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Cardiovascular risk factors and diseases in women undergoing hysterectomy with ovarian conservation

Shannon K. Laughlin-Tommaso, MD MPH[1,2], **Zaraq Khan, MBBS**[3], **Amy L. Weaver, MS**[4], **Cathy D. Schleck, BS**[4], **Walter A. Rocca, MD, MPH**[5,6], and **Elizabeth A. Stewart, MD**[2,3]

[1]Division of Gynecology, Department of Obstetrics & Gynecology, Mayo Clinic, Rochester, MN.

[2]Department of Surgery, Mayo Clinic, Rochester, MN.

[3]Division of Reproductive Endocrinology and Infertility, Department of Obstetrics & Gynecology, Mayo Clinic, Rochester, MN.

[4]Division of Biomedical Statistics and Informatics, Department of Health Sciences Research, Mayo Clinic, Rochester, MN.

[5]Division of Epidemiology, Department of Health Sciences Research, Mayo Clinic, Rochester, MN.

[6]Department of Neurology, College of Medicine, Mayo Clinic, Rochester, MN.

Abstract

Objective—To study the association of preexisting cardiovascular risk factors and diseases in women who underwent hysterectomy with bilateral ovarian conservation compared with controls.

Methods—Using the Rochester Epidemiology Project records-linkage system, we identified all Olmsted County, Minnesota women who underwent hysterectomy with ovarian conservation between January 1, 1965 and December 31, 2002 (cases). Each case was aged-matched (±1 year) to a woman selected randomly who resided in the county and did not undergo hysterectomy or oophorectomy prior to the index date (date of hysterectomy in her matched case). Using electronic codes, we identified cardiovascular risk factors (diabetes, hypertension, hyperlipidemia, obesity, metabolic syndrome, and polycystic ovarian syndrome) and diseases (coronary artery disease, congestive heart failure, myocardial infarction, and stroke) that occurred before the index date. Analyses were stratified by age at hysterectomy and surgical indication.

Results—During the study period, 3,816 women underwent hysterectomy with ovarian conservation for a benign indication. Preexisting hyperlipidemia, obesity, and metabolic syndrome were significantly more frequent in cases than controls in univariable analyses. Obesity remained significantly associated in multivariable analyses overall, for nearly all age groups, and across all indications. Stroke was significantly more frequent in cases than controls in the women <36 years. Congestive heart failure and stroke were significantly less common in cases than controls in the women >50 years.

Corresponding Author: Shannon Laughlin-Tommaso, MD MPH, Division of Gynecology, Department of Obstetrics and Gynecology, 200 1st Street SW, Rochester, MN 55905, telephone: 507-538-5783, laughlintommaso.shannon@mayo.edu..

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Conclusions—Hysterectomy with ovarian conservation is associated with cardiovascular risk factors, particularly obesity. Obesity may contribute to the underlying gynecologic conditions leading to hysterectomy; however, surgical selection may also play a role.

Keywords

Hysterectomy; ovarian conservation; leiomyomas; cardiovascular disease; stroke; epidemiology

Although cardiovascular disease (CVD) is the leading cause of morbidity and mortality in US women, strategies for its early recognition and prevention are limited.[1] The 2007 American Heart Association's update on cardiovascular prevention encouraged the assessment of cardiovascular risk during routine medical visits and the exploration of risk associated with gynecologic conditions.[1] For most women 18 - 64 years old, gynecologic visits are the main point of contact with medical providers, and may offer an opportunity for early recognition of cardiovascular risk factors or disease.[2] Moreover, gynecologists perform as well or better than general medical physicians in providing preventive services including counseling on tobacco cessation, diet and exercise, and colorectal screening.[2] Screening specific to CVD prevention, such as evaluation of blood pressure and lipids was also improved if a woman saw a gynecologist in addition to a general medical physician.[3]

To optimize CVD screening by gynecologists, it is important to determine which gynecologic conditions predispose women to CVD. Gestational diabetes mellitus is a good example of this paradigm. Research has shown that having gestational diabetes puts women at higher risk for type II diabetes later in life.[4] Currently, gynecologists are more likely than family medicine physicians to screen women who experienced gestational diabetes for diabetes following pregnancy, and to counsel women on the future risk of diabetes.[5] Knowledge about the obstetric condition and its future risks was cited as a reason why gynecologists outperformed other physicians in preventive screening in this area.[5]

Hysterectomy has been associated with a higher frequency of cardiovascular risk factors, such as hypertension, hyperlipidemia, and obesity at the time of the surgery.[6-9] However, these studies were limited by small sample sizes and lack of generalizability.[6-9] In addition, the cardiovascular risk factors considered varied across studies. Most studies of long-term outcomes following hysterectomy were retrospective and did not have information about preexisting cardiovascular risk factors and CVD.[10, 11] Not accounting for these baseline risk factors or conditions may lead to confounding.

