Pulmonary function in diabetes: a metaanalysis.

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Pulmonary Function in Diabetes

A Metaanalysis

Bram van den Borst, MD; Harry R. Gosker, PhD; Maurice P. Zeegers, PhD;
and Annemie M. W. J. Schols, PhD

Background: Research into the association between diabetes and pulmonary function has resulted in inconsistent outcomes among studies. We performed a metaanalysis to clarify this association.

Methods: From a systematic search of the literature, we included 40 studies describing pulmonary function data of 3,182 patients with diabetes and 27,080 control subjects. Associations were summarized pooling the mean difference (MD) (standard error) between patients with diabetes and control subjects of all studies for key lung function parameters.

Results: For all studies, the pooled MD for FEV₁, FVC, and diffusion of the lungs for carbon monoxide were -5.1 (95% CI, -6.4 to -3.7 ; $P < .001$), -6.3 (95% CI, -8.0 to -4.7 ; $P < .001$), and -7.2 (95% CI, -10.0 to -4.4 ; $P < .001$) % predicted, respectively, and for FEV₁/FVC 0.1% (95% CI, -0.8 to 1.0 ; $P = .78$). Metaregression analyses showed that between-study heterogeneity was not explained by BMI, smoking, diabetes duration, or glycated hemoglobin (all $P > .05$).

Conclusions: Diabetes is associated with a modest, albeit statistically significant, impaired pulmonary function in a restrictive pattern. Since our results apply to the diabetic subpopulation free from overt pulmonary disease, it would next be interesting to investigate the potential clinical implications in those patients with diabetes who carry a pulmonary diagnosis, such as COPD or asthma.

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Abbreviations: DLCO = diffusion of the lungs for carbon monoxide; HbA1c = glycated hemoglobin; MD = mean difference; VC = vital capacity

The World Health Organization estimates that >180 million people worldwide have diabetes, and by 2030 it is expected that this number will have doubled.¹ Diabetes is known to affect various organ systems, such as the kidneys, retinae, nerves, and cardiovascular system.² Recently, in the context of ongoing

research into the pulmonary safety of inhaled insulin,^{3–5} the pulmonary function in diabetes has also become a subject of interest.^{6–8}

Considering its large vascular network and richness in collagen and elastin, the pulmonary system is prone to undergoing microvascular damage and non-enzymatic glycation in diabetes. Many authors investigated the pulmonary function and diffusion capacity of patients with diabetes, but there have been repeatedly inconsistent findings.⁹

Earlier reviews of the pulmonary function in diabetes have been reported but are limited by being qualitative rather than quantitative.^{9–12} Therefore, we

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performed a metaanalysis on observational studies aimed at investigating the association between diabetes and FEV₁, (forced) vital capacity (F)/VC, FEV₁/FVC, and diffusion capacity of the lungs (DLCO) in patients without pulmonary diseases. Because of the different etiopathology of type 1 and type 2 diabetes, we investigated the association for both types separately. Furthermore, we investigated whether the duration of diabetes or glycemic state, as derivative measures for diabetes severity, influenced the association.

MATERIALS AND METHODS

Data Sources and Searches

This metaanalysis was performed according to the guidelines of the Meta-analysis of Observational Studies in Epidemiology.¹³ We conducted a systematic search in PubMed (1966 through September 2009), EMBASE (1989 through September 2009), The Cochrane Library (through September 2009), and in online conference databases of the American Diabetes Association (2004-2009), European Association for the Study of Diabetes (2001-2008), International Diabetes Federation (2003), American Thoracic Society (2006-2009), European Respiratory Society (2001-2008), and American College of Chest Physicians (2003-2005). For PubMed and EMBASE, combinations were constructed from controlled vocabulary terms and free text words (e-Table 1). Searches in The Cochrane Library and conference databases were performed using ([diabetes] and [FEV₁ or FVC or VC or TLCO or DLCO]), or were hand searched. Reference lists of selected studies were hand searched to find more studies. There was no language restriction.

