Glycemic Exposure Is Associated With Reduced Pulmonary Function in Type 2 Diabetes

The Fremantle Diabetes Study

WENDY A. DAVIS, MPH[1,2]
MATTHEW KNUIMAN, PHD[2]
PETER KENDALL, MB, BS[3]
VALERIE GRANGE, EN[1]
TIMOTHY M.E. DAVIS, DPHIL[1]

OBJECTIVE — To examine prospectively the relationship between diabetes, glycemic control, and spirometric measures.

RESEARCH DESIGN AND METHODS — From a community-based cohort, 495 Europid (i.e., of European descent) patients with type 2 diabetes who had no history of pulmonary disease underwent baseline spirometry between 1993 and 1994. A subset of 125 patients was restudied a mean of 7.0 years later. The main outcome measures included forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), vital capacity (VC), and peak expiratory flow (PEF) corrected for body temperature, air pressure, and water saturation and were expressed either in absolute terms or as percentage-predicted value for age, sex, and height.

RESULTS — Mean percentage-predicted values of each spirometric measure were decreased >10% in the whole cohort at baseline and absolute measures continued to decline at an annual rate of 68, 71, and 84 ml/year and 17 l/min for FVC, FEV_1, VC, and PEF, respectively, in the 125 prospectively studied patients. Declining lung function measures were consistently predicted by poor glycemic control in the form of a higher updated mean HbA_{1c}, follow-up HbA_{1c}, or follow-up fasting plasma glucose. In a Cox proportional hazards model, decreased FEV_1 percentage-predicted value was an independent predictor of all-cause mortality.

CONCLUSIONS — Reduced lung volumes and airflow limitation are likely to be chronic complications of type 2 diabetes, the severity of which relates to glycemic exposure. Airflow limitation is a predictor of death in type 2 diabetes after adjusting for other recognized risk factors.

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Several cross-sectional studies have shown that type 2 diabetes is associated with reduced lung function (1–3). Although this relationship could be interpreted as demonstrating the damaging effects of diabetes on the lung (4), a small-scale Scandinavian prospective study has provided some evidence that reduced pulmonary function is present before type 2 diabetes is diagnosed (5). This may mean that diabetes and impaired lung function share common pathophysiologic determinants rather than the lung being a target organ in diabetes. Consistent with this hypothesis, duration of diabetes has been found to have a much stronger negative correlation with spirometric measures than does metabolic control (2,3). There has, however, been no prospective evaluation of the interrelationship between type 2 diabetes, glycemic exposure, and lung function. Such studies have an added importance with the development of inhaled insulin preparations, the long-term pulmonary toxicity of which is yet to be established (6). We have, therefore, measured lung function in a large community-based cohort of patients with type 2 diabetes and repeated spirometry in a subgroup of these patients an average of 7 years later.

RESEARCH DESIGN AND METHODS

— We studied participants in the Fremantle Diabetes Study (FDS), a prospective observational study of care, metabolic control, and complications in patients recruited from a postcode-defined community of 120,097 people in Western Australia. The FDS protocol was approved by the Human Rights Committee, Fremantle Hospital, and all patients gave witnessed informed consent to participation. Descriptions of recruitment strategies, demographic characteristics of the sample, methods of defining diabetes type, and details of identified but nonrecruited patients have been published elsewhere (7,8). Of 2,258 subjects identified in the catchment area between 1993 and 1996, 1,426 (63%) were recruited to the FDS and 1,294 had type 2 diabetes.

The present study involved follow-up of a total of 495 FDS patients with type 2 diabetes (38% of all FDS patients with type 2 diabetes) who underwent spirometry between May 1993 and September 1994. The baseline cross-sectional characteristics and lung function in a subset of 421 patients (86%) have been reported

From the [1]University of Western Australia, School of Medicine and Pharmacology, Fremantle Hospital, Fremantle, Australia; the [2]University of Western Australia, School of Population Health, Perth, Australia; and the [3]Department of Respiratory Medicine, Fremantle Hospital, Fremantle, Australia.

Address correspondence and reprint requests to Professor T.M.E. Davis, School of Medicine and Pharmacology, Fremantle Hospital, P.O. Box 480, Fremantle, Western Australia 6959, Australia. E-mail: tdavis@cyllene.uwa.edu.au.

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Abbreviations: CHD, coronary heart disease; FDS, Fremantle Diabetes Study; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; PEF, peak expiratory flow; VC, vital capacity.

