Exploration of Endocrine and Metabolic Diseases

Open Exploration

Open Access Original Article

Prevalence and incidence of co-morbid lung disease associated with type 2 diabetes from the UK Biobank

Roanne Lecky, Kathryn Christie, Priyank Shukla, Paula L. McClean, Catriona Kelly*

Personalised Medicine Centre, School of Medicine, Ulster University, BT47 6SB Derry/Londonderry, UK

***Correspondence:** Catriona Kelly, Personalised Medicine Centre, School of Medicine, Ulster University, C-TRIC Building, Altnagelvin Hospital Campus, Glenshane Road, Northern Ireland, BT47 6SB Derry/Londonderry, UK. c.kelly@ulster.ac.uk

Academic Editor: Gulali Aktas, Abant Izzet Baysal University, Turkey

Received: April 28, 2025 **Accepted:** June 2, 2025 **Published:** July 3, 2025

Cite this article: Lecky R, Christie K, Shukla P, McClean PL, Kelly C. Prevalence and incidence of co-morbid lung disease associated with type 2 diabetes from the UK Biobank. Explor Endocr Metab Dis. 2025;2:101436. https://doi.org/10.37349/eemd.2025.101436

Abstract

Aim: This analysis examined the prevalence and incidence of type 2 diabetes mellitus (T2DM) and co-morbid lung disease in the UK Biobank population.

Methods: Non-communicable inflammatory lung diseases, body mass index (BMI), age, glycated haemoglobin (HbA1c), sex, smoking status, diabetes status, forced expiratory volume in one second (FEV1), and forced vital capacity (FVC) data were obtained. Participants were categorised by BMI: lean (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obese (≥ 30 kg/m^2). Fisher's exact test identified lung disease prevalence and incidence. Kruskal-Wallis assessed lung function variance and its correlation with HbA1c. Cox regression analysed the impact of confounders on time to lung disease events.

Results: Overweight and obesity increased the prevalence and incidence of chronic obstructive pulmonary disease, asthma, and bronchitis, but this was not evident in cases of bronchiectasis in those without T2DM (P < 0.05–0.0001). Conversely, T2DM increased lung disease risk across all BMIs (P < 0.0001) and reduced FEV1 and FVC even after HbA1c normalisation (P < 0.0001). FEV1 and FEV1/FVC were negatively correlated with HbA1c. Age, diabetes, being a woman, smoking, reduced FEV1 and FEV1/FVC ratio, but not BMI, were factors in lung disease development in T2DM.

Conclusions: Inflammatory lung conditions are more common in T2DM patients, regardless of BMI. The pattern of lung decline suggests restrictive impairment, despite a high risk of obstructive disorders. This data adds to the evidence that the lungs are a target organ of diabetes damage.

Keywords

Diabetes, obesity, body mass index (BMI), lung disease, UK Biobank, prevalence

Introduction

People with type 2 diabetes mellitus (T2DM) have a high prevalence of lung disease [1], but lung function is not routinely measured in this population. It has been shown that there are negative associations between

both forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) with insulin resistance and T2DM [2]. FEV1 and FVC, but not the FEV1/FVC ratio, are reduced in people with T2DM, which suggests a restrictive lung phenotype [3]. Yet, the risk of obstructive lung conditions, including asthma and chronic obstructive pulmonary disease (COPD), is high in those with T2DM [4]. Furthermore, lung impairment in T2DM may be confounded by obesity, which is both a major contributor to T2DM development and associated with the risk of some lung diseases, including 15–38% of asthma cases in the US [5].

Several mechanisms may contribute to the "Diabetic Lung". Glycosylation of the chest wall and bronchial tree end-products in people with T2DM results in a build-up of collagen in the connective tissue, which restricts the ability of the lungs to expand [6]. Systemic inflammation may be a linking mechanism for T2DM and lung impairment, which is associated with endothelial dysfunction [7]. For example, it has been reported that an increase in interleukin 6 is associated with the development of restrictive lung disease in people with T2DM, which is independent of body mass index (BMI) [8]. However, adipose tissue is an endocrine organ that produces pro-inflammatory adipokines, and obesity may therefore contribute to the inflammatory pathways in lung disease development in people with T2DM. Although mechanisms for the association of T2DM with lung function have been established, the pathways driving this association are not well characterised.

The UK Biobank is a long-term biomedical database of 500,000 people aged 40–69 recruited within the UK. This database allows large-scale investigations of biological data, enabling the discovery of new scientific findings with generalisable consequences across the population. Therefore, the objective of this analysis is to quantify the prevalence and incidence of chronic inflammatory lung disease in people with T2DM and/or obesity using the UK Biobank.

Materials and methods

Participant data

UK Biobank data (https://www.ukbiobank.ac.uk/) was extracted using R software [9] and the ukbtools R package [10] in a Linux and RStudio [11] environment. All participants were included in this analysis, separated according to the presence or absence of T2DM. T2DM was confirmed by a Field-ID of 130708, described as "date E11 first reported (non-insulin-dependent diabetes mellitus)". All other participants were regarded as population controls. Data obtained were age at recruitment [Field-ID 21022], HbA1c level [Field-ID 30750], sex [Field-ID 31], BMI [Field-ID 21001], smoking status [Field-ID 20116], FEV1 [Field-ID 3063], FVC [Field-ID 3062], FEV1% predicted [Field-ID 20154], ethnicity [Field-ID 21000], waist circumference [Field-ID 48], and date of consenting to join UK Biobank [Field-ID 200]. Correlation analysis showed BMI and waist circumference were largely concordant in this population (r = 0.8017, P < 0.0001, 95% CI 0.8007 to 0.8027). Therefore, BMI was used to stratify participants for obesity consistent with NICE recommendations (NICE 2023). Participants were divided into lean (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obese (≥ 30 kg/m^2) categories using BMI Field-ID 21001. Groups were further divided based on the confirmed presence or absence of an inflammatory lung disease (asthma [Field-ID 131494], chronic obstructive pulmonary disease (COPD) [Field-ID 131492], bronchiectasis [Field-ID 131498], chronic bronchitis [Field-ID 131484], and emphysema [Field-ID 131490]). This led to the generation of the following categories of participants for analysis: (1) population controls with lean BMI ± lung disease; (2) population controls with overweight BMI ± lung disease; (3) population controls with obese BMI ± lung disease; (4) T2DM with lean BMI ± lung disease; (5) T2DM with overweight BMI ± lung disease; (6) T2DM with obese BMI ± lung disease. Data was examined from time of initial recruitment until April 2021.