Hysterectomy with bilateral ovarian conservation is increasing in frequency because several studies have shown the cardiovascular and neurologic benefits of conserving the ovaries.[12-15] However, the long-term effects of hysterectomy with ovarian conservation are understudied. In this manuscript, we describe the baseline cardiovascular risk factors and CVD in women undergoing hysterectomy with ovarian conservation using a case-control design. These findings will allow us to differentiate baseline risk factors or conditions from long-term CVD outcomes following hysterectomy with ovarian conservation.

METHODS

Study population

As part of the Mayo Clinic Study of Uterine Disease and Health (MCUD), we studied all of the Olmsted County, Minnesota women who underwent hysterectomy with ovarian conservation (and without prior unilateral or bilateral oophorectomy) for a benign indication during a 38-year period (January 1, 1965 through December 31, 2002). The cohort was identified through the medical records-linkage system of the Rochester Epidemiology Project (REP) using methods that were described in detail elsewhere.[16-21] In brief, the REP electronic indexes were searched for the procedural codes for hysterectomy and for the diagnostic codes for indication. The REP is a population-based medical records-linkage system that includes the records of all inpatient and outpatient medical providers in the local community.[22] The REP includes the Olmsted Medical Center, Mayo Clinic, their three affiliated hospitals, and several smaller care providers. Mayo Clinic is a major tertiary care center, thus, referrals outside of Olmsted County are limited. Details of the Olmsted County population have been reported elsewhere, and the generalizability of this population to other populations in the United States has been studied.[23-25]

Using the resources of the REP, each woman undergoing hysterectomy with ovarian conservation (case) was individually matched by age (± 1 year) to a control woman residing in Olmsted County in the index year (year of hysterectomy in her matched case). Control women were selected randomly from the complete list of all women included in the population in any given year (REP census enumeration).[25] Control women were excluded if they underwent a hysterectomy or oophorectomy (either unilateral or bilateral) prior to the index date. Both cases and controls were excluded if they had not provided authorization for the use of their medical records for research, or if they were under age 18 at the index date. The study was approved by the institutional review boards at Olmsted Medical Center and Mayo Clinic.

Collection of clinical data

All cardiovascular risk factors prior to the index date were obtained electronically using diagnostic codes for diabetes, hypertension, hyperlipidemia, obesity, and polycystic ovary syndrome. Because the diagnostic code for metabolic syndrome was not in use for a large segment of our study period, we defined metabolic syndrome indirectly in subjects who received diagnostic codes for at least three of the following four conditions: diabetes, hypertension, hyperlipidemia, or obesity. We also used diagnostic codes for metabolic syndrome, when available. Diagnostic codes for CVD including myocardial infarction, coronary artery disease (CAD, which included codes for atherosclerosis), congestive heart failure (CHF), and stroke that occurred prior to the index date were also obtained electronically. We combined myocardial infarction, CAD, and CHF into a composite measure of cardiac disease (cardiac disease composite). We then added stroke to create a second composite measure of the full spectrum of CVD (CVD composite). To decrease the risk of false-positive diagnoses, only women who received at least 2 codes for a given risk factor or condition separated by more than 30 days were considered exposed. For diagnostic codes received before 1994, we required a one year separation because during that time

frame a finer dating of the codes was impossible in our system. A detailed list of the diagnostic codes used in this study can be obtained from the authors upon request.

Statistical analyses

Consistent with the matched case-control study design, conditional logistic regression models were used to estimate the odds ratio (OR) and the corresponding 95% confidence interval (CI) for each cardiovascular risk factor and cardiovascular disease. We also fit multivariable logistic regression models that included all cardiovascular risk factors with the exception of metabolic syndrome (because it was defined using the same cardiovascular risk factors). All p-values were two-sided, and p-values less than 0.05 were considered statistically significant. Analyses were performed using the SAS version 9.3 software package (SAS Institute, Inc., Cary, NC).

Analyses were also stratified by age (≤ 35, 36 - 40, 41 - 45, 46 - 50, and > 50 years) and by indication for surgery. We present data for uterine leiomyomas and uterine prolapse. These indications were chosen because uterine leiomyomas are common in younger women, whereas uterine prolapses are common in older women, and the two indications have a different pathophysiology. Pre-cancerous conditions, menstrual disorders, endometriosis, menopausal disorders, inflammatory diseases, and obstetrical complications were grouped together as other indications because they were either too heterogeneous or too uncommon to analyze separately.

RESULTS

Population description

During the 38-year study period, 9,893 women underwent hysterectomy with or without oophorectomy; however, 878 women (8.9%) were excluded because they did not authorize the use of their medical records for research. Of the remaining 9,015 women, 3,816 had hysterectomy performed for a benign indication with bilateral ovarian conservation and were included as cases. The median age at the time of hysterectomy with ovarian conservation was 41.0 years (interquartile range (IQR), 36.1 - 46.7); 24.6% of women (n = 939) were ≤ 35 years, 25.6% (n = 978) were 36-40, 22.8% (n = 870) were 41-45, 10.2% (n = 390) were 46 - 50, and 16.8% (n = 639) were older than 50 years at the time of hysterectomy. Leiomyomas were the most common indication (n = 1,125, 29.5%), followed by precancerous conditions of the endometrium or cervix (n = 878, 23.0%), prolapse (n = 805, 21.1%), menstrual disorders (n = 678, 17.8%), and endometriosis (n = 191, 5.0%). The remaining 139 (3.6%) women had less frequent diagnoses including menopausal disorders, inflammatory disease, and obstetrical complications.

