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Original Research

Reduced lung function and cause-specific mortality: A population-based study of Norwegian men followed for 26 years

Lucia Cestelli [a,*], Amund Gulsvik [a], Ane Johannessen [b], Knut Stavem [c,d,e], Rune Nielsen [a,f]

[a] Department of Clinical Science, University of Bergen, Bergen, Norway
[b] Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway
[c] Pulmonary Department, Akershus University Hospital, Lørenskog, Norway
[d] Institute of Clinical Medicine, University of Oslo, Oslo, Norway
[e] Health Services Research Unit, Akershus University Hospital, Lørenskog, Norway
[f] Department of Thoracic Medicine, Haukeland University Hospital, Bergen, Norway

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ABSTRACT

Background and aim: Reduced lung function is associated with increased mortality, but it is unclear how different spirometric patterns are related to specific deaths. Aim of this study was to investigate these associations in a large general population cohort.

Methods: The study population consisted of 26,091 men aged 30–46 years from the Pneumoconiosis Survey of Western Norway conducted in 1988–1990 with follow-up on date and cause of death for 26 years. Cox proportional hazard models were used to estimate the association between baseline FEV_1, FVC, obstructive (OSP) and restrictive spirometric pattern (RSP) (z-scores calculated according to GLI-2012 equations) and mortality (European 2012 shortlist classification (E−2012)), after adjustment for age, body mass index, smoking habits, and education.

Results: In total, 2462 (9%) subjects died. A predominant reduction of FEV_1 (and OSP) were associated with respiratory non-cancer (E−8) (HR for one unit FEV_1 z-score decrease 2.29 (95% CI 1.90, 2.77) and lung cancer mortality (E−2.1.8) (1.27(1.12, 1.44)). A similar reduction of FEV_1 and FVC (and RSP) were associated with diabetes (E−4.1) (FEV_1 2.21(1.67, 2.92), FVC 2.41(1.75, 3.32)), cerebrovascular (E−7.3) (1.52(1.21, 1.91), 1.54 (1.19, 1.98)), ischemic heart disease (E−7.1) (1.22(1.10, 1.35), 1.21(1.08, 1.36)), neurological (E−6.3) (1.56 (1.21, 2.01), 1.61(1.22, 2.13)), suicide (E−17.2) (1.37(1.13, 1.65), 1.29(1.04, 1.59)) and hematological cancer mortality (E−2.1.19–21) (1.29(1.05, 1.58), (1.26(1.00, 1.58)). No association was found between reduced lung function and mortality due to accidents, alcohol abuse, digestive and genitourinary cancer.

Conclusions: Spirometric obstruction was mainly related to pulmonary mortality. Spirometric restriction was mainly related to extra-pulmonary mortality.

1. Introduction

There is extensive evidence that reduced lung function is associated with mortality [1–7], but only few studies have investigated the relationship of both Forced Expiratory Volume in 1 s (FEV_1) and Forced Vital Capacity (FVC) with all-cause and cause-specific mortality [8–13].

Some authors have reported FEV_1 as a stronger predictor of all-cause mortality [9,10,13], while others have shown similar performances of FEV_1 and FVC [12]. Yet other studies favor FVC as a predictor of all-cause mortality in asymptomatic subjects [8] and middle-aged never-smokers [11]. Most of these studies took place in small or selected population samples with limited follow-up time, which limits the generalizability of the results.

With regard to cause-specific mortality, studies have reported conflicting findings regarding the association of FEV_1 and FVC with respiratory, cardiovascular and cancer mortality [9–12], possibly because of differences in characteristics of the populations or definitions of cause-specific mortality. Moreover, these studies have not explored specific subgroups of cause-specific death.

Other studies have investigated the relationship of obstructive (OSP) and restrictive spirometric pattern (RSP) with mortality [6,14] and suggested distinct mortality profiles between the two conditions. OSP

* Corresponding author. Department of Clinical Science, University of Bergen, PO Box 7804, 5020, Bergen, Norway.
E-mail address: lucia.cestelli@uib.no (L. Cestelli).

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showed strong associations with respiratory mortality, while RSP showed strong associations with diabetes mortality [6]. Findings regarding cardiovascular, cancer and dementia mortality appeared more uncertain, possibly due to the limited sample size of the studies [6,14].

We hypothesized that FEV_1 and FVC relate differently to specific types of mortality, and that the association might reflect different pathophysiological mechanisms regarding lung function impairment and death, such as predominant airflow obstruction or predominant restriction. The main aim of the study was to investigate the relationship of FEV_1, FVC, OSP and RSP with all-cause and cause-specific mortality in a general population cohort of over 25,000 men followed for 26 years.

2. Methods

2.1. Study population

The Pneumoconiosis Survey of Western Norway was a general population survey conducted between October 1988 and September 1990 in Hordaland county and Sauda municipality (Rogaland county) in Norway [15]. All men born 1944–1958 (aged 30–46 years, n = 45,380) living in the study area on January 1, 1988 received a postal invitation with a self-administered questionnaire, and a mobile unit from the National Health Screening Service (NHSS) performed chest radiographs and spirometry of the attendees; 29,611 subjects (65% of eligible) participated and 26,803 (91% of attendees) performed spirometry [16,17].