Statistical analysis

Data was tested for normality with the Shapiro-Wilk test in the first instance or with the D'Agostino-Pearson test in the second. Fisher's exact test was used to determine if the presence of T2DM and/or

obesity significantly increases the likelihood of developing a lung disease between cases at time of recruitment (prevalence) and cases diagnosed at time points after initial recruitment (incidence). The Kruskal-Wallis test with post hoc Dunn's multiple comparison test was performed for all comparisons of significance between FEV1 (% of predicted), FEV1/FVC ratio, BMI (kg/m^2), HbA1c (mmol/mol), and age (years) at time of recruitment. Spearman's correlation analysis was performed between HbA1c and lung function data to explore the relationship between the variables. Lung function data was normalised for HbA1c by scaling the mean of each category using the lean population control group as the reference standard. Cox regression multivariable analysis was performed to account for any independent predictive effect of ethnicity, sex, smoking status, age, BMI, waist circumference, FEV1% of predicted, FEV1/FVC ratio, and the presence of T2DM on time to a lung disease event. The Exact method was used for all the estimations [12]. Smoking was categorised as never smokers, current smokers, previous smokers, and prefer not to answer. Waist circumference was classed as normal fat (< 80 cm women, < 94 cm men), moderate fat (80–87.9 cm women, 94–101.9 cm men), or high fat (≥ 88 cm women, ≥ 102 cm men) [13]. The FEV1% of predicted was classified as normal (≥ 80%), mild (70–79%), moderate (50–69%), or severe (< 50%) according to the American Thoracic Society and European Respiratory Society [14]. The severity of lung disease based on FEV1/FVC ratio was defined as normal (≥ 0.7), mild (≥ 0.6 and < 0.7), moderate (> 0.5 and < 0.6), and severe (≤ 0.5). Significance was accepted at a *P*-value of < 0.05. Statistical analysis was performed using GraphPad PRISM 10.0.0 (GraphPad Software, San Diego, California, USA, www.graphpad.com) and R software [9].

Results

The presence of T2DM and chronic inflammatory lung disease in the UK Biobank population

At recruitment, 17,187 participants had T2DM, with 3,576 cases of co-morbid lung disease (Table 1A). Population controls comprised those who did not have T2DM; 479,449 participants, of whom 65,968 had a lung disease (Table 1A). The odds of having prevalent lung disease in individuals with T2DM are 1.65 times higher than in individuals without T2DM ($P < 0.0001$, 95% CI: 1.59 to 1.71). Incident cases of T2DM amounted to 17,393, while incident cases of lung disease in those with and without T2DM were 1,459 (8.5% of total at recruitment) and 19,606 (4.1% of total at recruitment), respectively (Table 1B). Therefore, the odds of incident lung disease in the T2DM population were 2.41 times higher than the population controls ($P < 0.0001$, 95% CI: 2.28 to 2.55). In all instances of comparison, total numbers are further stratified according to BMI (Table 1A and B).

Table 1. Prevalence and incidence of people with T2DM and/or chronic inflammatory lung disease in the UK Biobank population

Population grouping		Population controls			T2DM		
		Lean	Overweight	Obese	Lean	Overweight	Obese
		n (% of total)	*n* (% of total)	*n* (% of total)	*n* (% of total)	*n* (% of total)	*n* (% of total)
A	Total	160,723	206,438	112,288	1,629	5,624	9,934
	COPD	702 (0.4)	866 (0.4)	641 (0.6) ****	21 (1.3) $^{\Delta\Delta\Delta\Delta}$	87 (1.5) $^{\Delta\Delta\Delta\Delta}$	164 (1.7) $^{\Delta\Delta\Delta\Delta}$
	Asthma	15,436 (9.6)	21,603 (10.5) ****	14,468 (12.9) ****	179 (11.0)	642 (11.4) $^{\Delta}$	1,475 (14.8) *** $^{\Delta\Delta\Delta\Delta}$
	Bronchitis	1,520 (0.9)	2,121 (1.0) *	1,363 (1.2) ****	17 (1.0)	56 (1.0)	146 (1.5) $^{\Delta}$
	Emphysema	116 (0.1)	150 (0.1)	63 (0.1)	2 (0.1)	7 (0.1)	14 (0.1) $^{\Delta\Delta}$
	Bronchiectasis	403 (0.3)	307 (0.1) ****	127 (0.1) ****	7 (0.4)	11 (0.2)	15 (0.2) *
	≥ 2 lung diseases	1,781 (1.1)	2,340 (1.1)	1,961 (1.7) ****	65 (4.0) $^{\Delta\Delta\Delta\Delta}$	176 (3.1) $^{\Delta\Delta\Delta\Delta}$	492 (5.0) $^{\Delta\Delta\Delta\Delta}$
B	COPD	1,782 (1.1)	2,265 (1.1)	1,403 (1.2) ***	52 (3.2) $^{\Delta\Delta\Delta\Delta}$	165 (2.9) $^{\Delta\Delta\Delta\Delta}$	352 (3.5) $^{\Delta\Delta\Delta\Delta}$
	Asthma	2,047 (1.3)	3,224 (1.6) ****	2,190 (2.0) ****	34 (2.1) $^{\Delta\Delta}$	131 (2.3) $^{\Delta\Delta\Delta\Delta}$	248 (2.5) $^{\Delta\Delta\Delta}$
	Bronchitis	222 (0.1)	344 (0.2) *	257 (0.2) ****	2 (0.1)	22 (0.4) $^{\Delta\Delta\Delta}$	22 (0.2)
	Emphysema	312 (0.2)	368 (0.2)	157 (0.1) ***	8 (0.5) $^{\Delta}$	14 (0.2)	30 (0.3) $^{\Delta\Delta\Delta}$
	Bronchiectasis	534 (0.3)	538 (0.3) ****	273 (0.2) ****	8 (0.5)	29 (0.5) $^{\Delta\Delta\Delta}$	39 (0.4) $^{\Delta\Delta}$
	≥ 2 lung diseases	1,225 (0.8)	1,610 (0.8)	855 (0.8)	20 (1.2) $^{\Delta}$	92 (1.6) $^{\Delta\Delta\Delta\Delta}$	191 (1.9) $^{\Delta\Delta\Delta\Delta}$

