Dairy and related nutrient intake and risk of uterine leiomyoma: a prospective cohort study

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STUDY QUESTION: Is there an association between consumption of dairy foods and related nutrients and risk of uterine leiomyoma?

SUMMARY ANSWER: While dairy consumption was not consistently associated with uterine leiomyoma risk, intake of yogurt and calcium from foods may reduce risk of uterine leiomyoma.

WHAT IS KNOWN ALREADY: Two studies have examined the association between dairy intake and uterine leiomyoma risk with inconsistent results. Dairy foods have been inversely associated with inflammation and tumorigenesis, suggesting that vitamins and minerals concentrated in these dietary sources may influence uterine leiomyoma risk.

STUDY DESIGN, SIZE, DURATION: A prospective cohort study was carried out using data collected from 81 590 premenopausal women from 1991 to 2009 as part of the Nurses' Health Study II cohort.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Diet was assessed with a validated food frequency questionnaire every 4 years. Cases were restricted to self-reported ultrasound or hysterectomy-confirmation uterine leiomyoma. Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% CI.

MAIN RESULTS AND THE ROLE OF CHANCE: Eight thousand one hundred and forty-two cases of ultrasound or hysterectomy-confirmed uterine leiomyoma were diagnosed over an 18-year period. When compared to participants who consumed two servings a week of total dairy foods, participants who consumed four or more servings had a borderline significant 8% reduced risk of uterine leiomyoma (HR = 0.92, 95% CI = 0.85, 1.00; $p_{\text{trend}} = 0.19$). When the association between specific dairy foods and uterine leiomyoma was examined, the relation between dairy-food intake and uterine leiomyoma appeared to be driven primarily by yogurt consumption (HR for 2+ servings/day = 0.76; 95% CI = 0.55, 1.04 compared to ≤ 4 servings/week; $p_{\text{trend}} = 0.03$); however, there was a small number of cases in the 2+ servings/day group ($n = 39$). Of the nutrients examined, the association was strongest for calcium from foods (HR fifth quintile = 0.92, 95% CI = 0.86, 0.99; $p_{\text{trend}} = 0.04$).

LIMITATIONS, REASONS FOR CAUTION: Some cases of uterine leiomyoma were likely misclassified, particularly those that were asymptomatic. It is possible that dairy product constituents reduce uterine leiomyoma symptomology rather than development, giving the appearance of a protective effect on leiomyoma development: no data on uterine leiomyoma symptomology were available. We did not have vitamin and mineral concentrations from actual blood levels. Similarly, there is the potential for misclassification of participants based on predicted 25(OH)D, and changes in vitamin D supplementation over time may have impacted prediction models for 25(OH)D. Further, some error in the self-reporting of dietary intake is expected. Given our prospective design, it is likely that these misclassifications were non-differential with respect to the outcome, likely biasing estimates toward the null.

WIDER IMPLICATIONS OF THE FINDINGS: While no clear association between overall dairy consumption and uterine leiomyoma risk was observed, our findings suggest that intake of yogurt and calcium from foods may reduce risk of uterine leiomyoma.

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Key words: calcium / dairy foods / vitamin D / yogurt / diet / fibroids / uterine leiomyoma

Introduction

Uterine leiomyoma, also known as fibroids, are benign tumors in the smooth muscle of the uterus that are the leading cause of hysterectomy in the USA (Farquhar and Steiner, 2002). Approximately 70–80% of women will develop ultrasound-detectable fibroids before menopause (Baird et al., 2003). Symptoms can include severe pelvic pain, abnormal uterine bleeding and anemia (Stewart, 2001), and direct costs, including surgery, hospital admission, outpatient visits and medication, account for an estimated 4–9 billion US dollars annually (Cardozo et al., 2012). Despite the high prevalence, morbidity and associated costs, the etiology of uterine leiomyomas is poorly understood and few modifiable risk factors have been identified. Steroid hormones and growth factors are thought to play a role (Rein et al., 1995, Sozen and Arici, 2006) and diet may be an important factor due to its effects on inflammation and endogenous hormones.

Dairy foods have been inversely associated with inflammation and tumorigenesis (Lordan and Zabetakis, 2017), suggesting that vitamins and minerals concentrated in these dietary sources may influence uterine leiomyoma risk (Parazzini et al., 2015). For example, vitamin D has been shown to reduce fibroid cell proliferation in *in vitro* human cells and tumor growth in animal models (Brakta et al., 2015). Diet-induced vitamin D deficiency has also been shown to induce inflammation of uterine smooth muscle in mice (Elhusseini et al., 2018). However, few studies have examined the association between dairy food consumption and uterine leiomyoma. One case–control study of Italian women (843 histologically confirmed uterine leiomyoma cases and 1557 hospital-based controls) reported no association with increasing milk and cheese consumption (Chiaffarino et al., 1999). In contrast, a large prospective study of US black women reported a strong inverse association between surgically and ultrasound-diagnosed uterine leiomyoma and greater milk and total dairy consumption (Wise et al., 2010). Further confirmation of this inverse relationship, and an investigation into other dairy constituents, is warranted.

In this study, we investigated whether intake of total and specific dairy foods, nutrients concentrated in dairy foods (calcium, vitamin D and magnesium) and predicted plasma 25(OH)D levels were associated with incident uterine leiomyoma confirmed by ultrasound or hysterectomy in a large cohort of premenopausal women over an 18-year follow-up period.

