

## Lung Function and Glucose Metabolism: An Analysis of Data from the Third National Health and Nutrition Examination Survey

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Although people with diabetes have decreased lung function, the dose-response relation between measures of glucose control and lung function in nondiabetic people is not known. The authors used data from the Third National Health and Nutrition Examination Survey (1988–1994) to investigate the relation between glucose tolerance test response and other measures of glucose homeostasis and lung function in an adult population without a clinical diagnosis of diabetes. Plasma glucose level 2 hours after oral administration of 75 g of glucose was inversely related to forced expiratory volume in 1 second (FEV<sub>1</sub>), with a difference of –144.7 ml (95% confidence interval: –231.9, –57.4) for persons in the highest quintile of postchallenge glucose compared with the lowest. Similar inverse associations with FEV<sub>1</sub> were found for other measures of glucose autoregulation. Lung function did not appear to be related to fasting glucose level. Similar associations were seen for forced vital capacity (FVC) but not for the FEV<sub>1</sub>:FVC ratio. In the total study population, persons with previously diagnosed diabetes had an FEV<sub>1</sub> 119.1 ml (95% confidence interval: –161.5, –76.6) lower than persons without diabetes. This effect was greater in those with poorly controlled diabetes. These findings suggest that impaired glucose autoregulation is associated with impaired lung function.

glucose; hemoglobin A, glycosylated; insulin; lung; respiratory function tests

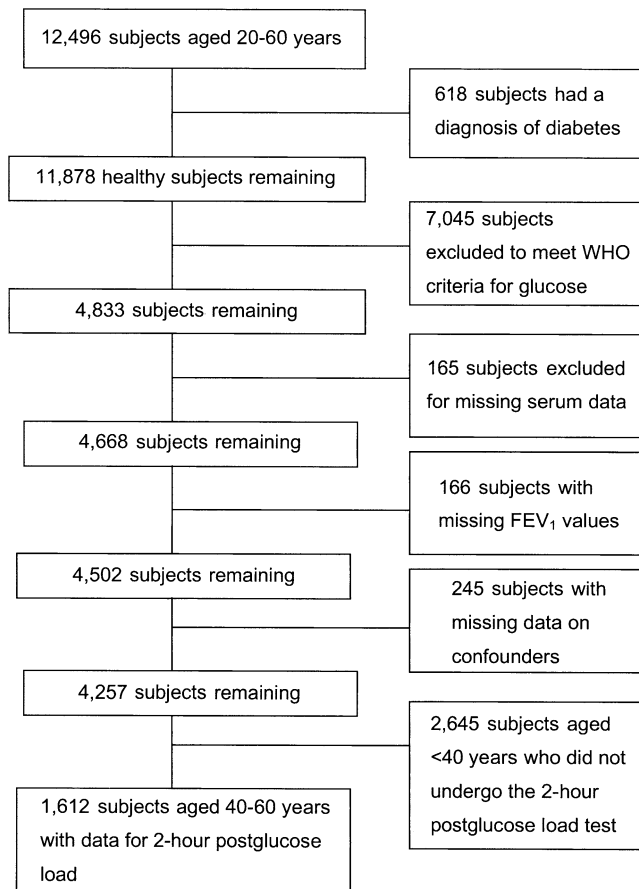
Abbreviations: CI, confidence interval; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; NHANES III, Third National Health and Nutrition Examination Survey.

Chronic obstructive pulmonary disease affects up to 24 million people in the United States and is a major cause of morbidity and mortality (1). Chronic obstructive pulmonary disease is characterized by increased respiratory symptoms such as cough and phlegm and obstructive airways disease, as defined by reduced forced expiratory volume in 1 second (FEV<sub>1</sub>) and a reduced ratio between FEV<sub>1</sub> and forced vital capacity (FVC) (2). Cigarette smoking is the main risk factor for chronic obstructive pulmonary disease, but other nutritional and environmental factors may be important, including those acting early in life, such as low birth weight. Diabetes mellitus and insulin resistance (3–17) have been independently associated with impaired lung function, but what is not known is the dose-response relation between

lung function and response to an oral glucose load in persons with no clinical diagnosis of diabetes.

The prevalence of smoking is declining and that of diabetes is increasing, so it is important to understand the effects of other exposures that may negatively affect lung function. For this reason, we used data from the Third National Health and Nutrition Examination Survey (NHANES III) in a population without a diagnosis of diabetes to investigate the relation between response to a glucose tolerance test and lung function as measured by FEV<sub>1</sub> and the FEV<sub>1</sub>:FVC ratio. We hypothesized that an increase in markers of impaired glycemic control would be associated with a reduction in both FEV<sub>1</sub> and FEV<sub>1</sub>:FVC ratio.

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**FIGURE 1.** Flow diagram for selection of study subjects, Third National Health and Nutrition Examination Survey, 1988–1994. Of the 7,045 subjects excluded to meet World Health Organization (WHO) criteria for glucose tolerance testing, 79% of those who did not meet the WHO criteria were excluded for having an afternoon or evening examination, and the remaining 21% were excluded because of missing data on the time of examination or the period of fasting. FEV<sub>1</sub>, forced expiratory volume in 1 second.

## MATERIALS AND METHODS

We used data from NHANES III, a survey designed to examine the health and nutrition of a randomly selected sample of the noninstitutionalized US population. The survey was conducted between 1988 and 1994. Full details on the survey design and examination procedure have been published by the National Center for Health Statistics (18). All adults aged 20–60 years were eligible for inclusion in the analyses. In the main analysis, persons with a known diagnosis of diabetes (defined as a physician's diagnosis or the regular use of diabetic medications) were excluded, as were those with missing data for lung function, plasma glycemic markers, and potentially confounding variables (figure 1). However, persons who had undiagnosed diabetes, as demonstrated by their fasting plasma glucose level or glucose tolerance test response, were included in the study population. In addition, to comply with standardized

procedures for the measurement of fasting plasma glucose level and glucose tolerance testing (19), we included in these analyses only those participants who had undergone examination in the morning and had fasted for 8 hours or more.

