

Increased stroke risk among adult asthmatic patients

Wei-Sheng Chung^{*,†}, Cheng-Li Lin^{‡,§}, Yung-Fu Chen[†], Feng-Ming Ho[¶], Wu-Huei Hsu^{**} and Chia-Hung Kao^{**,††}

^{*}Department of Internal Medicine, Taichung Hospital, Ministry of Health and Welfare, Taichung, Taiwan, [†]Department of Healthcare Administration, Central Taiwan University of Science and Technology, Taichung, Taiwan, [‡]Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan, [§]Department of Public Health, China Medical University, Taichung, Taiwan, [¶]Department of Internal Medicine, Taoyuan General Hospital, Ministry of Health and Welfare, Taoyuan, Taiwan, ^{**}Graduate Institute of Clinical Medical Science and School of Medicine, College of Medicine, China Medical University, Taichung, Taiwan, ^{††}Department of Nuclear Medicine and PET Center, China Medical University Hospital, Taichung, Taiwan

ABSTRACT

Background We conducted a nationwide population-based cohort study to investigate the effects of asthma on the risk of stroke development in an Asian population.

Materials and methods Newly diagnosed asthmatic patients aged ≥ 18 years were identified, and asthma-free controls were randomly selected from the general population and frequency matched according to age, sex and index year using records obtained from the National Health Insurance Research Database between 2000 and 2010. Both cohorts were followed up until the end of 2011 to measure the incidence of stroke. The risk of stroke was analysed using Cox proportional hazard regression models, including factors such as sex, age and comorbidities.

Results We followed the asthmatic patients for 104 697 person-years and followed the nonasthmatic people for 426 729 person-years. The incidence density rate of stroke increased in all of the groups of asthmatic patients compared with that of the controls when stratified according to sex, age and comorbidities. The hazard ratio (HR) of stroke was 1.37-fold greater for the asthmatic cohort, compared with that for the nonasthmatic cohort, after adjusting for sex, age and comorbidities. The adjusted HR of developing stroke substantially increased with older age and the increased frequency of asthmatic exacerbation and hospitalization. The patients receiving beta-2 agonists as a treatment exhibited a significantly greater risk of stroke compared with the patients receiving only inhaled corticosteroids, after adjusting for covariates.

Conclusion Asthma may be an independent risk factor for stroke, and its severity exhibits a dose response of stroke development.

Keywords Adult asthma, beta-2 agonists, population-based cohort study, stroke.

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- 1 The number of studies on the risk of stroke in asthmatic patients is scant.
- 2 Additional studies have reported that asthma is associated with prothrombotic factors and endothelial dysfunction in the development of atherothrombosis.

- 1 The hazard ratio (HR) of stroke was 1.38-fold greater for the asthmatic cohort, compared with that for the nonasthmatic cohort.
- 2 The adjusted HR of developing stroke substantially increased with older age and the increased frequency of asthmatic exacerbation and hospitalization.
- 3 The patients receiving beta-2 agonists as a treatment exhibited a significantly greater risk of stroke compared with the patients receiving only inhaled corticosteroids.

Introduction

Stroke is referred to as a cerebrovascular accident (CVA) and can be classified into ischaemic stroke and haemorrhagic stroke. The burden of stroke increased considerably based on the absolute number of ischaemic and haemorrhagic stroke events that occurred worldwide in the past decades [1]. Stroke causes death and impairs gross physical function. Stroke is the leading cause of adult disability and the third leading cause of death in Taiwan [2,3].

Asthma is a common chronic inflammatory disease of the airways, which is characterized by reversible airway obstruction and bronchospasm. An estimated 300 million people of all ages and all racial backgrounds suffer from asthma, which is increasingly affecting healthcare systems, families and patients worldwide [4]. The purpose of current asthma treatments, whether preventative or medicinal, is to control rather than cure the disease.

