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ORIGINAL ARTICLE

Metformin use and asthma outcomes among patients with concurrent asthma and diabetes

CHUN-YI LI,[1] STEVEN R. ERICKSON[2] AND CHUNG-HSUEN WU[3,4]

[1]*Medical Affairs, AstraZeneca Taiwan Limited,* [3]*School of Pharmacy, College of Pharmacy and* [4]*Research Center for Pharmacoeconomics, College of Pharmacy, Taipei Medical University, Taipei, Taiwan,* [2]*Department of Clinical Pharmacy, College of Pharmacy, University of Michigan, Ann Arbor, Michigan, USA*

ABSTRACT

Background and objective: **Metformin is a first-line treatment for patients with diabetes. Recent animal studies indicated that metformin can reduce airway inflammation. However, it remains unclear whether the use of metformin can help patients maintain asthma control. The purpose of this study was to evaluate the association between the use of metformin and asthma-related outcomes, which include asthma-related hospitalization, asthma-related emergency room visits and asthma exacerbation, among patients with concurrent asthma and diabetes.**

Methods: **We conducted an 11-year (2001–2011) retrospective cohort study using the Taiwan National Health Insurance Research Database. Patients with concurrent asthma and diabetes were included. The date of the first observed prescription of metformin was defined as the index date. For each metformin user, two matched metformin non-users of the same age and gender were randomly selected. Patients were followed for 3 years to measure the occurrence of asthma-related outcomes. Multivariable logistic regression models were used to assess the association between metformin use and asthma-related outcomes.**

Results: **Of 1332 patients with concurrent asthma and diabetes, 444 (33.3%) were metformin users. Compared with non-users, metformin users had a lower risk of asthma-related hospitalization (OR = 0.21, 95% CI: 0.07–0.63) and asthma exacerbation (OR = 0.39, 95% CI: 0.19–0.79).**

Conclusion: **The risk of asthma-related outcomes was lower for metformin users than non-users. Health-care providers should consider metformin as a treatment strategy for patients with concurrent asthma and diabetes.**

Key words: asthma, claims data, diabetes, metformin, The National Health Insurance Research Database.

Correspondence: Chung-Hsuen Wu, School of Pharmacy, College of Pharmacy, Taipei Medical University, 250 Wu-Hsing Street, Xinyi District, Taipei 11031, Taiwan. Email: chunghwu@tmu.edu.tw

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SUMMARY AT A GLANCE

Metformin is commonly used for diabetic patients and has recently been found to reduce airway inflammation in animal studies. We evaluated the association between metformin use and asthma exacerbation among patients with concurrent asthma and diabetes and found that the risk of exacerbation was lower among metformin users than non-users.

Abbreviations: AMPK, 5 adenosine monophosphate-activated protein kinase; CCI, Charlson comorbidity index; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; LABA, long-acting-β-agonist; NHIRD, National Health Insurance Research Database; OR, odds ratio.

INTRODUCTION

Asthma, a chronic disease involving inflammation in the small airway of the lungs, is a prevalent disease with considerable burden worldwide.[1] Asthma affects more than 300 million people around the world.[2] In the USA, an estimated 25.9 million people had asthma in 2011.[3] In Taiwan, asthma affects about 12% of the population.[4] The mean cost of hospitalizations for patients with asthma in Taiwan is 2.7 times higher than for patients without asthma.[5,6]

Asthma is treatable, even though it remains a lifelong disease. Medications for treating asthma are grouped in two major classes: controller and reliever medications.[7] Controller medications suppress inflammation or provide long-acting bronchodilation. Reliever medications have quick-onset bronchodilating effects and are used to treat acute asthma symptoms. Even though asthma is treatable, poor asthma control has often been reported in clinics.[8,9] For example, Carlton *et al.* conducted a survey of 60 000 patients in multiple primary care practice sites and reported that 74% of patients reported a lack of asthma control.[10]

Diabetes is a common comorbid condition among adult patients with asthma. For example, previous population-based studies reported that the range of the prevalence of comorbid diabetes was from 5% to

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16%.[11,12] Compared with patients without diabetes, patients with diabetes are also at increased risk for other respiratory diseases such as asthma, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis and pneumonia.[13] Furthermore, studies also showed that patients with concurrent asthma and diabetes had poorer glycemic control,[14] quality-adjusted life expectancy[15] and higher risk of pneumococcal disease[16] when compared with patients who only have asthma or diabetes.

