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Asthma Is Associated With a Subsequent Risk of Peripheral Artery Disease

A Longitudinal Population-Based Study

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Abstract: Asthma has been associated with the atherosclerosis risk, but not clear of peripheral artery disease (PAD). We attempted to examine the risk of PAD in patients with asthma.

From the insurance claims data of Taiwan, we identified 28,158 newly diagnosed asthma patients in 2000 to 2005 and 56,316 persons without asthma randomly selected into the comparison cohort, frequency matched by sex, age, and the date of diagnosis. Both cohorts were followed up until the end of 2011 to estimate the incident PAD. Adjusted hazard ratios (aHRs) of PAD were estimated using the Cox proportional hazards model after controlling for sex, age, and comorbidities.

The incidence of PAD was 1.46 times higher in the asthma cohort than in the comparison cohort, with an aHR of 1.34 [95% confidence interval (CI) = 1.24–1.45]. Incidence of PAD was higher in men, the aged, and those with comorbidities in both cohorts. The aHRs of PAD remained significant for the asthma cohort in all subgroups of sex, age, and the presence of comorbidity. The aHRs of PAD were 14.1 (95% CI = 8.18–24.5) in asthma patients with multiple emergency visits and 22.3 (95% CI = 15.6–31.9) for those with multiple hospitalizations.

Although smoking is a potential confounding factor, this study suggests patients with asthma have a significantly higher risk of developing PAD than the general population. The results also support the notion that poor control of asthma status is a key factor in subsequent PAD development.

(*Medicine* 95(3):e2546)

Abbreviations: ABI = ankle brachial index, ACS = acute coronary syndrome, CAD = coronary artery disease, CI = confidence interval, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, HR = hazard ratio, ICD-9-CM = International Classification of Disease, 9th Revision, Clinical Modification, IRR = incidence rate ratio, NHI = National Health Insurance, NHRI = National Health Research Institutes, PAD = peripheral artery disease.

INTRODUCTION

Characterized by atherosclerotic occlusion of the extremities, patients with peripheral artery disease (PAD) are at higher risk of cardiovascular complications and mortality.[1–3] Prevalence of PAD has been reported to be in the range of 3% to 10% in general populations, or of 15% to 20% in the elderly.[2,3] The most typical symptom of PAD is intermittent claudication, a crampy pain occurring during exercise, particularly from a long distance walk. The blocked arteries reduce blood flow in the limbs and cause pain. It is well known that inflammation plays a critical role in the association with the pathogenesis of atherosclerosis, increasing risks of coronary artery disease (CAD), PAD, and stroke.[4–6] Therefore, chronic inflammatory airway diseases, most notably chronic obstructive pulmonary disease (COPD), have been strongly associated with cardiovascular diseases.[7,8]

Asthma is another common chronic inflammatory airway disease affecting 1% to 18% of the population among countries.[9] Asthma patients have the evidence of variable airflow limitation, in addition to the characteristic symptoms of breath shortness. Enhanced atherosclerosis has been demonstrated among patients with asthma in previous studies.[10,11] The Atherosclerosis Risk in Communities Study has shown that the carotid artery intima-media thickness is significantly increased for women with adult-onset asthma.[11] Several studies have shown an association between asthma and atherosclerotic diseases, such as CAD, stroke, and heart failure.[12,13] A recent nationwide population-based cohort study in Taiwan also demonstrated asthma an independent risk factor for acute coronary syndrome (ACS).[14] A recent multicase-control study showed asthmatic patients with

Editor: Dai Yamanouchi.
Received: September 2, 2015; revised: November 30, 2015; accepted: December 21, 2015.
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Manuscript writing: CWY, TCS, CRL, YCW, CLL, FCS.
Manuscript revision: TCS, FCS.
Final approval of manuscript: all authors.
T-CS and F-CS contributed equally to this work.
The authors have no conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000002546

rhinitis were at higher risk of intermittent claudication, but not significant.[15] However, the association between asthma and PAD has been less investigated.

The National Health Insurance (NHI) database of Taiwan is a nationwide chornological dataset, which provides reliable data and has been used for various studies on either asthma or PAD.[16–18] In the present study, we aimed to determine whether asthma is associated with a subsequent development of PAD. To the best of our knowledge, this is the first longitudinal population-based study to investigate the risk of developing PAD for patients with asthma.

