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Hysterectomy associated with de novo lower urinary tract symptoms in a Taiwanese population: a nationwide, population-based study

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Abstract

Introduction and hypothesis The effect of hysterectomy on vesicourethral functions remains controversial. The objective of this study was to examine the association between hysterectomy and de novo lower urinary tract symptoms (LUTSs).
Methods We identified 8514 patients who had undergone hysterectomy between January 1, 2000, and December 31, 2012, from Taiwan's National Health Insurance (NHI) Research Database. A control cohort, comprising 34,056 age-matched patients who had not undergone hysterectomy, was created for comparison. All hysterectomy and control patients were followed up until diagnosis as having LUTSs (dysuria, urinary retention, incontinence, and increased urinary frequency and urgency), withdrawal from the NHI system, death, or December 31, 2013. Patients were excluded if LUTSs were diagnosed before or at the time of hysterectomy.
Results The adjusted hazard ratio (aHR) of subsequent de novo LUTSs was higher in the hysterectomy patients [1.57, 95% confidence interval (CI) 1.46–1.70] than in the controls during the follow-up period. Compared with the controls, the highest risk of de novo LUTSs was noted in patients who had undergone vaginal hysterectomy (VH; aHR 1.89, 95% CI 1.57–2.28) followed by those who had undergone laparoscopy-assisted VH (LAVH; aHR 1.74, 95% CI 1.56–1.94).
Conclusions We found that undergoing hysterectomy was associated with increased risks of developing lower urinary tract symptoms in women. This association was more pronounced for women undergoing the vaginal or laparoscopically assisted hysterectomy. Further large-scale prospective studies or clinical trials are needed to explore whether causality exists.

Keywords Hysterectomy · Lower urinary tract function · Incontinence · Dysuria · Population

Introduction

Hysterectomy is one of the most commonly performed gynecological surgical procedures for treating benign conditions [1]. The incidence of hysterectomy among Taiwanese women is 2.68–3.03 per 1000 women and is 3.0 per 10,000 women in the US [2, 3].

Some studies have reported an association between hysterectomy and lower urinary tract dysfunction and lower urinary tract symptoms (LUTSs) [4–6]. Anderson et al. showed increased urinary incontinence after subtotal abdominal hysterectomy (SAH) than total abdominal hysterectomy (SAH) [4]. Lakeman et al. showed LUTSs are more common in vaginal hysterectomy (VH) than TAH [6]. de Tayrac et al. reported that there was no risk of developing stress urinary incontinence (SUI) after VH compared with the conservative treatment group [5].

Most studies have shown a relatively high risk of urinary incontinence and stress urinary incontinence (SUI) after hysterectomy [7–9]. Altman et al. showed SUI was increased after surgery after a 30-year follow-up [7]. Thakar et al. reported urinary frequency, nocturia and SUI were decreased after compared with before hysterectomy [8]. Hsieh et al. reported urinary incontinence (UI) was also increased after hysterectomy and there was no relationship between UI and route of hysterectomy [9].

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The development of LUTSs could be due to damage to the innervation and supportive tissues of the pelvis during surgery [10]. However, the effect of hysterectomy on LUTSs has not been adequately studied, and the results of previous studies are inconsistent.

We investigated the incidence of de novo LUTSs after hysterectomy in Taiwan by using a single-payer, nationwide, population-based health insurance database.

Materials and methods

Data sources

Taiwan's National Health Insurance (NHI) program is a single-payer health insurance system launched on March 1, 1995. This program is mandatory, and it covers more than 99% of the Taiwanese population. Taiwan's National Health Research Institutes provides anonymized reimbursement claims data contained in the NHI Research Database (NHIRD) for research purposes. The present study was conducted using data from the Longitudinal Health Insurance Database 2000 (LHID2000), which is a subset of the NHIRD. The LHID2000 contains the claims data of 1 million people who were randomly and systemically sampled from the year 2000 registry of the entire Taiwanese population. Personal identification was encrypted by the NHI Administration to protect patient privacy before publishing the database. All medical records of inpatient, outpatient and emergency services used in our study were retrieved from the LHID2000. This study was approved by the Institutional Review Board of Hualien Tzu Chi Hospital (REC No. IRB 104-118-C).

