

Diabetes mellitus risk after hysterectomy

A population-based retrospective cohort study

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Abstract

We explored whether hysterectomy with or without bilateral oophorectomy was associated with the increasing incidence of diabetes mellitus (DM) in an East Asian population. This was a retrospective population-based cohort study that analyzed DM risk in Taiwanese women, using a health insurance research database of 1998 to 2013 containing nearly 1 million people. We identified 7088 women aged 30 to 49 years who had undergone hysterectomy with or without oophorectomy. The comparison group included 27,845 women without a hysterectomy who were randomly selected from the population and matched to women in the hysterectomy group by age (exact year) and year of the surgery. DM comorbidities were identified. The incidence and hazard ratios for DM were calculated with Cox proportional hazard regression models. The median ages of patients in the hysterectomy and comparison groups were both approximately 44 years. After a median 7.1 years of follow-up, the incidence of DM was 40% higher in the hysterectomized women as compared with the comparisons (9.12 vs 6.78/1000 person-years, $P < .001$), with an adjusted hazard ratio (aHR) of 1.37 (95% confidence interval [CI] = 1.23–1.52). However, the DM risk was not increased in the women with hysterectomy plus oophorectomy (aHR=1.28, 95% CI=0.93–1.76). Furthermore, among women aged 30 to 39 years, 40 to 49 years, the risk in hysterectomized women was higher than the comparisons (aHR = 1.75, 95% CI = 1.27–2.41; aHR = 1.33, 95% CI = 1.19–1.49, respectively). Our study provides essential and novel evidence for the association between hysterectomy and DM risk in women aged 30 to 49 years, which is relevant to these women and their physicians. Physicians should be aware of the increased DM risk associated with hysterectomy and take this into consideration when evaluating a patient for a hysterectomy. The current results might help gynecologists prevent DM and encourage diagnostic and preventive interventions in appropriate patients.

Abbreviations: aHR = adjusted hazard ratio, BSO = bilateral salpingo-oophorectomy, CAD = coronary artery disease, CKD = chronic kidney disease, DM = diabetes mellitus, HR = hazard ratio, ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification, NHI = National Health Insurance, NHIRD = NHI Research Database, NT = New Taiwan dollars.

Keywords: cohort, diabetes mellitus, hysterectomy, menopause, oophorectomy

1. Introduction

Diabetes mellitus (DM) is a metabolic disease characterized by hyperglycemia caused by insulin resistance, inappropriate insulin secretion, and excessive glucagon secretion.^[1] To diagnose DM, serum level of fasting glucose should be ≥ 126 mg/dL and 2 hour after 75 g glucose water intake ≥ 200 mg/dL.^[2] The risk factors for DM are including obesity,

family history, an unhealthy dietary mode, low level of education, decreased physical behavior, history of hypertension, gestational diabetes, and metabolic syndrome.^[3] The sex hormones may be associated with the impairment of glucose metabolism. The higher level of endogenous testosterone or estrogen is associated with an increased risk of DM in women.^[4,5] Polycystic ovary syndrome is also associated with

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The dataset is not available for public access but is available from the Taiwan National Health Insurance Department on reasonable request.

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an increased risk of DM in middle-aged women as it causes insulin resistance.^[6]

Hysterectomy, a major cause of surgical menopause, is the most prevalent surgical gynecological intervention in the United States, China, and Taiwan (5.1–5.8, 1.12, and 2.68–3.03 per 1000 person-years, respectively).^[7–10] It is performed to treat endometriosis, uterine myoma, uterine prolapse, and genital malignancies (cervical, endometrial, and ovarian cancer).^[7–9] Oophorectomy causes an abrupt stop of endogenous estrogen production. This ovarian hormone is thought to be a regulator of insulin sensitivity, which might be related to DM occurrence.^[11] Obviously, hysterectomy is associated with cardiovascular disease (CVD) and its pre-existing risk factors including metabolic syndrome (i.e., obesity, hyperlipidemia, and hypertension).^[12–16]

Studies regarding the association of hysterectomy and oophorectomy with DM are limited and inconclusive. A previous study recruited 2597 postmenopausal women without DM as baseline. After a follow-up of 9.2 years, women who underwent both hysterectomy and bilateral salpingo-oophorectomy (BSO) showed a hazard ratio (HR) of 1.57 (95% confidence interval [CI]=1.03–2.41) for association of an elevated DM risk; but women with hysterectomy alone were not associated with DM risk (HR=1.38, 95% CI=0.94–2.04).^[17] Another study however suggested BSO did not increase the DM risk in postmenopausal women underwent hysterectomy.^[18] A cohort study also showed postmenopausal hysterectomized women were not associated with an increased risk of DM.^[19]

The above studies were limited in the postmenopausal hysterectomized women. In premenopausal women, however, the ovary may still produce hormones. Hysterectomy and oophorectomy may hamper ovarian hormone production, prompting to menopause.^[20,21] Thus, BSO may put women predispose to DM.^[22] Moreover, oophorectomy may worsen glucose tolerance and insulin resistance.^[23] Menopausal hormone therapy with estrogen and progesterone can decrease DM incidence.^[24,25] Thus, we hypothesized that hysterectomy with or without oophorectomy may also cause endocrine dysfunction (alter sex hormones regulation) in premenopausal women, subsequently leading to the development of type 2 DM.

