Consumption of caffeinated and artificially sweetened soft drinks is associated with risk of early menarche[1,2]

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ABSTRACT

Background: Early menarche has been linked to risk of several chronic diseases. Prospective research on whether the intake of soft drinks containing caffeine, a modulator of the female reproductive axis, is associated with risk of early menarche is sparse.

Objective: We examined the hypothesis that consumption of caffeinated soft drinks in childhood is associated with higher risk of early menarche.

Design: The National Heart, Lung, and Blood Institute Growth and Health Study recruited and enrolled 2379 (1213 African American, 1166 Caucasian) girls aged 9–10 y (from Richmond, CA; Cincinnati, OH; and Washington, DC) and followed them for 10 y. After exclusions were made, there were 1988 girls in whom we examined prospective associations between consumption of caffeinated and noncaffeinated sugar- and artificially sweetened soft drinks and early menarche (defined as menarche age <11 y). We also examined associations between intakes of caffeine, sucrose, fructose, and aspartame and early menarche.

Results: Incident early menarche occurred in 165 (8.3%) of the girls. After adjustment for confounders and premenarcheal percentage body fat, greater consumption of caffeinated soft drinks was associated with a higher risk of early menarche (RR for 1 serving/d increment: 1.47; 95% CI: 1.22, 1.79). Consumption of artificially sweetened soft drinks was also positively associated with risk of early menarche (RR for 1 serving/d increment: 1.43; 95% CI: 1.08, 1.88). Consumption of noncaffeinated soft drinks was not significantly associated with early menarche (RR for 1 serving/d increment: 0.88; 95% CI: 0.62, 1.25); nor was consumption of sugar-sweetened soft drinks (RR for 1 serving/d increment: 1.15; 95% CI: 0.95, 1.39). Consistent with the beverage findings, intakes of caffeine (RR for 1-SD increment: 1.22; 95% CI: 1.08, 1.37) and aspartame (RR for 1-SD increment: 1.20; 95% CI: 1.10, 1.31) were positively associated with risk of early menarche.

Conclusion: Consumption of caffeinated and artificially sweetened soft drinks was positively associated with risk of early menarche in a US cohort of African American and Caucasian girls. *Am J Clin Nutr* 2015;102:648–54.

Keywords: puberty, epidemiology, diet, caffeine, aspartame, sugar-sweetened beverages

INTRODUCTION

There is growing evidence that early menarche onset is associated with a risk of myriad chronic diseases, including type 2 diabetes (1, 2), nonalcoholic fatty liver disease (3), cardiovascular disease (4, 5), and hormone-related cancers (6, 7). In light of the evidence that early menarche may be a harbinger for adult chronic disease, and evidence that the average age at menarche onset continues to decrease (8, 9), there is increasing need to identify modifiable factors that might prevent early onset of menarche.

Childhood diet is a modifiable factor that may play a role in pubertal timing (10). A recent study reported that sugar-sweetened soft drink consumption was associated with higher risk of earlier menarche (11). However, compared with regular soft drinks, diet soft drinks showed a similar, if not stronger, association in this study (11). Caffeine intake in this study was also independently associated with earlier menarche (11), which suggests that it may be partly responsible for the associations between sugar- and artificially sweetened soft drinks and menarcheal timing.

Children may be susceptible to the effects of soft drinks containing caffeine because specific regions of their brain—including the hypothalamic-pituitary-adrenocortical axis, which regulates pubertal timing (12)—are still developing. Because of caffeine's potentially negative effect on neurological and other physiological systems, the American Academy of Pediatrics has indicated that intake of caffeinated drinks should be discouraged for all children (13). The purpose of our investigation was to examine the prospective association between consumption of soft drinks, particularly those that are caffeinated, and risk of early menarche in a biracial sample of girls from the United States. We hypothesized that consumption of caffeinated soft drinks is associated with higher risk of early menarche.

