Original Article

Endometriosis and Risk of Coronary Heart Disease

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Background—Endometriosis is a prevalent gynecologic disease associated with systemic chronic inflammation, heightened oxidative stress, and atherogenic lipid profile that may increase women's risk for coronary heart disease (CHD).

Methods and Results—We examined the prospective association between laparoscopically confirmed endometriosis and subsequent CHD among 116 430 women in the Nurses' Health Study II (1989–2009). Participants with a history of heart disease and stroke were excluded. When compared with women without endometriosis, women with laparoscopically confirmed endometriosis had a higher risk of myocardial infarction (relative risk, 1.52; 95% confidence interval, 1.17–1.98), angiographically confirmed angina (1.91; 1.59–2.29), coronary artery bypass graft surgery/coronary angioplasty procedure/stent (1.35; 1.08–1.69), or any of these CHD end points combined (1.62; 1.39–1.89), independent of potential demographic, anthropometric, family history, reproductive, and lifestyle confounders. Relative risk for the combined CHD end point was highest among women aged ≤40 years (3.08; 2.02–4.70) and decreased as age increased (40<age≤50 years, 1.65; 1.35–2.02; 50<age≤55 years, 1.44; 1.07–1.94; and age >55 years, 0.98; 0.56–1.72; *P* value, test for heterogeneity=0.001). Having had a hysterectomy/oophorectomy was associated with higher risk of combined CHD compared with not having had a hysterectomy/oophorectomy (1.51; 1.34–1.71). A percentage of 42 of the association between endometriosis and CHD could be explained by greater frequency of hysterectomy/oophorectomy and earlier age at surgery after endometriosis diagnosis.

Conclusions—In this large, prospective cohort, laparoscopically confirmed endometriosis was associated with increased risk of CHD. The association was strongest among young women. Hysterectomy/oophorectomy was associated with higher risk of CHD and could partially explain the association between endometriosis and CHD. (*Circ Cardiovasc Qual Outcomes*. 2016;9:00-00. DOI: 10.1161/CIRCOUTCOMES.115.002224.)

Key Words: endometriosis ■ coronary artery disease ■ epidemiology

Endometriosis is a chronic and estrogen-dependent gynecologic disorder that affects ≈10% of women of reproductive age in the United States.[1] It is defined as the presence of endometrium-like tissue thriving outside the uterus, primarily on the pelvic peritoneum and ovaries.[2] Signs and symptoms include chronic pelvic pain, dysmenorrhea, dyspareunia, and reduced fertility.[3]

Endometriosis has been linked to systemic chronic inflammation, heightened oxidative stress, and an atherogenic lipid profile. Various inflammatory factors, eg, interleukin-1, interleukin-6, tumor necrosis factor-α, have been observed to be elevated both in the peritoneal fluid[4–6] and in the peripheral blood[4,5,7] of women with endometriosis compared with controls. Studies also have suggested an increase of markers of oxidative stress but a decrease of antioxidants in the peritoneal fluid[8,9] and peripheral blood[10,11] among women with endometriosis. Moreover, women with

endometriosis have been suggested to have higher serum levels of low-density lipoprotien[10–12] but lower high-density lipoprotein.[10,11]

Inflammation, oxidative stress, and an atherogenic lipid profile play key roles in the pathogenesis of atherosclerotic CHD.[13–15] Chronic systemic inflammation contributes to vascular insult and atheromatous plaque progression.[16] Increasing evidence supports that reactive oxygen species contributes to the process of atherogenesis, as important mediators of signaling pathways that lead to vascular inflammation.[15] Elevated concentration of low-density lipoprotein enhances its retention under the arterial wall[17]; retention and oxidation of low-density lipoprotein are fundamental events in atherogenesis.[18] In contrast, high-density lipoprotein is antiatherogenic, removing cholesterol from cells in the arterial intima.[19] Therefore, the presence of endometriosis may promote coronary artery atherosclerosis formation and progression, increasing the risk of CHD.