Data was extracted for participants from the UK Biobank and grouped based on BMI category and the presence or absence of T2DM: (**A**) Prevalence of chronic inflammatory lung conditions in those with and without T2DM in the UK Biobank at time of recruitment and (**B**) Incident cases of chronic inflammatory lung conditions in those with and without T2DM in the UK Biobank. Incident cases were defined as those that were not present at recruitment but were recorded subsequently. Fisher's exact test was performed. Data are presented as the total number (*n*) and the % of the total number at recruitment. * $P < 0.05$, *** $P < 0.001$, **** $P < 0.0001$ compared with corresponding lean controls with and without T2DM. Δ $P < 0.05$, ΔΔ $P < 0.01$, ΔΔΔ $P < 0.001$, and ΔΔΔΔ $P < 0.0001$ compared with those who did not have T2DM within the same BMI category. BMI: body mass index; COPD: chronic obstructive pulmonary disease; T2DM: type 2 diabetes mellitus

T2DM increases the prevalence and incidence of total lung disease

When compared with people who are lean, obesity and overweight increase the prevalence of total lung disease, bronchitis, and asthma in the absence of T2DM (Table 1A; Supplementary Figure S1A and C). Furthermore, obesity, but not overweight, was significantly associated with COPD (OR 1.31, $P < 0.0001$, 95% CI: 1.18 to 1.46) and the presence of two or more lung conditions concurrently (OR 1.59, $P < 0.0001$, 95% CI: 1.49 to 1.69) compared to lean controls. In the absence of T2DM, being lean was significantly associated with bronchiectasis compared to both overweight and obese categories (OR 1.69, $P < 0.0001$, 95% CI: 1.46 to 1.96 and OR 2.22, $P < 0.0001$, 95% CI: 1.82 to 2.71, respectively). Being lean without T2DM was also associated with incident emphysema and bronchiectasis compared to obese individuals (OR 1.39, $P < 0.001$, 95% CI: 1.15 to 1.68 and OR 1.37, $P < 0.0001$, 95% CI: 1.18 to 1.58, respectively), and incident bronchiectasis only in overweight individuals (OR 1.28, $P < 0.0001$, 95% CI: 1.13 to 1.44) (Table 1B; Supplementary Figure S1B and D).

In the presence of T2DM, the prevalence of total lung disease (lean OR 1.53, $P < 0.0001$, 95% CI: 1.35 to 1.74; overweight OR 1.38, $P < 0.0001$, 95% CI: 1.29 to 1.48; obese OR 1.52, $P < 0.0001$, 95% CI: 1.45 to 1.60), COPD (lean OR 3.0, $P < 0.0001$, 95% CI: 1.92 to 4.61; overweight 3.73, $P < 0.0001$, 95% CI: 2.99 to 4.66; obese OR 2.92, $P < 0.0001$, 95% CI: 2.46 to 3.48) and two or more concurrent lung diseases (lean OR 3.71, $P < 0.0001$, 95% CI: 2.88 to 4.77; overweight OR 2.82, $P < 0.0001$, 95% CI: 2.41 to 3.29; obese OR 2.93, $P < 0.0001$, 95% CI: 2.65 to 3.24) were significantly elevated in all BMI categories in comparison to those without T2DM (Table 1A; Figure 1A, C and E). Obesity in T2DM significantly increases the prevalence of asthma compared to people who are lean with T2DM (OR 1.41, $P < 0.0001$, 95% CI: 1.20 to 1.67) (Supplementary Figure S2C). However, the prevalence of asthma is also significantly increased in people with T2DM and obesity compared to people with obesity without T2DM (OR 1.18, $P < 0.0001$, 95% CI: 1.11 to 1.25; Table 1A; Figure 1E). Individuals with T2DM who were lean were more likely to have bronchiectasis than those with T2DM who had obesity (OR 2.85, $P < 0.05$, 95% CI: 1.09 to 6.72; Table 1A; Supplementary Figure S2C).

The presence of T2DM significantly increases the incidence of total lung disease in all BMI categories in comparison to their respective BMI categories in people without T2DM (Table 1B; Figure 1B, D, and F). In comparison to those without T2DM, incident cases of total lung disease (lean OR 2.08, $P < 0.0001$, 95% CI: 1.73 to 2.50; overweight OR 2.08, $P < 0.0001$, 95% CI: 1.88 to 2.29; obese OR 2.03, $P < 0.0001$, 95% CI: 1.89 to 2.19), COPD (lean OR 2.94, $P < 0.0001$, 95% CI: 2.22 to 3.89; overweight OR 2.73, $P < 0.0001$, 95% CI: 2.32 to 3.20; obese OR 2.90, $P < 0.0001$, 95% CI: 2.58 to 3.27), asthma (lean OR 1.65, $P < 0.01$, 95% CI: 1.17 to 2.33; overweight OR 1.50, $P < 0.0001$, 95% CI: 1.26 to 1.79; obese OR 1.29, $P < 0.001$, 95% CI: 1.13 to 1.47) and having 2 or more lung diseases concurrently (lean OR 1.62, $P < 0.05$, 95% CI: 1.04 to 2.52; overweight 2.12, $P < 0.0001$, 95% CI: 1.71 to 2.62; obese OR 2.56, $P < 0.0001$, 95% CI: 2.18 to 2.99) were significantly higher in the T2DM population.

