# Pulmonary Function Reduction in Diabetes With and Without Chronic Obstructive Pulmonary Disease

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## OBJECTIVE

**Diabetes damages major organ systems through disrupted glycemic control and increased inflammation. The effects of diabetes on the lung have been of interest for decades, but the modest reduction in pulmonary function and its nonprogressive nature have limited its investigation. A recent systematic review found that diabetes was associated with reductions in forced expiratory volume in 1 s ($FEV_1$), forced vital capacity (FVC), and diffusing capacity for carbon monoxide of the lung and increased $FEV_1$/FVC. They reported pooled results including few smokers. This study will examine measures of pulmonary function in participants with extensive smoking exposure.**

## RESEARCH DESIGN AND METHODS

**We examined pulmonary function in participants with a >10–pack-year history of smoking with and without diabetes with and without chronic obstructive pulmonary disease (COPD). We measured pulmonary function, exercise capacity, and pulmonary-related quality of life in 10,129 participants in the Genetic Epidemiology of Chronic Obstructive Pulmonary Disease (COPDGene) Study.**

## RESULTS

**Participants with diabetes were observed to have reduced pulmonary function after controlling for known risk factors and also significant reductions in exercise capacity and quality of life across functional stages of COPD.**

## CONCLUSIONS

**Pulmonary function in patients with ≥10 pack-years of smoking and diabetes is reduced, and this decrease is associated with significant reductions in activity-related quality of life and exercise capacity.**

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Reduced pulmonary function has been observed in patients with both type 1 and type 2 diabetes (1–4). This functional impairment has been shown primarily through cross-sectional associations between diabetes status and pulmonary function measures, including the forced vital capacity (FVC), forced expiratory volume in 1 s ($FEV_1$), and their ratio. van den Borst et al. (5) recently conducted a systematic review and meta-analysis investigating pulmonary function in diabetes, which

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supports observations of a modest reduction in $FEV_1$, FVC, and diffusing capacity for carbon monoxide of the lung associated with both type 1 and type 2 diabetes. This reduced lung function manifests as a reduction in $FEV_1$% predicted of 2.8% in type 1 diabetes and 4.9% in type 2 diabetes and a reduction of FVC% predicted of 3.8% in type 1 diabetes and 6.7% in type 2 diabetes. These reductions have not been examined in patients with extensive smoking exposure or a diagnosis of chronic obstructive pulmonary disease (COPD) (6,7). Diabetes has not been shown to be a strong predictor of pulmonary function decline over time (8–10), suggesting that pulmonary complications of diabetes are not progressive, as is the case with other complications of diabetes with microvascular origins such as retinopathy, nephropathy, and peripheral neuropathy. Reversal of diabetes through simultaneous pancreas and kidney transplantation has been shown to ameliorate $FEV_1$ and FVC reductions in a select population (7).

The origins of pulmonary function impairment in diabetes are thought to derive from four primary sources: nonenzymatic glycosylation of lung collagen and elastin by advanced glycosylation end products (AGEs) generated by disrupted glycemic control resulting in reduced elasticity of the lung (1,11). Of potentially equal importance, thickened alveolar epithelial basal lamina and microvascular changes in pulmonary capillary beds resulting in reduced pulmonary capillary blood volume and reduced diffusing capacity have been reported (1,3,12). Autonomic neuropathy affecting the phrenic nerves, resulting in reduced muscle tone and control of the diaphragm, has been observed (13,14). Finally, hyperglycemia resulting in increased glucose in airway surface liquid (ASL) serving as fuel for bacteria and a subsequent increase in the frequency of bacterial pathogens isolated in the sputum. Increased bacterial colonization has been shown to lead to more frequent acute exacerbations of COPD (AECOPD) and worse outcomes from those exacerbations (15–17). Each of these pathways may work synergistically with other pulmonary disorders, such as COPD, potentially resulting in negative outcomes for patients with both disorders.

