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Pulmonary function tests in type-2 diabetes. A meta-analysis

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Contributor statement

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

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Disclosure

The authors declare no conflict of interest.

PULMONARY FUNCTION TESTS IN TYPE-2 DIABETES. A META-ANALYSIS

ABSTRACT

Objectives: To determine the association between type 2 diabetes (T2D) 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 sex, body mass index (BMI), smoking and geographical region. We also conducted a sensitivity analysis according to the studies' publication date, size of the T2D group and the study quality, excluding the study with the greatest weight in the effect.

Results: The meta-analysis included 66 studies, one longitudinal, 2 case-control and 63 cross-sectional ones, with 11,134 patients with T2D and 48,377 control participants. The pooled MD (95%CI) for the predicted percentage of FEV₁, FVC, FEF_{25-75%}, PEF and DL_{CO} were -7.15 (95%CI -8.27, -6.03; $p<0.001$), -9.21 (95%CI -11.15, -7.26; $p<0.001$), -9.89 (95%CI -14.42, -5.36; $p<0.001$), -9.79 (95%CI -13.42, -6.15; $p<0.001$) and -7.13 (95%CI -10.62, -3.64; $p<0.001$), respectively. There was no difference in the ratio of FEV₁/FVC (95%CI -0.27; -1.63, 1.08; $p=0.69$). In all cases, there was considerable heterogeneity. The meta-regression analysis showed that between studies heterogeneity was not explained by patient sex, BMI, smoking or geographical region. The findings were consistent in the sensitivity analysis.

Conclusions: T2D is associated with impaired pulmonary function, independently of sex, smoking, BMI, and geographical region. Longitudinal studies are needed to investigate outcomes for patients with T2D and impaired pulmonary function.

Keywords: Type-2 diabetes; Pulmonary function test; meta-analysis.

INTRODUCTION

Diabetes is a chronic disease that affects 463 million people worldwide over the age of 20 years and is expected to affect more than 570 million by 2030 [1]. Diabetes is a leading cause of cardiovascular disease, blindness, kidney failure and lower limb amputation [2]. It is estimated that 4.2 million deaths worldwide were due to type-2 diabetes (T2D) and its complications in 2019 [1].

T2D affects all organs in the human body. It usually develops relatively slowly, and it is frequent the existence of target organ damage when T2D is diagnosed. A number of studies have shown fibrotic changes in the lungs [3] and pulmonary microcirculation disorders in patients with diabetes [4]. There have been persistent attempts investigating abnormal respiratory conditions in general diabetic patients [5-6]. However, pulmonary function impairment has not been well studied in patients with T2D. Although interest in this condition has increased in recent years, the findings of studies reflect high variability. A 2010 meta-analysis by van den Borst et al showed an association between T2D and a restrictive pattern [7]. Recently, Saini et al have conducted a new systematic review including exclusively English language studies published in PubMed between 2010 and 2018 [8]. Both meta-analysis reported data about forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and FEV_1/FVC ratio, and van den Borst et al also data about diffusing capacity of the lungs for carbon monoxide (DL_{CO}).

We hypothesize that lung may be a target organ of T2D. To contribute to advance the knowledge in this field, we decided to perform a new meta-analysis including literature published in all languages and analyzing the influence of publication date, study quality and number of individuals included. Furthermore, as novelty, we determined the influence of sex, tobacco use, geographical area and body mass index. The aim of this meta-analysis was to investigate the abnormal pulmonary function test results for patients with T2D incorporating the most recent studies. In addition to the parameters reported in the two previous

systematic reviews, 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 T2D on the following parameters of pulmonary function tests: FEV_1 , FVC, FEV_1/FVC ratio, $FEF_{25-75\%}$, PEF and DL_{CO} .

The protocol for this meta-analysis was recorded in the PROSPERO registry (number CRD42020145456) and was conducted according to the guidelines of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group.

Data sources and search strategy

We performed a systematic search in PubMed, EMBASE, The Cochrane Library and Virtual Health Library databases from their inception to August 1st, 2019. The search strategy was “(*pulmonary function test* OR FEV_1 OR FVC OR DL_{CO} OR PEF OR $FEF_{25-75\%}$) AND *diabetes*”. We performed an additional search in Google and ResearchGate. The reference lists of the selected studies were screened manually to find more studies.

Study selection

To be included in this review, the studies had to meet the following inclusion criteria:

- (i) Presence of a T2D 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.

The exclusion criteria were studies on cystic fibrosis-related diabetes, type-1 diabetes, studies that did not differentiate between type-1 and type-2 diabetes, studies that included patients with respiratory diseases as asthma or chronic

obstructive pulmonary disease, studies that did not report data on mean and standard deviation, studies published in predatory journals, conference abstracts, theses and articles published in Chinese language. 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. Any discrepancy was resolved by consensus.

When a study's full text was not accessible online or supplemental data were required, we made an attempt to contact the authors by email; unfortunately, these attempts were not successful.

Quality assessment

We independently assessed the risk of bias 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 T2D 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 age, sex, body mass index, tobacco use, T2D duration, fasting blood glucose, glycated hemoglobin and microangiopathy. The extracted results were FEV₁ (liters, L), percentage of predicted (%) FEV₁, FVC (L), %FVC, FEV₁/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 T2D 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 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 T2D group and study quality and by eliminating the study with the greatest weight on the effect. We established three categories of publication year, before 2000, 2000-2009 and 2010-2019, and two categories of T2D group size, < 50 and ≥ 50 patients. 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 and grey literature.

Results

Study selection

We identified 17,662 records. Figure 1 shows the study selection flowchart. Our initial search strategy produced 17,549 articles. With the manual search of the reference lists and the additional search in Google and ResearchGate, we added 115 articles. After eliminating the duplicated and irrelevant articles, we were left with 263 articles. We excluded 191 articles for the following reasons: 62 had no control group, 49 included patients with types 1 and 2 diabetes without differentiating them, 30 provided insufficient numerical data to be included in the meta-analysis, 26 originated from predatory journals, 10 presented overlapping data, six came from grey literature (theses and proceedings), four were in Chinese language, one included patients with respiratory diseases, two were meta-analyses and one was an editorial. There was no inter-rater agreement in study selection and consensus was necessary for eight studies. Furthermore, the full-text of six papers was not found (supplementary material). Ultimately, we included 66 studies in the meta-analysis [9-74], one longitudinal, 2 case control and 63 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 1991 and 2018. Three studies were conducted in Africa, 11 in America, 33 in Asia, 18 in Europe and one in Oceania. Fifty-eight studies were written in English, 4 in Turkish, 2 in Spanish, one in German and one in Japanese. After the quality assessment, we classified 60 studies as good, six as fair and four as poor. The inter-rater agreement was full. A total of 59,511 participants were included, 11,134 in the T2D group and 48,377 in the control group. The age range of T2D patients was 39.8-79 years, and 35.1% 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.

FEV₁

A total of 41 studies included data on %FEV₁, and 34 included data on FEV₁(L). Figures 2A and S1 (supplementary material) show the comparison forest plot. The pooled effect estimates for the patients with T2D were -7.15 (95%CI -8.27 to -6.03; $p < 0.0001$) for %FEV₁ and -0.34 (95%CI -0.42 to -0.27; $p < 0.0001$) for FEV₁(L).

FVC

A total of 35 studies included data on %FVC, and 23 included data on FVC(L). Figures 2B and S2 (supplementary material) show the effect estimates. The pooled estimates for the patients with T2D were -9.21 (95%CI -11.15 to -7.26; $p < 0.0001$) for %FVC and -0.36 (95%CI -0.43 to -0.29; $p < 0.0001$) for FVC(L).

FEV₁/FVC ratio

A total of 45 studies included data on the FEV₁/FVC ratio (%). Figure 3 shows the comparison forest plot. The pooled effect estimate for the patients with T2D was -0.27 (95%CI -1.63 to 1.08; $p < 0.69$).

FEF_{25-75%}

A total of 13 studies included data on %FEF_{25-75%}, and 12 included data on FEF_{25-75%} (L/s). Figures 4A and S3 (supplementary material) show the forest plots of the effect estimates. For the patients with T2D, the pooled estimates for %FEF_{25-75%} and FEF_{25-75%}(L/s) were -9.89 (95%CI -14.42 to -5.36; $p < 0.0001$) and -0.48 (95%CI -0.71 to -0.24; $p < 0.0001$), respectively.

PEF

A total of 15 studies included data on %PEF, and 19 included data on PEF(L/s). Figures 4B and S4 (supplementary material) show the comparison forest plot. The pooled effect estimates for the patients with T2D were -9.79 (95%CI -13.42 to -6.15; $p<0.0001$) for %PEF and -1.07 (95%CI -1.43 to -0.71; $p<0.0001$) for PEF(L/s).

DL_{CO}

A total of 12 studies included data on %DL_{CO}, and ten 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 patients with T2D were -7.13 (95%CI -10.62 to -3.64; $p<0.0001$) for %DL_{CO} and -3.42 (95%CI -5.14 to -1.70; $p<0.0001$) for DL_{CO} (mL/min/mmHg).

There was significant heterogeneity for all parameters of the pulmonary function tests (I^2 , 80–100%).

Subgroup analysis

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

Sex

Fifteen studies reported data differentiated by sex. A comparison could be established for %FEV₁, FEV₁(L), %FVC, FVC(L), FEV₁/FVC ratio and PEF (L/s). There were no differences by sex ($p>0.25$ for all cases).

Tobacco use

Fourteen studies included patients who smoked and those who did not, and 43 studies included exclusively nonsmokers. Another nine studies did not report

data on tobacco use. There was heterogeneity between the groups; the effect estimate for the patients with T2D who did not smoke presented a reduction in %FEV₁, %FVC, FVC(L) ($p \leq 0.01$ for all) and PEF(L/s) ($p < 0.001$), which was higher than in the other studies that included smokers and nonsmokers.

Geographical region

The same abnormal pulmonary function test results were observed in the patients with T2D in all continents. However, we observed heterogeneity between the various continents in %FEV₁, %FVC, FEV₁/FVC ratio, FEF_{25-75%}(L/s), %PEF, DL_{CO}(mL/min/mm Hg) (all $p < 0.001$) and PEF(L/s) ($p = 0.004$).