2.2. Baseline lung function and covariates

Pre-bronchodilator FEV_1 and FVC were measured with a dry-wedge spirometer (Vitalograph *S*-model, Vitalograph Ltd., Buckingham, UK). Three acceptable and reproducible spirometry recordings were required, with a difference between the two highest FVC values < 300 mL, in line with guidelines at the time [18]. Values were corrected to body temperature and pressure-saturated conditions (BTPS) using twice daily recordings of room temperature and barometric pressure. Z-scores of FEV_1 and FVC were calculated using GLI-2012 reference equations [19] adjusted for sex, age, height, and ethnicity. Height and weight were measured in all participants. Body mass index (BMI) was defined as weight (kg)/height squared (m^2) and grouped in four categories (<18.5, 18.5–24.9, 25–29.9, ≥30) according to the WHO nutritional status categories [20]. Information on smoking status was provided in a self-administered questionnaire and categorized as never, former, or current. Maximal attained education was retrieved from the national census for years 1970, 1980, 1990, 2001 and grouped in three categories (low= <11 years, medium = 11–13 years, high = 14+ years).

2.3. Follow-up and mortality

Mortality and emigration data up to December 31, 2016 were obtained from the Norwegian Cause of Death Registry and the National Population Register. The baseline was defined as the date of spirometry. Subjects were followed until death or censored at the date of emigration or end of follow-up, whichever came first. The European Shortlist for Causes of Death 2012 (E−2012) was used for classification of the underlying cause of death [21,22]. The main causes of death examined were: cancer, cardiovascular, respiratory, non-natural, and other. In the main analysis lung cancer was included among respiratory and not cancer deaths. We also analyzed the following subgroups of cause-specific deaths: lung cancer, non-cancer respiratory disease, ischemic heart disease, heart failure, cerebrovascular disease, diabetes, accidents, suicides, nervous system disease, alcohol abuse, cancer of the digestive, genitourinary, and hematological system. The exact coding and correspondence with ICD-9 and 10 classifications are shown in Table 1.

Table 1
Classification of underlying cause of death.

Underlying cause of death	E−2012 code	ICD-10 code	ICD-9 code
Main groups			
Cancer	2 except 2.1.8	C00-D48 except C33–C34	140-239 except 162
Cardiovascular	7	I00–I99	390–459
Respiratory	8 and 2.1.8	J00-J99 and C33–C34	460-519 and 162
Non-natural	17	V01–Y89	E800-E999
Other	All others	All others	All others
Selected subgroups			
Lung cancer	2.1.8	C33–C34	162
Respiratory diseases	8	J00-J99	460–519
Ischemic heart disease	7.1	I20–I25	410–414
Heart failure	7.2	I30–I51	420–429
Cerebrovascular disease	7.3	I60–I69	430–438
Diabetes	4.1	E10-E14	250
Accidents	17.1	V01-X59, Y85–Y86	E800-E929
Suicides	17.2	X60-X84, Y87.0	E950-E959
Nervous system disease	6.3	G00-G12, G14, G21-G25, G31-H95	320-330, 331.1–331.9, 332.1–389
Alcohol abuse	5.2	F10	291, 303
Digestive cancer	2.1.2–2.1.6	C15, C16, C18–C22, C25	150, 151, 153–154, 155, 157
Genitourinary cancer	2.1.14–2.1.16	C61, C64, C67	185, 189.0, 188
Hematological cancer	2.1.19–2.1.21	C81–C86, C91–C95, C88, C90, C96	200-201, 204–208, 202-203

E−2012 = European Shortlist 2012. ICD-10 and 9 = International Classification of Disease 10th and 9th revision.

2.4. Ethics

The study was approved by the Regional Committee on Medical Research Ethics (2017/1679), The Norwegian Data Inspectorate (07/00414) and The Norwegian Directorate of Health (07/948).

2.5. Statistical analysis

We used Cox proportional hazard models to estimate the association of FEV_1 and FVC z-scores with all-cause and cause-specific mortality (main groups and subgroups). Time since inclusion was used as time scale. Hazard ratios (HR) indicated the risk of mortality per one unit decrease of FEV_1 and FVC z-scores, i.e. corresponding to a decrease of 1 SD in the distribution of the norm population. The analyses were adjusted for the following covariates selected with the use of directed acyclic graphs (DAGs) [23] (Fig. S1): age, BMI, smoking status, and education. Additionally, we used Cox proportional hazard models to

estimate the association of OSP and RSP with all-cause and cause-specific mortality. OSP was defined as $FEV_1/FVC <$ lower limit of normal (LLN), corresponding to the 5th percentile of the adjusted reference population (z-score < -1.645). RSP was defined as $FEV_1/FVC \geq$ LLN and FVC $<$ LLN. These analyses were adjusted for the same covariates mentioned previously. We performed all analyses in the total population and in never smokers, in order to investigate the role of smoking in the associations studied. We were unable to study the association between OSP/RSP and subgroups of cause-specific mortality in never smokers because of the low number of events. Missing values in the study population were minimal and therefore not imputed. The proportional hazards assumption was tested using Schoenfeld residuals as well visual inspections of log-log plots, and was found to be acceptable (Fig. S2). All analyses were conducted using Stata 17 (StataCorp LLC, College Station, TX, USA).

