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# The impact of therapy on the risk of asthma in type 2 diabetes

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## Abstract

**Background and Objectives:** There are limited data about the risk of asthma in people with diabetes. We examined the incidence of asthma in subjects with type 2 diabetes (T2DM) compared to controls, and the association with metformin, sulphonylureas and insulin therapy.

**Materials and Methods:** We conducted a retrospective cohort study using a representative UK primary care database ($N = 894\,646$ adults). We used 1:1 propensity score matching (age, gender, socio-economic deprivation, body mass index and smoking status) to match 29 217 pairs of T2DM cases and controls. We used Cox proportional hazard regression to compare the incidence of asthma in both groups over 8 years of follow-up. In those with T2DM, we used Cox proportional hazard regression to assess for any impact of antidiabetic medications on asthma incidence.

**Results:** Individuals with T2DM were less likely to develop asthma than matched controls (hazard ratio [HR] 0.85, 95% CI 0.77-0.93). Insulin increased the risk of incident asthma (HR 1.25, 95% CI 1.01-1.56), whilst metformin and sulphonylureas were associated with reduced risk (HR 0.80, 95% CI 0.69-0.93 and HR 0.76, 95% CI 0.60-0.97, respectively). There was no association with diabetes duration, complications or glycaemic control.

**Conclusions:** T2DM may have a protective effect against asthma development. Insulin use was associated with an increased risk of asthma, while metformin and sulphonylureas reduced the risk in those with T2DM.

**KEYWORDS**
asthma, computerised medical records, metformin, type 2 diabetes

## 1 | INTRODUCTION

Asthma is a condition that arises from the complex interaction between environmental and genetic factors.[1] Obesity is a recently understood risk factor for asthma development, and cluster analyses have shown "obese asthma" to be a distinct subtype with a different treatment response to other forms.[2]

Obesity is a component of the metabolic syndrome, a cluster of biochemical and physiological parameters that predispose to cardiovascular disease and systemic inflammation.[3] This has led to interest in whether other components of the metabolic syndrome, such as type 2 diabetes, may be independently associated with asthma development.[4]

Prevalence studies involving hospitalised patients have shown T2DM and asthma to coexist more frequently than would be expected by chance.[5] Additionally, an American retrospective cohort study of 1.8 million patients demonstrated a modest increase in asthma incidence (HR 1.08, 1.03-1.12) in those with T2DM compared to healthy controls,[6] and a recent Taiwanese retrospective cohort study yielded similar

  

results (HR 1.30, 1.24-1.38).[7] These studies were limited by the use of asthma-related hospitalisation as the primary end point and potentially confounded by body mass index (BMI).

There is also emerging evidence to suggest that antidiabetic agents may have effects on airways disease. Insulin receptors are present in the lung and when activated, may lead to smooth muscle contraction.[8] Conversely, metformin has antiinflammatory properties, which may reduce airways hyperresponsiveness.[7]

The main aim of this study was to investigate the incidence of asthma in people with T2DM compared with matched controls over 8 years of follow-up. We also examined the impact of metformin, sulphonylureas and insulin on the risk of asthma incidence in a secondary analysis.

## 2 | MATERIALS AND METHODS

### 2.1 | Data source and study design

We conducted a retrospective cohort study using the Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) database. The RCGP RSC comprises pseudonymised data collected from 160 English primary care practices, representing the computerised medical records (CMRs) of over 1.7 million patients.[9] "Read" codes are used to code detailed clinical information in a consistent manner between clinicians and CMR systems.

The data completeness is high due to GP pay-for-performance incentives for chronic disease management and has electronic links to pathology results and prescriptions.[10] The RCGP RSC has been shown to be a representative sample of the population of England in terms of demographics and clinical outcomes and we have conducted a number of studies to demonstrate its utility for studies in diabetes.[11] This study is one of a pair of studies we conducted looking at respiratory disease in T2DM, and utilises the same patient sample and study protocol.[12]

### 2.2 | Study population and definition of variables

The study covered an 8-year period from December 31, 2008 to December 31, 2016. We included all registered patients aged over 18 without a baseline diagnosis of asthma, COPD or T1DM and who remained in the database for the study duration. Baseline COPD formed part of our exclusion criteria due to the high prevalence of asthma-COPD overlap in adults aged over 40.[13]

Included participants were categorised into those with and without T2DM at baseline. T2DM cases were detected using an ontology-based algorithm, which has been repeatedly utilised and validated by our department.[14] Misclassification of diabetes type is common when diagnostic codes alone are used to identify patients with T1DM and T2DM.[15] The first three steps of our categorisation algorithm allow overriding of diagnostic codes where clinical characteristics are highly likely to indicate a specific type of diabetes.

