ORIGINAL RESEARCH

Comparison of five major airflow limitation criteria to identify high-risk individuals with COPD: a contemporary population-based cohort

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ABSTRACT

Background Different airflow limitation criteria are often used to diagnose COPD. We investigated head-to-head whether Global Initiative for Chronic Obstructive Lung Disease (GOLD) (FEV_1/FVC <0.70) and four lower limit of normal (LLN) (FEV_1/FVC <LLN) criteria to diagnose airflow limitation differ in identifying individuals at risk of COPD exacerbations and mortality.

Methods 108 246 individuals aged 20–100 years randomly selected from the general population were followed from 2003 through 2018 to determine risk of COPD exacerbations, respiratory mortality and all-cause mortality. LLN criteria used equations from Global Lung Initiative (GLI), National Health and Nutrition Examination Survey (NHANES), European Community for Steel and Coal (ECSC) and Copenhagen City Heart Study (CCHS)/Copenhagen General Population Study (CGPS).

Results Prevalence of airflow limitation was 17% for GOLD, 8.6% for GLI, 10% for NHANES, 8.2% for ECSC and 14% for CCHS/CGPS. During 14.4 years follow-up, we observed 2745 COPD exacerbations, 762 respiratory deaths and 10 338 all-cause deaths. Comparing individuals with versus without airflow limitation, HRs for COPD exacerbations were 17 (95% CI 14 to 20) for GOLD, 21 (18 to 24) for GLI, 20 (17 to 23) for NHANES, 21 (18 to 24) for ECSC and 18 (16 to 21) for CCHS/CGPS. Corresponding HRs for respiratory mortality were 3.7 (3.1 to 4.3), 6.4 (5.6 to 7.5), 5.7 (4.9 to 6.6), 6.2 (5.3 to 7.2) and 4.5 (3.9 to 5.2), and for all-cause mortality 1.5 (1.4 to 1.5), 1.9 (1.8 to 2.0), 1.8 (1.7 to 1.9), 1.9 (1.8 to 2.0) and 1.7 (1.6 to 1.7), respectively. Differences in Harrell's C were minute for these outcomes; nonetheless, Harrell's C was slightly higher for LLN criteria compared with GOLD for mortality outcomes.

Conclusions The prevalence of airflow limitation ranged from 8% to 17% using GOLD and four different LLN criteria; however, identified individuals with the five different criteria had similar risk of COPD exacerbations and mortality.

Key messages

What is the key question?

► Do Global Initiative for Chronic Obstructive Lung Disease (GOLD) and four lower limit of normal (LLN) criteria to diagnose airflow limitation differ in identifying individuals at risk of COPD exacerbations and mortality in individuals in a contemporary population-based cohort?

What is the bottom line?

► Individuals had similar risk of COPD exacerbations and mortality according to GOLD and four different LLN criteria for airflow limitation, although the prevalence of airflow limitation by these definitions varied from 8% to 17%. Among LLN criteria, locally derived criteria seem optimal for identifying high-risk individuals.

Why read on?

► This is the first study that has investigated differences between various LLN criteria relative to GOLD criteria to diagnose airflow limitation against clinical outcomes of COPD in the general population.

INTRODUCTION

Different airflow limitation criteria are often used indiscriminately to diagnose COPD, that is, without careful judgement of the evidence for clinical usefulness of the various criteria. Currently, airflow limitation defined as a fixed ratio of FEV_1/FVC <0.70 is recommended to confirm the diagnosis of COPD according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) in subjects with respiratory symptoms and a relevant exposure.[1] However, airflow limitation according to lower limit of normal (LLN), defined as FEV_1/FVC <5th percentile of the predicted value for FEV_1/FVC, has alternatively been recommended to identify susceptible individuals at risk of developing COPD later in life by proposing an operational definition of early COPD.[2–6] Recently, we found that 15% fulfil criteria of early COPD in the general population, defined as FEV_1/FVC <LLN in individuals aged <50 years with smoking exposure ≥10 pack-years, and individuals with early COPD had an increased risk of acute respiratory hospitalisations and early death.[7] Furthermore, we recently also showed that young and middle-aged adults with airflow limitation according to LLN but not fixed ratio according to GOLD had an increased risk of respiratory and cardiovascular morbidity and early death.[8]

Airflow limitation according to LLN is often defined using different lung function reference equations due to lack of standardisation. That

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said, major efforts were made towards standardisation with the Global Lung Initiative (GLI) lung function reference equations,[9] which is now accepted as the standard given the comprehensiveness of the sampling and analyses underlying the derivation of the equations. Nonetheless, no study has investigated differences between various LLN criteria relative to GOLD criteria to diagnose airflow limitation against clinical outcomes of COPD.[10]

We investigated head-to-head whether GOLD and four LLN criteria to diagnose airflow limitation differ in identifying individuals at risk of COPD exacerbations and mortality in individuals in a contemporary population-based cohort.

