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RESPIRATORY EPIDEMIOLOGY

Combined effect of lung function level and decline increases morbidity and mortality risks

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Abstract Lung function level and decline are each predictive of morbidity and mortality. Evaluation of the combined effect of these measurements may help further identify high-risk groups. Using Copenhagen City Heart Study longitudinal spirometry data (n = 10,457), 16–21 year risks of chronic obstructive pulmonary disease (COPD) morbidity, COPD or coronary heart disease mortality, and all-cause mortality were estimated from combined effects of level and decline in forced expiratory volume in one second (FEV_1). Risks were evaluated using Cox proportional hazards models for individuals grouped by combinations of baseline predicted FEV_1 and quartiles of slope. Hazard ratios (HR) and 95 % confidence intervals (CI) were estimated using stratified analysis by gender, smoking status, and baseline age (≤45 and >45). For COPD morbidity, quartiles of increasing FEV_1 decline increased HRs (95 % CI) for individuals with FEV_1 at or above the lower limit of normal (LLN) but below 100 % predicted, reaching 5.11 (2.58–10.13) for males, 11.63 (4.75–28.46) for females, and 3.09 (0.88–10.86) for never smokers in the quartile of steepest decline. Significant increasing trends were also observed for mortality and in individuals with a baseline age ≤45. Groups with 'normal' lung function (FEV_1 at or above the LLN) but excessive declines (fourth quartile of FEV_1 slope) had significantly increased mortality risks, including never smokers and individuals with a baseline age ≤45.

Keywords Chronic obstructive pulmonary disease · Morbidity · Mortality · Respiratory symptoms · Spirometry

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

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Introduction

Lung function is a significant predictor of chronic obstructive pulmonary disease (COPD) and coronary heart disease (CHD) morbidity and mortality and all-cause mortality [1–19]. Although COPD is multifactorial by nature, it is generally caused by inflammatory response to inhaled hazardous exposures that may lead to chronic bronchitis, small airways disease, or emphysema [20, 21]. Changes leading to COPD are usually progressive, starting many years before abnormality can be detected with spirometry or radiology. Early markers suitable for detection of the disease processes are not yet available [22, 23]. Furthermore, there is also a strong association between COPD and CHD which is not fully understood [24].

Generally, the level of forced expiratory volume in one second (FEV_1) in relation to a predicted value is an indicator of the presence and severity of airflow impairment, while an excessive rate of FEV_1 decline is an indicator of ongoing adverse health effects (e.g. COPD progression, increasing abdominal obesity, decreasing fitness) [20]. Lung function decline has been assessed with regard to morbidity and mortality [25], but none of the published studies we are aware of have evaluated the combined effect of the level of lung function and the rate of lung function decline on morbidity and mortality. Evaluating the combined effect of the level and the rate of decline on morbidity or mortality risk provides information relevant in clinical and occupational settings where periodic spirometry may provide an opportunity for prevention of further excessive decline through intervention on preventable risk factors or medical treatment [26–29].

The purpose of this study was to evaluate the morbidity and mortality risks associated with the combined effect of the level and rate of lung function decline. Study participants were placed in lung function categories using baseline forced expiratory volume in one second (FEV_{1b}) compared to predicted values [30], and quartiles of FEV_1 slope measured over the subsequent years of follow-up. Within the categories, the prevalence rates of respiratory symptoms were also investigated. Because the purpose of our study was to evaluate the effect of lung function on morbidity and mortality outcomes, covariates known to be associated with decreasing lung function (e.g. smoking, diet, exposures, or obesity) were not included in the models, but the analysis were repeated in never smokers.

Methods

Study population

The Copenhagen City Heart Study is a 28-year cardiovascular disease study with four examinations of males and females age 20 years and older. The primary sample (n = 19,698) was drawn randomly from the Copenhagen Population Register in five-year age groups. Clinical examinations (with spirometry) and a self-administered questionnaire were conducted. An electronic spirometer (N 403 Monaghan, United States) was used during examinations one (1976–78) and two (1981–83). At each examination, three spirometric measurements were obtained with at least two within 5 % of one another. If airflow obstruction was identified ($FEV_1 < 80$ % and/or the ratio of FEV_1 and forced vital capacity [FVC] < 0.7), bronchial reversibility testing was performed and spirometric measurements were repeated after 30 min. The highest values of FEV_1 and FVC were retained in the data set. Age and gender data were obtained at study enrollment from the Copenhagen Population Register and height was measured during the clinical examination. Smoking status and current respiratory symptoms of chronic bronchitis were ascertained by questionnaire at each examination, and shortness of breath was ascertained at examination two [31, 32].

Morbidity data were obtained from the National Patient Register with discharges from all Danish acute-care, non-psychiatric hospitals since 1977 [33]. Mortality data were from the Civil Registration System (where vital status is continuously updated) [34], and cause-specific mortality data were from the National Register of Causes of Death. In the current study, health outcomes are (1) primary and secondary COPD hospital diagnoses (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 the underlying or contributing cause; and (3) all-cause mortality. (Denmark transitioned directly from the 8th to the 10th revision of ICD in 1993.) Use of lung function measurements at examinations one and two (1976–78 and 1981–83) permitted a 16–21 year follow-up that lasted through 5/8/2009 for COPD morbidity, 12/31/2006 for cause-specific mortality, and 5/17/2009 for all-cause mortality. Additional Copenhagen City Heart Study information is available elsewhere [31, 35].

