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What is the impact of different spirometric criteria on the prevalence of spirometrically defined COPD and its comorbidities? Results from the population-based KORA study

Stefan Karrasch,[1–3] Irene Brüske,[1] Maia P Smith,[1] Barbara Thorand,[4] Cornelia Huth,[4,5] Karl-Heinz Ladwig,[4] Florian Kronenberg,[6] Joachim Heinrich,[1,7] Rolf Holle,[8] Annette Peters,[4] Holger Schulz[1,7]

[1]Institute of Epidemiology I, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, [2]Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, Ludwig-Maximilians-Universität, [3]Institute of General Practice, University Hospital Klinikum rechts der Isar, Technische Universität München, Munich, [4]Institute of Epidemiology II, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, [5]German Center for Diabetes Research (DZD), Munich/Neuherberg, Germany; [6]Division of Genetic Epidemiology, Department of Medical Genetics, Molecular and Clinical Pharmacology, Medical University of Innsbruck, Innsbruck, Austria; [7]Comprehensive Pneumology Center Munich (CPC-M), Member of the German Center for Lung Research, [8]Institute of Health Economics and Health Care Management, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany

Correspondence: Stefan Karrasch
Institute of Epidemiology I, Helmholtz Zentrum München, German Research Center for Environmental Health (GmbH), Ingolstädter Landstraße 1, D-85764 Neuherberg, Germany
Tel +49 89 3187 4578
Fax +49 89 3187 3380
Email stefan.karrasch@helmholtz-muenchen.de

Background: There is an ongoing debate about the appropriate spirometric criterion for airway obstruction to detect COPD. Furthermore, the association of different criteria with comorbidity prevalence and inflammatory biomarkers in advanced age is unclear.

Materials and methods: Spirometry was performed in a population-based study (n=2,256) covering an age range of 41–90 years. COPD was spirometrically determined either by a fixed ratio (FR) of <0.7 for forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) or by FEV_1/FVC below the lower limit of normal (LLN). Comorbidity prevalences and circulating biomarker levels (C-reactive protein [CRP], interleukin [IL]-6) were compared between subjects with or without COPD by the two criteria using logistic and multiple regression models, adjusting for sex and age.

Results: The prevalence of spirometrically defined COPD by FR increased with age from 10% in subjects aged <65 years to 26% in subjects aged ≥ 75 years. For LLN-defined COPD, it remained below 10% for all age groups. Overall, COPD diagnosis was not associated with specific comorbidities, except for a lower prevalence of obesity in both FR- and LLN-defined cases. Both CRP and IL-6 tended to be higher in cases by both criteria.

Conclusion: In a population-based cohort of adults up to the age of 90 years, the prevalence of spirometrically defined COPD was higher for the FR criterion than for the LLN criterion. This difference increased with age. Neither prevalences of common comorbidities nor levels of the biomarkers, CRP or IL-6, were conclusively associated with the selection of the COPD criterion. Results have to be considered in light of the predominantly mild cases of airway obstruction in the examined study population.

Keywords: chronic obstructive pulmonary disease, spirometry, prevalence, comorbidity, biomarkers

Background

According to current recommendations, a clinical diagnosis of COPD is primarily based on the detection of airflow obstruction in spirometric measures.[1,2] However, the spirometric criteria defining airflow obstruction in COPD are still subject to lively debate.[3,4] The Global Initiative for Chronic Obstructive Lung Disease recommends the use of a fixed ratio (FR) of 0.7 for postbronchodilator forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) to confirm the diagnosis.[1] This approach has been criticized as arbitrary and argued to particularly overestimate prevalences in advanced age.[5] Alternatively, the use of the fifth percentile of the predicted value (lower limit of

normal, LLN) for FEV_1/FVC has been proposed by respiratory societies, eg, the American Thoracic Society and European Respiratory Society.[6,7] It has been shown that the two COPD definitions lead to deviating prevalences.[8] In addition, data and subjects in advanced age beyond 75 years are often underrepresented in the studied population-based samples.

Besides airflow obstruction, COPD is accompanied by a variety of systemic impairments.[9] Comorbidities of COPD include cardiovascular disease, diabetes, depression, and cancer,[10] and it has been reported that COPD may accelerate the progression of some of these comorbidities.[9] Moreover, COPD is characterized by low-grade systemic inflammation.[11] Different biomarkers such as C-reactive protein (CRP)[12] and interleukin (IL)-6[13] have been associated with a poor prognosis in COPD participants. Celli et al[14] showed that using a whole panel of inflammatory biomarkers (eg, CRP, IL-6, IL-8, and fibrinogen) improved the clinical prediction of mortality in COPD participants. Still, in how far circulating biomarker levels are affected by spirometric criteria is less investigated.

The aim of this investigation was 1) to quantify the impact of disease definition by different spirometric criteria (FR vs LLN) on COPD prevalence in a population-based sample and 2) to evaluate the association of FR vs LLN criteria with comorbidity prevalences and selected inflammatory biomarkers.

Materials and methods
Study participants

Within a population-based cohort from the Augsburg region (KORA, Cooperative Health Research in the Augsburg Region, Germany),[15] two follow-up studies, KORA-F4[16] and KORA-Age,[17] were launched from the MONICA/KORA surveys S1–S4. The KORA-F4 and KORA-Age studies were approved by the ethics committee of the Bavarian Medical Association, and written informed consent was obtained from all participants. Details of the KORA platform and surveys have been described earlier.[15,18] Briefly, spirometry was performed in 1,321 subjects aged 41–63 years in KORA-F4 (2006–2008) and in 935 subjects aged 65–90 years in KORA-Age (2009). Measurement conditions for spirometry and the examiners were the same in both studies. Standing height and weight were measured with subjects wearing only light clothes and no shoes.

Spirometry

Details on spirometric measurements have been reported earlier.[16] In short, standard spirometry without bronchodilation was performed in line with the American Thoracic

Society/European Respiratory Society recommendations in an upright sitting position, while subjects were wearing nose clips using a pneumotachograph-type spirometer (MasterScope PC; CareFusion, Höchberg, Germany). The participants performed at least three spirometric maneuvers in order to obtain a minimum of two acceptable and reproducible values. Subjects were classified as having COPD if FEV_1/FVC was <0.7 for the FR criterion and if FEV_1/FVC was < LLN for the LLN criterion. Reference values of the Global Lungs Initiative for FVC, FEV_1, and FEV_1/FVC were used.[19] The severity of COPD was graded according to the stages of disease based on FEV_1 results into categories as defined by the Global Initiative for Chronic Obstructive Lung Disease.[1]

Comorbidities and biomarkers

Self-reported information on myocardial infarction (MI), stroke, cancer, diabetes, inflammatory joint disease/rheumatic disease, gastrointestinal disease (GID), and COPD/chronic bronchitis diagnosis was collected in standardized interviews, which were partly performed via telephone and self-administered questionnaires within the comprehensive KORA assessments.[20] Information on current medication was assessed by asking all study participants to bring original packaging of their medications used during the last 7 days before the study examination.

