Lung function, forced expiratory volume in 1 s decline and COPD hospitalisations over 44 years of follow-up

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ABSTRACT The use of baseline lung function in the prediction of chronic obstructive pulmonary disease (COPD) hospitalisations, all-cause mortality and lung function decline was assessed in the population-based "Men Born in 1914" cohort.

Spirometry was assessed at age 55 years in 689 subjects, of whom 392 had spirometry reassessed at age 68 years. The cohort was divided into three groups using fixed ratio (FR) and lower limit of normal (LLN) criterion: forced expiratory volume in 1 s (FEV_1)/vital capacity (VC) $\geqslant$70%, FEV_1/VC <70% but $\geqslant$LLN (FR^+LLN^-), and FEV_1/VC <70% and <LLN (FR^+LLN^+).

Over 44 years of follow-up, 88 men were hospitalised due to COPD and 686 died. Hazard ratios (95% CI) for incident COPD hospitalisation were 4.15 (2.24–7.69) for FR^+LLN^- and 7.88 (4.82–12.87) for FR^+LLN^+ (reference FEV_1/VC $\geqslant$70%). Hazard ratios for death were 1.30 (0.98–1.72) for FR^+LLN^- and 1.58 (1.25–2.00) for FR^+LLN^+. The adjusted FEV_1 decline between 55 and 68 years of age was higher for FR^+LLN^- and FR^+LLN^+ relative to the reference. Of those with FR^+LLN^- at 55 years, 53% had progressed to the FR^+LLN^+ group at 68 years.

Airflow obstruction at age 55 years is a powerful risk factor for future COPD hospitalisations. The FR^+LLN^- group should be carefully evaluated in clinical practice in relation to future risks and potential benefit from early intervention. This is reinforced by the increased FEV_1 decline in this group.

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Introduction

Many population-based studies have shown that all-cause mortality and incidence of cardiovascular diseases are increased in individuals with low forced expiratory volume in 1 s (FEV_1) and/or forced vital capacity (FVC), even after many years of follow-up [1–5]. In contrast, the risk of chronic obstructive pulmonary disease (COPD) over a life course has been sparsely assessed in studies from the general population [5, 6]. As such, the use of spirometry measures as long-term predictors of future COPD hospitalisation could be important in identifying at-risk individuals and targeting prevention strategies.

Spirometry cut off values for the diagnosis of COPD remain an area where consensus has not been reached. The fixed ratio (FR) cut-offs (FEV_1/FVC <70%), as proposed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD), and a statistically defined lower fifth percentile of a reference population for the FEV_1/FVC ratio lower limit of normal (LLN) have both been used in the diagnosis of COPD. Many of the comparisons made between the two criteria and outcomes have been in population-based studies assessing prevalence of COPD or other adverse outcomes [7–17], and the optimal criteria for prediction of future COPD hospitalisations in the general population could be different from those used to define COPD. There is a need for more prospective research studies that can evaluate the use of both tests in relation to clinical outcomes in the future [18, 19].

In the older population, there is likely to be an intermediate group that falls between the two definitions, a subpopulation that may require special consideration. Those with FEV_1/FVC <70% but who do not meet the threshold for diagnosis by LLN (hence defined as "normal" by the LLN) comprise an intermediate group, and there has been some debate around this group and its profile [20]. Some longitudinal studies have found that this group has a higher risk of mortality and COPD-related hospital admissions relative to those with normal lung function, and so the LLN approach can "miss" those with early risks of future events who, as such, can be the target for early intervention if identified [4, 6].

A recent paper from the cohort Men Born in 1914 reported a nonsignificantly increased risk of all-cause mortality over 26 years of follow-up of men fulfilling the FR but not LLN criterion [21]. The aim of the present study was to assess the incidence and risk of COPD hospitalisations in relation to spirometry results at baseline in a population-based sample of 55-year-old men, followed up prospectively over a 44-year period. We also assessed changes in spirometry results for individuals reassessed in this follow-up period and subsequent reclassification of their lung function at the later time period.