Lung function is reduced in people with T2DM in the absence of a lung disease, irrespective of BMI

FEV1, FEV1/FVC, HbA1c, BMI, and age data for total participants are shown in Table 2. Expectedly, HbA1c in all categories was significantly higher in the presence of T2DM ($P < 0.0001$). BMI was also significantly higher in all T2DM categories compared to population controls, except for lean individuals with a lung disease [lean (total lung disease and without lung disease) $P < 0.05$; overweight (total and without lung disease) $P < 0.0001$ and (with lung disease) $P < 0.001$; obese $P < 0.0001$]. Those with T2DM were older in age in all categories ($P < 0.0001$). This has been accounted for in the Cox regression.

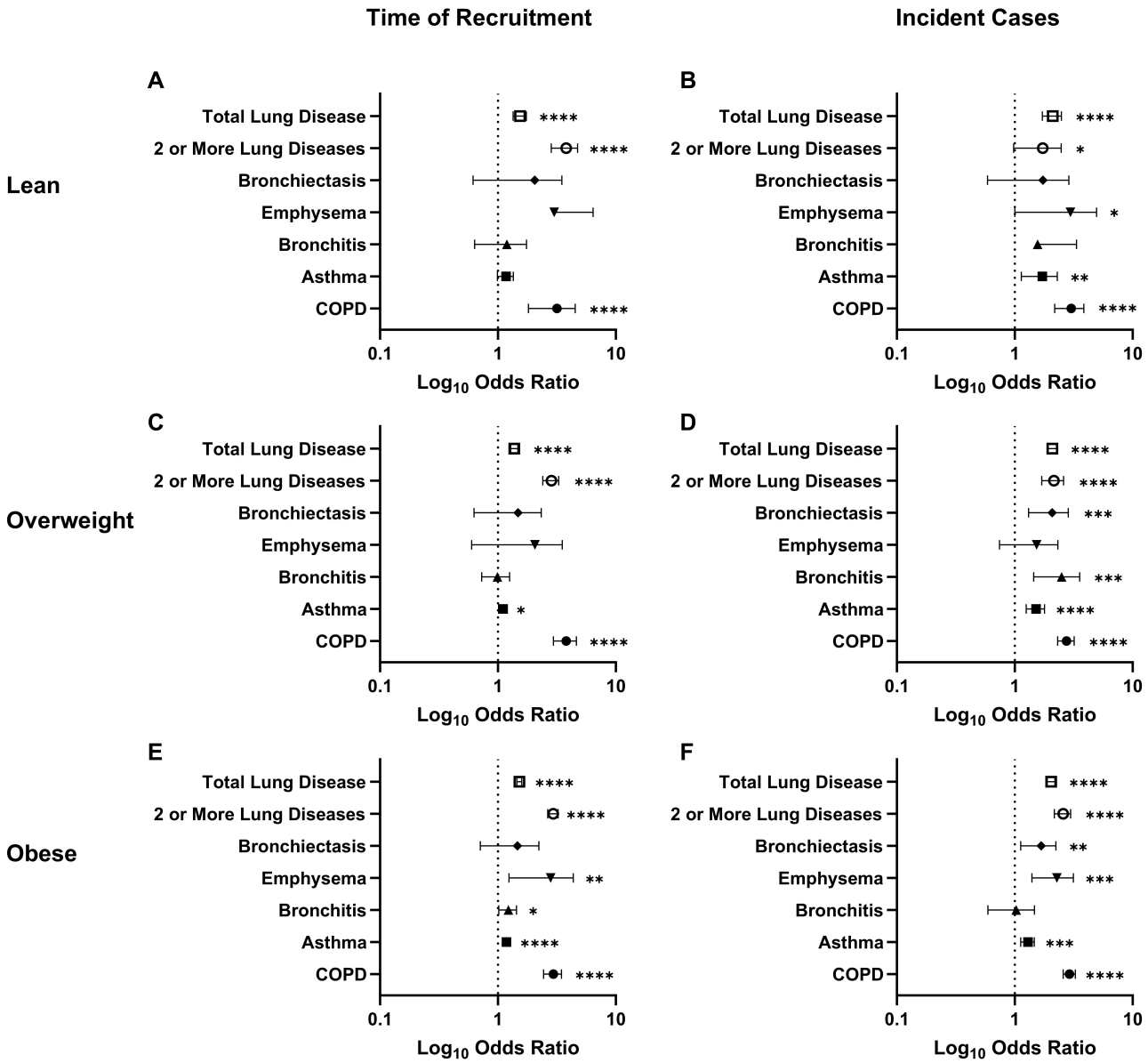

Figure 1. Risk of chronic lung disease in participants from the UK Biobank with T2DM. Log_{10} odds ratios were calculated for the presence of chronic inflammatory lung conditions at the time of recruitment (**A**, **C**, and **E**) and for incident cases (**B**, **D**, and **F**) in those with T2DM in comparison to those who did not have T2DM. Incident cases were those diagnosed after the initial recruitment period. Data was further categorised according to BMI [lean (**A**, **B**), overweight (**C**, **D**), and obese (**E**, **F**)]. *P < 0.05, ** P < 0.01, *** P < 0.001, **** P < 0.0001 compared with those who did not have T2DM within the same BMI category. BMI: body mass index; COPD: chronic obstructive pulmonary disease; T2DM: type 2 diabetes mellitus

Overall, there is a significantly lower FEV1 and significantly higher FEV1/FVC in those with T2DM without a lung condition in overweight and obese categories in comparison to lean controls (P < 0.0001, Table 2; Figure 2). Nevertheless, all lung function categories were significantly different between people with T2DM and those without T2DM in the absence of a lung disease (P < 0.0001; Table 2). Even after adjustment for HbA1c, people with T2DM have consistently lower FEV1 and FEV1/FVC values than population controls across all BMI categories (P < 0.0001; Figure 2). Once a lung disease has been established in people with T2DM, there is no significant difference in FEV1% of predicted and FEV1/FVC ratio in those who are overweight compared with those who are lean (Table 2). Although FEV1% of predicted was comparable between those who had T2DM with obesity and those who had T2DM and were lean, FEV1/FVC was significantly different (P < 0.001, Table 2). Once a chronic lung disease is present, FEV1% of predicted for those with T2DM who are overweight or obese is significantly lower than in population controls (P < 0.01 and P < 0.0001, respectively, Table 2). However, this is not significant in the lean category, nor is the FEV1/FVC significant in any BMI category between those with and without T2DM.

