

Diet and risk of endometriosis in a population-based case–control study

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Abstract

Diet plausibly has a role in the aetiology of endometriosis through effects on steroid hormone levels; however, few published studies have examined the diet and endometriosis risk. We evaluated dietary risk factors for endometriosis in a population-based case–control study. Cases were 284 Group Health (GH) enrollees aged 18–49 years with newly diagnosed, surgically confirmed endometriosis between 1996 and 2001. Controls were 660 randomly selected age-matched female GH enrollees without a history of endometriosis. Nutrients and selected food groups were assessed using the Women's Health Initiative FFQ. OR of endometriosis risk associated with dietary exposures were estimated using unconditional logistic regression and adjusted for identified covariates. Increased total fat consumption was associated with decreased endometriosis risk (fourth quartile *v.* lowest: OR 0.5, 95% CI 0.2, 1.0, *P*-trend=0.12). Increased β -carotene consumption and servings/d of fruit were associated with increased risk (β -carotene third quartile *v.* lowest: OR 1.7, 95% CI 1.1, 2.6; fourth quartile *v.* lowest: OR 1.6, 95% CI 1.0, 2.5, *P*-trend 0.16; fruit > 2 servings/d *v.* < 1: OR 1.5, 95% CI 1.0, 2.3, *P*-trend=0.04). We also found a suggestion of decreased endometriosis risk associated with the consumption of dairy products (2 servings/d *v.* \leq 1: OR 0.6, > 2 servings/d *v.* \leq 1: OR 0.7), but this association was not statistically significant for the highest tertile. The present study suggests that specific dietary components may be associated with endometriosis risk.

Key words: Case–control studies: Population-based studies: Diet: Endometriosis

Endometriosis is a gynaecological disorder characterised by the presence of functioning endometrial glands and stroma outside the uterus. The best population-based estimates of prevalence suggest that endometriosis affects 8–10% of reproductive-aged women in the United States⁽¹⁾. Symptoms associated with endometriosis include severe menstrual pain, excessive menstrual bleeding, chronic and severe pelvic pain, dyspareunia and subfertility.

Increased exposure to oestrogens is a common link among several known risk factors for endometriosis. Local oestrogen production coupled with circulating oestrogen stimulates the proliferation of ectopic endometrial tissue potentially leading to endometriosis^(2,3). Menarche at early age, shorter menstrual cycle length, nulliparity and greater height are all risk factors for endometriosis that are also associated with increased levels of circulating oestrogen concentrations^(4–8).

The relationship between diet and endometriosis risk is not well characterised. Diet may have a role in the

aetiology of endometriosis through its influence on steroid hormone levels, among other potential mechanisms. Some observational studies have shown that plant-based diets and diets high in fibre increase oestrogen excretion and decrease concentrations of bioavailable oestrogen, and thus may lower endometriosis risk^(9,10). Additionally, high-fat diets have been associated with increased serum oestrone, oestrone sulphate and oestradiol levels in premenopausal women^(9,11), suggesting that diets low in fat and high in fibre may modify endometriosis risk by altering steroid hormone metabolism.

The few published reports evaluating dietary risk factors for endometriosis have been somewhat contradictory. In the first of two case–control studies of endometriosis and specific foods published to date, increased consumption of ham, beef and red meat was associated with increased endometriosis risk in women visiting gynaecology clinics in northern Italy⁽¹²⁾. Conversely, in that study, green vegetable, fresh fruit and oil were all associated with

Abbreviation: GH, Group Health.

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decreased risk⁽¹²⁾. In the second study, a Belgian clinic-based case–control study, butter was marginally associated with an increased risk of peritoneal endometriosis⁽¹³⁾. Recently, a large US cohort study evaluated dietary fat consumption and endometriosis risk using 12 years of prospectively collected data⁽¹⁴⁾. The authors of that study reported that total dietary fat intake was not associated with endometriosis risk, but increased long-chain *n*-3 fatty acid consumption was associated with decreased risk of endometriosis and *trans*-fat intake was associated with increased risk of endometriosis⁽¹⁴⁾. The purpose of this analysis was to further investigate the role of diet – assessing both nutrients and a wide variety of food groups – as a risk factor for endometriosis in a population-based case–control study of US women.

