



Original Article

Adult asthmatics increase the risk of acute coronary syndrome: A nationwide population-based cohort study[☆]



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ABSTRACT

Objectives: Few studies have examined the risk of acute coronary syndrome (ACS) in asthmatics. We investigate the effects of asthma on the risk of ACS development in an Asian population.

Methods: Asthma patients aged ≥ 18 years were identified, and asthma-free controls were randomly selected from the general population and frequency-matched according to age, sex, index year, and baseline comorbidity by using the National Health Insurance Research Database. Both cohorts were followed up until the end of 2011 to measure the incidence of ACS. The risk of ACS was analyzed using Cox proportional hazards regression models. **Results:** We observed the asthmatic patients for 97,506 person-years and followed the nonasthmatic people for 193,423 person-years. The incidence density rate of ACS increased in all groups of the asthmatic patients compared with those of the controls when the data were stratified according to sex, age, and comorbidities. The hazard ratio (HR) of ACS was 1.66-fold greater in the asthmatic cohort than in the nonasthmatic cohort, after adjusting for sex, age, and comorbidities (95% confidence interval [CI]: 1.31–2.11). The adjusted HR of developing ACS increased substantially as age and the frequency of asthmatic exacerbation and hospitalization increased.

Conclusions: Asthma is an independent risk factor of ACS, and poor control of asthma increases the risk of ACS development in a dose-dependent manner.

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What is already known about this subject?

Few studies have examined the risk of acute coronary syndrome (ACS) in asthmatics. Systemic inflammation associated with acute exacerbation in addition to the presence of shared risk factors.

What does this study add?

We investigate the effects of asthma on the risk of ACS development in an Asian population. Asthma is an independent risk factor of ACS, and poor control of asthma increases the risk of ACS development in a dose-dependent manner.

1. Introduction

Acute coronary syndrome (ACS) represents a group of symptoms attributed to sudden reductions in blood flow in the coronary arteries. This syndrome, which includes unstable angina and myocardial infarction with or without ST-segment elevation, is a life-threatening disorder that leads to high morbidity and mortality despite advances in treatment [1,2]. Hypertension, diabetes, and hyperlipidemia are well-established major cardiovascular risk factors of atherosclerosis progression, which contributes to the development of ACS [3,4]. Cerebrovascular diseases and cardiovascular diseases share similar risks in the disorders of the circulatory system [5]. Studies have recently reported that chronic obstructive pulmonary disease (COPD) associated

Abbreviations: ACS, Acute coronary syndrome; COPD, chronic obstructive pulmonary disease; NHIRD, National Health Insurance Research Database; NHI, National Health Insurance; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; SABAs, short-acting beta-2 agonists; LABAs, long-acting beta-2 agonists; HRs, hazard ratios; CIs, confidence intervals; ER, emergency-room.

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with reduced lung function is a strong risk factor for cardiovascular events, independent of smoking [6,7]. This can be explained by systemic inflammation associated with acute exacerbation in addition to the presence of shared risk factors [8].

Asthma is a common chronic inflammatory disease of the airway that is characterized by airway hyperresponsiveness to irritative stimuli and reversible airflow obstruction. Asthma can cause symptoms of recurrent episodes of wheezing, breathlessness, chest tightness, and coughing [9]. As many as 300 million people of all ages and racial backgrounds are currently estimated to have asthma, and the impact of which on health-care systems, families, and patients is increasing worldwide [9]. Current asthma treatments, whether preventative or medicinal, are intended to control rather than cure the disease.

Inflammatory processes are key participants in the pathophysiology of atherosclerotic disease and hypertension [10–12]. Studies have recently detected elevated concentrations of thrombin in the sputum of asthmatic patients [13,14]. Furthermore, studies have reported that asthma is connected with prothrombotic factors and endothelial dysfunction in the development of atherothrombosis [15–17]. However, few studies have examined the risk of ACS in asthmatics [18,19]. We conducted a Taiwan-wide population-based cohort study to investigate whether the asthmatic patients increase the risk of ACS development in an Asian population.