METHODS

Data Source

Established in 1996, the NHI has provided health care coverage for more than 99% of the 23.72 million population of Taiwan since 1998. The National Health Research Institutes (NHRI) is responsible to maintain the claims data and to establish data files for research. Patient identifications are scrambled before releasing the data to users in order to protect the privacy of insured people. We obtained a representative subset of Longitudinal Health Insurance Database 2000, consisting of claims data from 1996 to 2011 for one million randomly selected people. Information on demographics, dates of clinical visits, diagnostic codes, prescriptions, and treatment procedures including surgeries were available in the claims data. Diseases are coded using the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM). This study was exempted from full ethical review by the research ethical committee at China Medical University and Hospital (IRB permit number: CMUH-104-REC2-115). Patient records/information in the database was anonymized and deidentified prior to analysis.

Study Participants

We identified a cohort of patients newly diagnosed with asthma (ICD-9-CM code: 493) between January 1, 2000 and December 31, 2005. Subjects who had at least 1 hospitalization or at least 3 visits for outpatient medical services for asthma were eligible for inclusion in the asthma cohort. The date of the initial diagnosis was defined as the index date. Patients with a history of PAD (ICD-9-CM code: 443.81, 443.9, 440.2, 444.2, and 444.89), and aged under 20 years, or those with missing age or sex information were excluded. For each asthma case identified, 2 insured participants adhering to the same inclusion criteria were randomly selected into the comparison cohort. The subjects were frequency matched by age (within 5 years), sex, and index year to reduce the confounding effects of age and sex and to reduce measurement bias of follow-up.

Outcome and Relevant Variables

All study subjects were followed from the index date to the date when PAD was diagnosed, the date of withdrawal from the NHI program, or the end of 2011, whichever came first. PAD-related blockages in the arteries may reduce blood flow to the legs and lead to low blood pressures in the ankles. The leg pressure to arm pressure ratio (ankle blood pressure divided by arm blood pressure) is called ankle brachial index (ABI). Clinically, the patient was diagnosed with PAD if the ABI is ≤ 0.9.[19,20] The baseline comorbidities considered for adjustment in this study included hypertension (ICD-9-CM code 401-405), hyperlipidemia (ICD-9-CM code 272), diabetes (ICD-9-CM code 250), stroke (ICD-9-CM code 430-438), CAD (ICD-9-CM code 410-413, 414.01-414.05, 414.8, and 414.9), and chronic kidney disease (CKD) (ICD-9-CM code 585).

Statistical Analysis

The distributions of demographic status and comorbidities between the asthma and comparison cohorts were compared and examined using the χ^2 test. The mean ages were measured and examined using the Student t test. We calculated the incidence density rates of PAD for the 2 cohorts by sex, age, and comorbidity and used Poisson regression model to measure the asthma cohort to comparison cohort incidence rate ratio (IRR). With valid proportional hazard assumption (P value = 0.1072), multivariable Cox proportional-hazards regression model was used to calculate the adjusted hazard ratios (aHRs) and the 95% confidence intervals (CIs) of PAD associated with asthma. We used the Kaplan–Meier method to estimate the cumulative incidence rates of PAD in both cohorts and compared them with the log-rank test.

We also used the Cox model to estimate the aHRs of PAD associated with annual numbers of emergency visits and hospitalizations for asthma exacerbations, compared with the comparison cohort. In addition, we assessed the trend of PAD duration the follow-up period using time-dependent covariates (<1, 1–3, 3–5, 5–7, and ≥ 7 years) as the sensitivity analysis.

The data management procedure and statistical analyses were performed using SAS 9.3 statistical package (SAS Institute, Cary, NC), with P value <0.05 in 2-tailed tests considered significant. The Kaplan–Meier estimates and the log-rank test were performed using the R software (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

We identified 28,158 asthma patients between 2000 and 2005 as the asthma cohort and 56,316 nonasthma subjects as the comparison cohort. In both cohorts, 53.7% were woman and 40.4% were aged between 20 and 49 years (Table 1). The mean age of subjects in the asthma cohort was slightly higher than that in the comparison cohort [54.7 ($\pm$17.7) vs. 54.4 ($\pm$17.8) years, $P < 0.01$]. Subjects in the asthma cohort tended to have higher prevalence rates of hypertension, hyperlipidemia, diabetes, stroke, and CAD than those in the comparison cohort. Figure 1 shows that the cumulative PAD incidence was significantly higher in the asthma cohort than in the comparison cohort (log-rank test, $P < 0.001$).

