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Association between Endometriosis and Hypercholesterolemia or Hypertension

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Abstract

An altered hormonal or chronic systemic inflammatory milieu characterizing endometriosis may result in a higher risk of hypercholesterolemia and hypertension. Conversely, elevated low-density lipoprotein in hypercholesterolemia and chronic systemic inflammation resulting from hypertension may increase the risk of endometriosis.

We assessed the association of laparoscopically-confirmed endometriosis with hypercholesterolemia and hypertension in a large prospective cohort study. In 1989, 116,430 registered female nurses aged 25–42 completed the baseline questionnaire and were followed for 20 years. Multivariable Cox proportional hazards models were applied.

In 1989, there were 4,244 women with laparoscopically-confirmed endometriosis and 91,554 women without. After adjusting for demographic, anthropometric, family history, reproductive, dietary, and lifestyle risk factors prospectively, comparing women with laparoscopically-confirmed endometriosis to women without, the relative risks were 1.25 (95% confidence interval=1.21–1.30) for development of hypercholesterolemia and 1.14 (1.09–1.18) for hypertension. Conversely, the relative risks of developing laparoscopically-confirmed endometriosis were 1.22 (1.15–1.31) comparing women with hypercholesterolemia to women without and 1.29 (1.18–1.41) comparing women with hypertension to women without. The strength of associations of laparoscopically-

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confirmed endometriosis with hypercholesterolemia or hypertension was strongest among women age ≤40 and weakened as age increased (p-values for interaction<0.001). We observed that ~45% of the associations between endometriosis and hypercholesterolemia and hypertension could be accounted for by treatment factors following endometriosis diagnosis, including greater frequency of hysterectomy/oophorectomy and earlier age for this surgery.

In this large cohort study, laparoscopically-confirmed endometriosis was prospectively associated with increased risk of hypercholesterolemia and hypertension. Conversely, hypercholesterolemia and hypertension were prospectively associated with higher risk of laparoscopically-confirmed endometriosis.

Keywords

Etiology [8] Epidemiology; Hypertension [14] Other hypertension

INTRODUCTION

Endometriosis is a common gynecological disorder that affects 6–10% of women of reproductive age in the United States (US).[1,2] It is defined as the presence of endometrium-like tissue in sites outside the uterine cavity, primarily on the pelvic peritoneum and ovaries.[3] Signs and symptoms include chronic pelvic pain, dysmenorrhea and reduced fertility.[1] There is general agreement that endometriosis is a pelvic inflammatory process, however, research has suggested that endometriosis is also characterized by systemic inflammation.[4,5] Various kinds of inflammatory factors have been found to be elevated in peritoneal fluid and in the peripheral blood among women with endometriosis compared with controls.[5–8]

Several case-control studies have found that women with endometriosis had higher serum levels of low-density lipoprotein (LDL) or oxidized LDL (ox-LDL) compared with controls.[9–11] It is possible that chronic inflammation, such as that associated with endometriosis, could impact lipid metabolism through various mechanisms and lead to high LDL levels[12,13]—the primary form of hypercholesterolemia.[14] On the other hand, elevated LDL in peripheral blood may cause a corresponding elevation of LDL in the peritoneal fluid and the oxidization of LDL may increase adhesion and growth of endometrial cells in the pelvic cavity, promoting the development of endometriosis.[15,16]

A pathophysiologic connection has been established between inflammation and hypertension.[17] Cross-sectional studies showed that, compared to normotensives, the plasma levels of inflammatory markers were increased in patients with essential hypertension and no evidence of cardiovascular diseases.[17–20] On one hand, hypertension is a major determinant of vascular remodeling, promoting an inflammatory response in the arterial wall,[17,21] which may increase the levels of circulating inflammatory markers and therefore in pelvic cavity, facilitating the adhesion, implantation, proliferation and infiltration of endometrial cells in the peritoneal environment.[22] On the other hand, inflammatory responses in the vasculature play key roles in the vascular remodeling process, which may be contributing to blood pressure elevation.[23] Hence the chronic systemic inflammation in endometriosis may predispose women with endometriosis to a higher risk of hypertension.

In sum, women with endometriosis may have higher risk of hypercholesterolemia or hypertension and women with hypertension or hypercholesterolemia may have a higher risk of endometriosis. We examined these hypotheses in the Nurses' Health Study II (NHSII), an ongoing prospective cohort study.