Study Selection

From the search results, one reviewer (B. B.) selected potentially relevant articles based on the title and obtained the abstracts from these articles. These were independently screened by two reviewers (B. B., H. R. G.) to find original studies measuring pulmonary function in a diabetes group. In this step, the second reviewer (H. R. G.) was blinded for journal, authors, publication language (all abstracts were in English), and year. The reviewers reached consensus on selecting abstracts for detailed full-text reviewing. For non-English language articles native speakers were consulted. All full-text articles and conference abstracts were independently judged by the two reviewers according to inclusion and exclusion criteria with any discrepancies being resolved by consensus between the reviewers. Inclusion criteria were the presence of a diabetes group as well as a control group in combination with the presence of % predicted values of either FEV₁, FVC (or VC), and/or DLCO, and/or the FEV₁/FVC ratio of these groups. Exclusion criteria were pulmonary comorbidity, postintervention without preintervention pulmonary function data, no data on smoking, and overlapping data. When pulmonary function parameters are presented as % predicted, this means that pulmonary function is given as a percentage of the normal value as expected for a healthy subject with the same age, sex, and height according to local references.¹⁴ Thus, by using only % predicted pulmonary function data from each individual study, we accounted for between-study differences in ethnicity, sex, age, and height. In an attempt to increase the number of included studies, authors were contacted (in their

own language whenever possible) to complete our data set in case one or more of the % predicted pulmonary function values or the FEV₁/FVC ratio were missing or the percentage of current smokers was unknown. When overlapping data were suspected, this was also verified with the corresponding authors. With respect to publication year, no limitations were applied in contacting authors, and multiple attempts were undertaken. When the requested information was not provided and because of this articles did not fulfill inclusion criteria, these articles were excluded. Permission for publication of new data was obtained in every case.

Data Extraction

We separated studies presenting type 1 diabetes or type 2 diabetes from studies presenting average values for a mixed-type group or in which the type of diabetes was unknown. For case and control groups, the mean (SD) FEV₁, FVC, FEV₁/FVC, and DLCO were extracted along with age, number of current smokers, and BMI. For the case group of each study, the mean (SD) duration of diabetes and glycated hemoglobin (HbA1c) were extracted along with information on insulin dependency and microvascular complications. When only a range was presented for certain variables, this was divided by four to estimate the SD. Whenever the case or control group was divided into subgroups, a pooled mean and SD for these combined subgroups was calculated. For each study the mean difference (MD) of FEV₁, FVC, FEV₁/FVC, and DLCO between diabetes and control groups was calculated. The corresponding pooled standard errors were calculated by taking the square root of the summed variances for cases and control subjects, respectively.

Data Synthesis and Analysis

For each pulmonary function parameter, pooled estimates were calculated for all studies, and for type 1 diabetes and type 2 diabetes separately. A pooled MD was calculated by means of empirical-Bayes random-effects metaanalysis to take into account any observed between-study heterogeneity. The amount of heterogeneity was quantified using the I² index.¹⁵

The within-study differences between the case and control groups in the percentage of current smokers (Δ smokers) and mean BMI (Δ BMI), and the mean duration of diabetes and the mean HbA1c of the diabetes group in each study were evaluated as potential sources of heterogeneity of results by using meta-regression analyses.

Assessment of publication bias was performed with the Egger test,¹⁶ and analyses for the presence of potential outliers were performed. *P* values < .05 were considered to be statistically significant. Analyses were performed using Stata, version 10 (StataCorp LP; College Station, TX).

RESULTS

A flowchart of study selection is presented in Figure 1. Briefly, the PubMed search yielded 732 hits, from which 133 potentially relevant hits were identified. The EMBASE search yielded 498 hits, from which another 15 unique potentially relevant articles were identified. The search in The Cochrane Library did not yield any new citations. Scanning of reference lists added another 21 unique hits. Based on the abstracts from these 169 hits, we excluded 37 titles. Searches in online conference databases added another 23 potentially

