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The Association of Lung Clearance Index with COPD and FEV^1 Reduction in 'Men Born in 1914'

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Title: The association of lung clearance index with COPD and FEV$_1$ reduction in "Men born in 1914"

(Running title: LCI, COPD and FEV1 reduction)

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ABSTRACT

Lung Clearance Index (LCI) provides an over-all measurement of ventilation inhomogeneity. This population-based study examines whether LCI predicts pulmonary obstruction and incidence of COPD events over a long-term follow-up.

Multiple breath nitrogen washout and spirometry were performed in 674 men from the cohort "Men born in 1914" at age 55 years. Subjects were classified into quartiles (Q) of LCI and according to LCI above and below upper limit of normal (ULN). Incidence of COPD events (COPD hospitalizations or COPD related deaths) were monitored over the remaining life span of the men, by linkage with national hospital registers. In addition, development of pulmonary obstruction (i.e., FEV_1/VC below lower limit of normal (LLN)) was studied in 387 men who were re-examined with spirometry at 68 years of age. Over 44 years of follow-up, there were 85 incident COPD events. Hazards ratios for COPD across quartiles of LCI were: Q1 1.00 (reference), Q2 1.30 (95% confidence interval: 0.61-2.74), Q3 1.97 (0.97-3.98) and Q4 3.99 (2.06-7.71) (p value for trend <0.001). This relationship remained significant after adjustments for confounding factors, including smoking and FEV_1 (HR, Q4 vs Q1: 2.34 (1.17-4.69) p value for trend 0.006). In men who were re-examined with spirometry, reduction of FEV_1 between 55 and 68 years of age and new cases with pulmonary obstruction was highest in those with high LCI.

High LCI is associated with future development of pulmonary obstruction and incidence of COPD hospitalisations in men from the general population.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) entails bronchial obstruction as well as emphysema. Both processes usually have a non-uniform distribution, the consequence of which is ventilation inhomogeneity within the diseased lung. Although spirometry has long been used to assess the presence and severity of COPD, it is not known to be sensitive to problems of ventilation distribution where considerable structural damage needs to occur before forced expiratory volume in 1 second (FEV_1) becomes impaired[1].

Lung Clearance Index (LCI) provides an over-all measurement of ventilation inhomogeneity and LCI can be affected by structural changes in both small and large airways along with changes in anatomical dead space[2]. However, although much is known about LCI as a measure of ventilation inhomogeneity, its role in COPD and its potential use in prediction alongside spirometry remains largely unknown.

The cohort 'Men born in 1914' was examined in 1969, when the men were 55 years old, and the subjects were re-examined with spirometry at 68 years of age. The cohort has been followed with respect to incidence of COPD hospitalisations over the remaining life span of the men[3]. The aim of the present paper is to assess the role of LCI with regards to the future risk of COPD hospitalisations. We attempt to ascertain whether there is an added value of using LCI along with existing lung function parameters such as FEV_1 and FEV_1/vital capacity (VC) to predict future COPD events in a population-based follow-up study. We also assess FEV_1 and VC at 55 and 68 years in relation LCI to ascertain if baseline LCI is associated with future development of pulmonary obstruction.

METHODS

Study population

The study population consists of subjects from the cohort "Men born in 1914". This cohort includes men living in Malmö during 1968 and who were born in even-numbered months in 1914. Details of questionnaires and examinations carried out have been published previously[4]. Baseline examinations were taken at age 55 years for all study subjects. A total of 703 men attended the examinations (participation rate: 87%). Six hundred and seventy-five subjects had information on both LCI and FEV_1 at baseline examination. One individual was excluded due to data irregularities; therefore all analyses were performed on 674 subjects.

A re-examination was performed in 1982, when the men were 68 years old. Of the 470 men eligible to re-participate (were alive and still living in Malmö), 387 had FEV_1 and VC measured again (participation rate: 82%). Of the 287 men who were not reassessed, 129 men had died before the re-examination, 75 had moved away from the city of Malmö and 83 declined to participate. Those who moved away or declined to participate (75+83=158) had a similar baseline prevalence of smoking (62% versus 58%, p=0.43), $FEV_{1\%pred}$ (96±17 versus 98±17, p=0.14) and $VC_{\%pred}$ (100±13 versus 102±13, p=0.12) compared to the 387 participants. As expected, those who died before the re-examination had lower $FEV_{1\%pred}$ and $VC_{\%pred}$ (92±19 and 98±16, respectively) and higher prevalence of smoking (71%). The study was approved by the regional ethics committee (Dnr 1982-111; 2013/443). Written consent was not available in 1969, however verbal consent was taken for all study participants.