Recent *in vitro* and *in vivo* studies showed that the anti-inflammatory effect of metformin can reduce airway inflammation.[17,18] The plausible mechanism of anti-inflammatory effect of metformin on the airway is believe to be mediated through metformin activated 5 adenosine monophosphate-activated protein kinase (AMPK).[18] Activation of AMPK inhibits inflammatory processes associated with conditions such as colitis, cystic fibrosis and autoimmune encephalomyelitis.[19–22] AMPK activity may also decrease oxidative stress, through the regulation of the cellular proliferation and protein synthesis and its effects on nicotinamide adenine dinucleotide phosphate-oxidases.[23] For example, Calixto *et al.* conducted a study among obese mice model fed with a high-fat diet and found that metformin attenuated the exacerbation of the allergic eosinophilic inflammation.[17] Another activity of metformin includes inhibition of tumour necrosis factor-α-induced inflammatory signalling and nuclear factor-kB-mediated inducible nitric oxide synthase expression.[18]

Given metformin is recommended as a first-line treatment for patients with diabetes,[24] it may become a better treatment option for better asthma control among patients with concurrent asthma and diabetes. However, it is unclear whether the use of metformin can help patients maintain better asthma control. Therefore, the purpose of this study was to evaluate the association between the use of metformin and asthma-related outcomes among patients with concurrent asthma and diabetes. We hypothesized that the risk of asthma-related adverse outcomes would be lower in metformin users than in non-users.

METHODS

Data source

The National Health Insurance Research Database (NHIRD) in Taiwan was used to conduct this study. In 1995, the Taiwanese government launched its National Health Insurance programme that covered 23 million citizens, which accounted for 98% of the population in Taiwan.[25–27] The health information recorded in the National Health Insurance programme was used to build the NHIRD, which is maintained by the Bureau of National Health Insurance of Taiwan and National Health Research Institute.[27] The NHIRD is a de-identified, administrative claims database that contains beneficiaries' demographics, diagnosis, inpatient and outpatient procedures, prescription drugs and enrollment information.

We used the 2005 Longitudinal Health Insurance Database, which is a sample containing one million Taiwanese beneficiaries in 2005 randomly selected from the NHIRD to conduct this study.[27] The overall length of the data in our study was 11 years from 1 January 2001 to 31 December 2011.

Study population and design

A retrospective cohort study design was used to conduct this study. Figure 1 describes the overall study design. Adult patients aged ≥18 years with concurrent asthma and diabetes were included in our study population. The International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes were used to identify patients. To be included in the population, patients needed to have had at least one inpatient or two outpatient diagnoses of asthma (ICD-9-CM: 493.x) and diabetes (ICD-9-CM: 250.x)

