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## Original Article

## Association between oophorectomy and depression in patients with comorbidities: A nationwide cohort study in Taiwan

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## ABSTRACT

**Objective:** This study investigated the long-term rates of depression after oophorectomy for benign gynecological conditions with or without comorbidities.**Materials and methods:** This retrospective cohort study examined data from the National Health Insurance Research Database (NHIRD) involving 8199 women aged  $\geq 20$  years who underwent unilateral or bilateral oophorectomy for benign gynecological conditions (cases) between 2000 and 2013 (index date). A second cohort consisted of 32,796 women who did not undergo oophorectomy (controls) who were matched 4:1 to cases by age and index year. The follow-up time was more than 10 years. For all participants, the analysis accounted for comorbidities including hypertension, diabetes mellitus, hyperlipidemia, stroke, chronic obstructive pulmonary disease (COPD), chronic liver disease and cirrhosis, chronic kidney disease, and anxiety. Crude hazard ratios, adjusted hazard ratios, and 95% confidence intervals (CIs) were calculated according to multivariable Cox proportional hazard regression models adjusting for age, comorbidity, and the combination of oophorectomy with one comorbidity.**Results:** Our results show that unilateral or bilateral oophorectomy, whether performed by laparotomy or laparoscopy, increases the overall risk of depression (aHR: 1.36, 95%CI: 1.19–1.55). Compared with controls, women aged  $< 50$  years had a significantly higher incidence of depression. Having diabetes (aHR: 1.66, 95%CI: 1.09–2.51), hypertension (aHR: 1.56, 95%CI: 1.14–2.14), hyperlipidemia (aHR: 1.46, 95%CI: 1.04–2.05), stroke (aHR: 1.91, 95%CI: 1.01–3.60), COPD (aHR: 2.06, 95%CI: 1.3–3.26), chronic liver cirrhosis (aHR: 1.99, 95%CI: 1.52–2.61), or anxiety (aHR: 5.01, 95%CI: 3.74–6.70) increased higher risk of depression compared with not having these comorbidities after oophorectomy. The likelihood of depression was highest within the first 6 years following oophorectomy (3–5 years: aHR: 1.26, 95%CI: 1.00–1.58).**Conclusions:** Oophorectomy increases the overall risk of depression. We offer useful information for surgical decision-making and preoperative assessments of women undergoing oophorectomy. It is concluded that a synergistic effect exists between oophorectomy and the comorbidities. Post-surgery, physicians should carefully evaluate the risk of depression developing amongst women with comorbidities. A postoperative follow-up time of at least 6 years is recommended, as this period was associated with a significantly higher rate of depression during our over 10-year follow-up.© 2020 Taiwan Association of Obstetrics & Gynecology. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Introduction

Oophorectomy is a gynecological surgery in which one or both ovaries are removed for treatment or prophylactic management of women with ovarian disease, including those with ovarian endometriomas, necrotic ovarian torsion, ovarian malignancies, or deleterious mutations in the *BRCA1* and *BRCA2* genes that increase

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the risk of ovarian cancer [1–4]. Much clinical evidence [5] shows that certain types of ovarian cancers, specifically high-grade serous ovarian cancer, originate in the fallopian tube and migrate to the ovary, which offers surgeons the option of salpingectomy or salpingo-oophorectomy for risk reduction.

The ovary produces sex steroid hormones including estrogens, progestogens, and androgens. These sex steroids were initially considered to be confined to major effects upon reproductive physiology [6]. Nowadays, it is increasingly recognized that sex steroids are also involved in other vital functions. For instance, estrogen is now known to play a role in the immune response, blood circulation, bone metabolism, cognitive function, and emotion [7–9]. Thus, the decision to perform ovarian removal must be carefully considered for its possible adverse effects.

