ORIGINAL RESEARCH

Association of Metformin Initiation and Risk of Asthma Exacerbation
A Claims-based Cohort Study

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Abstract

Rationale: Diabetes and metabolic syndrome have been associated with worsened asthma control. Metformin improves insulin resistance and metabolic function. Experimental studies suggest that metformin may improve pathologic features of asthma, but evidence of clinical benefit is limited.

Objectives: To determine if treatment with metformin in a cohort of individuals with asthma and diabetes is associated with lower risk of asthma exacerbation.

Methods: A 6-year retrospective cohort of individuals over age 18 with asthma and diabetes was assembled from a national administrative claims database. New users of metformin were matched to nonusers by propensity score on the basis of demographic, comorbidity, and medication-use characteristics. An exacerbation was defined as an asthma-related hospitalization, emergency department visit, or filling of a systemic corticosteroid prescription within 14 days of an asthma-related ambulatory visit. Cox proportional hazards estimated the change in hazard of asthma exacerbation associated with metformin initiation.

Results: In a cohort of 23,920 individuals with asthma and diabetes, metformin initiation was associated with lower hazard of asthma exacerbation (hazard ratio [HR], 0.92; 95% confidence interval [CI], 0.86–0.98), driven by lower hazards of asthma-related emergency department visits (HR, 0.81; 95% CI, 0.74–0.88) and hospitalization (HR, 0.67; 95% CI, 0.50–0.91), without differences in corticosteroid use (HR, 0.96; 95% CI, 0.86–1.03).

Conclusions: In an administrative cohort of individuals with asthma and diabetes, metformin initiation was associated with a lower hazard of asthma-related emergency department visits and hospitalizations. These findings suggest a possible benefit of metformin in more severe asthma exacerbations. Investigation within cohorts with more detailed participant characterization is necessary.

Keywords: metformin; pharmacoepidemiology; metabolic dysfunction; administrative data

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Asthma, diabetes, and metabolic syndrome are highly prevalent worldwide. In this decade, an estimated 339 million people are living with asthma, and 422 million adults are living with diabetes (1, 2). The substantial majority of individuals with type 2 diabetes also meet diagnostic criteria for metabolic syndrome, which defines a combination of insulin resistance, truncal obesity, and dyslipidemia (3, 4).

Diabetes and metabolic syndrome are associated with increased incidence of asthma (5, 6), asthma-like symptoms (7), and asthma severity (8, 9). Metformin, the recommended first-line treatment for diabetes, improves insulin sensitivity, metabolic dysfunction, and inflammation (10). In animal models of asthma,

metformin reduces lung tissue eosinophilic infiltration and improves inflammatory biomarkers associated with the allergic response (11, 12). *In vitro* work suggests that metformin inhibits airway smooth muscle proliferation and fibroblast activity, pathologic features associated with chronic asthma (12, 13).

A recent study using the Taiwan National Health Insurance Research Database reported that metformin use may be associated with lower odds of exacerbation among those with asthma (14). To date, the association between metformin use and asthma has not been investigated in other populations.

The availability of a large U.S.-based health services administrative database provided an opportunity to address this research question. We constructed a cohort of individuals with asthma and diabetes and compared asthma-related healthcare use between new users (initiators) and nonusers of metformin. We hypothesized that initiation of metformin would be associated with a lower risk of asthma exacerbations.

Methods

Data Source

We used the IBM MarketScan Research Databases. The Commercial Claims and Encounters Database includes inpatient, outpatient, and prescription drug claims that are submitted by private health plans and employers from all 50 states and the District of Columbia (15). Individuals in these plans were employees, their spouses and dependents, and a small number of COBRA (Consolidated Omnibus Budget Reconciliation Act of 1985) continuees. Prescription claims include those from retail, mail-order, and specialty pharmacies. This study used claims from January 1, 2010, to December 31, 2016.

Cohort Definition

A cohort was assembled of adult participants (aged ⩾18 yr) with both asthma and diabetes based on the recorded *International Classification of Diseases, 9th and 10th Revisions, Clinical Modification codes* (ICD-9-CM and ICD-10-CM, respectively; *see* Table E1 in the online supplement). Participants were considered to have diabetes or asthma if they had at least two compatible outpatient codes or one inpatient code during enrollment. We required qualifying outpatient claims to be within 1 year; this approach has been validated in claims databases to have high specificity for asthma (16) and diabetes (17, 18).

