

Sugar-sweetened beverage consumption and age at menarche in a prospective study of US girls

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STUDY QUESTION: Is sugar-sweetened beverage (SSB) consumption associated with age at menarche?

SUMMARY ANSWER: More frequent SSB consumption was associated with earlier menarche in a population of US girls.

WHAT IS KNOWN ALREADY: SSB consumption is associated with metabolic changes that could potentially impact menarcheal timing, but direct associations with age at menarche have yet to be investigated.

STUDY DESIGN, SIZE, DURATION: The Growing up Today Study, a prospective cohort study of 16 875 children of Nurses' Health Study II participants residing in all 50 US states. This analysis followed 5583 girls, aged 9–14 years and premenarcheal at baseline, between 1996 and 2001. During 10 555 person-years of follow-up, 94% ($n = 5227$) of girls reported their age at menarche, and 3% ($n = 159$) remained premenarcheal in 2001; 4% ($n = 197$) of eligible girls were censored, primarily for missing age at menarche.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Cumulative updated SSB consumption (composed of non-carbonated fruit drinks, sugar-sweetened soda and iced tea) was calculated using annual Youth/Adolescent Food Frequency Questionnaires from 1996 to 1998. Age at menarche was self-reported annually. The association between SSB consumption and age at menarche was assessed using Cox proportional hazards regression.

MAIN RESULTS AND THE ROLE OF CHANCE: More frequent SSB consumption predicted earlier menarche. At any given age between 9 and 18.5 years, premenarcheal girls who reported consuming > 1.5 servings of SSBs per day were, on average, 24% more likely [95% confidence interval (CI): 13, 36%; P -trend: < 0.001] to attain menarche in the next month relative to girls consuming ≤ 2 servings of SSBs weekly, adjusting for potential confounders including height, but not BMI (considered an intermediate). Correspondingly, girls consuming > 1.5 SSBs daily had an estimated 2.7-month earlier menarche (95% CI: $-4.1, -1.3$ months) relative to those consuming ≤ 2 SSBs weekly. The frequency of non-carbonated fruit drink (P -trend: 0.03) and sugar-sweetened soda (P -trend: 0.001), but not iced tea (P -trend: 0.49), consumption also predicted earlier menarche. The effect of SSB consumption on age at menarche was observed in every tertile of baseline BMI. Diet soda and fruit juice consumption were not associated with age at menarche.

LIMITATIONS, REASONS FOR CAUTION: Although we adjusted for a variety of suspected confounders, residual confounding is possible. We did not measure SSB consumption during early childhood, which may be an important window of exposure.

WIDER IMPLICATIONS OF THE FINDINGS: More frequent SSB consumption may predict earlier menarche through mechanisms other than increased BMI. Our findings provide further support for public health efforts to reduce SSB consumption.

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Key words: diet / menarche / sugar-sweetened beverage

Introduction

Age at menarche (first menses) in the USA and Western Europe is thought to have decreased substantially between the mid-19th and 20th centuries, and, to a lesser extent, over the second half of the 20th century (Euling et al., 2008; Cheng et al., 2012). During adolescence, early-maturing girls may be disadvantaged by the discordance of their physical appearance and chronological age (Waylen and Wolke, 2004); younger age at menarche is also a risk factor for breast (Hsieh et al., 1990; Rosner et al., 1994; Rosner and Colditz, 1996; Berkey et al., 1999) and endometrial cancer (Karageorgi et al., 2010). The occurrence of later menarche in girls who have experienced severe caloric restriction (Frisch and McArthur, 1974) and earlier menarche in girls with a high body mass index (BMI) (Biro et al., 2006; Dunger et al., 2005) (i.e. positive energy balance) supports the importance of nutritional factors in menarcheal timing.

Previous studies have reported associations between intake of certain nutrients, including animal and vegetable protein, but not others (e.g. total energy), with earlier age at menarche (recently reviewed by Cheng et al., 2012). Most foods and food groups, however, remain unexplored. Of particular interest are soda and other sugar-sweetened beverages (SSBs), which have experienced an upward trend in popularity (Popkin, 2010) over the same interval during which age at menarche has decreased, and may impact certain predictors of pubertal onset. Consumption of SSBs by children has been convincingly linked to weight gain (Ludwig et al., 2001; Fiorito et al., 2009), a consistent predictor of earlier menarche (Dunger et al., 2005). Pathways independent of weight gain are also possible; intake of highly glycemic foods like SSBs (Janssens et al., 1999; Ludwig, 2002) results in a rapid and immediate increase in circulating insulin concentrations, which could up-regulate hormones involved in the initiation of menarche [e.g. bioavailable sex hormones and insulin-like growth factor I (IGF-1)]. Both proposed biological pathways suggest an association between SSB consumption and earlier menarche.

We explored the association of total and individual SSBs and age at menarche in a large, prospective cohort of premenarcheal girls with up to 5 years of follow-up.