## Data collection

Blood samples were obtained for biochemical assays, and anthropometric measurements were taken, including measurement of height and weight and spirometric factors (including FEV<sub>1</sub> and FVC), using standardized techniques. We extracted data on various markers of glucose regulation, including levels of fasting glucose, glycosylated hemoglobin (hemoglobin A1c), insulin, and C-peptide and, for people over age 40 years, results of oral glucose tolerance testing, in which the subject's initial plasma glucose level was measured at baseline and 2 hours after oral administration of 75 g of glucose (Dextol™ or Trutol™). Insulin resistance was calculated from the measurements by means of a formula devised for use in epidemiologic studies: fasting glucose (mmol/liter) × fasting insulin (μU/ml)/25 (20). A detailed description of laboratory methods has been published elsewhere (21).

## Statistical analyses

The main population studied was persons with no clinical diagnosis of diabetes. We also studied a larger population including persons with a clinical diagnosis of diabetes to assess the impact of diabetes on lung function. Using self-reported information on smoking history, we classified subjects as never smokers, ex-smokers, or current smokers and quantified total cigarette smoking in pack-years. We modeled measures of lung function with adjustment for age, sex, height, smoking (status and pack-years), and race/ethnicity to derive the most parsimonious model that minimized variance. We examined a variety of more complex models for lung function that included higher-order variables for age, height, pack-years of smoking, and body mass index (weight (kg)/height (m)<sup>2</sup>), including interaction terms, but these did not improve the fit of the model; therefore, we chose the simplest model.

Glycemic markers were arbitrarily categorized into quintiles, and the relations between measures of glycemic status and lung function were explored using multiple linear regression. We fitted the models with quintiles of glycemic markers as both ordered and unordered factors and compared the two models for evidence of departure from linearity. The *p* value for linear trend is presented where there was no departure from linearity, and the *p* value from a test of heterogeneity is presented where the data demonstrated evidence of departure from linearity. Many of the markers demonstrated nonlinear relations; therefore, the results are presented in quintiles. We also divided the fasting blood glucose values according to the World Health Organization definitions of normal glucose tolerance, impaired glucose tolerance, and diabetes (19). Normal values for fasting plasma glucose are those less than 110 mg/dl; impaired fasting glucose values are 110–125.99 mg/dl; and

**TABLE 1. Demographic characteristics of the study population and of subjects excluded from the study, Third National Health and Nutrition Examination Survey, 1988–1994**

Characteristic	Included subjects (n = 4,257)			Excluded subjects* (n = 8,239)		
	Mean (SD)†	No.	%	Mean (SD)	No.	%
Sex						
Male		1,943	45.6		3,899	47.3
Female		2,314	54.4		4,340	52.7
Age (years)	37.0 (11.2)			37.5 (11.4)		
Smoking status						
Never smoker		2,225	52.3		4,020	48.8
Ex-smoker		784	18.4		1,587	19.3
Current smoker		1,248	29.3		2,626	31.9
Race/ethnicity						
Non-Hispanic White		1,523	35.8		2,756	33.5
Non-Hispanic Black		1,270	29.8		2,609	31.7
Mexican-American		1,288	30.3		2,508	30.4
Other		176	4.1		366	4.4
Height (cm)	167.6 (9.7)			166.3 (9.9)		
Body mass index‡	27.0 (5.8)			27.3 (6.3)		
Waist:hip ratio	0.90 (0.08)			0.90 (0.09)		
FEV <sub>1</sub> †	3.27 (0.82)			3.24 (0.95)		
FVC†	4.06 (1.00)			4.01 (1.03)		
FEV <sub>1</sub> :FVC ratio	0.81 (0.08)			0.81 (0.08)		

\* Data were missing for some excluded subjects.

† SD, standard deviation; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity.

‡ Weight (kg)/height (m)<sup>2</sup>.

values equal to or above 126 mg/dl indicate diabetes. The normal values for plasma glucose 2 hours after a 75-g oral glucose challenge are those less than 140 mg/dl; values for impaired glucose tolerance are 140–199.99 mg/dl; and values equal to or above 200 mg/dl indicate diabetes. The impact of these clinical definitions of impaired glycemic control on FEV<sub>1</sub>, FVC, and FEV<sub>1</sub>:FVC ratio was examined. We examined a number of confounding factors, such as body mass index, waist:hip ratio, poverty index ratio, and levels of serum triglycerides, serum antioxidants, and C-reactive protein (fitted as continuous or categorical variables as appropriate), to determine whether they altered the regression coefficients.

To obtain additional data, we also used the same modeling strategies to study the effect of a known diagnosis of diabetes on lung function using all persons with and without diagnosed diabetes who had data available. In addition, we examined the impact of the degree of glucose regulation in persons with known diabetes by stratifying these persons into two groups defined by a glycosylated hemoglobin concentration of <7 percent versus ≥7 percent. A factor was considered a confounding factor if its addition to the model changed the size of the effect by 15 percent or more. Because of the complex, multistage probability sample design of NHANES III, we accounted for the survey design in calculating estimates, using the specialized survey

command within Stata/SE 8.0 (Stata Corporation, College Station, Texas). Because certain age groups and ethnic groups were oversampled in the NHANES III study population, we also repeated the analyses using weighting variables to establish the descriptive population corrected to be representative of the general US population.

## RESULTS

A total of 12,496 adults were eligible for the initial analyses. Reasons for exclusion are outlined in figure 1. Six hundred and eighteen (5 percent) of those excluded from the initial analysis had a clinical diagnosis of diabetes, and 7,045 subjects (56 percent) were excluded because they failed to meet World Health Organization criteria for glucose testing. Our study population was similar to the excluded population in terms of demographic characteristics (table 1). A total of 4,257 participants (34 percent) had data on serum measures of glucose control, and 1,612 (13 percent) had data on serum glucose level 2 hours after a glucose load. The mean age of the population was 37 years; 54 percent were female. The mean levels and distributions of the various glycemic markers are presented in table 2.

