Stroke risk in women with or without hysterectomy and/or bilateral oophorectomy: evidence from the NHANES 1999-2018 and meta-analysis

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Abstract

Objective: We aimed to assess the relationship between hysterectomy and/or bilateral oophorectomy and the risk of stroke—a topic of ongoing debate in current research.

Methods: We utilized data from the National Health and Nutrition Examination Survey (NHANES) 1999-2018 to estimate both crude and multivariable-adjusted hazard ratios (HRs) and 95% CIs, applying survey-weighted Cox proportional hazards regression model. The modeling incorporated sampling weights and design variables to address NHANES's multistage probability sampling framework. In addition, a meta-analysis was conducted, incorporating findings from NHANES with those from other cohort studies identified through database search.

Results: This unweighted NHANES cohort included 21,240 women with 8.3 median follow-up years, documenting 193 stroke-related deaths. Compared with no hysterectomy, hysterectomy was not significantly associated with stroke mortality (HR: 1.28, 95% CI: 0.89-1.85). However, a meta-analysis of 2,065,490 participants from NHANES and 15 other studies demonstrated hysterectomy was linked to a 9% higher stroke risk (HR: 1.09, 95% CI: 1.04-1.15) compared with no hysterectomy. Similar finding was identified for bilateral oophorectomy (HR: 1.13, 95% CI: 1.09-1.17) compared with no bilateral oophorectomy. Subgroup analyses stratified by surgical indication, ovarian conservation status, and reference population consistently demonstrated elevated risks.

Conclusions: In summary, the data from NHANES and other studies indicate women with hysterectomy and/or bilateral oophorectomy may be associated with an increased stroke risk. Additional prospective studies are needed to confirm the association between hysterectomy and/or bilateral oophorectomy and stroke risk.

Key Words: Cohort, Epidemiology, Hysterectomy, Oophorectomy, Stroke.

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The NHANES data are publicly accessible and can be found on this website: https://wwwn.cdc.gov/nchs/nhanes/Default.aspx, initially accessed April 18. 2024. Meta-analysis is based on published studies.
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Stroke is the third dominant cause of death and the fourth dominant cause of disability around the world, representing a significant public health challenge.[1] The Global Burden of Disease Study 2021 reports ~11.9 million new stroke cases, 93.8 million existing events, 160.5 million disability-adjusted life years lost, and 7.3 million stroke-related deaths.[1] Therefore, ongoing prevention efforts that address modifiable risk factors are essential to reduce the burden of this disease.

Women of reproductive age exhibit lower stroke risk, whereas postmenopausal women experience an approximately 2-fold increase within a decade of menopause,[2,3] likely mediated by abrupt estrogen decline. Estrogen confers atheroprotection through vasodilation enhancement, fibrosis reduction, and mitochondrial/antioxidant optimization.[4-6] Hysterectomy and oophorectomy—common gynecologic surgeries— significantly impact estrogen levels.[7-9] Hysterectomy may accelerate ovarian failure through damage to the ovarian tissue or its blood supply.[10-14] This may result in lower ovarian sex steroid levels and precipitating earlier menopause. An oophorectomy can reduce premenopausal serum estradiol by up to 80% and androgen levels by about 50% in both premenopausal and postmenopausal women.[8,9] Therefore, understanding the consequences of these procedures is crucial, as they entail remarkable hormonal changes that can influence stroke risk similarly to natural menopause.

Despite pathophysiological plausibility, existing studies report inconsistent stroke risk associations with these procedures.[15-36] These inconsistent results may stem from variations in study design and participant characteristics. For instance, 2 cross-sectional studies analyzing the National Health and Nutrition Examination Survey (NHANES) data from 2007 to 2018[33] and 2005 to 2018[34] identified a positive link between hysterectomy and stroke, yet the role of oophorectomy remains undetermined. To provide additional evidence for this relationship, this study incorporates NHANES 1999-2018 data[37-40] with a cohort design and other studies.