Sensitivity analysis

When we applied the fixed effects model, we observed the same abnormal pulmonary function test results. The same result occurred when we performed an analysis separated by publication year, size of the T2D group, study quality and even when we included the articles from predatory journals and from the proceedings of congresses (Tables 3 and S2 supplementary material). The magnitude of the effect estimates was higher for %FEV₁, %FVC, %FEF_{25-75%}, %PEF and %DL_{CO} when only good quality studies were included in the meta-analysis. The removal of the study with greatest weight in each pulmonary function test did not change the results.

Publication bias

The funnel plots showed asymmetry, indicating the presence of potential publication biases (figures 5 and S6 supplementary material).

DISCUSSION

The results of our meta-analysis show that all of the pulmonary function test results, except the FEV₁/FVC ratio, were decreased for the patients with T2D. This pulmonary function impairment in T2D is observed worldwide, also in nonsmokers and is independent of sex.

Various qualitative reviews have been published on the influence of diabetes on pulmonary function [75-80], all of which have reported the presence of a reduction in FEV₁ and FVC in patients with diabetes. In 2010, van den Borst et al published a meta-analysis on pulmonary function in patients with diabetes [7], which included 16 studies with 1695 patients with T2D and 10,260 controls. The pooled difference in the %FEV₁, %FVC and %DL_{CO} was -4.86, -6.67 and -9.30, respectively, with no difference in the FEV₁/FVC ratio. Their results are consistent with those observed in our meta-analysis.

Recently, Saini et al reported another meta-analysis with 22 studies that included 7526 patients with T2D and 43,641 controls [8]. The pooled difference in the %FEV₁ and %FVC was -6.37 and -6.56 respectively, with no difference in the FEV₁/FVC ratio. The meta-analysis also presented data on FEV₁(L), FVC(L), with differences of -0.27 and -0.31 L, respectively, which were consistent with those observed in our meta-analysis. However, our meta-analysis and that of Saini et al. differ in the included studies. In our meta-analysis there are 20 studies that Saini et al did not include [38,40,43,44,47-50,53,57,59-68]. Moreover, we did not include 9 of the studies in the Saini et al meta-analysis because we considered that the studies did not clearly state that they only included patients with T2D [supplementary material, references S86-S88, S96, S98, S103, S104, S106, S108]. Unlike the studies by van den Borst et al and Saini et al, our meta-analysis included data on PEF and FEF_{25-75%}. The patients with T2D have a reduction of almost 10% in both of these tests, which indicates that there was impairment both in the large and small airways.

The functional impairment observed in patients with T2D for FEV₁ and FVC appear modest but is approximately 300 mL. Much lower differences (100–150 mL) have been considered significant in clinical trials with bronchodilators in patients with chronic obstructive pulmonary disease [81,82]. Therefore, pulmonary function impairment in T2D is relevant, although prospective longitudinal studies are still necessary to elucidate the progression of patients with diabetes and pulmonary impairment. It is widely known that patients with T2D have more diseases and pulmonary infections, including pneumonia and tuberculosis [83,84].

The prevalence of T2D varies according to geographical region and is higher in North America, Southeast Asia and the Middle East [1]. Age, sex, weight, height, body position and ethnicity are factors that affect pulmonary function [85]. We therefore proposed a prespecified analysis of pulmonary function tests for patients with T2D from various continents. Patients with T2D from all geographical regions presented reduced FEV₁, FVC, PEF, FEF_{25-75%} and DL_{CO}. We also found that impairment of T2D in the pulmonary function tests was observed in both sexes and did not change when we included only those studies with nonsmoker patients. In fact, the decrease of pulmonary function tests was higher in studies that included only nonsmokers than in the studies with a mixture of smokers and nonsmokers. We don't have an explanation for this finding, but we have observed that most of studies including smokers were conducted in Europe and America. It is possible that patients included in studies from Asia and Africa were nonsmokers but had more environmental exposure to biomass fuel, air pollution or other noxious particles or gases.

Overweight and obesity are associated with a detriment of lung function [86,87]. Therefore, we could consider that BMI is a confounder. Interestingly, we have observed that the reduction in pulmonary function tests, specifically FEV₁, FVC, FEF_{25-75%} and DL_{CO}, is present in normal, overweight and obese patients with T2D. FEV₁ reflects the airway resistance, and FVC the total compliance from both the chest wall and the lungs. The fat accumulation on the chest wall and in

abdomen substantially alters the movement of thoracic cage and diaphragm and impairs the lung compliance [88].

Including PEF and $FEF_{25-75\%}$ is one of novel findings in this meta-analysis. The decrease of %PEF and %FEV₁ in patients with T2D was -9.79% y -7.15% respectively. It is known that there is high correlation between both parameters. However, while FEV₁ is a good indicator of peripheral and proximal airway resistance, PEF reflects the status of proximal airway and is more effort dependant. $FEF_{25-75\%}$ is a function of the small airway obstruction. The structural changes of airway and the destruction of the lung parenchyma can modify $FEF_{25-75\%}$. Thus, other mechanisms, and not only obesity or tobacco use, must be involved in the decrease of lung function in patients with T2D and normal or overweight.

There are structural abnormalities in the lungs of patients with diabetes that could help explain the abnormal pulmonary function test results. Studies on the lungs of obese diabetic rats have observed thickening of alveolar basal lamina [88]. Autopsies of human patients with diabetes have also observed thickening of the capillary and epithelial basement membrane [89,90]. This thickening is due to inflammatory and fibrotic changes [91]. Fibrosis causes reduced pulmonary elasticity and can decrease lung volumes in T2D. The deterioration of alveolar integrity has also been shown through lung scans following radionuclide inhalation [92]. Alteration of the capillary microcirculation structure can impair pulmonary perfusion and change the ventilation/perfusion ratio [93], which would explain the reduction in DL_{CO} in patients with T2D.

Various biochemical mechanisms have been proposed to explain the pulmonary damage observed in T2D [94]. Sustained hyperglycemia causes reduced superoxide dismutase activity and increased oxidative stress. The oxidative stress increases nonenzymatic glycosylation, contributing to pulmonary fibrosis. 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 [91,94].

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 T2D patients ranged from 39.8 to 79 years, the T2D duration from 0.35 to 12.9 years, the mean glycated hemoglobin from 6.1 to 9.5% and 0-92% 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. 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 T2D 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, by including only the good quality studies and even when we excluded the study with the greatest weight, 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 66 studies included in the meta-analysis, only half included 50 or more cases in the T2D 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, T2D 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 T2D, specifically progression and possible therapies.

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Table 1. Characteristics of the included studies and patients with type 2 diabetes												
Ref	Study, author, year	Country (continent)	DM group size (men/women)	Mean age, years	Smokers, %	BMI (kg/m ²)	Fasting blood glucose, mmol/L	Glycated Hb (%)	T2D duration, years	Patients with microangiopathy (%)	Pulmonary function tests	Study quality
9	Matsubara, 1991	Japan (As)	53 (29/23)	58.0	NR	NR	NR	9.5	7.4	NR	FEV ₁ , DL _{CO}	Fair
10	Lara-Rodríguez, 1995	Venezuela (Am)	12 (7/5)	47.0	0	NR	NR	NR	NR	83	FEV ₁ , FVC, FEV ₁ /FVC, FEF _{25-75%} , DL _{CO}	Fair
11	Barrett-Connor, 1996	USA (Am)	139 (71/68)	75.9	5.7	26.3	6.94	NR	NR	NR	FEV ₁ , FVC	Good
12	Katoh, 1996	Japan (As)	19 (10/9)	50.5	NR	27.8	7.49	7.5	NR	NR	FEV ₁	Fair
13	Isotani, 1999	Japan (As)	54 (23/31)	54.9	0	22.2	9.77	9	11.0	68.5	FEV ₁ , DL _{CO}	Good
14	Benbassat, 2001	Israel (As)	12 (8/4)	60	0	29.6	NR	9.0	12.8	33	FEV ₁ , FVC, FEF _{25-75%} , DL _{CO}	Good
15	Zamarrón, 2001	Spain (Eu)	31 (5/26)	71.1	0	NR	NR	NR	NR	NR	FEV ₁ , FVC, FEV ₁ /FVC, FEF _{25-75%} , DL _{CO}	Good
16	Ari, 2002	Turkey (Eu)	25 (5/20)	55.6	0	25.8	NR	7.5	9.4	25	FEV ₁ , FVC, FEV ₁ /FVC, FEF _{25-75%} , PEF, DL _{CO}	Good
17	Guazzi, 2002	Italy (Eu)	15 (8/7)	62.3	0	NR	7.6	6.1	NR	NR	FEV ₁ , DL _{CO}	Good
18	Maiolo, 2002	Italy (Eu)	12 (0/12)	50.3	0	32.6	11.43	NR	NR	NR	FEV ₁ , FVC, FEV ₁ /FVC, PEF	Good
19	Boulbou, 2003	Greece (Eu)	33	NR	0	27.3	NR	NR	NR	NR	FEV ₁ , FVC, FEV ₁ /FVC, DL _{CO}	Good
20	Guvener, 2003	Turkey (Eu)	25 (9/16)	56.3	0	29.9	NR	7.4	5.8	63.6	FEV ₁ , FVC, PEF, DL _{CO}	Good
21	Melo, 2003	Brazil (Am)	17 (8/9)	47.0	0	NR	NR	NR	7.5	47	FEV ₁ , FVC, FEV ₁ /FVC, FEF _{25-75%}	Good
22	Lau, 2004	China (As)	40 (26/14)	49.8	10	25.9	NR	7.9	7.8	50	FEV ₁ , FVC, FEV ₁ /FVC, DL _{CO}	Poor
23	Sinha, 2004	India (as)	29 (21/8)	46.7	0	24.9	14.54	8.6	4.4	41.4	FEV ₁ , FVC, PEF, DL _{CO}	Good
24	Weisbrod, 2005	Australia (Oc)	8 (5/3)	56.2	0	29.9	9.1	7.9	5.1	0	FEV ₁ , FVC, FEV ₁ /FVC	Good
25	Meo, 2006	Saudi Arabia (As)	32 (32/0)	52.6	0	NR	NR	NR	10	NR	FEV ₁ , FVC, FEV ₁ /FVC, FEF _{25-75%} , PEF	Good
26	Ortiz-Aguirre, 2006	Mexico (Am)	144 (54/90)	57.7	36.8	28.8	9.16	NR	9.2	NR	FEV ₁ , FVC, FEV ₁ /FVC, PEF	Poor
27	Ozsahin, 2006	Turkey (Eu)	25 (6/19)	55	0	24.3	NR	NR	9.3	92	DL _{CO}	Fair
28	Chance, 2008	USA (Am)	69 (38/31)	46.1	0	31.1	NR	8.3	7.8	38	FEV ₁ , FVC, FEV ₁ /FVC	Good
29	Dennis, 2008	Colombia (Am)	262 (107/155)	50.9	15.3	NR	NR	NR	NR	NR	FEV ₁ , FVC, FEV ₁ /FVC	Good
30	Kabitz, 2008	Germany (Eu)	21 (21/0)	63.6	NR	28.5	NR	7.3	12.9	52.4	FEV ₁ , FVC, FEV ₁ /FVC	Good
31	Yeh, 2008	USA (Am)	1100 (528/572)	55	19	30.9	NR	NR	NR	NR	FEV ₁ , FVC, FEV ₁ /FVC	Good
32	Ali, 2009	Bangladesh (As)	60 (60/0)	51.8	0	21.3	NR	6.8	10.6	NR	FEV ₁ , FVC, FEV ₁ /FVC	Good
33	Saler, 2009	Turkey (Eu)	68 (19/49)	52.4	0	27.0	NR	7.4	7.6	44	DL _{CO}	Good
34	Verma, 2009	India (As)	50 (30/20)	50.2	0	NR	NR	NR	NR	NR	FEV ₁ , FVC, FEV ₁ /FVC, FEF _{25-75%} , PEF	Good
35	Agarwal, 2010	India (As)	30 (17/13)	44.6	0	22.0	NR	8.7	5.4	50	FEV ₁ , FVC, FEF _{25-75%} , PEF, DL _{CO}	Good
36	Ali, 2010,	Bangladesh (As)	60 (60/0)	51.8	0	21.3	NR	6.8	10.6	NR	FEF _{25-75%} , PEF	Good
37	Lecube, 2010	Spain (Eu)	25 (0/25)	44.0	0	49.2	8.6	7.5	NR	16	FEV ₁ , FVC, FEV ₁ /FVC, FEF _{25-75%}	Good
38	Ozoh, 2010	Nigeria (Af)	101 (47/54)	46.1	0	28.3	NR	7.8	1m-18y	NR	FEV ₁ , FVC, FEV ₁ /FVC, PEF	Good
39	Buyukhatipoglu, 2011	Turkey (Eu)	80 (40/40)	47.8	0	26.7	10.77	9.3	5	50	DL _{CO}	Good
40	Ceylan, 2011	Turkey (Eu)	37 (16/21)	39.8	0	NR	NR	8.2	7	NR	FEV ₁ , FVC, FEV ₁ /FVC, FEF _{25-75%} , PEF, DL _{CO}	Good

