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Hysterectomy With and Without Oophorectomy, Tubal Ligation, and Risk of Cardiovascular Disease in the Nurses' Health Study II

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Abstract

Background: Hysterectomy, oophorectomy, and tubal ligation are common surgical procedures. The literature regarding cardiovascular disease (CVD) risk after these surgeries has focused on oophorectomy with limited research on hysterectomy or tubal ligation.
Materials and Methods: Participants in the Nurses' Health Study II ($n = 116,429$) were followed from 1989 to 2017. Self-reported gynecologic surgery was categorized as follows: no surgery, hysterectomy alone, hysterectomy with unilateral oophorectomy, and hysterectomy with bilateral oophorectomy. We separately investigated tubal ligation alone. The primary outcome was CVD based on medical-record confirmed fatal and nonfatal myocardial infarction, fatal coronary heart disease, or fatal and nonfatal stroke. Our secondary outcome expanded CVD to include coronary revascularization (coronary artery bypass graft surgery, angioplasty, stent placement). Cox proportional hazard models were used to calculate hazard ratios (HR) and 95% confidence intervals (CIs) and were adjusted *a priori* for confounding factors. We investigated differences by age at surgery (≤50, >50) and menopausal hormone therapy usage.
Results: At baseline, participants were on average, 34 years old. During 2,899,787 person-years, we observed 1,864 cases of CVD. Hysterectomy in combination with any oophorectomy was associated with a greater risk of CVD in multivariable-adjusted models (HR hysterectomy with unilateral oophorectomy:1.40 [95% CI: 1.08–1.82]; HR hysterectomy with bilateral oophorectomy:1.27 [1.07–1.51]). Hysterectomy alone, hysterectomy with oophorectomy, and tubal ligation were also associated with an increased risk of combined CVD and coronary revascularization (HR hysterectomy alone: 1.19 [95% CI: 1.02–1.39]; HR hysterectomy with unilateral

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oophorectomy: 1.29 [1.01–1.64]; HR hysterectomy with bilateral oophorectomy: 1.22 [1.04–1.43]; HR tubal ligation: 1.16 [1.06–1.28]). The association between hysterectomy/oophorectomy and CVD and coronary revascularization risk varied by age at gynecologic surgery, with the strongest association among women who had surgery before age 50 years.

Conclusion: Our findings suggest that hysterectomy, alone or in combination with oophorectomy, as well as tubal ligation, may be associated with an increased risk of CVD and coronary revascularization. These findings extend previous research finding that oophorectomy is associated with CVD.

Keywords: hysterectomy, oophorectomy, tubal ligation, cardiovascular disease

Introduction

Hysterectomy, oophorectomy, and tubal ligation are common surgical procedures that are used for the treatment of gynecologic diseases such as fibroids, pelvic pain/endometriosis, abnormal uterine bleeding, pelvic organ prolapse, adnexal masses, predisposition to cancer, or desire for permanent sterilization.[1] Indeed, hysterectomy has historically been the second most common surgery in women and it is estimated that one in nine women will undergo hysterectomy in their lifetimes[2,3] and nearly 20% of women indicate tubal ligation as their form of contraception.[4] It is well documented that early age at menopause, which can be induced directly through oophorectomy, can substantially modify cardiometabolic disease onset.[5–7]

The literature regarding cardiovascular disease (CVD) risk after gynecologic surgery has produced varied results,[5,6,8–16] with research emphasizing the role of ovarian conservation in the context of hysterectomy.[5,9,10,17] Prior research in this area, some of which utilizes data from the Nurses' Health Study cohort,[5,17] has suggested that women who underwent hysterectomy with oophorectomy are at greater risk of CVD compared to women who underwent hysterectomy with ovarian conservation.[5,10,17] However, few studies have looked separately at the association of hysterectomy alone[6,11–14] or tubal ligation with risk of CVD, and among those that have, they have not been able to adjust for CVD risk factors,[11,14] had short duration of follow-up[13,14] or had limited statistical power.[12]

There are several potential mechanisms supporting the possible association between these gynecologic surgeries and risk of CVD. Timing of menopausal transition is one potential mechanism as bilateral oophorectomy without menopausal hormone therapy induces menopause. Pooled and meta-analyses have reported that early age of menopause is associated with a 40% greater risk of CVD,[18] a 23% greater risk for stroke, and a 20% greater risk of CVD mortality.[19] The risk between early menopause and CVD varies by natural and surgical menopause, as well as menopausal hormone therapy usage.[20] It has also been suggested that hysterectomy even with ovarian conservation may influence age at menopause.[21–23]

In addition, risk for CVD among women who underwent gynecologic surgery may be driven by clinical risk factors for CVD, including hypertension, high cholesterol, obesity, and type 2 diabetes,[6,15,24,25] which may act as confounders[26] or mediators,[27] depending on the temporality of the association. Indeed, some research has found that women with hysterectomy and oophorectomy are at increased risk of diabetes,[25] obesity,[12] hypercholesterolemia,[6] and/or hypertension,[15] after gynecologic surgery. However, some studies have found no change in incident CVD risk-factors after gynecologic surgery.[24,28] Uterine fibroids, the leading indication for hysterectomy, are associated with increased risk of obesity and hypertension.[29–31]

Prior research on the association between gynecologic surgeries and CVD has important limitations, including an emphasis on ovarian conservation without investigating the influence of hysterectomy alone or tubal ligation alone,[5,9,10,17] short duration of follow-up,[13,14] lack of consideration for important cardiovascular risk-factors,[11,14] and inability to investigate heterogeneity by age at surgery.[6,14] To overcome these prior limitations, we utilized data from Nurses' Health Study II (NHSII), a prospective cohort study of over 116,000 women aged 25–42 years in 1989 at cohort enrollment followed for nearly 30 years. We investigated the association between gynecologic surgery and CVD risk considering CVD risk factors over time and also thoroughly investigating how age at surgery may modify risk.

Materials and Methods

The NHSII is a prospective cohort study beginning in 1989 when 116,429 registered nurses in the United States, who were between the ages of 25–42 years, returned a mailed questionnaire that asked detailed information on their health and lifestyle.[32] Follow-up questionnaires that collect data on environmental, dietary, and lifestyle risk factors have been sent every 2 years. The cumulative follow-up rate from the original cohort is ≥90%. The study was approved by the Institutional Review Board of Brigham and Women's Hospital.