METHODS

Study Population

The Nurses' Health Study II (NHSII) is a prospective cohort study with 116,430 registered female nurses who were 25 to 42 and resided in 14 of the United States at enrollment in 1989. At baseline, participants completed a detailed questionnaire and every 2 years thereafter completed follow-up questionnaires regarding the incidence of disease outcomes and on a variety of biologic, reproductive, environmental, dietary, and lifestyle risk factors. This research was approved by the Institutional Review Boards of Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health, Boston, Massachusetts, US. All nurses participated in the NHSII gave informed consent. All the study procedures followed in this study were in accordance with institutional guidelines. All NHS2 data collection tools are publicly available. In addition, data are available to be accessed following the process established within the external collaboration guidelines: http://www.nurseshealthstudy.org/researchers

Assessment of endometriosis

In 1993, women were first asked if they had "ever had physician-diagnosed endometriosis." If "yes," they were asked during which follow-up period the diagnosis had occurred: before September 1989, September 1989-May 1991, and June 1991-May 1993, and if it had been confirmed by laparoscopy – the gold standard for diagnosing endometriosis.[24,25] These questions were asked again in each subsequent questionnaire cycle.

As previously reported,[2] in 1994 we conducted a study to validate self-reported endometriosis diagnosis. Supplementary questionnaires were mailed to 200 women who were randomly selected from the 1766 cases who had reported endometriosis diagnosis. Among those who reported laparoscopic confirmation and for whom medical records were received and reviewed (n=105), a laparoscopic diagnosis of endometriosis was confirmed in 96%. However, among those women without laparoscopic confirmation (n =26), evidence of clinical diagnosis was found in only 54% of the records. Based upon these validation results, self-reported physician-diagnosed endometriosis without laparoscopic confirmation may be substantially misclassified. Therefore, when studying endometriosis as a risk factor for hypercholesterolemia or hypertension, those who reported endometriosis diagnosis but never laparoscopic confirmation were censored at the report of clinical diagnosis; when studying endometriosis as an outcome, the endometriosis cases were restricted to women who reported laparoscopic confirmation to reduce misclassification.

Assessment of hypercholesterolemia

Hypercholesterolemia diagnosis by a physician was self-reported biennially. The diagnosis date of hypercholesterolemia was set to the middle of the questionnaire cycle during which

incident physician-diagnosed hypercholesterolemia was reported. The validity of self-reported hypercholesterolemia was assessed by obtaining medical records in a validation study in the original Nurses' Health Study (NHS).[26] Of the 84 women who reported elevated cholesterol levels and were recontacted, one refused to participate in the validation study and 10 denied the diagnosis.[26] Records were obtained for 47 of the 66 women who gave permission for record review. Using >240 mg/dl[27] as defining an elevated cholesterol level, record review confirmed the self-reports in all but one woman.

Assessment of hypertension

Hypertension diagnosis by a physician was also self-reported biennially. The diagnosis date of hypertension was set to the middle of the questionnaire cycle during which incident physician-diagnosed hypertension was reported. Of the 85 NHS cohort members who had reported elevated blood pressure and responded to the validation questionnaire, only one subsequently denied elevated blood pressure reporting that she, in fact, had hypotension.[26] Of 51 women who reported hypertension for whom we obtained medical records, hypertension defined as blood pressure greater than 140/90 mmHg was confirmed in all cases.[26] In addition, baseline blood pressure was also self-reported by the participants.

Statistical Analysis

Those who reported hypercholesterolemia, hypertension or endometriosis prior to enrollment into NHSII in 1989 were excluded from the respective endpoint-specific analyses. Person-months at risk were calculated from age at enrollment to age at death, incidence of endpoint of interest, or end of follow-up for the present aims, whichever occurred first. When endometriosis was the endpoint, women were censored at the first report of hysterectomy.

