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Original Article

Higher risk of hyperthyroidism in people with asthma: evidence from a nationwide, population-based cohort study

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All the authors involved in drafting or revising the article and approved of the submitted version. Dr. James Cheng-Chung Wei is the corresponding author who is responsible for the accuracy and integrity of data analysis.

Study conception and design: Gau SY, Yong SB and Wei JC

Data acquisition: Wei JC, Huang JY

Data analysis and demonstration: Gau SY, Huang JY, Yong SB and Wei JC

Original draft preparation: Gau SY and Wei JC

Statement of Ethics and Data Sharing Statement:

Datasets from the Longitudinal Health Insurance Database (LHID) 2000 were retrieved in this retrospective cohort study, and the data are available from the Taiwan National Health Insurance (NHI) Bureau. The data is not publicly available because of legal restrictions regarding the “Personal Information Protection Act” in Taiwan. However, requests for data can be formally sent to the NHI bureau. (<https://dep.mohw.gov.tw/DOS/cp-2516-3591-113.html>)

This study conformed to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of Chung Shan Medical University (IRB permit number CS15134).

Individual identification numbers were encrypted to protect the personal privacy of subjects.

Since data in NHIRD were de-identified, patient consent was exempted.

Abstract**Background:**

Studies have indicated that hyperthyroidism exacerbates asthma; however, the influence of asthma in the development of hyperthyroidism has not been adequately studied.

Objective:

The aim of this population-based, retrospective cohort study was to investigate the association between asthma and the development of hyperthyroidism.

Methods:

In this retrospective cohort study, datasets from the Longitudinal Health Insurance Database 2000 in Taiwan during 1997–2013 were retrieved. Patients newly diagnosed with asthma (ICD-9: 493) during 2000–2013 were identified as the exposure cohort. The 1:1 propensity-score-matched non-asthma individuals were selected as the comparison cohort. The hazard ratio (HR) of development of hyperthyroidism in patients with asthma and its association with age and follow-up time were examined.

Results:

A total of 45,182 individuals were included in the study, including 22,591 and 22,591 patients with (asthma group) and without (control group) asthma, respectively. Incidence rates (per 100,000 person-months) of hyperthyroidism in the study groups were 12.88 in the control group and 16.95 in asthma group. The adjusted HR for developing hyperthyroidism was 1.31(95% confidence interval, 1.12–1.53) in patients with asthma compared with controls. The risk of developing hyperthyroidism was higher in patients with asthma aged >30 years old and with a follow-up of <3 years than in other subgroups.

Conclusion:

Patients with asthma had a higher risk of developing hyperthyroidism, especially those over 30 years of age and in the first 3 years after diagnosis of asthma. Clinicians caring for patients with asthma should be aware of this increased risk

Highlights box:

1. What is already known about this topic?

→ Studies have indicated that hyperthyroidism exacerbates asthma; however, the influence of asthma in the development of hyperthyroidism has not been adequately studied.

2. What does this article add to our knowledge?

→ Patients with asthma were at higher risk of developing hyperthyroidism, especially those above 30 years old.

3. How does this study impact current management guidelines?

→ Clinicians caring for with asthma should be aware of an increased risk of hyperthyroidism developing in the future.

4. Key words:

→ asthma, hyperthyroidism, NHIRD, population-based study, cohort study

Abbreviations used:

LHID: longitudinal health insurance database

HR: hazard ratio

ICD-9 CM:

International classification of diseases, ninth revision, clinical modification

aHR: adjusted hazard ratio

C.I.: confidence interval

PTDM: prescription time-distribution matching

PSM: propensity score matching

Introduction:

Hyperthyroidism causes multiple symptoms such as palpitations, dyspnea, and polydipsia¹. Possible etiologies of hyperthyroidism include thyroiditis, thyroid dysfunction, and Graves' disease. Additionally, Graves' disease is considered to be the most common precursor of hyperthyroidism^{1,2}. Although factors contributing to Graves' disease remain uncertain, environmental factors such as infection, genetics, and endogenous factors have been implicated^{2,3}.

Asthma is associated with morbidity and mortality⁴. More than 300 million people were estimated to be affected by asthma worldwide in 2016⁵. According to epidemiological studies in Taiwan, 15.7% of individuals <20 years old have the possibility of being diagnosed with asthma, whereas 10.6% of adults are diagnosed with asthma^{6,7}. Exacerbations due to infection or allergens trigger cellular inflammation and tissue remodeling, and resulting symptoms include wheezing, cough, or shortness of breath⁸.

Asthma and autoimmune thyroid conditions were considered to be Th2- and Th1-mediated diseases, respectively^{9,10}. However, recent studies have reported that some asthma phenotypes are non-T2 or T2-low asthma. Th1 and Th17 pathways are associated with non-T2 asthma^{11,12}. These pathways have also been reported in the pathogenesis of hyperthyroidism¹³. However, large-scale studies evaluating the relationship between asthma and subsequent hyperthyroidism are lacking. Therefore, this retrospective population-based cohort study determined whether

144 asthma increases the risk of hyperthyroidism using the National Health Insurance Research

145 Database (NHIRD) in Taiwan.

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162 **Methods:**

Data source

Datasets from the Longitudinal Health Insurance Database (LHID) 2000 in Taiwan were retrieved. This database contains one million beneficiaries randomly sampled from the NHIRD. It comprised the claims data of each outpatient visit and hospital stay. Records, including diagnoses identified by ICD9 CM codes, medical prescriptions, and examination items during ambulatory care and hospitalizations, were available. The patients' or caregivers' identities were censored prior to the release of the data to protect privacy.

