American Journal of Epidemiology

Vol. 185, No. 9
DOI: 10.1093/aje/kwx023
Advance Access publication:
March 6, 2017

Original Contribution

Risk of Diabetes After Hysterectomy With or Without Oophorectomy in Postmenopausal Women

Juhua Luo*, JoAnn E. Manson, Rachel Peragallo Urrutia, Michael Hendryx, Erin S. LeBlanc, and Karen L. Margolis

* Correspondence to Juhua Luo, Department of Epidemiology and Biostatistics, School of Public Health–Bloomington, Indiana University, 1025 East 7th Street, Bloomington, IN 47405 (e-mail: juhluo@indiana.edu).

Initially submitted March 8, 2016; accepted for publication June 6, 2016.

The aim of this study was to determine the associations between hysterectomy, bilateral salpingo-oophorectomy (BSO), and incidence of diabetes in postmenopausal women participating in the Women's Health Initiative (WHI), a series of trials conducted in the United States, during the period 1993–1998. A total of 67,130 postmenopausal women aged 50–79 years were followed for a mean of 13.4 years. Among them, 7,430 cases of diabetes were diagnosed. Multivariable Cox proportional hazards models were used to assess the association between hysterectomy/oophorectomy status and diabetes incidence. Compared with women without hysterectomy, women with hysterectomy had a significantly higher risk of diabetes (hazard ratio = 1.13, 95% confidence interval: 1.06, 1.21). The increased risk of diabetes was similar for women with hysterectomy only and for women with hysterectomy with concomitant BSO. Compared with hysterectomy alone, hysterectomy with BSO was not associated with additional risk of diabetes after stratification by age at hysterectomy and hormone therapy status. In our large, prospective study, we observed that hysterectomy, regardless of oophorectomy status, was associated with increased risk of diabetes among postmenopausal women. However, our data did not support the hypothesis that early loss of ovarian estrogens is a risk factor for type 2 diabetes. The modest increased risk of diabetes associated with hysterectomy may be due to residual confounding, such as the reasons for hysterectomy.

diabetes; hysterectomy; oophorectomy; postmenopausal women

Abbreviations: BSO, bilateral salpingo-oophorectomy; CI, confidence interval; HR, hazard ratio; WHI, Women's Health Initiative.

Hysterectomy is the second most common surgery among women in the United States, and approximately 600,000 hysterectomies are performed in the United States annually (1). Almost 90% of surgeries are for benign gynecologic conditions, including symptomatic uterine fibroids or abnormal uterine bleeding (2, 3). Approximately 44% of women have concomitant bilateral salpingo-oophorectomy (BSO) at the time of hysterectomy in order to prevent the subsequent development of ovarian cancer, treat medical conditions, or prevent the need for future adnexal surgery (4). In premenopausal women, BSO induces menopause, but hormonal effects may also be present in postmenopausal women (5, 6). In addition, hysterectomy without BSO has been associated with a shorter time to menopause (7) and has been found to have similar, but less dramatic, hormonal changes as BSO (5, 8, 9). Increased knowledge about the long-term effects of hysterectomy and BSO on women's health will improve medical decision-making for women and their providers (10).

BSO before age 50 years is significantly associated with death from all causes (11). Some have attributed this to a higher risk of cardiovascular disease (12). It has been postulated that women who undergo early BSO may subsequently experience a higher risk of type 2 diabetes mellitus (hereafter referred to as diabetes) compared with women who do not undergo oophorectomy (13). According to Mauvais-Jarvis et al. (14), ovarian hormones regulate both insulin secretion and survival of pancreatic beta cells. In animal studies, an absence of female sex hormones after BSO leads to decreased whole-body insulin-mediated glucose uptake (15, 16). Oophorectomy worsens glucose tolerance and insulin resistance in mice (17). Furthermore, several randomized clinical trials have indicated that exogenous menopausal hormone therapy (either estrogen alone or estrogen plus progestin) reduces the risk of diabetes (18–20). Thus, we hypothesized that early BSO would be associated with an increased risk of diabetes and that hysterectomy without BSO might be associated with an intermediate risk compared with undergoing neither BSO nor hysterectomy.

Epidemiologic studies investigating the associations between hysterectomy, BSO, and diabetes incidence are sparse. Appiah et al. (21), using data from 2,597 postmenopausal women enrolled in the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study, reported that hysterectomy with BSO was significantly associated with diabetes risk (hazard ratio (HR) = 1.57, 95% confidence interval (CI): 1.03, 2.41), while hysterectomy alone was associated with a nonsignificantly increased risk of diabetes (HR = 1.38, 95% CI: 0.94, 2.04). In another small, prospective study (only 33 women with BSO), Lejsková et al. (22) found that women with BSO had a significant increase in fasting glycemia compared with women with natural menopause. In a third study, a secondary analysis of a randomized controlled trial among glucose intolerant adults, Kim et al. (23) reported no association between diabetes risk and bilateral oophorectomy. In that study, analysis of the subgroup that was randomized to a lifestyle intervention indicated that diabetes risk was lower among women with BSO compared with premenopausal women (23). However the population was women at high risk of diabetes, and investigators were unable to assess the effects of hormone use due to the lack of diabetes cases.

