Association of diabetes medication and asthma attacks: self-controlled case series and population-based cohort

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Subtitle: Diabetes medication and asthma attacks

Revision date: 29th August 2024

Social media post: Metformin (affordable, safe, diabetes drug) was associated with 30% lower asthma attacks. GLP1 (diabetes, weight loss drug) was associated with a further 40% reduction. Associations were not influenced by glycaemic control, weight or asthma phenotype.

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Key Points

Question: In patients with asthma and diabetes is metformin (the first-line diabetes medication) or any add-on antidiabetic medications associated with a reduced risk of asthma attacks?

Findings: In our self-controlled case series and population-based new-user cohort, metformin was associated with a lowered risk of asthma attacks by approximately 30%, adding GLP-1RA was associated with an additional lowered risk of approximately 40%; associations were found regardless of glycaemic control, weight or asthma phenotype.

Meaning: Metformin was associated with a significant lowering of asthma attacks and the addition of GLP-1RA was associated with a synergistic additive effect.

Abstract

Importance

Elevated body mass index (BMI) and type-2 diabetes are prevalent in asthma and increase the risk of asthma attacks. In experimental studies, the diabetes medications, metformin and glucagon-like peptide-1 receptor agonists (GLP-1RA), mitigate airway inflammation, hyperresponsiveness and remodelling. However, epidemiological evidence is limited.

Objective

To estimate the association of metformin and add-on antidiabetic medications (GLP-1RA, dipeptidyl peptidase-4 inhibitors, sulphonylureas, sodium-glucose co-transporter-2 inhibitors and insulin) with asthma attacks.

Design, Setting, and Participants

We used the United Kingdom's Clinical Practice Research Datalink (CPRD) Aurum linked hospital admissions and mortality data, 2004-2020. We used a triangulation approach, applying two distinct approaches to enhance robustness, a self-controlled case series (SCCS) and metformin new-user cohort with inverse-probability of treatment weighting

(IPTW cohort). Eligible participants were new-users of metformin with type-2 diabetes. To evaluate the influence of metabolic phenotypes (BMI, glycaemic control) and asthma phenotypes (type-2 inflammation, asthma severity), we conducted interaction analyses. Negative control analyses were conducted to assess for bias.

Exposure

The primary exposure was metformin; secondary exposures included add-on antidiabetic medications.

Main Outcomes

The primary outcome was first asthma exacerbation (short course of oral corticosteroids, unscheduled asthma-related hospital attendance or death) during 12-months follow-up. Incidence rate ratios (IRRs) with 95%CIs were estimated using fixed-effect conditional Poisson models in the SCCS and hazard ratios (HRs) were estimated using weighted Cox proportional hazards models in the cohort.

Results

Of over 2 million adults with asthma, we identified 4,278 patients for the SCCS and 8,424 patients for the IPTW cohort. Metformin was found to be associated with lower asthma attacks, of similar magnitude in both approaches (SCCS: IRR 0.68, [95%CI 0.62-0.75]; IPTW: HR 0.76 [0.67-0.85]). Negative control analyses did not find evidence of significant bias. HbA1c, BMI, blood eosinophil count and asthma severity did not modify the association ($p>0.05$). The only add-on antidiabetic medication to have an additive association was GLP-1RA (SCCS: IRR 0.60 [95%CI 0.49-0.73]).

Conclusions and Relevance

Metformin was associated with a lower rate of asthma attacks with further reduction with use of GLP-1RA. This appeared to be driven by mechanisms other than through glycaemic control or weight loss and occurred across asthma phenotypes.

Introduction

One in three adults with asthma are obese, of whom nearly half have type-2 diabetes mellitus (T2DM).[1] T2DM, insulin resistance and metabolic syndrome are independent risk factors for poor asthma control and asthma attacks.[2,3] These comorbidities hence lead to increased use of corticosteroids, which may exacerbate the underlying metabolic condition.

Globally, metformin is the first-line treatment for T2DM due to its effectiveness, excellent safety profile and affordability.[4,5] Although metformin has been used for decades, and has pleiotropic effects on multiple different organs, including the lungs, heart and nervous system, its mechanism of action is still not well understood.[6,7,8] Its pulmonary actions include anti-inflammatory effects and abrogation of airway remodelling and hyperresponsiveness, which may occur through several possible mechanisms.[9] First, through activation of AMP-activated protein kinase, a regulator of insulin signalling and glucose metabolism, shown to suppress murine airway inflammation and remodelling.[6,10,11] Second, through repression of the fatty acid-binding protein-4 pathway, a key regulator of murine eosinophilic airway inflammation and hyperresponsiveness.[12,13] Third, by downregulating insulin-like growth factor-1, which enhances airway inflammation, hyperresponsiveness, and smooth muscle hyperplasia.[14,15]

Although there is limited epidemiological evidence, three earlier studies found potential beneficial effects in asthma. A Taiwanese study found metformin was associated with 60% decrease in asthma attacks, but they did not account for smoking, weight and glycaemic control.[16] A US study found metformin was associated with 40% reduction in hospitalised asthma attacks, but had no effect on asthma-related oral corticosteroid use.[17] This study did not account for glycaemic control, therefore, in a population with available metabolic data, the same authors showed the association was independent of glycaemic control and

obesity.[18] No study considered the influence of asthma severity, type-2 inflammation, or other antidiabetic medications.

Of the add-on antidiabetic medications, glucagon-like peptide-1 receptor agonists (GLP-1RA) have shown the most promise in asthma.[19] GLP-1 has an excess number of receptors expressed in the lungs and reduces bronchial hyperresponsiveness in isolated airways.[20,21] One observational study found a 2-3 lower incidence of asthma attacks with GLP-1RA when compared to other antidiabetic medications.[22] The effect of metformin on this association was not evaluated.