Materials and Methods

Study population

The Growing up Today Study (GUTS) is a prospective cohort of 16 875 children (9033 girls) of women enrolled in the Nurses' Health Study II (Rockett et al., 2001). The Nurses' Health Study II was composed of female nurses who were 25–42 years of age and living in one of 14 US states at study initiation in 1989; GUTS participants now live throughout the USA. A baseline questionnaire assessing physical characteristics and behaviors was administered in 1996 when children were aged 9–14 years; relevant follow-up questionnaires were administered annually through 2001, and again in

2003. In 2005, postcards were mailed to girls who had not yet reported age at menarche.

Of the 9033 girls who returned the baseline questionnaire (68% of those contacted), we excluded 39 girls who failed to answer at least 75% of the individual food items or who reported an energy intake < 500 or > 5000 kcal in 1996, 3133 girls who had attained menarche by 1996 or whose baseline status was unknown, and 278 girls who never updated their menarcheal status. The 5583 girls who were considered eligible were followed through 2001, when all but 159 had reported menarche.

Ethical approval

Parents provided written informed consent for their child's participation. This study was approved by the Brigham and Women's Hospital Institutional Review Board.

Dietary assessment

We assessed diet in 1996, 1997 and 1998 using a self-administered, semi-quantitative 132-item youth/adolescent food frequency questionnaire (YAQ). The validity and reproducibility of the YAQ has been demonstrated in children 9–18 years (Rockett et al., 1995, 1997). Abbreviated questionnaires were administered after 1998, which did not allow for calculation of nutrient intake; therefore, 1998 data were carried forward for all dietary items for 1 year for the 774 girls ($n = 14\%$) who were followed between 1999 and 2000 and for 2 years for the additional 324 girls (6%) who were followed between 2000 and 2001. Participants were asked how frequently, on average, they consumed a typical portion size of a specified food during the past year. A serving was specified as 1 can/glass for soda and diet soda, 1 glass for non-carbonated fruit drinks (including Hawaiian Punch, lemonade, Koolaid and other non-carbonated fruit drinks) and 1 glass/can/bottle for sweetened iced tea. Total SSBs were calculated as the sum of non-carbonated fruit drinks (56% of total SSB intake during follow-up), non-diet soda (32%) and sweetened iced tea (10%) (percentages do not sum to 100 due to rounding). Alcohol, coffee and hot tea were not investigated since consumption was very low, and it was unknown whether they were consumed sweetened. In addition to total and individual SSBs, we investigated diet soda and fruit juice to assess the impact of artificially and naturally sweetened beverages, respectively.

Intakes of caffeine, added sugar (i.e. sugars added to food during processing or preparation), total sugar (i.e. added and naturally occurring), protein and animal protein (in all foods and beverages) were calculated by multiplying the frequency that a unit of food or drink was consumed by the nutrient content of the specified portion, then summing across all relevant foods and beverages. Nutrient composition values for foods were obtained from the US Department of Agriculture and other sources (Rockett et al., 1995). We adjusted nutrients for total energy using the residuals from the regression of nutrient intake on total caloric intake (Willett et al., 1997).

Assessment of age at menarche

Each questionnaire queried girls on whether her menstrual periods had begun and, if so, her age at initiation, reported in age in years and calendar month. Calendar month was not reported on the 2001 or 2003 questionnaires. Menarche is a salient event that is recalled accurately, especially over short intervals of time (Koo and Rohan, 1997). To reduce potential

misclassification, we used only first reported age at menarche. When menarcheal status was not reported for ≥ 1 years, age at menarche was retrospectively assigned using data from a later questionnaire, when possible ($n = 521$, 10%). The percentage of participants whose age at menarche was retrospectively assigned was equally distributed across categories of SSB consumption (data not shown). We obtained similar results when we censored girls with missing data on menarcheal status at the time of their last status report instead of retrospectively assigning their age at menarche (data not shown). If a participant reported her year, but not month of age at menarche, the month was imputed as 6 months later than the reported integer age at menarche.

Assessment of non-dietary factors

Data on physical activity, inactivity, frequency of eating dinner as a family, household composition, height and weight were collected via self-report at baseline, and updated using subsequent questionnaires. Race was self-reported at baseline. The participants' mothers self-reported their own age at menarche in 1989 and the birthweight of their child in 1996. Activity was calculated as hours per week spent in 17 activities and team sports and inactivity was calculated as the average time spent watching TV or videos and playing video and computer games (Berkey *et al.*, 2004).

Statistical analysis

First, we used Cox proportional hazards regression to calculate the hazard ratio (HR) and 95% confidence interval (CI) for the association between SSB consumption and the event of menarche. We used a time scale of calendar time in months; person-months were calculated for participants from the time at the return of the 1996 questionnaire to menarche, June 2001, or, if they were lost to follow-up, the date of the last returned questionnaire, whichever came first. All analyses were stratified by age in months and questionnaire cycle, making the time scale equivalent to age in months.

We calculated the hazard of menarche for participants in each category of cumulatively averaged SSB consumption (Hu *et al.*, 1999). We modeled exposure categories using indicator variables, with the category of lowest consumption considered the reference group. We further explored the association between SSB consumption and age at menarche among girls of different ages by calculating a series of HRs for increasingly longer intervals of follow-up, with the end of follow-up defined as the maximum age at questionnaire return (e.g. ≤ 12 years) (Hernan, 2010).