The median duration of enrollment in the records-linkage system preceding the index year was 19.3 years (IQR 11.4 - 28.1 years) for cases and 16.8 years (IQR 9.2 - 23.5 years) for controls (median difference = 1.9 years; Wilcoxon signed rank test, $p < 0.001$). In addition, 92.6% of cases and 91.2% of controls had at least three years of continuous enrollment within the records-linkage system preceding the index year (McNemar's test, $p = 0.03$).

Cardiovascular risk factors and disease

The odds ratios for hyperlipidemia, obesity, and metabolic syndrome were significantly elevated in women undergoing hysterectomy with ovarian conservation compared with controls in univariable analyses of the entire sample (Table 1). By contrast, hypertension, diabetes, polycystic ovary syndrome, and CVD diseases did not differ significantly between cases and controls in univariable analyses. In a multivariable model of the cardiovascular risk factors, results were attenuated and only obesity remained significant (Table 1).

Age stratification

Hysterectomy with ovarian conservation was significantly associated with obesity in univariable analyses for all of the age groups except over 50 years (Table 2). In multivariable analyses, the association with obesity remained significant for women in the age strata of <36 years, 41-45, and 46-50 years. Women who underwent hysterectomy at age 36-40 years also had increased frequency of hypertension, hyperlipidemia, and metabolic syndrome in univariable analyses. Results were attenuated and only hypertension remained significant in multivariable analyses.

The youngest age stratum showed a strong association between hysterectomy and stroke. The other CVD conditions were too rare to evaluate. Polycystic ovary syndrome, a rare risk factor in our sample, had a particularly strong association with hysterectomy with ovarian conservation in the youngest age stratum; however, the association was not statistically significant. The frequency of surgical indications for hysterectomy in the age stratum younger than 36 years differed slightly from the overall cohort: uterine leiomyomata (14.8%) and prolapse (16.4%) were less common, whereas menstrual disorders were more common (29.5%). Obstetrical causes of hysterectomy were uncommon (included among other conditions which comprised 7.9% of surgical indications).

Women who underwent hysterectomy with ovarian conservation after age 50 had a significantly lower frequency of congestive heart failure and stroke than controls (Table 2). There were no significant associations between hysterectomy with ovarian conservation and CVD conditions in women in the age strata between 36 and 50 years.

Surgical indication

Obesity was significantly associated with hysterectomy with ovarian conservation in both univariable and multivariable analyses across all surgical indications (Table 3). Women who had hysterectomy with ovarian conservation for prolapse also had a higher frequency of hyperlipidemia and a lower frequency of diabetes compared with controls, in multivariable analyses. In the stratum of other surgical indications, cases had a higher frequency of hyperlipidemia, hypertension, obesity, and metabolic syndrome compared with controls in univariable analyses; only obesity remained significant in multivariable analyses.

DISCUSSION

Women who underwent hysterectomy with ovarian conservation for a benign condition had a higher frequency of cardiovascular risk factors; however, after adjustment for other risk

factors, obesity appeared to be the primary driver of these associations. These findings provide an opportunity for women's healthcare providers to improve screening for cardiovascular health. Obesity was associated with hysterectomy across all surgical indications and in most age strata. Obesity is a risk factor for several gynecologic indications for hysterectomy including fibroids, prolapse, abnormal uterine bleeding, and precancerous conditions.[26-30] Thus, preventing or treating obesity may not only improve cardiovascular health but may also reduce hysterectomy rates.

Because obesity is associated with hyperlipidemia and hypertension, we observed some significant associations with these risk factors in our univariable analyses and in some of the multivariable analyses. For example, hypertension remained significant in multivariable analyses in one age stratum, and hyperlipidemia was significantly associated with hysterectomy with ovarian conservation for prolapse. The frequency of metabolic syndrome, a marker for women with multiple co-morbidities, was elevated in cases for nearly all strata, but the association was significant only in the overall cohort, in women 36-40 years old, and in women who underwent hysterectomy for indications other than leiomyomas or prolapse.

It initially seems counterintuitive that women with obesity, hypertension, hyperlipidemia, and metabolic syndrome were selected as surgical patients. However, during our study time period (1965 – 2002), the most common alternative to hysterectomy for many gynecologic conditions, including leiomyomas, abnormal uterine bleeding, and precancerous conditions including endometrial hyperplasia, was medical treatment with high-dose estrogen formulations such as oral contraceptives. Estrogen treatment would have been discouraged in women with these significant co-morbidities, particularly in the youngest women who were years away from natural menopause. Thus, hysterectomy may have been the best choice for these patients.