Materials and methods

Study population

The present study was conducted within the Women's Risk of Endometriosis study, the details of which have been described elsewhere⁽¹⁵⁾. In brief, Women's Risk of Endometriosis was a population-based case–control study of reproductive-age, premenopausal women enrolled in Group Health (GH) Cooperative, a large mixed-model healthcare organisation in Washington State. The cases were 18–49-year-old female GH enrollees with an incident endometriosis diagnosis (International Classification of Disease 9th Revision diagnostic codes 617.0–617.5, 617.8 and 617.9; individuals with International Classification of Disease 9th Revision code 617.0, uterine endometriosis, who did not meet the disease definition of endometriosis were excluded) between 1 April 1996 and 31 March 2001. Inpatient and outpatient medical record reviews confirmed the cases' lesion characteristics and diagnostic treatment details and provided their reference date (the date of the first GH visit for symptoms leading to the endometriosis diagnosis). Population-based controls were randomly selected from 18–49-year-old GH female enrollees without an endometriosis diagnosis during the study period; they were frequency matched on 5-year age intervals and assigned a reference date to correspond with the distribution of cases' reference dates. Women who did not speak English or who reported a hysterectomy or bilateral oophorectomy upon initial telephone eligibility screening were excluded from the participation. The present study was conducted according to the guidelines established in the Declaration of Helsinki, and all procedures involving human subjects were approved by the GH Institutional Review Board. A written informed consent was obtained from all the subjects. All the participants were interviewed using a structured questionnaire with questions regarding demographics, employment, prior medical conditions, menstrual history, pregnancy history, contraceptive methods, hormone use, tobacco and alcohol use, and

family and personal history of endometriosis. A total of 340 cases (73% of those eligible) and 741 controls (73% of those eligible) completed the interview on endometriosis risk factors. As a result of information captured on the interview, twelve cases and fourteen controls with a self-reported history of surgically confirmed endometriosis who were interviewed were excluded. While International Classification of Disease 9th Revision codes denoting any amount of endometriosis were the basis for initial case group selection, for the analyses presented here, we utilised a published case definition that emphasised definite or probable endometriotic disease, that is, endometriosis causing structural or functional damage or substantial symptoms⁽¹⁶⁾. As defined by Holt & Weiss⁽¹⁶⁾, 'definite endometriotic disease' included ovarian endometriomas, pelvic endometriotic lesions over 5 mm deep and pelvic endometriotic lesions with adhesions not attributable to other causes. 'Probable endometriotic disease' included other endometriotic implants with at least one major endometriosis symptom (infertility, moderate or severe dysmenorrhoeal, dyspareunia or pelvic pain)⁽¹⁶⁾. As a result, cases without surgical evidence of disease and asymptomatic cases with superficial or ambiguous pelvic lesions were excluded (*n* 12), as were three cases of extrapelvic scar endometriosis. After these exclusions, 313 cases and 727 controls remained.

Cases (93%, *n* 291) and controls (93.1%, *n* 677) who participated in the main study interview and satisfied the case and control definitions outlined above also completed a self-administered Women's Health Initiative FFQ about their usual diet during the year preceding the interview⁽¹⁷⁾. Using the FFQ, participants classified their consumption of specific food items into predefined frequency categories, ranging from never or less than once a month to two or more times a day, with corresponding serving size categories (small, medium and large). Summary questions were asked about usual overall intake of fruits and vegetables⁽¹⁸⁾. As a supplement to the Women's Health Initiative FFQ, women were asked to complete a brief questionnaire (thirty-five line-items and one summary question) about their usual frequency of fish and shellfish consumption.

Average daily intakes for twenty-seven nutrients were calculated from the FFQ using the University of Minnesota Nutrient Data System for Research database of food composition (Minneapolis, MN, USA)⁽¹⁹⁾. Questions related to food purchasing and preparation (e.g. fat added at table and while cooking) were used to adjust the calculations of nutrient content in specific line items. Vitamin and mineral intakes were determined from dietary sources as well as from dietary combined with supplementation sources. The latter showed associations with endometriosis similar to the former; therefore, we present findings for vitamins and minerals based on only dietary sources.

Selected food groups were created by calculating average daily intake for each line item of the FFQ

using predefined frequency and portion categories and summing across line items to create the following categories: dairy, vegetable, fruit (excluding fruit juice), whole grains, legumes, red meat, poultry, fatty fish, non-fatty fish and seafood.

Approximately, 2.4% of cases (7/291) and 2.7% of controls (17/677) were excluded because their reported total energy intake was <2092 or >20920 kJ; 284 cases and 660 controls were used for the present analyses.

Statistical analysis

Unconditional logistic regression models, using the standard multivariate method to control for energy consumption⁽²⁰⁾, were used to estimate OR and 95% CI for the association between dietary factors and endometriosis, separately for nutrients and for food groups. Nutrient variables were included in the models as categorical variables, using quartiles based on the controls' distribution. To assess the linear trend in the log odds of nutrient quartile, the median value for each quartile was entered into the logistic regression model as an ordinal variable. Food group variables were included as servings/d or servings/week. To assess the linear trend in the log odds of food group serving, the ordinal variable was entered into the logistic regression model.