For reasons including control of confounding by physical activity and body size, we adjusted for energy intake (quintiles) in all models (Willett *et al.*, 1997). Pubertal timing has a strong racial (Herman-Giddens *et al.*, 1997; Chumlea *et al.*, 2003) and genetic component (Dvornyk and Wagar-ul-Hag, 2012), but is also influenced by childhood growth trajectory and body size (dos Santos Silva *et al.*, 2002; Dunger *et al.*, 2005), physical activity level (Chavarro *et al.*, 2004) and family relationships, including father absence (Ellis, 2004). We therefore included the following covariates in multivariable models: birthweight (quintiles), height (quintiles), physical activity (quintiles), inactivity (quintiles), race (non-Hispanic white, other), household composition (no father or stepfather, father, stepfather), frequency of eating dinner as a family (never, sometimes, often, always) and maternal age at menarche (≤ 11 , 12, 13, ≥ 14 years). Additionally, non-diet soda, non-carbonated fruit beverages and sweetened iced tea were mutually adjusted for each other when appropriate (e.g. analyses of non-diet soda were adjusted for non-carbonated fruit beverage and sweetened iced tea consumption in addition to other covariates). To explore which component, if any, of SSBs could be responsible for a possible association with menarche, we examined the SSB–menarche association after including individual nutrients (i.e. caffeine, total sugar or added sugar) in the model. We also explored whether results were modified by (i) 1996 BMI tertiles (< 17.3 , $17.3–20.0$, > 20.0 kg/m²) or (ii) race (non-Hispanic white, other): analyses were

repeated within strata and we tested for effect modification using the likelihood ratio test. In an additional sensitivity analysis, we restricted our analysis to the 4485 participants whose follow-up ended in 1999 or earlier, and therefore we did not carry forward their 1998 diet.

Increases in BMI may mediate the association between SSB consumption and earlier menarche; therefore, we did not include BMI as a covariate in primary models (Schisterman *et al.*, 2009). Under this assumption, we calculated the proportion of the SSB consumption–age at menarche association mediated by BMI by comparing a model that included SSB consumption (modeled as a trend variable), BMI and covariates to a model in which BMI was omitted (Lin *et al.*, 1997). Heavier girls have been shown to consume more diet soda (Berkey *et al.*, 2004); therefore, we considered BMI to precede diet soda consumption rather than mediate the association of diet soda and menarche.

We additionally estimated multivariable-adjusted average age at menarche in the interval between 9 years, the youngest age at menarche observed, and 18.5 years, the oldest observed age at menarche using baseline survival probabilities (Carwile *et al.*, 2013). Bootstrapping was used to obtain the confidence limits of the estimated average age at menarche within each category of beverage intake, and for the difference in average age at menarche between categories of beverage intake relative to the reference. We drew 500 samples of the same size as the original data set with replacement from the data, computed the estimated years to menarche and the difference in average age at menarche between categories of beverage intake relative to the reference as described above, and took the 2.5th and 97.5th percentiles of the empirical distribution of these estimates as the 95% confidence bounds.

Statistical tests were two-sided and performed at the 0.05 level of significance (SAS version 9.2; SAS Institute, Cary, NC, USA).

Results

Study population

Of the 5583 girls included in this analysis, the majority ($n = 5227$, 94%) reported reaching menarche during the study interval, 159 (3%) remained premenarcheal in June 2001 and the remaining 4% ($n = 197$) were censored. The unadjusted median age at menarche in our sample was 13.1 years (25th and 75th percentiles: 12.4, 13.8 years). This was somewhat later than the median of 12.7 years (25th and 75th percentiles: 12.1, 13.5 years) in the entire cohort (8538 of 9033 girls reporting age at menarche), many of whom were excluded from our analysis because they had experienced menarche by 1996. Between 1996 and 2001, 10 555 person-years of follow-up were accumulated, with a median length of follow-up of 1.8 years for girls reporting menarche. Girls consuming SSBs tended to consume more calories and caffeine and less milk than non-consumers (Table I). Both physical activity and inactivity increased with SSB intake.

Total SSBs

Proportional hazards models indicated that more frequent SSB consumption predicted a higher rate of reaching menarche. Specifically, at any given age between 9 and 18.5 years, premenarcheal girls who reported consuming > 1.5 servings of SSBs per day were, on average, 26% more likely (95% CI: 15%, 38%; P -trend < 0.001) to attain menarche in the next month relative to girls who reported consuming ≤ 2 servings of SSBs weekly, adjusting for total calories only (Table II). Similar effect estimates (HR = 1.24; 95% CI: 1.13, 1.36) were obtained following additional adjustment for the following known or suspected determinants of

Table 1 Baseline characteristics^a of 5583 premenarcheal girls aged 9–14 years across categories of 1996 SSB consumption.

