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Asthma is associated with endometriosis: A retrospective population-based cohort study

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ABSTRACT

Background: Evidence regarding the association between asthma and endometriosis is limited and inconsistent. The goal of the study was to investigate whether women diagnosed as having asthma were at a greater risk of endometriosis than age-matched unaffected women.

Methods: We conducted a nationwide population-based retrospective study by using data retrieved from the Taiwan National Health Insurance Research Database during the period of 2000–2005 with follow-up through 2013. The current analysis included 7337 women aged 12–50 years with newly diagnosed asthma and using asthma-related medications and 29,348 age-matched women without asthma. A Cox proportional hazards regression model was used to estimate the risks of endometriosis in women with asthma as compared with those without asthma.

Results: The overall risk of endometriosis in the asthma group was 1.50-fold higher (95% confidence interval = 1.33–1.70) than that in the nonasthma group. A stratified analysis by age further revealed that patients with asthma were associated with a higher risk of endometriosis in age groups of 21–50 years.

Conclusion: Compared with women without asthma, women with asthma of reproductive age are at a higher risk of endometriosis. Additional studies are warranted to elucidate the mechanism(s) underlying the association between asthma and a higher risk of endometriosis.

1. Introduction

Epidemiological studies have indicated that in adult populations, asthma prevalence, morbidity, and severity are higher in women than in men [1–3]. Endometriosis is an estrogen-dependent disorder affecting 6%–10% of the female population of reproductive age [4,5]. However, its exact pathogenesis is not yet fully understood [5–7].

Although the relationship between asthma and endometriosis has been explored, the corresponding evidence is limited and inconsistent. For example, Sinaii et al. and Smorgick et al. have reported that asthma is more common in women with endometriosis [8,9]. However, a case-control study by Ferrero et al. revealed that asthma had a similar prevalence in women with and without endometriosis [10]. In addition, the association between asthma and endometriosis risk has yet to be examined in a cohort study.

Although the underlying mechanisms linking asthma and

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endometriosis remain unclear, a large body of evidence suggests that the overproduction of T helper (Th) cytokines by Th2 cells plays a crucial role in the pathophysiology of asthma [11]; moreover, endometriosis was reported to involve a possible shift toward Th2 immune response as demonstrated by the relative increase in Th2-related cytokines [12]. Notably, women with endometriosis tend to have higher levels of estrogen or a greater lifetime exposure to estrogen, which has also been linked to asthma onset [13,14].

Collectively, these observations led to the hypothesis that women diagnosed as having asthma were at a greater risk of endometriosis than their nonasthmatic counterparts. The current study was therefore conducted to test the proposed hypothesis by investigating whether asthma is associated with endometriosis in women of reproductive age; the investigation was conducted using data retrieved from the National Health Insurance Research Database (NHIRD) of Taiwan.

2. Methods

2.1. Data source

The Taiwan National Health Insurance (NHI) program was launched in 1995 and now covers more than 99% of the population of Taiwan. This study cohort was established on the basis of the Longitudinal Health Insurance Database (LHID 2000), a subset of the NHIRD. To protect patient privacy, the NHIRD procedure for releasing individuals' files involves the removal of the original identification number and the provision of a scrambled, anonymous number. The LHID 2000 dataset consists of claims data collected from 1 million people randomly selected from among the total population of insurants in the period of 1996–2013. The NHIRD of Taiwan is a database of all registry and claims data, including patients' demographic characteristics, dates of clinical visits, details of prescriptions, and diagnoses. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) was used to construct the disease record system. This study was approved by the Institutional Review Board of China Medical University (CMUH-104-REC2-115).

2.2. Study population

Using a retrospective population-based cohort study design, we investigated the association between asthma and endometriosis. The patient was defined as having received the ICD-9-CM diagnostic code 493.xx and the corresponding treatment (including inhaled corticosteroids or systemic [oral or intravenous] corticosteroids, inhaled short-acting beta-2 agonists, or inhaled long-acting beta-2 agonists). The asthma group consisted of patients who received a new diagnosis of asthma between 2000 and 2005. To further increase the validity of asthma diagnosis, only patients with at least three outpatient services or inpatient hospitalization claims of asthma diagnosis were included. The index date for the patients in the asthma group was the date of their first diagnosis of asthma. For each patient with asthma, four insured enrollees were frequency matched for age (every 1 year) and index years among insured enrollees who did not conform to the diagnosis condition of asthma. These enrollees constituted the nonasthma group. Any patient with a history of endometriosis at the baseline and aged less than 12 years or more than 51 years was excluded from both groups.