Identification of patients with asthma

Asthma and non-asthma cohorts were used to compare the future risk of developing hyperthyroidism. Patients diagnosed with asthma (ICD-9-CM: 493) between 1997 and 2013 were included in the asthma cohort. To improve the validity of the definition, inhaled prescriptions including fluticasone, fluticasone propionate with salmeterol, and budesonide with formoterol prescribed for at least 28 days within 3 months following the diagnosis of asthma were included as additional criteria. The date of the first asthma diagnosis was set as the index date for the asthma cohort.

Selection of comparison cohort

Prescription time-distribution matching (PTDM)¹⁴ and propensity score matching (PSM) matched each patient in the asthma cohort with a control patient using a logistic regression model with predictors (age, sex, urbanization, hospital stay 1 year prior to the index date, and

comorbidities). Individuals with (1) an index date before 2000, (2) diagnosis of hyperthyroidism prior to the index date, and (3) no match with appropriate controls were excluded. Data between 1997 and 1999 were not included in the analysis for the following two reasons: (1) In Taiwan, ICD-9 CM codes have been applied to recorded diagnoses since 2000. However, in the NHIRD dataset, data prior to 2000 were not completely recorded with ICD-9 CM codes. (2) If the data since 1997 were included, the time frame would be limited as the data did not cover a complete time range. In this case, left censoring bias or left truncation bias would occur. These types of biases are more difficult to solve compared to right-censoring biases. We set the index after a specific year (in this study, 2000) so that we could obtain sufficient preliminary data to confirm the sequences of the diseases on an appropriate timeline as well as the precise time of occurrence. Moreover, in the estimation of time-to-event risk, left censoring bias or left truncation bias can be considered as much as possible¹⁵. Absolute standardized differences (ASDs) were used to evaluate the balance of baseline covariates. The $ASD < .10$ indicated no difference. PTDM was used to assign index dates for matched non-asthma individuals, rather than assigning all controls a random index date and then matching by wait time. The index date (“Time 0 for the follow up”) represents the date of first diagnosis of asthma in asthma cohort, which was random between 2000 and 2013. For non-asthma cohort, the index date (“Time 0 for the follow up”) was the time assigned according to the distribution of date of asthma diagnosis in matched asthma case. Hence, the “Time 0” was the exactly same

date in both asthma and non-asthma cohort. Description of PTDM model could be found in **Figure E1** in the online repository (available in this article's Online Repository at www.jaci-inpractice.org). The rationale of applying PTDM to identify controls was to avoid the survival bias which could be potentially caused by the imbalance of prescription time distribution between asthma and non-asthma cohorts¹⁴. After PTDM, in the 1:2 age- and sex-matched population prior to PSM, we found non-balanced covariates. This included longer hospital stays in the asthma cohort and comorbidities of esophageal reflux, hypertension, coronary artery disease, gastritis, and duodenitis. After PSM, all covariates included were balanced between the cohorts.

Identification of subsequent hyperthyroidism

The primary endpoint of this study was the diagnosis of hyperthyroidism (ICD-9-CM: 242) after the index date. To increase accuracy, only patients with at least one inpatient or two outpatient visits with a diagnosis of hyperthyroidism were included. The definition of hyperthyroidism was identical in both the control and asthma cohort groups. All participants were followed from the index date until the first occurrence of hyperthyroidism, death, or December 2013. To the best of our knowledge, no validation study regarding hyperthyroidism in the Taiwanese NHIRD is available. However, we attempted to precisely define the occurrence of hyperthyroidism. The definition and inclusion criteria applied in the current study have been applied in previous studies¹⁶⁻¹⁹.

Statistical analysis

PTDM were applied to make the index date for a non-asthma patient assigned based on a randomly-selected asthma patient's time between cohort entry and their own index date (which in their case, the time of asthma diagnosis). We identified patients who were newly diagnosed with asthma between 2000 and 2013 as the asthma cohort. The index date was the date when the patient was first diagnosed with asthma. At the index date, according to the algorithm of time distribution matching, 2 non-asthma individuals were randomly selected (without replacement) and exactly matched with the sex and birth year of an asthma individual. After each sampling iteration, the exclusion criteria were checked for non-asthmatic individuals. The non-asthmatic individuals were removed from the un-paired pool if they met the exclusion criteria at the specific index date. The procedure of first-round matching was completed when each asthma patient was paired with two non-asthmatic individuals. A total of 45,470 hyperthyroidism-free non-asthmatic individuals were paired with asthma patients after time distribution matching.