Hypertension was defined as blood pressure values ≥140/90 mmHg measured during the visit and/or intake of antihypertensive medication, given that the participant was aware of having hypertension as assessed in the standardized interview or questionnaire. Diabetes mellitus was defined as having a self-reported physician diagnosis of diabetes and/or intake of antidiabetic medication. The presence of an anxiety disorder was defined using the Generalized Anxiety Disorder Scale-7[21] in the standardized interview or questionnaire with a score of ≥10 indicating the presence of an anxiety disorder. Depression was assessed using the depression module of the Brief Patient Health Questionnaire-D (PHQ-D) in KORA-F4 (age 41–63 years), whereas in KORA-Age (age 65–90 years) it was assessed using the Geriatric Depression Scale-15 (GDS-15) during the standardized interview, where participants with a score of ≥10 were classified as being depressive.[22] Smoking habits and symptoms of chronic bronchitis, defined as cough and sputum on most days during 3 or more months per year, were assessed within the standardized interview or questionnaire. Furthermore, information on the presence of a physician diagnosis of COPD or chronic bronchitis was assessed during the standardized interview. Information on medication against obstructive

respiratory disease comprised sympathomimetics, anticho-linergics, xanthines, leukotriene receptor antagonists, and corticosteroids.

Serum and ethylenediaminetetraacetic acid (EDTA) plasma samples were obtained from all study participants and were stored at −80°C until analysis. Levels of high-sensitivity CRP were measured in serum (KORA-Age) or EDTA plasma samples (KORA-F4) using Cardio Phase® hsCRP (Siemens, Eschborn, Germany). Serum IL-6 was measured using Quantikine HS Elisa (R&D Systems, Inc., Minneapolis, MN, USA). IL-6 measurements were available only for the KORA-Age cohort.

Statistical analysis

Prevalences are expressed as numbers and percentages of subjects with the trait. Subject characteristics and spirometric indices are expressed as mean (standard deviation). Basic study results are presented according to three age groups (<65 years/≥65 years and <75 years/≥75 years) and spirometric results on the basis of FEV_1/FVC categories. As the distributions of the biomarker levels were skewed, results were log_{10} transformed before further analysis. For the outcome variables of comorbidities, self-reported physician diagnosis of COPD/chronic bronchitis, use of lung medica-tion, chronic bronchitis symptoms, and ever-smoking logistic regression models were generated including sex and age as factors. The influence of the following dichotomous variables was then tested by separately including them into these basic models: 1) cases vs healthy subjects by the FR criterion, 2) cases vs healthy subjects by the LLN criterion, and 3) cases by the FR criterion only vs cases by the LLN criterion. All LLN-defined COPD cases were included in the respective FR-defined group except for one subject in the age group of 40–44 years who was excluded from these analyses. For the outcome variables, log_{10}(CRP) and log_{10}(IL-6) general linear models were generated including sex and age as predictors. The influence of the dichotomous variables for COPD defini-tion was then tested analogously. Analyses were performed using the commercially available software SAS 9.3 (SAS Institute Inc., Cary, NC, USA) and Statgraphics Centurion XVII (Statpoint Technologies Inc., Warrenton, VA, USA); additional plots were done using SigmaPlot 12.0 (Systat Software Inc., San Jose, CA, USA).

Results

In total, 2,256 individuals were included: 1,321 from KORA-F4 (618 men and 703 women) and 935 from KORA-Age (474 men and 461 women). Table 1 summarizes descriptive data of our study participants from both cohorts separately and combined. All study participants from KORA-F4 were younger than 65 years (41–63 years), and all participants from KORA-Age were 65 years and older (65–90 years).

The prevalence of COPD defined by spirometry without bronchodilation according to the FR criterion increased with age from ~10% for the age group below 65 years to 21% for the age group between 65 years and 75 years, and finally 26% for individuals in the age group of 75 years and older (Table 2), but was predominantly confined to mild and moderate stages of COPD. Severe and very severe COPD grades were rare in our population-based study (nine cases in total) and did not differ between FR and LLN criteria for all age groups. The prevalence of COPD on the basis of the LLN criterion remained stable below 10% up to an age of 90 years. The drifting apart with increasing age between both COPD definitions, depending on the diagnostic criteria used (FR vs LLN), became most prominent at age beyond 65 years (Figure 1).

As shown in Table 3, the presence of a self-reported physician diagnosis of COPD/chronic bronchitis in cases of spirometrically defined COPD was generally rather low ranging between 14% and 38%. However, it was pre-dominantly higher for LLN-defined COPD than for the FR criterion as was true for the current use of lung medication and the presence of chronic bronchitis symptoms. In the logistic regression model, this difference between the spiro-metric criteria was observed for all three aspects (Table 4). Regarding ever smoking, differences of cases vs no COPD by both criteria were most prominent in the youngest age group (Table 3), while no differences between the two COPD criteria were observed.

Table 5 shows the odds ratio estimates for the influence of COPD according to FR and LLN criteria on disease prevalence from the logistic regression models; primary prevalences of comorbidities are given in Figure S1A–C. By trend, differences between subjects with and without COPD were most prominent in males for the LLN criterion for MI, cancer, stroke, and anxiety in the middle and oldest age group and for GID in the youngest age group. Although a similar trend was observed for GID in females in the youngest age group, other comorbidities did not show consistent tenden-cies in women. On the other hand, as shown in Table 5, the prevalence of obesity was consistently lower in COPD cases, which was independent of the criterion. Beyond this observa-tion, no firm pattern was observed regarding the prevalence of the examined comorbidities. Still, the occurrence of two

Table 1 General characteristics of the KORA-F4 and KORA-Age study participants with spirometric data