The outcome measure of interest, which was defined as at least three outpatient services or inpatient hospitalization claims, was based on ICD-9-CM 617.xx during the follow-up period. All subjects were followed from the index date to the endpoint—that is, until the onset of endometriosis, withdrawal from the insurance system, or the end of 2013. Comorbidities that existed before the index date, including infertility (ICD-9-CM 628.xx), leiomyoma of the uterus (ICD-9-CM 218.xx), and inflammatory diseases of the cervix, vagina, or vulva (ICD-9-CM 616.xx) were considered pre-existing comorbidities. Concomitant use of estrogen that could be a confounding factor was also considered.

2.3. Statistical analyses

The distributions of baseline characteristics between the asthma and nonasthma groups were compared using Student's *t*-test for continuous variables and the chi-squared test for categorical variables. The incidence rates of endometriosis (per 1000 person-years) were calculated for the asthma and nonasthma groups. We used the Kaplan–Meier method to estimate the cumulative incidence of endometriosis between the asthma and nonasthma groups during the follow-up period. The significance of the differences between both curves was assessed using the log-rank test. Univariate and multivariate Cox proportional hazards regression models were used to estimate the hazard ratios (HRs) with confidence intervals (CIs) of endometriosis to compare the asthma and nonasthma groups. The multivariate model was adjusted for age; infertility; leiomyoma of the uterus; inflammatory diseases of the cervix, vagina, or vulva; estrogen use; and annual outpatients department (OPD) visits to gynecologists. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., NC, USA). Two-tailed $p < 0.05$ was considered significant.

3. Results

Table 1 presents the characteristics of demographic factors and history of comorbidity in the asthma and nonasthma groups. After frequency matching, the distribution of age groups did not differ significantly between the two groups. Compared with the nonasthma group, the asthma group exhibited a significantly higher prevalence of estrogen use and inflammatory diseases of the cervix, vagina, and vulva. The mean numbers of annual OPD visits to gynecologists in the asthma and nonasthma groups were 2.32 (SD = 3.07) and 1.77 (SD = 2.53), respectively (Student's *t*-test, $p < 0.001$).

During the mean follow-up period of 10.9 years, 371 (5.06%) of 7337 patients with asthma and 926 (3.16%) of 29,348 enrollees without asthma developed endometriosis. The cumulative incidence curves of endometriosis according to asthma status are illustrated in Fig. 1. The cumulative incidence of endometriosis was higher in the asthma group than in the nonasthma group (log-rank test, $p < 0.001$).

The incidence rate of endometriosis in the asthma group was 4.63 per 1000 person-years, which was higher than that in the nonasthma group (2.88 per 1000 person-years, Table 2). After adjustment for age, comorbidities, estrogen use, and the mean number of annual OPD visits to gynecologists, the asthma group exhibited a 1.50-fold higher risk of endometriosis than the nonasthma group (95% CI = 1.33–1.70).

Table 1
Comparisons of baseline demographic factors and comorbidities between participants with and without asthma.

Characteristics	Nonasthma group N = 29348		Asthma group N = 7337		p-value
	n	%	n	%	
Age, years					> 0.99
12-20	4168	14.2	1042	14.2	
21-30	6408	21.8	1602	21.8	
31-40	8208	28.0	2052	28.0	
41-50	10564	36.0	2641	36.0	
Mean (SD)[a]	34.8	(11.0)	34.9	(11.0)	0.83
Comorbidities					
Infertility	673	2.29	183	2.49	0.33
Leiomyoma of the uterus	972	3.31	260	3.54	0.34
Inflammatory disease of cervix, vagina, or vulva	8384	28.6	2777	37.9	< 0.001
Estrogen use	11319	38.6	3611	49.2	< 0.001
Annual OPD visits for gynecology, mean (SD)[a]	1.77	(2.53)	2.32	(3.07)	< 0.001

Abbreviations: OPD, outpatients department; SD, standard deviation.
[a] Student's *t*-test.

