Type-1 diabetes and pulmonary function tests. A meta-analysis

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Contributor statement

Jesús Díez-Manglano and Uxua Asìn Samper participated in study design, literature search, data collection, data analysis, and data interpretation. Jesús Díez-Manglano drafted the manuscript, and Uxua Asìn Samper contributed and approved the final version of the manuscript.

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TYPE-1 DIABETES AND PULMONARY FUNCTION TESTS. A META-ANALYSIS

ABSTRACT

Objectives: To determine the association between type-1 diabetes (T1D) and pulmonary function tests.

Methods: After conducting an exhaustive literature search, we performed a meta-analysis. We employed the inverse variance method with a random effects model to calculate the effect estimate as the mean difference (MD) and 95% confidence interval (CI). We calculated the heterogeneity with the I^2 statistic and performed a meta-regression analysis by age, sex, body mass index (BMI), smoking and geographical region. We also conducted a sensitivity analysis according to the studies' publication date, size of the T1D group and the study quality, excluding the study with the greatest weight in the effect.

Results: The meta-analysis included 38 studies, one longitudinal, three case-control and 34 cross-sectional ones, with 1199 patients with T1D and 1278 control participants. The pooled MD (95%CI) for the predicted percentage of FEV_1, FVC, $FEF_{25-75\%}$, PEF and DL_{CO} were –6.48 (95%CI -8.69, -4.26; p<0.001), -2.21 (95%CI -2.45, -1.78; p<0.001), -6.19 (95%CI -11.39, -0.99; p=0.02), -8.82 (95%CI -15.37, -2.27; p=0.008) and -0.64 (95%CI -1.12, -0.16; p=0.008), respectively. There was no difference in the ratio of FEV_1/FVC (-0.77 95%CI -2.15; 0.62; p=0.28). There was considerable heterogeneity. The meta-regression analysis showed that between studies heterogeneity was not explained by patient age, sex, BMI, smoking or geographical region. The findings were consistent in the sensitivity analysis.

Conclusions: T1D is associated with impaired pulmonary function, independently of age, sex, smoking, BMI, and geographical region. Longitudinal studies are needed to investigate outcomes for patients with T1D and impaired pulmonary function.

Keywords: type-1 diabetes; pulmonary function test; meta-analysis.

INTRODUCTION

Type-1 diabetes (T1D) is the major cause of diabetes in childhood, but it can develop at any age. In 2019, it is estimated that over one million of children and adolescents have T1D [1]. The incidence of T1D is increasing worldwide. There is considerable geographical variation in prevalence and incidence of T1D [2].

Microvascular complications of T1D include neuropathy, retinopathy and nephropathy. Diabetes is a leading cause of cardiovascular disease, blindness, kidney failure and lower limb amputation [3]. T1D is a significant cause of death and disability [4]. Mortality of T1D patients is 4-5 times that of the general population and more than 30% of all deaths are caused by chronic complications [5,6].

T1D affects all organs in the human body. A number of studies have shown pulmonary microcirculation disorders [7] and fibrotic changes in the lungs [8] and in patients with diabetes. Diabetes has been associated with impaired pulmonary function [9-11]. However, pulmonary function impairment has not been well studied in patients with T1D, and the findings of studies reflect high variability. A 2010 meta-analysis by van den Borst et al showed an association between T1D and a restrictive pattern [9]. This meta-analysis reported data about forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), FEV_1/FVC ratio, and diffusing capacity of the lungs for carbon monoxide (DL_{CO}).

Our hypothesis is that lung may be a target organ of T1D. To enhance the knowledge in this field, we resolved to perform a meta-analysis including literature published in all languages and analyzing the influence of study quality, publication date and number of individuals included. Furthermore, we determined the influence of age, sex, tobacco use, geographical area and body mass index. The purpose of this meta-analysis was to investigate the pulmonary function test results for patients with T1D incorporating the most recent studies. In addition to

FEV_1, FVC, FEV_1/FVC and DLCO, we included forced expiratory flow between 25% and 75% of total lung capacity ($FEF_{25-75\%}$) and peak expiratory flow (PEF).

METHODS

We designed this meta-analysis to determine the influence of T1D on the following parameters of pulmonary function tests: FEV_1, FVC, FEV_1/FVC ratio, $FEF_{25-75\%}$, PEF and DL_{CO}.

We recorded the protocol for this meta-analysis in the PROSPERO registry (number CRD42020175178), and reported it following the recommendations of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group.

Data sources and search strategy

We searched four databases (PubMed, EMBASE, The Cochrane Library and Virtual Health Library) from their inception to June 30th, 2021. The search strategy was "(*pulmonary function test* OR FEV_1 OR *FVC* OR DL_{CO} OR *PEF* OR FEF_{25-75}) AND *diabetes*". The full search strategy for Embase was ('pulmonary function test'/exp OR 'pulmonary function test' OR (pulmonary AND ('function'/exp OR function) AND ('test'/exp OR test)) OR FEV1 OR FVC OR DLCO OR PEF OR 'FEF25 75') AND ('diabetes'/exp OR diabetes). We performed a supplemental search in Google Scholar and ResearchGate. The reference lists of the selected studies were screened manually to find more studies.

