The Journal of Nutrition
Nutritional Epidemiology

Milk Consumption after Age 9 Years Does Not Predict Age at Menarche[1–3]

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Abstract

Background: Regular milk consumption during childhood and adolescence is recommended for bone health. However, milk consumption increases circulating insulin-like growth factor I concentrations, and may also accelerate puberty.

Objective: We prospectively investigated the association between milk consumption and age at menarche in the Growing Up Today Study.

Methods: Study participants were 5583 US girls who were premenarcheal and ages 9–14 y in 1996. Girls were followed through 2001, at which time 97% of noncensored participants had reported menarche. Frequency of milk and meat consumption was calculated with the use of annual youth/adolescent food frequency questionnaires from 1996–1998. Intake of related nutrients was also measured. Age at menarche was self-reported annually through 2001.

Results: During follow-up, 5227 girls attained menarche over 10,555 accrued person-years. In models adjusted for dietary and sociodemographic predictors of menarche, frequency of milk consumption did not predict age at onset of menarche (for >3 glasses of milk/d vs. 1.1–4 glasses/wk, HR: 0.93; 95% CI: 0.83, 1.04). After additional adjustment for body size, premenarcheal girls consuming >3 glasses of milk daily were 13% less likely (95% CI: −3%, −23%; *P*-trend: <0.01) to attain menarche in the next month relative to those consuming 1.1–4 glasses/wk. Neither total meat nor red meat consumption was associated with age at menarche.

Conclusions: Our findings suggest that regular consumption of milk in girls aged ≥9 y is unlikely to substantially affect age at onset of menarche. Studies assessing associations between diet in early childhood and pubertal timing may be more illuminating. *J Nutr* 2015;145:1900–8.

Keywords: dairy products, diet, Growing Up Today Study, meat, menarche, milk

Introduction

Low-fat dairy is promoted as a healthy choice for children, with the USDA Dietary Guidelines for Americans recommending 3 8-ounce servings daily (1). Benefits of childhood consumption include increased bone-mineral content and density (2, 3), characteristics important for the prevention of osteoporosis. However, hormones and growth factors are also endogenous to dairy foods (4), leading to speculation that consumption of dairy foods could be associated with accelerated pubertal development, an established risk factor for breast (5) and possibly endometrial cancer (6).

Multiple components of milk have the potential to influence age at menarche. Intake of animal protein, found in meat as well as dairy, has been related to earlier menarche in several prospective studies (7). Other factors may be unique to milk; in prepubertal children, consumption of milk is associated with elevations in plasma insulin-like growth factor I (IGF-I)[12] that have not been observed for macronutrient substitutes (8) or meat (9, 10). IGF-I is a central regulator of growth and development also associated with

[1] The Growing Up Today Study was supported by the NIH (grant R03 CA 106238) and the Breast Cancer Research Foundation. JL Carwile was supported by the Breast Cancer Research Foundation, the National Institute for Environmental Health Sciences at the NIH (Training Grant T32ES007069), and the National Institute of Child Health and Human Development at the NIH (Training Grant T32HD060454). AL Frazier was supported by the American Cancer Society, Research Scholar Grant in Cancer Control, and the NIH (grant R03 CA 106238). KB Michels was supported in part by the National Cancer Institute at the NIH (Public Health Service grants R01CA158313 and R03CA170952).
[2] Author disclosures: JL Carwile, WC Willett, M Wang, J Rich-Edwards, AL Frazier, and KB Michels, no conflicts of interest.
[3] Supplemental Tables 1–3 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://jn.nutrition.org.
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[12] Abbreviations used: GUTS, Growing Up Today Study; IGF-I, insulin-like growth factor I; YAQ, youth/adolescent food frequency questionnaire.

Manuscript received March 24, 2015. Initial review completed May 1, 2015. Revision accepted June 8, 2015.
First published online July 1, 2015; doi:10.3945/jn.115.214270.

the initiation of menarche; thus, we hypothesized that girls who consumed milk most frequently would have the highest IGF-I concentrations and the earliest menarche.

We examined the associations between milk (total, skim, low-fat, and whole milk) and related nutrients (dairy fat and protein, animal fat and protein, calcium, and vitamin D) and menarche in a large prospective cohort of premenarcheal US girls. To further investigate whether an association between milk and menarche, if observed, was common to other sources of animal protein, we also examined associations between meat and menarche.

Methods

Study population. Established in 1996, the Growing Up Today Study (GUTS) is an ongoing prospective cohort study of 16,875 children (9033 girls) of women enrolled in the Nurses' Health Study II (11). Participants were aged 9–14 y at baseline. Baseline and follow-up questionnaires assessed diet, activity, smoking, and other behaviors. Relevant questionnaires (completed online or via post) were completed annually through 2001, and again in 2003. In 2005, postcards were mailed to girls who had failed to report their age at menarche. The GUTS was approved by the institutional review board of the Brigham and Women's Hospital in Boston.

Follow-up for the present study began in 1996 and ended in 2001, when all but 159 eligible girls had reported menarche. Of the 9033 girls who completed the 1996 questionnaire, 8994 responded to at least 75% of the individual food items and reported an energy intake between 500 and 5000 kcal/d in 1996. Of these, 5861 were premenarcheal in 1996. After further exclusion of 278 girls who never updated their menarcheal status, 5583 girls were eligible for analysis.