Materials and Methods

Study population

The Nurses' Health Study II (NHSII) is an ongoing prospective cohort study established in 1989. At baseline, 116 429 US female registered nurses aged 25–42 years completed a questionnaire that collected

information on demographic and lifestyle factors, anthropometric variables and disease history. Follow-up questionnaires are sent biennially to update information on exposures and disease status. Further study details have been provided elsewhere (Solomon et al., 1997). Questionnaire response rates remain at >90%. Ongoing consent was assumed upon return of each completed questionnaire. This study was approved by the institutional review boards of the Harvard T.H. Chan School of Public Health and the Brigham and Women's Hospital, Boston, MA, USA.

Follow-up for the current analyses began in 1991 when 97 813 NHSII participants first returned the food frequency questionnaire (FFQ) and concluded in 2009, the last year uterine leiomyoma incidence was assessed on the biennial questionnaire—at which time the youngest participant was age 45 years. Criteria for exclusion were as follows: implausible total energy intake (<600 kcal/day or >3500 kcal/day), blank entries for more than 70 food items on the 1991 FFQ and a uterine leiomyoma or cancer diagnosis (other than nonmelanoma skin cancer) prior to June 1991. The analytical cohort was limited to nurses who were premenopausal and had intact uteri. After these exclusions, 81 590 premenopausal nurses with dietary information remained.

Dietary assessment

Diet was assessed in 1991, 1995, 1999, 2003 and 2007 using an FFQ that listed over 130 food items, including 11 individual dairy foods. Participants were asked how often, on average, they consumed each type of food or beverage during the previous year. For each food item, nine responses were possible, ranging from never or less than once per month to six or more times per day. Participants were also asked to report whether they used nutrient supplements and to provide the brand and dose. Intakes of total and specific dairy foods were calculated by multiplying the portion size of a single serving of each dairy item by its reported frequency of intake. Intakes of the nutrients of interest (vitamin D, calcium and magnesium) were calculated by first multiplying the portion size of a single serving of each food by its reported frequency of intake for the total amount of food consumed, and then multiplying the total amount consumed by the nutrient content of the food, and then summing the nutrient contributions of all food items using food composition data from the US Department of Agriculture (Nutrient Data Laboratory), while also taking dietary supplements into account. The specific types of milk, yogurt and cheese assessed on the FFQ were as follows: whole milk, 1% or 2% milk, skim milk, plain yogurt, flavored yogurt, cottage or ricotta cheese, cream cheese and other cheese (e.g. American i.e. a processed cheese, cheddar).

The reproducibility and validity of the NHSII FFQ have been reported in detail elsewhere (Salvini et al., 1989, Willett et al., 1985, Yuan et al., 2017). The FFQ has been shown to provide valid estimates of dairy food and nutrient intake, with deattenuated correlation

coefficients between the FFQ and 1-week diet records of 0.57 for hard cheeses (Salvini *et al.*, 1989), 0.75 for calcium intake (Willett, 1998), 0.62 for whole milk (Salvini *et al.*, 1989), 0.71 for magnesium (Rimm *et al.*, 1992), 0.80 for cottage cheese (Salvini *et al.*, 1989), 0.81 for skim milk (Salvini *et al.*, 1989) and 0.94 for yogurt (Salvini *et al.*, 1989). Vitamin D levels have been validated using plasma concentrations of 25(OH)D, with reported correlations of 0.25 ($P < 0.0001$) (Feskanich *et al.*, 2003, Wu *et al.*, 2009). Intakes of all nutrients were adjusted for total energy intake using the residual method (Willett, 1998).

Predicted plasma 25(OH)D levels

A model for predicting plasma 25(OH)D levels was developed using 1498 NHSII participants with no prior history of cancer who previously served as controls in nested case-control studies and who donated blood between 1996 and 1999. Plasma 25(OH)D was measured using an enzyme immunoassay, as previously described (Bertrand *et al.*, 2012), and a linear regression model was then developed to predict plasma 25(OH)D levels on the basis of race/ethnicity, geographical region, dietary vitamin D intake, supplementary vitamin D intake, BMI, alcohol intake and physical activity (Bertrand *et al.*, 2012). From the predictors' regression coefficients, a predicted 25(OH)D score was calculated for each participant. R-squared for the prediction model was 0.25 for the NHSII (Bertrand *et al.*, 2012).

Ascertainment and definition of uterine leiomyoma

Starting in 1993, participants were asked on each biennial questionnaire if they ever received a physician diagnosis of uterine leiomyoma and, if so, the date of diagnosis and whether the diagnosis was confirmed by pelvic exam, ultrasound or hysterectomy. Cases were defined on the basis of self-reported ultrasound or hysterectomy confirmation. Participants who reported fibroids not confirmed by ultrasound or hysterectomy (pelvic exam only) did not contribute person time to that study period but were allowed to re-enter the analysis if confirmed by ultrasound or hysterectomy in the future.

In a previous validation study, a subset of newly diagnosed cases confirmed by ultrasound or hysterectomy after 1989 ($N = 243$, 100 Caucasian and 143 African-American) were mailed a questionnaire on symptoms and a review of their medical records was requested (Marshall *et al.*, 1997). Of the 216 who responded (89%), 6% denied the diagnosis and 34% confirmed the diagnosis but did not release their medical records. Among the cases in which medical records could be obtained, 93% were confirmed. The proportion diagnosed by hysterectomy, myomectomy, examination under anesthesia or ultrasound did not differ between those who did and did not give permission for medical record release. The proportion confirmed by medical record did not differ comparing Caucasian (94%) and African-American (92%) participants.