Material and methods

Study population

Study subjects were from the cohort "Men Born in 1914". The study base consisted of all men who were born in even-numbered months in 1914 and who lived in Malmö, Sweden, in 1968. A total of 703 men attended the examinations at 55 years of age, out of an eligible population of 809 individuals (participation rate 87%). 689 men took part in lung function tests at baseline. Details of questionnaires and other examinations have been published previously [22].

A re-examination with spirometry was performed in 1982–1983, when the men were 68 years old. Of the 482 men who were eligible to participate (were alive and still living in Malmö), 392 took part in re-examination (participation rate 81%). Of the 297 men who were not reassessed, 132 died before the re-examination, 75 had moved away from the city of Malmö and 90 did not participate in whole or parts of the examination. Those who moved away or declined to participate (75+90=165) had a similar baseline prevalence of smoking (62 *versus* 59%, p=0.41), FEV_1 (3.30±0.63 *versus* 3.35±0.63 L, p=0.34) and VC (4.33±0.62 *versus* 4.38±0.67 L, p=0.39) compared to the 392. All participants were informed and gave verbal consent to participate in the study. The study was approved by the Regional Ethics Committee in Lund, Sweden (numbers 1982-111 and 2013-443).

Lung function data

A Bernstein-type spirometer was used to measure FEV_1 and vital capacity (VC), without prior bronchodilation. At least two acceptable manoeuvres were required. The measurements were performed by experienced staff from the Dept of Clinical Physiology at the Malmö University Hospital.

689 subjects were classified into three groups based on the FR criteria for COPD and the LLN approach; FEV_1/VC ratio ⩾70% (normal (N)), FEV_1/VC <70% but ⩾LLN (FR^+LLN^-), and FEV_1/VC <70% and <LLN (FR^+LLN^+). There were no men in the FR^-LLN^+ group. European reference values were used for the calculation of predicted FEV_1, VC and LLN [23]. FEV_1 and VC were then expressed as percentages of the predicted values. Restrictive lung function pattern was defined as FEV_1/VC ratio ⩾70% with VC ⩽80% predicted [24]. Subjects were divided into quartiles (Q) for both FEV_1 and VC % predicted values. Q4 was used as the reference group.

Men with lung function data measured in both 1969 and 1982 (n=392) were also divided into three groups (N, FR^+LLN^- and FR^+LLN^+) for both time periods. FEV_1 decline and reclassification between groups at the different time-points was assessed.

Outcomes

Incidence of COPD (*i.e.* hospitalisation or mortality related to COPD) and mortality (all causes) was followed up until 2013, when the last participant died. COPD incidence was established from hospital discharge summaries, outpatient data from Swedish hospitals and information from death certification. The Swedish inpatient registry had been operating in the south of Sweden during the entire follow-up period and the registry became nationwide in 1987. Data from the Swedish inpatient registry has been found to be of acceptable validity for epidemiological research including the diagnosis of COPD [25]. International Classification of Diseases (ICD)-8 (1968–1986; codes 490–492), ICD-9 (1987–1997; codes 490–492 and 496) and ICD-10 (1997–2013; codes J40–J44) were used to define COPD as a cause of hospitalisation (primary or secondary cause) or death.

Analysis of data

All analyses were carried out in SPSS version 22.0 (IBM, Armonk, NY, USA) or STATA version 12.0 (StataCorp, College Station, TX, USA). One-way ANOVA, Pearson's Chi-squares test and Fisher's exact test were used to compare baseline characteristics between subjects in the three groups (N, FR^+LLN^- and FR^+LLN^+). Cox proportional hazards regression was used to compare incidence of COPD and deaths from any cause between groups N, FR^+LLN^- and FR^+LLN^+, and between quartiles of lung function (FEV_1 % predicted and VC % predicted). The time from the baseline examination until death or emigration from Sweden was used in the analysis of all-cause mortality. For incidence of COPD, we used the time from baseline examination until the first COPD event, mortality or emigration from Sweden. Adjustments were made for potential confounding factors including smoking, diabetes, body mass index, height and physical activity. Cox proportional hazards assumptions were tested using Kaplan–Meier and log–log plots, and time-dependent covariate analysis in SPSS. A sensitivity analysis was carried out by excluding those with restrictive lung function patterns from the N group. To correct for the potential effect of other causes of death in old age, we also performed competing risks regression according to Fine and Gray's proportional subhazards model. Subhazard ratios for COPD incidence with death from any cause (non-COPD related and with no COPD diagnosis) as a competing event was obtained (adjusted for potential confounding factors). One-way ANOVA was used to compare mean decline in lung function for 392 subjects who had lung function measured in both 1969 and 1982. Univariate linear regression was used to adjust the decline in FEV_1 for initial FEV_1 and smoking.