Lung function data

Measurements were performed at the Department of Clinical Physiology at the Malmö University Hospital. Multiple-breath nitrogen washout was performed using an Ohio 700 nitrogen meter (Biomedical Products, Houston, Texas, USA). The subject was breathing room

air through a mouthpiece until a stable breathing level was attained. A stopcock was then turned at functional residual capacity and the subject continued tidal breathing of pure oxygen until the end-expiratory N_2-concentration reached 2 %. Wash-out-volume was collected in a diffusion-tight aluminium-plastic polylaminated bag. The exhaled volume was measured with a wet gas meter (Dehm and Zinkeisen, Frankfurt, Germany) having an accuracy of < 1%[5]. LCI were calculated according to Bouhuys et al [6]. A Bernstein type spirometer was used to measure FEV_1 and VC with no prior bronchodilation. At least two acceptable manoeuvres were required. FEV_1 volumes were standardised for height (age was the same for all subjects) and expressed as a percentage of the predicted value ($FEV_{1\%pred}$)[7]. Lower limit of normal was calculated for FEV_1 and FEV_1/VC[7].

Six hundred and seventy-four subjects were divided into quartiles (Q) of LCI. Q1 was used as the reference group for LCI. LCI was also categorized as abnormal (i.e., above upper limit of normal (ULN)) and normal (below ULN). ULN was calculated from the distribution in 104 55-year-old male never smokers in the present cohort (mean±SD; 7.63±1.36; ULN=9.86). Four categories based on LCI (above versus below ULN) and $FEV_{1\%pred}$ (above and below LLN) were created to study the combined effects of poor $FEV_{1\%pred}$ and LCI in terms of incidence of COPD. An additional 4 groups were then made based on quartiles of LCI (above versus below ULN) and FEV_1/VC (above and below LLN).

Outcomes

All men were followed from the baseline examination at 55 years of age until the date of the first COPD event, death or emigration. At the end of follow-up in 2013, all men had died, except for three individuals who were lost for follow-up due to emigration from Sweden. Incident COPD (hospital diagnosis of COPD or mortality related to COPD) was the main outcome. The Swedish patient register and the Swedish cause of death register were used for case retrieval. The Swedish patient register includes diagnoses, set by board certified

physicians, from hospital discharge summaries from all Swedish hospitals. The registry had been in operation during the entire follow-up period (which became nation-wide in 1987) and data from this registry has been found to be of acceptable validity for epidemiological research including the diagnosis of COPD[8]. International Classification of Diseases (ICD) codes: ICD 8 (1968-1986; codes 490-492), ICD-9 (1987-1997; codes 490-492, 496) and ICD-10 (1997-2013, codes J40-44) were used to define COPD as a cause for hospitalisation or death.

Statistics

All analyses were carried out on SPSS v22.0 and STATA v12.0. One way analysis of variance, Pearson's chi-squared test and Fisher's exact test were used to compare baseline characteristics between subjects in Q1-4 of LCI and between subjects with normal LCI and LCI>ULN. Cox' proportional hazards regression was used to compare the incidence of COPD events between categories of lung function at 55 years of age. Adjustments were made for potential confounding factors. Proportional hazards assumptions were tested using Kaplan-Meier survival curves, log-log plots and time dependent covariate analysis. The added value of LCI to survival models using other lung function parameters was assessed using the Harrell's C-statistic (corresponds to the area under the receiver operating characteristics curve) and the likelihood ratio test (LR test) (provides a measure of the goodness of fit of the Cox regression models). LCI, FEV1 and FEV1/VC were fitted as continuous variables in these analyses, together with BMI, diabetes, smoking, height and physical activity. One-way analysis of variance was used to compare mean reduction in lung function for 387 subjects who had lung function measured at both 55 and 68 years of age, in categories based on LCI. Univariate linear regression was used to adjust the change in FEV_1 for initial FEV_1 and smoking.

The proportion of new cases with pulmonary obstruction in relation to LCI was analysed using logistic regression (dependent variable: pulmonary obstruction at 68 years), among men with normal FEV_1/VC at 55 years.

