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Original Contribution

Dairy-Food, Calcium, Magnesium, and Vitamin D Intake and Endometriosis: A Prospective Cohort Study

Holly R. Harris*, Jorge E. Chavarro, Susan Malspeis, Walter C. Willett, and Stacey A. Missmer

* Correspondence to Dr. Holly R. Harris, Ob/Gyn Epidemiology Center, Brigham and Women's Hospital, 221 Longwood Avenue, Boston, MA 02115 (e-mail: hharris3@partners.org).

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The etiology of endometriosis is poorly understood, and few modifiable risk factors have been identified. Dairy foods and some nutrients can modulate inflammatory and immune factors, which are altered in women with endometriosis. We investigated whether intake of dairy foods, nutrients concentrated in dairy foods, and predicted plasma 25-hydroxyvitamin D (25(OH)D) levels were associated with incident laparoscopically confirmed endometriosis among 70,556 US women in Nurses' Health Study II. Diet was assessed via food frequency questionnaire. A score for predicted 25(OH)D level was calculated for each participant. During 737,712 person-years of follow-up over a 14-year period (1991–2005), 1,385 cases of incident laparoscopically confirmed endometriosis were reported. Intakes of total and low-fat dairy foods were associated with a lower risk of endometriosis. Women consuming more than 3 servings of total dairy foods per day were 18% less likely to be diagnosed with endometriosis than those reporting 2 servings per day (rate ratio = 0.82, 95% confidence interval: 0.71, 0.95; $P_{trend} = 0.03$). In addition, predicted plasma 25(OH)D level was inversely associated with endometriosis. Women in the highest quintile of predicted vitamin D level had a 24% lower risk of endometriosis than women in the lowest quintile (rate ratio = 0.76, 95% confidence interval: 0.60, 0.97; $P_{trend} = 0.004$). Our findings suggest that greater predicted plasma 25(OH)D levels and higher intake of dairy foods are associated with a decreased risk of endometriosis.

dairy foods; diet; endometriosis; magnesium; phosphorus; vitamin D

Abbreviations: BMI, body mass index; CI, confidence interval; FFQ, food frequency questionnaire; NHS II, Nurses' Health Study II; 25(OH)D, 25-hydroxyvitamin D; OR, odds ratio; RR, rate ratio.

Endometriosis is a disorder characterized by the presence of endometrial tissue outside the uterine cavity. It has an estimated prevalence of 10% (1) and is the third-leading cause of gynecological hospitalization in the United States (2). Signs and symptoms vary in severity and include dysmenorrhea, dyspareunia, infertility, dysuria, and dyschezia (3). Despite its prevalence and associated morbidity, the etiology of endometriosis is poorly understood, and few modifiable risk factors have been identified. One factor that may influence endometriosis is diet, which can act through multiple pathways, including effects on inflammation, smooth muscle contractility, immune function, and estrogenic effects.

Recent studies have suggested that vascular inflammation is present among persons with endometriosis (4–6). Intakes of dairy foods and dietary calcium have been inversely related to inflammatory stress (7), suggesting that dairy foods and nutrients concentrated in these foods may influence endometriosis risk. Magnesium relaxes smooth muscle (8, 9) and may thus be related to endometriosis through its influence on retrograde menstruation.

Endometriosis risk may also be influenced by dietary vitamin D intake and plasma 25-hydroxyvitamin D (25(OH)D) concentration. Beyond its role in calcium and bone homeostasis, vitamin D has been shown to influence immune function (10). Women with endometriosis exhibit changes in cell-mediated immunity, with altered T-helper cell:T-suppressor cell ratios and concentrations (11–13), and vitamin D may influence the development of endometriosis through its immunomodulatory effects.

Few studies have examined the relationship between diet and endometriosis, and only 2 have examined associations with dairy foods or nutrients. In the first human study that examined dietary intake, Parazzini et al. (14) found no association between milk or cheese intake and endometriosis risk. Most recently, in a population-based case-control study, Trabert et al. (15) reported a nonsignificant inverse association between dairy-food and calcium consumption and surgically confirmed endometriosis. In this study, we investigated whether intake of dairy foods, nutrients concentrated in dairy foods (calcium, vitamin D, magnesium, and phosphorus), and predicted plasma 25(OH)D levels were associated with incident laparoscopically confirmed endometriosis in a prospective cohort study over a 14-year follow-up period. We also examined whether the association between these factors and endometriosis varied according to the fertility status of endometriosis patients and whether this association was modified by body mass index (BMI; weight (kg)/height $(m)^2$), parity, or smoking.

MATERIALS AND METHODS

Study population

Nurses' Health Study II (NHS II) is an ongoing prospective cohort study that was established in 1989 when 116,430 US female registered nurses aged 25–42 years completed a baseline questionnaire that collected information on demographic and lifestyle factors, anthropometric variables, and disease history. Follow-up questionnaires are sent biennially to participants, with questions requesting updated information on incident disease risk factors. Questionnaire response rates through 2005 were approximately 90%. Further details on the study have been provided elsewhere (16).

Follow-up for the current analyses began in 1991, when NHS II participants ($n = 97,807$) returned the dietary assessment, and concluded in 2005. We excluded participants who had an implausible total energy intake (<800 kcal/day or >4,200 kcal/day) or left more than 70 food items blank on the 1991 food frequency questionnaire (FFQ). Participants were also excluded if they reported a diagnosis of endometriosis, a history of infertility, or a cancer diagnosis (other than nonmelanoma skin cancer) prior to June 1991. The analytical cohort was limited to women who were premenopausal and had intact uteri, since endometriosis rarely occurs incidentally among postmenopausal women or subsequent to a hysterectomy. After these exclusions, 70,556 premenopausal women with dietary information remained. Implied consent was assumed upon return of the completed questionnaire. This study was approved by the institutional review boards of the Harvard School of Public Health and Brigham and Women's Hospital, Boston, Massachusetts.