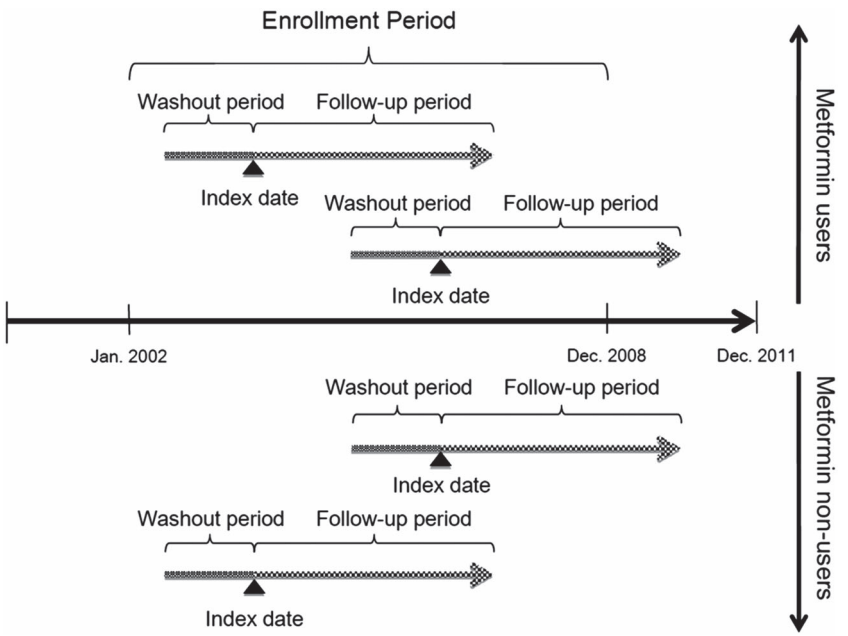

Figure 1 Description of the study design.

during the enrollment period (i.e. 1 January 2002 to 31 December 2008). In addition to the disease diagnosis, patients were included if they had at least one prescription for asthma and diabetes medication during the enrollment period. The index date of the metformin users was defined as the date of the first observed prescription record of metformin during the enrollment period. For each metformin user, two matched metformin non-users of the same age and gender were selected, and they were assigned the same index date as the matched metformin users. To ensure the patients included in our study were with concurrent asthma and diabetes, we further restricted that the date of the asthma and diabetes diagnosis must be earlier than the index date. Patients were followed for 3 years (i.e. the follow-up period) from the index date to measure asthma-related outcomes. Figure 2 describes the process of identifying the study population.

We excluded patients who had a metformin prescription within 1 year before the index date (i.e. the pre-index period). We furthered excluded patients if they had been diagnosed with COPD (ICD-9CM codes 491.xx, 492.xx or 496.xx), any respiratory tract cancer (ICD-9-CM codes 161, 161.x, 162, 163, 163.x, 231, 231.x),or bronchiectasis (ICD-9-CM code 494.xx) during the pre-index period.[28–30] Patients were also excluded if they had an asthma-related hospitalization or emergency room visit during the pre-index period. Finally, patients with invalid or missing information of age, gender, diagnosis codes, medication prescriptions and enrollment records were excluded.

Dependent variables

Three dependent variables were measured in our study: asthma-related hospitalization, asthma-related emergency room visits and the risk of asthma exacerbation.[30–32] We only used the primary diagnosis of asthma to identify asthma-related outcomes. The asthma-related hospitalization was defined as a patient with an asthma-related hospital admission during the follow-up period. The asthma-related emergency room visit was defined as a patient having an asthma-related emergency room visit during the follow-up period. Asthma exacerbation was defined as a patient who used a systemic corticosteroid plus had an asthma-related hospital admission or a systemic corticosteroid plus had an emergency room visit during the follow-up period.[32,33] To ensure the validity of the outcome, we further required that the systemic corticosteroid use and hospitalization (or emergency room visit) for asthma occurred for the same event.

