Stroke

ORIGINAL CONTRIBUTION

Laparoscopically Confirmed Endometriosis and Risk of Incident Stroke: A Prospective Cohort Study

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BACKGROUND: Prior research suggests that women with endometriosis are at greater risk of coronary heart disease. Therefore, our objective was to prospectively investigate the association between laparoscopically confirmed endometriosis and risk of incident stroke during 28 years of follow-up.

METHODS: Participants in the NHSII cohort study (Nurses' Health Study II) were followed from 1989 when they were between the ages of 25 to 42 until 2017 for development of incident stroke (ischemic and hemorrhagic). Cox proportional hazard models were used to calculate hazard ratios and 95% CI, with adjustment for potential confounding variables (alcohol intake, body mass index at age 18, current body mass index, age at menarche, menstrual cycle pattern in adolescence, current menstrual cycle pattern, parity, oral contraceptive use history, smoking history, diet quality, physical activity, NSAID use, aspirin use, race/ethnicity, and income). We estimated the proportion of the total association mediated by history of hypertension, hypercholesterolemia, hysterectomy/oophorectomy, and hormone therapy. We also tested for effect modification by age (<50, ≥50 years), infertility history, body mass index (<25, ≥25 kg/m^2), and menopausal status.

RESULTS: We documented 893 incident cases of stroke during 2 770 152 person-years of follow-up. Women with laparoscopically confirmed endometriosis had a 34% greater risk of stroke in multivariable-adjusted models (hazard ratio, 1.34 [95% CI, 1.10–1.62]), compared to those without a history of endometriosis. Of the total association of endometriosis with risk of stroke, the largest proportion was attributed to hysterectomy/oophorectomy (39% mediated [95% CI, 14%–71%]) and hormone therapy (16% mediated [95% CI, 5%–40%]). We observed no differences in the relationship between endometriosis and stroke by age, infertility history, body mass index, or menopausal status.

CONCLUSIONS: We observed that women with endometriosis were at elevated risk of stroke. Women and their health care providers should be aware of endometriosis history, maximize primary cardiovascular prevention, and discuss signs and symptoms of cardiovascular disease.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: body mass index ■ cardiovascular disease ■ endometriosis ■ heart disease ■ menstrual cycle

Endometriosis is a chronic inflammatory gynecologic condition that burdens ≈10% of women.[1] Cardiovascular disease (CVD) is known to present differently among men and women, including later age at onset for women,[2,3] and a higher incidence of stroke as the first cardiovascular event in women.[4] Female specific risk factors for CVD are increasingly being recognized. Mounting evidence suggests that women with endometriosis may be at greater risk for CVDs later in life.[5,6] Endometriosis may influence risk of cardiometabolic diseases, including stroke, through alterations in the endogenous inflammatory, immunologic, and hormonal milieu.[7–9] Further, treatments for endometriosis, such as hormonal medications, hysterectomy, and oophorectomy, may modify CVD

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Nonstandard Abbreviations and Acronyms

BMI	body mass index
CVD	cardiovascular disease
NHSII	Nurses' Health Study II

risk.[6] Previous research has suggested that women with endometriosis may have greater risk of hypertension,[10,11] hypercholesterolemia,[10] and coronary heart disease.[12,13]

Despite plausible mechanisms and prior research on coronary heart disease that suggest a possible association between endometriosis and elevated risk of stroke, there is a paucity of prospective research with longitudinal follow-up for stroke. Recently, analyses from the Health Improvement Network database in the UK observed that women with endometriosis had a 19% increased risk of cerebrovascular disease.[14] Additionally, retrospective data from Taiwan National Health Insurance reported approximately a 16% greater risk of acute ischemic or hemorrhagic stroke for women with endometriosis compared to women without endometriosis.[13] However, current research on endometriosis and risk of long-term health outcomes, including stroke, is limited by short durations of follow-up, limited accounting for potential confounding factors and reproductive health history, or cross-sectional analyses ignoring temporality that negate potential for causal inference.[6,15] To overcome these prior limitations, the current study investigated the association between endometriosis and risk of incident stroke among participants in the NHSII (Nurses' Health Study II) who have been followed for nearly 30 years.