To the authors' knowledge, there are no reports of pulmonary function reduction in patients with diabetes and overt COPD. Given the importance of smoking in COPD development, we sought to investigate whether diabetes was associated with pulmonary function reduction in three groups of smokers: the first is a population at risk for COPD ($>$45 years of age and $>$10 pack-years of smoking history with postbronchodilator $FEV_1/FVC \geq 0.70$ and $FEV_1 > 80\%$, control subjects), the second is a group with frank COPD ($FEV_1/FVC < 0.70$ and $FEV_1 < 80\%$) staged by the Global initiative for chronic Obstructive Lung Disease (GOLD) (COPD subjects), and a third group with lung function impairment characterized by reduced $FEV_1$ and preserved $FEV_1$/FVC ratio (unclassified spirometric abnormality subjects) (Fig. 1). We investigated whether diabetes, type 1 or 2, was associated with reduced pulmonary function in each of these groups, separating the frank COPD group by spirometric GOLD classification for severity. We also investigated whether these groups differed in functional capacity and quality of life.

## RESEARCH DESIGN AND METHODS

The Genetic Epidemiology of Chronic Obstructive Pulmonary Disease (COPDGene) Study is a large, observational study designed to identify genetic risk factors for COPD in a biracial population of non-Hispanic white (NHW) (approximately two-thirds) and African American (approximately one-third) smokers with at least a 10–pack-year history of cigarette use. COPDGene participants are between 45 and 80 years of age, span COPD disease severity, and include both sexes from 21 study clinical centers (18). This study presents results from the baseline visit completed by 10,129 participants.

COPDGene conducted an extensive study visit for each participant, collecting demographic data, measures of pulmonary function before and after inhaled bronchodilator, health-related quality of life, and chest CT. Demographic data were collected using a modified American Thoracic Society (ATS) Respiratory Epidemiology Questionnaire. Diabetes status was determined using the question, "Has a doctor ever told you that you have diabetes?" or diabetes-specific medication use was determined with an open-ended question, "List all medications, including those for your lungs, you take that have been prescribed by your health care provider

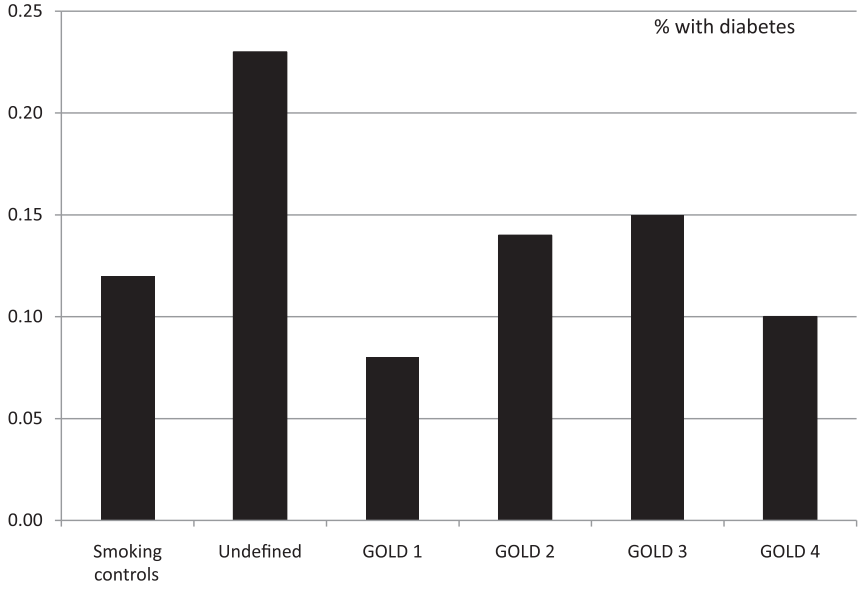


**Figure 1—**The prevalence of diabetes (type 1 or type 2) by GOLD classification.

(physician, nurse practitioner, physician assistant)." This open-ended question was queried for any drugs specific to diabetes by drug name and class. Common misspellings were considered where observed. All drugs in the biguanide, thiazolidinedione, sulfonylurea, meglitinide, α-glucosidase inhibitor, incretin mimetic, DPP-4 inhibitor, amylin analogue, and insulin families were identified, and if a patient did not report diabetes but did report one of these drugs, they were classified as having diabetes. Type 1 and 2 diabetes were combined for these analyses given the similarity in pulmonary function reduction reported in the literature. The age structure of the COPDGene population and medication use pattern suggest that the majority of diabetes in this population is likely type 2 diabetes.