	KORA-F4[16]		KORA-Age[17]		Cohorts combined	
	Men	**Women**	**Men**	**Women**	**Men**	**Women**
Subjects, N	618	703	474	461	1,092	1,164
Age, years: mean (SD)	51.7 (5.8)	51.6 (5.6)	75.6 (6.3)	75.7 (6.3)	62.1 (13.3)	61.1 (13.2)
Age category N (%)						
Age <65 years	618 (100.0)	703 (100.0)	0	0	618 (56.6)	703 (60.4)
Age 65–74 years	0	0	210 (44.3)	207 (44.9)	210 (19.2)	207 (17.8)
Age ≥75 years	0	0	264 (55.7)	254 (55.1)	264 (24.2)	254 (21.8)
Height, cm: mean (SD)	177.0 (6.4)	163.3 (6.1)	171.0 (6.9)	157.7 (6.1)	174.4 (7.2)	161.1 (6.7)
Weight, kg: mean (SD)	87.9 (15.4)	71.6 (14.1)	83.1 (12.7)	70.6 (12.0)	85.8 (14.5)	71.2 (13.3)
BMI, kg/m^2: mean (SD)	28.0 (4.5)	26.8 (5.2)	28.4 (3.9)	28.4 (4.6)	28.2 (4.2)	27.4 (5.1)
Non-lung diseases, N (%)	365 (59.1)	409 (58.2)	430 (90.7)	414 (89.8)	795 (72.8)	823 (70.7)
Number of non-lung diseases, N: median (IQR)	1 (0–2)	1 (0–1)	2 (1–3)	2 (1–3)	1 (0–2)	1 (0–2)
Smoking status: N (%)						
Current	155 (25.1)	151 (21.5)	26 (5.5)	18 (3.9)	181 (16.6)	169 (14.5)
Ex	283 (45.8)	255 (36.3)	266 (56.1)	97 (21.0)	549 (50.3)	352 (30.2)
Never	180 (29.1)	297 (42.2)	182 (38.4)	346 (75.1)	362 (33.2)	643 (55.2)
Lung function: mean (SD)						
FEV$_1$ (L)	3.92 (0.71)	2.84 (0.52)	2.92 (0.69)	2.06 (0.45)	3.48 (0.86)	2.53 (0.62)
FVC (L)	5.07 (0.80)	3.64 (0.62)	3.99 (0.79)	2.73 (0.57)	4.60 (0.96)	3.28 (0.75)
FEV$_1$/FVC	0.77 (0.06)	0.78 (0.06)	0.73 (0.09)	0.76 (0.08)	0.75 (0.08)	0.77 (0.07)
FEV$_1$/FVC category: N (%)						
FEV$_1$/FVC ≥80%	222 (35.9)	295 (42.0)	83 (17.5)	118 (25.6)	305 (27.9)	413 (35.5)
70%≤ FEV$_1$/FVC <80%	327 (52.9)	345 (49.1)	261 (55.1)	249 (54.0)	588 (53.8)	594 (51.0)
FEV$_1$/FVC <70%	69 (11.2)	63 (9.0)	130 (27.4)	94 (20.4)	199 (18.2)	157 (13.5)
FEV$_1$/FVC < LLN	45 (7.3)	52 (7.4)	36 (7.6)	20 (4.3)	81 (7.4)	72 (6.2)
GLI Z-scores: mean (SD)						
FEV$_1$	0.212 (1.142)	0.272 (1.178)	0.335 (1.249)	0.443 (1.108)	0.265 (1.190)	0.340 (1.153)
FVC	0.297 (0.936)	0.401 (0.996)	0.488 (1.071)	0.500 (0.965)	0.380 (1.001)	0.440 (0.985)
FEV$_1$/FVC	−0.200 (0.892)	−0.305 (0.888)	−0.285 (1.014)	−0.216 (0.912)	−0.235 (0.947)	−0.269 (0.898)

Note: LLN and Z-scores were calculated according to GLI reference values.
Abbreviations: BMI, body mass index; FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; GLI, Global Lungs Initiative; LLN, lower limit of normal; IQR, interquartile range.

Table 2 COPD based on FR (FEV$_1$/FVC <0.7) and LLN (FEV$_1$/FVC < LLN) criteria by age and sex (N, % of group)

	Total		Male		Female	
	FR	**LLN**	**FR**	**LLN**	**FR**	**LLN**
Age <65 years						
All subjects (N)	1,321		618		703	
No COPD	1,189 (90.0)	1,224 (92.7)	549 (88.8)	573 (92.7)	640 (91.0)	651 (92.6)
COPD	132 (10.0)	97 (7.3)	69 (11.2)	45 (7.3)	63 (9.0)	52 (7.4)
Mild (FEV$_1$ ≥80%)	83 (6.3)	57 (4.3)	42 (6.8)	25 (4.0)	41 (5.8)	32 (4.6)
Moderate–very severe (FEV$_1$ <80%)	49 (3.7)	40 (3.0)	27 (4.4)	20 (3.2)	22 (3.1)	20 (2.8)
Age 65–74 years						
All subjects (N)	417		210		207	
No COPD	330 (79.1)	390 (93.5)	162 (77.1)	195 (92.9)	168 (81.2)	195 (94.2)
COPD	87 (20.8)	27 (6.5)	48 (22.9)	15 (7.1)	39 (18.8)	12 (5.8)
Mild (FEV$_1$ ≥80%)	61 (14.6)	15 (3.6)	32 (15.2)	6 (2.9)	29 (14.0)	9 (4.3)
Moderate–very severe (FEV$_1$ <80%)	26 (6.2)	12 (2.9)	16 (7.6)	9 (4.3)	10 (4.8)	3 (1.4)
Age ≥75 years						
All subjects (N)	518		264		254	
No COPD	381 (73.6)	489 (94.4)	182 (68.9)	243 (92.0)	199 (78.3)	246 (96.9)
COPD	137 (26.4)	29 (5.6)	82 (31.1)	21 (8.0)	55 (21.7)	8 (3.1)
Mild (FEV$_1$ ≥80%)	89 (17.2)	6 (1.2)	49 (18.6)	4 (1.5)	40 (15.7)	2 (0.8)
Moderate–very severe (FEV$_1$ <80%)	48 (9.3)	23 (4.4)	33 (12.5)	17 (6.4)	15 (5.9)	6 (2.4)

Abbreviations: FEV$_1$, forced expiratory volume in 1 second; FR, fixed ratio; FVC, forced vital capacity; LLN, lower limit of normal.
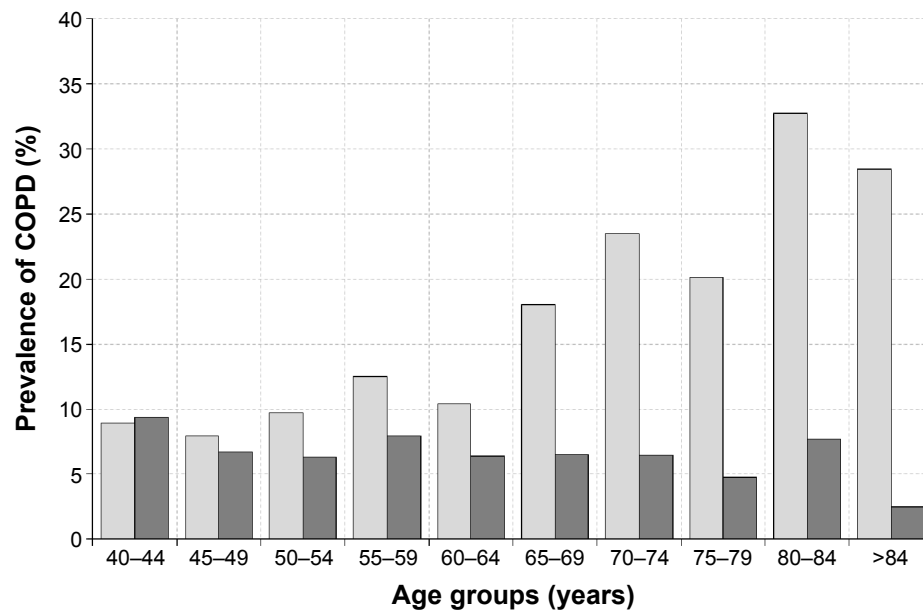
Figure 1 Prevalence of spirometrically defined COPD based on FR (light gray) or LLN (dark gray) criterion.
Note: All LLN-defined COPD cases were included in the respective FR-defined group, except for one subject in the age group of 40–44 years.
Abbreviations: FR, fixed ratio; LLN, lower limit of normal.