METHODS

Study population

We examined individuals aged 20–100 years from the Copenhagen General Population Study (CGPS), a Danish contemporary population-based cohort initiated in November 2003 with ongoing enrolment.[11] In the present study, we included 108 246 individuals recruited up to April 2015 with complete information on lung function. In Denmark, all individuals are assigned a unique identification number at birth or immigration (Central Person Registration number) and recorded in the national Danish Civil Registration System. Individuals living in the Capital Region of Denmark were randomly invited from the national Danish Civil Registration System to reflect the adult white Danish population (response rate 43%); non-responders were more likely men (48% vs 45%) and slightly younger (median age: 56 vs 58 years). All participants completed a comprehensive questionnaire and underwent a physical health examination. Questionnaires were reviewed at the day of attendance by a healthcare professional together with the participant. All individuals provided written informed consent.

Airflow limitation

Detailed description of lung function measurement is provided in the online supplementary material. In brief, spirometry measured prebronchodilator FEV_1 and FVC.[12] Predicted values for FEV_1/FVC were calculated according to (1) GLI derived reference equations.[9] (2) The National Health and Nutrition Examination Survey (NHANES) derived reference equations.[13] (3) The European Community for Steel and Coal (ECSC) derived reference equations.[14] (4) The Copenhagen City Heart Study (CCHS)/CGPS derived reference equations (a subset of 716 individuals from CCHS and 10 572 individuals from CGPS were previously included in the derivation of the equations).[12] Airflow limitation was defined according to a fixed ratio, that is FEV_1/FVC <0.70, denoted as GOLD,[1] and according to four LLN criteria, that is, FEV_1/FVC <LLN, denoted as GLI, NHANES, ECSC and CCHS/CGPS, respectively. The LLN was defined as the bottom fifth percentile of the predicted value for FEV_1/FVC, calculated as the mean value minus 1.645 SD.[15] GOLD recommends use of postbronchodilator airflow limitation to diagnose COPD.[1] Since postbronchodilator spirometry was not performed in the present study, a slight modification of the GOLD criterion was a necessity. Nonetheless, we were also interested in whether prebronchodilator airflow limitation could identify individuals at risk of COPD exacerbations and mortality, as spirometry in general is underused in clinical practice,[16] and if spirometry is used, postbronchodilator measurements are often omitted.

Other characteristics

Description of other characteristics is provided in the online supplementary material.

COPD exacerbations, respiratory mortality and all-cause mortality

COPD exacerbations (International Classification of Diseases (ICD)−10: J41-J44) were defined as acute emergency department visits and/or hospitalisations with the mentioned primary discharge diagnosis. Information was obtained from the national Danish Patient Registry, which covers all public and private hospitals in Denmark, recorded from baseline until 10 April 2018. Information on vital status was obtained from the national Danish Civil Registration System, which contains date of death and emigration for all residents in Denmark, recorded from baseline until 19 April 2018. Information on cause of death was obtained from the national Danish Causes of Death Registry, which contains causes of death for all residents in Denmark, recorded from baseline until 31 December 2016. Death due to respiratory disease (ICD-10: J00-J99) was based on the primary cause of death. Since COPD is under-reported on death certificates in the national Danish Causes of Death Registry,[17] we have deliberately chosen not to restrict on death due to COPD alone. Since the national Danish Causes of Death Registry lags the national Danish Civil Registration System by approximately 1 year, not all deaths could be classified by cause. As follow-up was done using the above-mentioned register linkage based on the unique Central Person Registration number provided to everyone in Denmark at birth or immigration, no person was lost to follow-up, and individuals who emigrated were censored at the date of emigration (n=452). All diagnoses recorded in the registries are strictly made by a medical doctor at discharge or death according to national Danish law using the WHO's ICD-codes.

Statistical analyses

Cox proportional regression models were used to determine risk of COPD exacerbations, respiratory mortality and all-cause mortality. We used age as the underlying timescale (=age adjusted) and also adjusted for sex with left truncation (=delayed entry) at study examination. On purpose, we did not adjust for other covariates, as our aim was to imitate clinical practice, and not exclude confounders. Risk of COPD exacerbations was investigated using multiple failure-time analysis according to the method of Andersen-Gill.[18] To avoid counting a single event multiple times, we chose that individuals experiencing an acute emergency department visit or hospitalisation had to be clinically stable for at least 4 weeks after discharge before they could be considered at risk again for a subsequent event, in accordance with recommendations.[19–21] Risk of respiratory and all-cause mortality was investigated using single failure-time analysis. Age differences between airflow limitation diagnosis by different LLN criteria were visualised through local polynomial smooth plots of LLN for FEV_1/FVC. Differences in the predictive capability by the different airflow limitation criteria and its clinical significance was investigated by determining the discriminative accuracy for an outcome using Harrell's C statistic, a goodness-of-fit measure for predictive models with censoring;[22 23] in this regard, risk of COPD exacerbation was investigated using single failure-time analysis. Area-proportional Venn diagrams were used to visualise overlaps between individuals diagnosed with different airflow limitation criteria. Due to the recently proposed operational definition of early COPD, we also investigated differences in airflow limitation criteria in young versus old individuals using age 50 years as cut-off.[3] Other subgroup analyses included those with low versus high tobacco consumption and those with versus without chronic respiratory