Assessment of gynecologic surgery status

Assessment of hysterectomy and oophorectomy. On the baseline questionnaire in 1989 and every 2 years subsequently, participants were asked whether their menstrual periods had ceased permanently, whether menstrual periods cessation was due to surgery, and if so, how many ovaries were removed. If a woman reported natural menopause, she was asked whether she had a subsequent surgery to remove her ovaries and/or uterus. On the 1995 questionnaire, and subsequently, participants were asked if they ever had their uterus or either/both ovaries removed. Hysterectomy and oophorectomy were categorized as hysterectomy alone, hysterectomy with unilateral oophorectomy, hysterectomy with bilateral oophorectomy, and no hysterectomy or oophorectomy. Information on indication for gynecologic surgery was not collected in our data. Gynecologic surgery status was updated over time and a participant could contribute person-time to multiple categories. Person-time of participants who reported oophorectomy without hysterectomy was not tabulated in the analyses. All hysterectomy/oophorectomy analyses were adjusted for tubal ligation.

Assessment of tubal ligation. On the baseline and all biennial questionnaires, participants were asked about methods of contraception utilized, including tubal ligation. On the 1997 questionnaire, NHSII women were asked what type of tubal ligation they had undergone, and were given the options: cautery/coagulation, ligation, clip/band/ring, or other/do not know. Participants with tubal ligation were compared to participants with no history of tubal ligation and all analyses were adjusted for hysterectomy and oophorectomy status.

Assessment of outcomes

We assessed incident myocardial infarction (MI), fatal coronary heart disease (CHD), stroke cases, as well as Coronary Artery Bypass Graft (CABG), angioplasty, and stent placement that occurred between enrollment and the 2017 questionnaire cycle (which ended in May 2019). Clinicians blinded to the questionnaire information reviewed medical records from self-reported nonfatal MI events. Nonfatal MIs were classed as ''confirmed'' if they met the criteria of the World Health Organization: symptoms and either diagnostic electrocardiographic changes or elevated cardiac enzymes,[33] as ''probable'' if hospital records were not obtained, but they were corroborated in writing or a telephone interview. Fatal CHD was confirmed by hospital records or autopsy. Participants reported incident physician diagnosed ''stroke (cerebrovascular accident) or transient ischemic attack'' events at enrollment in 1989 and biennially. Permission was requested from participants or next of kin to obtain and review medical records following self-reported stroke.

Stroke was classified as ischemic or hemorrhagic by the National Survey of Stroke criteria, requiring atypical neurological deficit of rapid or sudden onset lasting ≥24 hours or until death attributable to a vascular cause.[34] Pathology attributable to infection, trauma, or malignancy was excluded, as were silent strokes discovered only by radiological imaging. Physician-diagnosed CABG/coronary angioplasty/stent and time of diagnosis were self-reported. When MI, fatal CHD, stroke, and CABG/angioplasty/stent cases were combined as the outcome, we used the time of the first event among those three to determine the age of occurrence of the endpoint. The primary outcome was CVD based on medical record confirmed fatal and nonfatal myocardial infarction, fatal CHD, or fatal and nonfatal stroke. Our secondary outcome expanded CVD to include coronary revascularization (CABG surgery, angioplasty, stent placement).

Covariate data

On the 1989 baseline questionnaire, participants reported a number of characteristics, including their height, current weight, weight at age 18, physical activity, smoking history, age at menarche, oral contraceptive (OC) use, parity (number of pregnancies lasting ≥6 months), family history of myocardial infarction, family history of stroke, physician-diagnosed type 2 diabetes, physician-diagnosed cancer, physician-diagnosed elevated cholesterol, physician-diagnosed elevated blood pressure, menopausal status, and their history of bilateral oophorectomy.

Statistical analysis

Those who experienced cancer, MI, chronic ischemic disease, stroke, or CABG/angioplasty/stent before enrollment into NHSII in 1989 were excluded from this study. Person-months at risk were calculated from age at enrollment to age at death, CVD incidence, whichever occurred first, or administrative end of the study in 2017. We used multivariable Cox proportional hazards model, jointly stratified by age (months) and calendar time from start of study follow-up in 1989 (months) to obtain ''crude'' relative risks (RR).

We adjusted for potential confounders between surgery and CVD (Multivariable model 2),[26] including family history of MI, family history of stroke, age at menarche, body mass index (BMI; kg/m^2) (categories and continuous; time varying), BMI at 18, smoking history (time varying), alcohol intake (time varying), oral contraceptive use history (time varying), parity (time varying), Alternative Healthy Eating Index diet (quintiles; time varying), physical activity (metabolic equivalent of task hours/week; time varying), history of diabetes at baseline, history of hypertension at baseline, history of high cholesterol at baseline, tubal ligation (hysterectomy and oophorectomy analysis; time varying), hysterectomy and oophorectomy (tubal ligation analysis; time varying), menopausal hormone therapy use (never, estrogen only current, estrogen + progesterone current, other current, past use; time varying), and age at menopause (time varying). All time-varying covariates were updated prospectively. In sensitivity analyses, we adjusted for all covariates listed except menopausal hormone therapy use and age at menopause (Supplementary Table S1).

We additionally categorized our exposure by age at surgery (≤50, vs. >50). We also examined the effect modification by menopausal hormone therapy usage (ever vs. never) for the association between gynecologic surgery and CVD and tested the significance of the interactions with likelihood ratio tests.

Results

At study baseline, in 1989, participants who never reported hysterectomy/oophorectomy were more likely to be younger, nulliparous, ever smokers, leaner at time of the questionnaire, and were less likely to report family history of CVD compared to participants reporting gynecologic surgery. Women reporting no hysterectomy or oophorectomy were also less likely to report endometriosis diagnoses and uterine fibroids compared to women reporting hysterectomy with or without oophorectomy (Table 1). Participants who reported tubal ligation were more likely to be older, parous, to have a family history of MI or stroke, and to have a personal history of type 2 diabetes, high cholesterol, and hypertension across follow-up compared to participants with no history of tubal ligation.