Table 1—Patient Characteristics of Included Type 1 Diabetes Studies

Study/Year	Source	No. (m/f)	Age, Mean (SD), y	Current Smokers, No. (%)	Duration of Diabetes, Mean (SD), y	HbA1c, Mean (SD), %	BMI, Mean (SD), kg/m ²	Microvascular Complications	FEV ₁ , Mean (SD), % Predicted	FVC, Mean (SD), % Predicted	FEV ₁ /FVC, Mean (SD), % Predicted	DLCO, Mean (SD), % Predicted
Schnyer et al ³⁵ /1976	Outpatients	11 (11/0)	24 (1)	0 (0)	17 (5)	NA	NA	Retinopathy (n = 4)	NA	NA	NA	136 (23)
Sandler et al ³⁴ /1986	Outpatients	22 (11/11)	19 (5)	0 (0)	5 (6)	11.6 (2.8)	NA	Neuropathy (n = 9) Retinopathy (n = 0) LJM (n = 0)	NA	102 (13)	88 (6)	NA
Sandler et al ³⁵ /1987	Outpatients	40 (NA)	31 (2)	0 (0)	11 (1)	10.9 (0.4)	All < 30	Neuropathy (n = 1) LJM (n = 7) Retinopathy (n = 22) Nephropathy (n = 3) Neuropathy (n = 20)	NA	98 (14)	NA	NA
Prinhak et al ³⁶ /1987	Outpatients	88 (48/40)	12 (3)	0 (0)	5 (4)	NA	NA	LJM (n = 1)	87 (6)	92 (9) ^a	87 (6)	NA
Baraldi et al ³⁷ /1992	Outpatients	33 (17/16)	13 (2)	0 (0)	5 (3)	8.9 (1.8)	NA	NA	97 (9)	100 (9)	NA	NA
Strojek et al ³⁸ /1992	Outpatients	31 (17/14)	31 (5)	0 (0)	13 (5)	9.0 (1.2)	24 (2)	Retinopathy (n = 6) Neuropathy (n = 2) Neuropathy (n = 4)	97 (13)	98 (12)	NA	95 (18)
Quatraro et al ³⁹ /1993	NA	27 (27/0)	23 (6)	0 (0)	NA	NA	19 (2)	None	96 (10)	94 (9)	NA	NA
Innocenti et al ⁴⁰ /1994	Outpatients	23 (9/14)	32 (13)	0 (0)	9 (9)	7.6 (1.5)	NA	Retinopathy (n = 7) Autonomic	91 (18)	88 (13)	NA	82 (21)
Fuso et al ¹⁹ /1996	NA	20 (11/9)	29 (7)	6 (30)	14 (8)	6.5 (0.9) ^b	23 (2) ^b	neuropathy (n = 7) Retinopathy (n = 3) Combination (n = 2)	102 (10)	105 (14)	82 (7) ^b	116 (23) ^b
Schnack et al ⁴¹ /1996	Outpatients	39 (23/16)	37 (15)	2 (5)	19 (10)	8.1 (1.2)	25 (3)	Retinopathy (n = 12) Neuropathy (n = 18)	85 (15) ^c	87 (13) ^c	82 (6) ^c	88 (16) ^c
Pieron et al ⁴² /1997	NA	20 (10/10)	45 (13) ^c	0 (0)	21 (8) ^c	NA	25 (5) ^c	Autonomic	97 (8) ^c	101 (10) ^{c,d}	80 (19) ^c	NA
Niranjan et al ³⁰ /1997	Outpatients	18 (11/7)	39 (2) ^c	0 (0)	21 (2)	7.2 (0.4) ^c	25 (3) ^b	neuropathy (n = 10) 15 patients had no complications ^b	103 (15) ^c	98 (14) ^c	84 (5) ^c	82 (20) ^b
Scano et al ⁴³ /2000	Outpatients	9 (4/5)	31 (11)	0 (0)	9 (5)	6.1 (1.0)	23 (1)	8 patients had no complications ^b	100 (8)	95 (10) ^d	87 (5) ^e	85 (7) ^f
Makkar et al ⁴⁴ /2000	Outpatients	50 (NA)	21 (5)	0 (0)	NA	NA	NA	25 patients had no complications	87 (17)	87 (17)	NA	NA
Benbassat et al ³² /2001	Outpatients	15 (9/7)	40 (11)	0 (0)	25 (10)	8.6 (1.7)	26 (5)	Microangiopathy (n = 6)	98 (14)	98 (12)	NA	96 (16)

(Continued)