We used Cox proportional hazards models, initially adjusted for age in month and calendar time to obtain crude relative risks (RR) and confidence intervals (CI). We adjusted for the following risk factors for each endpoint: race, birth weight, age at menarche, body mass index (BMI) at age 18, and time-varying risk factors: current BMI, parity, total months of breast feeding, oral contraceptive (OC) use, smoking history, alcohol consumption, alternate healthy eating index 2010 (AHEI-2010, minimum score=0, maximum score=110),[28] physical activity, multivitamin use and health care utilization rate. For hypertension as the endpoint, we also adjusted for family history of hypertension. Marginal structural models (MSMs) with inverse probability weighting (IPW) were used to adjust for potential time-dependent confounding that could have been affected by previous exposure status.[29,30]

We examined modification of observed effects by age and tested the significance of modification with partial likelihood ratio tests. In addition, we calculated the proportions of associations between endometriosis and hypercholesterolemia/hypertension that were statistically accounted for by hysterectomy/oophorectomy, postmenopausal hormone use (PMH) and duration of use, and analgesic use, using the difference method[31].

RESULTS

Analysis 1: Endometriosis in Relation to the Risk of Hypercholesterolemia and Hypertension

Compared with women who did not have endometriosis at baseline, those who did had earlier age at menarche, were more likely to be nulliparous and had lower parity (Table 1). Women who had endometriosis were also more likely to have had a hysterectomy and/or oophorectomy and to have had these at an earlier age, and were more likely to be postmenopausal and use PMH and analgesics.

In multivariable-adjusted models, women with laparoscopically-confirmed endometriosis, as compared with those who did not, had a greater risk of hypercholesterolemia (RR=1.25, 95% CI=1.21–1.30) and hypertension (RR=1.14, 95%CI=1.09–1.18) (Table 2). The observed associations were unchanged when using MSMs to adjust for potential time-dependent confounding.

The RRs of endometriosis in relation with hypercholesterolemia decreased as age increased. Comparing women with laparoscopically-confirmed endometriosis to women without: the RR of hypercholesterolemia was 1.43 (95%CI=1.33–1.54) among women age≤40, 1.35 (1.27–1.45) among women age 40-≤45, 1.22 (1.14–1.30) among women age 45-≤50, and 1.07 (1.00–1.15) among women age>50; the RR of hypertension was 1.37 (95%CI=1.24–1.52) among women age≤40, 1.18 (1.09–1.27) among women age 40-≤45, 1.12 (1.04–1.20) among women age 45-≤50, and 1.04 (0.96–1.12) among women age>50 (both p-values for interaction<0.001) (Table 5).

We observed that 37% (95% CI=30–45%) of the association between endometriosis and hypercholesterolemia was statistically accounted for by greater frequency of hysterectomy/oophorectomy and earlier age at these surgeries among women with endometriosis. 18% (95% CI=14–23%) of the association could be statistically accounted for by greater frequency and longer duration of PMH use, 6% (95% CI=4–7%) by greater frequency of analgesic use, and 44% (95% CI=36–53%) by all of these factors combined. Similarly, 30% (95% CI=17–44%) of the association between endometriosis and hypertension could be statistically accounted for by greater frequency of hysterectomy/oophorectomy and earlier age at these surgeries, 26% (95% CI=15–37%) by PMH use and duration, 13% (95% CI=9–18%) by analgesic use, and 45% (95% CI=28–63%) by all of these combined.

Analysis 2: Hypercholesterolemia, Hypertension in Relation to the Risk of Endometriosis

Compared with women who did not have hypercholesterolemia and hypertension at baseline, women with either hypercholesterolemia or hypertension had a higher BMI at age 18 and at baseline, had earlier age at menarche, were more likely to be nulliparous, had lower parity, had a shorter duration of breastfeeding, and had less alcohol consumption (Table 3).

In multivariable-adjusted models, the risk of laparoscopically-confirmed endometriosis was greater for women who had hypercholesterolemia compared with those who did not (RR=1.22, 95%CI=1.15–1.31) and also for women who had hypertension compared with

those who did not (RR=1.29, 95%CI=1.18–1.41) (Table 4). The observed associations were unchanged when using MSMs to adjust for potential time-dependent confounding. The association of hypercholesterolemia and hypertension in relation to endometriosis risk were not modified by age (Table 5).

DISCUSSION

Analysis 1: Endometriosis in Relation to the Risk of Hypercholesterolemia and Hypertension

In this prospective cohort study involving 116,430 women, we found that women with laparoscopically-confirmed endometriosis had an increased risk of hypercholesterolemia and hypertension, compared with women without endometriosis. It has been found in prospective cohort studies that those with higher plasma levels of inflammatory response proteins, such as fibrinogen and haptoglobin, were at higher risk for developing future hypertension.[32–34] The chronic systemic inflammation associated with endometriosis may predispose women with endometriosis to a higher risk of hypercholesterolemia and hypertension.