2. Methods

2.1. Data source

We conducted a nationwide retrospective cohort study based on data obtained from the universal Taiwan National Health Insurance Research Database (NHIRD), which contains health-care claims filed between 1996 and 2011. The National Health Insurance (NHI) program covers 99.9% of the 23.74 million people in the Taiwanese population [20]. The NHIRD contains registration data on the outpatient visits, hospital admissions, prescriptions, and disease status of all insureds. The data used in this study were derived from a subdataset of the NHIRD that comprises one million randomly sampled beneficiaries enrolled in the NHI program in 2011 and contains all records on these insureds from 1996 to 2011. In this study, secondary data were analyzed after deidentification; therefore, no informed consent was required. This study was approved by the Ethics Review Board of China Medical University (CMU-REC-101-012) and the Research Ethics Committee of the National Health Research Institutes, Taiwan.

2.2. Sampled patients

Patients aged 18 years and older with newly diagnosed asthma (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] Code 493) were identified based on the 2000–2010 claims dataset, and the date of diagnosis of asthma was defined as the index date. To ensure the accuracy of asthma diagnosis, we included patients treated with inhaled corticosteroids (ICSs), inhaled short-acting beta-2 agonists (SABAs), or inhaled long-acting beta-2 agonists (LABAs) in the asthmatic cohort. Patients with ACS (ICD-9 Codes 410–411.1) or chronic ischemic heart disease (ICD-9 Code 414) before the index date were excluded. Controls were selected among people without a history of asthma, ACS, or chronic ischemic heart disease recorded in the claims dataset. The people in the nonasthmatic cohort were randomly assigned index dates as in the case of the asthmatic cohort and were frequency-matched according to age (5-year strata), sex, baseline comorbidity history of hypertension (ICD-9 Codes 401–405), diabetes (ICD-9 Code 250), hyperlipidemia (ICD-9 Code 272), stroke (ICD-9 Codes 430–438), heart failure (ICD-9 Code 428), COPD (ICD-9 Codes 490–492, 494 and 496) and smoking (ICD-9 Code 305.1), and index year at an approximate ratio of 2:1.

2.3. Diagnosis of asthma

The diagnosis of asthma in this study is based on physicians. The physicians took a history of variable respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough. The physicians conducted physical examination and may arrange a pulmonary function test including bronchodilator test or twice-daily measurements of peak expiratory flow rate over two weeks. National Health Insurance Administration can audit the diagnosis and management codes by the physicians. Several Taiwan-based studies have demonstrated the high accuracy and validity of the diagnoses in cardiology and pulmonology used here [21,22].

2.4. Main outcome

To compare the incidence of ACS between the 2 cohorts, the participants were followed from the index date until the occurrence of ACS, record termination because of death or withdrawal from the insurance system, or the end of 2011.

2.5. Statistical analysis

The differences in the distributions of sex, age, and baseline comorbidities between the asthmatic and nonasthmatic cohorts were assessed using chi-square tests and *t* tests. The incidence for ACS (per 1000 person-years) was calculated in both cohorts. The univariable and multivariable Cox proportional hazards regression analyses were used to assess the ACS risk associated with asthma, and the hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated. The multivariable model was developed by controlling for age, sex, and comorbidities of hypertension, diabetes, hyperlipidemia, stroke, heart failure and COPD. We further analyzed the data to assess the effect of the dose response of asthmatic exacerbation on the risk of ACS according to the number of emergency-room (ER) visits and hospitalizations required for asthma. We divided the asthmatic cohort into 4 mutually exclusive groups according to the drug-treatment status: [1] treatment with ICS; [2] treatment with ICS and inhaled SABA; [3] treatment with ICS and inhaled LABA; and [4] treatment with any above medicine and oral or IV steroids. The Kaplan–Meier analysis was used to plot the cumulative incidence, and the log-rank test was used to examine the differences between the 2 cohorts. All analyses were performed using SAS 9.3 software (SAS Institute Inc., Cary, NC, USA) and the Kaplan–Meier survival curve was plotted using R software (R Foundation for Statistical Computing, Vienna, Austria). The significance level was set at $P < .05$ in 2-sided tests.

