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ORIGINAL RESEARCH

Health Outcomes Associated with Lung Function Decline and Respiratory Symptoms and Disease in a Community Cohort

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***Background*: In workplace respiratory disease prevention, a thorough understanding is needed of the relative contributions of lung function loss and respiratory symptoms in predicting adverse health outcomes. *Methods*: Copenhagen City Heart Study respiratory data collected at 4 examinations (1976–2003) and morbidity and mortality data were used to investigate these relationships. With 15 or more years of follow-up for a hospital diagnosis of chronic obstructive pulmonary disease (COPD) morbidity, COPD or coronary heart disease (CHD) mortality, and all-cause mortality, risks for these outcomes were estimated in relation to asthma, chronic bronchitis, shortness of breath, and lung function level at examination 2 (1981–1983) or lung function decline established from examinations 1 (1976–1978) to 2 using 4 measures (FEV_1 slope, FEV_1 relative slope, American College of Occupational and Environmental Medicine's Longitudinal Normal Limit [LNL], or a limit of 90 milliliters per year [ml/yr]). These risks were estimated by hazard ratios (HR) and 95% confidence intervals (CI) adjusted for age, height-adjusted baseline forced expiratory volume in 1 second (FEV_1/height^2), and height. *Results*: For COPD morbidity, the increasing trend in the HR (95% CI) by quartiles of the FEV_1 slope reached a maximum of 3.77 (2.76–5.15) for males, 6.12 (4.63–8.10) for females, and 4.14 (1.57–10.90) for never-smokers. Significant increasing trends were also observed for mortality, with females at higher risk. *Conclusion*: Lung function decline was associated with increased risk of COPD morbidity and mortality emphasizing the need to monitor lung function change over time in at-risk occupational populations.**

Keywords: Spirometry, Respiratory symptoms, COPD, Mortality, Morbidity

INTRODUCTION

Studies of various populations demonstrate that lung function can predict adverse health outcomes, such as chronic obstructive pulmonary disease (COPD) morbidity and mortality, coronary heart disease (CHD) mortality, and all-cause mortality (1–16). COPD is a costly disease, with high prevalence rates in the United States and internationally, high associated healthcare costs, early retirement from work, and excess premature mortality. COPD is also associated with CHD, another costly disease (17–24). While the principal risk factor for COPD is tobacco smoking, occupational exposures also contribute to the development of COPD and its cost (22,25–33). Industry-based studies identify increased healthcare utilization and disability associated with COPD, and demonstrate the need for prevention of excessive loss of lung function (34,35). In workers with potential exposure to occupational respiratory hazards, effective monitoring of longitudinal lung function changes is one approach to early recognition of lung function impairment and provides opportunities for developing prevention strategies to reduce potentially modifiable risk factors associated with long-term adverse health outcomes.

Periodic lung function evaluation can support effective prevention strategies in the workplace. Important issues to consider are: the critical rate at which lung function decline becomes a significant predictor of morbidity and mortality; the measures of lung function decline that best predict morbidity and mortality; and the role of respiratory symptoms and asthma in the prediction. Specific cut-off points in the forced expiratory volume in 1 second (FEV_1) rate of decline were considered in a previous study of mortality in coal miners (36). This study showed increased mortality risk with

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rates of decline above about 60 ml/yr in never-smokers and with declines of 90 ml/yr in all miners; furthermore, the decline of 60 ml/yr or more was associated with increased disability and early retirement (22).

The aim of this study was to evaluate the risks of COPD morbidity based on hospitalizations, COPD or CHD mortality, and all-cause mortality associated with excessive lung function decline, current respiratory symptoms of chronic bronchitis and shortness of breath, and current asthma in an aging community cohort. Specific objectives were to evaluate the usefulness of various measures of lung function decline in predicting morbidity and mortality, to investigate the critical rate of lung function decline that becomes a significant predictor of morbidity and mortality, and to assess the usefulness of current respiratory symptoms and asthma in predicting morbidity and mortality relative to lung function level and decline.

MATERIALS AND METHODS

Study Population and Definitions

Our study used data from the Copenhagen City Heart Study, a prospective study of cardiovascular disease in 23,000 men and women aged 20 years and older (37, 38). The study involved 4 clinical examinations (including spirometry) and a self-administered questionnaire conducted over a 28-year period (1976–78, 1981–83, 1991–94, and 2001–03). A minimum of 3 spirometry tests were performed at each session, in a sitting position, using an electronic spirometer (N 403 Monaghan, United States). At least 2 measurements had to be within 5% of one another (37,38). For analysis of lung function decline, we selected subjects who had spirometry tests at examinations 1 and 2, approximately 5 years apart. Change in FEV_1 was evaluated because it is the most useful measurement for assessing the rate of lung function decline (39). Height measurements were collected as part of the physical examination. Age and gender data were obtained from the Copenhagen Population Register at the time of study enrollment. Smoking status was self-reported at each examination.

Current respiratory symptoms of chronic bronchitis and current asthma were self-reported at examinations 1 and 2, while shortness of breath was initially ascertained at examination 2. In preliminary univariate analyses, we identified asthma ("Do you suffer from asthma?") (40), chronic bronchitis ("Do you bring up phlegm, in the morning or during the day, for as long as 3 months each year?"), and shortness of breath ("Do you often feel out of breath?") as the best predictors of future morbidity and mortality.

Morbidity data were from the National Patient Register, mortality data from the Civil Registration System, and causes of death from the National Register of Causes of Death. Three health outcomes were studied: 1) primary and secondary hospital diagnoses of COPD morbidity (International Classification of Diseases [ICD]-8 491–492, and ICD-10 J41–J44); 2) COPD or CHD mortality (ICD-8 410–414, and ICD-10 I20–I25) as an underlying or contributing cause; and 3) all-cause mortality. COPD morbidity follow-up was until 12/31/2003. Mortality follow-up was until 12/31/2006 for cause-specific mortality, and until 8/11/2007 for all causes.