This results that endometriosis was associated with higher risk of hypercholesterolemia/hypertension were in line with a previous study which showed that endometriosis was associated with higher risk of coronary heart disease (CHD),[35] as it has been well established that hypercholesterolemia and hypertension are among the strongest risk factors for CHD.[36,37] In addition, the association observed between endometriosis and hypercholesterolemia was consistent with earlier case-control studies.[9–11] The largest sample size among these studies, however, was 40 cases and 80 controls.

Comparing women with endometriosis with women without, the RRs for both hypercholesterolemia and hypertension were highest among women younger than 40 and decreased as age increased. This age modification was again consistent with the endometriosis and CHD study which found the hazard ratios of CHD associated with endometriosis were highest among women younger than age 40 and decreased as age increase.[35] Inflammatory cytokines levels in human plasma have been shown to increase as age increases, and monocytes, dendritic cells and microglia produce more inflammatory cytokines in stimulated conditions[38–40]. In contrast, anti-inflammatory cytokine production decreases as age increases, which may be explained by aging-induced methylation that mediates the decrease in expression of genes of monocytes[38,41]. It is possible that as inflammation increases with age in women with and without endometriosis, the incremental risk associated with endometriosis in young women diminishes in the older women as age takes the dominated role in inflammation.

Other mechanisms may also be at play in addition to the inflammatory pathway mentioned above. 37% of the association between endometriosis and hypercholesterolemia and that 30% of the association between endometriosis and hypertension could be statistically accounted for by hysterectomy/oophorectomy and earlier age at these surgeries. Data on association between hysterectomy/oophorectomy and risk of subsequent hypercholesterolemia/hypertension are sparse. However, results are consistent that bilateral

oophorectomy younger than age 50 is associated with an increased risk of cardiovascular diseases (CVD) and CVD mortality (results have been inconclusive for bilateral oophorectomy at age older than 50).[42–44] Similarly, hysterectomy without oophorectomy has been shown to be associated with an increased risk of CVD in women age<50 but not in women age ≥50.[44] In addition, this finding was consistent with the previous endometriosis and CHD study which found that hysterectomy/oophorectomy and earlier age at these surgeries accounted for 40% of the overall association.[35]

Compared to women without endometriosis, women with endometriosis were more likely to use PMH and used PMH at an earlier age and for a longer duration due to more prevalent and earlier bilateral oophorectomy. It is likely that the proportion of association explained by PMH use was because that PMH use and duration of use was a marker for greater frequency of hysterectomy/oophorectomy and earlier age at surgery.

Women with endometriosis were also more likely to use analgesics due to pain symptoms. A review of randomized trials and observational studies showed that non-steroidal anti-inflammatory drugs (NSAIDs) use increased the risk of non-fatal MI with no substantial effect on fatal events[45]. This finding may in part explain that the association between endometriosis and hypercholesterolemia/hypertension can be partially accounted for by analgesics use. In addition, it is also possible that the use of analgesics was an indicator of chronic pain, which has been linked to increased risk of cardiovascular diseases[46,47].

Analysis 2: Hypercholesterolemia, Hypertension in Relation to the Risk of Endometriosis

Compared with women who did not have hypercholesterolemia, women who did had a higher risk of subsequent laparoscopically-confirmed endometriosis. This association was also consistent with earlier case-control studies discussed above,[9–11] which found that women with endometriosis had higher level of LDL compared to women without endometriosis. Because the previous studies were cross-sectional, it was unknown whether higher LDL could increase the risk of endometriosis or the presence of endometriosis could result in higher level of LDL. This present study investigated both directions of associations prospectively and found positive associations in both directions.

Compared with women without hypertension, women with hypertension had a higher risk of subsequent laparoscopically-confirmed endometriosis. Cross-sectional studies showed that the plasma levels of inflammatory markers, such as C-reactive protein, cytokines, chemokines, and adhesion molecules were increased in patients with hypertension and no evidence of CVD.[17–20] The chronic inflammation associated with hypertension can lead to increased cytokine levels in the retrograde menstrual blood, potentially facilitating the adhesion, implantation, proliferation and infiltration of endometrial cells in the peritoneal environment.[22] In the other direction, as discussed above, women with endometriosis may have higher risk of hypertension through the inflammation pathway. This was the first study to evaluate the prospective association between endometriosis and hypertension and the association between hypertension and endometriosis prospectively, and found significant associations in both directions.

