Bilateral Oophorectomy and the Risk of Incident Diabetes in Postmenopausal Women

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OBJECTIVE

Ovarian hormones regulate glucose uptake and insulin sensitivity. Despite the high frequency of surgical menopause, its relationship with diabetes has not been extensively investigated. We assessed the association between hysterectomy with or without bilateral oophorectomy (BSO) status, menopausal age, and reproductive life span with incident diabetes.

RESEARCH DESIGN AND METHODS

Data were from a cohort of 2,597 postmenopausal women enrolled in the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study without diabetes mellitus at baseline. Cox proportional hazards regression models were used to calculate adjusted hazard ratios (HRs) and 95% CIs.

RESULTS

After a median follow-up time of 9.2 years, the incidence of diabetes (in cases per 1,000 person-years) was 7.4 for women with no hysterectomy or BSO, 8.2 for hysterectomy alone, and 8.5 for hysterectomy with BSO. Hysterectomy status was associated positively with diabetes (HR 1.66, 95% CI 1.23–2.23). However, the elevated risk was restricted to women with both hysterectomy and BSO after adjustment for relevant confounders (HR 1.57, 95% CI 1.03–2.41). An earlier age at menopause and a shorter reproductive life span also exhibited a linear relationship with the development of diabetes irrespective of type of menopause (*P* for trend = 0.001).

CONCLUSIONS

Women with hysterectomy concomitant with BSO may represent a unique population with elevated risk for diabetes and other chronic diseases. Therefore, the decision to remove the ovaries at the time of hysterectomy for benign conditions during the premenopausal years should be balanced with the risk of diabetes and its potential complications. Furthermore, the mechanism linking BSO to diabetes mellitus needs to be clarified.

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Diabetes mellitus is common in postmenopausal women and is a major risk factor for cardiovascular disease, the leading cause of mortality in women in industrialized countries (1). In the United States, at least 1.8 million women of reproductive age (18–44 years) are estimated to have diabetes, compared with 3.8 million among women aged 45–65 years (2). With >2 million women reaching menopause each year, together with improvement in life expectancy (3), the prevalence of diabetes in postmenopausal women is expected to increase, making it a significant public health issue.

The postmenopausal years are associated with a rise in fasting insulin and glucose levels, and with increasing visceral adiposity (4). Although several investigations into the impact of menopause, when compared with aging, on diabetes have been undertaken, the association remains equivocal (1,5–7). The relationship between estrogens and diabetes is also uncertain in that circulating estradiol levels appear to be higher in postmenopausal women with diabetes than in those without diabetes (8), whereas estrogen therapy has been reported to reduce diabetes risk in postmenopausal women (9). The marked decline in endogenous estrogen production after menopause, resulting in increased relative androgenicity and changes in body composition, is suggested to influence pancreatic β-cell function (10), insulin-induced glucose transport (11), and hepatic glucose output (5,12).

Bilateral oophorectomy (BSO) abruptly decreases the production of estrogens, and is followed by post–glucose challenge hyperinsulinemia, implying insulin resistance (13). In rats, BSO decreased insulin-mediated glucose uptake via an impaired insulin-stimulated translocation of GLUT4 to the plasma membrane (11,14) and decreased protein expression of glycogen synthase (14). Despite these observations, the impact of BSO on diabetes risk has not been extensively studied.

Hysterectomy is the second most common surgery performed on women of child-bearing age after cesarean section, and more than half of the 600,000 women undergoing a hysterectomy annually also have both ovaries removed (BSO), usually as primary prevention for ovarian cancer (15). Despite the high frequency of surgical menopause in the United States, investigation into the effect of hysterectomy with or without oophorectomy on diabetes risk compared with women with natural menopause is sparse. In the current study, we investigated the association of hysterectomy and oophorectomy status, age at menopause, and reproductive life span (i.e., a marker of total endogenous estrogen exposure), with the incidence of diabetes in a national cohort of postmenopausal women.