See accompanying editorial, p. 837.

previously (3), and we added an additional 74 FDS patients to this sample. All patients were of European ethnic background and were between 25 and 85 years of age. They had no self-reported history of respiratory illness and were not being treated for respiratory disease.

Clinical assessment

All FDS subjects underwent initial comprehensive assessment and were invited for subsequent yearly reviews until late in 2001. Each assessment comprised a comprehensive medical history and physical examination, automated biochemical analyses of fasting blood and urine samples, and other tests. The same assay methodology was used throughout the study for key measures, including HbA_{1c}. Patients were classified as having coronary heart disease (CHD) if there was a self-reported history of myocardial infarction, angina, coronary artery bypass grafting, angioplasty, and/or definite/probable ischemic changes on Minnesota coding of baseline electrocardiography. Retinopathy, defined as at least one microaneurysm in either eye or worse, was assessed from direct and/or indirect ophthalmoscopy through dilated pupils and/or more detailed data in patients assessed for photocoagulation. Neuropathy was defined as a score of >2/8 using the Michigan Neuropathy Screening Instrument clinical portion (9). Microalbuminuria or worse was defined as a urinary albumin-to-creatinine ratio ≥3.0 mg/mmol.

Pulmonary function testing

Baseline spirometry was performed using a Vitalograph Model S bellows spirometer (Vitalograph, Buckingham, U.K.) (3). Each subject provided at least three acceptable tracings, from which forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), vital capacity (VC), and peak expiratory flow (PEF) were measured. All values were corrected for body temperature, air pressure, and water saturation. Before analysis, spirometric data were normalized by both dividing by the square of the patient's height (10) and expressing them as a percentage of those predicted for age, sex, and height based on data from healthy nonsmoking Caucasian subjects aged 25–79 years for PEF (11) and 25–84 years for VC, FVC, and FEV_1 (12).

Follow-up spirometry was performed between June 2000 and July 2001 in all available consenting patients from the original sample of 495. The same standardized protocol was followed (13), except that a MicroLab 3300 spirometer (Micro Medical, Gillingham, Kent, U.K.) was used. This instrument calculated predicted values using the same equations as the Vitalograph machine (11,12). Both spirometers have been validated to American Thoracic Society Spirometry Standards.

Because the normative equations used by the two spirometers were derived from U.S. studies performed by Knudson and coworkers (11,12) >20 years ago, we used lung function data obtained in 1994–1995 from Busselton, a regional Western Australia population center (14,15), as a source of local contemporaneous percentage-predicted values. Spirometric measures from 565 male and 928 female Europid Busselton residents who had never smoked and had no asthma, bronchitis, wheeze, or dyspnea were used to derive predictive equations for FEV_1 and FVC based on age, sex, and height.

Death ascertainment

The Western Australia death register is part of the larger Western Australia Health Services Research Linked Database. In addition, hospital records and primary health care physician contact were used to provide as much information as possible relating to details of death of FDS patients. These sources provided mortality data from the beginning of the study to death or study end (January 2002).

Statistical analysis

The computer software SPSS for Windows (version 10.0; SPSS, Chicago, IL) was used for statistical analysis. Data are presented as proportions, means ± SD, median (interquartile range), or geometric mean (SD range). Updated means were calculated from yearly values to provide a single measure of blood pressure and glycemic and lipid exposure during follow-up. For waist circumference, categories of normal, overweight, and obese were defined for men (using 94 and 102 cm as cut points) and women (80 and 88 cm cut points) (16).

Comparisons of two related samples were performed using McNemar's test, paired Student's *t* test, or the Wilcoxon's signed-rank test. Comparisons of multiple independent samples were performed by χ^2 test, one-way ANOVA, or Kruskal-Wallis with post-hoc pairwise comparisons by Fisher's exact test, the least significant difference test, or Mann-Whitney *U* test, respectively. To minimize Type I error, a significance level of 0.01 was used. Associations between measures of glycemic control and lung function were assessed using multiple linear regression. Cox proportional hazards modeling was used to identify predictors of all-cause mortality in the baseline cohort, with variables significant at $P < 0.2$ in the univariate analysis included. For multiple linear and Cox proportional hazards regressions, variables were entered and removed at $P < 0.05$ and > 0.10, respectively.