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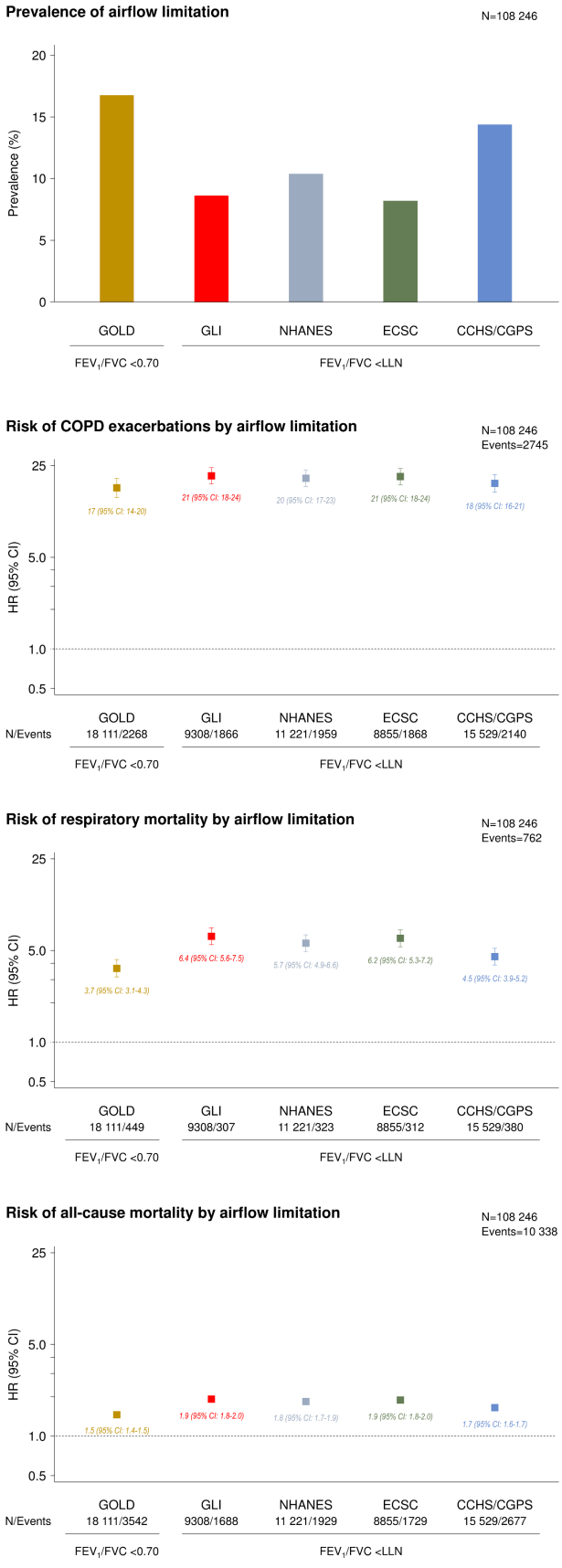

Figure 1 Prevalence of airflow limitation and risk of COPD exacerbations and mortality by airflow limitation using different criteria in individuals in the general population. Risk estimates obtained from Cox proportional regression models adjusted for age and sex. Based on 108 246 individuals from the CGPS. CCHS, Copenhagen City Heart Study; CGPS, Copenhagen General Population Study; ECSC, European Coal and Steel Community; GLI, Global Lung Initiative; GOLD, Global Initiative for Chronic Obstructive Lung Disease; LLN, lower limit of normal; NHANES, National Health and Nutrition Examination Survey.

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symptoms due to risk of potential overestimation and underestimation in clinical practice.

Our main analysis included all individuals, as smoking is not the only risk factor for COPD.[24] In a sensitivity analysis, we investigated the risk in a more clinically defined study population, that is, current and former smokers reporting at least one chronic respiratory symptom in the form of dyspnoea, chronic mucus hypersecretion, wheezing and/or cough. This is also a sensitivity analysis related to exclusion of healthy asymptomatic never-smoking individuals like those that were previously included in the derivation cohort of reference equations for CCHS/CGPS. In another sensitivity analysis, we excluded individuals with asthma. Analyses were performed using STATA/SE V.13.1 for Windows (StataCorp, College Station, Texas, USA), and a two-sided value of $p<0.05$ was considered statistically significant.