3. Results

In total, 26,118 subjects were identified with three complete recordings of FEV_1 and FVC satisfying reproducibility criteria. After further exclusions due to missing date of attendance (n = 12), missing height (n = 12), $FEV_1/FVC>1$ (n = 2), inconsistency between date of attendance and date of death (n = 1), the final sample consisted of 26,091 subjects. Detailed characteristics are reported in Table 2. Mean age at baseline was 38.2 years (range 30–46 years). Mean follow-up was 26.3 years, for a total of 685,163 person-years. In total, 2462 (9%) subjects died during follow-up, and 262 (1%) emigrated. Overall, 786 (32%) were cancer deaths, 609 (25%) cardiovascular deaths, 350 (14%) respiratory deaths and 283 (11%) non-natural deaths. The remaining deaths were grouped together and classified as 'other' (n = 434, 18%), of which n = 72 had unknown or missing cause. The causes most represented in the other category were: diseases of the nervous system (n = 59), alcohol abuse (n = 42), and diabetes mellitus (n = 41).

Table 2
Baseline characteristics of the study population.

No. subjects (all men)	26,091
Age (years)	38.2 (4.3)
Height (cm)	178.8 (6.3)
BMI (kg/m^2)	
<18.5	199 (1)
18.5–24.9	15,183 (58)
25–29.9	9259 (35)
≥30	1446 (6)
Smoking status	
Never	8133 (31)
Former	6395 (25)
Current	11,488 (44)
Education level	
Low (<11 years)	3476 (13)
Medium (11–13 years)	15,449 (59)
High (14+ years)	6785 (26)
FEV_1 z-score	−0.08 (0.96)
FVC z-score	0.04 (0.90)
OSP	1585 (6.1)
RSP	725 (2.8)

Continuous variables reported as mean (SD), categorical data as frequency (percentage). BMI= Body Mass Index, FEV_1= Forced Expiratory Volume in the 1st second, FVC= Forced Vital Capacity, OSP = obstructive spirometric pattern, RSP = restrictive spirometric pattern.

3.1. FEV_1, FVC and main groups of cause-specific mortality

We found significant associations of both FEV_1 and FVC with all-cause, cancer, cardiovascular, respiratory, and other cause mortality in the total population (HRs ranging 1.14–1.50 per one unit z-score decrease), after adjustment for age, BMI, smoking status, and education (Table 3). The strongest association was with respiratory mortality, with higher HRs for FEV_1 compared to FVC. No significant association of FEV_1 or FVC was found with non-natural deaths. In never smokers, associations with all-cause, cardiovascular and other cause mortality were confirmed, with higher HRs for FVC compared to FEV_1.

3.2. FEV_1, FVC and subgroups of cause-specific mortality

In the total population (Table 4), subgroup analyses of respiratory mortality showed stronger associations of FEV_1 and FVC with non-cancer respiratory deaths (HRs 2.29 and 1.78, per one unit z-score decrease) compared to lung cancer deaths (HRs 1.27 and 1.14). In both cases, HRs were higher for FEV_1 compared to FVC. Baseline smoking habits were similar among subjects who died of lung cancer and non-cancer respiratory cause (current smokers 90% and 80%, former smokers 6% and 15%, respectively), while baseline airflow obstruction was more prevalent in the non-cancer respiratory mortality group (33%) compared to the lung cancer mortality group (14%).

Significant associations of FEV_1 and FVC were also found with cardiovascular and diabetes deaths. In absolute terms, the strongest association for both lung function parameters was with diabetes mortality (HR 2.21 and 2.41, per one unit z-score decrease), followed by cerebrovascular disease (HR 1.52 and 1.54), heart failure (HR 1.39 and 1.44) and ischemic heart disease (HR 1.22 and 1.21). The magnitude of these associations was comparable for FEV_1 and FVC.

Subgroup analyses of non-natural cause mortality showed no association of FEV_1 or FVC with deaths due to accidents, but significant association of FEV_1 and FVC with deaths due to suicides (HRs 1.37 and 1.29, per one unit z-score decrease). Moreover, as part of the other cause of death category, we found strong associations of both FEV_1 and FVC with mortality from diseases of the nervous system (HRs 1.56 and 1.61), but not with mortality due to alcohol abuse.

Subgroup analyses of cancer mortality showed no association between FEV_1 or FVC with deaths due to digestive or genitourinary cancer, but significant associations of both FEV_1 (HR 1.29) and FVC (HR 1.26) with deaths due to hematological cancer.