The purpose of this study was to use a large prospective data set (the Women's Health Initiative (WHI)) to examine the associations between hysterectomy, BSO, and incidence of diabetes while adjusting for important confounders. We also tested the hypothesis that early loss of ovarian estrogens is a risk factor for diabetes by comparing diabetes risk among women who had hysterectomy with BSO with the risk among women who underwent hysterectomy only, stratified by age at hysterectomy and hormone therapy status.

METHODS

Women's Health Initiative

The WHI was designed to address the major causes of morbidity and mortality in postmenopausal women (24). It includes both multicenter clinical trials and an observational study. Details of the scientific rationale, eligibility requirements, and baseline characteristics of the participants in the WHI have been published elsewhere (25–29). Briefly, a total of 161,808 women aged 50 to 79 years were recruited at 40 clinical centers throughout the United States between September 1, 1993, and December 31, 1998. The current study uses the WHI Observational Study data. Participants in the Observational Study included 93,676 women who were screened for the clinical trial but were ineligible or unwilling to participate or who were recruited through a direct invitation for the Observational Study. The study was overseen by institutional review boards at all 40 clinical centers and at the coordinating center as well as by a study-wide data and safety monitoring board. All WHI participants gave signed informed consent and were followed prospectively.

The following participants were excluded from the Observational Study cohort of 93,676 for this analysis: 10,197 women who had a history of cancer (except nonmelanoma skin cancer) at baseline; 549 who joined but provided no follow-up information; 4,517 who had prevalent diabetes (defined as a positive answer to the question, "Did a doctor ever say that you had sugar diabetes or high blood sugar when you were not pregnant?") at baseline; 1,667 women with missing data on hysterectomy or oophorectomy; 6,109 women who had unilateral or partial oophorectomy; and 3,507 women with missing data on other covariates. After exclusions, 67,130 women remained for further analysis.

WHI cohort follow-up

The WHI Observational Study enrollment period was 1994 through 1998. Observational Study participants were followed for 6–10 years in the main study depending on when they enrolled in the study. WHI extension studies continued to follow consenting participants, the first for an additional 5 years (2005–2010) and the second for another 5 years (2010–2015). Consent rates to the WHI extension studies were 82.4% for clinical trials and 72.9% for the Observational Study for the first extension (2005–2010) and 85.2% for clinical trials and 88.2% for the Observational Study for the second extension (2010–2015). Annual updates on health outcomes were collected by mail from the participants. The annual follow-up response rate was over 94% each year. The reasons that participants were censored included death, nonconsent to the extensions, or end of follow-up. The maximum length of follow-up was 20 years.

Measurements of exposure and outcome

Exposures. Hysterectomy status at baseline was determined via self-report at enrollment by asking the following question: "Did you ever have a hysterectomy? (This is a surgery to take out your uterus or womb.)" The responses to this question were categorized as no or yes. Oophorectomy status at baseline was determined by asking "Have you ever had an operation to remove one or both of your ovaries?" The responses to this question were categorized as no; yes, one was taken out; yes, both were taken out; yes, part of an ovary was taken out; yes, unknown number taken out; and don't know. The validities of self-reported hysterectomy and BSO experience have been confirmed with a sensitivity of 91% and positive predictive value of 97% for hysterectomy status and sensitivity of 64% and positive predictive value of 100% for BSO (30). Age at hysterectomy and age at BSO were collected at baseline. WHI also collected the hysterectomy status and the date of the operation during follow-up. Oophorectomy status was not collected during follow-up.

Outcome. The primary outcome was incidence of diabetes during follow-up. This was defined via self-report by a positive report of a new diagnosis of diabetes treated with insulin or oral medications during follow-up. Self-reported diabetes in the WHI has been found to be valid based on medication inventories, fasting glucose levels, and medical record review (31, 32).

Covariates. In the multivariable models, we considered potential confounders, including age at enrollment (continuous), race/ethnicity (American Indian or Alaska Native, Asian or Pacific Islander, black or African American, Hispanic/Latino, non-Hispanic white, and other), education (high school or less, some college/technical training, college or some graduate work, and master's degree or higher), body mass index (weight divided by the square of height (kg/m^2), continuous), smoking (never smoker, former smoker, current smoker), alcohol intake (no alcohol consumption, past alcohol consumption, current and <7 alcoholic beverages/week, current and ≥7 alcoholic beverages/week), physical activity (metabolic equivalent (MET) hours/week: <5, 5–<10, 10–<20, 20–<30, ≥30), history of hormone therapy use (none, estrogen alone, estrogen and progestin, mixed), age at first birth (never had term pregnancy, <20 years, 20–<30 years, ≥30 years), age at menarche (<12 years, 12–14 years, ≥15 years), parity (never had term pregnancy, 1–2, ≥3), family history of diabetes (no, yes), waist circumference (centimeters), hypertension (yes, no), and high serum cholesterol requiring medication (yes, no).

Statistical analysis

Our primary analysis focused on the association between hysterectomy/oophorectomy status at baseline and risk of diabetes, because the WHI did not collect information on oophorectomy status during follow-up. Hysterectomy/oophorectomy status was divided into 4 categories: no hysterectomy or oophorectomy, no hysterectomy but BSO, hysterectomy alone, and hysterectomy with BSO.

Baseline characteristics were described using percentages for categorical variables and mean values (with standard deviations) for quantitative variables. Comparisons between the 4 groups (according to hysterectomy/oophorectomy status) were made using the χ^2 test for categorical variables and analysis-of-variance test for quantitative variables.