3. Results

3.1. Demographic characteristics and comorbidities of asthmatic and nonasthmatic cohorts

We analyzed 2000–2010 data on the 13,049 newly diagnosed asthmatic patients in the asthmatic cohort and 25,791 nonasthmatic people in the comparison cohort (Table 1). Both cohorts had similar sex and age distributions. The mean age ($\pm$ SD) was 50.9 ± 17.4 years in the asthmatic cohort and 50.5 ± 17.5 years in the nonasthmatic cohort. Comorbidities were also similar in the asthmatic cohort and in the nonasthmatic cohort, except heart failure and smoking.

3.2. Incidence and hazard ratios of acute coronary syndrome stratified according to sex, age, and comorbidity: comparison between the asthmatic cohort and the nonasthmatic cohort

The overall incidence of ACS was 1.66-fold greater in the asthmatic cohort than in the nonasthmatic cohort (1.30 vs 0.78 per 1000 person-years), with a crude HR of 1.66 (95% CI = 1.56–1.79) (Table 2). After

Table 1
Demographic characteristics and comorbidity between asthmatic patients and nonasthmatic cohort.

Variable	Asthma		P-value
	No N = 25,791	Yes N = 13,049	
Gender	n (%)	n (%)	0.98
Female	14,037 (54.4)	7104 (54.4)	
Male	11,754 (45.6)	5945 (45.6)	
Stratify age			0.81
≤34	5850 (22.7)	2931 (22.5)	
35–49	6823 (26.5)	3427 (26.3)	
50–64	6786 (26.3)	3426 (26.3)	
65–74	4025 (15.6)	2052 (15.7)	
75+	2307 (8.94)	1213 (9.30)	
Age, mean (SD) ^a	50.5 (17.5)	50.9 (17.4)	0.01
Comorbidity			
Hypertension	8348 (32.4)	4273 (32.8)	0.45
Diabetes	2971 (11.5)	1546 (11.9)	0.34
Hyperlipidemia	4263 (16.5)	2194 (16.8)	0.48
Stroke	2216 (8.59)	1179 (9.04)	0.14
Heart failure	560 (2.17)	392 (3.00)	<0.001
COPD	6929 (26.9)	3604 (27.6)	0.11
Smoking	519 (2.01)	557 (4.27)	<0.001

Chi-square test.

^a Two sample *t*-test.

adjusted for age, sex, and comorbidities of hypertension, diabetes, hyperlipidemia, stroke, heart failure, COPD and smoking, asthmatic patients compared to patients without asthmatic had a 1.66-fold risk of ACS (95% CI = 1.31–2.11). The incidence of ACS was greater in men than in women in both cohorts. The adjusted HRs of ACS were 1.79 (95% CI = 1.23–2.59) and 1.58 (95% CI = 1.16–2.14) in women and men, respectively. Comparing the asthmatic cohort with the nonasthmatic cohort showed that the adjusted HR of ACS were significant for all age groups, excluding the ≤49 year-old age group (adjusted HR = 1.67, 95% CI = 1.10–2.52, for the group aged 50–64 years; adjusted HR = 1.54, 95% CI = 1.02–2.34, for the group aged 65–74 years; and adjusted HR = 2.11, 95% CI = 1.26–3.52, for the elderly patients aged 75 years or more). The asthmatic patients with comorbidity were associated with significantly higher risk of ACS than the nonasthmatic patients were (adjusted HR = 1.68, 95% CI = 1.31–2.16).

Table 2
Comparison of incidence and hazard ratio of ACS stratified by sex, age and comorbidity between asthmatic patients and nonasthmatic cohort.