RESULTS

Subject characteristics are presented in Table 1. Median LCI was 8.0 for the total sample (8.2 for smokers and 7.6 for non-smokers). The proportion of current and ever smokers increased as LCI increased. Mean FEV_1 was lowest in quartiles with higher LCI. The Pearson's correlation coefficient between LCI and FEV_1 was -0.265 (p<0.001). Out of the 674 subjects, 81 had a $FEV_1/VC<LLN$ at baseline.

Mortality and incident COPD

All-cause mortality rates was significantly higher in men with poor LCI (Table 2). A total of 85 men had COPD diagnosed during the follow up period of 1969-2013, of which 77 were diagnosed from hospital admissions; 2 from hospital outpatient clinics only; and 6 from the death certificate only (5 of these had autopsy confirmation of the causes of death). The adjusted hazard ratio (HR) for incident COPD hospitalisations increased gradually with higher LCI (Figure 1). The adjusted HR was 2.24 (CI:1.3-3.9), comparing LCI>ULN with normal LCI (Table 2). The adjusted risk of incident COPD hospitalisations for those with $FEV1_{\%pred}$ below LLN was HR=3.7 (CI:2.2-6.2) (not shown in table). The adjusted HR for COPD per 1 standard deviation (SD) increase in LCI was 1.62 (CI:1.29-2.03), whereas the adjusted HR for COPD per 1 standard deviation decrease in $FEV_{1\%pred}$ was 2.04 (CI:1.63-2.56) (not shown in table). LCI was significantly associated with risk of COPD hospitalisations after further adjustment for baseline FEV_1 (table 2).

The HRs of COPD according to categories of LCI and $FEV_{1\%pred}$ and of LCI and

$FEV_1/VC<LLN$ are shown in Table 3 and 4, respectively. The HR of COPD was higher for

individuals with $FEV_1/VC<LLN$ and LCI>ULN compared to $FEV_1/VC<LLN$ and normal

LCI (adjusted HR: 11.75 (5.8-23.8) vs 5.15 (3.0-9.0), p=0.041) (Table 4).

Sensitivity analysis

A sensitivity analysis was performed, which only included COPD cases who were diagnosed

as hospitalized in-patients (n=77). The relationship between LCI and incidence of COPD

became slightly stronger (HR for LCI>ULN vs normal LCI: 2.53, CI:1.44-4.45; HR for Q1 vs

Q4:3.6, CI:1.8-7.3, after adjustment for smoking status, diabetes, BMI, height, and physical

activity).

Added value of LCI

The LR test showed improved goodness of fit after adding LCI to a model with $FEV_{1\%pred}$

(change after adding LCI: Chi-square= 6.74; p value 0.009) and also showed improved

goodness of fit after adding LCI to a model with FEV_1/VC (change after adding LCI: Chi-

square=5.89; p value 0.015). Harrell's C statistic increased from 0.73 to 0.74 (p-value for

difference: 0.192) and from 0.74 to 0.76 (p-value for difference: 0.174) after adding LCI to a

survival model already containing $FEV_{1\%pred}$ and FEV_1/VC respectively, along with other

confounding variables.

Pulmonary obstruction at 68 years of age

FEV_1 and VC at 55 and 68 years of age for the 387 subjects measured on both occasions is

shown in Table 5, classified according to quartiles of LCI and LCI>ULN. The greatest

reductions were found in men with poor LCI (LCI>ULN vs normal LCI: 0.61 L versus 0.43

L, p=0.004).

A total of 347 men had normal FEV_1/VC at 55 years of age, and 35 of them had developed

pulmonary obstruction ($FEV_1/VC <LLN$) at 68 years of age. The proportion of new cases

with pulmonary obstruction at 68 years of age increased significantly across quartiles of LCI at 55 years of age (Table 6). This relationship remained significant after adjustment for smoking and FEV_1. The proportion with pulmonary obstruction at 68 years was 20.7% vs 9.1%, respectively, in men with LCI>ULN and normal LCI at 55. However, this comparison was based on small number of exposed cases (n=6) (Table 6).

DISCUSSION

Although many advances in non-invasive physiological lung measurements have been made, spirometry remains the mainstay in terms of measures used to detect the presence of and severity of COPD[9]. COPD is a condition where development of strategies to enable early detection makes disease prevention a realistic goal[10]. Exploring the role of LCI earlier in life in otherwise healthy individuals can assess its value in the prediction of future COPD events, where it has been repeatedly proposed that spirometry alone cannot accomplish[11-13]. We have found that the risk of incident COPD events was predicted by LCI even after adjustment for FEV_1. The reduction in FEV_1 between 55 and 68 years of age and the proportion of new cases with pulmonary obstruction at 68 years was highest for those with poor LCI. High LCI was found to be a risk factor in the prediction of COPD.