Multivariable Cox proportional hazards models were used to assess the association between hysterectomy/oophorectomy status and diabetes incidence. In all multivariable models, potential confounders included variables listed in Table 1. To further test the hypothesis of whether early loss of ovarian estrogens is a risk factor for diabetes, we examined the association between hysterectomy with concomitant BSO and risk of diabetes according to age at hysterectomy (<45 years or ≥45 years) and hormone therapy status (never use, ever use), using women with hysterectomy alone as the reference group. In this way, we could further control for the confounding related to indications for hysterectomy. We also analyzed exposure (hysterectomy status) as a time-varying variable using time-dependent covariate Cox models.

We used SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina), for all analyses.

RESULTS

Among 67,130 women, 24,352 women (36.3%) had had hysterectomy at baseline. Among these, 13,761 (56.5%) had had concomitant BSO. As of September, 30, 2015, over a mean of 13.4 years of follow-up, 7,430 women (10.5%) developed diabetes. Among women who had not had hysterectomy at baseline, 4,387 (10.32%) developed diabetes, compared with 3,043 (12.5%) of women who had had hysterectomy at baseline and 1,731 (12.6%) of women who had had hysterectomy and BSO at baseline.

Baseline characteristics by hysterectomy and oophorectomy status at enrollment are shown in Table 1. Compared with women who did have hysterectomy or oophorectomy, women who had hysterectomy only or with concomitant BSO were more likely to be older, to be nonwhite (non-Hispanic), to be less educated, and to have higher body mass index. They were less physically active and were more likely to be a nonsmoker, to be a nondrinker of alcohol, to report a family history of diabetes, to have history of hormone use of estrogen alone, to have a longer duration of hormone therapy use, to have had menarche at a younger age, and to have been younger at their first childbirth. Compared with women had not had hysterectomy or oophorectomy, women who had not had hysterectomy but had had BSO had similar patterns as women with hysterectomy except for the following characteristics: they were more educated, more likely to be current smokers, and more likely to be nulliparous. Compared with women who had had hysterectomy alone, women with BSO regardless of hysterectomy were more likely to have had low parity and have had surgery at early age (Table 1).

In age-adjusted models, hysterectomy was associated with an increased risk of diabetes regardless of BSO status. The association between hysterectomy and risk of diabetes was attenuated but remained significant after adjusting for all potential confounders. The increased risk of diabetes was similar for women who had undergone hysterectomy only and for women who had had hysterectomy plus BSO. Women who had not had hysterectomy but had had BSO had no significant increased risk of diabetes compared with women who had not had hysterectomy or oophorectomy (Table 2). When stratified by age at oophorectomy (<45 years or ≥45 years), no significantly increased risk of diabetes was observed in women with no hysterectomy but with BSO in either stratum.

When analyzed according age at time of hysterectomy and hormone therapy use, compared with women who had had hysterectomy alone, women who had had hysterectomy plus BSO did not show an additional risk of diabetes (Table 3). The results were similar when stratified by age at time of hysterectomy at 50 years. We also performed analysis for hysterectomy and age at hysterectomy according to hormone therapy use by using no hysterectomy or BSO as the referent. Hazard ratios were similar and approximately 1.1–1.4 (Appendix Table 1).

In addition, we did not observe that the age of women at time of hysterectomy was associated with diabetes diagnosis. When hysterectomy status was analyzed as a time-varying variable using time-dependent covariate Cox models, a similarly increased risk of diabetes was observed in women who had had hysterectomy compared with women who had not had hysterectomy after adjusting for potential risk factors (HR = 1.12, 95% CI: 1.06, 1.18). Finally, we performed several sensitivity analyses. First, we performed an analysis for women who had had partial oophorectomy.

Table 1. Characteristics of Study Participants According to Hysterectomy/Oophorectomy Status Among 67,130 Participants in the Women's Health Initiative Observational Study, United States, 1993–1998

Characteristic	No Hysterectomy/ Oophorectomy (*n* = 42,535)		No Hysterectomy But Bilateral Oophorectomy (*n* = 243)		Hysterectomy Only (*n* = 10,591)		Hysterectomy and Bilateral Oophorectomy (*n* = 13,761)	
	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)
Age at baseline, years		63.1 (7.3)		64.2 (7.2)		63.4 (7.4)		63.7 (7.3)
Race/ethnicity								
American Indian or Alaskan Native	0.3		0.8		0.5		0.4	
Asian or Pacific Islander	3.4		3.3		1.9		2.7	
Black or African American	5.4		5.8		8.3		8.2	
Hispanic/Latino	3.3		2.5		4.7		3.1	
Non-Hispanic white	86.2		85.2		83.4		84.2	
Other	1.4		2.5		1.3		1.4	
College graduate or more education	21.6		24.3		14.6		17.0	
Body mass index[a]		26.6 (5.6)		27.0 (5.5)		27.3 (5.5)		27.3 (5.8)
Physical activity, MET-hours/week		14.6 (14.7)		14.2 (14.9)		13.4 (14.2)		13.2 (13.9)
Smoking status								
Never smoker	50.7		49.0		52.8		51.6	
Former smoker	43.3		42.8		41.1		42.8	
Current smoker	6.1		8.2		6.2		5.6	
Alcohol intake								
No alcohol	10.0		12.4		12.0		11.1	
Past alcohol use	15.8		18.1		19.7		19.0	
<7 alcoholic beverages/week	60.1		57.6		56.6		58.1	
≥7 alcoholic beverages/week	14.1		11.9		11.8		11.8	
Family history of diabetes, yes	28.2		31.7		32.0		32.0	
History of hormone therapy use								
None	49.5		37.9		26.5		15.4	
Estrogen alone	6.7		20.2		65.0		71.6	
Estrogen and progestin	38.5		29.2		2.4		2.8	
Mixed	5.4		12.8		6.2		10.3	
Duration of hormone therapy, years		6.6 (5.9)		8.6 (8.4)		11.3 (9.0)		13.4 (9.2)
Age at menarche, years								
<12	20.8		24.7		22.7		23.4	
12–14	69.5		65.0		67.7		67.6	
≥15	9.7		10.3		9.7		9.0	
Age at first birth, years[b]								
Never had term pregnancy	13.4		22.6		6.5		13.6	
<20	8.4		7.8		16.1		12.6	
20 to <30	60.0		51.4		63.4		59.3	
≥30	9.1		9.5		4.8		5.8	
Parity								
Never had term pregnancy	13.4		22.6		6.5		13.6	
1–2	35.7		40.7		32.6		37.6	
≥3	50.8		36.6		60.9		48.8	

