Pulmonary Function Is a Long-term Predictor of Mortality in the General Population*

29-Year Follow-up of the Buffalo Health Study

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Study objectives: **Results from several studies have described a relationship between pulmonary function and both all-cause and cause-specific mortality. The purpose of this study was to investigate the predictive value of pulmonary function by gender after 29 years of follow-up.**
Design: **Prospective study with 29-year follow-up of the Buffalo Health Study cohort.**
Participants: **Randomly selected sample of 554 men and 641 women, aged 20 to 89 years, from all listed households of the city of Buffalo, NY.**
Measurements and results: **Baseline measurements were performed in 1960 to 1961. Pulmonary function was assessed based on FEV_1 expressed as the normal percent predicted (FEV_1%pred). FEV_1%pred adjusted by age, body mass index, systolic BP, education, and smoking status was inversely related to all-cause mortality in both men and women ($p < 0.01$). A sequential survival analysis in participants who had a survival time of at least 5, 10, 15, 20, and 25 years after enrollment in the study was also performed. Except for men who survived for > 25 years, we observed a statistically significant negative association between FEV_1%pred and all-cause mortality. FEV_1%pred was also inversely related to ischemic heart disease (IHD) mortality. When participants were divided into quintiles of FEV_1%pred, participants in the lowest quintile of FEV_1%pred experienced significantly higher all-cause mortality compared with participants in the highest quintile of FEV_1%pred. For the entire follow-up period, the adjusted hazard ratios for all-cause mortality were 2.24 (95% confidence interval [CI], 1.60 to 3.13) for men and 1.81 (95% CI, 1.24 to 2.63) for women, respectively. Hazard ratios for death from IHD in the lowest quintile of FEV_1%pred were 2.11 (95% CI, 1.20 to 3.71) and 1.96 (95% CI, 0.99 to 3.88) for men and women, respectively.**
Conclusions: **These results suggest that pulmonary function is a long-term predictor for overall survival rates in both genders and could be used as a tool in general health assessment.**

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Key words: cohort study; FEV_1; ischemic heart disease; lung function; mortality

Abbreviations: BMI = body mass index; BTPS = body temperature pressure saturation; CI = confidence interval; FEV_1%pred = FEV_1 expressed as the normal percent predicted; IHD = ischemic heart disease; $QFEV_1$%pred = quintiles of FEV_1 percent predicted; SBP = systolic BP

Results from several studies have described a significant relationship between pulmonary function and both all-cause mortality as well as cause-specific mortality (*ie*, ischemic heart disease [IHD] mortality).[1–4] Pulmonary function was assessed from the FEV_1 expressed as the normal percent predicted (FEV_1%pred) in most of these studies. It has been suggested that the observed association between pulmonary function and mortality may be explained by smoking status.[5] However, several authors reported FEV_1 to be a risk factor for mortality independent of smoking status,[4,6] and others have found the association also in never-smokers[3,6,7];

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therefore, direct exposure to cigarette smoke cannot be the underlying cause. The period over which pulmonary function remains a predictor of mortality is unknown. Previous studies report follow-up periods of 10 to 25 years.[3–6,8–12] These studies showed an increased risk associated with lower levels of pulmonary function, but follow-up periods of > 25 years have not been examined, to our knowledge.

Despite numerous reports, little is known about whether or not there is a causal relationship between impaired pulmonary function and increased mortality. A recognized problem with the interpretation of this association is that study participants at baseline may have undiagnosed or asymptomatic disease that is associated with both lower levels of pulmonary function and short-term mortality risk.[1,8] In fact, it has been suggested that pulmonary function is a proxy for other disease conditions that lead to mortality and, therefore, that pulmonary function is not causally related to mortality. In an effort to overcome this concern, Hole et al[3] stated that the exclusion of participants who died during the first 5 or 10 years after follow-up did not significantly alter results, but periods of exclusion of > 10 years have not been examined until now. Persistent elevated risk levels after the exclusion of participants who die earlier during follow-up would suggest a direct effect.

The purpose of this study was to investigate the association between pulmonary function and mortality for periods of > 25 years of follow-up and, in particular, to examine this relationship for follow-up of > 15 years in women. We also sought to determine the time span over which pulmonary function remains a significant predictor of mortality by sequential survival analysis in participants who had minimum survival times of 5, 10, 15, 20, and 25 years after enrollment in the study.