Statistical methods

We used Cox proportional hazards models to estimate morbidity and mortality risks associated with the combined effect of the FEV_{1b} level and subsequent FEV_1 slope (difference in FEV_1 between the first two examinations, divided by time between the examinations) with an average follow-up of 5 years (Fig. 1). Baseline lung function results were divided into three groups: (1) FEV_{1b} at or above 100 % predicted; (2) FEV_{1b} at or above the lower limit of normal (LLN) but <100 % predicted; or (3) FEV_{1b} below the LLN. The predicted values and LLN were derived using Quanjer's published population-based reference equation [30]. The LLN approximates the one-sided 95 % confidence limit for

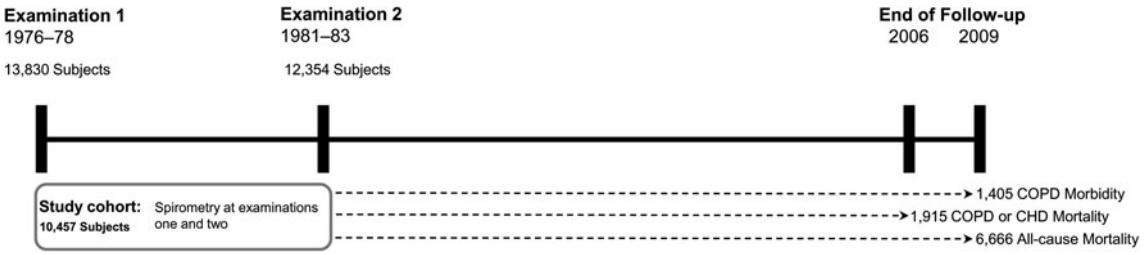

Fig. 1 Sample size and morbidity and mortality follow-up. Above the timeline are the numbers of subjects who participated in spirometry testing by Copenhagen City Heart Study examination. Below the timeline is the number of subjects who participated in spirometry testing at examinations one and two and the numbers of health outcomes that occurred during the morbidity and mortality follow-up periods. Note that the follow-up periods are represented as dashed lines and that follow-up for COPD or CHD mortality ended in 2006

the expected value, where 5 % of apparently healthy individuals who have never smoked would be identified as abnormal. Eight lung function categories were formed from combinations of FEV_{1b} (groups 1 and 2 only) and quartiles of FEV_1 slope (Fig. 2). The ninth category included individuals in group 3, whose FEV_{1b} was below the LLN. The reference category included individuals with FEV_{1b} at or above 100 % predicted and in the first (i.e. lowest) quartile of FEV_1 decline. Analyses were based on FEV_1 measurements because these are the most effective for evaluation of longitudinal lung function changes [36].

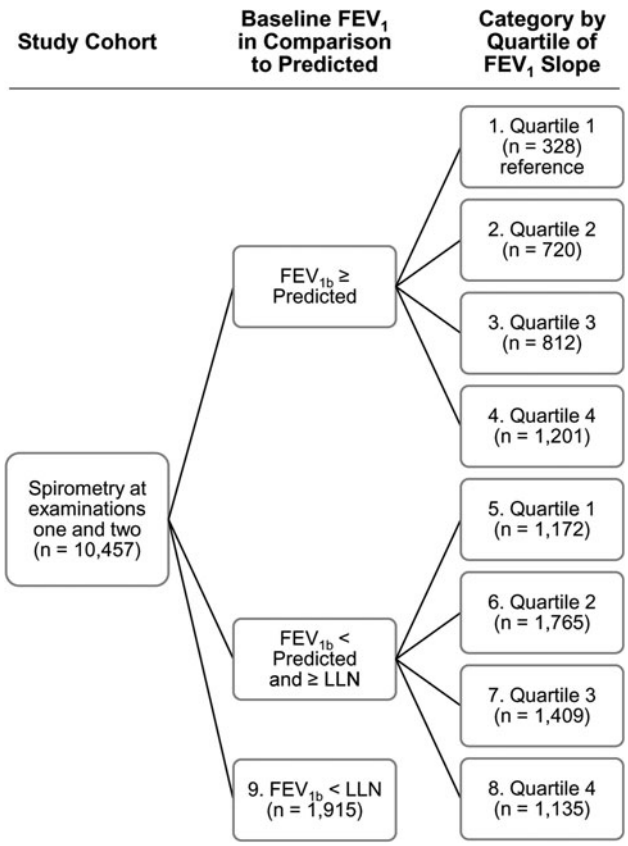

Fig. 2 Nine lung function categories based on baseline FEV_1 values in comparison to predicted values and quartiles of FEV_1 slope. European reference equations were used to calculate the predicted FEV_1 values[29]. *FEV_{1b}* baseline forced expiratory volume in one second; *LLN* lower limit of normal

Hazard ratios (HR) and 95 % confidence intervals (CI) were estimated overall, by gender, for never smokers, and by baseline age (≤45 and >45). The stratification was in recognition of the importance of age, gender, and smoking as determinants of lung function and risk factors for morbidity and mortality. Although not all models were gender-specific, all models used gender-specific quartile values for the FEV_1 slope to account for differences due to gender. All models were adjusted for baseline age and height to account for their potential effect on the level as well as decline in lung function and because these are essential covariates that would typically be available and taken into consideration in a clinical context [37]. However, smoking was not included in the models as a risk factor because the interest was to determine the effect of lung function and its decline on morbidity and mortality for application in prevention. Additional analyses were conducted in never smokers to demonstrate risk in the absence of smoking. The single cut point at age 45 was selected because it is an age related to COPD development [38, 39] and the 16–21 year morbidity and mortality follow-up permitted estimation of morbidity and mortality risks associated with lung function decline earlier in life, which is less well-known. Time to event (or censor) was from examination two until: (1) COPD hospital diagnosis, death, or end of follow-up for COPD morbidity; and (2) death or end of follow-up for mortality.