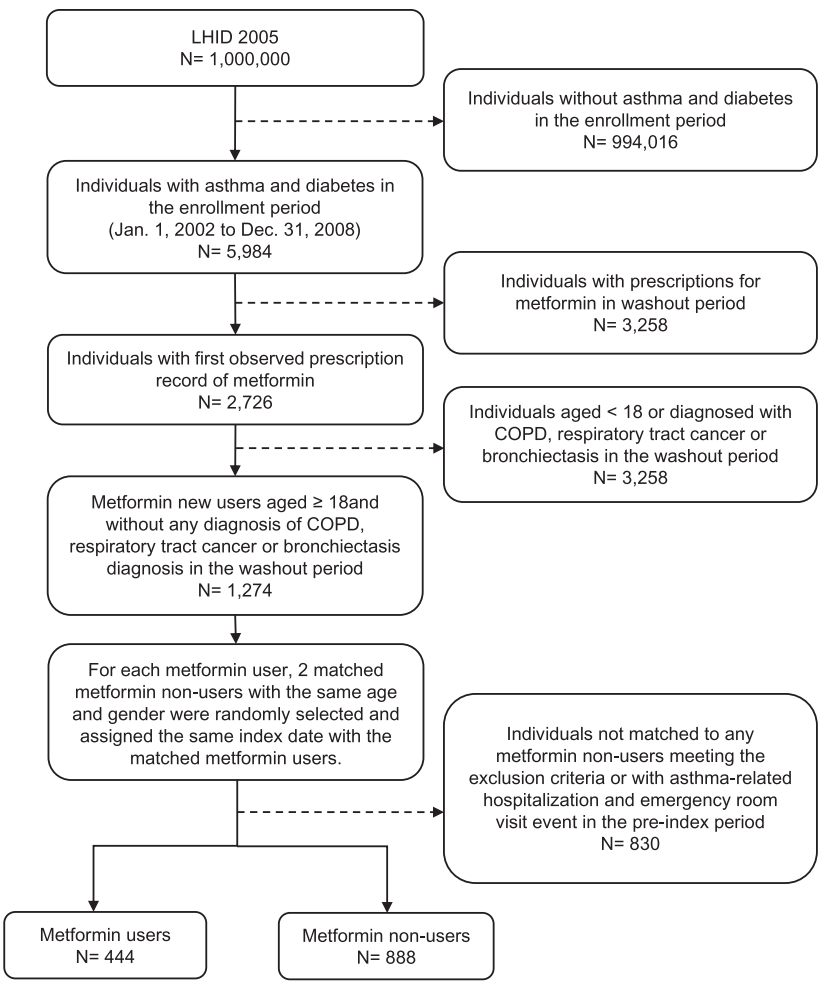

Figure 2 Flow chart: the identification process of the study population.

Table 1 Baseline characteristics of the study population

Characteristics	Overall population (N = 1332)	
	Estimated population	Percentage
Age (mean, SD)†	64	10.1
Age†		
18–39	24	1.8%
40–59	402	30.2%
60–79	906	68.0%
Gender		
Female	804	60.4%
Male	528	39.6%
Region†		
Northern	342	25.7%
North-west	202	15.2%
Central	247	18.5%
South-western	204	15.3%
Southern	213	16.0%
Eastern and other	124	9.3%
Charlson comorbidity index (mean, SD)‡	1.3	1.8
Duration of asthma (mean of months, SD)§	41.9	21.2
All cause events‡		
Hospital admission		
Yes	316	23.7%
Emergency room visit		
Yes	381	28.6%
Cardiovascular disease¶		
Yes	76	5.7%
Metformin-related discontinue diseases††		
Yes	90	6.7%
Medication for asthma‡		
Inhaled corticosteroid		
Yes	93	7.0%
Long-acting β-agonist		
Yes	189	14.2%
Short-acting β2-agonist		
Yes	348	26.1%
Leukotriene modifiers		
Yes	20	1.5%
Methyl-xanthine		
Yes	481	36.1%
Systemic corticosteroid		
Yes	272	20.4%
Anticholinergics		
Yes	49	3.7%
Medication for diabetes‡		
Sulfonylurea		
Yes	513	38.5%
Meglitinide		
Yes	72	5.4%
Thiazolidinedione		
Yes	77	5.8%
α-glucosidase inhibitor		
Yes	111	8.3%
Insulin		
Yes	147	11.0%
Asthma-related outcome variables‡‡		
Hospital admission		
Yes	33	2.5%
Emergency room visit		
Yes	30	2.3%
Exacerbation		
Yes	133	10.0%

†Calculated on the index date.
‡Calculated during the pre-index period.
§Duration between the date of first diagnosis with asthma and the index date in the enrollment period.
¶Including cardiovascular disease, dyslipidemia or metabolic syndrome.
††Including end stage renal disease, heart failure or chronic liver disease.
‡‡Calculated during the follow-up time.