We required that all individuals be continuously enrolled for at least 1 calendar year and participate in a health plan that submitted prescription claims during the entire enrollment period. We excluded individuals with any diagnosis of chronic obstructive pulmonary disease, bronchiectasis, or interstitial lung disease, as well as those with a contraindication for metformin use (stage IV or V chronic kidney disease or dialysis status), type 1 diabetes, and a rheumatologic condition that may require systemic corticosteroids for symptoms unrelated to asthma (Table E1).

Study Design

We conducted a retrospective cohort study using a new-user design to assess the association between metformin initiation and asthma exacerbations (19). New users of metformin entered the study upon fill of a metformin prescription without a prior fill in the preceding 365 days. Those with a prior fill were classified as prevalent users and were excluded. New users who filled a combination pill of metformin and another oral hypoglycemic were also excluded to limit confounding by diabetes severity and nonmetformin drug effects. Nonusers entered the study at a randomly assigned time after 1 year of enrollment and the fill of any prescription medication. These requirements were instituted to provide sufficient person-time for covariate assessment and to demonstrate engagement with health care. By design, nonusers could not later become new users, and new users remained new users even if they later discontinued metformin. Individuals were followed until occurrence of the study endpoint or were censored at the end of their insurance enrollment, whichever came first. We required all participants to have satisfied asthma criteria by study entry to ensure uniform possibility of observing the outcome.

Covariate and Outcome Definitions

Baseline covariates were collected in the 1 year before study entry. Comorbid illnesses were quantified with the Charlson comorbidity index and with the number of all-cause hospitalizations (20, 21). Asthma severity and control were represented by the number of asthma-related outpatient visits, exacerbations (defined below), and classes of asthma medications used. Structural variation in access to care, affecting both probability of metformin initiation and healthcare use, was represented by geographic region, insurance plan type, and months of eligible enrollment. These covariates, in addition to age, were selected as plausible confounders. We also recorded season and classes of diabetes medications used (other than metformin) as covariates that may plausibly relate to risk of asthma exacerbation. Drugs were identified by their National Drug Codes (Table E2). The conceptual relationships of these covariates are displayed in Figure E2.

The primary outcome was an asthma exacerbation, defined as an asthma-related systemic corticosteroid use (filling of a corticosteroid prescription of duration ⩾3 d within ±14 d of an outpatient visit at which asthma was a diagnosis), an emergency department encounter at which asthma was a diagnosis, or a hospitalization in which asthma was the principal admission diagnosis. This composite outcome, which is similar to those used in other claims-based asthma studies, was chosen because of an anticipated low number of events (22–24). Each component was examined as a secondary outcome.

Statistical Analysis

Our primary analysis involved matching metformin initiators and nonusers on propensity score to establish a cohort similar in measured covariates. As sensitivity analyses, we also performed stratification and inverse probability of treatment weighting by propensity score and traditional covariate adjustment, as described later.

A propensity score, representing the estimated probability of initiating metformin, was calculated for each participant using a nonparsimonious logistic regression model that included all covariates. Covariates believed to be related only to the outcome were included because this has been shown to improve precision (25). Distributions were trimmed to areas of common support where there is overlap in scores between new users and nonusers. Each new user was matched to one nonuser without replacement based on the logit of the propensity score using a caliper width equal to 0.2 times its standard deviation (26). We used a 1:1 ratio to limit incomplete

matching bias (27). Baseline characteristics between new users and nonusers were considered balanced if the standardized difference was less than 0.1 (28).

Cox proportional hazards models were fit to estimate the association between initiation of metformin and the hazard for the primary and secondary outcomes, using a robust variance estimator that accounted for clustering within matched pairs (29). The proportional hazards assumption was evaluated by testing for absence of correlation of Schoenfeld residuals with time. We also examined the association of metformin initiation with a panel of negative control outcomes (30). These outcomes were chosen *a priori* so as not to be plausibly attributable to metformin or diabetes control but to be potentially influenced by related participant characteristics, such as health-seeking behavior or frailty. We examined time to encounter for vaccinations, screening for malignant neoplasm (principally colonoscopy or mammography), diagnostic skin biopsy, and falls.

