was measured by ion-exchange chromatography using the Adams A1c, HA-8160 HPLC Auto analyzer (Menarini Diagnostics Benelux, Valkenswaard, The Netherlands). This analyzer was standardized on Diabetes Control and Complications Trial standards.

Weight, height, and waist circumference were measured in cm during clinical assessments at ages 8, 12, and 16 years. Body mass index (BMI) (kg/m^2) was used in the analysis as age- and sex-specific SDS (z scores), calculated using the reference growth curves of the Dutch Fourth Nationwide Growth Study carried out in 1997.¹⁶ Waist-to-height ratio was calculated. Overweight (including obesity) and thinness were defined based on international cut-off values.¹⁷

Characteristics used to describe the study population besides pubertal development were child's ethnicity, age (months), and maternal and paternal education. Ethnicity was based on country of birth of the child's parents and was categorized as Dutch, non-Dutch Western, or non-Western. Mother's and father's educational level were categorized as low (primary school, lower vocational, or lower secondary education), intermediate (intermediate vocational education or intermediate/higher secondary education) or high (higher vocational education and university).

Statistical Analyses

Mean levels of cardiometabolic markers and other characteristics were compared between groups with early and late pubertal timing, stratified by sex. Differences in cardiometabolic markers between adolescents with early or late vs intermediate pubertal timing, or menarche, were assessed by multiple linear regression analyses. The regression models were run separately for boys and girls and included groups of pubertal timing or menarcheal age as an independent variable and the cardiometabolic marker as dependent variable. Regression models were adjusted for age at the clinical assessment, ethnicity, height, and maternal and paternal education in the first adjusted model. These potential confounders were selected based on prior knowledge and their associations with the outcome of interest. We considered the potentially confounding role of smoking because it is an important risk factor for adult CVD, but the prevalence of smoking (at least once a day) was low in our study population of 16-year-olds (5%) and was not associated with pubertal timing in an exploratory analysis. Therefore, we did not include smoking in the regression models.

There is evidence that increased childhood adiposity is related to earlier pubertal timing in girls,⁵ whereas in boys the relationship is less clear.⁶ As childhood adiposity is also related to unfavorable cardiometabolic outcomes, it may act as a confounder in the relationship between pubertal timing and cardiometabolic markers; we investigated this by separately including and excluding childhood (age 8 years) BMI z score or waist circumference z score as a covariate in the linear regression models and comparing the regression coefficients. Furthermore, increased adiposity at the time of cardiometabolic marker assessment may explain part of the association with pubertal timing; therefore, we subsequently included BMI or

waist circumference at the time of clinical assessment (age 16 years) in the linear regression models. All of the data analysis was performed by using SAS software (v 9.3; SAS Institute Inc, Cary, North Carolina).

Results

The mean PDS increased with age from 3.4 (age 11 years) to 4.0 (age 16 years) in girls with early pubertal timing, and from 1.1 (age 11 years) to 2.8 (age 16 years) in girls with late pubertal timing (**Table I**). The mean PDS increased from 1.5 (age 11 years) to 3.8 (age 16 years) in boys with early pubertal timing, and from 1.1 (age 11 years) to 2.0 (age 16 years) in boys with late pubertal timing. Girls with early pubertal timing were consistently more often overweight/obese than girls with intermediate pubertal timing, from age 8 years (24% vs 10%), and age 12 years (20% vs 8%) to age 16 years (18% vs 8%). Boys with early pubertal timing were more often overweight than boys with intermediate pubertal timing at age 8 years (18% vs 12%), but no longer at age 12 years (8% vs 13%) and age 16 years (7% vs 10%).

After adjustment for confounders, girls with early pubertal timing had 1.54 cm larger waist circumference (95% CI .05; 3.03) and had 3.98 mm Hg higher systolic BP (95% CI 1.69; 6.27) at age 16 years than those with intermediate pubertal timing (**Table II**). Levels of other cardiometabolic markers did not differ between girls with early vs intermediate pubertal timing. When we additionally adjusted for childhood BMI z score (age 8 years), the association with systolic BP remained, at a difference of 3.69 mm Hg (95% CI 1.18; 6.21). After adjusting for BMI z score at the time of cardiometabolic assessment (age 16 years), the association with systolic BP attenuated to a difference of 2.67 mm Hg (95% CI 0.43; 4.92) (**Table II**). Because waist circumference may be a better proxy for adiposity than BMI, we repeated analyses adjusting for waist circumference z score instead of BMI. This resulted in similar effect sizes and did not change interpretations (data not presented).