For the 1,612 participants who had data on glucose tolerance testing, an inverse dose-response relation with

**TABLE 2. Mean levels of various markers of glycemic status, Third National Health and Nutrition Examination Survey, 1988–1994**

Variable and units	No. of subjects	Mean (SD)*
Fasting plasma glucose level	4,257	
mg/dl		96.5 (20.2)
mmol/liter		5.4 (1.1)
Hemoglobin A1c concentration (%)	4,257	5.3 (0.7)
C-peptide level	4,257	
nmol/liter		0.7 (0.4)
pmol/liter		0.7 (0.4)
Insulin level	4,257	
$\mu$ U/liter		11.1 (7.8)
pmol/liter		66.5 (46.6)
Insulin resistance†	4,257	2.5 (2.1)
Glucose level 2 hours post-glucose-load	1,612‡	
mg/dl		121.5 (58.7)
mmol/liter		6.7 (3.2)

\* SD, standard deviation.

† Insulin resistance = fasting glucose (mmol/liter)  $\times$  fasting insulin ( $\mu$ U/ml)/25.

‡ Data were available only for 1,612 people aged 40–60 years.

FEV<sub>1</sub> was found, such that those in the highest quintile of plasma glucose after oral glucose loading had a decrease of 144.7 ml (95 percent confidence interval (CI): –231.9, –57.4) compared with those in the lowest quintile (table 3). A similar relation was seen with increasing fasting insulin, plasma C-peptide, insulin resistance, and glycosylated hemoglobin, although there was no clear association between fasting plasma glucose and FEV<sub>1</sub>.

Adjusting the above associations for body mass index (in categories) and waist:hip ratio slightly decreased these associations between measures of glucose control and FEV<sub>1</sub>. Adjusting for other possible confounders, such as plasma antioxidants, vitamins A, C, and E, poverty index ratio, C-reactive protein, and triglycerides, did not appreciably alter these associations (data not shown). Stratifying the results according to age did not produce any noticeable difference in effect across the age categories, and there were no significant interactions between smoking and glycemic markers. Restricting the analysis to persons who had never smoked did not significantly alter these associations.

The relation between glycemic markers and FVC was similar to the results shown for FEV<sub>1</sub>, although the size of the effect was greater for FVC (table 4). However, no consistent association was seen between the different glycemic markers and the FEV<sub>1</sub>:FVC ratio (table 5).

When we compared persons with impaired glucose tolerance and persons who had clinical diabetes defined by glucose tolerance testing with persons whose values fell within the normal range, the differences in FEV<sub>1</sub> were –34.3 ml (95 percent CI: –114.5, –45.9) and –108.8 ml (95

percent CI: –217.3, –0.3), respectively (table 6). Impaired fasting glucose and diabetes as defined by fasting glucose level were associated with decreases in FEV<sub>1</sub> of 60.8 ml (95 percent CI: –95.7, –25.8) and 93.8 ml (95 percent CI: –127.4, –60.2), respectively. Persons with an elevated hemoglobin A1c concentration had an associated decrease in FEV<sub>1</sub> of 75.0 ml (95 percent CI: –231.0, 80.9).

In examining the effect of diagnosed diabetes on lung function, we found that persons with diabetes had a 119.1 ml (95 percent CI: –161.5, –76.6) reduction in FEV<sub>1</sub> in comparison with the rest of the population (table 7). Persons with suboptimal diabetic control, as determined by a glycosylated hemoglobin concentration of  $\geq 7$  percent, had lower lung function than persons with well-controlled diabetes.

Correction for the selective oversampling of certain age and ethnic groups in NHANES III using models that included the weighting variables did not change the qualitative nature of the results. Correction for weighting did increase the effect size of the association between measures of glycemic control and lung function, and it also increased the confidence intervals in the analyses of a smaller sample population, as shown in tables 6 and 7. We thus elected to present the data using the more conservative regression models derived from the data available for each eligible individual.

## DISCUSSION

We have demonstrated that in adults without a diagnosis of diabetes, impaired glucose regulation as indicated by glucose tolerance testing, higher levels of glycosylated hemoglobin, plasma insulin (a marker of insulin resistance (22)), and C-peptide (a by-product of insulin production), and an epidemiologic measure of insulin resistance are associated with impaired lung function in a dose-response manner. However, fasting plasma glucose was not associated with lung function. We have also demonstrated that persons with a clinical diagnosis of diabetes have impaired lung function, a finding that is consistent with previous work in this area (3–17). These findings were not explained by obesity or increasing age. This relation was seen throughout the nondiabetic values of these markers of glucose auto-regulation, which suggests that the relation between glucose and lung function is not just an association seen in persons with overt diabetes. A similar association was also seen between glycemic markers and FVC but was not seen consistently with the FEV<sub>1</sub>:FVC ratio; this suggests that the effect is primarily an effect on lung function and does not influence the development of obstructive lung disease (as seen in chronic obstructive pulmonary disease).