METHODS

Study design

The NHANES study prospectively collects data on health, diet, and personal, social, and economic characteristics, and is linked to the National Death Index, enabling the assessment of the relationship between individual exposures and public health. We assessed the relationship between hysterectomy and/or bilateral oophorectomy and stroke risk using a retrospective cohort design in NHANES 1999-2018 and adheres to the strengthening the reporting of observational studies in epidemiology (STROBE) statement.[41] In addition, the meta-analysis was performed following the Preferred Reporting Items for Systematic reviews and Meta-Analyses.[42]

Data sources

The NHANES, conducted by the Centers for Disease Control and Prevention, is a series of research initiatives designed to assess the health and nutritional status of both adults and children across the United States. Data from this cross-sectional survey have been made available biennially since 1999. All participants furnished written informed consent, and ethical approval was obtained from the National Center for Health Statistics (NCHS) Ethics Review Board (Protocol #98-12, Protocol #2005-06, Protocol #2011-17, and Protocol #2018-01).

Study population

Supplemental Figure 1 (Supplemental Digital Content 1, http://links.lww.com/MENO/B397) illustrates the participant selection process from 10 survey cycles (1999-2018). Among 101,316 initial participants, we sequentially excluded: 49,893 males; 20,768 aged younger than 18 years; 1,551 with incomplete mortality/follow-up data; and 7,864 lacking hysterectomy records. The final analytic cohort included 21,240 women.

Exposure data

Hysterectomy and bilateral oophorectomy data were collected from reproductive health questions: "rhd280: Had a hysterectomy?" "rhq290 and rhq291: age when had hysterectomy," "rhq300: Had at least one ovary removed?" "rhq310: Were both ovaries removed or only one?" "rhq305: Had both ovaries removed?" Responses of "Refused" or "Don't know" to "rhd280: had a hysterectomy?" were classified as "missing and excluded."

Follow-up and outcomes

NCHS has linked the National Death Index to obtain death certificate records. Stroke was identified with the 10th edition of the International Classification of Diseases codes I60-I69. The follow-up period began on the date when the interview was completed and continued until 31 December 2019, or until the participant's death, whichever occurred first.

Covariates

Based on previous investigations, 3 types of covariates, including the basic demographic characteristics, traditional risk factors, and female-specific factors associated with hormone exposure, were considered in the current analysis. Participants were initially categorized into 5 racial/ethnic groups: non-Hispanic White (n = 9,457), non-Hispanic Black (n = 4,372), Mexican American (n = 3,543), other Hispanic (n = 1,946), and other/multiracial (n = 1,922). We combined the latter 2 groups as "others." The basic demographic characteristics included age (continuous), race [non-Hispanic White, non-Hispanic Black, Mexican American, others (other accounts for other Hispanic and other/multiracial)], marital (married or living with partner, never married, widowed/divorced/separated, unknown), education (up to high school, some college, college graduate or above, unknown), and family poverty income ratio (PIR; $\leq$1.30, 1.31-3.5, $>$3.5, unknown).[43] The traditional risk factors involved history of hypertension (no, yes, unknown), high cholesterol (no, yes, unknown), diabetes (no, yes, borderline, unknown), stroke (no, yes, unknown), coronary heart disease (no, yes, unknown), smoking (never, former, current, unknown), alcohol consumption (never, former, current, unknown), and body mass index (BMI, $<$25, 25-29.9, $\geq$30 kg/m^2). The female-specific factors associated with hormone exposure involved oral contraception (OC) use (never, ever, unknown), hormone therapy (HT) use (never, ever, unknown), age at menarche ($\leq$11, 12-13, $\geq$14, unknown), age at menopause ($<$40, 40-44, 45-49, $\geq$50, unknown), and number of live births (0, 1, 2, 3, 4, $\geq$5, unknown).

Statistical analyses

Considering the NHANES survey employs a complex, multistage probability sampling method, we conducted all statistical analyses accounting for sample weights using R software (version 3.4.3; https://www.r-project.org/). In this study, we analyzed data from 10 cycles spanning 1999-2018. According to the guidelines, we applied the mobile examination center (MEC) weights during the analysis. The weighting formula for 1999-2000 and 2001-2002 was 2/10 multiplied by "wtmec4yr," and for 2003-2018, it was adjusted to 1/10 times "wtmec2yr."