Table 2. UK Biobank participant demographics

Population grouping		Lean					Overweight					Obese				
		FEV1% of predicted	FEV1/FVC ratio	HbA1c (mmol/mol)	BMI (kg/m^2)	Age (years)	FEV1% of predicted	FEV1/FVC ratio	HbA1c (mmol/mol)	BMI (kg/m^2)	Age (years)	FEV1% of predicted	FEV1/FVCL ratio	HbA1c (mmol/mol)	BMI (kg/m^2)	Age (years)
Population Controls	Total	97.6 ± 16.7	75.0 ± 7.5	34.6 ± 4.5	22.9 ± 1.5	55.6 ± 8.2	96.5 ± 16.6 ****	75.9 ± 7.2 ****	35.4 ± 5.1 ****	27.3 ± 1.4 ****	56.9 ± 8.1 ****	92.6 ± 16.7 ****	76.8 ± 7.1 ****	37.2 ± 6.7 ****	33.8 ± 3.8 ****	56.6 ± 7.9 ****
	Without lung disease	99.0 ± 15.7	75.5 ± 7.2	34.5 ± 4.5	22.9 ± 1.5	55.6 ± 8.2	97.8 ± 15.8 ****	76.3 ± 6.8 ****	35.4 ± 5.1 ****	27.3 ± 1.4 ****	56.9 ± 8.0 ****	94.1 ± 15.9 ****	77.2 ± 6.8 ****	37.1 ± 6.7 ****	33.7 ± 3.6 ****	56.6 ± 7.9 ****
	With lung disease	88.2 ± 19.8	71.5 ± 9.2	34.7 ± 4.4	22.9 ± 1.5	55.6 ± 8.4	88.6 ± 18.9	72.7 ± 8.7 ****	35.5 ± 5.0 ****	27.3 ± 1.4 ****	56.6 ± 8.2 ****	85.8 ± 18.3	74.6 ± 8.3 ****	37.3 ± 6.4 ****	34.4 ± 4.3 ****	56.4 ± 8.0 ****
T2DM	Total	91.1 ± 18.5 ΔΔΔΔ	73.5 ± 9.1 ΔΔΔΔ	51.1 ± 14.8 ΔΔΔΔ	23.3 ± 1.4 Δ	60.8 ± 7.0 ΔΔΔΔ	89.6 ± 17.3 ΔΔΔΔ	75.1 ± 8.2 **** ΔΔΔΔ	51.9 ± 13.9 ΔΔΔΔ	27.8 ± 1.4 **** ΔΔΔΔ	61.1 ± 6.5 ΔΔΔΔ	86.0 ± 17.1 **** ΔΔΔΔ	76.2 ± 7.7 **** ΔΔΔΔ	54.0 ± 14.7 **** ΔΔΔΔ	35.7 ± 4.9 **** ΔΔΔΔ	59.7 ± 6.9 **** ΔΔΔΔ
	Without lung disease	92.8 ± 17.9 ΔΔΔΔ	74.1 ± 8.7 ΔΔΔΔ	51.4 ± 15.1 ΔΔΔΔ	23.3 ± 1.4 Δ	60.8 ± 7.0 ΔΔΔΔ	90.9 ± 16.6 ΔΔΔΔ	75.6 ± 7.7 **** ΔΔΔΔ	52.0 ± 13.9 ΔΔΔΔ	27.8 ± 1.4 **** ΔΔΔΔ	61.2 ± 6.5 ΔΔΔΔ	88.0 ± 16.0 **** ΔΔΔΔ	76.7 ± 7.3 **** ΔΔΔΔ	54.1 ± 14.7 **** ΔΔΔΔ	35.4 ± 4.7 **** ΔΔΔΔ	59.8 ± 6.9 **** ΔΔΔΔ
	With lung disease	84.5 ± 19.3	70.6 ± 10.5	49.8 ± 13.4 ΔΔΔΔ	23.2 ± 1.4	61.1 ± 6.9 ΔΔΔΔ	83.9 ± 19.1 ΔΔ	72.2 ± 9.8	51.4 ± 13.9 ΔΔΔΔ	27.8 ± 1.4 **** ΔΔΔ	60.7 ± 6.9 ΔΔΔΔ	79.5 ± 19.1 ΔΔΔΔ	74.2 ± 8.5 ***	53.6 ± 14.8 ΔΔΔΔ	36.6 ± 5.4 **** ΔΔΔΔ	59.5 ± 7.1 ΔΔΔΔ

Kruskal-Wallis test of total participants for FEV1, FEV1/FVC, HbA1c, BMI, and age data with and without T2DM for lean, overweight, and obese individuals. Data presented as mean ± standard deviation. *** $P < 0.001$, **** $P < 0.0001$ compared with corresponding lean controls with and without T2DM. Δ $P < 0.05$, ΔΔ $P < 0.01$, ΔΔΔ $P < 0.001$, and ΔΔΔΔ $P < 0.0001$ compared with those without T2DM within the same BMI category. FEV1 forced expiratory volume in one second percentage of predicted; FVC forced vital capacity (L/L%); HbA1c glycated haemoglobin (mmol/mol); BMI, body mass index (kg/m^2); COPD: chronic obstructive pulmonary disease; T2DM: type 2 diabetes mellitus

HbA1c correlation with FEV1 and FEV1/FVC

HbA1c is negatively associated with both FEV1 and FEV1/FVC in the absence of T2DM in those with and without a lung disease ($P < 0.0001$; Table 3). However, total participant numbers FEV1/FVC were positively associated with HbA1c in the absence of T2DM ($P < 0.0001$). In the presence of T2DM, there is a significant and negative correlation between HbA1c and FEV1 in overweight and obese BMI categories in those without a lung disease ($P < 0.001$; Table 3A). This negative association was not significant in people with T2DM who were lean. Consistently, FEV1/FVC was positively correlated with HbA1c in overweight and obese BMI categories ($P < 0.05$) (Table 3B). Lean T2DM individuals' FEV1/FVC was not significantly associated with HbA1c.