Study population

The study population consisted of a hysterectomy (case) cohort and a nonhysterectomy (control) cohort. All women who were aged > 20 years and had undergone hysterectomy for benign indications between 2000 and 2012 were included in the hysterectomy cohort. All procedures of hysterectomy in the LHID2000 were identified and classified according to International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) procedure codes and the NHIRD operation codes. The hysterectomy techniques were categorized as follows: subtotal abdominal hysterectomy (SAH), total abdominal hysterectomy (TAH), vaginal hysterectomy (VH) and laparoscopy-assisted vaginal hysterectomy (LAVH). Patients who had previously received diagnoses of cervical, ovarian or endometrial cancer (ICD-9-CM codes: 179–180 and 182–183) or those who had undergone radical hysterectomy were excluded to ensure that only patients who had undergone hysterectomy for benign indications were

included. The index date was defined as the date of admission for hysterectomy, and the index hospitalization was defined as the concurrent hospitalization for hysterectomy. Patients with diagnoses of LUTSs (ICD-9-CM codes: 788.1–788.4 and 788.63) before the index date were excluded.

The control cohort was also selected from the LHID2000. Each patient from the hysterectomy cohort was matched exactly, according to age and index year, with four patients who had not undergone hysterectomy (1:4 exact matching) to create the control cohort. Patients who had received diagnoses of cervical, ovarian, or endometrial cancer or LUTSs before the index date were excluded. The index date of each control patient was defined as the same index date of the matched hysterectomy patient.

Outcome measures

The primary outcome was defined as developing LUTSs (ICD-9-CM codes: 788.1–788.4 and 788.63) during the follow-up period. Patients with LUTSs were defined as any patients who received diagnoses of LUTSs in at least one inpatient service or two outpatient visits within the study period. All patients were followed up from the index date to the occurrence of LUTSs, death, withdrawal from the NHI program or December 31, 2013 (the last date in the database). Individual urinary symptoms, such as dysuria (ICD-9-CM code: 788.1), urinary retention (788.2), urinary incontinence (788.3) and increased urinary frequency and urgency (788.4 and 788.63), were also analyzed as individual outcomes. We mainly compared the risk of LUTSs between the hysterectomy and control cohorts. In addition, to enable the evaluation of the effects of different hysterectomy techniques, the hysterectomy cohort was further categorized into four groups, namely SAH, TAH, VH and LAVH, according to technique.

Covariates

The following baseline comorbidities of the patients were retrieved using the ICD-9-CM codes on the inpatient and outpatient claims in the LHID: hypertension (401–405), diabetes mellitus (250), chronic obstructive pulmonary disease (COPD) (490–496), chronic kidney disease (582–583, 585–586 and 588), depression (296.2, 296.3, 298.0, 300.4, 309.0, 309.1 and 311), urinary tract infection (590, 595, 597 and 599.0) and menopause (627). The comorbidities were identified only when the patients sought medical help from the inpatient or outpatient service and were defined when such diagnosis was made in at least one inpatient or two outpatient services during the year prior to the index date. Income and urbanization levels were assessed according to the data of the NHIRD to represent the proxies of socioeconomic status. Four income levels were defined (≥ NT$40000, NT$20000–NT$39999, NT$1–NT$19999 and financially dependent),

which were determined according to NHI premiums. Five urbanization levels were identified for analysis. The income and urbanization levels were defined as described previously [11, 12].

Sensitivity analysis

Urinary tract infection is one of the common causes of LUTS, and it is also a common complication after hysterectomy. The prevalence of urinary tract infection in each individual's baseline condition as well as the prevalence of urinary tract infection after hysterectomy may cause a confounding effect and lead to bias. Therefore, to evaluate whether the prevalence of urinary tract infection caused bias, we performed a sensitivity analysis that excluded patients with previous diagnosis of UTI prior to the index date or developing UTI during index hospitalization or within 14 days after hysterectomy.