Statistical analysis

Participants contributed follow-up time from the return of the 1991 questionnaire until self-report of a uterine leiomyoma, diagnosis of any cancer (except non-melanoma skin cancer), death, loss to follow-up, hysterectomy, menopause or until return of the 2009 questionnaire—whichever occurred first. Cox proportional hazards regression models

were used with age and the questionnaire period as the time scale for the estimation of hazard ratios (HRs) and 95% CI. For nutrients, which were categorized into quintiles, the lowest category of intake was used as the reference group. For foods, which were categorized by servings/month, week or day, the category of intake with the most participants was used as the reference. Cumulative average consumption, in which uterine leiomyoma incidence between each 2-year questionnaire cycle is related to the cumulative average of dietary intake calculated from all of the preceding dietary measures, is the primary method reported as it captures long-term dietary intake and minimizes measurement error due to within-person variation over time (Hu *et al.*, 1999). In addition, as undiagnosed uterine leiomyomas have the potential to influence dietary intake before diagnosis we examined dietary intake in multiple ways; baseline intake (1991) and varying lag time. For example, it is plausible that heavy bleeding due to fibroids could lead to iron deficiency anemia and changes in dietary patterns (Puri *et al.*, 2014). The lagged analyses allow us to examine dietary intake that is potentially before or closer to fibroid onset and should capture dietary intake that is not influenced by fibroid symptoms (e.g. menstrual bleeding). We examined lag times of 2–4 (simple update), 4–6 and 6–8 years. For example, for a lag time of 6–8 years before diagnosis we used dietary intake from the 1991 questionnaire for a uterine leiomyoma diagnosis reported from June 1997 to June 2001, and intake from 1995 for follow-up from 2001 to 2005. Covariate adjusted models included known and purported uterine leiomyoma risk factors (age at menarche, infertility, ancestry, parity, age at first birth, time since last birth, age at first oral contraceptive (OC) use, BMI, length of menstrual cycle, smoking status, recent gynecologic/breast exam, use of anti-hypertensive medications/diastolic blood pressure) as well as total caloric intake (Boynnton-Jarrett *et al.*, 2005, Terry *et al.*, 2010, Terry *et al.*, 2007). Separate categories were created for those who were nulliparous for the age at first birth and time since last birth variables. For age at first OC use, those who never used OCs were included in a separate category. Menstrual cycle length was assessed in the 1993 questionnaire. The questionnaire response did not have a category option for those not experiencing menses but did have a category that was 51+ days or too irregular to estimate. Covariates were updated throughout the analysis as new information became available for the biennial questionnaires. Missing data were handled via the missing indicator method, with categories created for missing data included in the regression model (Mu *et al.*, 2016, Song *et al.*, 2016). Tests for linear trend of the exposures of interest were performed by assigning the median value of each category to all participants in that group.

Effect modification by parity (nulliparous versus parous) was assessed using likelihood ratio tests that compared the model with the cross-product between the exposure variable and parity to the main effects only model. This analysis was conducted as uterine leiomyomas may be diagnosed for different reasons in parous versus nulliparous women, with potentially more incidental uterine leiomyomas found on ultrasound among parous women.

The influence of misclassification on the outcome was assessed using methods by Duffy *et al.* (2004). We calculated a corrected log HR by dividing the uncorrected log HR by the sum of the positive predictive value, the negative predictive value and -1 . For this correction, we assumed that self-reported uterine leiomyoma had a positive predictive value of 93% based on the validation study performed earlier in this

study population (Marshall et al., 1997) and a negative predictive value of 51% based on a study by Baird et al. (2003) that demonstrated half of women in a randomly selected population who reported no uterine leiomyoma had uterine leiomyoma on ultrasound screening. All statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA) and all tests of statistical significance were two-sided. A value of $P < 0.05$ was considered significant.

Results

During 1 536 355 person years of follow-up contributed by 81 590 women, 81 42 incident cases of ultrasound or hysterectomy-confirmed uterine leiomyomas were reported. Women with the greatest intake of total dairy foods were slightly younger, had shorter time since last birth, were more likely to be overweight, Caucasian, and to have reported a recent gynecological examination and less likely to be current smokers and nulliparous than those with lower total dairy food intake (Table I).

Higher intake of total dairy foods was associated with lower risk of uterine leiomyoma in the age-adjusted model (Table II). When compared to participants who consumed two servings a day, participants who consumed greater than four servings per day had an 18% lower risk of uterine leiomyoma (95% CI = 0.75, 0.89; $p_{\text{trend}} < 0.0001$), and after adjustment for covariates the estimates were attenuated to an 8% lower risk (95% CI = 0.85, 1.00; $p_{\text{trend}} = 0.19$) and were borderline significant. This attenuation was primarily driven by adjustment for parity, time since last birth and age at first birth. When low-fat and high-fat dairy foods were included in the same model, there were no differences in the effects of these two types of dairy foods ($p_{\text{difference}} = 0.18$). When the association between specific dairy foods and uterine leiomyoma was examined, the relation between dairy-food intake and uterine leiomyoma appeared to be driven primarily by yogurt consumption (HR = 0.76 for 2+ servings/day; 95% CI = 0.55, 1.04; $p_{\text{trend}} = 0.03$) (Table III) and when yogurt consumption was adjusted for total dairy intake the association remained (HR = 0.77 for 2+ servings/day; 95% CI = 0.56, 1.06; $p_{\text{trend}} = 0.04$).