RESEARCH DESIGN AND METHODS

Study Population

The first National Health and Nutrition Examination Survey (NHANES I) was conducted from 1971 to 1975 by the National Center for Health Statistics to assess trends in health and nutritional status among noninstitutionalized U.S. civilians. Participants from this survey who were observed as part of the National Health and Nutrition Examination Epidemiologic Follow-up Survey (NHEFS) were eligible for the current study. The NHEFS is a longitudinal study that includes all participants aged 25–74 years who completed the medical examination in NHANES 1. These participants were contacted in four waves during 1982–1984, 1986, 1987, and 1992. During these periods, medical and health care records were abstracted. Approximately 93% of study participants of the original cohort were successfully traced through to 1992 (16). A detailed description of the study design and sampling methods is available elsewhere (17). The 1982–1984 NHEFS assessment included more detailed questions regarding reproductive health. Therefore, women who were alive at this wave of follow-up formed the baseline for this present study. Women were asked whether they were still having menstrual periods, whether the periods were regular or irregular, and, if irregular, whether this was because they were going through the change of life or because of some other reasons. Participants whose menstrual cycles had ceased were further asked whether this occurred naturally or by reason of surgery. Women who responded that their period had ceased spontaneously were considered to be menopausal with age at the last menstrual period—whether menses stopped naturally or surgically—considered to be the age at natural menopause or surgery. To prevent misclassification by the inclusion of women who were perimenopausal and to use a definition of menopause consistent with World Health Organization criteria (18), participants whose age at menopause was <1 year or within 1 year of their age at study enrollment were excluded. From the 3,759 postmenopausal women who were within the ages of 40–79 years, the following exclusions were made, in order: 105 women with unknown age at menopause or type of menopause; 248 women who had undergone unilateral oophorectomy; 48 women with intact uterus but had undergone BSO; 117 women with missing body weight measurement; and 18 women with “other” race/ethnicity. Finally, we excluded women with the following prevalent conditions: diabetes (n = 308); cardiovascular disease (n = 222); and gynecological cancers, defined as breast, cervical, ovarian, or uterus cancer (n = 96), since oophorectomy among these participants with neoplasms would likely have been therapeutic rather than prophylactic. These exclusions resulted in an analytic sample of 2,597 women.

Measurements

Baseline information included self-reported sociodemographic and lifestyle characteristics, reproductive and medical history, anthropometric measures, and physical activity. Sociodemographic and lifestyle factors obtained included age, race (white or African American), educational level (less than high school, high school, and some college or greater), and smoking status (never, former, current). Participants were weighed at home using a portable spring scale after removing extra articles of clothing, such as heavy sweaters or jackets. BMI was calculated by dividing weight in kilograms by height in meters squared. Waist circumference was calculated using the method proposed by Bozeman et al. (19). Physical activity was categorized into three levels (low, moderate, and high), based on self-reported daily and recreational activities (20). Women with low physical activity were considered sedentary. Blood pressure was measured by trained physicians while participants were seated. Hypertension (HT) was defined as a systolic blood pressure $>$140 mmHg, diastolic blood pressure $>$90 mmHg, or a previous physician diagnosis. Family history of medical conditions was self-reported, and total cholesterol level was obtained from a nonfasting blood sample.

Hysterectomy status was ascertained by asking "Do you still have your womb or uterus?" Additionally, participants were also asked whether they had one or both ovaries removed. Women who responded that both of their ovaries were removed surgically were considered to have BSO. Age at menarche was defined as self-reported age at first menstrual period. Reproductive life span was calculated by subtracting age at menarche from age at menopause. Postmenopausal hormone use was determined from the question "Did you ever take female hormone pills for reasons related to menopause, including hot flashes or mood changes around the time you were beginning the change of life? This would include hormone pills taken for natural change of life or because your periods stopped due to an operation." Specific hormone regimens, types, or routes of administration were not recorded. Parity, number of miscarriages, and oral contraceptive use were also ascertained via personal interview.

Incident Diabetes

Incident diabetes was defined by the report of this condition on any of the following: *1*) self-report of physician diagnosed diabetes; *2*) death certificate (*International Classification of Diseases*, ninth revision, codes 250.0–250.9; or *3*) health care facility stay with a discharge diagnosis of diabetes. The diagnosis date for diabetes was the date recorded on death certificates or facility discharge records or personal interview questionnaire.

