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James L. Nodler, MD, Holly R. Harris, ScD, MPH, Jorge E. Chavarro, MD, ScD, ScM, A. Lindsay Frazier, MD, ScM, Stacey A. Missmer, ScD, ScM

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Dairy consumption during adolescence and endometriosis risk

James L. Nodler, MD(1,2,*), Holly R. Harris, ScD, MPH(3,4,*), Jorge E. Chavarro, MD, ScD, ScM(5,6,7), A. Lindsay Frazier, MD, ScM (6,8), Stacey A. Missmer, ScD, ScM(5,9,10)

1. Department of Obstetrics, Gynecology, and Reproductive Biology, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, United States

2. Houston IVF, Houston, Texas, United States

3. Program in Epidemiology, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington, United States

4. Department of Epidemiology, University of Washington, Seattle, Washington, United States

5. Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston, Massachusetts, United States

6. Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, United States

7. Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, United States

8. Dana-Farber Children's Cancer Care, Boston, Massachusetts, United States

9. Division of Adolescent and Young Adult Medicine, Department of Medicine, Boston Children's Hospital and Harvard Medical School, Boston, Massachusetts, United States

10. Department of Obstetrics, Gynecology, and Reproductive Biology, College of Human Medicine, Michigan State University, Grand Rapids, Michigan, United States

*Contributed equally as co-first authors

Corresponding author: Dr Holly Harris, Program in Epidemiology, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, M4-B859, Seattle, WA 98109-1024, Telephone: 206-667-2712, E-mail: hharris@fredhutch.org

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Preliminary results from this study were presented at the American Society of Reproductive Medicine (ASRM) 69th Annual Meeting, October 12-17, 2013, Boston, Massachusetts. Since this time the analysis has been updated with additional years of follow-up.

Condensation: This study examined the association between dairy consumption in adolescence – a potentially critical window of exposure – and subsequent risk of laparoscopically-confirmed endometriosis diagnosis.

Short Title: Adolescent Dairy and Endometriosis

AJOG at a Glance:

- **Why was the study conducted?** Higher intake of dairy in adulthood has been associated with lower risk of endometriosis diagnosis but no previous studies have examined whether dairy intake during adolescent influences endometriosis risk.
- **What are the key findings?** In the first study to examine the association between adolescent dairy intake and endometriosis risk, higher dairy consumption was associated with a lower risk of laparoscopically-confirmed endometriosis
- **What does this study add to what is already known?** These results may be the first steps in identifying adolescent dietary counseling guidelines and could be effective in reducing the number of women affected by this devastating disease. Future prospective studies in adolescent populations with detailed dietary data are needed to confirm these results.

Abstract

Background: Modifiable risk factors such as diet may be important in both the etiology and progression of endometriosis as well as the prevalence of pain symptoms and infertility associated with this condition. In adults, higher intake of dairy has been associated with lower risk of endometriosis diagnosis. There is currently no literature on whether dairy intake during adolescence - a potentially critical window of exposure - influences endometriosis risk.

Objective: To evaluate the association between consumption of dairy foods in adolescence and risk of laparoscopically-confirmed endometriosis.

Study Design: A prospective cohort study, the Nurses' Health Study II (NHSII), which has prospectively collected data since 1989. In 1998, when participants were ages 34 to 51, they completed a 124-item food frequency questionnaire about their high school diet (HS-FFQ). Cases were defined as those who self-reported laparoscopically-confirmed endometriosis. Cox proportional hazard models were used to calculate hazard ratios and 95% confidence intervals for the association between dairy foods and laparoscopically-confirmed endometriosis.

Results: Among women who completed the HS-FFQ in 1998, 581 cases of laparoscopically-confirmed endometriosis were diagnosed among 32 868 premenopausal women from 1998 to 2013. Women who consumed more than four servings/day of dairy foods during adolescence had a 32% lower risk of laparoscopically-confirmed endometriosis during adulthood (95% CI=0.47-0.96; p_{trend}=0.04) compared to women consuming one or fewer servings/day. The association was similar for low-fat and high-fat dairy foods. Yogurt and ice cream consumption, specifically,

were associated with a lower risk of endometriosis. Those who consumed two or more servings of yogurt per week as an adolescent had a 29% lower risk of endometriosis diagnosis (95% CI=0.52-0.97; P_{trend}=0.02) compared to those consuming less than one serving per week. In addition, women who consumed one or more servings/day of ice cream per day during adolescence had a 38% lower risk of endometriosis diagnosis (95% CI=0.40-0.94; P_{trend}=0.20) compared to those consuming less than one serving per week.

Conclusion: Our findings suggest that dairy consumption, specifically yogurt and ice cream intake, in adolescence may reduce the risk of subsequent endometriosis diagnosis. Future studies in adolescent populations are needed to confirm these results.

Keywords: endometriosis, diet, adolescence, dairy, yogurt, ice cream

Introduction

Endometriosis is a common, estrogen-dependent disorder characterized by endometrial-like implants located outside of the uterus. It is a chronic inflammatory condition associated with pelvic pain and infertility. The prevalence of endometriosis is estimated to be ~10% in reproductive aged women, and as high as 50% in women with infertility[1, 2]. Endometriosis often has an early life presentation that can afflict adolescent girls and young women who may suffer from debilitating pain and risk future infertility[3].

Dietary factors have been implicated in the development and severity of endometriosis [1, 4-12]. The effect of diet on endometriosis may be due to changes in estrogen, prostaglandin metabolism, inflammation, or smooth muscle contractility[4]. To date, the literature relating to diet and endometriosis has focused primarily on incident diagnosis of endometriosis among women based on dietary intake in adulthood. However, adolescence may be the critical window for etiologically-influential exposures. Since there is a delay in diagnosis (average: seven years)[13], resulting in a reported peak of incidence at 25-29 years of age[14], and since case series suggest endometriosis symptom onset is most often during adolescence[15, 16], the true onset of the disease is likely to occur even earlier in life. Therefore, childhood and adolescence, may be a critical or sensitive etiologic window for endometriosis onset, and exploration of exposures during this time period may help identify early predictors of endometriosis risk. Exposures during adolescence have been associated with risk of adult-onset estrogen-related conditions, often even more strongly than those same exposures during adulthood. For example, early body size and early life exposure to dietary factors have been shown to have effects on the development of breast cancer[17-22] and benign breast disease[23, 24].

