Association between Glycemic State and Lung Function
The Framingham Heart Study

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Diabetes mellitus has been inconsistently associated with a reduced level of pulmonary function. To elucidate this association further, we analyzed the relationship of diabetes and of fasting blood glucose to the level of pulmonary function assessed by spirometry in the 3,254 members of the Framingham Offspring Cohort. Diabetes was defined as a fasting blood glucose of 126 mg/dl or more or pharmacologic treatment. Subjects were classified as current, former, or never smokers based on questionnaire responses. Predicted pulmonary function was determined from the coefficients of a regression of pulmonary function on age, sex, and body habitus in the 1,110 never smokers. Both the diagnosis of diabetes and a higher level of fasting blood glucose were associated with lower than predicted levels of pulmonary function. The adverse effect of diabetes and glycemic level on pulmonary function was stronger among ever smokers than never smokers, suggesting an interaction between the level of fasting glycemia and tobacco smoking.

Keywords: lung diseases, obstructive; diabetes mellitus; blood glucose; epidemiology; lung diseases

The current model for the pathogenesis of chronic obstructive pulmonary disease (COPD) involves upregulated inflammation in response to tobacco smoking in the majority of cases; this inflammation results in parenchymal destruction and narrowing of the airways (1). As only a minority of smokers develops clinically significant COPD (2), other factors likely influence the risk of developing disease. Diabetes mellitus (DM) has been associated with markers of systemic inflammation and with increased risk of other diseases in which inflammation plays a role, such as cardiovascular disease. Several studies have suggested that diabetes is associated with impaired pulmonary function (3–9), but this relationship has been inconsistent (10–14). Using the Offspring Cohort of the Framingham Heart Study, we examined the cross-sectional relationship of diabetes and the level of fasting blood glucose to pulmonary function.

METHODS

Subjects

Recruitment of the Offspring Cohort of the Framingham Heart Study has been previously described (15); this cohort was recruited from 1971 to 1975, enrolling 3,544 children of the Framingham Heart Study Original Cohort and 1,580 spouses of these offspring. Informed consent for participation was obtained from all participants, in accordance with the protocol approved by the institutional review board. The subjects included in this analysis are Offspring Cohort participants who had measurements of the variables of interest at examination 5 (1991–1994).

Blood Glucose, Smoking Status, and Body Habitus

Blood glucose was measured after an overnight fast (A-gent glucose test; Abbott, South Pasadena, CA), assays were run in duplicate, and the intra-assay coefficient of variation was less than 3% (16). DM was defined as a fasting blood glucose of 126 mg/dl or more or treatment with either insulin or an oral hypoglycemic agent (17, 18). Subjects were asked at their initial visit if they had ever smoked cigarettes, and at each subsequent visit they were asked to quantify their smoking if they had smoked regularly in the previous 12 months. Subjects reporting no cigarette use at every visit were classified as never smokers. Those not currently smoking but reporting smoking at any time before examination 5 were classified as former smokers, and those smoking at examination 5 were classified as current smokers. Participants undergo physician examination at each cycle and examiners review symptoms, medications, and medical problems. Based on these data, the physician is asked whether a subject has asthma; subjects classified by the examining physician as "yes" were considered to have asthma, and those classified as "maybe" or "no" were considered not to have asthma. Chronic obstructive lung disease was defined by a FEV_1 to FVC ratio of 0.70 or less (19), in accordance with the recommendations of Global Initiative for Chronic Obstructive Lung Disease. Weight and standing height were measured without shoes. Waist and hip girths were measured standing, at the level of the umbilicus and the level of maximal gluteal protrusion, respectively.

Spirometry

Spirometric data were obtained using a Collins Survey II spirometer, interfaced to pulmonary function data acquisition and quality control software (SandM Instruments, Doylestown, PA), and calibrated daily. Spirometric maneuvers were performed according to American Thoracic Society standards (20, 21). The largest FEV_1 and FVC of acceptable maneuvers were used in this analysis; the FEV_1/FVC ratio was obtained from the maneuver with the largest sum of FEV_1 plus FVC.

Statistical Analyses

All statistical analyses were performed using SAS software (SAS Institute, Cary, NC). Predicted lung function was obtained using the coefficients obtained from regression models in which each of the three spirometric measures (FEV_1, FVC, and FEV_1/FVC ratio) was individually regressed on age, sex, and body habitus in the 1,100 nonsmokers for whom spirometric information was available. Multiple prediction models, with clinical measures known to be associated with level of pulmonary function, were tested, including all combinations of age, height, height^2 (to test for a quadratic relationship to the variable of interest), weight, sex, and first-order interaction terms (to test for effect modification). Interaction terms were included when appropriate. The most parsimonious models for FEV_1 ($R^2 = 0.73$) and FVC ($R^2 = 0.77$) included sex, age, height, weight, and age $\times$ height, and for FEV_1/FVC ratio ($R^2 = 0.09$) included sex, age, height, and weight. The waist/hip ratio was included in a second model but did not improve the predictive value of the model. Residual pulmonary function was determined by subtracting the predicted from the measured value; negative values thus reflect pulmonary function less than expected.