Covariates

All covariates were measured during the pre-index period. They were age, gender, geographic region, the Charlson comorbidity index (CCI),[34,35] duration of asthma, use of asthmatic medications, use of diabetic medications, all-cause hospitalization and all-cause emergency room visits. We created a covariate called cardiovascular and metformin-related discontinue diseases, which includes cardiovascular diseases, dyslipidemia, metabolic syndrome end stage renal disease, heart failure or chronic liver disease. We adjusted the variable in addition to CCI to better control the confounding effect from comorbidity. Geographic areas in Taiwan were grouped into six regions: northern, north-western, central, south-western, southern, eastern and other. The use of the asthmatic medications was defined as the documentation of patients having at least one prescription for any of the following asthma medications in the pre-index period: inhaled corticosteroids, long-acting-β-agonists (LABAs), leukotriene modifiers, methyl-xanthine, short-acting β-agonists, Cromones, anti-immunoglobulin E and systemic corticosteroids. The diabetic medication use was defined as patients having at least one prescription for the following diabetes medications during the pre-index period: sulfonylurea, meglitinide, thiazolidinedione, α-glucosidase inhibitors, inhibitors of dipeptidyl peptidase 4, glucagon-like peptide-1 agonists and insulin. Each drug name in the category was listed in Appendix S1.

Statistical analysis

Descriptive statistics were used to describe patient characteristics of the overall study population, metformin users and metformin non-users. The Student's t-test and chi-square test were used to compare differences in means of continuous variables and percentage

Table 2 Comparisons of patient characteristics between metformin users and non-users

Characteristics	Metformin users (*N* = 444)		Metformin non-users (*N* = 888)		*P*
	Estimated population	Percentage	Estimated population	Percentage	
Age (mean, SD)†	64	10.1	64	10.1	0.98
Age†					1.00
18–39	8	1.8%	16	1.8%	
40–59	134	30.2%	268	30.2%	
60–79	302	68.0%	604	68.0%	
Gender					1.00
Female	268	60.4%	536	60.4%	
Male	176	39.6%	352	39.6%	
Region†					0.05
Northern	97	21.9%	245	27.6%	
North-west	82	18.0%	120	13.5%	
Central	76	17.1%	171	19.3%	
South-western	69	15.5%	135	15.2%	
Southern	72	16.2%	141	15.9%	
Eastern and other	48	10.8%	76	8.6%	
Charlson comorbidity index (mean, SD)‡	1.3	10.81	1.4	1.86	0.46
Duration of asthma (mean of months, SD)§	39.7	21.95	43.0	20.73	<0.01*
All cause events‡					
Hospital admission					0.74
Yes	103	23.2%	213	24.0%	
Emergency room visit					0.69
Yes	124	27.9%	257	28.9%	
Cardiovascular disease¶					0.15
Yes	31	7.0%	45	5.1%	
Metformin-related discontinue diseases††					0.81
Yes	31	7.0%	59	6.6%	
Inhaled corticosteroid					0.11
Yes	38	8.6%	55	6.2%	
Long-acting β-agonist					0.86
Yes	64	14.4%	125	14.1%	
Short-acting β2-agonist					0.02
Yes	134	30.2%	214	24.1%	
Leukotriene modifiers					0.75
Yes	6	1.4%	14	1.6%	
Methyl-xanthine					<0.01*
Yes	190	42.8%	291	32.8%	
Systemic corticosteroid					0.02
Yes	107	24.1%	165	18.6%	
Anticholinergics					0.09
Yes	11	2.5%	38	4.3%	
Medication for diabetes‡					
Sulfonylurea					0.12
Yes	184	41.4%	329	37.1%	
Meglitinide					<0.01*
Yes	15	3.4%	57	6.4%	
Thiazolidinedione					0.16
Yes	20	4.5%	57	6.4%	
α-glucosidase inhibitor					0.67
Yes	39	8.8%	72	8.1%	
Insulin					<0.01*
Yes	27	6.1%	120	13.5%	
Asthma-related outcome variables‡‡					
Hospital admission					<0.01*