WHAT IS KNOWN

Endometriosis has been associated with systemic chronic inflammation, heightened oxidative stress, and atherogenic lipid profile that may increase women's risk for coronary heart disease.

However, to our knowledge, no previous studies have explored the association between endometriosis and risk of coronary heart disease.

WHAT THE STUDY ADDS

This is the first study investigating the association between endometriosis and risk of coronary heart disease, and our data show that endometriosis is associated with higher risk of coronary heart disease independent of known and hypothesized confounders and coronary heart disease risk factors, especially among younger women.

Moreover, we observed that a portion of this association could be explained by treatment factors associated with endometriosis diagnosis, particularly hysterectomy/oophorectomy.

In addition, the treatments of endometriosis, such as hysterectomy or oophorectomy[20–24] and analgesics,[25] may confer increased risk of CHD to women with endometriosis. Hysterectomy or oophorectomy is a surgical treatment for endometriosis, thus women with endometriosis are much more likely to undergo hysterectomy or oophorectomy and also receive the surgery at a much younger age than the general population. The surgically induced menopause before a natural menopause may increase risk of CHD among women, and this elevated risk may be most evident at a younger age (ie, before all women reach natural menopause).[20–24]

In sum, women with endometriosis may have higher risk of CHD than women without endometriosis,[26] and this association may differ by age group. To test these hypotheses, we examined the prospective associations between endometriosis and myocardial infarction, angiographically confirmed angina, and coronary artery bypass graft surgery/coronary angioplasty procedure/stent within the Nurses' Health Study II, a large prospective cohort study.

Methods

Study Population

Nurses' Health Study II 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 on demographic, medical, lifestyle, reproductive, and other information and have continued to do so biennially. 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, MA.

Assessment of Endometriosis

In 1993, women were first asked whether they had ever had physician-diagnosed endometriosis. If yes, they were asked during which 2-year follow-up period the diagnosis had occurred and whether it had been confirmed by laparoscopy—the gold standard for diagnosing endometriosis.[27,28] They were asked again in each subsequent biennial questionnaire.

As previously detailed,[1] the surgical report validation for self-reported laparoscopically confirmed endometriosis cases within this cohort is 96% (n=101/105). Among women without laparoscopic confirmation, evidence of clinical diagnosis or symptoms was found in only 54% (n=14/26) of the records. Thus, self-reported physician-diagnosed endometriosis without laparoscopic confirmation may be substantially misclassified, and therefore, endometriosis exposure was restricted to women who reported laparoscopic confirmation. Those who reported endometriosis diagnosis but never laparoscopic confirmation were censored at the report of clinical diagnosis. In addition, this validation study determined that the average diagnostic delay (from symptom onset to surgical diagnosis) was 4 years in this cohort, whereas a study in 10 countries observed an average delay of 6.7 years.[29] A shorter diagnostic delay within Nurses' Health Study II compared with the general population may be attributed to the medical knowledge and greater access to care of this cohort of registered nurses.

Assessment of CHD

We assessed incident myocardial infarction cases (fatal and nonfatal), angiographically confirmed angina, and coronary artery bypass graft surgery/angioplasty/stent cases that occurred between enrollment and the 2007 questionnaire cycle (which ended in May 2009). Clinicians blinded to the questionnaire information reviewed medical records from self-reported nonfatal myocardial infarction events. Nonfatal myocardial infarctions were classed as confirmed if they met the criteria of the World Health Organization: symptoms and either diagnostic electrocardiographic changes or raised cardiac enzymes,[30] as probable if hospital records were not obtained but they were corroborated in writing or a telephone interview. Fatal myocardial infarction was confirmed by hospital records, the National Death Index, or autopsy. Physician-diagnosed angina confirmed by angiography, coronary artery bypass graft surgery/angioplasty/stent, and time of diagnosis were self-reported. When myocardial infarction, angiography-confirmed angina, and coronary artery bypass graft surgery/angioplasty/stent cases were combined as the outcome (the combined CHD), we used the time of the first CHD event among those 3 to define the first age of occurrence.