Many studies have confirmed a relationship between depression and oophorectomy for benign conditions; all of those studies theorized that a decline in ovarian hormones was the main reason for depression [10–13]. One cohort study [11] included 666 premenopausal women who underwent bilateral oophorectomy for benign conditions. After a median 24 years of follow-up, these women were at increased risk of depression and anxiety symptoms compared with an age-matched group of women from the same population who did not undergo oophorectomy. Notably, the physicians found that symptoms of depression and anxiety were worse in women with surgically-induced menopause than in those who had undergone natural menopause [14].

Interestingly, some clinical evidence is inconsistent with the outcomes reported above [15–17]. For example, in one study, 503 Norwegian women carrying the *BRCA1* or *BRCA2* mutation or were at risk for hereditary breast/ovarian cancer had undergone risk reduction salpingo-oophorectomy (RRSO) following genetic counseling [16]. Post-surgery, they were followed-up for a mean 5.3 years by mailed questionnaire, to evaluate their levels of mental distress and somatic complaints. Compared with age-matched controls, RRSO was associated with a higher incidence of physical comorbidities and lower levels of depression and total mental distress. Another study performed annual assessments of depressive and anxiety symptoms amongst 1970 women for up to 10 years [18]. During follow-up, 1793 women reached a natural menopause, 76 reported a hysterectomy with ovarian conservation, and 101 reported a hysterectomy with bilateral oophorectomy. Women who underwent a hysterectomy with bilateral oophorectomy did not experience more negative mood symptoms in the years after surgery compared with the 76 women who had hysterectomy alone. This finding might be explained by outcomes in a recent study showing that hysterectomy is an independent risk factor for depression [19].

Previous studies have evaluated the influence of oophorectomy upon mental health in different age groups of women [11,20]. However, the sample sizes or mean follow-up times were either too small or too short in those studies. We therefore designed our study to assess the long-term consequences of oophorectomy on depression incidence in a large sample size. Since hormone therapy [21] and hysterectomy [22] are known to influence psychological symptoms, we considered these to be potential confounders. Moreover, since unilateral and bilateral oophorectomy are often discussed separately, scant data are available comparing mental outcomes from women who have undergone either procedure. We therefore sought to determine whether removal of one or both ovaries is associated with depression. In addition, while much clinical evidence demonstrates that many chronic diseases such as diabetes, hypertension and COPD can lead to depression [23–26], so far, there had no studies examine the possible risk of depression after oophorectomy in women who had underlying diseases. Limited evidence shows that women with preoperative

depression or sexual problems are at increased risk for worsening psychological well-being after surgically-induced menopause [27]. The scant evidence base makes it difficult for physicians to discuss the possible risk of depression after oophorectomy with their patients who have comorbidities.

This investigation compared long-term rates of depression amongst women with or without comorbidities undergoing oophorectomy. It also compared the rates of depression between women who underwent oophorectomy and those who did not.