Materials and Methods

Study Population

The Buffalo BP/Erie County Air Pollution-Pulmonary Function Study enrolled 2,273 men and women aged 15 to 96 years from 1960 to 1961. This epidemiologic study engaged a randomly selected population sample of the city of Buffalo, NY, and was designed initially to investigate factors related to hypertension and pulmonary function. The details of the study design, participation, follow-up, and ascertainment of vital status have been described elsewhere.[13–15] In brief, a random sample of 1,369 households was selected, which is equivalent to a sampling ratio of 7.7 households per 1,000. At least one member of the 1,082 participating households agreed to participate, and the overall participation rate was 79.0%.[14] The specific objectives of the study were to explore how social and lifestyle factors, including occupation, education, ethnic background, exercise habits, diet, and smoking status influence BP. Another purpose of the study was to investigate how environmental exposure to air pollution and tobacco use influence pulmonary function. Therefore, spirometric measurements were performed.

A total of 369 participants (16.2%) were African American or other minorities and are not included in this analysis because of incomplete follow-up for this group and limitations in establishing reference equations for pulmonary function in race-gender subgroups from a relatively small sample. Of the remaining 1,904 participants, 156 (8.2%) had insufficient data available to initiate follow-up. We excluded another 254 participants (13.3%) because of their refusal to perform pulmonary function tests, an inability to perform the forced expiration maneuver, or a lack of spirometry curves to confirm the pulmonary function test data retrieved from magnetic tapes. Vital status was determined beginning in 1990; participants were followed up until their death or until the end of the study. The primary outcome of this analysis was vital status and cause of death, and no longitudinal measurements of covariates were performed.

Pulmonary Function Testing

Pulmonary function measurements were obtained with a spirometer (Vitalor; McKesson; Toledo, OH) adapted for field use. FVC and FEV_1 were recorded for at least three FVC maneuvers, as described.[13] Each of the test records was evaluated, and the FEV_1 was calculated by a physician with experience in pulmonary function testing using back extrapolation. The best FEV_1 test result was used for analysis according to the current American Thoracic Society standardized protocol.[16] Of the 1,494 participants with complete pulmonary function test data, 21 had unsatisfactory tracings of the spirometry curves, which exhibited insufficient expiratory times to calculate the FEV_1 (1.4%). We excluded 145 participants (9.7%) who were < 20 years of age at baseline, because pulmonary function in this age group shows variation owing to differences among participants in growth and because of the possibility that participants < 20 years would not have reached their adult height for body mass index (BMI) calculation.[17] Baseline data (*eg*, weight, height, and smoking status) were incomplete for 44 participants (2.9%), and vital status at any time during follow-up could not be confirmed in 69 women (4.6%) and 20 men (1.3%). The remaining 1,195 subjects, 641 women and 554 men, were included in the current analysis. Raw FEV_1 values were multiplied by 1.10 to correct for body temperature pressure saturation (BTPS) for better comparison with other published data, as previously described by Sorlie et al.[18] A constant correction factor for BTPS was used because no measurements of internal spirometer or room temperature were available. The use of this adjustment, is likely to introduce random error in the determination of FEV_1, but it is unlikely to cause bias.[18] FEV_1 relative to the predicted value was used to estimate pulmonary function impairment. Predicted values of FEV_1 were calculated from linear regression on age and height. The following equations were obtained,

$$\text{predicted } FEV_1 = -1.861 - (0.039 \times \text{age}) + (4.119 \times \text{height}) \text{ for men}$$

and,

$$\text{predicted } FEV_1 = 1.137 - (0.027 \times \text{age}) + (1.588 \times \text{height}) \text{ for women.}$$

Age was measured in years, and height was measured in meters. These coefficients were derived from pulmonary function records of 57 men and 288 women who never smoked, and they are in good agreement with other published prediction equations.[19] Percentages of the predicted FEV_1 (FEV_1%pred) were calculated, and each participant was classified into quintiles of FEV_1%pred ($QFEV_1$%pred). The corresponding quintile points

were 80.2%, 89.9%, 98.4%, and 108.8% for men and 80.5%, 93.8%, 104.1%, and 113.6% for women. The use of nonlinear prediction equations did not significantly alter the results. The maximum recorded volume of the employed spirometer was limited to 4.80 L before BTPS correction. Only one man (0.2%) reached this limit. After calculation of the FEV_1%pred for this participant, he was assigned into the highest $QFEV_1$%pred. Therefore, the limitation of the spirometer to 4.8 L of measurable volume did not influence the results presented for quintiles and was small when FEV_1%pred was used as a continuous variable. The maximum achieved FEV_1 for women was 4.57 L.