All the analyses were adjusted for matching variables age-group and reference year, total energy intake as a continuous variable and confounding factors such as income, BMI, smoking status and alcohol consumption. BMI was included as an *a priori* confounding factor because of its known associations with dietary patterns and endometriosis^(5,21). Other covariates considered in the models included race, education, first-degree family history of endometriosis, physical activity, age at menarche, parity, history of breastfeeding and marijuana use. The addition of these covariates to a model controlling for age, reference year and BMI did not result in a 10% change in the β coefficient of at least one quartile of total dietary fat, thus they were not included in the statistical analyses presented.

Endometriosis, as defined in the present study, included ovarian and non-ovarian cases and may be considered a heterogeneous disease entity. Therefore, in one subanalysis, we evaluated the association between dietary factors and ovarian and non-ovarian pelvic endometriosis separately. Since women who seek treatment for infertility may have endometriosis discovered incidentally as part of the diagnostic process, rather than because of symptomatic disease, we also considered separately the cases who reported seeking care only for reasons other than infertility. Finally, because of the possibility that there may be undiagnosed symptomatic cases in our population-based control group, we also conducted a subanalysis comparing endometriosis cases only with asymptomatic controls.

Results

The distributions of selected demographic and health characteristics for women who completed a dietary questionnaire are provided in Table 1. Cases and controls were similar with regard to age and race. A higher percentage of controls than cases reported household incomes of greater than \$70 000, while a higher percentage of cases than controls smoked and drank alcohol.

Cases consumed slightly less energy than controls and had lower median intakes of total fat, cholesterol and Ca (Table 2). In multivariable adjusted analyses, increased total fat consumption was associated with a decreased endometriosis risk (fourth quartile *v.* lowest: OR 0.5, 95% CI 0.2, 1.0, *P*-trend 0.12) (Table 3). We observed similar inverse associations with endometriosis risk for saturated-, monounsaturated- and *trans*-fat intake.

Table 1. Demographic and health characteristics of the study population stratified by case-control status* (Number and percentage values)

Characteristics	Cases (n 284)		Controls (n 660)	
	n†	%	n†	%
Age (years)				
18–24	23	8.1	58	8.8
25–34	55	19.4	125	18.9
35–44	138	48.6	329	49.9
45–49	68	23.9	148	22.4
Race				
Caucasian	230	81.0	547	82.9
African American	9	3.2	29	4.4
Asian American	19	6.7	41	6.2
Other	25	8.8	41	6.2
Income (\$)				
< 35 000	83	29.2	180	27.3
35 000–49 999	60	21.1	145	22.0
50 000–69 999	71	25.0	134	20.3
70 000 +	60	21.2	183	27.8
Education (years)				
< 12	6	2.1	21	3.2
12	47	16.6	119	18.0
> 12	231	81.3	520	78.8
BMI (kg/m ²)				
Underweight (<18.5)	7	2.5	13	2.0
Normal (18.5–24.9)	144	50.7	345	52.3
Overweight (25–29.9)	72	25.4	164	24.9
Obese (>30)	60	21.1	133	20.2
Smoking				
Present	55	19.4	103	15.6
Former	66	23.2	162	24.6
Never	163	57.4	395	59.9
Alcohol use				
Present	154	54.2	292	44.2
Former	51	18.0	140	21.2
Never	78	27.5	228	34.6
Parity (any live births)				
Parous	148	52.1	467	70.8
Nulliparous	136	47.9	192	29.1
History of infertility				
Yes	66	23.2	86	13.0
No	218	76.8	574	87.0

* Restricted to participants who reported consuming between 2092 and 20 920 kJ/d.
† Cell counts may not sum to column total because of missing data.

Table 2. Median daily intake of nutrients stratified by case and control status

Nutrients	Cases (<i>n</i> 284)	Controls (<i>n</i> 660)
Total energy (kJ)	6237.50	6378.93
Protein (g)	64.4	65.2
Animal protein (g)	45.4	45.2
Vegetable protein (g)	17.7	18.9
Carbohydrates (g)	178.8	186.0
Total fat (g)	54.8	58.3
Saturated fat (g)	19.2	21.1
Monounsaturated fat (g)	20.3	21.7
Polyunsaturated fat (g)	11.1	11.2
<i>Trans</i> -fat (g)	3.2	3.4
Cholesterol (mg)	190.9	197.6
<i>n</i> -3 Fatty acids (g)	1.2	1.2
<i>n</i> -6 Fatty acids (g)	9.8	9.9
Fibre (g)	13.9	14.7
Total folate (μg)	311.0	316.8
β-Carotene (μg)	1941.2	1878.5
Vitamin A – retinol (μg)	366.1	359.4
Vitamin C (mg)	69.2	66.8
Vitamin D (μg)	3.7	3.7
Vitamin E (mg)	6.7	7.1
Vitamin B ₆ (mg)	1.4	1.4
Vitamin B ₁₂ (μg)	5.4	5.0
Thiamin (mg)	1.2	1.2
Riboflavin (mg)	1.8	1.8
Niacin (mg)	15.9	15.7
Ca (mg)	754.4	796.2
Fe (mg)	10.6	10.9