Study selection

Eligible studies had to meet the following inclusion criteria:

(i) Presence of a T1D group and a control group without diabetes.
(ii) Provide values either of FEV_1, FVC, PEF, $FEF_{25-75\%}$, DL_{CO} and/or FEV_1/FVC ratio for both patient groups.

We excluded studies on cystic fibrosis-related diabetes, type-2 diabetes, studies that did not differentiate between type-1 and type-2 diabetes, studies that included patients with respiratory diseases, studies that did not report data on mean and standard deviation or these measures could not be calculated, studies published in predatory journals, conference abstracts, and theses. We considered predatory all journals that appeared in the List of Predatory Journals (https://predatoryjournals.com/journals/). When two studies referred to the same population, in the same period and showed overlapping data, we selected the most recent study for inclusion.

We independently screened the articles by reviewing the titles and abstracts. We recovered the studies that met the inclusion criteria and those with abstracts that lacked crucial information to evaluate the full text. Disagreements were resolved by consensus.

We made an attempt to contact the authors by email when a study's complete text was not accessible online or required supplemental data. Unfortunately, these attempts were not successful.

Quality assessment

We independently evaluated the quality of all the studies included using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (National Heart, Lung, and Blood Institute at the National Institutes of Health, USA), available from https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools. It includes 14 items about objective, population, rate of eligible persons, sample size, exposure, outcomes, blinded assessors, follow-up and confounding variables. The two authors classified the studies as good, fair or poor. Any discrepancy was resolved by consensus. We considered a study as poor when T1D patients and controls were not selected from the same population or in a different time or place, and fair when we cannot determine this and there were doubts about a selection bias. All studies were included in the meta-analysis; however, we conducted a sensitivity study only on those studies of good quality.

Data extraction

From each included study, we extracted the following information: first author, year of publication, country, sample size, patient mean age, sex, body mass index, tobacco use, T1D duration, fasting blood glucose, glycated hemoglobin and microangiopathy. The extracted results were FEV_1 (liters, L), percentage of predicted (%) FEV_1, FVC (L), %FVC, FEV_1/FVC ratio(%), $FEF_{25-75\%}$ (L/s), $\%FEF_{25-75\%}$, PEF (L/s), %PEF, DL_{CO} (mL/min/mm Hg) and $\%DL_{CO}$. Whenever the T1D or control group was divided into subgroups, a pooled mean and standard deviation for these combined subgroups was calculated.

Data synthesis and statistical analysis

We performed the statistical analysis using Review Manager version 5.3 (Cochrane Collaboration, Baltimore, MD, USA). The results are expressed as mean differences with 95% confidence intervals. Throughout the analysis, we applied the inverse variance method with a random effects model. To assess the heterogeneity and inconsistency between the studies, we employed the tau squared and I squared (I^2) statistics. Data with $p \geq 0.10$ and $I^2 \leq 50\%$ were defined as low heterogeneity. We evaluated the publication bias with a funnel plot. We planned a meta-regression analysis by subgroup according to age, sex, geographical area, tobacco use and body mass index. We performed a sensitivity analysis by applying a fixed effects model and calculating the effect estimates according to publication date, size of T1D group and study quality. We established two categories of publication year, before and after 2000, and two categories of T1D group size, < 50 and ≥ 50 patients. In the main analysis we included good, fair and poor quality studies and excluded studies published in predatory journals. For the sensitivity analysis according study quality, we calculated the effect estimates in two ways, including only the good quality studies and including all studies adding predatory journals.

Results

Study selection

Figure 1 shows the study selection flowchart. We identified 24,332 records. Our initial search strategy produced 24,311 articles. With the manual search of the reference lists and the additional search in Google and ResearchGate, we added 22 articles. After eliminating the duplicated and irrelevant articles, we were left with 136 articles. We excluded 97 articles for the following reasons: 20 had no control group, 45 included patients with types 1 and 2 diabetes without differentiating them, 19 provided insufficient numerical data to be included in the meta-analysis, three originated from predatory journals, two presented overlapping data, one was a meta-analysis and one included exclusively patients with type 2 diabetes. Furthermore, the full-text of six papers was not found (supplementary material). There was no inter-rater agreement in study selection and consensus was necessary for eight studies. Ultimately, we included 39 studies in the meta-analysis [12-50], one longitudinal, 35 case control and three cross-sectional ones. From the longitudinal study, we extracted only the baseline pulmonary function test data.

Study characteristics

Table 1 lists the characteristics of the included studies, which were published between 1976 and 2020. Twenty-two studies were conducted in Europe, eight in Asia, five in America, and five in Africa. Thirty-seven studies were written in English, one in Polish and one in French. After the quality assessment, we classified 24 studies as good, 11 as fair and four as poor. The inter-rater agreement was full. A total of 2627 participants were included, 1274 in the T1D group and 1353 in the control group. The age range of participants was 10.0-50.7 years, and 42.3% were women.

Pulmonary function tests

We provide here data on predicted percentages of pulmonary function tests. Data about absolute values are reported in supplementary material.