METHODS

Study Population

The NHSII is an ongoing prospective cohort study that began in 1989 when 116 429 female registered nurses between the ages of 25 to 42 returned a mailed questionnaire. Participants were recruited from 14 states where the investigators contacted state nursing boards to contact female nurses within the appropriate age range, recruitment details have been described in detail previously.[16] Participants have since moved to all 50 states and have received mailed questionnaires every 2 years that collected detailed information on a variety of chronic diseases and risk factors. For the present study, NHSII participants were excluded if they had a history of stroke, myocardial infarction, cancer (other than nonmelanoma skin cancer), or coronary artery bypass grafting before June 1989, when the cohort began or had endometriosis that was not confirmed by laparoscopy. Leaving 112 056 women followed from 1989 until June 2017 (Figure S1). The NHSII protocol was approved by the Institutional Review Board of the Partners Health Care System, Boston, MA, and this analysis was reviewed by the Institutional Review Board of the University of Arizona. Completion of the baseline and subsequent biennial questionnaires implied consent of the cohort participants. Because of the sensitive nature of the data collected for this study, requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to Channing Division of Network Medicine (nhsaccess@channing.harvard.edu). This study follows STROBE guidelines (Strengthening the Reporting of Observational Studies in Epidemiology; Supplemental Material).[17]

Endometriosis Definition

From 1993 and on each biennial questionnaire, participants were asked whether they had physician-diagnosed endometriosis. If participants responded "yes," they reported the year of diagnosis and whether the endometriosis diagnosis had been confirmed by laparoscopy, the clinical gold standard for endometriosis diagnosis.[18–20] Among a subgroup of participants, self-reported endometriosis was validated at 2 time points in 1994 (n=200) and 2011 (n=711), and a diagnosis of endometriosis was confirmed via medical records of 95% to 100% of women reporting laparoscopically confirmed endometriosis in the first and second validations studies, respectively, but in only 56% of women without laparoscopic confirmation.[21] Therefore, we restricted our endometriosis definition to those with laparoscopic confirmation, to reduce misclassification of our exposure. Laparoscopically confirmed endometriosis diagnosis was updated over time, but once a woman reported laparoscopically confirmed endometriosis, she was categorized as having a history of endometriosis for the remainder of follow-up.

Stroke Definition

At enrollment in 1989 and biennially, participants reported all incident physician-diagnosed stroke (cerebrovascular accident) or transient ischemic attack events. Permission was requested from participants or next of kin to obtain and review medical records following self-reported stroke. Stroke was confirmed by physician review of medical records (International Classification of Diseases, 430.0–437.0)

when available and classified as ischemic or hemorrhagic by the National Survey of Stroke criteria, requiring a typical neurological deficit of rapid or sudden onset lasting ≥24 hours or until death attributable to a vascular cause.[22] For reports of stroke for which medical records were not available/ permitted, strokes were corroborated by nurse participant information. Pathology attributable to infection, trauma, or malignancy was excluded, as were silent strokes discovered only by radiological imaging.

Covariate Data

On the baseline questionnaire in 1989 and subsequent questionnaires, participants reported several health characteristics including their height, current weight, weight at age 18, age at menarche, menstrual cycle pattern in adolescence, and currently, parity (number of pregnancies lasting ≥6 months), oral contraceptive use, smoking history, physical activity (modeled as metabolic equivalents from recreational and leisure-time activities), race and ethnicity, pretax annual household income, family history of myocardial infarction or stroke, history of infertility (>12 months trying to conceive without success), NSAID use, aspirin use, menopausal status, history of oophorectomy or hysterectomy and physician-diagnosed type 2 diabetes, CVD, cancer, hypercholesterolemia or physician-diagnosed hypertension, and postmenopausal hormone use. All time-varying characteristics were updated every 2 years. Diet in the past year was reported via food frequency questionnaire every 4

years,[23] from which the Alternative Health Eating Index diet score was calculated.[24,25]