Here, we assessed the association of metformin with asthma attacks, the influence of metabolic and asthma phenotypes and evaluated synergistic associations of add-on antidiabetic medications.

Methods

Data sources and participants

This study is reported following the recommendations of STROBE (Strengthening the Reporting of Observational Studies in Epidemiology).[23] The research was approved by Clinical Practice Research Datalink (CPRD) Research Data Governance for MHRA Database Research (protocol 22_002086). All patient data were deidentified; thus, the requirement for patient consent was waived by CRPD.

U.K.'s CPRD Aurum is a nationally representative database of primary care electronic healthcare records (using Read code and the SNOMED-CT classification systems), covering about 20% of the population and well-validated for epidemiological research.[24] Patient records were linked to Office for National Statistics (ONS) mortality data and Hospital Episode Statistics (HES) English hospital admission data. All code lists used are available (https://github.com/BoheeLEE/MetforminAsthma).

Our cohort included adults (>17 years) diagnosed with asthma, based on the presence ≥2 asthma codes within two years of cohort entry. Patients diagnosed with type-1 diabetes, chronic obstructive pulmonary disease and chronic kidney disease were excluded. Patients' '*cohort entry date'* was the latest date of their first asthma code, 1 January 2004, registry at a CPRD-linked GP practice and having ≥1 year of data. Patients '*cohort end date'* was the earliest date of transfer out of their GP practice, death, or 31 December 2020.

From this asthma cohort, we drew the '*metformin new-user cohort'*; consisting of people with T2DM who had not yet been prescribed metformin (**eFigure 1 in Supplement 1**). T2DM was defined as the presence ≥1 before cohort entry.

Study design

To increase robustness, we used a triangulation approach, applying two different designs, each with different biases: self-controlled case series (SCCS) and cohort design with propensity score methodology (**eFigures 2-3 in Supplement 1**).[25]

Self-controlled case series

In SCCS, each patient acts as their own control, implicitly controlling for confounding that is constant throughout the observation period (including genetics, socioeconomic status, metabolic dysfunction); time-varying confounding (e.g. age) is adjusted for within the model.[26] Only patients experiencing both exposure and the outcome were therefore eligible. We drew eligible patients from the metformin new-user cohort. The observation period started 12 months before exposure and ended 12 months after exposure or at the cohort end date.

To ensure valid and unbiased estimates, certain assumptions must be met.[26] First, the outcome should be independent of previous outcomes. Therefore, only incident outcome events were included by having a '*wash-out'* period of 12 months before the observation period, and only patients without an asthma attack during this wash-out period were eligible. But all patients had to have an asthma attack in the 24-month observation period. Second, the outcome should not change the probability of exposure. If the outcome only affects the

risk of the exposure within a short timeframe, any bias can be removed by using a '*pre-exposure period*' which is excluded from the analysis. We included a 31-day pre-exposure period as an asthma attack will lead to a GP practice visit, which in turn may precipitate reassessment of their diabetes and initiation of metformin. Third, the outcome should not censor the observation period, for example, death; this did not occur during the observation period.

Inverse probability of treatment weighting (IPTW) cohort

We drew eligible patients from the metformin new-user cohort. Patients' exposure status was defined during the first 12 months of cohort entry: exposed if metformin was initiated and unexposed if they were metformin-naïve. The IPTW cohort follow-up started on the index date (first metformin prescription for exposed, and cohort entry date for the unexposed). To reduce the risk of indication bias, patients were only eligible to be unexposed if they were eventually prescribed metformin (within 24 months of the end of the cohort). As a sensitivity analysis, we included all unexposed patients, regardless of if they went on to receive metformin or not. The IPTW cohort was censored at the earliest of 12 months follow-up, change of exposure status (either starting metformin if unexposed, or stopping metformin if exposed), first asthma attack, or cohort end date.

Exposures

Primary exposure (SCCS and IPTW)

Metformin: Exposure date was their first prescription. Only regular metformin users were included, defined as receiving prescriptions for metformin at least every 2 months until censored. A 30-day grace period was allowed to accommodate late prescription renewals. Patients who initiated inhaled corticosteroids and metformin concurrently, or were using other antidiabetic medications, were excluded.

Control exposures (SCCS only)

Dietary advice: As metformin is the only first-line diabetes medication, we could not conduct an active comparator study. Diet is often used as first-line diabetes management in the UK,[4,27,28] therefore, we used first code for 'diabetic diet review' in those not yet initiated on metformin as a control exposure.

Other drug exposures: To provide insight into possible bias, we evaluated two negative control exposures, using commonly prescribed medications in asthma, proton pump inhibitors and the antidepressant, citalopram.

Add-on antidiabetic medication exposures (SCCS only)

These included GLP-1RA, dipeptidyl peptidase 4 (DPP-4) inhibitors, sulphonylureas, sodium-glucose co-transporter-2 (SGLT-2) inhibitors and insulin. Patients had to have a prescription at least every two months to be included.

Outcomes

Primary outcome (SCCS and IPTW)

Our primary outcome was an asthma attack, defined as a short course of oral corticosteroids (5-7 days), asthma-related emergency department visit, hospital admission or death (ICD-10 codes J45 and J46).

Control outcomes (SCCS only)

As above, to further provide insight into possible bias, we also conducted several negative control outcomes. The controls were selected as common reasons for hospital admission and GP consultation in our study population that were not thought to be related to metformin use: hospitalisation for abdominal pain (ICD-10 K57), cellulitis (ICD-10 L03), arm fracture (ICD-10 S52) and GP minor ailments (sore throat, cold sore, coryzal symptoms, headaches and tiredness).