Girls with early (≤ 11 years) menarche had 3.24-cm larger waist circumference (95% CI 1.32; 5.17) at age 16 years than those with intermediate (12-14 years) menarche, and a tendency for higher systolic BP, although this effect estimate attenuated after adjustment for confounders (2.10 mm Hg; 95% CI -0.92; 5.13) (**Table III**).

In boys, those with early pubertal timing had 0.79 mmol/mol lower HbA1c (95% CI -1.38; -0.20) at age 16 years than those with intermediate pubertal timing (**Table II**). Levels of other cardiometabolic markers did not differ between boys with early vs intermediate pubertal timing.

Girls and boys with late pubertal timing had a tendency for lower waist circumference, although the effect estimates were not statistically significant after adjustment for confounders (**Table II**). Girls with late (≥ 15 years) menarche had a borderline significantly lower waist circumference of 1.83 cm (95% CI -3.63; -.03, $P = .05$) at age 16 years than those with intermediate menarche (**Table III**).

Table I. Characteristics of the study population within categories of pubertal timing

	Girls (n = 413)			Boys (n = 384)		
	Early pubertal timing (n = 84) Mean (SD) or %	Intermediate pubertal timing (n = 240) Mean (SD) or %	Late pubertal timing (n = 89) Mean (SD) or %	Early pubertal timing (n = 88) Mean (SD) or %	Intermediate pubertal timing (n = 211) Mean (SD) or %	Late pubertal timing (n = 85) Mean (SD) or %
Sociodemographic characteristics						
Ethnicity						
% Dutch	91.6	91.1	92.9	93.0	95.2	91.5
% Non-Dutch Western	2.4	3.8	4.7	2.3	3.4	1.2
% Non-Western	6.0	5.1	2.4	4.7	1.4	7.3
Maternal education						
% Low	17.9	10.8	15.7	20.5	15.2	16.5
% Intermediate	36.9	42.9	40.5	35.2	39.3	35.3
% High	45.2	46.3	43.8	44.3	45.5	48.2
Paternal education						
% Low	16.9	18.1	16.9	21.6	12.0	15.3
% Intermediate	37.4	29.5	30.3	34.1	33.7	36.5
% High	45.8	52.3	52.8	44.3	54.3	48.2
Pubertal assessment						
Puberty development scale at age 11 y (1-4)						
Puberty development scale at age 11 y (1-4)	3.4 (0.8)	1.5 (0.7)	1.1 (0.6)	1.5 (0.9)	1.2 (0.6)	1.1 (0.5)
Puberty development scale at age 14 y (1-4)	3.9 (0.5)	3.4 (0.8)	2.5 (1.3)	4.1 (0.4)	2.6 (0.7)	1.6 (1.0)
Puberty development scale at age 16 y (1-4)	4.0 (0.3)	3.8 (0.4)	2.8 (0.6)	3.8 (0.5)	3.4 (0.5)	2.0 (0.6)
Pubertal assessment at age 16 y						
Growth spurt (1-4)	4.0 (0)	4.0 (0.2)	3.4 (1.1)	3.8 (0.5)	3.7 (0.5)	3.0 (0.8)
Skin change (1-4)	3.5 (0.5)	3.4 (0.5)	2.7 (0.9)	3.4 (0.5)	3.2 (0.4)	2.5 (0.7)
Pubic hair (1-4)	3.9 (0.4)	3.8 (0.4)	3.1 (0.4)	3.6 (0.5)	3.3 (0.5)	3.0 (0.4)
Breast development (1-4)	3.7 (0.5)	3.4 (0.5)	2.9 (0.4)	-	-	-
Age at menarche (y)	11.9 (1.0)	13.2 (1.0)	13.9 (1.2)	-	-	-
Facial hair (1-4)	-	-	-	3.0 (0.5)	2.6 (0.6)	2.0 (0.6)
