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Original article

Metformin and risk of chronic obstructive pulmonary disease in diabetes patients

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ABSTRACT

Purpose. – This study aimed to investigate whether metformin can affect risk of chronic obstructive pulmonary disease (COPD) in type 2 diabetes (T2D) patients.
Methods. – T2D patients newly diagnosed during 1999–2005 were enrolled from the reimbursement database of Taiwan's National Health Insurance system and followed up to 31 December 2011. Analyses were conducted in an unmatched cohort (92,272 ever-users and 10,697 never-users of metformin) and a propensity score (PS) matched pair cohort (10,697 ever-users and 10,697 never-users). Cox regression incorporated into the inverse probability of treatment weighting using the PS was used to estimate hazard ratios (HRs).
Results. – In the unmatched cohort, 2573 never-users and 13,840 ever-users developed COPD with respective incidences of 5994.64 and 3393.19 per 100,000 person-years. The overall HR was 0.560 (95% confidence interval [CI]: 0.537–0.584). HRs for the first (< 25.27 months), second (25.27–55.97 months) and third (> 55.97 months) tertiles of cumulative duration were 1.021 (0.975–1.070), 0.575 (0.548–0.603) and 0.265 (0.252–0.280), respectively. Analyses of the matched cohort showed an overall HR of 0.643 (0.605–0.682), with HRs of 1.212 (1.122–1.309), 0.631 (0.578–0.689) and 0.305 (0.273–0.340) for the respective tertiles.
Conclusion. – A reduced risk of COPD is observed in metformin users with T2D.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by progressive airways obstruction and may be the cause of three million deaths per year (approximately 5% of all deaths) in the world [1]. The most important risk factor of COPD is cigarette-smoking (either active or passive). In non-smokers, other risk factors include genetic profile, indoor or outdoor air pollution, occupational dust and chemical exposures, recurrent lower respiratory infections during childhood, long-standing asthma and pulmonary tuberculosis [1,2]. Patients with obesity and/or diabetes may also have higher risks of developing COPD [3].

Currently, there is no way to cure COPD, and prevention remains the best strategy to reduce its morbidity and mortality. Metformin is now recommended as the first-line treatment for patients with type 2 diabetes (T2D), and recent studies have suggested that, in addition to its glucose-lowering effects, this biguanide may exert anti-inflammatory, anti-atherogenic, anti-cancer and anti-ageing effects as well [4]. Also, because COPD is closely related to ageing, it has been proposed that some geroprotectors, such as metformin, melatonin, rapamycin and resveratrol, might provide a novel strategy for prevention and treatment of COPD [5].

Indeed, some animal and clinical studies have revealed a potentially beneficial effect of metformin on lung function. For example, a recent animal study suggested that activation of 5'-adenosine monophosphate-activated protein kinase (AMPK) by metformin could reduce inflammatory responses in mice with elastase-induced emphysema [6]. In humans, an early retrospective study investigating lung function through spirometry in two groups of diabetes patients with COPD, and treated (n = 29) or not (n = 32) with insulin sensitizers, showed an improvement in lung function in those treated with insulin sensitizers [7]. A prospective open-label observational study evaluating the effects of 6-month treatment with metformin in 17 patients with T2D and moderate-to-severe COPD also suggested improvements in dyspnoea and health status [8]. Another clinical study retrospectively evaluated patients with T2D admitted to hospital for COPD exacerbations

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with or without the use of metformin, and found that metformin was safe and did not increase the risk of lactic acidosis. However, patients treated with metformin had significantly better rates of survival (median survival: 5.2 vs. 1.9 years; hazard ratio (HR): 0.57, 95% confidence interval [CI]: 0.35–0.94) [9]. Although the survival benefit was difficult to explain, Yasar et al. [10] hypothesized that it might be ascribed to effects on the autonomic nervous system. On the other hand, the survival benefit may also have resulted from a reduction in airways infection, as metformin has been shown to reduce both airways glucose permeability and *Staphylococcus aureus* load induced by hyperglycaemia [11].