Results

Subject characteristics are presented in table 1. The proportion of current smokers was higher in the groups with lower lung function. Mean FEV_1 was lowest in subjects in the FR^+LLN^+ group. The intermediary group (FR^+LLN^-) had an intermediary mean FEV_1. Only 2.8% of men reported dyspnoea above grade 2 (as per the Medical Research Council breathlessness scale) at baseline.

TABLE 1 Subject details by group of lung function classification method (n=689)

Group	Normal	FR^+LLN^-	FR^+LLN^+	p-value
Subjects n (%)	545 (79.1)	56 (8.1)	88 (12.8)	
Height m	1.75±0.06	1.75±0.07	1.76±0.07	0.115
BMI kg·m^{-2}	24.6±3.0	24.6±3.3	23.7±3.2	0.025
Current smokers	58.5	75.0	75.0	0.001
Ever-smokers	83.0	87.5	92.0	0.089
Diabetes	1.7	1.8	3.4	0.700
Cholesterol$^{\#}$ mmol·L^{-1}	6.39±1.14	6.48±1.03	6.21±1.10	0.297
SBP mmHg	139±22	141±23	139±21	0.772
DBP mmHg	85±12	84±14	84±12	0.771
VC L	4.4±0.7	4.2±0.6	4.2±0.8	0.016
FEV_1 L	3.5±0.5	2.9±0.4	2.5±0.6	<0.001

Data are presented as mean±SD or %, unless otherwise stated. FR: fixed ratio; LLN: lower limit of normal; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; VC: vital capacity; FEV_1: forced expiratory volume in 1 s. $^{\#}$: n=687.

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Incidence of mortality and COPD hospitalisations

A total of 686 out of 689 men died during the follow-up and three were lost to follow-up due to emigrating from Sweden. 88 men had COPD diagnosed during the follow-up. Of the 88 cases of COPD, 80 were diagnosed from hospital admissions; another two were diagnosed from a hospital outpatient clinic and six were diagnosed from the death certificate only (of whom five had autopsy confirmation of the causes of death).

Incidence rates and hazard ratios (HR) according to the classification by FR and LLN criteria are presented in table 2. The HR (95% CI) for COPD was 4.15 (2.24–7.69) in the FR^+LLN^- group relative to the reference group. This risk almost doubles (HR 7.88 (4.82–12.87)) for those meeting both criteria for COPD (FR^+LLN^+). The HR for all-cause mortality showed an increased risk for both the FR^+LLN^- and FR^+LLN^+ group (for the FR^+LLN^- group, however, this risk became nonsignificant after adjustment) (table 2). The subhazards ratio for COPD, after taking into account the competing risk of non-COPD related deaths, was 3.31 (1.80–6.09) for the FR^+LLN^- group and 5.53 (3.34–9.15) in the FR^+LLN^+ group. The HR for COPD hospitalisations and all-cause mortality increased in both the FR^+LLN^- and FR^+LLN^+ groups after excluding restrictive subjects in a sensitivity analysis (table 2). Figure 1 illustrates the marked difference in the incidence of COPD events between the normal and FR^+LLN^- or FR^+LLN^+ over 44 years of follow-up.

Incidence rates and HR for COPD and all-cause mortality according to quartiles of FEV_1 % predicted and VC % predicted are presented in tables 3 and 4, respectively.

Subjects in Q1 of FEV_1 % predicted had almost four times the risk of COPD relative to subjects in the reference group (Q4) after taking into account potential confounding factors. There was not found to be any significant increase in risk of COPD in quartiles of VC % predicted but there was a 26% increase in risk of all-cause mortality in Q1 (HR 1.26 (1.01–1.57)).