We aimed to determine whether hysterectomy for treating benign diseases, with or without BSO, increases the DM risk using the present population-based cohort study involving nationwide health insurance data from Taiwan.

2. Methods

2.1. Data source

The Taiwan National Health Insurance (NHI) program is a government-run program that was launched on March 1, 1995. It covers more than 99% of the population of Taiwan and has contracts with 93% of the country's medical institutions. Individuals were continuously enrolled in the NHI Research Database (NHIRD), and they did not have an opportunity for care outside of the program. The NHIRD is an electronic database that includes the registration files and original claims data of individuals insured under the NHI program (details available at <http://nhird.nhri.org.tw/en/index.htm>). All data are de-identified through encryption of the identification numbers of beneficiaries and medical facilities. We used a sub-dataset of 1 million people who were randomly selected from those in the NHIRD in 2000 to investigate the association between

hysterectomy and DM. Complete NHIRD medical records from 1996 to 2013 were obtained by linking the scrambled identification of each insurant. Diseases were diagnosed using International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes. A disease diagnosis without valid supporting clinical findings might be considered medical fraud by the NHI program, and this might involve a penalty of 100 times the payment claimed by the physician or hospital that had provided the treatment. This study was approved by the Institutional Review Board of China Medical University and the Hospital Research Ethics Committee (IRB permit number: CMUH-104-REC2-115). Informed consent has been waived by the approval of the committee. All methods were performed in accordance with the relevant guidelines and regulations.

2.2. Study participants

The study included different patient groups. The hysterectomy group included hysterectomized women between 2000 and 2013. The index date was the date of hysterectomy. Women who had undergone oophorectomy before or after hysterectomy were not included in this study. In total, 12,763 women underwent hysterectomy between 2000 and 2013. Among these women, 472 who had undergone oophorectomy before or after hysterectomy and 3811 aged <30 years (too few patients) or >50 years (might experience menopause) were excluded (Fig. 1). Additionally, women who had any cancer diagnosis at baseline (n=276) or within 1 year after hysterectomy (n=330), had DM at baseline or within 1 year after the index date (n=470), and were withdrawn from the database at baseline (n=312) and were unmatched (n=4) were excluded. The comparison group included women who did not undergo hysterectomy and did not have cancer or DM at baseline or within 1 year before the index date. The index date for the comparison group without oophorectomy was randomly assigned. The index date for the without hysterectomy with oophorectomy comparison subgroup was the oophorectomy date. The size of the comparison group was 4-fold greater than that of the hysterectomy, and both groups were propensity score-matched by age, hysterectomy date, urbanization, income, occupation, oophorectomy, and comorbidities listed in Table 1.

2.3. Outcome measures

The assessed outcome was DM (ICD-9-CM: 250). To improve the validity of the DM diagnosis, we considered patients with DM as those who made at least 2 clinic visits for DM within 1 year. For every patient, the assessment ended at DM diagnosis, death, withdrawal from the NHI program, or December 1, 2013, whichever was first. We followed the DM occurrence after 1 year of hysterectomy due to DM happening within 1 year of hysterectomy may be not related to the surgical procedure.

2.4. Sociodemographic characteristics and comorbidities

The sociodemographic characteristics assessed in this study were age, residential area urbanization, income, and occupation. Urbanization was divided into 4 levels according to the population density (people/km²) of the residential area (most urbanized [level 1] to least urbanized [level 4]). Occupations were classified as white-collar (government or office work), blue-collar (manual labor), and others (retired, unemployed, or low income). Income was divided into 3 levels according to income-related

