Prospective Association Between Lung Function and the Incidence of Diabetes

Findings from the National Health and Nutrition Examination Survey Epidemiologic Follow-Up Study

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OBJECTIVE — To determine whether impaired pulmonary function is a significant predictor of the incidence of diabetes.

RESEARCH DESIGN AND METHODS — Using data from the National Health and Nutrition Examination Survey Epidemiologic Follow-Up Study, a cohort study of a representative sample of U.S. adults, we examined the prospective associations between pulmonary function and incidence of diabetes. Our analyses included 4,830 U.S. men and women aged 25–74 years who had a baseline interview and examination (including spirometry) from 1971 through 1975 and were followed through 1992–1993. Incident diabetes (n = 443) was based on self- or proxy reports, hospitalization, or death certificates.

RESULTS — After multiple adjustment, forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), percentage of predicted FEV_1, and percentage of predicted FVC were significantly and inversely associated with the incidence of diabetes, but the ratio of FEV_1 to FVC was not. Obstructive lung disease (defined by the Global Initiative for Chronic Obstructive Lung Disease classification) was not significantly associated with the incidence of diabetes, but restrictive lung disease was (hazard ratio = 1.45, 95% CI 1.04–2.03). The association did not differ significantly by smoking status.

CONCLUSIONS — Although several prospective studies have found that impaired pulmonary function may increase the risk for developing diabetes, additional research is needed to better understand these relationships and their possible implications.

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Lung function may predict the development of insulin resistance or diabetes (1–4). In the Normative Aging Study (2), forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), and maximal mid-expiratory flow rate (MMEF) were associated with insulin resistance over a period of 20.9 years. In addition, three Swedish studies with follow-ups of 6–13.9 years found that impaired lung function predicted the development of diabetes (1,3,4). In all three studies, low levels of FVC were associated with increased risk; in one, FEV_1 was inversely associated with incidence.

To provide another perspective on the possible association between lung function and incidence of diabetes, we analyzed data from the National Health and Nutrition Examination Survey Epidemiologic Follow-Up Study (NHEFS), a cohort study. We studied possible prospective associations between measures of pulmonary function, including FEV_1, FVC, percentage of predicted FEV_1, percentage of predicted FVC, and the ratio of FEV_1 to FVC, and incidence of diabetes. In addition, we examined the association between different forms of lung disease—chronic obstructive pulmonary disease as classified by the Global Initiative for Chronic Obstructive Lung Disease (GOLD), restrictive lung disease, and respiratory symptoms—and the incidence of diabetes.

RESEARCH DESIGN AND METHODS

In 1971–1975, a representative sample of the U.S. civilian population received a baseline examination and interview as part of the first National Health and Nutrition Examination Survey (NHANES I). The sample was selected using a complex sampling design so that results would be representative of the noninstitutionalized civilian population. Participants aged 25–74 years (n = 14,407) were followed up through 1992–1993 and thus became part of the NHEFS. Details of the NHANES I and the NHEFS are available elsewhere (5–11).

During the follow-up study, up to four attempts were made to contact participants or their surrogates in person and, during later follow-ups, by telephone as well; this occurred in 1982–1984, 1986 (only participants aged ≥55 years), 1987, and 1992–1993. Permission was requested to obtain hospital records. Deaths were identified through searches of the National Death Index, enrollee files of the Health Care Financing Administration, and other tracing mechanisms. A participant was considered deceased only if a death certificate had been received or a proxy interview had been

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Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; MMEF, maximal mid-expiratory flow rate; NHANES I, National Health and Nutrition Examination Survey I; NHEFS, National Health and Nutrition Examination Survey Epidemiologic Follow-Up Study; RLD, restrictive lung disease.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

completed to verify the death. Death certificates have been obtained for 97% of participants who died through 1993.

Participants had incident diabetes if *1*) during any of the four follow-up contacts, they reported that they had ever been told by a doctor that they had diabetes; *2*) a hospitalization record listed the ICD-9-CM code 250 as any 1 of 10 diagnoses on the hospital discharge sheet; or *3*) the death certificate included the ICD-9 code 250. Participants who reported that they had diabetes were asked the year of disease onset. The midpoint of that year was designated as the date of onset. For participants who did not report a year of onset, we assigned the midpoint between the last date of known contact and the date of the most recent interview. The date of onset was chosen as the date the condition was first reported or recorded on institutional records or death certificates.