In multivariable-adjusted models (Table 2), hysterectomy in combination with unilateral or bilateral oophorectomy was associated with a statistically significant greater risk of combined CVD (hysterectomy and unilateral oophorectomy RR: 1.40 [1.08–1.82]; hysterectomy and bilateral oophorectomy RR: 1.27 [1.07–1.51]). Hysterectomy alone and tubal ligation were not associated with CVD (hysterectomy RR: 1.14 [0.95–1.36]; tubal ligation RR: 1.09 [0.98–1.22]).

When investigating the combined outcomes of CVD and coronary revascularization, we observed that hysterectomy

TABLE 1. CHARACTERISTICS OF WOMEN IN THE NURSES' HEALTH STUDY II AT BASELINE IN 1989

	History of hysterectomy and oophorectomy surgery				*History of tubal ligation surgery*	
	No hysterectomy or oophorectomy (n = 108,448)	*Hysterectomy (n = 2,960)*	*Hysterectomy with unilateral oophorectomy (n = 878)*	*Hysterectomy with bilateral oophorectomy (n = 2,153)*	*No ligation (n = 96,826)*	*Tubal ligation (n = 17,613)*
Age, years[a]	34.6 (4.6)	38.9 (3.1)	38.9 (3.2)	38.8 (3.3)	34.3 (4.7)	37.5 (3.6)
Non-Hispanic white, %	91.6	91.2	91.0	91.5	91.6	91.4
Pregnancies ≥6 months						
Nulliparous, %	31.0	11.9	9.7	33.2	34.3	4.5
Parity 1, %	19.3	13.1	18.8	18.5	20.8	8.0
Parity 2+, %	49.8	75.0	71.6	48.3	44.9	87.5
Smoking status						
Never, %	85.0	87.5	82.1	87.0	85.0	85.6
Past, %	6.5	5.2	7.6	6.2	6.6	6.0
Current, %	8.5	7.3	10.3	6.8	8.4	8.4
Oral contraceptive use						
Never, %	17.1	11.1	8.3	10.5	17.8	10.7
Past or current %	82.9	88.9	91.7	89.5	82.2	89.3
BMI (current), kg/m^2	24.0 (5.0)	25.0 (5.4)	24.8 (5.2)	24.8 (5.4)	24 (5.1)	24.6 (5.1)
BMI (current), kg/m^2						
<18.5, %	3.4	4.6	5.8	3.4	3.5	2.9
18.5–<25, %	66.9	53.8	52.8	60.9	67.0	62.0
25–<30, %	18.5	26.4	24.1	20.4	18.2	21.9
30+, %	11.2	15.2	17.4	15.3	11.3	13.2
Family history of MI, %	17.8	24.1	27.2	22.4	17.8	19.9
Family history of stroke, %	17.2	17.2	22.8	18.8	17.2	17.7
Type 2 diabetes at baseline, %	0.8	1.6	1.2	1.3	0.7	1.6
High cholesterol at baseline, %	10.8	12.4	18.4	22.6	11.2	10.6
Hypertension at baseline, %	5.3	11.0	11.5	11.4	5.5	6.6
Type 2 diabetes during follow-up, %	7.3	13.8	14.3	12.8	7.5	9.0
High cholesterol during follow-up, %	51.4	60.6	63.1	71.2	51.5	54.9
Hypertension during follow-up, %	37.4	49.6	51.2	47.9	37.2	42.9
Endometriosis, %	3.7	10.0	30.7	40.6	4.9	3.6
Uterine Fibroids,[b] %	3.6	20.7	20.2	17.5	4.7	4.2

Values are means (SD) or medians (Q25, Q75) for continuous variables; percentages for categorical variables, and are standardized to the age distribution of the study population, unless otherwise noted.
Values of polytomous variables may not sum to 100% due to rounding.
[a]Value is not age adjusted.
[b]Uterine fibroids from 1993 questionnaire.
BMI, body mass index; MI, myocardial infarction; SD, standard deviation.

alone and in combination with oophorectomy was associated with a statistically significant increased risk of MI, stroke, and coronary revascularization in multivariable-adjusted models (hysterectomy alone RR: 1.19 [1.02–1.39]; hysterectomy and unilateral oophorectomy RR: 1.29 [1.01–1.64]; hysterectomy and bilateral oophorectomy RR: 1.22 [1.04–1.43]). Participants with tubal ligation had a greater risk of combined CVD and coronary revascularization compared to participants with no history of tubal ligation (RR: 1.16 [1.06–1.28]).

In analyses incorporating information on age at surgery, the association with CVD and coronary revascularization varied across age groups (Table 3). Participants who experienced hysterectomy with unilateral and bilateral oophorectomy before age 50 had an elevated risk of CVD and coronary revascularization in multivariable models adjusted for menopausal hormone therapy use (hysterectomy and unilateral oophorectomy RR: 1.58 [1.07–2.33]; hysterectomy and bilateral oophorectomy RR: 1.63 [1.27–2.08]); but no difference was observed for hysterectomy alone. Among women older than 50 years of age, the

Table 2. Hysterectomy in Combination with Oophorectomy and Risk of Cardiovascular Disease in the Nurses' Health Study II