Dietary assessment

Diet was assessed in 1991, 1995, 1999, and 2003 using an FFQ listing over 130 food items, including 11 individual dairy foods. Participants were asked how often, on average, they had consumed each type of food or beverage during the previous year. Nine responses were possible, ranging from never or less than once per month to 6 or more times per day. Intakes of the nutrients of interest (vitamin D, calcium, magnesium, and phosphorus) were calculated by multiplying the portion size of a single serving of each food by its reported frequency of intake, then multiplying the total amount consumed by the nutrient content of the food, and summing the nutrient contributions of all food items using US Department of Agriculture food composition data (17), while also taking dietary supplements into account. The reproducibility and validity of the NHS II FFQ have been reported elsewhere (18–20). The FFQ has been shown to provide valid estimates of dairy-food and nutrient intake, with deattenuated correlation coefficients for dairy foods between the FFQ and 1-week diet records ranging from 0.57 for hard cheeses (18) to 0.94 for yogurt (18), 0.75 for calcium intake (21), 0.63 for phosphorus (22), and 0.71 for magnesium (22). Vitamin D intake has been validated using plasma concentrations of 25(OH)D, with reported correlations of 0.25 ($P < 0.001$) (23, 24). Intakes of all nutrients were adjusted for total energy intake using the residual method (21).

Predicted plasma 25(OH)D level

A model for predicting plasma 25(OH)D levels was developed using 1,498 NHS II participants with no prior history of cancer who gave blood samples between 1996 and 1999 and had served as controls in previous nested case-control studies. Plasma 25(OH)D concentration was measured by means of an enzyme immunoassay, and a linear regression model was then developed to predict plasma 25(OH)D levels on the basis of age, season of blood draw, race/ethnicity, geographical region, dietary vitamin D intake, BMI, alcohol intake, and physical activity, as previously described (25, 26). R^2 for the prediction model ranged from 0.25 to 0.33 (26). From the predictors' regression coefficients, a predicted-25(OH)D score was calculated for each cohort member.

Ascertainment and definition of endometriosis

Starting in 1993, participants were asked on each biennial questionnaire if they had "ever had physician-diagnosed endometriosis," and if so, the date of diagnosis and whether it had been confirmed by laparoscopy. The validity of self-reported endometriosis in this cohort has been described previously (27). Briefly, a diagnosis of endometriosis was confirmed by medical records in 96% of women who reported laparoscopic confirmation. However, a review of the medical records of women without laparoscopic confirmation indicated a clinical diagnosis of endometriosis in only 54%. In addition, a diagnosis of endometriosis at the time of hysterectomy was confirmed in 80% of the cases, but endometriosis was the primary indication for hysterectomy in only 6% of those for whom an indication was available. Therefore, to minimize the magnitude of misclassification and prevent confounding by indication for hysterectomy, we restricted our definition of incident diagnosis of endometriosis

to women who reported laparoscopic confirmation of their diagnosis ($n = 1,385$).

Because of the complex relationship between endometriosis and infertility within this restricted case definition, we examined risk factors according to 2 "subtypes" of endometriosis: 1) women who never reported infertility and 2) women with concurrent infertility. At baseline, the prevalence of infertility was greater among women with laparoscopic confirmation (20%) than among those who were clinically diagnosed without laparoscopic confirmation (4%). This may result in oversampling of persons with otherwise "asymptomatic" endometriosis. Because endometriosis with infertility may be indicative of asymptomatic disease secondary to other primary causes of infertility, the etiology of (and thus risk factors for) endometriosis with infertility could differ from that of endometriosis without concurrent infertility.

Statistical analysis

Participants contributed follow-up time from the return of the 1991 questionnaire to self-report of a laparoscopically confirmed endometriosis diagnosis, diagnosis of any cancer (except nonmelanoma skin cancer), death, loss to follow-up, hysterectomy, menopause, or the end of follow-up on June 1, 2005—whichever occurred first. In addition, women were censored at the time of self-report of infertility, because infertility in this population is strongly correlated with diagnosis of endometriosis via laparoscopy.

We used Cox proportional hazards regression models with age and questionnaire period as the time scale to estimate incidence rate ratios and 95% confidence intervals, using the lowest category of intake of each food or nutrient as the reference group. Because the temporal relationship between these foods/nutrients and risk of endometriosis is uncertain, dietary intake was examined in 3 ways: baseline intake (1991 FFQ), most recently reported intake, and cumulative average intake. The results observed for each approach were similar. Therefore, we present the results for the cumulative average models only, as this method captures long-term dietary intake and reduces measurement error due to within-person variation over time (28).

Potential confounders considered were age at menarche, parity, length of the menstrual cycle, BMI, physical activity, caffeine intake, cigarette smoking, alcohol intake, and oral contraceptive use. These covariates were included in the final regression model if they changed the effect estimate by more than 10% when included in the model. Thus, the regression models were adjusted for the following factors: age at menarche, parity, length of the menstrual cycle, and BMI. Covariates were updated throughout the analysis whenever new information became available from the biennial questionnaires. Total caloric intake was included in all models.