FEV_1

A total of 25 studies included data on %FEV_1, and 14 included data on FEV_1(L). Figures 2A and S1 (supplementary material) show the effect estimates. The pooled estimates for the difference between T1D and controls groups were -6.40 (95%CI -8.55 to -4.25; p<0.0001) for %FEV_1 and -0.56 (95%CI -0.71 to -0.41; p<0.0001) for FEV_1(L).

FVC

A total of 23 studies included data on %FVC, and 13 included data on FVC(L). Figures 2B and S2 (supplementary material) show the comparison forest plot. The pooled differences between T1D patients and controls were -6.39 (95%CI -8.46 to -4.33; p<0.0001) for %FVC and -0.64 (95%CI -0.87 to -0.41; p<0.0001) for FVC(L).

FEV_1/FVC ratio

A total of 19 studies included data on the FEV_1/FVC ratio (%). Figure 3 shows the forest plot. The pooled difference for the patients with T1D was -0.33 (95%CI -1.70 to 1.03; p<0.63).

$FEF_{25-75\%}$

A total of 10 studies included data on %$FEF_{25-75\%}$, and six included data on $FEF_{25-75\%}$ (L/s). Figures 4A and S3 (supplementary material) show the comparison forest plots. The pooled estimates for the difference between patients with T1D and controls were -6.14 (95%CI -10.73 to -1.56; p=0.009) for %$FEF_{25-75\%}$ and -0.65 (95%CI -1.07 to -0.23; p=0.002) for $FEF_{25-75\%}$ (L/s).

PEF

A total of five studies included data on %PEF, and six included data on PEF(L/s). Figures 4B and S4 (supplementary material) show the forest plots of the effect estimates. For the patients with T1D, the pooled differences for %PEF and PEF(L/s) were -9.32 (95%CI -14.15 to -4.50; p=0.0002) and -1.32 (95%CI -2.41 to -0.24; p=0.02), respectively.

DL_{CO}

A total of 14 studies included data on $\%DL_{CO}$, and six included data on DL_{CO}(mL/min/mm Hg). Figures 4C and S5 (supplementary material) show the comparison forest plot. The pooled effect estimates for the difference between T1D patients and controls were -0.64 (95%CI -1.12 to -0.16; p=0.008) for $\%DL_{CO}$ and -3.87 (95%CI -7.02 to -0.71; p=0.02) for DL_{CO} (mL/min/mmHg).

There was significant heterogeneity for all parameters of the pulmonary function tests (I^2, 60–98%).

Subgroup analysis

Tables 2 and S1 (supplementary material) present the meta-regression analysis prespecified by subgroup.

Age

Thirty-seven studies reported data about age. Eleven studies were conducted in children or adolescents (13-19 years) and 26 in adults (≥ 20 years). It was not possible a comparison for %PEF and DL_{CO}. There were no difference by age in $\%FEV_1$, FEV_1(L), %FVC, FVC (L/s), FEV_1/FVC ratio, $\%FEF_{25-75\%}$, $FEF_{25-75\%}$(L/s) and PEF(L/s), $\%DL_{CO}$ (all p≥0.05).

Sex

Ten studies reported data differentiated by sex. A comparison could be established for $\%FEV_1$, FEV_1(L), FVC(L) and FEV_1/FVC ratio. There were no differences by sex in $\%FEV_1$, FEV_1(L) and FEV_1/FVC ratio (p>0.35 for all cases), but the decrease of FVC(L) in T1D patients was higher in men than in women (-0.80 95%CI -1.14, -0.47, and -0.33 95%CI -0.50, -0.17 respectively; p=0.01).

Body mass index

Data on BMI were reported in 25 studies and a comparison could be established for %FEV_1, FEV_1(L), %FVC, FVC(L), FEV_1/FVC, %$FEF_{25-75\%}$ and %DL_{CO}. There was no difference among groups (all $p>0.05$) but there was heterogeneity in FVC(L) and %$FEF_{25-75\%}$.

Tobacco use

Twenty-eight studies included exclusively nonsmokers, and five studies included patients who smoked and those who did not. Two studies reported disaggregated data of smokers and nonsmokers. Another six studies did not report data on tobacco use. It was no possible to establish a comparison between groups.

Geographical region

The same abnormal pulmonary function test results were observed in the patients with T1D in all continents. However, we observed heterogeneity between the various continents in %FEV_1, %FVC, %$FEF_{25-75\%}$, $FEF_{25-75\%}$(L/s), %PEF and PEF(L/s).

Sensitivity analysis

We observed the same abnormal pulmonary function test results when we applied the fixed effects model. The same result occurred when we performed an analysis separated by size of the T1D group, publication year, and study quality and even when we included the articles from predatory journals (Tables 3 and S2 supplementary material). The magnitude of the effect estimates was higher for %FEV_1, %FVC, FVC(L), %PEF, %DL_{CO} and DL_{CO}(mL/min/mmHg) when only good quality studies were included in the meta-analysis. The results did not

change with the removal of the study with greatest weight in each pulmonary function test.