(*Continues*)

Table 2 (Continued)

Characteristics	Metformin users ($N = 444$) Estimated population	Percentage	Metformin non-users ($N = 888$) Estimated population	Percentage	*P*
Yes	4	0.9%	29	3.3%	
Emergency room visit					0.43
Yes	8	1.8%	22	2.5%	
Exacerbation					0.02
Yes	10	2.3%	44	5.0%	

Difference of the covariates between metformin users and non-metformin users, using Student *t*-test and chi-square test.
**P*-value with two-tailed significance level was set to 0.05.
†Calculated on the index date.
‡Calculated during the pre-index period.
§Duration between the date of first diagnosis with asthma and the index date in the enrollment period.
¶Including cardiovascular disease, dyslipidemia or metabolic syndrome.
††Including end stage renal disease, heart failure or chronic liver disease.
‡‡Calculated during the follow-up time.

differences of categorical variables between metformin users and non-users.

Multivariable logistic regression models were used to estimate adjusted odds ratios (ORs) between the use of metformin and the three dependent variables in our study. In the multivariable regression models, we evaluated the association between asthma-related outcomes and metformin use after adjusting the variables listed in the aforementioned covariates section including age, gender, region, the CCI, all-cause-related hospitalization, all-cause-related emergency room visit, duration of asthma, medications for asthma and medications for diabetes.

The asthma exacerbation measurement in our main analysis was patients using systemic corticosteroids plus asthma-related hospitalization or patients using systemic corticosteroids plus asthma-related emergency rom visit. In addition to the main analysis, we further conducted a sensitivity analysis to define the asthma exacerbation as a composite outcome of the occurrence of systemic corticosteroids use, asthma-related hospitalization or asthma-related emergency rom visit.

SAS proprietary software, Release 9.3 (SAS Institute, Cary, NC, USA) was used for data management and statistical analyses. A *P*-value with two-tailed significance level was set to 0.05. This study was reviewed and approved by the Taipei Medical University Joint Institutional Review Board.

RESULTS

Table 1 shows characteristics of the study population. The mean age was 64 years, and more than half were women (60.4%). The mean score of the CCI was 1.3. About 23.7% and 28.6% had a hospital admission and emergency room visit, respectively, during the 1-year pre-index period. About 14.2% took a LABA, 26.1% took a short-acting β-agonist and 20.4% took a systemic corticosteroid. More than one-third (38.5%) of the study population took sulfonylurea during the pre-index period.

Table 2 presents the comparison of the patient characteristics between metformin users and non-users. Metformin users took more short-acting β2-agonist (30.2% vs 24.1%, $P < 0.05$) and methyl-xanthine (42.8% vs 32.8%, $P < 0.01$). The use rate of insulin was lower among metformin users (6.1% vs 13.5%, $P < 0.01$). Metformin users had fewer asthma-related hospital admissions (0.9% vs 3.3%, $P < 0.01$) than metformin non-users during the follow-up period.

Table 3 shows the results of the adjusted multivariable logistic regression models. Results showed that metformin users were less likely to have asthma-related adverse outcomes. Compared with metformin non-users, metformin users had a lower risk of asthma-related hospitalization (OR = 0.21, 95% CI: 0.07–0.63) and asthma exacerbation (OR = 0.39, 95% CI: 0.19–0.79) but not emergency room visits for asthma (OR = 0.62, 95% CI 0.26–1.44)

Results from the sensitivity analysis showed that the risk of asthma exacerbation was not significantly different between metformin users and non-users (OR = 0.68, 95% CI: 0.45–1.02).