The study outcome measure was a new diagnosis of asthma during the follow-up period. A patient was classified as an asthma "case" if they had an asthma diagnostic code recorded (eg, atopic asthma) or if they had a process of care code recorded (eg, "asthma medication review").[16] A full list of the Read codes used to detect cases is included in the Supplementary Materials. Additional data collected included: age, gender, BMI, socioeconomic status as measured using IMD score (the official national measure of social deprivation), baseline smoking status and comorbidities (angina, previous stroke or transient ischaemic attack, previous myocardial infarction and hypertension).

For individuals with T2DM, data pertaining to baseline antidiabetic medications (insulin, metformin and sulphonylureas (full list in Supplementary Materials), years of diabetes, HbA1c values (in the preceding 2 years to study end) and presence of diabetic complications (chronic kidney disease [CKD], peripheral neuropathy and retinopathy [inclusive of background retinopathy]) were also examined. Participants with any missing data for the variables of interest were excluded from the analysis. To improve accuracy of the documented onset date of the index conditions, the first date a code consistent with that diagnosis was entered in the patient record was taken.[12]

### 2.3 | Statistical analysis—primary outcomes

To adjust for potential confounding factors between patients with and without a diagnosis of T2DM at baseline, propensity score matching in a 1:1 ratio was used with the following variables included in the propensity score: age, gender, BMI, IMD decile and smoking status.[12] The propensity score matching was conducted using SQL Server software and is explained further in Supplementary Materials.

All individuals entered the study on the December 31, 2008 and accumulated time until the date of asthma diagnosis or the study end. We calculated the incidence of asthma per 1000 person-years of follow-up for both groups. We generated cumulative incidence analysis curves grouped by T2DM status and then calculated adjusted hazard ratios (HRs) with accompanying 95% confidence intervals (95% CI) using Cox proportional hazards analysis.[12] Given that baseline variables were balanced between the propensity-matched groups, only the exposure variable of interest, T2DM, was included as an independent variable.

As a sensitivity analysis, we produced Cox proportional hazard regression models using the entire study population. We adjusted the models for age, gender, BMI, smoking status and IMD score.[12] Models were replicated without adjustment

for BMI to assess the impact of this variable on the overall results.

### 2.4 | Statistical analysis—secondary outcomes

In the T2DM group (from the propensity-matched pairs), we assessed the impact of the following variables on the asthma incidence as per the study protocol: antidiabetic medications at baseline (insulin, metformin, sulphonylureas), length of diabetes diagnosis, presence of diabetic complications and HbA1c.

Each predictor variable was initially examined using unadjusted cumulative incidence analysis. The variables were subsequently assessed simultaneously in a multivariate model. We also adjusted the model for age, gender, BMI, IMD score and smoking status. Backward stepwise elimination of variables was performed for the multivariate model selection with removal of variables to minimise the Akaike information criterion (AIC), the marker of relative statistical model quality.

The data analysis was performed using the statistical package R version 3.2.5 with use of the "Survival" package.

## 3 | RESULTS

### 3.1 | Baseline characteristics

A total of 894 646 adults were included in the study. A total of 29 222 (3.7%) of these had a diagnosis of T2DM at baseline and were classified as T2DM cases (see Figure S1).

The characteristics of those with and without T2DM are shown in Table 1.

Propensity score matched controls were found for 29 217 of the 29 222 T2DM cases (99.9%). There were no significant differences between the matched pairs on any of the matching criteria (age, BMI, IMD decile and smoking status) (see Table S1).

Additional characteristics of the T2DM cases are shown in Table 2.