RESULTS

Baseline patient characteristics

Of the original 495 patients, valid follow-up spirometric data were available for 125 (25.3%). The 370 patients for whom follow-up data were not available comprised 102 (20.6%) who died and 268 (54.1%) who were unable or unwilling to reattend for annual FDS reviews. Baseline details of patients classified according to follow-up status are shown in Table 1. The 102 patients who died were significantly older and had longer duration of diabetes than the 393 patients who were alive at study end (January 2002). They also had higher mean systolic blood pressure, greater prevalence of complications, and worse lung function. For the survivors, there were no significant differences between the 125 patients who were restudied and the 268 patients who were not restudied, except for shorter median duration of diabetes in the former group. At baseline, 29 of the 125 follow-up subjects (23.2%) had FEV_1 percentage-predicted values <70% and/or VC percentage-predicted value <80% without recognized respiratory disease.

Changes in glycemic control and pulmonary function during follow-up

The 125 prospective study patients were followed for 7.0 ± 0.5 years. Absolute and percentage-predicted lung function measures at baseline and follow-up are summarized in Table 2. All four values decreased significantly. The mean rate of decrease was 68 ml/year (1.1% predicted/year) for FVC, 71 ml/year (1.5% predict-

Table 1—*Baseline characteristics of FDS participants who had baseline spirometry only and those who had baseline and follow-up spirometry*

	Baseline only			
	Deceased by 31 January 2002	Alive on 31 January 2002	Baseline and follow-up	Trend *P* value
n	102	268	125	
Age (years)	71.0 ± 8.9	62.1 ± 10.6*	61.5 ± 8.6*	**<0.001**
Duration of diabetes (years)	7.6 (3.0–17.0)	4.7 (1.4–10.0)*	2.3 (0.6–6.5)*†	**<0.001**
Sex (% men)	60.8	47.8	48.8	0.07
BMI (kg/m^2)	29.0 ± 4.9	29.9 ± 5.4	29.9 ± 5.0	0.29
Waist: normal/overweight/obese (%)	13.0/21.0/66.0	12.5/24.2/63.4	12.0/20.0/68.0	0.89
Supine systolic blood pressure (mmHg)	160 ± 25	150 ± 21*	146 ± 20*	**<0.001**
Supine diastolic blood pressure (mmHg)	82 ± 12	82 ± 10	82 ± 9	0.87
Any exercise in the previous 2 weeks (%)	66.3	73.2	84.8*	**0.005**
Alcohol consumption (standard drinks/day)	0 (0–1.2)	0 (0–0.4)	0 (0–0.8)	0.63
Current/ex-/never smokers (%)	15.8/49.5/34.7	15.7/39.3/44.9	14.4/38.4/47.2	0.33
Fasting plasma glucose (mmol/l)	8.6 (6.6–11.8)	8.7 (7.0–11.0)	8.0 (6.7–9.9)	0.17
HbA_{1c} (%)	7.9 (6.5–9.2)	7.6 (6.6–9.1)	7.3 (6.3–8.5)	0.03
Total serum cholesterol (mmol/l)	5.6 ± 1.1	5.5 ± 1.0	5.6 ± 1.1	0.70
Serum HDL cholesterol (mmol/l)	1.00 ± 0.29	1.00 ± 0.31	1.06 ± 0.31	0.20
Serum triglycerides (mmol/l)	1.8 (1.1–2.9)	1.9 (1.1–3.2)	1.7 (1.0–3.0)	0.20
Microalbuminuria or worse (%)	63.6	38.5*	30.1*	**<0.001**
Retinopathy (%)	33.3	15.4*	14.4*	**<0.001**
Neuropathy (%)	61.3	27.4*	15.7*	**<0.001**
Coronary heart disease (%)	57.8	26.0*	29.0*	**<0.001**
FVC percentage predicted value				
Knudson	82.6 ± 20.0	90.7 ± 17.1*	94.3 ± 19.3*	**<0.001**
Busselton	81.3 ± 18.9	87.8 ± 14.9*	90.1 ± 16.9*	**<0.001**
FEV_1 percentage predicted value				
Knudson	79.6 ± 21.0	90.5 ± 18.2*	94.7 ± 22.0*	**<0.001**
Busselton	82.2 ± 20.5	91.3 ± 17.2*	94.2 ± 21.3*	**<0.001**
VC percentage predicted value	80.4 ± 20.2	89.7 ± 19.5*	92.9 ± 17.7*	**<0.001**
PEF percentage predicted value	69.7 ± 25.8	84.0 ± 25.5*	87.7 ± 24.6*	**<0.001**