In our study, age at the time of surgery and indication modified the association with cardiovascular conditions. Women who underwent hysterectomy before age 36 years had more preexisting stroke compared with controls. By contrast, women who underwent hysterectomy after age 50 has significantly less preexisting stroke and congestive heart failure than controls. Similarly, women who underwent hysterectomy with ovarian conservation for prolapse had a non-significant lower frequency of most CVD conditions. These findings may be attributed to surgical selection. Young women with a history of stroke would not be candidates for oral contraceptives, whereas older women with co-morbidities may have been encouraged to avoid hysterectomy until menopause. During our study period, there were alternatives to hysterectomy for the treatment of prolapse, including pessaries or colpocleisis, which were often preferentially used over major surgery in women with multiple co-morbidities.

Our findings are consistent with prior studies reporting pre-operative cardiovascular risk factors. In a prospective study of women older than 41 years, body mass index was significantly higher in women undergoing hysterectomy compared with women who underwent a natural menopause.[8, 9] Similarly, self-reported hypertension was associated with more than a 2-fold increased risk of hysterectomy or gynecological surgery.[6, 7] In addition, more women in the hysterectomy group were on lipid-lowering medications prior

to surgery.[8] Our study extends these studies which were limited by small numbers of women who underwent hysterectomy (n<200) or by restrictive inclusion criteria (e.g., narrow age ranges).[6-9]

Our study differs from several prior studies in which hysterectomy for leiomyomas was associated with hypertension and atherosclerosis. [31-35] These associations have biologic plausibility because hypertension, atherosclerosis, and leiomyomas may share similar mechanisms involving inflammatory pathways, vascular dysfunction, or plaque formation.[32, 36, 37, 38]. However, most previous studies did not control for body mass index, or showed greatly attenuated results when body mass index was used in multivariable analyses. A recent study compared women who had surgically treated fibroids with women who underwent gynecologic surgery for other reasons and with population controls; hypertension was significantly more common in women undergoing surgery for fibroids independent of body mass index.[39] Finally, carotid intimal thickness, a predictor of atherosclerosis, was significantly elevated in non-obese women with leiomyomas compared with age-matched controls.[40] Thus, we hypothesized that women who underwent hysterectomy with ovarian conservation for leiomyomas would have higher cardiovascular risk factors. Despite the biological plausibility, we found no significant association of the leiomyoma indication with hypertension or CVD conditions, and obesity was similarly associated across all three groups of indications. Our study included predominantly white women who tend to have a lower prevalence of hypertension than other race or ethnic groups, and we did not screen controls to exclude women with fibroids. These methodological differences may have contributed to the divergence in findings from prior studies. Surprisingly, hyperlipidemia was more strongly associated with the prolapse indication than with the leiomyoma indication.

Strength and limitations

Our study was population-based and included all incident events of hysterectomy with ovarian conservation over 38 years. This study design reduced the risk of selection bias or incidence-prevalence bias. In addition, all data pertaining to the dependent variable (case-control status) and the independent variables (preexisting cardiovascular risk factors or diseases) were obtained passively from medical records. These methodological features reduced the risk of recall bias or of interviewer bias. On the other hand, the study had some limitations. This study was specifically designed to investigate the long-term effects of hysterectomy with ovarian conservation; therefore, we excluded women with concurrent unilateral or bilateral oophorectomy. This restriction may have shifted the sample toward younger women. In addition, our study may reflect changes in surgical practice over time. For example, in the study time frame, hysterectomy with concurrent oophorectomy was more common than in recent years.

A second limitation was the use of electronic codes to define both the dependent variable (case-control status) and the independent variables (cardiovascular risk factors or diseases). A small scale validation study showed adequate agreement between electronic codes and manual abstraction of the full text of the records for the definition of hysterectomy with ovarian conservation (sample of 100 women; 99% agreement).[16] Similarly, other validation

studies including both men and women showed agreements between electronic codes (at least 2 codes for a given condition) and manual abstraction of the records of 82% for myocardial infarction and of 83% - 90% for cerebrovascular disease (unpublished data). These findings suggest that the electronic codes may be a reasonable surrogate for the actual risk factors or diseases of interest. In addition, we used the same coding definitions for both cases and control, thus reducing possible biases (non-differential misclassification). Finally, to avoid the risk of false-positive diagnoses for the cardiovascular risk factors and the cardiovascular diseases, we considered women to be exposed only when they received at least 2 codes for a given condition separated by more than 30 days. However, for diagnostic codes received before 1994, we required a one year separation because a finer dating of the codes was impossible in our system. This requirement of 2 codes has been used in other studies[41, 42]

A third limitation was the difference in length of enrollment in the records-linkage system prior to hysterectomy for cases and controls. Although the median difference was only 1.9 years, this asymmetry may have caused some bias. This difference was unexpected given the random sampling of the control women from the general population. However, prior studies have documented that women with lower socioeconomic status have a higher risk of undergoing hysterectomy. These women may also have lower mobility in and out of the county related to education or occupation, thus resulting in longer continuous enrollment in our system.[43] To address the potential bias, we conducted a set of sensitivity analyses in which the diagnoses for each case-control pair were considered only for the shorter of the 2 capture times. The findings did not change noticeably (data not shown).