Statistical Analysis

Those who experienced myocardial infarction, stroke, angiographically confirmed angina, or coronary artery bypass graft surgery/angioplasty/stent before enrollment into Nurses' Health Study II in 1989 were excluded from this study. Person-months at risk were calculated from age at enrollment to age at death, CHD incidence, and end of follow-up for the present aims, whichever occurred first.

Association Between Endometriosis and CHD

First, as the main analysis, we quantified the association between endometriosis and CHD using multivariable Cox proportional hazards models. To evaluate potential confounding, we adjusted for age at the beginning of each questionnaire cycle and calendar time and then additionally adjusted for demographic, anthropometric, family history, reproductive, and lifestyle potential confounders including known risk factors for CHD to calculate crude and adjusted relative risks and 95% confidence intervals. All time-varying covariates were updated prospectively. Given that most questions were asked in every questionnaire across the ≈20 years of follow-up, we observed little missing data. For example, there were <1% missing data for age at menarche (asked at baseline) and smoking history (asked in each questionnaire) among 2 019 360 person-years. The highest percentage of missing values observed was for birth weight (5%), body mass index (5%), and postmenopausal hormone use (6%). Missing covariate values were handled by the missing indicator method.[31] Multiple imputation to handle the missing data was also performed as a sensitivity analysis. Standard multivariable Cox models may be

biased when there exist time-dependent confounders that are also affected by previous exposure.[32] For example, diet and physical activity change over time and can be influenced by previous endometriosis diagnosis. Therefore, we also applied marginal structural models with inverse probability weighting to adjust for potential time-dependent confounding.

Age as a Modifier on the Association Between Endometriosis and CHD

Second, we examined whether and how age modifies the association between endometriosis and CHD. To do so, we stratified the association between endometriosis and combined CHD by age groups (<40, 40–50, 50–55, ≥55 years) and tested the statistical significance of the interaction between age and endometriosis with likelihood ratio tests.[33] We plotted the absolute incidence rate of combined CHD against age for women with and without laparoscopically confirmed endometriosis, calculated by multivariable adjusted pooled logistic regression. This incidence rate was calculated at the mean or mode of all covariates.

Relationship Between Endometriosis, Hysterectomy/oophorectomy, and Combined CHD

Third, we investigated the relationship between endometriosis, hysterectomy/oophorectomy, and combined CHD. As the first step, we assessed the association between hysterectomy/oophorectomy and combined CHD. In addition to the covariates adjusted in the main analysis, to further account for risk factors of hysterectomy, we added adjustment for household income, husband's education, and geographic region of residence. We also further adjusted for potential indication for hysterectomy including infertility history and analgesics use (in addition to oral contraceptive) as indicators of endometriosis clinical severity.

As the second step, we calculated whether proportions of the association between endometriosis and combined CHD could be statistically accounted for by the surgical treatments hysterectomy/oophorectomy. To do so, we added adjustment for hysterectomy/oophorectomy to the base multivariate model (ie, now a surgery-adjusted model). Then, we calculated the proportion of the association between endometriosis and combined CHD that was statistically accounted for by hysterectomy/oophorectomy by dividing the log relative risk for combined CHD in relation to endometriosis estimated from the surgery-adjusted model by the log relative risk for combined CHD in relation to endometriosis from the base model. Confidence intervals for these estimated proportions account are calculated as per Lin et al.[34] We repeated this method to calculate the proportions of association between endometriosis and combined CHD that were statistically accounted for by postmenopausal hormone use (estrogen, progesterone/progestin, or estrogen and progesterone/progestin combined) and duration of use, and analgesic use.

Results

Association Between Endometriosis and CHD

At baseline in 1989, 116 430 women were enrolled in this cohort. The response rate across the 20 years since enrollment has been consistently over 90% for each questionnaire cycle and did not vary by endometriosis status. During the 20-year follow-up among 1 971 574 person-years, there were 1438 incident combined CHD cases. At baseline (1989), women who had laparoscopically confirmed endometriosis history (n=5296) were slightly older, had earlier age at menarche, were more likely to be nulliparous, had lower parity, were more likely to use oral contraceptives, and more likely to have a family history of myocardial infarction aged <60 years old compared with women who had not been diagnosed with endometriosis at baseline (Table 1). Women with

endometriosis were also much more likely to have had a hysterectomy and/or oophorectomy and to have had these at an earlier age, be surgically postmenopausal, and use postmenopausal hormones and analgesics.