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TABLE 1. SUBJECT CHARACTERISTICS

	Individuals without Diabetes (*n = 2,974*)	Individuals with Diabetes (*n = 280*)	p Value
Male (%)	1,379 (46.4)	168 (60.0%)	< 0.001
Age, yr	53.9 (9.7)	59.6 (8.8)	< 0.001
Height, m	1.68 (0.09)	1.69 (0.09)	0.045
Weight, kg	77.0 (16.2)	87.6 (17.8)	< 0.001
Smoking status			
Never, n (%)	1,023 (34.4%)	87 (31.1%)	0.521
Former, n (%)	1,381 (46.4%)	138 (49.3%)	
Current, n (%)	570 (19.2%)	55 (19.6%)	
Blood glucose	94.8 (9.4)	164.6 (64.7)	< 0.001
FEV_1	2.92 (0.79)	2.70 (0.77)	< 0.001
FVC	3.95 (0.97)	3.66 (0.98)	< 0.001
FEV_1/FVC	0.74 (0.07)	0.74 (0.07)	0.710
Pack-years, former smokers	19.2 (19.1)	28.2 (24.2)	< 0.001
Pack-years, current smokers	36.9 (21.3)	54.2 (23.4)	< 0.001
Patients with asthma, n (%)	93/2,969 (3.1)	11 (3.9%)	0.469
COPD diagnosis, n (%)	634 (21.3)	73 (26.1%)	0.065

Definition of abbreviation: COPD = chronic obstructive pulmonary disease.

SDs are in parentheses, except where otherwise noted; p values are for those with diabetes versus those without, using *t* tests and chi-square statistical testing when appropriate.

Using linear regression, residual pulmonary function was adjusted for sex and smoking history (pack-years). Exclusion of patients with asthma and further adjustment for body mass index or waist/hip ratio did not change the model. Patients with diabetes were compared with those without diabetes for all subjects (without adjustment for smoking status) and for strata of smoking status using analysis of covariance. Restricting analysis to the subjects not on pharmacologic therapy for diabetes, the mean residual pulmonary function level was compared across quartiles of fasting blood glucose (first quartile, 48–88 mg/dl; second quartile, 89–94 mg/dl; third quartile, 95–101 mg/dl; and fourth quartile, 102–305 mg/dl) using analysis of covariance to adjust for sex and pack-years of tobacco smoking. This analysis was done for all subjects combined and was also stratified by smoking status. Finally, logistic regression was used examine the relationship between the diagnosis of diabetes to COPD, adjusting for sex and pack-years of cigarette smoking.

RESULTS

Subject Characteristics

Of the 3,799 subjects attending examination 5, 3,261 had acceptable spirometric data. Seven participants were excluded because of a lack of information on smoking status, anthropomorphic measurements, or blood glucose levels. The characteristics of the remaining 3,254 subjects are described in Table 1. Men were 46.5% of the subjects without diabetes and 60% of the subjects with diabetes; 280 of the subjects were classified as having DM (fasting blood glucose of 126 mg/dl or more or pharmacologic treatment for DM). Those with diabetes were slightly older than those without diabetes (59.6 versus 53.9 years) and were heavier (87.6 versus 77.0 kg). Although subjects with diabetes were no more likely to have been smokers, they had longer pack-years exposure to tobacco smoke.

Relationship of DM to Pulmonary Function

Among current smokers, mean residual FEV_1 was 139 ml lower among individuals with diabetes ($p = 0.04$) than among individuals without (Table 2). Compared with individuals without diabetes, the diagnosis of DM was associated with a mean residual FEV_1 that was 64 ml lower in former smokers and 27 ml lower in never smokers, although these differences did not achieve statistical significance.

The diagnosis of diabetes was also associated with a lower level of FVC, adjusted for sex and pack-years, across all strata of smoking status. Compared with those without diabetes of corresponding smoking status, individuals with diabetes who smoked had a lower mean residual FVC by 251 ml ($p < 0.001$); those with diabetes who were former smokers had a lower mean residual FVC by 163 ml ($p < 0.001$), and those with diabetes who were smokers a lower mean residual FVC by 109 ml ($p = 0.047$). The adjusted residual FEV_1/FVC ratio was approximately 1.5% higher in individuals with than without diabetes, a small but statistically significant ($p < 0.001$) difference. This small effect was seen in each stratum of smoking status.