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[2] Supplemental Tables 1–3 are available from the "Supplemental data" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

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METHODS

Study design

The National Heart, Lung, and Blood Institute Growth and Health Study (NGHS)[7] was formed in 1987–1978 to investigate racial differences in diet, physical activity, and familial and psychosocial factors in relation to obesity. The details of the study cohort—including design, eligibility criteria, sources, methods of recruitment and data collection, and means of assessing pubertal status—were described elsewhere (14).

Study participants

The study enrolled 2379 (1213 African American, 1166 Caucasian) girls 9–10 y of age from 3 centers: University of California, Berkeley; University of Cincinnati/Cincinnati Children's Medical Center; and Westat, Rockville, MD. The choice of these clinical centers was informed by census track information to ensure a wide distribution of household income and parental education within each race. Girls were eligible for enrollment in the NGHS if they self-identified as non-Hispanic African American or Caucasian, had racially concordant parents or guardians, and were 9–10 y of age (or within 2 wk of their 9th or 10th birthdays) at the time of the first clinical visit. Girls in the study gave assent, and their parents or guardians gave consent. The institutional review boards of each participating institution approved the study protocol, and an independent monitoring board provided study oversight. The procedures followed were in accordance with the ethical standards of the Declaration of Helsinki of 1975.

NGHS participants were followed annually for 10 visits, between 1986 and 1997. Annual follow-up rates through year 10 varied from 74% to 95%; almost 90% of the girls originally enrolled in the cohort participated through year 10. Girls attended an average of 8.8 visits (8.6 for Caucasian girls and 9.0 for African American girls).

Of the 2379 girls enrolled in the NGHS at baseline, we excluded those who had already reached menarche at the time of the baseline examination (n = 96), because we were interested in exposures before the onset of menarche. We also excluded those who never reported menarche onset during the 10-y follow-up (n = 22). We further excluded girls with diabetes at baseline (n = 5) and those who were missing information on diet (n = 210), BMI (n = 10), percentage body fat from skinfold thicknesses (n = 7), physical activity (n = 40), and parent education (n = 1), which yielded a final sample of 1988 for the current analyses.

Diet assessment

Dietary assessment for this study included a 3-d food record that provided high reporting accuracy, as documented in the initial validation study (15). We used baseline (age 9–10 y) dietary assessment to allow for temporality between diet and incident menarche. Dietitians were trained at the University of Minnesota Nutrition Coordinating Center (NCC) by staff using age-appropriate materials to instruct girls to record all food and drink for 3 consecutive days (2 weekdays and 1 weekend day). Dietitians reviewed the completed food records individually with the girls and used standardized probes to clarify incomplete responses. Default values from the NCC were used for missing information on food amounts or preparations. Study staff had a notebook of labels and pictures to help girls describe the foods and thereby minimize the amount of defaults. Food records were coded and analyzed for nutrients and other food chemicals by using the Food Table version 19 of the NCC nutrient database (16). The research dietitian excluded diet records that were considered unreliable.

Sugar-sweetened soft drinks were defined as the sum of nondiet soft drinks [cola, root beer, ginger ale, and Sprite (Coca-Cola Company)]. Artificially sweetened soft drinks were defined as the sum of diet cola, diet noncola soft drinks, and diet root beer. Intakes of sugar-sweetened and artificially sweetened colas were summed to create a variable for caffeinated soft drinks (there were no other caffeinated soft drinks reported by participants at baseline). Intakes of sugar-sweetened and artificially sweetened soft drinks without caffeine (e.g., noncolas) were then summed to create a variable for noncaffeinated soft drinks. Intakes of naturally sweetened juices (i.e., those without added sugar) were summed to create a group for natural juices.

Caffeine intake at baseline was derived from 101 items, but most of the intake (55.9%) came from sugar-sweetened or artificially sweetened soft drinks (only 17 girls in our sample consumed caffeinated coffee at time of the first clinic visit). Aspartame intake at baseline was derived from 20 items, with most (86.4%) coming from artificially sweetened drinks. Sucrose and fructose were found in 822 and 666 items in the diet, respectively.