Statistical methods

The Cox proportional hazards model was used to estimate the hazard (instantaneous event rate) of morbidity or mortality in relation to lung function level and decline, respiratory symptoms, and asthma, while adjusting for essential covariates that would typically be available and taken into consideration in a clinical context (41). Analyses were conducted by gender and for never-smokers. Additional Cox models using penalized splines were conducted for the overall cohort to identify the rate of FEV_1 slope at which morbidity and mortality risk began to increase. For COPD morbidity, time to event (or censor) was calculated from examination 2 until COPD diagnosis, death, or end of follow-up. For mortality, time to event (or censor) was calculated from examination 2 until death or end of follow-up.

First, we evaluated the relationships of the level of lung function measurements by examination (1 or 2) with morbidity and mortality. Models included quartiles of lung function level ($FEV_1/height^2$) (42), respiratory symptoms, asthma, and age. The highest lung function level (75th percentile and above) served as the reference category. As the results were generally similar, only examination 2 results are presented, because shortness of breath was often statistically significant ($p < 0.05$) and was unavailable at examination 1.

Second, we evaluated the relationship of the rate of lung function decline, and respiratory symptoms and asthma ascertained at examination 2 with morbidity and mortality, adjusted for baseline age, height-adjusted baseline lung function ($FEV_1/height^2$), and height. In separate analyses, we evaluated 4 measures of lung function decline: 1) the FEV_1 slope (the difference in FEV_1 between examinations 1 and 2, divided by the time between the examinations) in quartiles; 2) the FEV_1 relative slope (slope divided by baseline FEV_1) in quartiles; 3) the American College of Occupational and Environmental Medicine's (ACOEM) Longitudinal Normal Limit (LNL) decline based on the American Thoracic Society's (ATS) 15% annual limit and an expected decline of 30 ml/yr (43); and 4) a FEV_1 decline of 90 ml/yr or more (44).

The ACOEM LNL is designed to identify excessive declines during early years of spirometry follow-up (1–8 years) when data are sparse and a reliable slope cannot be estimated (43). To identify trends in risk, we categorized the slopes into quartiles and used the quartiles with the lowest rates of decline (75th percentile and above) as the reference categories. The risks associated with excessive lung function decline, defined by the 2 longitudinal limits (LNL and a decline of 90 ml/yr or more), were compared to subjects with "normal" decline. The 2 limits were compared for predicting risk, and for model fit using the Akaike's information criterion (AIC) (45).

Preliminary analysis of mean FEV_1 values by year of examination revealed a slightly excessive increase in mean FEV_1 in 1981 (n = 4,319), but not in 1982 (n = 5,353) or 1983 (n = 2,593), as compared to mean FEV_1 for baseline examinations in 1976–78. It is unknown to the authors whether this increase in 1981 was due to early difficulties with the

Monaghan spirometer that was replaced with a dry wedge spirometer by examination 3 or to other issues (38). To adjust for this increase, we reduced the individual FEV_1 measurements for 1981 by a fixed value of 289 ml for males and 201 ml for females to align the 1981 values with the 1976–78 and 1982–83 values. The fixed values represent the average difference in FEV_1 values from examination 1 to 2 (for 1982 only), minus 30 ml to correct for annual loss from 1981 to 1982. Models excluding the 1981 values were conducted for a sensitivity analysis regarding this adjustment.

Copenhagen City Heart Study participants gave informed consent to participate and the study was performed in accordance with the 2nd Helsinki Declaration and approved by the Danish regional ethics committee. The present study was approved by the National Institute for Occupational Safety and Health Human Subjects Review Board and the West Virginia University Institutional Review Board. Analyses were conducted with PROC PHREG ($p < 0.05$) in SAS, version 9.2 (SAS Institute Inc, Cary, NC, USA). Penalized splines were prepared in R software (version 2.7.2).

RESULTS

Three sub-cohorts (males, females, and never-smokers) used in the Cox models are described in Table 1. The table shows the duration of follow-up for morbidity and mortality (15–20 years), the mean and quartile values for FEV_1/height^2 (level of lung function) and the 2 types of slopes (lung function decline), and the frequency of symptoms and asthma. For never-smokers, we presented gender-specific quartiles

Table 1. Characteristics of the sub-cohorts for Cox proportional hazards model analysis using data for lung function level and decline