Variables	Asthma						Crude HR* (95% CI)	Adjusted HR† (95% CI)
	No	Yes		No	Yes			
	Event	PY	Rate#	Event	PY	Rate#		
All	151	193,423	0.78	127	97,506	1.30	1.67 (1.56, 1.79)***	1.66 (1.31, 2.11)***
Gender								
Female	59	106,550	0.55	53	53,995	0.98	1.77 (1.61, 1.95)***	1.79 (1.23, 2.59)**
Male	92	86,873	1.06	74	43,511	1.70	1.61 (1.45, 1.77)***	1.58 (1.16, 2.14)**
Stratify age								
≤49	20	96,427	0.21	15	49,271	0.30	1.47 (1.32, 1.64)***	1.46 (0.75, 2.87)
50–64	50	52,621	0.95	42	26,307	1.60	1.68 (1.48, 1.91)***	1.67 (1.10, 2.52)*
65–74	52	30,576	1.70	40	14,982	2.67	1.57 (1.33, 1.85)***	1.54 (1.02, 2.34)*
75+	29	13,800	2.10	30	6947	4.32	2.06 (1.67, 2.54)***	2.11 (1.26, 3.52)**
Comorbidity‡								
No	18	89,634	0.20	14	44,435	0.32	1.57 (1.40, 1.75)***	1.62 (0.80, 3.25)
Yes	133	103,789	1.28	113	53,071	2.13	1.66 (1.52, 1.82)***	1.68 (1.31, 2.16)***

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 hypertension, diabetes, hyperlipidemia, stroke, heart failure, COPD and smoking.

Comorbidity‡: Only to have one of comorbidities classified as the comorbidity group.

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

3.3. Relationship between the number of annual cases of asthma exacerbation and the risk of acute coronary syndrome development

The data in Table 3 show that asthmatic patients presenting with exacerbation who visited an ER more than 2 times per year exhibited a 3.25-fold increased risk of ACS development, after we adjusted for covariates (95% CI = 2.49–4.25), compared with the patients in the nonasthmatic cohort. The risk of ACS development increased from 1.59 (95% CI = 1.25–2.02) in patients presenting with 2 or fewer hospitalizations to 10.0 (95% CI = 4.65–21.7) in the case of those exhibiting 3 and more hospitalizations compared with those in the nonasthmatic cohort (trend test, *P* < .0001). The risk trends calculated for ER visits or hospitalizations and for ER visits were similar.

3.4. Relationship between asthmatic treatment and the risk of acute coronary syndrome development

Table 4 shows the results of an analysis of the ACS risk associated with treatments among the asthmatic patients. Compared with asthmatic patients who received ICS treatment, the patients who received ICS and inhaled SABA treatment did not exhibit significantly lower risk of ACS (adjusted HR = 0.43, 95% CI = 0.09–2.01). Compared with asthmatic patients who received ICS treatment, the patients who received any ICS, inhaled SABA, inhaled LABA, and oral or IV steroids treatment did not exhibit significantly higher risk of ACS (adjusted HR = 1.14, 95% CI = 0.28–4.65).

3.5. Cumulative incidence of acute coronary syndrome in asthmatic patients and nonasthmatic people

The Kaplan–Meier analysis showed that the cumulative incidence rate of ACS was higher in the asthmatic patients than in the nonasthmatic cohort (log-rank test: *P* < .001) (Fig. 1).

4. Discussion

This is the first study to investigate the effects of asthma on the risk of developing ACS in an Asian population; we conducted a Taiwan-wide population-based cohort investigation. Our study shows that, after we adjusted for age, sex, and comorbidities, compared with the general population, asthmatic patients exhibit a 1.66-fold greater risk of ACS development. Iribarren et al. indicated that asthma was associated

Table 3

Hazard ratios and 95% confidence intervals of ACS risk associated with the number of annual asthma exacerbation.