As additional sensitivity analyses, we fit models using stratification and inverse probability of treatment weighting by the propensity score (31), as well as covariate adjustment with regression. For stratification, propensity scores were divided into 10 strata of equal size, and models included strata as a categorical variable. For weighting, propensity scores among new users and nonusers were adjusted such that the distribution of covariates in each group was the same as the distribution of the entire sample. For

Table 1. Baseline characteristics

Characteristic	Unmatched Cohort (n = 40,343)		Propensity Score–matched Cohort (n = 23,920)	
	Metformin Initiators (n = 14,641)	Metformin Nonusers (n = 25,702)	Metformin Initiators (n = 11,960)	Matched Nonusers (n = 11,960)
Age, yr, mean (SD)	51.4 (9.3)*	53.2 (9.6)*	51.9 (9.3)	51.9 (9.9)
Female sex, *n* (%)	9,643 (66)	17,346 (68)	7,894 (66)	7,902 (66)
Asthma controller class, *n* (%)				
Inhaled corticosteroid	7,350 (50)*	10,660 (42)*	5,724 (48)	5,675 (47)
Long-acting β-agonist	5,533 (38)*	8,031 (31)*	4,289 (36)	4,268 (36)
Leukotriene modifier	4,606 (32)*	6,609 (26)*	3,576 (30)	3,495 (29)
Long-acting muscarinic antagonist	334 (2)	522 (2)	260 (2)	262 (2)
Theophylline	120 (1)	194 (1)	96 (1)	89 (1)
Asthma exacerbations†, mean (SD)	0.16 (0.6)	0.17 (0.6)	0.16 (0.6)	0.17 (0.6)
Asthma outpatient visits†, mean (SD)	1.6 (1.9)	1.6 (1.9)	1.6 (1.9)	1.6 (2.0)
Diabetes medication class, *n* (%)				
Sulfonylurea	3,017 (21)*	2,800 (11)*	1,951 (16)	1,973 (17)
Dipeptidyl peptidase-4 inhibitor	1,714 (12)*	1,502 (6)*	1,038 (9)	1,049 (9)
Incretin mimetic	1,005 (7)*	943 (4)*	647 (5)	612 (5)
Thiazolidinedione	570 (4)	1,079 (4)	451 (4)	457 (4)
Glycosuric	826 (6)*	513 (2)*	412 (3)	394 (3)
Meglitinide	85 (1)	151 (1)	63 (1)	58 (1)
α-Glucosidase inhibitor	27 (0.2)	42 (0.2)	22 (0.2)	19 (0.2)
Amylin analog	1 (<0.1)	5 (<0.1)	1 (<0.1)	2 (<0.1)
Insulin	1,597 (11)	3,396 (13)	1,262 (11)	1,282 (11)
Geographic region, *n* (%)				
Northeast	2,903 (20)*	6,043 (24)*	2,512 (21)	2,523 (21)
North Central	3,047 (21)	5,247 (20)	2,449 (21)	2,446 (21)
South	5,554 (38)	9,459 (37)	4,476 (37)	4,422 (37)
West	2,934 (20)	4,475 (17)	2,328 (20)	2,374 (20)
Unknown	203 (1)	478 (2)	195 (2)	195 (2)
Plan type, *n* (%)				
Health maintenance organization	2,388 (17)	4,061 (17)	1,932 (17)	1,958 (17)
Preferred provider organization	8,617 (62)	14,908 (63)	7,044 (62)	7,086 (63)
Other‡	2,900 (21)	4,638 (20)	2,317 (21)	2,280 (20)
Season of entry, *n* (%)				
Winter	3,607 (25)	6,952 (27)	2,981 (25)	2,905 (24)
Spring	3,785 (26)	5,880 (23)	3,054 (25)	3,074 (26)
Summer	3,690 (25)	6,018 (23)	2,990 (25)	3,016 (25)
Fall	3,559 (24)	6,852 (27)	2,935 (25)	2,965 (25)
Hospitalizations†, mean (SD)	0.2 (0.6)*	0.4 (0.9)*	0.3 (0.7)	0.3 (0.7)
CCI, mean (SD)	0.9 (1.1)*	1.4 (1.6)*	1.0 (1.2)	1.0 (1.1)

Definition of abbreviations: CCI = Charlson comorbidity index; SD = standard deviation.
*Standardized difference greater than 0.1 (for geographic region, denotes overall category).
†In the year before study entry.
‡Includes major medical, comprehensive, noncapitated point of service, capitated point of service, consumer-driven health plan, high-deductible health plan, or not reported.

covariate adjustment, only variables believed to be associated with the exposure and outcome in Figure E2 were included. These sensitivity analyses were performed in the unmatched cohort.