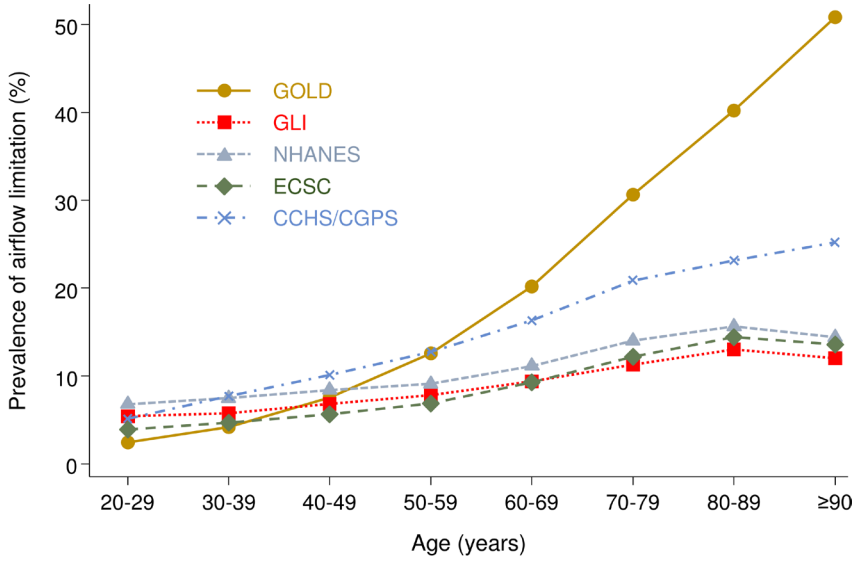
RESULTS

GOLD versus four LLN criteria using prebronchodilator spirometry

In 108 246 individuals from the general population, 18 111 (17%) had airflow limitation according to GOLD, 9308 (8.6%) according to GLI, 11 221 (10%) according to NHANES, 8855 (8.2%) according to ECSC and 15 529 (14%) had airflow limitation according to CCHS/CGPS (figure 1, upper panel). Overall, compared with GOLD, all criteria based on LLN identified more individuals with airflow limitation at younger age and fewer individuals at older age; however, differences could also be observed between the different LLN criteria (figure 2 and online supplementary figure S1). Regardless of the chosen criteria, individuals identified with airflow limitation had a higher prevalence of chronic respiratory symptoms and smoking with high tobacco consumption compared with those without airflow limitation (table 1). Also, the distribution of airflow limitation severity was similar between GOLD and four LLN criteria (online supplementary table S1).

During up to 14.4 years of follow-up (median: 8.7 years), we observed 2745 COPD exacerbations and 10 338 deaths, of which 762 had respiratory disease as the primary cause. Individuals with airflow limitation according to GOLD or one of the four LLN criteria had increased risk of COPD exacerbations, respiratory mortality and all-cause mortality compared with those without airflow limitation (figure 1, middle and lower panels). Compared with individuals without airflow limitation, age and sex adjusted HR for COPD exacerbations in individuals with airflow limitation was 17 (95% CI 14 to 20) according to GOLD, 21 (95% CI 18 to 24) according to GLI, 20 (95% CI 17 to 23) according to NHANES, 21 (95% CI 18 to 24) according to ECSC and 18 (95% CI 16 to 21) according to CCHS/CGPS. Corresponding HRs for respiratory mortality were 3.7 (95% CI 3.1 to 4.3), 6.4 (95% CI 5.6 to 7.5), 5.7 (95% CI 4.9 to 6.6), 6.2 (95% CI 5.3 to 7.2) and 4.5 (95% CI 3.9 to 5.2), and for all-cause mortality 1.5 (95% CI 1.4 to 1.5), 1.9 (95% CI 1.8 to 2.0), 1.8 (95% CI 1.7 to 1.9), 1.9 (95% CI 1.8 to 2.0) and 1.7 (95% CI 1.6 to 1.7), respectively.

Predictive capability for risk of COPD exacerbation was slightly higher for CCHS/CGPS compared with GOLD and the other three LLN criteria (all p values<0.05), while GOLD did not differ compared with the other three LLN criteria (all p values ≥0.05) (online supplementary figure S2, upper panel).



N	2134	5215	24 804	27 187	28 200	15 778	4678	250
GOLD	52	218	1878	3421	5700	4835	1880	127
GLI	116	300	1691	2127	2654	1781	609	30
NHANES	145	390	2087	2476	3143	2212	732	36
ECSC	84	245	1406	1873	2617	1920	676	34
CCHS/CGPS	110	403	2507	3465	4604	3295	1082	63

Figure 2 Prevalence of airflow limitation according to age using different criteria in individuals in the general population. Based on 108 246 Individuals from the CGPS. CCHS, Copenhagen City Heart Study; CGPS, Copenhagen General Population Study; ECSC, European Coal and Steel Community; GLI, Global Lung Initiative; GOLD, Global Initiative for Chronic Obstructive Lung Disease; NHANES, National Health and Nutrition Examination Survey.