Population attributable risks (PAR) were calculated with Levin's formula [40] for category 9 and jointly for categories 8 and 9 to demonstrate the potential contribution of an excessive FEV_1 slope in those with a 'normal' FEV_{1b} beyond that of FEV_{1b} below the LLN. We also plotted the relationship between the nine categories and the overall prevalence rates of current respiratory symptoms of chronic bronchitis and shortness of breath at examination two. As in our previous study, we conducted sensitivity analyses to assess the effect of an adjustment to FEV_1

measurements for 1981 by a mean difference with respect to years 1982 and 1983 [41]. Preliminary analysis of mean FEV_1 values had revealed a slightly excessive increase in mean FEV_1 in 1981, but not in 1982 or 1983, as compared to mean FEV_1 for baseline examinations in 1976–78. It is unknown to the authors whether the increase was due to early difficulties with the Monaghan spirometer that was replaced with a dry wedge spirometer by examination three or to other issues [42]. To adjust for the increase, we reduced the individual FEV_1 measurements for 1981 by a fixed value (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 are the average difference in FEV_1 values from examination one to two (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 the adjustment.

All Copenhagen City Heart Study subjects gave informed consent to participate. The Study was performed in accordance with the 2nd Helsinki Declaration and approved by the regional ethics committee (100.2039/91). Current analyses were approved by the National Institute for Occupational Safety and Health Human Subjects Review Board (08-DRDS-03XP) and the West Virginia University Institutional Review Board (H-21909). All analyses were conducted with PROC PHREG ($p < 0.05$) using SAS version 9.2 (SAS Institute Inc, USA).

Results

The characteristics of the 10,457 individuals with spirometry testing at examinations one and two are summarized by subcohort (males, females, and never smokers) in Table 1. The table describes the sample sizes, duration of morbidity and mortality follow-up (16–21 years), gender-specific values for baseline FEV_1 (FEV_{1b}), the frequencies by the level of FEV_{1b} and quartiles of FEV_1 slope, the quartiles of FEV_1 slope, and smoking status. For the combined COPD or CHD mortality events, the causes of death were CHD in 70 %, COPD in 25 %, and both causes in 5 % of these deaths. Of note are the high prevalence rates of current and former smoking. Individuals lost to follow-up by examination two (22.9 %) were older, had lower average height-adjusted FEV_1, and higher prevalence of self-reported respiratory symptoms of chronic bronchitis, current asthma, and smoking at baseline.

Morbidity and mortality risks by gender, for never smokers, and by age at baseline

Morbidity and mortality risks by gender and for never smokers are presented in Table 2. For categories with FEV_{1b} at or above 100 % predicted, only females in the fourth quartile of the slope had statistically significant morbidity and mortality risks. Categories with FEV_{1b} below 100 % predicted showed increasing trends in morbidity and mortality risk with increasing quartiles of the slope, most often significant in females. Females demonstrated higher COPD or CHD mortality risks than males; this pattern was not as clearly seen for all-cause mortality. Among never smokers, there was a clear trend for increasing COPD morbidity risk with worsening lung function category, however the risk was only significant with category 9 (FEV_{1b} below the LLN). Only all-cause mortality risk could be evaluated for never smokers by gender. There were no clear trends and only category 8 (FEV_{1b} below 100 % predicted and the fourth quartile of the slope) was statistically significant with HRs of 2.58 (1.04–6.40) for males and 1.74 (1.12–2.70) for females (not shown).

Morbidity and mortality risks estimated by age categories ($\leq$45 and >45) at baseline spirometry testing are shown in Table 3. The general increasing trend in the HRs across the lung function categories 1 to 9 was found in both age groups, but all-cause mortality risks were higher among the younger group. Among each subcohort (males, females, never smokers, and ages $\leq$45 and >45), cause-specific and all-cause mortality risks were significantly increased for those with 'normal' lung function (FEV_{1b} at or above the LLN but below 100 % predicted) and with excessive FEV_1 decline (fourth quartile of the slope).

Overall morbidity and mortality risks and attributable risk

Significant overall trends in the risk of morbidity and mortality outcomes across the nine categories for the combined effect of the lung function level and decline are demonstrated in Fig. 3a–c. Risks were higher for COPD morbidity as compared to the mortality outcomes. Statistically significant increases in the morbidity and mortality risks began at category 4 (FEV_{1b} at or above 100 % predicted and the fourth quartile of the slope). By category 8 (FEV_{1b} at or above the LLN but below 100 % predicted and the fourth quartile of the slope), HRs reached 7.29 (4.24–12.52) for COPD morbidity, 4.07 (2.70–6.13) for COPD or CHD mortality, and 2.13 (1.80–2.53) for all-cause mortality.