In age- and calendar year–adjusted analyses, the relative risks—comparing women with laparoscopically confirmed endometriosis (n=11 903 by end of follow-up) to women without—were 1.63 (95% confidence interval, 1.27–2.11) for myocardial infarction, 2.07 (1.73–2.47) for angiographically confirmed angina, 1.49 (1.19–1.86) for coronary artery bypass graft surgery/angioplasty/stent, and 1.73 (1.49–2.00) for combined CHD (Table 2). Results remained statistically significant after adjustment for potential confounders (myocardial infarction, 1.52, 1.17–1.98; angina, 1.91, 1.59–2.29; coronary artery bypass graft surgery/angioplasty/stent, 1.35, 1.08–1.69; combined CHD, 1.62, 1.39–1.89; Table 2). Results were unchanged when using marginal structural models. Results were also unchanged when multiple imputation was applied instead of the missing indicator method to address missing data in any covariate. The significant association between endometriosis and combined CHD remained after adjustment for each treatment factor.

Age as a Modifier on the Association Between Endometriosis and CHD

We observed a statistically significant interaction between endometriosis and age for the combined CHD end point. The relative risk was highest among women age ≤40 years (3.08; 2.02–4.70) and decreased as age increased (40<age≤50 years, 1.65; 1.35–2.02; 50<age≤55 years, 1.44, 1.07–1.94; age >55, 0.98; 0.56–1.72; *P* test for heterogeneity=0.001). The Figure demonstrates that women with endometriosis had a higher absolute incidence rate of combined CHD than women without endometriosis across ages before late the 50s; the 2 absolute incidence rates crossed at ages in the late 50s—after which the 2 groups had similar incidence rates (Figure). The incidence rate difference between women with endometriosis and women without endometriosis increased slowly as age increased until around the age 50 years.

Relationship Between Endometriosis, Hysterectomy/Oophorectomy, and Combined CHD

We observed that women who had a hysterectomy/oophorectomy had higher age-standardized incidence rates of CHD. Having had a hysterectomy/oophorectomy was associated with higher age-standardized absolute incidence rates of CHD than those who had not: 139 versus 60 per 100 000 person-years; having had a hysterectomy/oophorectomy was associated with higher risk of combined CHD compared with not having had a hysterectomy/oophorectomy (1.51; 1.34–1.71). Adjustment for potential risk factors and indication for hysterectomy/oophorectomy did not attenuate this association.

We observed that 42% of the association between endometriosis and CHD was statistically significantly accounted for by greater frequency of hysterectomy/oophorectomy and earlier age at these surgeries among women with endometriosis (Table 3). Although 31% of the association could be statistically accounted for by greater frequency and longer duration of postmenopausal hormone use, this was

Table 1.   Age-Standardized Baseline Characteristics of Women in the Nurses' Health Study II in 1989 by Laparoscopically Confirmed Endometriosis History