TABLE 2. MEAN RESIDUAL PULMONARY FUNCTION, ADJUSTED FOR SEX AND PACK-YEARS

	Individuals without Diabetes (*n = 3,030*)	DM (*n = 279*)	Difference (*95% CI*)	p Value
$rFEV_1$				
All	−112	−173	−61 (−116, −6)	0.031
Smoking status				
Never	2	−25	−27 ml (−118, 63)	0.552
Former, ml	−101	−165	−64 ml (−145, 17)	0.119
Current, ml	−339	−479	−139 ml (−275, −4)	0.043
rFVC				
All	−56	−217	−160 (−222, −99)	< 0.001
Smoking status				
Never, ml	9	−100	−109 ml (−216, −2)	0.047
Former, ml	−39	−202	−163 ml (−252, −74)	< 0.001
Current, ml	−211	−463	−251 ml (−395, −108)	< 0.001
$rFEV_1$/FVC ratio				
All	−0.020	−0.004	0.016 (0.008, 0.024)	< 0.001
Smoking status				
Never	−0.001	0.014	0.015 (0.003, 0.028)	0.017
Former	−0.021	−0.007	0.014 (0.003, 0.026)	0.014
Current	−0.051	−0.035	0.015 (−0.006, 0.037)	0.160

Definition of abbreviations: CI = confidence interval; DM = diabetes mellitus; $rFEV_1$ = residual FEV_1; rFVC = residual FVC.

The 95% confidence intervals for the difference in pulmonary function between those with diabetes and those without are included in parentheses. Among participants without diabetes, there were 1,023 never smokers, 1,381 former smokers, and 570 current smokers. Among participants with diabetes, there were 87 never smokers, 138 former smokers, and 55 current smokers.

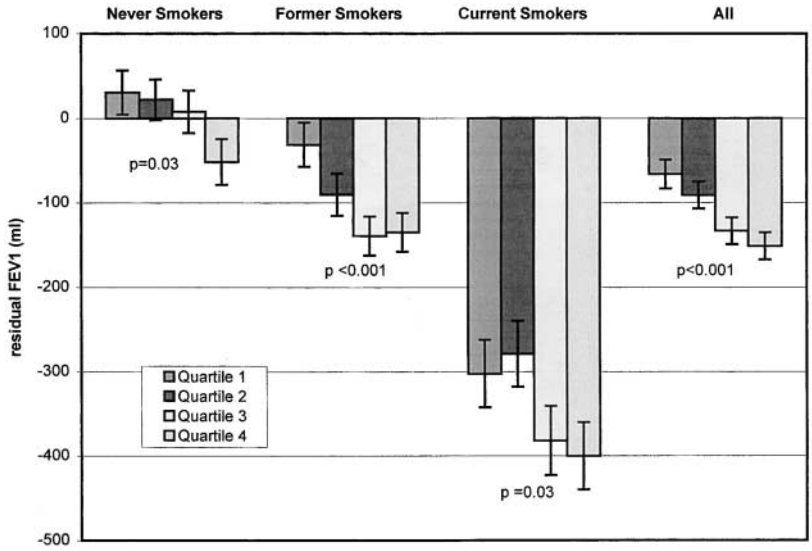

Figure 1. Relationship of *residual FEV_1* to level of fasting glucose. Quartiles of blood glucose: first quartile, 48–88 mg/dl; second quartile, 89–94 mg/dl; third quartile, 95–101 mg/dl; and fourth quartile, 102–305 mg/dl; p values are for linear trend across quartiles. *Error bars* are SDs.

Relationship of Fasting Blood Glucose to Pulmonary Function

Inclusion of treated individuals with diabetes, with consequent improved glycemic control, may have mitigated some of the relationship between lung function and blood sugar. To assess directly the relationship of pulmonary function to fasting blood sugar across a broad range of blood glucose values, we examined this relationship excluding only those subjects on either insulin or oral hypoglycemic agents. For this analysis, mean residual pulmonary function, adjusted for sex and pack-years, was compared across quartiles of fasting blood glucose.

The mean residual FEV_1 decreased (Figure 1) with increasing quartile of blood glucose, regardless of smoking status. In each stratum of smoking status, there was a negative linear association between quartile of fasting blood glucose and level of residual FEV_1 (for linear trend, $p < 0.001$ for all subjects, $p = 0.03$ for current smokers, $p < 0.001$ for former smokers, $p = 0.03$ for never smokers). Compared with subjects in the lowest quartile of fasting blood glucose, subjects in the highest quartile of fasting blood glucose had a residual FEV_1 that was on average 98 ml lower among current smokers, 104 ml lower among former smokers, and 82 ml lower among never smokers. When all strata of smoking status were combined, subjects in the highest quartile of fasting blood glucose had a residual FEV_1 that was on average 85 ml lower than subjects in the lowest quartile.

Similarly, there were negative linear associations (Figure 2) between quartile of fasting blood glucose and level of residual FVC (for linear trend, $p = 0.18$ for current smokers, $p < 0.001$ for former smokers, and $p = 0.04$ for never smokers). Current smokers in the highest quartile of fasting blood glucose had a mean adjusted residual FVC that was 69 ml lower than the lowest quartile. Former smokers in the highest quartile of fasting blood glucose had an average adjusted FVC that was 125 ml less than those in the lowest quartile, and never smokers in the highest quartile of fasting blood glucose had an average adjusted FVC that was 90 ml less than those in the lowest quartile. When all strata of smoking status were combined, subjects in the highest quartile of fasting blood glucose had a mean residual FVC that was 94 ml lower than those in the lowest quartile.