Statistical Analyses

Descriptive statistics (e.g., frequencies, percentages, and means) were calculated to describe study participants according to hysterectomy and oophorectomy status. For categorical variables, comparisons between groups were assessed using the χ^2 test. Comparisons for continuous variables were tested using ANOVA and *t* test when comparisons by ovarian status were undertaken among women with surgical menopause. Nonparametric equivalent tests, namely Kruskal-Wallis and Mann-Whitney *U* tests, were used for non-normally distributed continuous variables.

In the analysis of time to event, the cumulative probability of incident diabetes was calculated using Kaplan-Meier methods with the log-rank test used to test for differences in survival curves. Adjustment for multiple comparisons for the log-rank test was based on a Tukey Studentized range test. Women in whom diabetes did not develop were censored at date of death, date last known to be alive, or 19 July 1993 (the last day of follow-up). Finally, Cox proportional hazards regression was used to calculate relative risks and 95% CIs of incident diabetes by hysterectomy and oophorectomy status. All risk factors that were significant at or less than $P = 0.2$ were included in the multivariable analyses. Multiple models with progressive degrees of covariate adjustment were used and are presented to provide clarity regarding the effect of confounding. Covariates adjusted for were sociodemographic status (age, race, and education), health behaviors (smoking status and physical activity), general vascular health status (HT), reproductive factors (parity, postmenopausal estrogen use, age at menarche, and age at menopause), and adiposity (BMI and waist circumference). The presence of potential effect modifiers was evaluated using likelihood ratio test to compare models with and without interaction terms. A two-tailed probability value $<$0.05 was considered to be statistically significant. We tested and confirmed the validity of the proportional hazards assumption by using cumulative sums of Martingale residuals with a Kolmogorov-type supremum test and visually inspecting plots of Schoenfeld residuals versus time. The time scale for all survival analyses was age in years. The advantages of using age instead of years since enrollment, apart from it being recommended for the analyses of longitudinal studies such as NHEFS (21), is that it has a more straightforward interpretation because it is free of the confounding effect of age, which is intrinsically taken into account as a measure of survival time (22). A reoccurring dilemma in analyzing NHEFS concerns the use of sample weights and clustering (23,24). The use of weights and clustering enhances the calculation of national prevalence estimates. However, the objective of the current study was to examine the association between specific risk factors and the risk of the development of diabetes, and not to provide national estimates. Additionally, inconsistencies and changes in sampling strategies used during the original NHANES 1 may render weighted results less representative (24). We ran the analyses with and without the sampling weights and clusters, and found the results to be consistent. Therefore, we present here unweighted estimates. All analyses were performed using SAS software, version 9.3 (SAS Institute, Inc., Cary, NC).

RESULTS

A description of the cohort according to hysterectomy and oophorectomy status is shown in Table 1. The mean ± SD age at baseline of participants included in the analysis was 60 ± 10.7 years; 87% of participants were white. Approximately 40% of participants had undergone a hysterectomy. Of this number, almost half (47%) had undergone concomitant BSO, at a mean age of 41.9 years (95% CI 41.2–42.5 years). Perhaps because surgery was often conducted as a treatment for uterine fibroid tumors, a greater proportion of women with surgical menopause (hysterectomy with/or without oophorectomy) reported more episodes of miscarriage, and there were more ever-users of postmenopausal hormone therapy as

Table 1—Baseline characteristics of study participants by hysterectomy/oophorectomy status