Participants who reported at baseline that they had diabetes were considered prevalent cases, as were participants who during later follow-up contacts reported a date of onset that occurred in the year of their baseline interview or earlier, and they were excluded from the analyses.

The pulmonary symptoms included in the analysis, which were used to define an asymptomatic subset of the population to calculate equations for lung function and define a subset of the cohort with only respiratory symptoms, were cough (defined as a positive response to "Have you ever had a cough first thing in the morning in the winter?" or "Have you ever had a cough first thing in the morning in the summer?"), sputum (defined as a positive response to "Have you ever had any phlegm from your chest first thing in the morning in the winter?" or "Have you ever had any phlegm from your chest first thing in the morning in the summer?"), and wheeze (defined as a positive response to "Have you ever had wheezy or whistling sounds in your chest?").

Spirometry was obtained by using an Ohio Medical Instruments 800 spirometer. The procedures used have been documented previously (6). Individuals were excluded from this analysis if they either did not perform spirometry or had results that were not reliable. We included data from participants who did not have "reproducible" measures (12). (To be reproducible the FEV_1 and FVC from two reliable measurements had to be within 5% for most participants.) Values used in this analysis included the FVC, FEV_1, and the FEV_1-to-FVC ratio. We determined predicted values of FEV_1 and FVC by performing linear regression (stratified by sex and by using age and height as predictors) on a subgroup of participants who were white never smokers who did not report respiratory symptoms or physician-diagnosed lung disease. The results from these regression models (men: $FEV_1 = -4.3806 - \text{age} \times 0.031767 + \text{height} \times 0.13827$, $r^2 = 0.626$, and $FVC = -7.49837 - \text{age} \times 0.03071 + \text{height} \times 0.19794$, $r^2 = 0.589$; women: $FEV_1 = -0.75683 - \text{age} \times 0.02475 + \text{height} \times 0.07131$, $r^2 = 0.539$, and $FVC = -2.2086 - \text{age} \times 0.02394 + \text{height} \times 0.10381$, $r^2 = 0.451$) were applied to the data from all participants to obtain predicted values of FEV_1 and FVC. We used an adjustment factor of 0.88 to estimate predicted values for African-American participants.

Using the percentage of predicted FEV_1, percentage of predicted FVC, the FEV_1-to-FVC ratio, and the presence of respiratory symptoms, we used a modification of the GOLD criteria to classify participants as having chronic obstructive pulmonary disease (COPD). Participants had mild COPD if they had a FEV_1-to-FVC ratio <0.70 and a percentage of predicted FEV_1 $\geq 80\%$). Because too few participants had severe or very severe COPD, we combined them and participants who had moderate COPD into a single group (FEV_1-to-FVC ratio <0.70 and percentage of predicted FEV_1 $<80\%$). In addition, we assigned participants as having restrictive lung disease (RLD) (FEV_1-to-FVC ratio ≥ 0.70 and FVC $<80\%$ predicted), symptoms only (presence of respiratory symptoms in the absence of any lung function abnormality), and no lung disease. As per GOLD criteria, we assigned participants who met the criteria for having both COPD and RLD to the COPD group.

Covariates included age, race or ethnicity (nonwhite or white), education (years), cigarette smoking (never, former, or current), systolic blood pressure (mmHg), use of antihypertensive medication (yes/no), serum cholesterol concentration (mg/dl), BMI (kg/m^2), alcohol consumption (0, 1–2, ≥ 3 drinks/day), recreational exercise (much, moderate, little, or no exercise), and nonrecreational exercise (very active, moderately active, or quite inactive).

Two-sample comparisons of categorical and continuous variables were made by using χ^2 tests and *t* tests, respectively. Baseline characteristics and age-adjusted incidence rates were directly standardized to the age distribution from the 2000 census. Person-time was calculated for each participant from the time of entry into the study until one of the following conditions occurred: the participant developed diabetes (1), the participant died or left the study (2), or follow-up was completed in 1992/1993 (3). The independent association between pulmonary function parameters or lung disease, as assessed with the GOLD classification scheme, at baseline and incidence of diabetes was examined using proportional hazard models. To account for the complex sampling design, SUDAAN software was used in all analyses except for the evaluation of proportionality assumptions, which was done with SAS. Analyses showed that the proportionality assumption was satisfied.