Yet, it is also acknowledged that the benefits of metformin for COPD failed to be demonstrated in a multicentre randomized, double-blind, placebo-controlled trial. That small trial randomized 52 non-diabetes patients hospitalized for COPD exacerbations to receive either metformin (n = 34) or placebo (n = 18) treatment for 1 month. The investigators could find no significant changes in either the primary endpoint of blood glucose or secondary endpoints of C-reactive protein or scores on the COPD Assessment Test [12]. Thus, whether metformin can be used as an adjunctive therapy for COPD remains inconclusive.

To the best of my knowledge, whether long-term use of metformin in patients with T2D might affect the risk of COPD has not been previously investigated. Therefore, the present population-based study examined the risk of COPD associated with metformin use in T2D patients along with careful consideration of the potential biases and confounding factors commonly encountered in pharmaco-epidemiological studies derived from administrative databases.

Materials and methods

The present retrospective cohort study used the reimbursement database of Taiwan's National Health Insurance (NHI) system. This unique and universal healthcare system covers > 99% of the Taiwan population and has been implemented since March 1995. All inpatient-care hospitals and nearly 93% of all medical settings have contracts with the Bureau of NHI (BNHI), and its reimbursement database keeps records of all patients' disease diagnoses, medication prescriptions and clinical procedures. Academic research using the reimbursement database of the BNHI is allowed if approved after an ethics review: the present study's approval number is 99,274.

Diseases were coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) during the study period. Diabetes was coded as 250.XX and COPD as 490–496. A more detailed description of the database can be found in a previous paper [13].

The present study enrolled an unmatched original cohort and a matched cohort from the database for all analyses according to the procedures presented in Fig. 1. Initially, 423,949 patients with a new diagnosis of diabetes between 1999 and 2005 from outpatients' clinics, with prescriptions for anti-diabetic drugs filled