Covariates

Confounders (IPTW only)

The following variables were considered *a priori* to be potential confounders (**eFigure 4 in Supplement 1**): sex, age, socioeconomic deprivation (Index of Multiple Deprivation[29]), ethnicity, GP practice, year entered the IPTW cohort, body mass index (BMI, kg/m^2, categorised as normal:18.5-24.9, overweight: 25.0-29.9, obese: ≥30.0), HbA1c (<48mmol/mol [<6.5%] versus ≥48mmol/mol [≥6.5%]; most recent value within six months before study start), smoking history, cardiovascular disease and in the previous year: annual asthma review (yes/no), inhaled asthma medication (reliever only, ICS only, and ICS with '*add-on'* of long-acting bronchodilator or leukotriene receptor antagonist, further subcategorised by frequency: <4 prescriptions or ≥4) and asthma attack (none, 1, and ≥2).

Effect modifiers (SCCS and IPTW)

Potential modifiers assessed included sex, BMI, HbA1c blood eosinophil count (<0.3 and ≥0.3 $x10^9$/L [eosinophilia], highest value within 3 years) and asthma medication.

Statistical analysis

SCCS: We used fixed-effect conditional Poisson models to derive incidence rate ratios (IRR), comparing the control period (12-months before exposure) and the risk period (12-months after exposure or until censored). To examine for longitudinal associations, the risk period was segmented 0-90, 91-180 and 181-365 days. We adjusted models for the time-varying confounder, age. To calculate the number needed to treat, we used the event rate from the control and risk periods.[30] To investigate for effect modification, we fitted interactions and compared the interaction model with the main model using likelihood ratio tests.

IPTW: To achieve exchangeability between the exposed and unexposed, we used stabilised IPTW with crump trimming (propensity score trimming <0.1 and >0.9).[31] Weights were

estimated using probability of exposure assignment derived from multivariable logistic regression models, accounting for confounders (**eFigure 4 in Supplement 1**). Where variables had missing values, these were modelled with an unknown category. Absolute standardised differences were calculated to assess covariate balance, <0.10 indicating good balance.[32] To visually observe unadjusted and weighted cumulative incidence we applied Kaplan-Meier methodology. Weighted Cox proportional hazard models were fit to estimate the relative risk. No violations of the proportional hazard assumption were noted on visual inspection of Schoenfeld plots. Stratified analyses were conducted for potential effect modifiers. When multiple HbA1c values were available during follow-up, we analysed the association of the change in HbA1c, based on a minimum clinically important difference of 5.5 mmol/mol.

All statistical analysis was performed using STATA software version 17 (StataCop, College Station, Texas, USA).

Results

Obesity and T2DM prevalence in asthma

Of the adult asthma cohort (2,021,469) 81.5% had a recorded BMI (**eFigure 1 in Supplement 1**). Of those with a recorded BMI (1,648,396, median age 43.4 years [IQR 27.1-58.4]), 888,485 (53.9%) were overweight or obese (56.1% women). 114,375 (6.9%) had T2DM (38,859 [7.4%] in overweight and 50,594 [14·0%] in obese).

In the 799,286 overweight/obese asthma patients without a T2DM diagnosis, 230,194 (28.8%) had a documented HbA1c or blood glucose level; therefore, 71.2% had no glycaemic assessment. Of those with an elevated HbA1c (≥48 mmol/mol, 394,855 patients), only 16,189 (4.1%) received T2DM diagnosis within 2 years.

Patient characteristics: SCCS

4,278 patients were eligible; mean age was 52.9 years (SD 13.6), 61.2% were women, most were overweight (23.2%) or obese (70.8%); 37.3% were using ICS+add-on inhalers and just over half had eosinophilia (**Table1**).

Patient characteristics: IPTW cohort

8,424 were eligible: 5,892 metformin new-users (median follow-up 365 days, IQR 220-365) and 2,537 unexposed (median follow-up 365 days, IQR 341-365) (**Table2**). The median time to first metformin prescription from diabetes diagnosis was 394 days (IQR 291-498).

Association between metformin, diabetic diet review and asthma attacks

SCCS

Metformin was associated with a reduced risk of asthma attacks (adjusted IRR, aIRR, days 0-365: 0.68 [95%CI 0.62-0.75] p<0.001). The reduction occurred within three months (days 0-90, aIRR 0.66 [95%CI 0.58-0.74]) and remained for the subsequent nine months (days 91-180, 0.70 [0.61-0.79]; days 181-365, 0·73 [0.64-0.83]; **Figure1 and eTable 1 in Supplement 1**). The NNT with 12 months of metformin use to prevent one asthma attack was estimated at 14.

There was no association between diabetic diet review and asthma attacks (days 0-90, aIRR 0.93 [95% CI 0.84-1.04]; days 91-180, 1.02 [0.91-1.14]; days 181-365, 1.14 [1.01-1.28]).

IPTW cohort

The reduced risk of asthma attacks in the metformin new-users were visualised in the Kaplan-Meier plot and weighted cumulative incidence graph (**eFigures 5-6 in Supplement**

1). Incidence of first asthma attack per person-year were 0.26 (95% CI 0.24-0.27) in metformin-users and 0.32 (95% CI 0.28-0.35) in non-users.

Metformin was associated with a 24% lower risk of an asthma attack (weighted-HR 0.76 [95% CI 0.67-0.85]; **Figure2 and eTable 2 in Supplement 1**). In the sensitivity analysis (n=78,546), including all unexposed patients regardless of whether they eventually receive metformin or not, the risk remained similar (weighted-HR 0.80 [95% CI 0.75-0.87]).

Negative control analyses

Negative control exposures: There was no association between proton pump inhibitors and asthma attacks (**eTable 3 and eFigure 7 in Supplement 1).** In the citalopram model, asthma attacks were not reduced between 3 and 12 months but were reduced in the first three months.