	Laparoscopically Confirmed Endometriosis (Yes/No)	
	Yes (n=5296)	No (n=109 161)
Age at baseline, y,* mean (SD)	36.0 (4.2)	34.7 (4.7)
White race, %	94	92
Body mass index at baseline, kg/m^2		
<18.5 (underweight), %	4	3
18.5–22.4, %	45	44
22.5–24.9, %	23	22
25.0–29.9 (overweight), %	19	19
≥30.0 (obese), %	9	12
Age at menarche, %		
≤11 y old, %	29	24
12–13 y old, %	56	58
≥14 y old, %	15	18
Parity		
Nulliparous, %	42	30
1 pregnancy >6 mo, %	23	19
2 pregnancy >6 mo, %	26	33
≥3 pregnancy >6 mo, %	9	18
Oral contraceptive use, ever, %	89	83
Cigarette smoking history, never, %	64	65
Alcohol intake, g, mean (SD)	2.9 (5.8)	3.1 (6.1)
Alternate healthy eating index 2010,† mean (SD)	48.0 (11.0)	48.6 (11.0)
Physical activity, (metabolic equivalents/wk),‡ mean (SD)	24.6 (35.0)	24.9 (36.9)
Multivitamin use, %	47	44
Parental myocardial infarction <age 60 y, %	20	18
Healthcare usage, %	98	95
Physician-diagnosed hypertension, %	7	5
Physician-diagnosed hypercholesterolemia, %	14	11
Physician-diagnosed type 2 diabetes mellitus, %	1	1
Menopausal status		
Premenopausal, %	86	98
Postmenopausal, %	14	2
Ever use postmenopausal hormones, %	32	10
Hysterectomy, %	21	4
Oophorectomy		
Unilateral, %	4	1

(*Continued*)

Table 1.   Continued

	Laparoscopically Confirmed Endometriosis (Yes/No)	
	Yes (n=5296)	No (n=109 161)
Bilateral, %	13	1
Analgesic use§ (≥2 d/wk), %	51	41

Values are mean (SD) or percentages and are standardized to the age distribution of the study population. Values of categorical variables may not sum to 100% because of rounding.

*Value is not age adjusted.

†Alternate healthy eating index 2010[35] is a score that measures adherence to a diet pattern based on foods and nutrients most predictive of disease risk in the literature (minimum score=0, maximum score=110).

‡Metabolic equivalents from recreational and leisure-time activities.

§Analgesic included acetaminophen, aspirin, ibuprofen, indometacin, naproxen, nabumetone, ketoprofen, celecoxib, rofecoxib, and valdecoxib.

primarily driven by greater frequency and earlier age at hysterectomy/oophorectomy.

Discussion

When compared with women without endometriosis, laparoscopically confirmed endometriosis was associated with a significantly increased risk of myocardial infarction, angiographically confirmed angina, and coronary artery bypass graft surgery/angioplasty/stent. Adjustment for potential confounders did not attenuate this association. Hysterectomy/oophorectomy was associated with a higher risk of CHD and explained a portion of the association between endometriosis and CHD.

To our knowledge, this is the first prospective cohort study investigating the association between endometriosis and CHD. One case–control study found null results when investigating whether women with endometriosis (n=66) had greater subclinical atherosclerosis than controls (n=66), measured by intima-media thickness on the common carotid artery.[36] As noted by the author, the mean age of the study population was only 41 years. Given the small sample size, the study had insufficient statistical power to detect increased atherosclerosis at such early age. Also, the control group was defined as women with uterine myomas, ovarian cysts, or pelvic pain, who may have greater risk of subclinical atherosclerosis than the general population. Another case–control study also investigated the association between carotid intima-media thickness and endometriosis and found null results.[37] However, this study similarly had a young age group (mean age, 33 years in cases and 35 years in controls) and very small sample size (37 cases and 31 controls).

Systemic chronic inflammation, heightened oxidative stress, and atherogenic lipid profile associated with endometriosis and the synergistic effect of the 3 may underpin the biological mechanism for the association between endometriosis and CHD. In addition, endometriosis and CHD may share common genetic susceptibilities. Multiple independent loci in the CDKN2B-AS1 (also known as antisense non-coding RNA in the INK4 locus (ANRIL)) region on chromosome 9p21 have been robustly associated with endometriosis in genome-wide association studies in Japanese and European ancestry populations[38,39] and has also

Table 2.   Relative Risks and 95% Confidence Intervals of Incident Myocardial Infarction, Angiographically Confirmed Angina, Coronary Artery Bypass Graft Surgery/Coronary Angioplasty Procedure/Stent and Combined Coronary Heart Disease Events According to Laparoscopically Confirmed Endometriosis History