Characteristics	No hysterectomy/ oophorectomy (*N* = 1,562)	Hysterectomy only (*N* = 551)	Hysterectomy and oophorectomy (*N* = 484)	*P* value*	*P* value†
Age (years)	62.9 (9.8)	58.0 (11.9)	56.4 (10.0)	0.001	0.127
Race (%)				0.028	0.034
White	85.9	86.2	90.5		
Black	14.1	13.8	9.5		
Education (%)				0.059	0.796
Less than high school	23.8	19.1	19.8		
High school	56.2	61.2	62.0		
Some college or higher	20.0	19.7	18.2		
Current smoking status (%)	24.3	25.2	30.4	0.028	0.070
Sedentary lifestyle (%)	34.3	31.9	34.5	0.100	0.032
Waist circumference (cm)	91.3 (11.8)	90.3 (10.9)	90.6 (11.5)	0.176	0.744
BMI (kg/m^2) (%)				0.797	0.475
$<$25.0	46.9	48.6	46.7		
25.0–29.9	32.1	32.1	31.0		
$\geq$30.0	21.0	19.3	22.3		
Age at menarche (years)	13.2 (1.5)	12.9 (1.5)	12.9 (1.5)	0.001	0.844
Parity (%)				0.001	0.031
None	17.9	12.0	14.4		
1 live birth	12.7	11.4	11.8		
2–3 live births	37.8	41.9	46.9		
$\geq$4 live births	31.6	34.7	26.9		
Miscarriage (%)				0.036	0.371
None	72.2	69.2	70.9		
One	18.8	18.5	15.9		
Two	5.6	7.6	6.6		
Three or more	3.5	4.7	6.6		
Reproductive life span (years)	35.7 (5.2)	28.9 (7.3)	29.0 (7.1)	0.001	0.902
Age at menopause (years)	48.9 (5.0)	41.8 (7.2)	41.9 (7.1)	0.001	0.935
Ever-use of hormone therapy (%)	19.0	33.2	65.5	0.001	0.001
Ever-use of oral contraceptives (%)	14.5	31.0	27.9	0.001	0.306
Family history of female cancers (%)‡	10.4	12.7	11.8	0.311	0.704
HT (%)	44.6	39.2	45.7	0.056	0.038
Total cholesterol (mg/dL)	231.6 (47.5)	223.1 (46.9)	222.6 (47.0)	0.001	0.872

**P* value comparing all three groups. †*P* value comparing women with hysterectomy by ovarian status. ‡Family history of breast, ovarian, uterine, and cervical cancer.

well as oral contraceptives than women with natural menopause. Furthermore, surgically menopausal women had an earlier age at menarche (12.9 vs. 13.2 years) and a lower reproductive life span (28.9 vs. 35.7 years). Interestingly, there was no difference in waist circumference or BMI among women in the three groups, and the prevalence of HT was similar in women with hysterectomy concomitant with oophorectomy and natural menopause, although it was lower in those with hysterectomy alone. Comparing women with hysterectomy concomitant with oophorectomy to those with hysterectomy alone, the former were less likely to report black race (*P* = 0.034), but were more likely to be have a sedentary lifestyle (*P* = 0.032) and to be nulliparous (*P* = 0.031).

During a mean follow-up time of 8.7 years (median 9.2 years, SD 1.9 years), diabetes developed in 176 participants (6.8%). Of the incident cases, 61% were self-reported as physician-diagnosed diabetes, and 22.1% were based on hospital discharge diagnosis at a health care facility. Furthermore, 15.8% of participants were identified by both of these sources, with only two case patients (1.2%) recorded from death certificates. The unadjusted cumulative incidence of diabetes (in cases per 1,000 person-years) was 7.4 among women with no hysterectomy or oophorectomy, 8.2 among women with hysterectomy alone, and 8.5 among women with both hysterectomy and oophorectomy. Estimates based on the Kaplan-Meier procedure showed a higher risk of diabetes among women with both hysterectomy and oophorectomy (*P* = 0.002) with increasing age (Fig. 1). Differences in unadjusted survival curves among women with hysterectomy alone and women with both hysterectomy and oophorectomy did not attain statistical significance (*P* = 0.725). Multiple models with progressive adjustments were constructed to assess the influence of hysterectomy and ovarian status,