Table 3 Frequency (%) of self-reported physician diagnosis of COPD or chronic bronchitis, current use of lung medication, symptoms of chronic bronchitis, and ever smoking in subjects classified by FR (FEV$_1$/FVC <0.7) and LLN (FEV$_1$/FVC < LLN) criteria

	Physician diagnosis of COPD or chronic bronchitis	Current use of lung medication	Symptoms of chronic bronchitis	Ever smoked
Age <65 years				
No COPD				
FR	6.2	2.5	3.2	61.6
LLN	6.5	2.9	3.1	62.2
COPD				
FR	26.2	16.7	3.8	84.9
LLN	29.2	17.5	5.2	85.6
Age 65–74 years				
No COPD				
FR	4.6	3.3	3.9	44.2
LLN	5.6	4.6	4.9	45.9
COPD				
FR	13.8	13.8	14.9	56.3
LLN	18.5	18.5	25.9	59.3
Age ≥75 years				
No COPD				
FR	6.3	2.9	5.0	36.0
LLN	8.8	4.9	6.1	40.1
COPD				
FR	21.9	19.0	14.6	54.7
LLN	37.9	44.8	31.0	55.2

Abbreviations: FEV$_1$, forced expiratory volume in 1 second; FR, fixed ratio; FVC, forced vital capacity; LLN, lower limit of normal.

or more comorbidities was lower in subjects with vs without COPD defined by the LLN criterion (Table 5).

The estimates for the effect of COPD on levels of CRP and IL-6 are presented in Table 6; median CRP and IL-6 levels are shown in Figure S2A and B. Levels of both biomarkers slightly increased with age in all participants without COPD, but consistent differences between FR- and LLN-defined COPD were not detectable. Still, both CRP and IL-6 tended to be higher in cases by both criteria (Table 6).

Discussion

In epidemiology, the definition of COPD disease status is frequently based on either spirometric results, often without bronchodilation, or questionnaire data of physician diagnosis. In this population-based observational study, the impact of disease definition by different spirometric criteria (FR vs LLN) on COPD prevalence was evident and increased with age (Figure 1). The tendency of COPD being possibly over-diagnosed by the FR criterion becomes more pronounced in advanced age, most prominently beyond 65 years in our sample. However, neither the prevalence of common comorbidities nor levels of the inflammatory biomarkers CRP and IL-6 were affected by the selection of the COPD criterion. Our results have to be considered in light of the fact that in our epidemiological cohort we predominantly observed participants with mild-to-moderate airflow obstruction based on spirometry without bronchodilation.

Table 4 Odds ratio estimates (95% CI) for lung-associated parameters by spirometric criterion (FR: FEV$_1$/FVC <0.7; LLN: FEV$_1$/FVC <lower limit of normal) from adjusted logistic regression models

Lung-associated parameters	FR criterion (COPD vs healthy subjects)		LLN criterion (COPD vs healthy subjects)		LLN vs FR criterion (LLN-defined COPD vs LLN-defined healthy subjects within FR-defined COPD subjects)	
	Odds ratio estimate	P-value	Odds ratio estimate	P-value	Odds ratio estimate	P-value
Physician diagnosis of COPD or chronic bronchitis	4.458 (3.204; 6.204)	<0.001	5.777 (3.901; 8.553)	<0.001	2.57 (1.425; 4.636)	0.002
Current lung medication	6.913 (4.605; 10.378)	<0.001	8.280 (5.292; 12.955)	<0.001	2.560 (1.349; 4.860)	0.004
Symptoms of chronic bronchitis	2.681 (1.749; 4.109)	<0.001	3.916 (2.340; 6.554)	<0.001	3.422 (1.589; 7.370)	0.002
Ever smoked	2.230 (1.724; 2.886)	<0.001	2.463 (1.668; 3.637)	<0.001	1.145 (0.653; 2.008)	0.636

Note: Results with $P<0.05$ are indicated in bold.
Abbreviations: CRP, C-reactive protein; FR, fixed ratio; IL-6, interleukin-6; LLN, lower limit of normal.

The prevalence of respiratory obstruction we observed for both spirometric criteria compared well with recent population-based analyses that were performed in a similar fashion. For example, in a large Canadian sample, an overall obstruction prevalence of 17% by the FR criterion has been reported for the age range of 40–93 years,[23] Turkeshi et al[24] found an FR-based prevalence of 27% in a Belgian sample of very old adults aged 80 years or older. However, the prevalence of ~7% we found for LLN was slightly lower than the range of 9%–11% reported in these studies.

Unexpectedly, study participants with spirometrically defined COPD generally did not suffer from more comorbidities than participants of the same age without COPD irrespective of the applied spirometric criterion. Although a tendency toward higher prevalences of MI, cancer, stroke,

and anxiety was observed in participants with LLN-defined COPD compared with participants without LLN-defined COPD, there was no distinct difference after taking account of the sex and age in logistic regression models. On the contrary, we found a lower prevalence of obesity in COPD subjects for both criteria, which might be explained by a higher fraction of smokers among these subjects.[25] None of the other comorbidities evaluated were more prevalent among COPD participants, which is in contrast to findings from other studies.[26–28] The lack of a difference may partly be explained by the fact that our study was conducted in the general population with predominantly mild cases as opposed to a clinical setting with more severe stages of COPD. The prevalences we found in spirometrically defined COPD for MI, stroke, anxiety, and diabetes compared well

Table 5 Odds ratio estimates (95% CI) for comorbidities by spirometric criterion (FR: FEV$_1$/FVC <0.7; LLN: FEV$_1$/FVC < LLN) from adjusted logistic regression models