	Sugar-sweetened beverages (servings) ^b				
	≤2/week (n = 1615)	2.1–3/week (n = 187)	3.1–5/week (n = 1234)	5.1/week–1.5/day (n = 1373)	>1.5/day (n = 1174)
Age (years) ^c	11.1 (1.2)	11.3 (1.3)	11.2 (1.2)	11.3 (1.3)	11.4 (1.3)
Non-Hispanic white (%)	94	95	95	95	92
Birthweight (g)	3442 (531)	3430 (546)	3443 (530)	3424 (506)	3427 (517)
Maternal age at menarche (years)	12.6 (1.4)	12.4 (1.4)	12.6 (1.4)	12.6 (1.4)	12.6 (1.4)
BMI (kg/m ²)	18.2 (3.3)	18.5 (3.8)	18.0 (3.1)	18.1 (3.3)	18.3 (3.3)
Height (in.)	57.8 (4.1)	58.3 (4.1)	57.8 (4.0)	57.7 (4.1)	57.8 (4.1)
Diet soda (servings/day)	0.1 (0.4)	0.2 (0.4)	0.1 (0.3)	0.1 (0.4)	0.1 (0.4)
Total white milk (servings/day)	1.9 (1.3)	1.8 (1.2)	1.7 (1.2)	1.6 (1.1)	1.5 (1.2)
Fruit juice (servings/day)	0.8 (0.8)	0.7 (0.7)	0.7 (0.7)	0.8 (0.7)	0.9 (0.9)
Total energy (kcal/day)	1776 (568)	1928 (592)	1970 (581)	2135 (586)	2435 (673)
Caffeine (mg/day)	16.4 (24.2)	24.2 (27.0)	22.5 (22.5)	31.4 (26.1)	38.5 (35.2)
Total protein (g/day)	85.2 (12.3)	84.1 (11.8)	80.3 (11.3)	76.9 (10.6)	69.6 (10.9)
Animal protein (g/day)	58.6 (14.9)	58.2 (13.7)	55.2 (13.0)	52.4 (12.1)	47.3 (11.4)
Always eat dinner with family (%)	48	41	47	42	43
Household composition ^d					
Father/stepfather not present (%)	7	5	7	8	8
Father present (%)	91	93	90	89	90
Stepfather present (%)	2	1	4	2	3
Activity (hours/week)	12.6 (7.7)	13.3 (7.6)	13.1 (8.0)	14.1 (8.3)	14.4 (8.5)
Inactivity (hours/week)	21.3 (13.2)	24.4 (14.9)	24.1 (13.5)	26.3 (14.2)	28.4 (14.5)

^aValues are means(SD) or percentages and are standardized to the age distribution of the study population.

^bSum of non-carbonated fruit beverages (56% of total SSB consumption during follow-up), non-diet soda (32%) and sweetened iced tea (10%).

^cAll variables except age are age-standardized.

^dValues do not sum to 100 due to rounding.

age at menarche: race/ethnicity, activity, inactivity, birthweight, maternal age at menarche, frequency of eating dinner as a family, household composition and height. We obtained similar results when we restricted analyses to girls 12, 13 or 14 years of age or younger (Supplementary data, Table S1). Correspondingly, using baseline survival probabilities, we calculated that girls consuming >1.5 servings of SSBs per day reported an average age at menarche of 12.8 years (95% CI: 12.7, 13.0 years), 2.7 months earlier (95% CI: -4.1, -1.3 months) than those consuming ≤2 servings weekly [13.0 years (95% CI: 12.9, 13.2 years)] (Fig. 1). Similar effect sizes were observed for girls between the ages of 12.25 and 16 years (Supplementary data, Fig. S1).

Individual SSBs

When SSBs were modeled individually, more frequent consumption of non-carbonated fruit beverages and non-diet soda, but not sweetened iced tea, predicted an increased likelihood of attaining menarche in the next month, holding covariates constant (*P*-trend: 0.03, 0.001, 0.49, respectively). Neither fruit juice nor (after adjustment for covariates including BMI) diet soda was associated with likelihood of menarche (Table III). Consumption of SSBs, non-carbonated fruit beverages, and non-diet

soda remained associated with earlier menarche when models were (i) additionally adjusted for consumption of French fries, fried foods, milk, total meat, or red meat, or total or animal protein intake or (ii) not adjusted for height (data not shown).

Related nutrients

To explore which component of SSBs may be responsible for the observed association with earlier menarche, we investigated associations of total caffeine and sugar intake with menarche and repeated analyses of SSB consumption and menarche after adjustment for intake of individual nutrients. The intake of caffeine and added sugar, but not total sugar, each predicted an increased likelihood of menarche in the next month; however, none of the nutrients could fully explain observed associations of more frequent SSB consumption and earlier menarche (Supplementary data, Table SII).

Sensitivity analyses

Next, under the assumption that the relation between BMI and age at menarche is exclusively that of a mediator of the SSB consumption–age at menarche association, we estimated the direct effect of SSB

Table II HRs and 95% CIs for associations between cumulatively updated SSB consumption and menarche ($n = 5583$)^a.