Inflammatory processes are crucial in the pathophysiology of atherosclerotic disease and hypertension [5–7]. In recent studies, elevated concentrations of thrombin

have been detected in the sputum of asthmatic patients [8,9]. Additional studies have reported that asthma is associated with prothrombotic factors and endothelial dysfunction in the development of atherothrombosis [10–12]. In addition, several epidemiological studies have reported that asthma is associated with the risk of pulmonary thromboembolism and cardiovascular diseases [13–15]. However, asthma is not generally considered as a risk factor for stroke, although asthmatic patients may exhibit an elevated concentration of coagulation factors [8,11]. Therefore, we investigated whether asthma increases the risk of stroke using a retrospective nationwide population-based cohort study.

Methods

Data source

A single-payer compulsory National Health Insurance (NHI) programme was implemented in Taiwan in 1995, covering nearly 99% of 23.74 million residents in Taiwan by the end of 2009 [16]. The National Health Research Institute (NHRI), Ministry of Health and Welfare, established and manages the National Health Insurance Research Database (NHIRD). To protect patient privacy, the NHRI had encrypted in advance all personal identification numbers into unique numbers before releasing the data files to users. With approval from the NHRI, we were able to use the scrambled patient identification to link files, including the registry of medical facilities, details of inpatient orders, ambulatory cares, dental services and prescriptions. In this study, we obtained a subdata set for one million people randomly selected from the entire

registered population. This subdata set is similar to the entire population in the distributions of sex, age and average payroll-related insurance payment. The disease criteria were defined according to the International Classifications of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). To ensure the accuracy of the claims data, the Bureau of National Health Insurance (BNHI) would invite experts to review claims on a random sample basis for every one hundred outpatient claims and of every fifteen inpatient claims. False claims or unnecessary treatment would result in severe penalty from BNHI. This study was exempted from full ethical review by China Medical University (IRB Permit Number: CMU-REC-101-012).

Sampled patients

Figure 1 shows the selection process of the participants in the two study cohorts. We enrolled patients who were 18 years of age and older with newly diagnosed asthma (ICD-9 code 493) based on claims data between 1 January 2000 and 31 December 2010. To ensure the accuracy of the asthma diagnosis, we selected patients who had received treatment involving inhaled corticosteroids, inhaled short-acting beta-2 agonists (SABA) or inhaled long-acting beta-2 agonists (LABA) as the asthmatic cohort. The date of diagnosis of asthma was defined as the index date for initiating follow-up person-years measurement. For each asthmatic patient, four reference individuals were selected from the people without a diagnosis of asthma as the nonasthmatic comparison cohort and were frequency matched according to sex, age (every 5-years span) and index year of diagnosed asthma. We excluded the patients with a history of stroke (ICD-9 codes 430–438) and those with incomplete age or sex information at the baseline. The baseline comorbidity history was determined for each patient; these comorbidities included atrial fibrillation (ICD-9 code 427.31), hypertension (ICD-9 codes 401–405), diabetes (ICD-9 code 250), hyperlipidemia (ICD-9 code 272), heart failure (ICD-9 code 428), alcoholism (ICD-9 codes 303, 305.0, A215 and V113), obesity (ICD-9 code 278), chronic obstructive pulmonary disease (COPD; ICD-9 codes 491, 492, 496), deep vein thrombosis (DVT; ICD-9 code 453.8) and coronary artery disease (CAD; ICD-9 codes 413, 414.0, 414.3, 414.8, 414.9).

Main outcome

The primary outcome was newly diagnosed stroke reported in hospitalization records, including haemorrhagic stroke (ICD-9 codes 430–432) and ischaemic stroke (ICD-9 codes 433–438). The follow-up person-years were determined by calculating the interval between the index date and the date on which any of the following occurred first: the date of stroke diagnosis, the date of withdrawal from the NHI programme, the date of death or 31 December 2011.