Dietary assessment. Between 1996 and 1998, diet was assessed with the use of a 132-item youth/adolescent food frequency questionnaire (YAQ), a self-administered semiquantitative FFQ developed for use in older children and adolescents. Intake of nutrients, including total energy, could not be calculated between 1999 and 2001 because of the use of an abridged YAQ; therefore, for the 1098 girls (20%) who were followed during this interval, we used 1998 values for all dietary items. Participants were asked, on average, how frequently they consumed a typical portion size (for milk, "1 glass") of specified foods over the past year. Participants additionally selected the type of milk consumed most frequently (whole, 2%, 1%, skim (nonfat), soy, "don't know," or "don't drink milk"); consumption of less frequently consumed types of milk was assumed to be 0. Chocolate milk and soy milk, both of which were infrequently consumed, were excluded from total white milk calculations. If a food item was left blank, intake was set to zero (12). Individual food items included in each food group of interest are listed in **Supplemental Table 1**.

Dietary nutrient intake was calculated by multiplying the frequency of consumption of each unit of food by the nutrient content of the specified portion and summing across all foods. Nutrient composition values for each food were obtained from the USDA and other sources (13). To calculate nutrient intake, ingredients in all foods were considered. Vitamin and supplement use were also included in total calcium and vitamin D intake. To reduce extraneous variation in nutrient intake, nutrients were energy-adjusted with the use of the residuals from the regression of nutrient intake on total caloric intake (14).

When administered to children ages 9–18 y, the YAQ has good validity and reproducibility (13, 15). Comparison of YAQ nutrient estimates with those from 3 24-h recalls yielded a mean correlation of 0.54. Although food items and groups were not similarly validated in this population, a similar youth FFQ had high correlations with 7 d dietary records for milk and dairy foods (16).

Assessment of menarche. On each questionnaire, girls were asked to report whether their menstrual periods had begun, and, if they had, their age in years and, except for the 2001 and 2003 questionnaires, the calendar month at attainment. To reduce the potential for outcome misclassification, we used only the first reported age at menarche. Girls who never reported their age at menarche were censored at the time of last status report. Girls reporting menarche after ≥1 y of nonreport had their age at menarche retrospectively assigned (n = 521; 10%). We obtained similar findings when we instead censored these girls at their last report of being premenarcheal (i.e., did not include follow-up when menarcheal status was missing) (data not shown). If menarche was first reported during 2001 or 2003 or never reported, month of age at menarche was imputed as 6 mo after the integer age at menarche. Age at menarche has not been validated in the GUTS; other studies support high validity and reliability of recalled menarche (17).

Assessment of nondietary factors. The girls' mothers reported their own age at menarche in 1989, and their daughters' birthweight in 1996. Children self-reported their race at baseline by marking each of 6 race/ethnic groups (white, black, Hispanic, Asian or Pacific Islander, American Indian/Alaskan Native, or other). Physical activity and inactivity, frequency of eating dinner as a family, household composition, height, and weight were self-reported at baseline, and on all subsequent questionnaires. BMI was calculated as weight in kilograms divided by height in meters squared. Physical activity was calculated as the typical amount of time per season (hours per week) spent during the past year in 17 activities and team sports, not including gym class. Annual estimates of physical activity (hours per week) were calculated by summing across each season and then across seasons. Inactivity was calculated as the mean time a child reported watching television or videos and playing video and computer games (not including those assigned as homework). Characteristics that changed over time (i.e., physical activity and inactivity, frequency of eating dinner as a family, household composition, height, weight, and BMI) were updated with the use of data from the 1997–2000 questionnaires.

Statistical analysis. We used Cox proportional hazards regression to examine associations of cumulative averaged milk and meat consumption with 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 last questionnaire return, whichever came first. We evaluated the proportional hazards assumption with the use of a likelihood ratio test; proportional hazards assumptions were met in all of our analyses. To address decreased milk consumption in older girls, we accounted for age (months) and questionnaire cycle in all of our analyses, making the time scale equivalent to age (months) and ensuring that all comparisons were made within groups of same-age girls.

To minimize reverse causation, cumulative averaged intake of foods and food groups were calculated with the use of data collected between 1996 and the year before menarche or 1998, which ever came first. Cumulative averaged intake was categorized and modeled with the use of indicator variables. HRs and 95% CIs were calculated by comparing the rate of menarche in each category of intake to the reference category.

Total energy intake (quintiles) was included in all models for reasons including control for more frequent milk consumption by larger and more active girls (14). Family history, race (18, 19), and body size and associated factors (20, 21) have been consistently associated with age at menarche; therefore, we adjusted for maternal age at menarche (≤11, 12, 13, and ≥14 y), race (non-Hispanic white, other), physical activity (quintiles), inactivity (quintiles), and birthweight (quintiles). We adjusted for sugar-sweetened beverage consumption [≤2 servings (1 can or glass)/wk, 2.1–3 servings/wk, 3.1–5 servings/wk, 5.1 servings/wk–1.5 servings/d, and >1.5 servings/d] because it is associated with more frequent milk consumption and earlier menarche in this cohort (22). Girls with an absent father and/or stepfather mature earlier than those who live with their father (23), and we suspected smaller changes may be observed for intermediate levels of father presence; therefore, we adjusted for household composition (no father or stepfather, father, and stepfather) and frequency of eating dinner as a family (never, sometimes, often, and always). In analyses of individual milk types, we were unable to mutually adjust for other milk types because we obtained data on the most commonly consumed milk type only.