Spirometry was measured using the ndd EasyOne Spirometer, and all tests were performed according guidelines published by the ATS (19). A successful session included three acceptable maneuvers where the two best measures for $FEV_1$ and FVC were within 150 mL of each other. Based on a standardized review process, spirometry studies that did not meet these criteria were selected for inclusion or exclusion. Other assessments included a measure of quality of life—the St. George's Respiratory Questionnaire (SGRQ). Overall and subscores were calculated using the appropriate standard protocol (20). Dyspnea was measured using the Modified Medical Research Council Dyspnea Scale (MMRC) using the standard scoring protocol. Exercise capacity was assessed using the maximum distance a study subject could walk on an unobstructed, flat, indoor course in 6 min. Subjects were supervised by a trained researcher according to ATS guidelines (21).

Statistical analyses were performed using the SAS system, version 9.3 (2002–2008 by SAS Institute Inc., Cary, NC). Univariate comparisons were performed in normally distributed variables using a Student *t* test, nonnormally distributed variables were compared using Kruskal-Wallis test, and categorical variables were compared using $\chi^2$. Multivariable comparisons were performed using Proc GLIMMIX least squares means controlled for the random effect of study center, and all *P* values were two sided, with $P < 0.05$ considered significant. Multivariate models of pulmonary function, quality of life, and 6-min walk distance across COPD GOLD stages were conducted using the method above, controlling for age, sex, current smoking status, pack-years of smoking, ethnicity, and BMI, and the levels of each measure were obtained using least squares means. Multivariate models using $FEV_1$% predicted and FVC% predicted did not include sex and ethnicity as these covariates were accounted for in the sex- and race-specific prediction equations (22).

## RESULTS

Thisanalysis reports on 10,129 participants recruited by the COPDGene Study with GOLD stage 1, 2, 3, or 4 (*n* = 4,484; 13% with diabetes), smoking controls without COPD (*n* = 4,388; 12% with diabetes), and unclassified spirometric abnormalities (GOLD undefined) (*n* = 1,257; 22% with diabetes). Fifty-four participants without physician diagnosis of diabetes were classified as having diabetes using their medications alone, and 80% (*n* = 43) reported use of biguanides alone (metformin or glucophage) and none reported using insulin. In the participants reporting physician diagnosis of diabetes, 41% reported no medication use and 71% reported treatment with a single drug. Of those reporting single drug use, 63% (*n* = 329) reported use of a biguanide alone and 17% reported insulin alone.

As expected, those having diabetes were older, were more likely to be male, had a greater average BMI, had a greater report of breathlessness (higher dyspnea score), and were more likely to have serious pulmonary exacerbations (AECOPD) and pulmonary exacerbations more frequently if they had COPD or were GOLD undefined (Table 1). Among COPD case subjects and smoking control subjects, African Americans had a greater prevalence of diabetes than NHW (16 vs. 12%, *P* = 0.001, and 13 vs. 11%, *P* = 0.002). Those with diabetes had greater pack-years of smoking history

**Table 1—Demographic measures**

| | Control subjects | | | GOLD undefined | | | COPD (GOLD 1, 2, 3, 4) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Diabetes | No diabetes | *P* | Diabetes | No diabetes | *P* | Diabetes | No diabetes | *P* |
| *n* | 523 | 3,865 | NA | 282 | 975 | NA | 576 | 3,908 | NA |
| Age (years ± SD) | 58.8 ± 8.4 | 56.4 ± 8.3 | <0.0001 | 58.8 ± 7.7 | 56.8 ± 8.3 | 0.0003 | 64.7 ± 8.1 | 62.9 ± 8.7 | <0.0001 |
| Sex (% male) | 57.0 | 52.3 | 0.045 | 52.1 | 44.4 | 0.02 | 62.5 | 55.0 | 0.0007 |
| Ethnicity (% NHW) | 54.1 | 59.5 | 0.02 | 57.1 | 56 | 0.7 | 72.2 | 78.1 | 0.002 |
| Pack-years (years ± SD) | 40.7 ± 22.8 | 36.7 ± 19.8 | 0.0002 | 49.0 ± 28.0 | 40.8 ± 22.7 | <0.0001 | 58.5 ± 33.7 | 50.6 ± 26.0 | <0.0001 |
| BMI (years ± SD) | 31.7 ± 6.2 | 28.5 ± 5.6 | <0.0001 | 35.4 ± 7.2 | 30.7 ± 7.0 | <0.0001 | 31.4 ± 6.5 | 27.4 ± 5.9 | <0.0001 |
| MMRC dyspnea scale (median, range) | 0 (4) | 0 (4) | <0.0001 | 2 (4) | 1 (4) | <0.0001 | 3 (4) | 2 (4) | <0.0001 |
| AECOPD (% AECOPD+) | 16.0 | 9.7 | 0.004 | 6.1 | 4.1 | 0.03 | 24.1 | 18.9 | 0.003 |
| Exacerbation frequency (median, range) | 0 (6) | 0 (6) | 0.09 | 0 (6) | 0 (6) | 0.001 | 0 (6) | 0 (6) | <0.0001 |