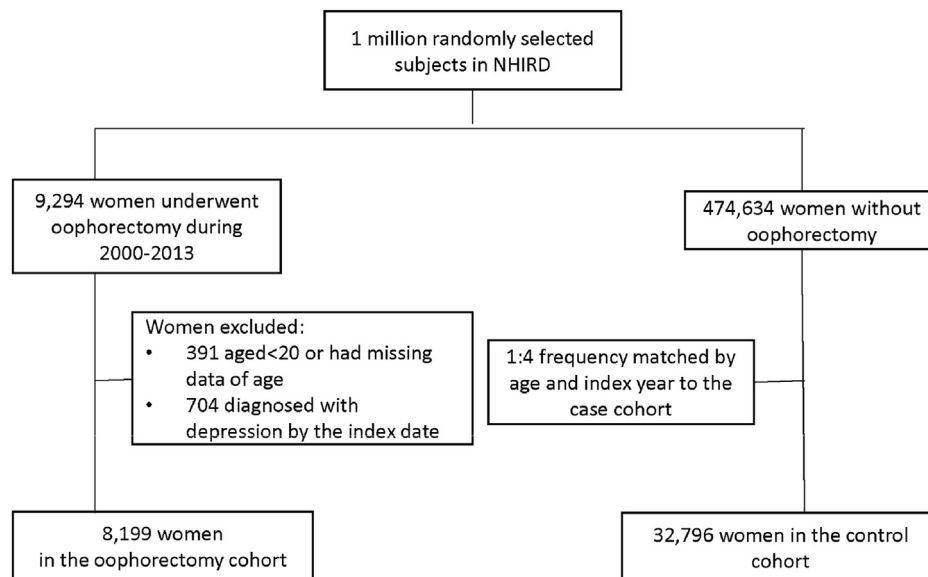
## Materials and Methods

### Data source

Taiwan's National Health Insurance Research Database (NHIRD) contains almost all medical information of its entire population. Since its implementation in 1995, the National Health Insurance (NHI) program has provided comprehensive medical care, including outpatient and inpatient care, for approximately 99% of the country's 23.74 million citizens. The data used in this study were obtained from one of the data subsets of the NHIRD, the Longitudinal Health Insurance Database 2000 (LHID2000), which contains all claims data from 2000 through 2013 for 1 million representative beneficiaries randomly selected from the NHIRD. The LHID2000 records the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes of patients' diagnoses and procedures, prescription details and expenditures relating to all outpatient and inpatient medical benefit claims. This study was approved by the Research Ethics Committee of China Medical University and Hospital, Taichung, Taiwan (CMUH-104-REC2-115). The requirement for informed consent was waived in respect of the retrospective nature of the study design and because the datasets analyzed provide only anonymized patient records.

### Sample design

This study included women aged  $\geq 20$  years who were registered in the NHIRD from 2000 through 2013. Women who underwent bilateral or unilateral oophorectomy served as the case cohort. Each woman in the oophorectomy cohort was age- and index date-matched with 4 women in the control group (women who did not undergo oophorectomy). The diagnosis of depression was defined by ICD-9-CM codes 296.2, 296.3, 300.4, or 311, by at least 3 visits to the outpatient clinic, or psychiatric inpatient admission. The index date for the case cohort was the date of oophorectomy and that for the control cohort was a random month, day, and an index year. Any patient diagnosed with depression by the index date or were missing data for sex or age was excluded. Follow-up continued until one of the following conditions was met: a diagnosis of depression, censored for death, withdrawal from the NHIRD, or the data collection period ended. The flowchart of the study subject selection process is presented in Fig. 1. In this study, the oophorectomy and non-oophorectomy cohorts are described by age, hysterectomy, hormone use, and comorbidities of hypertension (HTN; ICD-9-CM codes 401–405, A260, A269), diabetes mellitus (DM; ICD-9-CM codes 250, A181), hyperlipidemia (ICD-9-CM codes 272, A182), stroke (ICD-9-CM codes 433–436), chronic obstructive pulmonary disease (COPD; ICD-9-CM codes 491, 492, 496), chronic liver disease and cirrhosis (ICD-9-CM codes 571, A347), chronic kidney disease (CKD; ICD-9-CM code 585), and anxiety (ICD-9-CM codes 300.00). The incidence rate was defined as the number of events divided by person-years. Patient belonging to a comorbidity group had one of the comorbidities.



**Fig. 1.** The flowchart of the study subject selection process for establishing the oophorectomy cohort and controls obtained from the Longitudinal Health Insurance Database 2000 (LHID2000).

### Statistical analysis

The Chi-square test was used to analyze categorical variables of age, hysterectomy, hormone use, and strata of comorbidity, while the Student's *t*-test was used to analyze means of continuous variables (age and follow-up period). Crude hazard ratios (cHRs), adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) were calculated using multivariable Cox proportional hazard regression models accounting for age, comorbidity, and the combination of oophorectomy and one of the comorbidities. The Kaplan–Meier method was used to derive cumulative incidences of depression in the oophorectomy and non-oophorectomy cohorts, and the log-rank test was used to detect its significance. All statistical analyses used SAS software version 9.4 (SAS Institute, Cary, NC, USA). The level of significance was defined as  $p < 0.05$ .