T2DM is a significant predictor of lung disease development

Regression analysis in people who did not have a diagnosis of either T2DM or a lung disease at recruitment, who developed incident lung disease, revealed the presence of T2DM to be a significant predictor of lung disease development (HR 1.61, $P < 0.0001$; Table 4). Having a moderate or high waist circumference was an independent predictor (HR 1.12, $P < 0.01$ and HR 1.19, $P < 0.0001$, respectively), as was obesity defined by BMI (HR 1.17, $P < 0.001$). Cox regression of lung disease development in those with previously established T2DM showed that both obesity and waist circumference did not have a predictive effect on lung impairment.

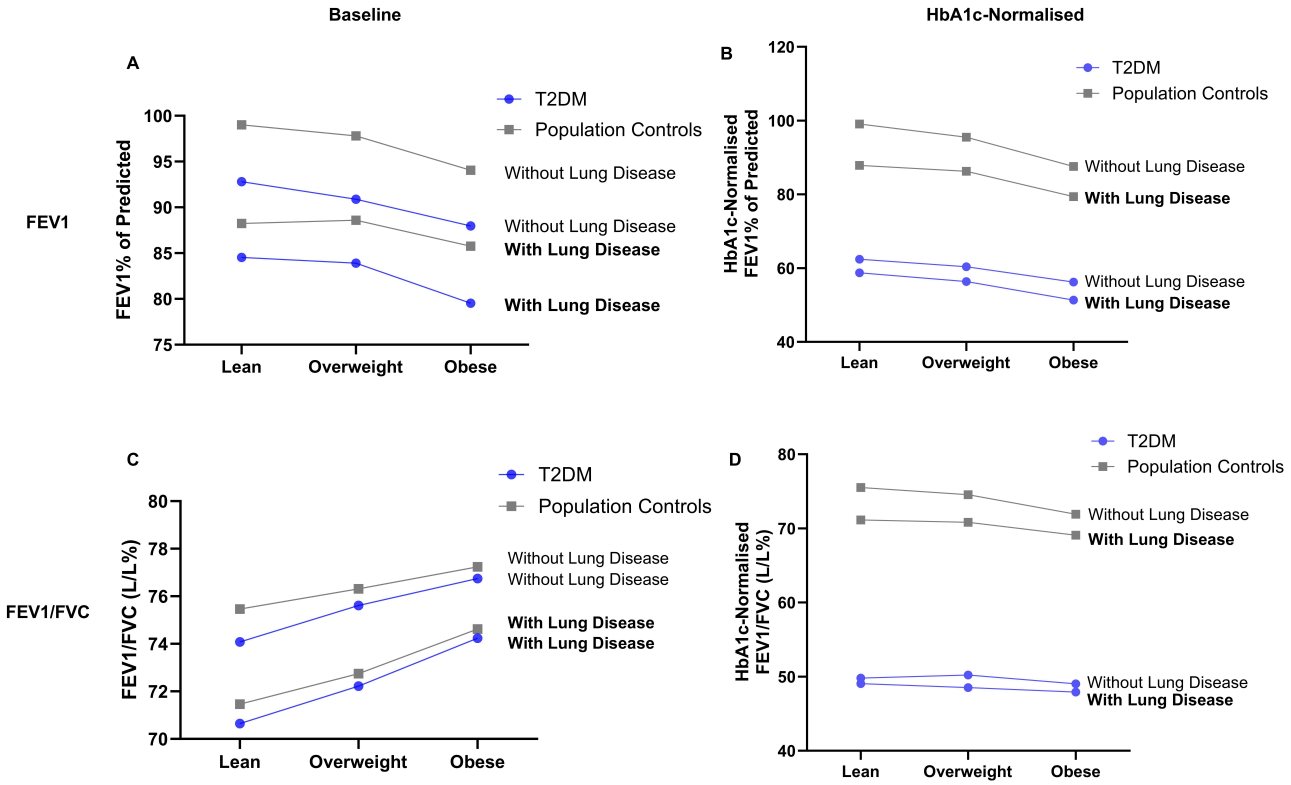

Figure 2. Impact of HbA1c on lung function measurements. Presented are the uncorrected baseline (**A**, **C**) and HbA1c-normalised (**B**, **D**) FEV1% of predicted (**A**, **B**) and FEV1/FVC (L/L%) (**C**, **D**) in people with T2DM (blue circles) and population controls (grey squares). Data is further divided by BMI and by those with (in bold) and without a lung disease. Data is presented as the mean. BMI: body mass index; T2DM: type 2 diabetes mellitus

This may be due to the fact that there is already lung decline in people with T2DM, and a significant additive effect of obesity on lung function decline is not seen in these cases. In both comparisons of lung disease development, women, having an FEV1 below 80% and a FEV1/FVC below 70%, were independent predictors. In those with an established lung disease, increasing BMI and increasing waist circumference were independent predictors for T2DM development. Having reduced FEV1 was predictive of T2DM development. Having normal FEV1/FVC was found to be more predictive of T2DM development than a reduced ratio. Men were more predictive of T2DM development (HR 1.319, $P < 0.0001$). Age and being a current or previous smoker increased risk across all three comparisons for lung disease and T2DM development ($P < 0.0001$).

Discussion

Here we have shown that T2DM increases both the prevalence and incidence of inflammatory lung disease, irrespective of BMI. People with T2DM have significantly lower FEV1% of predicted and FEV1/FVC (L/L) ratio compared to people without T2DM, which are negatively and positively associated with HbA1c, respectively. Demographics, including age, diabetes status, being a woman, reduced FEV1% of predicted and reduced FEV1/FVC ratio, and being a current or previous smoker, are all potential contributing factors for lung disease development in people with T2DM from this analysis.