Subsequent propensity score matching (PSM) was performed to balance the baseline characteristics of the study groups using the PSMATCH procedure in the SAS software. PSM was performed using “greedy nearest neighbor matching”. The propensity score of having asthma was estimated using logistic regression. The covariates included age, sex, urbanization, hospital stays 1 year prior to the index date and comorbidities (including esophageal reflux,

hypertension, coronary artery disease, diabetes mellitus, hyperlipidemia, systemic lupus erythematosus, Sjogren's syndrome, chronic kidney disease, chronic liver diseases, gastritis and duodenitis, malignancies, and depression as defined by ICD-9-CM codes). The balance of the baseline covariates between cohorts was evaluated using standardized differences. The absolute standardized difference $<.10$ was considered as no difference at the covariate. The absolute standardized difference was used to evaluate the differences in baseline characteristics between the asthma and non-asthma groups. The incidence rate, crude relative risk, and 95% confidence interval (95% CI) were calculated using univariate Poisson modeling. The cumulative incidence rate of hyperthyroidism was estimated using the Kaplan–Meier method. The log-rank test was performed to compare the difference in cumulative incidence between the groups. Statistical tests were considered significant when the p value was $<.05$. The adjusted hazard ratio (aHR) with 95% CI was used to determine the association between the study factors and hyperthyroidism events. Additionally, multiple Cox proportional hazard regressions for the paired study design were conducted to analyze the relationship between asthma and hyperthyroidism. Age- and sex-subgroup analyses were performed to determine the sensitivity of the study results and to explore the potential interaction between study variables. SAS (version 9.4; SAS Institute, Cary, NC, USA) was used to analyze the data.

Results:

After excluding cases not at risk at baseline, 22,591 patients and an equal number of matched controls were included in the study (**Figure 2**). **Table 1** summarizes the distribution of baseline characteristics in the asthma and control cohorts. After PSM, potential confounders selected in this study were balanced between the two cohorts. The cumulative incidence of hyperthyroidism was examined using Kaplan–Meier analysis (**Figure 1**). The asthma cohort showed a significantly higher cumulative probability of hyperthyroidism than the non-asthma cohort ($p<.01$), with an adjusted hazard ratio (aHR) of 1.31 (95% CI, 1.12–1.53). The incidence rates (per 100,000 person-months) of hyperthyroidism in patients with and without asthma were 16.95 (95% CI, 15.31–18.78) and 12.88 (95% CI, 11.44–14.5), respectively.

The frequency of patient visits to various medical departments within 3 months prior to the index date were reported in **Table E1** (available in this article's Online Repository at www.jaci-inpractice.org). For the asthma cohorts, Pediatrics, Family Medicine, Non-differentiated Divisions, General Medicine and Otolaryngology were departments that received high patient visits. In the asthma cohort, patients had a higher rate than the non-asthma cohort for visits to hospital departments related to an asthma diagnosis (**Table E2**, available in this article's Online Repository at www.jaci-inpractice.org). In the model, considering the amount of hospital visits to related divisions (3 months prior to the index date), the asthma cohort showed a higher risk of developing hyperthyroidism. The risk was statistically significant, with an aHR of 1.22 (**Table 2**).

In the stratified analysis, subgroups with various follow-up times, sex, and age at the index date were analyzed (**Table 3**). Patients with a relatively short follow-up time (<36 months) demonstrated a significant risk of hyperthyroidism (aHR, 1.59; 95% CI, 1.25–2.03). Asthma patients aged <30 years showed an insignificant association with future hyperthyroidism. Compared with the younger population, patients aged >30 years at the index date presented a significantly higher risk of developing future hyperthyroidism.

Stratification by pre-index medical visits was intended to assess bias by surveillance. For asthma patients visiting related departments 1 to 2 times prior to the index date, the risk of developing hyperthyroidism was significantly higher. However, the subgroup with more than 3 visits prior to the index date did not show a significantly higher risk of hyperthyroidism. The *p* for interaction was above 0.05. Three additional models were used in the sensitivity analysis to provide delaying periods. We excluded any near-index incident hyperthyroidism events that occurred within 6, 12, and 18 months to assess for bias caused by reverse causation. According to the results of the sensitivity analysis, all 3 models had a statistically significant risk for the asthma patients to develop hyperthyroidism. There was an increased risk from 19.9% to 23.8%, compared with the non-asthma cohort.

Discussion

This study suggests that patients with asthma are at an increased risk of subsequent development of hyperthyroidism, especially in those >30 years old. Furthermore, in the first 3 years after the diagnosis of asthma, asthma patients were more likely to develop hyperthyroidism.

The term “non-T2 asthma” refers multiple types of inflammation in the airway with a mechanism different from T2 inflammation. This also includes neuron-related abnormalities in signaling²⁰. Based on histological evidence, non-T2 asthma is associated with non-eosinophilic airway inflammation^{20,21}. Previous studies have suggested that Th17 cells and related cytokines such as IL-17 A could influence asthma patients’ airways. This implies that the Th17 pathway plays a potential role in the pathogenesis of severe asthma^{22,23}. Accordingly, in subtypes of non-T2 asthma, Th17 cell differentiation and alterations in cytokine levels, including IL-17 A, IL-17 F, and related chemokines, were observed in patients with neutrophilic airway inflammation²⁰. In this case, we suggest that the observed association with hyperthyroidism in the present study could be related to the Th17 pathway in non-T2 asthma. Plasma levels of IL-17 were reported to be elevated in patients with Graves’ disease²⁴. A previous study also indicated that increased Th17 could be involved in the pathogenesis of thyroid disease²⁵. The influence of the non-T2 pathway in asthma could be less younger patients who are more likely to be allergic than older patients (need reference). However, the hypothesized relationship between non-T2 asthma and hyperthyroidism could not be evaluated in this study since

endotypes and phenotypes of asthma patients in this study were not determined.