Beverage consumption (servings)	≤2/week	2.1–3/week	3.1–5/week	5.1/week–1.5/day	>1.5/day	P-trend ^b	Proportion of effect mediated by BMI, % (95% CI) ^c
Sugar-sweetened beverages ^d							
Events/person-y	1115/2720	423/760	1016/2167	1555/2901	1118/2007		
Model 1 HR (95% CI) ^e	1 (ref)	1.04 (0.92, 1.17)	1.09 (1.00, 1.20)	1.09 (1.00, 1.18)	1.26 (1.15, 1.38)	<0.001	
Model 2 HR (95% CI) ^f	1 (ref)	0.99 (0.87, 1.11)	1.08 (0.99, 1.18)	1.09 (1.00, 1.18)	1.24 (1.13, 1.36)	<0.001	
Model 3 HR (95% CI) ^g	1 (ref)	0.99 (0.88, 1.11)	1.08 (0.99, 1.18)	1.10 (1.01, 1.19)	1.22 (1.11, 1.35)	<0.001	9.2 (–2.2, 20.6)
Non-carbonated fruit drinks							
Events/person-y	2424/5057	505/795	1106/2335	686/1372	506/997		
Model 1 HR (95% CI) ^e	1 (ref)	1.06 (0.96, 1.17)	1.08 (1.00, 1.16)	1.04 (0.95, 1.14)	1.16 (1.05, 1.29)	0.007	
Model 2 HR (95% CI) ^f	1 (ref)	1.04 (0.94, 1.15)	1.09 (1.01, 1.18)	1.04 (0.95, 1.14)	1.13 (1.02, 1.26)	0.03	
Model 3 HR (95% CI) ^g	1 (ref)	1.04 (0.94, 1.16)	1.10 (1.01, 1.18)	1.04 (0.95, 1.14)	1.11 (1.00, 1.24)	0.05	6.5 (–16.6, 29.5)
Non-diet soda							
Events/person-y	3202/6894	497/809	954/1928	413/673	161/251		
Model 1 HR (95% CI) ^e	1 (ref)	1.00 (0.90, 1.10)	1.03 (0.96, 1.12)	1.23 (1.11, 1.37)	1.20 (1.02, 1.42)	0.001	
Model 2 HR (95% CI) ^f	1 (ref)	0.95 (0.86, 1.05)	1.03 (0.95, 1.11)	1.25 (1.12, 1.39)	1.21 (1.02, 1.43)	0.001	
Model 3 HR (95% CI) ^g	1 (ref)	0.96 (0.87, 1.06)	1.04 (0.96, 1.13)	1.24 (1.11, 1.39)	1.17 (0.99, 1.39)	0.002	8.6 (–6.0, 23.2)
Sweetened iced tea ^h							
Events/person-y	4456/9092	394/792	377/671				
Model 1 HR (95% CI) ^e	1 (ref)	1.00 (0.90, 1.12)	1.04 (0.94, 1.17)			0.48	
Model 2 HR (95% CI) ^f	1 (ref)	1.00 (0.89, 1.11)	1.05 (0.94, 1.17)			0.49	
Model 3 HR (95% CI) ^g	1 (ref)	0.98 (0.88, 1.09)	1.01 (0.90, 1.13)			0.98	35.8 (–16.8, 88.5)

BMI, body mass index; CI, confidence interval; HR, hazard ratio; SSB, sugar-sweetened beverage.

^aDiet was assessed in 1996, 1997 and 1998. Food intakes were cumulatively updated over follow-up.

^bCalculated using the median as a continuous term.

^cFor calculations of the proportion of effect mediated by BMI, exposure was modeled using the median as a continuous term, and models were adjusted for Model 2 covariates.

^dSum of non-carbonated fruit beverage (56% of total SSB consumption during follow-up), non-diet soda (32%) and iced tea (10%) consumption.

^eModel 1 is a Cox proportional hazards model stratified by age in months and questionnaire cycle and adjusted for total caloric intake (quintiles).

^fModel 2 is a Cox proportional hazards model adjusted for the same covariates as Model 1 as well as for race/ethnicity (non-Hispanic white, other), activity (quintiles), inactivity (quintiles), birthweight (quintiles), maternal age at menarche (≤11, 12, 13, ≥14 years), frequency of eating dinner as a family (ordinal), household composition (no father or stepfather, father, stepfather), and height (quintiles). Additionally, non-diet soda, non-carbonated fruit beverages and sweetened iced tea were mutually adjusted for each other.

^gModel 3 is a Cox proportional hazards model adjusted for the same covariates as Model 2 as well as for BMI (deciles).

^hMaximum frequency of consumption was 5 servings/week.

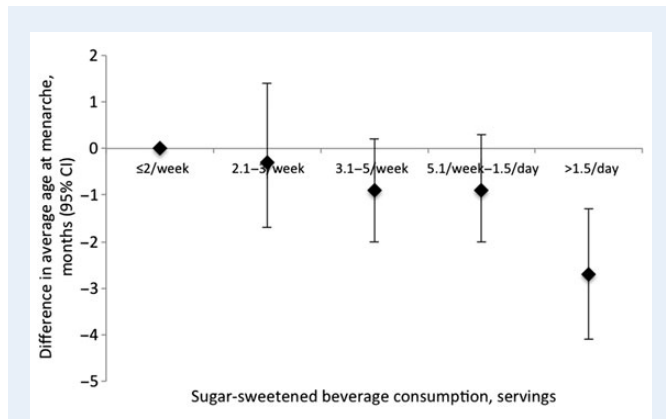


Figure 1 Difference in estimated average age at menarche by consumption of SSBs ($n = 5583$) calculated using baseline survival probabilities. Values for questionnaire cycle and categorical variables categorized using quantiles (total energy, birthweight, activity, inactivity) were set to their median value, and values of other risk factors (race, maternal age at menarche, frequency of eating dinner as a family, household composition) were set to their mode in the study population. CI, confidence interval.

consumption on menarche by adding BMI to multivariable models (Model 3). Adjustment for BMI resulted in attenuated, but statistically significant effect estimates (for > 1.5 servings per day versus ≤ 2 serving per week, HR: 1.22; 95% CI: 1.11, 1.35; P -trend: < 0.001). BMI did not explain a statistically significant proportion of the association of SSBs with menarche.