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Table 1 Baseline characteristics according to clinical groups of airflow limitation by using different criteria in individuals in the general population*

		GOLD		GLI		NHANES		ECSC		CCHS/CGPS	
	All individuals n=108 246	FEV_1/FVC≥0.70 n=90 135	FEV_1/FVC<0.70 n=18 111	FEV_1/FVC≥LLN n=98 938	FEV_1/FVC<LLN n=9308	FEV_1/FVC≥LLN n=97 025	FEV_1/FVC<LLN n=11 221	FEV_1/FVC≥LLN n=99 391	FEV_1/FVC<LLN n=8855	FEV_1/FVC≥LLN n=92 717	FEV_1/FVC<LLN n=15 529
General characteristics											
Age – years	58.2 (48.2–67.5)	56.3 (47.0–65.7)	66.3 (57.5–74.2)	57.8 (47.9–67.1)	61.7 (51.1–70.5)	57.7 (47.9–67.1)	61.7 (50.8–70.7)	57.7 (47.9–67.0)	63.4 (52.7–71.8)	57.3 (47.6–66.7)	63.0 (52.7–71.4)
Men – no. (%)	48 671 (45)	40 026 (44)	8645 (48)	44 797 (45)	3874 (42)	44 352 (46)	4319 (38)	45 243 (46)	3428 (39)	41 022 (44)	7649 (49)
Body mass index – kg/m^2	25.6 (23.2–28.4)	25.6 (23.3–28.5)	25.1 (22.9–27.9)	25.6 (23.3–28.5)	24.8 (22.6–27.7)	25.6 (23.3–28.5)	24.8 (22.6–27.6)	25.6 (23.3–28.5)	24.8 (22.5–27.6)	25.6 (23.3–28.5)	25.1 (22.8–27.8)
FEV_1 – L	2.93 (2.37–3.57)	3.04 (2.51–3.67)	2.28 (1.76–2.87)	2.99 (2.45–3.61)	2.19 (1.61–2.79)	3.00 (2.46–3.63)	2.25 (1.67–2.83)	2.99 (2.45–3.62)	2.11 (1.57–2.69)	3.01 (2.48–3.64)	2.36 (1.79–2.96)
FVC – L	3.80 (3.14–4.59)	3.84 (3.20–4.63)	3.56 (2.83–4.42)	3.82 (3.16–4.60)	3.60 (2.82–4.46)	3.82 (3.16–4.61)	3.61 (2.86–4.43)	3.82 (3.17–4.61)	3.51 (2.75–4.33)	3.81 (3.16–4.60)	3.70 (2.94–4.55)
FEV_1/FVC	0.77 (0.73–0.82)	0.79 (0.75–0.82)	0.66 (0.61–0.68)	0.78 (0.74–0.82)	0.62 (0.56–0.65)	0.78 (0.74–0.82)	0.63 (0.58–0.66)	0.78 (0.74–0.82)	0.61 (0.56–0.65)	0.79 (0.75–0.82)	0.65 (0.60–0.68)
Current smokers – no. (%)	18 456 (17)	13 493 (15)	4963 (27)	15 418 (16)	3038 (33)	14 963 (15)	3493 (31)	15 601 (16)	2855 (32)	13 796 (15)	4660 (30)
Former smokers – no (%)	44 139 (41)	35 725 (40)	8414 (46)	40 133 (41)	4006 (43)	39 295 (41)	4844 (43)	40 240 (40)	3899 (44)	37 240 (40)	6899 (44)
Tobacco consumption – pack-years†	15.4 (6.0–30.0)	14.0 (5.0–27.0)	25.0 (12.0–40.2)	15.0 (5.5–28.9)	26.3 (13.0–41.3)	15.0 (5.4–28.6)	25.2 (12.5–40.0)	15.0 (5.5–29.0)	27.0 (13.4–42.0)	14.3 (5.0–27.1)	25.7 (12.5–40.5)
Clinical characteristics											
Airway medication use – no. (%)	6501 (6)	3742 (4)	2759 (15)	4531 (5)	1970 (21)	4341 (4)	2160 (19)	4583 (5)	1918 (22)	3917 (4)	2584 (17)
Asthma – no. (%)	7447 (7)	4860 (5)	2587 (14)	5610 (6)	1837 (20)	5404 (6)	2043 (18)	5689 (6)	1758 (20)	4968 (5)	2479 (16)
Symptoms											
Dyspnoea – no. (%)	34 365 (32)	26 247 (29)	8118 (45)	29 800 (30)	4565 (49)	29 015 (30)	5350 (48)	29 891 (30)	4474 (51)	27 420 (30)	6945 (45)
mMRC ≥2 – no. (%)	8924 (8)	6016 (7)	2908 (16)	7188 (7)	1736 (19)	6983 (7)	1941 (17)	7177 (7)	1747 (20)	6502 (7)	2422 (16)
Chronic mucus hypersecretion – no. (%)	9540 (9)	6476 (7)	3064 (17)	7714 (8)	1826 (20)	7502 (8)	2038 (18)	7773 (8)	1767 (20)	6820 (7)	2720 (18)
Wheezing – no. (%)	18 236 (17)	13 027 (14)	5209 (29)	14 867 (15)	3369 (36)	14 435 (15)	3801 (34)	15 041 (15)	3195 (36)	13 366 (14)	4870 (31)
Cough – no. (%)	13 047 (12)	9631 (11)	3416 (19)	10 793 (11)	2254 (24)	10 482 (11)	2565 (23)	10 897 (11)	2150 (24)	9813 (11)	3234 (21)
Any symptom – no. (%)	46 096 (43)	35 611 (40)	10 485 (58)	40 176 (41)	5920 (64)	39 173 (40)	6923 (62)	40 392 (41)	5704 (64)	36 930 (40)	9166 (59)
Number of acute bronchitis/pneumonia episodes in the last 10 years											
None – no. (%)	83 286 (77)	70 896 (79)	12 390 (68)	77 351 (78)	5935 (64)	76 001 (78)	7285 (65)	77 714 (78)	5572 (63)	72 764 (78)	10 522 (68)
1–5 – no. (%)	22 847 (21)	17 931 (20)	4916 (27)	20 034 (20)	2813 (30)	19 544 (20)	3303 (29)	20 122 (20)	2725 (31)	18 581 (20)	4266 (27)
≥6 – no. (%)	2113 (2)	1308 (1)	805 (4)	1553 (2)	560 (6)	1480 (2)	633 (6)	1555 (2)	558 (6)	1372 (1)	741 (5)
Number of GP visits in the last 12 months											
None – no. (%)	22 580 (21)	19 436 (22)	3144 (17)	20 899 (21)	1681 (18)	20 596 (21)	1984 (18)	21 049 (21)	1531 (17)	19 777 (21)	2803 (18)
Once – no. (%)	24 132 (22)	20 728 (23)	3404 (19)	22 327 (23)	1805 (19)	21 941 (23)	2191 (20)	22 459 (23)	1673 (19)	21 051 (23)	3081 (20)
Twice or more – no. (%)	61 534 (57)	49 971 (55)	11 563 (64)	55 712 (56)	5822 (63)	54 488 (56)	7046 (63)	55 883 (56)	5651 (64)	51 889 (56)	9645 (62)