History of surgery[a]	*Cases/person-years*	*Age and calendar time-adjusted Model 1*	*Multivariable-adjusted Model 2*
Hazard Ratio (95% CI)[b]			
CVD (MI[b] and Stroke)			
No surgery	1,067/1,975,025	1.0 (Referent)	1.0 (Referent)
Hysterectomy alone	146/156,962	1.25 (1.05–1.49)	1.14 (0.95–1.36)
Hysterectomy + unilateral oophorectomy	63/52,318	1.54 (1.19–1.98)	1.40 (1.08–1.82)
Hysterectomy + bilateral oophorectomy	360/260,694	1.58 (1.39–1.78)	1.27 (1.07–1.51)
No ligation	1,304/2,211,187	1.0 (Referent)	1.0 (Referent)
Tubal ligation	583/710,397	1.13 (1.03–1.25)	1.09 (0.98–1.22)
CVD + coronary revascularization[c]			
No surgery	1,357/1,974,703	1.0 (Referent)	1.0 (Referent)
Hysterectomy alone	192/156,918	1.32 (1.13–1.54)	1.19 (1.02–1.39)
Hysterectomy + unilateral oophorectomy	75/52,303	1.44 (1.14–1.82)	1.29 (1.01–1.64)
Hysterectomy + bilateral oophorectomy	442/260,599	1.57 (1.40–1.75)	1.22 (1.04–1.43)
No ligation	1,620/2,210,827	1.0 (Referent)	1.0 (Referent)
Tubal ligation	771/710,178	1.19 (1.09–1.30)	1.16 (1.06–1.28)
MI[b]			
No surgery	529/1,975,538	1.0 (Referent)	1.0 (Referent)
Hysterectomy alone	80/157,024	1.31 (1.04–1.66)	1.16 (0.91–1.48)
Hysterectomy + unilateral oophorectomy	39/52,336	1.82 (1.31–2.53)	1.55 (1.11–2.17)
Hysterectomy + bilateral oophorectomy	204/260,845	1.70 (1.44–2.01)	1.34 (1.06–1.68)
No ligation	678/2,211,763	1.0 (Referent)	1.0 (Referent)
Tubal ligation	328/710,645	1.19 (1.04–1.35)	1.08 (0.93–1.25)
Stroke			
No surgery	541/1,975,479	1.0 (Referent)	1.0 (Referent)
Hysterectomy alone	67/157,037	1.19 (0.92–1.54)	1.13 (0.87–1.47)
Hysterectomy + unilateral oophorectomy	24/52,350	1.22 (0.80–1.83)	1.19 (0.78–1.81)
Hysterectomy + bilateral oophorectomy	158/260,866	1.45 (1.21–1.75)	1.19 (0.91–1.54)
No ligation	631/2,211,763	1.0 (Referent)	1.0 (Referent)
Tubal ligation	256/710,655	1.07 (0.92–1.24)	1.10 (0.93–1.28)
Coronary revascularization			
No surgery	449/1,975,572	1.0 (Referent)	1.0 (Referent)
Hysterectomy alone	64/157,045	1.42 (1.09–1.85)	1.24 (0.94–1.62)
Hysterectomy + unilateral oophorectomy	28/52,342	1.66 (1.13–2.44)	1.38 (0.93–2.05)
Hysterectomy + bilateral oophorectomy	150/260,880	1.80 (1.49–2.18)	1.22 (0.90–1.65)
No ligation	500/2,211,867	1.0 (Referent)	1.0 (Referent)
Tubal ligation	300/710,620	1.46 (1.26–1.69)	1.45 (1.24–1.71)

Model 1: Jointly stratified by age and calendar time.

Model 2: Model 1 + additionally adjusted for family history of MI, family history of stroke, history of diabetes at baseline in 1989, history of hypertension at baseline in 1989, history of high cholesterol at baseline in 1989, age at menarche, BMI (kg/m^2) (categories and continuous), BMI at 18, smoking history, alcohol intake, oral contraceptive use history, parity, AHEI diet (quintiles), physical activity (MET hours/week), tubal ligation (hysterectomy and oophorectomy analysis), hysterectomy and oophorectomy (Tubal ligation analysis), menopausal hormone therapy use (Never, estrogen only current, estrogen + progesterone current, other current, past use), and age at menopause.

[a]Women with oophorectomy without hysterectomy not tabulated.

[b]Fatal and non-fatal MI, and fatal CHD.

[c]CABG, surgery, angioplasty, stent placement.

AHEI, Alternative Healthy Eating Index; CABG, coronary artery bypass graft; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; MET, metabolic equivalent of task.

association between hysterectomy with bilateral oophorectomy and CVD with revascularization was also statistically significant, however, the magnitude of the association was more modest (RR:1.23) compared to women ≤50 years old. We observed no statistically significant difference in the association between gynecologic surgery and risk of CVD endpoints stratified by menopausal hormone therapy use (Table 4).

Discussion

We observed that women who underwent hysterectomy alone or in combination with oophorectomy, and women who underwent tubal ligation were at greater risk of the composite outcome of CVD and coronary revascularization compared to women who had not undergone those respective surgeries. These patterns of risk were consistent after adjustment for potential confounders, as well as clinical factors that may be on the causal pathway between surgery and CVD (*e.g.*, hypertension, hypercholesterolemia). We also observed that the association between hysterectomy with oophorectomy and CVD was strongest among women <50 years old.

Given the direct influence of oophorectomy on menopause, the relationship between oophorectomy on CVD risk has been well characterized,[7] but has often compared

Table 3. Hysterectomy in Combination with Oophorectomy and Risk of Cardiovascular Disease in the Nurses' Health Study II Stratified by Participant Age at Surgery

History of surgery[a]	*Cases/person-years*	*Age and calendar time-adjusted Model 1*	*Multivariable-adjusted Model 2*
Hazard Ratio (95% CI)[b]			
CVD + coronary revascularization[b]			
No surgery	1,357/1,974,703	1.0 (Referent)	1.0 (Referent)
≤50 at surgery			
Hysterectomy alone	61/72,466	1.35 (1.03–1.75)	1.18 (0.90–1.53)
Hysterectomy + unilateral oophorectomy	27/22,764	1.82 (1.23–2.67)	1.58 (1.07–2.33)
Hysterectomy + bilateral oophorectomy	120/82,629	2.12 (1.74–2.58)	1.63 (1.27–2.08)
>50 at surgery			
Hysterectomy alone	131/84,452	1.29 (1.07–1.55)	1.21 (1.00–1.46)
Hysterectomy + unilateral oophorectomy	48/29,540	1.27 (0.95–1.71)	1.18 (0.88–1.59)
Hysterectomy + bilateral oophorectomy	322/177,970	1.40 (1.22–1.59)	1.23 (1.05–1.44)
No ligation	1,620/2,210,827	1.0 (Referent)	1.0 (Referent)
≤50 at tubal ligation			
Tubal ligation	291/384,007	1.29 (1.12–1.49)	1.25 (1.08–1.45)
>50 at tubal ligation			
Tubal ligation	480/326,171	1.14 (1.02–1.27)	1.11 (0.99–1.25)