Comorbidities	FR criterion (COPD vs healthy subjects)		LLN criterion (COPD vs healthy subjects)		LLN vs FR criterion (LLN-defined COPD vs LLN-defined healthy subjects within FR-defined COPD subjects)	
	Odds ratio estimate	P-value	Odds ratio estimate	P-value	Odds ratio estimate	P-value
Hypertension	1.017 (0.779; 1.328)	0.901	0.836 (0.570; 1.224)	0.356	0.617 (0.365; 1.042)	0.071
MI	1.036 (0.654; 1.640)	0.881	1.457 (0.748; 2.839)	0.268	1.719 (0.716; 4.127)	0.225
Stroke	0.779 (0.436; 1.390)	0.397	1.143 (0.479; 2.728)	0.763	1.247 (0.404; 3.849)	0.701
Cancer	0.905 (0.609; 1.345)	0.621	1.183 (0.661; 2.118)	0.571	1.604 (0.732; 3.517)	0.238
Diabetes	0.767 (0.518; 1.137)	0.187	0.492 (0.224; 1.081)	0.077	0.547 (0.220; 1.357)	0.193
Obesity	**0.671 (0.511; 0.882)**	**0.004**	**0.606 (0.400; 0.920)**	**0.019**	0.756 (0.423; 1.350)	0.344
Arthritis	0.864 (0.595; 1.255)	0.442	0.942 (0.531; 1.674)	0.839	1.022 (0.473; 2.208)	0.956
Anxiety	1.033 (0.666; 1.602)	0.885	0.886 (0.456; 1.722)	0.722	0.907 (0.356; 2.312)	0.838
Depression	1.203 (0.482; 3.000)	0.692	0.922 (0.218; 3.897)	0.912	0.475 (0.064; 3.532)	0.467
GID	1.053 (0.729; 1.521)	0.782	1.114 (0.667; 1.859)	0.680	0.834 (0.381; 1.824)	0.650
≥2 comorbidities	0.791 (0.612; 1.022)	0.073	**0.650 (0.440; 0.960)**	**0.030**	0.689 (0.410; 1.159)	0.161

Note: Results with $P<0.05$ are indicated in bold.
Abbreviations: CRP, C-reactive protein; FEV$_1$, forced expiratory volume in 1 second; FR, fixed ratio; FVC, forced vital capacity; GID, gastrointestinal disease; IL-6, interleukin-6; LLN, lower limit of normal; MI, myocardial infarction.

Table 6 Parameter estimates (95% CI) for CRP and IL-6 levels from general linear models by FR and LLN criterion

Biomarkers	FR criterion (COPD vs healthy subjects)		LLN criterion (COPD vs healthy subjects)		LLN vs FR criterion (LLN-defined COPD vs LLN-defined healthy subjects within FR-defined COPD subjects)	
	Parameter estimate as factor	P-value	Parameter estimate as factor	P-value	Parameter estimate as factor	P-value
CRP	**1.154 (1.016; 1.311)**	**0.027**	1.121 (0.934; 1.346)	0.220	0.989 (0.758; 1.292)	0.937
IL-6	1.036 (0.935; 1.148)	0.498	1.178 (0.979; 1.418)	0.083	1.163 (0.937; 1.443)	0.171

Notes: Parameter estimates (95% CI) for CRP and IL-6 have been back-transformed from the model based on $\log_{10}$-transformed biomarker values and thus have to be regarded as factors on the respective biomarker levels. Results with $P<0.05$ are indicated in bold.
Abbreviations: CRP, C-reactive protein; FR, fixed ratio; IL-6, interleukin-6; LLN, lower limit of normal.

with findings described by Divo et al[29] in a recent analysis of COPD patients based on the BODE registry, when considering comparable age groups. However, our prevalences for hypertension were markedly higher, while those for depression were lower, which might be attributed to differences in the assessment of those comorbidities. Furthermore, the COPD cases as defined in our study were predominantly mild and mostly not yet confirmed by a physician, as indicated by the rather poor overlap with physician diagnoses, (Table 3) suggesting early undiagnosed cases to a large degree. Moreover, the increased fraction of ever smokers especially in the youngest age group points to the fact that this factor is of importance predominantly in COPD at comparably young age. It might be speculated that possible concomitant systemic impairments in these cases are in a comparably early stage and thus are not or not yet diagnosed by a physician. Alternatively, a limitation in airway function may precede the affections of other organs that are later described as comorbidities in COPD. The exploration of a possible sequence in this regard, however, would require a longitudinal evaluation, which was beyond the scope of the current cross-sectional study.

In recent years, systemic inflammation has come into the focus of COPD research, and increased serum levels of IL-6 and CRP in COPD participants have been reported.[30] Although we found a tendency toward elevated values for both markers in COPD participants, the overall effect was comparatively small. The lack of findings, particularly in the aged, may, in our case, be partly explained by harvesting, where subjects in poor health did not survive or did not participate in the study as they were unable to get into the study center. A recent study by Silva et al[31] did not find markedly elevated CRP in nonsmoking COPD patients compared to a control group indicating the possible impact of active smoking on this parameter. However, the tendency toward higher IL-6 levels in LLN-defined COPD cases in older age for males suggests that this criterion may be diagnostically more specific in identifying participants with

(early stage) systemic inflammation than the FR and needs confirmation in longitudinal settings.

Consequently, these findings indicate that the application of the LLN criterion in epidemiological or clinical settings will result in an identification of subjects with more concomitant typical characteristics of COPD, eg, chronic bronchitis symptoms, and a higher probability of a physician diagnosis of COPD compared to FR (Table 4). However, since no consistent differences in comorbidity prevalences or biomarker levels were observed, the preference of one criterion over the other in this regard could not be derived from our study. Beyond the FEV_1/FVC ratio, the use of more advanced lung function measurements such as body plethysmography[32] could provide a refined characterization of patient subgroups with a higher number or specific patterns of comorbidities.

The limitation of the current study might be the fact that the definition of COPD cases here, as a rather common epidemiological approach, was solely based on spirometric results as opposed to a usually more comprehensive approach in clinical practice including anamnesis, symptoms, risk factors, and individual clinical history. However, the restriction to different interpretations of a spirometric measure allowed us to specifically focus on the impact of this particular component of the diagnostic sequence in predominantly early, often undiagnosed cases of airway obstruction according to our research question. A clear strength of our study is the inclusion of participants from the general population up to an advanced age of 90 years, an age group that is often underrepresented in COPD studies.

Conclusion

In a population-based sample of adults in middle and advanced age, we found that the prevalence of spirometrically defined COPD was higher when using the FR criterion as opposed to LLN and this difference increased with increasing age. However, for the predominantly mild cases observed in our cohort, there was no conclusive impact of the different

spirometric criteria on the prevalence of comorbidities and on common inflammatory biomarker levels.