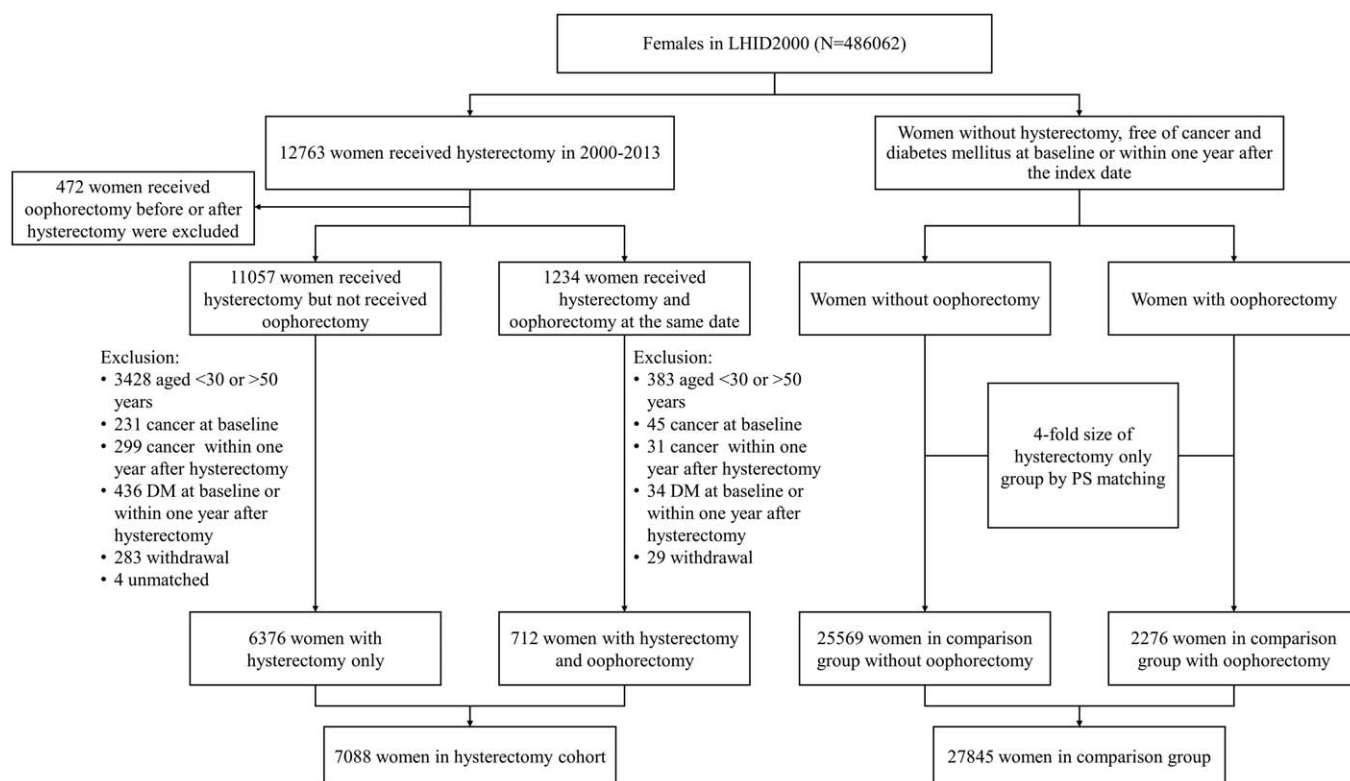


Figure 1. Study flow: the patient population enrolled from the National Health Insurance Research Database.

NHI premiums New Taiwan dollars (NT\$ ≥30000, NT\$ 15000–29999, and NT\$ 1–14999). Detailed descriptions of the assessments of urbanization, occupation, and income have been previously published.^[26]

Type 2 DM patients have risk factors such as endothelial dysfunction, vascular inflammation, and hyperlipidemia;^[27] they will cause cardiovascular complications,^[28] chronic kidney disease (CKD),^[29] and hypertension.^[30] Besides, DM patients are also found to have higher risk for depression and sleep disorders.^[31,32] Menopause may be associated with a rapid progression of glucose intolerance.^[33] Therefore, we accounted for baseline comorbidities, namely menopause (ICD-9-CM: 627.2), hypertension (ICD-9-CM: 401–405), hyperlipidemia (ICD-9-CM: 272), (CKD; ICD-9-CM: 585, 586, 588.8, and 588.9), coronary artery disease (CAD; ICD-9-CM: 410–414), heart failure (ICD-9-CM: 428), stroke (ICD-9-CM: 430–438), depression (ICD-9-CM: 296.2, 296.3, 296.82, 300.4, 309.0, 309.1, 309.28, and 311), and insomnia (ICD-9-CM: 780).

2.5. The number of clinic visits

We considered the number of clinic visits as confounding factors. We counted the clinic visits and hospitalizations involving the gynecology and Endocrine Departments.