Statistical analysis

Categorical variables were analyzed using the chi-square test. Cumulative incidence curves were estimated using the Kaplan-Meier method, and the differences between curves were analyzed using the log-rank test. The hazard ratios (HRs) and 95% confidence intervals (CIs) for developing LUTSs were calculated using univariate and multivariate Cox proportional hazards regression models. All baseline characteristics listed in Table 1 were used for adjustment during the execution of multivariate analysis by using Cox proportional hazards regression models. Stata software (version 13; Stata Corp., College Station, TX, USA) was used for statistical analyses. A two-tailed p value < 0.05 was considered statistically significant.

Results

Patient characteristics

After 1:4 exact matching according to age and index year, 8514 and 34,056 patients constituted the hysterectomy and control cohorts, respectively. The mean age of the study population was 47.1 years, and the median follow-up time was 7.7 years. The differences between the hysterectomy and control cohorts in baseline characteristics including income levels, urbanization levels and comorbidities were noted. The prevalence of baseline comorbidities, such as hypertension, diabetes mellitus, COPD, chronic kidney disease, depression, urinary tract infection and menopause, was higher in the hysterectomy cohort than in the control cohort (Table 1).

Table 1 Baseline characteristics of patients with and without hysterectomy

	Hysterectomy		P value
	Yes ($n = 8514$)	No ($n = 34,056$)	
Age (years)			1.000
< 40	1071 (12.6%)	4284 (12.6%)	
40–49	5216 (61.3%)	20,864 (61.3%)	
50–59	1418 (16.7%)	5672 (16.7%)	
≥ 60	809 (9.5%)	3236 (9.5%)	
Income level (NTD)			< 0.001
Financially dependent	1527 (17.9%)	6605 (19.4%)	
1–19,999	4852 (57.0%)	18,434 (54.1%)	
20,000–39,999	1490 (17.5%)	6338 (18.6%)	
≥ 40,000	645 (7.6%)	2679 (7.9%)	
Urbanization level			< 0.001
1 (Most urbanized)	2815 (33.1%)	12,076 (35.5%)	
2	2521 (29.6%)	10,013 (29.4%)	
3	1480 (17.4%)	5854 (17.2%)	
4	1055 (12.4%)	3837 (11.3%)	
5 (Least urbanized)	643 (7.6%)	2276 (6.7%)	
Comorbidities			
Hypertension	1218 (14.3%)	3221 (9.5%)	< 0.001
Diabetes mellitus	460 (5.4%)	1438 (4.2%)	< 0.001
COPD	196 (2.3%)	662 (1.9%)	0.035
Chronic kidney disease	48 (0.6%)	135 (0.4%)	0.035
Depression	235 (2.8%)	564 (1.7%)	< 0.001
Urinary tract infection	809 (9.5%)	1502 (4.4%)	< 0.001

Categorical data were expressed as number (%)

COPD, chronic obstructive pulmonary disease; NTD, New Taiwan dollars

Risk of LUTS

During the median follow-up time of 7.7 years, 939 patients developed LUTSs in the hysterectomy cohort (14.9/1000 person-years), and 2240 patients in the control cohort (8.5/1000 person-years). The cumulative incidence curves revealed that the hysterectomy cohort had a significantly higher cumulative incidence of LUTSs than the control cohort (log-rank test, $p < 0.001$) (Fig. 1). Hysterectomy was associated with an increased risk of LUTSs in both univariate analysis (crude HR = 1.75, 95% CI = 1.62–1.88, $p < 0.001$) and multivariate analysis [adjusted HR (aHR) = 1.57, 95% CI = 1.46–1.70, $p < 0.001$] conducted using Cox proportional hazards regression models (Table 2).