Age at menarche assessment

Girls were queried annually by a female research assistant about the age (to the closest month) at which their menses started. Early menarche was defined as first menses at $<$11 y of age. This definition has been associated with an increased risk of chronic diseases, including type 2 diabetes (2) and all-cause and cause-specific mortality (17).

Covariate assessment

Demographic information was collected at baseline from girls and their parents (or guardians). Race (African American or Caucasian) was defined by self-report on the basis of US Census categories. The participants' ages were recorded as their age at last birthday. Highest parental educational achievement (of either parent) ranged from 0 y of education to graduate school. The girls completed a habitual physical activity questionnaire that assessed frequencies of several activities described previously (18). The questionnaire asked about usual activities in and out of school during the school year and in the summer. Activities were given an activity code of 0 to 5 based on the intensity of the activity. Duration and frequency of the activity were also taken into account to derive an overall physical activity score. The score was shown to have internal validity in this population (18).

At each annual visit, the study participants underwent anthropometric measurements by trained female examiners. Techniques for measuring skinfold thicknesses were described in detail previously (19). Triceps and subscapular skinfold thicknesses were measured twice, and a third measurement was taken if the first 2 differed by 1.0 mm. When 3 measurements were taken, the closest

[7] Abbreviations used: GUTS, Growing Up Today Study; NCC, Nutrition Coordinating Center; NGHS, National Heart, Lung, and Blood Institute Growth and Health Study.

2 were averaged. Percentage body fat was derived from the triceps and subscapular skinfold thickness measurements according to the Slaughter et al. formula (20). A stadiometer and a calibrated scale were used to measure height and weight while the girls were in stocking feet and wearing light indoor clothing. BMI was calculated as weight (in kg) divided by height (in m) squared (kg/m^2).

Statistical analysis

Intakes of beverages were converted into fluid ounces (fl oz). The total consumed for each girl, on each day of the 3-d food record, was calculated, and mean beverage consumption over this time span was then computed to obtain the girl's mean beverage intake (per fl oz) per day. One serving was equivalent to 12 fl oz. We subsequently categorized nutritional exposures into tertiles or 3-level categories, which allowed for sufficient cases of early menarche in each level. We used age at menarche onset <11 y as an outcome because we were interested in whether our exposures of interest were associated with early menarche as opposed to menarcheal timing. We used Poisson regression models with robust variances (21) to estimate RR and 95% CIs for risk of early menarche. We began with an unadjusted model (model 1) then added variables if the literature and our data indicated that they were associated with the exposure of interest and early menarche and not on the causal pathway of this association. In our first multivariable model (model 2), we adjusted for age at baseline (y), study center, race, highest parental education (<college, college, graduate school) in the household, total calories (continuous), and physical activity score (continuous). We further adjusted for percentage body fat at baseline (model 3). Finally (in model 4), we additionally adjusted for aspartame in the caffeine model, caffeine in the aspartame model, and caffeine and aspartame in the sucrose and fructose models. We also evaluated confounding by parental (either parent) smoking reported at the baseline examination, and nutrients that were associated with caffeinated soft drink intake and early menarche (fiber, vitamin E, saturated fat, polyunsaturated fat), but we did not include these covariates in the final model because they did not alter the effect estimates by >10%.

We evaluated effect modification by including in the models cross-product terms for our exposures and race (African American vs. Caucasian) and BMI at baseline (median split: 17.5). All statistical tests were 2 sided, and significance was defined at $P < 0.05$. All analyses were performed by using SAS 9.4 (SAS Institute).

RESULTS

Girls included in the current analyses ($n = 1988$) were 9–10 y of age at baseline. At the end of follow-up, they had a mean ± SD age at menarche of 12.4 ± 1.1 y. A total of 165 (8.3%) girls had their first menses before 11 y of age (but after their baseline examination). Girls with earlier menarche were on average younger at enrollment into the study, taller, heavier, more physically fit, and more likely to be African American and born to parents of lower educational status ($P < 0.05$ for all) (**Supplemental Table 1**).