Interview

Information on anthropometric, demographic, and lifestyle variables was obtained at baseline by an interviewer-administered questionnaire, and systolic BP (SBP) and diastolic BP were measured three times in a standardized manner, as previously described in detail.[15] BMI was calculated from self-reported weight divided by height squared.

Follow-up and Outcome Measures

Participants were enrolled from June 1960 through December 1961 and were followed up for an average length of 29 years until the end of the follow-up on December 31, 1989. Baseline data and measurements were obtained at enrollment, and participants were followed up until their death or the end of the study, respectively. Details of the follow-up and ascertainment of vital status have been described by Dorn et al.[15] Briefly, vital status was determined with computer-based searches of the New York State Department Health Vital Records Death Registry, the Cancer Tumor Registry, the Department of Motor Vehicle records of drivers' licenses and automobile registrations, the US Social Security Administration Death Master Files, and manual searches of the telephone and Polk directories of the city of Buffalo, including its suburbs. We also attempted to contact the participant's last employer, neighbor, church, or other contact address if recorded in the original questionnaire. Living participants were followed up either through direct telephone contact or mail correspondence or through contact with relatives or other immediate contact persons (*eg*, nursing home personnel). Rigid matching criteria (exact spelling of the name and exact date of birth) were used and were manually reviewed to determine the death of participants from death certificates. The primary aim of this study was to assess mortality from all causes. The date and underlying cause of death were obtained from the death certificate. A trained nosologist upgraded *Ninth International Classification of Diseases* codes, as previously described.[15] All recorded deaths during the follow-up period from the day of the interview until the end of 1989 were taken into account for the current analysis. *Ninth International Classification of Diseases* codes 410 through 414 were classified as IHD (acute myocardial infarction, 410; other acute and subacute forms of IHD, 411 [*eg*, postmyocardial infarction syndrome, 411.0; intermediate coronary syndrome, 411.1]; old myocardial infarction, 412; angina pectoris, 413; other forms of chronic IHD, 414), codes 390 through 459 were classified as cardiovascular, codes 140 through 209 were classified as cancer, and codes 460 through 520 were classified as respiratory deaths.

Statistical Analysis

Student's *t* test and χ^2 analysis were utilized to compare the included participants to those persons excluded or unavailable for follow-up. We used the Cox proportional hazards model[20] to calculate the hazard ratios associated with pulmonary function status (FEV_1%pred or $QFEV_1$%pred) and mortality rate, with adjustment for known risk factors. Age, education, smoking status (never, former, or current smoker), SBP, and BMI were utilized as covariates because other studies showed these to be predictors of mortality. In the models exploring the subgroups with longer survival times, these covariates were included independently of the level of statistical significance. No statistically significant interactions were observed. Never-smokers were defined as those who smoked < 100 cigarettes in their lifetime. Hazard ratios were calculated utilizing FEV_1%pred as continuous variable or in quintiles ($QFEV_1$%pred) with the highest $QFEV_1$%pred serving as the reference category. Survival analysis was repeated after the exclusion of participants who survived < 5, 10, 15, 20, and 25 years. Computer software (SPSS; SPSS Inc; Chicago, IL)[21] was used for the analyses. Statistical significance was considered for p values < 0.05 (two-tailed), and 95% confidence intervals (CI) were computed around the risk-point estimates.

Results

There was no statistically significant difference in baseline variables between the 254 participants without pulmonary function records and the remaining 1,494 participants with pulmonary function data. Participants without pulmonary function data were less likely to be women than men (49.8% vs 55.8%, respectively), were slightly older (45.7 vs 44.2 years, respectively), and had higher SBP (141.4 vs 139.0 mm Hg, respectively) but showed similar height, education, and smoking habits.

Baseline characteristics of study participants included in the analysis are shown separately for men and women in Table 1. The age ranges were 20 to 89 years in men and 20 to 84 years in women. On average, men were slightly older and taller than women. BMI and SBP were higher in men. Overall smoking prevalence was high, and men were more likely to be current or ex-smokers than women. The number of years of education was similar in both

Table 1—*Demographic and Lung Function Variables at Baseline, Buffalo Health Study/Erie County Air Pollution-Respiratory Function Study, 1960 to 1961

Variable	Men (n = 554)	Women (n = 641)
Age, yr	47.5 (16.1)	46.2 (15.8)
Height, m	1.75 (0.08)	1.62 (0.06)†
BMI, kg/m^2	25.5 (3.8)	24.7 (4.6)
SBP, mm Hg	143.2 (23.2)	138.8 (27.6)†
Education, yr	10.5 (5.2)	10.2 (3.0)
FEV_1	3.23 (0.95)	2.43 (0.70)†
FEV_1 %pred	93.2 (19.8)	97.3 (22.2)†
Current smoker, %	73.3	45.3‡
Ex-smoker, %	16.4	9.8
Never-smoker, %	10.3	44.9‡

*Values given as mean (SD).
†$p < 0.05$ (Student's *t* test).
‡$p < 0.05$ (χ^2 analysis).

sexes. While absolute FEV_1 was higher in men, FEV_1%pred was lower in men than in women.