In the analyses for each symptom, hysterectomy was associated with increased risks of all individual symptoms, namely dysuria (aHR = 1.50, 95% CI = 1.22–1.85, $p < 0.001$), urinary retention (aHR = 1.66, 95% CI = 1.26–2.18, $p < 0.001$), urinary incontinence (aHR = 2.03, 95% CI = 1.74–2.37,
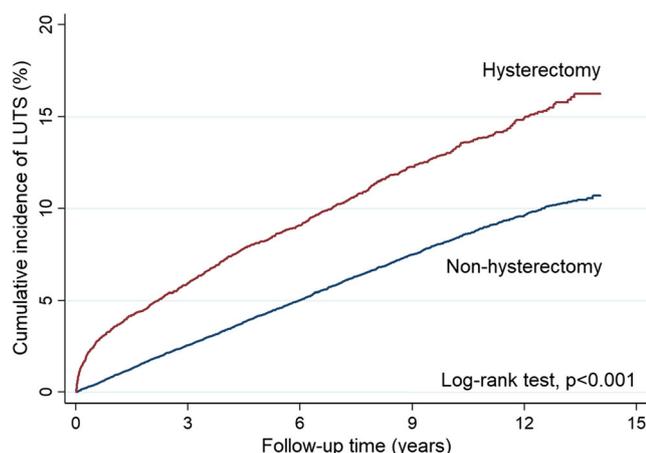
Fig. 1 Cumulative incidence of lower urinary tract symptoms in the hysterectomy and control patients

$p < 0.001$) and increased urinary frequency and urgency (aHR = 1.41, 95% CI = 1.28–1.56, $p < 0.001$) (Table 3). The cumulative incidence curves for each symptom are illustrated in Fig. 2A–D, respectively.

Risk of LUTSs stratified by hysterectomy technique

The effects of different hysterectomy techniques on the risk of LUTSs were further analyzed. Compared with the control patients, the risk of LUTSs was significantly higher in patients who underwent TAH, LAVH and VH. The highest risk of LUTSs was observed in patients who underwent VH (aHR = 1.89, 95% CI = 1.57–2.28, $p < 0.001$) followed by those who underwent LAVH (aHR = 1.74, 95% CI = 1.56–1.94, $p < 0.001$) and TAH (aHR = 1.38, 95% CI = 1.23–1.54, $p < 0.001$). Although the risk of LUTSs was higher in patients who underwent SAH than in the control patients, the difference was not statistically significant (aHR = 1.36, 95% CI = 0.97–1.90, $p = 0.073$) (Table 3).

Results of sensitivity analysis and other information

After excluding patients who were diagnosed with urinary tract infection prior to the index date, during index hospitalization or within 14 days after hysterectomy, we still observed similar results showing that hysterectomy was significantly associated with increased risk of LUTS (aHR =1.57, 95% CI = 1.44–1.71, $p < 0.001$). The sub-analyses for different hysterectomy techniques also revealed a similar pattern. The risks of LUTS were significantly higher in patients who underwent TAH (aHR =1.39, 95% CI = 1.23–1.57, $p < 0.001$), LAVH (aHR =1.74, 95% CI = 1.54–1.96, $p < 0.001$) and VH (aHR =1.81, 95% CI = 1.45–2.27, $p < 0.001$) compared with the control patients (Supplementary Table S1 in Supplementary Materials).

Table 2 Risk of developing lower urinary tract symptoms for patients with and without hysterectomy

	Events	Incidence rate*	Univariate model		Multivariate model[†]	
			Crude HR (95% CI)	p value	Adjusted HR (95% CI)	p value
Any symptoms[§]						
Non-hysterectomy	2240	8.5	1 (Ref.)		1 (Ref.)	
Hysterectomy	939	14.9	1.75 (1.62–1.88)	< 0.001	1.57 (1.46–1.70)	< 0.001
Dysuria						
Non-hysterectomy	322	1.2	1 (Ref.)		1 (Ref.)	
Hysterectomy	129	2.0	1.67 (1.36–2.05)	< 0.001	1.50 (1.22–1.85)	< 0.001
Urinary retention						
Non-hysterectomy	169	0.6	1 (Ref.)		1 (Ref.)	
Hysterectomy	76	1.2	1.87 (1.43–2.46)	< 0.001	1.66 (1.26–2.18)	< 0.001
Urinary incontinence						
Non-hysterectomy	464	1.8	1 (Ref.)		1 (Ref.)	
Hysterectomy	252	4.0	2.26 (1.94–2.64)	< 0.001	2.03 (1.74–2.37)	< 0.001
Urinary frequency or urgency						
Non-hysterectomy	1454	5.5	1 (Ref.)		1 (Ref.)	
Hysterectomy	546	8.7	1.56 (1.42–1.73)	< 0.001	1.41 (1.28–1.56)	< 0.001