### Results

The study population consists of 8199 women who underwent oophorectomy and 32,796 women who did not. Table 1 demonstrates significant between-group differences in the rates of hysterectomy ( $p < 0.001$ ), hormone use ( $p < 0.001$ ), and comorbidities of DM ( $p = 0.02$ ), HTN ( $p < 0.001$ ), hyperlipidemia ( $p = 0.01$ ), chronic liver disease and cirrhosis ( $p < 0.001$ ), and anxiety ( $p < 0.001$ ). Mean ages (standard deviation [SD]) for the oophorectomy and non-oophorectomy cohorts were 38.3 (11.7) and 38.1 (12.4) years, respectively ( $p = 0.09$ ). Corresponding mean (SD) follow-up periods were 6.44 (4.10) and 6.59 (4.07) years, respectively ( $p = 0.004$ ).

Table 2 demonstrates that oophorectomized patients were 1.36 times more likely to suffer from depression than non-oophorectomized ones ( $p < 0.001$ ). Oophorectomized patients in the 20–34-year-old age group ( $p < 0.01$ ) and in the 35–49-year-old group ( $p < 0.01$ ) were at increased risk of depression compared with their respective controls. The risk of incident depression was significantly greater for women aged between 35 and 49 years compared with all other age groups (incidence rates: non-oophorectomized cohort, 4.50 vs. oophorectomized cohort, 6.83, cHR: 1.52, aHR: 1.39, 95% CI: 1.14–1.70). Oophorectomized women with and without comorbidities were 1.29 ( $p < 0.05$ ) and 1.39

( $p < 0.001$ ) times more likely to suffer depression, respectively, than non-oophorectomized women. Notably, in analyses that kept all other covariates constant, patients aged  $\geq 65$  years who underwent oophorectomy were not more likely to suffer depression than women in any other age group.

Table 3 reveals that oophorectomized patients with and without DM were, respectively, 1.66 and 1.36 times more likely to suffer depression than oophorectomized patients without those comorbidities (IR: yes–yes: yes–no: no–no = 10.8: 6.32: 4.35; yes–yes, 95% CI: 1.09–2.51; yes–no, 95% CI: 1.19–1.55). Oophorectomized patients with and without HTN were, respectively, 1.56 and 1.36 times more likely to suffer depression than those without oophorectomy and HTN (IR: yes–yes: yes–no: no–no = 9.84: 6.17: 4.25; yes–yes, 95% CI: 1.14–2.14; yes–no, 95% CI: 1.19–1.57). Oophorectomized patients with and without hyperlipidemia were, respectively, 1.46 and 1.37 times more likely to suffer depression than those without oophorectomy and hyperlipidemia (IR: yes–yes: yes–no: no–no = 10.3: 6.21: 4.26; yes–yes, 95% CI: 1.04–2.05; yes–no, 95% CI: 1.19–1.57). Oophorectomized patients with and without stroke were, respectively, 1.91 and 1.35 times more likely to suffer depression than those without oophorectomy and stroke (IR: yes–yes: yes–no: no–no = 13.5: 6.42: 4.46; yes–yes, 95% CI: 1.01–3.60; yes–no, 95% CI: 1.18–1.54). Oophorectomized patients with and without COPD were, respectively, 2.06 and 1.34 times more likely to suffer depression than those without oophorectomy and COPD (IR: yes–yes: yes–no: no–no = 13.6: 6.32: 4.45; yes–yes, 95% CI: 1.30–3.26; yes–no, 95% CI: 1.17–1.53). Oophorectomized patients with and without chronic liver disease and cirrhosis were, respectively, 1.99 and 1.36 times more likely to suffer depression than those without them (IR: yes–yes: yes–no: no–no = 10.7: 6.01: 4.18; yes–yes, 95% CI: 1.52–2.61; yes–no, 95% CI: 1.18–1.57). Non-oophorectomized patients with chronic liver disease and cirrhosis were 1.48 times more likely to suffer depression than those without oophorectomy and those comorbidities (IR: no–yes: no–no = 7.77: 4.18; no–yes, 95% CI: 1.24–1.78). Oophorectomized patients without CKD were 1.36 times more likely to suffer depression than those without oophorectomy and CKD (IR: yes–no: no–no = 6.50: 4.49; yes–no, 95% CI: 1.20–1.55). Oophorectomized patients with and without anxiety were, respectively, 5.01 and 1.36 times more likely to suffer depression than those without oophorectomy and anxiety