	Males		Females		Never-smokers	
Data for lung function level (Examination 2)						
Subjects (n,*%)	5,494	44.8	6,771	55.2	2,555	20.8
Age at examination two (mean, SD†)	56.1	12.6	56.7	12.1	56.4	13.8
Follow-up, years (mean, SD)						
COPD morbidity	15.4	6.9	17.3	6.0	18.1	5.7
COPD or CHD mortality	16.9	7.9	19.3	7.0	20.0	6.7
All-cause mortality	17.1	8.1	19.5	7.2	20.3	7.0
Height, cm† (mean, SD)	174	7	161	6	164	9
FEV_1, l† (mean, SD)	2.82	0.91	2.05	0.63	2.39	0.85
FEV_1/height^2 × mean height^2, l (mean, SD)	2.57	0.75	2.17	0.60	2.42	0.67
25th percentile	2.07		1.78		2.43; 1.87‡	
Median	2.56		2.17		2.92; 2.23‡	
75th percentile	3.08		2.58		3.41; 2.65‡	
Asthma (n,%)	172	3.1	218	3.2	59	2.3
Chronic bronchitis (n,%)	872	15.9	722	10.7	148	5.8
Shortness of breath (n,%)	543	9.9	728	10.8	159	6.2
Never-smokers (n,%)	629	11.5	1,926	28.5	629; 1,926‡	24.6; 75.4‡
Former smokers (n,%)	1,352	24.6	1,244	18.4		
Current smokers (n,%)	3,510	63.9	3,592	53.1		
Data for lung function decline (Examination 1 to 2)§						
Subjects (n,*%)	4,253	43.9	5,426	56.1	1,822	18.8
Baseline age (mean, SD)	52.5	11.4	52.7	10.8	52.8	12.2
Follow-up, years (mean, SD)						
COPD morbidity	15.2	6.9	17.3	6.0	18.2	5.6
COPD or CHD mortality	16.7	7.9	19.3	6.9	20.1	6.7
All-cause mortality	16.9	8.1	19.6	7.1	20.4	6.9
Baseline FEV_1, l (mean, SD)	3.09	0.82	2.25	0.55	2.56	0.79
Baseline FEV_1/height^2 × mean height^2, l (mean, SD)	2.83	0.67	2.40	0.53	2.62	0.62
Slope FEV_1, ml/yr† (mean, SD)	−62	94	−45	71	−43	80
25th percentile	−118		−95		−114; −94‡	
Median	−60		−57		−57; −40‡	
75th percentile	0		0		19; 0‡	
Slope FEV_1/baseline FEV_1,%/yr (mean, SD)	−2.0	3.4	−1.9	3.4	−1.5	3.4
25th percentile	−4.1		−4.1		−3.2; −3.8‡	
Median	−2.2		−2.2		−1.5; −2.0‡	
75th percentile	0.0		0.0		0.4; 0.0‡	
FEV_1 below LNL† (n,%)	743	17.4	1,016	18.7	346	19.0
FEV_1 decline of 90 ml/yr or more (n,%)	1,717	40.4	1,444	26.6	505	27.7
Asthma (n,%)	125	2.9	168	3.1	40	2.2
Chronic bronchitis (n,%)	665	15.6	558	10.3	96	5.3
Shortness of breath (n,%)	401	9.4	550	10.1	104	5.7

*A total of 12,265 subjects at examination 2 and 9,679 subjects at both examinations 1 and 2.
†SD (standard deviation), cm (centimeters), l (liters), ml/yr (milliliters/year), and LNL (Longitudinal Normal Limit).
‡Males; females.
§Includes subjects with approximately 5 years between spirometry tests.

because females represented 75% of the never-smoker subcohort. (Sample sizes for the analysis of lung function decline were smaller because members had to participate at both examinations 1 and 2.) Baseline characteristics for subjects who were lost to follow-up by examination 2 were a higher average age, lower average $FEV_1/height^2$, and a higher percentage of self-reported current asthma, symptoms of chronic bronchitis, and smoking.

COPD morbidity

Estimated HRs for COPD morbidity (hospital diagnosis of COPD) are presented in Table 2. The level of lung function ($FEV_1/height^2$) was a significant predictor of COPD morbidity for males and females starting from the second quartile. A similar, but less significant trend was observed in never-smokers, where significance was observed only at the fourth quartile.

A similar increasing trend in COPD morbidity risk was seen for the FEV_1 slope, except significance began at the third quartile for never-smokers. Females had the highest HRs for COPD morbidity for the slope, the relative slope, the LNL, and the 90 ml/yr limit (Figure 1a). Results from the penalized spline analysis showed that the log HR for COPD morbidity (males and females combined) started to increase at an FEV_1 slope of –54 ml/yr (Figure 2a). The parameter for the linear rate was highly significant ($p < 0.0001$).

Comparing results for the dichotomous outcomes, the LNL was significantly associated with COPD morbidity for all 3 sub-cohorts, as was the 90 ml/yr limit. When compared using the AIC (45), the fit of these 2 models were similar. The LNL limit provided a slightly better fit for females, but the 90 ml/yr limit was slightly better for males and never-smokers.

Respiratory symptoms and asthma were often significantly associated with COPD morbidity in the models with

Table 2. Cox proportional hazards models for COPD morbidity (hospital diagnosis of COPD [ICD-8 491–492, ICD-10 J41–J44])