The strength of this study was the use of biologic markers of glycemic control and physiologic measurements of lung function in a well-defined population with no clinical diagnosis of diabetes and no knowledge of the hypothesis being tested. NHANES III had a high participation rate, with 86 percent and 78 percent of those invited to participate in the questionnaire survey and the medical examination, respectively, taking part (18). However, the population studied for the effect of fasting glucose, C-peptide, insulin

**TABLE 3. Association between various markers of glycemic status and forced expiratory volume in 1 second, Third National Health and Nutrition Examination Survey, 1988–1994**

Glycemic marker and quintile	Model 1*		Model 1* with additional adjustment for body mass index† and waist:hip ratio	
	β (ml)	95% CI‡	β (ml)	95% CI
Fasting plasma glucose level (mg/dl)				
52.0–86.6	0		0	
86.7–91.4	40.1	0.7, 79.5	39.6	1.1, 78.0
91.5–96.1	28.1	–15.2, 71.3	27.4	–16.0, 70.8
96.2–102.0	–6.0	–53.7, 41.7	0.2	–47.0, 47.5
102.1–445.2	–36.0	–99.8, 27.7	–17.2	–83.9, 49.5
Test for heterogeneity§	0.0041		0.0240	
Glucose level (mg/dl) 2 hours post-glucose-load				
36–84.5	0		0	
84.6–100.7	–81.8	–173.8, 10.1	–83.0	–175.7, 9.7
100.8–118.1	–77.4	–158.3, 3.6	–70.4	–153.3, 12.4
118.2–143.2	–56.1	–134.5, –22.3	–43.2	–121.4, 35.0
143.3–548.9	–144.7	–231.9, –57.4	–108.4	–201.1, –15.7
<i>p</i> value for trend§	0.005		0.079	
Hemoglobin A1c concentration (%)				
3.3–4.8	0		0	
4.9–5.1	9.5	–32.6, 51.6	6.0	–36.0, 48.0
5.2–5.3	–14.5	–58.1, 29.0	–16.6	–60.5, 27.4
5.4–5.6	–67.9	–113.2, –27.7	–64.8	–110.1, –19.4
5.7–15.7	–152.2	–206.5, –97.8	–136.3	–192.2, –80.4
Test for heterogeneity§	0.0001		<0.0001	
Insulin level (μU/liter)				
1.8–6.06	0		0	
6.07–8.03	–43.3	–85.3, –1.4	–60.5	–104.4, –16.5
8.04–10.51	–83.5	–128.3, –38.7	–105.5	–152.0, –58.9
10.52–14.34	–64.1	–111.5, –16.8	–92.3	–143.4, –41.2
14.35–175.8	–171.4	–211.8, –130.9	–190.9	–238.9, –142.8
Test for heterogeneity§	<0.0001		<0.0001	
C-peptide level (pmol/ml)				
0.02–0.34	0		0	
0.35–0.51	–12.3	–62.1, 37.5	–27.9	–78.2, 22.4
0.52–0.71	–34.4	–84.9, 16.1	–52.0	–103.2, –0.9
0.72–0.98	–51.7	–99.8, –3.6	–66.9	–122.1, –11.6
0.99–3.71	–137.5	–183.6, –91.4	–142.1	–201.7, –82.4
Test for heterogeneity§	<0.0001		0.0003	
Insulin resistance¶				
0.27–1.22	0		0	
1.23–1.65	–13.5	–50.8, 23.8	–34.4	–72.6, 3.8
1.66–2.22	–58.5	–104.9, –12.0	–81.9	–131.3, –32.6
2.23–3.19	–60.1	–107.5, –12.7	–91.1	–142.4, –39.8
3.20–47.34	–159.1	–197.7, –120.6	–179.8	–223.9, –135.7
<i>p</i> value for trend§	<0.0001		<0.0001	

\* Results were adjusted for age, sex, height, smoking (status and pack-years), and race/ethnicity.

† Weight (kg)/height (m)<sup>2</sup>. Modeled as a categorical variable (<20, 20–24.9, 25–29.9, >30).

‡ CI, confidence interval.

§ A *p* value for trend is presented for associations that showed no departure from linearity, and a *p* value from a test of heterogeneity is given for nonlinear associations.

¶ Insulin resistance = fasting glucose (mmol/liter) × fasting insulin (μU/ml)/25.

**TABLE 4. Association between various markers of glycemic status and forced vital capacity, Third National Health and Nutrition Examination Survey, 1988–1994**

Glycemic marker and quintile	Model 1*		Model 1* with additional adjustment for body mass index† and waist:hip ratio	
	β (ml)	95% CI‡	β (ml)	95% CI
Fasting plasma glucose level (mg/dl)				
52.0–86.6	0		0	
86.7–91.4	54.2	3.7, 104.7	52.5	2.6, 102.5
91.5–96.1	16.8	–34.0, 67.5	11.8	–38.5, 62.1
96.2–102.0	–24.1	–76.9, 28.7	–20.5	–73.4, 32.3
102.1–445.2	–70.2	–139.9, –0.61	–54.1	–124.3, 16.1
Test for heterogeneity§	0.001		0.0023	
Glucose level (mg/dl) 2 hours post-glucose-load				
36–84.5	0		0	
84.6–100.7	–89.9	–198.6, 19.6	–81.0	–193.7, 31.8
100.8–118.1	–93.6	–182.1, –5.1	–70.3	–164.2, 23.7
118.2–143.2	–103.6	–187.7, –19.6	–70.4	–159.5, 18.7
143.3–548.9	–224.0	–327.0, –121.0	–159.2	–268.1, –50.2
p value for trend§	0.001		0.009	
Hemoglobin A1c concentration (%)				
3.3–4.8	0		0	
4.9–5.1	30.1	–15.8, 76.1	25.7	–20.0, 71.3
5.2–5.3	18.5	–32.3, 69.3	15.3	–36.6, 67.3
5.4–5.6	–48.8	–101.0, 3.3	–44.4	–97.9, 9.1
5.7–15.7	–157.1	–220.6, –93.6	–137.8	–203.1, –72.5
Test for heterogeneity§	<0.0001		<0.0001	
Insulin level (μU/liter)				
1.8–6.06	0		0	
6.07–8.03	–57.0	–105.9, –8.1	–89.3	–139.3, –39.2
8.04–10.51	–96.3	–147.2, –45.5	–143.0	–197.0, –89.1
10.52–14.34	–87.8	–137.1, –38.4	–147.4	–203.6, –91.2
14.35–175.8	–243.1	–295.2, –191.1	–300.2	–362.3, –238.2
Test for heterogeneity§	<0.0001		<0.0001	
C-peptide level (pmol/ml)				
0.02–0.34	0		0	
0.35–0.51	–14.1	–68.0, 39.8	–42.4	–98.8, 14.0
0.52–0.71	–30.4	–78.1, 17.4	–68.4	–119.1, –17.7
0.72–0.98	–64.7	–115.7, –13.6	–105.8	–165.2, –46.4
0.99–3.71	–196.4	–247.8, –145.0	–229.1	–293.6, –164.7
Test for heterogeneity§	<0.0001		<0.0001	
Insulin resistance¶				
0.27–1.22	0		0	
1.23–1.65	–40.6	–90.3, 9.0	–78.1	–129.6, –25.6
1.66–2.22	–65.5	–118.4, –12.7	–115.3	–174.7, –55.8
2.23–3.19	–90.0	–140.9, –39.1	–154.5	–210.9, –98.0
3.20–47.34	–238.6	–290.6, –186.6	–298.6	–361.0, –236.2
p value for trend§	<0.001		<0.001	