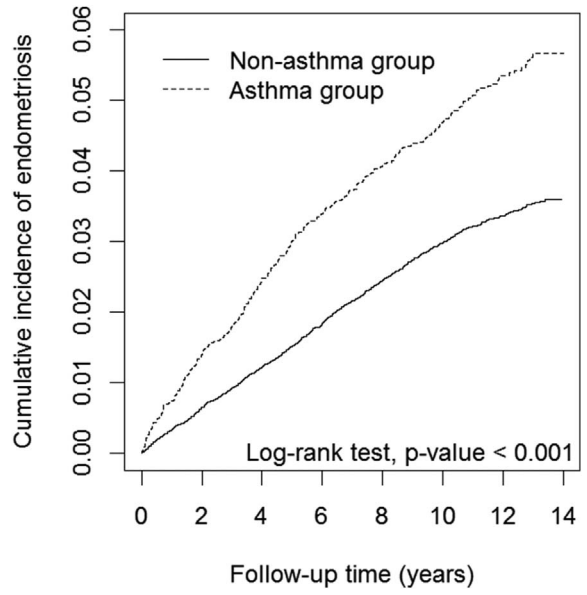


Fig. 1. Cumulative incidence curves of endometriosis for groups with and without asthma.

Table 2
Cox model measured hazard ratios and 95% confidence intervals of endometriosis associated with asthma and covariates.

Characteristics	Event no	Person-years	IR	HR (95% CI)	
				Univariate	Multivariate[a]
Asthma					
No	926	321083	2.88	1.00	1.00
Yes	371	80141	4.63	1.61 (1.42–1.81)***	1.50 (1.33–1.70)***
Age, years					
12-20	122	58280	2.09	1.00	1.00
21-30	337	85741	3.93	1.87 (1.52–2.30)***	1.46 (1.18–1.80)***
31-40	562	110416	5.09	2.42 (1.99–2.95)***	1.94 (1.58–2.37)***
41-50	276	146786	1.88	0.90 (0.73–1.11)	0.78 (0.63–0.97)*
Comorbidity					
Infertility					
No	1233	392302	3.14	1.00	1.00
Yes	64	8922	7.17	2.25 (1.75–2.90)***	1.38 (1.07–1.79)*
Leiomyoma of the uterus					
No	1210	388756	3.11	1.00	1.00
Yes	87	12468	6.98	2.20 (1.77–2.73)***	2.21 (1.76–2.77)***
Inflammatory disease of cervix, vagina, or vulva					
No	727	284378	2.56	1.00	1.00
Yes	570	116846	4.88	1.87 (1.68–2.09)***	1.39 (1.23–1.57)***
Estrogen use					
No	840	231939	3.62	1.00	
Yes	457	169285	2.70	0.75 (0.67–0.85)***	0.57 (0.50–0.64)***
Annual OPD visits for gynecology (each increment one visit)				1.10 (1.09–1.11)***	1.10 (1.09–1.11)***

Abbreviations: IR, incidence rate, per 1000 person-years; HR, hazard ratio; CI, confidence interval.
*p < 0.05, **p < 0.01, ***p < 0.001.
[a] Multivariate Cox proportional hazards regression model including asthma; age (categorical); infertility; leiomyoma of the uterus; inflammatory diseases of the cervix, vagina, or vulva, estrogen use, and annual OPD visits to gynecologists (continuous).

Multivariate Cox proportional hazards analysis indicated that individuals aged 21–30 and 31–40 years who had infertility; leiomyoma of the uterus; and inflammatory diseases of the cervix, vagina, or vulva and those with 1-OPD visit increments to gynecologists were associated with an increased risk of endometriosis (HR = 1.46, 95% CI = 1.18–1.80; HR = 1.94, 95% CI = 1.58–2.37; HR = 1.38, 95% CI = 1.07–1.79; HR = 2.21, 95% CI = 1.76–2.77; HR = 1.39, 95% CI = 1.23–1.57; and HR = 1.10, 95% CI = 1.09–1.11, respectively). Nevertheless, individuals aged 41–50 years were significantly associated with a lower risk of endometriosis, compared with individuals aged 12–20 years (HR = 0.78, 95% CI = 0.63–0.97). In addition, individuals with estrogen use were associated with a lower risk of endometriosis, compared with those without estrogen use (HR = 0.57, 95% CI = 0.50–0.64).