Table 1—Continued

Study/Year	Source	No. (m/f)	Age, Mean (SD), y	Current Smokers, No. (%)	Duration of Diabetes, Mean (SD), y	HbA1c, Mean (SD), %	BMI, Mean (SD), kg/m ²	Microvascular Complications	FEV ₁ , Mean (SD), % Predicted	FVC, Mean (SD), % Predicted	FEV ₁ /FVC, Mean (SD), % Predicted	DLCO, Mean (SD), % Predicted
Boulbou et al ²⁰ /2003	NA	16 (8/8)	37 (13)	0 (0)	17 (9)	9.4 (1.8)	24 (3)	Retinopathy (n = 10) Nephropathy (n = 3) ^b	99 (13)	93 (13)	NA	90 (21)
Villa et al ¹⁴ /2004	Outpatients	39 (21/18)	11 (3)	0 (0)	4 (2)	7.7 (0.7) ^c	20 (3) ^c	None	103 (12) ^c	103 (13) ^c	NA	93 (16) ^c
Cazzato et al ¹⁷ /2004	Outpatients	38 (19/19)	10 (2)	0 (0)	3 (3)	9.7 (3.2) ^b	18 (2)	Nephropathy (n = 8) LJM (n = 0)	99 (2) ^b	98 (2) ^b	88 (7) ^b	85 (10) ^b

DLCO = diffusion capacity of the lungs for carbon monoxide; f = female; HbA1c = glycated hemoglobin; LJM = limited joint mobility; m = male; NA = not available.

^aDepicted from a graph.

^bData obtained from personal communication with author.

^cPooled from subgroups.

^dVital capacity.

^eCalculated from individual patient data.

^fNot included in metaanalysis because no DLCO data from control group was available.

relevant hits. Full texts of 133 articles and the 23 conference abstracts were judged for inclusion criteria. Consultancy of the third reviewer was not required.

Personal communication with authors (e-Table 2) enabled inclusion of an additional 15 articles¹⁷⁻³¹ in the different analyses. Fourteen articles were excluded from the metaanalysis because of overlapping data (e-Table 3).

After applying exclusion criteria, 40 independent articles were suitable for inclusion in the metaanalysis. Collectively, these articles present pulmonary function data of 3,182 patients with diabetes and 27,080 control subjects. One study³² had available data for type 1 diabetes and type 2 diabetes separately, so this study was included in both subanalyses. Patient characteristics of included studies are presented in Tables 1-3. Characteristics of the corresponding control groups are presented in e-Tables 4-6.

Plots of pooled estimates for FEV₁, FVC, FEV₁/FVC, and DLCO are presented in Figures 2-5. For all studies, the pooled estimates for FEV₁, FVC, and DLCO were -5.1 (95% CI, -6.4 to -3.7 ; $P < .001$), -6.3 (95% CI, -8.0 to -4.7 ; $P < .001$), and -7.2 (95% CI, -10.0 to -4.4 ; $P < .001$) % predicted, respectively. Pooled estimates for type 1 diabetes for FEV₁, FVC, and DLCO were -2.8 (95% CI, -4.2 to -1.4 ; $P < .001$), -3.8 (95% CI, -6.0 to -1.7 ; $P < .001$), and -6.3 (95% CI, -9.6 to -2.9 ; $P < .001$) % predicted, respectively. Pooled estimates for type 2 diabetes for FEV₁, FVC, and DLCO were -4.9 (95% CI, -7.4 to -2.3 ; $P < .001$), -6.7 (95% CI, -9.0 to -4.3 ; $P < .001$), and -9.3 (95% CI, -14.5 to -4.1 ; $P < .001$) % predicted, respectively. Pooled estimates of FEV₁/FVC for all studies, type 1 diabetes studies, and type 2 diabetes studies were 0.1 (95% CI, -0.8 to 1.0; $P = .46$), -0.2 (95% CI, -1.3 to 0.9; $P = .69$), and 0.9 (95% CI, -0.6 to 2.4; $P = .22$) percent, respectively.

For all analyses except two (DLCO and FEV₁/FVC in type 1 diabetes, $P = .21$ and $P = .40$, respectively), tests of homogeneity indicated that there was significant heterogeneity ($P \leq .03$). This was accounted for using random-effects metaanalyses. The metaregression analyses for FEV₁, FVC, FEV₁/FVC, and DLCO, respectively, showed no significance for Δ smokers ($P = .61$, $P = .65$, $P = .92$, $P = .69$), Δ BMI ($P = .16$, $P = .40$, $P = .62$, $P = .54$), disease duration ($P = .20$, $P = .89$, $P = .66$, $P = .50$), or HbA1c ($P = .99$, $P = .19$, $P = .79$, $P = .23$), indicating that heterogeneity could not be explained by any of these variables. Egger tests for publication bias were not significant for FVC ($P = .12$), FEV₁/FVC ($P = .05$), and DLCO ($P = .25$), whereas for FEV₁ this test was significant ($P = .01$), indicating publication bias for FEV₁ outcomes. There were no outliers ($P > .05$).