Strengths and Limitations

This study has several potential limitations. Firstly, the assessment of endometriosis, hypertension and hypercholesterolemia were self-reported. Although the validation studies demonstrated that the 96%-100% of the self-reported diagnosis were confirmed by medical records among women whose medical records were reviewed, these validation studies were conducted in a small subset of the entire cohort and the confirmation status is unknown for those whose medical records were not available. Therefore, it is possible if all the medical records for the women with endometriosis, or hypertension or hypercholesterolemia were reviewed, the confirmation rate could be lowered than 95%-100%, although the participant characteristics of those with and without records procured were not different. If a larger proportion of those defined as having endometriosis or hypertension or hypercholesterolemia was misclassified, then this would have biased the results towards the null (i.e., the true association is stronger than the observed association presented here).

Moreover, expanding the definition of endometriosis cases by including endometriosis without laparoscopic confirmation did not alter the associations. Most importantly, as Zondervan[48] et al. quantified, the likely prevalence of undiagnosed endometriosis should not exceed 2% of the unexposed population, and therefore too low to impact on the results of this study. On the other hand, results could have been biased upward if having had been diagnosed with hypercholesterolemia/hypertension increased the diagnosis of endometriosis and vice versa. However, we adjusted for health care use in multivariable models, and it was highly unlikely hypercholesterolemia/hypertension increased endometriosis diagnosis and vice versa, because there have not been previous reports of this bidirectional association.

Secondly, we lacked information on non-contraceptive hormonal treatments for endometriosis, such as danazol (a synthetic androgen) and Leuprolide (lupron, gonadotropin-releasing hormone analog) to assess to what extent the association between endometriosis and hypercholesterolemia and hypertension could have been explained by these hormonal treatments. We also lacked information on the excision of endometriotic lesions during laparoscopy to evaluate whether having had the excision had an impact on the association seen between endometriosis and hypercholesterolemia/hypertension.

Thirdly, the NHSII population is representative of the population of women who were registered nurses at the time of enrollment, which may not be representative of all US women (e.g., there was a higher proportion of Caucasian women in NHSII). However, there is no evidence that the NHSII population differs biologically from the general US population. Many cardiovascular discoveries have been made in this cohort that are consistently replicated in other studies.[49]

Fourthly, as with all observational studies, there may be unobserved differences between the study groups that were not adjusted for in the analyses, such as detailed dietary factors (e.g., phytoestrogens in diet) and other medication use (e.g., the use of aromatase inhibitors). However, the wealth of time-varying data collected from the Nurses' cohort participants allowed for detailed adjustment for known and suspected risk factors for CHD, and minimal confounding was observed. Moreover, MSMs were employed to address potential time-

dependent confounding, and results were identical to those obtained from the standard multivariable Cox model.

Finally, the timing of exposure and outcome were not precisely quantified, because the initiation of endometriosis, hypercholesterolemia and hypertension at a cellular level is currently impossible to define and measure. However, clinical manifestation of these diseases endpoints are also reasonable targets of interest.

This study has many strengths. The longitudinal study design, large sample size and 20 years of follow-up allowed us to document, for the first time, the association between surgically diagnosed endometriosis and hypercholesterolemia/hypertension in two temporal directions. In addition, this study was able to investigate to what extent the association between endometriosis and hypercholesterolemia/hypertension were explained by treatment factors.

Perspectives

In this large prospective cohort study we found that women with laparoscopically-confirmed endometriosis had increased risks of hypercholesterolemia and hypertension. On the other hand, women with hypercholesterolemia and women with hypertension had higher risks of laparoscopically-confirmed endometriosis. These data suggest the need for greater awareness of the increased risks for hypercholesterolemia and hypertension among women with endometriosis and greater awareness of increased endometriosis risk among women with hypercholesterolemia or hypertension. However, because this is study is the first study to study these associations prospectively, these findings should be replicated in other populations.

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Novelty and Significance

What Is New?

