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 population 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 (alpha) of .05, a clinically relevant difference[13] 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 plots[14] 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,