In never smokers (Table 5), FEV_1 and FVC had strong associations with diabetes (HRs 2.77 and 2.65, per one unit z-score decrease) and suicide mortality (HR 1.59 for FEV_1). Associations with the other subgroups of cause-specific mortality were not significant, but the analyses were limited by the low number of events.

3.3. OSP, RSP and main groups of cause-specific mortality

In the total population (Table 6), RSP had strong associations (1.5–2-fold increase in HR, compared to absence of RSP) with all types of mortality, except for non-natural cause. OSP had generally weaker associations, except for respiratory mortality (HR 2.77, compared to absence of OSP). In never smokers, OSP showed no association with any mortality cause, while RSP was strongly associated with all-cause, cancer, cardiovascular, and other cause mortality (HRs ranging from 2.3 to 3.1).

Table 3
Associations of FEV_1 and FVC z-scores (HRs with 95% CIs) with all-cause and cause-specific mortality in the total population and in never smokers.

	All-cause	Cancer (excl. lung cancer)	Cardiovascular	Respiratory (incl. lung cancer)	Non-natural	Other
Total population (n = 26,091)						
No. deaths	n = 2462	n = 786	n = 609	n = 350	n = 283	n = 434
z-FEV_1 *one unit decrease*	1.27 (1.22, 1.32)	1.17 (1.08, 1.26)	1.25 (1.16, 1.36)	1.50 (1.35, 1.67)	1.13 (0.99, 1.28)	1.38 (1.26, 1.52)
z-FVC *one unit decrease*	1.21 (1.16, 1.27)	1.14 (1.05, 1.23)	1.26 (1.15, 1.38)	1.27 (1.13, 1.43)	1.08 (0.94, 1.23)	1.33 (1.19, 1.48)
Never smokers (n = 8133)						
No. deaths	n = 444	n = 183	n = 109	n = 15	n = 59	n = 78
z-FEV_1 *one unit decrease*	1.27 (1.15, 1.40)	1.16 (0.99, 1.35)	1.38 (1.13, 1.68)	1.06 (0.62, 1.80)	1.23 (0.94, 1.61)	1.45 (1.16, 1.82)
z-FVC *one unit decrease*	1.32 (1.20, 1.47)	1.17 (0.99, 1.38)	1.44 (1.17, 1.76)	1.37 (0.79, 2.36)	1.26 (0.96, 1.67)	1.60 (1.27, 2.02)

Cox proportional hazard models of FEV_1 and FVC z-scores adjusted for age, BMI, smoking status (total population only), and education. Abbreviations: FEV_1= Forced Expiratory Volume in the 1st second, FVC= Forced Vital Capacity, HR = hazard ratio, CI = confidence interval.

Table 4
Associations of FEV_1 and FVC z-scores (HRs with 95 % CIs) with subgroups of cause-specific mortality in the total population (n = 26,091).

	Respiratory deaths			
	Lung cancer	Respiratory non-cancer		
No. deaths	n = 264	n = 86		
z-FEV_1 *one unit decrease*	1.27 (1.12, 1.44)	2.29 (1.90, 2.77)		
z-FVC *one unit decrease*	1.14 (0.99, 1.30)	1.78 (1.41, 2.25)		
	Cardiovascular and diabetes deaths			
	Ischemic heart disease	Heart failure	Cerebrovascular disease	Diabetes mellitus
No. deaths	n = 390	n = 91	n = 73	n = 41
z-FEV_1 *one unit decrease*	1.22 (1.10, 1.35)	1.39 (1.12, 1.71)	1.52 (1.21, 1.91)	2.21 (1.67, 2.92)
z-FVC *one unit decrease*	1.21 (1.08, 1.36)	1.44 (1.14, 1.82)	1.54 (1.19, 1.98)	2.41 (1.75, 3.32)
	Non-natural and other cause deaths			
	Accidents	Suicides	Nervous system disease	Alcohol abuse
No. deaths	n = 164	n = 114	n = 59	n = 42
z-FEV_1 *one unit decrease*	1.00 (0.85, 1.18)	1.37 (1.13, 1.65)	1.56 (1.21, 2.01)	1.09 (0.78, 1.51)
z-FVC *one unit decrease*	0.97 (0.82, 1.16)	1.29 (1.04, 1.59)	1.61 (1.22, 2.13)	1.18 (0.83, 1.68)
	Cancer deaths			
	Digestive cancer	Genitourinary cancer	Hematological cancer	
No. deaths	n = 324	n = 116	n = 97	
z-FEV_1 *one unit decrease*	1.03 (0.92, 1.15)	1.10 (0.91, 1.34)	1.29 (1.05, 1.58)	
z-FVC *one unit decrease*	1.01 (0.90, 1.15)	1.20 (0.97, 1.48)	1.26 (1.00, 1.58)	

Cox proportional hazard models of FEV_1 and FVC z-scores adjusted for age, BMI, smoking status, and education. Abbreviations: FEV_1= Forced Expiratory Volume in the 1st second, FVC= Forced Vital Capacity, HR = hazard ratio, CI = confidence interval.