Surgeries categorized by age (≤50 years old, >50 years old) as reported on the questionnaire.
Model 1: Jointly stratified by age and calendar time.
Model 2: Model 1 + additionally adjusted for family history of MI, family history of stroke, history of diabetes at baseline in 1989, history of hypertension at baseline in 1989, history of high cholesterol at baseline in 1989, age at menarche, BMI (kg/m^2) (categories and continuous), BMI at 18, smoking history, alcohol intake, oral contraceptive use history, parity, AHEI diet (quintiles), physical activity (MET hours/week), tubal ligation (hysterectomy and oophorectomy analysis), hysterectomy and oophorectomy (Tubal ligation analysis), and menopausal therapy use (Never, estrogen only current, estrogen + progesterone current, other current, past use).
[a]Women with oophorectomy without hysterectomy not tabulated.
[b]CABG, surgery, angioplasty, stent placement.

hysterectomy with ovarian conservation to hysterectomy with bilateral oophorectomy. Prior research in our companion cohort, the Nurses' Health Study, found that compared to women who had undergone hysterectomy with ovarian conservation, women who had undergone hysterectomy with bilateral oophorectomy had a 17% greater risk of myocardial infarction and CHD and a 14% greater risk of stroke.[5] This was supported by research from over 113,000 women with records in the English Hospital Episode Statistics.[10] The Women's Health Initiative found no difference in CVD endpoints between women with and without ovarian conservation and hysterectomy,[9] however, this may be partially influenced by both groups being at an elevated risk.

Indeed, one of the largest studies to date that studied over 800,000 women from the Swedish National Health Registers found that women <50 years who underwent hysterectomy with ovarian conservation (hazard ratio [HR]: 1.18, 95% CI: 1.13–1.23) and women who underwent hysterectomy with bilateral oophorectomy (HR: 2.22, 95% CI: 1.01–4.83) were at increased risk of CVD,[11] however, they were unable to adjust for many CVD risk factors. This association between hysterectomy with ovarian conservation and greater risk of CVD among young women has also been reported in other studies.

Among participants in the Rochester Epidemiology Project, with median follow-up of 22 years, participants who had undergone hysterectomy ≤35 had a 4.6-fold greater risk of congestive heart failure and a 2.5-fold greater risk of coronary artery disease compared to women who had no surgery.[12] In the Taiwan National Health Insurance cohort, individuals who underwent hysterectomy ≤45 had a 2.3-fold risk of stroke and 1.14-fold risk of CHD compared to individuals who did not have a hysterectomy.[13]

We observed that hysterectomy with unilateral oophorectomy and with bilateral oophorectomy was associated with a greater risk of MI, stroke, and coronary revascularization compared to no surgery. Hysterectomy alone was associated with a greater risk of combined CVD and coronary revascularization. Tubal ligation was also associated with a greater risk of combined CVD and coronary revascularization. These relationships attenuated slightly after adjustment for potential confounding factors. The literature has been mixed as to the relationship between gynecologic surgery and CVD risk-factors (*e.g.*, hypertension, hypercholesterolemia, type 2 diabetes). Some research has suggested an adverse cardiometabolic profile among women who have had gynecologic surgery,[6,35,36] while other prospective research has suggested no meaningful change in cardiometabolic biomarkers after surgery.[24]

There also may be underlying demographic and socioeconomic differences among women who undergo hysterectomy and tubal ligation that contributes directly or indirectly to CVD risk, as differences in gynecologic surgery utilization by race, education, and income have been reported.[37–43] Research from the Women's Health Initiative suggested that education, income, obesity, exercise, hypertension, high cholesterol, and diabetes differed by gynecologic surgery status at baseline when participants were between the ages of 50 and 79 years old.[6] Disentangling causality can be challenging given the cross-sectional nature of many studies, but some prospective research has suggested that women undergoing gynecologic surgery may be more likely to develop hypertension,[12,15] hyperlipidemia,[12,44] and type 2 diabetes[25] and to experience arterial stiffening.[45]

However, the CARDIA study[28] observed that hysterectomy was not associated with subsequent changes in CVD risk

TABLE 4. HYSTERECTOMY IN COMBINATION WITH OOPHORECTOMY AND RISK OF CARDIOVASCULAR DISEASE IN THE NURSES' HEALTH STUDY II STRATIFIED BY MENOPAUSAL HORMONE THERAPY USE

	No menopausal hormone therapy use		*Menopausal hormone therapy use*		
History of surgery[a]	*Cases/person year*	*Multivariable-adjusted Model 2*	*Cases/person year*	*Multivariable-adjusted Model 2*	p-*value, test for Model 2 heterogeneity*[e,f]
Hazard ratio (95% CI)[b]					
CVD (MI[c] and stroke)					
No Surgery	861/1,794,351	1.0 (Referent)	206/180,675	1.0 (Referent)	0.20
Hysterectomy alone	125/139,580	1.18 (0.98–1.43)	21/17,382	0.81 (0.51–1.29)	
Hysterectomy + unilateral oophorectomy	51/46,524	1.42 (1.06–1.90)	12/5,793	1.35 (0.74–2.44)	
Hysterectomy + bilateral oophorectomy	35/34,026	1.07 (0.76–1.51)	325/226,668	1.21 (1.00–1.47)	
No ligation	907/1,893,158	1.0 (Referent)	397/318,030	1.0 (Referent)	0.86
Tubal ligation	381/569,103	1.12 (0.98–1.28)	202/141,293	1.06 (0.88–1.27)	
CVD + coronary revascularization[d]					
No surgery	1,095/1,794,093	1.0 (Referent)	262/180,611	1.0 (Referent)	0.18
Hysterectomy alone	169/139,541	1.26 (1.06–1.49)	23/17,377	0.74 (0.48–1.13)	
Hysterectomy + unilateral oophorectomy	63/46,510	1.34 (1.03–1.73)	12/5,793	1.08 (0.60–1.94)	
Hysterectomy + bilateral oophorectomy	43/34,021	1.10 (0.80–1.50)	399/226,578	1.11 (0.94–1.32)	
No ligation	1,138/1,892,897	1.0 (Referent)	482/317,930	1.0 (Referent)	0.95
Tubal ligation	517/568,951	1.21 (1.08–1.36)	254/141,227	1.06 (0.90–1.25)	

Model 2: Jointly stratified by age and calendar time and additionally adjusted for family history of MI, family history of stroke, history of diabetes at baseline in 1989, history of hypertension at baseline in 1989, history of high cholesterol at baseline in 1989, age at menarche, BMI (kg/m2) (categories and continuous), BMI at 18, smoking history, alcohol intake, oral contraceptive use history, parity, AHEI diet (quintiles), physical activity (MET hours/week), tubal ligation (hysterectomy and oophorectomy analysis), hysterectomy and oophorectomy (Tubal ligation analysis), and menopausal hormone therapy use (Never, estrogen only current, estrogen + progesterone current, other current, past use).