To illustrate the effect of excessive decline on morbidity and mortality in a population, we estimated the PARs for the increased risk in category 9 and then jointly for categories 8 and 9 to quantify the additional increase in risk due to excessive decline in those with 'normal' lung function, using estimated HRs from the overall analysis. Table 4 shows that the additional contribution of category 8 is 12.0 % for COPD morbidity (49.6–37.6 %), 9.6 % for COPD or CHD mortality, and 7.1 % for all-cause mortality. The increasing categories of lung function impairment were also associated

Table 1 Characteristics of the subcohorts for the Cox proportional hazards model analysis

	Males		Females		Never smokers	
Subjects at examinations one and two[a]						
Subjects (n, %[b])	4,598	44.0	5,859	56.0	1,949	18.6
Baseline age (mean, SD)	52.2	11.6	52.4	11.0	52.3	12.4
Subjects with baseline age ≤45 (mean, SD)	37.5	6.0	37.6	5.9	36.4	6.4
Subjects with baseline age >45 (mean, SD)	57.8	7.5	57.4	7.2	58.8	7.5
Events (n, %)						
COPD morbidity	616	13.4	789	13.5	75	3.8
COPD or CHD mortality	1,053	22.9	862	14.7	208	10.7
All-cause mortality	3,217	70.0	3,449	58.9	987	50.6
Years of follow-up (mean, SD)						
COPD morbidity	17.0	8.8	19.6	7.9	21.1	7.7
COPD or CHD mortality	16.7	7.9	19.2	6.9	20.1	6.7
All-cause mortality	17.5	8.7	20.2	7.8	21.3	7.6
FEV_{1b}, l (mean, SD)	3.09	0.83	2.25	0.55	3.48; 2.31[c]	0.85; 0.55[c]
FEV_{1b}, % predicted (mean, SD)	88.6	18.2	91.9	17.8	95.0; 96.6[c]	15.9; 18.0[c]
FEV_{1b} ≥ predicted (n, %)	1,189	25.9	1,872	32.0	791	40.6
Q1 Slope FEV_1 (n, %)	170	14.3	158	8.4	78	9.9
Q2 Slope FEV_1 (n, %)	253	21.3	467	24.9	179	22.6
Q3 Slope FEV_1 (n, %)	317	26.7	495	26.4	212	26.8
Q4 Slope FEV_1 (n, %)	449	37.8	752	40.2	322	40.7
FEV_{1b} < predicted and ≥LLN (n, %)	2,420	52.6	3,061	52.2	962	49.4
Q1 Slope FEV_1 (n, %)	528	21.8	644	21.0	241	25.1
Q2 Slope FEV_1 (n, %)	735	30.4	1,030	33.6	320	33.3
Q3 Slope FEV_1 (n, %)	606	25.0	803	26.2	248	25.8
Q4 Slope FEV_1 (n, %)	551	22.8	584	19.1	153	15.9
FEV_{1b} < LLN (n, %)	989	21.5	926	15.8	196	10.1
Slope FEV_1, ml/year (mean, SD)	−61	91	−44	69	−48; −40[c]	95; 71[c]
25th percentile	−117		−94		−113; −81[c]	
Median	−59		−55		−57; −39[c]	
75th percentile	0		0		−16; 0[c]	
Never smokers (n, %)[d]	453	9.9	1,496	25.5	453; 1,496[c]	23.2; 76.8[c]
Former smokers (n, %)[d]	1,210	26.3	1,224	20.9		
Current smokers (n, %)[d]	2,922	63.5	3,082	52.6		

FEV_{1b} baseline forced expiratory volume in one second, *l* liters, *LLN* lower limit of normal, *ml/yr* milliliters/year, *Q1* first quartile, *SD* standard deviation

[a] Spirometry tests were 4 to 7 years apart from examination one to two with a mean follow-up of 5 years

[b] A total of 10,457 subjects were present for examinations one and two

[c] Males; females

[d] Ascertained at examination two

with increasing prevalence of symptoms of chronic bronchitis and shortness of breath (Fig. 4).

Given that individuals with abnormal baseline lung function were included in the models, several additional Cox models were conducted post hoc. These models excluded individuals with: (1) a ratio of FEV_{1b} to baseline FVC (FEV_{1b}/FVC_b) below the LLN, (2) FEV_{1b} and FEV_{1b}/FVC_b below the LLN, and (3) FVC below the LLN and FEV_{1b}/FVC_b above the LLN. Differences occurred mainly in category 9, with lower HRs in the first two models and a higher HR for COPD morbidity in the last model, but overall patterns were not affected.

Discussion

This study shows that the combined effect of the baseline FEV_1 and excessive rate of FEV_1 decline is associated with

Table 2 Cox proportional hazards models for morbidity and mortality risks by lung function category and subcohort[a]