Tests for linear trend for the exposures of interest were performed by assigning the median value of each category to all participants in that group. Tests for heterogeneity (Wald statistic) were used to assess whether the associations between nutrient intake and endometriosis differed among cases with no past or current infertility and cases with concurrent infertility. Effect modification was assessed by means of a likelihood ratio test that compared the model with the cross-product term between the exposure variable and each potential effect modifier with the model with main effects only. All tests of statistical significance were 2-sided, and all statistical analyses were performed using SAS, version 9.1 (SAS Institute Inc., Cary, North Carolina).

RESULTS

During 737,712 person-years of follow-up contributed by 70,556 women, 1,385 incident cases of laparoscopically confirmed endometriosis with no past infertility were reported. Of these cases, 1,129 women never reported infertility and 235 reported undergoing an infertility evaluation during the same follow-up period as their laparoscopic confirmation of endometriosis. Women with the greatest intake of total dairy foods were slightly younger, more likely to be Caucasian and to have had a recent gynecological examination, and less likely to be current smokers and nulliparous than those with lower total dairy-food intake (Table 1).

Intake of total dairy foods was associated with a lower risk of endometriosis (Table 2). After adjustment for covariates, an increase in total dairy-food intake of 1 serving per day was associated with a 5% reduction in the risk of endometriosis (rate ratio (RR) = 0.95, 95% confidence interval (CI): 0.91, 1.00). When low-fat dairy foods were considered separately, a similar association was observed. High-fat dairy foods were not associated with endometriosis. The relationships between dairy-food intake and endometriosis were similar in women who had never reported infertility and women who reported a concurrent laparoscopic endometriosis diagnosis and infertility (Table 2). When the association between specific dairy foods and endometriosis risk was examined (Table 3), the relationship between dairy-food intake and endometriosis appeared to be driven primarily by the association of skim/low-fat milk with the disease.

Predicted plasma 25(OH)D level was inversely associated with endometriosis (Table 4). Women in the highest quintile of predicted vitamin D level had a 24% lower risk of endometriosis than women in the lowest quintile, and there was no evidence of heterogeneity according to case definition. Total intakes of calcium and vitamin D (including intake from supplements) were not associated with endometriosis. However, calcium and vitamin D intakes from food were inversely related to endometriosis. Women in the highest quintile of calcium intake from food had a multivariable adjusted rate ratio of 0.79 (95% CI: 0.66, 0.94; $P_{trend} = 0.001$). The corresponding figure for vitamin D intake from foods was 0.79 (95% CI: 0.66, 0.94; $P_{trend} = 0.003$). The associations between both calcium and vitamin D intakes from foods and endometriosis were attenuated after adjustment for milk consumption. Calcium and vitamin D intakes from dairy-food sources only were unrelated to endometriosis. When the relationships of calcium and vitamin D intake with endometriosis were evaluated

Table 1. Distribution of Potential Risk Factors for Endometriosis According to Total Dairy Food Intake Among Women in Nurses' Health Study II ($n = 70,556$), 1991–2005[a]

	No. of Servings of Total Dairy Foods											
	≤4/Week ($n = 3,332$)		5–6/Week ($n = 5,482$)		1/Day ($n = 3,771$)		2/Day ($n = 24,155$)		3/Day ($n = 13,888$)		>3/Day ($n = 19,928$)	
	%	Mean	%	Mean	%	Mean	%	Mean	%	Mean	%	Mean
Age, years		36.6		36.3		36.2		35.8		35.6		35.0
Caucasian race	84.1		88.3		89.5		92.2		93.7		94.2	
Body mass index[b]												
25–29.9 (overweight)	16.7		17.2		17.5		18.6		18.8		18.0	
≥30 (obese)	12.1		12.9		12.8		12.4		12.3		11.1	
Cigarette smoking												
Never smoker	64.1		64.6		66.4		65.8		67.1		67.1	
Past smoker	19.2		20.0		19.7		21.9		22.9		22.5	
Current smoker	16.6		15.3		13.8		12.2		9.9		10.3	
Age at menarche, years												
<12	24.4		24.6		23.4		23.7		23.6		22.9	
12	29.5		31.0		31.5		30.5		30.3		30.1	
13	26.9		26.1		27.9		27.9		28.4		28.2	
≥14	18.9		18.1		16.9		17.7		17.4		18.7	
Menstrual cycle length, days												
<26	14.5		13.5		12.5		11.8		10.8		9.8	
26–31	64.8		66.0		66.9		66.7		67.4		67.6	
32–50	15.8		16.4		17.0		17.1		17.3		17.9	
Ever use of oral contraceptives	81.7		83.6		84.7		84.1		83.5		82.4	
Nulliparous	32.4		31.8		29.9		28.1		26.2		21.9	
Duration of lactation (among parous women), months												
None	14.1		13.5		12.8		11.1		9.6		8.5	
≥12	18.6		20.0		21.7		25.3		30.3		37.3	
No recent gynecological examination	18.5		16.5		16.1		14.5		13.4		13.3	

[a] All data shown are standardized to the age distribution of the 1991 cohort.
[b] Weight (kg)/height $(m)^2$.

separately by case status, these associations were more pronounced in women who had never reported infertility; the test for heterogeneity between the two case types reached statistical significance for calcium intake from foods and vitamin D intake from dairy foods.

Total magnesium intake and total phosphorus intake had inverse relationships with endometriosis risk that approached statistical significance (Table 4). When intake from food sources was examined, there was a statistically significant inverse relationship between magnesium intake and endometriosis (RR = 0.86, 95% CI: 0.73, 1.01; $P_{trend} = 0.007$). The association of phosphorus intake from foods with endometriosis was similar to the association for total phosphorus intake. When intakes of magnesium and phosphorus from foods were mutually adjusted for each other, the association between phosphorus and endometriosis was attenuated and the association between magnesium and endometriosis did not materially change. The association between magnesium intake from foods and endometriosis was not altered by adjustment for milk consumption. The associations of these two nutrients with endometriosis appeared to be more pronounced in the never-infertile group. However, none of the tests for heterogeneity reached statistical significance.