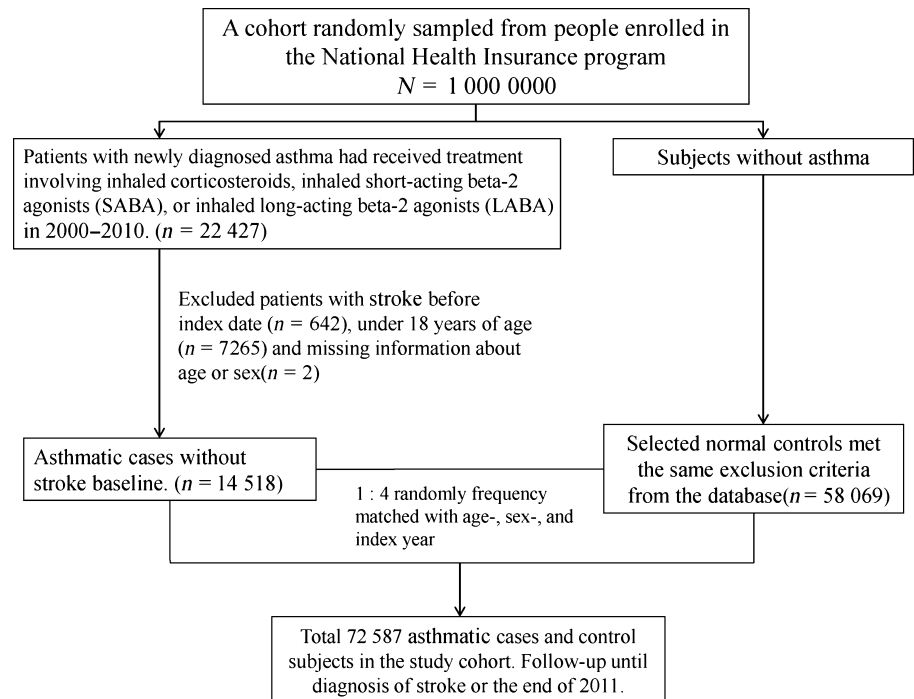


Figure 1 Shows the selection process of the participants in the 2 study cohorts.

Statistical analysis

The proportionate distributions of demographic status and comorbidity between the asthmatic and nonasthmatic cohorts were compared and examined using the chi-squared test. The mean ages and standard deviations (SDs) were measured and examined using a *t*-test. Similarly, the incidence density rates based on demographic variables and comorbidity were calculated for each cohort and the subgroups. Univariable and multivariable Cox proportional hazard regression models were used to estimate the hazard ratio (HR) and 95% confidence interval (CI) to assess the effects of asthma on the risk of stroke. The multivariable models were simultaneously adjusted for demographic characteristics and comorbidities. Further analysis was performed to assess the dose response of asthmatic exacerbation on the risk of stroke according to the number of emergency room (ER) visits and hospitalizations for asthma.

We divided the asthmatic cohort into three mutually exclusive groups, according to drug treatment status, as follows: (i) treatment with inhaled corticosteroids, (ii) treatment with inhaled SABA or LABA and (iii) both inhaled corticosteroids and inhaled SABA or LABA. To estimate the cumulative incidence of stroke risk in the asthmatic and nonasthmatic cohorts, we performed survival analysis using the Kaplan–Meier method, and significance was determined using the log-rank test. The entire matching procedure and all statistical analyses were performed using SAS 9.2 software (SAS Institute, Cary, NC, USA). A two-tailed *P*-value of < 0.05 was considered statistically significant.

Results

Demographic characteristics and comorbidity between the asthmatic patients and nonasthmatic controls

We analysed the data collected from a total of 58 069 people in the nonasthmatic cohort and 14 518 patients in the asthmatic cohort. The average follow-up duration was 7.21 years for the asthmatic cohort and 7.35 years for the nonasthmatic cohort. In the asthmatic cohort, 54.3% of the patients were female. The mean age of the study patients was 52.6 ± 17.6 years for the asthmatic cohort and 52.0 ± 17.6 years for the nonasthmatic cohort. Compared with those of the nonasthmatic cohort, the comorbidities of atrial fibrillation (0.97% vs. 0.43%), hypertension (38.1% vs. 26.9%), hyperlipidemia (20.4% vs. 15.1%), heart failure (4.90% vs. 1.33%), alcoholism (1.10% vs. 0.56%), obesity (1.60% vs. 0.82%), COPD (28.9% vs. 5.12%), DVT (0.14% vs. 0.11%) and CAD (21.1% vs. 11.9%) were more prevalent in the asthmatic cohort (Table 1).