Data are means ± SD, median (interquartile range), or proportions or geometric means (SD range). *$P < 0.01$ versus baseline only and deceased by 31 January 2002; †$P < 0.01$ versus baseline only and alive on 31 January 2002. Boldface data indicate significance.

ed/year) for FEV_1, 84 ml/year (1.6% predicted/year) for VC, and 17 l/min per year (3.1% predicted/year) for PEF. The rate of decrease in lung function for each measure was associated with its baseline value ($0.28 < r < 0.49$ for absolute measures and $0.41 < r < 0.49$ for percentage-predicted value; $P \leq 0.002$ in each case). At both baseline and follow-up, the Busselton-derived percentage-predicted values were similar to the Knudson-derived values for FEV_1 ($P \geq 0.47$), but FVC values were lower ($P < 0.001$). However, the magnitude of the change in percentage predicted over time was similar for FVC and FEV_1 using the two different methods ($P \geq 0.06$).

When mean Knudson-derived percentage-predicted values for each measure were plotted against median duration of diabetes at each time point (see Fig. 1), linear extrapolation gave an intercept at 100% lung function of between 1.1 and 2.8 years before diagnosis. The equivalent Busselton-derived inter-

Table 2—*Lung function measures as absolute values and as percentage of predicted values*

	Absolute measures			Percentage predicted			
	Baseline	Follow-up	Change	Equation	Baseline	Follow-up	Change
FVC	3.20 ± 0.89	2.72 ± 0.83*	−0.48 ± 0.51	Knudson	94.3 ± 19.3	86.4 ± 18.9*	−7.7 ± 17.8
				Busselton	90.1 ± 16.9	83.4 ± 17.7*	−6.7 ± 16.2
FEV_1	2.58 ± 0.78	2.08 ± 0.70*	−0.50 ± 0.51	Knudson	94.7 ± 22.0	83.7 ± 22.1*	−10.8 ± 20.5
				Busselton	94.2 ± 21.3	84.5 ± 22.2*	−9.7 ± 21.1
VC	3.15 ± 0.79	2.54 ± 0.85*	−0.58 ± 0.66	Knudson	92.9 ± 17.7	81.6 ± 20.1*	−10.9 ± 19.4
PEF	378 ± 129	260 ± 122*	−118 ± 109	Knudson	87.7 ± 24.6	66.2 ± 26.8*	−21.5 ± 26.8

Data are means ± SD. Absolute units of measurement were liters for FVC, FEV_1, and VC and liters per minute for PEF. For FVC and FEV_1, the percentage of predicted values are shown for both the Knudson and Busselton equations. *$P < 0.001$ versus baseline.

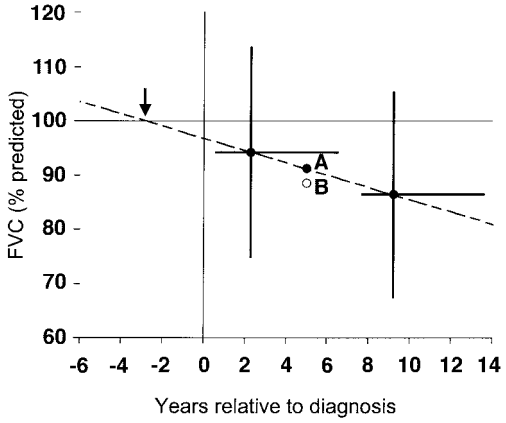

Figure 1—*FVC percentage-predicted values (mean ± SD) at both baseline and follow-up (median and interquartile range) using the predictive equations of Knudson and coworkers (see text). The trend line intersects the 100% FVC value at a point corresponding to −2.8 years on the x-axis. Point A is the FVC percentage-predicted value interpolated to a duration of diabetes of 5.0 years in the prospective cohort. Point B is the FVC percentage-predicted value in cross-sectional study patients who were not followed but who had a median duration of diabetes of 5.0 years.*

cepts were >1.8 years before diagnosis. Linear interpolation to a duration of 5.0 years generated Knudson-derived (and Busselton-derived) percentage-predicted estimates of 91.2 (87.5), 90.3 (90.4), 88.5, and 79.2% for FVC, FEV_1, VC, and PEF, respectively. The equivalent values for cross-sectional study patients who were not followed and whose median duration of diabetes was 5.0 years were 88.5 (87.0), 87.5 (90.2), 87.1, and 80.1%, respectively.