Negative control outcomes: Metformin was not associated with a risk of hospital admission for abdominal pain, cellulitis, fracture, or GP visit for a minor ailment, **eTable 3 and eFigure 8 in Supplement 1**).

Additive associations of the add-on antidiabetic drugs

Only GLP-1RA was associated with a significant additional and persistent decrease in asthma attacks (days 0-365: IRR 0·60 [95% CI 0·49 to 0·73]; days 0-90: 0·45 [0·31-0·65]; days 91-180: 0·62 [0·45-0·87]; days 181-365: 0·66 [0·52-0·84]; **eFigure 9 and eTable 4 in Supplement 1**).

Influence of metabolic and asthma phenotypes

In the SCCS interaction analyses and the IPTW stratified analyses, there was no modification by markers of metabolic phenotype (BMI, HbA1c), asthma phenotype (eosinophil count, asthma severity) or sex (**Figure 2 and eTable5 and eTable2 in**

294 **Supplement 1**). Additionally, change in HbA1c did not modify the association between
295 metformin and asthma attacks (**eTable 6 in Supplement 1**).

Discussion

In this population-based asthma cohort, we found metformin, the first-line, affordable and effective antidiabetic drug, was associated with an approximate 30% reduction in asthma attacks. The magnitude and direction of the association were consistent and reproducible using two completely different analysis approaches, each with distinct advantages and potential biases; as well as being robust to multiple negative control analyses. Of the add-on antidiabetic medications, GLP-1RA was associated with an additional approximate 40% reduction in asthma attacks.

In our asthma cohort of around two million patients, over half were overweight/obese, often with inadequate glycaemic control, yet T2DM was frequently not diagnosed, and treatment delayed. Therefore, our study findings suggest dual benefit, potential for repurposing metformin to reduced asthma attacks and benefit of early pharmacological intervention for adults with asthma and metabolic dysfunction.

The observed association could be confounded by asthma medication adherence, occurring as an indirect result of the medical review that led to the instigation of metformin. However, a diabetic diet review, the first-line non-pharmacological intervention for diabetes in the UK, did not reduce asthma attacks. Moreover, metformin's association lasted for at least one year.

We found no evidence of significant residual confounding when conducting the broad range of negative control analyses. Only in the citalopram analysis, we found a smaller reduction in asthma attacks in the first 3 months, but there was no association between 3 and 12 months. The initial, non-sustained, citalopram-related reduction is in keeping with findings from three small clinical trials[33]; as such, the first three months of the analysis acted as a positive control and the following nine months as a negative control.

Glycaemic control (HbA1c) and baseline weight did not modify the association between metformin and asthma attacks in either analysis. We also evaluated the change in HbA1c, but improvement in glycaemic control did not affect the association. Altogether, these findings imply that metformin's mechanism of action in reducing asthma attacks was not related to its anti-glycaemic or weight loss actions.

We studied the influence of asthma phenotype and found that metformin was associated with reduced asthma attacks in all phenotypes, including those with blood eosinophilia or not, and in all levels of asthma severity.

Many of our findings are consistent with the three earlier observational studies.[16,17,18] While a US study only found a reduction in hospitalised asthma attacks,[17] a Taiwanese study found a significant reduction in oral corticosteroids but not in emergency department visits.[16] This unexplained discrepancy in their findings could have been related to bias from missing confounders, including BMI, HbA1c, smoking and asthma characteristics. The US group later conducted another study, including metabolic variables, but due to sample size, were unable to employ a new-user design, and found the same findings.[18]

Our findings align with experimental evidence of GLP-1's pulmonary effects. In animal studies, GLP-1 reduces glucose-mediated oxidative stress, aeroallergen-induced neutrophilia, and lung protein excretion of interleukin(IL)-4, IL-5, IL-13 and IL-33.[34,35,-36] An epidemiology study in asthma found GLP-1RA (448 patients) was associated with reduced asthma attacks by 2-3 fold, in comparison to other add-on antidiabetic drugs.[22] GLP-1RA shows great potential, but metformin has considerable advantages, including global availability and affordability.

Although insulin was initially associated with reduced asthma attacks, this association was not sustained. The temporary reduced risk in the first six-months was approximately half that of GLP1-RA, comparable to the U.S. study directly comparing GLP1-RA to insulin.[22] In that same study, the authors compared GLP1-RA to other add-on antidiabetic medications and

found only GLP1-RA was associated with a reduction in asthma attacks, again comparable to our findings.

Our study has several strengths. We utilised one of the largest longitudinal healthcare databases worldwide. We applied a triangulation approach to increase the reproducibility and robustness of our findings including SCCS design which completely mitigates confounding that remains constant over the observation period and a new-user cohort design, as well as multiple negative control analyses. Our dataset offers the opportunity to compare metformin to diet review, an intervention that may not be available in other healthcare systems.

We also acknowledge some limitations. Like all observational studies, a risk of residual confounding. To reduce indication bias in the IPTW cohort, we only included unexposed patients who started metformin shortly after their follow-up ended. We reduced time-varying confounding by only including 12-months follow-up. We could not assess medication adherence, but only included patients with consecutive prescriptions. We could not assess metformin dose as this was often missing. We could not examine change in weight; however, the magnitude of weight loss is relatively low with metformin (2-5% per year),[37,38] so is unlikely to explain the observed association. Some patients may have been misdiagnosed as asthma, but the association was observed across asthma phenotypes, those on higher inhaler doses with eosinophilia were less likely to be misclassified. We do not have information on asthma biologics as these are prescribed through an external system for high-cost medications.