	Males		Females		Never-smokers	
	(n = 5,442, COPD = 563)		(n = 6,735, COPD = 678)		(n = 2,548, COPD = 73)	
Data for lung function level* (Examination 2)	HR	95% CI	HR	95% CI	HR	95% CI
Q1 $FEV_1/height^2$	1.00		1.00		1.00	
Q2 $FEV_1/height^2$	2.69	(1.73–4.18)	2.66	(1.85–3.83)	1.64	(0.55–4.87)
Q3 $FEV_1/height^2$	6.10	(3.99–9.33)	5.09	(3.57–7.25)	1.41	(0.46–4.34)
Q4 $FEV_1/height^2$	16.36	(10.67–25.07)	16.55	(11.65–23.53)	5.18	(1.81–14.80)
Asthma†	2.21	(1.66–2.93)	1.20	(0.91–1.58)	3.69	(1.67–8.15)
Chronic bronchitis†	2.04	(1.68–2.47)	2.05	(1.70–2.48)	2.35	(1.26–4.38)
Shortness of breath†	2.48	(2.00–3.08)	2.77	(2.29–3.36)	2.36	(1.21–4.58)
	(n = 4,214, COPD = 442)		(n = 5,402, COPD = 537)		(n = 1,817, COPD = 49)	
Data for lung function decline‡ (Examination 1 to 2)	HR	95% CI	HR	95% CI	HR	95% CI
Q1 FEV_1 slope	1.00		1.00		1.00	
Q2 FEV_1 slope	1.61	(1.18–2.19)	2.48	(1.89–3.27)	1.80	(0.73–4.45)
Q3 FEV_1 slope	2.54	(1.87–3.45)	3.37	(2.55–4.44)	2.53	(1.01–6.33)
Q4 FEV_1 slope	3.77	(2.76–5.15)	6.12	(4.63–8.10)	3.58	(1.34–9.62)
Asthma	1.41	(1.00–1.99)	0.80	(0.58–1.12)	4.45	(1.40–14.11)
Chronic bronchitis	1.92	(1.53–2.40)	2.24	(1.82–2.77)	2.00	(0.84–4.79)
Shortness of breath	2.00	(1.54–2.61)	2.22	(1.76–2.78)	0.69	(0.21–2.22)
Q1 FEV_1 relative slope§	1.00		1.00		1.00	
Q2 FEV_1 relative slope	1.50	(1.09–2.07)	1.99	(1.48–2.68)	1.73	(0.68–4.41)
Q3 FEV_1 relative slope	2.17	(1.58–3.00)	2.60	(1.95–3.46)	1.65	(0.60–4.57)
Q4 FEV_1 relative slope	3.48	(2.59–4.67)	5.27	(4.06–6.85)	3.92	(1.63–9.44)
Asthma	1.32	(0.93–1.86)	0.80	(0.57–1.11)	4.39	(1.38–13.92)
Chronic bronchitis	1.95	(1.56–2.44)	2.26	(1.82–2.79)	2.03	(0.87–4.73)
Shortness of breath	2.04	(1.57–2.65)	2.21	(1.76–2.78)	0.69	(0.22–2.18)
FEV_1 below LNL§	2.32	(1.86–2.88)	3.01	(2.49–3.64)	2.33	(1.22–4.44)
Asthma	1.52	(1.08–2.14)	0.86	(0.62–1.20)	4.49	(1.46–13.78)
Chronic bronchitis	1.98	(1.58–2.48)	2.37	(1.91–2.93)	2.18	(0.93–5.10)
Shortness of breath	2.10	(1.62–2.74)	2.27	(1.81–2.86)	0.76	(0.24–2.39)
FEV_1 decline of ≥90 ml/yr	2.11	(1.73–2.57)	2.87	(2.37–3.48)	2.32	(1.19–4.53)
Asthma	1.48	(1.05–2.09)	0.82	(0.59–1.15)	4.74	(1.56–14.46)
Chronic bronchitis	2.02	(1.61–2.52)	2.34	(1.89–2.89)	1.97	(0.81–4.80)
Shortness of breath	2.12	(1.63–2.75)	2.38	(1.90–2.98)	0.78	(0.25–2.41)

*Models adjusted for age at examination 2.
†Asthma, chronic bronchitis, and shortness of breath represented as dichotomous variables in all models.
‡Models adjusted for baseline age, height-adjusted baseline lung function ($FEV_1/height^2$), and height. See Table 1 for slope and relative slope quartile values.
§FEV_1 relative slope (slope FEV_1/baseline FEV_1) and LNL (Longitudinal Normal Limit).