Statistical significance was accepted at a two-sided P value less than 0.05. Cohort extraction and matching were performed in SAS 9.3 software (SAS Institute), and analysis was performed in Stata 15 software (StataCorp). The Johns Hopkins School of Medicine Institutional Review Board deemed this study exempt from institutional review.

Results

Of 45,419,637 enrollees who were initially examined, we identified 97,006 individuals with concurrent asthma and diabetes who met our inclusion criteria (Figure E1). Of these, 66,922 (69%) individuals used metformin, of whom 14,641 were new users. New users compared with prevalent users were younger, had fewer comorbidities, used fewer diabetes medications, and had a higher number of asthma exacerbations (Table E3).

The unmatched cohort included 40,343 individuals, comprised of 14,641 new users and 25,702 nonusers of metformin. Baseline covariates were unbalanced before matching (Table 1 and Figure E3). Notably, nonusers compared with new users were older, had more comorbidities and hospitalizations, and used fewer asthma and diabetes medications. Unadjusted analyses within the unmatched cohort are presented in Table 2.

Of all new users, 11,960 (82%) were successfully matched to nonusers. Thus, the final propensity score–matched cohort had 23,920 individuals. Mean participant age was 52, two-thirds were female, and 11% had had at least one asthma exacerbation in the prior year (Table 1). The Charlson comorbidity index was 1.0, reflecting a low comorbidity burden. Median follow-up time per individual was 0.84 years (interquartile range, 0.36–1.63 yr).

During 27,577 person-years of follow-up, 3,872 individuals experienced an asthma exacerbation, for an overall incidence rate of 14.0 events per 100 person-years. Metformin initiation was associated with a lower hazard of the composite outcome of asthma exacerbation (hazard ratio [HR], 0.92; 95% confidence interval [CI], 0.86–0.98; $P < 0.01$) (Figure 1 and Table 2). When examining each outcome separately, we observed that metformin initiation was associated with lower hazards of asthma-related emergency department encounters (HR, 0.81; 95% CI, 0.74–0.88; $P < 0.01$) and hospitalizations (HR, 0.67; 95% CI, 0.50–0.91; $P < 0.01$) but not with corticosteroid use (HR, 0.96; 95% CI, 0.90–1.03; $P = 0.22$) (Figure 2). There was no association between metformin initiation and the negative control outcomes (Table 3). Inferences were unchanged using stratification on the propensity score, inverse probability of treatment weighting by the propensity score, and traditional covariate adjustment within the full unmatched cohort (Table E4). *Post hoc* analyses investigating the association of metformin initiation and any corticosteroid fill (thereby not requiring a window of an asthma-related ambulatory visit) and corticosteroid fill conditioned on an asthma-related emergency department encounter or hospitalization were not qualitatively different from the original definition (not shown).

Table 2. Association of metformin initiation and study outcomes

Outcome	Unmatched Cohort		Propensity-matched Cohort	
	Events	Hazard Ratio (95% CI)	Events	Hazard Ratio (95% CI)
Asthma exacerbation*	5,594	1.04 (0.98–1.09)	3,872	**0.92 (0.86–0.98)**
Corticosteroid use	4,623	**1.10 (1.04–1.17)**	3,220	0.96 (0.90–1.03)
Emergency room visit	2,797	**0.86 (0.80–0.93)**	1,907	**0.81 (0.74–0.88)**
Hospitalization	266	**0.74 (0.58–0.94)**	174	**0.67 (0.50–0.91)**

Definition of abbreviation: CI = confidence interval.
Bolded values indicate statistical significance.
*Primary outcome.

Discussion

In this cohort of adults with asthma and diabetes, initiation of metformin was associated with a lower hazard of asthma exacerbation. This result was driven by lower hazards of asthma-related emergency department visits and hospitalizations. These findings suggest a potential role for metformin in lowering risk of more severe asthma exacerbations and highlight the need for further investigation using data with

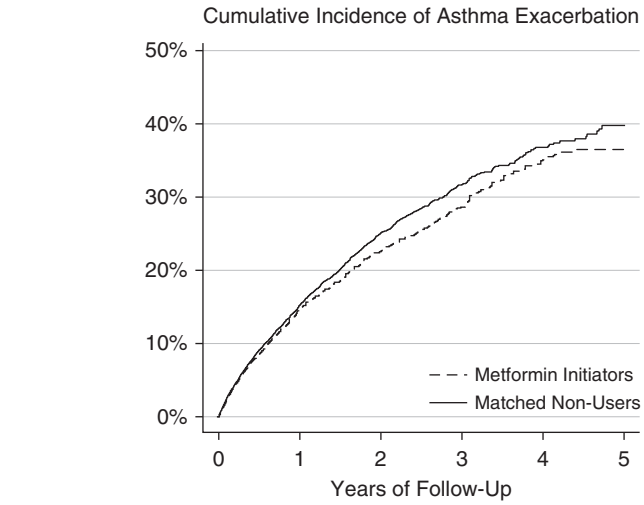

Figure 1. Kaplan-Meier cumulative incidence estimates of asthma exacerbations among the propensity score–matched cohort. Follow-up time is truncated at 5 years, with approximately 1% of the cohort remaining.