Publication bias

Figures 5 and S6 (supplementary material) show the funnel plots. They revealed asymmetry, indicating the presence of potential publication biases.

DISCUSSION

Our meta-analysis shows that all of the pulmonary function test results, except the FEV_1/FVC ratio, were decreased for the patients with T1D. This pulmonary function impairment in T1D is observed worldwide and also in nonsmokers.

Various qualitative reviews have described the effect of diabetes on lung function [51-54], all of which have reported the presence of a reduction in FEV_1 and FVC in patients with diabetes. To our knowledge, only a meta-analysis on pulmonary function in patients with T1D has been published [9], which included 18 studies with 539 patients with T1D and 624 controls. The pooled difference in the $\%FEV_1$, %FVC and $\%DL_{CO}$ was -2.78, -3.83 and -6.25, respectively, with no difference in the FEV_1/FVC ratio. Our results are consistent with those observed in that meta-analysis. Unlike the study by van den Borst et al, our meta-analysis included data on PEF and $FEF_{25-75\%}$. The patients with T1D had a reduction of more than 5% in both of these tests, which indicates that there was impairment both in the large and small airways.

The significance of impaired lung function in patients with T1D remain yet occult. The decrease of FEV_1 and FVC appear modest but is approximately 500 mL. These differences are much higher than those (100–150 mL) considered significant in clinical trials with bronchodilators in patients with chronic obstructive

pulmonary disease [55,56]. Therefore, we think that pulmonary function impairment in T1D is relevant, and prospective longitudinal studies are necessary to elucidate the progression of patients with diabetes and pulmonary impairment. Patients with T1D have more lung diseases, as asthma, fibrosis or chronic obstructive pulmonary disease, and more pulmonary infections, including pneumonia and tuberculosis [57,58]. It has been suggested that this increase may be a consequence of declining lung function [57].

The prevalence of T1D varies according to geographical region and is higher in Europe, North America, and the Middle East [1]. We therefore proposed a prespecified analysis of pulmonary function tests for patients with T1D from various continents. Patients with T1D from all geographical regions presented reduced FEV_1, FVC, PEF, $FEF_{25-75\%}$ and DL_{CO}. Age, sex, ethnicity, body position, weight and height are factors that affect pulmonary function [59]. We found that impairment in the pulmonary function tests of T1D patients was observed in adults, but children and adolescents also had some impaired tests. Besides the impairment did not change when we included only those studies with nonsmoker patients. We think that impairment of pulmonary function test in T1D is tobacco independent. However, due to the low number of studies and participants, we must be cautious to interpret the results of the meta-regression with subgroup analysis.

A novelty in this meta-analysis is including PEF and $FEF_{25-75\%}$. While PEF reflects the status of proximal airway and is more effort dependant, $FEF_{25-75\%}$ is a function of the small airway obstruction. We estimated a decrease of 9.32% and 6.14% of %PEF and % $FEF_{25-75\%}$ in patients with T1D respectively. These findings suggest that proximal, distal and small airways are damaged in patients with T1D.

The structural changes of airway and the destruction of the lung parenchyma of patients with T1D could help explain the abnormal pulmonary function test results. Autopsies of human patients with diabetes have also observed thickening

of the capillary and epithelial basement membrane [60,61]. This thickening is due to inflammatory and fibrotic changes [62,63]. Fibrosis causes reduced pulmonary viscoelasticity resulting in alveolar collapsibility and can decrease lung volumes in T1D [64].

Various biochemical mechanisms have been proposed to explain the pulmonary damage observed in T1D [65,66]. Redox imbalance, mitochondrial abnormality and oxidative stress contribute to this damage [67]. Sustained hyperglycemia causes reduced superoxide dismutase activity and increased oxidative stress. The oxidative stress increases nonenzymatic glycosylation, contributing to pulmonary fibrosis. There are high expression levels of signal transducer and activator of transcription 3 with enhaced connective tissue growth factor expression in the lung tissues [68]. Abnormalities in the polyol pathways have also been involved, as well as abnormalities in the protein kinase B and nuclear factor KB signaling pathways and in transforming growth factor beta [66].

Heterogeneity is an important finding in our meta-analysis. There are several possible reasons for it. Firstly, there are differences in participants of studies. The mean age of T1D patients ranged from 9.5 to 47.4 years, the T1D duration from 2.4 to 26 years, the mean glycated hemoglobin from 7.2 to 11.6% and 0-85.7% patients had microangiopathy. Even in each continent, there are differences among patients from various geographical regions, for example between Japanese and Iranian in Asia, or Canadian and Venezuelan in America, or German and Greek people in Europe. However, the subgroup analysis shows that large amounts of heterogeneity are still present even within these subgroups so while these factors may contribute to heterogeneity, there is clearly a lot of unexplained heterogeneity. Secondly, it is possible a publication bias. Probably there are small studies with negative results that have not been published.

One of our study’s strengths is the exhaustive literature comprehensive literature search that only excluded Chinese articles. Our additional search provided a large number of articles not collected in the main databases. However, there was

a notably high number of articles published in predatory journals, which leads us to think that there are a significant number of studies on pulmonary function in patients with T1D that have not been published, probably due to their low methodological quality. We also performed a sensitivity analysis, observing that the abnormalities in the pulmonary function test results were maintained when we changed statistical analysis method, both with a fixed and a random effects model. The results also did not change when we differentiated them by study publication date, or included only the good quality studies, all of which reinforces the results of the meta-analysis.