The association between SSB consumption and earlier menarche was not significantly modified by race or baseline BMI (heterogeneity test P -value: 0.63 and 0.51, respectively). While the heaviest girls (BMI in 1996 ≥ 20.0 kg/m²) had the earliest menarche, more frequent SSB consumption was associated with earlier menarche in every tertile of baseline BMI (Fig. 2) (for BMI < 17.3 kg/m², P -trend = 0.02, for BMI 17.3–20.0 kg/m² and ≥ 20.0 kg/m², P -trend < 0.0001). We observed similar results when we restricted our study population to participants for whom we did not carry forward dietary intake (data not shown).

Discussion

In this prospective study with up to 5 years of follow-up, we found that girls consuming > 1.5 servings of SSBs daily reported menarche an average of 2.7 months earlier than girls consuming SSBs ≤ 2 times weekly, even after adjusting for total energy intake, height and BMI. The intake of highly glycemic foods such as SSBs results in a rapid increase in circulating insulin concentrations (Janssens et al., 1999; Ludwig, 2002). While the direct impact of SSB consumption on other hormones requires further investigation (DeLellis-Henderson et al., 2007), insulin is known to down-regulate sex-hormone binding globulin and insulin-like growth factor binding protein-1 production (Holly et al., 1989; Caprio, 1999), resulting in higher concentrations of bioavailable sex hormones and IGF-1. Large alterations to circulating hormone concentrations have been compellingly linked to earlier menarche (Tam et al., 2006; Thankamony et al., 2012). For instance, delayed puberty has been observed in individuals with rare disorders of GH/IGF-1 axis inadequacy (Veldhuis et al., 2006), and metformin, an insulin sensitizer, has been found to

reverse precocious puberty in randomized controlled trials (Ibanez et al., 2006). It is plausible that smaller changes, for instance those induced by consumption of highly glycemic foods, could impart more modest changes in pubertal timing.

The observed decrease in age at menarche was specific to beverages with added sugar; consumption of naturally sweetened beverages such as fruit juice was not associated with menarche. Similarly, we observed associations of added, but not total sugar with earlier menarche. Fruit juices typically have a lower glycemic index than SSBs (Foster-Powell et al., 2002), and likely have a different overall metabolic effect (Schulz et al., 2004). Greater caffeine intake was associated with earlier menarche, which was not unexpected since non-diet soda was the largest source of caffeine intake. However, observed associations of SSB consumption and earlier menarche were not explained by caffeine or sugar intake. Diet soda consumption predicted earlier menarche only when BMI was not included in multivariable models, consistent with higher diet soda consumption among heavier girls.

BMI is a strong predictor of menarche, and the observed association of more frequent SSB consumption and earlier menarche may be partially explained by increases in BMI (Ludwig et al., 2001; Dungen et al., 2006; Fiorito et al., 2009). However, in addition to observing a direct effect of SSB consumption on earlier menarche using models adjusted for BMI, we found that BMI explained only 9.2% of the total observed association. These results should be interpreted cautiously as these methods can introduce bias if there is unmeasured confounding of either the association between SSBs and menarche or BMI and menarche (Cole and Hernan, 2002). Although some misclassification of height and weight, particularly underestimation of weight, is possible, adolescents have been found to self-report their height and weight validly (Brooks-Gunn et al., 1987; Strauss, 1999). We modeled BMI as an intermediate variable based on previously reported associations with age at menarche (Buyken et al., 2009; Cheng et al., 2012) and because other measures of adiposity were not available for this cohort; however, this variable may be an imperfect measure of body fatness or another aspect of body composition that mediates the SSB–menarche association. In addition, it is possible that BMI is (i) a confounder, but not a mediator or (ii) both a confounder and a mediator. More frequent SSB consumption predicted earlier menarche in girls in every tertile of baseline BMI.

Strengths and limitations

Girls in our study were 9–14 years at the start of follow-up, and were therefore likely to have already initiated puberty, although they had not yet reported menarche. Reverse causation could occur if early-maturing girls consumed SSBs more frequently as a consequence of their maturation. We minimized the potential for reverse causation by relating menarche to diet reported the previous year and earlier. Future studies should examine the impact of early childhood diet on age at menarche.

Our questionnaire suggested portion sizes for soft drinks, but did not specify the number of ounces in a portion. Indeed, SSBs are often consumed in very large portion sizes (averaging 19.9 ounces in the mid-1990s) (Nielsen and Popkin, 2003), with considerable variation in size (Nielsen and Popkin, 2003), which could lead to further misclassification. However, due to the prospective nature of our study, any misclassification of diet should be unrelated to menarche, resulting in decreased precision and underestimated HRs. While menarche is the

Table III HRs and 95% CIs for associations between cumulatively updated beverage and nutrient intake and menarche (n = 5583)^a.