Table 3 presents the incidence rates and HRs of endometriosis according to asthma status stratified by age and comorbidity. In age stratifications, patients with asthma had a significantly higher risk of endometriosis than did enrollees without asthma, except for the 12–20 years age group. The adjusted HRs of endometriosis were 1.57 (95% CI = 1.24–1.99) in the 21–30 years age group, 1.41 (95% CI = 1.17–1.71) in the 31–40 years age group, and 1.91 (95% CI = 1.48–2.46) in the 41–50 years age group. In each comorbidity stratification, the association between asthma and endometriosis remained similar.

4. Discussion

In this nationwide population-based cohort study, we observed that during a mean follow-up period of 10.9 years, women with asthma had a 1.50-fold higher risk of endometriosis than did those without asthma. Although infertility; leiomyoma of the uterus; inflammatory diseases of the cervix, vagina, or vulva and the number of annual OPD visits to gynecologists were associated with an increased risk of endometriosis, asthma remained an independent risk factor after adjustment for these covariates. A further stratified analysis revealed that the risk of endometriosis was significantly higher in women with asthma than in women without asthma in all age groups between 21 and 50 years.

The results of previous studies regarding the association between asthma and endometriosis appear inconsistent. A cross-sectional survey reported that asthma is more common in women with endometriosis than in women in the general population of the United States; however, these data were obtained using self-reported questionnaires, and the comparison groups from general populations were not adjusted for potential confounders [8]. Smorgick et al. reported that in 138 adolescent or young women with endometriosis, 31 (22%) were found to have asthma. However, the women with endometriosis included in this study were all from a tertiary care center; the prevalence of comorbidities might therefore be higher than that in a community-based sample, making generalization of results difficult [9]. By contrast, Ferrero et al. observed that in 879 women of reproductive age who underwent surgery for benign gynecological conditions, asthma prevalence was similar in women with and without endometriosis (4.9% vs. 5.3%) [10]. However, in that case-controlled study, the authors only included women who had undergone gynecological surgery as the study population, thereby rendering the study results inapplicable to general population.

Our study has several advantages over the aforementioned studies. First, we used specialist-validated diagnosis to define each disease rather than self-administered questionnaires. In the NHI program, auditors may scrutinize and validate claims randomly to ensure the accuracy of the claims. Miscoded diagnoses are subject to punitive actions. Therefore, it is reasonable to assume that the accuracy of disease diagnosis was higher in this study than in other studies.

Second, to increase the validity of the results, we included comorbidities to minimize potential confounders and the number of OPD visits to gynecologists to minimize surveillance bias. Third, the data we

Table 3
Incidence rates and hazard ratios of endometriosis stratified by age and comorbidity.

Characteristics	Nonasthma group			Asthma group			HR (95% CI)	
	Event no.	Person-years	IR	Event no.	Person-years	IR	Crude	Adjusted[a]
Age, years								
12-20	94	46596	2.02	28	11684	2.40	1.19 (0.78–1.81)	1.09 (0.71–1.68)
21-30	236	68397	3.45	101	17345	5.82	1.69 (1.34–2.13)***	1.57 (1.24–1.99)***
31-40	408	88400	4.62	154	22016	6.99	1.52 (1.26–1.83)***	1.41 (1.17–1.71)***
41-50	188	117690	1.60	88	29096	3.02	1.89 (1.47–2.44)***	1.91 (1.48–2.46)***
Comorbidities								
Infertility								
No	883	314001	2.81	350	78301	4.47	1.59 (1.41–1.80)***	1.49 (1.32–1.69)***
Yes	43	7082	6.07	21	1840	11.4	1.88 (1.12–3.17)*	1.84 (1.07–3.14)*
Leiomyoma of the uterus								
No	864	311207	2.78	346	77548	4.46	1.61 (1.42–1.82)***	1.49 (1.31–1.69)***
Yes	62	9876	6.28	25	2593	9.64	1.54 (0.97–2.46)	1.68 (1.05–2.68)*
Inflammatory disease of cervix, vagina, or vulva								
No	541	233056	2.32	186	51322	3.62	1.57 (1.33–1.85)***	1.55 (1.31–1.84)***
Yes	385	88027	4.37	185	28819	6.42	1.47 (1.23–1.75)***	1.43 (1.20–1.70)***

Abbreviations: IR, incidence rate, per 1000 person-years; HR, hazard ratio; CI, confidence interval.
*p < 0.05, **p < 0.01, ***p < 0.001.
[a] Mutually adjusting for age (continuous), infertility, leiomyoma of the uterus, inflammatory diseases of the cervix, vagina, or vulva, estrogen use, and annual OPD visits to gynecologists (continuous).

used were retrieved from a nationwide database rather than from a single institution. Finally, the large sample size and long follow-up period provided us with sufficient statistical power to differentiate the incidence of endometriosis in the two groups and generalize the results.