\* Results were adjusted for age, sex, height, smoking (status and pack-years), and race/ethnicity.

† Weight (kg)/height (m)<sup>2</sup>. Modeled as a categorical variable (<20, 20–24.9, 25–29.9, >30).

‡ CI, confidence interval.

§ A p value for trend is presented for associations that showed no departure from linearity, and a p value from a test of heterogeneity is given for nonlinear associations.

¶ Insulin resistance = fasting glucose (mmol/liter) × fasting insulin (μU/ml)/25.

**TABLE 5. Association between various markers of glycemic status and the ratio of forced expiratory volume in 1 second to forced vital capacity, Third National Health and Nutrition Examination Survey, 1988–1994**

Glycemic marker and quintile	Model 1*		Model 1* with additional adjustment for body mass index† and waist:hip ratio	
	β (ml)	95% CI‡	β (ml)	95% CI
Fasting plasma glucose level (mg/dl)				
52.0–86.6	0		0	
86.7–91.4	–0.18	–0.78, 0.42	–0.17	–0.77, 0.43
91.5–96.1	0.14	–0.45, 0.73	0.21	–0.43, 0.84
96.2–102.0	0.17	–0.52, 0.86	0.23	–0.49, 0.95
102.1–445.2	0.37	–0.45, 1.19	0.47	–0.46, 1.39
Test for heterogeneity§	0.235		0.205	
Glucose level (mg/dl) 2 hours post-glucose-load				
36–84.5	0		0	
84.6–100.7	–0.30	–1.47, 0.87	–0.53	–1.75, 0.69
100.8–118.1	–0.47	–1.70, 0.77	–0.79	–2.08, 0.50
118.2–143.2	0.81	–0.24, 1.85	0.43	–0.67, 1.52
143.3–548.9	0.85	–0.49, 2.19	0.44	–1.11, 1.99
p value for trend§	0.054		0.263	
Hemoglobin A1c concentration (%)				
3.3–4.8	0		0	
4.9–5.1	–0.30	–0.96, 0.36	–0.29	–0.97, 0.38
5.2–5.3	–0.78	–1.44, –0.13	–0.77	–1.44, –0.11
5.4–5.6	–0.64	–1.33, 0.04	–0.66	–1.35, 0.03
5.7–15.7	–0.99	–1.77, –0.22	–1.03	–1.82, –0.24
Test for heterogeneity§	0.009		0.007	
Insulin level (μU/liter)				
1.8–6.06	0		0	
6.07–8.03	0.06	–0.63, 0.75	0.28	–0.42, 0.98
8.04–10.51	–0.16	–0.95, 0.63	0.22	–0.56, 0.99
10.52–14.34	0.22	–0.56, 1.01	0.70	–0.15, 1.55
14.35–175.8	0.73	0.01, 1.45	1.36	0.56, 2.16
Test for heterogeneity§	0.054		0.263	
C-peptide level (pmol/ml)				
0.02–0.34	0		0	
0.35–0.51	–0.04		0.14	–0.57, 0.85
0.52–0.71	–0.24	–0.75, 0.66	0.07	–0.79, 0.94
0.72–0.98	0.04	–1.03, 0.56	0.46	–0.26, 1.18
0.99–3.71	0.63	–0.58, 0.66	1.14	0.28, 2.01
Test for heterogeneity§	0.063	–0.02, 1.29	0.003	
Insulin resistance¶				
0.27–1.22	0		0	
1.23–1.65	0.44	–0.25, 1.13	0.66	–0.03, 1.35
1.66–2.22	–0.30		0.09	–0.73, 0.91
2.23–3.19	0.40	–1.13, 0.53	0.88	0.07, 1.69
3.20–47.34	0.86	–0.36, 1.15	1.50	0.70, 2.30
p value for trend§	0.012	–0.12, 1.61	0.002	

\* Results were adjusted for age, sex, height, smoking (status and pack-years), and race/ethnicity.

† Weight (kg)/height (m)<sup>2</sup>. Modeled as a categorical variable (<20, 20–24.9, 25–29.9, >30).

‡ CI, confidence interval.

§ A p value for trend is presented for associations that showed no departure from linearity, and a p value from a test of heterogeneity is given for nonlinear associations.

¶ Insulin resistance = fasting glucose (mmol/liter) × fasting insulin (μU/ml)/25.

**TABLE 6. Association between various clinical definitions of diabetes\* and forced expiratory volume in 1 second, Third National Health and Nutrition Examination Survey, 1988–1994**

Definition of diabetes and glucose tolerance	Model 1†		Model 1† with additional adjustment for body mass index‡ and waist:hip ratio	
	β (ml)	95% CI§	β (ml)	95% CI
Fasting plasma glucose level				
Normal (<110 mg/dl) (n = 3,877)	0		0	
Impaired (110–125.99 mg/dl) (n = 262)	–75.2	–109.4, –41.1	–60.8	–95.7, –25.8
Diabetic (≥126 mg/dl) (n = 118)	–126.2	–160.1, –92.3	–93.8	–127.4, –60.2
Glucose level 2 hours post-glucose-load				
Normal (<140 mg/dl) (n = 1,258)	0		0	
Impaired (140–199.99 mg/dl) (n = 250)	–60.5	–134.8, 13.9	–34.3	–114.5, –45.9
Diabetic (≥200 mg/dl) (n = 104)	–154.5	–265.6, –43.4	–108.8	–217.3, –0.3
Hemoglobin A1c concentration				
<7% (n = 4,196)	0		0	
≥7% (n = 61)	–110.3	–269.7, 49.0	–75.0	–231.0, 80.9

\* According to the World Health Organization (19).