This is the first study investigating the prospective association between endometriosis and risk of hypercholesterolemia/hypertension and also the first study assessing the prospective association between hypercholesterolemia/hypertension and risk of endometriosis. Our data show that endometriosis is associated with higher risk of hypercholesterolemia and hypertension independent of known and hypothesized hypercholesterolemia/hypertension risk factors, especially among younger women. Moreover, we observed that these associations could be partially explained by treatment factors associated with endometriosis diagnosis, particularly hysterectomy/oophorectomy.

Conversely, women with hypercholesterolemia had higher risk of endometriosis compared to women without hypercholesterolemia and similarly, women with hypertension had higher risk of endometriosis compared to women without hypertension.

What Is Relevant?

This study evaluated hypertension as a risk factor as well as as an outcome in relation to endometriosis.

Summary

In this large prospective cohort study we found that women with laparoscopically-confirmed endometriosis had increased risks of hypercholesterolemia and hypertension. On the other hand, women with hypercholesterolemia and women with hypertension had higher risks of endometriosis.

Table 1.

Baseline characteristics of women in the Nurses' Health Study II in 1989 by laparoscopically-confirmed endometriosis

Baseline characteristics	Laparoscopically-Confirmed Endometriosis	
	Yes (n=4,244)	No (n=91,554)
Age (years) *, mean(SD)	35.8(4.1)	34.5(4.6)
White race, %	94	93
BMI † at age 18 (kg/m^2)	20.7(3.0)	21.1(3.2)
BMI at baseline (kg/m^2)	23.3(4.2)	23.7(4.6)
Age at menarche		
- ≤ 11 years old, %	27	24
- 12–13 years old, %	57	58
- ≥ 14 years old, %	16	18
Parity		
- Nulliparous, %	42	30
- 1 pregnancy >6 months, %	24	19
- 2 pregnancies >6 months, %	26	33
- 3+ pregnancies >6 months, %	10	18
Oral contraceptive use, ever %	89	83
Cigarette smoking history, never, %	66	66
Alcohol intake (grams), mean(SD)	3.0(6.0)	3.2(6.1)
Alternate health eating index 2010 ‡, mean(SD)	1.9(1.4)	2.0(1.4)
Physical activity, (METS/week) §, mean(SD)	24.9(35.5)	25.2(37.0)
Multivitamin use, %	48	44
Family history of hypertension, %	52	51
Health care usage, %	98	95
Menopausal status, premenopausal, %	88	99
Postmenopausal hormone use, %	30	9
Hysterectomy, %	18	4
Oophorectomy		
- Unilateral, %	3	1
- Bilateral, %	11	1
Analgesic use (>=2 day/week) ‖, %	49	39
Systolic blood pressure		
- < 115 mmHg, %	65	65
- 115–125 mmHg, %	27	26
- 125–135 mmHg, %	7	7
- ≥135 mmHg, %	2	2
Diastolic blood pressure		
- < 90 mmHg, %	99	99

Baseline characteristics	Laparoscopically-Confirmed Endometriosis	
	Yes (n=4,244)	No (n=91,554)
- ≥90 mmHg, %	1	1
Serum cholesterol level		
- <240 mg/dl, %	99	99
- ≥240 mg/dl, %	1	1

Values are means (SD) or percentages and are standardized to the age distribution of the study population.

Values of categorical variables may not sum to 100% due to rounding.

[*] Value is not age adjusted

[†] BMI=body mass index

[‡] AHEI-2010[28] is a score that measures adherence to a diet pattern based on foods and nutrients most predictive of disease risk in the literature

[§] METS=metabolic equivalents from recreational and leisure-time activities

[//] Analgesic included acetaminophen, aspirin, ibuprofen, indometacin, naproxen, nabumetone, ketoprofen, celecoxib, rofecoxib and valdecoxib.

Table 2.

Relative risks and 95% confidence intervals for hypercholesterolemia and hypertension in relation to history of laparoscopically-confirmed endometriosis

Outcome	**Exposure**	
Hypercholesterolemia	**Endometriosis**	
	No	**Yes**
No. of cases	34,626	3,708
Person-years	1,373,691	105,236
Age and calendar time-adjusted model	1.00	1.31 (1.27–1.36)
Multivariable-adjusted[1]	1.00	1.25 (1.21–1.30)
Hypertension	**Endometriosis**	
	No	**Yes**
No. of cases	26,034	2,871
Person-years	1,582,120	132,355
Age and calendar time-adjusted model	1.00	1.16 (1.11–1.20)
Multivariable-adjusted[1]	1.00	1.14 (1.09–1.18)

Table 3.