A final limitation was that the Olmsted County population is predominantly of central and northern European descent, and our findings may not be generalizable to other ethnic groups; however, the social and demographic characteristics of this population are similar to a large segment of the U.S. population.[24]

CONCLUSION

Our study extends the evidence for an association between hysterectomy with ovarian conservation and preexisting cardiovascular risk factors as well as cardiovascular diseases. The association with preexisting cardiovascular diseases is age-related; young women had a higher frequency of stroke, and older women had a lower frequency of stroke and congestive heart failure compared with matched controls. Our findings may stimulate the engagement of gynecologists in the prevention of CVD. Women who are considered for hysterectomy may have co-morbidities in addition to obesity, and should undergo diagnostic tests and preventive interventions, when indicated. Further analyses are being conducted in our population to study the effect of hysterectomy with ovarian conservation on the long-term risk of CVD after adjusting for the baseline cardiovascular risk factors or diseases described in this article.

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Table 1

Case-control analyses on the association of preexisting cardiovascular risk factors and cardiovascular disease with hysterectomy with ovarian conservation in the overall sample (3,816 cases; 3,816 controls)

Risk Factor or Disease	Women with Hysterectomy n (%)	Referent Women n (%)	Univariable Analyses			Multivariable Analyses[a]		
			OR	95% CI	p-value	OR	95% CI	p-value
Cardiovascular risk factor								
Diabetes	89 (2.3)	93 (2.4)	0.96	(0.71-1.28)	0.76	0.84	(0.62-1.13)	0.25
Hyperlipidemia	135 (3.5)	98 (2.6)	1.41	(1.08-1.84)	0.01	1.27	(0.96-1.67)	0.09
Hypertension	307 (8.0)	267 (7.0)	1.19	(0.99-1.44)	0.06	1.06	(0.87-1.28)	0.56
Obesity	637 (16.7)	469 (12.3)	1.44	(1.26-1.64)	<0.001	1.42	(1.24-1.62)	<0.001
Metabolic syndrome[b]	59 (1.5)	32 (0.8)	1.93	(1.23-3.02)	0.004	...	...	...
Polycystic ovary syndrome	10 (0.3)	6 (0.2)	1.67	(0.61-4.59)	0.32	1.42	(0.51-3.95)	0.50
Cardiovascular disease								
CAD	47 (1.2)	44 (1.2)	1.07	(0.70-1.64)	0.74	...	...	...
CHF	7 (0.2)	16 (0.4)	0.44	(0.18-1.06)	0.07	...	...	...
Myocardial infarction	12 (0.3)	14 (0.4)	0.86	(0.40-1.85)	0.70	...	...	...
Cardiac disease composite[c]	55 (1.4)	56 (1.5)	0.98	(0.66-1.45)	0.92	...	...	...
Stroke	27 (0.7)	28 (0.7)	0.96	(0.57-1.64)	0.89	...	...	...
CVD composite[d]	76 (2.0)	75 (2.0)	1.01	(0.73-1.42)	0.93	...	...	...

OR, odds ratio; CI, confidence interval; CAD, coronary artery disease; CHF, congestive heart failure; CVD, cardiovascular disease.

[a] Cardiovascular risk factors were evaluated in a full multivariable logistic regression model that included diabetes, hyperlipidemia, hypertension, obesity, and polycystic ovary syndrome. Metabolic syndrome was not included because it was defined using variables already included in the model.

[b] Metabolic syndrome was defined indirectly as 3 or more of the following 4 conditions: hyperlipidemia, hypertension, diabetes, or obesity, or as a diagnosis of metabolic syndrome.

[c] The cardiac disease composite included CAD, myocardial infarction, and CHF.

[d] The CVD composite included CAD, myocardial infarction, CHF, and stroke.

Table 2

Case-control analyses on the association of preexisting cardiovascular risk factors and cardiovascular disease with hysterectomy with ovarian conservation stratified by age of the surgery