In addition, no statistically significant differences in any of these variables were observed between the subjects included in the study and those who were excluded because vital status could not be confirmed (*ie*, 20 men and 69 women). Subjects with information on follow-up in the group included in the study were slightly older than those without (men, 2.5 years older; women, 3.0 years older) and had higher SBPs (men, 2.3 mm Hg higher; women, 5.8 mm Hg higher). Years of education, BMI, height, and FEV_1%pred were similar for both included and excluded subjects.

Table 2 shows the vital status and underlying cause of death for all participants included in the present study. During the entire follow-up period, 54.5% of the men and 43.4% of the women died. Cardiovascular disease and IHD, in particular, represented the predominant causes of death in both genders. Respiratory disease was found to be the underlying cause of death in 9.6% of the deceased men but in only 3.6% of the deceased women.

Baseline characteristics for participants with different lengths of survival (entire follow-up, survival > 5, 10, 15, 20, or 25 years) are shown in Table 3. As expected, mean age, BMI, and SBP were inversely related to length of survival, while education and FEV_1%pred were positively related to length of survival. These results were statistically significant when all included participants were analyzed, but not all variables remained statistically significant in all survival groups. Height did not differ significantly between the survival groups.

The results of the Cox proportional hazards survival analyses for different survival periods are summarized in Tables 4 and 5. The results of the survival analysis indicated that hazard ratios remained proportional over time (data not shown). Table 4 shows the hazard ratios and 95% CIs for all-cause mortality by FEV_1%pred (continuous variable) and $QFEV_1$%pred after adjustment for age, BMI, smoking status, SBP, and education. FEV_1%pred was a statistically significant predictor for all-cause mortality in men and women for the entire 29 years of follow-up (all survival groups). The hazard ratios were 0.985 for men and 0.990 for women, indicating a 1 to 1.5% decrease in mortality risk associated with a 1% increase in FEV_1%pred. In men, FEV1%pred was statistically significantly associated with all-cause mortality for all the survival periods examined except after the exclusion of participants who died ≥ 25 years after enrollment. In women, FEV_1%pred was a statistically significant predictor in all but one survival group (survival for > 20 years; $p = 0.053$). The analysis of $QFEV_1$%pred indicated that for the 29-year follow-up period as a whole compared to the highest quintile, the relative hazard ratio for those in the lowest quintile was 2.24 for men and 1.81 for women. Increased risks also were observed for participants with moderately lower levels of FEV_1 (in the second quintile). Similar results were observed for men when participants who survived for < 5 or 10 years were excluded, but hazard ratios declined and did not reach statistical significance after the exclusion of participants with survival times of < 15 years. In women, the risk for all-cause mortality for the first quintile of FEV_1%pred was significantly elevated in all survival groups except after the exclusion of participants who survived for > 20 years.

The hazard ratios for death from IHD for FEV_1%pred and $QFEV_1$%pred are shown in Table 5. FEV_1%pred as a continuous variable was a statistically significant predictor of IHD mortality in both men and women for the 29-year follow-up period as a whole (all survival groups), and the corresponding hazard ratios were 0.987 for men and 0.990 for women. In both men and women, there was a statistically significant or borderline statistically significant negative association of FEV_1%pred with IHD mortality in all survival periods. In quintile analyses, compared to the highest quintile, participants in the lowest quintile of FEV_1%pred exhibited an overall hazard ratio for IHD death of 2.11 in men and 1.96 in women. The risk remained statistically significant in men only for the survival groups of > 5 and 10 years where the risk was elevated also in the second quintile compared to the highest. In women, all hazard ratios indicated an excess risk but did not reach statistical significance.