RESULTS — Of the 14,407 participants in the NHEFS, 6,913 were included in the cardiorespiratory subset and were thus eligible for spirometry. After participants who were lost to follow-up were excluded, 6,672 remained. Excluding participants with prevalent diabetes reduced the sample size to 6,260, and further exclusion of participants with insufficient data to establish whether they developed diabetes during follow-up left 6,112 participants. After excluding pregnant women, 6,069 participants remained, and additional elimination of participants with missing data for covariates left 5,913 for analysis. Of this group, 4,830 participants had pulmonary function tests available; this group thus constituted our final analytic sample. Of the group, 443 developed diabetes during the course of the study.

Participants who developed diabetes were older than those who remained free of the disease (Table 1). After adjustment for age, participants who developed diabetes were less likely to be white, had fewer years of education, had higher systolic blood pressure, were more likely to be taking antihypertensive medication, were heavier, and were more likely to be sedentary than participants who remained free of diabetes. In addition, par-

Table 1—*Selected characteristics at baseline examination among adults aged 25–74 years by diabetes status, NHEFS, 1971–1976 to 1992–1993*

	Incident diabetes		
	Yes	No	*P*
n	443	4,387	
Age (years)	50.0 ± 0.8	45.2 ± 0.3	<0.001
Men (%)	49.7 ± 2.8	47.4 ± 0.9	0.438
White (%)	83.9 ± 2.3	91.0 ± 0.7	0.002
Education (years)	11.0 ± 0.2	11.9 ± 0.1	<0.001
Current smoker (%)	41.2 ± 3.1	38.3 ± 0.9	0.344
Systolic blood pressure (mmHg)	136.7 ± 1.4	128.6 ± 0.5	<0.001
Antihypertensive medication (%)	18.0 ± 2.7	11.1 ± 0.6	0.013
Cholesterol concentration (mg/dl)	222.1 ± 2.8	220.3 ± 1.0	0.545
BMI (kg/m^2)	29.7 ± 0.4	25.1 ± 0.1	<0.001
Alcohol intake (drinks/day)	0.7 ± 0.1	0.7 ± 0.0	0.692
Recreational exercise (% little or no exercise)	45.5 ± 3.3	37.9 ± 1.3	0.021
Nonrecreational activity (% quite inactive)	9.3 ± 1.8	9.3 ± 0.5	0.982
FEV_1 (% predicted)	91.9 ± 1.0	95.8 ± 0.5	<0.001
FVC (% predicted)	93.6 ± 1.0	97.9 ± 0.5	<0.001
FEV_1-to-FVC ratio	77.7 ± 0.4	77.3 ± 0.1	0.347
Respiratory health (%)			<0.001
COPD (moderate or severe)	7.5 ± 1.3	8.0 ± 0.5	
COPD (mild)	4.2 ± 0.9	7.6 ± 0.5	
Symptoms	19.0 ± 2.3	15.8 ± 0.8	
RLD	13.6 ± 1.7	7.4 ± 0.5	
Normal	55.7 ± 3.2	61.1 ± 1.0	

Data are age-adjusted means ± SE or percent ± SE.

ticipants who developed diabetes had lower mean percentage of predicted FEV_1 and percentage of predicted FVC. The groups had similar FEV_1-to-FVC ratios. Finally, participants who developed diabetes were more likely to have restrictive lung disease at baseline.

The FEV1, FVC, percentage of predicted FEV_1, and percentage predicted FVC were significantly and inversely associated with the incidence of diabetes in fully adjusted proportional hazards regression models (Table 2). In contrast, the ratio of FEV_1 to FVC was not.

In unadjusted models, participants with moderate or severe COPD or RLD were at increased risk for developing diabetes (Table 3). In addition, participants with symptoms had a borderline increased risk. After age adjustment, only participants with symptoms or RLD were at increased risk for developing diabetes. After full adjustment, however, only participants with RLD were at increased risk for developing diabetes (hazard ratio [HR] 1.45, 95% CI 1.04–2.03). Additional adjustment for BMI^2 did not materially affect the HR. Risk estimates did not differ by sex ($P = 0.324$ for the interaction between sex and lung status) or race or ethnicity ($P = 0.261$ for the interaction between race or ethnicity and lung status). In addition, age (HR per year 1.03, 1.02–1.04), sex (HR for men versus women 1.42, 1.08–1.88), education (HR per year 0.96, 0.92–1.00), smoking status (HR for current versus never smoking 1.36, 1.06–1.76), and BMI (HR per kg/m^2 1.12, 1.10–1.14) were significantly associated with diabetes in the fully adjusted proportional hazards regression model. Adjusting for the number of pack years smoked instead of the three levels of smoking had very little effect on the HR for RLD. However, using pack years reduced the sample size because of missing data. To maximize sample size, we used smoking status as a three level variable.