Although higher levels of fasting blood glucose were associated with reductions in both residual FEV_1 and residual FVC, among the individual strata of smoking status, higher levels of fasting blood glucose were associated with significantly lower mean residual FEV_1/FVC ratios (Figure 3) only among current smokers (lowest quartile to highest quartile difference = 1.8%,

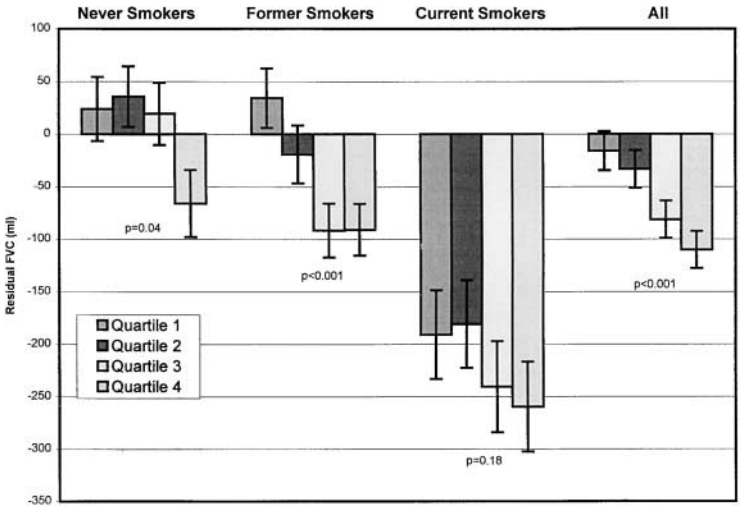

Figure 2. Relationship of *residual FVC* to level of fasting glucose. Quartiles of blood glucose: first quartile, 48–88 mg/dl; second quartile, 89–94 mg/dl; third quartile, 95–101 mg/dl; and fourth quartile, 102–305 mg/dl; p values are for linear trend across quartiles. *Error bars* are SDs.

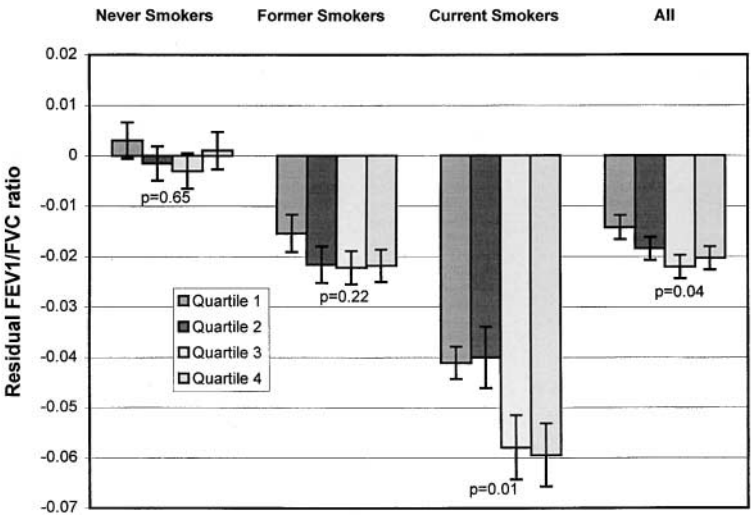

Figure 3. Relationship of *residual FEV_1/FVC* to level of fasting glucose. Quartiles of blood glucose: first quartile, 48–88 mg/dl; second quartile, 89–94 mg/dl; third quartile, 95–101 mg/dl; and fourth quartile, 102–305 mg/dl; p values are for linear trend across quartiles. *Error bars* are SDs.

test for linear trend, p = 0.012). A similar effect was seen when the subgroups were combined; the residual ratio was 1% lower in the highest quartile compared with the lowest quartile of fasting blood glucose (test of linear trend, p = 0.04).

Finally, we investigated whether the diagnosis of DM was associated with the diagnosis of COPD. More subjects with diabetes than without diabetes had COPD (*see* Table 1; 21 versus 26%, p = 0.07); however, after adjustment for sex and tobacco consumption, there was no significant association between the diagnosis of DM and COPD. Exclusion of individuals with asthma from the analysis did not significantly alter the results.

DISCUSSION

The current paradigm for the pathogenesis of COPD involves the upregulation of neutrophil and macrophage activity with consequent connective tissue degradation, usually in response to smoking (1, 22). The FEV_1 of cigarette smokers declines approximately 15–30 ml per year faster than that of nonsmokers, but there is a spectrum of sensitivity to tobacco smoke (23–31). Markers of systemic inflammation (32–34) and levels of cytokines that regulate neutrophil function, including interleukin (IL)-1 (35), IL-4 (36), IL-6 (37), IL-8 (38), and tumor necrosis factor (35, 38–41), have been associated with COPD, and heterogeneity in expression of inflammatory mediators may affect the risk of developing COPD (42).

Although our understanding of the pathogenesis of type I diabetes has long included a significant role for inflammation and other immune mechanisms (43), recent epidemiologic studies have also demonstrated an association between type II diabetes and higher levels of markers of systemic inflammation. Elevated serum ferritin (44) and other inflammatory markers (45–47) have been associated with an increased risk for the development of diabetes. A variety of mediators of inflammation, including IL-1, IL-6, and tumor necrosis factor, that have also been implicated in the pathogenesis of COPD have been associated with insulin resistance (48, 49). Systemic inflammation related to cigarette smoking might therefore independently influence both lung function and glycemia (50, 51).