3.4. OSP, RSP and subgroups of cause-specific mortality

In the total population (Table 7), OSP was mainly related to respiratory non-cancer (HR 6.20) and lung cancer mortality (HR 1.95), while RSP was mainly related to diabetes (HR 5.62), cerebrovascular disease (HR 4.16), neurological (HR 2.84), and hematological cancer mortality (HR 3.29). Both OSP and RSP were similarly related to ischemic heart disease mortality (HRs 1.51 and 1.90).

3.5. Supplementary data

In supplementary data (Tables S1–S8) we reported the analyses presented in Tables 3 and 6, with full covariates detail. Of note, low education was strongly and consistently associated with all types of mortality. Obesity was strongly associated with cardiovascular mortality, while underweight was strongly associated with the other cause of death category, which includes diabetes and nervous system disease mortality.

4. Discussion

Our study examined the relationship between baseline spirometric measurements and mortality in a large general population sample of 30–46 year-old men followed for 26 years. Overall, a predominant reduction of FEV_1, and OSP, were strongly associated with respiratory mortality. A predominant (or similar) reduction of FVC and FEV_1, and RSP, were strongly associated with diabetes, cerebrovascular disease, neurological and hematological cancer mortality. FVC and RSP were

Table 5
Associations of FEV_1 and FVC z-scores (HRs with 95% CIs) with subgroups of cause-specific mortality in never smokers (n = 8133).

	Respiratory deaths			
	Lung cancer	Respiratory non-cancer		
No. deaths	n = 11	n = 4		
z-FEV_1 *one unit decrease*	1.02 (0.55, 1.91)	1.15 (0.41, 3.20)		
z-FVC *one unit decrease*	1.46 (0.78, 2.74)	1.11 (0.37, 3.32)		
	Cardiovascular and diabetes deaths			
	Ischemic heart disease	Heart failure	Cerebrovascular disease	Diabetes mellitus
No. deaths	n = 63	n = 18	n = 19	n = 7
z-FEV_1 *one unit decrease*	1.15 (0.41, 3.20)	0.92 (0.55, 1.54)	0.92 (0.55, 1.54)	2.77 (1.43, 5.37)
z-FVC *one unit decrease*	1.11 (0.37, 3.32)	1.20 (0.71, 2.02)	1.20 (0.71, 2.02)	2.65 (1.40, 5.01)
	Non-natural and other cause deaths			
	Accidents	Suicides	Nervous system disease	Alcohol abuse
No. deaths	n = 37	n = 22	n = 11	n = 3
z-FEV_1 *one unit decrease*	1.05 (0.74, 1.48)	1.59 (1.04, 2.42)	1.23 (0.67, 2.27)	1.25 (0.37, 4.21)
z-FVC *one unit decrease*	1.14 (0.79, 1.63)	1.50 (0.96, 2.32)	1.36 (0.73, 2.55)	0.72 (0.19, 2.70)
	Cancer deaths			
	Digestive cancer	Genitourinary cancer	Hematological cancer	
No. deaths	n = 70	n = 26	n = 28	
z-FEV_1 *one unit decrease*	0.95 (0.74, 1.22)	1.34 (0.88, 2.02)	1.23 (0.83, 1.82)	
z-FVC *one unit decrease*	1.04 (0.80, 1.35)	1.48 (0.97, 2.27)	1.28 (0.85, 1.93)	

Cox proportional hazard models of FEV_1 and FVC z-scores adjusted for age, BMI, and education. Abbreviations: FEV_1= Forced Expiratory Volume in the 1st second, FVC= Forced Vital Capacity, HR = hazard ratio, CI = confidence interval.

Table 6
Associations of OSP and RSP (HRs with 95% CIs) with all-cause and cause-specific mortality in the total population and in never smokers.

	All-cause	Cancer (excl. lung cancer)	Cardiovascular	Respiratory (incl. lung cancer)	Non-natural	Other
Total population (n = 26,091)						
No. deaths	n = 2462	n = 786	n = 609	n = 350	n = 283	n = 434
OSP	1.56 (1.37, 1.79)	1.07 (0.80, 1.43)	1.37 (1.03, 1.82)	2.77 (2.11, 3.63)	1.11 (0.70, 1.75)	1.97 (1.47, 2.64)
RSP	1.75 (1.45, 2.12)	1.51 (1.05, 2.18)	1.97 (1.39, 2.79)	1.69 (1.01, 2.85)	1.18 (0.60, 2.29)	2.26 (1.51, 3.37)
Never smokers (n = 8133)						
No. deaths	n = 444	n = 183	n = 109	n = 15	n = 59	n = 78
OSP	0.92 (0.54, 1.56)	1.11 (0.52, 2.37)	0.83 (0.26, 2.63)	- *	0.45 (0.06, 3.26)	1.13 (0.36, 3.62)
RSP	2.32 (1.58, 3.42)	2.42 (1.31, 4.47)	2.62 (1.27, 5.43)	- *	1.09 (0.27, 4.51)	3.11 (1.41, 6.82)

Cox proportional hazard models of OSP and RSP adjusted for age, BMI, smoking status (total population only), and education. Abbreviations: OSP = obstructive spirometric pattern, RSP = restrictive spirometric pattern, HR = hazard ratio, CI = confidence interval. * Not calculated because of absence of observations.

more important determinants among never smokers. A summary of the findings is presented in Fig. 1.