Several theories exist to describe a link between dairy foods and endometriosis. Women

with endometriosis have high peripheral and peritoneal levels of several inflammatory factors including interleukin-6 (IL)-6, IL-8, and tumor necrosis factor-α (TNFα)[25-27]. Studies have shown that intake of dairy foods and dietary calcium is inversely related to oxidative and inflammatory stress[28]. Vascular endothelial growth factor (VEGF) has been found in higher levels in the peritoneal fluid of women with endometriosis[29]. High dairy intake has been shown to reduce vascular inflammation[28]. Retrograde menstruation is postulated to be the potential etiologic catalyst for endometriosis[30], and magnesium, which is found at high levels in dairy foods, relaxes smooth muscle and may reduce retrograde menstruation[31]. The consumption of dairy foods and associated nutrients during adulthood has been associated with risk of endometriosis[6-8]. Of the two prior case-control studies that examined adult dairy intake and endometriosis risk one generally suggested non-significant inverse associations between dairy foods and endometriosis risk[11] while the second observed a non-significant decreased risk with increasing cheese intake, and non-significant increased risk with increasing milk and butter intake[6]. In the only prior prospective study to examine this association, this same NHSII cohort, total adult dairy intake was associated with a significant decreased risk of endometriosis[32]. This investigation provides the first data on the relation between adolescent dairy consumption and the subsequent risk of endometriosis diagnosis in adulthood.

Materials and Methods

Study Population

The Nurses' Health Study II (NHSII) prospective cohort was established in 1989, when 116 429 US female nurses between the ages of 25-42 completed a baseline questionnaire on demographic, medical history, and lifestyle information. Follow-up questionnaires are sent to

participants every two years to collected update information on disease diagnosis, lifestyle factors, and other health related topics. 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, Massachusetts.

In 1997, participants were asked to complete a food frequency questionnaire about diet during high school (HS-FFQ). Details about the HS-FFQ are provided elsewhere.[33] The HS-FFQ was completed by 47 355 women (83% of those sent the questionnaire) in 1998. For the current analysis, women were excluded if they had a diagnosis of endometriosis (with or without laparoscopic confirmation; n=4727), a diagnosis with cancer other than non-melanoma skin cancer (n=1290), a hysterectomy (n=2766), or reported being postmenopausal (n=4576) prior to return of the HS-FFQ (1998). In addition, those with implausible daily caloric intake on the HS-FFQ (<500 or >=5000 kcal; n=980), or who did not return any subsequent questionnaires (n=148) were also excluded. After exclusions, 32 868 participants comprised the study population.

Endometriosis Definition

Starting with the 1993 questionnaire participants were asked if they "had ever had physician-diagnosed endometriosis" at each questionnaire cycle. If they reported "yes", they were asked if their endometriosis diagnosis was confirmed by laparoscopy, which is the gold standard for diagnosis of endometriosis[34]. A validation study was conducted among 200 randomly selected cases from the 1766 incident cases identified from the initial questionnaire [35]. Endometriosis diagnosis was confirmed through medical record review of surgical reports in 96.2% of women who self-reported laparoscopic confirmation. We also looked at the association

between dairy consumption and endometriosis in two subtypes of endometriosis patients – those diagnosed with endometriosis in the context of an infertility evaluation, and those who never reported infertility. As women who are diagnosed with endometriosis outside of an infertility evaluation usually present with pain, they may represent a different endometriosis phenotype or may highlight an impact of diet specific to the pain symptoms of endometriosis.

Dietary Assessment

Adolescent diet was measured using a 124-item HS-FFQ specifically designed to include foods that were commonly consumed between 1960 and 1980 when the women would have been in high school. Participants were asked to indicate how often, on average, they consumed a specified amount of each food between the ages of 13-18 years. Nine responses were possible, ranging from never to six or more times a day. Participants were between the ages of 34-51 when they completed the HS-FFQ.

The HS-FFQ has been previously validated in a different study population comparing two prospectively collected 131-item self-administered Youth/Adolescent Questionnaires (YAQ) that were completed when the participants were ages 13-18 to recalled adolescent diet using the HS-FFQ ten years later[36]. The mean corrected correlation between the HS-FFQ and the YAQs was 0.58 (range=0.40-0.88). Calcium and vitamin D were the only dairy-specific nutrients examined, with correlation coefficients of 0.84 and 0.68, respectively. These mean correlations are comparable to those obtained in validations of current diet assessment[37-40]. Adult diet was assessed in 1991 and every four years thereafter with similar methods using a food frequency questionnaire (FFQ) listing over 130 food items. Previous validation studies of the adult diet FFQ have been reported elsewhere with good correlations between foods and nutrients assessed

by the FFQ compared to food records[37, 40].

Analyses for adolescent dairy consumption were conducted using the following categories: total dairy (milk, yogurt, cheese, instant breakfast, ice cream, milkshake, sherbet, butter), high-fat dairy (whole milk, ice cream, milkshake, cream cheese, other cheese, butter) and low-fat dairy (low fat or skim milk, yogurt, cottage cheese, instant breakfast, sherbet).

Statistical Analysis

In our primary analysis, follow-up time began in 1998 with completion of the HS-FFQ and continued until self-report of laparoscopically-confirmed endometriosis, diagnosis of cancer, death, loss to follow-up, hysterectomy, menopause, or end of follow-up on June 1, 2013, whichever occurred first (described hereafter as the prospective analysis). This analysis only includes cases of endometriosis diagnosed after return of the HS-FFQ. In secondary analyses, follow-up started in 1989 with return of the baseline questionnaire and continued until self-report of laparoscopically-confirmed endometriosis, diagnosis of cancer, death, loss to follow-up, hysterectomy, menopause, or end of follow-up on June 1, 2013, whichever occurred first (described hereafter as the combined analysis). This analysis combined cases of endometriosis diagnosed before and after return of the HS-FFQ, allowing for greater power to examine subtypes of endometriosis defined by fertility status. In both analyses, participants who reported physician-diagnosed endometriosis with no laparoscopic confirmation were censored at the time of that report but were allowed to reenter the analysis population if they reported laparoscopic confirmation on a subsequent questionnaire. We used Cox proportional hazards models to estimate hazard ratios (HR) and 95% confidence intervals (CI), using the lowest category of intake as the reference category. Tests for linear trend across intake categories were performed

by assigning the median intake value of each category to all participants in that group and including as a continuous variable in the regression models. We *a priori* adjusted for characteristics that would have occurred prior to or contemporaneous with adolescent dietary intake: age, BMI at age 18, age at menarche, adolescent physical activity, smoking in adolescence, adolescent hormonal contraceptive use, and total high school caloric intake. Missing data were handled with the missing indicator method, with categories created for missing data included in the regression model[41]. Adolescent physical activity had 5% missing and all other adjustment variables had <0.8% missing. Statistical analyses were performed using SAS Version 9.4 (SAS Institute Inc, Cary, NC).