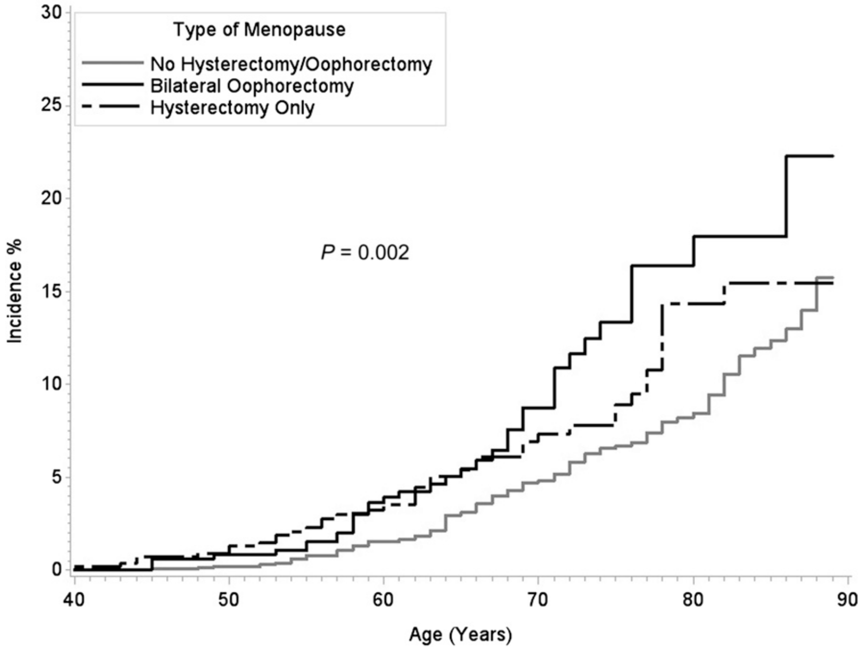

Figure 1—Kaplan-Meier cumulative incidence estimates of incident diabetes according to hysterectomy/oophorectomy status. The log-rank *P* value of 0.002 represents differences among all three groups. Hysterectomy only vs. hysterectomy with BSO: *P* = 0.725 (adjusted for multiple comparisons).

reproductive life span, and age at natural menopause or surgery with incident diabetes. In age-adjusted analysis, hysterectomy regardless of ovarian status was associated with diabetes (Table 2). Women with both hysterectomy and oophorectomy had a higher risk of incident diabetes (hazard ratio [HR] 1.89 [95% CI 1.29–2.76]) than women with hysterectomy alone (1.49 [1.03–2.15]) when compared with women who had not undergone hysterectomy or oophorectomy. After adjustment for reproductive factors, diabetes risk was limited to women with both hysterectomy and oophorectomy (1.59 [1.03–2.43]), whereas the risk for women who had undergone hysterectomy alone failed to attain statistical significance (1.41 [0.95–2.07]).

The further addition of physical activity and adiposity measures (BMI and waist circumference) had little effect on the HRs for women with hysterectomy alone (1.38 [95% CI 0.94–2.04]) or hysterectomy with BSO (1.57 [1.03–2.41]) in the fully adjusted model. Interaction analyses showed that the association of hysterectomy and ovarian status with incident diabetes did not differ by BMI, waist circumference, and smoking status. An early age at natural menopause/surgery was associated with a higher risk of diabetes, which exhibited a linear relationship (*P* for trend = 0.009) with HRs of 1.83, 1.02, 0.89, and 0.64 for ages $<$40, 40–44, 45–49, and $\geq$55 years, respectively (Fig. 2). Additionally, the duration of natural menses was positively associated with diabetes (Fig. 2), with women who had fewer years of menstrual cyclicity having elevated risks, yielding HRs of 14.89, 5.41, 2.09, 0.51, and 0.31 for reproductive life span of $\geq$20, 21–25, 26–30, 36–40, and $>$40 years, respectively (*P* for trend $\leq$ 0.001).

CONCLUSIONS

The major finding in this prospective cohort of postmenopausal women is that hysterectomy concomitant with BSO is associated with incident diabetes mellitus independent of confounding factors as women grow older. Moreover, BMI, waist circumference, and smoking status did not moderate this relationship. Additionally, a shorter exposure to endogenous estrogens as well as an earlier age at menopause, whether natural or surgical, elevates the risk of incident diabetes.

Menopause is a milestone in the life of women, with $>$2 million U.S. women reaching this state of ovarian functional loss each year (3). This period is characterized by an increase in several chronic conditions, with diabetes being a notable example. Several investigations into the effect of menopausal status on the incidence of diabetes have been undertaken, but the association remains inconclusive. One reason that may partly explain the inconsistencies is that in the few studies that included women with surgical menopause, the definition of surgical menopause was inconsistent. For instance, while some studies defined surgical menopause by hysterectomy and oophorectomy (1), others excluded entirely in their analyses women with the former or latter (6,7). These discrepancies led to misclassification bias since women who had undergone hysterectomy and at least one intact ovary may have a different diagnosis and exhibit a different hormonal profile than women who had undergone hysterectomy alone or those who had undergone hysterectomy and BSO (2,25). The current study created mutually exclusive groups of women