Next, we examined dairy protein, dairy fat, and lactose to explore what component of dairy foods might explain the association between milk intake and endometriosis. Adjustment for dairy protein and lactose strengthened the inverse association between milk intake and endometriosis, while adjustment for dairy fat did not materially alter the

Table 2. Rate Ratios for Laparoscopically Confirmed Endometriosis According to Dairy Food Intake and Infertility Status Among Women in Nurses' Health Study II, 1991–2005

Type of Dairy Food and No. of Servings	Case Definition											$P_{heterogeneity}$[a]
	All Women ($n = 1,385$)					Never Infertile[b] ($n = 1,129$)			Concurrent Infertility[b] ($n = 235$)			
	No. of Cases	Age-adjusted RR	95% CI	MV RR[c]	95% CI	No. of Cases	MV RR[c]	95% CI	No. of Cases	MV RR[c]	95% CI	
Total dairy foods[d]												
≤4/week	49	0.93	0.69, 1.26	0.94	0.70, 1.27	45	1.12	0.82, 1.53	3[e]			0.10
5–6/week	104	0.99	0.80, 1.23	0.99	0.80, 1.22	86	1.04	0.82, 1.31	16	0.52	0.34, 0.81	
1/day	66	0.79	0.61, 1.02	0.80	0.62, 1.03	56	0.85	0.64, 1.12	8			
2/day	532	1.00	Referent	1.00	Referent	425	1.00	Referent	102	1.00	Referent	
3/day	301	0.83	0.72, 0.96	0.84	0.72, 0.97	245	0.84	0.71, 0.98	51	0.85	0.61, 1.20	
>3/day	333	0.79	0.68, 0.91	0.82	0.71, 0.95	272	0.82	0.70, 0.97	55	0.84	0.59, 1.19	
P_{trend}[f]		0.006		0.03			0.01			0.55		
Low-fat dairy foods[d]												
≤4/week	250	0.87	0.74, 1.02	0.89	0.76, 1.05	214	0.98	0.83, 1.17	33	0.52	0.35, 0.79	0.13
5–6/week	257	1.14	0.98, 1.33	1.14	0.98, 1.33	208	1.18	0.99, 1.40	43	0.89	0.61, 1.29	
1/day	156	1.12	0.93, 1.34	1.12	0.93, 1.34	124	1.14	0.92, 1.40	30	1.00	0.66, 1.53	
2/day	432	1.00	Referent	1.00	Referent	342	1.00	Referent	84	1.00	Referent	
>2/day	290	0.79	0.68, 0.92	0.83	0.71, 0.97	241	0.86	0.73, 1.02	45	0.75	0.52, 1.09	
P_{trend}[f]		0.008		0.03			0.02			0.45		
High-fat dairy foods[d]												
≤4/week	339	1.07	0.92, 1.26	1.04	0.89, 1.22	275	1.08	0.90, 1.28	62	0.98	0.67, 1.41	0.88
5–6/week	357	1.01	0.87, 1.17	1.00	0.87, 1.16	295	1.04	0.88, 1.23	59	0.91	0.64, 1.31	
1/day	170	1.06	0.88, 1.27	1.05	0.88, 1.27	144	1.12	0.92, 1.37	24	0.84	0.52, 1.34	
2/day	365	1.00	Referent	1.00	Referent	290	1.00	Referent	65	1.00	Referent	
>2/day	154	0.93	0.77, 1.13	0.91	0.75, 1.10	125	0.93	0.76, 1.15	25	0.82	0.51, 1.30	
P_{trend}[f]		0.19		0.21			0.18			0.61		

Abbreviations: CI, confidence interval; MV, multivariable; RR, rate ratio.

[a] Test for heterogeneity comparing nutrient consumption among women with no past or current infertility with that among women with concurrent infertility.

[b] Infertility was defined as attempting to become pregnant for at least 1 year without success. Cases with "no past or concurrent infertility" were women who never reported infertility. Cases with "concurrent infertility" were women who reported undergoing an infertility evaluation in the same follow-up cycle as laparoscopic confirmation of endometriosis.

[c] The multivariate model was stratified by age (in months) at the start of follow-up and calendar year of the current questionnaire cycle. Results were simultaneously adjusted for age at menarche (<10, 10, 11, 12, 13, 14, 15, 16, or >16 years), length of the menstrual cycle (<26, 26–31, 32–50, or ≥51 days), parity (nulliparous or 1, 2, 3, or ≥4 pregnancies lasting more than 6 months), body mass index (weight (kg)/height $(m)^2$; <19, 19–20.4, 20.5–21.9, 22–24.9, 25–29.9, or ≥30), and energy intake (kcal/day; continuous).

[d] Intakes of individual dairy foods were summed to obtain intakes of low-fat dairy foods (skim/low-fat milk, sherbet, yogurt, and cottage cheese), high-fat dairy foods (whole milk, cream, ice cream, cream cheese, other cheese, and butter), and total dairy foods (all low-fat and high-fat dairy foods).

[e] Three categories were combined because of small numbers of cases.

[f] Determined using category median values.