Table 2—*Vital Status and Cause of Death After 29-Year Follow-up, Buffalo Health Study/Erie County Air Pollution-Respiratory Function Study, 1960 to 1961

Variable	Male (n = 554)	Female (n = 641)
Vital status		
Alive	252 (45.5)	363 (56.6)
Deceased	302 (54.5)	278 (43.4)
CVD†	163 (53.4)	149 (53.6)
IHD†	118 (39.1)	79 (28.4)
Stroke†	20 (6.6)	33 (11.9)
Cancer†	67 (22.2)	63 (22.7)
Injury†	4 (1.3)	4 (1.4)
Respiratory†	29 (9.6)	10 (3.6)
Other†	39 (12.9)	52 (1.9)

*Values given as No. (%). CVD = cardiovascular disease.
†Percentages given as percent of all-cause mortality.

Discussion

The findings of this cohort study suggest that FEV_1 is a risk factor for all-cause and for IHD

Table 3—*Characteristics Measured by Length of Minimum Survival and Gender, Buffalo Health Study/Erie County Air Pollution-Respiratory Function Study, 1960 to 1961

Variable	Total Included Cohort	Survival > 5 yr	> 10 yr	> 15 yr	> 20 yr	> 25 yr
Age, yr						
Men	47.5 (16.1)	45.7 (15.5)	43.6 (14.6)	41.1 (13.6)	39.3 (12.6)	36.6 (10.9)
Women	46.2 (15.8)	45.2 (15.4)	44.1 (15.1)	42.6 (14.4)	40.9 (13.7)	38.6 (12.5)
Height, m						
Men	1.75 (0.1)	1.75 (0.1)	1.75 (0.1)	1.75 (0.1)	1.76 (0.1)	1.75 (0.1)
Women	1.62 (0.1)	1.62 (0.1)	1.62 (0.1)	1.62 (0.1)	1.62 (0.1)	1.62 (0.1)
BMI, kg/m^2						
Men	25.5 (3.8)	25.6 (3.8)	25.6 (3.8)	25.4 (3.6)	25.3 (3.3)	25.3 (3.3)
Women	24.7 (4.6)	24.7 (4.6)	24.5 (4.5)	24.4 (4.4)	24.3 (4.4)	24.1 (4.3)
SBP, mm Hg						
Men	143.2 (23.2)	142.1 (22.7)	140.1 (21.1)	138.1 (19.7)	136.2 (17.9)	135.1 (16.3)
Women	138.8 (27.6)	137.2 (26.2)	135.4 (25.2)	133.3 (23.9)	131.0 (22.5)	128.5 (20.7)
Education, yr						
Men	10.5 (5.2)	10.5 (3.5)	10.7 (3.4)	11.0 (3.2)	11.3 (3.1)	11.4 (3.0)
Women	10.2 (3.0)	10.3 (3.0)	10.4 (2.9)	10.5 (2.8)	10.6 (2.8)	10.8 (2.7)
FEV_1%pred						
Men	93.2 (19.8)	93.9 (18.6)	94.4 (17.9)	95.1 (17.4)	94.9 (16.9)	95.2 (16.5)
Women	97.3 (22.2)	97.6 (22.2)	97.7 (22.0)	98.9 (21.4)	99.5 (21.3)	99.7 (21.4)
Included participants, No.†						
Men	554	500	444	383	345	285
Women	641	614	571	531	479	420

*Values given as mean (SD), unless otherwise indicated.
†Total number of participants alive.

mortality for a follow-up period of 29 years after adjustment for other risk factors. The exclusion of participants who die early during follow-up does not seem to alter the results. Only after the exclusion of participants who died within 25 years of follow-up does FEV_1 not predict the all-cause mortality rate in men, although power was limited after the exclusion of this group of participants, and the lack of an association may be due to chance.

The results of this study confirm previous reports that pulmonary function is an independent risk factor for overall all-cause mortality and IHD mortality and suggest that this risk is evident for longer periods than those studied to date.[1,3,5,8,9,18,22,23] Previous studies with long follow-up periods are limited by the characteristics of the study population. Both the study by Beaty et al,[8] which examined a follow-up period of 24 years in volunteers, and the study by Weiss et al,[4] which examined a follow-up period averaging 25 years, are restricted to men. Other studies that included women had significantly shorter follow-up periods.[2,3,6,7,9,18] No previous study has reported an association of lower levels of pulmonary function with all-cause mortality for a follow-up period of 29 years. Our risk estimates for FEV_1%pred and all-cause mortality for both men and women are similar to those in other studies.[3,4,9,10] As a continuous variable, FEV_1%pred was a significant predictor of IHD mortality in both men and women. The risk estimates for death from IHD in the lowest $QFEV_1$%pred of 2.11 for men and 1.96 in women are in agreement with the study by Hole et al,[3] which examined participants in terms of $QFEV_1$. It is important to note that elevated hazard ratios were observed also for participants with lower levels of lung function in the second quintile. This observation suggests that the increased risk is not confined to a small fraction of the population with severely reduced pulmonary function.