2.6. Statistical analysis

For between-group (hysterectomy group vs comparison group) comparisons of categorical and continuous variables, the chi-squared test and Wilcoxon rank-sum test were applied, respectively. The proportional hazards assumption was examined by

adding an interaction term, group*follow-up time, in the Cox proportional hazards model to test whether the 2 groups have the same effect on hazard at any point in time. A comparison of hysterectomy and matched cohort satisfied the proportional hazards assumption ($P = .0811$). Multivariable Cox proportional hazard regression models were used to calculate HRs with 95% CIs, and the variables considered were age, urbanization, income, occupation, oophorectomy, and all aforementioned comorbidities. Interactions between comorbidities and hysterectomy were examined by putting the interaction term, hysterectomy*the comorbidity, in the Cox regression model. Due to the large sample size in the database, we estimated the power of this study will be more than 80%. We did a retrospective power analysis. We used the POWER procedure of SAS software to calculate the power. To calculate the power, 3 key values were input: the observation numbers, hazard rates, and follow-up duration. The hazard rate refers to the rate of events for a group of a given time. Kaplan–Meier survival curves were used to assess the cumulative incidences of DM in the 2 groups, and differences between the groups were assessed using the log-rank test. All statistical analyses were performed using SAS (version 9.4; SAS Institute INC., Cary, NC). A 2-tailed P -value <.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

The present study enrolled 7088 women who underwent a hysterectomy in the hysterectomy group and 27,845 who did not undergo a hysterectomy in the comparison group. The median patient ages in the hysterectomy and comparison groups were

Table 1
Baseline characteristics in women with and without hysterectomy.

	Hysterectomy (n=7088)	Matched cohort (n=27845)	P-value
Age, yr			
30–39	1226 (17.3)	5487 (19.7)	<.0001
40–49	5862 (82.7)	22358 (80.3)	
Median (Q1, Q3)	44.2 (41.3, 46.7)	44.3 (41.0, 47.2)	.0008
Urbanization			
1	2328 (32.8)	9245 (33.2)	.4041
2	2228 (31.4)	8548 (30.7)	
3	1214 (17.1)	4683 (16.8)	
4	1318 (18.6)	5369 (19.3)	
Income			
0–15000	1587 (22.4)	6587 (23.7)	.0003
15000–30000	4121 (58.1)	15452 (55.5)	
≥30000	1380 (19.5)	5806 (20.9)	
Occupation			
White collar	3887 (54.8)	15738 (56.5)	<.0001
Blue collar	2712 (38.3)	9938 (35.7)	
Other	489 (6.9)	2169 (7.8)	
Follow-up duration, years			
Median (Q1, Q3)	7.1 (3.8, 10.7)	7.1 (4.4, 10.1)	.0001
Oophorectomy	712 (10.0)	2276 (8.2)	<.0001
Comorbidity, n (%)			
Menopause	361 (5.1)	1434 (5.1)	.8466
Hypertension	832 (11.7)	2933 (10.5)	.0035
Hyperlipidemia	630 (8.9)	2304 (8.3)	.0962
CKD	50 (0.7)	198 (0.7)	.9596
CAD	389 (5.5)	1395 (5.0)	.1025
Heart failure	52 (0.7)	191 (0.7)	.6662
Stroke	220 (3.1)	835 (3.0)	.6444
Depression	503 (7.1)	1835 (6.6)	.1277
Insomnia	2927 (41.3)	11008 (39.5)	.0068

P-values were calculated by Chi-squared tests for categorical variables, such as age groups, urbanization, level of income, occupation, oophorectomy, and comorbidities.

For continuous variables, median age and follow-up duration, the P-values were calculated by Wilcoxon rank-sum tests.

P-values less than .05 were considered significant.

CAD = coronary artery disease, CKD = chronic kidney disease.

both approximately 44 years (Table 1). The distributions of urbanization levels, incomes, occupations, and clinic visits did not differ between the groups (Table 1, Fig. 2). The frequency of comorbidities in the hysterectomy group was also no different from that in the comparison group.

3.2. DM risk in hysterectomy and comparison groups

During median follow-up periods of 7.1 years, 462 women in the hysterectomy group and 1389 women in the comparison group developed DM, respectively (Table 2). Kaplan–Meier analysis revealed that the cumulative DM incidence in the hysterectomy group was higher than that in the comparison group (9.12 vs 6.78 per 1000 person-years; log-rank test, $P < .0001$; Fig. 3). The DM risk in the hysterectomy group was significantly higher than that in the comparison group in multivariable Cox proportional hazard regression models (adjusted HR [aHR] = 1.37, 95% CI=1.23–1.52) (Table 2). The following variables: age, urbanization, income, occupation, oophorectomy, menopause, hypertension, CKD, CAD, heart failure, stroke, depression, and insomnia, were put in the Cox regression model for adjustment.

3.3. Effect of oophorectomy on the DM risk in the hysterectomy group

The DM risk in the hysterectomy without oophorectomy subgroup was significantly higher than that in the comparison group (aHR = 1.35, 95% CI=1.21–1.51) (Table 2). However, the DM risk in the hysterectomy with oophorectomy was not significantly higher than that in the comparison group (aHR = 1.28, 95% CI=0.93–1.76). Notably, the DM risk was not significant in the without hysterectomy with oophorectomy comparison subgroup (aHR=0.79, 95% CI=0.61–1.01).