Risk Factor or Disease	Women with Hysterectomy n (%)	Referent Women n (%)	Univariable Analyses			Multivariable Analyses[a]		
			OR	95% CI	p-value	OR	95% CI	p-value
Age ≤ 35 years (939 cases; 939 controls)								
Cardiovascular risk factor								
Diabetes	9 (1.0)	10 (1.1)	0.90	(0.37-2.21)	0.82	1.04	(0.41-2.64)	0.93
Hyperlipidemia	12 (1.3)	12 (1.3)	1.00	(0.45-2.23)	1.00	0.82	(0.36-1.88)	0.64
Hypertension	20 (2.1)	21 (2.2)	0.94	(0.49-1.83)	0.87	0.72	(0.36-1.44)	0.36
Obesity	113 (12.0)	63 (6.7)	1.86	(1.35-2.56)	<0.001	1.89	(1.37-2.62)	<0.001
Metabolic syndrome[b]	1 (0.1)	0 (0.0)	...	...	...	...	...	...
Polycystic ovary syndrome	5 (0.5)	1 (0.1)	5.00	(0.58-42.80)	0.14	4.88	(0.54-43.76)	0.16
Cardiovascular disease								
CAD	0 (0.0)	1 (0.1)	...	...	...	...	...	...
CHF	1 (0.1)	0 (0.0)	...	...	...	...	...	...
Myocardial infarction	0 (0.0)	0 (0.0)	...	...	...	...	...	
Cardiac disease composite[c]	1 (0.1)	1 (0.1)	1.00	(0.06-15.99)	1.00	...	...	...
Stroke	7 (0.7)	0 (0.0)	9.61	(1.87-infinity)	0.02	...	...	...
CVD composite[d]	7 (0.7)	1 (0.1)	7.00	(0.86-56.89)	0.07	...	...	...
Age 36-40 years (978 cases; 978 controls)								
Cardiovascular risk factor								
Diabetes	17 (1.7)	10 (1.0)	1.70	(0.78-3.71)	0.18	1.31	(0.58-2.93)	0.51
Hyperlipidemia	39 (4.0)	22 (2.2)	1.77	(1.05-2.99)	0.03	1.46	(0.84-2.55)	0.18
Hypertension	54 (5.5)	26 (2.7)	2.22	(1.36-3.63)	0.002	1.92	(1.15-3.20)	0.01
Obesity	142 (14.5)	110 (11.2)	1.33	(1.02-1.74)	0.03	1.17	(0.88-1.54)	0.28
Metabolic syndrome[b]	14 (1.4)	4 (0.4)	3.50	(1.15-10.63)	0.03	...	...	...
Polycystic ovary syndrome	3 (0.3)	3 (0.3)	1.00	(0.20-4.95)	1.00	0.73	(0.14-3.80)	0.71
Cardiovascular disease								
CAD	1 (0.1)	2 (0.2)	0.50	(0.05-5.51)	0.57	...	...	...

Risk Factor or Disease	Women with Hysterectomy n (%)	Referent Women n (%)	Univariable Analyses			Multivariable Analyses[a]		
			OR	95% CI	p-value	OR	95% CI	p-value
CHF	0 (0.0)	0 (0.0)	...	...	...	...	...	...
Myocardial infarction	2 (0.2)	0 (0.0)	...	...	...	...	...	...
Cardiac disease composite[c]	2 (0.2)	2 (0.2)	1.00	(0.14-7.10)	1.00	...	...	...
Stroke	5 (0.5)	4 (0.4)	1.25	(0.34-4.65)	0.74	...	...	...
CVD composite[d]	7 (0.7)	6 (0.6)	1.17	(0.39-3.47)	0.78	...	...	...
Age 41-45 years (870 cases; 870 controls)								
Cardiovascular risk factor								
Diabetes	13 (1.5)	20 (2.3)	0.65	(0.32-1.31)	0.23	0.59	(0.29-1.20)	0.15
Hyperlipidemia	29 (3.3)	28 (3.2)	1.04	(0.61-1.76)	0.89	1.00	(0.59-1.72)	0.99
Hypertension	48 (5.5)	46 (5.3)	1.05	(0.68-1.62)	0.83	0.93	(0.59-1.45)	0.74
Obesity	141 (16.2)	107 (12.3)	1.40	(1.06-1.86)	0.02	1.44	(1.08-1.93)	0.01
Metabolic syndrome[b]	7 (0.8)	2 (0.2)	3.50	(0.73-16.85)	0.12	...	...	...
Polycystic ovary syndrome	2 (0.2)	1 (0.1)	2.00	(0.18-22.06)	0.57	1.57	(0.14-17.51)	0.71
Cardiovascular disease								
CAD	4 (0.5)	3 (0.3)	1.33	(0.30-5.96)	0.71	...	...	...
CHF	1 (0.1)	1 (0.1)	1.00	(0.06-15.99)	1.00	...	...	...
Myocardial infarction	2 (0.2)	1 (0.1)	2.00	(0.18-22.06)	0.57	...	...	...
Cardiac disease composite[c]	5 (0.6)	5 (0.6)	1.00	(0.29-3.45)	1.00	...	...	...
Stroke	5 (0.6)	1 (0.1)	5.00	(0.58-42.80)	0.14	...	...	...
CVD Composite[d]	10 (1.1)	6 (0.7)	1.67	(0.61-4.59)	0.32	...	...	...
Age 46-50 years (390 cases; 390 controls)								
Cardiovascular risk factor								
Diabetes	12 (3.1)	7 (1.8)	1.71	(0.67-4.35)	0.26	1.28	(0.48-3.38)	0.62
Hyperlipidemia	15 (3.8)	8 (2.1)	1.87	(0.79-4.42)	0.15	1.53	(0.63-3.71)	0.34
Hypertension	35 (9.0)	25 (6.4)	1.42	(0.84-2.39)	0.19	1.24	(0.72-2.13)	0.43
Obesity	74 (19.0)	48 (12.3)	1.63	(1.11-2.41)	0.01	1.52	(1.01-2.27)	0.04
Metabolic syndrome[b]	6 (1.5)	2 (0.5)	3.00	(0.61-14.86)	0.18	...	...	...
Polycystic ovary syndrome[c]	0 (0.0)	1 (0.3)	...	...	...	...	...	...