DISCUSSION

In this retrospective cohort study, we found a significant association between metformin use and asthma-related outcomes among patients with concurrent asthma and diabetes. Metformin users were less likely to have an asthma-related hospitalization and an asthma exacerbation than metformin non-users. Our findings confirmed that the anti-inflammatory effect of metformin may be associated with a reduced risk of airway inflammation, which was reported in previous animal studies.[17,18]

Although the plausible mechanism remains unclear, previous *in vitro* and *in vivo* studies showed that metformin could have anti-inflammatory effect.[17,18] Through the activation of the AMPK, metformin attenuates the exacerbation of the allergic eosinophilic

Table 3 The associations between metformin use and asthma outcomes (hospitalization, emergency room visit and exacerbation): results from multivariable logistic regression models[†]

	Asthma hospitalization		Asthma emergency room visit		Asthma exacerbation	
	Adjusted model		Adjusted model		Adjusted model	
Variable	Odds ratio	(95% CI)	Odds ratio	(95% CI)	Odds ratio	(95% CI)
Use of metformin						
Yes	0.21	(0.07–0.63)	0.62	(0.26–1.44)	0.39	(0.19–0.79)
No	Reference	Reference	Reference	Reference	Reference	Reference
Age	1.02	(0.99–1.06)	0.98	(0.94–1.01)	1.01	(0.98–1.03)
Gender[‡]						
Female	1.91	(0.83–4.37)	0.96	(0.45–2.04)	1.46	(0.79–2.69)
Region[‡]						
North-west	3.80	(1.23–11.73)	2.08	(0.72–5.97)	1.83	(0.81–4.11)
Central	1.58	(0.46–5.38)	1.12	(0.37–3.46)	1.07	(0.45–2.51)
South-western	1.56	(0.44–5.59)	0.67	(0.17–2.67)	0.98	(0.40–2.45)
Southern	1.48	(0.41–5.37)	0.74	(0.21–2.69)	0.79	(0.30–2.07)
Eastern and other	0.88	(0.16–4.81)	0.66	(0.13–3.29)	0.55	(0.15–2.03)
Charlson comorbidity index	0.86	(0.66–1.13)	1.01	(0.81–1.27)	0.91	(0.75–1.11)
Duration of asthma[§]	1.00	(0.99 - 1.02)	1.00	(0.98–1.02)	1.00	(0.99–1.01)
Cardiovascular and metformin-related discontinue disease[‡,¶]						
Yes	0.27	(0.03–2.16)	1.30	(0.41–4.18)	1.06	(0.41–2.74)
Medication for asthma						
Inhaled corticosteroid[‡]						
Yes	1.89	(0.64–5.60)	3.74	(1.34–10.4)	1.22	(0.49–3.05)
Long-acting β-agonist[‡]						
Yes	2.21	(0.90–5.41)	0.60	(0.20–1.80)	1.91	(0.95–3.85)
Short-acting β2-agonist[‡]						
Yes	1.87	(0.84–4.19)	1.44	(0.62–3.32)	1.77	(0.95–3.28)
Systemic corticosteroid[‡]						
Yes	2.21	(0.87–4.72)	1.86	(0.79–4.37)	1.64	(0.85–3.17)
Other medication[‡,††]						
Yes	1.05	(0.44–2.52)	1.10	(0.46–2.65)	1.26	(0.66–2.41)
Medications for diabetes[‡,‡‡]						
Yes	0.85	(0.41–1.77)	1.28	(0.6–2.77)	1.13	(0.64–2.00)

[†]Adjusted variables including age, gender, region, Charlson comorbidity index, duration of asthma, medications for asthma and medication for diabetes.

[‡]Reference groups: gender (male), region (northern), cardiovascular and metformin-related discontinue disease (No), inhaled corticosteroid (No), long-acting β-agonist (No), short-acting β2-agonist (No), systemic corticosteroid (No), other medications (No) and medications for diabetes (No).

[§]Duration between the date of first diagnosis with asthma and the index date in the enrollment period.

[¶]Including cardiovascular disease, dyslipidemia, metabolic syndrome, end stage renal disease, heart failure or chronic liver disease.