Comparison of the incidence and hazard ratio of stroke stratified by sex, age and comorbidity between the asthmatic patients and nonasthmatic controls

The overall incidence of stroke was greater in the asthmatic cohort than in the nonasthmatic cohort (10.9 and 7.13 per 1000 person-years, crude HR = 1.53, 95% CI = 1.47–1.60), with an

Table 1 Demographic characteristics and comorbidity in patient with and without asthma

Variable	Asthma		P-value
	No N = 58 069 n (%)	Yes N = 14 518 n (%)	
Sex			
Female	31 504 (54.3)	7876 (54.3)	0.99
Male	26 565 (45.7)	6642 (45.7)	
Age, mean(SD) [†]	52.0 (17.6)	52.6 (17.6)	0.0002
Stratify age			
≤ 34	11 752 (20.2)	2938 (20.2)	0.99
35–49	14 128 (24.3)	3532 (24.3)	
50–64	15 464 (26.6)	3866 (26.6)	
65–74	10 384 (17.9)	2596 (17.9)	
75+	6341 (10.9)	1586 (10.9)	
Comorbidity			
Atrial fibrillation	251 (0.43)	141 (0.97)	< 0.0001
Hypertension	15 632 (26.9)	5531 (38.1)	< 0.0001
Hyperlipidemia	8787 (15.1)	2963 (20.4)	< 0.0001
Heart failure	771 (1.33)	712 (4.90)	< 0.0001
Alcoholism	324 (0.56)	159 (1.10)	< 0.0001
Obesity	476 (0.82)	232 (1.60)	< 0.0001
COPD	2972 (5.12)	4189 (28.9)	< 0.0001
DVT	61 (0.11)	20 (0.14)	0.29
CAD	6925 (11.9)	3062 (21.1)	< 0.0001

COPD denotes chronic obstructive pulmonary disease; DVT denotes deep vein thrombosis; CAD denotes coronary artery disease.

Chi-squared test; [†]two sample *t*-test.

adjusted HR of 1.37 (95% CI = 1.27–1.48) when adjusting for age, sex and comorbidities (Table 2). Furthermore, patients with asthma were 1.38-fold more likely to develop ischaemic stroke (95% CI = 1.27–1.49) and were 1.31-fold more likely to develop haemorrhagic stroke (95% CI = 1.09–1.65) than were the non-asthmatic controls after adjusting for age, sex and comorbidities. The stroke incidence was greater in men than in women in both cohorts. However, the adjusted HR of stroke for the asthmatic cohort compared with that of the nonasthmatic cohort was greater for women than for men. The stroke incidence increased with age in both cohorts. However, the age-specific asthma-to-nonasthma relative risk was the greatest for the oldest group aged 75+ years (adjusted HR = 1.48; 95% CI = 1.29–1.70). The

comorbidity-specific asthmatic-cohort-to-nonasthmatic-cohort adjusted HR of stroke was significant for patients both without comorbidity (adjusted HR = 1.37, 95% CI = 1.13–1.67) and with comorbidity (adjusted HR = 1.33, 95% CI = 1.23–1.43).

Hazard ratios of stroke associated with the number of annual asthmatic exacerbations

Compared with the nonasthmatic cohort, patients in the asthmatic cohort visiting the ER visits more than three times were associated with a significantly higher risk of stroke (adjusted HR = 3.05, 95% CI = 2.75–3.38) (Table 3). Furthermore, the risk of stroke increased as the number of hospitalizations for asthma increased. The patients who were admitted for asthma more than five times exhibited the highest risk of stroke with an adjusted HR of 60.8 (95% CI = 42.8–86.3).