Categorical variables were shown as frequency numbers (percentages). The continuous variables were described as the mean ± SD. Weighted Cox proportional hazards regression analyses were conducted. Hazard ratios (HRs) and 95% CIs for 3 models were estimated. Model I was not adjusted for any covariates. Model II was adjusted for demographic characteristics and traditional risk factors for stroke, as detailed listed in the "covariate section." Model III was adjusted for model II plus female-specific factors associated with hormone exposure. To utilize all available data, missing values for classified covariates were reported as missing category in all analyses.[44] We also performed a sensitivity analysis restricted to individuals without a history of stroke.

In this study, we first analyzed hysterectomy status and age at surgery ($\leq$44, 45-49, $\geq$50 y) versus non-hysterectomy controls, regardless of ovarian status. Given frequent oophorectomy cooccurrence, sensitivity analyses compared 4 groups: (1) nonsurgical, (2) hysterectomy-only, (3) hysterectomy with unilateral oophorectomy, and (4) hysterectomy with bilateral oophorectomy.

Meta-analysis

We conducted a comprehensive literature search on PubMed and Embase databases (from their inception to April 4, 2024) to identify all original articles. The detailed search strategy is outlined in Supplemental Table 1 (Supplemental Digital Content 1, http://links.lww.com/MENO/B397). In addition, we reviewed the reference lists of the included articles, reviews, and meta-analyses/systematic reviews to supplement our initial search strategy. We restricted our search to human studies without specifying any further limits. Detailed methods regarding inclusion/exclusion criteria, data extraction, literature bias assessment, and GRADE evidence quality evaluation are presented in the Supplemental Text (Supplemental Digital Content 1, http://links.lww.com/MENO/B397).

Prior research focused on hysterectomy status (yes/no) and bilateral oophorectomy presence (yes/no); thus, we selected this as the main focus of our analysis. Two main categories were identified for bilateral oophorectomy: "bilateral oophorectomy with hysterectomy versus hysterectomy alone" and "bilateral oophorectomy versus no surgery (no hysterectomy or bilateral ovariectomy)." Initial pooled analysis compared bilateral oophorectomy versus nonexposed cohorts, followed by subgroup stratification based on reference groups. In women undergoing hysterectomy, we examined the stroke risk association with ovarian conservation (ovarian-conserving hysterectomy vs hysterectomy with bilateral oophorectomy). Subgroup analyses were also performed based on surgical indications (benign vs benign/malignant). In the current study, we did not assess the impact of age at surgery on stroke risk, as few studies have reported on this variable, and the cutoff values for age vary greatly.

We applied a random-effect model by DerSimonian and Laird et al[45] to combine the risk estimates with their corresponding 95% CIs when the I^2 statistic exceeded 50% or $P < 0.1$[46]; otherwise, we used a fixed-effect model. When studies separately reported risk estimates by age at surgery or stroke type, we initially pooled these estimates using a fixed-effect model before integrating them with other studies. Potential publication bias was evaluated by funnel plots and Egger test.[47,48] To evaluate the impact of each study on the overall findings, a sensitivity analysis was conducted by systematically excluding one study at a time. All meta-analyses were performed using STATA software (version 15.0, StataCorp LLC).

To tackle the issue of unmeasured confounding, we carried out an additional sensitivity analysis, using a newly accepted method proposed by VanderWeele et al.[49,50] E-values (https://www.evalue-calculator.com/) assist in gauging the stability of the overall findings by determining whether the residual confounding on a specific scale is reasonable.

AI statement

AI tools were employed in this study to optimize textual clarity, conciseness, and linguistic accuracy while mitigating redundancy.

RESULTS

National Health and Nutrition Examination Survey

The final unweighted cohort (n = 21,240, ages: 20-85 y) represented ~85.9 million US women. Over 8.3 median follow-up years, we documented 193 stroke-related deaths (population-weighted estimate: 554,167). As detailed in Supplemental Table 2 (Supplemental Digital Content 1, http://links.lww.com/MENO/B397), hysterectomy recipients were typically older and had higher rates of bilateral oophorectomy (52.02%), obesity, comorbidities, and parity (> 3 live births).