Voice change (1-4)	-	-	-	3.8 (0.4)	3.6 (0.5)	2.6 (0.7)
Cardiometabolic assessment						
At age 8 y						
BMI (z score)	0.4 (0.9)	-0 (0.9)	-0.2 (1.0)	0.2 (1.0)	0.1 (0.9)	-0.1 (0.9)
% Overweight/obese	24.0	9.8	10.4	17.6	12.1	4.2
% Thin or very thin	1.3	6.8	11.7	5.4	5.5	7.0
At age 12 y						
BMI (z score)	0.5 (1.0)	-0 (1.0)	-0.2 (1.0)	0.2 (0.9)	0.2 (1.1)	-0.1 (1.0)
% Overweight/obese	20.0	7.6	6.5	7.8	13.1	7.7
% Thin or very thin	2.7	8.1	15.6	6.5	9.1	9.0
At age 16 y						
BMI (z score)	0.4 (1.0)	0.1 (0.9)	-0.3 (1.0)	0.1 (0.9)	0.1 (1.0)	-0.3 (1.0)
% Overweight/obese	18.3	8.3	5.6	6.8	10.4	5.9
% Thin or very thin	6.1	8.8	15.7	3.4	9.0	17.7
Age at clinical assessment (y)	16.4 (0.2)	16.4 (0.2)	16.3 (0.2)	16.4 (0.2)	16.3 (0.2)	16.3 (0.2)
Height (cm)	170.1 (5.8)	170.4 (6.2)	168.9 (6.1)	183.6 (6.3)	182.0 (6.1)	179.6 (7.7)
Height-for-age (z score)	0.2 (0.9)	0.2 (1.0)	.0 (0.9)	0.5 (0.8)	0.3 (0.8)	-0 (1.0)
Waist circumference (cm)	71.9 (7.2)	70.4 (6.2)	68.9 (5.1)	74.8 (5.9)	74.6 (6.7)	73.0 (6.5)
Waist-to-height ratio	0.4 (0)	0.4 (0)	0.4 (0)	0.4 (0)	0.4 (0)	0.4 (0)
TC (mmol/L)	4.1 (0.7)	4.2 (0.7)	4.1 (0.8)	3.6 (0.8)	3.7 (0.6)	3.6 (0.6)
HDL cholesterol (mmol/L)	1.4 (0.3)	1.5 (0.4)	1.5 (0.3)	1.2 (0.3)	1.3 (0.3)	1.3 (0.3)
Total/HDL cholesterol ratio	3.0 (0.8)	3.0 (0.8)	3.0 (1.1)	3.0 (0.8)	3.0 (0.7)	2.8 (0.7)
Systolic BP (mm Hg)	116.5 (10.2)	112.4 (8.6)	111.9 (9.5)	121.6 (8.4)	119.3 (9.6)	118.2 (10.2)
Diastolic BP (mm Hg)	68.7 (6.5)	67.2 (6.8)	66.5 (6.6)	65.9 (6.0)	65.0 (6.5)	64.7 (7.2)
HbA1c (mmol/mol)	33.1 (4.2)	33.6 (4.2)	33.1 (2.3)	32.7 (2.0)	33.4 (2.2)	33.4 (2.5)

BP, blood pressure; HbA1c, glycated hemoglobin.

Discussion

We observed that 16-year-old girls with early puberty have higher systolic BP, which suggests that the increased cardiometabolic risk observed in adult women with early menarche manifests in adolescence. The systolic BP difference in our study (3.98 mm Hg) was comparable with the difference observed in American girls of around the same age; 4.3 mm Hg for early vs late maturing¹⁸ and 1.24 mm Hg for each 1-year earlier age at menarche.⁸ These findings are also consistent with

studies that observed increased risks for hypertension and CVD in adult women with early menarche.²⁻⁴

As an explanation for the increased risk of overweight and CVD in women with early menarche, it has been suggested that this association reflects earlier timing of puberty in girls who were already overweight in childhood.^{1,9} In our study, adjusting for childhood (age 8 years) BMI or waist circumference did not explain the association of early puberty with higher BP in girls. It may be that early pubertal timing influences cardiometabolic risk aside from adiposity by altering the timing of exposure to endogenous hormones or the lifetime