41	Dharwadkar, 2011	India (As)	40 (25/15)	52.3	0	22.7	8.2	NR	6.4	NR	FEV ₁ , FVC, PEF	Poor
42	Kim, 2011	South Korea (As)	2745 (2168/577)	55	29	25.1	NR	NR	NR	NR	FEV ₁ , FVC, FEV ₁ /FVC	Good
43	Klein, 2011	USA (Am)	76 (33/43)	63.1	29	34.2	NR	NR	6.7	NR	FEV ₁ , FVC	Good
44	Al-Habbo, 2012	Iraq (As)	45 (26/19)	46.7	NR	NR	NR	NR	NR	NR	FEV ₁ , FVC, FEV ₁ /FVC, FEF _{25-75%} , PEF	Good
45	Klein, 2012	USA (Am)	303 (178/125)	61.7	29.4	31.4	NR	NR	NR	NR	DL _{CO}	Good
46	Klein, 2012b	USA (Am)	560 (314/260)	62.0	27	31.7	NR	NR	NR	NR	FEV ₁ , FVC, DL _{CO}	Good
47	Nandhini, 2012	India (As)	45 (30/15)	47.1	NR	NR	7.1	NR	6.3	NR	FEV ₁ , FVC, FEV ₁ /FVC, FEF _{25-75%} , PEF	Good
48	Abd-El-Azeem, 2013	Egypt (Af)	30	NR	0	NR	NR	NR	NR	NR	FEV ₁ , FVC, FEV ₁ /FVC, FEF _{25-75%} , PEF, DL _{CO}	Good
49	Akber, 2013	Iraq (As)	63 (28/35)	51.0	0	30.0	NR	NR	NR	NR	FEV ₁ , FVC, FEV ₁ /FVC	Good
50	Alkinany, 2013	Iraq (As)	60 (60/0)	40-60y	0	NR	NR	NR	NR	NR	FEV ₁ , FVC	Poor
51	Anandhalakshmi, 2013	India (As)	30	44.8	0	26.1	NR	6.8	7.0	NR	FEV ₁ , FVC, FEV ₁ /FVC, FEF _{25-75%} , PEF, DL _{CO}	Good
52	Aparna, 2013	India (As)	40 (22/18)	49	0	25.2	NR	NR	NR	NR	FEV ₁ , FVC, FEV ₁ /FVC, PEF	Fair
53	Rajani, 2013	India (As)	40 (19/21)	46	0	NR	10.88	7.0	NR	NR	FEV ₁ , FVC, FEV ₁ /FVC, FEF _{25-75%} , PEF	Good
54	Shafiee, 2013	Iran (As)	80 (31/49)	53.6	0	28.8	NR	8.4	9.8	50	FEV ₁ , FVC, FEV ₁ /FVC, PEF	Good
55	Shah, 2013	India (As)	60 (60/0)	53.9	0	NR	NR	7.1	6.6	NR	FEV ₁ , FVC, FEV ₁ /FVC, FEF _{25-75%} , PEF	Good
56	Huang, 2014	China (As)	292 (181/111)	66.8	0	23.9	8.55	NR	5.2	NR	FEV ₁ , FVC, FEV ₁ /FVC	Good
57	Jamatia, 2014	India (As)	30 (19/11)	57.7	0	23.5	10.71	7.93	>2y	0	FEV ₁ , FVC, FEV ₁ /FVC, FEF _{25-75%} , PEF	Good
58	Uz-Zaman, 2014	India (As)	60	44.6	0	24.4	9.93	7.1	NR	NR	FEV ₁ , FVC, FEV ₁ /FVC, FEF _{25-75%} , PEF, DL _{CO}	Good
59	Zineldin, 2015	Egypt (Af)	45 (45/0)	51.1	0	24.5	NR	7.5	7.6	NR	FEV ₁ , FVC, FEV ₁ /FVC, PEF	Good
60	Buchmann, 2016	Germany (Eu)	91 (49/42)	67.9	9.6	29.2	NR	NR	NR	NR	FEV ₁ , FVC, FEV ₁ /FVC	Good
61	Kaur, 2016	India (As)	50	NR	0	NR	NR	NR	NR	NR	FEV ₁ , FVC, FEV ₁ /FVC, PEF	Good
62	Kumar, 2016	India (As)	40	50.7	0	25.4	10.6	8.5	11.1	50	FEV ₁ , FVC, FEV ₁ /FVC, DL _{CO}	Poor
63	Caron, 2017	Canada (Am)	10 (10/0)	55	NR	30.0	6.5	6.1	1.25y	0	FEV ₁ , FVC, DL _{CO}	Good
64	Khafaie, 2017	Iran (As)	347 (268/79)	54.6	21	26.7	7.98	8.8	NR	NR	FEV ₁ , FVC, FEV ₁ /FVC	Poor
65	Kim, 2017	South Korea (As)	1431 (814/617)	59.1	20	25.4	7.54	7.3	4.7	NR	FEV ₁ , FVC, FEV ₁ /FVC	Good
66	López-Cano, 2017	Spain (Eu)	49 (12/37)	51.3	0	42.0	9.2	8.0	NR	NR	FEV ₁ , FVC, FEF _{25-75%}	Good
67	Nidhianand, 2017	India (As)	100 (57/43)	46.6	0	NR	NR	NR	NR	NR	FEV ₁ , FVC, FEV ₁ /FVC, PEF	Good
68	Shergill, 2017	India (As)	50 (50/0)	52.6	NR	23.7	NR	NR	NR	NR	FEV ₁ , FVC, FEV ₁ /FVC, PEF	Good
69	Tai, 2017	China (As)	63 (34/29)	53.0	0	27.7	7.9	8.0	7.8y	NR	FEV ₁ , FVC, FEV ₁ /FVC, DL _{CO}	Good
70	Wilms, 2017	Switzerland (Eu)	65 (19/46)	46.9	27.7	44.0	8.9	7.9	NR	NR	FEV ₁ , FEV ₁ /FVC	Fair
71	Okur, 2018	Turkey (Eu)	58 (15/43)	53.3	NR	31.7	10.27	8.2	9.9y	NR	FEV ₁ , FVC, FEV ₁ /FVC, FEF _{25-75%} , PEF	Good
72	Rohling, 2018	Germany (Eu)	34 (21/13)	53.0	26.5	30.8	NR	6.4	0.35y	NR	FEV ₁ , FVC	Good
73	Tayarami, 2018	Iran (As)	50	58.3	0	NR	NR	NR	NR	NR	FEV ₁ , FVC, FEV ₁ /FVC, FEF _{25-75%} , PEF	Good
74	Van Eetvelde, 2018	Belgium (Eu)	110 (39/71)	79	NR	295	NR	6.7	10.3	74.5	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%; FEV₁, forced expiratory flow in one second; FVC, forced vital capacity; Hb, hemoglobin; m, months; PEF, peak expiratory flow; Oc, Oceania; NR, not reported; T²D, type-2 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	
Male	5	667	-13.10 (-22.57, -3.64)	96%	0.007	5	667	-13.71 (-22.02, -5.39)	95%	0.001	11	1099	2.69 (0.70, 4.67)	92%	0.008	
Female	3	473	-9.00 (-19.86, 1.85)	82%	0.10	3	473	-9.58 (-18.07, -1.09)	70%	0.03	7	737	2.84 (-1.89, 7.57)	96%	0.24	
Nonsmokers	25	2,357	-967 (-13.05, -629)	94%	<0.001	23	2,252	-10.84 (-14.12, -7.57)	93%	<0.001	32	3257	-0.21 (-3.35, 2.93)	100%	0.90	
Continent																
Africa	1	90	NA	NA	NA	1	90	NA	NA	NA	3	365	-2.70 (-9.01, 3.62)	99%	0.40	
America	5	11,966	-4.99 (-6.72, -3.26)	98%	<0.001	4	11,683	-8.77 (-13.43, -4.11)	99%	<0.001	6	12,238	2.48 (1.56, 3.40)	85%	<0.001	
Asia	21	36,202	-7.50 (-9.01, -6.00)	95%	<0.001	18	35,992	-7.91 (-9.40, -6.43)	95%	<0.001	26	36,944	0.02 -1.80, 1.83)	100%	0.99	
Europe	13	1432	-8.93 (-13.25, -4.62)	82%	<0.001	11	1372	-11.48 (-17.38, -5.57)	88%	<0.001	9	1149	-1.53 (-4.21, 1.16)	89%	0.26	
Oceania	1	15	NA	NA	0.50	1	15	NA	NA	NA	1	15	NA	NA	NA	
BMI (kg/m ²)																
< 25	9	1809	-10.95 (-16.58, -5.33)	96%	<0.001	5	927	-12.26 (-23.01, -1.51)	98%	0.03	7	1152	1.41 (-3.31, 6.14)	99%	0.56	
25-29.9	14	35,064	-3.46 (-5.54, -2.38)	94%	<0.001	14	35,515	-5.78 (-7.03, -4.53)	90%	<0.001	16	36,003	-0.28 (-1.61, 1.05)	99%	0.68	
30-39.9	6	11,856	-6.50 (-9.14, -3.86)	93%	<0.001	6	11,856	-9.66 (-13.67, -5.65)	98%	<0.001	5	11,649	3.25 (0.83, 5.68)	92%	0.009	
≥ 40	3	352	-10.40 (-20.45, -0.35)	85%	0.04	2	222	-11.44 (-16.63, -6.24)	0%	<0.001	1	75	NA	NA	NA	
	%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	
Male	2	210	-17.18 (-138.25, 3.89)	94%	0.11	3	300	-18.55 (-20.69, -16.40)	0%	<0.001	0	NA	NA	NA	NA	
Female	1	75	-25.30 (-42.63, -7.97)	NA	NA	1	24	-25.51 (-31.37, -19.65)	NA	NA	0	NA	NA	NA	NA	
Nonsmokers	10	742	-11.04 (-16.29, -5.78)	77%	<0.001	10	844	-11.03 (-15.25, -6.82)	92%	<0.001	12	851	-7.13 (-10.62, -3.64)	80%	<0.001	
Continent																
Africa	0	90	NA	NA	NA	1	90	NA	NA	NA	0	0	NA	NA	NA	
America	1	21	NA	NA	NA	0	0	NA	NA	NA	0	0	NA	NA	NA	
Asia	6	537	-11.44 (-17.07, -5.81)	77%	<0.001	10	972	-9.34 (-12.75, -5.93)	86%	<0.001	5	349	-5.60 (-11.83, -0.62)	78%	0.08	
Europe	6	476	-9.88 (-18.65, -1.11)	78%	0.03	4	229	-7.78 (-21.43, 5.88)	93%	0.26	7	502	-8.07 (-12.34, -3.79)	68%	<0.001	
Oceania	0	0	NA	NA	NA	0	0	NA	NA	NA	0	0	NA	NA	NA	
BMI (kg/m ²)																
< 25	3	255	-13.36 (-23.15, -3.57)	88%	0.007	4	345	-13.32 (-19.69, -6.96)	91%	<0.001	3	205	-11.83 (-16.30, -7.36)	0%	<0.001	
25-29.9	1	35	NA	NA	NA	3	250	-5.84 (-7.08, -4.60)	0%	<0.001	6	507	-5.20 (-9.72, -0.68)	59%	0.002	
30-39.9	1	110	NA	NA	NA	2	134	-13.12 (-37.47, 11.22)	97%	0.29	0	0	NA	NA	NA	
≥ 40	2	222	-26.04 (-34.93, -17.14)	0%	<0.001	0	0	NA	NA	NA	0	0	NA	NA	NA	