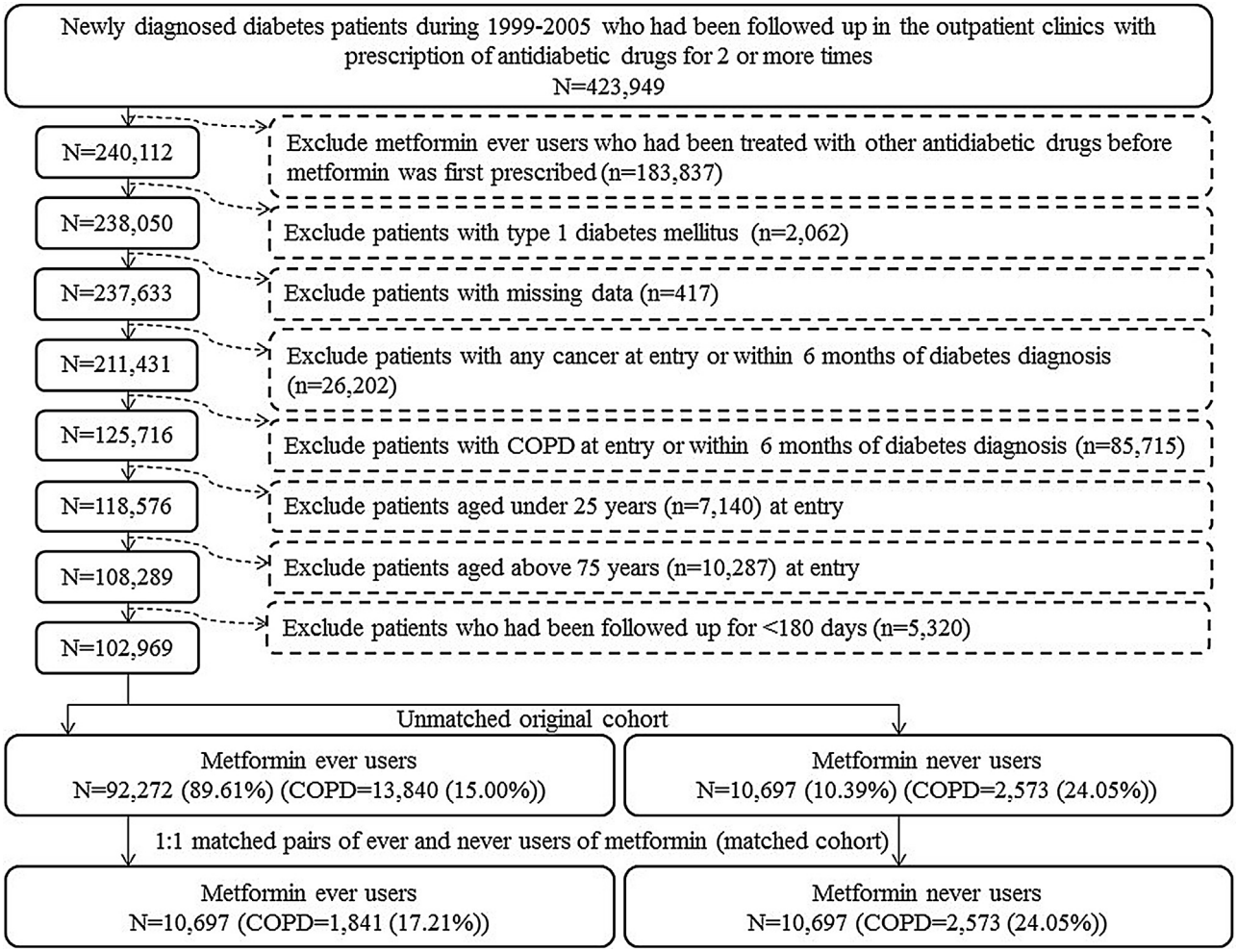

Fig. 1. Procedures used to create the unmatched original cohort and a cohort of 1:1 matched pairs of metformin ever-users and never-users from the reimbursement database of Taiwan's National Health Insurance system. COPD: chronic obstructive pulmonary disease.

at least twice, were identified in the database. The following exclusion criteria were then applied:

- ever-users of metformin who had received other anti-diabetic drugs before metformin was prescribed (n = 183,837);
- those with type 1 diabetes (n = 2062);
- those with missing data (n = 417);
- diagnosis of any cancer before study entry or within 6 months of diabetes diagnosis (n = 26,202);
- diagnosis of COPD before entry or within 6 months of diabetes diagnosis (n = 85,715);
- those aged < 25 years at entry (n = 7140);
- those aged > 75 years at entry (n = 10,287) and;
- those with follow-ups < 180 days (n = 5320).

As a result, 92,272 ever-users and 10,697 never-users of metformin were enrolled as the unmatched original cohort. A propensity score (PS) was constructed from each patient's characteristics (collected up to the end of follow-up; Table 1) plus the date of study entry by logistic regression, and a matched pairs (matched) cohort was created by matching the PS based on the Greedy 8→1 digit match algorithm [14]. This method has also been used in previous research as detailed elsewhere [14,15].

The following categories of variables were treated as potential confounders:

- demographic data: age, gender, occupation, region of residence;
- major comorbidities: hypertension, dyslipidaemia, obesity;
- diabetes-related complications: nephropathy, eye disease, stroke, ischaemic heart disease, peripheral artery disease;
- anti-diabetic drugs: insulin, sulphonylurea, meglitinide, acarbose, rosiglitazone, pioglitazone;
- commonly encountered comorbidities: tobacco use disorder, alcohol-related diagnoses, heart failure, gingival/periodontal

Table 1
Characteristics of metformin never-users and ever-users in the unmatched original cohort and propensity score-matched cohort.