**Table 1**

Demographic characteristics and comorbidities of the oophorectomy and non-oophorectomy study cohorts.

	Oophorectomy				p-value
	No		Yes		
	32,796		8199		
	N	%	N	%	
<b>Age, years</b>					0.99
20–34	14,488	44.2	3622	44.2	
35–49	13,996	42.7	3499	42.7	
50–64	3188	9.72	797	9.72	
65+	1124	3.43	281	3.43	
mean (SD) <sup>a</sup>	38.1	12.4	38.3	11.7	0.09
<b>Hysterectomy</b>	543	1.66	1221	14.9	<0.001
<b>Hormone use</b>	2494	7.60	1678	20.5	<0.001
<b>Comorbidity</b>					
Diabetes	1551	4.73	438	5.34	0.02
Hypertension	3140	9.57	896	10.9	<0.001
Hyperlipidemia	2623	8.00	732	8.93	0.01
Stroke	635	1.94	168	2.05	0.51
COPD	1027	3.13	270	3.29	0.45
Chronic liver disease and cirrhosis	3057	9.32	944	11.5	<0.001
Chronic kidney disease	134	0.41	40	0.49	0.32
Anxiety	1416	4.32	461	5.62	<0.001
<b>Mean follow-up time (years) for diagnosis of depression (SD)<sup>a</sup></b>	6.59	4.07	6.44	4.10	0.004

SD, standard deviation.

<sup>a</sup> Chi-Square Test.<sup>a</sup> t-test.

(IR: yes–yes: yes–no: no–no = 24.3: 5.78: 4.09; yes–yes, 95% CI: 3.74–6.70; yes–no, 95% CI: 1.18–1.56). Non-oophorectomized patients with anxiety were 3.65 times more likely to suffer depression than those without oophorectomy and anxiety (IR: no–yes: no–no = 17.9: 4.09; no–yes, 95% CI: 2.99–4.46).

Table 4 demonstrates that oophorectomized patients during the follow-up durations of <3 and 3–5 years were, respectively, 1.77 and 1.36 times more likely to suffer depression than non-oophorectomized patients (IR: <3, 7.68 vs. 4.33; 3–5, 7.03 vs. 5.19), with aHRs of 1.73 and 1.26, respectively (<3, 95% CI: 1.43–2.10; 3–5, 95% CI: 1.00–1.58). Notably, the likelihood of depression was not higher among oophorectomized patients compared with non-oophorectomized patients during the years of follow-up beyond 6 years. This finding emphasizes the importance of following women after oophorectomy for at least 6 years, due to the increased risk of incident depression during this time. Fig. 2

**Table 2**

Comparison of incidence rates of depression and hazard ratios between patients with and without oophorectomy, accounting for demographic characteristics and comorbidities.

	Oophorectomy						cHR	(95% CI)	aHR	(95% CI)
	No			Yes						
	Event	PY	Rate <sup>a</sup>	Event	PY	Rate <sup>a</sup>				
All	974	215,999	4.51	344	52,802	6.51	1.44	(1.28,1.63)***	1.36	(1.19,1.55)***
Age, years										
20–34	406	98,917	4.10	142	24,658	5.76	1.40	(1.16,1.70)***	1.37	(1.13,1.67)**
35–49	419	93,031	4.50	155	22,687	6.83	1.52	(1.26,1.82)***	1.39	(1.14,1.70)**
50–64	113	17,821	6.34	31	4215	7.36	1.16	(0.78,1.73)	1.19	(0.77,1.85)
65+	36	6230	5.78	16	1243	12.9	2.16	(1.20,3.89)*	1.56	(0.78,3.16)
Comorbidity <sup>b</sup>										
No	598	168,990	3.54	199	39,674	5.02	1.42	(1.21,1.67)***	1.39	(1.18,1.65)***
Yes	376	47,009	8.00	145	13,129	11.0	1.37	(1.13,1.66)**	1.29	(1.05,1.58)*