**TABLE 1** Characteristics of the study cohort

| | People with type 2 diabetes $n = 29\,222$ | People without type 2 diabetes $n = 865\,424$ |
|---|---|---|
| Age (Mean ± SD) | 69.83 (12.3) | 48.54 (18.3) |
| Sex = F (*n*, %) | 12 411 (42.5) | 469 059 (54.2) |
| BMI (Mean ± SD) | 30.30 (6.2) | 26.30 (5.7) |
| IMD Quintile (*n*, %) | | |
| 1 (most deprived) | 5303 (18.1) | 140 805 (16.3) |
| 2 | 5064 (17.3) | 148 678 (17.2) |
| 3 | 5393 (18.5) | 153 660 (17.8) |
| 4 | 6360 (21.8) | 189 634 (21.9) |
| 5 (least deprived) | 7102 (24.3) | 232 647 (26.9) |
| Smoking status (*n*, %) | | |
| Non-smoker | 9068 (31.0) | 425 393 (49.2) |
| Ex-smoker | 14 187 (48.5) | 236 054 (27.3) |
| Active smoker | 5967 (20.4) | 203 977 (23.6) |
| Comorbidities (*n*, %) | | |
| Angina | 3584 (12.3) | 16 872 (1.9) |
| Myocardial infarction | 2590 (8.9) | 13 840 (1.6) |
| Ischaemic stroke/TIA | 2776 (9.5) | 17 643 (2.0) |
| Hypertension | 21 068 (72.1) | 162 053 (18.7) |

**TABLE 2** Characteristics of the type 2 diabetes cases

| | Type 2 diabetes cases ($n = 29\,217$) |
|---|---|
| Years of diabetes[a] (Mean ± SD) | 13.92 years (5.6) |
| Mean HbA1c[b] (Mean ± SD) | 57.8 mmol/L (17.5) |
| Medications at baseline (*n*, %) | |
| Insulin | 3300 (11.30) |
| Metformin | 16 258 (55.8) |
| Sulphonylurea | 4159 (14.2) |
| Diabetic complications (*n*, %) | |
| Peripheral neuropathy | 3758 (12.9) |
| Retinopathy | 26 005 (89.0) |
| CKD stage 3+ | 9228 (31.6) |

[a]Up to December 31, 2016, years since code consistent with T2DM diagnosis first entered in GP record.
[b]From January 1, 2015 to December 31, 2016.

### 3.2 | The incidence of asthma in individuals with type 2 diabetes

During the follow up period (mean 7.89 years for T2DM cases and 7.87 years for controls), there was a total of 1739 new cases of asthma in the 58 434 matched pairs. The crude incidence rate of asthma in the T2DM and control groups per 1000 person-years was 3.47 (95% CI 3.23-3.71) and 4.09 (95% CI 3.83-4.35), respectively.

The reduced incidence of asthma in T2DM compared with controls can be seen in the cumulative incidence analysis curves in Figure 1.

In the Cox proportional hazards regression model, the HR for incident asthma was 0.85 (95% CI 0.77-0.93, $P < 0.001$) in the T2DM group in comparison to controls.

As per protocol, the Cox proportional hazard model was repeated on the entire study population ($n = 894\,646$) as a sensitivity analysis. A lower incidence of asthma was found in those with T2DM (HR 0.87; 95% CI 0.81-0.94) compared to those without after adjusting for age, gender, BMI, IMD

score and smoking status (see Table S2). When adjustment for BMI was removed from the model, this difference was lost (HR 0.98; 95% CI 0.92-1.06) (see Table S3).

### 3.3 | Secondary analysis

New onset asthma was more common in people with T2DM ($n = 29\,217$) who were prescribed insulin at baseline and less common in those prescribed metformin and sulphonylureas (see Table 3 and Figure S2). After adjustment for confounders in Cox regression models these differences remained.

Diabetes duration (years since diabetes first indicator), glycaemic control (most recent HbA1c to study end) and the presence of diabetic complications did not affect asthma risk (see Table S4).

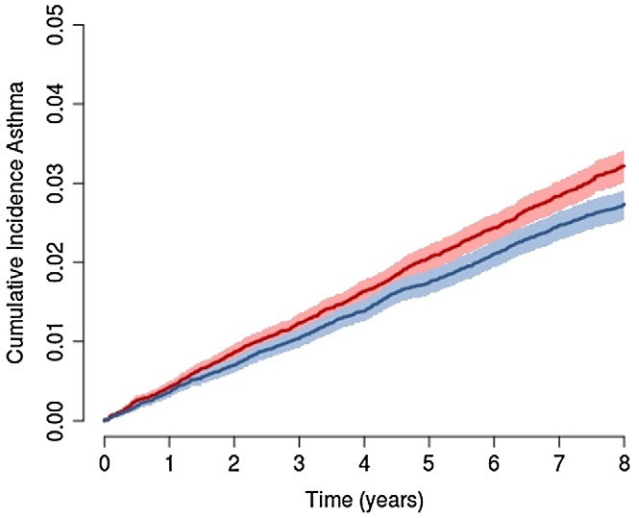


**FIGURE 1** Cumulative incidence of asthma over 8 years of follow-up in type 2 diabetes cases and matched controls Key: Red = controls, blue = type 2 diabetes cases.