Arnalich and colleagues (52) observed a reduction in serum markers of inflammation with the treatment of diabetes, however, suggesting that diabetes may itself be a cause of systemic inflammation. This could be due to the proinflammatory effects of advanced glycation end-points (AGEs). Advanced glycation end-points, the result of interaction of intracellular proteins and decomposing saccharides and polysaccharides, can alter matrix proteins, affect the expression of cytokines and growth by macrophages and mesangial cells, alter expression of inflammatory mediators by endothelial cells (53), and induce apoptosis (54). In addition, expression of the transmembrane receptor for advanced glycation end-points is seen in the lung, preferentially localized to the basal face of type I pneumocytes (55). If DM and hyperglycemia are themselves proinflammatory, impaired glycemic control may cause ventilatory impairment in either an independent or synergistic manner with tobacco smoke.

We have demonstrated an association between glycemic state and reduced lung function. The diagnosis of DM was associated with a lower mean adjusted residual FEV_1 and FVC. This effect was greater in ever smokers than never smokers and was greatest among current smokers, even after adjusting for pack-years of smoking. Overall, after adjusting for sex and pack-years of smoking, there was a progressive fall in residual pulmonary function across quartiles of fasting blood glucose, with a difference of approximately 85 ml in residual FEV_1 and 94 ml in residual FVC from highest to lowest quartile of fasting blood glucose. Although the effect was slightly greater in ever smokers than never smokers, there was no clear difference in the effect of fasting blood glucose across strata of smoking status. Although the diagnosis of diabetes was associated with a slightly increased FEV_1/FVC ratio, suggesting a restrictive pattern of ventilatory impairment, the residual FEV_1/FVC ratio of subjects not on therapy for diabetes fell with the increasing serum glucose concentration. This effect varied between strata of smoking status, with the most striking association among current smokers.

Diabetes has previously been inconsistently associated with spirometric abnormalities in a number of small retrospective cross-sectional studies. Several studies of fewer than 50 subjects with diabetes reported no differences in spirometric measures between type I (10–12), type II (13), or a mixed population of subjects (14) and controls. In contrast, Bell and colleagues (3) observed proportional reductions in FEV_1 and FVC in 28 young individuals with diabetes compared with age- and height-matched control subjects; these changes were more pronounced among those with diabetes who smoked tobacco. Schnack and colleagues (4) compared 31 individuals with type I diabetes who were never smokers to healthy control subjects and found significant reductions in lung function among those with diabetes, especially among those with microalbuminuria; this relationship was stronger for FEV_1 than for FVC. However, Innocenti and

colleagues (5) demonstrated nearly equal reductions in FEV_1 and FVC in 24 insulin-dependent nonsmokers compared with control subjects. Primhak and colleagues (6) observed a reduction in FVC among 88 pediatric individuals with diabetes compared with control subjects that did not correlate with duration of DM.

In these small studies, attempts to characterize the nature of the pulmonary function abnormalities of various groups of individuals with diabetes have produced inconsistent results. Most studies have reported a reduction in diffusion (3, 4, 7, 12, 14, 56) or FVC, either with concomitantly reduced FEV_1 (3, 4) or in isolation (4, 6, 7, 9, 12, 56, 57). Innocenti and colleagues (5) reported an isolated reduction in diffusion among only those with renal dysfunction.

Few larger studies have examined the impact of diabetes on pulmonary function. Cross-sectional analysis of participants in the Copenhagen City Heart Study (58), including 284 subjects with diabetes among 11,763 subjects, demonstrated some impairment of pulmonary function among subjects with diabetes, more pronounced in those treated with insulin. The average FEV_1 and FVC among insulin-treated patients with diabetes were 239 and 334 ml lower than control subjects, respectively, and 122 and 150 ml lower than individuals with diabetes treated with oral agents. In addition, among participants not known to have DM, there was a significant association between elevated plasma glucose and a reduction in lung function. Longitudinal analysis (59) of participants in the Copenhagen City Heart Study, including 326 subjects with diabetes and 9,051 control subjects, demonstrated an association between the new diagnosis of diabetes and impaired pulmonary function; after adjusting for confounders, those individuals who were newly diagnosed with diabetes annually lost 29 ml of FVC and 25 ml of FEV_1 more than control subjects. The Cardiovascular Health Study, in determining reference standards for a healthy population, found diabetes to be significantly associated with a decreased FEV_1 (60). These observations were not duplicated in the analysis of the Rancho Bernardo cohort, in which measures of lung function were not associated with fasting blood glucose (61). However, age differences between these studies and the younger Framingham Offspring Cohort may limit comparison.