When the association between specific nutrients found in dairy foods and uterine leiomyoma was examined, the relation between dairy-food intake and uterine leiomyoma appeared to be driven primarily by calcium from foods (Table IV). When compared to participants in the lowest quintile of calcium from foods, participants in the highest quintile of calcium from foods had an 8% lower risk of uterine leiomyoma (95% CI = 0.86, 0.99; $p_{\text{trend}} = 0.04$) (Table IV). When calcium from foods and total dairy intake were mutually adjusted for each other in the same regression model, the association with total dairy intake was attenuated (HR = 0.97 for >4 servings/day; 95% CI = 0.88, 1.07; $p_{\text{trend}} = 0.92$) while the association with calcium intake from foods did not materially change (HR for fifth quintile = 0.91; 95% CI = 0.82, 1.00; $p_{\text{trend}} = 0.10$). The results for dairy calcium were similar to calcium from foods, with a 7% lower risk of uterine leiomyoma (95% CI = 0.87–1.00; $p_{\text{trend}} = 0.06$) comparing highest to lowest quintile (Table IV). Total intake of calcium (including intake from supplements), total vitamin D intake (including intake from supplements), vitamin D from foods, predicted 25(OH)D, total magnesium intake (including intake from supplements) and magnesium from foods were not associated with uterine leiomyoma risk in the multivariable adjusted models (Table IV).

When stratified by parity, inverse associations observed for total dairy and calcium intake from foods were generally restricted to parous women (Supplementary Tables SI and SII). For example, a 10% lower risk of uterine leiomyoma was observed comparing parous participants with the highest total dairy intake (>4/day) to 2/day (reference) (HR = 0.90; 95% CI = 0.81, 0.98; $p_{\text{trend}} = 0.06$) while no difference was observed among nulliparous women (HR = 1.02; 95% CI = 0.88, 1.19; $p_{\text{trend}} = 0.47$). Similarly, when compared to parous participants in the lowest quintile of calcium intake from foods, parous participants in the highest quintile had a 10% lower risk of uterine leiomyoma (HR = 0.90; 95% CI = 0.83, 0.98; $p_{\text{trend}} = 0.03$). A similar inverse association was not observed among nulliparous women (HR = 0.99; 95% CI = 0.86, 1.14; $p_{\text{trend}} = 0.49$). However, the interactions were not statistically significant and this differential association was not observed for yogurt intake.

The associations with dairy intake were consistent across different time intervals between dietary intake and uterine leiomyoma diagnosis (Supplementary Table SIII). When we corrected our effect estimates for the misclassification of the outcome (assuming that half of the women who did not report uterine leiomyoma actually had undiagnosed uterine leiomyoma), we saw small changes in the effect estimates with the changes slightly strengthening the results but with wider CIs (Supplementary Tables SIV and SV).

Discussion

In this large prospective study, we observed suggestive evidence for a lower risk of uterine leiomyoma among participants with a higher intake of total dairy foods, irrespective of low- and high-fat sources. Calcium from foods and yogurt consumption appeared to be the strongest contributors to this association. No associations were observed with any other dairy foods or nutrients.

The epidemiologic data regarding the relationship between dairy intake and uterine leiomyoma are limited (Parazzini et al., 2015). To our knowledge, only two case-control studies and one prospective cohort study have examined the association between dairy intake and uterine leiomyoma (Chiaffarino et al., 1999; He et al., 2013; Wise et al., 2010). Case-control studies may be impacted by differential dietary recall from cases and controls, biasing estimates in both upward and downward directions from the null, and may reflect more recent dietary intake rather than intake prior to diagnosis. A case-control study in Italy found no association between weekly consumption of milk and cheese (defined as either low/intermediate/high) and clinically diagnosed uterine leiomyoma (odds ratios (ORs) comparing high to low categories for milk and cheese were 1.2 and 1.0, respectively) (Chiaffarino et al., 1999). Controls were women of comparable age who did not have hysterectomies and who were admitted to the hospital for acute non-gynecologic, non-hormonal, non-neoplastic conditions. Similarly, a case-control study in China found no association between average weekly dairy food consumption (defined as either low/intermediate/high) and hysterectomy-confirmed uterine leiomyoma from medical records (OR comparing high to low categories was 1.2) (He et al., 2013). Participants were recruited from a medical health checkup programme, but unfortunately the characteristics of the control women and their selection methods were not described. Models from these two studies did not adjust for total

Table 1 Distribution of potential risk factors for uterine leiomyomas according to total dairy intake among women in the Nurses' Health Study II at baseline.¹