Comparisons of normally distributed variables were performed using Student *t* test and reported as mean ± SD. Categorical variables were compared using $\chi^2$ and reported as percentages. Scales and counts were compared using Kruskal-Wallis one-way ANOVA and reported as median and range. NA, not applicable.

(59 vs. 51%, $P < 0.0001$ in COPD subjects; 41 vs. 37%, $P = 0.0002$ in control subjects; and 49 vs. 41%, $P < 0.0001$ in GOLD-undefined subjects).

Among smokers without obstructive disease, $FEV_1$%, FVC, and FVC% were significantly lower in those with diabetes (Table 2), and this was also true for spirometric measures in GOLD-undefined individuals. Among COPD case subjects (GOLD 1–4), $FEV_1$ (in liters) was not different by diabetes status overall (−0.02 L [95% CI −0.05 to 0.006], $P = 0.1$) or in individual comparisons within GOLD stages. FVC was significantly lower in participants with diabetes overall (−0.10 L [−0.14 to −0.05], $P < 0.0001$) and was significantly decreased in GOLD-undefined, smoking control, and GOLD 2 subjects. Both $FEV_1$% and FVC% were significantly decreased overall in participants with diabetes (−0.8% [95% CI −1.5 to −0.06], $P = 0.03$, and −2.8% [−3.7 to −1.9], $P < 0.0001$). Smoking control and GOLD-unclassified subjects showed reduction in $FEV_1$% and FVC%; however, $FEV_1$% was not reduced in COPD. FVC% was reduced in GOLD stages 2 and 3 but not stage 4. $FEV_1$/FVC ratio was increased in those with diabetes overall (0.13 [95% CI 0.009–0.02], $P < 0.0001$); statistically significant increases in $FEV_1$/FVC ratio were observed among GOLD 2 and 3 subjects but not among other COPD groups.

Exercise capacity, as measured by 6-min walk distance, was significantly reduced (−90.2 feet [95% CI −115.3 to −65.1], $P < 0.0001$) in individuals with diabetes across all lung function categories. Walk distance reduction ranged between 45.6 and 129.3 feet and was consistently decreased in participants with diabetes (Fig. 2). Quality of life as measured by SGRQ, a pulmonary-specific questionnaire, was significantly worse (higher score) in those with diabetes overall (3.3 points [95% CI 2.0–4.7], $P < 0.0001$) and among those participants with diabetes, without COPD, GOLD undefined, and GOLD 2–3 but not among those with GOLD 1 or 4.

**Table 2—Pulmonary function and outcome measures**

| | Control subjects | | GOLD undefined | | GOLD 1 | | GOLD 2 | | GOLD 3 | | GOLD 4 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Diabetes | No diabetes | Diabetes | No diabetes | Diabetes | No diabetes | Diabetes | No diabetes | Diabetes | No diabetes | Diabetes | No diabetes |
| Pulmonary function | | | | | | | | | | | | |
| $FEV_1$ (L) | 2.71*** | 2.76 | 1.94*** | 2.03 | 2.53 | 2.54 | 1.81 | 1.84 | 1.15 | 1.10 | 0.57 | 0.57 |
| $FEV_1$% predicted | 95.1**** | 97.0 | 67.9*** | 70.5 | 89.6 | 90.0 | 63.6* | 64.9 | 41.3 | 40.0 | 22.5 | 22.5 |
| FVC (L) | 3.42*** | 3.50 | 2.57*** | 2.70 | 3.83 | 3.90 | 3.00**** | 3.16 | 2.49 | 2.57 | 1.90 | 1.92 |
| FVC% predicted | 93.5**** | 95.8 | 69.6*** | 72.3 | 103.5 | 106.1 | 81.9**** | 86.0 | 68.3 | 70.9 | 51.9 | 54.6 |
| FEV/FVC | 0.79 | 0.78 | 0.76 | 0.76 | 0.67 | 0.66 | 0.60*** | 0.59 | 0.48**** | 0.45 | 0.35 | 0.33 |
| Study outcomes | | | | | | | | | | | | |
| SGRQ total score | 21.5**** | 18.2 | 34.2**** | 26.0 | 22.7 | 22.3 | 38.5**** | 33.5 | 49.1* | 46.1 | 57.2 | 57.3 |
| 6-min walk distance (feet) | 1,325**** | 1,397 | 1,182**** | 1,289 | 1,310* | 1,398 | 1,212* | 1,266 | 987** | 1,081 | 636** | 762 |