When we limited the proportional hazards model to participants who had never smoked (190 participants developed diabetes in this group of 2,013), the multiple-adjusted HRs were 1.38 (95% CI 0.67–2.84) for participants with moderate to severe COPD, 0.87 (0.47–1.63) for participants with mild COPD, 1.18 (0.71–1.94) for participants with respiratory symptoms, and 1.58 (0.94–2.66) for participants with RLD. Among participants who were current smokers (148 participants developed diabetes in this group of 1,750), the multiple-adjusted HRs were 1.13 (0.68–1.86) for participants with moderate to severe COPD, 0.53 (0.22–1.29) for participants with mild COPD, 1.10 (0.67–1.81) for participants with respiratory symptoms, and 1.69 (0.89–3.21) for participants with RLD. Among participants who were former smokers (105 participants developed diabetes in this group of 1,067), the multiple-adjusted HRs were 0.45 (0.20–1.00) for participants with moderate to severe COPD, 0.57 (0.22–1.44) for participants with mild COPD, 0.77 (0.41–1.44) for participants with respiratory symptoms, and 1.35 (0.73–2.50) for participants with RLD. The interaction between smoking status and pulmonary status was not significant ($P = 0.502$).

CONCLUSIONS — Because associations between lung disease using the GOLD classification and the incidence of diabetes had not been studied previously, our analyses provide new and unique in-

Table 2—*Results from proportional hazards analysis of parameters from spirometry and incidence of diabetes (443 events) among 4,830 participants aged 25–74 years, NHEFS 1971–1975 to 1992–1993*

Spirometry parameter	Regression coefficient ± SE*	*P*
FEV_1 (ml)	−0.00036 ± 0.00009	<0.001
FVC (ml)	−0.00032 ± 0.00008	<0.001
Ratio of FEV_1 to FVC	0.22781 ± 0.77576	0.769
% predicted FEV_1	−0.00874 ± 0.00295	0.003
% predicted FVC	−0.01032 ± 0.00342	0.003

*Adjusted for age, sex, race or ethnicity, education, smoking status, systolic blood pressure, use of antihypertensive medication, cholesterol concentration, BMI, alcohol use, recreational exercise, and nonrecreational activity.

Table 3—*Incidence rates and HRs for diabetes by pulmonary conditions among participants aged 25–74 years, NHEFS, 1971–1975 to 1992–1993*

Pulmonary conditions	No. of cases	Person-years	Unadjusted incidence per 100,000 person-years*	Age-adjusted incidence per 100,000 person-years*	HR (95% CI)		
					Unadjusted	Age-adjusted	Multiple-adjusted†
COPD (moderate or severe)	46	5,647	711	604	1.54 (1.03–2.30)	1.23 (0.84–1.81)	1.02 (0.68–1.53)
COPD (mild)	29	5,929	388	330	0.83 (0.51–1.35)	0.66 (0.40–1.10)	0.66 (0.39–1.12)
Symptoms	78	12,221	616	679	1.31 (0.98–1.76)	1.34 (1.00–1.81)	1.06 (0.76–1.48)
RLD	68	6,076	1,106	1047	2.38 (1.74–3.27)	2.04 (1.47–2.81)	1.45 (1.04–2.03)
Normal	222	47,466	475	516	1.00	1.00	1.00
P for overall test‡					<0.001	<0.001	0.032

Of 4,830 in the total sample, 443 people developed diabetes. *Estimate calculated using sampling weights. †Adjusted for age, sex, race or ethnicity, education, smoking status, systolic blood pressure, use of antihypertensive medication, cholesterol concentration, BMI, alcohol use, recreational exercise, and nonrecreational activity. ‡Wald χ^2 test.

formation about potential links between lung disease and diabetes. Our study of a representative sample of the U.S. population indicates that adults with RLD may be at increased risk for developing diabetes. Furthermore, as have other studies, we found that FEV_1 and FVC are significantly associated with the incidence of diabetes. However, we did not find that the ratio of these two parameters, which had not been previously studied and are associated with obstructive lung diseases, predicted the development of diabetes.