Table 2—Risk of incident diabetes by hysterectomy/oophorectomy status

Model no. and variables	HR	95% CI	*P* value	Adjustments
1				Age
No hysterectomy/oophorectomy	1	Referent		
Hysterectomy only	1.49	1.03–2.15	0.034	
BSO	1.89	1.29–2.76	0.001	
All hysterectomies	1.66	1.23–2.23	0.001	
2				Above plus race and education
No hysterectomy/oophorectomy	1	Referent		
Hysterectomy only	1.51	1.05–2.19	0.027	
BSO	1.98	1.35–2.90	0.001	
All hysterectomies	1.70	1.26–2.30	0.001	
3				Above plus smoking and HT
No hysterectomy/oophorectomy	1	Referent		
Hysterectomy only	1.54	1.07–2.23	0.021	
BSO	1.91	1.30–2.80	0.001	
All hysterectomies	1.69	1.28–2.29	0.001	
4				Above plus parity, postmenopausal estrogen use, age at menarche, and age at menopause
No hysterectomy/oophorectomy	1	Referent		
Hysterectomy only	1.41	0.95–2.07	0.087	
BSO	1.59	1.03–2.43	0.035	
All hysterectomies	1.48	1.06–2.06	0.023	
5				Above plus BMI, physical activity, and waist circumference
No hysterectomy/oophorectomy	1	Referent		
Hysterectomy only	1.38	0.94–2.04	0.105	
BSO	1.57	1.03–2.41	0.038	
All hysterectomies	1.46	1.04–2.04	0.028	

with natural menopause, hysterectomy alone, or hysterectomy with BSO to prevent overlapping hormonal profiles. To our knowledge, this is the first study to do so, and to also report an elevated diabetes risk among women after combined hysterectomy and oophorectomy.

During the natural menopausal transition, there is an increase in estradiol secretion followed by a continuous but irregular decline due to variation in cycle length and a reduction in ovulatory cycles, whereas testosterone levels are relatively unchanged (26). Hysterectomy with ovarian conservation was reported to cause a slight decrease in testosterone levels but not estradiol levels (27), whereas BSO produces an abrupt and marked decline in serum estradiol levels in premenopausal women and a decrease in testosterone levels (27).

It is well-known that ovarian hormones influence the function of pancreatic β-cells (10). Estrogens enhance insulin-induced glucose transport (11) by activating phosphatidylinositol 3 kinase/Akt signaling, leading to translocation of GLUT4 to the plasma membrane (28), and suppressing hepatic gluconeogenesis (5,12). Rincon et al. (14), observed a 25% reduction in insulin-mediated glucose uptake and protein expression of glycogen synthase in rats 8 weeks after ovariectomy, while Bailey and Ahmed-Sorour (10) reported a 40% increase in plasma glucose concentrations during glucose tolerance tests, and a 26% decrease in the plasma insulin response to glucose in ovariectomized mice compared with controls.

In women who had undergone oophorectomy, Dørum et al. (29) and Michelsen et al. (30) each reported a higher prevalence and incidence of metabolic syndrome, and women who undergo hysterectomy with or without BSO, because of anovulation, may have polycystic ovary disease. Although the cause of the association between hysterectomy with or without BSO and diabetes is uncertain, these findings offer a potential hormonal-metabolic mechanism to explain the elevated risk of diabetes among women with BSO in the current study.

Testosterone levels are higher in postmenopausal women with diabetes than in those without diabetes (31), and increased androgenicity is associated positively with an increased risk for the development of diabetes. Since women who have undergone BSO have lower androgen levels than women with intact ovaries, we began this study with the hypothesis that BSO would reduce diabetes risk. Correction of androgenicity among women with polycystic ovary syndrome by laparoscopic ovarian cautery did not improve insulin sensitivity (32), and reduction in ovarian sex steroid production by gonadotropin-releasing hormone analogs in girls with early puberty increased insulin resistance later in life (33). Thus, ovarian androgens are unlikely to explain our results.