Statistical Analyses

Person-months at risk were calculated from entry into the cohort in 1989 until confirmed (1) death, (2) cardiovascular event (myocardial infarction, stroke), or (3) their last returned questionnaire, whichever came first. To account for possible confounding by age, all variables presented in Table 1 (aside from age) were standardized to the age distribution of the study sample.[26] Cox proportional hazard models were stratified by calendar time (years) with age (months) as the time metameter and were used to calculate the hazard ratios and 95% CI of incident stroke diagnosis (model 1). The proportional hazards assumptions were tested using the likelihood-ratio test comparing a model with and without an interaction term for time; they were met. We adjusted for covariates that we hypothesized were potential confounders for the association between endometriosis and risk of stroke[27] with time-varying covariates updated biennially at every questionnaire cycle (Model 2): alcohol intake (0, 0–5, 5+ g/d), body mass index (BMI) at age 18 (<22, 22.5–<25, 25–<30+ kg/m^2), current BMI (<22, 22.5 to <25, 25–<30, 30–<35, 35+ kg/m^2), age at menarche (11 or younger, 12-13, 14+ years of age), menstrual cycle pattern in adolescence (regular, usually irregular, always irregular, no menses), current menstrual cycle pattern in adulthood (regular, irregular, no menses), parity (0, 1, 2, 3+ pregnancies >6 months), oral contraceptive use history (current, past, never), smoking history (never, past, current), Alternative Health Eating Index diet score (quintiles), physical activity (<3, 3–8.9, 9–17.9, 18–26.9, 27+ modeled as metabolic equivalent–hour/wk), NSAID use (nonuser, current user), aspirin use (nonuser, current user), race (White, non-White), pretax annual income (<$50 K, $50–<$100 K, $100 K+ per year), family history of myocardial infarction (no, yes), and family history of stroke (no, yes).

Mediation analyses were conducted to investigate the proportion of the association between endometriosis and risk of stroke that could be attributed to intermediate variables occurring after endometriosis diagnosis but before stroke.[28] The proportion mediated was estimated by comparing the hazard ratio with and without the time-varying proposed mediator.[29,30] Potential mediators of interest were: physician-diagnosed hypertension or hypercholesterolemia, age at menopause (≤45 years old, >45 years old), hysterectomy or oophorectomy, and hormone therapy use.

Effect modification by age and infertility history were observed in prior analyses of endometriosis and cardiometabolic conditions[12,31]; therefore, we assessed heterogeneity in the association between endometriosis and stroke by potential effect modifiers, including current age (<50 years old, ≥50 years old), BMI (<25, ≥25 kg/m^2), history of infertility (yes, no), menopausal status (premenopausal, postmenopausal), smoking status, history of hypertension, history of hypercholesterolemia, history of hormone therapy use, and history of age at menopause (≤45, >45). Women contributed person-time to the appropriate strata given their time-varying status over follow-up. Likelihood-ratio tests were used to test for statistically significant differences between groups.[27]

Sensitivity analyses were performed to investigate known complexities in endometriosis diagnosis. Women with endometriosis may wait many years between when their symptoms begin and when they receive a diagnosis of endometriosis. Therefore, due to the potential diagnostic delay between endometriosis symptom onset and disease diagnosis,[32,33] the date of endometriosis diagnosis was predated in sensitivity analyses by 4, 6, and 8 years. Additionally, we expanded our endometriosis exposure definition to include endometriosis cases both with and without laparoscopic confirmation.

RESULTS

During 2 770 152 person-years of follow-up, there were 893 incident cases of stroke. At baseline in 1989, women with laparoscopically confirmed endometriosis were more likely than women without a history of endometriosis to report a BMI <25 kg/m^2 at age 18, an earlier age at menarche, irregular menstrual cycles, a history of infertility, nulliparity, and to have been past or current oral contraceptive users (Table 1). We observed no difference between women with and without a history of endometriosis for physical activity patterns, alcohol intake, or Alternative Health Eating Index dietary intake score. Women with a history of endometriosis were more likely to report a family history of myocardial infarction and stroke.