† Results were adjusted for sex, age, height, race/ethnicity, and smoking (status and pack-years).

‡ Weight (kg)/height (m)<sup>2</sup>. Modeled as a categorical variable (<20, 20–24.9, 25–29.9, >30).

§ CI, confidence interval.

resistance, and response to glucose tolerance testing was a subsample of the original NHANES III population, since we excluded some participants in order to comply with standardized conditions for collecting the samples (19) (including only those who had attended a morning examination and had fasted for 8 hours or more). It is unlikely that those who were included in this group had lower lung function than those who did not fast for 8 hours or underwent examination in the afternoon. We do have to consider the potential for confounding, especially by

smoking, antioxidants, and early life development. Because an association between smoking and diabetes has been demonstrated (23, 24), smoking status may confound the relation between impaired glycemic control and lung function (25). However, we rigorously adjusted for self-reported smoking history using both current smoking status and total pack-years of smoking, additionally restricting our analysis to persons who had never smoked, and this did not alter our findings. Another risk factor that is associated with both diabetes (26) and reduced lung function (27) is

**TABLE 7. Association between known diagnosis of diabetes and forced expiratory volume in 1 second, Third National Health and Nutrition Examination Survey, 1988–1994**

Comparison	Model 1*		Model 1* with additional adjustment for body mass index† and waist:hip ratio	
	β (ml)	95% CI‡	β (ml)	95% CI
Diabetes status				
No diabetes (n = 4,257)	0		0	
Diabetes (n = 512)	–119.1	–161.5, –76.6	–78.8§	–118.7, –38.8
Level of control of diabetes				
No diabetes (n = 4,196)	0		0	
Well-controlled diabetes (hemoglobin A1c <7%) (n = 253)	–91.6	–157.4	–54.5¶	–116.2, 7.3
Poorly controlled diabetes (hemoglobin A1c ≥7%) (n = 395)	–144.9	–200.5, –89.2	–100.1#	–155.3, –44.9

\* Results were adjusted for sex, age, height, race/ethnicity, and smoking (status and pack-years).

† Weight (kg)/height (m)<sup>2</sup>. Modeled as a categorical variable (<20, 20–24.9, 25–29.9, >30).

‡ CI, confidence interval.

§ n = 489.

¶ n = 218.

# n = 259.

antioxidant status, although adjustment for serum vitamin C and vitamin E levels did not alter our findings.

One potentially confounding factor, which we are unable to exclude, is growth in early life. An association has been demonstrated between low body weight in early life and impaired glucose control, insulin resistance (28, 29), and decreased lung function (30). It is thus possible that our apparent association between poor glucose regulation and reduced lung function is a consequence of confounding by growth in early life, although no effect of birth weight on lung function was reported in a recent study (9). Alternatively, it may be that poor glycemic control lies within the causal pathway explaining the association between low birth weight and decreased lung function. The use of data from a cross-sectional study such as NHANES III does not permit temporal relations to be considered; therefore, we cannot exclude the possibility of reverse causality—that is, lower lung function's leading to impaired glucose regulation.

The absence of an effect of fasting plasma glucose on FEV<sub>1</sub> in the presence of a negative effect of increasing levels of other markers of poor glycemic control is anomalous and difficult to explain. Over 95 percent of our study population was in the nondiabetic ranges for fasting plasma glucose, and we theorize that there may be greater random variation of fasting plasma glucose within these levels, while the other measures of glycemic control provide a more consistent measure of glycemic control. Although we have been unable to find data in the literature to substantiate this, the association of a gradient of decreasing FEV<sub>1</sub> among persons with fasting plasma glucose levels in the "impaired" or diabetic ranges (table 4) demonstrates a consistency with the rest of the data, suggesting that this may be the case. The mechanism by which impaired glycemic control may lead to a reduction in lung function is uncertain, though it has been suggested that the increased systemic inflammation associated with diabetes (31) may result in pulmonary inflammation (4) and hence airway damage (32). Alternatively, a reduction in antioxidant defenses resulting from increased oxidative activity associated with diabetes (26) may lead to a secondary reduction in the antioxidant defenses of the lung and hence increased susceptibility to environmental oxidative insults, resulting in subsequent loss of lung function. In addition to an increase in intracellular oxidative stress, increased nuclear factor- $\kappa$ B, and inflammatory mediator expression, long-term hyperglycemia causes an increase in collagen molecule synthesis and cross-linking via the accumulation of advanced glycosylation end products, which may also adversely influence lung function (33). The observation that increasing insulin level and insulin resistance is associated with loss of lung function suggests that insulin may have a direct negative effect on airway function (34).