Variable	Unmatched original cohort						Matched cohort					
	Never-users (n = 10,697)		Ever-users (n = 92,272)				Never-users (n = 10,697)		Ever-users (n = 10,697)			
	n	%	n	%	P	SD	n	%	n	%	P	SD
Demographic data												
Age[a], (years)	61.58 ± 10.37		60.16 ± 9.94		< 0.0001	−13.78	61.58 ± 10.37		61.61 ± 10.05		0.7902	0.77
Gender, (male)	6360	59.46	51,743	56.08	< 0.0001	−7.64	6360	59.46	6314	59.03	0.5222	−1.02
Occupation[b]												
Class I	4407	41.20	37,915	41.09	< 0.0001		4407	41.20	4371	40.86	0.7478	
Class II	2165	20.24	21,666	23.48		8.38	2165	20.24	2170	20.29		0.11
Class III	2054	19.20	17,708	19.19		0.44	2054	19.20	2114	19.76		1.46
Class IV	2071	19.36	14,983	16.24		−9.29	2071	19.36	2042	19.09		−0.72
Residential region												
Taipei	3629	33.93	29,884	32.39	< 0.0001		3629	33.93	3609	33.74	0.8749	
Northern	1009	9.43	10,088	10.93		5.26	1009	9.43	979	9.15		−0.99
Central	1852	17.31	16,355	17.72		1.29	1852	17.31	1838	17.18		−0.39
Southern	1885	17.62	15,645	16.96		−1.92	1885	17.62	1933	18.07		1.23
Kao-Ping/Eastern	2322	21.71	20,300	22.00		0.68	2322	21.71	2338	21.86		0.40
Major comorbidities												
Hypertension	8281	77.41	72,354	78.41	0.0176	2.92	8281	77.41	8275	77.36	0.9219	−0.08
Dyslipidaemia	7402	69.20	75,201	81.50	< 0.0001	31.61	7402	69.20	7379	68.98	0.7337	−0.35
Obesity	237	2.22	3694	4.00	< 0.0001	10.54	237	2.22	221	2.07	0.4498	−1.04
Diabetes-related complications												
Nephropathy	3120	29.17	21,614	23.42	< 0.0001	−15.03	3120	29.17	3089	28.88	0.6405	−1.00
Eye diseases	1923	17.98	28,590	30.98	< 0.0001	30.47	1923	17.98	1776	16.60	0.0079	−4.00
Stroke	2855	26.69	23,053	24.98	0.0001	−4.35	2855	26.69	2835	26.50	0.7570	−0.43
Ischaemic heart disease	4130	38.61	35,167	38.11	0.3169	−0.60	4130	38.61	4166	38.95	0.6135	0.74
Peripheral artery disease	2033	19.01	20,655	22.38	< 0.0001	8.72	2033	19.01	2117	19.79	0.1464	1.81
Anti-diabetic drugs												
Insulin	871	8.14	2188	2.37	< 0.0001	−30.22	871	8.14	763	7.13	0.0054	−5.10
Sulphonylurea	8013	74.91	68,835	74.60	0.4872	4.74	8013	74.91	8229	76.93	0.0006	4.89
Meglitinide	807	7.54	3623	3.93	< 0.0001	−16.36	807	7.54	828	7.74	0.5889	0.63
Acarbose	1132	10.58	5157	5.59	< 0.0001	−17.78	1132	10.58	1103	10.31	0.5168	−2.27
Rosiglitazone	342	3.20	4794	5.20	< 0.0001	10.58	342	3.20	353	3.30	0.6714	0.09
Pioglitazone	245	2.29	2612	2.83	0.0013	−17.78	245	2.29	275	2.57	0.1829	−2.27
Commonly encountered comorbidities												
Tobacco use disorder	243	2.27	3131	3.39	< 0.0001	7.00	243	2.27	238	2.22	0.8176	−0.35
Alcohol-related diagnoses	789	7.38	6026	6.53	0.0009	−4.88	789	7.38	738	6.90	0.1756	−2.00
Heart failure	1593	14.89	11,067	11.99	< 0.0001	−9.43	1593	14.89	1594	14.90	0.9847	−0.11
Gingival/periodontal disease	8730	81.61	78,909	85.52	< 0.0001	11.97	8730	81.61	8766	81.95	0.5237	1.09
Pneumonia	1172	10.96	8347	9.05	< 0.0001	−8.09	1172	10.96	1130	10.56	0.3541	−1.48
Pulmonary tuberculosis	248	2.32	2007	2.18	0.3377	−1.32	248	2.32	270	2.52	0.3278	1.04
Osteoporosis	1889	17.66	14,861	16.11	< 0.0001	−4.48	1889	17.66	1836	17.16	0.3393	−1.18
HIV infection	6	0.06	60	0.07	0.7296	−0.10	6	0.06	9	0.08	0.4384	0.88
Commonly used medications in diabetes patients												
ACE inhibitor/ARB	6895	64.46	64,159	69.53	< 0.0001	11.51	6895	64.46	6887	64.38	0.9090	−0.21
Calcium-channel blocker	5982	55.92	49,867	54.04	0.0002	−3.64	5982	55.92	5975	55.86	0.9232	−0.08
Statin	5385	50.34	59,022	63.97	< 0.0001	29.62	5385	50.34	5377	50.27	0.9129	−0.20
Fibrate	3403	31.81	38,187	41.39	< 0.0001	21.44	3403	31.81	3425	32.02	0.7469	0.55
Aspirin	5436	50.82	51,962	56.31	< 0.0001	11.70	5436	50.82	5422	50.69	0.8482	−0.15