FEV_1 decline

Information of FEV_1 decline from 55 to 68 years of age is shown in table 5 for the 392 subjects assessed on both occasions. There was a larger decline in FEV_1 in the FR^+LLN^- and FR^+LLN^+ groups after adjustment for initial FEV_1 and smoking. The difference between groups was significant ($p<0.05$) for the N *versus* FR^+LLN^- and the N *versus* FR^+LLN^+ groups, but nonsignificant between the FR^+LLN^- and FR^+LLN^+ groups ($p=0.847$). Of the 317 subjects who were initially in the N lung function group ($FEV_1/VC \geqslant 70\%$), 72 were reclassified into the FR^+LLN^- group and 18 into the FR^+LLN^+ group at 68 years of age. In addition, 53% of subjects who were initially in the FR^+LLN^- group were found to be in the FR^+LLN^+ group on re-assessment. Of the 43 men with FR^+LLN^+ at 55 years, 10 (23%) were in a less severe category at 68 years.

Discussion

There has been a long-standing debate based on spirometry criteria for the diagnosis of COPD. The use of $FEV_1/FVC < 70\%$ (FR^+LLN^-) has been suggested to overdiagnose airflow obstruction in the elderly and underdiagnose in the young as this criterion is heavily influenced by age [15, 26]. It has also been

TABLE 2 Incidence and hazard ratios of chronic obstructive pulmonary disease (COPD) hospitalisation per group of lung function classification method for 689 participants at 55 years of age

	Normal	FR^+LLN^-	FR^+LLN^+	p-value
Subjects n	545	56	88	
COPD events n (n per 1000 person-years)	42 (3.3)	14 (12.7)	32 (22.1)	
COPD events unadjusted hazard ratio (95% CI)	1.00	4.22 (2.30–7.74)	7.87 (4.94–12.54)	<0.001
COPD events adjusted hazard ratio[#] (95% CI)	1.00	4.15 (2.24–7.69)	7.88 (4.82–12.87)	<0.001
COPD events with competing risks regression[#,¶] (95% CI)	1.00	3.31 (1.80–6.09)	5.53 (3.34–9.15)	<0.001
COPD events adjusted hazard ratio[#] excluding 30 restrictive[+] subjects from the normal group (95% CI)	1.00	4.50 (2.40–8.45)	8.80 (5.31–14.58)	<0.001
Deaths n (n per 1000 person-years)	542 (42.17)	56 (48.53)	88 (54.22)	
Deaths unadjusted hazard ratio (95% CI)	1.00	1.40 (1.04–1.84)	1.63 (1.30–2.05)	<0.001
Deaths adjusted hazard ratio[#,§] (95% CI)	1.00	1.30 (0.98–1.72)	1.58 (1.25–2.00)	<0.001
Deaths adjusted hazard ratio[#,§] excluding 30 restrictive[+] subjects from the normal group (95% CI)	1.00	1.34 (1.01–1.77)	1.65 (1.30–2.08)	<0.001

FR: fixed ratio; LLN: lower limit of normal. [#]: adjusted for smoking status (three groups: never, ex- and current smokers), diabetes, body mass index, height and physical activity (three groups: high, moderate and low physical activity); [¶]: 88 incident COPD cases as failure events and 598 deaths without COPD as competing risks; [+]: forced expiratory volume in 1 s/vital capacity (VC) $\geqslant$70%, VC $\leqslant$80% predicted; [§]: additionally adjusted for systolic blood pressure and cholesterol.