Hazard ratios of stroke associated with asthma treatment

Table 4 shows the analysis of treatment associated with stroke risk among the asthmatic patients. Compared with asthmatic patients who received inhaled corticosteroid treatment, the patients who received inhaled SABA or LABA treatment had a significantly increased risk of stroke (adjusted HR = 1.93, 95% CI = 1.63–2.27), followed by those who had received both inhaled corticosteroids and inhaled SABA or LABA treatment (adjusted HR = 1.33, 95% CI = 1.13–1.56).

Comparing the probabilities of stroke between the asthmatic and nonasthmatic cohorts using Kaplan–Meier analysis

The Kaplan–Meier analysis revealed that the risk of stroke increased during the follow-up period in both cohorts, and the cumulative incidences of stroke were significantly higher in the asthmatic cohort than in the nonasthmatic cohort (log-rank $P < 0.0001$) (Fig. 2).

Discussion

This is the first study to investigate whether asthma increases the risk of developing stroke by applying a longitudinal population-based cohort study to an Asian population. This study demonstrated that asthmatic patients exhibit a 1.38-fold greater risk of stroke development than that of the general population, after adjusting for age, sex and comorbidities. Onufrak *et al.* [15] demonstrated that women with adult-onset asthma experienced a twofold increase in the risk of stroke in four communities in the United States. Iribarren *et al.* [17] indicated that asthma is associated with a 1.2-fold hazard of cerebrovascular disease for adults in Northern Carolina. These two studies reported the stroke risk exhibited by asthmatic patients in local communities in the United States.

Table 2 Comparison of incidence and hazard ratios of stroke stratified by sex and age between asthmatic patients and nonasthmatic people

Variables	Asthma		Rate	Yes		Rate	Crude HR (95% CI)	Adjusted HR (95% CI)
	No	PY		Event	PY			
All [†]	3044	42 6729	7.13	1140	10 4697	10.9	1.53 (1.47, 1.60)***	1.37 (1.27, 1.48)***
Ischaemic stroke [†]	2614		6.13	992		9.47	1.55 (1.48, 1.62)***	1.38 (1.27, 1.49)***
Haemorrhagic stroke [†]	430		1.01	148		1.41	1.40 (1.33, 1.48)***	1.34 (1.09, 1.65)**
Sex [‡]								
Female	1280	235 309	5.44	513	58 037	8.84	1.62 (1.53, 1.73)***	1.42 (1.27, 1.58)***
Male	1764	191 420	9.22	627	46 660	13.4	1.46 (1.37, 1.55)***	1.33 (1.20, 1.48)***
Stratify age [§]								
≤ 34	24	86 610	0.28	10	22 243	0.45	1.62 (1.43, 1.85)***	1.33 (0.62, 2.88)
35–49	175	109 347	1.60	71	27 676	2.57	1.60 (1.45, 1.78)***	1.27 (0.95, 1.71)
50–64	702	117 486	5.98	299	28 600	10.5	1.75 (1.61, 1.90)***	1.44 (1.24, 1.68)***
65–74	1245	76 275	16.3	419	17 767	23.6	1.44 (1.31, 1.59)***	1.25 (1.10, 1.41)***
75+	898	37 010	24.3	341	8410	40.6	1.67 (1.49, 1.87)***	1.48 (1.29, 1.70)***
Comorbidity								
No	843	279 454	3.02	116	46 427	2.50	0.83 (0.68, 1.00)	1.37 (1.13, 1.67)***
Yes	2201	147 274	14.9	1024	58 270	17.6	1.18 (1.09, 1.27)***	1.33 (1.23, 1.43)***

PY, person-years; rate, incidence rate, per 1000 person-years; Crude HR, relative hazard ratio; Comorbidity: only to have one of comorbidities (including atrial fibrillation, hypertension, hyperlipidemia, heart failure, alcoholism, obesity, chronic obstructive pulmonary disease, deep vein thrombosis and coronary artery disease) classified as the comorbidity group.