The incidence of PAD in the asthma cohort was 1.46 times higher than that in the comparison cohort (4.45 vs. 3.06 per 1000 person-years), with an aHR of 1.34 (95% CI = 1.24–1.45) (Table 2). The sex-specific asthma cohort to comparison cohort aHRs of PAD were statistically significant for both women (aHR: 1.31, 95% CI = 1.17–1.47) and men (aHR: 1.38, 95% CI = 1.23–1.55). The age-specific incidence of PAD increased with age in both cohorts, the highest being in the elderly asthma patients (9.35 per 1000 person-years). However, the age-specific asthma cohort to comparison cohort aHR of PAD was the highest for those 20 to 49 years of age (1.47, 95% CI = 1.14–1.88). The corresponding aHR for the elderly was 1.28 (95% CI = 1.16–1.43). Subjects with comorbidity were at much higher risk of PAD than those without comorbidity. However, the asthma cohort to comparison cohort aHRs of PAD were 1.40 (95% CI = 1.14–1.71) for patients without comorbidity and 1.33 (95% CI = 1.22–1.46) for those with comorbidity. In the comorbidity-specific stratified analysis, similar patterns appeared in associations with hypertension, diabetes, and stroke.

TABLE 1. Comparisons in Demographic Characteristics and Comorbidities in Patients With and Without Asthma

	Asthma				
	No		Yes		
	N = 56,316		N = 28,158		*P* Value
	n	%	n	%	
Sex*					0.98
Women	30,230	53.7	15,115	53.7	
Men	26,086	46.3	13,043	46.3	
Age, yr*					0.98
20–49	22,772	40.4	11,386	40.4	
50–64	14,774	26.2	7387	26.2	
≥65	18,770	33.3	9385	33.3	
Mean (SD)†	54.4	(17.8)	54.7	(17.7)	0.01
Comorbidity*					
Hypertension	17,967	31.9	12,026	42.7	<0.0001
Hyperlipidemia	9460	16.8	6220	22.1	<0.0001
Diabetes	7671	13.6	4736	16.8	<0.0001
Stroke	8705	15.5	5929	21.1	<0.0001
CAD	5526	9.81	4353	15.5	<0.0001
CKD	202	0.36	92	0.33	0.46

CAD = coronary artery disease, CKD = chronic kidney disease.
* χ^2 test.
† Student *t* test.

Table 3 shows the interaction between asthma and age. Compared with the youngest group aged 20 to 49 years, the aHR of PAD increased with age to 6.80 (95% CI = 5.55–8.34) for ≥65-year group. Compared with those without asthma and comorbidity, the aHR showed that asthma and comorbidity had joint effect in developing PAD with an aHR of 3.86 (95% CI = 3.37–4.42). The comorbidity-specific analysis showed that comorbidity with joint effect included hypertension (aHR: 2.92, 95% CI = 2.59–3.28), hyperlipidemia (aHR: 2.87, 95% CI = 2.56–3.22), diabetes (aHR: 3.21, 95% CI = 2.84–3.63), stroke (aHR: 2.34, 95% CI = 2.07–2.64), and CAD (aHR: 2.39, 95% CI = 2.10–2.72).

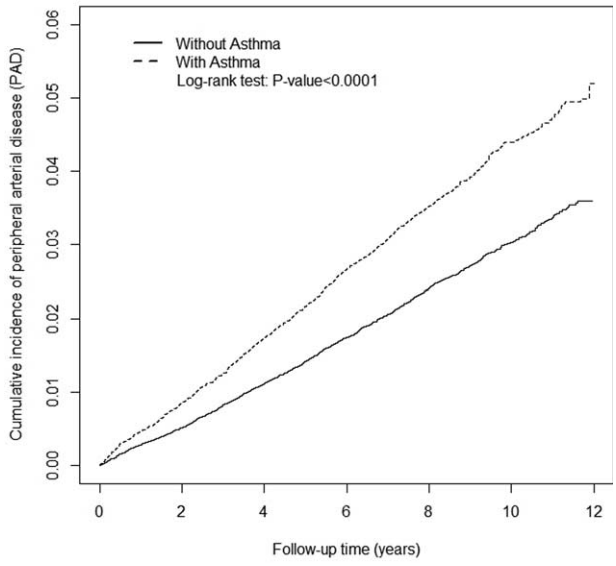

FIGURE 1. Cumulative incidence of peripheral artery disease for patients with (dashed line) and without (solid line) asthma.