FIGURE 1. Flowchart of selection of studies for inclusion in the metaanalysis. DLCO = diffusion capacity of the lungs for carbon monoxide; VC = vital capacity.

DISCUSSION

Our metaanalysis shows that diabetes, in the absence of overt pulmonary disease, is associated with a modest, albeit statistically significant, impaired pulmonary function in a restrictive pattern. The results were irrespective of BMI, smoking, diabetes duration, and HbA1c levels. In subanalyses, the association seemed to be more pronounced in type 2 diabetes than in type 1 diabetes. Our study adds evidence for yet another organ system to be involved in both type 1 and type 2 diabetes. As a consequence of exclusion criteria, the levels of functional impairment fell within values that are generally considered to be normal. However, to place this in perspective, the magnitude of impairment found in our study closely resembles that of smoking *per se*.⁵⁷ Similarly, given the relatively high prevalence of diabetes in COPD,⁵⁸ it is tempting to speculate that (uncontrolled) diabetes may accelerate progressive lung function decline. However, from our metaanalysis summarizing cross-sectional studies, it is difficult to draw conclusions on causality and progression into overt pulmonary diseases. In times of increased pulmonary demands, such as repeated respiratory infections, the loss of pulmonary reserves could eventually become clinically manifest. In those patients with diabetes who carry a pulmonary diagnosis, such as COPD or asthma, it would next be interesting to investigate potential clinical implications.

Two main pathophysiologic mechanisms have been proposed as underlying impaired pulmonary function in diabetes. First, because the thorax and lungs are rich in collagen and elastin, nonenzymatic glycation of these structural compounds could cause stiffening of the thorax and lung parenchyma.¹¹ This may lead to a restrictive pattern, which our findings support. One would expect that a longer exposure to diabetes would proportionally increase the chance of connective tissue being nonenzymatically glycated. However, our study suggests that a longer duration is not necessarily associated with additional loss of pulmonary reserves. This is in line with previous longitudinal studies on this topic.^{59,60} To further investigate whether nonenzymatic glycation attributes to this association, measurements of advanced glycation end products may be useful in future studies.

Second, diabetes-related microvascular damage may reside in the lungs in parallel to complications in the kidneys, retina, and nerves. A postmortem histologic study showed indeed thickening of both the alveolar epithelial and pulmonary capillary basal laminae in patients with diabetes.⁶¹ Also, reduced pulmonary capillary blood volume was found, suggesting the presence of pulmonary microangiopathy.³⁵ This could perhaps lead to a redistribution of the pulmonary circulation, potentially causing well-ventilated areas to become underperfused. A combination of increased thickness of the respiratory membrane and