However, our study also has a number of limitations. Firstly, we resolved the discrepancies in study selection and quality assessment by consensus, and did not calculate the Cohen´s kappa. However, the level of inter-rater agreement was high in study selection and total in quality assessment. Secondly, we observed considerable heterogeneity between the studies, even between those performed in the same geographical region. Although the implementation of a pulmonary function test is standardized, we cannot rule out that the heterogeneity is due to differing methods for measuring the pulmonary parameters. Thirdly, of the 39 studies included in the meta-analysis, only six included 50 or more cases in the T1D group, which leads us to think that many more studies might have been conducted with small groups that have not been published. The funnel plots also seem to indicate this idea. However, the results were consistent when we included only the studies with more patients. Finally, only a small number of the studies provided data separated by sex. The results of the analysis by sex should therefore be taken with caution and should be validated in future studies with a large number of patients.

In conclusion, T1D is associated with pulmonary function impairment; however, further studies with large numbers of patients from all geographical areas are needed to corroborate these data and to provide insight into the still pending issues on pulmonary impairment in patients with T1D, specifically progression and possible therapies.

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Table 1· Characteristics of the included studies

Ref	Study, author, year	Country (continent)	Sample size (men/women)	Mean age, years	Smokers, %	BMI (kg/m^2)	Fasting blood glucose (mmol/L) in T1D patients	Glycated Hb (%) in T1D patients	T1D duration, years	T1D patients with microangiopathy (%)	Pulmonary function tests	Study quality
12	Schuyler, 1976	USA (Am)	23 (23/0)	24.6	0	NR	NR	NR	17	NR	$FEF_{25-75\%}$, PEF, DL_{CO}	Fair
13	Schernthaner, 1977	Austria (Eu)	40	32.3	0	NR	NR	NR	10.9	NR	FEV_1, DL_{CO}	Fair
14	Sandler, 1986	South Africa (Af)	44 (22/22)	19.1	0	NR	NR	11.6	4.75	40.9	FVC, FEV_1/FVC	Good
15	Primhak, 1987	United Kingdom (Eu)	304 (163/141)	11.7	NR	NR	NR	7.8	4.6	NR	FEV_1, FVC	Good
16	Sandler, 1987	South Africa (Af)	81	30.9	0	<30	NR	10.9	11.0	65	FVC, FEV_1/FVC	Good
17	Bell, 1988	United Kingdom (Eu)	44 (44/0)	32.4	42.8	NR	NR	10	18.1	17.8	FEV_1, FVC, FEV_1/FVC	Poor
18	Heimer, 1990	Israel (As)	62 (34/28)	30.5	NR	NR	12.8	NR	11.1	NR	FEV_1, FVC, FEV_1/FVC	Fair
19	Wanke, 1991	Austria (Eu)	76 (64/12)	30.2	0	NR	NR	NR	NR	NR	FEV_1	Good
20	Baraldi, 1992	Italy (Eu)	80 (41/39)	12.9	NR	20.2	11.8	8.9	5.0	0	FEV_1, FVC, $FEF_{25-75\%}$	Good
21	Strojek, 1992	Poland (Eu)	49	30.5	0	23.5	NR	9.0	12.9	38.7	FEV_1, FVC, $FEF_{25-75\%}$, PEF, DL_{CO}	Fair
22	Wanke, 1992	Austria (Eu)	28 (28/0)	38	0	24.3	NR	8.8	26	NR	FEV_1	Good
23	Quatraro, 1993	Italy (Eu)	42 (42/0)	22.7	0	18.7	NR	NR	NR	0	FEV_1, FVC, FEV_1/FVC	Fair
24	Innocenti, 1994	Italy (Eu)	47 (21/26)	33	0	22.9	9.5	7.6	9.2	30.4	FEV_1, FVC, FEV_1/FVC, DL_{CO}	Poor
25	Ayça, 1996	Turkey (Eu)	40 (20/20)	12.5	NR	18.1	NR	8.5	2-5	NR	FEV_1, FVC, $FEF_{25-75\%}$	Poor
26	Fuso, 1996	Italy (Eu)	40 (23/17)	29.1	30	NR	NR	6.5	14	25	FEV_1, FVC, DL_{CO}	Poor

