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Type 2 diabetes: A protective factor for COPD?

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) and type 2 diabetes (T2DM) are common comorbidities. COPD is a known risk factor for incident T2DM, however few studies have examined the relationship in reverse. The primary aim of this study was to compare the incidence of COPD in people with and without T2DM.

Materials and methods: We conducted a retrospective case-control study using a long-established English general practice network database (n = 894,646). We matched 29,217 cases of T2DM with controls, adjusting for age, gender, smoking status, BMI and social deprivation, to achieve 1:1 propensity matching and compared the rate of incident COPD over eight years of follow-up. We performed a secondary analysis to investigate the effect of insulin, metformin and sulphonylureas on COPD incidence.

Results: People with T2DM had a reduced risk of COPD compared to matched controls over the follow-up period (HR 0.89, 95%CI 0.79–0.93). 48.5% of those with T2DM were ex-smokers compared with 27.3% of those without T2DM. Active smoking rates were 20.4% and 23.7% respectively. Insulin, metformin and sulphonylureas were not associated with incident COPD.

Conclusions: People with T2DM are less likely to be diagnosed with COPD than matched controls. This may be due to positive lifestyle changes, such as smoking cessation in those with T2DM.

1. Introduction

Type 2 diabetes (T2DM) is a common comorbidity in people with chronic obstructive pulmonary disease (COPD). The prevalence of T2DM in patients with COPD is estimated to be in the region of 18.7%, compared with 10.5% in the general population [1]. Epidemiological studies have demonstrated a 40–50% increased risk of incident T2DM in individuals with COPD, independent of traditional diabetes risk factors such as tobacco smoking [2–4]. Potential mechanisms for this include systemic inflammation, hypoxia and oxidative stress, all of

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which have been shown to induce dysglycaemia [4], alongside the diabetogenic effect of corticosteroid treatment [5]. The association between COPD and components of the metabolic syndrome, including T2DM, have led some experts to consider COPD as a chronic systemic inflammatory syndrome and not exclusively a respiratory pathology [6].

However, comparatively few studies have examined the relationship in reverse; that is to explore whether the incidence risk of COPD in individuals with T2DM. A large retrospective cohort study demonstrated a small but significant increased risk of incident COPD (HR 1.22, 95%CI 1.15–1.28) in individuals with diabetes in comparison with controls [7], after adjustment for Body Mass Index (BMI) and smoking status. Additionally, accelerated lung function decline has been observed in those with T2DM [8], and higher levels of insulin resistance are negatively associated with FEV1 and FVC on spirometry testing [9]. There is also emerging evidence to suggest that anti-diabetic medications, in particular metformin, may have an effect on airways disease. In two small studies, metformin treatment was associated with improved lung function and respiratory muscle strength in patients with T2DM and COPD [10,11].

The principal aim of this study was to compare the incidence of COPD in a large population of individuals with T2DM with matched controls over an eight year follow-up period. We performed secondary analyses to examine the effects of anti-diabetic medications: insulin, metformin and sulphonylureas on the risk of incident COPD.

2. Materials and methods

2.1. Data source and study design

We conducted a retrospective nested case-control study using the Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) database. This dataset is contributed to by 160 GP practices across England, and includes over 1.7 million patients. It contains pseudononymised electronic patient records with coded demographic, diagnostic, biochemical and prescription data at an individual patient level. The RCGP RSC has been shown to be a representative sample of the population of England in terms of demographics and clinical outcomes, and has been used extensively for studies in diabetes [12]. Furthermore, COPD is one of the major pay-for-performance (P4P) quality indicators in the UK. As part of this, GPs are remunerated based on the quality of their COPD data recording. Practices involved in the RCGP RSC achieve higher P4P scores than the national average, which is generally associated with better data quality [13].

2.2. Study population and definition of variables

The study covered an eight year period from 31st December 2008 to 31st December 2016. Eight years was selected to balance the benefits of an increased number of cases of T2DM at the study commencement, and to enable sufficient follow-up time to investigate the study outcomes. All individuals aged over 18 who were free from asthma, COPD and T1DM at baseline, and who remained registered in the RCGP RSC for the study duration were eligible for inclusion. A baseline diagnosis of asthma was added to the exclusion criteria due to considerable overlap between asthma and COPD in older adults [14]. Those who met the inclusion criteria were categorised into those with T2DM (the study exposure) and those without T2DM at baseline. Cases of T2DM were identified using a two-step ontology-based algorithm consistent with consensus definitions of diabetes, previously developed and validated by our department [15].