[a]Women with oophorectomy without hysterectomy not tabulated.

[b]Cox proportional hazard models used.

[c]Fatal and nonfatal MI, and fatal CHD.

[d]CABG, surgery, angioplasty, stent placement.

[e]Likelihood ratio test for heterogeneity between groups.

[f]Five-category exposure (No Surgery, Hysterectomy alone, *etc.*) test for interaction, tubal ligation exposure test for heterogeneity listed for each outcome.

factors and instead participants who underwent hysterectomy had less favorable CVD risk factors (*e.g.*, higher BMI, waist circumference, systolic blood pressure, and triglycerides levels and lower high density lipoprotein) before surgery compared to women who underwent natural menopause.

The association between hysterectomy with ovarian conservation and tubal ligation only reached the threshold of statistical significance for analyses that included coronary revascularization as part of the composite outcome. In our relatively young cohort, participants were between the ages of 53 and 70 at the end of follow-up, thus the endpoint of coronary revascularization may be representative of early-stage CVD among this group of young women. Indeed, we found that the association between hysterectomy and oophorectomy was stronger among women who experienced surgery before the age of 50 years. We also observed that the relationship with all gynecologic surgeries were stronger for the outcome of MI compared to stroke.

The majority of the research on gynecologic surgery and CVD risk has focused on the influence of oophorectomy with less emphasis on the role of hysterectomy and little to no research on tubal ligation. While hysterectomy and tubal ligation do not directly change endogenous hormonal levels and induce menopause, they may lead to compromised ovarian function and subsequently changes in hormone levels through reduced blood flow to the ovaries. Indeed, research has suggested that women who have undergone a hysterectomy, even with ovarian conservation, had earlier age at menopause,[21] lower AMH levels,[22] and were at greater risk of ovarian failure.[46] Tubal ligation has been associated with lower HDL-C and higher triglycerides[47] and with lower circulating estrogen and progesterone levels in some,[48,49] but not all studies.[49–52] Endogenous hormone levels have been associated with circulating lipids[53–55] and ultimately CVD risk.[56–58]

While this study has many strengths, including its large sample size and its ability to prospectively investigate the association between gynecologic surgery and CVD, we must also recognize its limitations. Women in our study were between the ages of 53 and 70 years at the end of follow-up and therefore they may be relatively young for the development of cardiovascular events. Thus, the reported associations may not be representative of the entire spectrum of CVD disease development in women or may be an underestimation of the cumulative risk. Our study does not have information on the indication for gynecologic surgery. We lacked detailed information on indication for surgery, as hysterectomy and oophorectomy may be chosen as treatments for benign gynecologic conditions, including endometriosis, fibroids, and adenomyosis,[59] and these conditions may also be associated with CVD.[60,61] This may be particularly pertinent to decisions regarding unilateral versus bilateral oophorectomy.

In addition, surgical techniques during our study may not be representative of techniques used today. Our data do not contain information on salpingectomy. Future research could incorporate indication for surgery and cardiovascular risk, as has been done in some of the prior literature.[8,12,62] In addition, whether a woman undergoes gynecologic surgery may be influenced by a variety of factors, including parity, family history of cancer, education, geographic region, and socioeconomic status. While *a priori* confounding factors were taken into account in multivariable models, we cannot rule out the possibility of residual confounding or mediation[27] by other covariates or residual confounding by indication for surgery which was not collected. Given the high proportion of non-Hispanic white cohort members ($\sim$91%), we were unable to investigate whether these associations vary by race/ethnicity.

Future work should investigate whether these results generalize to other racial/ethnic groups. While MI and stroke cases were verified with medical records, information on coronary revascularization were based on self-report and may be prone to misclassification. We would assume that any misclassification of the outcome of revascularization be nondifferential with respect to the exposures and therefore, attenuate effect estimates.

In summary, we found that women who underwent hysterectomy with ovarian conservation, hysterectomy with oophorectomy, or tubal ligation were at greater risk of CVD and coronary revascularization than women who had not undergone these respective surgeries. This research builds on prior research that suggests that gynecologic surgery may influence CVD risk. Importantly, many of these gynecologic interventions serve an important purpose in treating a medical condition, and may have other downstream effects that are beneficial to patient's overall health. Future research should further investigate mechanisms and protective factors to better council patients. Clinicians should incorporate a discussion of CVD risk when counseling patients about the use of gynecologic surgery as treatment for benign indications and tubal ligation as contraception methodology.

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Authors' Contributions

L.V.F., S.A.M., and M.S.R. conceived, designed, and supervised the study. W.J.D. performed the statistical analysis. L.V.F., J.E.M., W.J.D., K.M.R., E.B.R., J.R.-E., E.A.S., S.L.C.R., W.R.R., and S.A.M. drafted and critically reviewed the article and approved the final version.

Author Disclosure Statement

No competing financial interests exist.