Acknowledgments

Disclosure

The authors report no conflicts of interest in this work.

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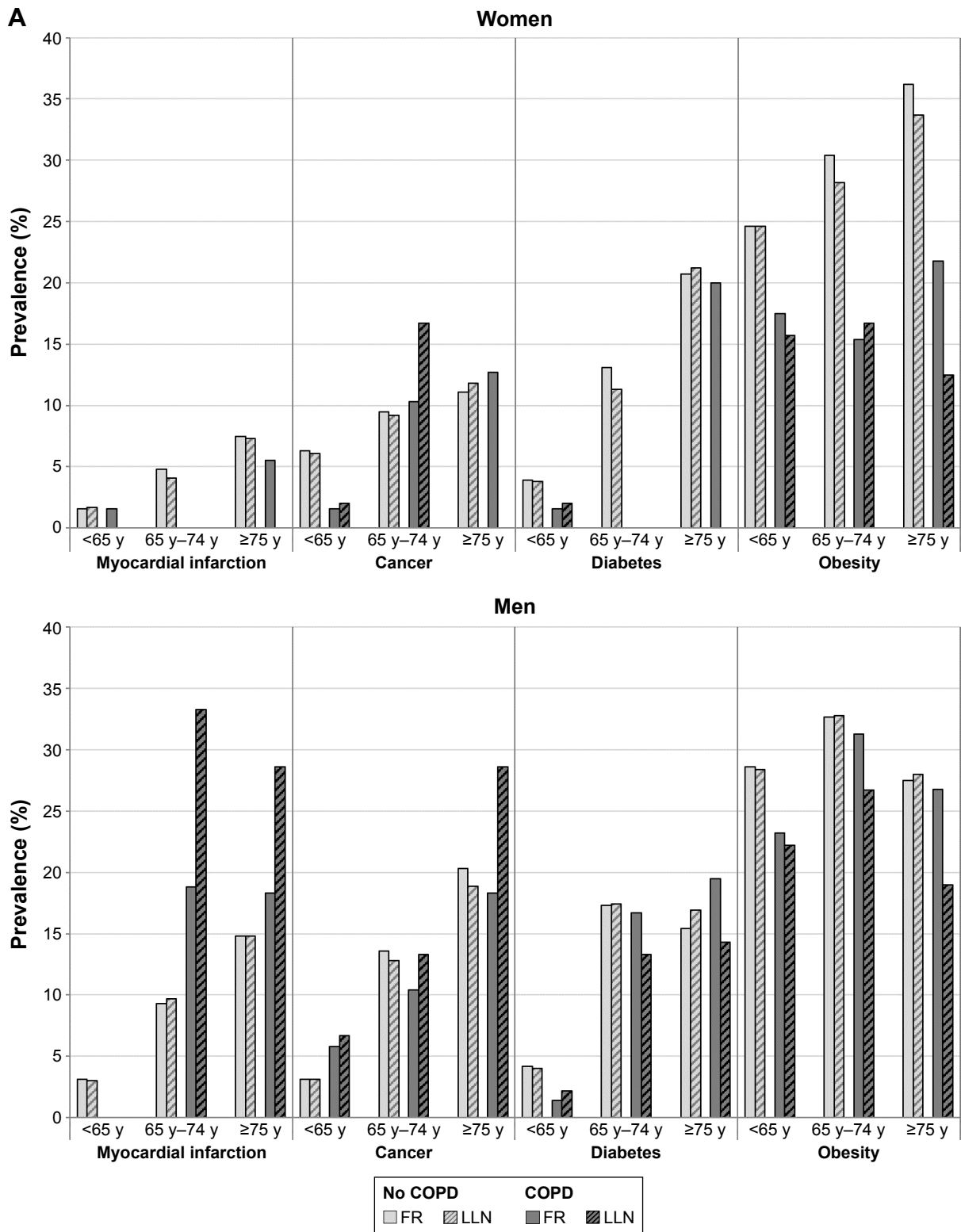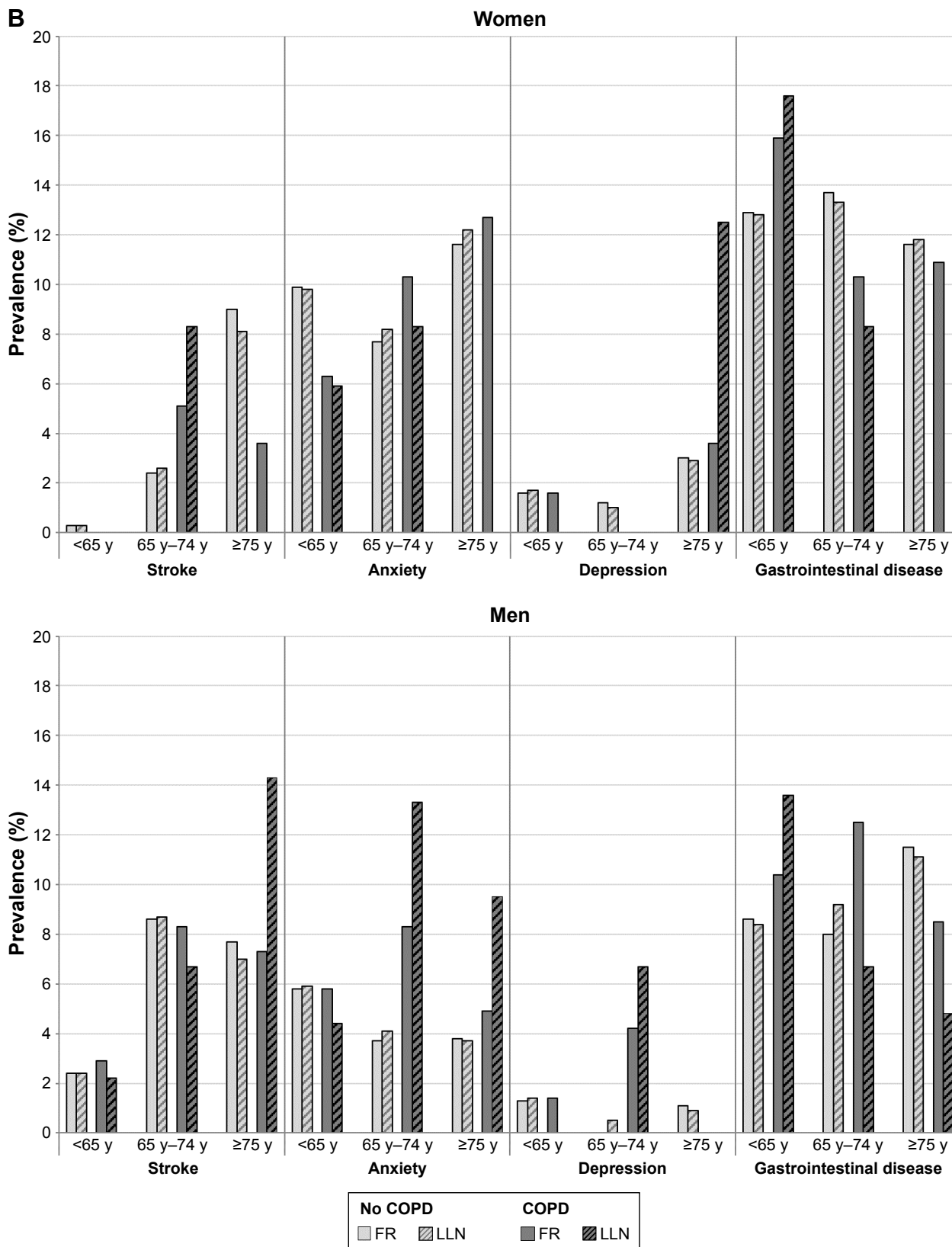
Supplementary materials