[a] Mean ± standard deviation.
[b] See main text (Materials and methods) for definition of classes. SD: standardized difference; HIV: human immunodeficiency virus; ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker.

diseases, pneumonia, pulmonary tuberculosis, osteoporosis, human immunodeficiency virus (HIV) infection and;
- commonly used medications in diabetes patients: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, calcium-channel blocker, statin, fibrate, aspirin.

Classifications of residential regions and occupations have been detailed elsewhere [16]. In brief, regions of residence were classified as Taipei, Northern, Central, Southern and Kao-Ping/Eastern Taiwan. Occupations were classified as: class I: civil servants, teachers, employees of government or private businesses, professionals, technicians; class II: people with no specific employers, self-employed people, seamen; class III: farmers, fishermen; and class IV: low-income families supported by social welfare, veterans. The ICD-9-CM codes used for the above-mentioned diagnoses were: hypertension (401–405); dyslipidaemia (272.0–272.4); obesity (278); nephropathy (580–589); eye diseases (250.5: diabetes with ophthalmic manifestations; 362.0: diabetic retinopathy; 369: blindness and poor vision; 366.41: diabetic cataract; 365.44: glaucoma associated with systemic syndromes); stroke (430–438); ischaemic heart disease (410–414); peripheral artery disease (250.7, 785.4, 443.81, 440–448); tobacco use disorder (305.1, 649.0, 989.84); alcohol-related diagnoses (291, 303, 535.3, 571.0–571.3, 980.0); heart failure (398.91, 402.11, 402.91, 404.11, 404.13, 404.91, 404.93, 428); gingival/periodontal diseases (523); pneumonia (486); pulmonary tuberculosis (011); osteoporosis (733.00); and HIV infection (042, 079.53, V08, V01.79, 795.71).

Age differences between never-users and ever-users of metformin were compared by Student's t tests and, for other variables, by chi^2 tests. The standardized difference as proposed by Austin and Stuart was calculated for all covariates as a test of balance diagnostics [17]. A value $> 10\%$ was taken to indicate potential confounding by the variable [17].

Cumulative duration of metformin therapy was calculated in months, and its tertiles were used for dose–response analyses. Incidence density of COPD was calculated according to the following subgroups of metformin use: never-users; ever-users; and tertiles of cumulative duration. The numerator was the number of cases of new COPD diagnoses observed during follow-up; the denominator was follow-up duration as expressed in person-years, ending on 31 December 2011 at the time of new diagnosis of COPD, the date of death or the last reimbursement on record.