Values are least squares means of each measure of pulmonary function or study outcome adjusted for study site, age, sex, smoking status, pack-years of smoking, BMI, diabetes, GOLD stage, and the interaction between diabetes and GOLD stage. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; ****$P < 0.0001$.

## CONCLUSIONS

In the COPDGene population, we found that diabetes is associated with

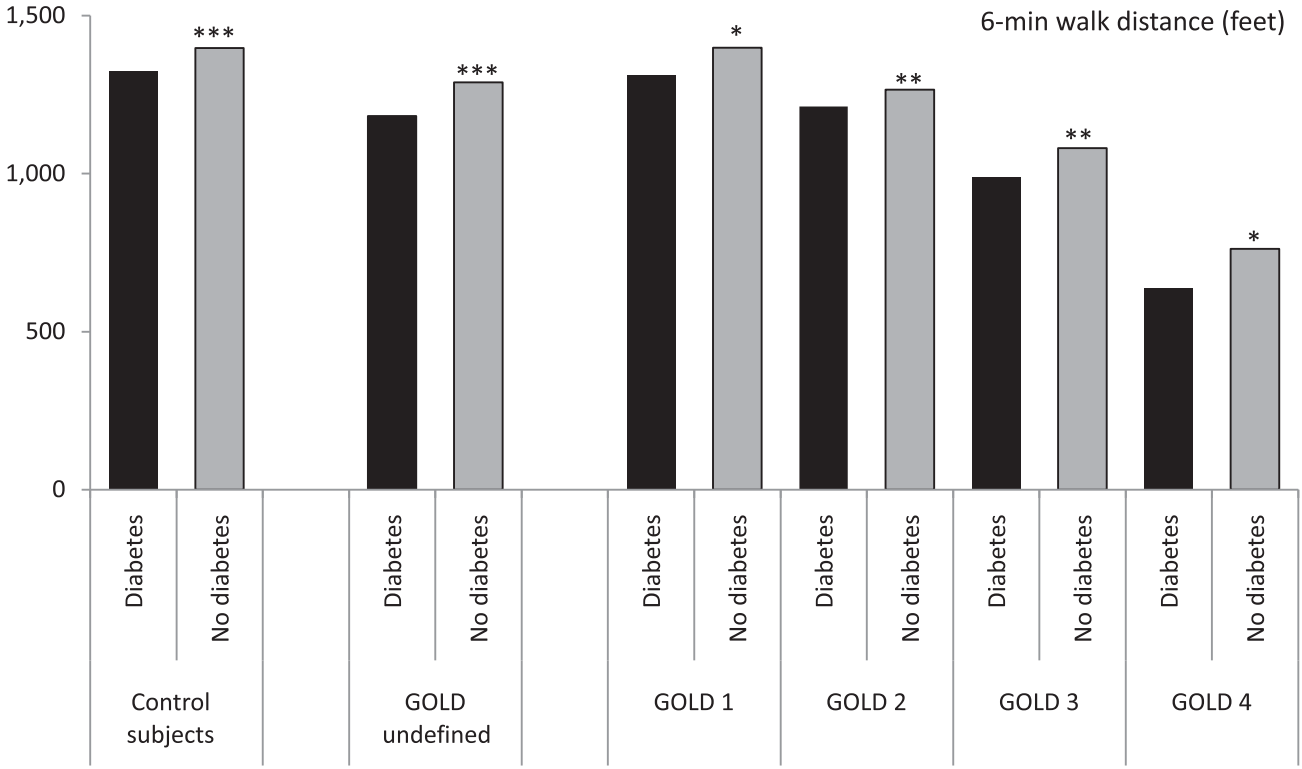


**Figure 2—**The results of the 6-min walk test in feet by GOLD classification and diabetes status. Levels are least squares means adjusted for study site, age, sex, smoking status, pack-years of smoking, BMI, diabetes, GOLD stage, and the interaction between diabetes and GOLD stage. *$P < 0.05$; **$P < 0.01$; ***$P < 0.0001$.