Unadjusted analyses demonstrated a significant association between hysterectomy and stroke (HR: 2.34, 95% CI: 1.66-3.30; Table 1 and Supplemental Table 3, Supplemental Digital Content 1, http://links.lww.com/MENO/B397). However, this association was not significant after sequential adjustments for basic demographic characteristics and traditional risk factors (HR: 1.16, 95% CI: 0.82-1.66), and further adjustment for female-specific factors (HR: 1.28, 95% CI: 0.89-1.85). Age-stratified analyses showed no significant association across subgroups: younger than 45 years (HR: 1.56, 95% CI: 0.92-2.65), 45-49 years (HR: 0.84, 95% CI: 0.30-2.32), and 50 years or older (HR: 1.18, 95% CI: 0.69-2.02).

To address ovarian hormone confounding, we stratified analyses by oophorectomy status. Compared with no surgery, hysterectomy alone (HR: 0.92, 95% CI: 0.52-1.64) and hysterectomy with unilateral ovariectomy (HR: 1.32, 95% CI: 0.45-3.90) were not significantly associated with stroke risk; however, hysterectomy combined with bilateral oophorectomy was associated with a 51% increased risk (HR: 1.55, 95% CI: 1.04-2.31). Moreover, a borderline association was identified for hysterectomy with bilateral ovariectomy compared with hysterectomy alone (HR: 1.62, 95% CI: 0.92-2.89).

We also performed a sensitivity analysis restricted to individuals without a history of stroke. Similarly, no significant association between hysterectomy and stroke risk was identified (Supplemental Table 4, Supplemental Digital Content 1, http://links.lww.com/MENO/B397).

TABLE 1. Hysterectomy and stroke risk in the NHANES data

	Model I		Model II		Model III	
Character	**HR and 95% CI**	***P***	**HR and 95% CI**	***P***	**HR and 95% CI**	***P***
Hysterectomy						
No	1.0 (Ref.)	—	1.0 (Ref.)	—	1.0 (Ref.)	—
Yes	2.34 (1.66-3.30)	< 0.001	1.16 (0.82-1.66)	0.404	1.28 (0.89-1.85)	0.182
Age at hysterectomy						
No	1.0 (Ref.)	—	1.0 (Ref.)	—	1.0 (Ref.)	—
< 45	1.73 (1.16-2.57)	0.007	1.21 (0.78-1.86)	0.395	1.56(0.92-2.65)	0.099
45-49	1.84 (0.72-4.69)	0.199	0.79 (0.33-2.08)	0.693	0.84 (0.30-2.32)	0.730
≥ 50	4.50 (2.72-7.44)	< 0.001	1.12 (0.68-1.85)	0.659	1.18 (0.69-2.02)	0.553
Status of ovarian conservation						
No any surgery	1.0 (Ref.)	—	1.0 (Ref.)	—	1.0 (Ref.)	—
Hysterectomy alone	1.62 (0.93-2.82)	0.086	0.88 (0.51-1.49)	0.626	0.92 (0.52-1.64)	0.784
Hysterectomy with unilateral ovariectomy	2.41 (0.90-6.46)	0.08	1.18 (0.45-3.09)	0.733	1.32 (0.45-3.90)	0.616
Hysterectomy with bilateral ovariectomy	2.77 (1.90-4.05)	< 0.001	1.36 (0.90-2.05)	0.148	1.55 (1.04-2.31)	0.032
Hysterectomy and bilateral ovariectomy						
Hysterectomy alone	1.0 (Ref.)	—	1.0 (Ref.)	—	1.0 (Ref.)	—
Hysterectomy with bilateral ovariectomy	1.74 (1.00-3.03)	0.051	1.41 (0.84-2.39)	0.197	1.62 (0.92-2.89)	0.095

Model I was not adjusted for any covariates.