Table 2—Patient Characteristics of Included Type 2 Diabetes Studies

Study	Source	No. (m/f)	Age, Mean (SD), y	Current Smokers, No. (%)	Duration of Diabetes, Mean (SD), y	Insulin-Dependent Patients, No. (%)		HbA1c, Mean (SD), %	BMI, Mean (SD), kg/m ²	Microvascular Complications	FEV ₁ , Mean (SD), %		FVC, Mean (SD), %		FEV ₁ /FVC, Mean (SD), %		DLCO, mean (SD), % Predicted
						No. (%)	No. (%)				Predicted	%	Predicted	%	Mean (SD), %	%	
Isotani et al ⁴⁵ /1999	NA	54 (23/31)	55 (10)	0 (0)	11 (7)	0 (0)	0 (0)	9.0 (2.3)	22 (3)	Retinopathy (n = 37)	NA	100 (11)	85 (7)	NA	NA	NA	
Benbassat et al ³² /2001	Outpatients	12 (8/3)	60 (8)	0 (0)	13 (6)	1 (8)	1 (8)	9.0 (2.1)	30 (3)	Microangiopathy (n = 4)	104 (16)	100 (16)	NA	114 (24)	NA	NA	
Maiolo et al ²⁹ /2001	NA	7 (0/7)	50 (3)	0 (0)	7 (7) ^a	NA	NA	7.6 (0.5) ^a	32 (4) ^a	Retinopathy (n = 1)	96 (9) ^a	97 (6) ^a	81 (4) ^a	NA	NA	NA	
Guazzzi et al ⁴⁶ /2002	NA	15 (8/7)	62 (7)	0 (0)	NA	5 (33)	5 (33)	6.1 (0.3)	NA	Neuropathy (n = 0)	95 (12)	91 (13) ^b	NA	87 (5)	NA	NA	
Boulbou et al ²¹ /2003	NA	33 (NA)	59 (7)	0 (0)	NA	33 (100)	33 (100)	8.4 (1.0) ^a	NA	Retinopathy (n = 25)	96 (13)	92 (14)	NA	91 (22)	NA	NA	
Lau et al ¹⁷ /2004	Outpatients	40 (26/14)	50 (7)	4 (10)	8 (5)	15 (38)	15 (38)	8.0 (1.4)	26 (4)	Nephropathy (n = 11) ^a	97 (13)	87 (30)	82 (5) ^c	NA	NA	NA	
Sinha et al ⁴⁸ /2004	Outpatients	29 (21/8)	46 (10) ^c	0 (0)	4 (6) ^c	NA	NA	8.6 (1.3) ^c	25 (3) ^c	12 patients had retinopathy and/or nephropathy	80 (14) ^c	81 (14) ^c	NA	NA	NA	NA	
Yu et al ⁴⁹ /2004	NA	70 (29/41)	54 (2)	0 (0)	8 (4)	NA	NA	NA	26 (4)	NA	88 (15)	97 (18) ^b	NA	87 (24)	NA	NA	
Weisbrod et al ³⁰ /2005	NA	8 (5/3)	56 (6)	0 (0)	5 (3)	2 (25)	2 (25)	7.9 (0.6)	29 (11)	None	90 (16)	84 (12)	83 (7)	NA	NA	NA	
El-Jundi et al ²⁴ /2005 ^d	NA	39 (11/28)	53 (10) ^a	0 (0)	7 (5)	NA	NA	7.9 (1.9) ^a	28 (4)	23 patients had no complication ^a	98 (18) ^a	100 (21) ^a	82 (9) ^a	107 (19) ^a	NA	NA	
Özşahin et al ⁵¹ /2006	NA	25 (6/19)	55 (6)	0 (0)	NA	NA	NA	9.3 (1.8)	24 (2)	2 patients had no complications	NA	NA	NA	92 (19)	NA	NA	
Chance et al ³⁹ /2006 ^d	NA	29 (NA)	44 (9)	0 (0)	7 (6)	NA	NA	7.2 (1.9)	NA	NA	94 (17)	94 (15)	NA	83 (15)	NA	NA	
Ortiz-Aguirre et al ³² /2006	Outpatients	144 (54/90)	58 (11)	53 (37)	9 (7)	NA	NA	NA	29 (5)	NA	87 (16)	78 (13)	88 (11)	NA	NA	NA	
Yeh et al ³⁵ /2008	Atherosclerosis Risk In Communities study	1,100 (528/572)	55 (6)	209 (19)	NA	NA	NA	NA	31 (6)	NA	93 (14)	97 (13)	77 (6)	NA	NA	NA	
Chance et al ³¹ /2008	Outpatients	69 (38/31)	47 (11)	0 (0)	8 (6)	37 (54)	37 (54)	8.3 (1.7)	31 (3)	Retinopathy (n = 22)	95 (10)	90 (14)	83 (5) ^c	103 (14) ^{a,c}	NA	NA	
Kabitz et al ²³ /2008	NA	21 (21/0)	64 (8)	0 (0) ^a	13 (10)	11 (52)	11 (52)	7.1 (1.0)	29 (4)	Nephropathy (n = 26) Neuropathy (n = 19) 1 patient had no complication ^a	103 (11)	107 (14)	78 (6)	NA	NA	NA	

See Table 1 for expansion of abbreviations.

^aData obtained from personal communication with author.^bVital capacity.^cPooled from subgroups.^dAbstract.