Table II. Differences* in levels of cardiometabolic markers at age 16 years among girls and boys with early or late pubertal timing compared with those with intermediate pubertal timing

	Waist circumference (cm)	TC (mmol/L)	HDL cholesterol (mmol/L)	TC/HDL cholesterol ratio	Systolic BP (mm Hg) [†]	Diastolic BP (mm Hg) [†]	HbA1c (mmol/mol)
Girls with intermediate pubertal timing—absolute level (reference)	70.4	4.2	1.5	3.0	112.4	67.2	33.6
Girls with early pubertal timing [‡]							
Crude	1.44 (−0.11; 2.99)	−.07 (−0.26; 0.12)	−.01 (−0.10; .08)	−.04 (−0.26; 0.18)	4.13 (1.84; 6.42) [§]	1.50 (−0.18; 3.17)	−0.51 (−1.51; 0.50)
Adjusted [¶]	1.54 (.05; 3.03)	−.09 (−0.28; 0.10)	−.01 (−0.10; .09)	−.08 (−0.30; 0.15)	3.98 (1.69; 6.27) [§]	1.43 (−0.27; 3.14)	−0.52 (−1.54; 0.51)
+ BMI (z score) age 8 y	—	−.09 (−0.30; 0.13)	−.01 (−0.11; .08)	−.07 (−0.31; 0.18)	3.69 (1.18; 6.21) [§]	0.84 (−0.99; 2.68)	−0.76 (−1.91; 0.39)
+ BMI (z score) age 16 y	—	−0.15 (−0.34; .04)	.01 (−.08; 0.10)	−0.15 (−0.38; .07)	2.67 (0.43; 4.92) [§]	0.73 (−0.98; 2.43)	−0.47 (−1.51; 0.57)
Girls with late pubertal timing [‡]							
Crude	−1.52 (−3.03; −.01)	−0.10 (−0.29; .09)	.01 (−.08; 0.10)	−.05 (−0.27; 0.17)	−0.70 (−2.95; 1.55)	−0.87 (−2.51; 0.78)	−0.48 (−1.48; 0.52)
Adjusted [¶]	−0.98 (−2.45; 0.49)	−.09 (−0.29; 0.10)	.001 (−.09; .09)	−.03 (−0.26; 0.19)	−0.55 (−2.83; 1.73)	−0.82 (−2.52; 0.87)	−0.66 (−1.69; 0.37)
+ BMI (z score) age 8 y	—	−.08 (−0.29; 0.13)	−.002 (−0.10; .09)	−.02 (−0.26; 0.23)	−0.57 (−3.04; 1.91)	−0.48 (−2.28; 1.33)	−0.79 (−1.92; 0.34)
+ BMI (z score) age 16 y	—	−.04 (−0.23; 0.15)	−.01 (−0.10; .08)	.03 (−0.19; 0.25)	−0.17 (−2.37; 2.03)	−0.67 (−2.34; 1.01)	−0.67 (−1.70; 0.36)
Boys with intermediate pubertal timing—absolute level (reference)	74.6	3.7	1.3	3.0	119.3	65.0	33.4
Boys with early pubertal timing [‡]							
Crude	0.26 (−1.36; 1.87)	−.07 (−0.23; .09)	−.03 (−0.10; .04)	.003 (−0.18; 0.19)	2.34 (−.03; 4.71)	0.86 (−0.77; 2.49)	−0.75 (−1.33; −0.18) [§]
Adjusted [¶]	−.05 (−1.71; 1.61)	−.02 (−0.18; 0.14)	−.04 (−0.11; .03)	.05 (−0.13; 0.24)	1.78 (−0.64; 4.20)	0.60 (−1.06; 2.25)	−0.79 (−1.38; −0.20) [§]
+ BMI (z score) age 8 y	—	−.08 (−0.25; .09)	−.04 (−0.11; .04)	.01 (−0.19; 0.21)	1.47 (−1.00; 3.95)	−.09 (−1.86; 1.69)	−0.61 (−1.23; .02)
+ BMI (z score) age 16 y	—	−.05 (−0.21; 0.11)	−.04 (−0.11; .03)	.03 (−0.15; 0.22)	2.00 (−0.31; 4.32)	0.80 (−0.86; 2.45)	−0.80 (−1.38; −0.21) [§]
Boys with late pubertal timing [‡]							
Crude	−1.57 (−3.22; .07)	−.07 (−0.22; .09)	.05 (−.02; 0.11)	−0.18 (−0.37; .0002)	−1.28 (−3.69; 1.13)	−0.45 (−2.11; 1.21)	.02 (−0.55; 0.59)
Adjusted [¶]	−1.18 (−2.88; 0.51)	−.09 (−0.25; .07)	.03 (−.04; 0.10)	−0.17 (−0.36; .02)	−1.22 (−3.68; 1.25)	−0.44 (−2.13; 1.25)	.08 (−0.51; 0.67)
+ BMI (z score) age 8 y	—	−.09 (−0.27; .09)	.05 (−.03; 0.12)	−0.18 (−0.39; .02)	−2.49 (−5.02; .04)	−1.50 (−3.31; 0.32)	0.41 (−0.23; 1.05)
+ BMI (z score) age 16 y	—	−.02 (−0.18; 0.14)	.02 (−.05; .09)	−.08 (−0.27; 0.10)	−0.48 (−2.86; 1.90)	−0.37 (−2.07; 1.33)	0.12 (−0.48; 0.71)