Results

During 584 086 person years of follow-up from 1998 to 2013, 581 NHSII participants reported a laparoscopically-confirmed endometriosis diagnosis. The average age of participants at the time of completion of the HS-FFQ in 1998 was 41 years (Table 1). Women who consumed greater amounts of total dairy as an adolescent were taller, consumed more calories, and had a higher level of adolescent physical activity.

Adolescent intake of total dairy foods was associated with a lower risk of endometriosis in adulthood in the prospective analysis. After adjustment for covariates, women who consumed >four servings/day of total dairy foods as an adolescent has a 32% lower risk of laparoscopically-confirmed endometriosis compared to women consuming ≤one servings/day (95% CI=0.47-0.96; p_{trend}=0.04)(Figure 1; Table 2). When low-fat dairy foods and high-fat dairy foods were included in the same model there was no differences in the associations between these two dairy types (p=0.56). No variation by infertility status was observed (all

$p_{heterogeneity}$>0.20) in this prospective analysis. However, the sample size in the concurrently infertile group was very small (n=36). The associations between adolescent dairy intake and endometriosis remained the same after adjusting for adult dairy intake (results not shown).

When the association between consumption of individual dairy foods as an adolescent and risk of endometriosis was examined in the prospective analysis (Table 3), a lower risk of endometriosis was seen with higher consumption of yogurt. After adjusting for intake of all other dairy foods, those who consumed ≥two servings of yogurt per week were 29% less likely to be diagnosed with endometriosis as an adult (95% CI=0.52-0.97; p_{trend}=0.02) than those consuming <one serving/week. There was also a lower risk of endometriosis with increasing ice cream consumption. Women consuming one or more servings/week had a 38% (95% CI=0.40-0.94; p_{trend}=0.20) lower risk of endometriosis compared to those consuming <one serving/week. We examined the effect of total dairy food consumption with yogurt and ice cream removed from the total dairy calculation, to see if either of these foods was driving the inverse association between total dairy consumption and endometriosis diagnosis. Those who consumed >four servings of total dairy (with yogurt and ice cream removed) per day as an adolescent had a 21% (95% CI=0.58-1.08; p_{trend}=0.29) lower risk of laparoscopically-confirmed endometriosis than those who consumed ≤one serving of total dairy per day.

Focusing on micronutrients that are rich in dairy foods, consumption as an adolescent of calcium from all sources was suggestively associated with a lower risk of endometriosis as an adult (Table 4). Milk was by far the largest contributor to calcium intake (40%) and vitamin D intake (42%), with all other individual foods contributing <10%. The association was similar when calcium from dairy and non-dairy sources was considered. No associations were observed with vitamin D intake (Table 4). We also examined whether dairy fat intake could explain the

association between total dairy, yogurt, and/or ice cream intake and endometriosis risk by including dairy fat in the model and did not observe any material changes in the effect estimates.

In the combined analysis that included women diagnosed with endometriosis beginning in 1989 (40 874 eligible participants; 2412 laparoscopically-confirmed endometriosis cases) results were similar but slightly attenuated for total dairy, yogurt, and ice cream (Supplemental Tables 1, 2, and 3). When the associations were evaluated by case subtype, the lower risk for total dairy intake was observed only among women who had never reported infertility (HR=0.74 for >four servings/day; 95% CI=0.61-0.91; p_{trend}=0.001) with a $p_{heterogeneity}$ between case subtypes of 0.06. The lower risk with increasing yogurt consumption was limited to women who had never reported infertility (HR=0.70 for ≥two servings/week; 95% CI=0.57-0.85; p_{trend}=0.0001; $p_{heterogeneity}$=0.02). When total dairy intake was examined removing yogurt or ice cream from the total dairy calculation the results were not materially changed. In regards to nutrients concentrated in dairy foods, in the combined analysis adolescent intake of calcium, particularly dairy calcium, was associated with a lower risk of endometriosis (Supplemental Table 3) and this association was robust to adjustment for total dairy food intake.

Comment

In this longitudinal cohort study, we observed lower rates of laparoscopically-confirmed endometriosis diagnosis during adulthood among those who, in adolescence, consumed greater amounts of total dairy foods, yogurt, or ice cream. When results were examined in an expanded population that included retrospective cases, we observed that the associations between total dairy foods, yogurt, and ice cream were strongest among women who had never reported infertility, suggesting that at least part of these associations may be driven by symptom

remediation. However, case numbers of those women with concurrent infertility in the primary analysis were small and robust associations could not be inferred from the data within this stratum.

Overall, the results of this study were similar to our previous evaluation in this cohort of diet during adulthood[7], where greater consumption of total dairy foods during adulthood (HR for >three servings/day=0.82; 95% CI=0.71-0.95; p_{trend}=0.03) was associated with a lower incidence of endometriosis diagnosis. That association appeared to be driven primarily by consumption of skim/reduced-fat milk, which was not associated with lower endometriosis risk in our adolescent diet analysis. We observed lower risk with adolescent consumption of yogurt or ice cream that were not observed for adult consumption. Calcium from food sources in adulthood was also associated with lower endometriosis risk, which is consistent with results for calcium from food sources in adolescence. In sensitivity analyses, we controlled for dairy fat and did not observe material change in the effect estimates which suggest that it is not dairy fat that is driving our observed associations.

To our knowledge, this is the first study to evaluate the relation between dairy intake and related nutrients during adolescence and risk of endometriosis diagnosis. In addition to the analyses of dairy intake during adulthood within this Nurses' cohort that are described above, two other studies have evaluated adult dairy consumption and endometriosis. Trabert et al. performed a case-control study in the United States, including 284 cases with endometriosis and 660 controls[8]. This study showed a trend toward lower odds of endometriosis with greater adult consumption of dairy (odds ratio [OR]=0.7; 95% CI=0.4-1.2; p_{trend}=0.13) and calcium (OR=0.7; 95% CI=0.4-1.2; p_{trend}=0.41), but the confidence intervals included 1.0. Parazzini et al. conducted two case-control studies in Italy between 1984-1999, that included 504 cases with

241 endometriosis and 504 controls[6]. The findings suggested a trend toward higher endometriosis
242 odds with greater consumption of milk (OR=1.4; 95% CI=0.9-2.0), butter (OR=1.5; 95%
243 CI=1.0-2.0), and margarine (OR=1.2; 95% CI=0.7-1.9), and a trend toward lower endometriosis
244 odds with greater consumption of cheese (OR=0.8; 95% CI=0.6-1.2), however but the
245 confidence intervals included 1.0 and total caloric intake was not accounted for.