Table 4 shows associations between PAD and annual number of emergency visits, hospitalizations, and summation of both for asthma exacerbations, compared with the comparison cohort. The aHRs increased to 14.1 (95% CI = 8.18–24.5) for asthma patients with ≥2 emergency visits, to 22.3 (95% CI = 15.6–31.9) for those with ≥2 hospitalizations, and to 28.2 (95% CI = 18.6–42.8) for those with ≥4 uses of emergency visit and hospitalization.

The incidence of PAD in the asthma cohort during the follow-up period did not change much, while it increased gradually in the comparison cohort (Table 5). The aHR of PAD for the asthma cohort relative to the comparison cohort declined from 1.42 (95% CI = 1.13–1.80) in the first year of follow-up to 1.24 (95% CI = 1.05–1.47) after 7 years of follow-up or longer.

DISCUSSION

The present longitudinal population-based study shows that patients with asthma exhibit a 1.34-fold greater risk of PAD development, compared with the general population, after controlling for sex, age, and comorbidities. Our findings are compatible to the well-known concept that the risk of PAD is higher in men, older patients, and those with diabetes, hyperlipidemia, and cardiovascular and cerebrovascular comorbidities, and this was observed in both cohorts. Moreover, the aHRs of PAD for the asthma group compared with the comparison group remained consistent and significant in all sex and age subgroups. Furthermore, the variable-specific aHRs were higher in men than in women (1.38 and 1.31), in younger than in older patients (1.47, 1.32, and 1.28), and in those without any comorbidity than those with any comorbidity (1.40 and 1.33). In addition, the aHRs of PAD for the asthma cohort compared with the comparison cohort were consistent and significant during the whole follow-up period (aHR = 1.24–1.44).

It is important to note that asthma patients without the comorbidities had higher HRs for PAD than asthma patients with comorbidities. This phenomenon reflects that asthma alone is associated with the PAD risk without comorbidity and comorbidity modifies the relationship. The incidence rates of PAD were 1.09 per 1000 person-years in nonasthmatics and 1.25 per 1000 person-years in asthmatics without comorbidity. The incidence of PAD elevated sharply to 5.95 per 1000 person-years in nonasthmatics and 7.36 per 1000 person-years in asthmatics with comorbidities. The absolute risk is in fact increased further for asthma patients than for nonasthma subjects due to the comorbidity.

Another important finding in this study is that asthma patients with a higher number of emergency visits or hospitalizations for their exacerbation have an extremely increased risk for developing PAD. Previous study has shown that viral and bacterial infections could contribute to atherosclerosis due to direct infecting on vascular cells, or indirect effects of cytokines. It is also possible that the infection at nonvascular sites may induce acute phase proteins and develop atherosclerosis.[21] It is well known that asthma exacerbations are often precipitated by infections.[22] In addition, asthma attacks and oxidative stress may decrease peripheral blood erythrocyte

TABLE 2. Incidences and Hazard Ratios of Peripheral Artery Disease for Asthma Cohort Compared With Nonasthma Cohort by Sex, Age, and Comorbidity