The study outcome measure was a new diagnosis of COPD during the follow-up period. We identified cases of COPD using an ontology-based algorithm consistent with international COPD diagnostic criteria previously tested for accuracy and validity by our department (see S1: Supplemental materials). We have long experience of identifying cases from routine data [16]. The prevalence of COPD and T2DM in our dataset was checked against nationally reported figures to ensure that our data was representative of the population.

Demographic and baseline clinical data were extracted for all included participants including: age, gender, BMI, socioeconomic status using the index of multiple deprivation (IMD) score [17], smoking status (most recent to baseline) and comorbidities (angina, previous stroke or transient ischaemic attack, previous myocardial infarction and hypertension). Those with missing data for the variables of interest were excluded. For individuals with T2DM, we also extracted data concerning baseline usage of insulin, metformin and sulphonylureas, duration of diabetes diagnosis, HbA1c values and presence of diabetic complications (chronic kidney disease (CKD), peripheral neuropathy and retinopathy).

2.3. Statistical analysis – primary outcomes

We used propensity score matching in a 1:1 ratio to adjust for potential confounding factors between participants with and without a baseline diagnosis of T2DM. Age, gender, BMI, IMD decile and smoking status were used in the matching process. Differences between the groups for the matching variables were examined with a two-tailed P value <0.05 considered to be significant. All individuals entered the study on the 31st December 2008 and accumulated time until the date of COPD diagnosis or the study end (31st December 2016).

We calculated the incidence of COPD 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) using Cox proportional hazards analysis. Only T2DM, the exposure variable, was included as an independent variable as baseline variables were balanced between both propensity-matched groups.

As a sensitivity analysis, we created Cox proportional hazard regression models using the entire study population to confirm the findings from the primary analysis. Models were adjusted for age, gender, BMI, smoking status and IMD score, and were replicated without adjustment for BMI to assess the impact of BMI on overall results.

2.4. Statistical analysis – secondary outcomes

In the T2DM group, the impact of anti-diabetic medications at baseline (insulin, metformin, sulphonylureas), length of dia-

Table 1 – Characteristics of the total study cohort.

	People with T2DM $n = 29,222$	People without T2DM $n = 865,424$
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*, %)		
Never smoked	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)

betes diagnosis, presence of diabetic complications and HbA1c on the risk of incident COPD was examined as per the study protocol. Each predictor variable was individually examined using unadjusted cumulative incidence analysis and then all variables of interest were assessed simultaneously in a multivariate model. The model was also adjusted for age, gender, BMI, IMD and baseline smoking status. The optimal multivariate model was selected using backward stepwise elimination of variables, with removal of variables to minimise the Akaike information criterion, the marker of relative statistical model quality.

The statistical package R Studio version 3.2.5 was used to perform the data analysis, with the use of the 'Survival' package [18,19].

2.5. *Ethics*

All data was pseudonymised at the point of extraction from clinical systems and no personally identifiable data was used. This study was approved by the RCGP RSC study review team (reference RSC_0517) and was deemed by the UK's Medical Research Council-Health Research Authority (MRC-HRA) tool as a service evaluation not requiring further ethical review. The study was conducted in accordance with STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines [20].

3. Results

3.1. *Baseline characteristics*

A total of 894,646 adults fulfilled the inclusion criteria, 29,222 of whom had a diagnosis of T2DM on or before 31st December 2008, and hence were classified as T2DM cases (crude prevalence 3.27%), (see S2: Supplemental materials).

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

Table 2 – Characteristics of the T2DM cases.

	T2DM 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 31st December 2016.
[b] From 1st January 2015 to 31st December 2016.

Propensity score matched controls were found for 29,217 of the 29,222 T2DM cases (99.9%) in the total cohort. There were no significant differences in the distribution of age, BMI, deprivation index (IMD decile) or smoking status at baseline between the 29,217 pairs of cases and controls (see S3: Supplemental materials).