There were 8514 and 34,056 patients in hysterectomy and non-hysterectomy cohort, respectively, after exact matching for age and index year

* Per 1000 person-years

[†] Multivariate Cox proportional hazards regression model, adjusting for all baseline characteristics listed in Table 1

[§] Any symptoms were defined as developing any of the following: dysuria, urinary retention, incontinence, frequency or urgency

CI, confidence interval; HR, hazard ratio

Table 3 Risk of developing lower urinary tract symptoms among patients receiving different hysterectomy procedures

Procedures	Events[§]	Incidence rate[*]	Univariate model		Multivariate model[†]	
			Crude HR[‡] (95% CI)	p value	Adjusted HR[‡] (95% CI)	p value
Non-hysterectomy (n = 34,056)	2240	8.5	1 (Ref.)		1 (Ref.)	
SAH (n = 475)	35	11.9	1.36 (0.98–1.90)	0.069	1.36 (0.97–1.90)	0.073
TAH (n = 3857)	372	12.7	1.49 (1.33–1.66)	< 0.001	1.38 (1.23–1.54)	< 0.001
LAVH (n = 3478)	405	15.9	1.86 (1.68–2.07)	< 0.001	1.74 (1.56–1.94)	< 0.001
VH (n = 704)	127	24.2	2.84 (2.37–3.39)	< 0.001	1.89 (1.57–2.28)	< 0.001

[§] Events were defined as developing any of the following symptoms: dysuria, urinary retention, incontinence, frequency or urgency

[*] Per 1000 person-years

[†] Multivariate Cox proportional hazards regression model, adjusting for all baseline characteristics listed in Table 1

[‡] The HR of each hysterectomy procedure was calculated using non-hysterectomy patients as reference