Risk Factor or Disease	Women with Hysterectomy n (%)	Referent Women n (%)	Univariable Analyses			Multivariable Analyses[a]		
			OR	95% CI	p-value	OR	95% CI	p-value
Cardiovascular disease								
CAD	3 (0.8)	0 (0.0)	...	...	...	...	...	...
CHF	0 (0.0)	1 (0.3)	...	...	...	...	...	...
Myocardial infarction	0 (0.0)	2 (0.5)	...	...	...	...	...	...
Cardiac disease composite[c]	3 (0.8)	3 (0.8)	1.00	(0.20-4.95)	1.00	...	...	...
Stroke	1 (0.3)	1 (0.3)	1.00	(0.06-15.99)	1.00	...	...	...
CVD composite[d]	3 (0.8)	4 (1.0)	0.75	(0.17-3.35)	0.71	...	...	...
Age > 50 years (639 cases; 639 controls)								
Cardiovascular risk factor								
Diabetes	38 (5.9)	46 (7.2)	0.82	(0.53-1.27)	0.37	0.73	(0.46-1.15)	0.17
Hyperlipidemia	40 (6.3)	28 (4.4)	1.55	(0.90-2.64)	0.11	1.55	(0.89-2.68)	0.12
Hypertension	149 (23.3)	149 (23.3)	1.00	(0.76-1.32)	1.00	0.92	(0.69-1.23)	0.57
Obesity	167 (26.1)	141 (22.1)	1.25	(0.97-1.63)	0.09	1.30	(0.99-1.71)	0.06
Metabolic syndrome[b]	31 (4.9)	24 (3.8)	1.33	(0.76-2.35)	0.32	...	...	...
Polycystic ovary syndrome[e]	0 (0.0)	0 (0.0)	...	...	...	...	...	...
Cardiovascular disease								
CAD	39 (6.1)	38 (5.9)	1.03	(0.65-1.64)	0.91	...	...	...
CHF	5 (0.8)	14 (2.2)	0.36	(0.13-0.99)	0.05	...	...	...
Myocardial infarction	8 (1.3)	11 (1.7)	0.73	(0.29-1.81)	0.49	...	...	...
Cardiac disease composite[c]	44 (6.9)	45 (7.0)	0.98	(0.63-1.52)	0.91	...	...	...
Stroke	9 (1.4)	22 (3.4)	0.41	(0.19-0.89)	0.02	...	...	...
CVD composite[d]	49 (7.7)	58 (9.1)	0.82	(0.55-1.24)	0.35	...	...	...

OR, odds ratio; CI, confidence interval; CAD, coronary artery disease; CHF, congestive heart failure; CVD, cardiovascular disease.

[a] Cardiovascular risk factors were evaluated in a full multivariable logistic regression model that included diabetes, hyperlipidemia, hypertension, obesity, and polycystic ovary syndrome. Metabolic syndrome was not included because it was defined using variables already included in the model.

[b] Metabolic syndrome was defined as 3 or more of the following 4 conditions: hyperlipidemia, hypertension, diabetes, or obesity, or as a diagnosis of metabolic syndrome.

[c] The cardiac disease composite included CAD, myocardial infarction, and CHF.

[d] The CVD composite included CAD, myocardial infarction, CHF, and stroke.

[e] Polycystic ovary syndrome was not included in the full multivariate model for the age strata 46-50 and > 50 years because of the small numbers.

Table 3

Case-control analyses on the association of preexisting cardiovascular risk factors and cardiovascular disease with hysterectomy with ovarian conservation stratified by indication for the surgery