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

3.2. *The incidence of COPD in individuals with T2DM*

In the 58,434 individuals included in the case control study, 2921 cases of incident COPD over a mean follow up period of 7.82 years (mean = 7.83 years for the T2DM cases and 7.82 years for the controls). The crude incidence rate of COPD for the T2DM group was 6.02 (95%CI 5.71–6.34) per 1000 person years, and 6.76 (95%CI 6.43–7.10) per 1000 person years for the control group.

Cumulative incidence analysis curves by T2DM status are shown in Fig. 1. In the Cox proportional hazards regression model, the hazard ratio for incident COPD was 0.89 (95%CI 0.77–0.93, $p < 0.001$) in the T2DM group in comparison with controls.

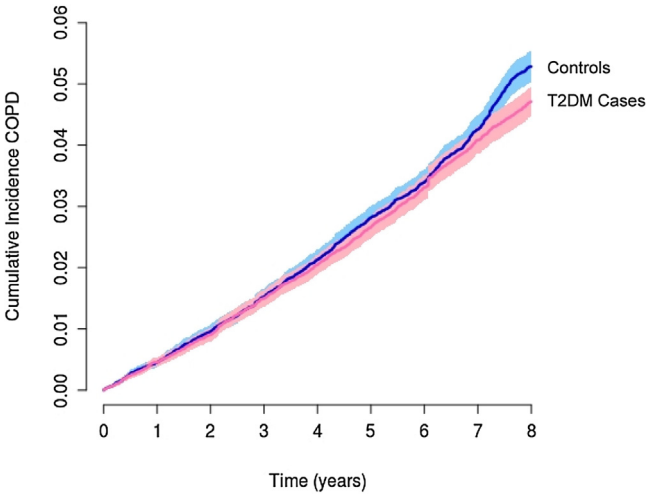

Fig. 1 – Cumulative incidence of COPD over 8 years of follow-up in T2DM cases and matched controls. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article). Pink = T2DM cases, blue = controls.

Table 3 – Hazard ratios of variables related to the incidence of COPD.

	Hazard ratio (95%CI)	Significance (p-value)
T2DM case	0.90 (0.85–0.95)	0.001
Sex = F	0.83 (0.81–0.87)	0.001
Age band		
18–44	0.021 (0.019–0.022)	0.001
45–54	0.13 (0.13–0.15)	0.001
55–64	0.37 (0.35–0.39)	0.010
65–74	0.75 (0.72–0.78)	0.010
75+	1.00 [reference]	–
IMD quintile		
1	2.41 (2.31–2.53)	0.001
2	1.85 (1.77–1.95)	0.001
3	1.37 (1.31–1.44)	0.001
4	1.16 (1.11–1.22)	0.001
5	1.00 [reference]	–
BMI band		
Underweight (<18.5)	1.95 (1.78–2.12)	0.001
Normal (18.5–24.9)	1.00 [reference]	–
Overweight (25–29.9)	0.89 (0.86–0.92)	0.001
Class 1 obese (30–34.9)	1.11 (1.06–1.16)	0.001
Class 2 obese (35–39.9)	1.32 (1.24–1.40)	0.001
Class 3 obese (>40)	1.42 (1.31–1.55)	0.001
Smoking status		
Never smoked	1.00 [reference]	–
Ex-smoker	3.70 (3.50–3.91)	0.001
Active smoker	11.01 (10.50–11.69)	0.001

These findings were consistent with results from the pre-specified sensitivity analyses. The Cox proportional hazards regression, performed on the entire study population (n = 894,646) also found a lower incidence of COPD in people with T2DM (HR 0.90, 95%CI 0.85–0.95) compared to those without after adjusting for age, gender, BMI, IMD and smoking status (see Table 3). Increasing age, greater social deprivation (lower IMD quintile) and being underweight or obese increased the risk of incident COPD. Active smoking was the greatest predictor of COPD development (HR 11.01, 95%CI 10.50–11.67), with an increased risk also seen in ex-smokers (HR 3.70, 95%CI 3.50–3.91). Those with T2DM were much more likely to be ex-smokers than those without T2DM (48.5% vs 27.3%). Active smoking rates were 20.4% and 23.7% respectively.

Table 4 – Impact of additional variables on incidence of COPD in T2DM cases.

