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Metformin Use and Asthma Outcomes among Patients with Concurrent Asthma and Diabetes

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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.

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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 three 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 1,332 patients with concurrent asthma and diabetes, 444 (33.3%) were metformin users. Compared to non-users, metformin users had a lower risk of asthma-related hospitalization (odds ratio (OR) = 0.21, 95% confidence interval (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.

Keywords: Asthma, claims data, diabetes, metformin, The National Health Insurance Research Database

Short Title: Metformin and asthma outcome reduction

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Abbreviations

ACOS	Asthma-Chronic Obstructive Pulmonary Disease Overlap Syndrome
CCI	Charlson Comorbidity Index
COPD	Chronic Obstructive Pulmonary Disease
DPP-4	Dipeptidyl Peptidase 4
GLP	Glucagon-Like Peptide
ICD-9-CM	International Classification Of Diseases, 9th Revision, Clinical Modification
ICS	Inhaled Corticosteroid
IgE	Anti-Immunoglobulin E
LABA	Long-Acting-B-Agonist
LHID	Longitudinal Health Insurance Database
NHI	National Health Insurance
NHIRD	National Health Insurance Research Database
NHRI	National Health Research Institute
OR	Odds Ratio
PCOS	Polycystic Ovarian Syndrome
SABA	Short-Acting B-Agonist

Introduction

Asthma, a chronic disease involving inflammation in the small airways 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 United States, 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 16%.^{11,12} Compared to patients without diabetes, diabetics are also at increased risk for other respiratory diseases such as asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, and pneumonia.¹³ Furthermore, studies also showed that patients with concurrent asthma and diabetes had poorer glycemic control¹⁴, quality-adjusted life expectancy¹⁵ and higher risk of pneumococcal disease¹⁶ 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 believed 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 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 tumor necrosis factor- α -induced inflammatory signaling 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 (NHI) program that covered 23 million citizens, which accounted for 98% of the population in Taiwan.²⁵⁻²⁷ The health information recorded in the NHI program was used to build the NHIRD which is maintained by the Bureau of National Health Insurance of Taiwan and National Health Research Institute (NHRI).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 (LHID 2005) 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 January 1, 2001 to December 31, 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) during the enrollment period (i.e.,

January 1, 2002 to December 31, 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 three 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 one year before the index date (i.e., the pre-index period). We further excluded patients if they had been diagnosed with chronic obstructive pulmonary disease (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.

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, northwestern, central, southwestern, 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 (ICSs), long-acting- β -agonists (LABAs), leukotriene modifiers, methyl-xanthine, short-acting β -agonists (SABAs), Cromones, anti-immunoglobulin E (IgE), 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 (DPP-4), glucagon-like peptide (GLP)-1 agonists, and insulin. Each drug name in the category was listed in the appendix (Appendix 1).

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 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 above 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 ER 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

ER visit.

SAS[®] Proprietary Software, Release 9.3 (SAS Institute, Cary, NC) 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.

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Results

Table 1 shows characteristics of the study population. The mean age was 64 years, and more than half were females (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 one 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 β 2-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 to 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 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 encephalomyelitis²² and LPS-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 design³⁸ 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 ICS, 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 (PCOS), 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, etc., 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 (BMI), 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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Table 1 Baseline characteristics of the study population*

Characteristics	Overall population (N=1,332)	
	Estimated population	Percentage
Age (mean, SD) ^a	64	10.1
Age ^a		
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 ^a		
Northern	342	25.7%
Northwest	202	15.2%
Central	247	18.5%
Southwestern	204	15.3%
Southern	213	16.0%
Eastern and other	124	9.3%
Charlson-Comorbidity-Index (mean, SD) ^b	1.3	1.8
Duration of asthma (mean of months, SD) ^c	41.9	21.2
All cause events ^b		
Hospital admission		
Yes	316	23.7%
Emergency room visit		
Yes	381	28.6%
Cardiovascular disease ^d		
Yes	76	5.7%
Metformin-related discontinue diseases ^e		
Yes	90	6.7%
Medication for asthma ^b		
Inhaled corticosteroid		
Yes	93	7.0%