The better prognostic ability of FVC compared to FEV_1 in "healthy" subjects was also observed in a previous study [8], where after mutual adjustment only FVC, but not FEV_1, was associated with survival in subjects without respiratory symptoms and chronic respiratory diseases. Similarly, a study conducted in two large British cohorts [11] evidenced stronger associations of FVC with all-cause mortality compared to FEV_1 among non-smokers.

In terms of cause-specific mortality, our study found stronger associations of FEV_1 with respiratory mortality compared to FVC, especially of non-cancer related deaths compared to lung cancer. This is in agreement with Gupta et al. [11], showing stronger associations of FEV_1 with respiratory mortality compared to FVC among former and current smokers, and Guerra et al. [6], showing a stronger association of obstructive rather than restrictive pattern with COPD deaths, and to a lower extent lung cancer. Other studies showed instead similar associations of FEV_1 and FVC with respiratory mortality [9,12]. This might be due to different definitions of respiratory deaths or the fact that these studies were mostly performed in middle- and low-income countries, with potentially different etiology of respiratory morbidity and mortality.

The relationship between reduced lung volumes and cardiovascular mortality is well established [3,7,24,25], but few studies have examined different subgroups of cardiovascular deaths in the same cohort. Our results suggest a similar association of FEV_1 and FVC with cardiovascular deaths, stronger in terms of magnitude for cerebrovascular disease, followed by heart failure and ischemic heart disease. Guerra et al. [6]

Table 7
Associations of OSP and RSP (HRs with 95 % CIs) with subgroups of cause-specific mortality in the total population (n = 26,091).

	Respiratory deaths			
	Lung cancer	Respiratory non-cancer		
No. deaths	n = 264	n = 86		
OSP	1.95 (1.37, 2.76)	6.20 (3.91, 9.82)		
RSP	1.19 (0.59, 2.41)	3.31 (1.52, 7.22)		
	Cardiovascular and diabetes deaths			
	Ischemic heart disease	Heart failure	Cerebrovascular disease	Diabetes mellitus
No. deaths	n = 390	n = 91	n = 73	n = 41
OSP	1.51 (1.07, 2.13)	1.22 (0.56, 2.66)	1.17 (0.47, 2.91)	3.77 (1.72, 8.27)
RSP	1.90 (1.22, 2.96)	1.15 (0.36, 3.65)	4.16 (1.98, 8.76)	5.62 (2.32, 13.63)
	Non-natural and other cause deaths			
	Accidents	Suicides	Nervous system disease	Alcohol abuse
No. deaths	n = 164	n = 114	n = 59	n = 42
OSP	0.95 (0.50, 1.80)	1.27 (0.64, 2.52)	1.64 (0.70, 3.86)	1.65 (0.64, 4.25)
RSP	0.86 (0.32, 2.32)	1.75 (0.71, 4.31)	2.84 (1.02, 7.91)	- *
	Cancer deaths			
	Digestive cancer	Genitourinary cancer	Hematological cancer	
No. deaths	n = 324	n = 116	n = 97	
OSP	0.90 (0.56, 1.46)	0.58 (0.21, 1.59)	0.71 (0.26, 1.95)	
RSP	1.48 (0.83, 2.64)	1.38 (0.51, 3.75)	3.29 (1.58, 6.84)	

Cox proportional hazard models of OSP and RSP adjusted for age, BMI, smoking status, and education. Abbreviations: OSP = obstructive spirometric pattern, RSP = restrictive spirometric pattern, HR = hazard ratio, CI = confidence interval. * Not calculated because of absence of observations.