Lifestyle could influence the development of hyperthyroidism in older patients. For instance, exposure to air pollutants could influence thyroid function more often in the older population than in the younger population²⁶. These differences could contribute to a higher risk of hyperthyroidism in patients asthma aged >30 years. Sex differences in the development of hyperthyroidism were not significant in the asthma cohort ($p>.05$). The incidence rate of hyperthyroidism in women was higher than that in men in both cohorts. This is in agreement with prior observations. Future clinical studies should determine the actual mechanism between asthma and hyperthyroidism to strengthen the association between these two conditions.

The strength of this study is that it describes an epidemiological relationship between asthma and the potential risk of hyperthyroidism. This study is the first to evaluate the real-world relationship between asthma and the future development of hyperthyroidism using a nationwide longitudinal population-based database. However, this study has some limitations that must be addressed. First, the ICD-9-CM codes may be insufficient in defining diseases, and this may result in misclassification of diseases. However, we attempted to define patients with asthma using the definition in previous studies^{27,28}. Inhaled steroid receipt was included as additional criterion to improve validity. Second, residual confounders may have caused a potential bias. In the NHIRD, only diagnosis records, related therapies, or prescribed drugs are accessible. Thus, information on smoking status, lifestyle, or detailed analysis of serological

examinations were unavailable. Nonetheless, the potential influences of age, sex, and related comorbidities were considered. Third, because short-term risk was reported, reverse causation bias could exist. Hyperthyroidism can complicate the existence of asthma or precipitate symptoms that mimic it. Moreover, causation was difficult to determine as 3 years could overlap with the subclinical stage. Nonetheless, to address this bias, we provided a period of delayed entry for patients in the sensitivity model. After ignoring any incident hyperthyroidism events that occurred within 6, 12, and 18 months after the index date in both cases and controls, the risk of developing hyperthyroidism in asthma patients remained statistically significant (**Table 3**). Fourth, surveillance bias could also exist. Serving as a definition of intervention, the diagnostic code for asthma and medication prescriptions related to asthma, could imply a high level of medical surveillance. The information in **Table E2** also implies that individuals with asthma have greater medical surveillance than those without asthma. However, we attempted to control potential surveillance bias by conducting a multiple Cox proportional hazard regression and stratification analysis under an additional model. This added the attribute of related hospital department visitations 3 months prior to the index date as an additional variable. We considered the number of visits to medical departments, including general medicine, pediatrics, otolaryngology, thoracic medicine or endocrinology 3 months prior to the index date. The rationale for limiting it to these specialties was because these specialties were related to patient visits due to asthma. In this analysis, we primarily focused on the differences in medical

surveillance that might impact the chance of discovering hyperthyroidism related to asthma visits. In the stratification analysis, we found that for asthma patients visiting related departments 1 to 2 times prior to the index date, the risk of developing hyperthyroidism was significantly higher. However, the subgroup with more than 3 visits prior to the index date did not show a significantly higher risk of hyperthyroidism. The p for interaction was above 0.05 (**Table 3**). In this case, we believe that the influence of medical surveillance could be addressed, as there were no significant differences in hyperthyroidism risk between the various subgroups related to hospital department visits. Moreover, after considering the confounder of the hospital visiting attribute in the model, the asthma cohort continued to show a statistically significant risk of developing hyperthyroidism (**Table 2**). This supported the reported association in the present study.

This study is the first to demonstrate the association between asthma and the risk of hyperthyroidism from a robust population-based database. Clinicians caring for patients with asthma should be aware of the increased risk of future development of hyperthyroidism in their patients

References

1. De Leo S, Lee SY, Braverman LE: **Hyperthyroidism**. *Lancet* 2016, **388**(10047):906-918.
2. Smith TJ, Hegedus L: **Graves' Disease**. *The New England journal of medicine* 2016, **375**(16):1552-1565.
3. Wemeau JL, Klein M, Sadoul JL, Briet C, Velayoudom-Cephise FL: **Graves' disease: Introduction, epidemiology, endogenous and environmental pathogenic factors**. *Annales d'endocrinologie* 2018, **79**(6):599-607.
4. Fergeson JE, Patel SS, Lockey RF: **Acute asthma, prognosis, and treatment**. *The Journal of allergy and clinical immunology* 2017, **139**(2):438-447.
5. **The global asthma report 2018**. Global Asthma Network; 2018. Available at [http://globalasthmareport.org/resources/Global_Asthma_Report_2018.pdf]. Accessed August 26, 2021.
6. Hwang CY, Chen YJ, Lin MW, Chen TJ, Chu SY, Chen CC *et al*: **Prevalence of atopic dermatitis, allergic rhinitis and asthma in Taiwan: a national study 2000 to 2007**. *Acta dermato-venereologica* 2010, **90**(6):589-594.
7. Ma YC, Lin CC, Yang SY, Chen HJ, Li TC, Lin JG: **Time Trend Analysis of the Prevalence and Incidence of Diagnosed Asthma and Traditional Chinese Medicine Use among Adults in Taiwan from 2000 to 2011: A Population-Based Study**. *PloS one* 2015, **10**(10):e0140318.
8. Mims JW: **Asthma: definitions and pathophysiology**. *International forum of allergy & rhinology* 2015, **5 Suppl 1**:S2-6.
9. Rapoport B, McLachlan SM: **Graves' hyperthyroidism is antibody-mediated but is predominantly a Th1-type cytokine disease**. *J Clin Endocrinol Metab* 2014, **99**(11):4060-4061.
10. Barnes PJ: **Th2 cytokines and asthma: an introduction**. *Respir Res* 2001, **2**(2):64-65.
11. Hudey SN, Ledford DK, Cardet JC: **Mechanisms of non-type 2 asthma**. *Curr Opin Immunol* 2020, **66**:123-128.
12. Raundhal M, Morse C, Khare A, Oriss TB, Milosevic J, Trudeau J *et al*: **High IFN-gamma and low SLPI mark severe asthma in mice and humans**. *J Clin Invest* 2015, **125**(8):3037-3050.
13. Li Q, Wang B, Mu K, Zhang JA: **The pathogenesis of thyroid autoimmune diseases: New T lymphocytes - Cytokines circuits beyond the Th1-Th2 paradigm**. *J Cell Physiol* 2019, **234**(3):2204-2216.
14. Zhou Z, Rahme E, Abrahamowicz M, Pilote L: **Survival bias associated with time-to-treatment initiation in drug effectiveness evaluation: a comparison of methods**. *Am J Epidemiol* 2005, **162**(10):1016-1023.
15. Cain KC, Harlow SD, Little RJ, Nan B, Yosef M, Taffe JR *et al*: **Bias due to left truncation and left censoring in longitudinal studies of developmental and disease**