The initial studies of diabetes and lung function were small and had little statistical power, which may explain why the results were inconsistent (6–8, 35–42). The subsequent larger population-based studies have been more coherent, demonstrating reduced pulmonary function in persons with an elevated plasma glucose level and a diagnosis of diabetes. Enright et al. (43) reported a small reduction in FEV<sub>1</sub> of 23 ml among persons with diabetes

in the Cardiovascular Health Study. Analysis of 3,254 members of the Framingham Offspring Cohort showed associations of both diagnosed diabetes and elevated plasma glucose with reduced FEV<sub>1</sub> (4). The results demonstrated that persons with diabetes had an FEV<sub>1</sub> 61 ml lower than that of persons without diabetes and that persons in the highest quartile of plasma glucose had an FEV<sub>1</sub> 85 ml lower than that of persons in the lowest quartile (4). The cross-sectional data from the Copenhagen City Heart Study demonstrated a reduction in FEV<sub>1</sub> of 239 ml among diabetics who required insulin and a reduction of 117 ml among diabetics treated with oral hypoglycemic agents (3) in comparison with nondiabetics. In an analysis of persons without diagnosed diabetes, an inverse association was observed between an elevated nonfasting plasma glucose level ( $\geq 200$  mg/dl) and lung function; there was a difference in FEV<sub>1</sub> of  $-218$  ml in comparison with persons with normal fasting plasma glucose levels (3). The longitudinal analyses of the same population demonstrated an association between a new diagnosis of diabetes and impaired pulmonary function, with the newly diagnosed diabetics having an annual decrease in FEV<sub>1</sub> of 25 ml more than control subjects (44). A similar increased decline in lung function among persons with poor diabetic control has been reported elsewhere (45), although follow-up at 15 years demonstrated that the decline in FEV<sub>1</sub> among those with diabetes was the same as that among those without the disease. Similarly, in the Normative Aging Study, Lazarus et al. (10) demonstrated an association between decreased FEV<sub>1</sub> and increased insulin resistance, although persons with lower baseline lung function were observed to be more likely to develop insulin resistance 20 years later (11)—a result that was also seen for the development of diabetes elsewhere (46). However, these relations were not seen in analysis of adults aged 51–95 years in the Rancho Bernardo Study (47), where lung function was not associated with fasting blood glucose level; this may have been a consequence of studying an older population. Interestingly, a small cohort study of 18 subjects with type I diabetes who were using an insulin pump to achieve normoglycemia in comparison with conventional therapy suggested that intensive insulin treatment, and hence better glycemic control, may preserve pulmonary function, although the absence of baseline pulmonary function measurements limited the interpretation of these data (48).

We have demonstrated that increases in the glucose response to a glucose tolerance test, glycosylated hemoglobin, serum insulin, and a marker of insulin resistance are all associated with a reduction in lung function as assessed by FEV<sub>1</sub> (and FVC). This effect is not explained by confounding due to obesity. The observation that persons with diagnosed diabetes that is poorly controlled have worse lung function than persons with diagnosed diabetes who have good glucose control is consistent with the hypothesis that good control of diabetes is associated with preserved lung function. Further understanding of the effect of glucose regulation on the lungs would be obtained by assessing lung function in participants from a trial of intensive glucose regulation, such as the Diabetes Control and Complications

Trial, where beneficial effects on diabetic nephropathy are seen 7–8 years after the end of the intervention (49). Although smoking is the main risk factor for loss of lung function, there is an urgent need to understand other factors that contribute to a reduction in lung function, as demonstrated by the 95 percent excess mortality among persons who have never smoked but have reduced lung function in comparison with those with normal lung function (50). In addition, the emergence of novel risk factors such as hyperglycemia will lead to increased understanding of the pathogenesis of worse lung function and hence new possibilities for intervention. In view of the public health importance of lung function in health and the increasing prevalence of diabetes, this is a subject that warrants further investigation.

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## REFERENCES

- Mannino D, Homa D, Akinbami L, et al. Chronic obstructive pulmonary disease surveillance—United States 1971–2000. *MMWR Surveill Summ* 2002;51:1–16.
- Pauwels R, Rabe K. Burden and clinical features of chronic obstructive pulmonary disease (COPD). *Lancet* 2004;364:613–20.
- Lange P, Groth S, Kastrup J, et al. Diabetes mellitus, plasma glucose and lung function in a cross-sectional population study. *Eur Respir J* 1989;2:14–19.
- Walter R, Beiser A, Givelber R, et al. The association between glycemic state and lung function: The Framingham Heart Study. *Am J Respir Crit Care Med* 2003;167:911–16.
- Hakala K, Stenius-Aarniala B, Sovijarvi A. Effects of weight loss on peak flow variability, airways obstruction, and lung volumes in obese patients with asthma. *Chest* 2000;118:1315–21.
- Schnack C, Festa A, Schwarzmaier-D'Assie A, et al. Pulmonary dysfunction in type 1 diabetes in relation to metabolic long-term control and to incipient diabetic nephropathy. *Nephron* 1996;74:395–400.
- Bell D, Collier A, Matthews D, et al. Are reduced lung volumes in IDDM due to defect in connective tissue? *Diabetes* 1988;37:829–31.
- Innocenti F, Fabbri A, Anichini R, et al. Indications of reduced pulmonary function in type 1 (insulin-dependent) diabetes mellitus. *Diabetes Res Clin Pract* 1994;25:161–8.
- Lawlor D, Ebrahim S, Davey Smith G. Associations of measures of lung function with insulin resistance and type 2 diabetes: findings from the British Women's Heart and Health Study. *Diabetologia* 2004;47:195–203.
- Lazarus R, Sparrow D, Weiss S. Impaired ventilatory function and elevated insulin levels in nondiabetic males: The Normative Aging Study. *Eur Respir J* 1998;12:635–40.
- Lazarus R, Sparrow D, Weiss S. 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;12:641–5.
- Davis T, Knudman M, Kendall P, et al. Reduced pulmonary function and its associations in type 2 diabetes: The Fremont Diabetes Study. *Diabetes Res Clin Pract* 2000;50:153–9.
- Cazzato S, Bernardi F, Salardi S, et al. Lung function in children with diabetes mellitus. *Pediatr Pulmonol* 2004;37:17–23.
- Mori H, Okubo M, Okamura M, et al. Abnormalities of pulmonary function in patients with non-insulin dependent diabetes mellitus. *Intern Med* 1992;31:189–93.
- Schnapf B, Banks R, Silverstein J, et al. Pulmonary function in insulin-dependent diabetes mellitus with limited joint mobility. *Am Rev Respir Dis* 1984;130:930–2.
- Sandler M, Bunn A, Stewart R. Cross-section study of pulmonary function in patients with insulin-dependent diabetes mellitus. *Am Rev Respir Dis* 1987;135:223–9.
- Burchfiel C, Curb D, Sharp D, et al. Distribution and correlates of insulin in elderly men: The Honolulu Heart Program. *Arterioscler Thromb Vasc Biol* 1995;15:2213–21.
- National Center for Health Statistics. Plan and operation of the Third National Health and Nutrition Examination Survey, 1988–94. (Vital and health statistics, series 1—programs and collection procedures, no. 32). Hyattsville, MD: National Center for Health Statistics, 1994.
- World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications, part 1: diagnosis and classification of diabetes mellitus. Report of a WHO Consultation. Geneva, Switzerland: World Health Organization, 1999.
- Duncan M, Singh B, Wise P, et al. A simple measure of insulin resistance. *Lancet* 1995;346:120–1.
- Gunter E, Lewis B, Koncickowski S. Laboratory procedures used for the Third National and Nutrition Examination Survey (NHANES III), 1988–1994. Hyattsville, MD: National Center for Health Statistics, 1996.
- Laakso M. How good a marker is insulin level for insulin resistance? *Am J Epidemiol* 1993;137:959–65.
- Sargeant L, Khaw K, Bingham S, et al. Cigarette smoking and glycaemia: The EPIC–Norfolk Study. *Int J Epidemiol* 2001;30:547–54.
- Will J, Galuska D, Ford E, et al. Cigarette smoking and diabetes mellitus: evidence of a positive association from a large prospective cohort study. *Int J Epidemiol* 2001;30:540–6.
- Fletcher C, Peto R, Tinker C, et al. Factors related to the development of airflow obstruction. In: *The natural history of chronic bronchitis and emphysema: an eight-year study of early chronic obstructive lung disease in working men in London*. 1st ed. New York, NY: Oxford University Press, 1976:70–102.
- Gazis A, Page S, Cockcroft J. Vitamin E and cardiovascular protection in diabetes. *BMJ* 1997;314:1845–6.
- Britton J, Pavord I, Richards K, et al. Dietary antioxidant vitamin intake and lung function in the general population. *Am J Respir Crit Care Med* 1995;151:1383–7.
- Hales C, Barker D, Clark P, et al. Fetal and infant growth and impaired glucose tolerance at age 64. *BMJ* 1991;303:1019–22.
- Ong K, Dunger D. Perinatal growth failure: the road to obesity, insulin resistance and cardiovascular disease in adults. *Best Pract Res Clin Endocrinol Metab* 2002;16:191–207.
- Barker D, Godfrey K, Fall C, et al. Relation of birth weight and childhood respiratory disease to adult lung function and death from chronic obstructive airways disease. *BMJ* 1991;303:671–5.