Table continues

Table 1. Continued

Characteristic	No Hysterectomy/ Oophorectomy (*n* = 42,535)		No Hysterectomy But Bilateral Oophorectomy (*n* = 243)		Hysterectomy Only (*n* = 10,591)		Hysterectomy and Bilateral Oophorectomy (*n* = 13,761)	
	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)
Age at hysterectomy/oophorectomy, years								
<40			63.8		17.6		32.5	
40 to <50			12.4		42.0		46.3	
≥50			21.8		40.0		21.0	

Abbreviations: MET, metabolic equivalent of task; SD, standard deviation.
[a] Body mass index was calculated as weight (kg)/height (m)^2.
[b] The numbers may not sum to the total because of missing values.

Compared with women who had had neither hysterectomy nor oophorectomy, women who had not had hysterectomy but had had partial oophorectomy had no increased risk of diabetes (HR = 0.92, 95% CI: 0.79, 1.07); women who had had hysterectomy and had had partial oophorectomy had a similarly increased risk of diabetes (HR = 1.17, 95% CI: 1.06, 1.29) as women who had had hysterectomy alone (HR = 1.14, 98% CI: 1.06, 1.22) or women who had had hysterectomy plus BSO (HR = 1.16, 95%CI: 1.08, 1.24). Second, we further adjusted for age at menopause, and results were similar. Third, analyses according to race/ethnicity showed that the association between hysterectomy and risk of diabetes was consistent across racial/ethnic groups.

DISCUSSION

In this large, prospective study of postmenopausal women, we observed that hysterectomy status regardless of oophorectomy status was associated with increased risk of diabetes. Compared with women who have undergone hysterectomy alone, concomitant BSO did not impart additional risk of diabetes regardless of the age at hysterectomy or the hormone therapy status.

A few epidemiologic studies have examined the associations between hysterectomy, BSO, and risk of diabetes, and they have yielded inconsistent results (21–23). Kim et al. (23) reported no increased risk of diabetes associated with

Table 2. Hazard Ratios for the Association Between Hysterectomy/Oophorectomy and Risk of Diabetes Among 67,130 Participants in the Women's Health Initiative Observational Study, United States, 1993–1998

Surgical Status	No. of Diabetes Cases	Person-Years	Crude Incidence Rates (per 1,000 Person-years)	Age-Adjusted		Adjusted for Age, Prior Hormone Use, and BMI		Multivariable-Adjusted[a]	
				HR	95% CI	HR	95% CI	HR	95% CI
Hysterectomy									
No	4,387	581,257	7.55	1	Referent	1	Referent	1	Referent
Yes	3,043	319,805	9.52	1.27	1.21, 1.33	1.25	1.17, 1.33	1.13	1.06, 1.21
Hysterectomy/oophorectomy									
None	4,360	578,146	7.54	1	Referent	1	Referent	1	Referent
No hysterectomy but bilateral oophorectomy	27	3,111	8.68	1.19	0.81, 1.74	1.20	0.82, 1.75	1.02	0.70, 1.49
Hysterectomy without oophorectomy	1,312	138,920	9.44	1.27	1.19, 1.35	1.25	1.16, 1.35	1.12	1.04, 1.21
Hysterectomy with bilateral oophorectomy	1,731	180,884	9.57	1.28	1.21, 1.35	1.26	1.17, 1.35	1.14	1.06, 1.23

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] In the multivariable-adjustment models, we adjusted for potential confounders, including age (continuous) at enrollment, race/ethnicity (American Indian or Alaska Native, Asian or Pacific Islander, black or African American, Hispanic/Latino, non-Hispanic white, and other), body mass index (continuous), education (high school or less, some college/technical training, college or some graduate work, and master's degree or higher), smoking (never, former, current), alcohol intake (no alcohol, past alcohol consumption, current and <7 alcoholic beverages/week, current and ≥7 alcoholic beverages/week), physical activity (metabolic equivalent hours/week: <5, 5–<10, 10–<20, 20–<30, ≥30), family history of diabetes (no, yes), age at first birth (never had term pregnancy, <20 years, 20–<30 years, ≥30 years), age at menarche (<12 years, 12–14 years, ≥15 years), parity (never had term pregnancy, 1–2, ≥3), waist circumference (continuous), hypertension (yes, no), and high serum cholesterol requiring medication (yes, no).