27	Schnack, 1996	Austria (Eu)	83 (50/33)	35.7	2.4	24.5	NR	8.2	19.3	46.1	FEV_1, FVC, FEV_1/FVC, PEF, DL_{CO}	Good
28	Niranjan, 1997	USA (Am)	32 (21/11)	35.5	0	25.3	NR	7.3	21	NR	FEV_1, FVC, FEV_1/FVC, $FEF_{25-75\%}$	Good
29	Pieron, 1997	Belgique (Eu)	30 (20/10)	44.7	0	25.3	NR	NR	20.5	50	FEV_1, FVC, FEV_1/FVC	Good
30	Makkar, 2000	India (As)	70	21.3	0	NR	NR	NR	NR	NR	FEV_1, FVC, FEV_1/FVC, PEF	Fair
31	Benbassat, 2001	Israel (As)	30 (18/15)	44	0	25.8	NR	8.6	25	40	FEV_1, FVC, $FEF_{25-75\%}$, DL_{CO}	Fair
32	Boulbou, 2003	Greece (Eu)	38 (16/22)	43.1	0	27.3	NR	9.4	16.6	NR	FEV_1, FVC, FEV_1/FVC, DL_{CO}	Fair
33	Cazzato, 2004	Italy (Eu)	79 (40/39)	10	0	18	NR	7.6	3.2	21	FEV_1, FVC, FEV_1/FVC, DL_{CO}	Faie
34	Villa, 2004	Italy (Eu)	69 (42/27)	10.8	0	19.5	NR	7.7	3.6	2.6	FEV_1, FVC, $FEF_{25-75\%}$	Good
35	Meo, 2005	Saudi Arabia (As)	54 (54/0)	39.8	0	26.0	NR	NR	11.6	0	FEV_1, FVC, FEV_1/FVC, $FEF_{25-75\%}$, PEF	Good
36	Saler, 2009	Turkey (Eu)	124 (37/87)	37.4	0	24.4	NR	7.5	6.8	31.8	DL_{CO}	Fair
37	Verma, 2009	India (As)	100 (60/40)	50.7	0	NR	NR	NR	NR	NR	FEV_1, FVC, FEV_1/FVC, $FEF_{25-75\%}$, PEF	Good
38	Baldi, 2010	USA (Am)	22 (18/4)	36.8	0	23	11.3	7.3	NR	NR	FEV_1, FVC	Good
39	Komatsu, 2010	Brazil (Am)	51	26.5	NR	23.1	NR	8.2	14.9	NR	FEV_1, FVC, DL_{CO}	Good
40	Al_Habbo, 2012	Iraq (As)	70 (38/32)	41.8	0	NR	NR	NR	5.5	0	FEV_1, FVC, FEV_1/FVC, $FEF_{25-75\%}$, PEF	Fair
41	Arif, 2012	Bangladesh (As)	60 (60/0)	23.5	NR	17.8	11.1	NR	NR	NR	FEV_1, FVC, FEV_1/FVC	Good
42	Pieniawska, 2012	Poland (Eu)	73 (39/34)	13.4	0	19.2	NR	8.1	3.3	NR	FEV_1, FVC, FEV_1/FVC, PEF	Good
43	Scaramuzza, 2012	Italy (Eu)	72 (40/32)	15.7	0	27	NR	8.3	8.3	NR	FEV_1, FVC, DL_{CO}	Good
44	Abd El-Azeem, 2013	Egypt (Af)	70	NR	0	NR	NR	NR	> 5	NR	FEV_1, FVC, FEV_1/FVC, $FEF_{25-75\%}$, PEF, DL_{CO}	Good
45	Baseer, 2013	Saudi Arabia (As)	100 (60/40)	11.5	0	16.5	NR	7.2	6.1	0	FEV_1, FVC, FEV_1/FVC, PEF	Good
46	Mohamad, 2015	Egypt (Af)	110 (61/49)	10.2	0	NR	NR	10.9	2.4	0	FEV_1, FVC, FEV_1/FVC, PEF	Good
47	Slim, 2015	Tunisia (Af)	28 (14/14)	48.6	17.9	27.7	10.3	10.7	21	85.7	FEV_1, FVC, FEV_1/FVC, $FEF_{25-75\%}$, DL_{CO}	Good

48	Durdik, 2016	Slovakia (Eu)	71 (38/33)	16.4	0	21.2	11.9	10.8	6.4	NR	FEV_1, FVC, $FEF_{25-75\%}$, PEF	Good
49	Lee, 2016	USA (Am)	48 (22/26)	24.0	0	22.5	NR	7.9	9.8	0	FEV_1, FVC	Good
50	Sánchez, 2020	Spain (Eu)	150 (44/106)	40.4	11.5	24.4	8.8	7.6	≥ 3	NR	FEV_1, FVC, FEV_1/FVC, $FEF_{25-75\%}$, PEF	Good

Abbreviations: Af, Africa; Am, America; As, Asia; BMI, body mass index; DL_{CO}, diffusion capacity of the lungs for carbon monoxide; DM, diabetes mellitus; Eu, Europe; $FEF_{25-75\%}$, forced expiratory flow between 25-75%; FEV_1, forced expiratory flow in one second; FVC, forced vital capacity; Hb, hemoglobin; m, months; PEF, peak expiratory flow; Oc, Oceania; NR, not reported; T1D, type-1 diabetes; y, years.