Model II was adjusted for age (continuous), race [non-Hispanic White, non-Hispanic Black, Mexican American, others (other accounts for other Hispanic and other/multiracial)], marital (married or living with partner, never married, widowed/divorced/separated, unknown), education (up to high school, some college, college graduate or above, unknown), and poverty income ratio (≤ 1.30, 1.31-3.5, > 3.5, unknown), history of hypertension (no, yes, unknown), high cholesterol (no, yes, unknown), diabetes (no, yes, borderline, unknown), stroke (no, yes, unknown), coronary heart disease (no, yes, unknown), smoking (never, former, current, unknown), alcohol consumption (never, former, current, unknown), and body mass index (< 25, 25-29.9, ≥ 30 kg/m^2, unknown).

Model III was adjusted for model II plus oral contraception use (never, ever, unknown), hormone therapy use (never, ever, unknown), age at menarche (≤ 11, 12-13, ≥ 14, unknown), age at menopause (< 40, 40-44, 45-49, ≥ 50, unknown), and number of live births (0, 1, 2, 3, 4, ≥ 5, unknown).

HR, hazard ratio; NHANES, National Health and Nutrition Examination Survey; Ref., reference.

Meta-analysis

Our systematic search identified 5,713 articles initially, with 124 proceeding to full-text review (Supplemental Fig. 2, Supplemental Digital Content 1, http://links.lww.com/MENO/B397). After exclusions (n = 110; Supplemental Table 5, Supplemental Digital Content 1, http://links.lww.com/MENO/B397) and adding one study from references,[36] 15 articles published between 2009 and 2023 were included.[15-28,36] The major characteristics of the included studies were listed in Supplemental Table 6 and Supplemental Table 7 (Supplemental Digital Content 1, http://links.lww.com/MENO/B397). The study populations originated from the USA, the UK, China, Sweden, Denmark, Australia, and Korea. Sample sizes varied between 3,474 and 833,484. Stroke outcomes were ascertained using various hospitalization records, death register, or self-report without validation.[24] The included studies exhibited heterogeneity in stroke outcome, with our study and 3 others[15,19,36] specifically examining fatal strokes, one study[24] reporting nonfatal strokes exclusively, while the remaining studies[16-18,20-23,25-28] presented composite fatal and nonfatal stroke cases. Hysterectomy and bilateral oophorectomy were confirmed using medical records[15,16,18,20-22,26,28] or self-reported questionnaires.[17,19,23-25,27,36] Most studies[15-20,22,25,26,28,36] reported benign diseases as the indication for surgery, with some exceptions[21,23,24,27] where the indication included benign/malignant conditions.

Our primary analysis assessed hysterectomy-associated stroke risk using non-hysterectomy as reference level, incorporating 9 studies including NHANES.[16,18,20,21,23,25-27,36] Pooled analysis demonstrated elevated stroke risk with hysterectomy (HR: 1.09, 95% CI: 1.04-1.15, P = 0.001; I^2 = 50.4%, P for heterogeneity = 0.034; Table 2). In subtype analyses by surgical indication, the significant association was only pronounced in benign indications (HR: 1.10, 95% CI: 1.04-1.17, P = 0.001; I^2 = 56.5%, P for heterogeneity = 0.042), but not in benign/malignant group (HR: 1.05, 95% CI: 0.92-1.20, P = 0.454; I^2 = 50.5%, P for heterogeneity = 0.109). When stratified by ovarian conservation status, elevated stroke risk was observed both in women with ovarian conservation (HR: 1.05, 95% CI: 1.01-1.08, P = 0.01; I^2 = 29.6%, P for heterogeneity = 0.182) and those with bilateral oophorectomy (HR: 1.18, 95% CI: 1.10-1.27, $P <$ 0.001; I^2 = 9.6%, P for heterogeneity = 0.355) compared with no surgery.

Thirteen studies examined bilateral oophorectomy's association with stroke risk.[15-17,19,21-28,36] Compared with no oophorectomy (regardless of hysterectomy status), pooled analysis showed significantly increased stroke risk (HR: 1.13, 95% CI: 1.09-1.17, $P <$ 0.001; I^2 = 17.3%, P for heterogeneity = 0.269). After excluding one study with unclear oophorectomy classification,[23] results remained consistent (HR: 1.13, 95% CI: 1.09-1.18, $P <$ 0.001; I^2 = 22.2%, P for heterogeneity = 0.225). Subgroup analyses by surgical indication and reference populations showed no significant differences across all subgroups (Table 2).