246 There are several hypotheses regarding the potential biochemical and physiologic impact
247 that dairy products, vitamin D, and calcium have, which may confer lower risk of endometriosis.
248 Endometriosis is an inflammatory condition[2]. It has been postulated that dairy and calcium may
249 reduce oxidative and inflammatory stress. Zemel, et al. demonstrated that inflammatory factors
250 such as reactive oxygen species (ROS), TNFα, and IL-6 were all decreased by high calcium and
251 high dairy diets[28]. Similarly, inverse relationships between vitamin D and levels of C-reactive
252 protein (CRP) have been seen in several conditions such as diabetes mellitus and atherosclerotic
253 vascular disease[42].

254 The adolescent dietary exposure window may be key. While the association between total
255 dairy consumption and incidence of endometriosis diagnosis was similar in adult and adolescent
256 diet, earlier exposure could impact disease progression. While there are no published studies
257 evaluating the effect of adolescent diet on the development of endometriosis, there are several
258 studies linking adolescent diet to breast cancer in adulthood, utilizing the HS-FFQ[18-21, 43, 44]. In
259 the combined analysis we observed that the associations with total dairy, yogurt, and ice cream
260 were strongest among women who had never reported infertility, the case group most likely to
261 have pain as the indication for their laparoscopic evaluation. This suggests that adolescent diet
262 may influence incidence of a more painful subtype of endometriosis and/or increase pain
263 symptoms that lead to endometriosis diagnosis. Regular consumption of yogurt has been

suggested to beneficially influence the intestinal microbiota due to its probiotic properties[45]. Some studies have demonstrated the potential for probiotics to improve symptoms among patients with irritable bowel syndrome (IBS)[46-48], a condition that often overlaps with, or is misdiagnosed for, endometriosis. While speculative, it is plausible that adolescent dairy consumption, particularly yogurt and ice cream, lead to a more beneficial microbiome, resulting in the dampening of endometriosis related pelvic pain during a critical window (adolescence), reducing the risk of visceral hypersensitivity[49], which may amplify symptoms of endometriosis over the lifetime[50].

A limitation of this study is that it depends on long-term recall of the participants. Participants were asked, in adulthood, to recall their dietary intake from adolescence. While some misclassification is likely, in the absence of prospective data collected during adolescence followed by decades of follow-up, this previously validated method[51, 52], provides an important opportunity to begin to examine adolescent diet and endometriosis risk. Also, the make-up and intake of dairy products in the period queried, 1960-1982, was different than what is currently available. When considering micronutrient evaluation, we were limited by the inability to quantify the contribution of sun exposure to vitamin D intake and were not able to examine magnesium intake. In future studies, we would benefit from validated biomarkers of dietary exposures, which would help to reduce exposure misclassification and may further clarify the underlying etiologic mechanism for the impact of dairy on endometriosis diagnosis.

A particular strength of this study is that in the primary analyses, only those cases who were laparoscopically diagnosed after the HS-FFQ was completed in 1998 were included in the primarily analysis. While it is unlikely that women diagnosed with endometriosis prior to completion of the HS-FFQ would be subject to recall bias and report their high school dietary

intake differently due to the endometriosis diagnosis, this analysis maintained the prospective nature of the cohort and avoids recall bias. Another strength of the study is the utilization of the large, longitudinal NHSII cohort. The extensive data collected in this cohort allowed for the adjustment of multiple confounders, including adjustment for adult dietary intake.

These results may be the first steps in identifying adolescent dietary counseling guidelines and could be effective in reducing the number of women affected by this devastating disease. Future prospective studies in adolescent populations with detailed dietary data are needed to confirm these results.

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Table 1. Age-adjusted adolescent and adult characteristics in 1997 by total adolescent dairy intake among women in the Nurses' Health Study II

	No. of servings of Total Dairy Foods				
	≤1/day (n=2,387)	2/day (n=6,698)	3/day (n=6,288)	4/day (n=7,308)	>4/day (n=9,924)
Age (years), Mean (SD)	41.5 (4.5)	41.1 (4.6)	41.1 (4.5)	41.5 (4.5)	41.7 (4.5)
Total adolescent calories/day (kcal), Mean (SD)	1992 (657)	2328 (656)	2640 (689)	2786 (673)	3228 (717)
Adolescent Physical Activity (MET hrs/week), Mean (SD) [a]	45.9 (34.6)	49.3 (35.3)	51.7 (36.2)	52.9 (36.0)	57.1 (38.0)
BMI at age 18, Mean (SD) [b]	21.2 (3.4)	21.3 (3.3)	21.2 (3.2)	21.1 (3.1)	21.1 (3.2)
Height in inches, Mean (SD)	64.5 (2.7)	64.7 (2.6)	64.8 (2.6)	65.0 (2.6)	65.1 (2.6)
BMI in 1997, Mean (SD)	25.8 (6.0)	25.9 (6.1)	25.6 (5.9)	25.5 (5.8)	25.6 (5.8)
Age at menarche (%)					
<12 years	23	24	23	23	23
12 years	31	31	31	30	30
13 years	28	27	28	28	29
>13 years	18	18	18	19	19
Menstrual cycle length between ages 18-22, %					
<26 days	13	11	10	10	9
26-31 days	64	67	66	65	66
32-50 days	18	17	18	19	20
>50 days or irregular	5	5	6	6	6
Adolescent cigarette smoking, %[c]	20.9	22.8	23.6	20.9	22.9
Adult cigarette smoking (%)					
Current smoker	8.0	9.5	8.6	8.2	7.8
Past smoker	23.3	24.3	25.1	22.6	24.7
Adolescent Hormonal Contraceptive Use, %[d]	22.0	23.1	21.5	20.8	22.0
Ever used oral contraceptives, %	85	86	86	84	85
Nulliparous, %	22	21	20	18	17
Adult dairy consumption (servings/day), Mean (SD)	1.5 (1.0)	2.0 (1.1)	2.3 (1.2)	2.6 (1.2)	3.1 (1.4)

[a] Grades 9 – 12, MET=Metabolic Equivalent of Task
[b] Body Mass Index, weight (kg)/height $(m)^2$
[c] Ages 15-19 years

[d] Age 18 years or below
Values are standardized to the age distribution of the study population (value of age is not age adjusted).