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

[†]Adjusted HR was calculated by Cox proportional hazard regression and adjusted for age, sex and comorbidities of atrial fibrillation, hypertension, hyperlipidemia, heart failure, alcoholism, obesity, chronic obstructive pulmonary disease, deep vein thrombosis and coronary artery disease.

[‡]Adjusted HR was calculated by Cox proportional hazard regression stratified by sex and adjusted for age, and comorbidities of atrial fibrillation, hypertension, hyperlipidemia, heart failure, alcoholism, obesity, chronic obstructive pulmonary disease, deep vein thrombosis and coronary artery disease.

[§]Adjusted HR was calculated by Cox proportional hazard regression stratified by age and adjusted for sex, and comorbidities of atrial fibrillation, hypertension, hyperlipidemia, heart failure, alcoholism, obesity, chronic obstructive pulmonary disease, deep vein thrombosis and coronary artery disease.

^{||}Adjusted HR was calculated by Cox proportional hazard regression stratified by comorbidity and adjusted for age and sex.

Although the asthmatic patients in this study presented a higher prevalence of comorbidities and coexisting conditions associated with the development of stroke than did the comparison cohort, asthma remained an independent risk factor for developing stroke after adjusting for covariates.

The mechanisms underlying the epidemiologic association between asthma and stroke remain unclear. A possible theory is that chronic airway inflammation may contribute to systemic inflammation and to the vulnerability to vascular disease [18,19]. Allergens are responsible for an inflammatory response in the lungs of asthmatic patients, in whom the response is aggravated by the proinflammatory effects of platelets and decreased cytoprotective effects [11]. Coagulation is activated in the airways of asthmatic patients by the leaking of clotting and tissue factors. Fibrin deposition is further facilitated by

decreased activity of the anticoagulant protein C and the inhibition of fibrinolysis [11]. In addition to chronic inflammation, other contributing thrombovascular risk factors and effects of asthma medications may also play vital roles in stroke development. Vijayakumar *et al.* [20] indicated that asthma is associated with increased arterial inflammation. Furthermore, Onufrak *et al.* reported that adult-onset asthma is associated with an increased risk of carotid atherosclerosis and stroke among women [12,15].

In this study, more than half of the patients in the asthmatic cohort were women. The finding of this study is consistent with that described in a previous report, indicating that women have a higher prevalence rate than that of men [21]. Onufrak *et al.* [15] indicated that adult-onset asthma may be a significant risk factor for stroke in women, but not in men. However, the

Table 3 Hazard ratios and 95% confidence intervals of stroke risk associated with the number of annual asthmatic exacerbation

	No. of Event	Crude HR (95% CI)	Adjusted HR (95% CI)
Nonasthma	3044	1 (Reference)	1 (Reference)
Times of emergency room visit			
≤ 3	668	1.05 (0.96, 1.14)	1.00 (0.92, 1.09)
> 3	472	4.34 (3.94, 4.78)***	3.05 (2.75, 3.38)***
<i>P</i> for trend		< 0.0001	< 0.0001
Times of hospitalization			
≤ 2	1058	1.42 (1.32, 1.52)***	1.28 (1.19, 1.39)***
3–4	48	50.2 (37.7, 66.9)***	18.9 (14.1, 25.4)***
≥ 5	34	220.3 (155.5, 312.0)***	60.8 (42.8, 86.3)***
<i>P</i> for trend		< 0.0001	< 0.0001
Times of hospitalization or emergency room visit			
≤ 2	562	0.96 (0.88, 1.05)	0.92 (0.84, 1.02)
3–5	153	1.90 (1.62, 2.24)***	1.67 (1.41, 1.97)***
≥ 6	425	5.33 (4.82, 5.90)***	3.65 (3.27, 4.06)***
<i>P</i> for trend		< 0.0001	< 0.0001

Crude HR, relative hazard ratio; Adjusted HR: multivariable analysis including age, sex and comorbidities of atrial fibrillation, hypertension, hyperlipidemia, heart failure, alcoholism, obesity chronic obstructive pulmonary disease, deep vein thrombosis and coronary artery disease.