Sensitivity analysis sequentially excluding each study confirmed the robustness of our findings, with no single study significantly influencing the overall results (Supplemental Table 8 and Supplemental Table 9, Supplemental Digital Content 1, http://links.lww.com/MENO/B397).

TABLE 2. Meta-analysis for the association between stroke risk and hysterectomy and/or bilateral ovariectomy

			Pooled results		Heterogeneity	
Exposure	**Group**	**Model**	**HR and 95% CI**	***P***	**I^2 (%)**	***P***
Bilateral ovariectomy vs nonbilateral ovariectomy	All studies	Fixed	1.13 (1.09-1.17)	< 0.001	17.3	0.269
	Surgery indication	—	—	—	—	—
	Benign	Fixed	1.13 (1.08-1.18)	< 0.001	39.8	0.102
	Benign/malignant	Fixed	1.12 (1.05-1.20)	0.001	0.0	0.753
	Reference populations	—	—	—	—	—
	No hysterectomy or bilateral ovariectomy	Fixed	1.16 (1.11-1.21)	< 0.001	0.5	0.430
	Hysterectomy alone	Fixed	1.08 (1.02-1.15)	0.007	10.5	0.341
Hysterectomy vs non-hysterectomy	All studies	Random	1.09 (1.04-1.15)	0.001	50.4	0.034
	Surgery indication	—	—	—	—	—
	Benign	Random	1.10 (1.04-1.17)	0.001	56.5	0.042
	Benign/malignant	Random	1.05 (0.92-1.20)	0.454	50.5	0.109
	Status of ovarian conservation	—	—	—	—	—
	Bilateral ovariectomy	Fixed	1.18 (1.10-1.27)	< 0.001	9.6	0.355
	Hysterectomy alone or ovarian conservation	Fixed	1.05 (1.01-1.08)	0.010	29.6	0.182

HR, hazard ratio.

Egger tests (*P* = 0.642 for bilateral oophorectomy; *P* = 0.676 for hysterectomy) and funnel plots (Supplemental Fig. 3, Supplemental Digital Content 1, http://links.lww.com/MENO/B397) both indicated no evidence of publication bias.

In another sensitivity analysis, we calculated E-values of 1.51 for bilateral ovariectomy and 1.40 for hysterectomy, suggesting the observed HR of 1.13 for bilateral ovariectomy and 1.09 for hysterectomy could be attributed to an unmeasured confounder that is linked with both exposures and stroke, with a risk ratio of 1.51-fold or 1.4-fold respectively, or above and beyond the measured confounders. However, weaker confounding could not account for this.

Based on the Newcastle Ottawa Scale, all included studies were classified as good quality with the exception of one study, which was rated as poor quality (Supplemental Table 10, Supplemental Digital Content 1, http://links.lww.com/MENO/B397). In addition, the GRADE evaluation indicated that the overall quality of evidence was "very low" for hysterectomy and bilateral oophorectomy (Supplemental Table 11, Supplemental Digital Content 1, http://links.lww.com/MENO/B397).

DISCUSSION

Principal findings

In the NHANES 1999-2018 study with follow-up until the end of 2019, hysterectomy was not significantly associated with stroke risk. However, a subsequent meta-analysis incorporating NHANES and other cohort data demonstrated elevated stroke risk with hysterectomy and/or bilateral oophorectomy.