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; FEV₁, 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	41	49,705	-7.15 (-8.27, -6.03)	99%	35	49,152	-9.21 (-11.15, -7.26)	100%	45	50,711	-0.27 (-1.63, 1.08)	100%
Fixed effect			-3.18 (-3.20, -3.16)				-4.82 (-4.85, -4.80)				0.01 (-0.00, 0.02)	
Publication year												
Before 2000	4	244	-1.59 (-3.19, 0.01)	0%	2	109	-2.81 (-6.84, 1.21)	0%	2	109	-1.94 (-4.92, 1.05)	0%
2000-2009	14	12,142	-8.14 (-10.96, -5.31)	93%	11	11,789	-11.96 (-18.66, -5.26)	95%	15	12,759	1.16 (0.27, 2.05)	86%
2010-2019	23	37,319	-8.00 (-9.48, -6.51)	99%	22	37,254	-8.67 (-11.04, -6.29)	100%	28	37,843	-0.53 (-2.39, 1.33)	100%
Type-2 diabetes group size												
<50 patients	21	1207	-10.29 (-13.88, -6.70)	86%	19	1155	-9.45 (-13.67, -5.22)	89%	20	1168	-1.69 (-4.86, 1.48)	99%
≥50 patients	20	48,498	-5.68 (-7.01, -4.34)	99%	16	47,997	-9.16 (-11.80, -6.51)	100%	25	49,543	0.69 (-0.93, 2.30)	100%
Study quality												
Only good quality studies	32	48,201	-7.95 (-9.30, -6.60)	99%	31	48,276	-9.53 (-11.59, -7.47)	100%	38	49,359	-0.52 (-2.13, 1.10)	100%
Including predatory journals and grey literature	57	51,845	-1.27 (-1.83, -0.71)	100%	48	50,973	-1.73 (-2.39, -1.08)	100%	69	53,875	0.13 (-0.02,-0.28)	96%
Excluding the highest weight study	40	40,921	-7.37 (-8.53, -6.20)	96%	34	40,368	-9.39 (-11.42, -7.36)	98%	44	26,029	-0.21 (-1.66, 1.23)	100%
	%FEF _{25-75%} 1				%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	13	1034	-9.89 (-14.42, -5.36)	76%	15	1291	-9.79 (-13.42, -6.15)	92%	12	851	-7.13 (-10.62, -3.64)	93%
Fixed effect			-9.02 (-10.68, -7.36)				-8.73 (-9.62, -7.85)				-3.79 (-4.78, -2.80)	
Publication year												
Before 2000	1	21	NA	NA	0	0	NA	NA	0	0	NA	NA
2000-2009	2	82	-2.80 (-13.85, 8.25)	42%	2	59	-15.15 (-36.78, 6.47)	90%	6	347	-8.26 (-14.58, -1.94)	72%
2010-2019	10	931	-11.85 (-16.68, -7.03)	78%	13	1232	-8.93 (-12.50, -5.36)	91%	6	504	-5.99 (-9.80, -2.18)	76%
Type-2 diabetes group size												
<50 patients	9	614	-9.01 (-15.84, -2.19)	72%	7	436	-9.47 (-17.73, -1.22)	93%	8	368	-7.29 (-11.66, -2.93)	66%
≥50 patients	4	420	-11.37 (-18.96, -3.78)	86%	8	855	-9.84 (-13.56, -6.12)	88%	4	486	-7.01 (-13.43, -0.58)	84%
Study quality												
Only good quality studies	12	1013	-10.60 (-15.03, -6.17)	75%	15	1291	-9.79 (-13.42, -6.15)	92%	10	749	-7.08 (-10.92, -3.25)	83%
Including predatory journals and grey literature	18	1722	-0.57 (-0.81, -0.32)	82%	21	1961	-0.73 (-1.01, -0.46)	88%	13	971	-0.51 (-0.76, -0.26)	69%
Excluding the highest weight study	12	914	-10.07 (-16.01, -4.13)	78%	14	1196	-10.10 (-14.20, -6.01)	89%	11	756	-7.91 (- 11.40, -4.43)	63%
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