Because the rate of decline in lung function was dependent on the baseline level, we investigated associations between glycemic control (updated mean and follow-up values of both fasting plasma glucose and HbA_{1c}) and lung function at the end of follow-up (both absolute and percentage-predicted values) after adjusting for the baseline value and other potential confounding or explanatory variables. Three linear regression models were fitted sequentially: model 1, independent variables with a potential influence on follow-up lung function (baseline lung function, sex, follow-up age, BMI, duration of diabetes, and smoking status); model 2, variables listed in model 1, together with vascular risk factors (updated mean systolic and diastolic blood pressures and serum total cholesterol, HDL cholesterol, and triglyceride levels); and model 3, variables listed in model 2 plus presence or absence of complications at follow-up (CHD, microalbuminuria, neuropathy, and retinopathy). After controlling for the variables included in these three models, stepwise forward selection was performed to identify the measure of glycemic control with the strongest association with each lung function measure. This single index of glycemic exposure was then added back into the three models above.

For both height squared–normalized and percentage-predicted measures, there were consistent significant, negative associations with glycemic exposure in each model, in the form of either updated mean HbA_{1c} or follow-up HbA_{1c} or fasting plasma glucose (see Table 3). For the fully adjusted model, for example, an increase of 1% in updated mean HbA_{1c} was associated with a decrease of 4% in FVC percentage-predicted value. The FEV_1-to-FVC ratio at follow-up was also significantly and negatively associated with follow-up HbA_{1c} ($P = 0.005$).

Baseline predictors of mortality

Significant univariate baseline predictors of mortality at study end (January 2002) in the whole cohort were older age, male sex, longer duration of diabetes, higher systolic blood pressure, retinopathy, neuropathy, micro- or macroalbuminuria, and CHD ($P < 0.02$), as well as each of the four percentage-predicted lung function measures ($P \leq 0.001$ in each case for both Knudson- and Busselton-derived values). The nonspirometric variables in this list, and two others (BMI and smoking status) significant at $P < 0.2$, were incorporated into a forward-conditional Cox proportional hazards regression model. After adjusting for each of these variables in the model and adding the spirometric measures, only the FEV_1 percentage-predicted value (hazard ratio [95% CI] 1.13 [1.02–1.26] for a decrease of 10%; $P = 0.025$) was a significant independent predictor of all-cause mortality. The findings when Busselton-derived percentage-predicted values were used were similar (data not shown).

CONCLUSIONS

— The present study is the largest to have examined prospectively the relationship between diabetes and pulmonary function and the only one in patients with type 2 diabetes. We found that, relative to values predicted for age, sex, and height, each of FVC, FEV_1, VC, and PEF decreased at an average of between 1.1 and 3.1%/year in our community-based cohort. FVC and FEV_1 decreased by means of 68 and 71 ml/year in absolute terms, rates that are approaching double those reported in prospective studies involving samples from the general population (≤40 ml/year) (10,17), including one from the Busselton study (15). These data provide evidence that reduced lung volumes and airflow limitation complicate diabetes.

Glycemic exposure (principally in the form of the updated mean or follow-up HbA_{1c}) was a strong and consistent negative predictor of follow-up lung function after adjusting for baseline values and potential confounding or explanatory variables. Previous studies assessing the relationship between blood glucose control and pulmonary function have produced inconsistent results. Cross-sectional associations between HbA_{1c} and spirometric measures were weak in our original study (3) and were not seen in the Rancho Bernado cohort (2). However, a large Danish cross-sectional population study (1) showed a negative association between plasma glucose and both FVC and FEV_1. In a small-scale, 6-year study of patients with type 1 diabetes, intensive treatment by subcutaneous insulin infusion improved both FVC and FEV_1 percentage-predicted values, whereas those allocated to twice-daily premixed insulin had >15% mean reductions in these measures (18). Thus, the only two prospective studies in diabetes have shown consistent results, albeit in different contexts.