	ACS No. of event	Hazard ratio (95% CI)	
		Crude	Adjusted [†]
Non-asthma	151	1 (Reference)	1 (Reference)
Times of emergency room visit			
≤2	41	0.79 (0.56, 1.11) *	0.83 (0.59, 1.17) **
>2	86	3.61 (2.77, 4.71) ***	3.25 (2.49, 4.25) ***
P for trend		<0.0001	<0.0001
Times of admission			
≤2	120	1.59 (1.25, 2.01) ***	1.59 (1.25, 2.02) ***
>2	7	19.2 (8.95, 41.0) ***	10.0 (4.65, 21.7) ***
P for trend		<0.0001	<0.0001
Times of admission or emergency room visit			
≤3	52	0.87 (0.63, 1.19)	0.91 (0.66, 1.25)
4–5	20	2.43 (1.52, 3.87) ***	2.30 (1.44, 3.67) ***
≥6	55	7.01 (5.15, 9.54) ***	5.49 (4.02, 7.51) ***
P for trend		<0.0001	<0.0001

Crude HR*, relative hazard ratio.

Adjusted HR[†]: multivariable analysis including age, sex, and comorbidities of hypertension, diabetes, hyperlipidemia, stroke, heart failure, COPD and smoking.

*** P < 0.001.

with a 1.4-fold increase in the hazard of coronary heart disease in adults in Northern California, USA [19].

The mechanisms underlying the epidemiological association between asthma and ACS remain unclear. One theory is that chronic airway inflammation may contribute to systemic inflammation and to the vulnerability to vascular disease [23,24]. Allergens are responsible for eliciting an inflammatory response in the lungs of asthmatic patients, and this response is aggravated by the proinflammatory effects of platelets and by diminished cytoprotective effects. Coagulation is activated in the airways of asthmatic patients as a result of the leakage of clotting factors and tissue factors, and fibrin deposition is facilitated by a reduction in the activity of the anticoagulant protein C and an inhibition of fibrinolysis [17]. Moreover, several studies have been reported that inflammation is linked with elevated blood pressure [25–27]. In addition to chronic inflammation, other factors that contribute to thrombovascular risk and the effects of asthma medications may play vital roles in ACS development. Vijayakumar et al. indicated that asthma is associated with increased arterial inflammation [28].

More than half of the patients in our asthmatic cohort were women. This finding is consistent with a previous report indicating that the prevalence rate of asthma is higher in women than in men [29]. Our study showed that the risk of ACS for asthmatic patients was significantly higher than that for the comparison cohort in both sexes after

adjusting for covariates. The incidence of ACS increased with age in both cohorts. The age-specific crude relative risk of ACS was significantly higher in the asthmatic cohort than in the nonasthmatic cohort. However, after we adjusted for sex and comorbidities, the risk of ACS was significantly higher in the asthmatic cohort than in the nonasthmatic cohort among patients aged 50 years and older. Asthma may accentuate vascular atherosclerosis and thrombosis, which contribute to ACS risk in elderly people.

The Global Initiative for Asthma has recommended asthma care that is based on the clinical asthma-control statuses of uncontrolled, partly controlled, and good control, instead of asthma severity [9]. No study has investigated the relationship between the number of asthma exacerbation and hospital admission and the risk of ACS development. Our study showed that the risk of developing ACS increased as the number of asthma exacerbations that required >2 ER visits per year and the number of hospitalizations increased. This result suggests that poor control of asthma is a key factor that affects ACS development in asthmatic patients. The mechanism by which the number of asthma exacerbation, ER visits, and hospitalizations may predispose a patient to ACS seems complex. Inflammation may alter the balance between procoagulant and fibrinolytic activities because inflammation and coagulation stimulate each other [30]. In addition to inflammation, hypoxemia during asthma exacerbation may contribute to ACS development [31]. Furthermore, the relationship between the number of asthma exacerbation that required hospitalization and the risk of ACS development exhibited a dose-response effect.