[††]Other medications including leukotriene modifier, methyl-xanthine and anticholinergic agent.

[‡‡]Medication for diabetes including sulfonylurea, meglitinide, thiazolidinedione, α-glucosidase inhibitor and insulin.

inflammation, which reduces the airway inflammatory.[18] The activation of the AMPK could also inhibit the inflammatory process in several other diseases such as colitis,[20] cystic fibrosis,[21] autoimmune encephalomyelitis[22] and lipopolysaccharide-induced lung inflammation.[36] Therefore, a lower risk of asthma exacerbation among metformin users that we observed in the study could result from this anti-inflammatory effect.

This study has several strengths. To our knowledge, this is the first study to evaluate the association between metformin use and asthma-related outcomes in a large, population-based cohort. Then, we used both the disease diagnoses and medication records, which can prevent the misclassification that was commonly reported in studies using administrative claims data, to ensure the accuracy and validity of identifying our study population.[37] Furthermore, we adopted the new user design[38] to prevent the immortal bias that was commonly reported in the observational studies.[39,40] Furthermore, we identified asthma-related medication use, which included the use of inhaled corticosteroid, LABA and short-acting β-agonists and adjusted the medication use in the regression model. The model allowed us to obtain a more comprehensive finding because the management of asthma-related medication was highly associated with the asthma outcomes. Finally, we also adjusted for diabetic patients' medication use including insulin in our regression analysis. Including diabetic medication use can

potentially serve as a proxy of the severity of the diabetic condition. The adjustment ensured that we obtained comprehensive and objective findings.

Moreover, we used asthma exacerbation because it is a more comprehensive and clinically meaningful outcome. We found that the risk of asthma exacerbation was lower among metformin users than non-users. Metformin is a first-line medication treatment that is widely used for patients with diabetes. Physicians may consider prescribing metformin or adding metformin to current diabetic medicines as a treatment strategy for patients with concurrent asthma and diabetes.

Previous studies indicated that metformin can reduce the risk of cancer, HIV lipodystrophy syndrome, polycystic ovarian syndrome and several chronic inflammatory diseases through its anti-inflammatory effect.[41,42] The association between metformin use and the reduced risk of the asthma exacerbation that we found in this study needs further investigation. Several ongoing randomized control trials may provide more evidence to support our findings.[43,44]

There are several limitations to this study. First, several risk factors, which can impact asthma control including obesity, allergens, infections, occupational sensitizers, smoking, air pollution and dietary habits, were not available in the administration claims data.[1] Second, the NHIRD does not have information regarding the socioeconomic status such as education, family income, race/ethnicity, marital status and so on, which are confounders for asthma exacerbation. The residual confounding effect can still exist. In addition, the NHRID did not provide the laboratory data or other clinical measures such as body mass index, which were potential confounders in this study. Third, symptom overlaps could exist between patients with chronic COPD and asthma.[45,46] We potentially eliminated patients with severe asthma when we excluded patients with COPD. This exclusion criterion would have lowered the generalizability and validity of our study. Fourth, bias created from confounding by indication may exist because the number of comorbid conditions and medication use were higher for metformin users than non-users. Fifth, actual medication adherence in the study population was unknown because a record of prescriptions filled might not mean a prescription taken by the patient. Finally, asthma is a heterogeneous disease,[47] and information regarding the phenotypes or severity of asthma was not available in the claims data.

In summary, metformin use is potentially associated with improvements in asthma control among patients with concurrent asthma and diabetes. From a clinical perspective, metformin can become a priority selection among patients with diabetes and asthma. Future studies can continue to investigate the underlying anti-inflammatory mechanism of metformin, and clinical trials are necessary to further confirm the effect of metformin on asthma control.

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Disclosure Statement

The study was from a part of C-YL Master's thesis at the Taipei Medical University, Taipei, Taiwan.

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Supplementary Information

Additional Supplementary Information can be accessed via the *html* version of this article at the publisher's website:

Appendix S1 Medication covariates