decreased lung function in current and former smokers with a >10–pack-year history of smoking who do not have obstructive lung disease. The magnitude of the differences we observed was small but in keeping with previous studies of pulmonary function conducted primarily in populations with less overall smoking exposure. This decrease in function is manifest in all Pulmonary Function Test (PFT)-based measures in our study, with the exception of $FEV_1$.These participants also exhibit reduced 6-min walk distance and worse quality of life.

Participants with COPD also show reduced pulmonary function by several measures, including reduced 6-min walk distance. GOLD-unclassified participants show the most consistent effect of diabetes, with all measures showing reduction. As COPD severity worsened, there were fewer differences in pulmonary function measures related to diabetes, with GOLD 2 showing significantly lower pulmonary function among three PFT parameters (FVC, FVC% predicted, and $FEV_1$/FVC ratio) (Table 2). Among GOLD 3 individuals, there were two functional parameters that were significantly reduced in diabetes (FVC% predicted and $FEV_1$/FVC). In GOLD 4 individuals, none of the functional measures were significantly lower in diabetes. The overall picture of the effect of diabetes on pulmonary function is of small reductions exhibiting important effects on functional capacity and quality of life. The pattern observed in these participants is restrictive, e.g., lower FVC and higher $FEV_1$/FVC, which is consistent with potential biological mechanisms, such as collagen cross-linking in the lung associated with glycemic dysregulation and AGE exposure.

A meta-analysis conducted by van den Borst et al. (5) demonstrated a pooled estimate of reduction in $FEV_1$% of 5.07%, reduction in FVC% of 6.31%, and increase in $FEV_1$/FVC of 0.12. This study included limited numbers of current smokers and lacked data regarding former smoke exposure. Our study explores a population exposed to substantial cumulative smoke exposure (≥10 pack-years) and reports smaller but comparable reductions in former smokers, reduction in $FEV_1$% of 1.90%, reduction in FVC% of 2.30%, and increase in $FEV_1$/FVC of 0.01. In participants with COPD, $FEV_1$% reduction was lower than in smoking control subjects and reduction in FVC% was higher than in smoking control subjects but did not reach the difference observed in the meta-analysis (Table 2). GOLD-unclassified subjects also showed similar levels of reduction that did not reach the levels observed in that study. The magnitude of the differences observed that is attributable to diabetes might be expected to be reduced given the large effect of smoking. This is also true of the COPD lung where the restrictive effect of diabetes might be hypothesized to be masked by smoking and obstructive disease. Our observation of significant functional reduction, worse quality of life, and 6-min walk distance in participants with COPD underscores the importance of diabetes on the pulmonary system, which may not be appreciated using spirometry alone.

The COPDGene Study differs in important ways from the studies used in the systematic review and meta-analysis, primarily in that it represents heavy smoking exposure and measures diabetes in a less than optimal fashion. The study design allows us to compensate somewhat for an imprecise measurement of diabetes in that self-report of diabetes in 10,129 participants is highly unlikely to be biased to such an extent that it influences the outcome, and incorrect report of diabetes diagnosis would bias our results in a conservative direction. Participants with undiagnosed and untreated diabetes would likely have worse glycemic control than participants who were treated, and this would likely also generate bias in a conservative direction. Our observation of medication use in participants reporting diabetes is comparable to that reported by the Centers for Disease Control and Prevention (23). The size of the study also allows a very precise measure of pulmonary function, and the emphasis of COPDGene on pulmonary outcomes ensures that the outcome was measured consistently. The data reported are cross-sectional and likely include a survival bias and are subject to the weaknesses inherent in that type of study design.