PDS, pubertal development scale; P75/P25, 75th/25th percentile.

*Regression coefficient (95% CI) of the mean level of the cardiometabolic marker among adolescents with early or late pubertal timing compared with the mean level among those with intermediate pubertal timing.

†Adjusted for cuff size in all models.

‡Early puberty was defined as a PDS > P75 at age 11 years for girls, and age 14 for years boys. Late puberty was defined as a PDS < P25 at age 16 years for girls and boys.

§P < .05.

¶Adjusted for age at clinical assessment, height, ethnicity, maternal education, and paternal education. Subsequently, models additionally adjusted for BMI (z score) either at age 8 or at age 16 years (excluding height).

Table III. Differences* in levels of cardiometabolic markers at age 16 years among girls with early or late menarche compared with girls with intermediate menarche

	Intermediate menarche (12-14 y) Absolute level (reference)	Early menarche (≤11 y) difference	Late menarche (≥15 y) difference
Waist circumference (cm)	70.5	3.24 (1.32; 5.17) [†]	-1.83 (-3.63; -.03)
TC (mmol/L)	4.1	-.01 (-0.26; 0.24)	-.03 (-0.27; 0.20)
HDL cholesterol (mmol/L)	1.4	.01 (-0.11; 0.13)	.01 (-0.10; 0.12)
TC/HDL cholesterol ratio	3.0	.01 (-0.28; 0.30)	.04 (-0.23; 0.30)
Systolic BP (mm Hg) [‡]	113.3	2.10 (-0.92; 5.13)	-1.92 (-4.81; 0.97)
Diastolic BP (mm Hg) [‡]	67.6	0.34 (-1.89; 2.57)	-1.82 (-3.95; 0.31)
HbA1c (mmol/mol)	33.4	-0.15 (-1.48; 1.19)	-0.30 (-1.54; 0.93)

*Regression coefficients (95% CIs) adjusted for age at clinical assessment, height, ethnicity, maternal education, and paternal education.

[†] $P < .05$.

[‡]Additionally adjusted for cuff size.

cumulative dose.¹⁹ However, we cannot exclude the possibility that other specific aspects of childhood adiposity (eg, proportion or distribution of body fat, or the proportion of visceral vs subcutaneous fat) may exert effects on BP beyond BMI or waist circumference.

Many previous studies investigated cardiometabolic markers at different ages during adolescence or assessed variation in cardiometabolic marker levels by pubertal stage. Such studies do not categorize individual adolescents as having early or late pubertal timing (taking in account their age), but categorize adolescents according to their pubertal stage at one time point (eg, those with Tanner stage II would be categorized as “early” puberty, irrespective of their age at that stage). We found only 4 studies that evaluated differences in cardiometabolic markers between adolescents categorized as early or late pubertal timing, while taking in account their age.^{7-9,18} Three studies assessed menarcheal age in girls,⁷⁻⁹ and one study assessed Tanner stages (a puberty scale similar to the PDS based on physical examination of external primary and secondary sex characteristics) in boys and girls.¹⁸ As in our study, girls with self-reported early menarche or early pubertal timing developed increased BP in late adolescence in 2 prospective studies,^{8,18} and this was independent of baseline BMI¹⁸ or changes in body composition.⁸ In the Young Finns Study⁹ and the Bogalusa Heart Study,⁷ early menarche was not associated with increased BP, but there were several methodological limitations to these studies that may have prevented the detection of associations. For example, a wide age range (9-18 years) and measurement of BP before onset of menarche,⁹ and high adiposity in girls with late menarche that may have obscured subtle differences in BP.⁷