Among the subjects included in our analysis, diagnosis of DM was associated with a larger reduction in residual FVC than FEV_1. The consequent larger residual FEV_1/FVC ratio in subjects with diabetes suggests restrictive physiology. In contrast, when those with diabetes on therapy were excluded, higher levels of fasting blood glucose were associated with larger reduction in FEV_1 than FVC. The resulting progressive decrement in level of residual FEV_1/FVC ratio with increasing level of blood sugar suggests that higher fasting blood sugar is associated with more obstructive physiology. When we explored the relationship of the diagnosis of DM to COPD, we found no significant association after adjusting for confounders. The relatively small number of participants with an abnormally low FEV_1/FVC ratio may limit the ability to demonstrate such an association. As described previously here, the existing literature provides an inconsistent picture of the overall nature of the impairment of pulmonary function among those with diabetes, and this study does not provide a definitive answer.

Our observation that decreased lung function is associated with diabetes and level of fasting blood glucose and that this effect appears greater in smokers than nonsmokers adds to a growing body of evidence that diabetes may increase susceptibility to the adverse pulmonary effects of tobacco smoking. This association may offer clues into the pathogenesis of both COPD and DM. It may be that host factors, presumably genetically determined, confer common susceptibility to both impaired glucose tolerance and ventilatory impairment. Alternatively, diabetes or subclinical hyperglycemia may alter the regulation of inflammatory pathways, augmenting inflammatory response in the lung with consequent development of chronic ventilatory impairment. Inflammatory mediators implicated in the pathogenesis of both COPD and diabetes, such as IL-1, IL-6, and tumor necrosis factor, represent the most promising candidates for future investigations.

Our understanding of the pathogenesis of COPD, especially as it relates to the variable risk of disease among those exposed, remains quite limited. Risk factors other than tobacco smoking likely contribute to the pathogenesis of COPD, although little is known about these. Improved understanding of the epidemiology of cardiovascular disease has improved understanding of its pathogenesis; interventions that improve mortality and even reverse the course of the disease have been developed as a consequence. At least in part due to these advances, a decline in the age-adjusted rates of cardiovascular disease has occurred (62). The exploitation of the potential for similar interventions in COPD will require a better understanding of the relationship of COPD to novel risk factors, such as hyperglycemia and diabetes.

References

1. Barnes PJ. Chronic obstructive pulmonary disease. *N Engl J Med* 2000; 343:269–280.
2. Higgins M, Keller J, Becker M, Howatt W, Landis JR, Rotman H, Weg J, Higgins I. An index of risk for obstructive airways disease. *Am Rev Respir Dis* 1982;125:144–151.
3. Bell D, Collier A, Matthews DM, Cooksey EJ, McHardy GJ, Clarke BF. Are reduced lung volumes in IDDM due to defect in connective tissue? *Diabetes* 1988;37:829–831.
4. Schnack C, Festa A, Schwarzmaier-D'Assie A, Haber P, Schernthaner G. Pulmonary dysfunction in type 1 diabetes in relation to metabolic long-term control and to incipient diabetic nephropathy. *Nephron* 1996; 74:395–400.
5. Innocenti F, Fabbri A, Anichini R, Tuci S, Pettina G, Vannucci F, De GL, Seghieri G. Indications of reduced pulmonary function in type 1 (insulin-dependent) diabetes mellitus. *Diabetes Res Clin Pract* 1994;25: 161–168.
6. Primhak RA, Whincup G, Tsanakas JN, Milner RD. Reduced vital capacity in insulin-dependent diabetes. *Diabetes* 1987;36:324–326.
7. Matsubara T, Hara F. The pulmonary function and histopathological studies of the lung in diabetes mellitus. *Nippon Ika Daigaku Zasshi* 1991;58:528–536.
8. Asanuma Y, Fujiya S, Ide H, Agishi Y. Characteristics of pulmonary function in patients with diabetes mellitus. *Diabetes Res Clin Pract* 1985; 1:95–101.
9. Cooper BG, Taylor R, Alberti KG, Gibson GJ. Lung function in patients with diabetes mellitus. *Respir Med* 1990;84:235–239.
10. Schernthaner G, Haber P, Kummer F, Ludwig H. Lung elasticity in juvenile-onset diabetes mellitus. *Am Rev Respir Dis* 1977;116:544–546.
11. Maccioni FJ, Colebatch HJ. Lung volume and distensibility in insulin-dependent diabetes mellitus. *Am Rev Respir Dis* 1991;143:1253–1256.
12. Strojek K, Ziora D, Sroczynski JW, Oklek K. Pulmonary complications of type 1 (insulin-dependent) diabetic patients. *Diabetologia* 1992;35: 1173–1176.
13. Katoh J, Hara Y, Kurusu M, Miyaji J, Narutaki K. Cardiorespiratory function as assessed by exercise testing in patients with non-insulin-dependent diabetes mellitus. *J Int Med Res* 1996;24:209–213.
14. Sandler M, Bunn AE, Stewart RI. Cross-section study of pulmonary function in patients with insulin-dependent diabetes mellitus. *Am Rev Respir Dis* 1987;135:1223–1229.
15. Kannel WB, Feinleib M, McNamara PM, Garrison RJ, Castelli WP. An investigation of coronary heart disease in families: the Framingham Offspring Study. *Am J Epidemiol* 1979;110:281–290.
16. Meigs JB, Ordovas JM, Cupples LA, Singer DE, Nathan DM, Schaefer EJ, Wilson PW. Apolipoprotein E isoform polymorphisms are not associated with insulin resistance: the Framingham Offspring Study. *Diabetes Care* 2000;23:669–674.
17. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications: part 1: diagnosis and classification