- processes. *Am J Epidemiol* 2011, **173**(9):1078-1084.
16. Wu TY, Wang CH, Tien N, Lin CL, Chu FY, Chang HY *et al*: **A Population-Based Cohort Study on the Association of Hyperthyroidism With the Risk of Hyperlipidemia and the Effects of Anti-thyroid Drugs on Hepatic Gene Expression.** *Front Med (Lausanne)* 2020, **7**:228.
 17. Man KM, Chen KB, Chen HY, Chiang JH, Su YC, Man SS *et al*: **Hyperthyroidism is not a significant risk of benign prostatic hyperplasia: A nationwide population-based study.** *Medicine (Baltimore)* 2018, **97**(39):e12459.
 18. L'Heureux A, Wieland DR, Weng CH, Chen YH, Lin CH, Lin TH *et al*: **Association Between Thyroid Disorders and Colorectal Cancer Risk in Adult Patients in Taiwan.** *JAMA Netw Open* 2019, **2**(5):e193755.
 19. Chan YH, Wu LS, See LC, Liu JR, Chang SH, Chao TF *et al*: **Direct Oral Anticoagulants in Atrial Fibrillation Patients With Concomitant Hyperthyroidism.** *J Clin Endocrinol Metab* 2020, **105**(9).
 20. Murphy RC, Pavord ID, Alam R, Altman MC: **Management Strategies to Reduce Exacerbations in non-T2 Asthma.** *The journal of allergy and clinical immunology In practice* 2021, **9**(7):2588-2597.
 21. Simpson JL, Scott R, Boyle MJ, Gibson PG: **Inflammatory subtypes in asthma: assessment and identification using induced sputum.** *Respirology* 2006, **11**(1):54-61.
 22. Ray A, Kolls JK: **Neutrophilic Inflammation in Asthma and Association with Disease Severity.** *Trends Immunol* 2017, **38**(12):942-954.
 23. Agache I, Ciobanu C, Agache C, Anghel M: **Increased serum IL-17 is an independent risk factor for severe asthma.** *Respir Med* 2010, **104**(8):1131-1137.
 24. Peng D, Xu B, Wang Y, Guo H, Jiang Y: **A high frequency of circulating th22 and th17 cells in patients with new onset graves' disease.** *PloS one* 2013, **8**(7):e68446.
 25. Qin J, Zhou J, Fan C, Zhao N, Liu Y, Wang S *et al*: **Increased Circulating Th17 but Decreased CD4(+)Foxp3(+) Treg and CD19(+)CD1d(hi)CD5(+) Breg Subsets in New-Onset Graves' Disease.** *BioMed research international* 2017, **2017**:8431838.
 26. Kim HJ, Kwon H, Yun JM, Cho B, Park JH: **Association Between Exposure to Ambient Air Pollution and Thyroid Function in Korean Adults.** *J Clin Endocrinol Metab* 2020, **105**(8).
 27. Wang YT, Tsai MC, Wang YH, Wei JC: **Association Between Proton Pump Inhibitors and Asthma: A Population-Based Cohort Study.** *Front Pharmacol* 2020, **11**:607.
 28. Fu LS, Lin CC, Wei CY, Lin CH, Huang YC: **Risk of acute exacerbation between acetaminophen and ibuprofen in children with asthma.** *PeerJ* 2019, **7**:e6760.

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446 **Figure Legends:**

447 **Figure 1.**

448 Comparison of cumulative probability of hyperthyroidism in overall patients with and without
449 asthma

450 **Figure 2.**

451 Study follow chart: Selection Protocol

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Table E1

Ranking of frequency regarding divisions the study groups included in this study visit within 3 months before index date.

Rank	Non-asthma cohort	Asthma cohort
1	Family Medicine	Pediatrics
2	Non-differentiated division ^a	Family Medicine
3	General Medicine ^b	Non-differentiated division ^a
4	Otolaryngology	General Medicine ^b
5	Chinese Medicine	Otolaryngology
6	Pediatrics	Thoracic Medicine
7	Dentistry	Chinese Medicine
8	Ophthalmology	Dentistry
9	Cardiovascular	Ophthalmology
10	Obstetrics and Gynecology	Cardiovascular

^a Within our study period, “non- differentiated division” could be an option for patients in Taiwan to visit.