Risk Factor or Disease	Women with Hysterectomy n (%)	Referent Women n (%)	Univariable Analyses			Multivariable Analyses[a]		
			OR	95% CI	p-value	OR	95% CI	p-value
Leiomyomas (1,125 cases; 1,125 controls)								
Cardiovascular risk factor								
Diabetes	25 (2.2)	31 (2.8)	0.81	(0.48-1.37)	0.42	0.66	(0.38-1.14)	0.14
Hyperlipidemia	44 (3.9)	40 (3.6)	1.11	(0.71-1.74)	0.65	1.06	(0.66-1.70)	0.80
Hypertension	97 (8.6)	92 (8.2)	1.07	(0.78-1.47)	0.68	0.94	(0.67-1.31)	0.70
Obesity	201 (17.9)	143 (12.7)	1.52	(1.20-1.93)	<0.001	1.59	(1.23-2.04)	<0.001
Metabolic syndrome[b]	25 (2.2)	15 (1.3)	1.77	(0.90-3.49)	0.10	...	...	...
Polycystic ovary syndrome	3 (0.3)	3 (0.3)	1.00	(0.20-4.95)	1.00	0.99	(0.20-4.97)	0.99
Cardiovascular disease								
CAD	10 (0.9)	15 (1.3)	0.64	(0.28-1.49)	0.30	...	...	...
CHF	1 (0.1)	7 (0.6)	0.14	(0.02-1.16)	0.07	...	...	...
Myocardial infarction	5 (0.4)	5 (0.4)	1.00	(0.29-3.45)	1.00	...	...	...
Cardiac disease composite[c]	14 (1.2)	19 (1.7)	0.71	(0.34-1.48)	0.36	...	...	...
Stroke	7 (0.6)	6 (0.5)	1.17	(0.39-3.47)	0.78	...	...	...
CVD composite[d]	21 (1.9)	24 (2.1)	0.86	(0.47-1.60)	0.64	...	...	...
Prolapse (805 cases; 805 controls)								
Cardiovascular risk factor								
Diabetes	22 (2.7)	33 (4.1)	0.66	(0.38-1.14)	0.13	0.57	(0.33-1.00)	0.05
Hyperlipidemia	26 (3.2)	13 (1.6)	2.08	(1.05-4.15)	0.04	2.03	(1.01-4.11)	0.05
Hypertension	96 (11.9)	86 (10.7)	1.16	(0.83-1.62)	0.39	1.02	(0.72-1.45)	0.90
Obesity	146 (18.1)	105 (13.0)	1.49	(1.13-1.97)	0.005	1.49	(1.12-1.99)	0.007
Metabolic syndrome[b]	7 (0.9)	7 (0.9)	1.00	(0.35-2.85)	1.00	...	...	...
Polycystic ovary syndrome	1 (0.1)	0 (0.0)	...	...	...	...	...	...
Cardiovascular disease								
CAD	19 (2.4)	19 (2.4)	1.00	(0.53-1.89)	1.00	...	...	...

Risk Factor or Disease	Women with Hysterectomy n (%)	Referent Women n (%)	Univariable Analyses			Multivariable Analyses[a]		
			OR	95% CI	p-value	OR	95% CI	p-value
CHF	3 (0.4)	6 (0.7)	0.50	(0.13-2.00)	0.33	...	...	...
Myocardial infarction	2 (0.2)	5 (0.6)	0.40	(0.08-2.06)	0.27	...	...	...
Cardiac disease composite[c]	21 (2.6)	22 (2.7)	0.95	(0.52-1.74)	0.88	...	...	...
Stroke	9 (1.1)	13 (1.6)	0.69	(0.30-1.62)	0.40	...	...	...
CVD composite[d]	27 (3.4)	28 (3.5)	0.96	(0.57-1.64)	0.89	...	...	...
Other indications (1,886 cases; 1,886 controls)								
Cardiovascular risk factor								
Diabetes	42 (2.2)	29 (1.5)	1.46	(0.91-2.37)	0.12	1.32	(0.80-2.15)	0.27
Hyperlipidemia	65 (3.4)	45 (2.4)	1.47	(0.99-2.16)	0.05	1.28	(0.86-1.91)	0.22
Hypertension	114 (6.0)	89 (4.7)	1.35	(0.99-1.84)	0.05	1.19	(0.86-1.63)	0.29
Obesity	290 (15.4)	221 (11.7)	1.37	(1.13-1.66)	0.001	1.30	(1.07-1.58)	0.01
Metabolic syndrome[b]	27 (1.4)	10 (0.5)	2.89	(1.35-6.16)	0.006	...	...	...
Polycystic ovary syndrome	6 (0.3)	3 (0.2)	2.00	(0.50-8.00)	0.33	1.69	(0.42-6.83)	0.46
Cardiovascular disease								
CAD	18 (1.0)	10 (0.5)	2.00	(0.86-4.67)	0.11	...	...	...
CHF	3 (0.2)	3 (0.2)	1.00	(0.20-4.95)	1.00	...	...	...
Myocardial infarction	5 (0.3)	4 (0.2)	1.25	(0.34-4.65)	0.74	...	...	...
Cardiac disease composite[c]	20 (1.1)	15 (0.8)	1.42	(0.68-2.97)	0.36	...	...	...
Stroke	11 (0.6)	9 (0.5)	1.22	(0.51-2.95)	0.66	...	...	...
CVD composite[d]	28 (1.5)	23 (1.2)	1.28	(0.69-2.37)	0.44	...	...	...

OR, odds ratio; CI, confidence interval; CAD, coronary artery disease; CHF, congestive heart failure; CVD, cardiovascular disease.

[a] The cardiovascular risk factors were evaluated in a full multivariable logistic regression model that included diabetes, hyperlipidemia, hypertension, obesity, and polycystic ovary syndrome. Metabolic syndrome was not included because it was defined using variables already included in the model.

[b] Metabolic syndrome was defined as 3 or more of the following 4 conditions: hyperlipidemia, hypertension, diabetes, or obesity, or as a diagnosis of metabolic syndrome.

[c] The cardiac disease composite included CAD, myocardial infarction, and CHF.

[d] The CVD composite included CAD, myocardial infarction, CHF, and stroke.