HR, hazard ratio; CI, confidence interval

SAH: Subtotal abdominal hysterectomy

TAH: Total abdominal hysterectomy

LAVH: Laparoscopy-assisted vaginal hysterectomy
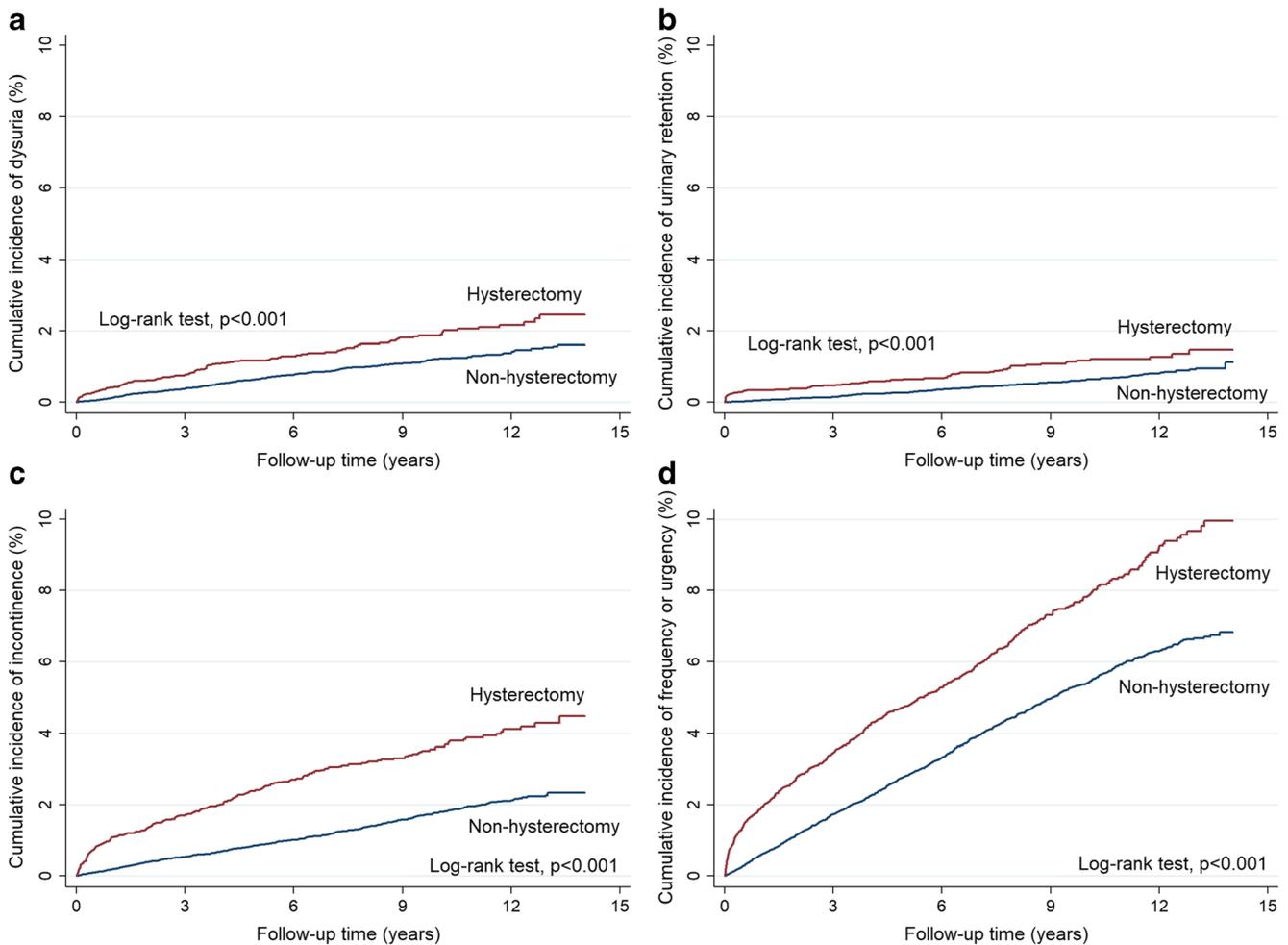
VH: Vaginal hysterectomy

Fig. 2 Cumulative incidence of individual urinary symptoms in the hysterectomy and control patients: (A) dysuria; (B) urinary retention; (C) urinary incontinence; (D) increased urinary frequency and urgency

In addition, we calculated the prevalence of several common complications after receiving hysterectomy, including UTI (5.3%), pneumonia (0.1%), cellulitis or other postoperative infection (3.6%), and ICU utilization (1.1%). The complication was defined as patients developing such an event during index hospitalization or within 14 days after hysterectomy.

Discussion

In this large-scale population-based cohort study, we observed a significant association between hysterectomy and the risk of de novo LUTSs. The median follow-up time was 7.7 years. The study population mainly comprised middle-age women, and more than 60% of all hysterectomies were performed in patients aged 40–49 years. This trend may be observed because the prevalence of uterine leiomyoma, the most common indication for hysterectomy, is the highest in this age group [13]. Our result indicates that women who had undergone hysterectomy were more likely to develop dysuria, urinary retention, urinary incontinence and increased urinary frequency and urgency. Among all LUTSs, the overall incidence of urinary incontinence was more than twice as high in women who had undergone hysterectomy than in the controls after adjustment for comorbidities. The results of a large-scale Swedish cohort study on 165,260 women who had undergone hysterectomy also revealed that hysterectomy predisposes women to requiring subsequent SUI surgery, particularly within 5 years of hysterectomy. Furthermore, the risk increased with parity and was relatively high in patients who had undergone hysterectomy for prolapse [7].

However, the association between hysterectomy and LUTSs has not been systematically investigated. Available studies have reported inconsistent findings regarding the aftereffects of hysterectomy in terms of urinary symptoms and bladder function [4, 14, 15]. Therefore, physicians face a dilemma regarding whether to inform patients of the potential risk of LUTSs associated with hysterectomy. Moreover, previous studies appear to have lacked sufficient statistical power to evaluate the correlation between hysterectomy and LUTSs. Our findings provide support for the clinical practice of informing patients who intend to undergo hysterectomy that LUTSs are more likely to occur, particularly after VH. This is also the first large cohort study to demonstrate an association between hysterectomy and LUTSs in Asian women.