Table 3. Hazard Ratios for Diabetes in Women With Hysterectomy and Bilateral Oophorectomy Compared With Women With Hysterectomy Alone, According to Age at Hysterectomy and Hormone Therapy Status, Women's Health Initiative Observational Study, United States, 1993–1998[a]

Hormone Therapy and Surgical Status	Hysterectomy Before Age 45					Hysterectomy After Age 45				
	No. of Cases	Person-Years	Crude Incidence Rates (per 1,000 Person-years)	HR	95% CI	No. of Cases	Person-Years	Crude Incidence Rates (per 1,000 Person-years)	HR	95% CI
Women who never used hormone therapy										
Hysterectomy alone	265	22,078	12.00	1	Referent	129	12,034	10.72	1	Referent
Hysterectomy with BSO	126	10,026	12.57	1.00	0.80, 1.24	166	15,002	11.07	1.01	0.80, 1.29
Women who ever used hormone therapy										
Hysterectomy alone	620	68,924	9.00	1	Referent	292	35,367	8.26	1	Referent
Hysterectomy with BSO	610	62,208	9.81	1.01	0.90, 1.13	825	93,218	8.85	0.99	0.86, 1.14

Abbreviations: BSO, bilateral oophorectomy; CI, confidence interval; HR, hazard ratio.

[a] In the multivariable-adjustment models, we adjusted for potential confounders, including age (continuous) at enrollment, race/ethnicity (American Indian or Alaska Native, Asian or Pacific Islander, black or African American, Hispanic/Latino, non-Hispanic white, and other), body mass index (continuous), education (high school or less, some college/technical training, college or some graduate work, and master's degree or higher), smoking (never, former, current), alcohol intake (no alcohol, past alcohol consumption, current and <7 alcoholic beverages/week, current and ≥7 alcoholic beverages/week), physical activity (metabolic equivalent hours/week: <5, 5–<10, 10–<20, 20–<30, ≥30), family history of diabetes (no, yes), age at first birth (never had term pregnancy, <20 years, 20–<30 years, ≥30 years), age at menarche (<12 years, 12–14 years, ≥15 years), parity (never had term pregnancy, 1–2, ≥3), waist circumference (continuous), hypertension (yes, no), and high serum cholesterol requiring medication (yes, no).

bilateral oophorectomy overall or a reduced risk associated with bilateral oophorectomy in a subgroup compared with premenopausal women. Two studies (21, 22) observed an increased risk of diabetes in women who underwent hysterectomy concomitant with BSO, which is in line with our finding. However, Lejsková et al. (22) did not examine the association between hysterectomy alone and risk of diabetes, and Appiah et al. (21) observed a nonsignificantly increased risk of diabetes associated with hysterectomy alone (HR = 1.38, 95% CI: 0.94, 2.04). In fact, the magnitude of the association found by Appiah et al. is greater than our adjusted point estimate of 1.15 (95% CI: 1.07, 1.24) for hysterectomy only. Thus, we think that the nonsignificant finding in Appiah et al. may be due to low statistical power to detect a modest association with hysterectomy.

To our knowledge, our study is the first epidemiologic study to directly compare risk of diabetes associated with BSO to that associated with hysterectomy alone according to age at hysterectomy and hormone therapy status. We considered age at hysterectomy for 2 reasons. First, the indications and reasons for younger women to undergo hysterectomy might differ from those of older women who were in perimenopausal or postmenopausal stages. Second, the impact of hormone changes following hysterectomy may be different on younger women than on older women, because women having surgery before the typical age at natural menopause may experience more substantial changes in hormone levels than women who are many years past menopause. We observed that among postmenopausal women (compared with women who underwent hysterectomy), concomitant BSO did not impart additional risk of diabetes regardless of the age at hysterectomy and hormone therapy status. Using hysterectomy alone as a reference group helped control for the confounding related to indications for hysterectomy. The results were also supported by the finding that women with BSO alone had no increased risk of diabetes compared with women who had had neither hysterectomy nor BSO. Our findings are consistent with those of a WHI study in which Jacoby et al. (3) reported that BSO was not associated with risks of cardiovascular disease, hip fracture, cancer, or total mortality when compared with hysterectomy and ovarian conservation.

Women who have had BSO represent a unique population because they have a sudden dramatic decrease in both their androgen and estrogen production (5, 33). Experimental data demonstrate a protective role for estrogens in glucose metabolism (34, 35). Hormone therapy has also been associated with a lower incidence of diabetes in postmenopausal women (18–20). We were able to control for the use of hormone therapy in our study; however, the null findings from our data did not support the hypothesis that early loss of ovarian estrogen is a risk factor for diabetes. This might be because BSO reduces both androgen and estrogen production (5, 33), and, while deficiency of estrogen may be associated with increased risk of diabetes, reduced androgen may also lead to lower risk of diabetes (36, 37). Therefore, the overall positive and negative effects of BSO on risk of diabetes may cancel out. Another explanation may be that circulating estrone and estradiol levels are derived primarily from peripheral aromatization of androstenedione and testosterone among postmenopausal women. Studies have shown that oophorectomy does not seem to influence peripheral estrogen production in older women (38). Therefore, the absolute difference in hormone levels between women who undergo hysterectomy with or without BSO may not be sufficient to demonstrate a significant difference on risk of diabetes in older women. In fact, 2 studies observed no difference in estradiol or estrone levels associated with BSO in postmenopausal women and no differential influence of timing of oophorectomy (e.g., before or after natural menopause) on estrogen levels (5, 6).