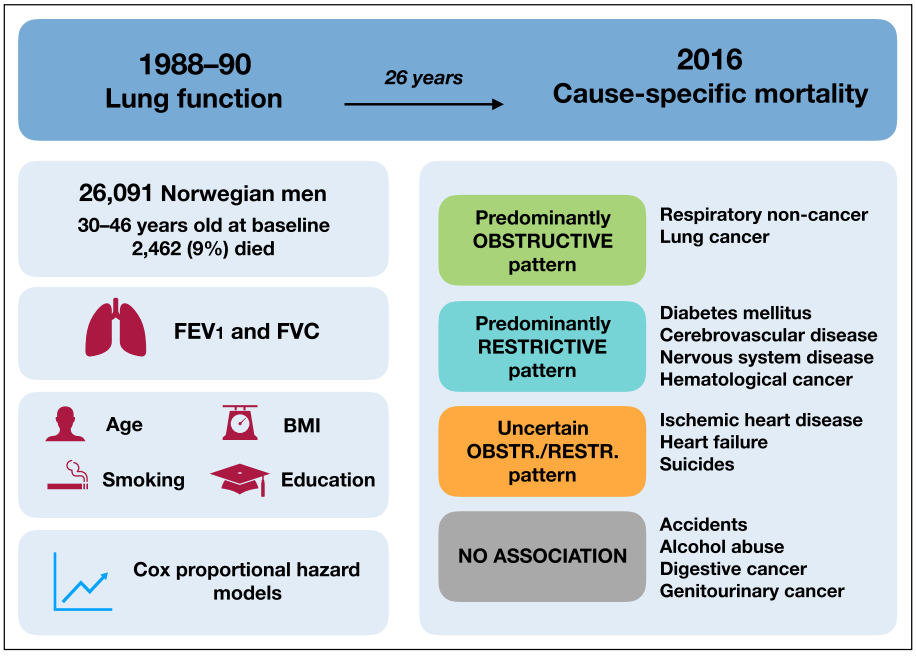

Fig. 1. Summary of the study.

also found a stronger association of restrictive and obstructive patterns with mortality due to stroke rather than heart disease. The strongest association of reduced FEV_1 and FVC in our study was however observed with diabetes mortality (over two-fold increase in HR for one unit z-score decrease, comparable to non-cancer respiratory deaths, and also confirmed in never smokers). This strong relationship is epidemiologically extensively documented [26–28], but mechanisms remain poorly understood.

We found no association of FEV_1 and FVC with mortality from non-natural causes in our study when considered as a single outcome, similarly to Vasquez et al. [10]. In stratified analyses, however, there was an association of both FEV_1 and FVC with deaths due to suicides, but not accidents. A relationship between reduced lung function and mental health problems has previously been reported [29], as well as increased risk of suicide in subjects with asthma and COPD [30,31]. A study of European middle-aged men followed for 40 years [32] found that low FVC and low FVC/height ratio were independently related to completed suicide. In contrast, another recent study reported no association between FEV_1 and suicide risk [33], although the analysis was limited to heavy smokers.

Of interest, is also the strong association of both FEV_1 and FVC with mortality from diseases of the nervous system. This is consistent with previous evidence of relationship between reduced lung function and cognitive impairment/incident dementia [34], cerebral small vessel disease [35], smaller brain volumes [36], and vascular brain lesions [37]. Lutsey et al. [34], in particular, showed that the magnitude of associations with both Alzheimer's disease-type and cerebrovascular dementia was more pronounced for restrictive impairment compared to COPD pattern, and that the association persisted in non-smokers. Kim et al. [35] found significant associations of FVC but not FEV_1 with cerebral small vessel disease markers. Results from Backman et al. [14] suggested higher associations of RSP than OSP with dementia mortality, although the findings were not significant, possibly due to the limited size of the study. Overall, it should be mentioned that in this subgroup of subjects it is possible that spirometry was performed with a less optimal technique.

Finally, we found a significant and similar association of FEV_1 and FVC with mortality from hematological cancer, but not digestive or genitourinary cancer. To our knowledge no study has investigated the association of lung function with subtypes of cancer mortality other than lung cancer [2,6]. The link with hematological cancer is in agreement with increasing evidence about dysregulation of immunity and inflammation being central to the pathogenesis of COPD and other clinical entities [38,39]. Moreover, a previous study described a significant association between myelodysplastic syndrome and reduced FVC [40].

We hypothesize that the stronger association of some types of mortality with FEV_1 reflects a predominant mechanism of airflow obstruction, especially due to cigarette smoking, while a stronger or comparable association with FVC, reflects a predominant role of restriction, due to reduced lung growth, potentially associated with other systemic abnormalities. Therefore, we also studied the associations of OSP and RSP with mortality, as they represent a more comprehensive view of spirometric abnormalities net of the correlation between FEV_1 and FVC. In the total population, OSP was mainly associated with respiratory mortality, while all other causes of death were more strongly associated with RSP (especially in never smokers). In particular, RSP was highly related to diabetes, cerebrovascular, neurological and hematological cancer mortality.

This supports spirometric obstruction as the predominant mechanism behind respiratory deaths, especially non-cancer related, and spirometric restriction as the predominant mechanism behind extra-pulmonary mortality. Consistently with this hypothesis, a recent population-based study [41] showed distinct risk factors profiles for spirometric restriction (e.g. *in utero* and childhood growth and nutritional status) and spirometric obstruction (e.g. childhood asthma). Another recent study showed significant associations between low FEV_1 and circulating biomarkers, such as CC16 (club cell secretory protein), HbA1c, leptin and others, supporting the role of multiple mechanisms, like inflammation, poor organ development and metabolic alterations, linking lung and systemic organ dysfunction [42].