3.4. Stratified analysis of menopause on DM risk

We compared the DM risk stratified by menopausal status. There was no significant risk for DM after menopause (aHR=0.92, 95% CI=0.77–1.10) (Table 2).

3.5. Effect of age on DM risk in the hysterectomy group

We compared the DM risk between the hysterectomy and comparison groups stratified by age. With regard to women aged 30 to 39 years and 40 to 49 years, there was a significant difference between the groups (aHR = 1.75, 95% CI=1.27–2.41, aHR = 1.33, 95% CI=1.19–1.49, respectively) (Table 2).

3.6. Effect of comorbidities on DM risk in the hysterectomy group

We compared the DM risk between the hysterectomy and comparison groups stratified by comorbidities (menopause, hypertension, hyperlipidemia, CKD, CAD, heart failure, stroke, obesity, depression, and insomnia) (Table 3). For the comorbidities like hypertension, CAD, stroke, depression, and insomnia, no matter with or without any one of these comorbidities, the hysterectomy group patients were associated with a higher risk of DM than the comparison group. For without the other comorbidities (menopause, hyperlipidemia, CKD, and heart failure), the hysterectomy group were also associated a higher risk of DM than the comparison group. Thus, patients who underwent hysterectomy and with one of these comorbidities (hypertension, CAD, stroke, depression, and insomnia) should be more cautious on diabetes.

3.7. The power of this study

The hazard rates of the 2 groups: 9.12 and 6.78 for hysterectomy and the comparison groups, respectively. The observation number: 7088 and 27,845 for hysterectomy and the comparison groups, respectively. And follow-up duration was 14 years for both 2 groups. Finally, we get a power 99%, which is greater than 80%.

4. Discussion

The present retrospective cohort study found that the risk of developing DM was high in hysterectomized women aged 30 to 39 and 40 to 50 years (aHR = 1.75, 95% CI=1.27–2.41; aHR = 1.33, 95% CI=1.19–1.49). The incidences of DM in this age group without and with hysterectomy were 6.78 and 9.12 per 1000 person-years, respectively. These incidences were higher than those in Western countries (3.4 per 1000 person-years).^[34]