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Supplementary Material

Supplementary Table S1

References

1. Stewart EA, Missmer SA, Rocca WA. Moving beyond reflexive and prophylactic gynecologic surgery. Mayo Clinic Proc 2021;96(2):291–294.
2. Wright JD, Herzog TJ, Tsui J, et al. Nationwide trends in the performance of inpatient hysterectomy in the United States. Obstet Gynecol 2013;122(2 Pt 1):233–241.
3. Wu JM, Wechter ME, Geller EJ, et al. Hysterectomy rates in the United States, 2003. Obstet Gynecol 2007;110(5): 1091–1095.
4. Daniels KAJ. Current Contraceptive Status Among Women Aged 15–49: United States, 2017–2019. Hyattsville, MD: National Institute for Health Statistics; 2020.
5. Parker WH, Broder MS, Chang E, et al. Ovarian conservation at the time of hysterectomy and long-term health outcomes in the nurses' health study. Obstet Gynecol 2009; 113(5):1027–1037.
6. Howard BV, Kuller L, Langer R, et al. Risk of cardiovascular disease by hysterectomy status, with and without oophorectomy: The Women's Health Initiative Observational Study. Circulation 2005;111(12):1462–1470.
7. Zhu D, Chung HF, Dobson AJ, et al. Age at natural menopause and risk of incident cardiovascular disease: A pooled analysis of individual patient data. Lancet Publ Health 2019;4(11):e553–e564.
8. Rivera CM, Grossardt BR, Rhodes DJ, et al. Increased cardiovascular mortality after early bilateral oophorectomy. Menopause (New York, NY) 2009;16(1):15–23.
9. Jacoby VL, Grady D, Wactawski-Wende J, et al. Oophorectomy vs ovarian conservation with hysterectomy: Cardiovascular disease, hip fracture, and cancer in the Women's Health Initiative Observational Study. Arch Intern Med 2011;171(8):760–768.
10. Mytton J, Evison F, Chilton PJ, et al. Removal of all ovarian tissue versus conserving ovarian tissue at time of hysterectomy in premenopausal patients with benign disease: Study using routine data and data linkage. BMJ 2017;356:j372.
11. Ingelsson E, Lundholm C, Johansson AL, et al. Hysterectomy and risk of cardiovascular disease: A population-based cohort study. Eur Heart J 2011;32(6):745–750.
12. Laughlin-Tommaso SK, Khan Z, Weaver AL, et al. Cardiovascular and metabolic morbidity after hysterectomy with ovarian conservation: A cohort study. Menopause (New York, NY) 2018;25(5):483–492.
13. Yeh JS, Cheng HM, Hsu PF, et al. Hysterectomy in young women associates with higher risk of stroke: A nationwide cohort study. Int J Cardiol 2013;168(3):2616–2621.

14. Ding DC, Tsai IJ, Hsu CY, et al. Hysterectomy is associated with higher risk of coronary artery disease: A nationwide retrospective cohort study in Taiwan. Medicine 2018;97(16):e0421.
15. Ding DC, Tsai IJ, Hsu CY, et al. Risk of hypertension after hysterectomy: A population-based study. BJOG 2018; 125(13):1717–1724.
16. Tuesley KM, Protani MM, Webb PM, et al. Hysterectomy with and without oophorectomy and all-cause and cause-specific mortality. Am J Obstet Gynecol 2020;223(5): 723.e1–723.e16.
17. Parker WH, Feskanich D, Broder MS, et al. Long-term mortality associated with oophorectomy compared with ovarian conservation in the nurses' health study. Obstet Gynecol 2013;121(4):709–716.
18. Atsma F, Bartelink ML, Grobbee DE, et al. Post-menopausal status and early menopause as independent risk factors for cardiovascular disease: A meta-analysis. Menopause 2006;13(2):265–279.
19. Muka T, Oliver-Williams C, Kunutsor S, et al. Association of age at onset of menopause and time since onset of menopause with cardiovascular outcomes, intermediate vascular traits, and all-cause mortality: A systematic review and meta-analysis. JAMA Cardiol 2016;1(7):767–776.
20. Zhu D, Chung HF, Dobson AJ, et al. Type of menopause, age of menopause and variations in the risk of incident cardiovascular disease: Pooled analysis of individual data from 10 international studies. Hum Reprod 2020;35(8): 1933–1943.
21. Farquhar CM, Sadler L, Harvey SA, et al. The association of hysterectomy and menopause: A prospective cohort study. BJOG 2005;112(7):956–962.
22. Trabuco EC, Moorman PG, Algeciras-Schimnich A, et al. Association of ovary-sparing hysterectomy with ovarian reserve. Obstet Gynecol 2016;127(5):819–827.
23. Yuan H, Wang C, Wang D, et al. Comparing the effect of laparoscopic supracervical and total hysterectomy for uterine fibroids on ovarian reserve by assessing serum anti-mullerian hormone levels: A prospective cohort study. J Minim Invasive Gynecol 2015;22(4):637–641.
24. Matthews KA, Gibson CJ, El Khoudary SR, et al. Changes in cardiovascular risk factors by hysterectomy status with and without oophorectomy: Study of Women's Health Across the Nation. J Am Coll Cardiol 2013;62(3):191–200.
25. Luo J, Manson JE, Urrutia RP, et al. Risk of diabetes after hysterectomy with or without oophorectomy in postmenopausal women. Am J Epidemiol 2017;185(9):777–785.
26. Correia KF, Dodge LE, Farland LV, et al. Confounding and effect measure modification in reproductive medicine research. Hum Reprod 2020;35(5):1013–1018.
27. Farland LV, Correia KFB, Dodge LE, et al. The importance of mediation in reproductive health studies. Hum Reprod 2020;35(6):1262–1266.
28. Appiah D, Schreiner PJ, Bower JK, et al. Is surgical menopause associated with future levels of cardiovascular risk factor independent of antecedent levels? The CARDIA study. Am J Epidemiol 2015;182(12):991–999.
29. Madika AL, MacDonald CJ, Gelot A, et al. Hysterectomy, non-malignant gynecological diseases, and the risk of incident hypertension: The E3N prospective cohort. Maturitas 2021;150:22–29.
30. Haan YC, Oudman I, de Lange ME, et al. Hypertension risk in dutch women with symptomatic uterine fibroids. Am J Hypertens 2014;28(4):487–492.
31. Haan YC, Diemer FS, Van Der Woude L, et al. The risk of hypertension and cardiovascular disease in women with uterine fibroids. J Clin Hypertens (Greenwich) 2018;20(4): 718–726.
32. Chavarro JE, Rich-Edwards JW, Gaskins AJ, et al. Contributions of the nurses' health studies to reproductive health research. Am J Public Health 2016;106(9):1669–1676.
33. Rose GA BH. Cardiovascular Survey Methods, 2nd ed. Geneva: World Health Organization; 1982; (WHO monograph series No 58.).
34. Walker AE, Robins M, Weinfeld FD. The National Survey of Stroke. Clinical findings. Stroke 1981;12(2 Pt 2 Suppl 1): I13–I44.
35. Laughlin-Tommaso SK, Khan Z, Weaver AL, et al. Cardiovascular risk factors and diseases in women undergoing hysterectomy with ovarian conservation. Menopause (New York, NY) 2016;23(2):121–128.
36. Halli SS, Singh DP, Biradar RA. Increased hypertension following hysterectomy among reproductive women in India. Am J Prev Cardiol 2020:100131.
37. Robinson WR, Cheng MM, Howard AG, et al. For U.S. Black women, shift of hysterectomy to outpatient settings may have lagged behind White women: A claims-based analysis, 2011–2013. BMC Health Services Res 2017; 17(1):526.
38. Kjerulff KH, Guzinski GM, Langenberg PW, et al. Hysterectomy and race. Obstet Gynecol 1993;82(5):757–764.
39. Kjerulff K, Langenberg P, Guzinski G. The socioeconomic correlates of hysterectomies in the United States. Am J Public Health 1993;83(1):106–108.
40. Price JT, Zimmerman LD, Koelper NC, et al. Social determinants of access to minimally invasive hysterectomy: Reevaluating the relationship between race and route of hysterectomy for benign disease. Am J Obstet Gynecol 2017;217(5):572.e1–572.e10.
41. Erekson EA, Weitzen S, Sung VW, et al. Socioeconomic indicators and hysterectomy status in the United States, 2004. J Reprod Med 2009;54(9):553–558.
42. Gartner DR, Delamater PL, Hummer RA, et al. Patterns of black and white hysterectomy incidence among reproductive aged women. Health Serv Res 2021;56(5):847–853.
43. Gartner DR, Delamater PL, Hummer RA, et al. Integrating surveillance data to estimate race/ethnicity-specific hysterectomy inequalities among reproductive-aged women: Who's at risk? Epidemiology 2020;31(3):385–392.
44. Li P-C, Tsai IJ, Hsu CY, et al. Risk of hyperlipidemia in women with hysterectomy—A retrospective cohort Study in Taiwan. Sci Rep 2018;8(1):12956.
45. Gavin KM, Jankowski C, Kohrt WM, et al. Hysterectomy is associated with large artery stiffening in estrogen-deficient postmenopausal women. Menopause 2012;19(9):1000–1007.
46. Moorman PG, Myers ER, Schildkraut JM, et al. Effect of hysterectomy with ovarian preservation on ovarian function. Obstet Gynecol 2011;118(6):1271–1279.
47. Ozkaya E, Gokmen O, Tosun A, et al. Unfavorable lipid profile and higher frequency of hot flashes during perimenopausal years after fallopian tube ligation. Gynecol Endocrinol 2013;29(6):559–562; doi: 10.3109/09513590.2013.788633
48. Alvarez-Sanchez F, Segal SJ, Brache V, et al. Pituitary-ovarian function after tubal ligation. Fertil Steril 1981; 36(5):606–609.