Early studies that first found LCI to be an important marker of ventilation inhomogeneity assessed its use in subjects with emphysema[14], where LCI was found to be the simplest marker and most efficient when separating normal from emphysematous subjects[14]. However although this index was thought to have good diagnostic sensitivity, it was also thought to have the greatest intra-subject variability[14]. Though since then the LCI has gained popularity for use in conditions such as cystic fibrosis [15,16] where it has been a valuable marker of ventilation inhomogeneity in both children and adults and studies have found it to have good intra-visit reproducibility in this population[17,18]. The majority of the literature on ventilation inhomogeneity in COPD patients has involved using markers such as phase III slope analysis from either single breath washout or multiple breath washout [19-23]. Verbanck et al[19] assessed the link between smoking history and non-invasive detection of ventilation heterogeneity and found that the multiple breath washout using conductive and acinar zone measurement could detect ventilation heterogeneity in the small airways from as early as 10 pack-years of smoking history when pathological changes could still be reversible. Indeed this study addressed much needed interest towards the early detection of ventilation

inhomogeneity in a population at risk of COPD and proposed the multiple breath washout as an eligible screening tool in smoking-induced lung disease[19]. A recent study of COPD patients reported relationships between COPD severity, dyspnea, exercise intolerance and poor ventilation distribution defined as the ratio of TLC to alveolar volume, suggesting that ventilation inhomogeneity could be of value in the clinical setting [24]. Our data was acquired long before conductive and acinar zone measurements were introduced; therefore these indices are not available for analysis in the data from the current cohort. Our study therefore assesses the value of measuring overall ventilation inhomogeneity in the lung and the future risk of COPD events using the LCI and subsequently we cannot comment on which structural part of the airway may be affected in those who have poor LCI at baseline.

Study limitations

All subjects were men aged 55 years at baseline. FEV_1, LCI and other measures of ventilation inhomogeneity are known to worsen substantially with increasing age[25,26]. The study design offers very good control for these effects, since age and follow-up periods were identical for all men. On the other hand, it is unclear to what extent the findings can be generalised to women and other age groups.

Although lung function tests were carried out by experienced staff at the Clinical Physiology unit at Malmö University Hospital it was before the current guidelines for spirometry were published so the spirometry methods may differ from the guidelines that exist today. As no prior bronchodilation was carried out all spirometry measurements were also "pre-bronchodilator" figures which can overestimate the prevalence of COPD in a population[27]. The Swedish patient registry was used to monitor incidence of COPD over 44 years of follow-up. The register has been operating in south of Sweden throughout the duration of the study and became nationwide in 1987. The register only recorded cases severe enough to be referred to hospital and milder cases of COPD would have been missed. However the data

available is of acceptable validity for epidemiological research[8]. Furthermore, LCI was also associated with reduction of FEV_1 between 55 and 68 years of age and development of pulmonary obstruction, which further supports the conclusion of a relationship between LCI and the increased incidence of COPD.

Some subjects did quit smoking during the follow-up period, thereby reducing the risk of COPD in their respective groups, however data was not available for all the 674 initially measured at baseline. Even though inhaled corticosteroids were not used at the time of the baseline examination, some men may have used these drugs during the follow-up. This would, if anything, reduce the risk of COPD hospitalisation for men with poor lung function. However, the long follow-up period over the life course of the individuals is unique and a strength of the study, since COPD is a disease mainly affecting older patients.

Another limitation is the relatively small number of individuals and events which may have affected the power of the study and hence resulted in a non-significant increase in the C-statistic when assessing the value of adding LCI to models using spirometry. However, as far as we are aware this is the only study that has assessed LCI as a predictive marker of incident COPD events and development of pulmonary obstruction and investigated its use in addition to normal spirometry over a long follow-up period.

CONCLUSION

LCI is associated with incidence of COPD events, independently of measures from conventional spirometry. High LCI was also associated with reduction of FEV_1 between 55 and 68 years of age and development of pulmonary obstruction.

CONFLICT OF INTEREST STATEMENTS

PW has a patent pending named "Device and Method for Pulmonary Function Measurement" and reports grants from Swedish Heart and Lung Foundation during the conduct of the study.

GE reports grants from the Swedish Heart and Lung foundation and grants from the Swedish Research Council during the conduct of the study.

SZ has no conflicts of interest to disclose.