of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998;15:539–553.
18. Diabetes mellitus: report of a WHO Study Group. *World Health Organ Tech Rep Ser* 1985;727:1–113.
19. Pauwels RA, Buist AS, Ma P, Jenkins CR, Hurd SS. GOLD Scientific Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: National Heart, Lung, and Blood Institute and World Health Organization Global Initiative for Chronic Obstructive Lung Disease (GOLD): executive summary. *Respir Care* 2001;46:798–825.
20. Anonymous. Standardization of spirometry, 1994 update: American Thoracic Society. *Am J Respir Crit Care Med* 1995;152:1107–1136.
21. Anonymous. Standardization of spirometry: 1987 update: statement of the American Thoracic Society. *Am Rev Respir Dis* 1987;136:1285–1298.
22. Barnes PJ. Mechanisms in COPD: differences from asthma. *Chest* 2000; 117:10S–14S.
23. Anthonisen NR, Connett JE, Kiley JP, Altose MD, Bailey WC, Buist AS, Conway WA Jr, Enright PL, Kanner RE, O'Hara P. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1: the Lung Health Study. *JAMA* 1994;272:1497–1505.
24. Sandford AJ, Chagani T, Weir TD, Connett JE, Anthonisen NR, Pare PD. Susceptibility genes for rapid decline of lung function in the lung health study. *Am J Respir Crit Care Med* 2001;163:469–473.
25. Pelkonen M, Notkola IL, Tukiainen H, Tervahauta M, Tuomilehto J, Nissinen A. Smoking cessation, decline in pulmonary function and total mortality: a 30 year follow up study among the Finnish cohorts of the Seven Countries Study. *Thorax* 2001;56:703–707.
26. Morgan WK, Reger RB. Rise and fall of the FEV(1). *Chest* 2000;118: 1639–1644.
27. Lange P, Parner J, Vestbo J, Schnohr P, Jensen G. A 15-year follow-up study of ventilatory function in adults with asthma. *N Engl J Med* 1998; 339:1194–1200.
28. Xu X, Dockery DW, Ware JH, Speizer FE, Ferris BG Jr. Effects of cigarette smoking on rate of loss of pulmonary function in adults: a longitudinal assessment. *Am Rev Respir Dis* 1992;146:1345–1348.
29. Sherman CB, Xu X, Speizer FE, Ferris BG Jr, Weiss ST, Dockery DW. Longitudinal lung function decline in subjects with respiratory symptoms. *Am Rev Respir Dis* 1992;146:855–859.
30. Bosse R, Sparrow D, Garvey AJ, Costa PT Jr, Weiss ST, Rowe JW. Cigarette smoking, aging, and decline in pulmonary function: a longitudinal study. *Arch Environ Health* 1980;35:247–252.
31. Kerstjens HA, Rijcken B, Schouten JP, Postma DS. Decline of FEV1 by age and smoking status: facts, figures, and fallacies. *Thorax* 1997; 52:820–827.
32. Dahl M, Tybjaerg-Hansen A, Vestbo J, Lange P, Nordestgaard BG. Elevated plasma fibrinogen associated with reduced pulmonary function and increased risk of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;164:1008–1011.
33. Stockley RA, O'Brien C, Pye A, Hill SL. Relationship of sputum color to nature and outpatient management of acute exacerbations of COPD. *Chest* 2000;117:1638–1645.
34. Dev D, Wallace E, Sankaran R, Cunniffe J, Govan JR, Wathen CG, Emmanuel FX. Value of C-reactive protein measurements in exacerbations of chronic obstructive pulmonary disease. *Respir Med* 1998; 92:664–667.
35. Soler N, Ewig S, Torres A, Filella X, Gonzalez J, Zaubet A. Airway inflammation and bronchial microbial patterns in patients with stable chronic obstructive pulmonary disease. *Eur Respir J* 1999;14:1015–1022.
36. Zhu J, Majumdar S, Qiu Y, Ansari T, Oliva A, Kips JC, Pauwels RA, De Rose V, Jeffery PK. Interleukin-4 and interleukin-5 gene expression and inflammation in the mucus-secreting glands and subepithelial tissue of smokers with chronic bronchitis: lack of relationship with CD8(+) cells. *Am J Respir Crit Care Med* 2001;164:2220–2228.
37. Bhowmik A, Seemungal TA, Sapsford RJ, Wedzicha JA. Relation of sputum inflammatory markers to symptoms and lung function changes in COPD exacerbations. *Thorax* 2000;55:114–120.
38. Aaron SD, Angel JB, Lunau M, Wright K, Fex C, Le Saux N, Dales RE. Granulocyte inflammatory markers and airway infection during acute exacerbation of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;163:349–355.
39. Keatings VM, Collins PD, Scott DM, Barnes PJ. Differences in interleukin-8 and tumor necrosis factor-alpha in induced sputum from patients with chronic obstructive pulmonary disease or asthma. *Am J Respir Crit Care Med* 1996;153:530–534.