A

Figure S1 (*Continued*)
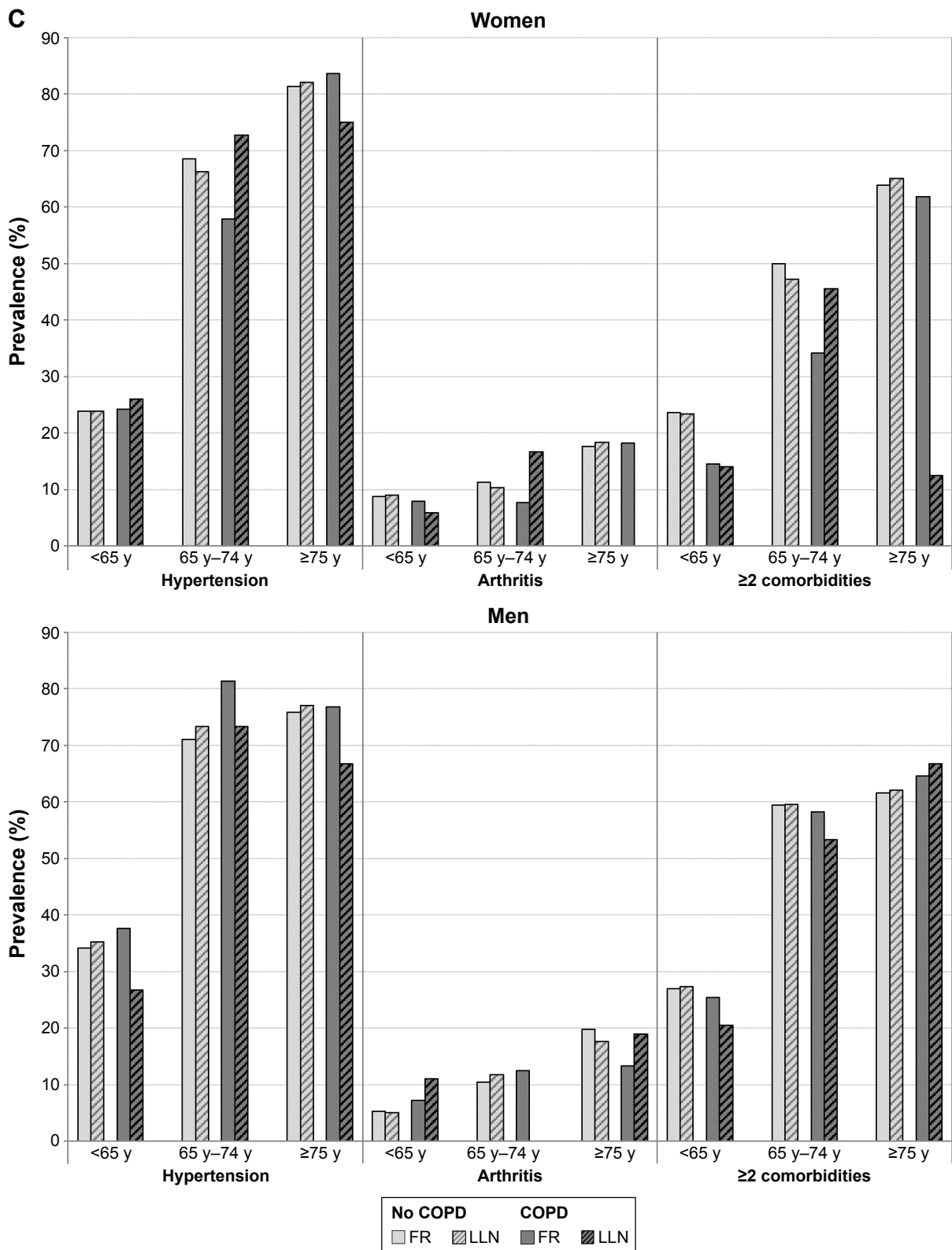
Figure S1 (*Continued*)