Although the exact pathophysiology underlying the association between asthma and endometriosis is unknown, several lines of evidence might offer plausible explanations. For example, while a large body of evidence has suggested that the overproduction of Th cytokines by Th2 cells plays a crucial role in the pathophysiology of asthma [11,15], an association between endometriosis and a predominant Th2 cytokine immune response was also reported in a prior study [12]. In addition, the association of asthma with persistent inflammation of the conducting airways is well-established. Some researchers have proposed that inflammatory reactions are also involved in the pathogenesis of endometriosis [16]. Levels of inflammatory cytokines have also been found to be higher in the peritoneum or serum of women with endometriosis than that of women without endometriosis. Specifically, many inflammatory cytokines, such as transforming growth factor-β, tumor necrosis factor-α, interleukin (IL)-4, IL-6, and vascular endothelial cell growth factor are involved in the inflammatory response and airway remodeling in asthmatic lungs [17–21]. These cytokines induce the proliferation of endometriotic cells, contributing to the development of endometriosis [22–25].

In our analyses, women with infertility; leiomyoma of the uterus; and inflammatory diseases of the cervix, vagina, and vulva were associated with an increased risk of endometriosis (Table 2), consistent with the findings of previous studies [26–28]. In addition, we found that the prevalence of inflammatory diseases of the cervix, vagina, and vulva was higher in women with asthma than in those without asthma (Table 1). Emerging evidence has suggested that in addition to local inflammation of the airway, systemic inflammation may also be present in certain phenotypes of asthma [29,30]. Thus far, studies on the relationship between asthma and inflammatory diseases of the cervix, vagina, and vulva are scant, and further research is merited.

We observed that the prevalence of estrogen use was higher in the asthma group than that in the nonasthma group, and the use of estrogen was associated with a lower risk of endometriosis. We assume that enrollees in this study may be prescribed estrogen for the purpose of contraception, menstruation-related pain relief, and bleeding control. The risk of endometriosis therefore concurrently decreased. However, evidence of the effect of prior exposure to oral contraceptives on future risk of endometriosis is inconclusive [31,32], and future research is required to clarify this issue.

According to our review of the relevant literature, this is the first cohort study to suggest that women with asthma are at an increased risk of endometriosis. However, several limitations should be considered. First, the NHIRD does not provide detailed personal information of enrollees such as early age at menarche, shorter menstrual cycles, heavy menstrual bleeding, and presence of lower body mass index, which are reportedly potential risk factors for endometriosis [4,33,34]. Second, because participants' clinical information, such as serum laboratory data, pulmonary function test, pathological findings, and various pain symptoms associated with endometriosis, are unavailable in the NHIRD, determining the severity and phenotype of both asthma and endometriosis was not possible. Third, the diagnoses of diseases were based on ICD-9-CM codes obtained from the nationwide administrative database; participants who did not seek medical care were not included in the study. However, given that the accessibility and availability of medical care within the NHI is high in Taiwan [35], we believe that any underestimation was very limited. Finally, although we included annual OPD visits for gynecology as a covariate for adjustment, the possibility that a higher degree of contact with the health care system may be associated with a higher risk of being diagnosed as having endometriosis cannot be fully ruled out. In addition, selection bias may still exist in our cohort study, although we meticulously designed the study to minimize selection bias by matching each asthmatic patient with a nonasthmatic enrollee for age and index year and by using multivariate models that included the number of OPD visits to gynecologists.

Despite these limitations, we believe that the relationship between asthma and endometriosis indicated in the study is reliable and applicable to the general population because of the large scale, nationwide population-based study design, validity of the database, and 13-year follow-up period.

5. Conclusion

In this nationwide study of 36,685 women, records for more than 80,140 follow-up person-years indicated that women of reproductive age with asthma are closely associated with the risk of endometriosis. Future studies can focus on different phenotypes of asthma and endometriosis and explore the underlying pathophysiology to clarify the association between these two diseases.

Conflict of interest

The authors report no conflict of interest.

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