There has been speculation about the underlying mechanism that could explain the predictive properties of pulmonary function with regard to mortality. The initial concerns that FEV_1%pred may be a proxy for smoking status have been solved by reports showing that this association is independent of smoking status and that it is present in never-smokers.[3,6,7] The number of never-smoking men (n = 57) in our study was too small for separate analysis. In the group of never-smoking women as a whole (n = 288), FEV_1%pred as a continuous variable was inversely related to all-cause mortality with a hazard ratio of 0.993 (95% CI, 0.985 to 1.000; p = 0.053) after adjustment for other risk factors. Compared to the highest quintile in this subgroup, the all-cause mortality risk in the lowest $QFEV_1$%pred was 1.58 (95% CI, 0.94 to 2.67; results not shown), which is similar to the results of Hole et al.[3]

It is not clear whether the observed association

Table 4—*Cox Proportional Hazards for All-Cause Mortality by FEV_1%pred as a Continuous Variable and in Quintiles, Buffalo Health Study, 1960 to 1989

	Survival					
FEV_1%pred	Total Included Cohort	≥ 5 yr	≥ 10 yr	≥ 15 yr	≥ 20 yr	≥ 25 yr
Men						
FEV_1%pred	0.985 (0.980–0.990)	0.985 (0.979–0.991)	0.983 (0.976–0.990)	0.986 (0.978–0.995)	0.987 (0.977–0.997)	0.998 (0.980–1.017)
$QFEV_1$%pred						
5th quintile	1	1	1	1	1	1
4th quintile	1.08 (0.74–1.58)	1.27 (0.84–1.91)	1.39 (0.87–2.24)	0.99 (0.54–1.82)	0.91 (0.43–1.92)	0.58 (0.17–1.97)
3rd quintile	1.09 (0.74–1.60)	1.14 (0.75–1.72)	1.13 (0.70–1.81)	0.85 (0.48–1.50)	0.66 (0.33–1.34)	0.41 (0.13–1.30)
2nd quintile	1.61 (1.13–2.29)	1.76 (1.19–2.61)	1.92 (1.23–3.00)	1.49 (0.90–2.49)	1.68 (0.93–3.02)	0.91 (0.32–2.62)
1st quintile	2.24 (1.60–3.13)	2.22 (1.51–3.26)	2.30 (1.47–3.61)	1.65 (0.95–2.87)	1.60 (0.82–3.09)	1.04 (0.34–3.15)
Participants alive, total No.	554	500	444	383	345	285
Mortality,† %	55	50	43	34	24	12
Women						
FEV_1%pred	0.990 (0.985–0.995)	0.990 (0.985–0.996)	0.988 (0.982–0.994)	0.992 (0.985–0.998)	0.992 (0.985–1.000)	0.987 (0.976–0.998)
$QFEV_1$%pred						
5th quintile	1	1	1	1	1	1
4th quintile	1.23 (0.81–1.86)	1.20 (0.78–1.84)	1.25 (0.78–1.99)	1.27 (0.77–2.10)	1.23 (0.68–2.23)	1.56 (0.66–3.69)
3rd quintile	1.43 (0.96–2.13)	1.33 (0.88–2.02)	1.30 (0.81–2.08)	1.46 (0.89–2.39)	1.20 (0.66–2.19)	1.69 (0.70–4.07)
2nd quintile	1.43 (0.96–2.12)	1.38 (0.92–2.09)	1.66 (1.06–2.61)	1.39 (0.84–2.31)	1.21 (0.67–2.19)	1.06 (0.42–2.63)
1st quintile	1.81 (1.24–2.63)	1.79 (1.21–2.63)	2.06 (1.34–3.17)	1.71 (1.05–2.77)	1.53 (0.87–2.70)	2.56 (1.17–5.64)
Participants alive, total No.	641	614	571	531	479	420
Mortality,† %	43	41	37	32	27	14

*Values given as hazard ratio (95% CI), unless otherwise indicated.
†All-cause mortality given as the percentage of the total number of participants who are alive.