In summary, we observed that metformin was associated with around 30% lowering of asthma attacks. GLP-1RA had a synergistic association of further 40% reduction. These findings suggest potential for repurposing antidiabetic drugs to much-needed alternative treatments for asthma. Further research, including randomised controlled trials and

mechanistic studies are now needed to confirm their effect and mechanism of action in asthma.

Acknowledgement

This study is supported by Asthma + Lung UK. We acknowledge and appreciate the support of the patient advisory members including Olivia Fulton, Viviene Tickle, Mary Gibbeson, Amanda Sayers and Sue Lang, for their review and feedback. We would also like to thank CPRD and HES for providing access to the datasets used for analysis. This study is based in part on data from the CPRD obtained under licence from the UK Medicines and Healthcare Products Regulatory Agency. The data are provided by patients and collected by the NHS as part of their care and support. HES data (Copyright © 2022) were re-used with the permission of The Health & Social Care Information Centre. All rights reserved. The interpretation and conclusions contained in this study are those of the authors alone.

Contributors

CIB conceived the research question and study design. BL and KKCM reviewed the study design. BL performed the data analysis. CIB, BL, KKCM, EW, TT and AS interpreted the data. BL wrote the first draft of the manuscript. All authors critically reviewed the manuscript. BL and CIB had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors had final responsibility for the decision to submit for publication.

Conflict of Interest Disclosures

CIB reports grants from Asthma + Lung UK and the National Institute for Health Research Imperial Biomedical Research Centre. BL reports grants from Asthma + Lung UK. All other authors declare no competing interests.

Funding/Support

This research was supported by Asthma + Lung UK (WADR22\100003).

Role of the Funder/Sponsor

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication

Data sharing statement

This study used anonymised electronic health records, CPRD obtained under license from the UK Medicines and Healthcare Products Regulatory Agency. According to the UK Data Protection Act, electronic health records are regarded as “sensitive data”, which prevents data sharing via public deposition. To access CPRD data and linked data such as Hospital Episodes Statistics, data from the Office for National Statistics, and multiple deprivation index data, it requires approval via CPRD’s Research Data Governance (RDG) Process (https://cprd.com/data-access). Data management was provided by the Big Data and Analytical Unit at the Institute of Global Health Innovation.

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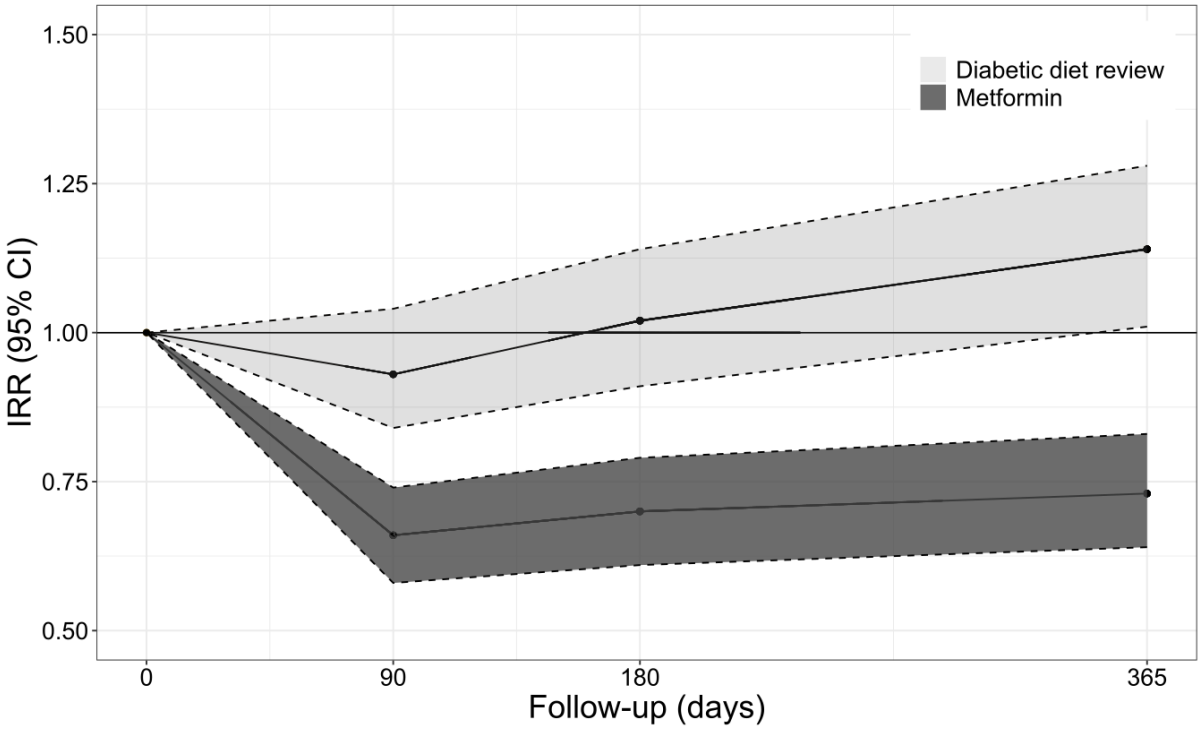

Figure 1. Association between metformin and diabetic diet review and asthma attacks (SCCS).

Abbreviations: SCCS=self-controlled case series, IRR=incidence rate ratio. 95% CI=95% confidence interval. Shaded area shows 95% confidence interval. Line graph shows the relative incidence rates of asthma attacks in the SCCS analysis: (dark grey) comparing rates after metformin was initiated to before, (light grey) comparing rates after first diabetic diet review to before the review.