Patients with diabetes receiving simultaneous pancreas and kidney transplantation showed significantly improved pulmonary function measured by $FEV_1$ but not measured by FVC or total lung capacity (7). This suggests that the elimination of diabetes improved pulmonary function without directly affecting lung structure, implying an effect of the diabetic milieu on pulmonary function irrespective of the pulmonary damage associated with smoking. Diabetes represents a disruption in glycemic control and increased exposure to AGEs. The receptor for AGEs (RAGE) has been shown to localize to the basal cell membrane of alveolar type 1 epithelial cells (24). Genetic studies confirm an association between polymorphisms in the *AGER* gene and reductions in pulmonary function without considering the effect of diabetes (25). This suggests that altered function of RAGE may play an important role in the restrictive lung disease observed in diabetes. A reduction in exercise capacity has been observed in patients with diabetes, and this reduction has been shown to be associated with microvascular blood flow defects at the muscle (26) as well as cardiac dysfunction (27). This reduction in capillary blood volume has also been observed in studies of gas transfer in people with diabetes (28). Diabetes is the leading cause of neuropathies in humans, and one target is the phrenic nerve. Diabetic phrenic neuropathy has been shown to present as respiratory weakness (14) or failure (29) and to occur before the onset of frank diabetes (13). Whereas this study is not able to assess phrenic neuropathy, future studies should consider subsymptomatic phrenic dysfunction related to diabetes. This study also shows significant dyspnea and AECOPD and a higher frequency of pulmonary exacerbations related to diabetes, suggesting that diabetes is directly related to serious lung problems beyond those discussed above. Lastly, 6-min walk distance measures both pulmonary and extrapulmonary manifestations of COPD. Spruit et al. (30) showed that patients that were unable to exceed 1,095 feet in walk distance were at increased risk of death, and an individual experiencing a reduction in walk distance of 98.4 feet has been shown to be at increased risk for death (31). Our study shows a decrease in walk distance in participants with diabetes overall of 90.2 feet (95% CI 115.3–65.1, $P < 0.0001$). The magnitude of this decreased functional capacity suggests serious increased risk of death for participants with diabetes and COPD. Annual assessment of 6-min walk distance in patients with diabetes may represent an important and cost-effective addition to commonly measured clinical markers.

Pulmonary function in patients with $\geq$10 pack-years of smoking and diabetes is reduced, and this decrease is associated with significant reductions in activity-related quality of life and exercise capacity. This reduction is evident in those with and without COPD and in participants without defined obstructive lung disease. Additional work is needed to understand the influence of the biological pathways linking diabetes and reduced pulmonary function in order to identify appropriate treatments that consider both diabetes and COPD.

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**Author Contributions.** G.L.K. designed the research, performed the statistical analysis, interpreted and discussed the results, and drafted the manuscript. J.L.B.-S., E.S.W., X.S., and J.E.H. interpreted and discussed the results and reviewed and edited the manuscript. B.M., E.R., E.K.S., and J.C. acquired clinical data, interpreted and discussed the results, and reviewed and edited the manuscript. S.L. interpreted and discussed the results and statistical analysis and reviewed and edited the manuscript. All authors approved the final version of the manuscript. G.L.K. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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## References

1. Sandler M. Is the lung a 'target organ' in diabetes mellitus? Arch Intern Med 1990; 150:1385–1388
2. Mirrakhimov AE. Chronic obstructive pulmonary disease and glucose metabolism: a bitter sweet symphony. Cardiovasc Diabetol 2012;11:132
3. Sandler M, Bunn AE, Stewart RI. Cross-section study of pulmonary function in patients with insulin-dependent diabetes mellitus. Am Rev Respir Dis 1987;135:223–229
4. Klein OL, Meltzer D, Carnethon M, Krishnan JA. Type II diabetes mellitus is associated with decreased measures of lung function in a clinical setting. Respir Med 2011;105: 1095–1098
5. van den Borst B, Gosker HR, Zeegers MP, Schols AM. Pulmonary function in diabetes: a metaanalysis. Chest 2010;138: 393–406
6. Kaparianos A, Argyropoulou E, Sampsonas F, Karkoulias K, Tsiamita M, Spiropoulos K.