Because change in BMI or height may mediate the association between milk consumption and age at menarche, we omitted these variables from primary models to avoid overadjustment and associated biases (24). In some models, under the assumption that body size was exclusively a mediator of the milk consumption–age at menarche association, we calculated the direct effect of milk consumption on menarche (i.e., not mediated through body size) by including updated BMI (deciles) and height (quintiles) in multivariable models.

We additionally estimated the multivariable-adjusted mean age at menarche in the interval between 9 y, the youngest age at menarche observed, and 18.5 y, the oldest observed age at menarche, with the use of baseline survival probabilities (25). To obtain the CIs of the estimated mean age at menarche within each category of beverage intake, 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 took the 2.5th and 97.5th percentiles of the empirical distribution of these estimates as the 95% CIs.

Because we excluded girls who had already reached menarche at baseline, girls with the earliest menarche may have been under-represented in our cohort. To assess whether results were similar for girls of different ages, particularly the youngest girls (i.e., the least affected by left-censoring), we repeated models with the use of events and person-time accrued by girls ≤12, ≤13, and ≤14 y of age. We also repeated analyses after restricting to the 4485 participants whose follow-up ended in 1999 or earlier, and did not have 1998 dietary data used for follow-up occurring after 1999. We additionally stratified by baseline BMI tertiles (<17.3, 17.3–20.0, and > 20.0 kg/m^2) and race (non-Hispanic white and other) and tested for effect modification with the use of the likelihood ratio test.

Statistical tests were 2-sided and performed at the 0.05 level of significance. We used SAS (version 9.2) for all analyses.

Results

Study population. Of the 9033 female GUTS participants (68% of those contacted), 5583 girls were premenarcheal at baseline and met other eligibility criteria. The majority reported menarche during follow-up (5227; 94%), 159 (3%) remained premenarcheal in June 2001, and the remaining 4% (n = 197) were censored because of missing data on age at menarche. A total of 10,555 person-years of follow-up were accumulated over 5 y. Girls reporting menarche accrued a median of 1.8 y of follow-up (25th and 75th percentiles: 0.8, 2.7 y) between study entry and report of menarche. The unadjusted median age at menarche was 12.7 in the entire cohort (n = 8538 reporting age at menarche) and, after excluding those who were postmenarcheal at baseline or failed to meet other eligibility criteria for the present analysis, 13.1 y. Total white milk consumption was higher among non-Hispanic whites and among girls who were taller, more active, and had a higher total caloric intake (**Table 1**). Birthweight and maternal age at menarche were positively associated with age at menarche (i.e., a decreased rate of menarche) (**Supplemental Table 2**). Factors predictive of a younger age at menarche (i.e., an increased rate of menarche) included BMI, height, living with a stepfather, nonwhite race, and inactivity.

Milk, dairy, and meat. Premenarcheal girls consuming >3 glasses/d of milk were, on average, 13% less likely (HR: 0.87; 95% CI: 0.78, 0.97; P-trend < 0.01) to attain menarche in the next month relative to girls consuming 1.1–4 glasses/wk of milk, holding total energy intake constant. However, the association lost statistical significance after additional adjustment for potential sociodemographic and nutritional predictors of menarche (Model 2, HR: 0.93; 95% CI: 0.83, 1.04; P-trend = 0.14). The corresponding estimated mean ages at menarche were 13.1 y (95% CI: 12.9, 13.3) for girls consuming >3 glasses/d of milk and 12.9 y (95% CI: 12.8, 13.1) for those consuming 1.1–4 glasses/wk (**Table 2**). When milk types were investigated individually, only low-fat milk was associated with later menarche at a statistically significant level (**Table 3**, Model 1). Consumption of dairy and meat was not associated with age at menarche.

Related nutrients. Intake of related nutrients did not predict age at menarche, with the exception of a modest association of higher dairy fat and dairy protein intake and later menarche in select models (**Table 4**).

Role of body size. For some models, we assumed that the role of body size was exclusively that of a mediator and estimated the direct effect of milk consumption on age at menarche by adjusting for height and BMI. Holding body size constant, more frequent milk consumption was associated with a slight increase in age at menarche (Table 3, Model 3, for 3 glasses/d vs. 1.1–4 glasses/wk, HR: 0.87; 95% CI: 0.77, 0.97). Results were not significantly modified by baseline BMI (data not shown).

TABLE 1 Age-standardized baseline characteristics of 5583 premenarcheal girls in the Growing Up Today Study across categories of 1996 total white milk consumption[1]

	Total white milk				
	≤1 serving/wk (n = 256)	1.1–4 servings/wk (n = 1556)	4.1–7 servings/wk (n = 1117)	1.1–3 servings/d (n = 2040)	>3 servings/d (n = 614)
Age,[2] y	11.5 ± 1.3	11.3 ± 1.3	11.3 ± 1.3	11.2 ± 1.2	11.3 ± 1.3
Non-Hispanic white, %	90	93	93	95	96
Birthweight, g	3420 ± 524	3420 ± 516	3420 ± 549	3450 ± 518	3460 ± 508
Maternal age at menarche, y	12.6 ± 1.5	12.6 ± 1.4	12.6 ± 1.4	12.6 ± 1.4	12.5 ± 1.4
BMI, kg/m^2	18.0 ± 3.0	18.5 ± 3.6	18.1 ± 3.1	18.0 ± 3.2	18.2 ± 3.0
Height, cm	146.4 ± 10.5	146.3 ± 10.3	146.7 ± 10.4	147.2 ± 10.4	147.3 ± 10.6
Total energy, kcal/d	1780 ± 614	1850 ± 618	1980 ± 609	2190 ± 615	2350 ± 665
Sugar-sweetened beverages, servings/d	3.3 ± 1.5	3.2 ± 1.5	3.2 ± 1.5	2.9 ± 1.5	2.6 ± 1.6
Always eat dinner with family, %	42	39	45	48	53
Household composition,[3] %					
Father/stepfather not present	7	9	8	6	6
Father present	90	88	90	91	92
Stepfather present	4	3	2	3	2
Activity, h/wk	12.4 ± 7.8	13.2 ± 8.2	13.2 ± 7.8	13.5 ± 8.0	15.5 ± 8.8
Inactivity, h/wk	25.5 ± 14.0	26.3 ± 14.2	24.9 ± 14.1	23.1 ± 13.6	25.4 ± 14.9