Cox regression incorporated into the inverse probability of treatment weighting (IPTW) using the PS was used to estimate HRs and their 95% CIs for ever-users and for each tertile of cumulative duration compared with never-users. As proposed by Austin, this method reduces potential confounding by differences in characteristics [18].

To examine whether the present study findings were consistent, analyses were conducted of the unmatched original cohort and matched cohort, and followed by three sensitivity analyses. The latter included analyses after excluding patients who filled at least two consecutive prescriptions of metformin spanning > 4 months and > 6 months. Because the BNHI permits no drug prescriptions for > 3 months at each outpatient visit, these analyses would also have excluded those not making regular drug refills. Furthermore, to avoid the potential impact of incretin-based therapies, which were not reimbursed by the BNHI until after 2009 in Taiwan, additional analyses were conducted after excluding patients treated with an incretin during follow-up.

All analyses were performed using SAS version 9.3 statistical software (SAS Institute, Cary, NC, USA). $P < 0.05$ was considered statistically significant.

Results

Characteristics of never-users and ever-users of metformin are presented in Table 1. Age and gender differed significantly in the unmatched original cohort, with an older mean age (61.58 ± 10.37 vs. 60.16 ± 9.94 years; $P < 0.0001$) and greater proportion of men (59.46% vs. 56.08%; $P < 0.0001$) observed in never-users. All other variables, except for ischaemic heart disease, sulphonylurea use, pulmonary tuberculosis and HIV infection, also differed significantly in the original unmatched cohort. However, after matching, age, gender and most of the other variables did not differ significantly, except for eye diseases, insulin and sulphonylurea use. None of the variables had a standardized difference value $> 10\%$ in the matched cohort.

The incidence of COPD and HRs according to metformin exposure are presented in Table 2. In general, HRs showed significantly lower risks of COPD in metformin users in both the unmatched and matched cohorts. Tertile analyses indicated a reduced risk with a dose–response pattern. Metformin use for > 2 years in the second and third tertiles consistently showed significantly reduced risks. However, in the first tertile, the risk was

Table 2
Incidence rates of chronic obstructive pulmonary disease (COPD) and hazard ratios (HRs) by metformin exposure.

Metformin use	n	N	Person-years	Incidence rate (per 100,000 person-years)	HR	95% CI	P
Unmatched original cohort							
Never-users	2573	10,697	42,921.65	5994.64	1.000		
Ever-users	13,840	92,272	407,875.56	3393.19	0.560	(0.537–0.584)	< 0.0001
Tertiles of cumulative duration of metformin therapy (months)							
Never-users	2573	10,697	42,921.65	5994.64	1.000		
< 25.27	6033	30,469	96,260.51	6267.37	1.021	(0.975–1.070)	0.3791
25.27–55.97	4858	30,436	138,107.48	3517.55	0.575	(0.548–0.603)	< 0.0001
> 55.97	2949	31,367	173,507.57	1699.64	0.265	(0.252–0.280)	< 0.0001
Matched cohort							
Never-users	2573	10,697	42,921.65	5994.64	1.000		
Ever-users	1841	10,697	47,583.68	3868.97	0.643	(0.605–0.682)	< 0.0001
Tertiles of cumulative duration of metformin therapy (months)							
Never-users	2573	10,697	42,921.65	5994.64	1.000		
< 27.13	863	3527	11,476.63	7519.63	1.212	(1.122–1.309)	< 0.0001
27.13–57.70	617	3533	16,121.64	3827.15	0.631	(0.578–0.689)	< 0.0001
> 57.70	361	3637	19,985.41	1806.32	0.305	(0.273–0.340)	< 0.0001

Cox regression was incorporated into the inverse probability of treatment weighting using propensity scores derived from variables in Table I plus date of entry. n: number of incident cases of COPD; N: number of cases followed; CI: confidence interval.

Table 3
Sensitivity analyses estimating hazard ratios (HRs) for chronic obstructive pulmonary disease in ever-users vs. never-users of metformin in the original cohort.