	Males		Females		Never Smokers	
	HR	95 % CI	HR	95 % CI	HR	95 % CI
COPD Morbidity	(n = 4,550 COPD = 616)		(n = 5,833 COPD = 789)		(n = 1,943 COPD = 75)	
FEV_{1b} ≥ pred. and Q1 slope	1.00		1.00		1.00	
FEV_{1b} ≥ pred. and Q2 slope	0.68	(0.27–1.71)	1.15	(0.42–3.15)	0.27	(0.05–1.64)
FEV_{1b} ≥ pred. and Q3 slope	1.18	(0.54–2.58)	1.52	(0.58–4.01)	0.12	(0.01–1.12)
FEV_{1b} ≥ pred. and Q4 slope	1.38	(0.65–2.90)	2.99	(1.20–7.44)	0.68	(0.18–2.57)
FEV_{1b} < pred. and ≥ LLN and Q1 slope	1.25	(0.60–2.60)	3.68[b]	(1.48–9.15)	0.80	(0.21–3.10)
FEV_{1b} < pred. and ≥ LLN and Q2 slope	1.85	(0.92–3.72)	4.90[b]	(2.00–11.97)	1.15	(0.32–4.08)
FEV_{1b} < pred. and ≥ LLN and Q3 slope	3.10	(1.56–6.17)	6.06	(2.47–14.86)	1.44	(0.41–5.11)
FEV_{1b} < pred. and ≥ LLN and Q4 slope	5.11[b]	(2.58–10.13)	11.63[b]	(4.75–28.46)	3.09[c]	(0.88–10.86)
FEV_{1b} < LLN	9.38[b]	(4.82–18.24)	18.05[b]	(7.44–43.78)	3.44[c]	(1.00–11.77)
COPD or CHD Mortality	(n = 4,598 Deaths = 1,053)		(n = 5,859 Deaths = 862)		(n = 1,949 Deaths = 208)[d]	
FEV_{1b} ≥ pred. and Q1 slope	1.00		1.00		1.00	
FEV_{1b} ≥ pred. and Q2 slope	1.33	(0.77–2.31)	1.93	(0.87–4.29)	2.33	(0.68–7.91)
FEV_{1b} ≥ pred. and Q3 slope	1.23	(0.72–2.10)	2.19	(0.99–4.84)	2.39	(0.71–7.99)
FEV_{1b} ≥ pred. and Q4 slope	1.43	(0.85–2.39)	3.04	(1.41–6.55)	2.10	(0.64–6.90)
FEV_{1b} < pred. and ≥LLN and Q1 slope	1.48	(0.90–2.45)	3.58	(1.65–7.75)	2.92	(0.88–9.61)
FEV_{1b} < pred. and ≥LLN and Q2 slope	1.53	(0.93–2.50)	3.46[b]	(1.62–7.40)	3.18	(0.98–10.33)
FEV_{1b} < pred. and ≥LLN and Q3 slope	1.96	(1.20–3.20)	4.22	(1.97–9.05)	2.78	(0.84–9.19)
FEV_{1b} < pred. and ≥LLN and Q4 slope	3.03	(1.86–4.95)	7.47[b]	(3.49–16.00)	4.90	(1.48–16.30)
FEV_{1b} < LLN	3.71	(2.30–5.96)	11.11[b]	(5.22–23.62)	4.50	(1.36–14.95)
All-cause Mortality	(n = 4,598 Deaths = 3,217)		(n = 5,859 Deaths = 3,449)		(n = 1,949 Deaths = 987)	
FEV_{1b} ≥ pred. and Q1 slope	1.00		1.00		1.00	
FEV_{1b} ≥ pred. and Q2 slope	1.03	(0.79–1.35)	1.05	(0.81–1.37)	1.05	(0.70–1.58)
FEV_{1b} ≥ pred. and Q3 slope	0.93	(0.72–1.21)	1.16	(0.90–1.51)	1.12	(0.76–1.66)
FEV_{1b} ≥ pred. and Q4 slope	1.12	(0.88–1.44)	1.34	(1.05–1.72)	1.22	(0.84–1.77)
FEV_{1b} < pred. and ≥LLN and Q1 slope	1.14	(0.90–1.45)	1.30	(1.01–1.68)	1.11	(0.75–1.64)
FEV_{1b} < pred. and ≥LLN and Q2 slope	1.34	(1.06–1.68)	1.55	(1.22–1.98)	1.38	(0.95–2.00)
FEV_{1b} < pred. and ≥LLN and Q3 slope	1.40	(1.11–1.77)	1.62	(1.26–2.07)	1.28	(0.88–1.88)
FEV_{1b} < pred. and ≥LLN and Q4 slope	2.01	(1.59–2.54)	2.40	(1.87–3.08)	1.89	(1.27–2.80)
FEV_{1b} < LLN	2.24	(1.79–2.80)	2.85	(2.23–3.63)	1.66	(1.12–2.47)

FEV_{1b} baseline forced expiratory volume in one second, *LLN* lower limit of normal, *pred.* predicted value, *Q1* first quartile of FEV_1 slope

[a] Adjusted for baseline age and height

[b] Sensitivity analysis, excluding the adjusted 1981 FEV_1 values, indicates there may be an underestimation of risk

[c] Sensitivity analysis indicates there may be an overestimation of risk

[d] Sensitivity analysis was not possible due to a lack of cases in the reference category after excluding the adjusted 1981 FEV_1 values

increased morbidity and mortality risks, even with a 'normal' baseline FEV_1 (at or above the LLN). The effect of an excessive decline was seen in males, females, never smokers, and with a baseline age of 45 or under or above 45, although all-cause mortality risks were higher in those 45 or under. The contribution of excessive FEV_1 decline in those with 'normal' FEV_1 has public health significance as illustrated by the additional contribution to the PAR of 12.0 % for COPD morbidity, 9.6 % for COPD or CHD mortality, and 7.1 % for all-cause mortality.