	Total Dairy Servings						
	≤4/week	5–6/week	1/day	2/day	3/day	4/day	>4/day
No. of Women	3072	5508	3925	26 300	16 527	14 031	11 607
Age (years)	37.1 (4.5)	36.8 (4.6)	36.7 (4.6)	36.3 (4.6)	36.2 (4.6)	35.7 (4.5)	35.5 (4.5)
Caucasian	84.1	88.8	89.9	92.2	93.8	94.7	93.7
BMI (kg/m ²), Mean (SD)	24.1 (5.2)	24.5 (5.4)	24.6 (5.5)	24.5 (5.3)	24.6 (5.3)	24.4 (5.1)	24.6 (5.3)
BMI (kg/m ²), %							
<25, %	69.0	67.8	66.8	66.9	66.3	67.1	65.6
25–29.9, %	18.6	18.4	19.7	20.1	20.3	20.3	21.2
30+, %	12.4	13.9	13.5	13.0	13.4	12.6	13.2
Cigarette smoking							
Never	64.8	65.1	66.4	66.2	66.2	68.5	64.4
Past	19.1	19.4	20.0	21.4	23.2	22.0	23.8
Current	16.1	15.5	13.6	12.4	10.6	9.5	11.9
Age at menarche							
<12 years	24.3	25.6	24.4	23.8	23.8	22.9	23.4
12 years	30.0	30.8	30.7	30.6	30.5	30.6	29.3
13 years	27.1	25.6	27.8	27.8	27.9	28.4	28.0
≥14 years	18.6	18.1	17.1	17.8	17.7	18.1	19.4
Menstrual cycle length							
<26 days	20.5	18.9	17.9	17.1	16.2	15.5	15.6
26–31 days	64.8	66.8	67.9	68.4	68.6	69.0	68.5
32–50 days	9.2	10.2	10.4	10.6	11.0	11.7	11.8
51+ or irregular	5.4	4.2	3.9	4.0	4.3	3.8	4.1
Ever use of oral contraceptives	82.2	84.8	85.7	84.7	83.9	83.5	82.1
Nulliparous	31.9	31.0	30.3	29.3	27.6	23.0	22.8
Infertility diagnosis	5.6	6.3	6.0	6.3	6.4	6.1	6.3
Total Calories (kcal), Mean (SD)	1322 (479)	1411 (462)	1474 (464)	1632 (466)	1855 (481)	1986 (482)	2260 (519)
Time since last birth							
<1 year	4.2	3.5	4.6	4.5	5.8	7.2	10.2
1–3 years	24.0	25.3	24.9	26.6	29.4	32.0	35.0
4–5 years	15.2	15.5	16.2	15.5	15.7	15.0	13.2
6–7 years	13.5	12.3	11.9	12.3	11.9	11.7	10.6
8–9 years	11.4	10.7	10.5	10.4	9.8	9.2	8.4
10+ years	31.7	32.7	31.9	30.5	27.4	24.9	22.7
Age at first use of oral contraceptives							
Never	18.2	15.6	14.6	15.7	16.5	16.9	18.3
13–16 years	5.9	5.3	5.5	5.3	5.4	4.8	5.3
17–20 years	40.4	41.6	41.7	41.1	40.4	39.6	40.1
21–24 years	25.7	28.7	28.5	28.5	28.2	29.2	27.4
25+ years	9.7	8.9	9.7	9.5	9.6	9.5	8.8
Recent gynecologic exam							
No exam	18.4	16.1	15.1	14.5	13.4	13.3	13.3
Anti-hypertensive medication use	3.7	3.2	3.1	2.9	2.6	2.3	2.2
Diastolic blood pressure (mm Hg)							
<65	22.8	21.7	20.7	22.1	22.3	22.3	23.8
65–74	47.1	47.1	47.0	47.7	47.6	49.2	48.5
75–84	23.2	24.4	25.2	23.8	24.0	23.1	21.8
85–89	4.0	4.2	4.7	3.9	4.0	3.3	3.6
90+	2.9	2.6	2.4	2.5	2.1	2.0	2.3

¹All data shown are standardized to the age distributions of the 1991 cohort. Percentages are shown for categorical variables, values are means (SD) for continuous variables.

Table II HR and 95% CIs for uterine leiomyomas according to dairy intake in the Nurses' Health Study II, 1991–2009.

	Cases	Age-adjusted HR (95% CI)		MV HR (95% CI) ¹	
Total Dairy					
≤4/week	168	1.08	(0.92, 1.26)	1.08	(0.92, 1.26)
5–6/week	422	1.05	(0.94, 1.16)	1.03	(0.93, 1.14)
1/day	350	0.90	(0.81, 1.01)	0.89	(0.80, 1.00)
2/day	2706	1.00	Referent	1.00	Referent
3/day	2139	0.93	(0.87, 0.98)	0.96	(0.90, 1.02)
4/day	1468	0.93	(0.87, 0.99)	1.00	(0.93, 1.07)
>4/day	889	0.82	(0.75, 0.89)	0.92	(0.85, 1.00)
<i>P</i> _{trend} ²		<0.0001		0.19	
Low Fat Dairy					
≤4/week	1435	1.01	(0.95, 1.08)	1.01	(0.94, 1.07)
5–6/week	1406	1.05	(0.98, 1.12)	1.02	(0.96, 1.09)
1/day	888	1.07	(1.00, 1.16)	1.06	(0.98, 1.14)
2/day	2630	1.00	Referent	1.00	Referent
3/day	1318	0.92	(0.86, 0.98)	0.96	(0.90, 1.03)
>3/day	465	0.89	(0.80, 0.98)	0.96	(0.87, 1.06)
<i>P</i> _{trend} ²		<0.0001		0.08	
High Fat Dairy					
≤4/week	1708	1.03	(0.96, 1.10)	0.99	(0.92, 1.05)
5–6/week	2064	0.95	(0.89, 1.01)	0.92	(0.87, 0.98)
1/day	1041	0.98	(0.91, 1.05)	0.96	(0.89, 1.03)
2/day	2332	1.00	Referent	1.00	Referent
3/day	644	0.99	(0.91, 1.08)	1.01	(0.92, 1.10)
>3/day	353	0.89	(0.79, 1.00)	0.92	(0.82, 1.03)
<i>P</i> _{trend} ²		0.20		0.72	

HR, hazard ratio; MV, multivariable.
¹Adjusted for age (continuous), total calories (continuous), age at menarche (<11, 11, 12, 13, 14–15, >15 years), infertility (yes, no), ancestry (Caucasian, African-American, Hispanic, Asian, other), parity (nulliparous, 1, 2, 3, 4+), age at first birth (<25, 25–30, >30 years), time since last birth (<1, 1–3, 4–5, 6–7, 8–9, 10–12, 13–15, 16+ years), age first oral contraceptive (OC) use (13–16, 17–20, 21–24, 25+ years), BMI (<20, 20–21.9, 22–23.9, 24–24.9, 25–26.9, 27–29.9, 30+ kg/m²), menstrual cycle length (<26, 26–31, 32–50 and >50 days), smoking (never, past, current), recent gynecologic/breast exam (no recent exam, recent exam) and use of anti-hypertensive medications/diastolic blood pressure (no meds <65, no meds 65–74, no meds 75–84, no meds 85–89, no meds 90+, meds <65, meds 65–74, meds 75–84, meds 85–89, meds 90+).
²Determined using category medians.

caloric intake. The extent to which low and high categories reflected actual number of dairy servings was unclear in the former case–control study (Chiaffarino et al., 1999), while low reflected ‘never/less than one day per week’ and high reflected ‘more than 3 days per week’ in the latter case–control study (He et al., 2013), representing a substantially lower intake of dairy, were observed in our study population.