[1] Values are means ± SDs or percentages and are standardized to the age distribution of the study population. Serving size is one glass.
[2] Values are not age-adjusted.
[3] Values do not sum to 100 because of rounding.

TABLE 2 Estimated mean age at menarche and 95% CI in 5583 girls in the Growing Up Today Study, 1996–2001[1]

	Events/person-years	Unadjusted estimated mean age at menarche,[2] y	Adjusted estimated mean age at menarche,[3] y
Total white milk			
≤1 serving/wk	171/318	12.8 (12.7, 12.8)	12.8 (12.6, 13.0)
1.1–4 servings/wk	1251/2489	12.7 (12.5, 12.8)	12.9 (12.8, 13.1)
4.1–7 servings/wk	917/1929	12.8 (12.7, 12.9)	12.9 (12.8, 13.1)
1.1–3 servings/d	2403/4709	12.8 (12.8, 12.9)	13.0 (12.8, 13.2)
>3 servings/d	485/1110	12.9 (12.8, 13.0)	13.1 (12.9, 13.3)
Whole milk[4,5]			
<1 serving/wk	2925/5921	12.8 (12.7, 12.9)	13.0 (12.8, 13.1)
1–4 servings/wk	765/1446	12.8 (12.7, 12.9)	12.9 (12.8, 13.1)
4.1–7 servings/wk	428/878	12.8 (12.7, 12.9)	13.0 (12.8, 13.2)
1.1–3 servings/d	954/1945	12.9 (12.8, 13.0)	13.0 (12.8, 13.2)
>3 servings/d	155/364	12.9 (12.7, 13.1)	13.0 (12.8, 13.3)
Low-fat milk[5]			
<1 serving/wk	3699/7541	12.8 (12.7, 12.9)	13.0 (12.8, 13.1)
1–4 servings/wk	486/896	12.8 (12.7, 12.9)	13.0 (12.8, 13.2)
4.1–7 servings/wk	296/535	12.8 (12.7, 12.9)	12.9 (12.7, 13.1)
1.1–3 servings/d	662/1361	12.9 (12.8, 13.0)	13.0 (12.9, 13.2)
>3 servings/d	84/222	13.0 (12.8, 13.3)	13.1 (12.9, 13.5)
Skim milk[5]			
<1 serving/wk	3370/7074	12.6 (12.5, 12.7)	13.0 (12.8, 13.2)
1–4 servings/wk	488/824	12.8 (12.8, 12.9)	12.8 (12.6, 13.0)
4.1–7 servings/wk	310/609	12.9 (12.7, 13.0)	13.0 (12.8, 13.3)
1.1–3 servings/d	891/1679	12.8 (12.7, 12.9)	13.0 (12.8, 13.2)
>3 servings/d	168/369	12.8 (12.7, 13.0)	13.0 (12.8, 13.3)
Low-fat dairy[4,6]			
≤0.5 servings/d	2219/4495	12.8 (12.7, 12.9)	12.9 (12.8, 13.1)
0.6–1 servings/d	865/1734	12.8 (12.7, 12.9)	13.0 (12.8, 13.1)
1.1–2 servings/d	855/1570	12.9 (12.8, 13.0)	13.0 (12.9, 13.2)
2.1–3 servings/d	839/1795	12.8 (12.7, 12.9)	13.0 (12.8, 13.1)
>3 servings/d	449/962	12.9 (12.7, 13.0)	13.0 (12.8, 13.2)
High-fat dairy[6]			
≤0.5 servings/d	606/1200	12.8 (12.7, 12.9)	13.0 (12.8, 13.2)
0.6–1 servings/d	1027/2097	12.8 (12.7, 12.9)	13.0 (12.8, 13.2)
1.1–2 servings/d	1715/3316	12.8 (12.7, 12.9)	12.9 (12.8, 13.1)
2.1–3 servings/d	874/1741	12.8 (12.7, 12.9)	13.0 (12.8, 13.2)
>3 servings/d	1005/2201	12.9 (12.8, 13.0)	13.0 (12.8, 13.2)
Meat[4,6]			
≤1 serving/wk	145/314	12.9 (12.7, 13.0)	13.0 (12.8, 13.3)
1.1–2 servings/wk	221/481	12.9 (12.7, 13.2)	13.0 (12.8, 13.3)
2.1–4 servings/wk	1020/1999	12.8 (12.7, 12.9)	13.0 (12.8, 13.1)
4.1–7 servings/wk	1985/3802	12.8 (12.7, 12.9)	13.0 (12.8, 13.1)
>1 servings/d	1856/3960	12.8 (12.8, 12.9)	13.0 (12.8, 13.2)
Red meat[4,6]			
≤1 serving/wk	433/930	12.7 (12.6, 12.8)	12.9 (12.7, 13.1)
1.1–2 servings/wk	742/1390	12.9 (12.8, 13.1)	13.1 (12.9, 13.3)
2.1–4 servings/wk	1850/3668	12.8 (12.7, 12.9)	13.0 (12.8, 13.1)
4.1–7 servings/wk	1635/3331	12.8 (12.8, 12.9)	13.0 (12.8, 13.2)
>1 servings/d	567/1237	12.8 (12.7, 12.9)	12.9 (12.7, 13.1)