Table 2. Meta-regression with subgroup analysis

	%FEV_1					%FVC					FEV_1/FVC(%)				
	Studies	Participants	Effect estimate	I^2	p	Studies	Participants	Effect estimate	I^2	p	Studies	Participants	Effect estimate	I^2	p
Age															
C & A	7	748	-3.65 (-6.56, -0.75)	88%	0.01	6	416	-1.72 (-4.22, 0.79)	51%	0.18	4	363	2.55 (-3.36, 8.46)	96%	0.40
Adults	17	824	-7.98 (-11.30, -4.66)	91%	<0.001	14	650	-5.26 (-7.72, -2.79)	73%	<0.001	13	723	-2.42 (-4.41, -0.43)	80%	0.02
Male	4	279	-19.10 (-41.89, 3.70)	86%	0.10	3	116	-24.18 (-45.65, -0.22)	96%	0.003	6	274	-0.97 (-3.62, 1.68)	56%	0.47
Female	2	155	-7.27 (-18.95, 4.40)	98%	0.22	1	14	NA	NA	NA	2	54	-3.03 (-6.04, -0.02)	0%	0.05
Nonsmokers	17	886	-4.78 (-7.00, -2.56)	77%	<0.001	16	816	-5.07 (-7.79, -2.35)	81%	<0.001	15	933	-0.59 (-2.14, 0.87)	95%	0.46
Continent															
Africa	1	28	NA	NA	NA	2	72	-6.60 (-19.14, 5.94)	82%	0.30	4	288	1.17 (-1.51, 3.85)	98%	0.39
America	3	131	-5.99 (-8.55, -3.44)	66%	<0.001	3	131	-1.79 (-2.16, -1.42)	0%	<0.001	1	32	NA	NA	NA
Asia	5	292	-14.01 (-30.19, 2.17)	97%	0.09	4	222	-17.41 (-35.5 ,0.75)	956	0.06	6	446	-2.79 (-6.43, 0.85)	83%	0.13
Europe	15	1121	-4.06 (-6.11, -2.00)	78%	<0.001	13	1737	-4.96 (-8.34, -1.57)	86%	<0.001	7	390	-1.23 (-4.71, 2.26)	78%	0.49
BMI (kg/m^2)															
< 20	5	323	-11.64 (-24.50, 1.21)	98%	0.08	5	323	-11.99 (-23.71, -0.27)	97%	0.04	4	275	1.11 (-3.52, 5.75)	69%	0.64
20-25	8	457	-5.86 (-9.05, -2.67)	73%	<0.001	8	457	-5.24 (-8.69, -1.78)	78%	0.003	5	283	-0.64 (-3.01, 1.74)	71%	0.60
25.1-30	5	206	7.41 (-13.68, -1.14)	84%	<0.001	6	246	-3.95 (-11.18, 3.28)	90%	0.28	3	142	-3.05 (-5.13, -0.96)	71%	0.004

	%FEF_{25-75}					%PEF					%DL_{CO}				
	Studies	Participants	Effect estimate	I^2	p	Studies	Participants	Effect estimate	I^2	p	Studies	Participants	Effect estimate	I^2	p
Age															
C & A	3	220	-0.53 (-5.57, 6.63)	10%	0.86	1	71	NA	NA	NA	3	220	-1.26 (-2.37, -0.14)	93%	0.03
Adults	6	232	-9.66 (-15.09, -4.22)	57%	<0.001	3	202	-9.73 (--19.95, 0.50)	77%	0.06	11	578	-0.46 (-0.98, 0.06)	88%	0.08
Male	2	37	-0.26 (-0.56, 0.05)	25%	0.07	0	0	NA	NA	NA	2	37	0.69 (-2.04, 3.42)	92%	0.62
Female	1	14	NA	NA	NA	0	0	NA	NA	NA	1	14	NA	NA	NA
Nonsmokers	8	366	-7.15 (-12.10, -2.21)	57%	0.005	3	190	-5.37 (-9.37, -1.36)	0%	0.009	10	596	-0.42 (-0.93, 0.09)	88%	0.10
Continent															
Africa	1	28	NA	NA	NA	0	0	NA	NA	NA	1	28	NA	NA	NA
America	2	55	-10.95 (-16.30, -5.59)	61%	<0.001	0	0	NA	NA	NA	3	106	-0.63 (-3.79, 2.52)	97%	0.69
Asia	2	100	-8.71 (-16.82, -0.60)	0%	0.04	1	70	NA	NA	NA	1	30	NA	NA	NA
Europe	4	269	1.12 (-4.12, 6.36)	0%	0.68	3	203	-11.30 (-18.95, -3.64)	57%	0.04	9	634	-0.62 (-1.03, -0.20)	84%	0.004
BMI (kg/m^2)															
< 20	1	69	NA	NA	NA	0	NA	NA	NA	NA	2	148	-0.64 (-0.97, -0.31)	0%	<0.001
20-25	4	228	-4.94 (-15.49, 5.60)	69%	0.36	3	203	-11.30 (-18.95, -3.64)	57%	0.004	6	382	-0.86 (-1.61, -0.10)	91%	<0.001
25.1-30	2	62	-8.15 (-12.10, -4.21)	0%	<0.001	0	NA	NA	NA	NA	4	205	-1.01 (-2.06, 0.04)	91%	<0.001

Abbreviations: BMI, body mass index; DL_{CO}, diffusion capacity of the lung for carbon monoxide; $FEF_{25-75\%}$, forced expiratory flow between 25% and 75% of total lung capacity; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; NA, not applicable; PEF, peak expiratory flow.