Approximately 40.4% of individuals diagnosed with bronchiectasis are lean, while 5.1% are underweight, 25.4% are overweight, and 29.3% are obese [15]. Consequently, it is not unexpected that this analysis found higher odds of bronchiectasis in lean individuals without T2DM compared to both overweight and obese individuals. This may reflect the association of cachexia in individuals with advanced bronchiectasis [16]. Prevalence and incidence of lung disease increase, irrespective of BMI, in the context of T2DM in this analysis. Consistently, there are higher odds of lung disease in the T2DM group, which suggests that T2DM alone is sufficient for increased prevalence and incidence of lung diseases. This is consistent with reported associations between T2DM and almost all respiratory diseases, including asthma [17]. Despite this, the risk of developing an obstructive lung condition is noted in both this analysis and in

Table 3. Correlation of HbA1c with FEV1% of predicted and FEV1/FVC from people in UK Biobank

Population grouping			Population controls			T2DM		
			Total	Without lung disease	With lung disease	Total	Without lung disease	With lung disease
A	Lean	Spearman's *r*	–0.1045	0.09238	–0.1781	0.05243	–0.05888	–0.1595
		P-value	< 0.0001	< 0.0001	< 0.0001	0.3232	0.3211	0.1838
	Overweight	Spearman's *r*	–0.1237	–0.1169	–0.1715	0.09451	–0.1025	–0.04244
		P-value	< 0.0001	< 0.0001	< 0.0001	0.0004	0.0005	0.4973
	Obese	Spearman's *r*	–0.1543	–0.1482	–0.1715	0.07979	–0.09566	–0.05579
		P-value	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	0.1532
B	Lean	Spearman's *r*	0.1036	–0.09967	–0.1402	0.009461	0.01239	–0.05094
		P-value	< 0.0001	< 0.0001	< 0.0001	0.738	0.6893	0.4628
	Overweight	Spearman's *r*	0.06826	–0.06741	–0.07867	0.04602	0.03467	0.08798
		P-value	< 0.0001	< 0.0001	< 0.0001	0.0021	0.0333	0.0203
	Obese	Spearman's *r*	0.05421	–0.0495	–0.07039	0.03964	0.04009	0.02379
		P-value	< 0.0001	< 0.0001	< 0.0001	0.0005	0.0018	0.3405

Spearman's correlation of HbA1c with FEV1% of predicted (**A**) and FEV1/FVC (**B**). Data has been separated into lean, overweight, and obese BMI categories. Data is further stratified according to the presence or absence (population controls) of T2DM and/or a chronic inflammatory lung disease. Spearman's correlation coefficient (*r*) and *P*-value (two tailed) are presented. T2DM: type 2 diabetes mellitus

Table 4. Cox regression analysis of predictor variables for lung disease and T2DM development from people in the UK Biobank

Variable		Population grouping								
		Lung disease → T2DM			Healthy → lung disease			T2DM → lung disease		
		HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
WC (cm)	Normal fat	1.00	-	-	1.00	-	-	1.00	-	-
	Moderate fat	1.608	1.331 to 1.947	< 0.0001	1.12	1.045 to 1.201	0.0014	1.143	0.8510 to 1.545	0.3807
	High fat	2.634	2.161 to 3.223	< 0.0001	1.188	1.094 to 1.290	< 0.0001	1.194	0.8781 to 1.640	0.2655
Smoking	Never	1.00	-	-	1.00	-	-	1.00	-	-
	Current	2.636	2.334 to 2.972	< 0.0001	3.444	3.242 to 3.657	< 0.0001	3.225	2.653 to 3.918	< 0.0001
	Previous	1.866	1.695 to 2.054	< 0.0001	2.11	1.993 to 2.234	< 0.0001	1.948	1.650 to 2.303	< 0.0001
	Prefer not to answer	2.5E–08	-	0.9991	1.1E–07	-	0.9984	8.821E–08	-	0.9994
FEV1 (% of predicted)	Normal	1.00	-	-	1.00	-	-	1.00	-	-
	Mild	1.431	1.275 to 1.603	< 0.0001	1.768	1.655 to 1.887	< 0.0001	1.709	1.434 to 2.030	< 0.0001

Table 4. Cox regression analysis of predictor variables for lung disease and T2DM development from people in the UK Biobank (*continued*)

Variable		Population grouping								
		Lung disease → T2DM			Healthy → lung disease			T2DM → lung disease		
		HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
	Moderate	1.636	1.435 to 1.861	< 0.0001	2.411	2.240 to 2.594	< 0.0001	1.964	1.618 to 2.375	< 0.0001
	Severe	2.101	1.662 to 2.636	< 0.0001	3.247	2.816 to 3.731	< 0.0001	2.312	1.519 to 3.401	< 0.0001
FEV1/FVC ratio	Normal	1.00	-	-	1.00	-	-	1.00	-	-
	Mild	0.6983	0.6245 to 0.7800	< 0.0001	2.02	1.906 to 2.141	< 0.0001	1.481	1.240 to 1.762	< 0.0001
	Moderate	0.5421	0.4473 to 0.6541	< 0.0001	3.354	3.040 to 3.698	< 0.0001	2.667	1.923 to 3.634	< 0.0001
	Severe	0.4415	0.3126 to 0.6145	< 0.0001	4.223	3.501 to 5.068	< 0.0001	2.693	1.306 to 5.069	0.0039
BMI (kg/m^2)	Lean	1.00	-	-	1.00	-	-	1.00	-	-
	Overweight	1.389	1.146 to 1.688	0.0009	0.9765	0.9115 to 1.046	0.499	0.9481	0.6989 to 1.299	0.7358
	Obese	3.159	2.555 to 3.921	< 0.0001	1.172	1.069 to 1.285	0.0007	0.9732	0.6919 to 1.382	0.8778
Sex	Women	1.00	-	-	1.00	-	-	1.00	-	-
	Men	1.319	1.209 to 1.438	< 0.0001	0.831	0.7923 to 0.8716	< 0.0001	0.7644	0.6627 to 0.8825	0.0002
T2DM	No	-	-	-	1.00	-	-	-	-	-
	Yes	-	-	-	1.614	1.502 to 1.733	< 0.0001	-	-	-
Age (years)		1.035	1.029 to 1.042	< 0.0001	1.039	1.035 to 1.042	< 0.0001	1.027	1.016 to 1.039	< 0.0001