	Univariate HR estimates (95%CI)	Adjusted HR following backward stepwise elimination (95%CI)
Years of diabetes[a]	1.00 (0.99–1.01)	1.01 (1.00–1.03)
Mean HbA1c[b]	0.99 (0.99–1.00)	–
Diabetic complications[c]	1.10 (0.89–1.39)	–
Medications at baseline		
Insulin	1.08 (0.92–1.27)	1.17 (0.98–1.40)
Metformin	1.01 (0.91–1.12)	0.91 (0.82–1.02)
Sulphonylurea	1.03 (0.89–1.20)	–

[a] On 31st December 2016.
[b] From 1st Jan 2015 to 31st Dec 2016.
[c] CKD/retinopathy/peripheral neuropathy.

When the model was repeated without adjustment for BMI, there was an increase in the HR for incident COPD in the T2DM group compared with controls, but the association remained significant (HR 0.93, 95%CI 0.88–0.98) (see S4: Supplemental materials).

3.3. *Secondary analysis*

In the T2DM group (n = 29,217), we found there was no difference in COPD incidence between those prescribed insulin (HR 1.16, 95%CI 0.98–1.40), metformin (HR 0.91, 95%CI 0.82–1.02) or sulphonylureas (unadjusted HR 0.97, 95%CI 0.88–1.20) at baseline (see Table 4 and S5: Supplemental materials).

Years of diabetes diagnosis, most recent HbA1c to study end and the presence of diabetic complications did not significantly alter the incidence of COPD (see S6: Supplemental materials).

4. Discussion

In this large nested case control study, we found a reduced incidence of COPD in individuals with T2DM after eight years of follow up. These findings were consistent in the sensitivity analysis. In the T2DM cohort, no relationship was seen between prescription of insulin, metformin or sulphonylureas at baseline and the subsequent incidence of COPD. Length of diabetes diagnosis, the presence of diabetic complications and glycaemic control were also not associated with COPD onset. The greatest predictor of developing COPD was current smoking. Previous smoking, increasing age, lower socio-economic status and being significantly underweight or obese also increased the risk of incident COPD. Smoking ces-

sation (ex-smoker status) was much more common in those with T2DM compared to those without T2DM.

4.1. *Reduced incidence of COPD in T2DM*

Whilst previous work has proposed COPD as a risk factor for T2DM, our results suggest that this is not a bidirectional relationship: T2DM was not a risk factor for COPD development in our study, and was actually associated with a reduced incidence. This finding may be considered to contradict that of Ehrlich et al. [7], who examined the risk of multiple pulmonary outcomes in diabetes in a large retrospective cohort. They found a higher risk of COPD (asthma, pulmonary fibrosis and pneumonia) in those with diabetes compared with controls. Age, BMI and smoking were controlled for. Notably the authors restricted cases of respiratory disease to those that required hospitalisation and had the pulmonary outcome documented as their primary discharge diagnosis or cause of death. Infective exacerbations are the commonest reason for hospitalisation in COPD [21], and the risk of common infections is substantially increased in those with diabetes [22]. It is therefore possible that their findings represent an increase in infective respiratory exacerbations in the people with diabetes, but not an increased incidence of stable pulmonary disease.

There are a number of different explanations for our findings. Smoking and BMI were shown in this study to be the biggest predictors of COPD development. Smoking cessation and optimised nutrition may occur more frequently in the T2DM group compared with similar controls due to regular contact with healthcare professionals and 'pay-for-performance' targets in UK primary care. In our study population, the T2DM group were much more likely to be ex-smokers than those without T2DM. Our results may therefore demonstrate a previously unmeasured benefit of lifestyle intervention in those with T2DM.

Additionally, both T2DM and COPD have an insidious onset and may be under-diagnosed [23,24]. Diagnosis of COPD in patients with T2DM may be further delayed by attribution of respiratory symptoms to their diabetes or lifestyle, and not to a distinct respiratory diagnosis [4]. COPD exacerbations may initially be considered to represent an increased predisposition towards respiratory tract infections due to reduced immunity in diabetes. Shortness of breath, productive cough and wheeze may be attributed to heart failure, which is more prevalent and severe in those with diabetes than in the general population [25]. Furthermore patients with T2DM may only undertake gentle exercise and hence be unaware of a reduced exercise capacity, which could signal a diagnosis of COPD.