40. Sandford AJ, Chagani T, Weir TD, Connett JE, Anthonisen NR, Pare PD. Susceptibility genes for rapid decline of lung function in the lung health study. *Am J Respir Crit Care Med* 2001;163:469–473.
41. Sakao S, Tatsumi K, Igari H, Shino Y, Shirasawa H, Kuriyama T. Association of tumor necrosis factor alpha gene promoter polymorphism with the presence of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;163:420–422.
42. Retamales I, Elliott WM, Meshi B, Coxson HO, Pare PD, Sciurba FC, Rogers RM, Hayashi S, Hogg JC. Amplification of inflammation in emphysema and its association with latent adenoviral infection. *Am J Respir Crit Care Med* 2001;164:469–473.
43. Jenson AB, Dobersen MJ. Etiopathology of diabetes mellitus. *Perspect Pediatr Pathol* 1982;7:167–184.
44. Ford ES, Cogswell ME. Diabetes and serum ferritin concentration among US adults. *Diabetes Care* 1999;22:1978–1983.
45. Duncan BB, Schmidt MI, Offenbacher S, Wu KK, Savage PJ, Heiss G. Factor VIII and other hemostasis variables are related to incident diabetes in adults: the Atherosclerosis Risk in Communities (ARIC) Study. *Diabetes Care* 1999;22:767–772.
46. Schmidt MI, Duncan BB, Sharrett AR, Lindberg G, Savage PJ, Offenbacher S, Azambuja MI, Tracy RP, Heiss G. Markers of inflammation and prediction of diabetes mellitus in adults (Atherosclerosis Risk in Communities study): a cohort study. *Lancet* 1999;353:1649–1652.
47. Rodriguez-Moran M, Guerrero-Romero F. Increased levels of C-reactive protein in noncontrolled type II diabetic subjects. *J Diabetes Complications* 1999;13:211–215.
48. Bloomgarden ZT. American Diabetes Association Annual Meeting, 1999: more on cardiovascular disease. *Diabetes Care* 2000; 23:845–852.
49. Moller DE. Potential role of TNF-alpha in the pathogenesis of insulin resistance and type 2 diabetes. *Trends Endocrinol Metab* 2000;11: 212–217.
50. Sargeant LA, Khaw KT, Bingham S, Day NE, Luben RN, Oakes S, Welch A, Wareham NJ. Cigarette smoking and glycaemia: the EPIC-Norfolk Study: European Prospective Investigation into Cancer. *Int J Epidemiol* 2001;30:547–554.
51. Will JC, Galuska DA, Ford ES, Mokdad A, Calle EE. Cigarette smoking and diabetes mellitus: evidence of a positive association from a large prospective cohort study. *Int J Epidemiol* 2001;30:540–546.
52. Arnalich F, Hernanz A, Lopez-Maderuelo D, Pena JM, Camacho J, Madero R, Vazquez JJ, Montiel C. Enhanced acute-phase response and oxidative stress in older adults with type II diabetes. *Horm Metab Res* 2000;32:407–412.
53. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. *Nature* 2001;414:813–820.
54. Roehlecke C, Kuhnt AK, Fehrenbach H, Werner C, Funk RH, Kasper M. Resistance of L132 lung cell clusters to glyoxal-induced apoptosis. *Histochem Cell Biol* 2000;114:283–292.
55. 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* 1998;44:1147–1157.
56. Asanuma Y, Fujiya S, Ide H, Agishi Y. Characteristics of pulmonary function in patients with diabetes mellitus. *Diabetes Res Clin Pract* 1985;1:95–101.
57. Heimer D, Brami J, Lieberman D, Bark H. Respiratory muscle performance in patients with type 1 diabetes. *Diabet Med* 1990;7:434–437.
58. Lange P, Groth S, Kastrup J, Mortensen J, Appleyard M, Nyboe J, Jensen G, Schnohr P. Diabetes mellitus, plasma glucose and lung function in a cross-sectional population study. *Eur Respir J* 1989;2:14–19.
59. Lange P, Groth S, Mortensen J, Appleyard M, Nyboe J, Schnohr P, Jensen G. Diabetes mellitus and ventilatory capacity: a five year follow-up study. *Eur Respir J* 1990;3:288–292.
60. Enright P, Kronmal R, Higgins M, Schenker M, Haponik E. Spirometry reference values for women and men 65 to 85 years of age. *Am Rev Respir Dis* 1993;147:125–133.
61. Barrett-Connor E, Frette C. NIDDM, impaired glucose tolerance, and pulmonary function in older adults: the Rancho Bernardo Study. *Diabetes Care* 1996;19:1441–1444.
62. Luepker R. Epidemiology of atherosclerotic diseases in population groups. In: Pearson T, Criqui M, Luepker R, Oberman A, Winston M, editors. Primer in preventive cardiology. Dallas, TX: American Heart Association; 1994. p. 1–11.