reflects a cause-effect relationship of reduced pulmonary function with mortality. The lung is a primary defense organ against environmental toxins, and impaired pulmonary function could lead to decreased tolerance against these environmental toxins. This hypothesis has been described in detail by Cohen,[24] who speculated that impaired pulmonary function contributes to a variety of disease processes that ultimately lead to disease and death. On the other hand, factors may be involved that affect both pulmonary function and mortality. Weiss et al[4] speculated that FEV_1 is an indicator of general health influenced by environmental toxic exposure and is, therefore, related to survival. FEV_1 levels could affect physical activity, which may prolong survival times through its influences on metabolism with decreased IHD mortality. These authors also hypothesized that oxidants, which influence FEV_1 and health status, might be responsible for the observed relationship.[4] In fact, oxidants have been shown to play a role in the etiology of various diseases, including IHD.[25] In 1997, we showed in a cross-sectional study[26] that indicators of oxidative stress are negatively correlated with FEV_1%pred. Several other authors have reported positive correlations between antioxidant vitamins and respiratory function,[27–32] but reduced pulmonary function also could be the underlying factor responsible for increased oxidative stress.[26] Further research is needed to investigate the hypothesis that oxidative stress is related to both pulmonary function and mortality.

In female participants in this study, pulmonary function was a predictor of all-cause mortality for a period of > 25 years, while in male participants, pulmonary function lost its predictive value after 20 years from baseline. The underlying reason for the observed difference between men and women needs to be explained. Men and women compared well with respect to baseline characteristics in the different survival groups except for smoking status. A change in lifestyle factors (*eg*, smoking cessation) after baseline measures were taken may have led to a shift between quintiles of FEV_1%pred. This shift, in turn, could have influenced the relative hazard associated with FEV_1%pred. We may have observed a decline in risk in men that was influenced by smoking but was not controlled for adequately in the analysis by utilizing smoking status alone. The latter is less likely, because when we included pack-years as a summary measure of smoking exposure in the analysis, the results did not change significantly. Finally, men die earlier than women, and the lack of

Table 5—*Cox Proportional Hazards for IHD Mortality by FEV_1%pred as Continuous Variable and in Quintiles, Buffalo Health Study, 1960 to 1989***

	Survival					
FEV_1%pred	Total Included Cohort	≥ 5 yr	≥ 10 yr	≥ 15 yr	≥ 20 yr	≥ 25 yr
Men						
FEV_1%pred	0.987 (0.979–0.996)	0.985 (0.975–0.995)	0.981 (0.969–0.993)	0.983 (0.967–1.000)	0.973 (0.952–0.993)	0.985 (0.946–1.025)
$QFEV_1$%pred						
5th quintile	1	1	1	1	1	1
4th quintile	1.21 (0.66–2.21)	1.52 (0.74–3.11)	1.84 (0.78–4.32)	1.08 (0.32–3.62)	0.90 (0.17–4.80)	1.00 (0.06–17.83)
3rd quintile	0.92 (0.47–1.81)	1.17 (0.55–2.50)	1.27 (0.52–3.13)	0.71 (0.22–2.27)	0.64 (0.14–3.01)	0.71 (0.05–10.86)
2nd quintile	2.62 (1.52–4.53)	3.30 (1.71–6.35)	4.49 (2.08–9.68)	2.46 (0.96–6.32)	3.75 (1.20–11.73)	3.16 (0.29–34.80)
1st quintile	2.11 (1.20–3.71)	2.72 (1.39–5.35)	3.21 (1.42–7.23)	2.06 (0.73–5.83)	3.07 (0.84–11.21)	1.86 (0.13–26.67)
Participants alive, total No.	554	500	443	383	345	285
Mortality,† %	21	18	15	10	8	3
Women						
FEV_1%pred	0.990 (0.980–0.999)	0.990 (0.980–0.999)	0.989 (0.979–0.999)	0.991 (0.980–1.003)	0.991 (0.977–1.004)	0.988 (0.970–1.006)
$QFEV_1$%pred						
5th quintile	1	1	1	1	1	1
4th quintile	1.13 (0.53–2.39)	1.13 (0.53–2.39)	1.17 (0.55–2.52)	1.20 (0.51–2.80)	0.97 (0.32–2.88)	0.84 (0.19–3.77)
3rd quintile	1.39 (0.66–2.93)	1.39 (0.66–2.93)	1.38 (0.64–2.97)	1.74 (0.75–4.02)	1.38 (0.46–4.11)	0.91 (0.17–4.99)
2nd quintile	1.17 (0.55–2.490)	1.17 (0.55–2.490)	1.05 (0.46–2.37)	0.86 (0.34–2.21)	1.11 (0.40–3.03)	1.11 (0.29–4.21)
1st quintile	1.96 (0.99–3.88)	1.96 (0.99–3.88)	2.03 (0.99–4.14)	1.89 (0.84–4.24)	1.74 (0.66–4.59)	2.36 (0.70–8.02)
Participants alive, total No.	641	614	571	531	479	420
Mortality,† %	13	13	12	11	8	5

*Values given as hazard ratio (95% CI), unless otherwise indicated.