^b In some cases, General Medicine in Taiwan were not clearly divided into different subspecialties

Table E2.

Analysis for the study group regarding the amount of hospital visiting 3 months before the index date for divisions related to the exposure or outcome in the present study.

Hospital visiting amount for asthma diagnosis related divisions ^a	Non-asthma	Asthma
0	13111 (58.0%)	3054 (13.5%)
1-2	4863 (21.5%)	6395 (28.3%)
3-5	2975 (13.2%)	6858 (30.4%)
≥6	1642 (7.3%)	6284 (27.8%)

^a Including “General Medicine”, “Pediatrics”, “Otolaryngology”, “Thoracic Medicine” or “Endocrinology”

Table 1.**Baseline characteristics among study groups**

	Before PSM (1:2 age-sex matching)			After 1:1 PSM		
	Control n=45,470	Asthma n=22,735	Standardized difference	Control n=22,591	Asthma n=22,591	Standardized difference
Sex			.00			<.01
Female	21,850(48.05%)	10,925(48.05%)		10,858(48.06%)	10,848(48.02%)	
Male	23,620(51.95%)	11,810(51.95%)		11,733(51.94%)	11,743(51.98%)	
Age			.00			.03
<30	15,350(33.76%)	7,675(33.76%)		7,587(33.58%)	7,668(33.94%)	
30-45	7,132(15.69%)	3,566(15.69%)		3,425(15.16%)	3,546(15.70%)	
45-65	12,028(26.45%)	6,014(26.45%)		5,832(25.82%)	5,943(26.31%)	
≥65	10,960(24.10%)	5,480(24.10%)		5,747(25.44%)	5,434(24.05%)	
Urbanization			.06			<.01
Urban	26,517(58.32%)	13,970(61.45%)		13,899(61.52%)	13,868(61.39%)	
Sub-urban	13,961(30.70%)	6,428(28.27%)		6,410(28.37%)	6,401(28.33%)	
Rural	4,992(10.98%)	2,337(10.28%)		2,282(10.1%)	2,322(10.28%)	
Low income	231(0.51%)	148(0.65%)	.02	130(0.58%)	148(0.66%)	.01
Length of hospital stays (Within 2 year before index date)			.20			.01
0 day	38,257(84.14%)	17,325(76.2%)		17,170(76%)	17,306(76.61%)	
1-6 days	4,044(8.89%)	2,874(12.64%)		2,893(12.81%)	2,827(12.51%)	
≥7 days	3,169(6.97%)	2,536(11.15%)		2,528(11.19%)	2,458(10.88%)	
Co-morbidity						

Esophageal reflux	827(1.82%)	960(4.22%)	.14	776(3.43%)	864(3.82%)	.02
Hypertension	9,097(20.01%)	5,954(26.19%)	.15	6,081(26.92%)	5,843(25.86%)	.02
Coronary artery disease	3,644(8.01%)	2,916(12.83%)	.16	2,789(12.35%)	2,825(12.50%)	<.01
Diabetes mellitus	4,381(9.63%)	2,276(10.01%)	<.01	2,300(10.18%)	2,253(9.97%)	<.01
Hyperlipidemia	4,815(10.59%)	3,040(13.37%)	.09	3,047(13.49%)	2,974(13.16%)	.01
SLE	47(0.10%)	59(0.26%)	.04	38(0.17%)	53(0.23%)	.02
Sjogren syndrome	203(0.45%)	182(0.80%)	.05	156(0.69%)	169(0.75%)	<.01
Chronic kidney disease	611(1.34%)	323(1.42%)	<.01	274(1.21%)	321(1.42%)	.02
Chronic liver diseases	3,913(8.61%)	2,609(11.48%)	.10	2,592(11.47%)	2,536(11.23%)	<.01
Gastritis and duodenitis	5,284(11.62%)	4,040(17.77%)	.17	4,014(17.77%)	3,926(17.38%)	.01
Malignancies	1368(3.01%)	884(3.89%)	.05	840(3.72%)	867(3.84%)	<.01
Depression	1147(2.52%)	906(3.99%)	.08	858(3.80%)	869(3.85%)	<.01

Table 2.

Multiple Cox proportional hazard regression for estimation of adjusted hazard ratios on hyperthyroidism^a.

Variable	aHR (95% C.I.)
Asthma (ref: Control)	1.22 (1.02-1.45)
Sex (ref: Female)	
Male	0.36 (0.30-0.43)
Age (ref: 30-45)	
<30	0.45 (0.35-0.58)
45-64	1.04 (0.83-1.30)
>=65	0.65 (0.49-0.87)
Urbanization (ref: Urban)	
Sub-urban	0.88 (0.73-1.06)
Rural	0.97 (0.74-1.25)
Length of hospital stays ^b (ref: 0 day)	
1-6 days	0.94 (0.74-1.19)
>=7 days	1.11 (0.86-1.44)
Co-morbidity	
Esophageal reflux	0.84 (0.49-1.44)
Hypertension	1.02 (0.83-1.26)
Coronary artery disease	1.31 (1.04-1.67)
Diabetes mellitus	1.02 (0.78-1.34)
Hyperlipidemia	1.07 (0.84-1.35)
Systemic Lupus Erythematosus	2.37 (0.96-5.83)
Sjogren syndrome	1.33 (0.65-2.72)
Chronic kidney disease	1.12 (0.57-2.19)
Chronic liver diseases	1.11 (0.88-1.39)
Gastritis and duodenitis	1.18 (0.97-1.44)
Malignancies	1.32 (0.91-1.91)
Depression	1.44 (1.06-1.96)
Hospital visiting amount for related divisions 3 months before the index date (ref: 0 day)	
1-2	1.14 (0.92-1.42)
3-5	1.25 (1.00-1.58)
≥6	1.14 (0.88-1.48)

^a Considering the amount of hospital visiting 3 months before the index date for asthma diagnosis related divisions, including “General Medicine”, “Pediatrics”, “Otolaryngology”, “Thoracic Medicine” or “Endocrinology”

^bLength of hospital stays, was the sum of the days in the hospitalization within 2 years before index date.