Previous studies have demonstrated associations between morbidity and mortality and FEV_1 and the rate of decline [1–19]. Our results confirm the well-recognized finding that FEV_1 is an important marker of risk for cardiovascular and respiratory outcomes. Similar to prior studies, we also identified higher morbidity and mortality risks among females [11, 17], which may result from increased susceptibility to the effects of smoking [43], and increased COPD morbidity risk with lower lung function at younger ages [44].

Table 3 Cox proportional hazards models for morbidity and mortality risks by lung function category and baseline age[a]

	Baseline age ≤45		Baseline age >45	
	HR	95 % CI	HR	95 % CI
COPD Morbidity	(n = 2,726 COPD = 269)		(n = 7,657 COPD = 1,136)	
FEV_{1b} ≥ pred. and Q1 slope	1.00		1.00	
FEV_{1b} ≥ pred. and Q2 slope	0.75	(0.23–2.47)	0.91	(0.41–2.02)
FEV_{1b} ≥ pred. and Q3 slope	1.19	(0.41–3.43)	1.35	(0.65–2.83)
FEV_{1b} ≥ pred. and Q4 slope	1.69	(0.63–4.50)	2.15	(1.07–4.31)
FEV_{1b} < pred. and ≥LLN and Q1 slope	1.92	(0.74–4.97)	2.35	(1.17–4.71)
FEV_{1b} < pred. and ≥LLN and Q2 slope	2.66	(1.06–6.71)	3.29[b]	(1.68–6.46)
FEV_{1b} < pred. and ≥LLN and Q3 slope	2.64	(1.03–6.76)	4.91	(2.51–9.60)
FEV_{1b} < pred. and ≥LLN and Q4 slope	4.79[b]	(1.88–12.17)	8.48[b]	(4.34–16.57)
FEV_{1b} < LLN	6.21[b]	(2.52–15.33)	15.26[b]	(7.88–29.54)
COPD or CHD Mortality	(n = 2,732 Deaths = 136)		(n = 7,725 Deaths = 1,779)	
FEV_{1b} ≥ pred. and Q1 slope	1.00		1.00	
FEV_{1b} ≥ pred. and Q2 slope	1.12	(0.27–4.67)	1.41	(0.88–2.27)
FEV_{1b} ≥ pred. and Q3 slope	1.69	(0.46–6.24)	1.47	(0.93–2.35)
FEV_{1b} ≥ pred. and Q4 slope	0.86	(0.22–3.44)	1.87	(1.19–2.91)
FEV_{1b} < pred. and ≥LLN and Q1 slope	1.71	(0.49–5.90)	2.10	(1.35–3.28)
FEV_{1b} < pred. and ≥LLN and Q2 slope	2.67[c]	(0.81–8.83)	1.98	(1.28–3.07)
FEV_{1b} < pred. and ≥LLN and Q3 slope	1.59	(0.45–5.64)	2.61	(1.69–4.03)
FEV_{1b} < pred. and ≥LLN and Q4 slope	3.77[c]	(1.12–12.71)	4.09[b]	(2.65–6.33)
FEV_{1b} < LLN	4.39[c]	(1.36–14.23)	5.46[b]	(3.56–8.37)
All-cause Mortality	(n = 2,732 Deaths = 715)		(n = 7,725 Deaths = 5,951)	
FEV_{1b} ≥ pred. and Q1 slope	1.00		1.00	
FEV_{1b} ≥ pred. and Q2 slope	1.17	(0.66–2.08)	0.97	(0.80–1.19)
FEV_{1b} ≥ pred. and Q3 slope	1.55	(0.90–2.66)	0.99	(0.82–1.21)
FEV_{1b} ≥ pred. and Q4 slope	1.62	(0.96–2.72)	1.14	(0.95–1.37)
FEV_{1b} < pred. and ≥LLN and Q1 slope	1.69	(1.02–2.81)	1.15	(0.95–1.38)
FEV_{1b} < pred. and ≥LLN and Q2 slope	2.00	(1.22–3.29)	1.35	(1.13–1.61)
FEV_{1b} < pred. and ≥LLN and Q3 slope	1.81	(1.09–3.02)	1.42	(1.19–1.70)
FEV_{1b} < pred. and ≥LLN and Q4 slope	2.66	(1.60–4.43)	2.06	(1.72–2.47)
FEV_{1b} < LLN	3.21	(1.98–5.23)	2.35	(1.97–2.80)

FEV_{1b} baseline forced expiratory volume in one second, *LLN* lower limit of normal, *pred.* predicted value, *Q1* first quartile of FEV_1 slope

[a] Adjusted for baseline age and height

[b] Sensitivity analysis, excluding the adjusted 1981 FEV_1 values, indicates there may be an underestimation of risk

[c] Sensitivity analysis indicates there may be an overestimation of risk

Evaluating the combined effect of the level and rate of decline is a new approach and adds to current knowledge regarding prevention. Because FEV_1 is considered the most useful of the spirometry tests for the evaluation of longitudinal changes in lung function, it was of interest to determine the combination of the level and the rate of decline on the future morbidity and mortality outcomes. Especially in individuals with normal levels of lung function, but excessive decline, who may not be considered at risk because their lung function level is within the normal limits. The three-tier classification of the level of lung function permits examination of results for individuals with FEV_{1b} at or above the LLN but less than 100 % predicted, a group of potential concern if rates of decline are excessive. The LLN cut point was used to initially delineate 'normal' versus 'abnormal' levels of lung function because the LLN is based on population-based reference values that account for age, height, gender, and race. For example, using the LLN for the FEV_1/FVC ratio was shown to be a better predictor of excessive rate of decline than a fixed ratio [25].