ETHICS APPROVAL AND CONSENT

The study was approved by The Regional Ethics committee in Lund (1982-111; 2013-443).

Written consent was not available in 1969 however verbal consent was taken for all study participants.

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Table 1 Subject details by quartiles of lung clearance index (674 participants)

	Q1 (best) (4.4-6.9)	Q2 (7.0-7.9)	Q3 (8.0-8.9)	Q4 (worst) (9.0-12.6)	P value
Number (=674)	162	171	173	168	-
Height (m)	1.74 (±0.06)	1.75 (±0.07)	1.75 (±0.07)	1.75 (±0.07)	0.334
BMI (kg/m^2)	25.1 (±2.6)	24.2 (±3.0)	24.6 (±3.2)	24.2 (±3.2)	0.013
Current smoker (%)	47.5	58.5	63.0	76.8	<0.001
Ever smoker (%)	82.1	80.1	86.1	89.9	0.062
Tobacco per day (%)					<0.001
Non-smoker	52.5	41.5	37.0	23.2	
1-14g/day	29.0	36.8	38.2	38.7	
15-24g/day	15.4	16.4	20.8	28.6	
≥25g/day	3.1	5.3	4.0	9.5	
Diabetes (%)	1.9	3.5	1.2	1.2	0.420
P-cholesterol mmol/L *	6.38 (±1.13)	6.39 (±1.13)	6.42 (±1.19)	6.31 (±1.10)	0.861
SBP (mmHg)	142 (±21)	139 (±22)	138 (±24)	137 (±21)	0.123
DBP (mmHg)	88 (±12)	85 (±12)	83 (±13)	82 (±12)	<0.001
LCI	6.1 (±0.7)	7.5 (±0.3)	8.4 (±0.3)	10.0 (±0.8)	<0.001
FEV_1 (L)	3.45 (±0.55)	3.45 (±0.61)	3.30 (±0.59)	3.03 (±0.73)	<0.001
$FEV_{1\%pred}$	101.2 (±14.8)	99.6 (±15.7)	96.3 (±15.4)	87.8 (±20.0)	<0.001

Data are presented as mean ± SD unless otherwise stated. BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; LCI: Lung clearance index; FEV1: forced expiratory volume in 1 s. *Data from 672 participants.

Table 2 Incidence rates and Hazard ratios of COPD by quartiles of LCI and LCI>ULN

	Q1 (reference) 4.4-6.9	Q2 7.0-7.9	Q3 8.0-8.9	Q4 9.0-12.6	P, trend	Normal LCI (n=589)	LCI>ULN (n=85)
All cause mortality, n (/1000 person years)	161 (40)	171 (42)	171 (44)	168 (49)		586 (43)	85 (54)
All cause mortality adjusted (95% CI)[a]	1.00	1.04 (0.83-1.3)	1.08 (0.87-1.35)	1.52 (1.2-1.9)	<0.001	1.00	1.78 (1.41-2.24)
COPD events, n (/1000 person years)	12 (3.1)	16 (4.0)	22 (5.9)	35 (10.9)	-	69 (5.2)	16 (10.6)
COPD events, unadjusted (95% CI)	1.00	1.30 (0.61-2.74)	1.97 (0.97-3.98)	3.99 (2.06-7.71)	<0.001	1.00	2.37 (1.36-4.10)
COPD events, adjusted (95% CI)[a]	1.00	1.21 (0.56-2.59)	1.73 (0.85-3.52)	3.40 (1.74-6.67)	<0.001	1.00	2.24 (1.29-3.92)
COPD events, adjusted (95% CI)[ab]	1.00	1.18 (0.55-2.53)	1.63 (0.80-3.32)	2.34 (1.17-4.69)	0.006	1.00	1.85 (1.05-3.27 [ac]

SD: Standard deviation

[a] Adjusted for smoking status (3 groups: never, ex and current smokers), diabetes, BMI, height, and physical activity (3 groups: high, moderate and low physical activity).

[b] Additionally adjusted for FEV_1 or [c] FEV1<LLN

Table 3 Hazard ratios of COPD by categories of $FEV_{1\%pred}$ and Lung clearance index

	Normal FEV_1 Normal LCI	Normal FEV_1 LCI>ULN	FEV_1<LLN Normal LCI	FEV_1<LLN, LCI>ULN	P value (3 df)
	(Reference)			(Highest risk Category)	
N (=674)	535	60	54	25	
COPD events, unadjusted (95% CI)	1.00	1.48 (0.67-3.26)	3.05 (1.59-5.83)	7.36 (3.61-15.0)	<0.001
COPD events, adjusted (95% CI)[a]	1.00	1.36 (0.61-3.00)	*2.63 (1.35-5.12)	*7.81 (3.78-16.1)	<0.001

[a] Adjusted for smoking status (3 groups: never, ex and current smokers), diabetes, BMI, height, and physical activity (3 groups: high, moderate and low physical activity).