	Asthma							
	No			Yes			Compared to Without Asthma	
Variables	Event	PY	Rate[#]	Event	PY	Rate[#]	IRR (95% CI)	Adjusted HR[†] (95% CI)
All	1429	467,655	3.06	1016	228,508	4.45	1.46(1.40–1.52)***	1.34(1.24–1.45)***
Sex								
Women	743	257,327	2.89	525	126,778	4.14	1.43(1.36–1.52)***	1.31(1.17–1.47)***
Men	686	210,328	3.26	491	101,731	4.83	1.48(1.39–1.57)***	1.38(1.23–1.55)***
Age, yr								
20–49	132	202,357	0.65	129	102,548	1.26	1.93(1.80–2.07)***	1.47(1.14–1.88)**
50–64	403	129,766	3.11	309	64,127	4.82	1.55(1.44–1.68)***	1.32(1.13–1.53)***
≥65	894	135,531	6.60	578	61,833	9.35	1.42(1.33–1.51)***	1.28(1.16–1.43)***
Comorbidity[‡]								
No	305	278,617	1.09	136	108,992	1.25	1.14(1.07–1.22)***	1.40(1.14–1.71)***
Yes	1124	189,038	5.95	880	119,516	7.36	1.24(1.17–1.31)***	1.33(1.22–1.46)***
Comorbidity, type								
Hypertension								
No	514	331,399	1.55	295	139,703	2.11	1.36(1.29–1.44)***	1.46(1.26–1.69)***
Yes	915	136,255	6.72	721	88,805	8.12	1.21(1.14–1.29)***	1.26(1.14–1.39)***
Hyperlipidemia								
No	915	391,737	2.34	585	179,090	3.27	1.40(1.33–1.47)***	1.31(1.18–1.45)***
Yes	514	75,917	6.77	431	49,418	8.72	1.29(1.18–1.40)***	1.35(1.19–1.54)***
Diabetes								
No	926	410,793	2.25	660	194,990	3.38	1.50(1.44–1.57)***	1.42(1.28–1.57)***
Yes	503	56,861	8.85	356	33,519	10.6	1.20(1.09–1.32)***	1.19(1.04–1.36)*
Stroke								
No	978	406,016	2.41	641	188,694	3.40	1.41(1.35–1.48)***	1.34(1.22–1.49)***
Yes	451	61,639	7.32	375	39,814	9.42	1.29(1.18–1.41)***	1.31(1.14–1.50)***
CAD								
No	1065	428,327	2.49	716	198,273	3.61	1.45(1.39–1.52)***	1.42(1.29–1.57)***
Yes	364	39,327	9.26	300	30,235	9.92	1.07(0.96–1.19)	1.12(0.96–1.30)
CKD								
No	1411	466,670	3.02	1012	228,065	4.44	1.47(1.41–1.53)***	1.35(1.24–1.46)***
Yes	18	984	18.3	4	444	9.01	0.49(0.23–1.05)	0.54(0.18–1.62)

CAD = coronary artery disease, CI = confidence interval, CKD = chronic kidney disease, HR = hazard ratio, IRR = incidence rate ratio, PY = person-years.

[#] Rate = incidence rate per 1000 person-years.

[†] Model was adjusted for age, sex, and comorbidities of hypertension, hyperlipidemia, diabetes, stroke, coronary artery disease, and chronic kidney disease.

[‡] Patients with any comorbidity of hypertension, hyperlipidemia, diabetes, stroke, coronary artery disease, and chronic kidney disease were defined as the comorbidity group.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

superoxide dismutase activity and contribute to the consequence of cardiovascular diseases.[23,24] Our study showed a dose–response relationship between the number of asthma exacerbations and the development of PAD. This finding suggests that poor asthma control is the key factor associating with the PAD development.

Several studies have evaluated the relationship between asthma and atherosclerosis. The results from Bruneck and ARMY studies show that patients with allergic disorders, such as allergic rhinitis and asthma, are at increased risks of high intima-media thickness in young men and of atherosclerosis in the older participants.[10] Onufrak et al[12] found that women with the asthma onset in their older ages could experience a 2-fold increased incident CAD and stroke, after controlling for smoking, obesity, and physical activity. In another prospective study, the results show 1.40-fold, 1.20-fold, and 2.14-fold elevated hazards of cerebrovascular disease, coronary heart disease, and heart failure, respectively, for adults with asthma.[13] In a recent retrospective cohort study, Chung et al[14] found in Taiwan that patients with asthma were at a 1.66-fold greater hazard to develop an acute coronary syndrome than those without the asthma history ($P < 0.001$). Ferrari et al[15] found patients with asthma are at higher risk of intermittent claudication, but not reach statistical significance. In the present study, we provide a relative ''real world'' scenario wherein the diagnosis of asthma and PAD are due to actual medical consultations.

Mechanisms of association between asthma and PAD remain largely uncertain. It is possible that the chronic airway inflammation can contribute to a systemic inflammatory response, leading to atherosclerosis.[25,26] In a cross sectional study, Vijayakumar et al[27] reported that patients with bronchial asthma are twice as likely to develop arterial inflammation than

TABLE 3. Adjusted Hazard Ratios of Peripheral Artery Disease Associated With Interaction Between Asthma and Age and Comorbidity