Table 3. Rate Ratios[a] for Laparoscopically Confirmed Endometriosis According to Intake of Specific Dairy Foods and Infertility Status Among Women in Nurses' Health Study II, 1991–2005

Dairy Food and No. of Servings	Case Definition									$P_{heterogeneity}$[b]
	All Women (n = 1,385)			Never Infertile[c] (n = 1,129)			Concurrent Infertility[c] (n = 235)			
	No. of Cases	RR	95% CI	No. of Cases	RR	95% CI	No. of Cases	RR	95% CI	
All types of milk										
≤4/week	236	1.00	Referent	185	1.00	Referent	50	1.00	Referent	0.46
5–6/week	78	0.94	0.72, 1.22	58	0.87	0.65, 1.18	19	1.17	0.69, 2.01	
1/day	190	1.00	0.82, 1.21	145	0.95	0.76, 1.18	44	1.27	0.83, 1.92	
2/day	546	0.81	0.66, 0.98	456	0.77	0.62, 0.96	86	1.14	0.72, 1.81	
>2/day	335	0.83	0.67, 1.04	285	0.81	0.63, 1.03	36	1.09	0.66, 1.70	
P_{trend}[d]			0.07			0.08			0.77	
Skim/low-fat milk										
≤4/week	298	1.00	Referent	238	1.00	Referent	58	1.00	Referent	0.006
5–6/week	138	1.13	0.92, 1.40	105	1.03	0.81, 1.31	32	1.70	1.09, 2.67	
1/day	332	0.98	0.82, 1.15	269	0.92	0.76, 1.10	62	1.36	0.93, 1.98	
2/day	546	1.07	0.84, 1.36	464	0.91	0.70, 1.18	66	3.34	1.67, 6.65	
>2/day	70	0.71	0.84, 1.36	53	0.68	0.50, 0.93	17	0.95	0.54, 1.67	
P_{trend}[d]			0.04			0.01			0.34	
Whole milk										
≤4/week	992	1.00	Referent	786	1.00	Referent	202	1.00	Referent	0.75
5–6/week	149	0.92	0.72, 1.19	134	0.95	0.72, 1.26	16	0.82	0.42, 1.59	
≥1/day	244	0.84	0.62, 1.13	209	0.83	0.59, 1.14	17	1.00	0.50, 2.00	
P_{trend}[d]			0.26			0.33			0.76	
Ice cream										
≤4/week	823	1.00	Referent	643	1.00	Referent	177	1.00	Referent	0.22
5–6/week	190	1.00	0.83, 1.22	162	0.98	0.79, 1.21	28	1.18	0.73, 1.91	
≥1/day	372	1.04	0.81, 1.34	324	0.96	0.73, 1.27	30	1.77	0.94, 3.33	
P_{trend}[d]			0.83			0.77			0.15	
Yogurt										
≤4/week	713	1.00	Referent	555	1.00	Referent	155	1.00	Referent	0.78
5–6/week	183	1.24	1.02, 1.50	151	1.24	1.00, 1.54	31	1.25	0.80, 1.95	
1/day	116	0.92	0.72, 1.16	99	0.94	0.72, 1.22	17	0.85	0.48, 1.51	
>1/day	373	0.95	0.71, 1.26	324	0.91	0.67, 1.25	32	1.24	0.63, 2.43	
P_{trend}[d]			0.78			0.66			0.69	
Cheese										
≤4/week	253	1.00	Referent	196	1.00	Referent	57	1.00	Referent	0.11
5–6/week	161	0.79	0.65, 0.97	119	0.73	0.58, 0.93	43	1.08	0.72, 1.62	
1/day	117	0.85	0.67, 1.07	98	0.88	0.68, 1.14	18	0.70	0.40, 1.21	
>1/day	854	0.85	0.68, 1.05	716	0.79	0.62, 1.01	117	1.12	0.71, 1.76	
P_{trend}[d]			0.49			0.25			0.52	

Abbreviations: CI, confidence interval; RR, rate ratio.

[a] Multivariate model stratified by age (in months) at the start of follow-up and calendar year of the current questionnaire cycle. Results were simultaneously adjusted for age at menarche (<10, 10, 11, 12, 13, 14, 15, 16, or >16 years), length of the menstrual cycle (<26, 26–31, 32–50, or ≥51 days), parity (nulliparous or 1, 2, 3, or ≥4 pregnancies lasting more than 6 months), body mass index (weight (kg)/height $(m)^2$; <19, 19–20.4, 20.5–21.9, 22–24.9, 25–29.9, or ≥30), and energy intake (kcal/day; continuous).

[b] Test for heterogeneity comparing nutrient consumption among women with no past or current infertility with that among women with concurrent infertility.

[c] Infertility was defined as attempting to become pregnant for at least 1 year without success. Cases with "no past or concurrent infertility" were women who never reported infertility. Cases with "concurrent infertility" were women who reported undergoing an infertility evaluation in the same follow-up cycle as laparoscopic confirmation of endometriosis.

[d] Determined using category median values.

Table 4. Rate Ratios[a] for Laparoscopically Confirmed Endometriosis According to Nutrient Intake and Infertility Status Among Women in Nurses' Health Study II, 1991–2005