* Difference between FEV_1<LLN/Normal LCI and FEV_1<LLN/LCI>LLN: p-value 0.019

Table 4 Hazard ratios of COPD by categories of FEV_1/VC and Lung clearance index

	Normal FEV_1/VC Normal LCI (Reference)	Normal FEV_1/VC LCI>ULN	FEV_1/VC<LLN Normal LCI	FEV_1/VC<LLN LCI>ULN (Highest risk Category)	P value (3 df)
N (=674)	530	63	59	22	
COPD events, unadjusted (95% CI)	1.00	1.45 (0.62-3.38)	5.38 (3.16-9.15)	10.32 (5.16-20.6)	<0.001
COPD events, adjusted (95% CI)[a]	1.00	1.34 (0.58-3.19)	*5.15 (2.95-9.01)	*11.75 (5.79-23.8)	<0.001

[a] Adjusted for smoking status (3 groups: never, ex and current smokers), diabetes, BMI, height, and physical activity (3 groups: high, moderate and low physical activity).
The categories are divided by FEV_1/VC (normal vs <LLN) and LCI (normal vs >ULN)
 * Difference between FEV_1/VC<LLN/ normal LCI and FEV_1/VC<LLN/ LCI>ULN: p-value 0.041

Table 5. FEV_1 at 55 and 68 years of age by quartiles of LCI and for LCI>ULN

	Q1 (best) 4.5-6.9	Q2 7.0-7.9	Q3 8.0-8.9	Q4 (worst) 9.0-12.6	P value† (trend)	Normal LCI	LCI>ULN
N (=387)	100	100	93	94		345	42
FEV1%pred (at 55 years)	102 (±14)	102 (±15)	97 (±14)	90 (±20)	<0.001	99 (±16)	86 (±20)**
FEV1%pred (at 68 years)	101 (±16)	101 (±17)	95 (±18)	83 (±27)	<0.001	97 (±20)	78 (±24)**
FEV_1 (55 years), L	3.46 (±0.53)	3.53 (±0.61)	3.33 (±0.58)	3.09 (±0.70)	<0.001	3.41 (±0.60)	2.91 (±0.68)**
FEV_1 reduction between 55 and 68 yrs, L	0.42 (±0.30)	0.42 (±0.31)	0.44 (±0.41)	0.54 (±0.43)	0.063	0.44 (±0.36)	0.56 (±0.40)*
Adjusted FEV_1 reduction, L (95% CI)[a]	0.42 (0.34-0.49)	0.40 (0.33-0.48)	0.43 (0.36-0.51)	0.56 (0.49-0.64)	0.011	0.43 (0.40-0.47)	0.61 (0.50-0.72)**

Data are presented as mean ± SD unless otherwise stated. [a]Adjusted for initial FEV_1 at 55 years and current smoking.

* p<0.05 and **p<0.01 for normal LCI vs LCI>ULN
† p-value for trend across quartiles of LCI

Table 6. Pulmonary obstruction at 68 years in relation to LCI at 55 years, among men with normal FEV_1/VC at 55 years.

	Q1 (best) 4.5-6.9	Q2 7.0-7.9	Q3 8.0-8.9	Q4 (worst) 9.0-12.6	P value† (trend)	Normal LCI	LCI>ULN
N (=347)	95	95	86	71		318	29
FEV/VC<LLN at 68 years n (%)	2 (2.1)	7 (7.4)	13 (15.1)	13 (18.3)	<0.001	29 (9.1)	6 (20.7)*
OR	1.00	3.65 (0.74-18)	7.9 (1.7-36)	9.8 (2.1-45)	<0.001		
OR[a]	1.00	4.1 (0.80-21)	7.2 (1.5-34)	8.1 (1.7-39)	0.004		

[a]OR adjusted for smoking.
*no multivariate analysis is presented due to small number of exposed cases.
† p-value for trend across quartiles of LCI

Figure 1. Incidence of COPD hospitalisations or COPD related deaths by quartiles of Lung Clearance Index: Q1 best LCI value, Q4 worst LCI value.