*Data presented as median (25th and 75th percentiles), or number (%). Numbers may not sum to 100% due to rounding
†Only for current and former smokers.
CCHS, Copenhagen City Heart Study; CGPS, Copenhagen General Population Study; ECSC, European Coal and Steel Community; GLI, Global Lung Initiative; GOLD, Global Initiative for Chronic Obstructive Lung Disease; GP, general practitioner; LLN, lower limit of normal; mMRC, modified Medical Research Council Dyspnoea Scale; NHANES, National Health and Nutrition Examination Survey.;

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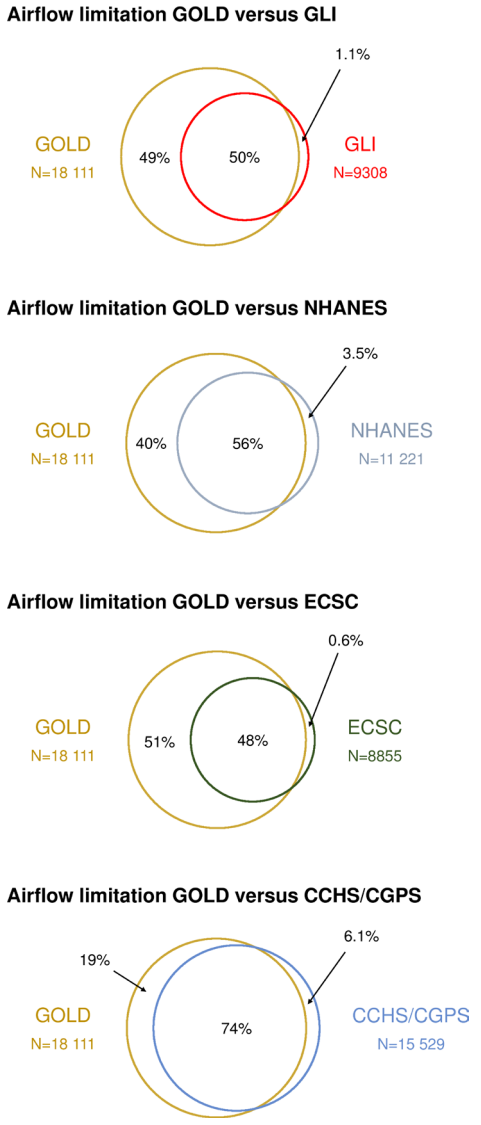

Figure 3 Overlap between individuals in the general population diagnosed with airflow limitation according to different criteria. Based on 108 246 individuals from the CGPS. CCHS, Copenhagen City Heart Study; CGPS, Copenhagen General Population Study; ECSC, European Coal and Steel Community; GLI, Global Lung Initiative; GOLD, Global Initiative for Chronic Obstructive Lung Disease; NHANES, National Health and Nutrition Examination Survey.