We further evaluated the dietary fat association using adjustment questions from the Women's Health Initiative FFQ and found that women who reported primarily using butter, shortening or margarine while cooking and at the table were also at a decreased risk of endometriosis (butter, shortening or margarine for cooking *v.* no-fat added while cooking: OR 0.4, 95% CI 0.2, 0.8; butter, shortening or margarine *v.* no-fat added at the table: OR 0.5, 95% CI 0.2, 1.0). Increased β-carotene consumption was associated with increased endometriosis risk (third quartile *v.* lowest: OR 1.7, 95% CI 1.1, 2.6; fourth quartile *v.* lowest: OR 1.6, 95% CI 1.0, 2.5, *P*-trend 0.16). Other macronutrients and micronutrients were not significantly associated with endometriosis risk.

We also evaluated daily or weekly servings of selected food groups as predictors of endometriosis risk (Table 4). Increased number of servings/d of fruit was associated with increased disease risk (>1–2 servings/d *v.* ≤1: OR 1.1, 95% CI 0.8, 1.6; >2 servings/d *v.* ≤1: OR 1.5, 95% CI 1.0, 2.3, *P*-trend 0.04). Analyses exploring the effect of specific types of fruit did not identify any one type that primarily accounted for the increased endometriosis risk. We also found a suggestion of decreased endometriosis risk associated with consumption of dairy products (2 servings/d *v.* ≤1: OR 0.6; >2 servings/d *v.* ≤1: OR 0.7), but this association was not statistically significant for the highest tertile. We did not observe significant associations with endometriosis risk for the other food groups evaluated.

Restricting analyses to cases with ovarian endometriosis only, the individual quartile associations between

endometriosis and the following dietary components, dietary fat, β-carotene, dairy and fruit, did not diminish (results not shown). Compared with the results in Tables 3 and 4, the OR did not substantially change in analyses restricted to asymptomatic controls, suggesting that the presence of undiagnosed symptomatic cases in our control group was unlikely to have affected the present study (results not shown).

Discussion

Within the Women's Risk of Endometriosis study population, we observed decreased endometriosis risk with increased intakes of total fat and dairy. Our findings also suggested that higher intake of β-carotene and fruit were associated with an increased risk of endometriosis. Our data were not supportive of a relationship between endometriosis and any of the other nutrients or food groups examined.

Previous case–control studies exploring diet and risk of endometriosis were limited and have yielded inconsistent results. One report combined data from two case–control studies of endometriosis in northern Italy⁽¹²⁾. Cases (*n* 504) were women with laparoscopically confirmed endometriosis selected from obstetric and gynaecology clinics and controls (*n* 504) were women admitted to the same clinics for acute non-gynaecological, non-hormonal, non-neoplastic conditions. Dietary assessment was via interview; women were asked to report the number of portions/week of selected food items (major sources of retinoids and carotenoids in the Italian diet, alcohol and coffee consumption) in the year before the interview. Fat intake and consumption of whole grain foods were estimated by respondents as low, intermediate or high in quantity.

The second was a clinic-based case–control study of risk factors for endometriosis in Belgium⁽¹³⁾. Cases were eighty-eight women diagnosed with peritoneal endometriosis and hospitalised for surgical treatment between January 2001 and December 2003; eighty-eight matched controls were recruited during the same time period from the same gynaecologists who referred the cases and had no clinical suspicion of peritoneal endometriosis. Consumption of selected foods was assessed with an FFQ; however, results of the present study were based on crude consumption frequencies, and nutrient consumption based on the FFQ was not reported.