Cohort characteristics by categories of caffeinated soft drink consumption are presented in **Table 1**. Girls with a higher caffeinated soft drink consumption were more likely to be Caucasian and had greater percentage fat measured by skinfold thickness (Table 1). Those with a higher caffeinated soft drink consumption also consumed more calories, with fewer of these calories coming from fiber and saturated fat and more coming from sugar. They also had higher intakes of aspartame and lower intakes of magnesium and vitamin C than did their

TABLE 1
Baseline characteristics according to categories of caffeinated soft drink consumption in a biracial cohort of US girls aged 9–10 y[1]

	Categories of caffeinated soft drink consumption			
Characteristics	0 servings/d (n = 1062)	>0 to <1 serving/d (n = 525)	≥1 serving/d (n = 401)	P[2]
Age at entry into study, y	10.0 ± 0.6	10.0 ± 0.5	10.1 ± 0.5	0.20
Race, % African American	54.4	41.0	36.7	<0.01
Height, cm	140.9 ± 7.5	140.4 ± 7.2	141.7 ± 7.5	0.17
Fat from skinfolds, %	20.8 ± 8.4	21.2 ± 8.0	22.2 ± 8.5	<0.01
BMI, kg/m^2	18.5 ± 3.8	18.2 ± 3.6	18.9 ± 3.8	0.19
Parent education ≥college, %	38.0	38.3	37.4	0.22
Television viewing, h/wk	30.8 ± 17.9	30.6 ± 15.9	30.4 ± 15.8	0.69
Activity score, METS[3]	32.0 ± 18.4	32.4 ± 20.0	32.8 ± 20.0	0.50
Diet variables				
Energy, kcal	1817.3 ± 551.9	1802.2 ± 462.0	1896.2 ± 524.5	0.04
Saturated fat, % of energy	15.1 ± 2.9	15.3 ± 2.7	14.5 ± 2.7	<0.01
Polyunsaturated fat, % of energy	6.9 ± 2.3	7.0 ± 2.3	6.8 ± 2.2	0.20
Fiber, g/1000 kcal	6.6 ± 2.1	6.0 ± 1.8	6.0 ± 2.0	<0.01
Magnesium, mg/1000 kcal	123.4 ± 27.7	114.8 ± 22.1	113.4 ± 26.1	<0.01
Vitamin C, mg/1000 kcal	52.4 ± 36.2	48.9 ± 30.6	46.2 ± 30.0	<0.01
Caffeine, mg/1000 kcal	3.6 ± 6.4	10.7 ± 8.3	20.3 ± 12.8	<0.01
Aspartame, mg/1000 kcal	2.4 ± 10.4	4.6 ± 17.6	12.5 ± 31.2	<0.01
Sugar, g/1000 kcal	61.5 ± 16.3	64.0 ± 15.8	70.0 ± 16.5	<0.01

[1]Values are means ± SDs unless otherwise indicated.
[2]Derived from ANOVA or chi-square test.
[3]METS, metabolic equivalents.

counterparts with a low caffeinated soft drink intake (Table 1). Cohort characteristics by categories of caffeine and aspartame intake can be found in **Supplemental Table 2** and **Supplemental Table 3**.

RRs and 95% CIs for early menarche according to consumption of soft drinks and natural fruit juice are shown in **Table 2**. After adjustment for confounders (study center, baseline age, race, parental education, total energy intake, physical activity score) and percentage body fat, greater consumption of caffeinated soft drinks was associated with higher risk of early menarche (RR for 1 serving/d increment: 1.47; 95% CI: 1.22, 1.79). Artificially sweetened soft drink consumption was also associated, in a monotonic fashion, with risk of early menarche (RR for 1 serving/d increment: 1.43; 95% CI: 1.08, 1.88). Sugar-sweetened soft drink consumption showed a less consistent association with early menarche. Compared with girls who consumed 0 sugar-sweetened beverages, those who consumed >0 but <1/d had a modestly elevated risk of early menarche (RR: 1.42; 95% CI: 1.01, 1.99). However, no association was found for those who consumed >1 sugar-sweetened beverage/d (RR: 1.21; 95% CI: 0.84, 1.73). Consumption of noncaffeinated soft drinks or natural fruit juice were not significantly associated with risk of early menarche (Table 2).