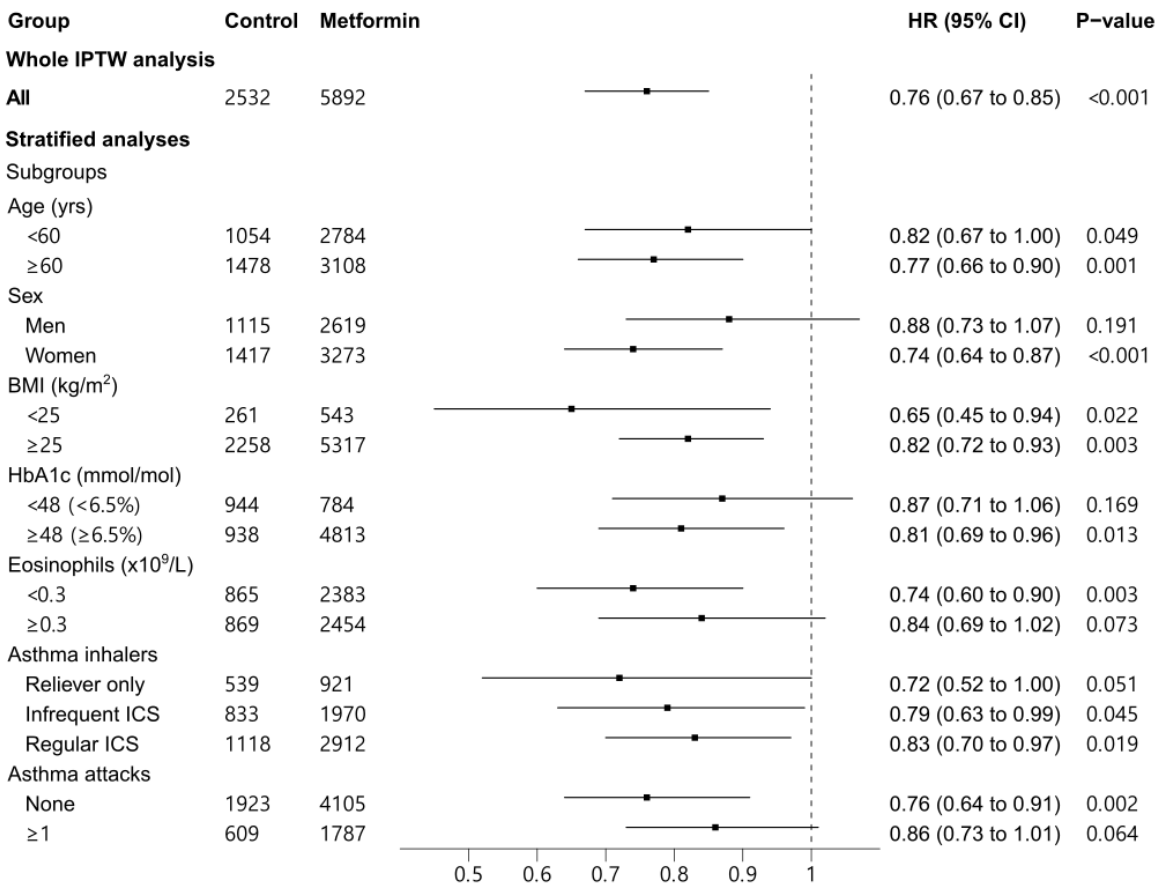

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Figure 2. Association between metformin and asthma attacks, main analysis and stratified analysis (IPTW)

Abbreviations: IPTW=inverse probability of treatment weighting, HR=hazard ratio, 95%CI= 95% confidence interval, BMI=body mass index (kg/m^2), HbA1c=haemoglobin A1C, ICS=inhaled corticosteroids