Women with a history of laparoscopically confirmed endometriosis had a 34% greater risk of stroke compared to women without a history of endometriosis in models adjusted for potential confounding factors (hazard ratio, 1.34 [95% CI, 1.10–1.62]; Table 2). This association was partially mediated by occurrence of hysterectomy or oophorectomy (percent mediated: 39%), postmenopausal hormone therapy (15.5%), age at menopause <45 (12.3%), history of hypertension (8.4%), or history of high cholesterol (4.9%; Table 3). We observed no difference in the association between endometriosis and risk of stroke by age, BMI, history of infertility, menopausal status, smoking history, history of hysterectomy/oophorectomy, history of hypertension, history of hypercholesterolemia, history of hormone therapy use, and history of age at menopause (Table S1). Sensitivity analyses that included all reports of endometriosis, with or without laparoscopic confirmation, did not meaningfully change the results (data not shown).

DISCUSSION

In this analysis, we observed that women with a history of endometriosis had a greater risk for stroke compared to women without a history of endometriosis. This association was found to be partially attributable to the influence of hysterectomy/oophorectomy occurrence, postmenopausal hormone therapy, menopausal status, and history of hypertension. We observed no difference in the association by infertility history, age, or BMI.

There are several different pathways through which endometriosis may be associated with risk of stroke. Women with

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Table 1. Age-Standardized Characteristics of the NHSII Population at 1989 Baseline by Laparoscopically Confirmed Endometriosis Diagnosis

	Laparoscopically confirmed endometriosis	
	Yes (n=5244)	No (n=106 812)
Age, y*	36 (4.2)	34.7 (4.7)
BMI at 18 y old, kg/m²		
<18.5, %	79.6	75.1
18.5–<22.5, %	12.6	14.3
22.5–<25, %	5.9	8.0
25+, %	1.9	2.6
BMI at baseline, kg/m²		
<18.5, %	3.9	3.4
18.5 to <22.5, %	45.2	44.1
22.5 to <25, %	22.8	22.4
25 to <30, %	18.9	18.6
30+, %	9.2	11.5
Age at menarche, years old		
≤11, %	28.8	24.4
12–13, %	56.1	57.6
14+, %	15.1	18.1
Menstrual cycle pattern in adulthood		
Regular, %	86.7	90.0
Irregular, %	7.8	6.3
No menses, %	5.4	3.6
Infertility		
Yes, %	54.0	16.5
No, %	46.0	83.5
Oral contraceptive use		
Current, %	9.3	11.7
Past, %	80.0	71.3
Never, %	10.7	17.0
No. of pregnancies ≥6 mo		
Nulliparous, %	41.5	29.7
Parity 1, %	23.1	18.8
Parity 2, %	25.8	33.1
Parity 3+, %	9.6	18.4
Race and ethnicity		
White, %	94.0	92.5
Smoking status		
Current, %	14.2	13.2
Cumulative average physical activity, met h/wk		
42+, %	16.6	16.2
Married		
Yes, %	82.1	77.3
Alcohol intake, g/d†		
>5, %	15.2	15.2
Family history of MI‡		
Yes, %	44.9	41.0
Family history of stroke§		
Yes, %	27.4	24.1
Aspirin use		
Current, %	12.7	11.0
NSAID use		
Current, %	26.3	18.9

(*Continued*)

Table 1. Continued

Values are means (SD) for continuous variables; percentages or ns or both for categorical variables, and are standardized to the age distribution of the study population. Values of polytomous variables may not sum to 100% due to rounding

BMI indicates body mass index; MI, myocardial infarction; and NHSII, Nurses' Health Study II.

*Value is not age adjusted.

†Alcohol intake from 1991 questionnaire.

‡Family history of MI cumulative through 2013 questionnaire.