Table 2. Hazard ratios and 95% CIs for laparoscopically confirmed endometriosis according to adolescent dairy intake among 32,868 women in the Nurses' Health Study II, 1998-2013

Type of Dairy Food and No. of Servings	No. of Cases	Hazard Ratio (95% confidence interval)	
		Age-Adjusted	MV[a]
Total dairy foods			
≤1/day	48	1.00 (Referent)	1.00 (Referent)
2/day	125	0.84 (0.60, 1.18)	0.83 (0.59, 1.16)
3/day	105	0.69 (0.49, 0.99)	0.69 (0.48, 0.98)
4/day	119	0.67 (0.47, 0.95)	0.66 (0.46, 0.93)
>4/day	184	0.68 (0.48, 0.97)	0.68 (0.47, 0.96)
P_{trend}[b]		0.04	0.04
High-fat dairy foods			
≤1/day	174	1.00 (Referent)	1.00 (Referent)
2/day	156	0.81 (0.65, 1.02)	0.81 (0.65, 1.02)
3/day	79	0.80 (0.61, 1.06)	0.81 (0.61, 1.06)
4/day	75	0.73 (0.55, 0.97)	0.73 (0.55, 0.97)
>4/day	97	0.83 (0.63, 1.10)	0.84 (0.64, 1.11)
P_{trend}[c]		0.17	0.20
Low-fat dairy foods			
<1/week	59	1.00 (Referent)	1.00 (Referent)
1/week	161	1.07 (0.79, 1.44)	1.06 (0.79, 1.44)
2-6/week	153	0.97 (0.71, 1.31)	0.95 (0.70, 1.28)
1-2/day	110	0.99 (0.72, 1.36)	0.97 (0.70, 1.34)
>2/day	98	0.90 (0.64, 1.25)	0.88 (0.63, 1.22)
P_{trend}[b]		0.59	0.66

Abbreviations: CI, Confidence Interval; MV, multivariable; HR, hazard ratio.

[a]Multivariable model adjusted for adolescent characteristics: BMI at age 18 (<19.0, 19.0-20.4, 20.5-21.9, 22.0-24.9, 25.0-29.9, ≥30 kg/m^2), age at menarche (<10, 10, 11, 12, 13, 14, 15, or ≥16 years), adolescent physical activity (<21, 21-35.9, 36-53.9, 54-80.9, ≥81 MET hours/week), smoking in adolescence (no, yes), adolescent hormonal contraceptive use (no, yes), and energy intake (kcal/day; continuous).

[b]Determined using category median values.

Figure 1. Association between total adolescent dairy intake and laparoscopically confirmed endometriosis among 32,868 women in the Nurses' Health Study II, 1998-2013. Dots represent hazard ratios, whiskers represent 95% confidence intervals.

Table 3. Multivariable adjusted hazard ratios and 95% CI for laparoscopically confirmed endometriosis according to adolescent intake of specific dairy foods among 32,868 women in the Nurses' Health Study II, 1998-2013

Dairy Food and No. of Servings	No. of Cases	MV HR[a]
Total milk		
<1/day	155	1.00 (Referent)
1/day	96	0.87 (0.67, 1.12)
2/day	100	1.01 (0.78, 1.30)
3/day	175	0.78 (0.62, 0.98)
≥4/day	55	0.97 (0.70, 1.35)
P_{trend}[b]		0.27
Whole Milk		
<1/month	264	1.00 (Referent)
1/month-6/week	75	1.42 (1.01, 2.00)
1-2/day	112	1.10 (0.80, 1.52)
>2/day	130	0.98 (0.71, 1.35)
P_{trend}[b]		0.12
Reduced fat/Skim Milk		
<1/month	377	1.00 (Referent)
1/month-6/week	37	1.12 (0.74, 1.70)
1-2/day	80	1.24 (0.88, 1.74)
>2/day	87	0.96 (0.68, 1.34)
P_{trend}[b]		0.15
Butter		
<1/month	263	1.00 (Referent)
1/month-6/week	174	1.01 (0.83, 1.22)
1-2/day	75	0.80 (0.62, 1.05)
>2/day	69	1.20 (0.91, 1.59)
P_{trend}[b]		0.47
Cheese		
<5/week	139	1.00 (Referent)
5-6/week	218	1.05 (0.84, 1.31)
1/day	123	1.00 (0.77, 1.29)
≥2/day	101	0.92 (0.69, 1.21)
P_{trend}[b]		0.41
Yogurt		
<1/week	407	1.00 (Referent)
1/week	128	0.84 (0.69, 1.04)
≥2/week	46	0.71 (0.52, 0.97)
P_{trend}[b]		0.02
Ice Cream		
<1/week	47	1.00 (Referent)
1/week	318	0.68 (0.49, 0.93)
2-6/week	163	0.66 (0.47, 0.93)
≥1/day	53	0.62 (0.40, 0.94)
P_{trend}[b]		0.20

Abbreviations: CI, Confidence Interval; MV, multivariable; HR, hazard ratio.

[a]Multivariable model was adjusted for BMI at age 18 (<19.0, 19.0-20.4, 20.5-21.9, 22.0-24.9, 25.0-29.9, ≥30 kg/m^2), age at

menarche (<10, 10, 11, 12, 13, 14, 15, or ≥16 years), adolescent physical activity (<21, 21-35.9, 36-53.9, 54-80.9, ≥81 MET hours/week), smoking in adolescence (no, yes), adolescent hormonal contraceptive use (no, yes), and energy intake (kcal/day; continuous). In addition, all foods/food groups are mutually adjusted for each other.
[b]Determined using category median values.