The differences between the two case–control studies and our population-based study in subject selection criteria, dietary assessment and type of analysis (selected food groups *v.* nutrients) are substantial and limit our ability to compare the results. Both of the previous case–control studies reported components of dietary fat (butter, margarine and/or oil) rather than total fat based on nutrient values from an FFQ as in the present study. The Italian study reported a decreased risk of

Table 3. Endometriosis and dietary nutrients among 284 cases and 660 controls
(Odds ratios and 95 % confidence intervals)

	Reference	Quartile 2		Quartile 3		Quartile 4		<i>P</i> -trend
		OR	95 % CI	OR	95 % CI	OR	95 % CI	
Protein								
Median (g)	37.78	55.68		72.86		102.89		
Case/control	76/161	73/168		61/161		74/170		
Multivariable adjusted*	1.0	1.0	0.6, 1.7	0.9	0.5, 1.7	1.2	0.6, 2.6	0.54
Protein (animal)								
Median (g)	22.3	37.93		52.28		75.58		
Case/control	76/164	65/165		76/172		67/159		
Multivariable adjusted*	1.0	0.8	0.5, 1.3	1.1	0.7, 1.8	1.1	0.6, 2.0	0.61
Protein (vegetable)								
Median (g)	10.81	16.56		21.46		33.21		
Case/control	84/173	76/159		63/164		61/164		
Multivariable adjusted*	1.0	1.0	0.7, 1.6	0.8	0.5, 1.3	0.8	0.4, 1.5	0.40
Carbohydrate								
Median (g)	104.70	160.42		209.44		296.90		
Case/control	72/165	82/165		62/165		68/165		
Multivariable adjusted*	1.0	1.3	0.8, 2.2	1.1	0.6, 2.0	1.3	0.6, 2.9	0.70
Fat								
Median (g)	31.78	49.44		67.74		100.17		
Case/control	90/166	66/159		63/167		65/168		
Multivariable adjusted*	1.0	0.6†	0.4, 1.0	0.6†	0.3, 1.0	0.5	0.2, 1.0	0.12
Saturated fat								
Median (g)	7.85	15.40		24.53		37.39		
Case/control	34/64	123/265		66/168		61/163		
Multivariable adjusted*	1.0	0.7	0.4, 1.1	0.5	0.3, 1.1	0.5	0.2, 1.1	0.13
Monounsaturated fat								
Median (g)	11.32	18.38		25.75		38.39		
Case/control	82/149	76/184		56/154		70/173		
Multivariable adjusted*	1.0	0.7	0.4, 1.0	0.5†	0.3, 0.9	0.6	0.3, 1.2	0.25
Polyunsaturated fat								
Median (g)	6.05	9.40		13.25		20.48		
Case/control	81/176	59/145		84/180		60/159		
Multivariable adjusted*	1.0	0.9	0.6, 1.4	1.0	0.6, 1.6	0.8	0.4, 1.6	0.65
Trans-fat								
Median (g)	1.60	2.70		4.16		7.39		
Case/control	95/171	55/155		73/169		61/165		
Multivariable adjusted*	1.0	0.6†	0.4, 1.0	0.7	0.4, 1.1	0.6	0.3, 1.1	0.22
Cholesterol								
Median (mg)	103.16	171.55		237.53		383.71		
Case/control	81/163	67/168		73/164		63/165		
Multivariable adjusted*	1.0	0.8	0.5, 1.2	0.9	0.5, 1.4	0.7	0.4, 1.2	0.33
<i>n</i>-3 Fatty acids								
Median (g)	0.68	1.05		1.42		2.11		
Case/control	81/187	62/124		80/183		61/166		
Multivariable adjusted*	1.0	1.1	0.7, 1.7	0.9	0.6, 1.5	0.7	0.4, 1.4	0.24
<i>n</i>-6 Fatty acids								
Median (g)	5.27	8.29		11.77		17.94		
Case/control	76/177	69/155		73/161		66/167		
Multivariable adjusted*	1.0	1.1	0.7, 1.7	1.1	0.6, 1.8	1.0	0.5, 2.0	0.99
Fibre								
Median (g)	8.03	12.48		16.82		24.26		
Case/control	82/161	74/169		55/167		73/163		
Multivariable adjusted*	1.0	0.9	0.6, 1.4	0.8	0.5, 1.2	1.0	0.6, 1.8	0.86
Folate								
Median (µg)	184.04	278.74		356.82		522.30		
Case/control	85/165	61/165		68/164		70/166		
Multivariable adjusted*	1.0	0.7	0.5, 1.2	0.8	0.5, 1.4	0.9	0.5, 1.5	0.87
β-Carotene								
Median (µg)	767.57	1473.65		2458.47		4804.61		
Case/control	60/163	75/166		79/166		70/165		
Multivariable adjusted*	1.0	1.4	0.9, 2.2	1.7†	1.1, 2.6	1.6	1.0, 2.5	0.16
Vitamin A								
Median (µg)	160.20	291.31		435.24		710.76		
Case/control	77/165	61/165		77/165		69/165		
Multivariable adjusted*	1.0	0.7	0.5, 1.2	1.1	0.7, 1.7	1.0	0.6, 1.7	0.67
Vitamin C								
Median (mg)	25.83	51.22		86.45		138.66		
Case/control	72/168	68/164		73/162		71/166		
Multivariable adjusted*	1.0	1.1	0.7, 1.7	1.3	0.8, 1.9	1.2	0.7, 1.8	0.53