The results for intake of nutritional elements found in soft drinks and risk of early menarche are shown in **Table 3**. After adjustment for confounders and percentage body fat, a 1-SD increment in caffeine intake was associated with a 1.22 (95% CI: 1.08, 1.37) higher risk of early menarche. A 1-SD increment in aspartame was associated with a 1.20 (95% CI: 1.10, 1.31) higher risk of early menarche. When caffeine and aspartame were included in the same model, both remained significantly associated with early menarche (model 4, Table 3). Sucrose and fructose intakes were not associated with early menarche (Table 3).

There was no evidence that our main findings differed across strata of race (African American vs. Caucasian) or BMI (<17.5 vs. ≥17.5) (*P*-multiplicative interaction > 0.10 for both).

DISCUSSION

In this prospective cohort of African American and Caucasian girls, after control for potential confounders and percentage body fat, consumption of caffeinated, but not noncaffeinated, soft drinks was positively associated with a risk of early menarche. Consumption of artificially sweetened drinks was also associated with a higher risk of early menarche. Consistent with these findings,

TABLE 2
RR of incident menarche before 11 y of age according to baseline consumption of selected beverages in a biracial cohort of US girls enrolled at 9–10 y of age

			RR (95% CI)		
Category	Subjects, *n*	Menarche age <11 y, *n* (%)	Model 1[1]	Model 2[2]	Model 3[3]
Caffeinated soft drinks					
0 servings/d	1062	74 (7.0)	1.0 (reference)	1.0 (reference)	1.0 (reference)
>0 to <1 serving/d	525	53 (10.1)	1.45 (1.03, 2.03)	1.64 (1.16, 2.32)	1.63 (1.15, 2.30)
≥1 serving/d	401	38 (9.5)	1.36 (0.94, 1.98)	1.69 (1.17, 2.45)	1.60 (1.11, 2.32)
P-trend[4]			0.67	0.23	0.29
1 serving/d increment	1988		1.29 (1.06, 1.58)	1.52 (1.26, 1.83)	1.47 (1.22, 1.79)
Noncaffeinated soft drinks					
0 servings/d	1406	128 (9.1)	1.0 (reference)	1.0 (reference)	1.0 (reference)
>0 to <1 serving/d	345	20 (5.8)	0.64 (0.40, 1.01)	0.70 (0.45, 1.11)	0.73 (0.46, 1.15)
≥1 serving/d	237	17 (7.2)	0.79 (0.48, 1.28)	0.86 (0.53, 1.41)	0.86 (0.53, 1.39)
P-trend[4]			0.09	0.25	0.26
1 serving/d increment	1988		0.80 (0.56, 1.14)	0.87 (0.62, 1.24)	0.88 (0.62, 1.25)
Artificially sweetened soft drinks					
0 servings/d	1749	138 (7.9)	1.0 (reference)	1.0 (reference)	1.0 (reference)
>0 to <1 serving/d	132	13 (9.9)	1.25 (0.73, 2.14)	1.52 (0.90, 2.56)	1.47 (0.87, 2.47)
≥1 serving/d	107	14 (13.1)	1.66 (0.99, 2.77)	2.28 (1.35, 3.86)	2.10 (1.23, 3.58)
P-trend[4]			0.09	0.01	0.02
1 serving/d increment	1988		1.21 (0.91, 1.59)	1.52 (1.15, 1.99)	1.43 (1.08, 1.88)
Sugar-sweetened soft drinks					
0 servings/d	837	63 (7.5)	1.0 (reference)	1.0 (reference)	1.0 (reference)
>0 to <1 serving/d	593	57 (9.6)	1.28 (0.91, 1.80)	1.37 (0.97, 1.93)	1.42 (1.01, 1.99)
≥1 serving/d	558	45 (8.1)	1.07 (0.74, 1.55)	1.23 (0.85, 1.77)	1.21 (0.84, 1.73)
P-trend[4]			0.60	0.21	0.22
1 serving/d increment	1988		1.05 (0.87, 1.27)	1.15 (0.95, 1.40)	1.15 (0.95, 1.39)
Natural fruit juices					
0 servings/d	523	51 (9.8)	1.0 (reference)	1.0 (reference)	1.0 (reference)
>0 to <1 serving/d	824	58 (7.0)	0.72 (0.50, 1.03)	0.72 (0.51, 1.02)	0.73 (0.51, 1.03)
≥1 serving/d	641	56 (8.7)	0.90 (0.62, 1.29)	0.88 (0.61, 1.27)	0.92 (0.63, 1.32)
P-trend[4]			0.22	0.73	0.66
1 serving/d increment	1988		0.99 (0.82, 1.20)	0.97(0.79, 1.17)	0.98 (0.80, 1.19)