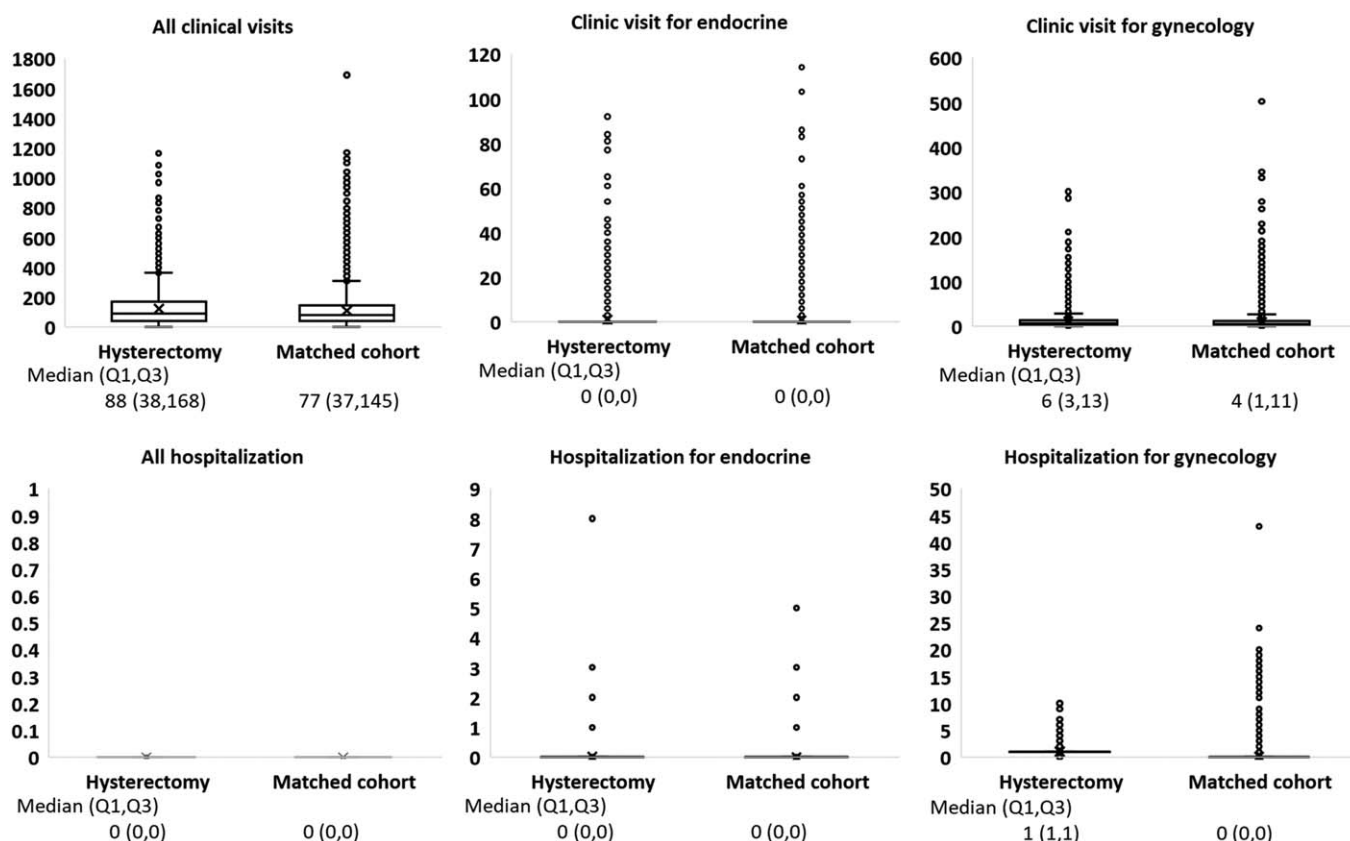


Figure 2. Box plot shows the distribution of all clinic visits, all hospitalization, clinic visit for gynecology, hospitalization for gynecology, clinic visit for endocrine, hospitalization for endocrine.

Additionally, our study found that oophorectomy did not affect the DM risk in hysterectomized women (aHR = 1.25, 95% CI = 0.91–1.72).

Menopause causes changes in body composition as well as metabolic and sex hormone profiles.^[35,36] Declines in ovarian

hormone levels negatively influence glucose metabolism by altering not only pancreatic beta-cell function^[37] but also glucose transportation.^[38] This is because of the impairment of the phosphatidylinositol 3 kinase/Akt signaling pathway, which causes GLUT4 translocation to the plasma membrane. More-

Table 2
Risk of diabetes mellitus in women with hysterectomy compared with the matched cohort.

	N	Event	Person-yr	Incidence per 1000 person-years	Adjusted* HR with 95% CI	P-value
All						
Matched cohort	27845	1389	205001.383	6.78	1 (reference)	
Hysterectomy	7088	462	50666.6639	9.12	1.37 (1.23, 1.52)	<.0001
All						
Matched cohort without oophorectomy	25569	1322	189082.39	6.99	1 (reference)	
Matched cohort with oophorectomy	2276	67	15918.9925	4.21	0.79 (0.61, 1.01)	.0575
Hysterectomy only	6376	423	46030.7953	9.19	1.35 (1.21, 1.51)	<.0001
Hysterectomy with oophorectomy	712	39	4635.86858	8.41	1.28 (0.93, 1.76)	.1314
All						
Non-menopause	33138	1714	241898.387	7.09	1 (reference)	
Menopause	1795	137	13769.6591	9.95	0.92 (0.77, 1.10)	.3499
Age 30–39						
Matched cohort	5575	122	41115.8001	2.97	1 (reference)	
Hysterectomy	1227	55	9860.83504	5.58	1.75 (1.27, 2.41)	.0007
Age 40–49						
Matched cohort	22270	1267	163885.582	7.73	1 (reference)	
Hysterectomy	5861	407	40805.8289	9.97	1.33 (1.19, 1.49)	<.0001

* Model was adjusted for age, urbanization, income, occupation, oophorectomy, and comorbidities listed in Table 1.
HR = hazard ratio.

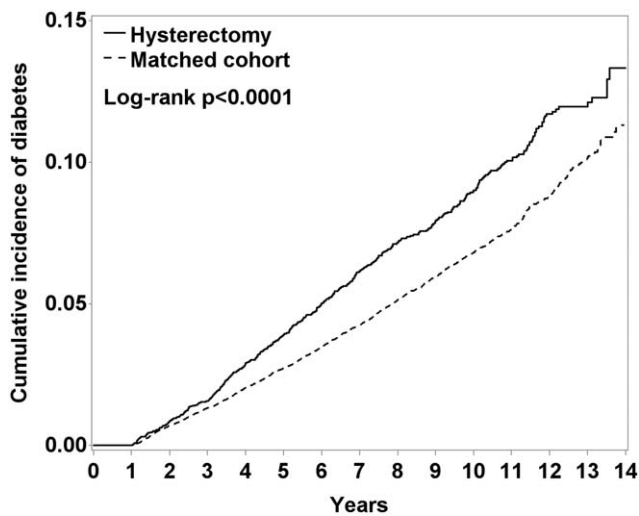


Figure 3. Kaplan–Meier curves showing the cumulative diabetes mellitus incidence in the hysterectomy group (dashed line) and comparison group (solid line) matched by age and comorbidities.