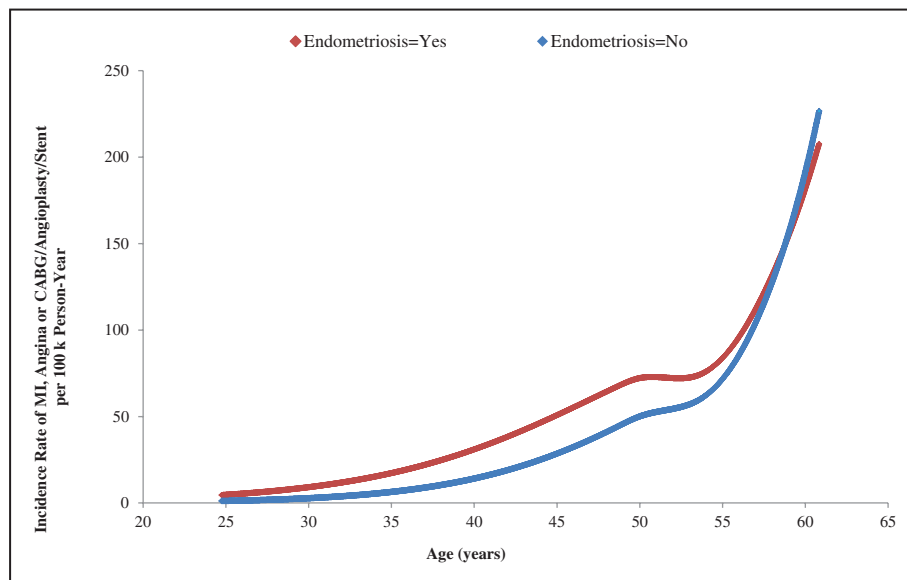|	Myocardial Infarction		Angina		Coronary Bypass/Angioplasty/Stent		Combined Coronary Heart Disease	
	Endometriosis Confirmed by Laparoscopy (No/Yes)							
	No	Yes	No	Yes	No	Yes	No	Yes
No. of CHD cases	429	69	742	149	599	91	1231	207
Person-years	1 822 783	154 696	1 820 499	153 892	1 821 888	154 555	1 818 018	153 556
Age and calendar year adjusted	1.00	1.63 (1.27–2.11)	1.00	2.07 (1.73–2.47)	1.00	1.49 (1.19–1.86)	1.00	1.73 (1.49–2.00)
Multivariable-adjusted*	1.00	1.52 (1.17–1.98)	1.00	1.91 (1.59–2.29)	1.00	1.35 (1.08–1.69)	1.00	1.62 (1.39–1.89)

CHD indicates coronary heart disease.

*Relative risks and 95% confidence intervals stratified by age in months and questionnaire cycle and adjusted for race (white, black, Asian, and other), age at menarche (≤11, 12–13, and ≥14 years old), birth weight (not full term, <5.5, 5.5–6.9, 7–8.3, and ≥8.4 lb), maternal or paternal history of myocardial infarction <60 years old (yes/no), body mass index at the age of 18 years (<18.5, 18.5–22.4, 22.5–24.9, 25–29.9, and ≥30 kg/m^2), and time-varying risk factors: current body mass index (<18.5, 18.5–22.4, 22.5–24.9, 25–29.9, 30–34.9, 35–39.9, and ≥40 kg/m^2), parity (nulliparous, 1, 2, 3, and ≥4 pregnancies that were longer than 6 months), total months of breast feeding (no breast feeding or <1 month, <6, 6–11, 12–23, and 24 months), oral contraceptive use (never, past, and current), smoking history (never, past, and current), alcohol consumption (none, <5, 5–10, and >10 g/d), alternate healthy eating index quintile 2010 (a score that measures adherence to a diet pattern based on foods and nutrients most predictive of disease risk in the literature), physical activity (<3, 3–8, 9–17, 18–26, 27–41, ≥42 metabolic equivalent, metabolic equivalents-hour/wk), multivitamin use (yes/no), and healthcare utilization rate (a cumulative score was calculated based on the answers to several questions that asked whether the nurse has had a physical examination, pap smear, pelvic examination, or a breast examination by a clinician).