Pulmonary complications in diabetes mellitus. Chron Respir Dis 2008;5:101–108

7. Dieterle CD, Schmauss S, Arbogast H, Domsch C, Huber RM, Landgraf R. Pulmonary function in patients with type 1 diabetes before and after simultaneous pancreas and kidney transplantation. Transplantation 2007;83:566–569
8. Yeh HC, Punjabi NM, Wang NY, et al. Cross-sectional and prospective study of lung function in adults with type 2 diabetes: the Atherosclerosis Risk in Communities (ARIC) study. Diabetes Care 2008;31:741–746
9. Lange P, Parner J, Schnohr P, Jensen G. Copenhagen City Heart Study: longitudinal analysis of ventilatory capacity in diabetic and nondiabetic adults. Eur Respir J 2002; 20:1406–1412
10. Lazarus R, Sparrow D, Weiss ST. Baseline ventilatory function predicts the development of higher levels of fasting insulin and fasting insulin resistance index: the Normative Aging Study. Eur Respir J 1998;12:641–645
11. Forbes JM, Cooper ME. Mechanisms of diabetic complications. Physiol Rev 2013; 93:137–188
12. Vracko R. Effects of aging and diabetes on basal lamina thickness of six cell types. In *Biology and Chemistry of Basement Membranes*. New York, Academic Press, Inc., 1978, p. 483–493
13. Yesil Y, Ugur-Altun B, Turgut N, et al. Phrenic neuropathy in diabetic and prediabetic patients without neuromuscular complaint. Acta Diabetol. 28 January 2012 [Epub ahead of print]
14. Brannagan TH, Promisloff RA, McCluskey LF, Mitz KA. Proximal diabetic neuropathy presenting with respiratory weakness. J Neurol Neurosurg Psychiatry 1999;67:539–541
15. Baker EH, Janaway CH, Philips BJ, et al. Hyperglycaemia is associated with poor outcomes in patients admitted to hospital with acute exacerbations of chronic obstructive pulmonary disease. Thorax 2006;61:284–289
16. Kalsi KK, Baker EH, Fraser O, et al. Glucose homeostasis across human airway epithelial cell monolayers: role of diffusion, transport and metabolism. Pflugers Arch 2009;457:1061–1070
17. Baker EH, Bell D. Blood glucose: of emerging importance in COPD exacerbations. Thorax 2009;64:830–832
18. Regan EA, Hokanson JE, Murphy JR, et al. Genetic epidemiology of COPD (COPDGene) study design. COPD 2010;7:32–43
19. Miller MR, Crapo R, Hankinson J, et al.; ATS/ERS Task Force. General considerations for lung function testing. Eur Respir J 2005;26: 153–161
20. Jones PSt. *George's Respiratory Questionnaire Manual.* Version 2.3. London, St. George's, University of London, 2009
21. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111–117
22. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med 1999;159:179–187
23. Centers for Disease Control and Prevention. *National Diabetes Fact Sheet: National Estimates and General Information on Diabetes and Prediabetes in the United States.* Atlanta, Georgia, U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2011
24. Fehrenbach H, Kasper M, Tschernig T, Shearman MS, Schuh D, Muller M. Receptor for advanced glycation endproducts (RAGE) exhibits highly differential cellular and subcellular localisation in rat and human lung. Cell Mol Biol (Noisy-le-grand) 1998; 44:1147–1157
25. Hancock DB, Eijgelsheim M, Wilk JB, et al. Meta-analyses of genome-wide association studies identify multiple loci associated with pulmonary function. Nat Genet 2010; 42:45–52
26. Bauer TA, Reusch JE, Levi M, Regensteiner JG. Skeletal muscle deoxygenation after the onset of moderate exercise suggests slowed microvascular blood flow kinetics in type 2 diabetes. Diabetes Care 2007;30: 2880–2885
27. Regensteiner JG, Bauer TA, Reusch JE, et al. Cardiac dysfunction during exercise in uncomplicated type 2 diabetes. Med Sci Sports Exerc 2009;41:977–984
28. Vracko R, Thorning D, Huang TW. Basal lamina of alveolar epithelium and capillaries: quantitative changes with aging and in diabetes mellitus. Am Rev Respir Dis 1979;120:973–983
29. Tang EW, Jardine DL, Rodins K, Evans J. Respiratory failure secondary to diabetic neuropathy affecting the phrenic nerve. Diabet Med 2003;20:599–601
30. Spruit MA, Polkey MI, Celli B, et al.; Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Study Investigators. Predicting outcomes from 6-minute walk distance in chronic obstructive pulmonary disease. J Am Med Dir Assoc 2012;13: 291–297
31. Polkey MI, Spruit MA, Edwards LD, et al.; Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Study Investigators. Six-minute-walk test in chronic obstructive pulmonary disease: minimal clinically important difference for death or hospitalization. Am J Respir Crit Care Med 2013;187:382–386