The modestly increased risk of diabetes associated with hysterectomy that we observed could have several explanations. First, the increased risk might be due to a true increased risk from surgery leading to lower estrogen levels. After hysterectomy without BSO, patients experience shorter time to ovarian failure and menopausal symptoms (8, 9). Farquhar et al. (7) demonstrated that the onset of menopause in women who underwent hysterectomy retaining both ovaries was nearly 4 years earlier than for women with intact uteri. Early menopause may lead to a shift toward androgen predominance, including a decrease in sex hormone–binding globulin levels. Increased androgenicity has been linked to glucose intolerance (39).

A second explanation for the modest increased risk of diabetes associated with hysterectomy may be residual confounding due to the indication for hysterectomy. For example, obesity has been suggested as a major risk factor for abnormal uterine bleeding (40) and fibroids (41), which are leading indications for hysterectomy. It is also a risk factor for diabetes. Although we were able to adjust for body mass index, there may be residual unmeasured confounding factors that predispose women to surgery and also to diabetes. If the association between hysterectomy and risk of diabetes truly operates via lower estrogen or early menopause, then we would have expected to observe a higher risk of diabetes in women who underwent BSO.

Another explanation for the modest increased risk of diabetes associated with hysterectomy might be surveillance bias. For example, women who undergo hysterectomy and/or BSO might be more likely to be under a doctor's care or might see medical professionals more frequently during follow-up, thereby making it more likely that they would be screened for diabetes and subsequently diagnosed with diabetes. There are no data about the rates of diabetes screening in this population; however, we compared the average number of cholesterol tests (a surrogate variable for receipt of medical care) over the follow-up period by hysterectomy or oophorectomy status and did not observe appreciable differences in the numbers, suggesting that our findings are unlikely to be due to surveillance bias.

Strengths of our study include the prospective design with detail about potential confounders, the large sample size and long-term follow-up, and the ability to observe the association across several racial/ethnic groups. However, several limitations deserve mention. First, although other studies have reported reasonable validity for self-report of hysterectomy, hysterectomy and oophorectomy status were self-reported rather than verified from records. The nondifferential misclassification of exposures would tend to attenuate the associations for extreme exposure levels. However, if the degree of misclassification between hysterectomy alone and hysterectomy plus BSO were very high, it is possible that biases due to the misclassification could distort an exposure-response relationship if it exists (none, hysterectomy alone, hysterectomy plus BSO). Second, we are unable to determine whether women who reported prior hysterectomy and BSO underwent these surgeries concomitantly or at different times. However, most women likely underwent BSO at the time of hysterectomy. Third, our analyses may also be affected by survival bias, because WHI participants began follow-up many years after they underwent hysterectomy. In our study, we required all participants to be free of diabetes at the start of our follow-up period; thus, women who underwent hysterectomy and developed diabetes earlier than the start of the follow-up period were excluded. Therefore, the relative risk of diabetes associated with hysterectomy may be underestimated. Fourth, we do not know the risk-factor status of participating women before hysterectomy or the reason for the surgery. Finally, the outcome measure is self-reported diagnosis of diabetes and/or diabetes medication use, which may lead to some nondifferential misclassification.

In conclusion, our large, prospective study observed that hysterectomy status regardless of oophorectomy status was associated with increased risk of diabetes among postmenopausal women. However, our data did not support the hypothesis that early loss of ovarian estrogens is a risk factor for diabetes. The modest increased risk of diabetes associated with hysterectomy may be due to residual confounding or indications for hysterectomy.

ACKNOWLEDGMENTS

Author affiliations: Department of Epidemiology and Biostatistics, School of Public Health, Indiana University, Bloomington, Indiana (Juhua Luo); Division of Preventive Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts (JoAnn E. Manson); Division of Women's Primary Healthcare, Department of Obstetrics and Gynecology, School of Medicine, University of North Carolina, Chapel Hill, North Carolina (Rachel Peragallo Urrutia); Department of Applied Health Science, School of Public Health, Indiana University, Bloomington, Indiana (Michael Hendryx); Kaiser Permanente Center for Health Research, Portland, Oregon (Erin S. LeBlanc); and HealthPartners Institute, Minneapolis, Minnesota (Karen L. Margolis).

The WHI program is funded by the National Heart, Lung, and Blood Institute through contracts HHSN268201100046C, HHSN268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C, and HHSN271201100004C.

A short list of WHI investigators: *Program Office:* National Heart, Lung, and Blood Institute, Bethesda, Maryland (Jacques Rossouw, Shari Ludlam, Dale Burwen, Joan McGowan, Leslie Ford, and Nancy Geller). *Clinical Coordinating Center:* Fred Hutchinson Cancer Research Center, Seattle, Washington (Garnet Anderson, Ross Prentice, Andrea LaCroix, and Charles Kooperberg).