Our results indicate that prevention of an excessive lung function decline has public health significance even in individuals who have normal levels of FEV_1. The results are particularly relevant to prevention in occupational settings

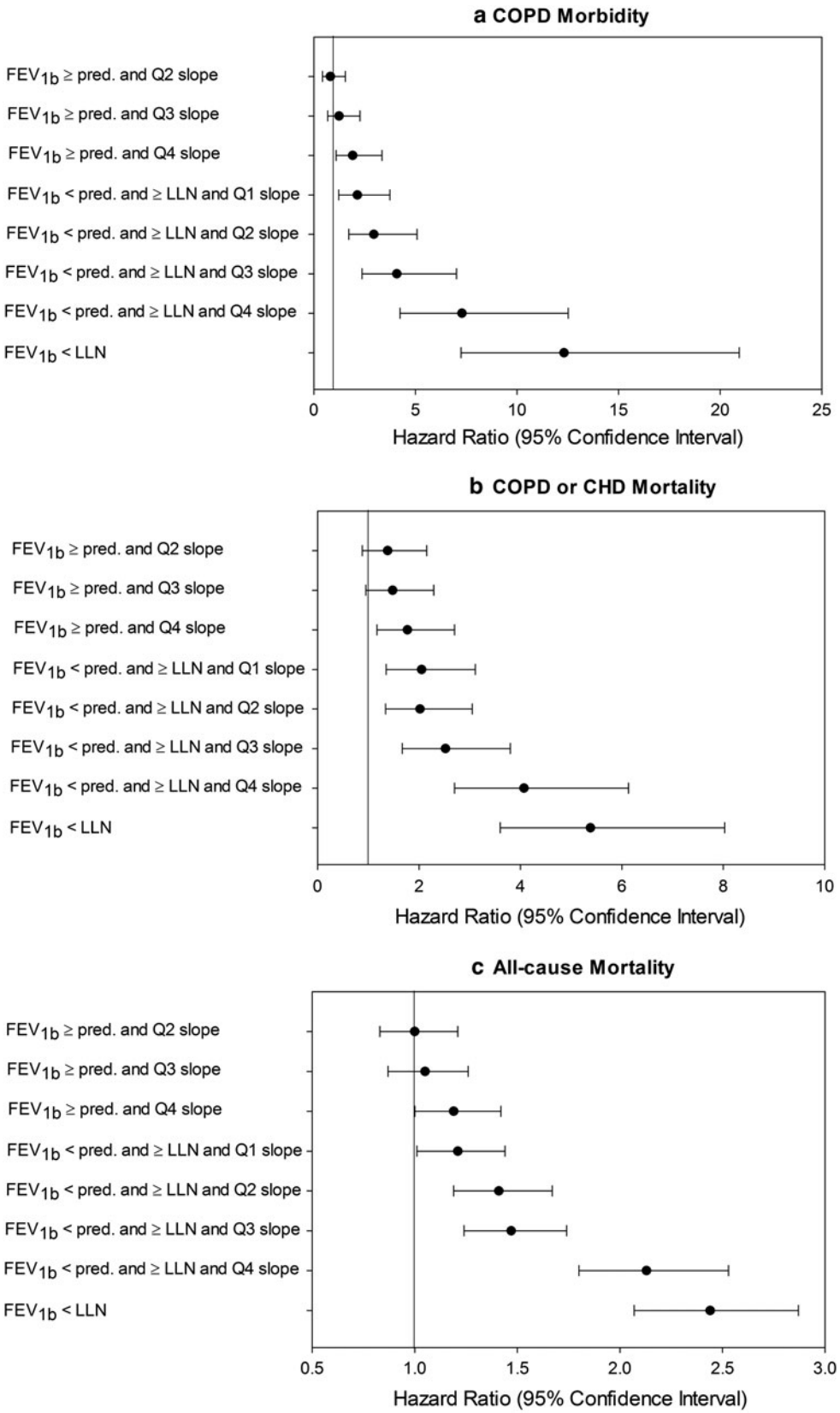

Fig. 3 Cox proportional hazards models for overall (**a**) morbidity and (**b** and **c**) mortality risks by lung function category. Models adjusted for baseline age and height. The scales for the hazard ratio differ for the morbidity and mortality outcomes and are not directly comparable. Sensitivity analyses, excluding the adjusted 1981 FEV_1 values, indicate there may be an underestimation of risk in the last three lung function categories for COPD morbidity and where $FEV_{1b} < LLN$ for COPD or CHD mortality. *FEV_{1b}* baseline forced expiratory volume in one second; *LLN* lower limit of normal; *pred.* predicted value; *Q1* first quartile of FEV_1 slope

Table 4 PAR for morbidity and mortality in the overall study cohort[a]

	HR[a]	95 % CI	PAR (%)
COPD Morbidity	(n = 10,383 COPD = 1,405)		
Categories 1–8	1.00		
Category 9	4.35	(3.90–4.85)	37.6
Categories 1–7	1.00		
Categories 8 and 9	4.42	(3.97–4.91)	49.6
COPD or CHD Mortality	(n = 10,457 Deaths = 1,915)		
Categories 1–8	1.00		
Category 9	2.48	(2.24–2.74)	21.3
Categories 1–7	1.00		
Categories 8 and 9	2.53	(2.31–2.78)	30.9
All-cause Mortality	(n = 10,457 Deaths = 6,666)		
Categories 1–8	1.00		
Category 9	1.80	(1.70–1.91)	12.8
Categories 1–7	1.00		
Categories 8 and 9	1.85	(1.75–1.95)	19.9