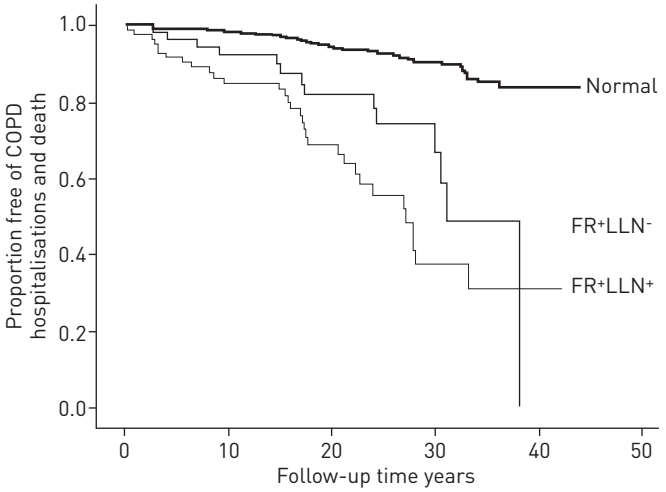

FIGURE 1 Kaplan–Meier survival curves of chronic obstructive pulmonary disease (COPD) in three groups: forced expiratory volume in 1 s (FEV_1)/vital capacity (VC) ⩾70% (normal), FEV_1/VC <70% but above the lower limit of normal (LLN) (fixed ratio (FR^+LLN^-), and FEV_1/VC <70% and <LLN (FR^+LLN^+). Incident COPD was defined as hospitalisation due to COPD or a COPD-related death.

suggested that the LLN of the FEV_1/FVC ratio is a more useful tool in identifying those with clinically relevant airflow obstruction [13, 26–30]. However, there could be a reason to use broader criteria for the purpose of prediction and prevention of future COPD hospitalisations. This study indicates that there is an increased risk of COPD hospitalisation in individuals who show signs of airflow obstruction, as defined by either the FR or LLN, relative to those with FEV_1/VC ⩾70% at baseline. Both definitions were also associated with increased all-cause mortality after excluding those with a restrictive pattern on baseline spirometry. The FEV_1/VC ratio cut-off of <70%, therefore, does seem to be an important predictor of both COPD hospitalisations and all-cause mortality, and supports the use of the GOLD criteria in middle-aged men for future risk prediction. The increase in risk of those in the intermediate group (FR^+LLN^-) indicates that these individuals should be carefully evaluated in clinical practice in relation to future risk and can be a target for early preventive treatment in an attempt to reduce this risk. Those with poor lung function at 55 years had more of a decline in lung function with age than those with better lung function. 53% of those in the FR^+LLN^- group were in the FR^+LLN^+ group at the follow-up at 68 years of age and another 34% were still in the FR^+LLN^- category. The significant FEV_1 decline in the FR^+LLN^- group reinforces the need to clinically evaluate this group earlier in life.

Comparison with existing literature

There are many longitudinal studies that have assessed the predictive ability of different lung function parameters to outcomes such as cardiovascular disease, mortality and airflow obstruction in the literature [2, 3, 5, 31]; however, there have been few longitudinal studies that have compared the predictive ability of the FR and LLN criteria. Bhatt *et al.* [32] compared the FR to the LLN approach to diagnose smoking

TABLE 3 Incidence rates and hazard ratios of death and hospitalisations due to chronic obstructive pulmonary disease (COPD) by quartile (Q) of forced expiratory volume in 1 s % predicted

	Q4[#,¶]	Q3	Q2	Q1[+]	p-value for trend
Subjects n	172	172	173	172	
COPD events n (n per 1000 person-years)	14 (3.35)	11 (2.67)	22 (5.75)	41 (13.52)	
COPD events unadjusted hazard ratio (95% CI)	1.00	0.86 (0.39–1.89)	1.86 (0.95–3.65)	4.88 (2.64–9.01)	<0.001
COPD events adjusted hazard ratio[§] (95% CI)	1.00	0.74 (0.33–1.63)	1.60 (0.81–3.16)	3.84 (2.03–7.27)	<0.001
Deaths unadjusted hazard ratio (95% CI)	1.00	1.18 (0.95–1.46)	1.29 (1.04–1.59)	1.96 (1.58–2.43)	<0.001
Deaths adjusted hazard ratio[§,f] (95% CI)	1.00	1.09 (0.87–1.35)	1.20 (0.97–1.49)	1.67 (1.34–2.10)	<0.001

Q4: 107–143% predicted; Q3: 98–107% predicted; Q2: 86–97% predicted; Q1: 42–86% predicted. [#]: highest quartile; [¶]: reference quartile; [+]: lowest quartile; [§]: adjusted for smoking status (three groups: never, ex- and current smokers), diabetes, body mass index, height and physical activity (three groups: high, moderate and low physical activity); [f]: additionally adjusted for systolic blood pressure and cholesterol.