Table 3. Continued

	Reference	Quartile 2		Quartile 3		Quartile 4		P-trend
		OR	95% CI	OR	95% CI	OR	95% CI	
Vitamin D								
Median (μg)	1.52	2.98		4.61		8.49		
Case/control	81/163	64/164		67/168		72/165		
Multivariable adjusted*	1.0	0.8	0.5, 1.2	0.8	0.5, 1.3	0.9	0.6, 1.5	0.99
Vitamin E								
Median (mg)	3.96	6.00		8.28		12.13		
Case/control	79/163	69/168		62/163		74/166		
Multivariable adjusted*	1.0	0.9	0.6, 1.5	0.8	0.5, 1.3	1.1	0.6, 2.0	0.64
Vitamin B ₆								
Median (mg)	0.83	1.23		1.61		2.27		
Case/control	73/162	68/168		77/162		66/168		
Multivariable adjusted*	1.0	1.0	0.6, 1.5	1.2	0.7, 2.0	1.1	0.6, 2.1	0.66
Vitamin B ₁₂								
Median (μg)	2.66	4.26		5.85		9.10		
Case/control	77/171	51/160		89/164		67/165		
Multivariable adjusted*	1.0	0.8	0.5, 1.2	1.4	0.9, 2.2	1.0	0.6, 1.8	0.53
Thiamin (vitamin B ₁)								
Median (mg)	0.69	1.05		1.36		1.97		
Case/control	70/145	78/175		65/168		71/172		
Multivariable adjusted*	1.0	1.0	0.6, 1.7	0.9	0.5, 1.5	1.0	0.5, 2.0	0.88
Riboflavin (vitamin B ₂)								
Median (mg)	1.03	1.52		2.05		2.90		
Case/control	87/162	59/171		64/146		74/181		
Multivariable adjusted*	1.0	0.6†	0.4, 0.9	0.8	0.5, 1.3	0.7	0.4, 1.3	0.68
Niacin								
Median (mg)	9.56	13.86		17.92		25.72		
Case/control	85/167	55/162		75/165		69/166		
Multivariable adjusted*	1.0	0.7	0.4, 1.1	1.0	0.6, 1.6	1.0	0.5, 1.9	0.72
Ca								
Median (mg)	379.97	647.65		927.15		1451.60		
Case/control	87/165	60/165		75/165		62/165		
Multivariable adjusted*	1.0	0.7	0.4, 1.0	0.8	0.5, 1.3	0.7	0.4, 1.2	0.41
Fe								
Median (mg)	6.26	9.56		12.31		18.08		
Case/control	83/165	64/169		74/160		63/166		
Multivariable adjusted*	1.0	0.7	0.5, 1.2	0.9	0.5, 1.5	0.8	0.4, 1.5	0.64

* Models adjusted for matching factors (age and year of enrolment), total energy, income, BMI, smoking and alcohol consumption.

† P-value for individual quartile <0.05.

endometriosis with 'intermediate' and 'high' servings/week of oil and the Belgian study reported no association of endometriosis risk with margarine and a marginally increased endometriosis risk associated with butter in unadjusted analyses^(12,13). We found a decreased risk of disease with increased total fat consumption and similar associations with saturated-, monounsaturated- and *trans*-fat consumption. Evaluating the type of fat used during cooking and at the table, we report a decreased disease risk with butter, shortening or margarine use.

The only available information on diet and endometriosis in a US population is a recent report from a large prospective cohort study, focussing on dietary fat intake. In that study, using data from the Nurses' Health Study II, 1199 subjects without infertility self-reported a laparoscopically confirmed diagnosis of endometriosis between 1991 and 2001, and their dietary intake was assessed via a 130-item FFQ at three time points during the follow-up. The total fat intake was not associated with endometriosis risk; however, the highest quintile of *trans*-fat intake was associated with an increased risk of endometriosis, while

the highest quintile of long-chain *n*-3 fatty acid was inversely associated with endometriosis risk. The present results are not consistent with those of Missmer *et al.*⁽¹⁴⁾; rather we found a decreased risk of endometriosis with some quartiles of total fat, monounsaturated fat and *trans*-fat consumption using an energy-substitution model. Using the carbohydrate-substitution model similar to Missmer *et al.*⁽¹⁴⁾, the OR for our estimates and corresponding 95% CI did not substantially change (results not shown). Furthermore, the present study used medical records to determine a surgically confirmed diagnosis of definite or probable endometriotic disease, while the Nurses' Health Study relied on self-report of laparoscopically confirmed endometriosis, a case definition that includes a more heterogeneous distribution of disease severity and potentially a number of non-cases. Unlike the present study, the Nurses' Health Study did not have information from cases' medical records and therefore could not evaluate the severity other than stratifying on self-reported fertility status (fertile *v.* infertile). Finally, we evaluated nutrients as well as a wide variety of food groups providing