been robustly associated with CHD outcomes.[40–42] Chr9p21 encodes the long noncoding RNA ANRIL, which has been demonstrated to regulate cell proliferation, adhesion, and apoptosis,[43,44]—central mechanisms of atherogenesis[13,43] and endometriosis.[2,3]

Apart from these biological mechanisms, it is possible that the crude association between endometriosis and CHD can be explained by CHD risk factors that predate and cause endometriosis (eg, diet). However, the small attenuation of relative risk from the crude models to the comprehensive multivariable models suggests that strong confounding is unlikely. Moreover, because the results of multivariable Cox models and marginal structural models were almost identical,

the potential bias that may remain within multivariable Cox models for adjustment of time-varying confounding[32] was negligible.

We observed that the increased risk of CHD in women with endometriosis was greatest among younger women, and there was no increased risk from endometriosis after women reached the late 50s. This association may have important clinical and public health implications among women in their early 40s to early 50s. It is possible that the observed increased risk associated with surgical menopause from hysterectomy/oophorectomy among women with endometriosis started to diminish with age partially because nearly every woman had reached menopause by the age of 55 years.

Figure. Incidence rate of myocardial infarction (MI), angina and coronary artery bypass graft surgery (CABG)/angioplasty/stent across age in years (covariates set to mean or mode value).

Table 3.   Proportions and 95% CIs* of the Association Between Endometriosis and Combined Coronary Heart Disease Event (Myocardial Infarction, Angiographically Confirmed Angina, and Coronary Artery Bypass Graft Surgery/Coronary Angioplasty Procedure/Stent) Mediated by Treatment Factors

Treatment Factors	Proportion (95% CI)*
Hysterectomy/oophorectomy and age at surgery†	42 (25–60)
Postmenopausal hormone use (yes/no)+postmenopausal hormone use duration (continuous years)	31 (17–44)
Analgesic use‡ (≥2 vs <2 times/wk)	5 (3–8)
All treatment factors combined	55 (33–77)

CI indicates confidence interval.

*Proportions and CIs were calculated following Lin et al,[34] comparing the full model that includes the exposure, treatment factor(s), and any covariates with a partial model without the treatment factor (ie, 1-log(relative risk of model 1)/log(relative risk of model 2)). The multivariable-adjusted model 2 (Table 2) represents the average effect of endometriosis given the distribution of age and treatment in the Nurses' Health Study. The mediation proportion estimated from the model presented here can be interpreted as the mediation proportion to be observed in this study population or any other study population with a similar proportion of treatment and a similar age distribution.

†Categorical variable, defined as: no hysterectomy/oophorectomy, hysterectomy/oophorectomy at age ≤45, 45–50, 50–55, and >55 years.

‡Analgesic included acetaminophen, aspirin, ibuprofen, indometacin, naproxen, nabumetone, ketoprofen, celecoxib, rofecoxib, and valdecoxib.

We observed higher risk of CHD among women who had a hysterectomy/oophorectomy than women who did not have a hysterectomy/oophorectomy. These associations were not altered when potential confounding factors, eg, age, parity, body mass index, and race/ethnicity,[45–47] were adjusted for in the multivariable analyses. Another important determinant of the decisions on hysterectomy/oophorectomy is education,[45,47] which is homogenous in this population of nurses, and so we additionally adjusted for husband's education level and household income, again with no evidence of confounding. Confounding by indication of this hysterectomy association could be because of severity of endometriosis disease. Therefore, we further adjusted for infertility history and analgesics use (in addition to oral contraceptive use) as proxies of endometriosis disease severity as the main presentations of endometriosis are infertility and pain.[1,3] Adjustment did not change the association between hysterectomy/oophorectomy and CHD. These results were supported by the literature: bilateral oophorectomy at ages younger than 50 years has been associated with an increased incidence and mortality of cardiovascular diseases although results have been inconclusive for bilateral oophorectomy at ages >50 years.[20–22] A nationwide study from Sweden showed that hysterectomy without oophorectomy was associated with an increased risk of cardiovascular diseases in women aged <50 years but not in women aged ≥50 years.[23,24] Loss of ovarian function and subsequent deficiency of endogenous estrogens may be the biological mechanism for association between bilateral oophorectomy and cardiovascular diseases, whereas simple hysterectomy can interfere with ovarian blood flow and may result in premature ovarian failure.[23]