Contrary to our findings in the NEFS, a low risk of diabetes was found among women who had undergone BSO compared with premenopausal women in the Diabetes Prevention Program (DPP) (6). In that cohort of women with glucose intolerance, however, the low risk with oophorectomy was restricted to those women randomized to receive intensive lifestyle intervention but was

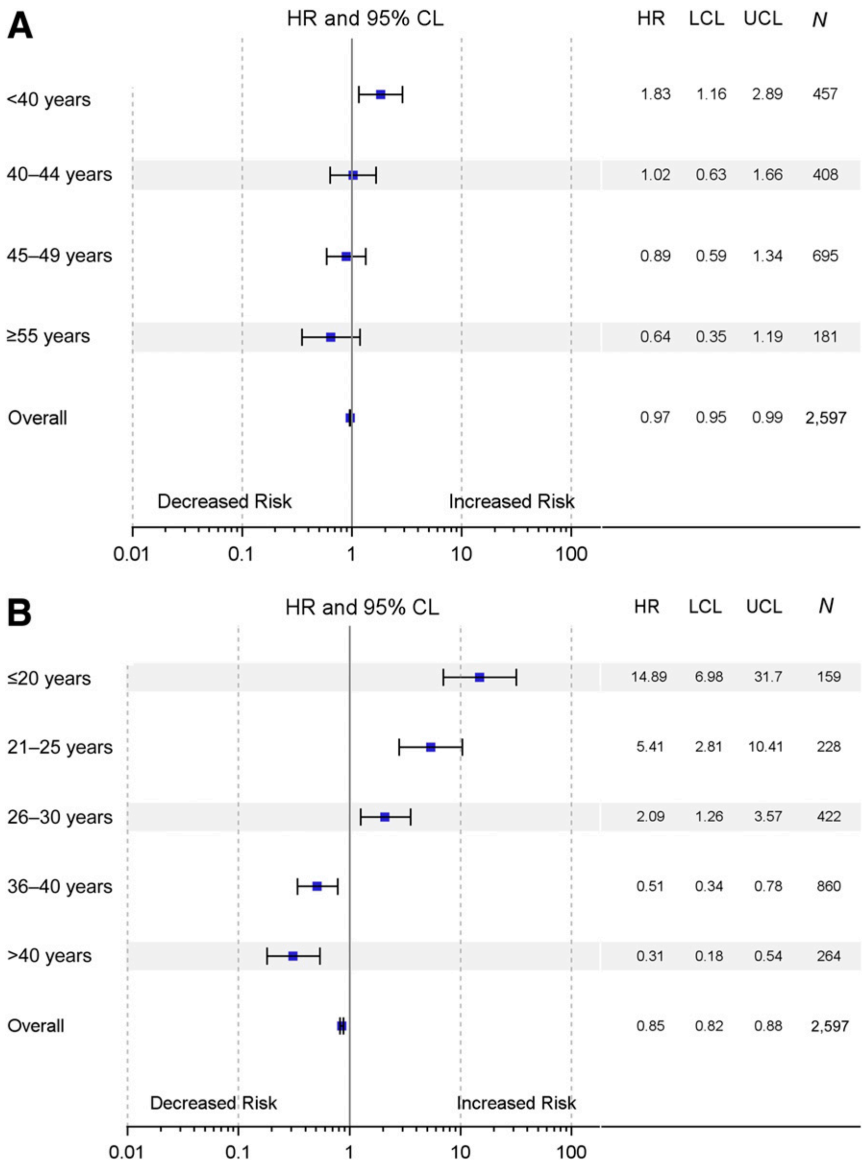

Figure 2—Summary estimates of the risk of incident diabetes according to age at natural menopause/surgery (50–54 years of age as referent, *n* = 856) (*A*) and reproductive life span (31–35 years of age as referent, *n* = 664) (*B*). CL, confidence limit; LCL, lower confidence limit; UCL, upper confidence limit.

not observed in those in the treatment arm of the study. A possible explanation for the divergent results may be that the DPP had a higher proportion of oophorectomized women with a history of hormone therapy (65% in NEFS vs. 88% in DPP). In the DPP, the moderating effect of hormone therapy could not be determined since diabetes did not develop in any hormone therapy users who had undergone oophorectomy within the lifestyle arm of the study. Nevertheless, not all investigations of the effect of hormone therapy on diabetes risk in women with surgical menopause support a protective effect of exogenous estrogens (9,34). Another explanation may be that those oophorectomized women who are at high risk for the development of diabetes may have benefitted from lifestyle interventions but not hormone therapy (6). For example, a Norwegian study (35) of women at risk for hereditary breast and/or ovarian cancer reported a favorable risk profile among oophorectomized women, including lower levels of total cholesterol, higher levels of HDL cholesterol, lower systolic blood pressure, more physical activity, and lower BMI. Those women had undergone risk-reducing salpingo-oophorectomy after genetic counseling and thus were also more likely to establish a healthier lifestyle. The DPP did not exclude women with a personal or family history of gynecological cancers, as was done in the NEFS, and perhaps may have included a large number of high-risk oophorectomized women who made beneficial lifestyle changes after surgery, leading to reduced diabetes incidence.