Investigators and Academic Centers: Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts (JoAnn E. Manson); MedStar Health Research Institute/Howard University, Washington, DC (Barbara V. Howard); Stanford Prevention Research Center, Stanford, California (Marcia L. Stefanic; The Ohio State University, Columbus, Ohio (Rebecca Jackson); University of Arizona, Tucson/Phoenix, Arizona (Cynthia A. Thomson); University at Buffalo, Buffalo, New York) Jean Wactawski-Wende; University of Florida, Gainesville/Jacksonville, Florida (Marian Limacher); University of Iowa, Iowa City/Davenport, Iowa (Robert Wallace); University of Pittsburgh, Pittsburgh, Pennsylvania (Lewis Kuller); Wake Forest University School of Medicine, Winston-Salem, North Carolina (Sally Shumaker). *Women's Health Initiative Memory Study:* Wake Forest University School of Medicine, Winston-Salem, North Carolina (Sally Shumaker).

Conflict of interest: none declared.

REFERENCES

1. Whiteman MK, Hillis SD, Jamieson DJ, et al. Inpatient hysterectomy surveillance in the United States, 2000–2004. *Am J Obstet Gynecol*. 2008;198(1):34.e1–34.e7.
2. Wu JM, Wechter ME, Geller EJ, et al. Hysterectomy rates in the United States, 2003. *Obstet Gynecol*. 2007;110(5):1091–1095.
3. 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 Int Med*. 2011;171(8):760–768.
4. Mikhail E, Salemi JL, Mogos MF, et al. National trends of adnexal surgeries at the time of hysterectomy for benign indication, United States, 1998–2011. *Am J Obstet Gynecol*. 2015;213(5):713.e1–713.e13.
5. Kotsopoulos J, Shafrir AL, Rice M, et al. The relationship between bilateral oophorectomy and plasma hormone levels in postmenopausal women. *Horm Cancer*. 2015;6(1):54–63.
6. Endogenous Hormones and Breast Cancer Collaborative Group, Key TJ, Appleby PN, et al. Circulating sex hormones and breast cancer risk factors in postmenopausal women: reanalysis of 13 studies. *Br J Cancer*. 2011;105(5):709–722.
7. Farquhar CM, Sadler L, Harvey SA, et al. The association of hysterectomy and menopause: a prospective cohort study. *BJOG*. 2005;112(7):956–962.
8. Moorman PG, Myers ER, Schildkraut JM, et al. Effect of hysterectomy with ovarian preservation on ovarian function. *Obstet Gynecol*. 2011;118(6):1271–1279.
9. Riedel HH, Lehmann-Willenbrock E, Semm K. Ovarian failure phenomena after hysterectomy. *J Reprod Med*. 1986;31(7):597–600.
10. 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.
11. 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.
12. Rivera CM, Grossardt BR, Rhodes DJ, et al. Increased cardiovascular mortality after early bilateral oophorectomy. *Menopause*. 2009;16(1):15–23.
13. Dørum A, Tonstad S, Liavaag AH, et al. Bilateral oophorectomy before 50 years of age is significantly associated with the metabolic syndrome and Framingham risk score: a controlled, population-based study (HUNT-2). *Gynecol Oncol*. 2008;109(3):377–383.
14. Mauvais-Jarvis F, Clegg DJ, Hevener A. The role of estrogens in control of energy balance and glucose homeostasis. *Endocr Rev*. 2013;34(3):309–338.
15. Kumagai S, Holmäng A, Björntorp P. The effects of oestrogen and progesterone on insulin sensitivity in female rats. *Acta Physiol Scand*. 1993;149(1):91–97.
16. Rincon J, Holmäng A, Wahlström EO, et al. Mechanisms behind insulin resistance in rat skeletal muscle after oophorectomy and additional testosterone treatment. *Diabetes*. 1996;45(5):615–621.
17. Riant E, Waget A, Cogo H, et al. Estrogens protect against high-fat diet-induced insulin resistance and glucose intolerance in mice. *Endocrinology*. 2009;150(5):2109–2117.
18. Margolis KL, Bonds DE, Rodabough RJ, et al. Effect of oestrogen plus progestin on the incidence of diabetes in postmenopausal women: results from the Women's Health Initiative Hormone Trial. *Diabetologia*. 2004;47(7):1175–1187.
19. Kanaya AM, Herrington D, Vittinghoff E, et al. Glycemic effects of postmenopausal hormone therapy: the Heart and Estrogen/Progestin Replacement Study. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med*. 2003;138(1):1–9.
20. Bonds DE, Lasser N, Qi L, et al. The effect of conjugated equine oestrogen on diabetes incidence: the Women's Health Initiative randomised trial. *Diabetologia*. 2006;49(3):459–468.
21. Appiah D, Winters SJ, Hornung CA. Bilateral oophorectomy and the risk of incident diabetes in postmenopausal women. *Diabetes Care*. 2014;37(3):725–733.
22. Lejsková M, Pit'ha J, Adámková S, et al. Bilateral oophorectomy may have an unfavorable effect on glucose metabolism compared with natural menopause. *Physiol Res*. 2014;63(suppl 3):S395–S402.
23. Kim C, Edelstein SL, Crandall JP, et al. Menopause and risk of diabetes in the Diabetes Prevention Program. *Menopause*. 2011;18(8):857–868.
24. Design of the Women's Health Initiative clinical trial and observational study. The Women's Health Initiative Study Group. *Control Clin Trials*. 1998;19(1):61–109.
25. Hays J, Hunt JR, Hubbell FA, et al. The Women's Health Initiative recruitment methods and results. *Ann Epidemiol*. 2003;13(9 suppl):S18–S77.
26. Jackson RD, LaCroix AZ, Cauley JA, et al. The Women's Health Initiative calcium–vitamin D trial: overview and baseline characteristics of participants. *Ann Epidemiol*. 2003;13(9 suppl):S98–S106.
27. Langer RD, White E, Lewis CE, et al. The Women's Health Initiative Observational Study: baseline characteristics of participants and reliability of baseline measures. *Ann Epidemiol*. 2003;13(9 suppl):S107–S121.
28. Ritenbaugh C, Patterson RE, Chlebowski RT, et al. The Women's Health Initiative Dietary Modification trial: overview and baseline characteristics of participants. *Ann Epidemiol*. 2003;13(9 suppl):S87–S97.
29. Stefanick ML, Cochrane BB, Hsia J, et al. The Women's Health Initiative postmenopausal hormone trials: overview