Beverage consumption (servings)	≤2/week	2.1–3/week	3.1–5/week	5.1/week–1.5/day	>1.5/day	P-trend ^b
Fruit juice						
Events/person-y	1726/3450	479/886	970/2025	1320/2598	732/1596	
Model 1 HR (95% CI) ^c	1 (ref)	0.97 (0.87, 1.08)	0.97 (0.90, 1.06)	0.94 (0.87, 1.01)	0.97 (0.88, 1.06)	0.34
Model 2 HR (95% CI) ^d	1 (ref)	0.99 (0.89, 1.10)	1.00 (0.92, 1.08)	0.95 (0.87, 1.02)	0.98 (0.89, 1.08)	0.45
Model 3 HR (95% CI) ^e	1 (ref)	0.97 (0.87, 1.08)	0.99 (0.91, 1.07)	0.94 (0.87, 1.02)	0.99 (0.90, 1.08)	0.52
Diet soda						
Events/person-y	4460/9180	184/279	360/720	151/268	72/109	
Model 1 HR (95% CI) ^c	1 (ref)	1.05 (0.90, 1.22)	1.12 (1.00, 1.25)	1.16 (0.98, 1.37)	1.55 (1.22, 1.97)	<0.001
Model 2 HR (95% CI) ^d	1 (ref)	1.03 (0.88, 1.20)	1.06 (0.94, 1.19)	1.02 (0.86, 1.21)	1.34 (1.04, 1.71)	0.02
Model 3 HR (95% CI) ^e	1 (ref)	0.95 (0.81, 1.11)	0.95 (0.85, 1.07)	0.90 (0.76, 1.07)	1.23 (0.96, 1.58)	0.73
Nutrient intake (quintiles)	1	2	3	4	5	P-trend ^b
Caffeine						
Events/person-y	1232/2856	1194/2556	1052/2111	964/1777	785/1255	
Model 1 HR (95% CI) ^c	1 (ref)	1.09 (1.00, 1.18)	1.10 (1.01, 1.20)	1.18 (1.08, 1.28)	1.30 (1.19, 1.43)	<0.001
Model 2 HR (95% CI) ^d	1 (ref)	1.05 (0.97, 1.14)	1.07 (0.98, 1.16)	1.15 (1.06, 1.26)	1.24 (1.13, 1.37)	<0.001
Model 3 HR (95% CI) ^e	1 (ref)	1.08 (1.00, 1.18)	1.08 (0.99, 1.18)	1.11 (1.02, 1.22)	1.17 (1.06, 1.30)	0.002
Total sugar						
Events/person-y ^f	1091/2338	1138/2315	1051/2151	1032/2023	915/1729	
Model 1 HR (95% CI) ^c	1 (ref)	1.04 (0.95, 1.13)	1.05 (0.96, 1.14)	1.07 (0.98, 1.17)	1.09 (0.99, 1.19)	0.06
Model 2 HR (95% CI) ^d	1 (ref)	1.02 (0.93, 1.11)	1.01 (0.93, 1.11)	1.03 (0.94, 1.12)	1.04 (0.95, 1.14)	0.34
Model 3 HR (95% CI) ^e	1 (ref)	1.01 (0.92, 1.10)	1.02 (0.94, 1.12)	1.02 (0.93, 1.11)	1.07 (0.97, 1.17)	0.18
Added sugar						
Events/person-y ^f	1099/2423	1099/2332	1100/2187	1015/1962	914/1652	
Model 1 HR (95% CI) ^c	1 (ref)	1.04 (0.95, 1.13)	1.08 (0.99, 1.18)	1.11 (1.01, 1.21)	1.17 (1.07, 1.28)	<0.001
Model 2 HR (95% CI) ^d	1 (ref)	1.03 (0.95, 1.13)	1.07 (0.98, 1.17)	1.12 (1.03, 1.23)	1.19 (1.09, 1.31)	<0.001
Model 3 HR (95% CI) ^e	1 (ref)	1.04 (0.95, 1.14)	1.08 (0.99, 1.18)	1.16 (1.06, 1.27)	1.21 (1.10, 1.33)	<0.001

CI, confidence interval; HR, hazard ratio.

^aDiet was assessed in 1996, 1997 and 1998. Food intakes were cumulatively updated over follow-up.^bCalculated using the median of each category as a continuous term.^cModel 1 is a Cox proportional hazards model stratified by age in months and questionnaire cycle and adjusted for total caloric intake (quintiles).^dModel 2 is a Cox proportional hazards model adjusted for the same covariates as Model 1 as well as for race/ethnicity (non-Hispanic white, other), activity (quintiles), inactivity (quintiles), birthweight (quintiles), maternal age at menarche (≤11, 12, 13, ≥14 years), frequency of eating dinner as a family (ordinal), household composition (no father or stepfather, father, stepfather) and height (quintiles).^eModel 3 is a Cox proportional hazards model adjusted for the same covariates as Model 2 as well as for BMI (deciles).^fPerson-years do not sum to total due to rounding.

easiest and arguably most reliable marker of pubertal development (Brooks-Gunn *et al.*, 1987; Desmangles *et al.*, 2006), consideration of earlier puberty markers (e.g. Tanner stage) may be used to confirm our findings and explore related outcomes such as pubertal tempo. We minimized misclassification of the outcome by choosing a salient pubertal event, and minimizing the interval over which age at menarche was recalled.