§Family history of stroke cumulative through 2013 questionnaire.

endometriosis have been found to have a hyperinflammatory milieu both locally (in the peritoneal cavity) and systemically[7,9] that may contribute to a greater risk of CVD. Specifically, several inflammatory markers have been found to be elevated in women with endometriosis, such as ICAM-1 (intracellular adhesion molecule 1), CRP (C-reactive protein), IL (interleukin)-1 and IL-6, TNF (tumor necrosis factor)-α, and VEGF (vascular endothelial growth factor)[34–36]; most of these biomarkers have also been associated with CVD risk. Additionally, some evidence supports lower risk of CVD among those with longer reproductive lifespan[37] and later menopause transition.[3] Early age at menopause, which can be surgically induced by oophorectomy, can substantially modify cardiometabolic disease onset.[38,39] Furthermore, there is growing evidence that hysterectomy with or without bilateral oophorectomy may impact CVD risk.[40,41] Individuals with endometriosis have a higher incidence of hysterectomy with and without oophorectomy and also of surgical menopause, which may contribute to stroke risk.[1,5,6]

We observed that women with endometriosis had a 34% greater risk for stroke compared to women without a history of endometriosis in multivariable models adjusted for detailed potential confounding factors. The findings from this manuscript are in agreement with previous findings. Prior research from NHSII with 20 years of follow-up observed that women with a history of endometriosis had a greater risk of coronary heart disease,[12] hypertension, and hypercholesterolemia.[10] Specifically, women with a history of endometriosis had a 52% greater risk of myocardial infarction, a 91% greater risk of angiographically confirmed angina, a 35% greater risk of coronary artery bypass graft surgery/coronary angioplasty/stent,[12] a 22% greater risk of hypercholesterolemia, and a 29% greater risk of hypertension.[10] Research from a retrospective cohort in Taiwan (median follow-up: 9.2 years), observed that women with endometriosis had a 1.2-fold greater risk of any major adverse cardiovascular and cerebrovascular events compared to women without endometriosis, with a 1.16-fold greater

Table 2. Laparoscopically Confirmed Endometriosis Diagnosis in Relation to Risk of Stroke Among Participants in the Nurses' Health Study II Followed From 1989 to 2017

Endometriosis	Cases/ person-years	Hazard ratio of incident stroke (95% CI)	
		Model 1*	Model 2†
No	765/2 517 730	1.0 (Referent)	1.0 (Referent)
Yes	128/252 422	1.49 (1.23–1.80)	1.34 (1.10–1.62)

AHEI indicates Alternative Health Eating Index; BMI, body mass index; and MI, myocardial infarction.

*Model 1: adjusted for age (months) and calendar time

†Model 2: Additionally adjusted for alcohol intake, BMI at age 18 y, current BMI, age at menarche, menstrual cycle pattern in adolescence, current menstrual cycle pattern in adulthood, parity, oral contraceptive use history, smoking history, AHEI diet score in quintiles, physical activity, race, income, family history of MI, family history of stroke, aspirin use, and NSAID use

Table 3. The Proportion Mediated (95% CI) of the Association Between Endometriosis and Risk of Stroke

Covariate	Proportion mediated (95% CI)*	*P* value†
History of hypertension	8.4% (3.6–18.1)	≤0.0001
History of high cholesterol	4.9% (1.8–12.4)	0.003
Hormone therapy use	15.5% (4.8–39.9)	0.01
Hysterectomy/oophorectomy	39.0% (14.3–71.0)	≤0.0001
Age at menopause <45, ≥45 y	12.3% (1.9–50.0)	0.06

AHEI indicates Alternative Health Eating Index; BMI, body mass index; and MI, myocardial infarction.

*Multivariable models adjusted for alcohol intake, BMI at age 18, current BMI, age at menarche, menstrual cycle pattern in adolescence, current menstrual cycle pattern in adulthood, parity, oral contraceptive use history, smoking history, AHEI diet score in quintiles, physical activity, race, income, family history of MI, family history of stroke, aspirin use, and NSAID use.

†The macro used to get the CI does not go below zero and, therefore, may not represent nonstatistically significant *P* values.

risk of cerebrovascular accident.[13] Similarly, a retrospective cohort from the Health Improvement Network in the United Kingdom (average follow-up: 5.7 years, maximum follow-up: 23 years) observed that women with endometriosis had a 1.24-fold greater risk of their composite CVD end point and a 1.19-fold greater risk of cerebrovascular disease. The cross-sectional Japan Nurses' Health Study reported a two-fold risk of either transient ischemic attack or cerebral infarction for women with endometriosis compared to women without endometriosis.[11]