PY, person-years; cHR, crude hazard ratio; aHR, adjusted hazard ratio, controlling for age, hormone use, hysterectomy, and comorbidities of diabetes, hypertension, hyperlipidemia, chronic liver disease and cirrhosis, and anxiety; \*p < 0.05, \*\*p < 0.01, \*\*\*p < 0.001.

<sup>a</sup> Incidence rate per 1000 person-years.<sup>b</sup> Patients with one of the following comorbidities: diabetes, hypertension, hyperlipidemia, stroke, COPD, chronic liver disease and cirrhosis, chronic kidney disease, or anxiety, were defined as the comorbidity group.

shows that the cumulative incidences of depression of patients with and without oophorectomy differed significantly (log-rank test: p < 0.001).

## Discussion

According to our findings, Taiwanese women of any age who undergo oophorectomy are at an overall higher risk for incident depression than age-matched women who do not undergo oophorectomy. This outcome is consistent with findings from previous studies [10–14]. However, those studies only investigated women with bilateral oophorectomy, whereas we included patients undergoing different types of oophorectomy.

In our study, women aged younger than 49 years had a significantly higher incidence of depression compared with older women, which corresponded with data reported by a previous study [11]. Compared with premenopausal women, perimenopausal women experience hormonal fluctuations and progressively declining ovarian function [28]. Thus, the risk of depression increases in premenopausal women with relatively greater alterations of hormones after oophorectomy compared with their counterparts who do not undergo oophorectomy.

Although women with comorbidities were at increased risk of depression, we found that oophorectomized women with diabetes, hypertension, hyperlipidemia, stroke, COPD, chronic liver cirrhosis or anxiety had higher risk of depression than those without comorbidities after oophorectomy. This finding indicates that a synergistic effect exists between oophorectomy and comorbidities in relation to incident depression.

The results of the present study provide helpful information for surgical decision-making when considering oophorectomy in women with comorbidities. In particular, women with symptoms of anxiety have a markedly high risk of depression than those without anxiety (IR: 24.3, 95% CI: 3.74–6.70). Interestingly, the latest study showed the synergetic effect of oophorectomy and comorbidities will increase higher rate of suicide. Our result is similar with Chiu et al. [29] However, the data were not significantly meaningful in this study for patients with CKD, due to the fact that only 2 such women were included in our analyses. Whether CKD does increase the risk of developing depression after oophorectomy should be further investigated.

Strengths of our study include its investigation of nationwide data involving a large number of participants over a wide age range, with a prolonged follow-up. We excluded women with

**Table 3**

Cox proportional hazard regression analysis examining the risk of depression in association with the interactions of oophorectomy and comorbidities.