Cox regression was performed for lung disease development both in those with (T2DM → lung disease) and without (Healthy → lung disease) established type 2 diabetes (T2DM) and for T2DM development in those with previously established lung disease (lung disease → T2DM). Analysis was adjusted for waist circumference (WC), smoking, forced expiratory volume in 1 second (FEV1), FEV1/forced vital capacity (FVC), glycated haemoglobin (HbA1c), body mass index (BMI), sex, presence of T2DM, and age. HR: hazard ratio; CI: confidence interval

several others [18]. In this analysis, an independent predictive effect of diabetes, age, smoking status, being a woman, and severity of lung disease on the time to lung disease development was found. Smoking and increasing age are well-established risk factors for lung disease [19, 20] and have also been linked to the development of T2DM [21, 22]. In this analysis, the T2DM groups were older than the population controls, which needs to be taken into consideration when interpreting these findings. There is a notable lack of studies focused on the young adult population with T2DM, which includes a lack of investigations of lung function impairment specific to younger cohorts.

Men have a higher risk of developing T2DM than women [23], which has also been reiterated in these results. Once T2DM has been diagnosed, women have an overall increased risk of experiencing secondary complications [24]. Moreover, in the general population, women experience lung disease more often than men [25]. In this analysis, even in the absence of a lung disease, FEV1 and the FEV1/FVC were significantly lower in people with T2DM compared to those without, irrespective of BMI. In initial analyses, when T2DM is present, there was evidence that obesity was potentially causing an additive effect on reducing lung function in certain cases. However, after regression analysis was performed to further investigate this, BMI did not prove to be a significant predictor of lung disease

development in people with T2DM. Therefore, it appears that obesity is not directly confounding lung function decline in people with T2DM, and this further supports that the presence of T2DM significantly deteriorates lung function, even without a confirmed lung disease. We observed a negative correlation between FEV1 and HbA1c in obese and overweight individuals without a lung disease, while FEV1/FVC was positively correlated with HbA1c in obese and overweight individuals. This is consistent with a restrictive phenotype, which is consistent with the literature [26]. In the presence of a lung disease, T2DM has a finite impact on the FEV1/FVC ratio, irrespective of BMI. This further suggests T2DM is restrictive in nature. However, there are significant differences between the FEV1 of people with T2DM who are overweight and obese compared to population controls, and considering BMI was not significant in the regression analysis, this suggests that the presence of T2DM exacerbates obstruction in those with an established lung disease. Other studies have also suggested that the presence of T2DM further exacerbates lung function in people with co-morbid lung disease [27, 28].

The effects of both diabetes and lung disease medication need to be considered when interpreting the correlation between HbA1c and lung function. Corticosteroids are the mainstay of several lung conditions and are known to increase HbA1c levels. Corticosteroids are thought to be associated with diabetes through increased insulin resistance in the liver and skeletal muscles [29] and impaired insulin secretion [30]. Meanwhile, diabetes medication can both alleviate and exacerbate lung impairment [17]. Therefore, the type of medication may influence the correlation between HbA1c and lung function and should be considered when interpreting cases of pulmonary impairment in people with T2DM. In this analysis, participant medication was not investigated and therefore, is a limitation to the investigation.

The UK Biobank cohort primarily represents the white ethnic UK population (94.6%) [31]. Those who participated were more likely to have ownership of their own property, they were taller, less likely to be obese, less likely to be smokers, had fewer self-reported health conditions, and had lower all-cause mortality compared to the general population [31]. Therefore, the UK Biobank cohort lacks ethnic, socio-demographic, and health-related data for generalisable prevalence and incidence rates. However, due to the large participant numbers, the UK Biobank has the ability to disclose exposure-disease associations that are still widely applicable to other populations [31].

Additionally, the UK Biobank cohort does not include any participants below the age of 40, which prevents the investigation of the effect of diabetes in younger age groups. Finally, adjusting the lung function data for HbA1c assumes a linear relationship and this might oversimplify the complex biological interactions that are occurring, potentially leading to inaccurate conclusions.

In conclusion, T2DM increases overall lung impairment compared to people without T2DM. In the absence of T2DM, BMI has a direct influence on total lung disease prevalence and incidence. Once diabetes has been established, T2DM increases both the prevalence and incidence of lung disease, irrespective of BMI. Moreover, the impact of T2DM is more readily noticeable in individuals without a pre-existing lung disease, as those with a lung condition already experience reduced pulmonary function. The current study adds to the weight of evidence suggesting that lung function monitoring may be warranted in the T2DM population.

Abbreviations

BMI: body mass index

COPD: chronic obstructive pulmonary disease

FEV1: forced expiratory volume in one second

FVC: forced vital capacity

HbA1c: glycated haemoglobin

T2DM: type 2 diabetes mellitus

Supplementary materials

The supplementary figures for this article are available at: https://www.explorationpub.com/uploads/Article/file/101436_sup_1.pdf.

Declarations

Author contributions

CK and PLM: Conceptualization, Writing—review & editing, Supervision. PS: Conceptualization, Supervision. KC: Data curation. RL: Data curation, Investigation, Formal analysis, Writing—original draft. All authors read and approved the submitted version.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

This research has been conducted using the UK Biobank Resource under application number 48433.

Consent to participate

All UK Biobank participants consented to take part in the UK Biobank project. Approved researchers working under approved projects can access the data for health-related research purposes. Participants were removed from analysis if they later revoked their consent.

Consent to publication

Not applicable.

Availability of data and materials

The data analysed in this study were obtained from UK Biobank. Requests for access to these datasets should be directed to the access management team (AMT), access@ukbiobank.ac.uk.

Funding

CK, PLM, and PS wish to acknowledge funding of a PhD studentship to RL from the Department for the Economy (DfE), Northern Ireland. PS wishes to acknowledge funding of a PhD studentship to KC from the Department for the Economy (DfE), Northern Ireland, and funding support from the Ulster University for the UK Biobank project number 48433. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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