49. Cibula D, Widschwendter M, Zikan M, et al. Underlying mechanisms of ovarian cancer risk reduction after tubal ligation. Acta Obstet Gynecol Scand 2011;90(6):559–563.
50. Garza-Flores J, Vazquez-Estrada L, Reyes A, et al. Assessment of luteal function after surgical tubal sterilization. Adv Contracept 1991;7(4):371–377.
51. Wu E, Xiao B, Yan W, et al. Hormonal profile of the menstrual cycle in Chinese women after tubal sterilization. Contraception 1992;45(6):583–593.
52. Gentile GP, Helbig DW, Zacur H, et al. Hormone levels before and after tubal sterilization. Contraception 2006; 73(5):507–511.
53. Chen Y, Zeleniuch-Jacquotte A, Arslan AA, et al. Endogenous hormones and coronary heart disease in postmenopausal women. Atherosclerosis 2011;216(2):414–419.
54. Karim R, Hodis HN, Stanczyk FZ, et al. Relationship between serum levels of sex hormones and progression of subclinical atherosclerosis in postmenopausal women. J Clin Endocrinol Metab 2008;93(1):131–138.
55. Manolio TA, Furberg CD, Shemanski L, et al. Associations of postmenopausal estrogen use with cardiovascular disease and its risk factors in older women. The CHS Collaborative Research Group. Circulation 1993;88(5 Pt 1):2163–2171.
56. Phillips GB, Pinkernell BH, Jing TY. Relationship between serum sex hormones and coronary artery disease in postmenopausal women. Arterioscler Thromb Vasc Biol 1997; 17(4):695–701.
57. Mudali S, Dobs AS, Ding J, et al. Endogenous postmenopausal hormones and serum lipids: The atherosclerosis risk in communities study. J Clin Endocrinol Metab 2005;90(2): 1202–1209.
58. Dai W, Li Y, Zheng H. Estradiol/testosterone imbalance: Impact on coronary heart disease risk factors in postmenopausal women. Cardiol 2012;121(4):249–254.
59. Farland LV, Harris HR. Long-term health consequences of endometriosis—pathways and mediation by treatment. Curr Obstet Gynecol Rep 2020;9(3):79–88.
60. Farland LV, Degnan WJ, 3rd, Bell ML, et al. Laparoscopically confirmed endometriosis and risk of incident stroke: A prospective cohort study. Stroke 2022:101161 strokeaha122039250
61. Mu F, Rich-Edwards J, Rimm EB, et al. Association between endometriosis and hypercholesterolemia or hypertension. Hypertension 2017;70(1):59–65.
62. Cusimano MC, Chiu M, Ferguson SE, et al. Association of bilateral salpingo-oophorectomy with all cause and cause specific mortality: Population based cohort study. BMJ 2021;375:e067528.

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