We observed that ≈40% of the observed significant association between endometriosis and CHD may be statistically

accounted for by hysterectomy/oophorectomy and age at surgery. This may be because (1) women with endometriosis were subsequently much more likely to have a hysterectomy/oophorectomy and had the surgery at a younger age than women without endometriosis; and (2) hysterectomy/oophorectomy is associated with higher risk of CHD. The mediation proportion estimated from this model can be interpreted as the mediation proportion to be observed in this study population or any other study population with a similar proportion of treatment and a similar age distribution. The remaining ≈50% of the significant association between endometriosis and CHD was not explained by endometriosis treatments.

These data raise concerns on treating endometriosis with hysterectomy/oophorectomy. Physicians need to consider the potential long-term impact that the surgeries may cause and weigh the risks and benefits of the treatment in dialogue with patients, particularly with respect to endometriosis where pain recurrence risk remains.[48] Although oophorectomy confers obvious prevention for ovarian cancer, with which endometriosis has been associated,[49] CHD is the leading cause of mortality and morbidity in women in the United States and United Kingdom. CHD incidence and mortality are orders of magnitude greater than ovarian cancer, with incidence 30 times greater and mortality 26 times greater in the United States in 2010.[50] However, we acknowledge that endometriosis management decisions are not random, and there are many individual issues that contribute to treatment decisions between a physician and patient.

Strengths and Limitations

About limitations, our unexposed group (ie, never clinically or surgically diagnosed with endometriosis) may include asymptomatic endometriosis or symptomatic without confirmatory diagnosis. If so, our results would be biased toward the null. However, in sensitivity analyses, expanded definition of endometriosis cases by attributing person time from endometriosis without laparoscopic confirmation to the exposed group did not alter the results. More importantly, as Zondervan et al[51] quantified, the likely prevalence of undiagnosed endometriosis should not exceed 2% of the unexposed population, and therefore too low to affect the results, particularly in our large study population among whom undiagnosed endometriosis become diluted among tens of thousands of those with no endometriosis. We did not have information on other 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 CHD could have been explained by those treatments. We also did not have information on the extent of excision of endometriosis lesions during laparoscopy to evaluate whether the excision could alter the elevated CHD risk associated with endometriosis although no current cohort of sufficient size has these data. About generalizability, these medical professionals have greater knowledge of and access to medical care, minimizing misclassification of the primary exposure (endometriosis) or the outcomes and thus maximizing precision of hazard ratio estimation; it is unlikely that the underlying biological relation observed between endometriosis and CHD, if true, would differ between these women and women in the general

population. Finally, the timing of exposure was defined by the time of surgical diagnosis, not by disease onset. However, this is true for all studies of endometriosis regardless of design; furthermore, sensitivity analyses predating diagnosis time of endometriosis for 2, 4, 6, or 8 years did not change our results.

Our study has many strengths. The longitudinal study design, large sample size, and 20 years of follow-up allowed us to document the prospective association between surgically diagnosed endometriosis and subsequent risk of CHD. The wealth of time-varying data allowed for detailed adjustment for known and suspected potential confounders and risk factors for CHD. Minimal confounding was seen. We were able to assess proportions of the association statistically accounted for by various treatment factors. Finally, the results were robust across multiple definitions of CHD.

Conclusions

In this large prospective cohort, laparoscopically confirmed endometriosis was associated with higher risk of CHD. The association was stronger among young women. Hysterectomy/oophorectomy was associated with higher risk of CHD and could explain a portion of the association between endometriosis and CHD. These data have implications for clinical management of endometriosis patients, suggesting that women with endometriosis may represent a high-risk group for CHD—particularly at a young age, indicating the need for risk awareness and subsequent screening for CHD and healthy lifestyle promotion among primary care and public health specialists.

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Disclosures

None.

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