[1] Estimated mean age at menarche in the interval between 9 and 18.5 y. Diet was assessed in 1996, 1997, and 1998. Food intake was cumulatively updated over follow-up. Milk serving size is one glass.
[2] Values of questionnaire cycle variables were set to their median value.
[3] Values of questionnaire cycle and ordinal categorical variables were set to their median value (total energy, birthweight, activity, and inactivity), and values of continuous and polytomous categorical risk factors were set to their observed mode in the study population (race, maternal age at menarche, frequency of eating dinner as a family, and household composition).
[4] Person-time does not sum to total because of rounding.
[5] Girls selected the type of milk typically consumed; consumption of other types was assumed to be zero.
[6] See Supplemental Table 1 for list of food items included in each food group.

TABLE 3 HRs and 95% CIs for associations between cumulative updated milk and meat consumption and menarche in 5583 girls in the Growing Up Today Study, 1996–2001[1]

	Events/person-years	Model 1	Model 2	Model 3
Total white milk, servings				
≤1/wk	171/318	1.07 (0.90, 1.26)	1.09 (0.92, 1.29)	1.13 (0.95, 1.33)
1.1–4/wk	1251/2489	1.00 (ref)	1.00 (ref)	1.00 (ref)
4.1/wk–1/d	917/1929	0.97 (0.89, 1.06)	0.99 (0.91, 1.09)	0.97 (0.88, 1.06)
1.1–3/d	2403/4709	0.93 (0.87, 1.00)	0.98 (0.91, 1.05)	0.93 (0.86, 1.00)
>3/d	485/1110	0.87 (0.78, 0.97)	0.93 (0.83, 1.04)	0.87 (0.77, 0.97)
P-trend		< 0.01	0.14	< 0.01
Whole milk,[2,3] servings				
<1/wk	2925/5921	0.98 (0.90, 1.06)	1.02 (0.94, 1.11)	0.98 (0.90, 1.06)
1–4/wk	765/1446	1.00 (ref)	1.00 (ref)	1.00 (ref)
4.1/wk–1/d	428/878	0.97 (0.86, 1.10)	1.01 (0.90, 1.15)	1.04 (0.92, 1.18)
1.1–3/d	954/1945	0.91 (0.82, 1.01)	0.97 (0.88, 1.07)	0.96 (0.87, 1.06)
>3/d	155/364	0.90 (0.75, 1.08)	0.97 (0.81, 1.17)	0.97 (0.80, 1.16)
P-trend		0.06	0.19	0.74
Low-fat milk,[3] servings				
<1/wk	3699/7541	1.03 (0.93, 1.13)	1.06 (0.95, 1.17)	1.03 (0.93, 1.14)
1–4/wk	486/896	1.00 (ref)	1.00 (ref)	1.00 (ref)
4.1/wk–1/d	296/535	1.04 (0.90, 1.21)	1.10 (0.94, 1.28)	1.09 (0.93, 1.27)
1.1–3/d	662/1361	0.93 (0.82, 1.05)	0.99 (0.87, 1.12)	0.95 (0.84, 1.08)
>3/d	84/222	0.86 (0.67, 1.09)	0.96 (0.75, 1.23)	0.87 (0.68, 1.11)
P-trend		0.01	0.14	0.04
Skim milk,[3] servings				
<1/wk	3370/7074	0.82 (0.74, 0.90)	0.82 (0.74, 0.91)	0.83 (0.75, 0.91)
1–4/wk	488/824	1.00 (ref)	1.00 (ref)	1.00 (ref)
4.1/wk–1/d	310/609	0.79 (0.68, 0.92)	0.78 (0.67, 0.91)	0.71 (0.61, 0.83)
1.1–3/d	891/1679	0.86 (0.76, 0.96)	0.86 (0.77, 0.97)	0.79 (0.70, 0.88)
>3/d	168/369	0.83 (0.69, 0.99)	0.84 (0.70, 1.01)	0.79 (0.66, 0.96)
P-trend		0.41	0.44	0.14
Total dairy,[4] servings				
≤0.5/d	102/168	1.24 (0.99, 1.56)	1.27 (1.01, 1.61)	1.26 (1.00, 1.59)
0.6–1/d	328/642	1.00 (ref)	1.00 (ref)	1.00 (ref)
1.1–2/d	1272/2515	1.08 (0.95, 1.23)	1.11 (0.98, 1.27)	1.05 (0.92, 1.19)
2.1–3/d	1278/2401	1.09 (0.96, 1.24)	1.15 (1.01, 1.31)	1.07 (0.93, 1.22)
>3/d	2248/4830	1.02 (0.89, 1.15)	1.12 (0.98, 1.29)	1.01 (0.88, 1.16)
P-trend		0.10	0.63	0.25
Low-fat dairy,[2,4] servings				
≤0.5/d	2219/4495	0.96 (0.88, 1.04)	0.95 (0.88, 1.03)	1.00 (0.92, 1.09)
0.6–1/d	865/1734	1.00 (ref)	1.00 (ref)	1.00 (ref)
1.1–2/d	855/1570	0.91 (0.82, 1.00)	0.91 (0.83, 1.01)	0.89 (0.80, 0.98)
2.1–3/d	839/1795	0.97 (0.88, 1.07)	1.00 (0.90, 1.10)	0.94 (0.85, 1.04)
>3/d	449/962	0.94 (0.83, 1.05)	0.98 (0.87, 1.11)	0.95 (0.84, 1.07)
P-trend		0.70	0.48	0.07
High-fat dairy,[4] servings				
≤0.5/d	606/1200	1.01 (0.91, 1.12)	1.01 (0.91, 1.13)	1.00 (0.90, 1.12)
0.6–1/d	1027/2097	1.00 (ref)	1.00 (ref)	1.00 (ref)
1.1–2/d	1715/3316	1.04 (0.96, 1.13)	1.05 (0.97, 1.14)	1.03 (0.95, 1.12)
2.1–3/d	874/1741	1.02 (0.93, 1.12)	1.04 (0.94, 1.14)	1.03 (0.93, 1.13)
>3/d	1005/2201	0.97 (0.88, 1.06)	1.01 (0.92, 1.12)	1.03 (0.93, 1.14)
P-trend		0.28	0.96	0.61
Meat,[2,4] servings				
≤1/wk	145/314	0.98 (0.79, 1.22)	1.04 (0.84, 1.30)	1.08 (0.87, 1.35)
1.1–2/wk	221/481	1.00 (ref)	1.00 (ref)	1.00 (ref)
2.1–4/wk	1020/1999	1.08 (0.93, 1.26)	1.09 (0.93, 1.27)	1.10 (0.94, 1.28)
4.1/wk–1/d	1985/3802	1.10 (0.95, 1.28)	1.09 (0.94, 1.28)	1.08 (0.93, 1.26)
>1/d	1856/3960	1.06 (0.90, 1.24)	1.07 (0.91, 1.25)	1.06 (0.90, 1.24)
P-trend		0.95	0.94	0.69