LUTSs are the most common symptoms in women in all age groups worldwide and adversely affect women's quality of life. The common postoperative urinary symptoms are urinary incontinence, increased urinary frequency and urgency, incomplete voiding and difficulty in initiating micturition due to bladder atony. Women with LUTSs also report sexual dysfunction disorders more frequently than do those without LUTSs. The prevalence of LUTSs varies widely from 13% to 76% [16]. According to a study by Chen et al., approximately 54% of Taiwanese women experience urinary incontinence and related symptoms, and the occurrence increases with age [17]. Despite the high prevalence of LUTSs in both Western and Asian countries, only a few affected women seek medical intervention to treat the condition. The negative effect of LUTSs is considerable but often ignored.

Among the different procedures of hysterectomy, the incidence of LUTSs was highest in hysterectomy performed through the vaginal route. Our findings corroborate the results of most studies (Table 3) [18]. The extent of neurological damage is associated with the severity of LUTSs. During VH, the peritoneum overlying the bladder is detached to allow access to the uterovesical pouch. The vesical plexus lies above the lower anterior part of the bladder and communicates with the uterine plexus. Damage to innervation and blood supply may occur during anterior colpotomy [19]. Consequently, bladder dysfunction was more common with the vaginal than with the transabdominal approach. Everaert et al. also reported that urinary retention after hysterectomy is associated with de-afferentiation of the bladder wall and is inversely correlated with the relative electrical sensory threshold of the bladder neck [20]. By contrast, by evaluating the effect of SAH and TAH in a randomized trial, Andersen et al. reported that at 14 years after hysterectomy, a significantly higher proportion of patients experienced urinary incontinence after SAH than after TAH (33% vs. 20%; relative risk = 1.67; 95% CI = 1.02–2.70; $p = 0.035$) [4]. Our result is partially consistent with the finding of Lethaby et al., who concluded that the occurrence of SUI, incomplete emptying of the bladder and urgency were not different in the SAH and TAH groups [21]. In our study, the LUTS risk in patients who underwent SAH did not differ significantly from that in the controls. The incidence of LUTSs was similar in the two groups.

The strengths of our study are its large-scale population-based design and constant classification of intervention and outcome. Near-complete registration that covered > 99.5% of the Taiwanese citizens reduces the risk for ascertainment and reporting bias. Several potential limitations of the retrospective study should be considered when interpreting these findings. Because of the lack of information on obstetric history on Taiwan's NHIRD, we did not report parity status and delivery modes. The relationship between the number of vaginal births and risk of LUTSs is well established. However, earlier studies have demonstrated inconsistent effects of delivery mode on the prevalence of urge incontinence and overactive bladder [22]. According to a recent large epidemiological study on hysterectomy in Chinese women by Liu et al., the parity status in hysterectomy and nonhysterectomy cohorts did not differ significantly [23]. Hence, in our study, the potential effects of parity status may be ignored because of similar distributions in both groups. Another confounder is

menopausal status, which may affect the prevalence of LUTSs. This can be explained by the crucial role of estrogen receptors in the urethra, bladder and pelvic floor [24]; the deficiency of estrogen in the urogenital tract causes atrophic changes [25]. Thus, we further adjusted several variables, including menopause, age, income level, urbanization level and other comorbidities, in our study. Our data are representative of the Asian population, and the controls were drawn from a homogeneous population by using data from highly reliable nationwide health care registers. That using an administrative database to collect data regarding symptoms may not be specific and precise is another shortcoming.

In conclusion, we found that undergoing hysterectomy was associated with increased risks of developing lower urinary tract symptoms in women. This association was more pronounced for women undergoing a vaginal or laparoscopically assisted hysterectomy. Considering the high prevalence of hysterectomy, our findings have crucial implications for public health. However, further large-scale prospective studies or clinical trials are needed to explore whether causality exists.

Compliance with ethical standards

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