Baseline characteristics of women in the Nurses' Health Study II in 1989 by hypercholesterolemia and hypertension history

Baseline characteristics	Hypercholesterolemia or Hypertension	
	Either (n=14,356)	Neither (n=89,200)
Age (years) *, mean(SD)	35.6(4.6)	34.4(4.6)
White Race, %	91	93
BMI † at age 18 (kg/m^2)	22.2(4.1)	21.1(3.2)
BMI at baseline (kg/m^2)	26.3(6.4)	23.6(4.6)
Age at menarche		
- ≤11 years old, %	28	23
- 12–13 years old, %	55	58
- ≥ 14 years old, %	16	18
Parity		
- Nulliparous, %	35	30
- 1 pregnancy >6 months, %	20	19
- 2 pregnancies >6 months, %	30	33
- 3+ pregnancies >6 months, %	15	19
Months of breast feeding		
- 0 or <1 month, %	25	19
- <6 months, %	20	17
- 6–11 months, %	20	20
- 12–23 months, %	21	24
- ≥24 months, %	14	19
Oral contraceptive use, ever, %	85	82
Smoking history, never, %	65	66
Alcohol intake (grams), mean(SD)	2.9(5.9)	3.2(6.1)
Alternate healthy eating index 2010‡, mean(SD)	1.9(1.4)	2.0(1.4)
Physical activity, (METS/week)§s, mean(SD)	23.9(36.8)	25.2(37.1)
Multivitamin use, %	44	44
Health care usage, %	97	95

Values are means (SD) or percentages and are standardized to the age distribution of the study population.

Values of categorical variables may not sum to 100% due to rounding.

*Value is not age adjusted

†BMI=body mass index

‡AHEI-2010[28] is a score that measures adherence to a diet pattern based on foods and nutrients most predictive of disease risk in the literature

§METS=metabolic equivalents from recreational and leisure-time activities

Table 4.

Relative risks and 95% confidence intervals for laparoscopically-confirmed endometriosis in relation to history of hypercholesterolemia or hypertension

Outcome	**Exposure**	
Endometriosis	**Hypercholesterolemia**	
	No	**Yes**
No. of cases	4,512	1,293
Person-years	1,288,476	381,098
Age and calendar time-adjusted model	1.00	1.31 (1.23–1.40)
Multivariable-adjusted	1.00	1.22 (1.15–1.31)
Endometriosis	**Hypertension**	
	No	**Yes**
No. of cases	5,167	638
Person-years	1,463,271	206,304
Age and calendar time-adjusted model	1.00	1.32 (1.21–1.43)
Multivariable-adjusted	1.00	1.29 (1.18–1.41)

Table 5.

Relative risks and 95% confident intervals stratified by age group at current questionnaire cycle for all associations

Outcome Hypercholesterolemia	**age ≤40**	**40<age ≤45**	**45<age ≤50**	**age >50**	$P_{interaction}$ *
No. of hypercholesterolemia cases	10,212	9,285	9,493	9,344	
Exposure endometriosis, multivariable[2]	1.43 (1.33–1.54)	1.35 (1.27–1.45)	1.22 (1.14–1.30)	1.07 (1.00–1.15)	<0.001
Outcome Hypertension	**age ≤40**	**40<age ≤45**	**45<age ≤50**	**age >50**	
No. of hypertension cases	4,847	7,422	8,699	7,937	
Exposure endometriosis, multivariable[2]	1.37 (1.24–1.52)	1.18 (1.09–1.27)	1.12 (1.04–1.20)	1.04 (0.96–1.12)	<0.001
Outcome Endometriosis	**age ≤35**	**35<age ≤40**	**40<age ≤45**	**age >45**	
No. of endometriosis cases	1,594	1,763	1,485	963	
Exposure hypercholesterolemia, multivariable	1.15 (1.00–1.33)	1.36 (1.21–1.53)	1.15 (1.02–1.30)	1.22 (1.06–1.39)	0.88
Exposure hypertension, multivariable	1.20 (0.95–1.51)	1.41 (1.19–1.67)	1.27 (1.09–1.49)	1.26 (1.08–1.48)	0.87

* P value from likelihood ratio tests of the interactions terms between age medians of each category and exposure variables.