The patients who received inhaled SABA or LABA added on ICS did not influence the risk of ACS than did those who received ICS alone. Although inhaled beta-2 agonists are typically absorbed at a low level systemically, increased plasma levels of the agonists have been reported in patients who used the medication [32]. Most of cardiac events reported after beta 2 agonist use were sinus tachycardia. Salpeter et al. indicated that the major cardiac events such as ventricular tachycardia, myocardial infarction and sudden cardiac arrest are not statistically associated with beta 2 agonist use compared to that of placebo use [33]. In addition, our results also did not find that oral or IV steroids significantly increased the risk of ACS compared than did those who received ICS alone.

The strength of this work is that it is a nationwide population-based longitudinal cohort study on the risk of subsequent ACS development in adults with asthma. However, several limitations must be considered when interpreting these findings. The NHIRD does not provide detailed

Table 4

Cox proportional hazards regression analysis measured hazard ratio of ACS among asthma patients by treatment.

Variables	Event	PY	Rate [#]	Crude HR* (95% CI)	Adjusted HR [†] (95% CI)
Asthma					
Only ICS	9	19,059	0.47	1 (Reference)	1 (Reference)
ICS + inhaled SABA	25	17,089	1.46	0.37 (0.08, 1.72)	0.43 (0.09, 2.01)
ICS + inhaled LABA	2	1579	1.27	1.16 (0.27, 4.88)	1.09 (0.26, 4.61)
Any above	91	59,779	1.52	1.20 (0.30, 4.88)	1.14 (0.28, 4.65)
medicine + oral or IV steroids					

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 hypertension, diabetes, hyperlipidemia, stroke, heart failure, COPD and smoking.

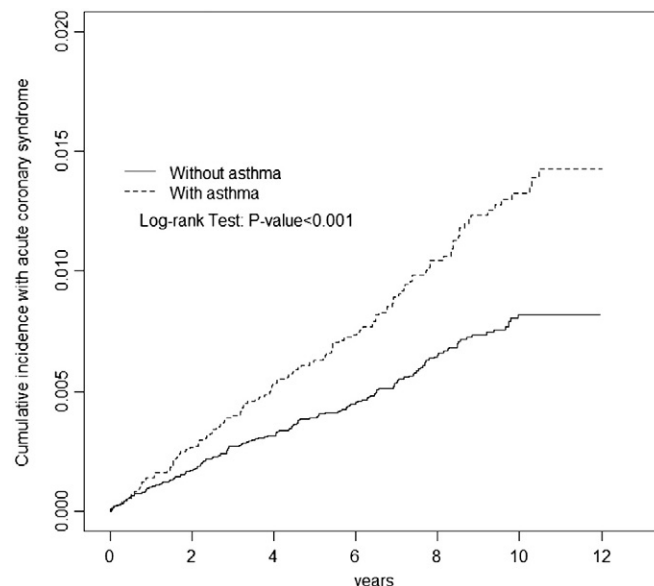


Fig. 1. Cumulative incidence of ACS for patients with and without asthma.

lifestyle information such as smoking habits, body mass index, physical activity levels, socioeconomic status, and family history, and all of which are potential confounding factors in this study. COPD and stroke are well-known comorbidities strongly correlated with smoking. We also used these comorbidities for adjustment to minimize the influence of smoking. Second, the study cases were selected according to ICD-9 codes, potentially causing a misclassification bias despite the ability of the auditing mechanism used by the National Health Insurance Administration to minimize diagnostic uncertainty and misclassification. Third, the age of the study participants enrolled was more than 18 years, and the selection bias of the general population may exist. In addition, the lack of drug-treatment data such as those on hormone-replacement therapy and the use of contraceptives, anticoagulants, and antiplatelet drugs may have influenced the primary outcomes of this study.

This nationwide study of 13,049 asthmatic patients with a follow-up of 97,506 person-years indicates that, compared with the comparison cohort, asthmatic patients exhibit a 66% increase in the risk of developing ACS. Moreover, we observed a dose-response relationship between the number of asthma exacerbation that necessitated hospitalization and the risk of ACS development. Thus, a multidisciplinary team should guide the assessment, treatment, and holistic care of asthmatic patients.

Conflict of interests

All authors report no conflicts of interest.

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