We observed that the association between endometriosis and risk of stroke was partially mediated by occurrence of oophorectomy or hysterectomy, hormone therapy, age at menopause, and history of hypertension. Prior research from the UK observed that when women with hysterectomy and oophorectomy were excluded from analyses, the relationship between endometriosis and CVD was attenuated,[14] implying that gynecologic surgery, or the indication for the surgery, may partially contribute to increased risk of CVD. Mu et al's[12] analysis in the NHSII observed that 42% of the association between endometriosis and coronary heart disease was mediated by hysterectomy/oophorectomy and age at surgery. Prior research has suggested that hysterectomy with and without ovarian conservation may influence CVD risk.[38,40–42] Research has also observed that women with endometriosis may have greater risk of hypertension than women without endometriosis.[10,11] In our analysis, hypertension was found to be a modest mediator of the association between endometriosis and risk of stroke. Although prior research in the NHSII observed the association between endometriosis and coronary heart disease was strongest among younger women (<40 years of age),[12] we observed no difference in the relationship between endometriosis and risk of stroke by age (<50 years of age).

This study has many strengths including its prospective design, large sample size, endometriosis confirmed by laparoscopy, nearly 30 years of longitudinal follow-up, and detailed evaluation of potential time-varying confounding, mediation, and effect modification of the association between endometriosis and stroke. However, there are also important limitations that must be considered. The exact onset of endometriosis cannot be determined—regardless of study design or population sampled, and the time from symptom onset to definitive diagnosis (laparoscopy) can be many years (NHSII mean=4 years, general population mean=7 years[32]). To reduce misclassification of endometriosis, we restricted our analyses to laparoscopic confirmation of endometriosis which has extremely high validity with the medical record (≥96%).[21] We also conducted 2 sensitivity analyses related to our endometriosis definition—we predated our endometriosis diagnoses by 4, 6, and 8 years, and we also expanded our endometriosis definition to include all women with any self-reported endometriosis. In both sensitivity analyses, the results did not meaningfully change. We were unable to differentiate between hemorrhagic and ischemic stroke using the current data set nor was ischemic stroke subtype available for analysis. Whether or not endometriosis is more strongly associated with a particular stroke subtype is an important area for future research that could inform strategies to reduce stroke risk among patients with endometriosis. Moreover, given limited statistical power in this data source, we are unable to investigate the influence of serious cardiovascular events, such as myocardial infarction and coronary artery bypass graft surgery, on the association between endometriosis and stroke risk.

Our unexposed group may include women who have never reported, recognized, or received a diagnosis for their endometriosis. We expect the prevalence of undiagnosed endometriosis to be sufficiently low and to have minimal impact on study results; however, their characteristics will be diluted among the ≈80 000 true unexposed women.[43] Our analysis was able to take into account the influence of hysterectomy and oophorectomy on risk of stroke; however, we were not able to incorporate information on all treatments for endometriosis that may influence stroke risk. The NHSII cohort is not a random sample of US women; thus, our findings may not be generalizable

to the entire population. However, it is unlikely that the biological associations observed in this cohort will differ from women in general.[16,44] The high level of education and interest in health are distinct advantages that aid our ability to collect valid, high-quality information, and reduce possible confounding by socioeconomic factors.

Our findings, along with previous research on endometriosis and CVD, suggest that clinicians should consider both reproductive and gynecologic health history when counseling patients regarding their CVD risk. Future research should focus on replicating these findings, looking separately at ischemic versus hemorrhagic stroke, and assessing the influence of reducing CVD risk factors among women with endometriosis.

CONCLUSIONS

Prior research has suggested that women with endometriosis may be at increased risk of CVDs such as myocardial infarction and hypertension. Our prospective analysis with nearly thirty years of longitudinal follow-up suggests that women with laparoscopically confirmed endometriosis may also be at increased risk of stroke. These findings should be replicated in other large, longitudinal cohorts to fully disentangle the contribution of endometriosis treatments on CVD risk. Women and their health care providers should be aware of their gynecologic and reproductive history when counseling patients and evaluate cardiovascular risk factors and primary prevention of CVD, as well as the signs and symptoms of CVD, including stroke.

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Supplemental Material

Figure S1
Table S1

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