Table 1. Characteristics of the patients eligible for the SCCS analysis

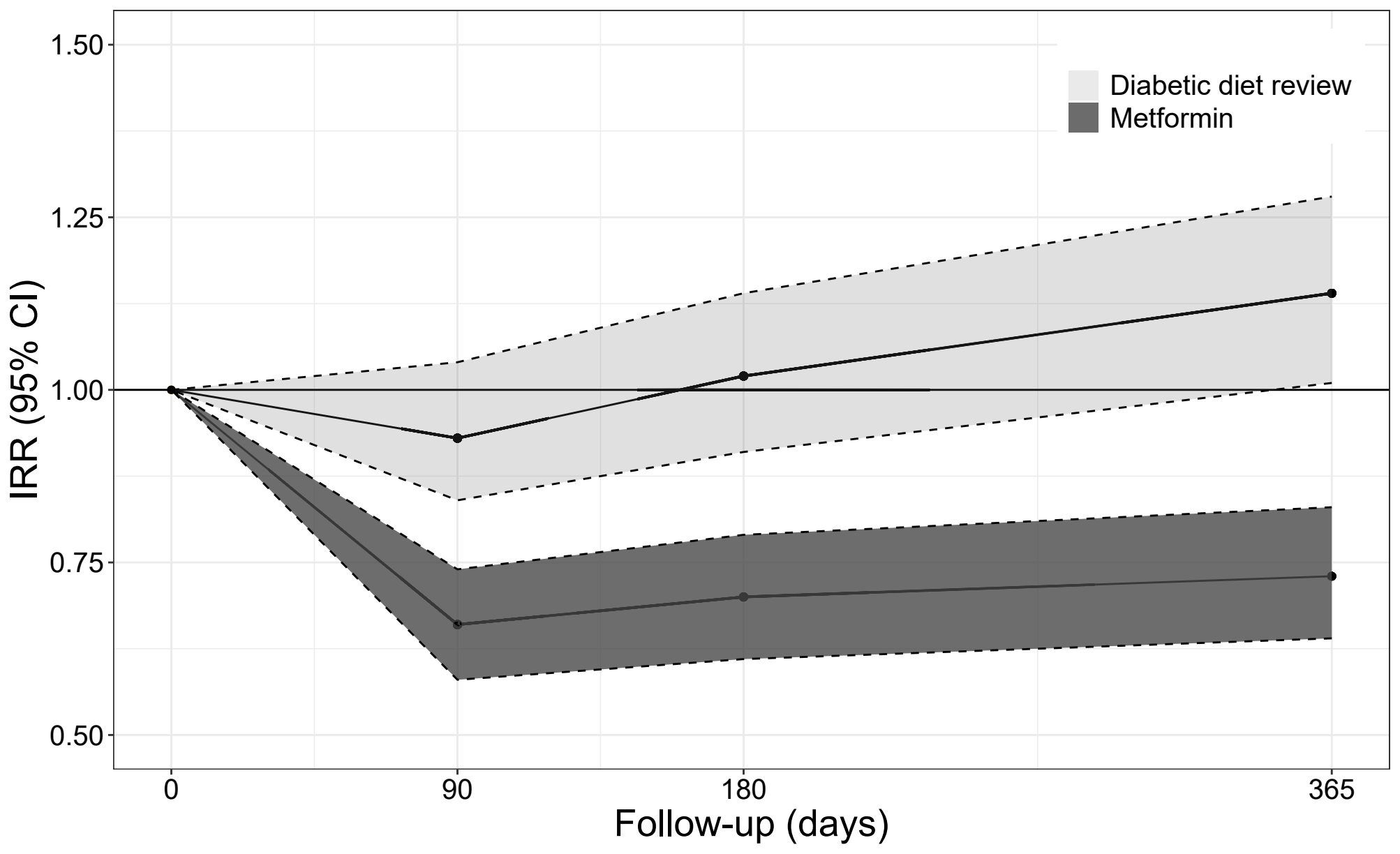
Characteristics	N (%)
Total	4,278 (100.0%)
Mean (SD) age (years)	52.9 (13.57)
Women	2,617 (61.2%)
Ethnicity	
Asian	478 (11.2%)
Black	162 (3.8%)
Mixed	47 (1.1%)
White	3,433 (80.3%)
Other	29 (0.7%)
Unknown	129 (3.0%)
IMD	
1 (least deprived)	654 (15.3%)
2	707 (16.5%)
3	764 (17.9%)
4	972 (22.7%)
5	1,176 (27.5%)
Unrecorded	5 (0.1%)
BMI (kg/m2)	
Normal (18.5 – 25)	248 (5.8%)
Overweight (25 - 30)	993 (23.2%)
Obese (>30)	3,030 (70.8%)
Unrecorded	7 (0.2%)
HbA1c (IPCC, mmol/mol)	
<48 (<6.5%)	1,253 (29.3%)
≥48 (≥6.5%)	2,848 (.66.6%)
Unrecorded	177 (4.1%)
Smoking status	
Never	1,503 (35.1%)
Ex-smoker	1,648 (.8.5%)
Current smoker	1,081 (25.3%)
Unrecorded	46 (1.1%)
Comorbidities	
Depression	1,083 (25.3%)
Gastroesophageal reflux disease	864 (20.2%)
Ischemic heart disease	316 (7.4%)
Heart failure	16 (0.4%)
Asthma variables	
Atopy	1,682 (39.3%)
Blood eosinophil count (x10^9/L)	
<0.3	1,596 (.37.3%)
≥0.3	1,735 (.40.6%)
Unrecorded	947 (22.1%)
Inhaled medication, year before exposure	
Reliever only	1,289 (30.1%)
Infrequent ICS only	704 (16.5%)
Regular ICS only	665 (15.5%)
Infrequent ICS+add-on	468 (10.9%)
Regular ICS+add-on	1,128 (26.4%)
Others	24 (0.6%)

Abbreviations: SD=standard deviation, SMD= standardised mean difference, IMD=index of multiple deprivation, HbA1c=haemoglobin A1C, ICS= inhaled corticosteroids, BMI = body mass index.

Table 2. Characteristics of the IPTW cohort (N=8,625)