Nutrient and Quintile of Intake	Case Definition									$P_{heterogeneity}$[b]
	All Women ($n = 1,385$)			Never Infertile[c] ($n = 1,129$)			Concurrent Infertility[c] ($n = 235$)			
	No. of Cases	RR	95% CI	No. of Cases	RR	95% CI	No. of Cases	RR	95% CI	
Calcium										
Total calcium										
1	256	1.00	Referent	213	1.00	Referent	36	1.00	Referent	0.34
2	310	1.13	0.95, 1.33	258	1.13	0.94, 1.36	48	1.28	0.83, 1.98	
3	297	1.05	0.88, 1.24	235	1.00	0.83, 1.21	58	1.46	0.96, 2.22	
4	256	0.92	0.77, 1.10	204	0.88	0.73, 1.07	49	1.35	0.87, 2.09	
5	266	1.03	0.86, 1.22	219	1.03	0.85, 1.24	44	1.25	0.80, 1.95	
P_{trend}[d]			0.46			0.45			0.47	
Calcium from food										
1	270	1.00	Referent	233	1.00	Referent	29	1.00	Referent	0.02
2	293	1.00	0.84, 1.18	235	0.93	0.77, 1.11	56	1.79	1.14, 2.81	
3	298	0.98	0.83, 1.15	248	0.95	0.79, 1.14	45	1.38	0.86, 2.21	
4	278	0.88	0.74, 1.04	214	0.79	0.66, 0.95	60	1.72	1.10, 2.68	
5	246	0.79	0.66, 0.94	199	0.74	0.61, 0.89	45	1.42	0.89, 2.28	
P_{trend}[d]			0.001			0.0004			0.39	
Dairy calcium										
1	236	1.00	Referent	202	1.00	Referent	28	1.00	Referent	0.09
2	301	1.17	0.99, 1.39	249	1.13	0.94, 1.36	47	1.56	0.97, 2.51	
3	316	1.19	1.00, 1.40	252	1.11	0.92, 1.34	61	1.95	1.24, 3.07	
4	278	1.02	0.86, 1.22	217	0.93	0.77, 1.13	57	1.81	1.15, 2.87	
5	254	0.94	0.78, 1.12	209	0.90	0.74, 1.10	42	1.39	0.86, 2.26	
P_{trend}[d]			0.07			0.04			0.41	
Vitamin D										
Total vitamin D										
1	273	1.00	Referent	231	1.00	Referent	39	1.00	Referent	0.18
2	281	1.00	0.85, 1.18	233	0.98	0.81, 1.17	45	1.17	0.76, 1.80	
3	302	1.04	0.88, 1.23	251	1.02	0.85, 1.22	45	1.17	0.76, 1.81	
4	266	0.90	0.76, 1.07	217	0.88	0.73, 1.07	42	0.98	0.63, 1.53	
5	263	0.92	0.77, 1.09	197	0.85	0.70, 1.02	64	1.42	0.94, 2.12	
P_{trend}[d]			0.14			0.04			0.15	
Vitamin D from food										
1	281	1.00	Referent	239	1.00	Referent	35	1.00	Referent	0.18
2	305	1.06	0.90, 1.25	249	1.01	0.85, 1.21	50	1.43	0.93, 2.21	
3	272	0.91	0.77, 1.08	223	0.88	0.73, 1.06	47	1.28	0.82, 1.98	
4	291	0.98	0.83, 1.15	229	0.91	0.76, 1.09	58	1.60	1.05, 2.44	
5	236	0.79	0.66, 0.94	189	0.75	0.62, 0.91	45	1.21	0.78, 1.89	
P_{trend}[d]			0.003			0.002			0.46	
Dairy vitamin D										
1	271	1.00	Referent	231	1.00	Referent	35	1.00	Referent	0.02
2	289	1.01	0.86, 1.19	237	0.97	0.81, 1.17	46	1.26	0.81, 1.97	
3	284	0.97	0.82, 1.15	226	0.91	0.75, 1.09	55	1.50	0.98, 2.30	
4	292	1.01	0.85, 1.19	226	0.90	0.75, 1.08	62	1.89	1.24, 2.88	
5	249	0.86	0.73, 1.03	209	0.84	0.69, 1.01	37	1.17	0.73, 1.86	
P_{trend}[d]			0.08			0.05			0.39	

Table continues

Table 4. Continued

Nutrient and Quintile of Intake	Case Definition									$P_{heterogeneity}$[b]
	All Women ($n = 1,385$)			Never Infertile[c] ($n = 1,129$)			Concurrent Infertility[c] ($n = 235$)			
	No. of Cases	RR	95% CI	No. of Cases	RR	95% CI	No. of Cases	RR	95% CI	
Predicted 25(OH)D level										
1	238	1.00	Referent	207	1.00	Referent	26	1.00	Referent	0.69
2	292	1.05	0.86, 1.29	253	1.10	10.89, 1.37	34	0.82	0.44, 1.51	
3	291	0.94	0.76, 1.18	239	0.98	0.77, 1.24	50	0.89	0.47, 1.68	
4	296	0.89	0.71, 1.12	236	0.93	0.72, 1.19	52	0.74	0.39, 1.41	
5	268	0.76	0.60, 0.97	194	0.76	0.58, 0.99	73	0.75	0.39, 1.44	
P_{trend}[d]			0.004			0.01			0.35	
Magnesium										
Total magnesium										
1	287	1.00	Referent	242	1.00	Referent	43	1.00	Referent	0.25
2	294	1.01	0.86, 1.19	238	0.95	0.80, 1.14	50	1.21	0.80, 1.82	
3	255	0.86	0.73, 1.02	203	0.80	0.67, 0.97	46	1.12	0.74, 1.71	
4	284	0.94	0.80, 1.11	240	0.94	0.79, 1.13	38	0.86	0.55, 1.33	
5	265	0.87	0.74, 1.03	206	0.83	0.68, 1.00	58	1.13	0.75, 1.68	
P_{trend}[d]			0.08			0.06			0.99	
Magnesium from food										
1	306	1.00	Referent	255	1.00	Referent	47	1.00	Referent	0.91
2	297	0.96	0.82, 1.13	245	0.93	0.78, 1.11	50	1.12	0.75, 1.68	
3	264	0.84	0.71, 0.99	212	0.79	0.66, 0.95	44	0.96	0.63, 1.45	
4	239	0.75	0.63, 0.89	191	0.71	0.59, 0.86	41	0.86	0.56, 1.32	
5	279	0.86	0.73, 1.01	226	0.84	0.70, 1.01	53	0.96	0.65, 1.44	
P_{trend}[d]			0.007			0.007			0.55	
Phosphorus										
Total phosphorus										
1	297	1.00	Referent	241	1.00	Referent	52	1.00	Referent	0.29
2	248	0.80	0.68, 0.95	210	0.83	0.69, 0.99	32	0.64	0.41, 1.00	
3	303	0.96	0.82, 1.13	248	0.96	0.80, 1.14	51	0.97	0.65, 1.43	
4	276	0.87	0.74, 1.03	221	0.84	0.70, 1.01	50	1.04	0.70, 1.54	
5	261	0.82	0.69, 0.97	209	0.80	0.66, 0.96	50	1.01	0.68, 1.50	
P_{trend}[d]			0.07			0.04			0.41	
Phosphorus from food										
1	295	1.00	Referent	242	1.00	Referent	48	1.00	Referent	0.46
2	258	0.85	0.71, 1.00	212	0.83	0.69, 1.00	42	0.91	0.60, 1.38	
3	296	0.95	0.81, 1.12	243	0.94	0.78, 1.12	48	0.99	0.66, 1.48	
4	273	0.87	0.74, 1.02	223	0.85	0.70, 1.02	46	1.04	0.69, 1.56	
5	263	0.84	0.71, 1.00	209	0.80	0.66, 0.96	51	1.17	0.79, 1.75	
P_{trend}[d]			0.08			0.04			0.33	