Models	*n*	*N*	HR	95% CI	*P*
Excluding two consecutive metformin prescriptions over > 4 months					
Never-users	2573	10,697	1.000		
Ever-users	4018	31,375	0.506	(0.482–0.532)	< 0.0001
Tertiles of cumulative duration of metformin therapy (months)					
Never-users	2573	10,697	1.000		
< 25.27	1470	9847	0.951	(0.891–1.015)	0.1335
25.27–55.97	1372	8719	0.619	(0.580–0.661)	< 0.0001
> 55.97	1176	12,809	0.269	(0.251–0.288)	< 0.0001
Excluding two consecutive metformin prescriptions over > 6 months					
Never-users	2573	10,697	1.000		
Ever-users	5623	41,764	0.517	(0.493–0.541)	< 0.0001
Tertiles of cumulative duration of metformin therapy (months)					
Never-users	2573	10,697	1.000		
< 25.27	1980	12,082	1.013	(0.955–1.076)	0.6618
25.27–55.97	1995	12,146	0.629	(0.593–0.667)	< 0.0001
> 55.97	1648	17,536	0.271	(0.255–0.289)	< 0.0001
Excluding patients treated with incretin-based therapies during follow-up					
Never-users	2546	10,173	1.000		
Ever-users	12,832	72,519	0.654	(0.627–0.682)	< 0.0001
Tertiles of cumulative duration of metformin therapy (months)					
Never-users	2546	10,173	1.000		
< 25.27	5797	26,355	1.096	(1.045–1.148)	0.0001
25.27–55.97	4521	23,932	0.664	(0.632–0.697)	< 0.0001
> 55.97	2514	22,232	0.313	(0.296–0.331)	< 0.0001

n: number of incident cases of COPD; *N*: number of cases followed; CI: confidence interval.

neutral in the unmatched cohort, but slightly higher with a significant *P* value in the matched cohort.

Sensitivity analyses conducted in the unmatched cohort after excluding patients not using regular refills of at least two consecutive prescriptions of metformin spanning > 4 months and > 6 months, or after excluding patients treated with an incretin during follow-up, did not change the study's conclusions (Table 3).

Discussion

This is the first population-based observational study to show a preventative effect of metformin on development of COPD in patients with T2D (Tables 2–3). Such a beneficial effect was especially significant when metformin was used for > 2 years (Table 2). The risk reduction showed a dose–response pattern and was consistent on sensitivity analyses (Table 3).

While the mechanisms underlying the reduced risk of COPD associated with metformin use remain unclear, certain biological actions of metformin might explain such a beneficial effect. Metformin inhibits mitochondrial respiratory-chain complex 1, leading to activation of the liver kinase B1 (LKB1)/AMPK pathway which, in turn, inhibits gluconeogenesis in the liver, thereby lowering blood glucose [19]. In addition, metformin improves insulin resistance by increasing expression of insulin receptors and activation of tyrosine kinase [20]. COPD is characterized by increased inflammation and oxidative stress, and upregulation of mammalian target of rapamycin (mTOR) [21], whereas metformin can protect the cardiovascular system against oxidative stress and inflammation via AMPK-dependent and -independent pathways [22]. A study of mice with induced emphysema confirmed that metformin improved lung function with a significant reduction in inflammatory responses and cellular senescence via activation of AMPK [6]. Metformin is also well known for its inhibitory effect on mTOR through activation of LKB1/AMPK, which may be responsible for its anti-cancer effect [20]. Advanced glycation end-products (AGEs) can exacerbate acute inflammatory lung injury [23], but metformin can reduce the formation of AGEs through improving glycaemic control and exert a scavenging effect on AGEs [24]. In addition, gut microbiota dysbiosis may play a role in COPD progression and exacerbation [25], whereas metformin use is associated with a compositional change in gut microbiota, resulting in an increase in *Akkermansia* species, which might be responsible for the improved insulin resistance and reduced tissue inflammation [26]. Subclinical atherosclerosis may also be closely linked to COPD [27], and clinical trials have suggested that metformin might have an anti-atherogenic effect [28]. Taken altogether, metformin may reduce the risk of COPD through multiple pathways.