		Event	PY	Rate <sup>a</sup>	aHR	(95% CI)	p-value <sup>b</sup>
Oophorectomy	Diabetes						0.72
No	No	900	206,777	4.35	1 (Ref.)		
No	Yes	74	9221	8.02	1.21	(0.93,1.58)	
Yes	No	319	50,478	6.32	1.36	(1.19,1.55)***	
Yes	Yes	25	2325	10.8	1.66	(1.09,2.51)*	
Oophorectomy	Hypertension						0.72
No	No	840	19,7492	4.25	1 (Ref.)		
No	Yes	134	18,507	7.24	1.18	(0.95,1.47)	
Yes	No	295	47,824	6.17	1.36	(1.19,1.57)***	
Yes	Yes	49	4979	9.84	1.56	(1.14,2.14)**	
Oophorectomy	Hyperlipidemia						0.59
No	No	855	200,785	4.26	1 (Ref.)		
No	Yes	119	15,214	7.82	1.14	(0.91,1.44)	
Yes	No	303	48,817	6.21	1.37	(1.19,1.57)***	
Yes	Yes	41	3986	10.3	1.46	(1.04,2.05)*	
Oophorectomy	Stroke						0.74
No	No	949	212,978	4.46	1 (Ref.)		
No	Yes	25	3021	8.28	1.10	(0.73,1.66)	
Yes	No	334	52,061	6.42	1.35	(1.18,1.54)***	
Yes	Yes	10	741	13.5	1.91	(1.01,3.60)*	
Oophorectomy	COPD						0.22
No	No	935	210,202	4.45	1 (Ref.)		
No	Yes	39	5797	6.73	1.04	(0.75,1.45)	
Yes	No	325	51,403	6.32	1.34	(1.17,1.53)***	
Yes	Yes	19	1399	13.6	2.06	(1.30,3.26)**	
Oophorectomy	Chronic liver disease and cirrhosis						0.75
No	No	819	196,057	4.18	1 (Ref.)		
No	Yes	155	19,941	7.77	1.48	(1.24,1.78)***	
Yes	No	283	47,088	6.01	1.36	(1.18,1.57)***	
Yes	Yes	61	5714	10.7	1.99	(1.52,2.61)***	
Oophorectomy	Chronic kidney disease						0.74
No	No	967	215,373	4.49	1 (Ref.)		
No	Yes	7	626	11.2	1.79	(0.84,3.79)	
Yes	No	342	52,642	6.50	1.36	(1.20,1.55)***	
Yes	Yes	2	161	12.4	1.66	(0.41,6.70)	
Oophorectomy	Anxiety						0.80
No	No	856	209,404	4.09	1 (Ref.)		
No	Yes	118	6595	17.9	3.65	(2.99,4.46)***	
Yes	No	293	50,699	5.78	1.36	(1.18,1.56)***	
Yes	Yes	51	2103	24.3	5.01	(3.74,6.70)***	

PY, person-years; aHR, adjusted hazard ratio, accounting for age, hormone use, hysterectomy, and comorbidities of diabetes, hypertension, hyperlipidemia, chronic liver disease and cirrhosis, and anxiety; \*p < 0.05, \*\*p < 0.01, \*\*\*p < 0.001.

<sup>a</sup> Incidence rate per 1000 person-years.

<sup>b</sup> p for interaction.

**Table 4**

Trend of depression risk stratified by follow-up period.

Follow-up periods examining incident depression	Oophorectomy						cHR	(95% CI)	aHR	(95% CI)
	No			Yes						
	Event	PY	Rate <sup>a</sup>	Event	PY	Rate <sup>a</sup>				
<3 years	372	85,913	4.33	163	21,213	7.68	1.77	(1.48,2.13)***	1.73	(1.43,2.10)***
3–5 years	324	62,452	5.19	107	15,217	7.03	1.36	(1.09,1.69)**	1.26	(1.00,1.58)
6–9 years	222	50,860	4.36	58	12,320	4.71	1.08	(0.81,1.44)	0.92	(0.68,1.26)
≥ 10 years	56	16,774	3.34	16	4053	3.95	1.19	(0.68,2.07)	1.24	(0.70,2.21)

PY, person-years; cHR, crude hazard ratio; aHR, adjusted hazard ratio, controlling for age, hormone use, hysterectomy, and comorbidities of diabetes, hypertension, hyperlipidemia, chronic liver disease and cirrhosis, and anxiety; \*p < 0.05, \*\*p < 0.01, \*\*\*p < 0.001.