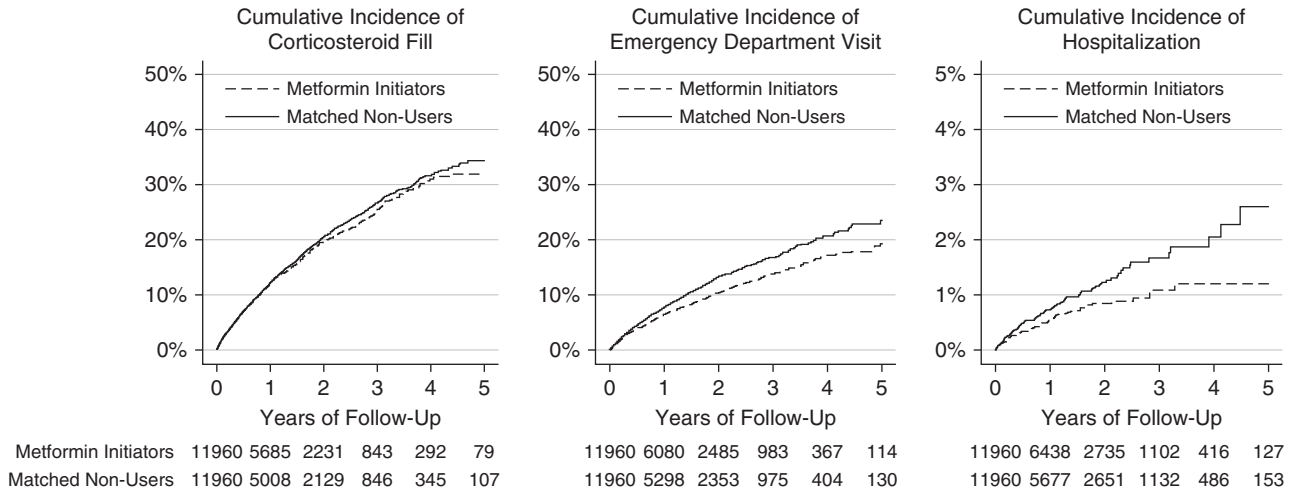

Figure 2. Kaplan-Meier cumulative incidence estimates of each secondary outcome among the propensity score–matched cohort. Follow-up time is truncated at 5 years, with approximately 1% of the cohort remaining. Please note the different *y*-axis scale for asthma-related hospitalizations.

more detailed participant characterization that overcome intrinsic limitations of administrative claims data.

To our knowledge, this is the largest study addressing the hypothesis that metformin, a common drug for the treatment of diabetes and metabolic syndrome, may be associated with improvements in asthma. Our findings extend those reported by Li and colleagues (14), who examined individuals with asthma and diabetes in the Taiwan National Health Insurance Research Database. These investigators found that, among 444 new users of metformin compared with 888 age- and sex-matched control subjects, metformin users had a 79% lower odds of asthma-related hospitalization and a 61% lower odds of emergency department– or hospitalization-associated corticosteroid use, results remarkably similar to ours. Our larger study had a longer follow-up time and allowed examination of corticosteroids associated with outpatient encounters as an outcome.

The relationship between metabolic dysfunction and asthma severity has received increasing scientific attention (32), particularly in the context of obesity-associated and nonallergic asthma, for which there are few specific treatments. Epidemiologic studies have demonstrated an association between metabolic dysfunction with incident asthma and with higher prevalence of more severe asthma (5–8, 33). These conditions are associated with increased systemic inflammation, altered adipokine balance, and hyperinsulinemia, which have each been implicated in inducing pathologic changes in the lung, leading to speculation that intervention in these disorders may improve asthma control and severity (34, 35).