Table 3. Sensitivity analysis

	%FEV_1				%FVC				FEV_1/FVC (%)			
	Studies	Participants	Effect estimate	I^2	Studies	Participants	Effect estimate	I^2	Studies	Participants	Effect estimate	I^2
Statistical analysis method												
Random effect	25	1722	-6.40 (-8.55, -4.25)	94%	23	1348	-6.39 (-8.46, -4.33)	91%	19	1306	-0.33 (-1.70, 1.03)	94%
Fixed effect			-6.39 (-6.68, -6.09)				-2.14 (-2.47, -1.80)				0.44 (0.26, 0.62)	
Publication year												
Before 2000	11	809	-3.48 (-5.44, -1.52)	53%	10	509	-3.81 (-7.32, -0.29)	75%	8	420	-1.62 (-3.09, -0.15)	58%
After 2000	13	763	-8.81 (-12.10, -5.51)	96%	12	689	-8.77 (-11.75, -5.78)	94%	10	736	-0.03 (-1.77, 1.70)	88%
Type-1 diabetes group size												
<50 patients	22	1198	-6.71 (-9.09, -4.32)	86%	22	1198	-6.51 (-8.66, -4.36)	91%	15	846	-1.30 (-2.75, 0.15)	94%
≥50 patients	2	374	-4.62 (-12.43, 3.18)	99%	1	150	NA	NA	3	310	1.54 (-5.36, 8.44)	89%
Study quality												
Only good quality studies	12	1001	-8.45 (-12.06, -4.85)	95%	13	741	-7.39 (-11.75, -3.03)	94%	12	820	0.02 (-1.56, 1.60)	95%
Including predatory journals	24	1572	-6.48 (-8.69, -4.26)	94%	22	1198	-2.12 (-2.45, -1.78)	91%	18	1156	-0.77 (-2.15, 0.62)	93%
	%$FEF_{25-75\%}$				%PEF				%DL_{CO}			
	Studies	Participants	Effect estimate	I^2	Studies	Participants	Effect estimate	I^2	Studies	Participants	Effect estimate	I^2
Statistical analysis method												
Random effect	10	602	-6.14 (-10.73, -1.56)	63%	5	423	-9.32 (-14.15, -4.50)	60%	14	798	-0.64 (-1.12, -0.16)	89%
Fixed effect			-7.58 (-10.02, -5.14)				-9.09 (-11.91, -6.27)				-0.57 (-0.72, -0.42)	
Publication year												
Before 2000	4	184	-5.03 (-10.06, -0.00)	78%	2	132	-14.14 (-24.73, -3.54)	53%	6	274	0.09 (-0.41, 0.59)	74%
After 2000	5	268	-7.01 (-16.01, 2.00)	61%	2	141	-5.01 (-9.28, -0.74)	0%	8	524	-1.23 (-1.90, -0.56)	91%
Type-1 diabetes group size												
<50 patients	10	602	-6.14 (-10.73, -1.56)	63%	4	141	-8.82 (-15.37, -2.27)	65%	14	798	-0.64 (-1.12, -0.16)	89%
≥50 patients	0	0	NA	NA	1	150	NA	NA	0	0	NA)	NA
Study quality												
Only good quality studies	5	280	-5.26 (-12.92, 2.40)	71%	2	154	-12.66 (-24.02, -1.31)	77%	6	335	-1.34 (-2.33, -0.35)	93%
Including predatory journals	9	452	-6.19 (-11.39, -0.99)	67%	4	273	-8.82 (-15.37, -2.27)	65%	14	798	-0.64 (-1.12, -0.16)	89%

Abbreviations: DL_{CO}, diffusion capacity of the lung for carbon monoxide; $FEF_{25-75\%}$, forced expiratory flow between 25% and 75% of total lung capacity; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; NA, not applicable; PEF, peak expiratory flow.

Figure legends

Figure 1. Flowchart of included studies

Figure 2. Forest plots of % predicted forced expiratory volume in one second (A) and % predicted forced vital capacity (B).

Figure 3. Forest plot of forced expiratory volume in one second/forced vital capacity ratio (%)

Figure 4. Forest plots of % predicted forced expiratory flow between 25% and 75% of total lung capacity (A), % predicted peak expiratory flow (B), and % predicted diffusion capacity of the lungs for carbon monoxide (C).

Figure 5. Funnel plots of % predicted forced expiratory volume in one second (A) and % predicted forced vital capacity (B), forced expiratory volume in one second/forced vital capacity ratio (%) (C), forced expiratory flow between 25% and 75% of total lung capacity (D), % predicted peak expiratory flow (E), and % predicted diffusion capacity of the lungs for carbon monoxide (F).

Key messages

- What is the key question?

What is the influence of type-1 diabetes on pulmonary function tests?

- What is the bottom line?

Type-1 diabetes is associated with impaired pulmonary function

- Why read on?

Lung is a target organ of type-1 diabetes, and clinicians should consider measuring lung function in patients with type-1 diabetes.