Table 3—Patient Characteristics of Included Mixed-Type Diabetes Studies

Study	Source	No. (m/f)	Age, Mean (SD), y	Current Smokers, No. (%)	Duration of Diabetes, Mean (SD), y	Insulin-Dependent Patients, No. (%)	HbA1c, Mean (SD), %	BMI, Mean (SD), kg/m ²	Microvascular Complications	FEV ₁ , Mean (SD), % Predicted	FVC, Mean (SD), % Predicted	FEV ₁ /FVC, Mean (SD), % Predicted	DLCO, Mean (SD), % Predicted
Lange et al. ²⁶ /1989	Copenhagen City Heart Study	284 (176/108)	58 (10) ^a	142 (50)	NA	68 (24)	NA	27 (5) ^a	NA	85 (23) ^a	89 (19) ^a	77 (12) ^a	NA
Cooper et al. ²⁵ /1990	Outpatients	35 (16/19)	35 (7) ^b	0 (0)	14 (9) ^b	35 (100)	9.5 (2.2) ^b	NA	Retinopathy (n = 7)	104 (46) ^b	100 (55) ^{b,c,d}	NA	102 (43) ^b
Tan et al. ²⁵ /1990	NA	60 (29/31)	NA	0 (0)	5 (4)	30 (50)	NA	NA	Neuropathy (n = 11)	NA	102 (16) ^b	86 (5) ^b	102 (15)
Tantucci et al. ²⁷ /1997	Outpatients	28 (28/0)	44 (11) ^b	NA ^e	17 (9) ^b	28 (100)	NA	NA	Autonomic neuropathy (n = 18)	99 (14) ^b	103 (13) ^{b,e}	82 (5) ^b	NA
Tantucci et al. ²⁸ /2001	Outpatients	45 (45/0)	46 (11) ^b	NA ^e	18 (10) ^b	45 (100)	7.6 (0.8)	24 (3) ^b	Retinopathy (n = 22)	100 (10) ^b	104 (13) ^{b,e}	82 (4) ^b	NA
Zamarrón et al. ²⁶ /2001	NA	65 (25/40)	68 (12)	0 (0)	NA	34 (52)	NA	NA	Nephropathy (n = 19)	68 (30)	64 (24)	NA	96 (7)
McKeever et al. ²⁵ /2005	National Health and Nutrition Examination Survey III	512 (187/325)	45 (8) ^a	124 (24) ^{a,f}	8 (8) ^a	146 (30) ^a	NA	31 (7) ^a	Autonomic neuropathy (n = 30)	92 (15) ^{g,g}	NA	81 (8) ^a	NA

See Table 1 for expansion of abbreviations.

^aData obtained from personal communication with author.

^bPooled from subgroups.

^cVital capacity.

^dDepicted from a graph.

^ePack-years of smoking did not differ significantly between case and control group.

^fSmoking data available for 493 patients.

^gFEV₁ data available for 431 patients.

FIGURE 2. Weighted mean difference (error bars indicate 95% CIs) in FEV₁ in patients with diabetes vs control subjects. The I^2 statistic describes the percentage of total variation across studies, which is due to heterogeneity rather than chance.¹⁵

a ventilation-perfusion mismatch is therefore suggested to be underlying impaired diffusion capacity in diabetes. Anemia, a common finding in patients with diabetes, especially in those with chronic kidney failure,⁶² could also be an explanation for a decreased DLCO. Others showed that diabetic polyneuropathy impairs respiratory neuromuscular function,^{23,63}

potentially affecting pulmonary volumes. Reduced diaphragm strength has been suggested to result from axonal loss of the phrenic nerve.²³ However, inconsistent outcomes have been reported from studies relating the presence and severity of diabetic nephropathy, retinopathy and neuropathy to pulmonary function.^{17,31,51,64} Discrepancies between studies might be

FIGURE 3. Weighted mean difference (error bars indicate 95% CIs) in FVC in patients with diabetes vs control subjects. The I^2 statistic describes the percentage of total variation across studies, which is due to heterogeneity rather than chance.¹⁵

explained by the different gradations of complications among studies, different assessments of complications, and different study designs (ie, some studies addressed only one complication and disregarded others). In our metaanalysis, we were not able to include a variable for microvascular complications

because of the heterogeneity of data presentation among the included studies, as holds true for diabetes treatment and previous respiratory infections. Therefore, we cannot rule out either of these variables as being explanatory for the observed heterogeneity. Yet, also for diabetes treatment, inconsistent

FIGURE 4. Weighted mean difference (error bars indicate 95% CIs) in FEV₁/FVC ratio in patients with diabetes vs control subjects. The I² statistic describes the percentage of total variation across studies, which is due to heterogeneity rather than chance.¹⁵

findings have been reported regarding its relationship with pulmonary function.^{44,46,51,53} It is intriguing to observe that the pulmonary system remains relatively spared in diabetes when compared with other organs with wide microvascular beds. It is speculated that the large pulmonary reserves protect against severe pulmonary dysfunction.