Figure S1 (**A–C**) Prevalence of comorbidities in subjects without COPD (light grey) or with COPD (dark grey) by FR (FEV$_1$/FVC <0.7; solid color) and LLN (FEV$_1$/FVC <lower limit of normal; hatched) criterion (percentages).
Abbreviations: FR, fixed ratio; LLN, lower limit of normal; FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; y, years.
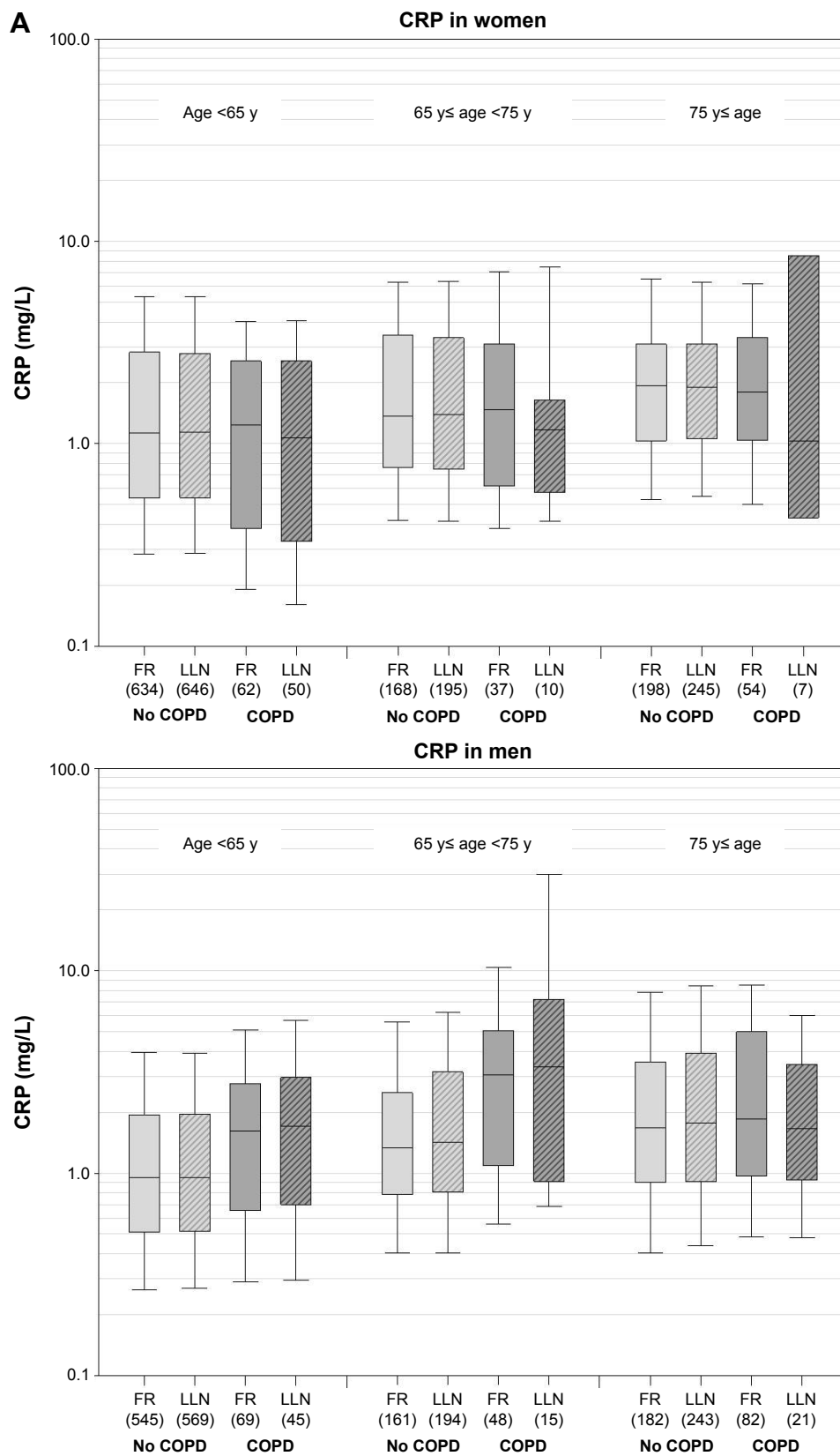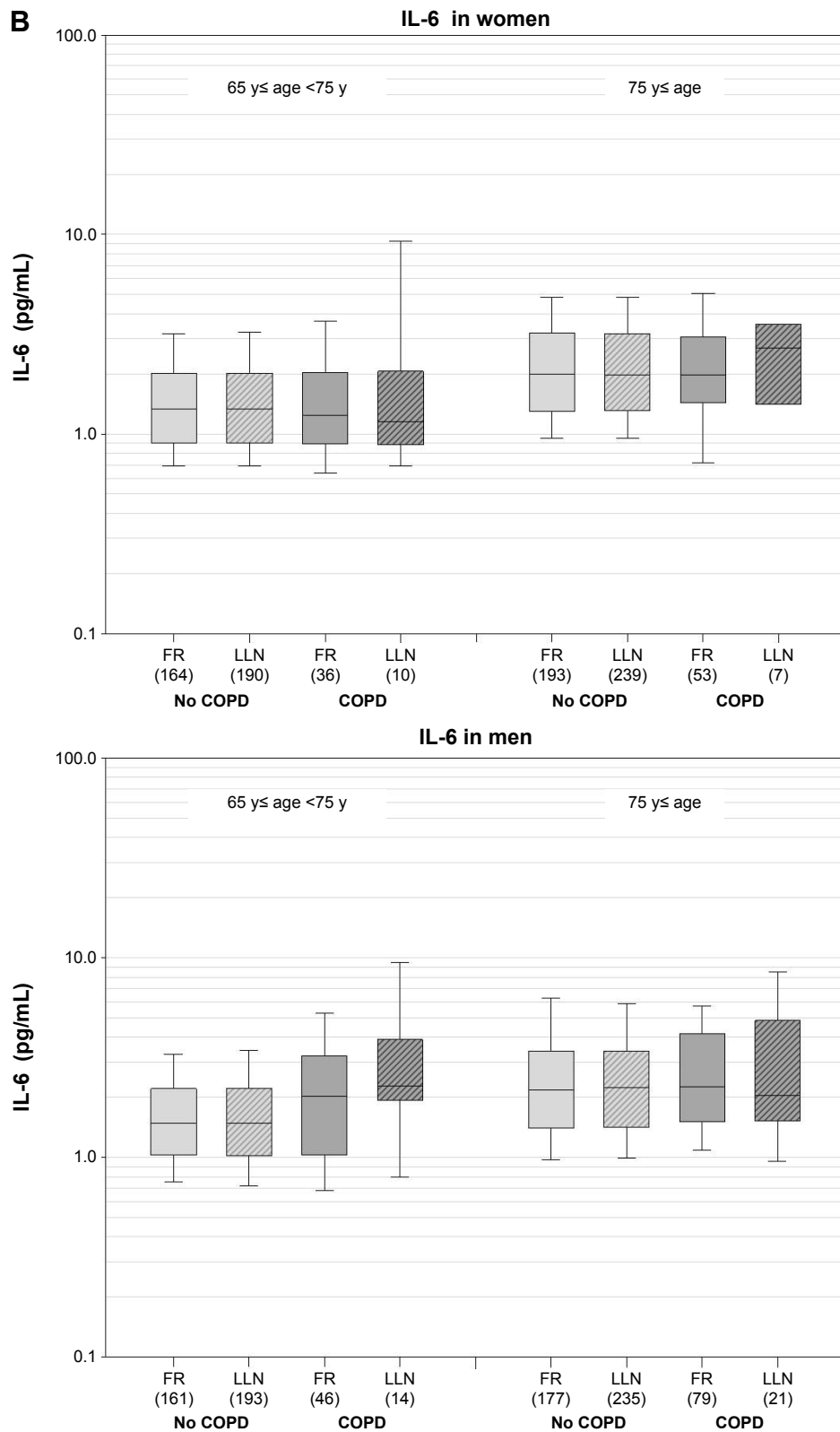
Figure S2 (*Continued*)

Figure S2 (**A–B**) Levels of CRP and IL-6 in subjects without COPD (light grey) and COPD cases (dark grey) based on FR (FEV$_1$/FVC <0.7; solid color) or LLN (FEV$_1$/FVC <lower limit of normal; hatched) criterion (number of subjects per group are given in brackets).
Abbreviations: FR, fixed ratio; LLN, lower limit of normal; FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; y, years.