Our study has limitations. First, the prospective study patients were healthy survivors. The percentage-predicted values of each spirometric measure at 5.0 years' duration of diabetes interpolated from our baseline and follow-up data were close to, but mostly greater than, those observed in the cross-sectional patients who were not followed and who had been diabetic for a median of 5.0 years. Second, because of the time between paired studies, we used two different spirometers and, despite validation to American Thoracic Society standards and the use of the same algorithms to generate percentage-predicted values, there may have been differences in performance. However, the potential discrepancies be-

Table 3—*Fitted regression models showing the best glycemic predictor of height squared–normalized (top) and percentage of predicted value (%pred) (bottom) follow-up lung function measures after multivariate adjustment*

	FVC/h^2			FEV_1/h_2			VC/h^2			PEF/h^2		
Model	β	SE	*P*	β	SE	*P*	β	SE	*P*	β	SE	*P*
1												
Updated mean HbA_{1c}	−0.042	0.013	0.002	−0.046	0.012	<0.001						
Follow-up HbA_{1c}										−5.83	2.23	0.010
Follow-up fasting plasma glucose							−0.025	0.007	<0.001			
2												
Updated mean HbA_{1c}	−0.051	0.013	<0.001	−0.055	0.012	<0.001						
Follow-up HbA_{1c}										−6.25	2.25	0.006
Follow-up fasting plasma glucose							−0.025	0.007	<0.001			
3												
Updated mean HbA_{1c}	−0.049	0.015	0.002	−0.053	0.013	<0.001						
Follow-up HbA_{1c}										−7.50	2.31	0.002
Follow-up fasting plasma glucose							−0.030	0.007	<0.001			

	FVC %pred			FEV_1 %pred			VC %pred			PEF %pred		
Model	β	SE	*P*	β	SE	*P*	β	SE	*P*	β	SE	*P*
1												
Updated mean HbA_{1c}	−3.20	1.21	0.009									
	−3.43*	1.14*	0.003	−5.12*	1.44*	0.001						
Follow-up HbA_{1c}				−4.02	1.17	0.001				−4.16	1.54	0.008
Follow-up fasting plasma glucose							−1.90	0.55	0.001			
2												
Updated mean HbA_{1c}	−3.89	1.20	0.002									
	−4.12*	1.13*	<0.001	−6.04*	1.41*	<0.001						
Follow-up HbA_{1c}				−4.54	1.14	<0.001				−4.49	1.55	0.004
Follow-up fasting plasma glucose							−1.87	0.56	0.001			
3												
Updated mean HbA_{1c}	−4.01	1.41	0.005									
	−3.91*	1.33*	0.004	−5.92*	1.56*	<0.001						
Follow-up HbA_{1c}				−5.63	1.24	<0.001				−5.47	1.54	0.001
Follow-up fasting plasma glucose							−2.14	0.63	0.001			

*Results derived from using the Busselton predictive equations.

tween spirometric measures obtained by the two instruments (0–5%) (19–22) do not account for the significantly greater changes we found in our diabetic patients compared with those predicted. In addition, preliminary 3-year follow-up data from the Atherosclerosis Risk in Communities study (23) also show a more rapid decrease in diabetic versus nondiabetic individuals. Our data suggest that lung function measures start to decrease several years before diagnosis, consistent with similar estimates from studies of retinopathy progression (24) and preliminary longitudinal spirometric data from a small European cohort (5).

Reduced spirometric measurements do not identify a specific underlying pathology, but there have been preliminary reports of histopathologic changes in the lungs of diabetic patients, including basal lamina thickening (25) and fibrosis (26). Other possible contributory factors include glycation of chest wall/bronchial tree proteins (27,28), autonomic and/or phrenic neuropathy causing alterations in bronchial reactivity and respiratory muscle function (29), and an increased propensity to, and severity of, respiratory infections (30,31). It is also possible that our spirometric data reflect the effects of chronic illness on effort-dependent measures, but duration of diabetes was not consistently associated with changes in lung function.

Several studies have found an association between impaired lung function and death (32–34). We found that a 10% decrease in FEV_1 was associated with a 12% increase in all-cause mortality, a figure very similar to the 11–15% increase found in the general population (14,35,36), including a report from Busselton (15). This indicates that, despite the presence of other strong diabetes-related causes of death, including CHD and microangiopathy, airflow limitation was an important predictor of mortality. This finding is consistent with Wisconsin Epidemiologic Study of Diabetic Retinopathy data showing an association between PEF and mortality (37).

Our data support the suggestion that the lung is a target organ in diabetes and that glycemic exposure is a strong determinant of reduced pulmonary function in type 2 patients. Furthermore, because measures of airflow limitation predict all-cause mortality in type 2 diabetes, intensive glycemic management may reduce

the risk of death through improved ventilatory function independent of other beneficial effects. In the light of the development of inhaled insulin preparations, our data emphasize the importance of control groups in the assessment of pulmonary toxicity so the effects of glycemic exposure per se can be differentiated from those related to therapy.

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