Metformin, a widely available medication for the treatment of diabetes, acts on the key pathways implicated in metabolic syndrome and has produced some evidence of benefit in asthma models. Metformin ameliorates hyperinsulinemia by improving peripheral and hepatic insulin sensitivity, reduces lipotoxicity by slowing fatty acid oxidation in adipose tissue and lowering levels of circulating triglycerides, and has direct antiinflammatory effects (10, 36–38). Among ovalbumin-challenged obese mice with insulin resistance, metformin reduced lung tissue eosinophilic infiltration and decreased levels of tumor necrosis factor-α, eotaxin-1, and nitrogen oxide levels in bronchoalveolar lavage fluid (11). In a chronic asthma mouse model, metformin was also associated with reduced tissue eosinophilic inflammation as well as decreased peribronchial fibrosis and airway remodeling, corroborated with reduced expression of fibronectin and collagen in cultured fibroblasts (12). In an *in vitro* study, metformin inhibited proliferation of cultured murine airway smooth muscle cells (13).

Our findings, taken together with experimental evidence, emphasize the need for further study of metformin in individuals with asthma and metabolic dysfunction. We note that although differences in hazard of exacerbation with metformin initiation were small, we did not have access to a number of important characteristics, especially allergic and T2/non-T2 polarization and body mass index, which may inform subgroups of individuals who may plausibly benefit more. Null findings with respect to systemic corticosteroid use may reflect a tendency for corticosteroid prescriptions in the outpatient setting to be less specific for

Table 3. Association of metformin initiation and negative control outcomes

Outcome	Unmatched Cohort		Propensity-matched Cohort	
	Events	Hazard Ratio (95% CI)	Events	Hazard Ratio (95% CI)
Vaccination	11,164	0.98 (0.94–1.01)	7,506	1.01 (0.97–1.06)
Malignancy screening	4,049	0.96 (0.90–1.02)	2,803	0.99 (0.92–1.06)
Skin biopsy	1,704	0.97 (0.88–1.07)	1,166	1.00 (0.89–1.12)
Fall	672	**0.77 (0.66–0.90)**	444	0.89 (0.74–1.07)

Definition of abbreviation: CI = confidence interval.
Bolded values indicate statistical significance.

treatment of asthma exacerbations. We only examined asthma exacerbations that led to emergent attention or systemic corticosteroid use, which does not represent the full spectrum of asthma morbidity. Our exacerbation rate was similar to those of other claims-based studies of asthma exacerbations within the United States and the United Kingdom (22), reflecting a cohort not enriched for severe disease.

Our study has a number of strengths. It was performed in a large dataset consisting of individuals from across the United States. The new-user design eliminated well-described biases associated with studying prevalent users of the medication (19). Allowing drug discontinuation within the new-user group produced conservative estimates more representative of real-world adherence patterns, reflective of the intent to examine metformin initiation rather than use. Propensity score matching ensured similarity in a comprehensive number of baseline covariates, enhancing the comparability between new users and nonusers, especially on the basis of asthma and diabetes treatment intensity. This includes thiazolidinediones, which have similar effects on insulin resistance and inflammation (39, 40). Medication use was assessed by pharmacy fill and not by prescription, substantially increasing the likelihood of reflecting true use.

These strengths are contrasted by intrinsic limitations of claims research, especially the absence of important covariates that would improve participant characterization and matching, especially body mass index and lung function. These factors, which associate with risk of exacerbation, may plausibly have a relationship with the probability of metformin initiation. Inaccuracies and missingness in claims data are likely to misclassify some outcomes and covariates, including some misclassification of chronic obstructive pulmonary disease as asthma, which may unpredictably bias estimates. Because study enrollment is dependent on participation in an employer-sponsored health plan, there may be informative loss to follow-up, and study results are not generalizable to all individuals with asthma. Glycemic measurements were also generally unavailable for these participants, increasing the risk that nonusers of metformin may not have had diabetes. This would likely be conservative, however, because such misclassification would be expected to identify a group less prone to exacerbations within the hypothesis of this study. Finally, the findings could reflect a healthy user bias whereby metformin initiators may also engage in other behaviors that reduce the need for asthma-related care, although there were no associations of metformin use and the negative control outcomes.

In an administrative claims–based cohort of individuals with asthma and diabetes, metformin initiation was associated with a lower risk asthma exacerbations, driven by asthma-related emergency department visits and hospitalizations. These findings add to the evidence that metabolic dysfunction is associated with asthma control. Future studies are needed to investigate effects of metformin in well-characterized participants with asthma, especially in those who are obese and have metabolic dysfunction. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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