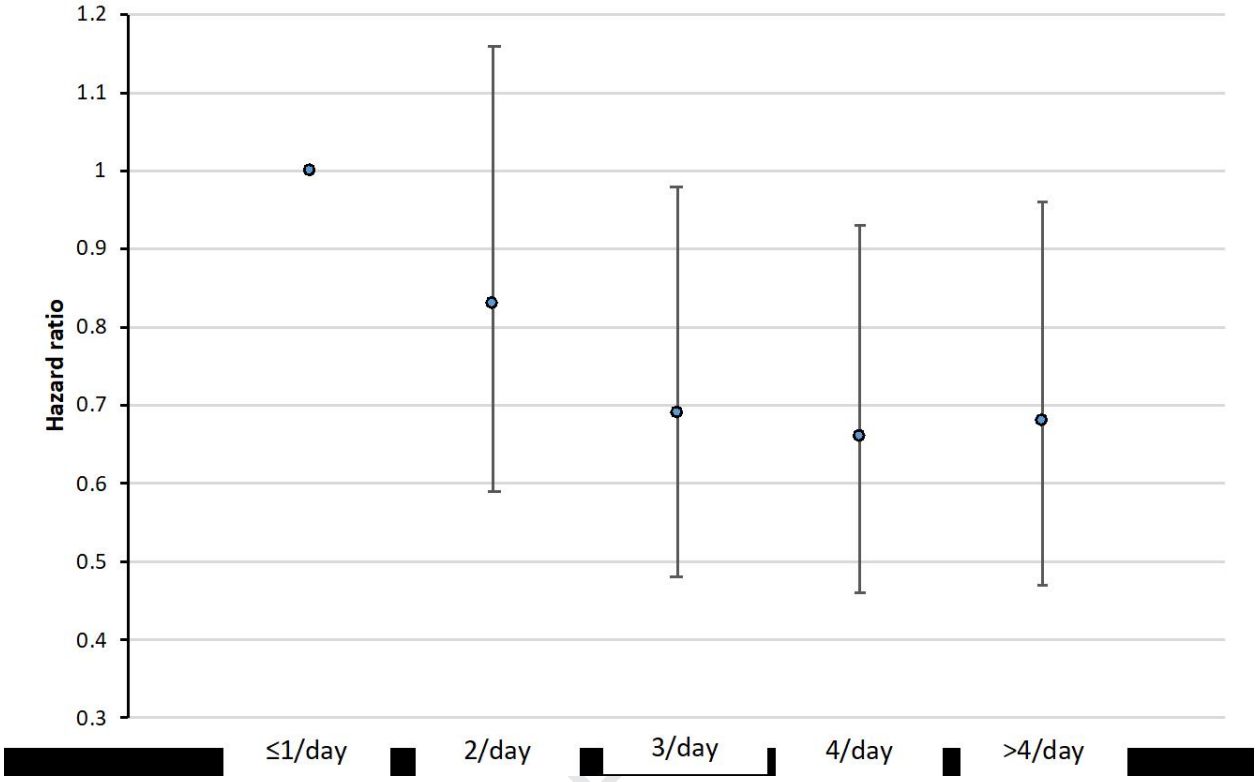
Table 4. Multivariable adjusted hazard ratios and 95% CI for laparoscopically confirmed endometriosis according to adolescent nutrient intake among 32,868 women in the Nurses' Health Study II, 1998-2013

Nutrient intake	No. of Cases	MV HR[a]
Calcium		
1	114	1.00 (Referent)
2	127	0.95 (0.74, 1.23)
3	112	0.82 (0.63, 1.07)
4	115	0.80 (0.61, 1.04)
5	113	0.81 (0.62, 1.06)
P_{trend}[b]		0.07
Dairy Calcium		
1	124	1.00 (Referent)
2	124	0.93 (0.72, 1.19)
3	107	0.80 (0.62, 1.04)
4	113	0.80 (0.61, 1.03)
5	113	0.87 (0.67, 1.12)
P_{trend}[b]		0.18
Non-Dairy Calcium		
1	88	1.00 (Referent)
2	104	0.96 (0.72, 1.28)
3	106	0.84 (0.62, 1.13)
4	123	0.82 (0.61, 1.10)
5	160	0.91 (0.69, 1.22)
P_{trend}[b]		0.54
Vitamin D		
1	106	1.00 (Referent)
2	120	1.11 (0.85, 1.44)
3	104	0.88 (0.67, 1.16)
4	111	1.01 (0.77, 1.32)
5	140	1.27 (0.98, 1.64)
P_{trend}[b]		0.09
Dairy Vitamin D		
1	125	1.00 (Referent)
2	134	1.10 (0.86, 1.41)
3	113	0.94 (0.73, 1.22)
4	104	0.81 (0.62, 1.06)
5	105	0.94 (0.72, 1.23)
P_{trend}[b]		0.18
Vitamin D from foods		
1	118	1.00 (Referent)
2	120	0.98 (0.76, 1.27)
3	120	0.91 (0.70, 1.18)
4	102	0.81 (0.62, 1.06)
5	121	1.03 (0.79, 1.33)
P_{trend}[b]		0.80

Abbreviations: CI, Confidence Interval; MV, multivariable; HR, hazard ratio.

[a]Multivariable model was adjusted for BMI at age 18 (<19.0, 19.0-20.4, 20.5-21.9, 22.0-24.9, 25.0-29.9, ≥30 kg/m^2), age at menarche (<10, 10, 11, 12, 13, 14, 15, or ≥16 years), adolescent physical activity (<21, 21-35.9, 36-53.9, 54-

80.9, ≥81 MET hours/week), smoking in adolescence (no, yes), adolescent hormonal contraceptive use (no, yes), and energy intake (kcal/day; continuous).
[b]Determined using category median values.



Supplemental Table 1. Multivariable adjusted hazard ratios and 95% CIs for laparoscopically confirmed endometriosis according to adolescent dairy intake among 40,874 women in the Nurses' Health Study II, 1989-2013, overall and by fertility status

Type of Dairy Food and No. of Servings	All women (n=2412)			Never Infertile (n=1744)[a]			Concurrent Infertility (n=549)[a]			$P_{heterogeneity}$[b]
	No. of Cases	MV HR[c]	95% CI	No. of Cases	MV HR[c]	95% CI	No. of Cases	MV HR[c]	95% CI	
Total dairy foods										
<1/day	186	1.00	Referent	144	1.00	Referent	30	1.00	Referent	0.06
1/day	505	0.94	0.80, 1.12	357	0.87	0.71, 1.06	118	1.36	0.90, 2.03	
2/day	470	0.89	0.74, 1.05	345	0.84	0.69, 1.03	105	1.24	0.81, 1.87	
3/day	483	0.77	0.65, 0.92	343	0.70	0.57, 0.86	121	1.25	0.83, 1.90	
≥4/day	768	0.81	0.68, 0.97	555	0.74	0.61, 0.91	175	1.28	0.85, 1.95	
P_{trend}[d]			0.002			0.001			0.75	
High-fat dairy foods										
≤1/day	642	1.00	Referent	461	1.00	Referent	151	1.00	Referent	0.79
2/day	676	0.96	0.85, 1.07	471	0.93	0.81, 1.06	171	1.04	0.83, 1.30	
3/day	381	1.00	0.87, 1.14	277	0.99	0.84, 1.15	85	1.00	0.76, 1.32	
4/day	319	0.78	0.68, 0.90	242	0.78	0.67, 0.92	64	0.76	0.56, 1.03	
>4/day	394	0.83	0.72, 0.95	293	0.81	0.69, 0.95	78	0.83	0.61, 1.12	
P_{trend}[d]			0.0008			0.003			0.06	
Low-fat dairy foods										
>1/week	282	1.00	Referent	216	1.00	Referent	56	1.00	Referent	0.68
1/week	649	0.97	0.85, 1.12	483	0.96	0.81, 1.13	130	0.98	0.71, 1.34	
2-6/week	688	1.03	0.89, 1.19	507	1.01	0.86, 1.19	141	1.05	0.76, 1.43	
1-2/day	408	0.99	0.85, 1.16	276	0.93	0.78, 1.12	111	1.19	0.85, 1.65	
>2/day	385	0.96	0.82, 1.13	262	0.92	0.76, 1.10	111	1.22	0.87, 1.70	
P_{trend}[d]			0.45			0.39			0.32	

Abbreviations: CI, Confidence Interval; MV, multivariable; HR, hazard ratio.