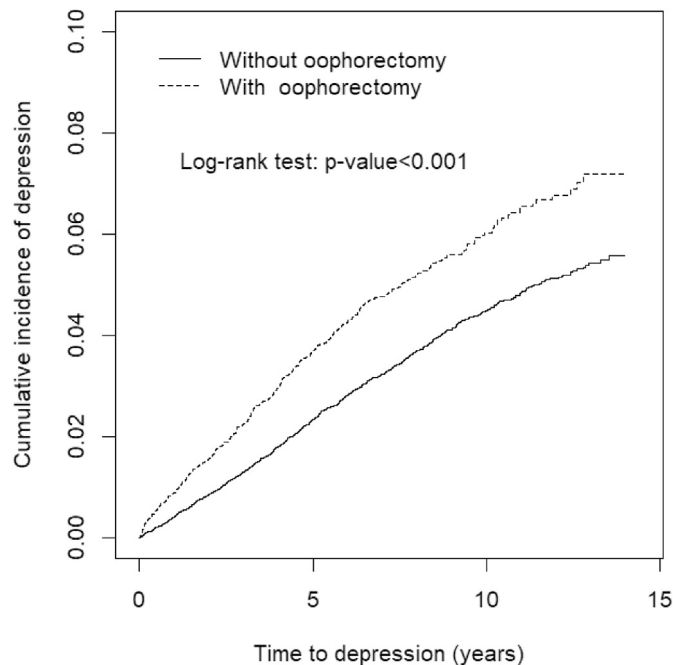
<sup>a</sup> Incidence rate per 1000 person-years.

malignancies, as these conditions adversely affect mental health, which is a strong confounding factor. Our study also evaluated different types of oophorectomy, including unilateral and bilateral, performed under laparotomy or laparoscopy procedures. The evidence from our study unequivocally shows that, regardless of the type of oophorectomy or comorbidities, women in Taiwan who

undergo oophorectomy are more likely to suffer from depression than their counterparts who do not undergo oophorectomy.

This study has several limitations. Our data were obtained from the NHIRD, which records de-identified patient information. Thus, the reason for performing oophorectomy for individual patients remains unknown. Undergoing prophylactic surgery for potential





**Fig. 2.** Cumulative incidence rates of depression among patients with and without oophorectomy.

development of carcinoma of the ovary may influence psychological well-being. Moreover, the ICD codes do not define the event of menopause, so the NHIRD records do not reveal actual menopause status. We have therefore included women aged <49 years as representing pre-menopausal condition, since the mean age for menopause in Taiwan is 51 years [30].

Although we considered hormone therapy as a confounding factor in our analyses, we may have missed unrecorded instances of estrogen use. In Taiwan, the oral contraceptive pill is obtainable over the counter and prescribed Chinese medicines may also contain estrogens. It is not possible to obtain information on these aspects from the NHIRD database. However, our large study sample size may offset the population variation. It would be worthwhile for a future study to explore the relationship between depression, oophorectomy and hormone therapy.

## Conclusions

In summary, oophorectomy increases the overall risk of depression. This study offers physicians useful information for consideration in preoperative assessments of women potentially undergoing gynecological surgery. A synergistic effect exists between oophorectomy and the comorbidities of diabetes, hypertension, hyperlipidemia, stroke, COPD, chronic liver cirrhosis and anxiety on the odds of incident depression. Patients with these comorbidities should be carefully considered for the risk of depression before surgery. Conversely, the physician should also carefully evaluate the postoperative risk of depression among women with these comorbidities. For postoperative follow-up, we recommend that patients are monitored for at least 6 years, as the risk of depression is significantly increased over this period of time.

## Author contributions

Conceptualization, K.Y.-H.L.; Data curation, K.Y.-H.L.; Funding acquisition, W.-C.L. and L.W.; Project administration, W.-C.L. and

L.W.; Resources, C.Y.-Y.C.; Writing—original draft, C.-Y.C.; Writing—review & editing, C.-Y.C., K.Y.-H.L.

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## Declaration of Competing Interest

The authors declare no conflicts of interest.

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## Abbreviations

CKD	chronic kidney disease
COPD	chronic obstructive pulmonary disease
DM	diabetes mellitus
HTN	hypertension
NHIRD	National Health Insurance Research Database

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