Table 4. Endometriosis and selected food groups among 284 cases and 660 controls (Odds ratios and 95% confidence intervals)

	OR	OR	95% CI	OR	95% CI	P-trend
Servings/d						
Dairy	≤1	>1–2		>2		
Case/control	84/145	135/352		54/130		
Multivariable adjusted*	1.0	0.6†	0.4, 0.9	0.7	0.4, 1.2	0.13
Vegetables	≤1	>1–3		>3		
Case/control	90/204	154/358		40/98		
Multivariable adjusted*	1.0	1.0	0.7, 1.5	1.0	0.6, 1.7	0.89
Fruit‡	≤1	>1–2		>2		
Case/control	110/297	85/165		89/198		
Multivariable adjusted*	1.0	1.1	0.8, 1.6	1.5†	1.2, 2.3	0.04
Servings/week						
Whole grains	<1	1–4		>4		
Case/control	99/226	97/203		88/222		
Multivariable adjusted*	1.0	1.0	0.7, 1.5	0.8	0.6, 1.2	0.36
Legumes	<1	1–2		>2		
Case/control	149/316	54/141		80/199		
Multivariable adjusted*	1.0	0.9	0.6, 1.3	0.9	0.6, 1.3	0.57
Red meat	≤2	>2–4		>4		
Case/control	102/209	69/185		112/260		
Multivariable adjusted*	1.0	0.7	0.5, 1.1	0.9	0.6, 1.4	0.74
Poultry	≤1	>1–2		>2		
Case/control	138/330	70/165		76/164		
Multivariable adjusted*	1.0	1.1	0.7, 1.5	1.2	0.8, 1.7	0.42
Fatty fish (includes halibut)	≤1	>1–2		>2		
Case/control	89/218	54/109		128/309		
Multivariable adjusted*	1.0	1.1	0.7, 1.7	1.0	0.7, 1.5	0.94
Non-fatty fish	≤1	>1–2		>2		
Case/control	133/277	70/195		65/157		
Multivariable adjusted*	1.0	0.7	0.5, 1.0	0.8	0.5, 1.1	0.11
Seafood	≤0.5	>0.5				
Case/control	149/321	123/318				
Multivariable adjusted*	1.0	0.8	0.6, 1.1			

* Models adjusted for matching factors (age and year of enrolment), total energy, income, BMI, smoking and alcohol consumption.

† P-value for individual quartile <0.05.

‡ Excluding fruit juice.

additional information about food consumption patterns of US women and endometriosis risk.

In our food group analyses, vegetable intake was not associated with endometriosis risk; however, increased disease risk was associated with increased fruit consumption. These findings are not consistent with the reduced risk of endometriosis associated with consumption of both green vegetables and fresh fruit reported by Parazzini *et al.*⁽¹²⁾. Our fruit consumption variable does not differentiate between fresh and canned fruit; however, we did find non-significantly elevated endometriosis risk with individual fresh fruit categories (results not shown). Although speculative, our findings could be related to increased pesticide consumption through fruits. Laboratory analyses have demonstrated that pesticides can remain at detectable levels after harvest and processing, and that pesticide residue is found more commonly in domestic fruits than in imported fruits and more commonly in fruits than in vegetables^(22,23). *In vitro* and *in vivo* studies have shown that certain classes of pesticides may produce oestrogenic effects^(24,25). Further, exposure of rats with induced endometriosis to high doses of a pesticide commonly used on orchard fruits exacerbates the existing endometriotic lesions and contributes to its recurrence⁽²⁶⁾. We also

observed an increased endometriosis risk with increased β -carotene consumption that could be related to the increase that we observed with servings/d of fruit.

Our other food group result of interest was a marginally significant inverse association between dairy intake and endometriosis. While this association has not previously been observed, decreased risk of breast cancer, another hormone-related disease, has been associated with increased dairy consumption⁽²⁷⁾. One hypothesis for the mechanism of this association relates to the ability of Ca and vitamin D to down-regulate growth-promoting factors, such as insulin-like growth factor-I and up-regulate negative growth factor regulators, such as transforming growth factor β . We did not see significantly decreased endometriosis risk associated with increased vitamin D intake; however, we saw a similar association, albeit not statistically significant, with Ca.