Variable		N	Event	Adjusted HR (95% CI)	*P* Value[#]
Asthma	Age group				0.0712
No	20–49	22,772	132	Reference[†]	
No	50–64	14,774	403	3.25 (2.66–3.97)***	
No	≥65	18,770	894	5.37 (4.42–6.52)***	
Yes	20–49	11,386	129	1.76 (1.38–2.24)***	
Yes	50–64	7387	309	4.28 (3.46–5.28)***	
Yes	≥65	9385	578	6.80 (5.55–8.34)***	
Asthma	Comorbidity[§]				0.7423
No	No	31,934	305	Reference[‡]	
No	Yes	24,382	1124	2.85 (2.50–3.26)***	
Yes	No	12,359	136	1.31 (1.07–1.60)*	
Yes	Yes	15,799	880	3.86 (3.37–4.42)***	
Asthma	Hypertension				0.1415
No	No	38,349	514	Reference[‡]	
No	Yes	17,967	915	2.19 (1.95–2.46)***	
Yes	No	16,132	295	1.52 (1.31–1.75)***	
Yes	Yes	12,026	721	2.92 (2.59–3.28)***	
Asthma	Hyperlipidemia				0.9066
No	No	46,856	915	Reference[‡]	
No	Yes	9460	514	1.99 (1.79–2.22)***	
Yes	No	21,938	585	1.45 (1.31–1.61)***	
Yes	Yes	6220	431	2.87 (2.56–3.22)***	
Asthma	Diabetes				0.0182
No	No	48,645	926	Reference[‡]	
No	Yes	7671	503	2.51 (2.25–2.80)***	
Yes	No	23,422	660	1.57 (1.42–1.73)***	
Yes	Yes	4736	356	3.21 (2.84–3.63)***	
Asthma	Stroke				0.3739
No	No	47,611	978	Reference[‡]	
No	Yes	8705	451	1.68 (1.50–1.89)***	
Yes	No	22,229	641	1.50 (1.36–1.66)***	
Yes	Yes	5929	375	2.34 (2.07–2.64)***	
Asthma	CAD				0.0046
No	No	50,790	1065	Reference[‡]	
No	Yes	5526	364	2.00 (1.77–2.26)***	
Yes	No	23,805	716	1.55 (1.41–1.70)***	
Yes	Yes	4353	300	2.39 (2.10–2.72)***	
Asthma	CKD				
No	No	56,114	1411	Reference[‡]	0.0556
No	Yes	202	18	5.09 (3.20–8.11)***	
Yes	No	28,066	1012	1.52 (1.41–1.65)***	
Yes	Yes	92	4	2.69 (1.01–7.17)*	

CAD = coronary artery disease, CI = confidence interval, CKD = chronic kidney disease, HR = hazard ratio.

[†] Model adjusted for sex and comorbidities

[‡] Model adjusted for age and sex,.

[§] Patients with any comorbidity of hypertension, hyperlipidemia, diabetes, stroke, coronary artery disease, and chronic kidney disease were defined as the comorbidity group.

[#] *P* value for interaction.

* $P < 0.05$.

*** $P < 0.001$.

control subjects with low Framingham risk scores without asthma. Asthma may activate the expression of bronchoalveolar coagulation, and further impair the procoagulant activities and attenuate fibrinolysis. The activities of the anticoagulant protein C system and fibrinolysis are impaired in the bronchoalveolar space.[28] Moreover, genetic factors, shared comorbidities, environmental exposures, frequent infections, inadequate lifestyles, and physical inactivity may also contribute to the occurrence of PAD for patients with asthma.[29]

The strength of this study is using population data to perform a longitudinal evaluation for the risk of developing PAD in asthma patients. It is generally very expensive to conduct a population-based prospective cohort study. This retrospective cohort study using claims data meets the

TABLE 4. Hazard Ratios of Peripheral Artery Disease Associated With Annual Emergency Visits and Hospitalizations for Asthma

Variables	N	Event	Crude HR (95% CI)	Adjusted HR* (95% CI)
Without asthma	56,316	1429	1.00	1.00
Annual number of emergency visits				
<2	28,040	1003	1.44 (1.33–1.56)***	1.32 (1.22–1.44)***
≥2	118	13	17.1 (9.92–29.6)***	14.1 (8.18–24.5)***
P value for trend			<0.0001	<0.0001
Annual number of hospitalizations				
<2	27,919	984	1.41 (1.30–1.53)***	1.30 (1.20–1.41)***
≥2	239	32	43.7 (30.7–62.3)***	22.3 (15.6–31.9)***
P value for trend			<0.0001	<0.0001
Annual number of emergency visits plus hospitalizations				
<2	27,797	969	1.39 (1.28–1.51)***	1.28 (1.18–1.39)***
2–4	184	24	15.5 (10.3–23.2)***	9.44 (6.29–14.2)***
≥4	177	23	45.8 (30.3–69.3)***	28.2 (18.6–42.8)***
P value for trend			<0.0001	<0.0001