(Continued)

TABLE 3 *Continued*

	Events/person-years	Model 1	Model 2	Model 3
Red meat,[2,4] servings				
≤1/wk	433/930	0.82 (0.72, 0.93)	0.85 (0.75, 0.96)	0.89 (0.78, 1.00)
1.1–2/wk	742/1390	1.00 (ref)	1.00 (ref)	1.00 (ref)
2.1–4/wk	1850/3668	0.92 (0.84, 1.00)	0.92 (0.84, 1.01)	0.91 (0.83, 0.99)
4.1/wk–1/d	1635/3331	0.92 (0.84, 1.01)	0.92 (0.83, 1.01)	0.89 (0.81, 0.99)
>1/d	567/1237	0.94 (0.83, 1.06)	0.94 (0.82, 1.07)	0.93 (0.82, 1.06)
P-trend		0.54	0.81	0.71

[1] Diet was assessed in 1996, 1997, and 1998. Food intake was cumulatively updated over follow-up. Model 1 is a Cox proportional hazards model stratified by age in months and questionnaire cycle and adjusted for total caloric intake (quintiles). Model 2 is a Cox proportional hazards model adjusted for Model 1 covariates, as well as sugar-sweetened beverage consumption (≤2 servings/wk, 2.1–3 servings/wk, 3.1–5 servings/wk, 5.1 servings/wk–1.5 servings/d, and >1.5 servings/d), activity (quintiles), inactivity (quintiles), race/ethnicity (non-Hispanic white and other), household composition (no father or stepfather, father, and stepfather), frequency of eating dinner as a family (ordinal), maternal age at menarche (≤11, 12, 13, and ≥14 y), and birthweight (quintiles). Model 3 is a Cox proportional hazards model adjusted for Model 2 covariates, as well as BMI (deciles) and height (quintiles). Milk serving size is one glass. *P*-trend is calculated by using the median of each category as a continuous term. ref, reference.

[2] Person-time does not sum to total because of rounding.

[3] Girls selected the type of milk typically consumed; consumption of other types was assumed to be zero.

[4] See Supplemental Table 1 for list of food items included in each food group.

Sensitivity analyses. We observed similar findings when we restricted our analyses to events and person-time contributed by girls under 12, 13, or 14 y of age (**Supplemental Table 3**), and in the sample in which follow-up ended in 1999 or earlier (i.e., 1998 dietary data were not used for 1999–2001 follow-up) (data not shown). Statistically significant effect modification by race was observed for the association of milk consumption and menarche (*P*-heterogeneity = 0.02), but not other exposures. Associations of more frequent milk consumption and later menarche in whites only were similar to those observed for the entire sample (data not shown).

Discussion

In this cohort of US girls, neither consumption of milk nor meat predicted age at menarche when examined using models adjusted for potential sociodemographic and nutritional confounders. After additional consideration for body size, we observed that more frequent consumption of total and low-fat milk and dairy protein predicted a modestly older age at menarche (i.e., a lower rate of menarche). This is in contrast to our a priori hypothesis that controlling for body size, a potential intermediate, would result in attenuated effect estimates. Milk is a nutritionally complex food that contains multiple hormonally active substances. Thus, it is possible that milk consumption activates numerous pathways—some of which accelerate menarche and others that delay it—that, when taken together, have no overall effect on menarcheal timing. However, observed effect estimates from models adjusted for body size were modest, and may be an artifact of confounding, which can be introduced by conditioning on an intermediate variable (24).