[1]Unadjusted.
[2]Adjusted for study center, baseline age, race (African American or Caucasian), parental education, total calories, and physical activity score.
[3]Adjusted as for model 2 plus percentage body fat.
[4]Calculated by treating categorical variables for beverages as continuous variables.

TABLE 3
RR of incident menarche before 11 y of age according to baseline intakes of caffeine, sugar, and aspartame in a biracial cohort of US girls enrolled at 9–10 y of age

			RR (95% CI)			
Category	No. of subjects	Menarche age <11 y, *n* (%)	Model 1[1]	Model 2[2]	Model 3[3]	Model 4[4]
Caffeine						
0 to <25 mg/d	1575	124 (7.9)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
25 to <50 mg/d	300	27 (9.0)	1.14 (0.77, 1.70)	1.45 (0.97, 2.18)	1.37 (0.92, 2.05)	1.32 (0.89, 1.98)
≥50 mg/d	113	14 (12.4)	1.57 (0.94, 2.64)	1.95 (1.19, 3.19)	1.72 (1.04, 2.85)	1.44 (0.84, 2.47)
P-trend[5]			0.14	0.01	0.03	0.12
1-SD increment	1988		1.13 (1.01, 1.26)	1.24 (1.12, 1.38)	1.22 (1.08, 1.37)	1.15 (1.02, 1.30)
Aspartame (mg/d)						
0 mg/d	1706	133 (7.8)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
<50 mg/d	154	14 (9.1)	1.17 (0.69, 1.97)	1.45 (0.87, 2.42)	1.41 (0.84, 2.35)	1.35 (0.80, 2.28)
≥50 mg/d	128	18 (14.1)	1.80 (1.14, 2.85)	2.67 (1.68, 4.24)	2.43 (1.51, 3.90)	2.17 (1.34, 3.50)
P-trend[5]			0.047	<0.01	<0.01	0.01
1-SD increment	1988		1.11 (1.01, 1.21)	1.23 (1.13, 1.34)	1.20 (1.10, 1.31)	1.14 (1.03, 1.26)
Sucrose						
Tertile 1 (0.8 to <35.5 mg/d)	662	51 (7.7)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Tertile 2 (35.5 to <55.2 mg/d)	663	61 (9.2)	1.19 (0.84, 1.70)	1.22 (0.86, 1.75)	1.22 (0.85, 1.73)	1.22 (0.83, 1.69)
Tertile 3 (55.2 to 216.6 mg/d)	663	53 (8.0)	1.04 (0.72, 1.50)	0.97 (0.65, 1.45)	0.98 (0.66, 1.48)	0.95 (0.63, 1.43)
P-trend[5]			0.84	0.88	0.94	0.79
1-SD increment	1988		1.08 (0.94, 1.25)	1.03 (0.86, 1.20)	1.04 (0.90, 1.21)	1.01 (0.86, 1.17)
Fructose						
Tertile 1 (0.9 to <17.1 mg/d)	662	56 (8.5)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Tertile 2 (17.1 to <28.2 mg/d)	663	56 (8.5)	1.00 (0.70, 1.42)	0.98 (0.68, 1.40)	0.98 (0.68, 1.39)	1.01 (0.71, 1.44)
Tertile 3 (28.2 to 102.2 mg/d)	663	53 (8.0)	0.95 (0.66, 1.35)	0.96 (0.65, 1.44)	0.94 (0.63, 1.40)	0.95 (0.64, 1.41)
P-trend[5]			0.76	0.86	0.77	0.71
1-SD increment	1988		0.98 (0.85, 1.13)	0.97 (0.84, 1.13)	0.97 (0.83, 1.13)	0.97 (0.83, 1.13)