Girls consuming the most SSBs may have a different overall dietary pattern than those consuming fewer SSBs, and it is possible that differences in intake of another food or nutrient may explain the observed association between SSB consumption and age at menarche. While girls with the greatest SSB consumption also reported drinking less milk and had lower total and animal protein intake, our findings were unchanged

after additional adjustment for these and many other dietary and lifestyle factors. While confounding is possible in any observational study, our effect estimates did not appreciably change even after adjustment for some of the strongest identified predictors of menarche (e.g. height), making substantial residual confounding unlikely.

We report a median age at menarche in the entire 93% white cohort of 12.7 years, similar to contemporary populations of white girls (Herman-Giddens *et al.*, 1997; Chumlea *et al.*, 2003; Adgent *et al.*, 2012). Generalizability of our results to Hispanics and blacks is uncertain, as these girls typically attain menarche earlier than whites (Herman-Giddens *et al.*, 1997; Chumlea *et al.*, 2003). Small sample sizes made it impossible to obtain stable stratum-specific estimates for blacks and Hispanics and limited power for detecting whether associations were modified by

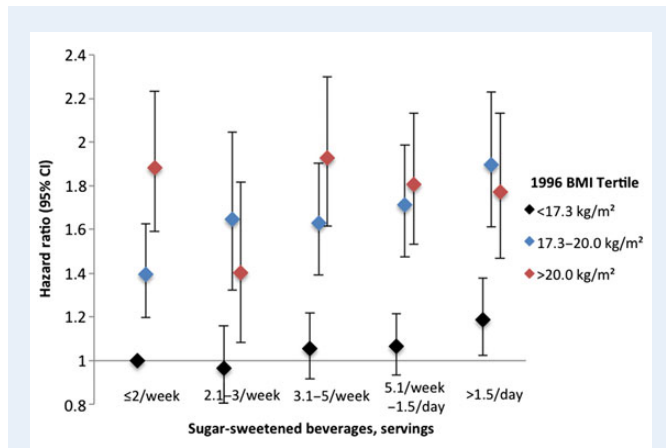


Figure 2 HRs of obtaining menarche in the next month depending on consumption of SSBs and baseline BMI among 5493 girls with non-missing BMI calculated using the Cox proportional hazards models. The reference group was girls consuming ≤ 2 SSBs/week with a 1996 BMI < 17.3 kg/m². BMI tertile 1: 2303 events/5666 person-years, tertile 2: 1651 events/2826 person-years; tertile 3: 1189 events/1893 person-years; 90 girls (84 events/170 person-years) were excluded for missing BMI. The Cox proportional hazards models were stratified by age in months and questionnaire cycle and adjusted for total caloric intake (quintiles), race/ethnicity (non-Hispanic white, other), activity (quintiles), inactivity (quintiles), birthweight (quintiles), maternal age at menarche (≤ 11 , 12, 13, ≥ 14 years), frequency of eating dinner as a family (ordinal), household composition (no father or stepfather, father, stepfather) and height (quintiles). BMI, body mass index; SSB, sugar-sweetened beverage.

race. As expected, we observed a higher median age at menarche (13.1 years) upon restriction to the girls who were premenarcheal at baseline and reported menarche during follow-up, as girls with earlier-than-average menarche would have been excluded at baseline. However, while our method of sampling limits our ability to generalize to girls younger than 9 years of age, it does not compromise the validity of our effect estimates.

Conclusions

Our findings suggest that frequent consumption of SSBs may be associated with earlier menarche. A 1-year decrease in age at menarche is estimated to increase the risk of breast cancer by 5% (Rosner and Colditz, 1996; Collaborative Group on Hormonal Factors in Breast Cancer, 2012); thus, a 2.7-month decrease in age at menarche likely has a modest impact on breast cancer risk. The amount of SSBs consumed by girls in our highest category of consumption, > 1.5 servings per day, however, is likely low compared with consumption in certain other populations, in which we would expect an even more dramatic decrease in age at menarche. Indeed, among female NHANES participants who reported recent SSB consumption, the mean daily SSB consumption was 18 oz for 6–11 year olds and 27 oz for 12–19 year olds (Wang et al., 2008). Most importantly, the public health significance of SSB consumption on age at menarche, and possibly breast cancer, should not be overlooked, since, unlike most other predictors of menarche, SSB consumption can be modified.

Supplementary data

Supplementary data are available at <http://humrep.oxfordjournals.org/>.

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Authors' roles

J.L.C., W.C.W., J.R.-E., A.L.F. and K.B.M. designed research; D.S. and E.H. developed statistical methods; J.L.C. performed statistical analysis and drafted the paper; W.C.W., D.S., E.H., J.R.-E., A.L.F. and K.B.M. critically reviewed the manuscript; K.B.M. had primary responsibility for final content. All authors read and approved the final manuscript. J.L.C. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflict of interest

None declared.

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