In the present study, matched cohort patients in the first tertile with short-term metformin exposures apparently had significantly higher risks of COPD (Table 2). Because obesity is one of the major risk factors of COPD [3] and metformin is strongly indicated for obese diabetes patients [28], the increased risk in short-term users could reflect the carry-over of obesity before metformin use into the initial period of metformin treatment.

The methodological problems commonly seen in pharmacoepidemiological studies, such as prevalent user bias, immortal time bias and confounding by indication, have been carefully addressed in the present study. Bias due to prevalent users has been avoided by enrolling newly diagnosed diabetes patients and new users of metformin. The effects of other anti-diabetic drugs used prior to metformin use were also avoided by including only ever-users of metformin who received this anti-diabetic drug as their initial treatment (Fig. 1).

immortal time refers to the follow-up period during which the outcome cannot happen [29], and a bias due to immortal time may be introduced when treatment status and follow-up duration are inappropriately assigned when calculating the follow-up period. In the present study, as only patients who had been prescribed anti-diabetic drugs two or more times were enrolled (Fig. 1), cases of ambiguous diagnoses were excluded. Misclassification of treatment status was also unlikely because, in Taiwan, the NHI is a universal healthcare system and all prescription information is available over even long follow-up periods. Therefore, diabetes misdiagnosis and misclassification of treatment status were not likely in the present study.

The immortal time between diabetes diagnosis and initiation of anti-diabetic drugs was not calculated in person-years, and the immortal time during the initial period of enrolment was avoided because patients with short follow-up durations of < 180 days were excluded (Fig. 1). As pointed out by Lévesque et al. [29], immortal time can also be introduced during the waiting period between drug prescription and its dispensation when patients are discharged from hospital. However, this would never happen in Taiwan because all the necessary drugs can be obtained directly from the hospital when patients are discharged.

Confounding by indication was considerably reduced in the PS-matched cohort (Table 2) and by Cox regression incorporated into the IPTW (Table 2). No standardized differences had values > 10% in the matched cohort (Table 1), thereby suggesting a lack of potential residual confounding from covariates.

The present study has the further merit of using a nationwide database covering > 99% of the Taiwanese population, thus allowing generalization of its findings to the entire population. Also, the use of medical records reduced any biases related to self-reporting. Detection biases due to different socioeconomic statuses are also less likely in Taiwan because drug co-pays are low in the NHI, and much of the cost can be waived in veterans, in patients with low incomes and in those requiring prescription refills for chronic diseases.

Nevertheless, several study limitations should be mentioned. First, the lack of data for major risk factors of COPD, such as smoking habits, and environmental and occupational exposures, makes it difficult to draw any definitive conclusions regarding a causal relationship between metformin use and incidence of COPD. Second, because COPD is often underdiagnosed, it is likely that a number of subjects, both users and non-users, were affected by obstructive airways disease, but had not yet been diagnosed with COPD and recorded as such in the database. Therefore, whether metformin increases the incidence of COPD or worsens airways obstruction in patients with preexisting but undiagnosed lung disease cannot be determined by this study. Third, there were no biochemical or AGEs data for the analyses, nor were there measurement data for some other potential confounders, such as anthropometric factors, alcohol intakes, lifestyle choices, nutritional status, dietary patterns, family history and genetic parameters. Yet, despite these limitations, this study does provide a rationale for conducting clinical trials to evaluate the potential benefit of metformin in COPD.

In summary, the present study supports the beneficial effect of metformin in preventing COPD in patients with T2D. These findings can also serve as a basis for conducting clinical trials to confirm such an effect. Given that metformin is safe and inexpensive, and does not cause hypoglycaemia when used as monotherapy, its usefulness for COPD prevention in both diabetes patients and non-diabetic subjects is worthy of further in-depth investigations.

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Contributions of authors

C.T. researched the data and wrote manuscript.

Disclosure of interest

The authors declare that they have no competing interest.

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