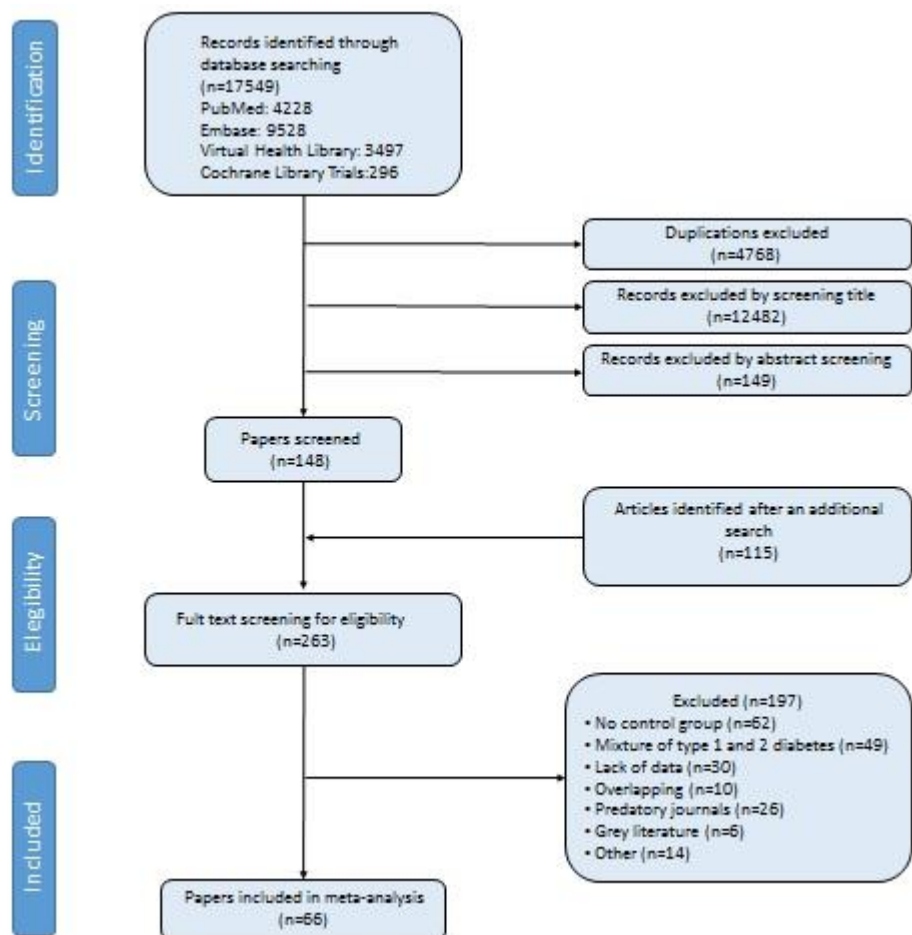
Figure 1. Flowchart of included studies

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

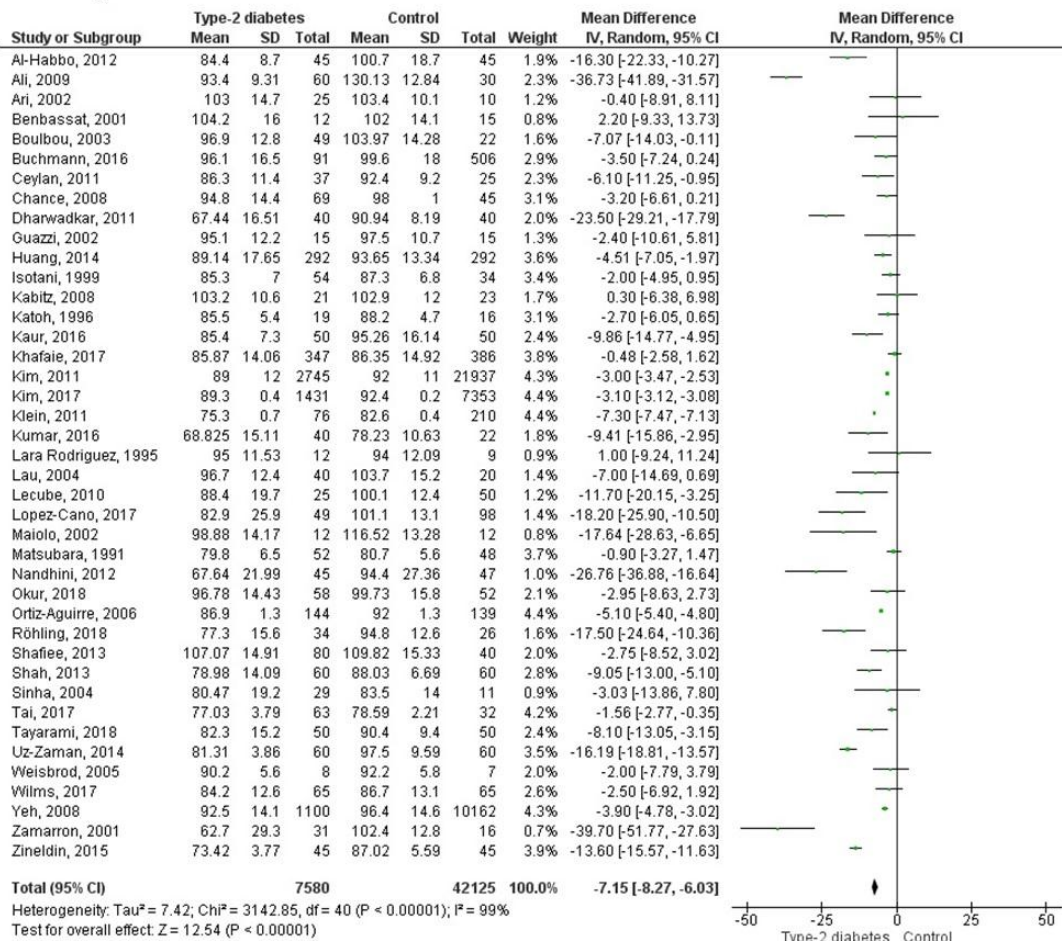
Figure 3. Forest plot of forced expiratory volume in one second/forced vital capacity ratio (%)

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).

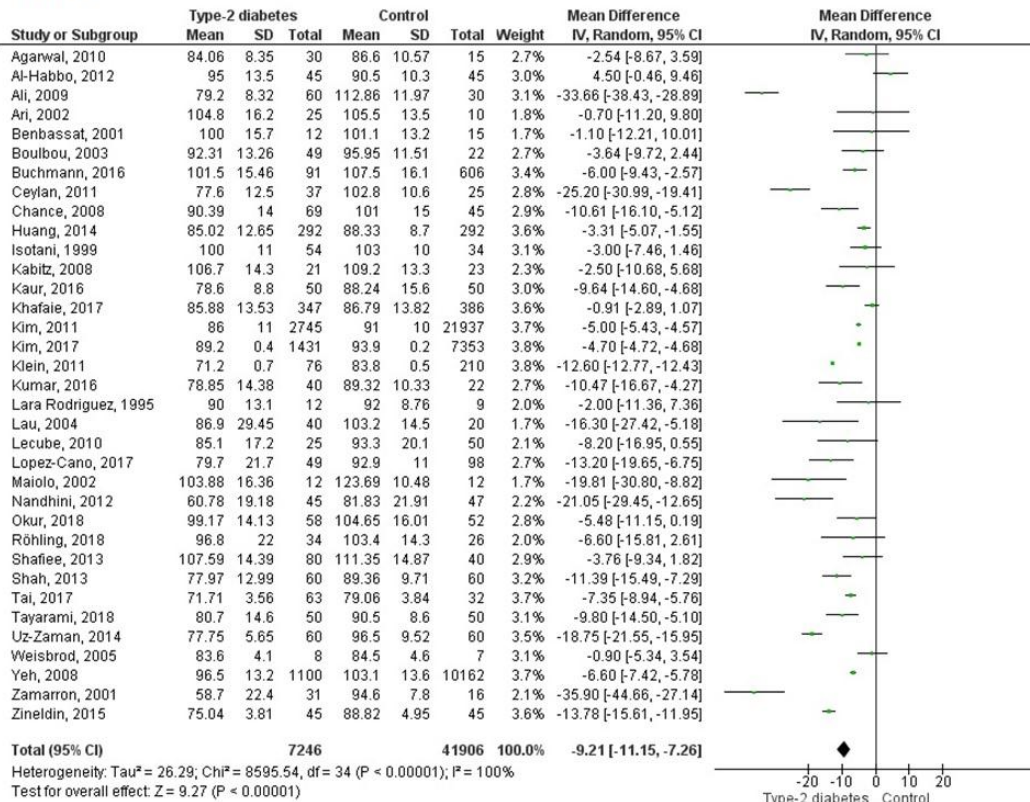
Figure 5. Funnel plots of % predicted forced expiratory volume in one second (A) and % predicted forced vital capacity (B), forced expiratory volume in one second/forced vital capacity ratio (%) (C), forced expiratory flow between 25% and 75% of total lung capacity (D), % predicted peak expiratory flow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