Previous studies. To our knowledge, our study is the largest and the first prospective study of the association between milk and menarche in a US population. General nutrition status, milk consumption (26), and age at menarche (27) vary by country, and the generalizability of previous findings to a contemporary population of US girls is uncertain. Our results are consistent with null findings from milk-supplementation studies of 757 Chinese 10-y-old children (3, 28) and 80 British 12-y-old children (2), prospective observational studies of 3298 British girls (29) and 2299 Canadian fifth graders (30), and cross-sectional analyses of 777 Spanish 8–16-y-old children (31) and 1008 US 9–12-y-old children (32). In contrast, milk consumption was associated with earlier menarche in a prospective study of 134 Iranian girls (33) and cross-sectional studies of 2657 20–49-y-old US women (32) and 411 North Korean refugees (mean age: 31.3 y) (34). Notably, studies with positive findings had the greatest potential for misclassification of the exposure and outcome because of a longer recall interval (32, 34) and poor dietary assessment (34). Previous investigations of nutrient intake (7) and meat (29–31) with age at menarche have yielded mixed results.

Biological mechanism. Consumption of milk, but not meat, has been found to raise concentrations of absolute and bioavailable IGF-I in prepubertal children (9, 10), although girls the age of our study participants have yet to be studied. Although dairy, especially milk (35), contains IGF-I, it is unknown whether the observed increase in IGF-I concentrations after milk consumption is due to the intact absorption and bioactivity of bovine IGF-I or the endogenous stimulation of human IGF-I by another constituent of milk, such as protein (36, 37). IGF-I is an important regulator of growth in prepubertal children, and many studies have observed positive associations between milk intake and linear growth (26) and weight gain (38), important predictors of age at menarche (20, 21). Higher IGF-I concentrations at 8 y of age are associated with earlier menarche (39); however, it is not known to what extent the association of IGF-I with earlier menarche is causal or the by-product of the association of greater height with earlier menarche. Steroid hormones are also endogenous to milk (4), but it is unclear whether consumption of milk could increase circulating estrogen concentrations (2) and how this would influence pubertal timing.

Strengths and limitations. Girls were aged 9–14 y at baseline and, although premenarcheal, were likely to have initiated puberty. This leads to 2 potential limitations: *1*) early-maturing girls may drink less milk as a consequence of their maturation (i.e., reverse causation), and *2*) if a critical window for exposure exists in early childhood (29), it may have been missed. Early-maturing girls may avoid milk if they perceive it as a "childish" food or because of its suspected association with acne (40). However, it is also possible that they may consume more milk to fulfill greater nutritional needs during a time of rapid growth. We minimized the potential for reverse causation by relating menarche to dietary consumption reported the previous year and earlier.

TABLE 4 HRs and 95% CIs for associations between cumulative updated nutrients and menarche among 5583 girls in the Growing Up Today Study, 1996–2001[1]

Nutrient	Events/person-years	Model 1	Model 2	Model 3
Dairy fat[2]				
Q1	899/1759	1.00 (ref)	1.00 (ref)	1.00 (ref)
Q2	982/1899	1.01 (0.92, 1.11)	1.00 (0.91, 1.10)	1.00 (0.91, 1.10)
Q3	1060/2153	0.95 (0.87, 1.04)	0.94 (0.85, 1.03)	0.94 (0.85, 1.03)
Q4	1108/2324	0.93 (0.85, 1.02)	0.95 (0.86, 1.04)	0.99 (0.91, 1.09)
Q5	1178/2421	0.91 (0.83, 1.00)	0.94 (0.86, 1.03)	0.98 (0.89, 1.08)
P-trend		0.01	0.12	0.80
Dairy protein[2]				
Q1	907/1773	1.00 (ref)	1.00 (ref)	1.00 (ref)
Q2	1065/2088	0.99 (0.90, 1.09)	1.03 (0.94, 1.13)	0.97 (0.88, 1.06)
Q3	1064/2197	0.95 (0.87, 1.05)	1.01 (0.92, 1.11)	0.95 (0.87, 1.04)
Q4	1115/2257	0.95 (0.86, 1.04)	1.00 (0.91, 1.10)	0.92 (0.83, 1.01)
Q5	1076/2241	0.94 (0.86, 1.03)	1.02 (0.93, 1.13)	0.92 (0.83, 1.01)
P-trend		0.13	0.86	0.05
Animal fat[2]				
Q1	897/1689	1.00 (ref)	1.00 (ref)	1.00 (ref)
Q2	999/2002	0.97 (0.88, 1.06)	0.96 (0.87, 1.05)	0.98 (0.89, 1.08)
Q3	1100/2146	1.00 (0.91, 1.09)	1.00 (0.91, 1.10)	1.01 (0.92, 1.11)
Q4	1058/2303	0.93 (0.84, 1.02)	0.93 (0.85, 1.03)	0.95 (0.86, 1.04)
Q5	1173/2414	0.94 (0.86, 1.03)	0.96 (0.88, 1.05)	0.98 (0.90, 1.08)
P-trend		0.11	0.33	0.57
Animal protein				
Q1	979/1891	1.00 (ref)	1.00 (ref)	1.00 (ref)
Q2	1068/2101	0.98 (0.90, 1.07)	1.04 (0.95, 1.14)	1.02 (0.93, 1.12)
Q3	1102/2193	0.98 (0.90, 1.08)	1.05 (0.96, 1.15)	1.03 (0.94, 1.12)
Q4	1022/2215	0.94 (0.86, 1.03)	1.02 (0.93, 1.12)	0.97 (0.88, 1.07)
Q5	1056/2155	0.97 (0.89, 1.06)	1.05 (0.95, 1.15)	0.95 (0.86, 1.05)
P-trend		0.35	0.47	0.16
Calcium[3]				
Q1	892/1739	1.00 (ref)	1.00 (ref)	1.00 (ref)
Q2	1085/2100	0.99 (0.90, 1.08)	1.02 (0.93, 1.12)	0.98 (0.89, 1.08)
Q3	1066/2220	0.93 (0.84, 1.02)	0.98 (0.89, 1.07)	0.92 (0.84, 1.02)
Q4	1107/2257	0.96 (0.88, 1.05)	1.02 (0.93, 1.12)	0.95 (0.86, 1.04)
Q5	1077/2239	0.93 (0.85, 1.02)	1.02 (0.92, 1.12)	0.93 (0.84, 1.02)
P-trend		0.11	0.78	0.12
Vitamin D[3]				
Q1	890/1629	1.00 (ref)	1.00 (ref)	1.00 (ref)
Q2	1025/2033	0.93 (0.85, 1.03)	0.97 (0.88, 1.06)	1.01 (0.91, 1.10)
Q3	1090/2217	0.92 (0.84, 1.01)	0.96 (0.87, 1.05)	0.96 (0.88, 1.06)
Q4	1091/2225	0.96 (0.88, 1.06)	1.02 (0.92, 1.12)	1.01 (0.92, 1.11)
Q5	1131/2451	0.89 (0.82, 0.98)	0.96 (0.87, 1.05)	0.97 (0.88, 1.06)
P-trend		0.06	0.69	0.53