In contrast, predictive capability for risk of respiratory mortality and all-cause mortality was slightly lower for GOLD compared with the four LLN criteria (all p values<0.05). However, the differences in Harrells' C statistic were small.

Discordance between GOLD and four LLN criteria

Among individuals diagnosed with airflow limitation according to GOLD (corresponding to n=18 111), 50% also fulfilled the diagnosis of airflow limitation according to GLI (n=9105); however, GLI only identified an additional 1.1% with airflow limitation (n=203) (figure 3). When GOLD was compared with the other three LLN criteria, corresponding proportions were 56% (n=10 565) and 3.5% (n=656) for NHANES, 48% (n=8745) and 0.6% (n=110) for ECSC, and 74% (n=14 361) and 6.1% (n=1168) for CCHS/CGPS.

A direct comparison of GOLD with each of the four LLN criteria showed that individuals with airflow limitation according to GOLD but not LLN criteria had increased risk of COPD exacerbations, respiratory mortality and all-cause mortality (figure 4). For the four LLN criteria, only NHANES and CCHS/CGPS identified additional individuals at risk of COPD exacerbations, respiratory mortality and/or all-cause mortality independent from GOLD.

Compared with individuals without airflow limitation according to GOLD or the four LLN criteria, individuals with airflow limitation according to GOLD but not each of the four LLN criteria were older with higher tobacco consumption and higher prevalence of chronic respiratory symptoms (table 2). Correspondingly, individuals with airflow limitation according each of the four LLN but not GOLD criteria were younger with higher prevalence of asthma and chronic respiratory symptoms. Interestingly, while those identified with airflow limitation according to GOLD but not each of the four LLN criteria had lower lung function, those identified with airflow limitation according each of the four LLN but not GOLD criteria were predominantly female.

Discordance between four LLN criteria

A direct comparison of the four LLN criteria showed that GLI identified individuals at risk of COPD exacerbations and all-cause mortality independent from ECSC and *vice versa*, but not independent from NHANES or CCHS/CGPS (online supplementary figure S3). NHANES identified individuals at risk of COPD exacerbations, respiratory mortality and all-cause mortality independent from GLI and ECSC, but not independent from CCHS/CGPS. Finally, CCHS/CGPS identified individuals at risk of COPD exacerbations, respiratory mortality and all-cause mortality independent from GLI, NHANES and ECSC.

Age-stratified and other subgroup analyses

Stratified by age, the prevalence of airflow limitation was 6.7% according to GOLD, 6.6% according to GLI, 8.2% according to NHANES, 5.4% according to ECSC, and 9.4% according to CCHS/CGPS for those aged <50 years, and 21% according to GOLD, 9.5% according to GLI, 11% according to NHANES, 9.4% according to ECSC and 16% according to CCHS/CGPS for those aged ≥50 years (figure 5, upper panel). Risk of COPD exacerbations, respiratory mortality and all-cause mortality were similar in individuals <50 years and ≥50 years (figure 5, middle and lower panels). The differences in Harrells' C statistic were again small; although, with lower statistical power (online supplementary figure S2, middle and lower panels).

Results were similar in a more clinically defined study population, that is, current and former smokers reporting at least one chronic respiratory symptom in the form of dyspnoea, chronic mucus hypersecretion, wheezing and/or cough (compare figure 4 and online supplementary figure S3 with online supplementary figures S4 and S5). Risk estimates were comparable between the different airflow limitation criteria in those with low versus high tobacco consumption and in those with versus without chronic respiratory symptoms (compare figure 1 with online supplementary figures S6 and S7). Results were also similar when individuals with asthma were excluded (compare figure 4 and figure S3 with online supplementary figures S8 and S9).