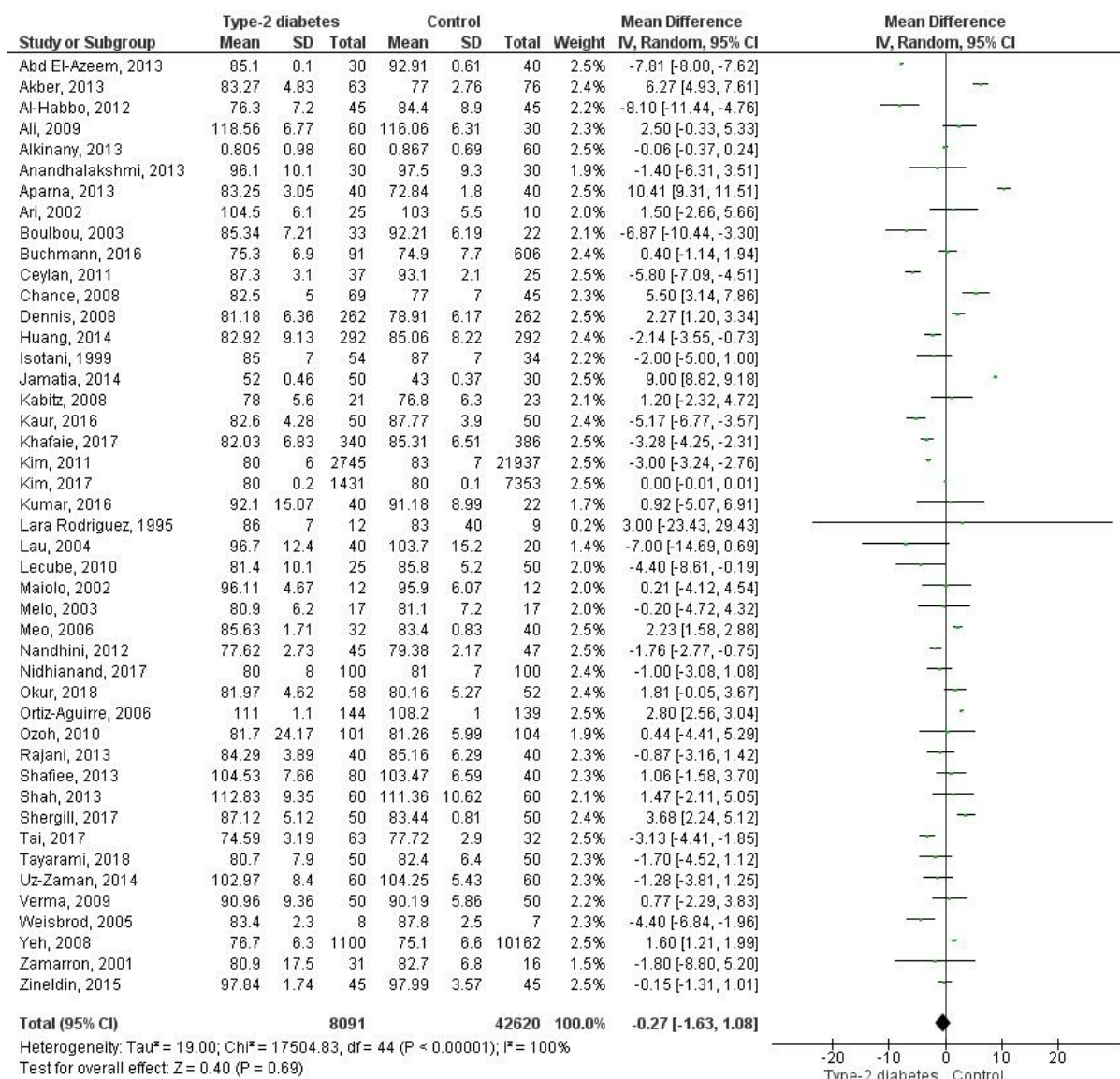


A. %FEV₁

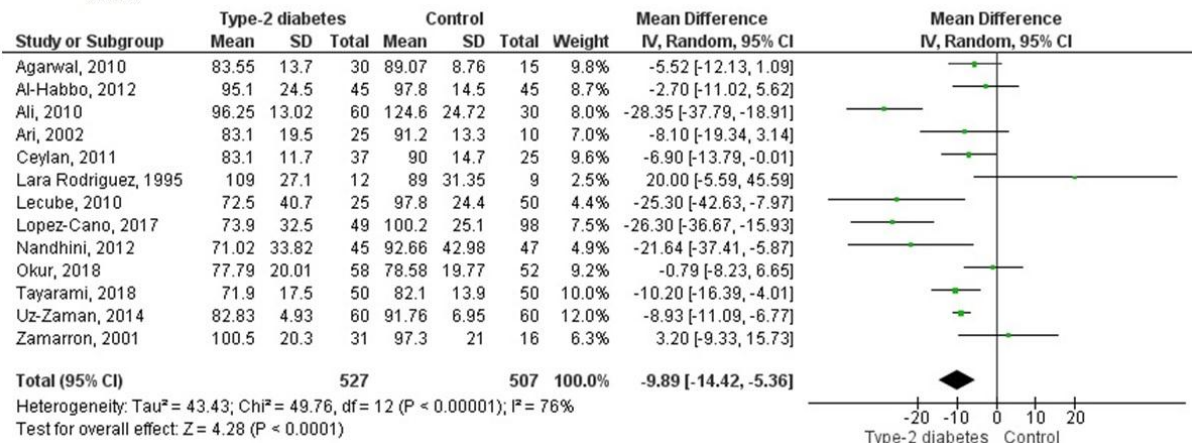


B. %FVC

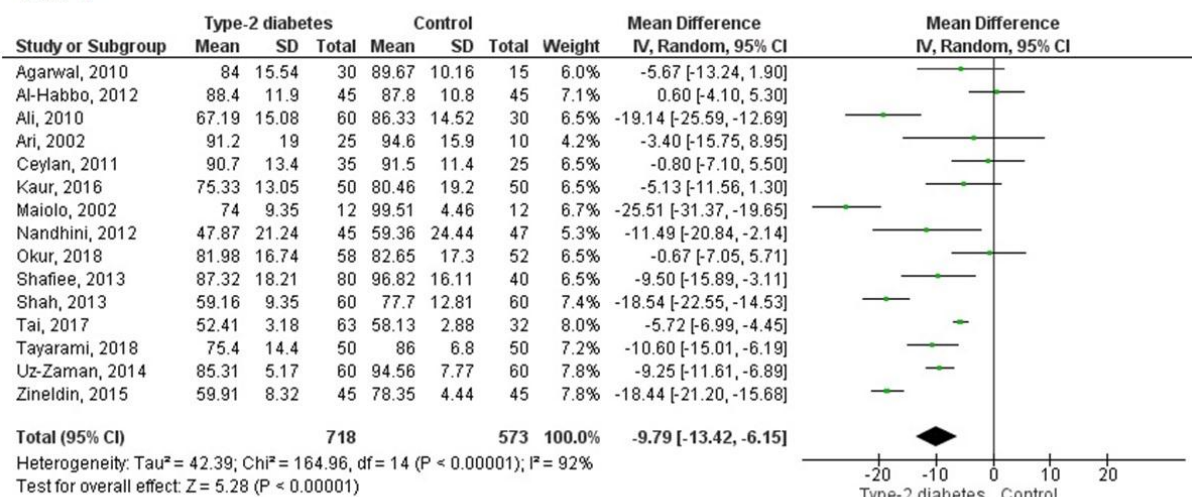




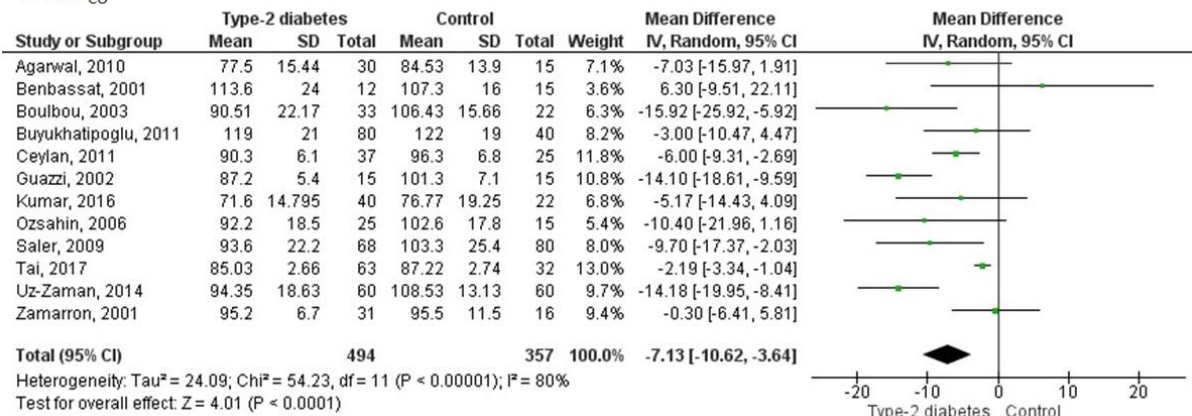
A. %FEF_{25-75%}



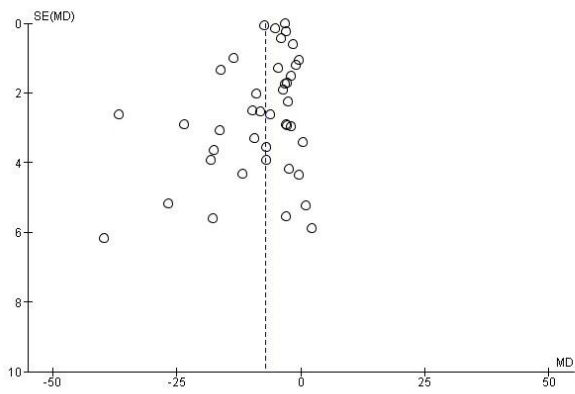
B. %PEF



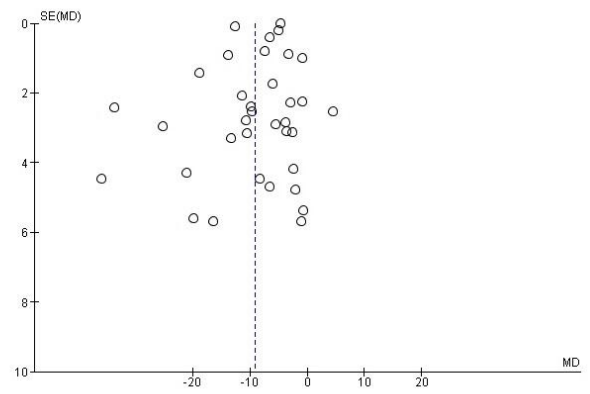
C. %DL_{CO}



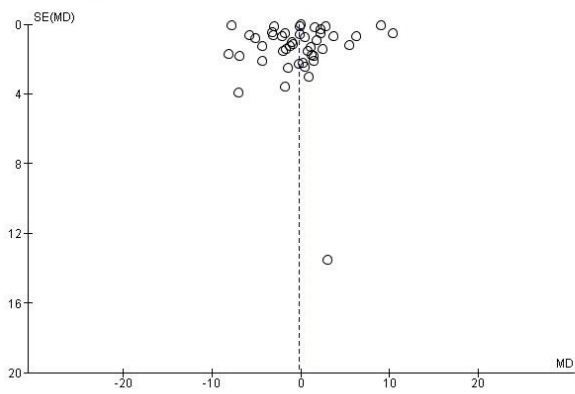
A. %FEV₁



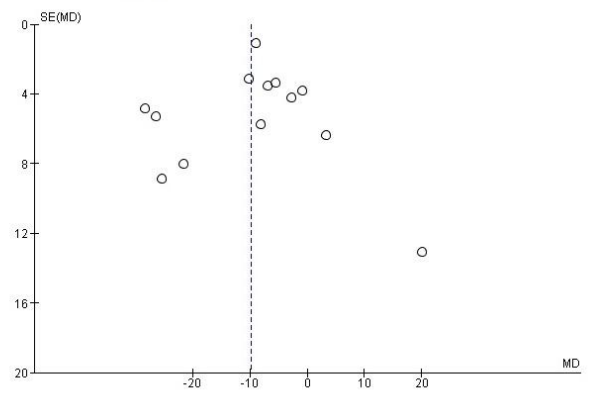
B. %FVC



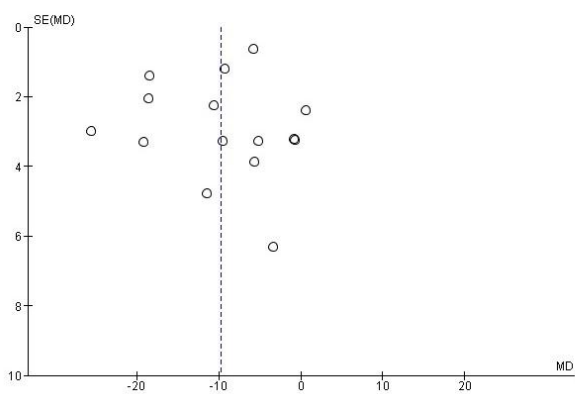
C. FEV₁/FVC



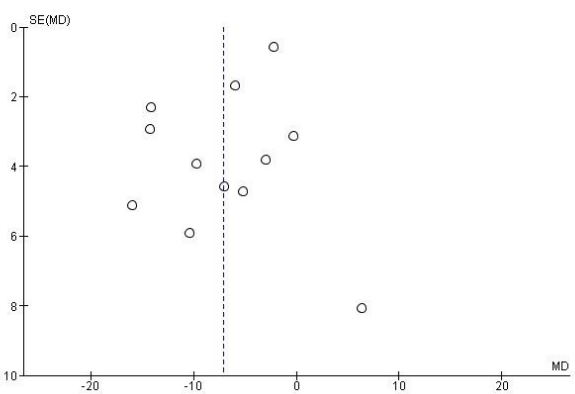
D. %FEF_{25-75%}



E. %PEF



F. %DL_{CO}



SUPPLEMENTARY MATERIAL

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Table S1A. Meta-regression with subgroup analysis										
	FEV ₁ (L)					FVC (L)				
	Studies	Participants	Effect estimate	I ²	p	Studies	Participants	Effect estimate	I ²	p
Male	10	1396	-0.28 (-0.41, -0.16)	89%	<0.001	10	1416	-0.36 (-0.59, -0.14)	95%	0.001
Female	7	1376	-0.29 (-0.43, -0.15)	88%	<0.001	7	1376	-0.42 (-0.69, -0.15)	96%	0.003
Nonsmokers	19	1490	-0.39 (-0.52, -0.27)	92%	<0.001	20	1614	-0.45 (-0.58, -0.32)	84%	<0.001
Continent										
Africa	2	275	-0.71 (-1.66, 0.24)	99%	0.14	2	275	-0.68 (-1.53, 0.16)	97%	0.11
America	8	17,639	-0.30 (-0.41, -0.19)	95%	<0.001	8	17,639	-0.25 (-0.33, -0.17)	85%	<0.001
Asia	15	2018	-0.35 (-0.42, -0.28)	78%	<0.001	15	2018	-0.37 (-0.48, -0.27)	80%	<0.001
Europe	8	1110	-0.28 (-0.40, -0.15)	51%	<0.001	6	950	-0.39 (-0.57, -0.22)	47%	<0.011
Oceania	1	15	NA	NA	NA	1	15	NA	NA	NA
BMI (kg/m ²)										
<25	4	285	-0.27 (-0.51, -0.02)	72%	0.03	4	285	-0.31 (-0.62, -0.00)	77%	0.05
25-29.9	11	3444	-0.39 (-0.51, -0.27)	95%	<0.001	11	3444	-0.32 (-0.43, -0.20)	84%	<0.001
30-39.9	7	15,832	-0.27 (-0.37, -0.17)	80%	<0.001	7	15,832	-0.37 (-0.45, -0.30)	55%	<0.001
≥ 40	1	130	NA	NA	NA	0	0	NA	NA	NA

Table S1B. Meta-regression with subgroup analysis															
	FEF ₂₅₋₇₅ (L)					PEF (L/s)					DL _{co}				
	Studies	Participants	Effect estimate	I ²	p	Studies	Participants	Effect estimate	I ²	p	Studies	Participants	Effect estimate	I ²	p
Male	1	72	NA	NA	NA	4	312	-1.31 (-1.98, -0.64)	95%	<0.001	1	19	NA	NA	NA
Female	0	NA	NA	NA	NA	3	169	-1.09 (-1.47, -0.71)	69%	<0.001	0	NA	NA	NA	NA
Nonsmokers	10	623	-0.52 (-0.81, -0.24)	86%	<0.001	14	1148	-1.14 (-1.55, -0.73)	94%	<0.001	6	400	-4.52 (-6.98, -2.06)	88%	<0.001
Continent															
Africa	1	70	NA	NA	NA	2	275	-1.69 (-3.58, 0.20)	97%	0.08	1	70	NA	NA	NA
America	1	34	NA	NA	NA	1	283	NA	NA	NA	3	4789	-1.74 (-2.95, -0.54)	74%	0.005
Asia	7	529	-0.38 (-0.52, -0.24)	27%	<0.001	11	969	-0.99 (-1.39, -0.60)	92%	<0.001	3	205	-3.62 (-4.86, -2.39)	0%	<0.001
Europe	3	192	-0.32 (-0.67, 0.03)	45%	0.07	5	351	-1.11 (-1.93, -0.29)	81%	0.008	3	225	-3.80 (-5.35, -2.24)	0%	<0.001
Oceania	0	NA	NA	NA	NA	0	NA	NA	NA	NA	0	NA	NA	NA	NA
BMI (kg/m ²)															
<25	2	125	-0.30 (-0.63, -0.03)	0%	0.08	4	285	-1.19 (-1.91, -0.48)	71%	0.01	1	45	NA	NA	NA