An earlier age at natural menopause/surgery and a shorter reproductive life span were also associated with diabetes in the NEFS. Previous studies regarding menopausal age are mixed, with some identifying no association after adjusting for confounders (36,37), while others observed a positive association (1,38). The risk of diabetes development in women with a shorter reproductive life span has been attributed to a shorter exposure to endogenous estrogens (1), thereby explaining the relatively higher estimates observed for reproductive life span compared with menopausal age, even though both measures were highly correlated (r = 0.975). With several experimental and mechanistic studies (9,34) supporting a protective effect of estrogen on insulin secretion, glucose homeostasis, and incident diabetes, reproductive life span may be a better measure for quantifying lifetime estrogen exposure than age at menopause. The significant effect of menopausal age on the incidence of diabetes may be relevant for the prevention of diabetes because women with early menopause will be targeted for screening. Of note, the lower tail of the distribution of age at menopause, either natural or surgical, may represent a subgroup of women with genetic or environmental factors that predispose them to early ovarian failure, thereby increasing their risk of development of diabetes. Future investigations into the mechanisms influencing ovarian senescence may have broader implications for understanding why such women are more susceptible to metabolic diseases and mortality.

This study has several notable strengths. A major strength is the use of a large population-based nationally representative cohort of postmenopausal women, which increases the generalizability of the findings. Additionally, this study was of sufficient sample size and duration of follow-up to allow associations with incident diabetes to be assessed with good precision. Several limitations of the present analyses deserve mention, however. Hysterectomy and oophorectomy status were self-reported and not confirmed by medical records. This may lead to the potential for misclassifications due to imprecise recall of the date of occurrence, which may be many years before study enrollment. Due to the prospective design of the study, any such random misclassification, if present, would be expected to bias the findings toward the null. On the other hand, many studies have reported reasonable validity for self-report of menopausal status, whether natural or surgical, with women's accuracy in recalling age at oophorectomy surpassing recall of age at natural menopause (39). We did not identify any effect modification by BMI, waist circumference, or smoking. This may be attributable to these measures not being assessed at the onset of menopause but during follow-up. Furthermore, estimating waist circumference by indirect calculation, rather than direct measurement may be a contributing factor. Regardless, other investigators (1,6) have also reported no significant interaction effect of these factors on incident diabetes risk.

Biochemical testing to detect diabetes was not available in NEFS; therefore, we could not eliminate participants who may have had undiagnosed diabetes at baseline, rendering the possibility of reverse causality to be present in our analyses. To overcome this, incident diabetes cases occurring within 2 years of baseline were excluded in sensitivity analyses, but this did not yield appreciably different results. Finally, even though we adjusted for a large number of covariates, residual confounding cannot be ruled out entirely.

The present report has both clinical and public health significance, showing that hysterectomy with oophorectomy, early age at natural menopause/surgery, and shorter duration of endogenous exposure to estrogen are positively associated with diabetes in postmenopausal women. Women who have undergone hysterectomy concomitant with oophorectomy represent a unique population due to the abrupt cessation of ovarian hormone production, perhaps making them susceptible to numerous chronic diseases and mortality. The choice of prophylactic oophorectomy at the time of hysterectomy is a complex decision requiring that patients and physicians consider multiple factors. Recognizing that the preservation of the ovaries at the time of hysterectomy during the premenopausal age may greatly influence the long-term health of women, gynecologists are less likely nowadays to recommend prophylactic BSO in younger women (40). Further research is essential to determine why type 2 diabetes is more likely to develop in women who have undergone BSO.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. D.A. researched data, conducted data analysis, and wrote the manuscript. S.J.W. contributed to discussion and reviewed and edited the manuscript. C.A.H reviewed and edited the manuscript. D.A. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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