[1] Diet was assessed in 1996, 1997, and 1998. Food intake was cumulatively updated over follow-up. Model 1 is a Cox proportional hazards model stratified by age in months and questionnaire cycle and adjusted for total caloric intake (quintiles). Model 2 is a Cox proportional hazards model adjusted for Model 1 covariates, as well as sugar-sweetened beverage consumption (≤2 servings/wk, 2.1–3 servings/wk, 3.1–5 servings/wk, 5.1 servings/wk–1.5 servings/d, and >1.5 servings/d), activity (quintiles), inactivity (quintiles), race/ethnicity (non-Hispanic white and other), household composition (no father or stepfather, father, and stepfather), frequency of eating dinner as a family (ordinal), maternal age at menarche (≤11, 12, 13, and ≥14 y), and birthweight (quintiles). Model 3 is a Cox proportional hazards model adjusted for Model 2 covariates, as well as BMI (deciles) and height (quintiles). *P*-trend is calculated by using the median of each category as a continuous term. Q, quintile; ref, reference.

[2] Person-time does not sum to total due to rounding.

[3] Includes intake from food and supplements.

Some within- and between-person error in dietary recall is inevitable in an FFQ. However, reporting errors in milk intake are likely unrelated to age at menarche, resulting in an underestimate of the true association. Furthermore, the use of cumulative averaged intake reduces measurement error because of within-person variation. Misclassification of the outcome was minimized by selecting a salient pubertal event and using only the first reported age at menarche. Reporting errors are likely to be unrelated to milk consumption, resulting in an underestimate of the true effect. Advantages of using age at menarche as a measure of pubertal timing include ease and reliability (17, 41); however, menarche is a relatively late pubertal event, and it is possible that different associations may exist with other markers of pubertal timing.

Girls with the most frequent milk consumption may differ in their overall dietary pattern, activity level, or other characteristics compared with girls consuming little or no milk. We addressed potential confounding by a variety of anthropomorphic, socio-demographic, and dietary factors using multivariable models. We observed only a small change in observed effect estimates after adjustment for strong predictors of menarche, reassuring us that the magnitude of any residual confounding is likely to be negligible.

Although study follow-up began almost 20 y ago, mean age at menarche in the United States has been relatively static since the turn of the 20th century (7, 42), and we expect our findings to be generalizable to contemporary US girls. Indeed, the unadjusted median age at menarche in the entire GUTS cohort (93% white) was 12.7 y, comparable to reports from other contemporary populations of white girls (18, 19). African-American and Hispanic girls typically experience menarche earlier than whites (18, 19), and the generalizability of our results to these populations is uncertain. We observed effect modification by race for the association of total milk consumption and age at menarche, but were unable to calculate stable effect estimates for Hispanics and African-Americans because of small sample sizes. In order to prospectively obtain data on age at menarche, we excluded girls who were menarcheal at baseline, resulting in a median age at menarche of 13.1 y in our study population. This decision should not affect the validity of our effect estimates, as evidenced by similar findings for the youngest girls in our cohort (i.e., the least affected by left-censoring).

In conclusion, in a large cohort of US girls whose follow-up began at ages 9–14 y, we observed an association between more frequent milk consumption and later menarche only after adjustment for body size. Effect estimates were modest and may have been due to residual confounding. Consumption of milk during late childhood is therefore unlikely to strongly affect menarcheal timing. Other studies have suggested that consumption of meat and dairy products can affect endocrine and reproductive outcomes (40, 43), and the health consequences of milk and meat consumption in prepubertal children, in particular, should continue to be closely examined.

Acknowledgments

We thank Donna Spiegelman, Ellen Hertmark, and Garrett Fitzmaurice, of Harvard T.H. Chan School of Public Health for their advice on statistical methods. JLC, WCW, ALF, and KBM designed the research; JLC analyzed the data and drafted the manuscript; WCW, MW, JR-E, ALF, and KBM provided significant consultation. JLC had primary responsibility for the final content. All authors read and approved the final manuscript.

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