Abbreviations: CI, confidence interval; RR, rate ratio.

[a] Multivariate model stratified by age (in months) at the start of follow-up and calendar year of the current questionnaire cycle. Results were simultaneously adjusted for age at menarche (<10, 10, 11, 12, 13, 14, 15, 16, or >16 years), length of the menstrual cycle (<26, 26–31, 32–50, or ≥51 days), parity (nulliparous or 1, 2, 3, or ≥4 pregnancies lasting more than 6 months), body mass index (weight (kg)/height $(m)^2$; <19, 19–20.4, 20.5–21.9, 22–24.9, 25–29.9, or ≥30), and energy intake (kcal/day; continuous).

[b] Test for heterogeneity comparing nutrient consumption among women with no past or current infertility with that among women with concurrent infertility.

[c] Infertility was defined as attempting to become pregnant for at least 1 year without success. Cases with "no past or concurrent infertility" were women who never reported infertility. Cases with "concurrent infertility" were women who reported undergoing an infertility evaluation in the same follow-up cycle as laparoscopic confirmation of endometriosis.

[d] Determined using category median values.

association. None of the dairy components (dairy protein, dairy fat, and lactose) were associated with endometriosis in these models (results not shown).

Finally, we assessed whether the associations between dairy-food intake and other nutrients were modified by BMI, parity, or cigarette smoking. The association between high-fat dairy-food intake and endometriosis differed by BMI ($P_{interaction} = 0.0004$). Among women who had a BMI less than 25, the risk of endometriosis was lowest among those in the highest intake category. In these women, we observed a multivariable rate ratio of 0.69 (95% CI: 0.53, 0.90) compared with women in the lowest quintile ($P_{trend} = 0.004$). No association was observed in women who were overweight (BMI ≥25) (RR = 1.25, 95% CI: 0.90, 1.75; $P_{trend} = 0.11$).

DISCUSSION

In this large prospective study, we observed a significantly lower rate of laparoscopically confirmed endometriosis among women with greater predicted plasma 25(OH)D levels and among women with a higher intake of dairy foods. Calcium, vitamin D, and magnesium intakes from foods (including fortified foods) were also inversely related to endometriosis.

The epidemiologic data regarding the relationship between diet and endometriosis are limited. Only 2 case-control studies have examined the association between dairy foods and nutrients. Parazzini et al. (14) examined 504 laparoscopically confirmed endometriosis cases and 504 controls with acute nongynecological, nonhormonal, nonneoplastic conditions and reported no association between milk or cheese intake and endometriosis (for the top tertile of intake, odds ratio (OR) = 1.4 (95% CI: 0.9, 2.0) for milk and OR = 0.8 (95% CI: 0.6, 1.2) for cheese). Differences between that study and ours include our prospectively collected data and our ability to adjust for total caloric intake. Furthermore, although that study did use laparoscopically confirmed cases of endometriosis, the associations were not examined separately by the fertility status of the cases. Finding results similar to ours, Trabert et al. (15) reported inverse associations between dairy foods and calcium intake from foods and endometriosis (for the top quartile of intake, OR = 0.7 (95% CI: 0.4, 1.2) for dairy foods and OR = 0.7 (95% CI: 0.4, 1.2) for calcium). However, they did not observe an association with vitamin D intake from foods.

Abnormal levels of proinflammatory cytokines have been observed in the peritoneal fluid and serum of women with endometriosis (29–31). Mouse models examining the development of endometriosis have suggested that interleukin-6 and tumor necrosis factor α may play a role through their influence on inflammatory angiogenesis (4). Accordingly, dietary factors such as dairy foods and specific nutrients may be related to the physiological processes associated with endometriosis through effects on inflammation. Our results are supported by mouse models in which a milk diet reduced markers of oxidative and inflammatory stress, including tumor necrosis factor α and interleukin-6 (7). Moreover, data in humans suggest that high magnesium intake may be associated with lower levels of inflammatory markers, including interleukin-6 and tumor necrosis factor α-R2 (32).