Because neither the duration of diabetes nor glycaemic state appeared to influence the association in our study, one might question whether there is a causal relationship between diabetes and impaired pulmonary function. Although inconclusive, further indications for this can be found in the literature. Multiple studies have consistently shown that a lower (F)VC is a risk factor for future development of type 2

diabetes.^{60,65-69} So, impaired pulmonary function might precede diabetes diagnosis, although no convincing explanations for this have been proposed yet. Moreover, a lower birth weight may be a common risk factor for both a modestly impaired pulmonary function⁷⁰ and the development of type 2 diabetes.⁷¹ Another possible link between lower pulmonary function and diabetes is suggested to be of inflammatory origin. In one large study,⁵³ patients with type 2 diabetes had higher systemic leukocyte and fibrinogen levels and had reduced FEV₁ and FVC compared with controls. However, inclusion of leukocyte and fibrinogen levels as covariates in their analyses did not help to explain lower pulmonary function in diabetes. Similarly, in the National Health and Nutrition Examination

FIGURE 5. Weighted mean difference (error bars indicate 95% CIs) in DLCO in patients with diabetes vs control subjects. The I^2 statistic describes the percentage of total variation across studies, which is due to heterogeneity rather than chance.¹⁵ See Fig 1 legend for expansion of abbreviation.

Survey III cohort, no cross-sectional relationship was found between increased plasma C-reactive protein levels and lower FVC in patients with diabetes.⁷² Furthermore, Liu et al⁷³ published data on bronchoalveolar lavage fluid cell counts and leukocyte differentiation in nonsmoking, respiratory healthy subjects with type 1 and 2 diabetes. They found levels within the normal range, concluding that diabetes itself does not increase inflammatory cellular composites in the lining fluid of the lungs. Considering this body of evidence so far, neither systemic nor local inflammation seems to underlie pulmonary function abnormalities in diabetes.

A strength of our study is that we performed a quantitative analysis of a comprehensive literature search on pulmonary function in a large diabetic population. This was partly facilitated by restricting our analyses to those studies with available % predicted pulmonary function data, enabling inclusion of a large number of studies across different ethnicities, age groups, and sexes. Therefore, we did not include any of these variables in the meta-regression analy-

ses. In addition, the extensive communication with corresponding authors provided a large and unique database with previously unpublished data. Personal communication resulted in the inclusion of 1,066 additional patients with diabetes in the different analyses. Finally, we prevented language bias by including non-English articles, which should increase the generalizability of our results.

Some limitations of the literature and our metaanalysis need to be commented on. First, although pulmonary function protocols for FEV₁ and FVC are fairly well-standardized tests, there are many accepted ways of measuring DLCO. To overcome between-study differences in pulmonary function test protocols, we restricted our analyses to pooling mean differences between the case and control groups from each study. Second, we were able to account for the number of current smokers in our analyses, but not for former smokers or the number of pack-years, as these were insufficiently presented in most studies. Nevertheless, most studies included only never-smokers. Third, since the Egger test for FEV₁ data was statistically

significant, FEV₁ results may be affected by publication bias. Fourth, our analyses regarding HbA1c levels should be interpreted with some caution. Worldwide, three different reference systems are used to quantify HbA1c levels.⁷⁴ Although converting equations are available, none of the included papers reported which reference system was used, and local reference values were hardly ever presented. Finally, although statistically there were no outliers, the study by Zamarrón et al⁵⁶ reports a remarkably lower FEV₁ and FVC than other studies. Since clear anthropometric data in this particular study were lacking, their outcomes might be attributable to differences in BMI between case and control groups.

In conclusion, when studied in the absence of overt pulmonary comorbidity, both type 1 and type 2 diabetes are associated with a modestly impaired pulmonary function in a restrictive pattern. More research is needed into possible pathophysiological mechanisms. At present, because of reasonable doubts that the decline in pulmonary function is actually caused by diabetes, it remains unclear whether tighter glycaemic control would be beneficial for the pulmonary function. Considering the rapidly increasing prevalence of lifestyle-related chronic diseases, such as diabetes and COPD, the potential implications for patients with diabetes with overt pulmonary diseases deserve further attention.

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Dr Gosker: contributed to designing the study, assisted in data analyses and interpretation of data, revised the manuscript, and assisted in technical support.

Dr Zeegers: contributed to designing the study, completed all analyses, assisted in data management and interpretation of data, revised the manuscript, and supervised the study.

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