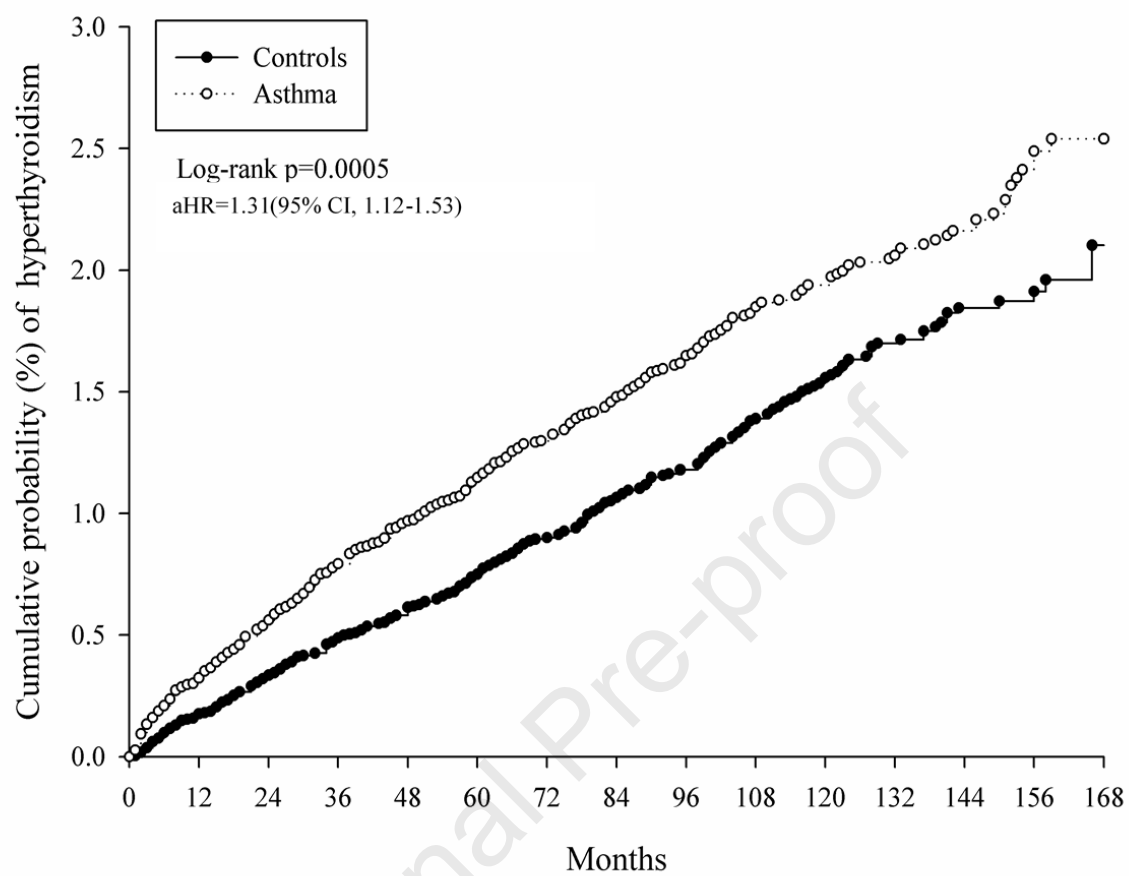
Table 3.

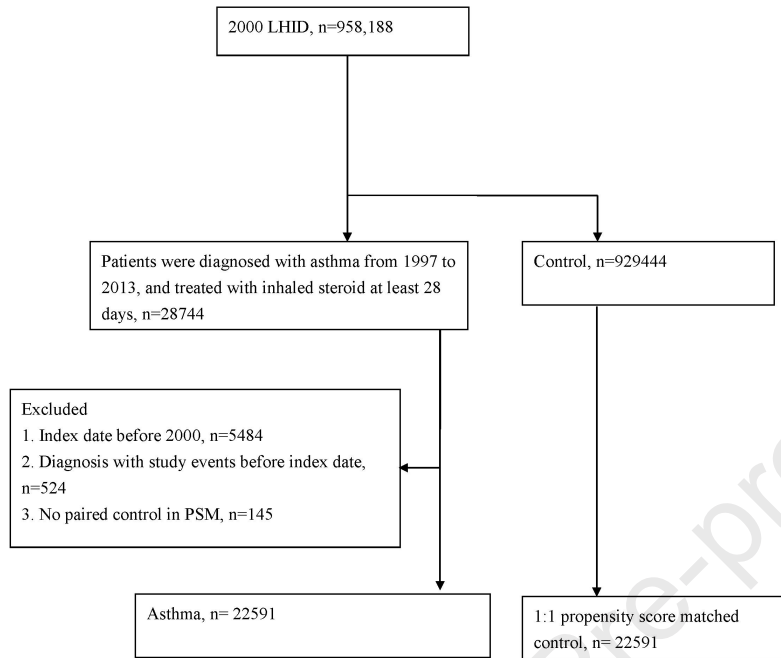
The sensitivity analysis for the adjusted hazard ratio (95% C.I.) stratified by follow up time, sex and age groups.