[a]Infertility is defined as attempting to become pregnant for >1 year without success. Cases who are classified as 'never infertile' are women who never reported infertility. Cases with 'concurrent infertility' are women who reported an infertility evaluation in the same follow-up cycle as laparoscopic-confirmation of endometriosis.

[b]Test for heterogeneity comparing the effect of dietary consumption among women with no past or current infertility to those with concurrent infertility.

[c]Multivariable model was adjusted for BMI at age 18 (<19.0, 19.0-20.4, 20.5-21.9, 22.0-24.9, 25.0-29.9, ≥30 kg/m^2), age at menarche (<10, 10, 11, 12, 13, 14, 15, or ≥16 years), adolescent physical activity (<21, 21-35.9, 36-53.9, 54-80.9, ≥81 MET hours/week), smoking in adolescence (no, yes), adolescent hormonal contraceptive use (no, yes), and energy intake (kcal/day; continuous).

[d]Determined using category median values.

Supplemental Table 2. Multivariable adjusted hazard ratios and 95% CIs for laparoscopically confirmed endometriosis according to adolescent intake of specific dairy foods among 40,874 women in the Nurses' Health Study II, 1989-2013, overall and by fertility status

Dairy Food and No. of Servings	All women (n=2412)			Never Infertile (n=1744)[a]			Concurrent Infertility (n=549)[a]			$P_{heterogeneity}$[b]
	No. of Cases	MV HR[c]	95% CI	No. of Cases	MV HR[c]	95% CI	No. of Cases	MV HR[c]	95% CI	
Total milk										
<1/day	679	1.00	Referent	482	1.00	Referent	152	1.00	Referent	0.46
1/day	376	0.81	0.71, 0.92	269	0.82	0.71, 0.96	91	0.85	0.65, 1.11	
2/day	379	0.88	0.78, 1.00	271	0.90	0.77, 1.04	88	0.90	0.68, 1.17	
3/day	757	0.80	0.71, 0.89	548	0.80	0.71, 0.91	180	0.88	0.70, 1.10	
≥4/day	221	0.90	0.76, 1.05	174	0.97	0.80, 1.16	38	0.75	0.52, 1.09	
P_{trend}[d]			0.02			0.20			0.19	
Whole Milk										
<1/month	1050	1.00	Referent	726	1.00	Referent	276	1.00	Referent	0.40
1/month-6/week	318	1.08	0.92, 1.27	223	1.02	0.85, 1.23	74	1.22	0.87, 1.71	
1-2/day	476	0.86	0.74, 0.99	352	0.86	0.73, 1.02	99	0.85	0.62, 1.17	
>2/day	568	0.80	0.69, 0.92	443	0.82	0.69, 0.97	100	0.73	0.53, 1.01	
P_{trend}[d]			0.0003			0.01			0.01	
Reduced fat/Skim Milk										
<1/month	1675	1.00	Referent	1246	1.00	Referent	341	1.00	Referent	0.16
1/month-6/week	146	0.98	0.80, 1.19	98	0.94	0.74, 1.20	39	1.07	0.71, 1.59	
1-2/day	241	0.86	0.73, 1.02	164	0.86	0.70, 1.05	66	0.94	0.68, 1.33	
>2/day	350	0.87	0.74, 1.01	236	0.84	0.69, 1.01	103	1.09	0.79, 1.49	
P_{trend}[d]			0.01			0.03			0.98	
Butter										
<1/month	1085	1.00	Referent	789	1.00	Referent	248	1.00	Referent	0.24
1/month-6/week	672	0.97	0.87, 1.06	489	0.97	0.87, 1.09	149	0.94	0.77, 1.16	
1-2/day	406	1.01	0.90, 1.14	285	0.96	0.83, 1.10	104	1.23	0.97, 1.55	
>2/day	249	0.92	0.80, 1.07	181	0.87	0.73, 1.03	48	0.97	0.70, 1.33	
P_{trend}[d]			0.47			0.11			0.53	
Cheese										
<5/week	591	1.00	Referent	447	1.00	Referent	119	1.00	Referent	0.13
5-6/week	896	1.08	0.97, 1.20	655	1.06	0.93, 1.19	189	1.10	0.87, 1.39	
1/day	499	1.07	0.94, 1.21	358	1.05	0.91, 1.21	120	1.18	0.90, 1.54	
≥2/day	426	1.07	0.93, 1.22	284	0.98	0.83, 1.15	121	1.35	1.02, 1.79	
P_{trend}[d]			0.59			0.66			0.04	
Yogurt										
<1/week	1785	1.00	Referent	1335	1.00	Referent	371	1.00	Referent	0.02
1/week	447	0.81	0.73, 0.90	299	0.78	0.69, 0.89	118	0.81	0.65, 1.00	
≥2/week	180	0.78	0.67, 0.91	110	0.70	0.57, 0.85	60	0.98	0.74, 1.30	
P_{trend}[d]			0.001			0.0001			0.92	
Ice Cream										
<1/week	156	1.00	Referent	120	1.00	Referent	27	1.00	Referent	0.11
1/week	1382	0.88	0.75, 1.05	1016	0.83	0.69, 1.01	308	1.17	0.79, 1.75	
2-6/week	687	0.88	0.73, 1.05	479	0.77	0.63, 0.95	173	1.36	0.89, 2.07	
≥1/day	187	0.70	0.56, 0.88	129	0.62	0.48, 0.81	41	0.91	0.55, 1.51	
P_{trend}[d]			0.007			0.0006			0.82	

Abbreviations: CI, Confidence Interval; MV, multivariable; HR, hazard ratio.