[a] Cox models adjusted for baseline age and height

where periodic spirometry is often conducted on relatively healthy workers to maintain workers' fitness to wear respirators and to prevent occupational injury. Generally, in occupational settings most of the workers have 'normal' levels of lung function and prevention of excessive decline in lung function by intervening on the preventable risk factors [17, 18, 20, 44] would be of public health significance in at risk worker populations. Also, of clinical significance is the increased prevalence of symptoms of chronic bronchitis and shortness of breath with increasing decline in lung function starting from the fourth quartile in those with FEV_1 at or above the predicted value.

Despite this study's strengths, such as a large, age-stratified population and long outcome follow-up, there were limitations including the adjustment of FEV_1 values for 1981 [41]. Sensitivity analyses excluding 1981 data indicated under- and overestimation of COPD morbidity and COPD or CHD mortality risks but was not possible for COPD or CHD mortality risk in never smokers because there were no events in the reference category of the comparison model. Underestimation of risk could also have occurred through self-selection of healthier subjects into the Copenhagen City Heart Study and survivor bias.

Chronic obstructive pulmonary disease (COPD) is generally thought to be under-diagnosed and mortality under-reported, such misclassification could have biased the results toward the null and decreased associations [45]. Thus, the COPD or CHD mortality outcome was used [19, 46, 47]. COPD morbidity defined as a hospital diagnosis limits the generalizability of the results to individuals with more severe disease. The FEV_1 slope calculated from only two measurements is vulnerable to regression to the mean, but adjustment for height may have lessened this effect. The duration of follow-up in the study was sufficient to estimate the slope, although the precision may have been somewhat improved by more frequent measurements [48].

Throughout these models, our method of stratification by combinations of lung function level and rate of decline created the potential for a relatively small sample size in

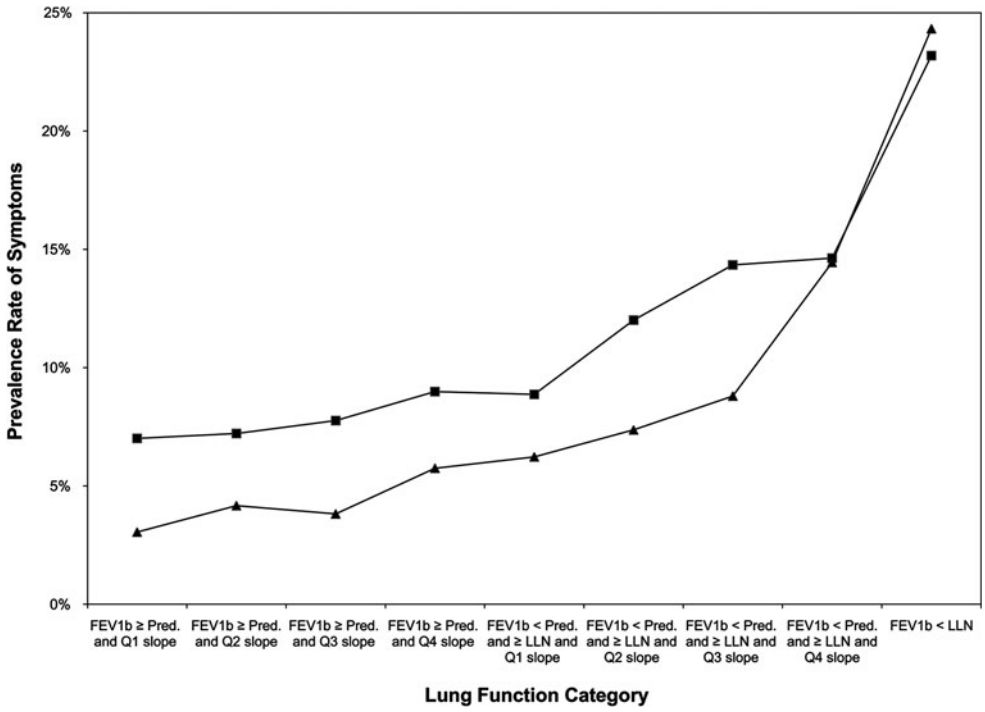

Fig. 4 Overall prevalence rates of self-reported respiratory symptoms (*filled square* chronic bronchitis; *filled triangle* shortness of breath) at examination two by lung function category. FEV_{1b} baseline forced expiratory volume in one second; *LLN* lower limit of normal; *pred.*, predicted value; *Q1* first quartile of FEV_1 slope

the reference category that could influence the results. For example, this may partially explain the gender-specific differences in the morbidity and mortality risks. To explore this issue, we created a new reference category by combining categories 1 and 2. The addition of category 2 narrowed the gender gap in risk slightly and reduced the HRs.

In conclusion, this study provides evidence that individuals with excessive longitudinal decline are at increased risk of morbidity and mortality even before the point when their spirometry values would be interpreted as abnormal. Recognition of this provides an earlier opportunity for prevention. These study results may be useful to health care providers who evaluate individuals at-risk for lung function impairment.

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Conflict of interest The authors declare that they have no conflict of interest.

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