25-29.9	2	95	-0.55 (-0.93, -0.17)	0%	0.005	7	845	-1.06 (-1.74, -0.38)	98%	0.002	2	208	-4.25 (-5.72, -2.77)	0%	<0.001
30-39.9	1	110	NA	NA	NA	2	134	-0.90 (-2.12, 0.32)	92%	0.15	3	4789	-1.74 (-2.95, -0.54)	74%	0.005
≥ 40	0	NA	NA	NA	NA	0	NA	NA	NA	NA	0	NA	NA	NA	NA
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 S2A. Sensitivity analysis								
	FEV ₁ (L)				FVC (L)			
	Studies	Participants	Effect estimate	I ²	Studies	Participants	Effect estimate	I ²
Statistical analysis method								
Random effect								
Fixed effect	34	21,057	-0.34 (-0.42, -0.27) -0.33 (-0.34, -0.32)	94%	32	20,987	-0.36 (-0.43, -0.29) -0.32 (-0.34, -0.31)	87%
Publication year								
Before 2000	1	1239	NA	NA	1	1239	NA	NA
2000-2009	14	12,637	-0.28 (-0.36, -0.21)	84%	13	12,607	-0.35 (-0.44, -0.26)	84%
2010-2019	19	7181	-0.34 (-0.46, -0.23)	94%	18	7051	-0.39 (-0.50, -0.28)	90%
Type-2 diabetes group size								
<50 patients	18	940	-0.40 (-0.53, -0.27)	91%	17	910	-0.47 (-0.63, -0.30)	81%
≥50 patients	16	20,117	-0.29 (-0.36, -0.2)	92%	15	19,987	-0.29 (-0.34, -0.23)	82%
Study quality								
Only good quality studies	27	19,574	-0.35 (-0.45, -0.25)	94%	26	19,544	-0.38 (-0.47, -0.29)	100%
Including predatory journals and grey literature	54	23,495	-1.18 (1.38, -0.98)	96%	52	23,335	-1.03 (-1.21, -0.85)	95%
Excluding the greatest weight study	33	20,774	-0.34 (-0.43, -0.26)	94%	31	16,733	-0.36 (-0.43, -0.29)	88%

Table S2B. Sensitivity analysis												
	FEF ₂₅₋₇₅ (L)				PEF (L/s)				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												
Fixed effect	12	825	-0.48 (-0.71, -0.24) -0.47 (-0.54, -0.39)	84%	19	1878	-1.07 (-1.73, -0.71) -0.60 (-0.64, -0.56)	97%	10	5289	-3.42 (-5.14, -1.70) -3.17 (-3.55, -2.80)	93%
Publication year												
Before 2000	0	NA	NA	NA	0	NA	NA	NA	1	100	NA	NA
2000-2009	5	288	-0.35 (-0.53, -0.17)	21%	6	551	-0.83 (-1.33, -0.32)	94%	3	225	-3.80 (-5.35, -2.24)	0%
2010-2019	7	537	-0.54 (-0.92, -0.16)	88%	13	1327	-1.18 (-1.67, -0.69)	94%	6	4964	-3.16 (-5.56, -0.77)	96%
Type-2 diabetes group size												
<50 patients	9	535	-0.57 (-0.85, -0.29)	86%	13	835	-1.24 (-1.60, -0.89)	88%	6	271	-3.58 (-6.59, -0.58)	91%
≥50 patients	3	290	-0.15 (-0.37, 0.07)	8%	6	1043	-0.62 (-0.90, -0.34)	79%	4	5018	-2.64 (-3.67, -1.61)	68%
Study quality												
Only good quality studies	12	825	-0.48 (-0.71, -0.24)	84%	16	1435	-1.09 (-1.51, -0.68)	92%	9	5189	-3.37 (-5.23, -1.50)	94%
Including predatory journals and grey literature	24	2027	-1.08 (-1.41, -0.74)	92%	35	3790	-1.06 (-1.31, -0.82)	92%	10	5289	-0.76 (-1.07, -0.45)	89%
Excluding the greatest weight study	11	753	-0.49 (-0.79, -0.20)	84%	18	1595	-1.12 (-1.47, -0.76)	93%	9	1125	-3.48 (-5.76, -1.20)	93%
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 S1. Forest plot of forced expiratory volume in one second (L)