[1]Unadjusted.
[2]Adjusted for study center, baseline age, race (African American or Caucasian), parental education, total calories, and physical activity score.
[3]Adjusted as for model 2 plus percentage body fat.
[4]Adjusted as for model 3 plus caffeine and aspartame (in sucrose and fructose models), aspartame (in caffeine model), and caffeine (in aspartame model).
[5]Calculated by treating categorical variables for caffeine, aspartame, sucrose, and fructose as continuous variables.

intakes of caffeine and aspartame—the predominant artificial sweetener used at the time this study was conducted—were independently positively associated with risk of early menarche.

Our findings largely agree with those of the one previous study that evaluated the association between caffeine intake and menarcheal timing (11). The Growing Up Today Study (GUTS) prospectively followed 5583 US girls aged 9–14 y who were premenarcheal at baseline. This study found that girls in the 5th vs. 1st quintile for caffeine intake had 17% (95% CI: 6%, 30%) greater risk of earlier menarche, after control for confounders and BMI. GUTS also found that intake of >1.5 artificially sweetened beverages/d (vs. ≤2/wk) was associated with 1.23 (95% CI: 0.96, 1.58) times higher risk of earlier menarche. Unlike our study, however, GUTS did not analyze and report the association between aspartame and menarcheal timing. GUTS also reported an association between sugar-sweetened beverages and added sugar and risk of earlier menarche that was independent of confounding factors and BMI. Other than GUTS, we are unaware of any studies that have examined the association between caffeine intake and risk of early menarche.

Whereas our findings on caffeine intake largely align with those from GUTS, differences between our findings and those of GUTS—such as the association between intake of sugar-sweetened beverages and age at menarche—may be due to incongruent study methods. Our study analyzed girls who were 9–10 y of age at the baseline examination. GUTS analyzed girls who were 9–14 y at baseline; thus, many of the girls in the GUTS sample were already beyond our early menarche (<11 y) designation. GUTS analyzed baseline dietary intake in relation to risk of menarche at any age, whereas we were interested in the prospective association between premenarcheal dietary intake and risk of menarche onset at <11 y of age, because this cutoff has been reported as a risk factor for chronic diseases, including type 2 diabetes (2) and all-cause and cause-specific mortality (17). Another difference is that GUTS derived intakes from a food-frequency questionnaire, whereas we derived intakes from 3-d dietary records.

Effects of caffeine on glucocorticoid secretion (22, 23), via modulation of the hypothalamic-pituitary-adrenocortical axis (22, 24), may be driving the association between caffeine intake and early onset of menarche. The hypothalamic-pituitary-adrenocortical axis has been shown to play a key role in pubertal timing (12). The association between caffeine intake and early menarche may also be due to insulin resistance induced by caffeine consumption (25). This idea is supported by evidence from a review which found that although caffeine increases athletic performance, it reduces insulin-mediated glucose disposal by ~30% (26), and in conjunction with the finding that hyperinsulinemia and impaired glucose homeostasis appear to be involved in menarcheal timing (27).