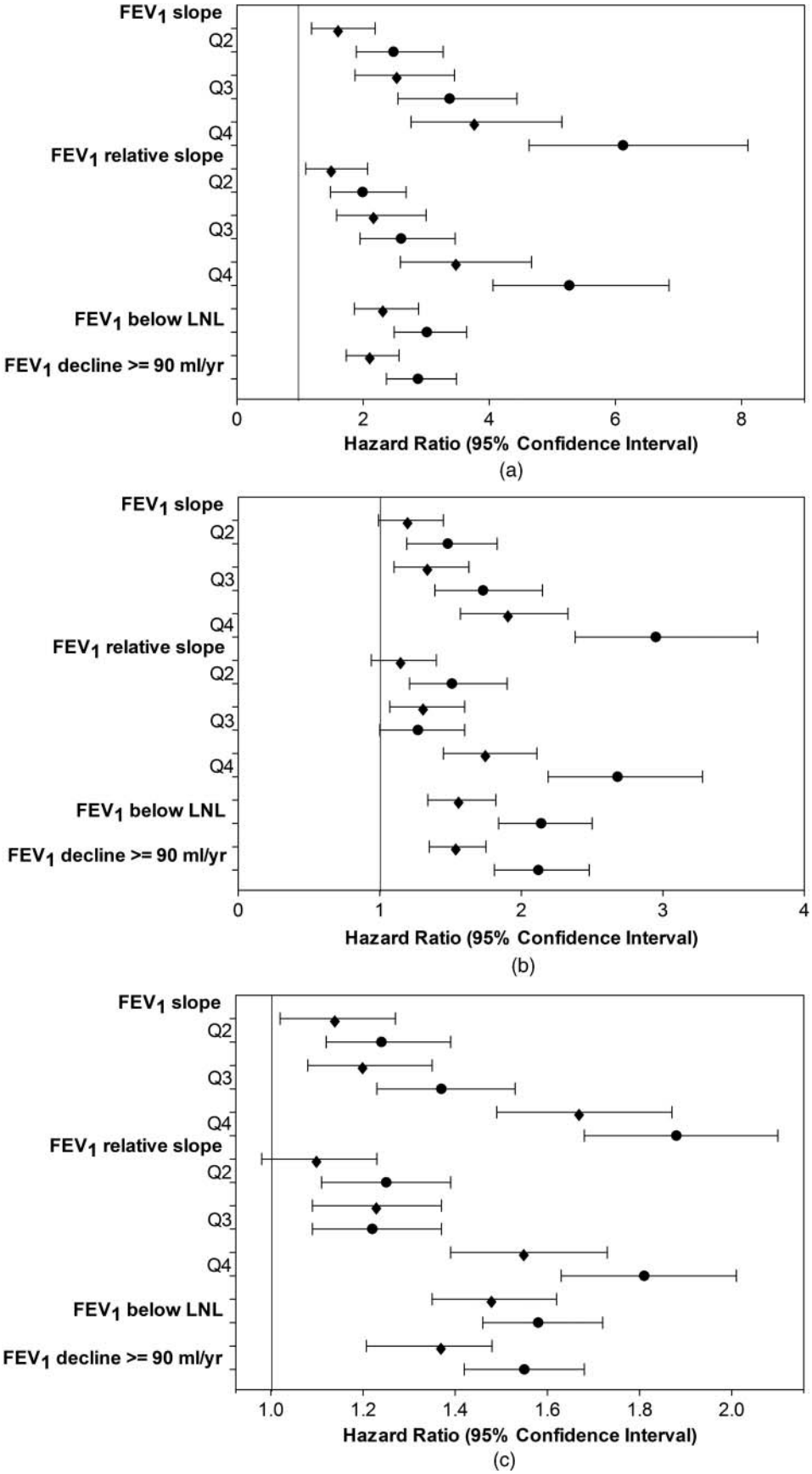

Figure 1. Cox proportional hazards model results by gender (♦ = males and • = females) for (a) COPD morbidity, (b) COPD or CHD mortality, and (c) all-cause mortality. Models adjusted for baseline age, height-adjusted baseline lung function (FEV_1/height^2), height, and respiratory symptoms and asthma as dichotomous variables. Relative slope is slope FEV_1/baseline FEV_1. LNL is the Longitudinal Normal Limit. See Table 1 for slope and relative slope quartile values.

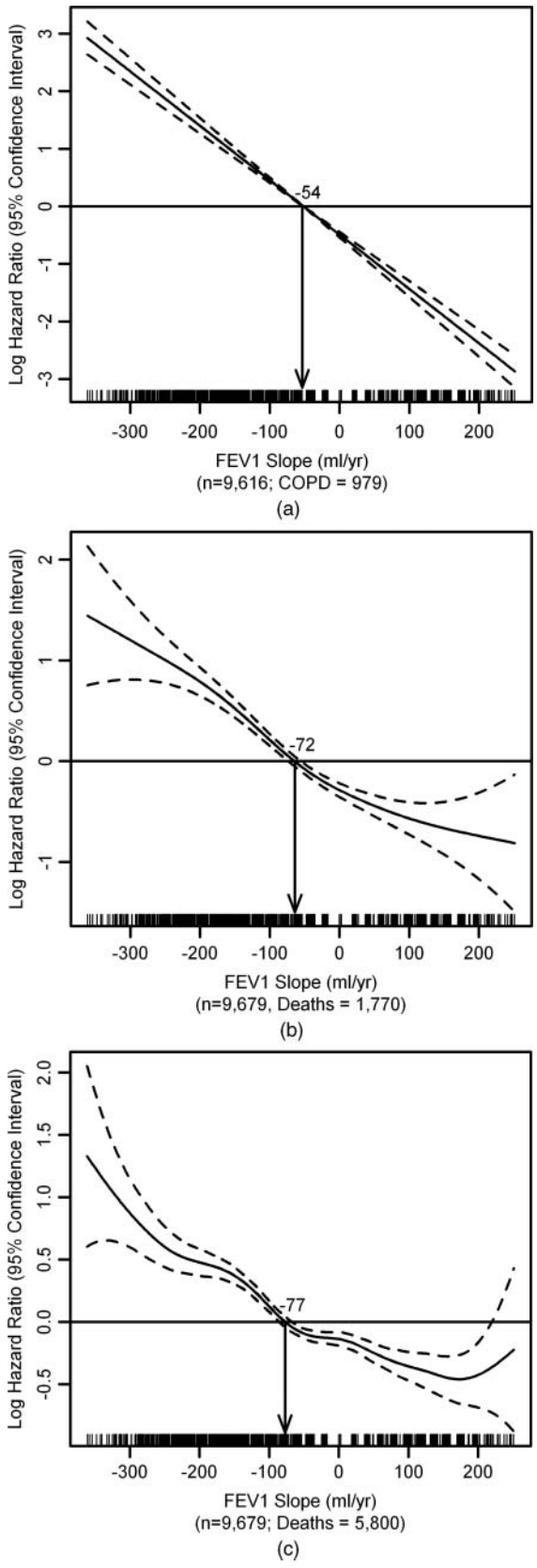

Figure 2. Cox proportional hazards model using a penalized spline for the FEV_1 slope, males and females combined. The spline crossed above zero for the log HR at –54 ml/yr for (a) COPD morbidity, at –72 ml/yr for (b) COPD or CHD mortality, and at –77 ml/yr for (c) all-cause mortality. Models adjusted for baseline age, height-adjusted baseline lung function (FEV_1/height^2), and height. Tick marks on the x axis represent the frequency of the various FEV_1 slope values.

the level of lung function and lung function decline. The risks associated with chronic bronchitis and shortness of breath were higher than for asthma for males and females. In never-smokers, the risk associated with asthma was the highest with a 4-fold increase.

Mortality due to COPD or CHD, and all-cause mortality

For mortality outcomes, there was significant association with decreasing level of lung function for all 3 sub-cohorts (Tables 3 and 4). The risk of COPD or CHD mortality in relation to the level of lung function was slightly higher than for all-cause mortality, with females and never-smokers often having higher risks than males. For COPD or CHD mortality, females in the fourth quartile had more than a 5-fold increase in risk, never-smokers a nearly 4-fold increase in risk, and males a 3-fold increase in risk as compared to the reference. Hazard ratios for all-cause mortality were more similar for the 3 sub-cohorts.

Increased risk of mortality began at the second quartile of the FEV_1 slope and relative slope for females, and most often at the third quartile for males and the fourth quartile for never-smokers. Figures 2b and 2c show the penalized splines for the slope for the mortality outcomes in males and females combined. The nonlinear terms were significant ($p = 0.01$ for COPD or CHD mortality and $p = 0.0001$ for all-causes) and the spline crossed above zero for the log HR at –72 ml/yr for COPD or CHD mortality and at –77 ml/yr for all-cause mortality.