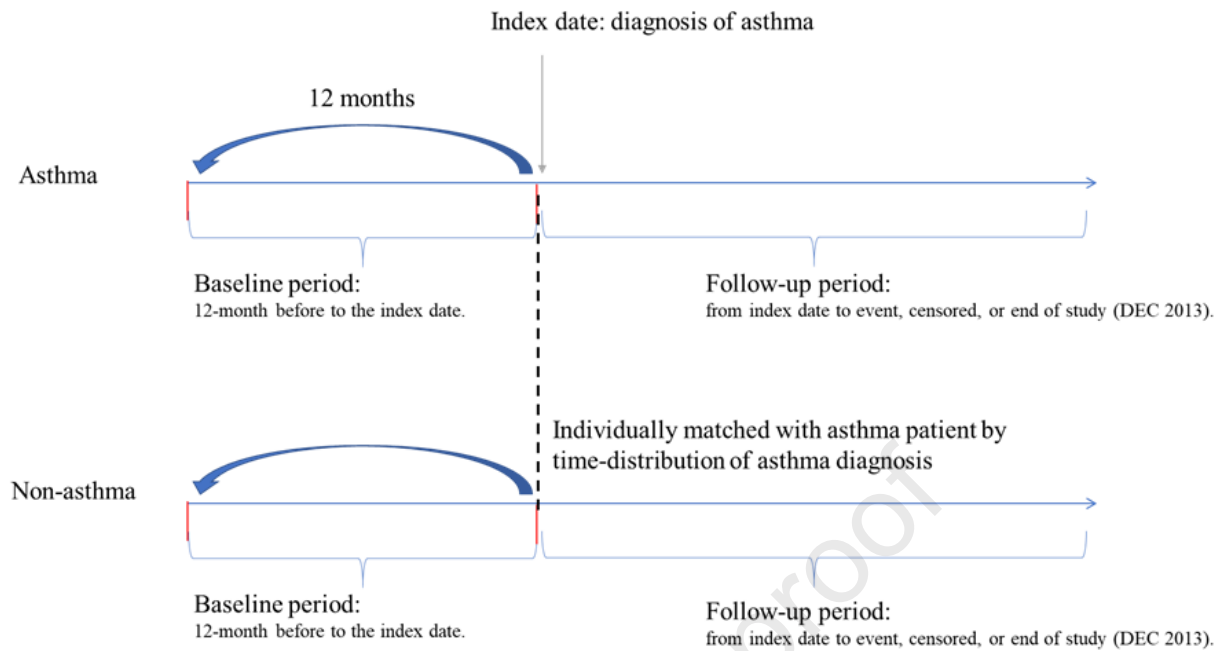
	Incidence rate (95% C.I.) of Hyperthyroidism		
Subgroups	Control	Asthma	aHR (95% C.I.)
Follow up time			
0-36 months	14.32(11.81-17.35)	22.99(19.76-26.74)	1.59(1.25-2.03)
>36 months	12.66(10.92-14.68)	14.29(12.45-16.39)	1.12(0.91-1.37)
p for interaction	0.0380		
Sex subgroups			
Male	5.43(4.23-6.98)	9.28(7.67-11.23)	1.69(1.24-2.32)
Female	21.20(18.54-24.25)	25.46(22.56-28.74)	1.20(1.00-1.43)
p for interaction	0.06		
Age at index date			
<30 years old	7.53(5.91-9.58)	7.53(5.93-9.57)	0.97(0.69-1.36)
30-44 years old	17.18(13.13-22.50)	25.27(20.35-31.37)	1.49(1.05-2.11)
45-64 years old	20.57(17.01-24.89)	27.38(23.28-32.20)	1.33(1.04-1.71)
>=65 years old	11.48(8.67-15.19)	17.24(13.71-21.68)	1.52(1.06-2.18)
p for interaction	0.31		
Amount^a (times)			
0	12.83 (10.97-15.00)	12.94 (9.45-17.70)	0.98 (0.69-1.39)
1-2	12.39 (9.56-16.07)	18.08 (15.01-21.78)	1.46 (1.06-2.01)
≥3	13.52 (10.5-17.42)	17.37 (15.21-19.83)	1.16(0.87-1.55)
p for interaction	0.2175		
Excluding events^b			
Events within 6 months after index	12.89(11.41-14.57)	16.00(14.36-17.84)	1.238(1.050-1.460)
Events within 12 months after index	12.82(11.30-14.56)	15.78(14.10-17.67)	1.224(1.031-1.453)
Events within 18 months after index	12.83(11.25-14.63)	15.39(13.67-17.33)	1.199(1.003-1.433)

^a Times of visiting related medical departments (including General Medicine, Pediatrics, Otolaryngology, Thoracic Medicine or Endocrinology) 3 months before the index date.

^b In the three additional models, any incident hyperthyroidism events that respectively occurred within 6, 12 and 18 months were excluded to address potential reverse causation bias







- 1 **Figure E1.**
- 2 PTDM model description
- 3