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TABLE 4 Incidence rates and hazard ratios of death and hospitalisations due to chronic obstructive pulmonary disease (COPD) by quartile (Q) of vital capacity % predicted

	Q4[#,¶]	Q3	Q2	Q1[+]	p-value for trend
Subjects n	172	172	173	172	
COPD events n (n per 1000 person-years)	22 (5.45)	15 (3.92)	23 (5.97)	28 (8.16)	
COPD events unadjusted hazard ratio (95% CI)	1.00	0.76 (0.39–1.46)	1.15 (0.64–2.07)	1.64 (0.94–2.87)	0.044
COPD events adjusted hazard ratio[§] (95% CI)	1.00	0.67 (0.35–1.31)	1.03 (0.57–1.88)	1.31 (0.74–2.32)	0.183
Deaths unadjusted hazard ratio (95% CI)	1.00	1.22 (0.98–1.50)	1.24 (1.00–1.53)	1.44 (1.16–1.78)	0.001
Deaths adjusted hazard ratio[§,f] (95% CI)	1.00	1.05 (0.84–1.31)	1.13 (0.91–1.40)	1.26 (1.01–1.57)	0.02

Q4: 109–139% predicted; Q3: 101–109% predicted; Q2: 93–101% predicted; Q1: 48–93% predicted. [#]: highest quartile; [¶]: reference quartile; [+]: lowest quartile; [§]: adjusted for smoking status (three groups: never, ex- and current smokers), diabetes, body mass index, height and physical activity (three groups: high, moderate and low physical activity); [f]: additionally adjusted for systolic blood pressure and cholesterol.

related airway obstruction. It was found that the LLN can misclassify participants as normal when they have been identified using the FR and found to have evidence of emphysema and gas trapping on CT. Vaz Fragoso *et al.* [33] compared the GOLD criteria to the "SR-tile strategy" (FEV_1 below the fifth or 10th standardised-residual percentile). They found that relative to the SR-tile strategy, older people with GOLD COPD did not have an increased risk of all-cause mortality or respiratory symptoms. A study from a Swedish population of men and women aged 65–100 years also did not find any increased mortality in individuals with FR^+ only [34]. This study also showed that the incidence of COPD varies greatly depending on which definition is used, with higher incidence rates when the FR^+ criterion is used instead of LLN [34]. This is in accordance with our results from men with repeated spirometry (table 5).

Much of the prospective research that compares the FR and LLN assesses mortality as an outcome [4, 6, 21, 35] or FEV_1 decline [35–38], which is thought to be an important marker of COPD prognosis [36]. There are few studies that have compared FR and LLN in their predictive abilities with respect to COPD as an outcome [6], or other related outcomes such as respiratory related hospital admissions [36] and evidence of airflow limitation [39, 40]. Our study attempts to add to this area where studies are sparse.

We are aware of only one other study with similar methodology and outcomes that compared the LLN and GOLD criteria to predict COPD in a longitudinal follow-up study where subjects were not already diagnosed with COPD at baseline. Mannino *et al.* [6] assessed different stages of the GOLD criteria *versus* the LLN criteria to predict COPD hospitalisation and all-cause mortality as outcomes in an 11-year follow-up study in subjects >65 years using "pre-bronchodilator" measurements. They found that the "potentially over-diagnosed group" (subjects who were classified as normal using the LLN but abnormal using the GOLD criteria stages 1–4) had an increased adjusted risk of death (HR 1.3 (1.1–1.5)) and COPD-related hospitalisation (HR 2.6 (2.0–3.3)) relative to asymptomatic individuals with normal lung function. We found similar risks of death in the FR^+LLN^- group and the risk of COPD hospitalisation was higher but comparable after adjusting for the competing risk of death in our analysis.

TABLE 5 Lung function decline from 55 to 68 years of age: information on 392 participants with repeated lung function measurements

	Lung function group at 55 years			
	Normal	FR^+LLN^-	FR^+LLN^+	p-value
Subjects n	317	32	43	
Initial FEV_1 at 55 years L	3.52±0.54	2.81±0.39	2.55±0.53	<0.001
FEV_1 decline from 55 to 68 years L	0.44±0.31	0.50±0.36	0.49±0.66	0.568
Adjusted[#] FEV_1 decline from 55 to 68 years L (95% CI)	0.42 (0.38–0.46)	0.58 (0.45–0.71)	0.60 (0.48–0.72)	0.009
Lung function group at 68 years n				
Normal	227	4	8	
FR^+LLN^-	72	11	2	
FR^+LLN^+	18	17	33	