The Black Woman’s Health Study (BWHS) is most comparable to our study in that it was prospective, thereby avoiding differential recall bias due to uterine leiomyoma diagnosis, and its FFQ reflected diet prior to diagnosis and included a number of different dairy sources, allowing for examination of dairy-associated vitamins and minerals. The BWHS found a strong inverse association between self-reported uterine leiomyoma (diagnosed by surgery or ultrasound) and total daily dairy intake (Wise et al., 2010). In multivariable models adjusted for total caloric intake and other factors, incidence rate ratios for 1, 2, 3 and ≥4 total dairy servings/day were 0.94, 0.87, 0.84 and

0.70, respectively, compared to the reference group of <1 total dairy servings/day (*P*_{trend} < 0.0001). In our study, we did not observe such a dose response, and the HR comparing the highest category of total dairy consumption (>4/day) to our reference group (2/day) was 0.92. Wise et al. (2010) also observed evidence for a protective effect from both high- and low-fat dairy sources. In a follow-up manuscript, Wise et al. (2013) examined the association between dairy products and uterine leiomyoma adjusting for percentage European ancestry (as African Americans may avoid dairy products due to a higher prevalence of lactose intolerance) and observed similar inverse associations. The predominantly white NHSII differed from the BWHS in the amount of dairy products consumed, with higher average dairy consumption among NHSII participants. This observation is consistent with other reports of fewer mean servings/day of dairy food consumption in African-Americans compared to whites (Fulgoni et al., 2007). However, despite these differences in dairy intake, a similar protective association was observed for the highest consumers of yogurt, and

Table III HR and 95% CIs for uterine leiomyomas according to specific dairy food intake in the Nurses' Health Study II, 1991–2009.

	Cases	Age-adjusted HR (95% CI)	Multivariable HR (95% CI) ¹
All Milk			
<=4/week	2594	1.00 (referent)	1.00 (referent)
5–6/week	1532	1.00 (0.94, 1.07)	1.01 (0.95, 1.08)
1/day	1175	0.93 (0.87, 1.00)	0.96 (0.89, 1.03)
2/day	1647	0.96 (0.90, 1.02)	1.02 (0.95, 1.08)
>2/day	1194	0.84 (0.79, 0.91)	0.95 (0.88, 1.02)
P_{trend}^2		<0.0001	0.22
Skim/low-fat milk			
<=4/week	2863	1.00 (referent)	1.00 (referent)
5–6/week	1461	1.00 (0.94, 1.07)	1.01 (0.94, 1.07)
1/day	1185	0.95 (0.88, 1.01)	0.97 (0.90, 1.03)
2/day	1518	0.98 (0.91, 1.04)	1.02 (0.96, 1.09)
>2/day	1115	0.85 (0.79, 0.91)	0.94 (0.88, 1.01)
P_{trend}^2		<0.0001	0.23
Whole milk			
<=4/week	7911	1.00 (referent)	1.00 (referent)
5–6/week	111	0.90 (0.75, 1.09)	0.97 (0.80, 1.17)
1/day	64	0.98 (0.76, 1.25)	1.07 (0.83, 1.36)
2/day	35	0.74 (0.53, 1.03)	0.81 (0.58, 1.14)
>2/day	21	0.83 (0.54, 1.27)	0.98 (0.64, 1.51)
P_{trend}^2		0.06	0.57
Ice Cream			
<=4/week	7958	1.00 (referent)	1.00 (referent)
5–6/week	142	0.89 (0.75, 1.05)	0.92 (0.78, 1.09)
1/day	24	0.87 (0.58, 1.30)	0.92 (0.61, 1.37)
2+/day	18	1.09 (0.69, 1.73)	1.12 (0.70, 1.78)
P_{trend}^2		0.30	0.57
Yogurt			
<=4/week	7443	1.00 (referent)	1.00 (referent)
5–6/week	547	0.94 (0.86, 1.02)	0.92 (0.84, 1.01)
1/day	113	1.00 (0.83, 1.20)	0.98 (0.81, 1.18)
2+/day	39	0.78 (0.57, 1.07)	0.76 (0.55, 1.04)
P_{trend}^2		0.08	0.03
Cheese			
<=4/week	3525	1.00 (referent)	1.00 (referent)
5–6/week	2882	1.00 (0.95, 1.06)	1.02 (0.97, 1.07)
1/day	827	0.94 (0.87, 1.01)	0.96 (0.89, 1.04)
2/day	810	0.95 (0.87, 1.03)	0.98 (0.91, 1.07)
>2/day	98	0.94 (0.76, 1.15)	0.97 (0.79, 1.19)
P_{trend}^2		0.10	0.51

¹Adjusted for age (continuous), total calories (continuous), age at menarche (<11, 11, 12, 13, 14–15, >15 years), infertility (yes, no), ancestry (Caucasian, African-American, Hispanic, Asian, other), parity (nulliparous, 1, 2, 3, 4+), age at first birth (<25, 25–30, >30 years), time since last birth (<1, 1–3, 4–5, 6–7, 8–9, 10–12, 13–15, 16+ years), age first OC use (13–16, 17–20, 21–24, 25+ years), BMI (<20, 20–21.9, 22–23.9, 24–24.9, 25–26.9, 27–29.9, 30+ kg/m²), menstrual cycle length (<26, 26–31, 32–50 and >50 days), smoking (never, past, current), recent gynecologic/breast exam (no recent exam, recent exam) and use of anti-hypertensive medications/diastolic blood pressure (no meds <65, no meds 65–74, no meds 75–84, no meds 85–89, no meds 90+, meds <65, meds 65–74, meds 75–84, meds 85–89, meds 90+).

