Age at Menarche and Cardiometabolic Risk in Adulthood: The Coronary Artery Risk Development in Young Adults Study

Jill Dreyfus, PhD, MPH[1], David R. Jacobs, Jr., PhD[1], Noel Mueller, PhD, MPH[2], Pamela J. Schreiner, PhD[1], Antoinette Moran, MD[1], Mercedes R. Carnethon, PhD[3], and Ellen W. Demerath, PhD[1]

Objective To examine the association of menarche timing with cardiometabolic risk factors into early to mid-adulthood, comparing African American and White women.

Study design Analyses included 2583 women (African American = 1333; White = 1250) from the Coronary Artery Risk Development in Young Adults cohort study over 25 years of follow-up (1985-2011). Outcomes included type 2 diabetes, metabolic syndrome, adiposity, glucose, insulin, blood pressure, and blood lipids. Cox models or repeated measures linear regression models estimated the association between age at menarche and the outcomes.

Results Each 1-year earlier age at menarche was associated with higher mean body mass index among African American (0.88 ± 0.12 kg/m^2, $P < .0001$) and White (0.89 ± 0.10 kg/m^2, $P < .0001$) women. After body mass index adjustment, each 1-year earlier age at menarche was associated with higher triglycerides (2.26 ± 0.68 mg/dL, $P = .001$) and glucose (0.34 ± 0.11 mg/dL, $P = .002$), and greater risk for incident impaired fasting glucose (hazard ratio = 1.13, 95% CI 1.04-1.20) and metabolic syndrome (hazard ratio 1.19, 95% CI 1.11-1.26) among White women only.

Conclusions Excess adiposity associated with earlier menarche is sustained through mid-adulthood, and primarily drives higher cardiometabolic risk factor levels. However, White women with earlier menarche had increased risk of a number of insulin-resistance related conditions independent of adiposity. The cardiometabolic impact of earlier menarche was weaker in African American women despite higher average adiposity. Weight maintenance would likely reduce but may not completely eliminate the elevated cardiometabolic risk of earlier menarche. *(J Pediatr 2015;167:344-52)*.

See editorial, p 225

A growing number of studies report associations between early age at menarche and increased risk for cardiovascular disease (CVD)-related risk factors, such as type 2 diabetes mellitus (T2DM), high blood pressure, and metabolic syndrome (MetS).[1-7] However, early menarche is also strongly associated with obesity, which increases the risk for these adulthood diseases.[8,9] Recent studies conflict about the confounding or mediating role of childhood and adulthood obesity in the relationship between earlier puberty and cardiometabolic risk factors,[1-3,6,10,11] possibly because childhood obesity and puberty may influence each other through common pathways such as hormonal changes and insulin resistance.[5,12] Longitudinal data on this topic are scarce[5] and would help clarify the relationship between the timing of menarche, adiposity accumulation, and other cardiometabolic risk factors.

Although race appears to be an independent risk factor for early menarche,[13,14] as well as for certain cardiometabolic conditions,[15] the relationship of age at menarche with cardiometabolic risk among African American women has not been well studied. Most reports have included women of European descent only[6,10,11,16-20] or did not look at risk specifically among African American women.[2,21,22] In the Atherosclerosis Risk in Communities (ARIC) study, age at menarche was

ARIC	Atherosclerosis Risk in Communities
BMI	Body mass index
CARDIA	Coronary Artery Risk Development in Young Adults
CVD	Cardiovascular disease
HDL-C	High-density lipoprotein-cholesterol
HR	Hazard ratio
IFG	Impaired fasting glucose
LDL-C	Low-density lipoprotein-cholesterol
MetS	Metabolic syndrome
T2DM	Type 2 diabetes mellitus

From the [1]University of Minnesota, School of Public Health, Minneapolis, MN; [2]Columbia University, Mailman School of Public Health, New York, NY; and [3]Northwestern University, Feinberg School of Medicine, Chicago, IL

The Coronary Artery Risk Development in Young Adults Study is supported by the National Heart, Lung, and Blood Institute and the Intramural Research Program of the National Institute on Aging (HHSN268201300025C, HHSN268201300026C, HHSN268201300027C, HHSN268201300028C, HHSN268201300029C, HHSN268200900041C). J.D. was supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health (T32HL007779); she currently is employed at Premier, Inc. The other authors declare no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2015.04.032

associated with T2DM among White, but not African American women during mid- to late-adulthood.[3]

The current study evaluates the association between age at menarche and CVD risk factors in a prospective cohort of young to middle-aged women with the following aims: (1) assess race-specific associations between age at menarche and incident T2DM, impaired fasting glucose (IFG), and MetS over 25 years of follow-up; and (2) examine associations of age at menarche with components of cardiometabolic risk (adiposity, glucose, insulin, blood pressure, and blood lipids) during follow-up. We also considered whether any observed associations were independent of body mass index (BMI) measured in young adulthood. We hypothesized an independent association of earlier age at menarche with cardiometabolic risk factors in adulthood, and given findings from ARIC, stronger associations among White women.