Long-acting β -agonist			
Yes	189	14.2%	
Short-acting β 2-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 ^b			
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 ^f			
Hospital admission			
Yes	33	2.5%	
Emergency room visit			
Yes	30	2.3%	
Exacerbation			
Yes	133	10.0%	

^a: Calculated on the index date

^b: Calculated during the pre-index period

^c: Duration between the date of first diagnosis with asthma and the index date in the enrollment period

- ^d. Including cardiovascular disease, dyslipidemia or metabolic syndrome
- ^e. Including end stage renal disease, heart failure or chronic liver disease
- ^f. Calculated during the follow-up time

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

Characteristics	Metformin users (N=444)		Metformin non-users (N=888)		P-value*
	Estimated population	Percentage	Estimated population	Percentage	
Age (mean, SD) ^a	64	10.1	64	10.1	0.98
Age ^a					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 ^a					0.05
Northern	97	21.9%	245	27.6%	
Northwest	82	18.0%	120	13.5%	
Central	76	17.1%	171	19.3%	
Southwestern	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) ^b	1.3	10.81	1.4	1.86	0.46
Duration of asthma (mean of months, SD) ^c	39.7	21.95	43.0	20.73	<0.01*
All cause events ^b					
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 ^d					0.15
Yes	31	7.0%	45	5.1%	
Metformin-related discontinue diseases ^e					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 β 2-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 ^b					
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 ^f					
Hospital admission					<0.01*
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%
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*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

- ^a. Calculated on the index date
- ^b. Calculated during the pre-index period
- ^c. Duration between the date of first diagnosis with asthma and the index date in the enrollment period
- ^d. Including cardiovascular disease, dyslipidemia or metabolic syndrome
- ^e. Including end stage renal disease, heart failure or chronic liver disease
- ^f. Calculated during the follow-up time

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

Variable	Asthma hospitalization		Asthma emergency room visit		Asthma exacerbation	
	Adjusted model		Adjusted model		Adjusted model	
	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 ^b						
Female	1.91	(0.83- 4.37)	0.96	(0.45 - 2.04)	1.46	(0.79 - 2.69)
Region ^b						
Northwest	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)
Southwestern	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 ^c	1.00	(0.99 - 1.02)	1.00	(0.98 - 1.02)	1.00	(0.99 - 1.01)

Cardiovascular and metformin-related discontinue disease ^{b,d}						
Yes	0.27	(0.03 - 2.16)	1.30	(0.41 - 4.18)	1.06	(0.41 - 2.74)
Medication for asthma						
Inhaled corticosteroid ^b						
Yes	1.89	(0.64 - 5.60)	3.74	(1.34 - 10.4)	1.22	(0.49 - 3.05)
Long-acting β -agonist ^b						
Yes	2.21	(0.90 - 5.41)	0.60	(0.20 - 1.80)	1.91	(0.95 - 3.85)
Short-acting β 2-agonist ^b						
Yes	1.87	(0.84 - 4.19)	1.44	(0.62 - 3.32)	1.77	(0.95 - 3.28)
Systemic corticosteroid ^b						
Yes	2.21	(0.87 - 4.72)	1.86	(0.79 - 4.37)	1.64	(0.85 - 3.17)
Other medication ^{b,e}						
Yes	1.05	(0.44 - 2.52)	1.10	(0.46 - 2.65)	1.26	(0.66 - 2.41)
Medications for diabetes ^{b,f}						
Yes	0.85	(0.41 - 1.77)	1.28	(0.6 - 2.77)	1.13	(0.64 - 2.00)

^a. Adjusted variables including age, gender, region, Charlson Comorbidity Index, duration of asthma, medications for asthma, medication for diabetes

- ^b. Reference groups: gender (male), region (northern), cardiovascular and metformin-related discontinue disease (No), inhaled corticosteroid (No), long-acting β -agonist (No), short-acting β 2-agonist (No), systemic corticosteroid (No), other medications (No), and medications for diabetes (No)
- ^c. Duration between the date of first diagnosis with asthma and the index date in the enrollment period
- ^d. Including cardiovascular disease, dyslipidemia, metabolic syndrome, end stage renal disease, heart failure or chronic liver disease
- ^e. Other medications including leukotriene modifier, methyl-xanthine and anti-cholinergic agent
- ^f. Medication for diabetes including sulfonylurea, meglitinide, thiazolidinedione, α -glucosidase inhibitor and insulin