Previous studies have found that magnesium deficiency is common among women with premenstrual syndrome (33) and among women with a history of miscarriage (34). This may indicate a role of magnesium in reproductive function. In a recent study, Mathias et al. (35) observed that the fallopian tubes of women with endometriosis contract not at regular intervals but more spasmodically, exhibiting "seizure activity." Magnesium has also been shown to relax smooth muscles (8, 9) and as a result may influence endometriosis through its effect on retrograde menstruation. Consistent with these findings, we observed a decreased risk of endometriosis with increasing magnesium intake, with the strongest association being with magnesium intake from foods.

Only a portion of vitamin D comes from diet; thus, plasma 25(OH)D is a more relevant indicator of vitamin D levels than dietary vitamin D, as it reflects not only dietary intake of vitamin D but also adiposity, skin pigmentation, and vitamin D produced from exposure to ultraviolet B radiation. To our knowledge, we are the first investigators to report an inverse association between predicted plasma 25(OH)D levels and endometriosis. In contrast, 2 previous studies found elevated levels of serum 1,25-dihydroxyvitamin D (36) and 25-hydroxyvitamin D_3 (37), while a third study found no differences in 25(OH)D serum levels between women with endometriosis and healthy controls (38). These studies measured vitamin D levels after (36, 38) and at the time of (37) endometriosis diagnosis; thus, in these studies it was unknown whether serum vitamin D levels influenced the development of endometriosis or whether the presence of endometriosis influenced serum vitamin D levels. We used predicted plasma levels prior to endometriosis diagnosis, which may represent the long-term average 25(OH)D level of an individual better than a single plasma measurement (25). In addition, using predicted levels had the benefit of increasing our statistical power by allowing us to examine the association with a larger sample size than if we had been limited to only those subjects with plasma 25(OH)D measurements.

The biological mechanism through which vitamin D may affect endometriosis risk is not yet fully understood, though it is hypothesized to involve immune system regulation, since there is strong circumstantial evidence that endometriosis is dependent not only on circulating steroid hormone levels but also on aberrant immunological response (39). Women with endometriosis have been demonstrated to exhibit altered immune surveillance, with depressed cell-mediated immunity and heightened humoral immune response (40). Vitamin D may influence endometriosis through suppression of proinflammatory processes. In vitro studies have demonstrated that 1,25-dihydroxyvitamin D_3 inhibits proliferation of T helper 1 cells (41) and production of interleukin-2 and interferon γ (42) and stimulates development of T helper 2 cells (41), suggesting a role of vitamin D in diseases such as endometriosis.

Our results suggest dissimilar associations between dietary intakes of total milk, skim/low-fat milk, and magnesium and

endometriosis risk between the 2 subtypes of endometriosis. In contrast, the inverse association between predicted plasma(OH)D levels and endometriosis risk was quite consistent in both women who had never reported infertility and women who reported concurrent infertility. This may suggest that these foods and nutrients may play different roles in chronic pelvic pain symptoms and/or the etiology of endometriosis. Among women who have had laparoscopically diagnosed endometriosis, the infertile women who are diagnosed with endometriosis during an infertility evaluation will include women who are "asymptomatic," while women with no infertility are all "symptomatic" with respect to pain; otherwise a surgical evaluation would not have been conducted. Thus, the stronger protective association for milk and magnesium intakes in women who have never reported infertility may be due to these factors' influence on chronic pelvic pain symptoms or due to differing endometriosis etiologies in women without infertility and women with infertility.

It is likely that there was some misclassification of predicted plasma 25(OH)D levels in our data. However, the prediction model has been validated among participants in 3 prospective cohort studies, including NHS II, providing evidence that it is appropriate for assessing an individual's long-term vitamin D status (26). Previous studies have found significant inverse associations between vitamin D estimates from this prediction model and Crohn's disease (43), pancreatic cancer (44), digestive-system cancer mortality (25, 45), total cancer incidence (25), and total cancer mortality (25, 45). We expect that any misclassification would have been random and would probably have caused attenuation of the true effect.

We observed stronger associations with intakes of calcium, vitamin D, and magnesium from foods than with total intake. This may indicate residual or unmeasured confounding by other dietary factors. However, we explored the association for foods that were the top contributors of these nutrients and observed an association with milk consumption. In addition, confounding by other lifestyle factors is a possibility. However, we adjusted for physical activity, cigarette smoking, and alcohol intake, and the associations did not materially change. Because the participants were primarily white nurses, it is unlikely that confounding by socioeconomic characteristics or access to health care influenced the results.

To our knowledge, this is the largest study to have examined the relationship between dairy foods and nutrients and endometriosis risk, allowing us the power to examine whether the association varied according to the fertility status of endometriosis cases. We also had high follow-up rates, cases that had been laparoscopically confirmed, and information on many important covariates, including known endometriosis risk factors on which data were collected and updated at 2-year intervals.

In conclusion, our findings suggest that greater predicted plasma 25(OH)D levels and higher intake of dairy foods are associated with a lower risk of endometriosis. While these findings need to be confirmed in future studies, dairy foods and vitamin D may be some of the first identifiable modifiable risk factors for endometriosis.

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Author affiliations: Department of Obstetrics, Gynecology, and Reproductive Biology, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts (Holly R. Harris, Stacey A. Missmer); Division of Nutritional Epidemiology, National Institute for Environmental Medicine, Karolinska Institutet, Stockholm, Sweden (Holly R. Harris); Departments of Epidemiology and Nutrition, Harvard School of Public Health, Boston, Massachusetts (Jorge E. Chavarro, Walter C. Willett); and Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts (Susan Malspeis, Stacey A. Missmer).

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