Methods

We used data from the Coronary Artery Risk Development in Young Adults (CARDIA) study. CARDIA included 5115 African American and White men (n = 2328) and women (n = 2787) aged 18-30 years at baseline and was designed to study the role of lifestyle and the evolution of CVD risk factors in young adults. The details of the study cohort, including eligibility criteria, sources and methods of recruitment, and follow-up have been described in detail elsewhere.[23] Briefly, participants were recruited from four US communities: Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California. Data for our analyses were collected during clinic visits at the baseline and follow-up exams over 25 years (1985-2011). The retention rates at years 2, 5, 7, 10, 15, 20, and 25 were 90%, 86%, 81%, 79%, 74%, 72%, and 72%, respectively. The institutional review boards at each of the study sites approved the study, and participants provided informed consent.

Analyses excluded women with missing age at menarche (n = 118), or who reported their age at menarche as <8 (n = 1) or >17 (n = 9) years as we were interested in studying women within the normal range of menarche timing. Other exclusions were those with diabetes (n = 20), missing diabetes status (n = 45), or missing BMI (n = 11) at the baseline visit, for an overall sample size of 2583 women (African American = 1333, White = 1250). For incident IFG and MetS, women with those conditions at baseline were also excluded (IFG: n = 38; MetS: n = 49) to ensure that onset was after completion of puberty (ie, incident cases instead of prevalent cases). The final samples for the IFG and MetS analyses were 2545 and 2534, respectively. For the analysis of changes in cardiometabolic risk factors during follow-up, time points were excluded for patients who were pregnant or missing an outcome variable, or who had developed diabetes at any time prior to the visit. The baseline demographic and cardiovascular risk factor characteristics of those included in these analyses were similar to those of the overall cohort before exclusions.[23]

Age at menarche was defined as the age in whole years at the first menstrual period. Age at menarche was assessed at baseline and at visit 2 by self-report on a questionnaire by asking "How old where you when you began menstruating?". Correlation between reported age at menarche at baseline and at visit 2 was high (r = 0.84). We used age at menarche reported at the baseline visit because it was closest in time to the event. We included age at menarche reported at baseline as both continuous and categorical (early [8-11 years], average [12-13 years], and late [14-17 years]) variables in separate models.

Diabetes status was assessed at baseline and at each CARDIA clinic visit. T2DM was defined among nonpregnant women as fasting (for 8 hours) glucose ≥7.0 mmol/L (126 mg/dL), hemoglobin A1c ≥6.5%, 2-hour oral glucose tolerance ≥11.1 mmol/L (200 mg/dL), or use of diabetes medication. The 2-hour oral glucose tolerance test was administered at visit years 10, 20, and 25 only, and hemoglobin A1c was measured at years 20 and 25 only.

IFG was defined as fasting glucose ≥5.6 mmol/L (100 mg/dL) but <7.0 mmol/L (126 mg/dL) and not taking diabetes medication. MetS was defined according to the National Cholesterol Education Program's Adult Treatment Panel III report revised criteria for women of 3 or more of the following factors: waist circumference >88 cm, systolic blood pressure ≥130/85 mm Hg (or use of antihypertensive medication), high-density lipoprotein-cholesterol (HDL-C) <2.8 mmol/L (50 mg/dL), triglycerides ≥8.3 mmol/L (150 mg/dL) (or use of lipid-lowering medication), or fasting glucose ≥5.6 mmol/L (100 mg/dL) (or use of hypoglycemic medication).[24]

Blood pressure was measured 3 times at each visit after a 5-minute rest, and the mean of the last 2 measurements were used in this analysis. Weight (kg), height (cm), and waist circumference (cm) were measured at each clinic visit while participants dressed in scrub suits and removed shoes. Body height (cm) and weight (kg) were measured with a calibrated scale and a vertical ruler. BMI was calculated as weight (kg)/height^2 (m^2) at each examination. An enzymatic method was used to measure plasma concentrations of total cholesterol, HDL-C, and triglycerides. HDL-C was measured after dextran-magnesium precipitation,[25] and low-density lipoprotein-cholesterol (LDL-C) was calculated by using the Friedewald equation.[26] The test-retest reliability coefficients for split specimens of total, HDL-C, LDL-C, and triglycerides were high, at >0.98.[27] Additional details of the CARDIA examination procedures were published previously.[27,28]

The covariates age (years), race (African American or White), parental history of diabetes (yes/no), oral contraceptive use (yes/no), smoking status (never, former, current), physical activity level (metabolic equivalent of task-h/wk), alcohol consumption (g/d), and education (<high school, high school, >high school) were all self-reported at baseline. Physical activity prior to high school and during high school was recalled at the baseline visit using an activity scale of 1 (physically inactive) to 5 (very active). Antihypertensive and hypoglycemic medication use was queried at all visits, and use of lipid-lowering