Contrary to the data published by Parazzini *et al.*, we did not report an increased risk of endometriosis with increasing servings/week of red meat⁽¹²⁾. Parazzini *et al.* categorised tertiles of red meat consumption as 0–3 servings/week (referent), 4–6 servings/week (intermediate), 7 or more servings/week (high)⁽¹²⁾. We categorised red meat consumption in servings/week as well; however, our

categories were 0–2 servings/week (referent), 2–4 servings/week and >4 servings/week. Only 15% of our population reported eating seven or more servings of meat/week compared with 33% of participants in the Parazzini study. We may not have found an increased risk because our population ate less meat than the Italian population. We re-evaluated the present results using the tertile categorisation that Parazzini *et al.* used and did not find an increased risk of endometriosis with frequent red meat consumption (results not shown).

There are several strengths to the present study, including its size and population-based design. Cases without surgical confirmation of endometriosis as well as participants who reported prior surgically confirmed endometriosis were excluded. This allowed us to capture the initial surgical diagnosis of endometriosis and to ascertain exposures before the first medical visit for onset of symptoms associated with that diagnosis. In an attempt to enhance the reproducibility of our findings, a well-defined set of criteria was used to evaluate the certainty of diagnosis. In addition, disease features and evidence were evaluated directly from medical records rather than relying on self-report.

The controls, chosen from the same well-enumerated population, had a race, income and educational profile similar to other western Washington state residents⁽²⁸⁾. We selected controls randomly from reproductive-age female GH enrollees rather than utilising GH gynaecological patients because the latter may introduce bias if dietary exposures are associated with other gynaecological pathology. One consequence of our choice was that some of our controls may have had undiagnosed endometriosis. From previous studies, we calculate that the presence of undiagnosed, symptomatic endometriosis in the control group was likely to have been >2%, resulting in a very small number of cases being misclassified as controls⁽¹⁶⁾. Partly to address this issue, we limited our case group to women with definite or probable endometriotic disease, and it is unlikely that participants with this extent of disease were included in the control group. To further address the issue, in one subanalysis, we excluded controls with endometriosis-type symptoms. In this analysis, we found no change in our effect estimates, suggesting that the potential presence of undiagnosed cases in our control group had little impact on the results of the analyses we present.

The most apparent limitation in the present study was the retrospective assessment of dietary factors, a problem inherent in all case–control studies of diet and chronic disease that can lead to measurement error if cases' recall of diet is different from that of the control group. Additionally, since diet in the 12 months before interview was assessed in the present study, cases may have reported healthier diets than controls as a result of post-diagnosis dietary changes. We think these biases are unlikely to have affected our findings for two reasons. First, at the

time of the Women's Risk of Endometriosis interviews, dietary recommendations for endometriosis prevention were limited. The first reports on soya and environmental contaminants were published in 2001, and dietary recommendations in published books are copyrighted in 2003 and later. Second, the specificity of the association, increased risk of endometriosis with β -carotene and fruit and not vegetables also argues against differential recall and post-diagnosis dietary changes with respect to fruit and vegetable consumption. We did not account for multiple comparisons in our analyses; we emphasise that our findings may be due to chance and require further investigation.

Changes in dietary patterns over time, limited recall of serving size and omission of certain foods can contribute to measurement error on the FFQ. It has been demonstrated that FFQ often underestimate energy and fat consumption⁽²⁹⁾. Measurement error may have occurred in the estimation of dietary intake in the present study; however, it is unlikely that there were systematic differences in dietary assessment by study group. Thus, non-differential misclassification of exposure would tend to underestimate any true associations.

Healthy individuals may be more willing to participate in research studies than less healthy individuals; therefore, we may have an incomplete characterisation of the entire range of dietary intake of all potential cases and controls. Because a high and equivalent percentage of cases and controls participated in the present study, this potential limitation, if present, is unlikely to have caused substantial bias. Given that the present study is a case–control study and information on dietary intake was collected after the diagnosis of endometriosis, we cannot rule out that post-diagnosis dietary changes may have resulted in cases reporting healthier diets than the controls, leading to the decreased risk observed for dietary fat intake and the increased risk with fruit intake.

In summary, the present study suggests a possible inverse risk of disease with dietary fat and dairy consumption and an increased risk of endometriosis with β -carotene and higher servings of fruit/d, but these findings have not been confirmed elsewhere and require further evaluation in a prospective investigation. A more detailed understanding on the impact of dietary components and patterns on endometriosis risk is urgently needed to inform the development of population-based strategies to prevent this serious and prevalent gynaecological disease.

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