²Determined using category medians.

associations with total calcium intake and vitamin D across the two studies were null. Unlike our study, the BWHS did not report associations with calcium from foods alone. Differences between the results

observed in our study compared to BWHS could be suggestive of a threshold effect, where increases beyond a certain level of intake are no longer detectable.

Table IV HR and 95% CIs for uterine leiomyomas according to quintiles of nutrient intake in the Nurses' Health Study II, 1991–2009.

Nutrient	Cases	Age-adjusted HR (95% CI)		MV ¹	HR (95% CI)
Calcium (mg)					
Total Calcium Intake					
194–718	1553	1.00	Referent	1.00	Referent
719–894	1570	0.95	0.89, 1.02	0.97	0.90, 1.04
985–1090	1650	0.94	0.87, 1.01	0.98	0.91, 1.05
1091–1340	1645	0.91	0.85, 0.97	0.97	0.91, 1.04
1341–5062	1724	0.95	0.88, 1.01	1.02	0.95, 1.10
P_{trend}^2		0.10		0.36	
Calcium from Foods					
200–649	1692	1.00	Referent	1.00	Referent
650–780	1724	0.97	0.90, 1.03	0.97	0.91, 1.04
781–916	1644	0.91	0.85, 0.97	0.93	0.87, 1.00
917–1107	1662	0.91	0.85, 0.98	0.96	0.90, 1.03
1108–4202	1420	0.84	0.78, 0.90	0.92	0.86, 0.99
P_{trend}^2		<0.0001		0.04	
Dairy Calcium					
0–330	1699	1.00	Referent	1.00	Referent
331–454	1743	0.99	0.92, 1.06	1.00	0.93, 1.07
455–587	1689	0.96	0.89, 1.02	0.98	0.91, 1.05
588–783	1649	0.94	0.88, 1.01	0.99	0.93, 1.06
784–4057	1362	0.85	0.79, 0.91	0.93	0.87, 1.00
P_{trend}^2		<0.0001		0.06	
Vitamin D (IU)					
Total Vitamin D Intake					
3–195	1565	1.00	Referent	1.00	Referent
196–291	1617	0.97	0.90, 1.04	1.00	0.93, 1.07
292–399	1736	0.99	0.92, 1.06	1.04	0.97, 1.11
400–557	1704	0.96	0.90, 1.03	1.04	0.97, 1.12
558–4984	1520	0.95	0.89, 1.02	1.05	0.97, 1.12
P_{trend}^2		0.18		0.13	
Vitamin D from foods					
3–146	1720	1.00	Referent	1.00	Referent
147–199	1740	0.99	0.93, 1.06	1.00	0.94, 1.07
200–252	1746	1.00	0.94, 1.07	1.04	0.97, 1.11
253–323	1560	0.92	0.86, 0.99	0.98	0.92, 1.05
324–2021	1376	0.90	0.84, 0.97	0.99	0.92, 1.06
P_{trend}^2		0.0006		0.53	
Dairy Vitamin D					
0–45	1688	1.00	Referent	1.00	Referent
46–84	1716	0.97	0.90, 1.03	0.97	0.90, 1.04
85–128	1655	0.94	0.88, 1.01	0.97	0.90, 1.04
129–198	1671	0.95	0.89, 1.02	1.01	0.94, 1.08
199–1907	1412	0.86	0.80, 0.92	0.95	0.88, 1.02
P_{trend}^2		<0.0001		0.38	
Predicted 25(OH)D (ng/mL)					
13.5–27.5	1947	1.00	Referent	1.00	Referent
27.6–30.0	1656	0.89	0.83, 0.95	1.00	0.93, 1.08
30.1–31.9	1513	0.83	0.77, 0.89	0.99	0.91, 1.08
32.0–33.9	1428	0.78	0.73, 0.84	0.95	0.87, 1.04
40.0–44.8	1471	0.82	0.77, 0.88	1.02	0.93, 1.12
P_{trend}^2		<0.0001		0.63	

Continued

Table IV Continued.

Nutrient	Cases	Age-adjusted HR (95% CI)		MV ¹	HR (95% CI)
Magnesium (mg)					
Total Magnesium Intake					
95–267	1434	1.00	Referent	1.00	Referent
268–300	1625	1.00	0.93, 1.08	1.02	0.95, 1.10
301–332	1615	0.95	0.88, 1.01	0.98	0.91, 1.05
333–374	1702	0.97	0.90, 1.04	1.01	0.94, 1.09
375–1685	1766	0.99	0.93, 1.07	1.03	0.96, 1.10
<i>P</i> _{trend} ²		0.79		0.51	
Magnesium from food					
95–259	1512	1.00	Referent	1.00	Referent
260–289	1614	0.95	0.89, 1.02	0.98	0.91, 1.05
290–315	1684	0.95	0.88, 1.02	0.98	0.91, 1.05
316–348	1649	0.91	0.85, 0.98	0.94	0.88, 1.01
349–1025	1683	0.93	0.87, 1.00	0.96	0.90, 1.04
<i>P</i> _{trend} ²		0.03		0.21	