†IHD mortality given as the percentage of the total number of participants who are alive.

statistical power in men after > 25 years of survival may be the most likely explanation for the observed difference, since only 44 men were classified into the quintile with the lowest FEV_1%pred.

In our study, as in other studies,[3] we included all participants independent of disease status at baseline. The presence of disease at baseline could have been related to both pulmonary function and mortality. However, we controlled for this bias by excluding those persons who died early in the sequential analysis. An advantage of this approach is that it also decreases the bias of including participants with undiagnosed disease, which could be responsible for an observed relationship in other studies in which only those persons with diagnosed disease at baseline were excluded.

For the proper analysis of pulmonary function data, the use of an adequate prediction equation and adjustment for known covariates is important. Neas and Schwartz[10] reported that the choice of an internal vs an external prediction equation for FEV_1 did not alter the observed results. We performed our analysis with an internal linear equation using age and height as predictors, because models that included nonlinear terms did not improve prediction. Given the relatively wide age range of participants and the association of reduced pulmonary function with mortality, older participants in this study could represent healthy survivors selected for superior pulmonary function. This selection could explain the observed linear relationship of FEV_1 with age. Additionally, the equation in men was derived from only 57 never-smokers. For these reasons, we repeated the analysis using external linear and nonlinear prediction equations. Our results did not change significantly when we used external linear or nonlinear equations, such as the ones used by Morris et al[33] or Dockery et al,[34] to predict FEV_1. It seems, therefore, that the observed results were not influenced by the choice of an internal prediction equation.

The present study has a number of limitations. Participant characteristics, except for vital status and underlying cause of death, were obtained at baseline only. Several variables (*eg*, smoking) could have changed during the follow-up period, as described above. Since we do not have this information, we are unable to determine how changes in the independent variables would affect survival. Our analysis was adjusted for significant risk factors, such as BMI, SBP, gender, education, and smoking status; however, no information was available on another important IHD risk factor, serum cholesterol level. Cholesterol levels at baseline have been shown to be a significant risk factor for IHD mortality in prospec-

tive studies.[35,36] Our criteria for the determination of vital status were rigid, and overall follow-up for vital status was high. A general problem in cohort studies is the exclusion of participants and the unavailability for follow-up. While the lack of baseline data, including missing spirometry curves, is less likely to be associated with pulmonary function status, we excluded a small percentage of participants because they were unable to perform or refused to perform spirometry. Although these participants did not differ significantly in baseline characteristics from those with available pulmonary function data, it has been shown that the refusal or inability to perform spirometry is a stronger risk factor of mortality than low FEV_1.[9] However, subjects who are unable to perform or refuse to perform spirometry would also be likely to have lower FEV_1 levels and would fall in the lower percentiles of the distribution. An exclusion of these subjects from the lower quintiles, despite their elevated mortality risk, could lead to an underestimation of the overall risk associated with poor pulmonary function. We were unable to follow-up on 69 women and 20 men who had sufficient data to be included at baseline. These participants did not significantly differ in baseline characteristics from those who were included. If the majority of these subjects died shortly after the baseline information was obtained and if their early death was the reason for the unavailability for follow-up, then our risk estimates would represent overestimates of the true risk because they were similar to included participants in baseline characteristics. Overall, the number of subjects with pulmonary function test information who were unavailable for follow-up is small. Therefore, the results are unlikely to be biased severely by the loss to follow-up. There is also the potential for inaccurate coding on death certificates. Such misclassification probably affected the mortality attributed to IHD, but a relationship of coding inaccuracy to baseline lung function is highly unlikely. Therefore, the finding that reduced pulmonary function is related to IHD mortality is less likely to be affected by coding errors on death certificates.

Conclusion

In summary, our results extend those from previous studies indicating that FEV_1%pred is a statistically significant predictor for both all-cause and IHD mortality in both genders in follow-up periods of 29 years. As has been pointed out by Persson et al,[11] there is an urgency to reach a better understanding of the relationship of impaired pulmonary function to disease in order to undertake preventive measures. From several studies, we know that smoking cessation does not seem to be the only solution because the risk is found also in never-smokers. At present, given the overall predictive value of reduced pulmonary function for mortality from various diseases, independent of smoking,[3] it is, in fact, surprising that this simple measurement has not gained more importance as a general health assessment tool, including testing for life insurance.

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