As for the dichotomous criteria (the LNL and the 90 ml/yr limit), there were significant associations with both mortality outcomes, with the exception of the LNL and COPD or CHD mortality in never-smokers. The AIC values for these 2 criteria were similar by sub-cohort and outcome, but the models with the LNL fit best overall, with the exceptions of COPD or CHD mortality in males and in never-smokers. A comparison of all of the results by sub-cohort demonstrates that females had the highest HRs for both mortality outcomes for all 4 measures of lung function decline.

Asthma was not significantly associated with increased risk of mortality. Chronic bronchitis was significantly associated with mortality, but not for never-smokers; COPD or CHD mortality was approximately 30% more likely for males and 60% for females who reported chronic bronchitis. In the models with the level of lung function, shortness of breath was significantly associated with mortality for all 3 sub-cohorts; doubling the risk of COPD or CHD mortality for males and females, and increasing the risk of all-cause mortality by 50%. Similar results were observed in the models with lung function decline.

DISCUSSION

Unlike studies concerned with identifying morbidity and mortality risk factors, our interest was examining the relationship of respiratory status (lung function, respiratory symptoms, and asthma) with morbidity and mortality. This study relates to clinical practice and prevention as it focuses on the predictive, rather than causative, nature of these

Table 3. Cox proportional hazards models for COPD (ICD-8 491–492, ICD-10 J41–J44) or CHD mortality (ICD-8 410–414, and ICD-10 I20–I25)

	Males		Females		Never-smokers	
	(n = 5,494, Deaths = 1,201)		(n = 6,771, Deaths = 983)		(n = 2,555, Deaths = 269)	
Data for lung function level* (Examination 2)	HR	95% CI	HR	95% CI	HR	95% CI
Q1 FEV_1/height^2	1.00		1.00		1.00	
Q2 FEV_1/height^2	1.46	(1.15–1.85)	1.88	(1.38–2.57)	1.92	(0.95–3.89)
Q3 FEV_1/height^2	2.02	(1.60–2.56)	2.79	(2.06–3.77)	2.54	(1.29–5.01)
Q4 FEV_1/height^2	3.02	(2.38–3.84)	5.49	(4.07–7.41)	3.94	(2.00–7.76)
Asthma†	1.14	(0.88–1.47)	0.87	(0.66–1.15)	1.03	(0.49–2.14)
Chronic bronchitis†	1.32	(1.14–1.53)	1.62	(1.37–1.93)	1.32	(0.88–1.99)
Shortness of breath†	2.15	(1.82–2.54)	2.30	(1.94–2.72)	1.57	(1.04–2.35)
	(n = 4,253, Deaths = 974)		(n = 5,426, Deaths = 796)		(n = 1,822, Deaths = 202)	
Data for lung function decline‡ (Examination 1 to 2)	HR	95% CI	HR	95% CI	HR	95% CI
Q1 FEV_1 slope	1.00		1.00		1.00	
Q2 FEV_1 slope	1.20	(0.99–1.45)	1.48	(1.19–1.83)	1.17	(0.77–1.78)
Q3 FEV_1 slope	1.34	(1.10–1.63)	1.73	(1.39–2.15)	1.42	(0.93–2.17)
Q4 FEV_1 slope	1.91	(1.57–2.33)	2.95	(2.38–3.67)	1.42	(0.90–2.25)
Asthma	0.94	(0.70–1.27)	0.74	(0.54–1.03)	1.30	(0.56–3.03)
Chronic bronchitis	1.29	(1.10–1.52)	1.58	(1.31–1.92)	1.33	(0.80–2.22)
Shortness of breath	1.92	(1.58–2.33)	1.86	(1.52–2.28)	1.21	(0.70–2.09)
Q1 FEV_1 relative slope§	1.00		1.00		1.00	
Q2 FEV_1 relative slope	1.15	(0.94–1.40)	1.51	(1.21–1.90)	1.08	(0.69–1.67)
Q3 FEV_1 relative slope	1.31	(1.07–1.60)	1.27	(1.00–1.60)	1.15	(0.74–1.80)
Q4 FEV_1 relative slope	1.75	(1.45–2.11)	2.68	(2.19–3.28)	1.61	(1.06–2.43)
Asthma	0.90	(0.67–1.22)	0.68	(0.49–0.94)	1.31	(0.56–3.04)
Chronic bronchitis	1.29	(1.10–1.53)	1.60	(1.32–1.95)	1.32	(0.79–2.19)
Shortness of breath	1.95	(1.61–2.37)	1.90	(1.56–2.33)	1.17	(0.68–2.02)
FEV_1 below LNL§	1.56	(1.34–1.82)	2.14	(1.84–2.50)	1.34	(0.97–1.85)
Asthma	0.95	(0.70–1.28)	0.73	(0.52–1.01)	1.27	(0.55–2.95)
Chronic bronchitis	1.31	(1.11–1.54)	1.63	(1.34–1.98)	1.32	(0.79–2.21)
Shortness of breath	1.95	(1.60–2.36)	1.86	(1.51–2.27)	1.22	(0.71–2.10)
FEV_1 decline of ≥90 ml/yr	1.54	(1.35–1.75)	2.12	(1.81–2.48)	1.43	(1.03–1.99)
Asthma	0.94	(0.70–1.27)	0.76	(0.55–1.05)	1.33	(0.57–3.08)
Chronic bronchitis	1.30	(1.11–1.54)	1.62	(1.33–1.96)	1.31	(0.78–2.18)
Shortness of breath	1.98	(1.63–2.39)	1.89	(1.55–2.31)	1.19	(0.69–2.05)

*Models adjusted for age at examination 2.
†Asthma, chronic bronchitis, and shortness of breath represented as dichotomous variables in all models.
‡Models adjusted for baseline age, height-adjusted baseline lung function (FEV_1/height^2), and height. See Table 1 for slope and relative slope quartile values.
§FEV_1 relative slope (slope FEV_1/baseline FEV_1) and LNL (Longitudinal Normal Limit).

respiratory factors. The level of lung function was associated with a high risk for morbidity and mortality, supporting the need for prevention. For example, in at-risk occupational populations, monitoring lung function over time can be used to identify individuals at risk of lung function impairment and initiate appropriate intervention. Our results add to current knowledge on lung function decline as a predictor of morbidity and mortality in aging populations.