## 4 | DISCUSSION

In this retrospective cohort study, we found a reduced incidence of asthma in individuals with T2DM compared with matched controls. In those with diabetes, insulin use was associated with a higher incidence of asthma after adjusting for potential confounders. Metformin and sulfonylurea use were both associated with a lower incidence of asthma.

### 4.1 | Reduced incidence of asthma in T2DM—a medication effect?

Potential explanations for a reduced incidence of asthma in those with T2DM include both medication-related and physician-related concepts. We observed an increased risk of incident asthma in those prescribed insulin at baseline compared to those who did not require insulin and a reduced incidence of asthma in those prescribed metformin and sulphonylureas. There was no relationship between length of T2DM diagnosis, presence of diabetic complications or HbA1c on asthma risk, suggesting that these findings may be reflective of a characteristic of the medications themselves and not of the underlying disease severity.

At baseline, metformin was taken by 55.8% of those with T2DM, sulphonylureas were taken by 14.2% and insulin was taken by 11.3%. No controls took these medications at baseline. Consequently, the reduced incidence of asthma observed in the T2DM patients may reflect the high prevalence of metformin and sulphonylurea use and its potential protective effect.

Metformin, which is thought to work by AMP-K enzyme activation, is known to have antiinflammatory properties.[17] In mice models it has been shown to reduce allergic eosinophillic airway inflammation and normalise AMP-K levels in lung tissue.[18] It may also reduce smooth muscle proliferation by AMP-K-mediated pathways.[19]

**TABLE 3** Impact of additional variables on incidence of asthma in type 2 diabetes cases

| | Univariate HR estimates (95% CI) | Adjusted HR from multivariate model with backward stepwise elimination (95% CI) |
|---|---|---|
| Years of diabetes[a] | 1.01 (0.99-1.02) | 1.01 (1.00-1.03) |
| Mean HbA1c[b] | 1.00 (0.99-1.01) | - |
| Diabetic complications[c] | 1.10 (0.82-1.48) | - |
| Medications at baseline | | |
| Insulin | 1.39 (1.15-1.69) | 1.25 (1.01-1.56) |
| Metformin | 0.85 (0.74-0.98) | 0.80 (0.69-0.93) |
| Sulphonylurea | 0.68 (0.54-0.85) | 0.76 (0.60-0.97) |

[a]On December 31, 2016.
[b]From January 1, 2015 to December 31, 2016.
[c]CKD/retinopathy/peripheral neuropathy.

Metformin has previously been shown in small studies to improve lung function in individuals with COPD,[20] and to reduce the rate of asthma exacerbations (OR 0.39, 95% CI 0.19-0.79) and hospitalisation frequency (OR 0.21, 95% CI 0.07-0.63) in those with asthma and co-morbid diabetes.[21] Our findings also align with previous observational studies which have demonstrated a reduced incidence of asthma in metformin users.[9]

To our knowledge, ours is the first study to demonstrate an association between asthma and sulphonylurea use in humans. In mouse models, glibenclamide has been shown to attenuate eosinophil-mediated airways inflammation and hyperresponsiveness.[22] Sulphonylureas stimulate insulin secretion from β cells by inhibiting ATP-sensitive potassium channels.[22] Our findings here may potentially demonstrate the difference between exogenous and endogenous insulin on the incidence risk of asthma, when considered alongside our results from insulin users. Another class of insulin secretagogue, glucagon-like peptide-1 analogues, also display promising antiinflammatory effects in mouse models,[23] and have recently been proposed as potential novel treatments for obesity-associated asthma.[24]