over, hepatic glucose output decreases because of gluconeogenesis suppression.^[39] Women with a short reproductive lifespan have a high DM risk because of reduced endogenous estrogen levels.^[17,40]

With regard to surgical menopause, patients typically undergo hysterectomy combined with oophorectomy as the primary prevention approach for ovarian cancer.^[41] This approach causes a sharp iatrogenic decline in estrogen production and early menopause, indicating it differs from those of natural menopause. Several studies have revealed the effects of post-hysterectomy menopause-related sudden estrogen loss on glycemic regulation. Hysterectomy combined with oophorectomy can cause carbohydrate metabolism impairment and eventually insulin-resistant

glucose tolerance.^[23,42,43] A previous study showed that hysterectomy with or without oophorectomy in postmenopausal women was associated with an increased DM risk (HR = 1.13, 95% CI = 1.06–1.21).^[18] Oophorectomy might not increase the DM risk in postmenopausal hysterectomized women. In the present study, hysterectomized women, without oophorectomy, were associated with an increased DM risk (HR = 1.5, 95% CI = 1.21–1.51). The effect of hysterectomy combined with oophorectomy was not obvious (aHR = 1.28, 95% CI = 0.93–1.76), probably because most women who underwent hysterectomy were near menopausal age (40–49 years) so that they potentially had compromised ovarian function. Moreover, we also found menopause was not associated with a higher risk of DM (aHR = 0.92, 95% CI = 0.77–1.10).

In the National Health and Nutrition Examination Survey I follow-up study, the DM risk was 57% higher in women who underwent both hysterectomy and bilateral oophorectomy when compared with women who experienced natural menopause (95% CI = 1.03–2.41).^[17] In women who underwent hysterectomy alone, no significant DM risk was observed after adjusting for relevant confounders.^[17] However, the ovarian function might be disrupted because of a decrease in ovarian blood supply after hysterectomy.^[13,40] Our study, with factor control including the exclusion of patients with DM history and adjustment of other cardiovascular risk factors, demonstrated that women with hysterectomy alone were associated with DM risk. Therefore, the potential for increased DM risk should be considered before hysterectomy in premenopausal women.

The association of hysterectomy with DM risk may be attributed to 3 possible reasons:

The first reason is the decrease in estrogen after hysterectomy^[44] or oophorectomy.^[15,17] It is hypothesized that the ovarian hormone decrease is associated with glucose intolerance. BSO causes dramatic decreases in both estrogen and androgen levels;^[20] estrogen protects glucose metabolism,^[45] and hormone therapy lowers the incidence of DM in postmenopausal

Table 3

Interaction between different comorbidities and hysterectomy on the risk of diabetes mellitus.

		Hysterectomy				Comparison group				adjusted HR	Interaction P
		N	Event	person-yr	Incidence per 1000 person-yr	N	Event	person-yr	Incidence per 1000 person-yr		
Menopause	No	6727	429	47991.272	8.94	26411	1285	193907.12	6.63	1.36 (1.22, 1.52)	.93
	Yes	361	33	2675.3922	12.3	1434	104	11094.267	9.37	1.37 (0.92, 2.04)	
Hypertension	No	6256	350	45356.783	7.72	24912	1056	184780.82	5.71	1.36 (1.21, 1.54)	.75
	Yes	832	112	5309.8809	21.1	2933	333	20220.567	16.5	1.34 (1.08, 1.67)	
Hyperlipidemia	No	6458	409	46916.441	8.72	25541	1213	189969.51	6.39	1.36 (1.21, 1.52)	.50
	Yes	630	53	3750.2231	14.1	2304	176	15031.871	11.7	1.34 (0.98, 1.83)	
CKD	No	7038	459	50346.921	9.12	27647	1379	203634.05	6.77	1.37 (1.23, 1.52)	.94
	Yes	50	3	319.74264	9.38	198	10	1367.3374	7.31	1.88 (0.40, 8.91)	
CAD	No	6699	416	47949.506	8.68	26450	1278	195116.45	6.55	1.34 (1.20, 1.05)	.47
	Yes	389	46	2717.1581	16.9	1395	111	9884.9281	11.2	1.63 (1.15, 2.31)	
Heart failure	No	7036	459	50352.26	9.12	27654	1369	203768.35	6.72	1.38 (1.24, 1.54)	.19
	Yes	52	3	314.40383	9.54	191	20	1233.0294	16.2	0.49 (0.13, 1.81)	
Stroke	No	6868	440	49127.159	8.96	27010	1330	198917.22	6.69	1.36 (1.22, 1.52)	.69
	Yes	220	22	1539.5044	14.3	835	59	6084.1588	9.70	1.68 (1.02, 2.77)	
Depression	No	6585	427	47924.271	8.91	26010	1296	193777.4	6.69	1.36 (1.21, 1.51)	.42
	Yes	503	35	2742.3929	12.8	1835	93	11223.986	8.29	1.62 (1.09, 2.41)	
Insomnia	No	4161	294	34630.615	8.49	16837	911	137236.41	6.64	1.28 (1.13, 1.47)	.12
	Yes	2927	168	16036.049	10.5	11008	478	67764.972	7.05	1.56 (1.31, 1.86)	