CI = confidence interval, HR = hazard ratio.
† Model was adjusted for age, sex, and comorbidities of hypertension, hyperlipidemia, diabetes, stroke, coronary artery disease, and chronic kidney disease.
*** $P < 0.001$.

requirements of longitudinal follow-up avoiding serious loss to follow-up and is economical.[30] However, there are several limitations to be considered when interpreting the present findings. First, this study used the ICD-9-CM algorithm to define asthma, PAD, and comorbidities. The accuracy of diagnoses depends on the physician-perceived evidences in the clinical practices. However, the insurance authority has established an ad hoc committee established to randomly review the claims data to prevent errors and violations. To increase the validity and accuracy of diagnosis, we also included only patients with repeated clinic visits to prevent coding errors. Second, NHIRD does not provide detailed information on smoking habits, occupation, body mass index, diet, environmental exposure, and family history, although these are potential confounding factors. Among these factors, smoking is of a greater concern in both asthma and PAD risks. However, a large population survey in Taiwan has found a lower smoking rate in asthmatic patients than in nonasthma subjects (13.1 vs. 24.0%).[31,32] Less than 5% of women in Taiwan were smokers. Smoking is likely playing no important role in the relationship between asthma and the PAD risk, as the HRs of PAD for asthmatic men and asthmatic women were alike. We are not clear whether occupation, body mass index, diet, environmental exposure, and family history play any role in the relationship between asthma and the PAD risk. In, relevant clinical variables, such as pulmonary function tests, ankle-brachial index, addition serum laboratory data, or imaging results were unavailable. These factors can be used to differentiate severity of asthma and PAD. We used numbers of emergency visits and hospitalizations to represent the severity of asthma and found severe cases were at much greater hazards for PAD. Last, the lack of drug-treatment information such as those on hormone-replacement therapy, and the use of contraceptives, anticoagulants, and antiplatelet drugs may have influenced the outcomes of this study.

TABLE 5. Trend of Peripheral Artery Disease Risk by Follow-Up Years

	Asthma						Asthma Cohort to Comparisons	
	No			Yes				
Variables	Event	PY	Rate#	Event	PY	Rate#	IRR (95% CI)	Adjusted HR† (95% CI)
Follow-up, yr								
<1	158	55,610	2.84	129	27,505	4.69	1.65(1.57–1.74)***	1.42(1.13–1.80)**
1–3	291	107,287	2.71	206	52,549	3.92	1.45(1.38–1.52)***	1.31(1.09–1.57)**
3–5	307	102,485	3.00	235	49,721	4.73	1.58(1.50–1.66)***	1.44(1.21–1.71)***
5–7	308	93,902	3.28	211	45,384	4.65	1.42(1.35–1.49)***	1.35(1.13–1.61)***
≥7	365	108,371	3.37	235	53,350	4.40	1.31(1.24–1.38)***	1.24(1.05–1.47)*

CI = confidence interval, HR = hazard ratio, IRR = incidence rate ratio, PY = person-years.
# Rate = incidence rate per 1000 person-years.
† Model was adjusted for age, sex, and comorbidities of hypertension, hyperlipidemia, diabetes, stroke, coronary artery disease, and chronic kidney disease.
* $P<0.05$.
** $P < 0.01$.
*** $P < 0.001$.

CONCLUSION

Although smoking is a potential confounding factor, this nationwide study based on 28,158 asthmatic patients with a follow-up time of 228,508 person-years indicates that, compared with the comparison cohort, asthmatic patients exhibit a 34% increase in the risk of developing PAD. Moreover, we observed a dose–response relationship between the annual number of asthma exacerbations and the risk of PAD development. Thus, a multidisciplinary team should guide the assessment, treatment, and holistic care for asthmatic patients.

ACKNOWLEDGMENT

This study was supported in part by Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (MOHW104-TDU-B-212-113002), China Medical University Hospital (1MS1), Academia Sinica Taiwan Biobank, Stroke Biosignature Project (BM104010092), NRPB Stroke Clinical Trial Consortium (MOST 103-2325-B-039-006), Tseng-Lien Lin Foundation, Taichung, Taiwan, Taiwan Brain Disease Foundation, Taipei, Taiwan, and Katsuzo and Kiyo Aoshima Memorial Funds, Japan.

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