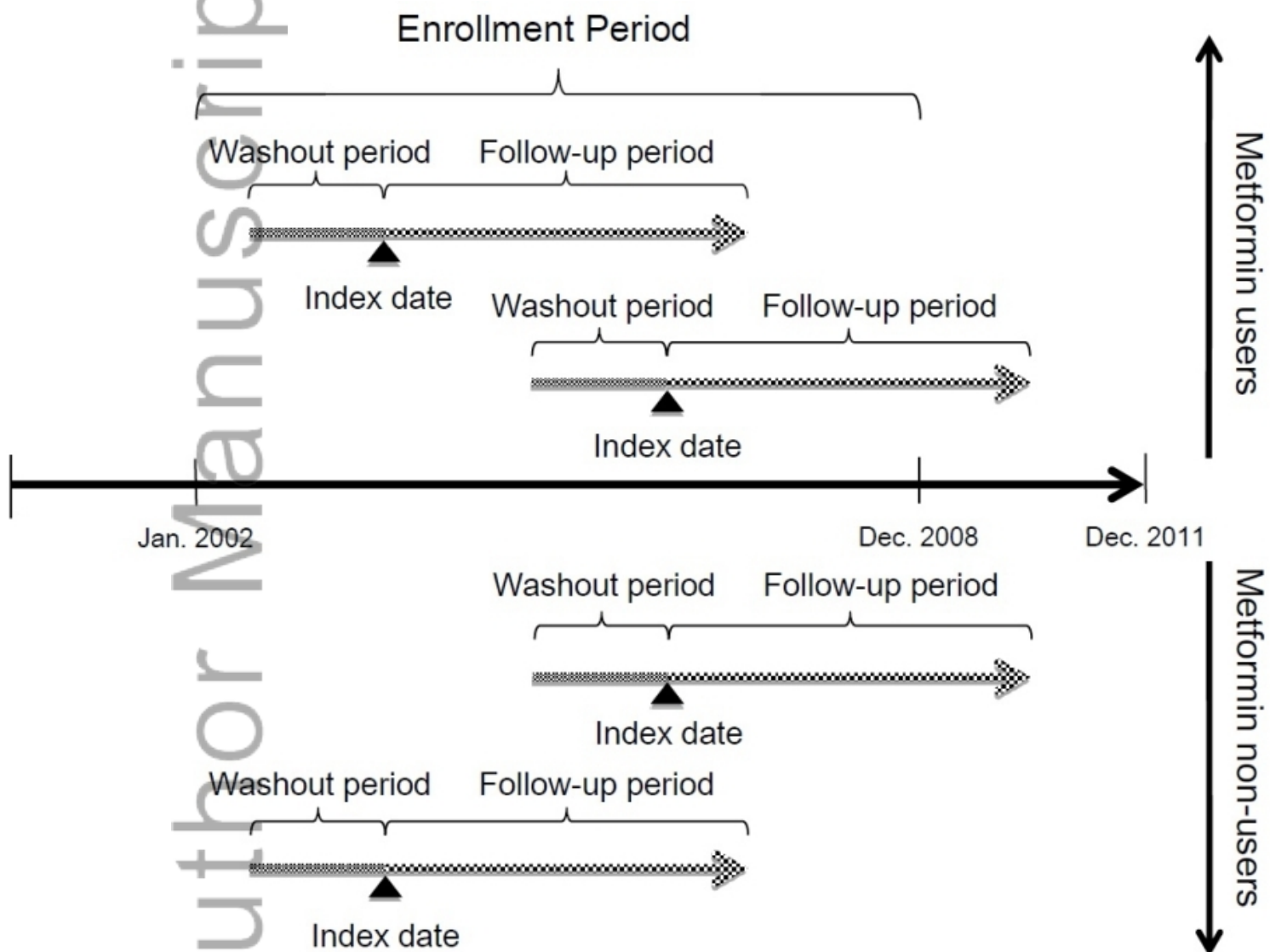
Figure legends

Figure 1 Description of the study design

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

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