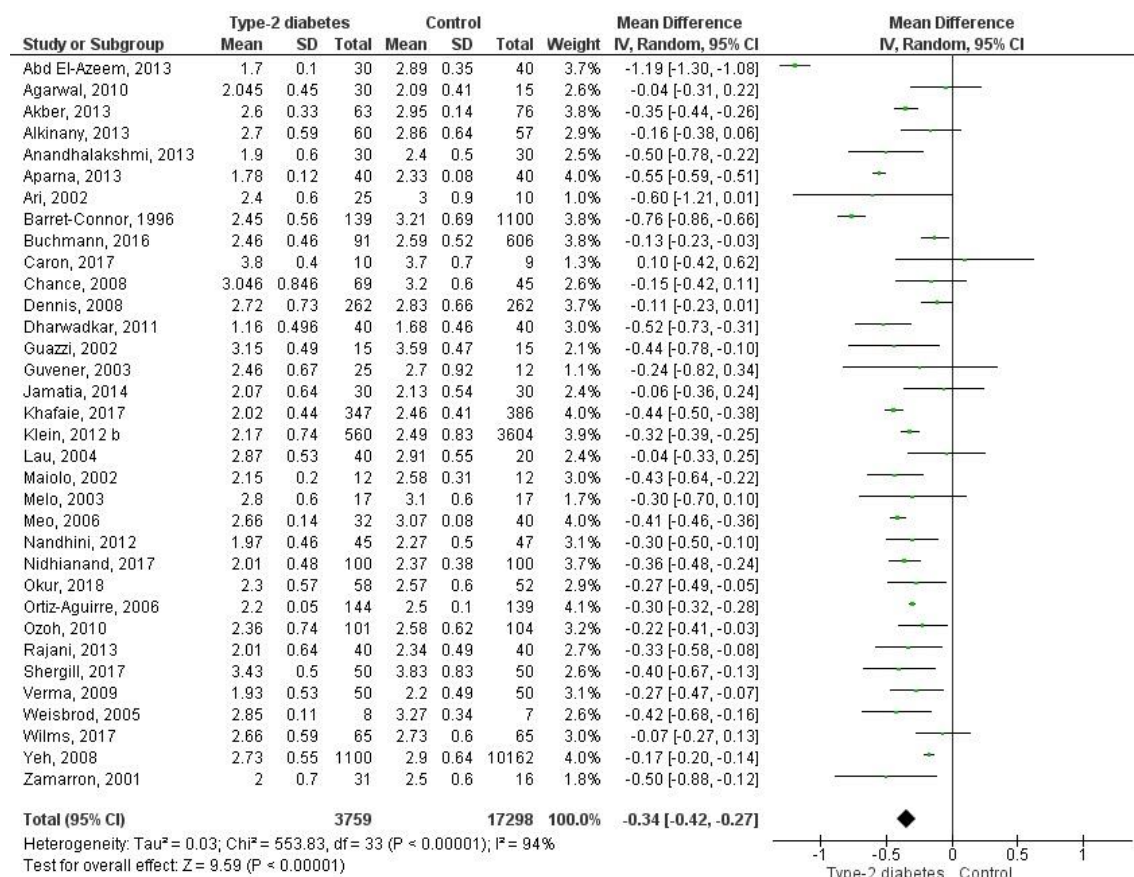


Figure S2. Forest plot of forced vital capacity (L)

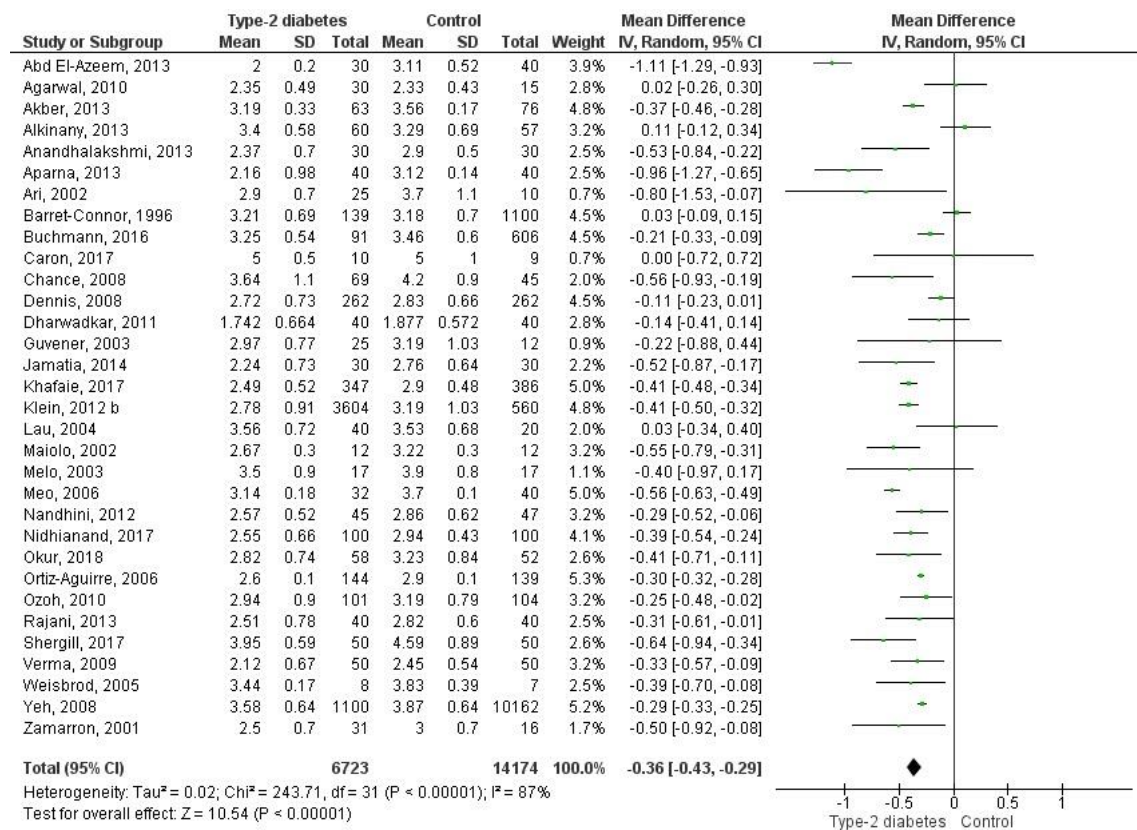


Figure S3. Forest plot of forced expiratory flow between 25% and 75% of total lung capacity (L/s)

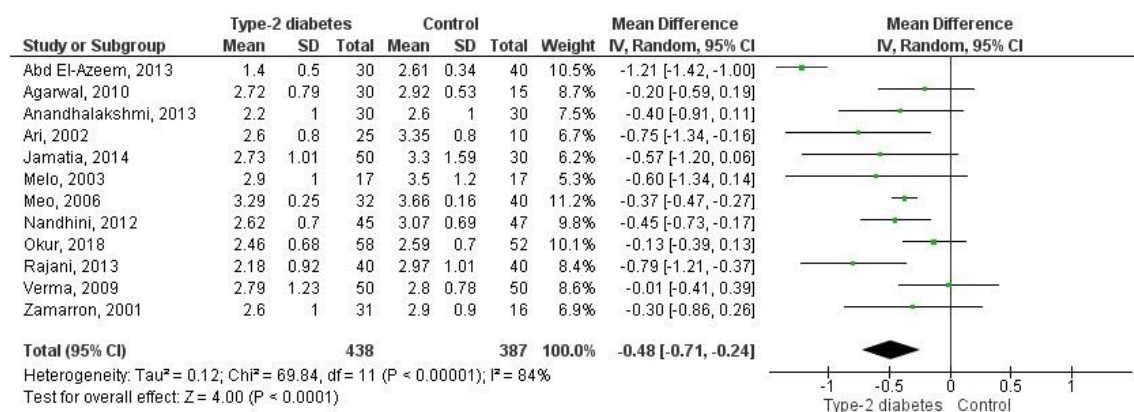


Figure S4. Forest plot of peak expiratory flow (L/s)

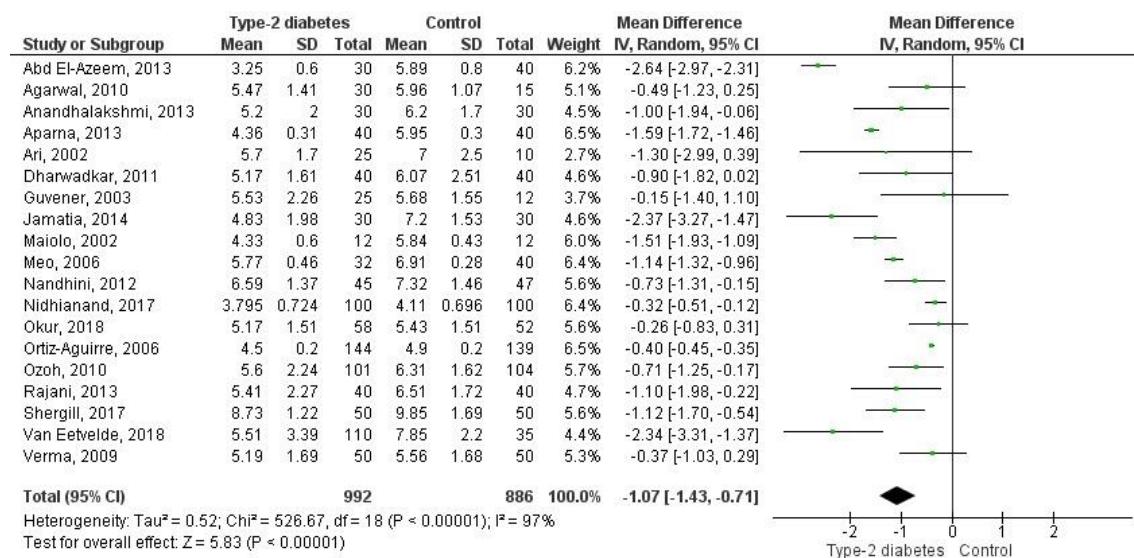


Figure S5. Forest plot of diffusion capacity of the lungs for carbon monoxide (mL/min/mm Hg)

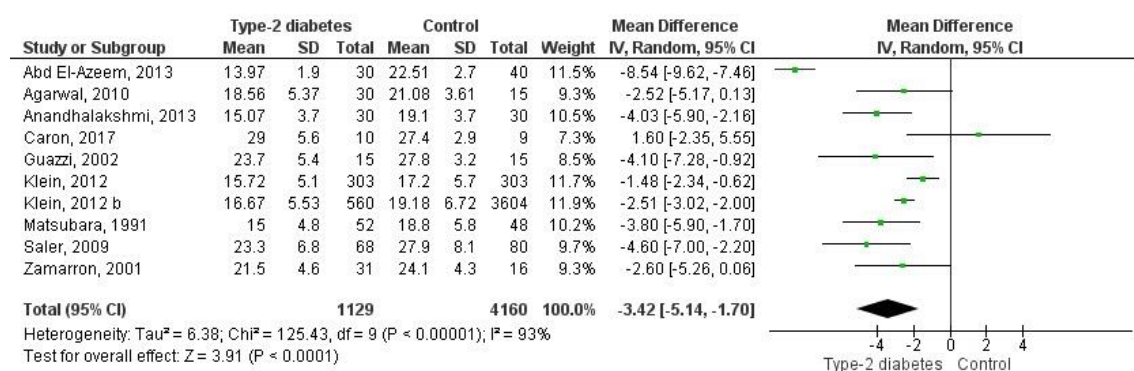


Figure S6. Funnel plot of FEV₁ (L), FVC (L), FEF_{25-75%} (L/s), PEF (L/s) and DL_{CO} (mL/min/mm Hg)