Our results in boys are consistent with 1 prospective study in African American boys, observing that early vs nonearly maturing boys did not develop unfavorable BMI, waist circumference, and BP.¹⁸ Mild transient insulin resistance occurs during normal puberty, with higher circulating insulin levels near the end of puberty (Tanner stage V).²⁰ Those with advanced puberty may have higher insulin levels and lower glucose levels earlier than those with later puberty, possibly explaining the lower HbA1c levels at age 16 years in boys with early compared with intermediate pubertal timing. Although this is an interesting

finding, it is difficult to interpret. It may be that these differences will diminish toward adulthood.

Although levels of cholesterol change with age during adolescence, we found no association of early or late pubertal timing with cholesterol levels (HDL cholesterol, TC, or TC/HDL cholesterol ratio), which is consistent with previous research in adolescent populations.^{1,7-9}

We observed that pubertal timing was inversely associated with waist circumference in girls, which is in line with previous findings.^{8,9} We found no evidence of unfavorable cardiometabolic markers in boys and girls with late pubertal timing or menarche. Previous studies, including the United Kingdom Million Women Study and Biobank Study, observed that adult women with late menarche (≥15 years) had increased risk of coronary heart disease,^{2,4} and women with menarche at 16-18 years had a slightly increased risk of all-cause and coronary heart disease mortality.^{21,22} Remarkably, women with late menarche had a 0.24 kg/m² lower BMI than women with menarche <15 years in a previous meta-analysis¹ and in these individual studies. Potential mechanisms may be inflammatory diseases²³ and childhood undernutrition and underweight,^{24,25} which are associated with delayed puberty and cardiometabolic risk. Our results indicate that the cardiometabolic risk in girls with late pubertal timing or menarche is not yet increased in 16-year-old girls, suggesting that exposures after adolescence might contribute to the increased CVD risk in adult women.

Some limitations should be addressed. Pubertal assessment was based on self-reports without external objective validation, but the PDS has reasonable agreement with physical examinations and is stable over time.^{12,26} It has been observed that adolescents who are substantially more physically developed than their same-aged peers underestimate pubertal maturation, whereas adolescents who are less physically developed overestimate pubertal maturation.²⁶ This may have resulted in an underestimation of the strength of associations, as the degree of misreporting pubertal development is unlikely to be related to levels of cardiometabolic markers or BMI.²⁶ Our study population consisted of only 20% (799/3963) of the original cohort, which is a potential weakness. However, power calculations indicated that the sample size was

sufficient to detect a clinically relevant difference of 2.4 cm in waist circumference. Adolescents with a lower socioeconomic position (as reflected by parental education) and of non-Western ethnicity were under-represented in the current study population, compared with the total study population. The mean age at menarche in our study population (13.1 years, SD 1.2) was comparable with the 50th percentile age at menarche in 6270 girls in The Netherlands in 2009 (13.1 years, 95% CI 12.9-13.2),²⁷ but our results may not be generalizable to other ethnic groups. Further, although socioeconomic disadvantage is strongly associated with adult CVD, associations of pubertal timing with cardiometabolic markers may be assumed to be in the same direction for adolescents of lower or higher socioeconomic position.

Early puberty may have negative consequences for adult cardiometabolic health, and has been associated with several other disorders (eg, polycystic ovarian syndrome, and breast, ovarian, and endometrial cancers).^{19,28,29} Overweight is a major risk factor for these disorders, which emphasizes the role of adiposity in associations with pubertal timing especially given our finding that girls with early pubertal timing have a higher BMI during childhood. Lifestyle factors such as physical activity may be intermediate factors on the pathway from pubertal timing to cardiometabolic markers. These topics should be further explored by future studies. ■

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