Our findings relating to insulin are consistent with those of Chen et al[7] who observed an increased risk of asthma in patients with diabetes who are regularly prescribed insulin compared with matched controls (OR 2.23, 1.52-3.58). Previous work by this group has yielded similar results.[25] The lung is known to have insulin receptors, and high levels of insulin binding may promote airway smooth muscle contraction and hyperresponsiveness.[8]

Our finding of a reduced incidence of asthma in those with T2DM may also represent diagnostic patterns. Both T2DM and asthma have an insidious onset and may be underdiagnosed. Recognition of asthma may be more difficult in patients with T2DM as exacerbations may initially be considered to be respiratory tract infections given the increased risk of infection in diabetes.[26] Furthermore, patients with T2DM may be less likely to exert themselves[27] and experience exercise-induced bronchospasm which could herald a diagnosis of asthma.

## 4.2 | Comparison with previous work

Our results contrast those seen in two previous studies on the risk of incident asthma in T2DM. Ehrlich et al[6] found a higher incidence of asthma in those with diabetes compared with controls in an American cohort of 1 811 220 individuals, after adjusting for age, BMI and smoking status. However, new cases of asthma were limited to those that required hospitalisation and had "asthma" documented as their primary discharge diagnosis or cause of death. Destabilisation of asthma tends to be caused by infections, and the risk of common infections is increased in those with diabetes.[26] These findings may therefore represent increased exacerbations, not new cases.

Chen et al[7] also reported an increased risk of asthma in those with diabetes ($n = 58\,284$) over a mean 8.6 years of follow-up in a Taiwanese cohort. Notably, only obesity (defined by a physician diagnostic code for obesity) and not BMI levels were controlled for. BMI may therefore remain as a residual confounder. Additionally, considerably higher incidence rates of asthma were observed in their population: 10.3-13.5 per 1000 person-years, compared with 3.47-4.09 per 1000 person-years seen in our study. Our reported incidence rate is in line with British Lung Foundation national estimates (2.72 per 1000 person-years).[28]

## 4.3 | Strengths and limitations

Use of a large well-validated database with clear case definitions and onset dates improves the reliability of our results and clarity around the temporal nature of the index conditions. The prevalence rates yielded from this study are comparable with national estimates, highlighting the data's utility as a representative sample. Propensity matching for the primary study outcome reduced the influence of confounding variables such as BMI, which have complicated previous studies.

Nonetheless, despite propensity score matching, some residual confounding may have remained. Furthermore, while we used a well-validated method for distinguishing cases of T1DM and T2DM, misclassification cannot be completely excluded. Additionally, for the secondary analysis, patients on each of the T2DM drugs studied were likely to have been on a combination of antidiabetic agents, making it difficult to isolate findings to one drug. Furthermore, it is possible that underlying prescribing choices could have influenced the results, eg, lower BMI in sulphonylurea group. Finally, incomplete data led to exclusion of 195 000 individuals, 15% of the total population.

## 4.4 | Recommendations for future research

In accordance with previous work, our findings suggest a potential ability for anti-diabetic medications to modify airways disease. We propose a meta-analysis of randomized controlled trials investigating insulin, metformin and sulphonylureas that report respiratory outcomes to determine if this is a causal association and to inform possible future interventional studies.

# 5 | CONCLUSIONS

In summary, we demonstrate a reduced incidence of asthma in those with T2DM compared with propensity-matched controls

in this large case-control study. This may suggest a possible protective effect of T2DM against the development of asthma.

In those with T2DM, prescription of insulin was associated with increased asthma incidence, while metformin and sulphonylureas were associated with a reduced incidence. The possible ability of these drugs to modulate airways disease represents an important and exciting target for future research.

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## CONFLICT OF INTERESTS

The authors declare that they have no conflict of interest with the contents of this article.

## AUTHOR CONTRIBUTIONS

All authors have approved the final manuscript for submission. LR developed the study protocol, conducted the analysis and was the primary author of the manuscript. AMcG contributed to study design, data analysis and manuscript writing. JS and AC performed the data extraction, assisted with the data analysis and reviewed the manuscript. PG and BC-B contributed to the study design and manuscript and review. SdeL contributed to study design, analysis and writing of the manuscript, and is the guarantor for the article.

## ETHICS

The RCGP RSC study review team approved the use of these data for this study. No personally identifiable data were available to researchers. The study is reported in accordance with STROBE guidelines for observational studies.[29]

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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