Evaluating the usefulness of the measures of lung function decline

The results demonstrate the predictive capacities of the 4 criteria for lung function decline (the FEV_1 slope and relative slope, the ACOEM LNL based on the ATS 15% year-to-year limit, and a FEV_1 decline of 90 ml/yr or more) for morbidity and mortality (43,44). Associations were stronger with COPD morbidity, as might be expected, given its identification using a hospital diagnosis which would focus on greater disease severity (Figure 1a). Also as expected, associations with mortality due to COPD or CHD were slightly higher than with all-cause mortality (Figures 1b and 1c); possibly due to a more direct relationship of COPD and CHD mortality with lung function.

Females were at greater risk of morbidity and mortality than males across all measures of lung function decline. This may be partially explained by smaller lung capacity in females; loss of lung function could pose more risk (46). Also, given that females in this study had lower tobacco consumption than males, this may suggest higher susceptibility in females. Other studies also find females more susceptible to the effects of smoking and with more rapid decline than males, and possibly with greater propensity for the development of COPD (47,48). HRs for never-smokers showed an

Table 4. Cox proportional hazards models for all-cause mortality

	Males		Females		Never-smokers	
	(n = 5,494, Deaths = 3,535)		(n = 6,771, Deaths = 3,632)		(n = 2,555, Deaths = 1,181)	
Data for lung function level* (Examination 2)	HR	95% CI	HR	95% CI	HR	95% CI
Q1 FEV_1/height^2	1.00		1.00		1.00	
Q2 FEV_1/height^2	1.27	(1.13–1.44)	1.39	(1.22–1.57)	1.54	(1.20–1.98)
Q3 FEV_1/height^2	1.60	(1.42–1.81)	1.83	(1.62–2.07)	1.70	(1.33–2.16)
Q4 FEV_1/height^2	2.31	(2.04–2.62)	2.65	(2.33–3.01)	2.15	(1.68–2.76)
Asthma†	0.98	(0.82–1.17)	0.99	(0.83–1.18)	1.13	(0.78–1.63)
Chronic bronchitis†	1.29	(1.18–1.40)	1.32	(1.20–1.46)	1.16	(0.94–1.44)
Shortness of breath†	1.52	(1.36–1.70)	1.50	(1.36–1.67)	1.38	(1.11–1.70)
	(n = 4,253, Deaths = 2,842)		(n = 5,426, Deaths = 2,958)		(n = 1,822, Deaths = 860)	
Data for lung function decline‡ (Examination 1 to 2)	HR	95% CI	HR	95% CI	HR	95% CI
Q1 FEV_1 slope	1.00		1.00		1.00	
Q2 FEV_1 slope	1.14	(1.02–1.27)	1.24	(1.12–1.39)	1.17	(0.95–1.43)
Q3 FEV_1 slope	1.20	(1.08–1.35)	1.37	(1.23–1.53)	1.31	(1.06–1.61)
Q4 FEV_1 slope	1.67	(1.49–1.87)	1.88	(1.68–2.10)	1.53	(1.23–1.91)
Asthma	0.87	(0.71–1.07)	0.96	(0.78–1.16)	1.15	(0.73–1.80)
Chronic bronchitis	1.24	(1.12–1.38)	1.27	(1.14–1.43)	1.10	(0.84–1.45)
Shortness of breath	1.43	(1.26–1.63)	1.36	(1.21–1.54)	1.27	(0.97–1.66)
Q1 FEV_1 relative slope§	1.00		1.00		1.00	
Q2 FEV_1 relative slope	1.10	(0.98–1.23)	1.25	(1.11–1.39)	1.18	(0.96–1.46)
Q3 FEV_1 relative slope	1.23	(1.09–1.37)	1.22	(1.09–1.37)	1.13	(0.91–1.40)
Q4 FEV_1 relative slope	1.55	(1.39–1.73)	1.81	(1.63–2.01)	1.59	(1.29–1.95)
Asthma	0.84	(0.68–1.04)	0.91	(0.74–1.10)	1.11	(0.71–1.74)
Chronic bronchitis	1.24	(1.12–1.37)	1.28	(1.15–1.44)	1.09	(0.83–1.44)
Shortness of breath	1.45	(1.28–1.65)	1.38	(1.22–1.55)	1.26	(0.97–1.65)
FEV_1 below LNL§	1.48	(1.35–1.62)	1.58	(1.46–1.72)	1.42	(1.22–1.66)
Asthma	0.87	(0.71–1.07)	0.94	(0.77–1.15)	1.11	(0.71–1.74)
Chronic bronchitis	1.25	(1.13–1.39)	1.30	(1.16–1.45)	1.11	(0.84–1.46)
Shortness of breath	1.44	(1.27–1.64)	1.36	(1.21–1.54)	1.29	(0.99–1.69)
FEV_1 decline of ≥90 ml/yr	1.37	(1.27–1.48)	1.55	(1.42–1.68)	1.37	(1.17–1.61)
Asthma	0.87	(0.70–1.07)	0.97	(0.80–1.18)	1.14	(0.73–1.79)
Chronic bronchitis	1.25	(1.13–1.39)	1.29	(1.15–1.44)	1.10	(0.83–1.45)
Shortness of breath	1.47	(1.30–1.67)	1.37	(1.22–1.55)	1.29	(0.99–1.68)

*Models adjusted for age at examination 2.
†Asthma, chronic bronchitis, and shortness of breath represented as dichotomous variables in all models.
‡Models adjusted for baseline age, height-adjusted baseline lung function (FEV_1/height^2), and height. See Table 1 for slope and relative slope quartile values.
§FEV_1 relative slope (slope FEV_1/baseline FEV_1) and LNL (Longitudinal Normal Limit).

increasing trend for all outcomes, but less statistical significance (Tables 2–4).