Several prospective studies have now shown that parameters of pulmonary function predict the onset of diabetes. In a study of 4,637 nondiabetic Swedish men (1) aged 48 years, 116 men who went on to develop diabetes over 6 years had 10% lower mean vital capacity at baseline than men who did not develop diabetes. In the Normative Aging Study (2), 1,050 nondiabetic men aged 21–80 years were followed for an average of 20.9 years. FVC, FEV_1, and MMEF were all inversely associated with the development of insulin resistance as measured with surrogate measures (2). In the Men Born in 1914 Study (3), 382 nondiabetic men had spirometry performed when they were 55 years of age. After 13 years of follow-up, 15 had developed diabetes. FEV_1 and FVC were inversely associated with incidence of diabetes. In the Malmo Preventive Study (4), 1,436 nondiabetic men aged 35–52 years, of whom 144 developed diabetes, were followed for 13.9 years, and 896 nondiabetic women aged 38–57 years, of whom 42 developed diabetes, were followed for 9.4 years. The percentage of predicted FVC was inversely associated with the incidence of diabetes.

The findings from these prospective studies may indicate that early in the course of diabetes, before it is diagnosed, lung function changes. If, in effect, the development of diabetes impairs lung function, the changes could be seen as risk markers rather than risk factors for diabetes. However, inflammation is present in obstructive and RLD (13), and several studies have shown that various indicators of inflammation predict the development of diabetes (14–19), although a couple of studies failed to find a significant association (20,21). Thus, inflammation associated with pulmonary disorders could conceivably contribute to the development of diabetes. If so, abnormal pulmonary function or lung disease could act as a risk factor for diabetes.

Several limitations of the present study merit mentioning. The incidence of diabetes was established from self-report, hospitalization discharge, and death certificates, all of which provide less rigorous definitions of diabetes than oral glucose tolerance tests or fasting glucose concentrations. If the resulting misclassification was nondifferential, the associations were most likely underestimated. Nevertheless, end points based on these data sources are commonly used, and known risk factors for diabetes, such as excess weight, are strongly associated with diabetes defined by using these data sources. An additional limitation was that participants with type 1 diabetes could not be distinguished from those with type 2 diabetes. However, the overwhelming majority of people who develop newly diagnosed diabetes after age 30 years have type 2 diabetes. We also did not have total lung capacity available to classify people according to the strictest criteria for RLD.

Our results may have been a spurious finding. The inability to adjust for all relevant confounding variables or residual confounding could have accounted for our results. Some relevant factors include occupation, birth weight, body weight distribution, and medication use, such as corticosteroid use. Furthermore, we cannot dismiss the possibility that detection or diagnostic bias may explain our findings. People who had abnormal pulmonary function tests may have seen a doctor more frequently during the follow-up period, thus having an increased opportunity to have diabetes diagnosed. If so, such bias must have affected people with chronic obstructive pulmonary disease and RLD differentially because we did not find a significant association between chronic obstructive pulmonary disease and diabetes. Also, RLD may have represented an unknown factor that was truly associated with the incidence of diabetes.

Conceivably, abnormal lung function at baseline may have been associated with worsening obesity rather than diabetes. Unraveling the complexities of such an association would require the availability of anthropometric data at various points in time during the follow-up period, especially at the time of diagnosis of diabetes. Such data were not available for the NHEFS. Other studies in which participants were periodically examined might be able to assess such an explanation.

In conclusion, we found that FEV_1, FVC, percentage of predicted FEV_1, and

percentage of predicted FVC were inversely associated with the risk of developing diabetes in a representative cohort of U.S. men and women, but the FEV_1-to-FVC ratio was not. Furthermore, RLD but not COPD was associated with a moderate increase in the risk of diabetes. Our results are consistent with results from four other prospective studies suggesting that abnormal lung function is associated with an increased incidence of diabetes. Even so, the association between lung disease and the development of diabetes requires further study. Possible mechanisms that link impaired lung function to diabetes also need clarification.

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