	Before weighting			After weighting		
Characteristics	**Unexposed (no metformin)**	**Exposed (metformin use)**	**SMD**	**Unexposed (no metformin)**	**Exposed (metformin use)**	**SMD**
Total	2,532	5,892	*N/A*	8600	8631	*N/A*
Mean (SD) age (years)	61.61 (13.18)	59.74 (13.70)	0.139	60.27 (13.36)	60.35 (13.79)	0.006
Cohort year entry (median)	2008	2009	0.206	2009	2009	0.011
Women	1,417 (56.0 %)	3,273 (55.6%)	0.008	4676 (55.7 %)	4682 (55.5 %)	0.004
Ethnicity						
Asian	268 (10.6%)	605 (10.3%)	0.010	890 (10.6 %)	894 (10.6 %)	<0.001
Black	84 (3.3%)	207 (3.5%)	0.011	294 (3.5 %)	295 (3.5 %)	<0.001
Mixed	18 (0.7%)	57 (1.0%)	0.028	92 (1.1 %)	76 (0.9 %)	0.015
White	1,911 (75.5%)	4,458 (75.7%)	0.004	6288 (74.9 %)	6352 (75.3 %)	0.009
Other	22 (0.9%)	52 (0.9%)	0.001	84 (1 %)	76 (0.9 %)	0.008
Unknown	229 (9.0%)	513 (8.7%)	0.012	747 (8.9 %)	742 (8.8 %)	0.005
IMD						
1 (least deprived)	315 (12.4%)	742 (12.6%)	0.005	1033 (12.3 %)	1038 (12.3 %)	0.001
2	423 (16.7%)	922 (15.6%)	0.029	1410 (16.8 %)	1358 (16.1 %)	0.019
3	489 (19.3%)	1,086 (18.4%)	0.023	1478 (17.6 %)	1569 (18.6 %)	0.028
4	593 (23.4%)	1,348 (22.9%)	0.013	1964 (23.4 %)	1949 (23.1 %)	0.006
5	712 (28.1%)	1,794 (30.4%)	0.051	2510 (29.9 %)	2514 (29.8 %)	0.002
BMI (kg/m^2)						
Normal	261 (10.3%)	543 (9.2%)	0.037	856 (10.2 %)	835 (9.9 %)	0.007
Overweight	725 (28.6%)	1,517 (25.7%)	0.065	2258 (26.9 %)	2227 (26.4 %)	0.01
Obese	1,533 (60.5%)	3,800 (64.5%)	0.082	5222 (62.2 %)	5323 (63.1 %)	0.018
Unrecorded	13 (0.5%)	32 (0.5%)	0.004	67 (0.8 %)	51 (0.6 %)	0.025
HbA1c (mmol/mol/%)						
<48 (<6.5%)	944 (37.3%)	784 (13.3%)	0.574	1746 (20.8 %)	1738 (20.6 %)	0.005
≥48 (≥6.5%)	938 (37.0%)	4,813 (81.7%)	1.020	5700 (67.9 %)	5745 (68.1 %)	0.005
Unrecorded	650 (25.7%)	295 (5.0%)	0.599	949 (11.3 %)	953 (11.3 %)	0.001
Smoking status						
Never	816 (32.2%)	1,755 (29.8%)	0.053	2577 (30.7 %)	2565 (30.4 %)	0.006
Ex-smoker	1,018 (40.2%)	2,464 (41.8%)	0.033	3518 (41.9 %)	3501 (41.5 %)	0.007
Current smoker	640 (25.3%)	1,620 (27.5%)	0.050	2199 (26.2 %)	2252 (26.7 %)	0.013
Unrecorded	58 (2.3%)	53 (0.9%)	0.111	109 (1.3 %)	110 (1.3 %)	0.002
Comorbidities						
Ischemic heart disease	217 (8.6%)	414 (7.0%)	0.058	680 (8.1 %)	658 (7.8 %)	0.008
Heart failure	17 (0.7%)	30 (0.5%)	0.021	50 (0.6 %)	51 (0.6 %)	0.001
Asthma characteristics in year before IPTW cohort entry						
Annual asthma review	512 (20.2%)	2,121 (36.0%)	0.356	2586 (30.8 %)	2624 (31.1 %)	0.007
Inhaled medication*						
Reliever only	539 (21.3%)	921 (15.6%)	0.146	1410 (16.8 %)	1443 (17.1 %)	0.007
Infrequent ICS only	600 (23.7%)	1,266 (21.5%)	0.053	1914 (22.8 %)	1898 (22.5 %)	0.008
Regular ICS only	461 (18.2%)	1,097 (18.6%)	0.011	1486 (17.7 %)	1552 (18.4 %)	0.018
Infrequent ICS+add-on	233 (9.2%)	704 (11.9%)	0.089	1007 (12.0 %)	953 (11.3 %)	0.021
Regular ICS+add-on	657 (25.9%)	1,815 (30.8%)	0.108	2451 (29.2 %)	2463 (29.2 %)	<0.001
Other	42 (1.7%)	89 (1.5%)	0.012	126 (1.5 %)	135 (1.6 %)	0.005
Asthma attacks						
None	1,923 (75.9%)	4,105 (69.7%)	0.141	5960 (71 %)	6023 (71.4 %)	0.01
One	340 (13.4%)	954 (16.2%)	0.078	1301 (15.5 %)	1291 (15.3 %)	0.005
More than one	269 (10.6%)	833 (14.1%)	0.107	1133 (13.5 %)	1114 (13.2 %)	0.008

Abbreviations: SD=standard deviation, SMD= standardised mean difference, IMD=index of multiple deprivation, HbA1c=haemoglobin A1C, ICS= inhaled corticosteroids. Note: Data are number (%) unless stated otherwise. After weighting shows the number of patients in the weighted pseudo population (the actual number of patients did not change).


1.50
1.25
1.00
0.75
0.50
IRR (95% CI)
0
90
180
365
Follow-up (days)
Diabetic diet review
Metformin

Group	Control	Metformin	HR (95% CI)	P−value
Whole IPTW analysis				
All	2532	5892	0.76 (0.67 to 0.85)	<0.001
Stratified analyses				
Subgroups				
Age (yrs)				
<60	1054	2784	0.82 (0.67 to 1.00)	0.049
≥60	1478	3108	0.77 (0.66 to 0.90)	0.001
Sex				
Men	1115	2619	0.88 (0.73 to 1.07)	0.191
Women	1417	3273	0.74 (0.64 to 0.87)	<0.001
BMI (kg/m^2)				
<25	261	543	0.65 (0.45 to 0.94)	0.022
≥25	2258	5317	0.82 (0.72 to 0.93)	0.003
HbA1c (mmol/mol)				
<48 (<6.5%)	944	784	0.87 (0.71 to 1.06)	0.169
≥48 (≥6.5%)	938	4813	0.81 (0.69 to 0.96)	0.013
Eosinophils (x10^9/L)				
<0.3	865	2383	0.74 (0.60 to 0.90)	0.003
≥0.3	869	2454	0.84 (0.69 to 1.02)	0.073
Asthma inhalers				
Reliever only	539	921	0.72 (0.52 to 1.00)	0.051
Infrequent ICS	833	1970	0.79 (0.63 to 0.99)	0.045
Regular ICS	1118	2912	0.83 (0.70 to 0.97)	0.019
Asthma attacks				
None	1923	4105	0.76 (0.64 to 0.91)	0.002
≥1	609	1787	0.86 (0.73 to 1.01)	0.064