*Model was adjusted for age, urbanization, income, occupation, oophorectomy, and comorbidities listed in Table 1. CAD = coronary artery disease, CKD = chronic kidney disease, HR = hazard ratio.

women.^[46] Although reduced estrogen levels may increase the DM risk, reduced androgen levels may decrease or neutralize the DM risk.^[47] The maintenance of circulating peripheral tissue-derived estrogen after BSO may help reduce DM risk; therefore, BSO may not be associated with DM risk. However, our study failed to show that BSO was a risk factor for DM.

There was a nearly 2-fold risk of ovarian failure after hysterectomy (HR = 1.92, 95% CI = 1.29–2.86).^[44] A prospective cohort study showed that the menopause age was 4 years earlier in a hysterectomy cohort than in a non-hysterectomy cohort.^[21] Early menopause can increase the androgen proportion and decrease sex hormone-binding globulin levels.^[48] Decreased estrogen production after hysterectomy can increase the incidence of DM and glucose intolerance.^[42] In our study, hysterectomy alone was associated with an increased risk of DM.

The second reason is the indication for hysterectomy. The indication might be a risk factor for DM development. For example, obesity is linked to dysfunctional uterine bleeding^[49] and uterine myoma,^[50] and it is a risk factor for DM development. This implied that obesity was not the only factor in DM development after hysterectomy. The higher obesity and hypertension prevalence in the hysterectomy group could be due to the indication of the hysterectomy. Over 60% of hysterectomies were performed because of uterine fibroids, which are associated with cardiovascular risk factors in particular hypertension but also obesity and diabetes. However, obesity was underreported in the database. Therefore, we did not analyze the influence of obesity in this study.

The third reason is the possible surveillance bias. Usually, after hysterectomy, women visit the clinic often for follow-up of their postoperative condition. Therefore, the chance of DM diagnosis is high in women who have undergone a hysterectomy. In this study, we found that the numbers of clinic visit and hospitalizations were higher in the hysterectomy group than in the comparison group. However, a previous study showed that the number of clinic visits was not different between hysterectomy and comparison cohorts.^[18] The surveillance bias could be eliminated by adjustment of the visit number.

The present study has several notable strengths. First, data were collected from 23 million people in Taiwan, and 1 million people with generalized ethnicities were selected randomly. Second, this population-based study included all hysterectomies for benign diseases during a 14-year period. Selection bias and incidence-prevalence bias were limited. Finally, both independent variables (presurgical cardiovascular risk factors) and dependent variables (case-control conditions) were available in the medical diagnosis system.

However, several limitations of our study need to be considered. First, population variables were clarified through ICD-9-CM codes, which could have caused diagnostic errors. Nevertheless, a previous report suggested consistency between diagnostic code use and manual diagnosis,^[51] and thus, ICD-9-CM codes are considered appropriate for detecting actual risk factors or diseases. Another shortage of using diagnostic codes was not entirely reflected in the comorbidities prevalence. Third, obesity, smoking/drinking, and body mass index data were underreported or not recorded in the database. High body mass index is considered a risk factor for DM. Lastly, although the comparison group was propensity-score-matched, some women in the hysterectomy group have no matched comparisons. There were some distributions of variables not quite similar in both groups. Nevertheless, we adjusted those variables in the later analysis.

In conclusion, our study provides essential and novel evidence for the association between hysterectomy and DM risk in middle-aged women, which is relevant to these women and their physicians. Physicians should be aware of the increased DM risk associated with hysterectomy and take this into consideration when evaluating a patient for a hysterectomy. The current results will help gynecologists prevent DM and encourage diagnostic and preventive interventions in appropriate patients.

Author contributions

CHC wrote the manuscript; DCD wrote the manuscript, was responsible for the concept design, and supervised the project; WC and IJT wrote the manuscript and were responsible for statistical analyses; JHW was responsible for the concept design and statistical analysis; CYH and SZL supervised the project, and all authors approved the final manuscript. DCD is the guarantor of this work and, as such, had full access to all the data and takes responsibility for the integrity of the data and accuracy of the data analysis.

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