Although previous studies have demonstrated impaired lung function on spirometry testing in those with diabetes compared with controls, the findings are not wholly consistent with spirometry findings in COPD. A meta-analysis of 40 studies evaluating pulmonary function in participants with diabetes free from overt pulmonary disease reported reductions in Forced Expiratory Volume in 1 s (FEV1) and Forced Vital Capacity (FVC) in a restrictive lung disease pattern [26], which is more fitting with spirometry seen in obesity [27], rather than the obstructive deficit seen in COPD. Furthermore, the aforementioned accelerated decline in lung function in diabetes may represent a greater propensity to infection and associated damage, or may be a subclinical finding which does not translate into evident pulmonary disease.

4.2. *The effect of anti-diabetic medications*

In this study we found no relationship between the prescription of insulin, metformin or sulphonylureas and the development of COPD after eight years of follow-up. To our knowledge, ours is the first study to assess the impact of these medications on COPD incidence.

Acute bronchospasm was a noted, but rare, side effect seen during clinical trials of inhaled insulin for diabetes [28]. Whilst we cannot comment on the direct effects of inhaled insulin on the lung, our results suggest that exogenous insulin administration does not appear to increase the long term risk of chronic obstructive airways disease.

There has been considerable research interest in the potential benefits of metformin in COPD. Metformin has been shown to improve spirometry readings in patients with comorbid COPD and T2DM [29]. However, a recent randomised controlled trial revealed no difference in clinical outcomes when metformin was administered to non-diabetic patients during COPD exacerbations [30], suggesting that the proposed beneficial effects of metformin may be related to improved glycaemic control and not an inherent property of the drug.

4.3. *Strengths and limitations*

This study benefits from the use of a large sample from a well-established UK primary care network. We used clear ontology based definitions for the index conditions, which have been validated in previous work [15], reducing the risks of missed cases and misclassification. Our reported prevalence rates are comparable with national figures [31], with only a slightly lower prevalence of COPD to the national average due to slight oversampling of higher socio-economic areas. Use of propensity matching for the primary study outcome reduced the influence of confounding variables such as smoking status and BMI, which have complicated previous studies.

However, our work is not without limitations. The study population was derived from real world evidence, with its inherent limitations diagnostic coding and inability to detect cases which do not present to medical attention. We were unable to include all possible variables which could impact upon one's risk of COPD, such as other respiratory illnesses excluding asthma and occupational exposure.

We were also unable to obtain data pertaining to the exact number of "pack-years" in an individual's smoking history, and hence were only able to classify individuals as ex, current or non-smokers, which may have introduced residual confounding. Furthermore, participants were matched at baseline and at baseline and study end, which represents an important consideration as their smoking status could have changed within this period. It would also be interesting to examine this data to see whether T2DM patients were more likely to become ex smokers during the study period and not just prior to its commencement. Pressure from medical staff on T2DM patients to stop smoking may result in false reporting of smoking status, which could also have affected the results.

In addition, our findings regarding medications are based upon prescription of the medication; we were not able to include a measure of adherence. Given the observational nature of the work, other medications patients may have been taking during the study was not assessed or controlled for, and may have had an effect on the results.

4.4. *Clinical implications*

A reduced incidence of COPD in the T2DM cases in this study raises the possibility of a protective factor against the development of COPD in these patients. We propose that this protective factor may be additional lifestyle advice and motivation for lifestyle changes. If so, our observations demonstrate a previously unmeasured positive outcome in diabetes public health. The findings may also represent a diagnostic "blind spot" for physicians when treating patients with long-term conditions, in which new symptoms are initially attributed to the existing disease, rather to new unrelated pathology.

5. Conclusions

In summary, we report a reduced incidence of COPD in individuals with T2DM compared with matched controls in this large retrospective case-control study. This suggests a potential protective effect of T2DM against the development of COPD, which may be due to positive lifestyle changes in this group, in particular successful smoking cessation.

Previous work has shown COPD to be a risk factor for T2DM. This study demonstrates that the relationship is not bidirectional.

Conflict of interest

AMcG has undertaken research funded by Eli Lilly and Company and AstraZeneca. SdeL has undertaken research funded by GlaxoSmithKline, AstraZeneca, Eli Lilly and Company, and Takeda.

The authors state that they have no conflict of interest.

Authorship contributions

LR developed the study protocol, conducted the analysis and was the primary author of the manuscript. JS and AC performed the data extraction and assisted with the analysis. AMcG assisted with the analysis. All authors contributed to the writing of the manuscript and all have approved the final manuscript for submission.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.pcd.2018.05.002.

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