Potential biological mechanisms

The biological mechanisms connecting stroke risk to hysterectomy and/or bilateral oophorectomy remain elusive. Potential mechanisms include:

- These surgeries lead to abrupt estrogen loss impairing cardiovascular protection.[4-14]
- Harmful hemorheologic changes occur after surgery. Evidence indicates that menopausal hematocrit elevation increasing blood viscosity, promoting endothelial damage and thrombogenesis through shear stress.[26,51-54]
- Hysterectomy induces menopausal transition, while postmenopausal iron dysregulation accelerates atherosclerosis through oxidative pathways.[55-58]
- Hysterectomy—especially when performed abdominally—can provoke a systemic inflammatory response,[59-62] contributing to endothelial dysfunction.
- Ovary-retaining hysterectomy elevating atherogenic lipids (total/LDL cholesterol) versus natural menopause.[63]

Current concerns

The primary concern regarding hysterectomy and stroke risk is the confounding effect of bilateral oophorectomy. While 2 studies showed nonsignificant increased risk for hysterectomy alone versus no surgery,[18,20] 5 studies provided separate comparisons.[21,23,25-27] The Korean cohort found no significant stroke risk increase with hysterectomy, regardless of oophorectomy status.[21] Four other studies consistently showed elevated stroke risk with hysterectomy (with or without oophorectomy),[23,25-27] though not always significant.[23,27] Our NHANES analysis similarly found an increased risk was identified for hysterectomy with bilateral oophorectomy, but not for hysterectomy alone or hysterectomy with unilateral oophorectomy, compared with no surgery. Furthermore, we observed a marginally significant association when comparing hysterectomy with bilateral oophorectomy versus hysterectomy alone. Finally, pooling analyses combining NHANES with other cohorts revealed an 18% higher risk of stroke for hysterectomy with bilateral oophorectomy, and a 5% higher risk of stroke for hysterectomy alone.

Surgical indication is another concern. While NHANES lacked surgical indication data, meta-analysis studies predominantly reported benign indications,[15-20,22,25,26,28] with 4 studies including benign/malignant cases.[21,23,24,27] Subgroup analysis revealed an increased risk of stroke across all surgical indications, though nonsignificant in the benign/malignant subgroup undergoing hysterectomy. Current evidence lacks differentiated stroke risk by specific indications (endometriosis, adenomyosis, fibroids, abnormal uterine bleeding, prolapse, and other rare conditions) with distinct pathogeneses. For instance, some evidence suggests that endometriosis is associated with an increased risk of stroke.[64,65] Hence, future research with indication-specific data is needed to clarify differential cerebrovascular risks.

Apart from ovarian conservation and surgical indications, the association between stroke risk and hysterectomy and/or bilateral oophorectomy appears to depend on the age at surgery or menopausal status. While NHANES and other cohorts found no age-specific associations,[15,17,19,22] three nationwide registries demonstrated elevated risk with younger surgical age,[16,18,25] without similar associations in groups around the menopausal age or older. Nevertheless, the use of varying prespecified age cut-offs (eg, <45, ≤ 49, and ≤ 50) across these studies was used.[16,18,25] Similarly, the Danish registers reported an increased stroke risk only in premenopausal and early postmenopausal women, but not in perimenopausal and late postmenopausal women.[28] Potential explanations for these discrepancies include: (1) possible chance findings, (2) selection bias, where older women undergoing elective surgery for benign reasons might be healthier and at lower stroke risk than younger women without surgery, may be present in previous studies,[16] (3) extended loss of hormonal protection in younger cohorts, (4) heightened sensitivity to hormonal shifts in younger women. Women around the menopausal age or older naturally experience a gradual decline in hormone levels due to aging, so the surgery has less impact on their hormonal balance. Moreover, the InterLACE study found that initiating HT after surgical menopause before age 45 was associated with modestly lower stroke risk compared with nonusers,[24] aligning with 2022 guidelines recommending HT until average menopause age (~52 y) for surgical menopause/primary ovarian insufficiency.[66] Hence, the menopausal status, age at surgery, the timeline of event since surgery, and interaction between HT use and age at surgery warrants further investigation.