Among the 4 criteria, quartiles for the slope had higher HRs, but goodness of fit (AIC) was generally better for the relative slope. The slightly lower risk and better fit for the relative slope are reasonable given the adjustment for baseline lung function level. As for the 2 limits (the LNL and the 90 ml/yr limit), the HRs were similar, but often slightly higher for the LNL, and the goodness-of-fit was often better for the LNL.

Investigating critical rates of lung function decline

HRs for COPD morbidity suggest a critical rate at the third quartile of the slope with risks greater than 2.5 times those for the reference (Figure 1a), corresponding to declines starting at 60 ml/yr for males and 57 ml/yr for females (Table 1). For COPD or CHD mortality, the critical rate is more likely at the fourth quartile of the slope, with risks nearly doubled for males and tripled for females (Figure 1b). For all-cause mortality, fourth quartile risks were increased by 67% and 88% for males and females, respectively (Figure 1c), corresponding to declines starting at 118 ml/yr for males and 95 ml/yr for females (Table 1).

Our results generally agree with several community-based and occupational studies of lung function decline and respiratory morbidity and mortality (11,14,16,22,36). Similarities include slightly higher increased risks in females of COPD hospitalization and all-cause mortality associated with rapid decline as compared to males (11, 16) and increased risk of cardiac mortality with increasing decline in males (14). Also similar to our results, underground coal miners had a 2-fold risk of cardiovascular and nonmalignant respiratory disease mortality with rapid decline (22), and declines above 90 ml/yr were statistically significant for mortality as were declines of 60 ml/yr or more in never-smokers (36).

Assessing the usefulness of respiratory symptoms and asthma relative to lung function

Risk associated with lung function decline was often greater than with respiratory symptoms and asthma, though their risks remained statistically significant after adjustment for lung function. Asthma predicted COPD morbidity in males and never-smokers. Chronic bronchitis and shortness of breath predicted morbidity and mortality in males and females, with higher HRs in females for chronic bronchitis, which could relate to increased susceptibility to the effects of respiratory hazards (48).

Other studies have also reported increased risk of morbidity and mortality in relation to reported respiratory symptoms (chronic bronchitis, cough, phlegm, and shortness of breath) and asthma (49–53), even after controlling for FEV_1 (54). In contrast, we did not find increased risk between asthma and respiratory mortality; however, our study targeted COPD specifically (49). Chronic bronchitis often remained a significant predictor of mortality in our study, even with adjustment for shortness of breath and height-adjusted baseline lung function (54).

There are several limitations including the necessary adjustment in the FEV_1 values collected in 1981. Therefore, influences of the adjusted data were investigated by excluding it from the analysis, and significant overestimation of the HRs was not identified. Rather, the inclusion of the adjusted data resulted in an underestimation of the HRs. In particular, COPD morbidity HRs were underestimated for the level of lung function, the slope, and the relative slope, but mainly for never-smokers and more often for females than for males. There was also underestimation of the HRs for COPD or CHD mortality for the level of lung function for never-smokers.

There are other possible limitations related to lung function decline. One is the use of only 2 spirometry measurements for the rate of change in FEV_1, leaving the slope vulnerable to instability in either measurement, but the quartile groupings could have reduced this effect. The limit of 90 ml/yr or more was from literature pertaining to males (44). Although females generally have smaller lungs (46), results using this criterion were similar to those for the LNL and the fourth quartile of the slope for females, a corresponding decline of 95 ml/yr or more. In studying lung function decline, we did not account for possible mixing between cause and effect with regard to steeply declining lung function and COPD outcomes, but our interest was in prediction rather than causation.

Underdiagnosis of COPD and underreporting of COPD as a cause of death could have resulted in misclassification, biasing the results toward the null, and reducing the associations (55). This was addressed by combining the often interrelated COPD and CHD mortality into 1 outcome (23, 24). As COPD morbidity was limited to a hospital diagnosis, our results generally represent risk for individuals with more severe disease, but also likely the highest costs. Other possible selection bias includes subjects lost to follow-up by examination 2, who were older at baseline, had a lower lung function level, and a higher proportion of self-reported current asthma, chronic bronchitis, and smoking as compared those who participated at examinations 1 and 2. This could have resulted in an underestimation of risk.

Our findings are relevant to clinical and workplace disease prevention and cost-reduction (34,35). Investment in health promotion and protection for COPD could create savings for employers (56, 57). The strong associations of COPD morbidity with lung function level and decline correspond with high medical costs for COPD and indicate that effective monitoring and interpretation of lung function decline for early disease detection could lead to cost-savings.

In conclusion, the risk of COPD morbidity, COPD or CHD mortality, and all-cause mortality showed an increasing trend with lung function decline after adjustment for baseline lung function, respiratory symptoms, and asthma. The level and rate of lung function decline generally demonstrated a higher risk of morbidity and mortality than the respiratory symptoms and asthma. These results provide further evidence that evaluation of lung function decline, in addition to the lung function level, is important in spirometry monitoring programs.

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DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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