Our findings on artificially sweetened soft drink consumption and early menarche are novel and may also be driven by insulin-mediated pathways. Some, but not all, human studies have linked consumption of diet beverages to hyperinsulinemia (28). Experimental administration of artificial sweeteners in mice (29, 30), and in a small number of humans (29), was shown to alter gut microbiota in

a manner that increased body weight and impaired glucose regulation. Yet, in an observational study of adults, de Koning and colleagues (31) found that the association between artificially sweetened beverages and diabetes was attenuated by adjustment for previous weight change and dieting behaviors, which suggests that the associations between diet soft drink consumption and metabolic outcomes may be confounded. Unfortunately, information on previous weight change or intent to diet was lacking in our study. Thus, future epidemiologic studies that control for childhood weight gain and intention to diet are warranted to determine whether the associations for artificially sweetened beverages and aspartame and early menarche can be replicated. If our findings hold up epidemiologically, then experiments in rodents and humans, which include measurements of gut microbiota and insulin-related pathways, should be considered to elucidate potential mechanisms.

If an insulin-mediated alteration in glucose metabolism is the mechanism of action by which caffeinated or noncaloric artificially sweetened beverages increase risk of early menarche, we might have expected to see a stronger and dose-dependent association between sugar-sweetened soft drink consumption and early menarche in our analysis. One reason why we did not observe such an association could have been due to differential misclassification of sugar-sweetened soft drinks. In another study, underreporting of "unhealthy" snacks, such as sugar-sweetened soft drinks, was found to be more common in overweight girls than in normal-weight girls (32). Because overweight girls were more likely to have early menarche in our sample, differential underreporting of sugar-sweetened soft drinks, according to weight status, could have led to a weaker association between early menarche and sugar-sweetened soft drink consumption. Whereas the NGHS did not have an objective measure of sugar-sweetened soft drink intake to determine whether underreporting was differential, we adjusted our regression model for percentage body fat at baseline, and the associations were not appreciably altered.

In addition to the potential misclassification of diet—a limitation of self-reported dietary intake not unique to dietary records—our study had several other limitations. First, it is possible that consumption of soft drinks before 9–10 y of age, the earliest assessment of diet in our study, may have a different association with early menarche, especially if an undetected prepubertal surge in estrogen influenced the dietary preferences of the NGHS participants. Second, results from our study cannot be generalized to other measures of pubertal onset or tempo, because onset of menarche, breast budding, and age at appearance of pubic hair do not represent parallel pubertal events (33). Third, our findings may not apply to nonaspartame artificially sweetened beverages, because all but one of the artificially sweetened drinks reported in our study were sweetened with aspartame. Fourth, we cannot be certain that our exclusion of girls who had menarche by the time the study started did not introduce selection bias (34). Fifth, it is possible that unmeasured or residual confounding, by dietary patterns for example, influenced our findings. Finally, we cannot rule out the possibility that one or more of the statistically significant results were false positive.

In light of these limitations, our investigation was strengthened by the use of a validated 3-d dietary recall that has been shown to perform better than a 24-h recall and a 5-d food-frequency questionnaire in this sample of 9- and 10-y-olds (15), the prospective measurement of age at menarche to the nearest month, and the socioeconomic and geographic diversity of NGHS participants.

In conclusion, in a cohort of African American and Caucasian girls from the United States, greater consumption of caffeinated and artificially sweetened soft drinks at 9–10 y of age is prospectively associated with a higher risk of early menarche, independent of adiposity. Further research is needed to replicate these associations and to determine the underlying biologic mechanisms. If these findings hold up, reducing consumption of these beverages in childhood may help curb the rise in early onset of menarche.

The authors' responsibilities were as follows—NTM and MAP: designed the analytic strategy, undertook the analyses, interpreted the results, and wrote, reviewed, and edited the manuscript; DRJ: contributed to the study design, data collection, results interpretation, and manuscript revision; RFM, EWD, and JGD: contributed to the analytic strategy, results interpretation, and manuscript revision; SPK: undertook the analyses and interpreted the results; and all authors: were involved in writing the manuscript and provided final approval of the manuscript. The authors had no conflicts of interest with the submitted work.

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