Two studies examining stroke subtype risks post-hysterectomy/oophorectomy yielded discordant findings: the Korean cohort data showed no elevated risk,[21] whereas the China Kadoorie Biobank identified increased ischemic stroke risk, without hemorrhagic stroke association.[25] This discrepancy may reflect pathophysiological distinctions between stroke subtypes—ischemic (87% of all stroke cases) and hemorrhagic (40% of stroke-related deaths) strokes exhibit differential risk factor profiles, including diabetes, atrial fibrillation, previous stroke, smoking, and alcohol consumption.[67,68] Therefore, these procedures may differentially affect stroke subtypes, warranting future studies to elucidate subtype-specific associations and mechanistic distinctions between ischemic and hemorrhagic strokes.

Several hysterectomy techniques—including total abdominal, total laparoscopic, and vaginal hysterectomy —remain under-researched. Only one study has examined laparoscopic hysterectomy and stroke risk, demonstrating significantly higher risk versus no hysterectomy.[26] In addition, current evidence points that ovarian reserve decline (anti-Müllerian hormone reduction) across techniques, most marked post-abdominal hysterectomy than laparoscopic method.[69] Given these findings, further research is crucial to establish procedure-specific risk profiles, informing personalized surgical selection.

Compared with previous meta-analyses

Several meta-analyses have explored the association between stroke risk and hysterectomy and/or bilateral oophorectomy.[70-72] The earliest analysis, which included 2 studies without adjustment for potential confounders, reported that hysterectomy might confer a 12% decrease in stroke risk for women.[70] Subsequent work in 2022, incorporating one cross-sectional and 5 cohort studies, found no statistically significant association between hysterectomy (regardless of oophorectomy status) and stroke risk.[71] The most recent 2024 meta-analysis of 4 cohort studies identified a significantly elevated stroke risk specifically for hysterectomy performed with concurrent bilateral oophorectomy relative to no surgery.[72] In our investigation, we conducted a pooled analysis of NHANES and 15 additional studies to enhance analytical comprehensiveness and statistical power. Our methodology specifically accounted for 3 critical domains: (1) reference population heterogeneity, (2) ovarian conservation status, and (3) surgical indications. The final results revealed that hysterectomy alone also elevates stroke risk, while combined hysterectomy-oophorectomy showed further risk elevation compared with hysterectomy alone.

Strengths and limitations

The NHANES study boasts several strengths, including its prospective data collection, extended follow-up period, and comprehensive adjustment for key confounders. Additional merits include the consideration of ovarian conservation status, surgical indications, and reference exposure variations, with consistent subgroup findings. However, notable weaknesses warrant consideration. First, potentially, misclassification may attenuate true associations. In NHANES study, bilateral oophorectomy ascertainment (2007-2018 cycles) focused solely on whether participants had "both ovaries removed," potentially including unilateral cases in the reference group. In the meta-analysis, the NHANES and some other studies assessed surgical history and covariates exclusively through self-reported questionnaires at baseline, failing to account for temporal changes during follow-up periods. Future studies should employ validated medical records to assess hysterectomy and oophorectomy, ensuring greater accuracy and reliability. Second, residual confounding persists (eg, drug use, education, and socioeconomic factors) as a persistent concern inherent to observational designs. Earlier research omitted key socioeconomic determinants (eg, education, income) influencing surgical decisions, potentially compromising validity. Third, the potential publication bias highlights the need for a cautious interpretation of the results, although no evidence of such bias was identified.

Perspectives and significance

Hysterectomy demonstrates cost-effectiveness for gynecologic disorders, performed in 20% of US women (50% with concurrent oophorectomy).[73,74] The high prevalence of this intervention necessitates comprehensive evaluation of its long-term health consequences. The current study indicates that hysterectomy and/or bilateral oophorectomy are associated with an increased risk of stroke, underscoring that women who have had these surgeries should be closely monitored and require proactive preventive health measures for early signs of stroke. Moreover, our findings encourage clinical researchers to explore new safer surgical techniques or alternative treatments for diseases related to hysterectomy/bilateral oophorectomy.

CONCLUSIONS

Women having a hysterectomy and/or bilateral oophorectomy had higher risks of stroke compared with those who did not have surgery. Future prospective studies with a large sample size and longer follow-up period are needed to address the disparities of type of stroke, age at surgery, surgical techniques, and menopause status on the association between stroke risk and hysterectomy and/or bilateral oophorectomy.

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