and baseline characteristics of participants. *Ann Epidemiol*. 2003;13(9 suppl):S78–S86.
30. Phipps AI, Buist DS. Validation of self-reported history of hysterectomy and oophorectomy among women in an integrated group practice setting. *Menopause*. 2009;16(3):576–581.
31. Margolis KL, Qi L, Brzyski R, et al. Validity of diabetes self-reports in the Women's Health Initiative: comparison with medication inventories and fasting glucose measurements. *Clin Trials*. 2008;5(3):240–247.
32. Jackson JM, Defor TA, Crain AL, et al. Self-reported diabetes is a valid outcome in pragmatic clinical trials and observational studies. *J Clin Epidemiol*. 2013;66(3):349–350.
33. Korse CM, Bonfrer JM, van Beurden M, et al. Estradiol and testosterone levels are lower after oophorectomy than after natural menopause. *Tumour Biol*. 2009;30(1):37–42.
34. Godsland IF. Oestrogens and insulin secretion. *Diabetologia*. 2005;48(11):2213–2220.
35. Le May C, Chu K, Hu M, et al. Estrogens protect pancreatic beta-cells from apoptosis and prevent insulin-deficient diabetes mellitus in mice. *Proc Natl Acad Sci USA*. 2006; 103(24):9232–9237.
36. Oh JY, Barrett-Connor E, Wedick NM, et al. Endogenous sex hormones and the development of type 2 diabetes in older men and women: the Rancho Bernardo Study. *Diabetes Care*. 2002;25(1):55–60.
37. Ding EL, Song Y, Manson JE, et al. Plasma sex steroid hormones and risk of developing type 2 diabetes in women: a prospective study. *Diabetologia*. 2007;50(10):2076–2084.
38. Laughlin GA, Barrett-Connor E, Kritz-Silverstein D, et al. Hysterectomy, oophorectomy, and endogenous sex hormone levels in older women: the Rancho Bernardo Study. *J Clin Endocrinol Metab*. 2000;85(2):645–651.
39. Pirimoglu ZM, Arslan C, Buyukbayrak EE, et al. Glucose tolerance of premenopausal women after menopause due to surgical removal of ovaries. *Climacteric*. 2011;14(4): 453–457.
40. Nouri M, Tavakkolian A, Mousavi SR. Association of dysfunctional uterine bleeding with high body mass index and obesity as a main predisposing factor. *Diabetes Metab Syndr*. 2014;8(1):1–2.
41. Pandey S, Bhattacharya S. Impact of obesity on gynecology. *Womens Health (Lond)*. 2010;6(1):107–117.

Appendix Table 1. Hazard Ratios for Diabetes in Women With Hysterectomy According to Age at Hysterectomy and Hormone Therapy Status, Women's Health Initiative Observational Study, United States, 1993–1998[a]

Hysterectomy	Never Used Hormone Therapy			Ever Used Hormone Therapy		
	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI
No	2,337	1		2,050	1	
Yes	689	1.12	1.03, 1.22	2,354	1.13	1.06, 1.20
Before age 45 years	391	1.12	1.01, 1.25	1,230	1.11	1.04, 1.20
After age 45 years	295	1.12	0.99, 1.27	1,117	1.14	1.06, 1.23

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] In the multivariable-adjustment models, we adjusted for potential confounders, including age (continuous) at enrollment, race/ethnicity (American Indian or Alaska Native, Asian or Pacific Islander, black or African American, Hispanic/Latino, non-Hispanic white, and other), body mass index (continuous), education (high school or less, some college/technical training, college or some graduate work, and master's degree or higher), smoking (never, former, current), alcohol intake (no alcohol, past alcohol consumption, current and <7 alcoholic beverages/week, current and ≥7 alcoholic beverages/week), physical activity (metabolic equivalent hours/week: <5, 5–<10, 10–<20, 20–<30, ≥30), family history of diabetes (no, yes), age at first birth (never had term pregnancy, <20 years, 20–<30 years, ≥30 years), age at menarche (<12 years, 12–14 years, ≥15 years), parity (never had term pregnancy, 1–2, ≥3), waist circumference (continuous), hypertension (yes, no), and high serum cholesterol requiring medication (yes, no).