Data are presented as mean±SD unless otherwise stated. FR: fixed ratio; LLN: lower limit of normal; FEV_1: forced expiratory volume in 1 s. [#]: linear regression models used to adjust FEV_1 decline; adjusted for initial FEV_1 (at 55 years) and current smokers. p-values for adjusted FEV_1 decline: p=0.025, normal *versus* FR^+LLN^-; p=0.847, FR^+LLN^- *versus* FR^+LLN^+; p=0.009, normal *versus* FR^+LLN^+.

LLN and FR have also been compared to an expert panel diagnosis. One study found that FR more accurately detects COPD than the LLN [41], whereas in another study [42], FR was found to overdiagnose and LLN underdiagnose COPD in the elderly, and either criteria coupled with FEV1 % predicted was thought to bring both definitions closer to the expert panel diagnosis.

In two studies by Akkermans and coworkers [36, 37] looking at FEV1 decline, it was found that pre-bronchodilator FEV1 decline per year showed a nonsignificant difference between the decline in the "normal" nonobstructed category and the FR^+LLN^- group, and a significant increase in the decline between the FR^+LLN^- and FR^+LLN^+ groups. Similar findings were seen for post-bronchodilator values, and in smokers and nonsmokers. This is in contrast to our results, where significant differences in decline were seen only between the normal nonobstructed group and the other two groups. However, our study looked at decline from 55 to 68 years overall, while Akkerman *et al.* [37] used a mean follow-up of 3.4 years in patients >40 years. As illustrated by our results, many subjects belong to a more severe category when they get older, and comparisons of FEV1 decline will probably be influenced by the studied populations, age groups and follow-up times.

Limitations of our study

Lung function tests were carried out by experienced persons from the Dept of Clinical Physiology at Malmö University Hospital; however, at the time of the baseline measurements, the current guidelines for spirometry were not published so we cannot assume spirometry was carried out in line with guidelines that exist today. VC measurements were used rather than FVC. FEV1/VC is thought to result in lower values than when FEV1/FVC is used, especially when more severe airflow limitation is present; however, the cut-off of 70% is still recommended [43]. The spirometry values can be considered pre-bronchodilation, which are thought to give a higher estimation of prevalence of COPD than post-bronchodilator values [14]. However, it has been found that both pre- and post-bronchodilator lung function predict mortality with similar accuracy and, as such, post-bronchodilator lung function may not be necessary in studies that predict long-term outcomes [44].

Hospital diagnoses of COPD were settled by board-certified specialist physicians, and it has been shown in validation studies that data from the Swedish inpatient registry is of acceptable validity for the diagnosis of COPD and other epidemiological research [25]; furthermore, this registry was in operation throughout the duration of the study. However, the registry recorded cases severe enough to be hospitalised and so milder cases of COPD that were never managed in hospital would be missed in our study end-point data. Six cases were based on death certificate data only and five of them were confirmed by autopsy, adding validity to the end-point ascertainment.

Due to the nature of longitudinal studies with long follow-up times, there are several baseline characteristics that may have changed during the duration of follow-up that may have affected the outcome, mainly smoking status. Some subjects may have quit smoking during the follow-up period, thereby reducing the risk of COPD in their respective groups, which probably would bias our results towards the null. Inhaled corticosteroids were not used in the late 1960s when the study started but some individuals may have received COPD medication during follow-up. This would if anything, reduce the HRs for the FR^+LLN^- and FR^+LLN^+ groups.

Our study sample was also smaller than that of those who have carried out studies with similar methodologies as ours. However, as far as we are aware this is the only longitudinal study that compares the FR and LLN criteria to predict the three outcomes of mortality, COPD and FEV1 decline over a very long follow-up period.

Conclusion

Signs of airflow obstruction on spirometry are powerful risk factors for future COPD hospitalisations, even after many years of follow-up. Careful evaluation may be needed of those in the FR^+LLN^- group as they may be a target for prevention to reduce their future risk. The increased FEV1 decline for those in the FR^+LLN^- group reinforces this.

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