¹Adjusted for age (continuous), total calories (continuous), age at menarche (<11, 11, 12, 13, 14–15, >15 years), infertility (yes, no), ancestry (Caucasian, African-American, Hispanic, Asian, other), parity (nulliparous, 1, 2, 3, 4+), age at first birth (<25, 25–30, >30 years), time since last birth (<1, 1–3, 4–5, 6–7, 8–9, 10–12, 13–15, 16+ years), age first OC use (13–16, 17–20, 21–24, 25+ years), BMI (<20, 20–21.9, 22–23.9, 24–24.9, 25–26.9, 27–29.9, 30+ kg/m²), menstrual cycle length (<26, 26–31, 32–50 and >50 days), smoking (never, past, current), recent gynecologic/breast exam (no recent exam, recent exam) and use of anti-hypertensive medications/diastolic blood pressure (no meds <65, no meds 65–74, no meds 75–84, no meds 85–89, no meds 90+, meds <65, meds 65–74, meds 75–84, meds 85–89, meds 90+).

²Determined using category medians.

The potential mechanism linking dairy foods and reduced risk of uterine leiomyoma is not well understood, although biologically plausible. Calcium, a major component of dairy foods, reduces cell proliferation by maintaining intracellular calcium concentrations (Jacobson *et al.*, 1989). However, the impact of calcium may not function independently of dairy, and other components of dairy foods may contribute to synergistic effects. For example, when calcium from foods and total dairy intake were mutually adjusted for each other, the association with total dairy intake was attenuated while the association with calcium intake remained, despite that no association was observed with total calcium intake (which includes calcium from foods and supplements). Dairy foods could also impact uterine leiomyoma through effects on inflammation. In mouse models, a milk diet has been shown to reduce tumor necrosis factor α and interleukin-6 (Zemel and Sun, 2008), markers of oxidative and inflammatory stress; however, unlike the BWHS, we did not observe a significant effect specifically related to milk consumption on uterine leiomyoma risk. Further, we did not observe an association between intake of total dairy foods or calcium intake from foods and uterine leiomyoma risk among women who were nulliparous. To our knowledge, we are the only study to have examined the association between dairy foods and nutrients and uterine leiomyoma stratified by parity. It may be that uterine leiomyoma incidence in nulliparous women is more strongly influenced by other risk factors (e.g. menstrual cycle length) and thus the influence of dietary factors on uterine leiomyoma may be more easily detectable among parous women.

The suggestion of an inverse association between yogurt intake and uterine leiomyoma risk in both our study and the BWHS is intriguing. Adults who regularly consume yogurt have a more beneficial intestinal microbiota profile compared to non-consumers

(Alvaro *et al.*, 2007). Further, significant correlations between the microbiome measured in stool samples to the microbiome of reproductive organs, including uterine microbiome, have been reported (Walther-Antonio *et al.*, 2016). While speculative, it is possible that a shared microbial environment from the gut to uterus could, in part, explain the inverse association observed between yogurt consumption and uterine leiomyoma risk.

Limitations of our study must be considered. It is likely that some uterine leiomyoma cases were misclassified, particularly those that were asymptomatic, likely biasing estimates toward the null due to our prospective study design. We did not have vitamin and mineral concentrations from actual blood levels. Similarly, there is the potential for misclassification of participants based on predicted 25(OH)D. However, the prediction model has been validated in three prospective cohort studies (Bertrand *et al.*, 2012), including NHSII, suggesting that it is an appropriate estimate of long-term vitamin D status. Therefore, misclassification would be expected to be random. We also excluded prevalent uterine leiomyoma at baseline, which could lead to bias if those who were diagnosed with uterine leiomyoma prior to baseline had a different dairy intake than those diagnosed after baseline. However, when we compared the distribution of dairy intake in cases diagnosed before and after study baseline, no material differences in dairy intake were observed. It is possible that dairy product constituents reduce uterine leiomyoma symptomology rather than development, giving the appearance of a protective effect on uterine leiomyoma development. We did not have data on uterine leiomyoma symptomology. Lastly, changes in vitamin D supplementation over time may have impacted prediction models for 25(OH)D.

Our study has a number of strengths including its prospective study design, large sample size and long follow-up period that was

longer than the BWHS prospective study on this topic. We also used ultrasound/hysterectomy confirmed cases, representing the most clinically relevant fibroids. Additionally, we adjusted for multiple uterine leiomyoma risk factors associated with diet and looked at multiple aspects of dairy diet: total and specific dairy foods, nutrients and predicted 25(OH)D that integrates multiple contributors to vitamin D status. Our study also may account for a wider range of dairy exposure compared to the only other prospective cohort study.

In conclusion, our findings are null by and large, but in the direction of our *a priori* hypotheses, suggestive of an inverse association with total dairy consumption, with potentially important contributions from yogurt and calcium intake from foods. Further replication of these findings utilizing prospective cohort studies that have detailed diet data are needed, as is exploration of the underlying physiology that may explain a role for yogurt and calcium in uterine leiomyoma incidence.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

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Authors' roles

H.R.H., K.L.T. and S.A.M. designed the research, H.R.H. performed statistical analyses, H.R.H., O.R.O., K.L.T. and S.A.M. interpreted the data, O.R.O. and H.R.H. wrote the paper and K.L.T. and S.A.M. edited manuscript drafts. All authors read and approved the final manuscript.

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Conflict of interest

None.

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