[a]Infertility is defined as attempting to become pregnant for >1 year without success. Cases who are classified as 'never infertile' are women who never reported infertility. Cases with 'concurrent infertility' are women who reported an infertility evaluation in the same follow-up cycle as laparoscopic-confirmation of endometriosis.

[b]Test for heterogeneity comparing the effect of dietary consumption among women with no past or current infertility to those with concurrent infertility.
[c]Multivariable model was adjusted for BMI at age 18 (<19.0, 19.0-20.4, 20.5-21.9, 22.0-24.9, 25.0-29.9, ≥30 kg/m^2), age at menarche (<10, 10, 11, 12, 13, 14, 15, or ≥16 years), adolescent physical activity (<21, 21-35.9, 36-53.9, 54-80.9, ≥81 MET hours/week), smoking in adolescence (no, yes), adolescent hormonal contraceptive use (no, yes), and energy intake (kcal/day; continuous). In addition, all foods/food groups are mutually adjusted for each other.
[d]Determined using category median values.

Supplemental Table 3. Multivariable adjusted hazard ratios and 95% CIs for laparoscopically confirmed endometriosis according to adolescent nutrient intake among 40,874 women in the Nurses' Health Study II, 1989-2013, overall and by fertility status

Nutrient and Quintile of Intake	All women (n=2412)[a]			Never Infertile (n=1744)[a]			Concurrent Infertility (n=549)[a]			$P_{heterogeneity}$[b]
	No. of Cases	MV HR[c]	95% CI	No. of Cases	MV HR[c]	95% CI	No. of Cases	MV HR[c]	95% CI	
Calcium										
1	504	1.00	Referent	373	1.00	Referent	100	1.00	Referent	0.63
2	508	0.95	0.84, 1.08	362	0.93	0.81, 1.08	113	1.01	0.77, 1.33	
3	475	0.86	0.76, 0.98	335	0.84	0.72, 0.97	123	1.07	0.82, 1.39	
4	474	0.85	0.75, 0.96	346	0.85	0.73, 0.98	108	0.96	0.73, 1.26	
5	451	0.81	0.71, 0.92	328	0.81	0.70, 0.94	105	0.91	0.69, 1.21	
P_{trend}[d]			0.0004			0.004			0.39	
Dairy Calcium										
1	536	1.00	Referent	387	1.00	Referent	113	1.00	Referent	0.64
2	500	0.91	0.80, 1.03	361	0.91	0.79, 1.05	114	0.98	0.75, 1.28	
3	459	0.82	0.73, 0.93	323	0.80	0.69, 0.93	113	0.98	0.75, 1.27	
4	482	0.85	0.75, 0.96	348	0.84	0.72, 0.97	116	1.00	0.77, 1.30	
5	435	0.79	0.69, 0.89	325	0.80	0.69, 0.93	93	0.83	0.62, 1.09	
P_{trend}[d]			0.0002			0.004			0.22	
Non-dairy calcium										
1	393	1.00	Referent	316	1.00	Referent	62	1.00	Referent	0.52
2	449	1.02	0.89, 1.17	333	0.96	0.82, 1.13	95	1.26	0.91, 1.74	
3	487	1.05	0.92, 1.21	345	0.98	0.83, 1.14	114	1.33	0.97, 1.83	
4	521	1.04	0.90, 1.19	367	0.99	0.85, 1.16	130	1.26	0.92, 1.73	
5	562	1.03	0.89, 1.18	383	0.99	0.84, 1.16	148	1.20	0.87, 1.65	
P_{trend}[d]			0.75			0.98			0.58	
Vitamin D										
1	514	1.00	Referent	366	1.00	Referent	118	1.00	Referent	0.92
2	481	0.92	0.81, 1.04	355	0.96	0.83, 1.11	108	0.87	0.67, 1.13	
3	463	0.87	0.76, 0.98	335	0.88	0.75, 1.02	106	0.88	0.68, 1.15	
4	448	0.86	0.75, 0.97	327	0.87	0.75, 1.01	100	0.84	0.64, 1.10	
5	506	0.96	0.85, 1.09	361	0.98	0.84, 1.13	117	0.95	0.73, 1.23	
P_{trend}[d]			0.61			0.64			0.83	
Dairy Vitamin D										
1	527	1.00	Referent	369	1.00	Referent	124	1.00	Referent	0.60
2	524	1.00	0.88, 1.13	378	1.01	0.88, 1.17	115	0.97	0.75, 1.26	
3	464	0.91	0.80, 1.03	337	0.92	0.79, 1.07	105	0.93	0.71, 1.21	
4	465	0.88	0.77, 1.00	332	0.87	0.75, 1.01	116	1.02	0.79, 1.32	
5	432	0.87	0.76, 0.99	328	0.91	0.78, 1.06	89	0.83	0.63, 1.10	
P_{trend}[d]			0.006			0.06			0.30	
Vitamin D from foods										
1	538	1.00	Referent	380	1.00	Referent	124	1.00	Referent	0.80
2	473	0.86	0.76, 0.98	350	0.91	0.78, 1.05	105	0.82	0.63, 1.06	
3	498	0.89	0.79, 1.01	348	0.89	0.76, 1.03	118	0.91	0.71, 1.18	
4	444	0.80	0.71, 0.91	324	0.82	0.71, 0.96	102	0.82	0.63, 1.07	
5	459	0.86	0.76, 0.98	342	0.91	0.78, 1.06	100	0.81	0.62, 1.06	
P_{trend}[d]			0.02			0.14			0.17	

Abbreviations: CI, Confidence Interval; MV, multivariable; HR, hazard ratio.

[a]Infertility is defined as attempting to become pregnant for >1 year without success. Cases who are classified as 'never infertile' are women who never reported infertility. Cases with 'concurrent infertility' are women who reported an infertility evaluation in the same follow-up cycle as laparoscopic-confirmation of endometriosis.

[b]Test for heterogeneity comparing the effect of dietary consumption among women with no past or current infertility to those with concurrent infertility.

[c]Multivariable model was adjusted for BMI at age 18 (<19.0, 19.0-20.4, 20.5-21.9, 22.0-24.9, 25.0-29.9, ≥30 kg/m^2), age at menarche (<10, 10, 11, 12, 13, 14, 15, or ≥16 years), adolescent physical activity (<21, 21-35.9, 36-53.9, 54-80.9, ≥81 MET hours/week), smoking in adolescence (no, yes), adolescent hormonal contraceptive use (no, yes), and energy intake (kcal/day; continuous).

[d]Determined using category median values.