31. Arnalich F, Hernanz A, Lopez-Maderuelo D, et al. Enhanced acute-phase response and oxidative stress in older adults with type II diabetes. *Horm Metab Res* 2000;32:407–12.
32. Cirillo D, Agrawal Y, Cassano P. Lipids and pulmonary function in the Third National Health and Nutrition Examination Survey. *Am J Epidemiol* 2002;155:842–8.
33. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. *Nature* 2001;414:813–20.
34. Tantisira K, Weiss S. Complex interactions in complex traits: obesity and asthma. *Thorax* 2001;56 (suppl 2):ii64–73.
35. Asanuma Y, Fujiya S, Ide H, et al. Characteristics of pulmonary function in patients with diabetes mellitus. *Diabetes Res Clin Pract* 1985;1:95–101.
36. Heimer D, Brami J, Lieberman D, et al. Respiratory muscle performance in patients with type I diabetes. *Diabet Med* 1990;7:434–7.
37. Katoh J, Hara Y, Kurusu M, et al. Cardiorespiratory function as assessed by exercise testing in patients with non-insulin-dependent diabetes mellitus. *J Int Med Res* 1996;24:209–13.
38. Maccioni F, Colebatch J. Lung volume and distensibility in insulin-dependent diabetes mellitus. *Am Rev Respir Dis* 1991;143:1253–6.
39. Strojek K, Sroczynski J, Oklek K. Pulmonary complications of type 1 (insulin-dependent) diabetic patients. *Diabetologia* 1992;35:1173–6.
40. Sandler M. Is the lung a “target organ” in diabetes mellitus? *Arch Intern Med* 1990;150:1385–8.
41. Cooper B, Taylor R, Alberti K, et al. Lung function in patients with diabetes mellitus. *Respir Med* 1990;84:235–9.
42. Primhak R, Whincup G, Tsanakas J, et al. Reduced vital capacity in insulin-dependent diabetes. *Diabetes* 1987;36:324–6.
43. Enright P, Kronmal R, Higgins M, et al. Spirometry reference values for women and men 65 to 85 years of age. *Am Rev Respir Dis* 1993;147:125–33.
44. Lange P, Groth S, Mortensen J, et al. Diabetes mellitus and ventilatory capacity: a five year follow-up study. *Eur Respir J* 1990;3:288–92.
45. Davis W, Knuiiman M, Kendall P, et al. Glycemic exposure is associated with reduced pulmonary function in type 2 diabetes: The Fremantle Diabetes Study. *Diabetes Care* 2004;27:752–7.
46. Engstrom G, Janzon L. Risk of developing diabetes is inversely related to lung function: a population-based cohort study. *Diabet Med* 2001;19:167–70.
47. Barrett-Connor E, Frette E. NIDDM, impaired glucose tolerance, and pulmonary function in older adults. *Diabetes Care* 1996;19:1441–4.
48. Ramirez L, Dal Nogare A, Hsia C, et al. Relationship between diabetes control and pulmonary function in insulin-dependent diabetes mellitus. *Am J Med* 1991;91:371–6.
49. Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: The Epidemiology of Diabetes Interventions and Complications (EDIC) Study. *JAMA* 2003;290:2159–67.
50. Hole D, Watt G, Davey Smith G, et al. Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. *BMJ* 1996;313:711–15.