P* < 0.05, *P* < 0.01, ****P* < 0.001.

Table 4 Cox proportional hazard regression analysis measured hazard ratio of stroke among asthma patients by treatment

Variables	Event	PY	Rate	Crude HR (95% CI)	Adjusted HR (95% CI)
Asthma					
Inhaled corticosteroids	221	37 356	5.92	1 (Reference)	1 (Reference)
Inhaled SABA or LABA	474	23 250	20.4	3.44 (2.94, 4.04)***	1.93 (1.63, 2.27)***
Both	445	44 091	10.1	1.71 (1.46, 2.01)***	1.33 (1.13, 1.56)***

PY, person-years; Rate, incidence rate, per 1000 person-years; Crude HR, relative hazard ratio; Adjusted HR: multivariable analysis including age, sex and comorbidities of atrial fibrillation, hypertension, hyperlipidemia, heart failure, alcoholism obesity, chronic obstructive pulmonary disease, deep vein thrombosis and coronary artery disease.

P* < 0.05, *P* < 0.01, ****P* < 0.001.

current study demonstrated that the asthmatic patients exhibited a significantly higher risk of stroke than that of the comparison cohort in patients of both sexes, after adjusting for covariates. A possible reason for the stroke risk differences among asthmatic patients between Western countries and Taiwan may be related to racial differences [22].

The stroke incidence increased with age in both cohorts. The age-specific crude relative risk indicated that stroke risk was significantly higher in the asthmatic cohort than in the nonasthmatic cohort. However, the risk of stroke was significantly higher in the asthmatic cohort than in the

nonasthmatic cohort for those aged 50 years or older, after adjusting for sex and comorbidities. As people age, activity levels decrease and cardiopulmonary systems deteriorate. Previous studies have reported that cerebral blood flow decreases during normal ageing [23,24]. Asthma may exacerbate cerebral vascular thrombosis and increase the vulnerability of the cerebral vessels, thereby contributing to stroke risk in elderly patients. The asthmatic patients exhibited an increased adjusted HR of stroke compared with the comparison cohort, irrespective of whether they had any comorbidity.

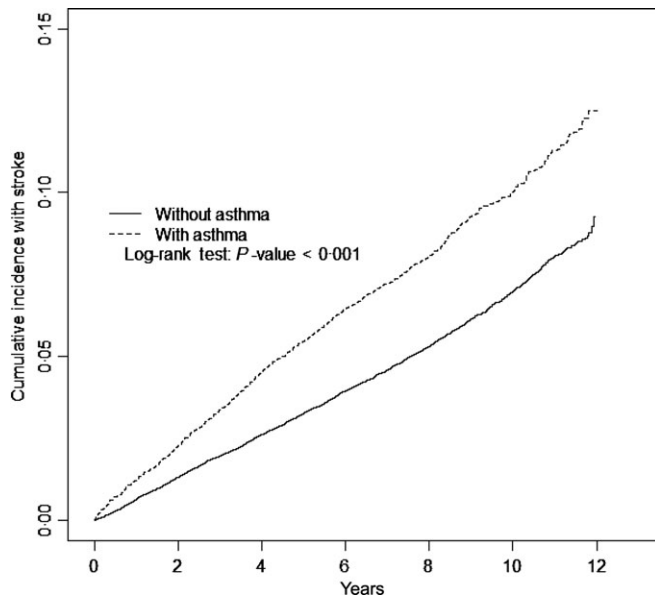


Figure 2 Comparing probabilities of stroke between asthmatic and nonasthmatic cohorts using Kaplan–Meier analysis.