In particular, it can be speculated that factors associated with reduced lung growth, (i.e. hyperglycemia, preterm birth, and developmental deficits in other organs, especially the brain), may explain many of the mortality causes of our study, such as diabetes, neurological, cerebrovascular, and cancer. Indeed, preterm birth is known to be related to cognitive impairment, behavioral sequelae [43], reduced spirometric indices in the long-term [44], mortality from cardiovascular, chronic lung disease, and diabetes [45]. Similarly, reduced fetal growth has been related to increased risk of stroke through several possible mechanisms [46].

Our study has many strengths, such as a prospective study design, large sample size and long follow-up, which allowed us to explore subgroups of cause-specific mortality not available in previous studies. Additionally, the study population was homogeneous, with a high initial response rate and almost complete endpoint registration in a high-quality national registry. Another strength is the young age of the participants, which enabled the observation of premature mortality, and the absence of healthy worker effect as in occupational surveys.

Our study has also some limitations. As in any mortality registry study there might be misclassification of causes of death. A previous study in the same area showed however substantial agreement between mortality statistics and autopsy findings of stroke and coronary deaths [47]. Another study comparing the validity of EU codes of respiratory diseases with autopsy findings, showed almost perfect agreement for lung cancer, substantial agreement for chronic lower respiratory disease, and fair agreement for pneumonia [48]. At the time of the study COPD was heavily underdiagnosed, which could underestimate the association between spirometry variables and respiratory deaths. Additionally, we had only information about mortality but not incident disease. Another limitation is that we used only spirometric data, while a more accurate assessment of restriction would require the measurement of total lung capacity. Furthermore, our study was limited to men, and covariates were available only at baseline. Spirometry curves were not stored and cannot be quality assured afterwards, which might limit the comparison with more recent studies.

Regarding the statistical analysis, studies of cause-specific mortality represent a traditional competing risks setting. A competing risk is an event whose occurrence precludes the occurrence of the primary event of interest [49]. Two approaches are usually adopted to analyse them: cause-specific hazard models or subdistribution hazard models. In the first case, subjects are censored when a competing event occurs, and the analysis continues in those event free; in the second case, the risk set includes both subjects who are event free and those who have previously experienced a competing event [49]. According to many authors, the first approach is suggested when the purpose of the study is to address etiological questions, while the second is suggested when estimating incidence or predicting prognosis [49–51]. Our study was aimed to investigate potential causal relationships, therefore we used cause-specific hazard ratios calculated with Cox regression models. The main interpretation of our estimates is therefore not quantitative, but rather as signal of epidemiological associations.

Our study included only men because the aim of the original survey was to investigate the impact on lung function of occupational exposures, which were at the time largely more prevalent in men than in women. It is difficult to say if the associations that we observed would be the same also in women. Most previous studies of lung function and cause-specific mortality were not stratified by sex [6,10,14]. In the Renfrew and Paisley study [2], reduced FEV_1 had stronger associations with respiratory mortality in men than in women, while the opposite was true for lung cancer, after adjustment for age, cigarette smoking, diastolic blood pressure, serum cholesterol, body mass index and social class. Associations with stroke mortality were instead similar in both sexes [2]. Future studies should investigate the relationship between reduced lung function and cause-specific mortality in both men and women, and the analyses of the current study should be repeated at a later time to investigate the associations in the elderly.

Short-term clinical implications of this study could be an increased awareness of the RSP in clinical practice. Our results might suggest the investigation of comorbidities, especially diabetes, in subjects with reduced FVC or RSP, and no apparent explanation. In the future, we hope that the mechanisms behind these associations could be clarified, contributing to better lung health and reduced mortality.

In conclusion, we found many significant associations of FEV_1 and FVC with cause-specific mortality in a general population of 30–46 year-old men followed for 26 years. Most notably, FEV_1 was strongly associated with respiratory mortality, especially non-cancer related. Both FEV_1 and FVC were associated with diabetes, cardiovascular, neurological, suicide, and hematological cancer mortality. We found no association with mortality due to accidents, alcohol abuse, digestive and genitourinary cancer. OSP was mainly related to pulmonary mortality, RSP was mainly related to extra-pulmonary mortality. Future studies should investigate the biological mechanisms of these associations.

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CRediT authorship contribution statement

Lucia Cestelli: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing, Visualization. **Amund Gulsvik:** Conceptualization, Resources, Writing – review & editing, Project administration. **Ane Johannessen:** Methodology, Writing – review & editing, Supervision. **Knut Stavem:** Methodology, Writing – review & editing, Supervision. **Rune Nielsen:** Conceptualization, Writing – review & editing, Supervision.

Declaration of competing interest

Lucia Cestelli has nothing to disclose.

Amund Gulsvik has nothing to disclose.

Ane Johannessen has nothing to disclose.

Knut Stavem reports fees from UCB Pharma and MSD, outside the submitted work.

Rune Nielsen reports funding from AstraZeneca, outside the submitted work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2023.107421.

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