The Global Initiative for Asthma recommended that asthma care be based on the clinical control status of uncontrolled, partly controlled and adequately controlled, instead of asthma severity [25]. No study has investigated the relationship between the number of asthmatic exacerbations and hospitalizations and the risk of stroke development. The present study demonstrated that the risk of developing stroke increased when the number of asthmatic exacerbations required for emergency room visits was > 3 times a year, and when the number of hospitalizations increased. This result suggests that poor control is a critical factor for stroke in asthmatic patients. The mechanism by which the number of asthmatic exacerbations, emergency room visits and hospitalizations may predispose stroke seems complex. Inflammation may alter the balance between procoagulant and fibrinolytic activities because inflammation and coagulation stimulate each other [26]. Moreover, the relationship between the number of asthmatic exacerbations necessary for hospitalization and the risk of stroke development exhibited a dose–response effect.

Considering the effect of asthma treatment on the risk of stroke development, the patients receiving SABA or LABA exhibited a significantly higher risk of stroke compared with the patients receiving only inhaled corticosteroids, after adjusting for covariates. Although beta-2 agonists are typically inhaled with low systemic absorption, increased plasma levels have been reported [27]. Beta-2 agonists are considered as a

significant risk factor for incident atrial fibrillation [28–30]. Subclinical atrial tachyarrhythmias were associated with a significantly increased risk of ischaemic stroke [31].

The strength of this study is that it provides a nationwide population-based longitudinal cohort study on the risk of stroke development in people with asthma. These findings can be generalized to the general population. However, several limitations must be considered when interpreting these findings. The NHIRD does not provide detailed lifestyle information, such as smoking, body mass index, physical activity levels, socioeconomic status and family history, which are all potential confounding factors for this study. Second, the study cases were physician-diagnosed asthmatic patients, thus potentially causing a misclassification bias despite the ability of the auditing mechanism of the Bureau of National Health Insurance to facilitate the minimization of diagnostic uncertainty and misclassification. The lack of drug data, such as those on hormone replacement therapy and the use of contraceptive, anticoagulant, and antiplatelet drugs, may also have influenced the primary outcomes of this study.

This nationwide study of 14 518 asthmatic patients with 104 697 person-year follow-ups indicates that asthmatic patients have a 38% increased risk of developing stroke compared with the general population. These findings emphasize the importance of clinician awareness of potential stroke development among asthmatic patients.

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Authors' contributions

All authors have contributed significantly, and that all authors are in agreement with the content of the manuscript: Wei-Sheng Chung and Chia-Hung Kao contributed in conception/design; Chia-Hung Kao contributed in provision of study materials; All authors contributed in collection and/or assembly of data; Wei-Sheng Chung, Cheng-Li Lin and Chia-Hung Kao performed data analysis and interpretation; All authors wrote the manuscript; All authors contributed in final approval of the manuscript.

Disclosure statement

All authors report no conflict of interests.

Address

Department of Internal Medicine, Taichung Hospital, Ministry of Health and Welfare, 400, Taichung, Taiwan (W. S. Chung); Department of Healthcare Administration, Central Taiwan University of Science and Technology, 400, Taichung, Taiwan (W. S. Chung, Y. F. Chen);

Management Office for Health Data, China Medical University Hospital, 400, Taichung, Taiwan (C. L. Lin);

Department of Public Health, China Medical University, 400, Taichung, Taiwan (C. L. Lin);

Department of Internal Medicine, Taoyuan General Hospital, Ministry of Health and Welfare, 330, Taoyuan, Taiwan (F. M. Ho); Graduate Institute of Clinical Medical Science and School of Medicine, College of Medicine, China Medical University, 400, Taichung, Taiwan (W. H. Hsu, C. H. Kao);

Department of Nuclear Medicine and PET Center, China Medical University Hospital, 400, Taichung, Taiwan (C. H. Kao).

Correspondence to: Chia-Hung Kao, MD, Graduate Institute of Clinical Medical Science and School of Medicine, College of Medicine, China Medical University, No. 2, Yuh-Der Road, Taichung 404, Taiwan. Tel.: +886 4 22052121x7412; fax: +886 4 22336174; e-mail: d10040@mail.cmuh.org.tw

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