DISCUSSION

Using a large Danish contemporary population-based cohort with 108 246 randomly sampled individuals with prebronchodilator

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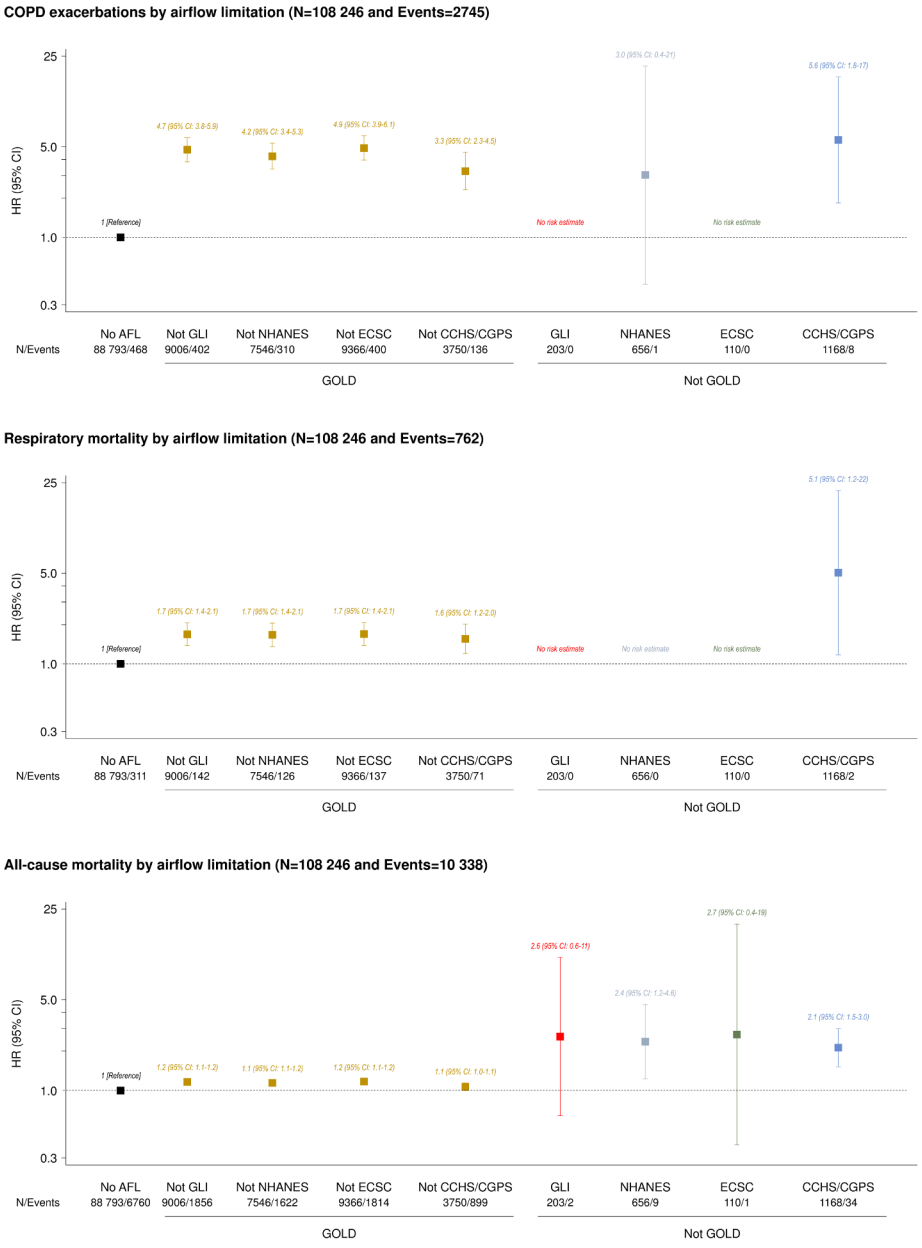

Figure 4 Direct comparison of GOLD with four LLN criteria to identify individuals in the general population at risk of COPD exacerbations and mortality. Risk estimates obtained from Cox proportional regression models adjusted for age and sex. Number of individuals are relative to GOLD. The reference group consisted of individuals without airflow limitation according to GOLD and four LLN criteria. Based on 108 246 individuals from the CGPS. AFL, airflow limitation; CCHS, Copenhagen City Heart Study; CGPS, Copenhagen General Population Study; ECSC, European Coal and Steel Community; GLI, Global Lung Initiative; GOLD, Global Initiative for Chronic Obstructive Lung Disease; LLN, lower limit of normal; NHANES, National Health and Nutrition Examination Survey.

spirometry, we found that prevalence of airflow limitation ranged from 8% to 17% using GOLD and four different LLN criteria; however, identified individuals with the five different criteria had similar risk of COPD exacerbations and mortality. Among LLN criteria, locally derived criteria seem optimal for identifying high-risk individuals. To our knowledge, this is the first study investigating differences between four LLN criteria relative to GOLD criteria for predicting clinical outcomes of COPD.

Based on current evidence, using a fixed ratio for the diagnosis of clinical COPD in the presence of symptoms and exposure seems reasonable, as individuals diagnosed with airflow limitation according to fixed ratio but not LLN experienced an increased risk of COPD exacerbations and mortality, as shown in the present study and in another recent study.[25 26] In addition, these individuals seem to have clinical findings compatible with COPD.[27 28] Thus, choosing LLN instead of fixed ratio for the diagnosis of airflow limitation among older individuals may lead to potential underdiagnosis of an important clinical group of COPD that will likely benefit from preventive treatment. Nonetheless, it may be prudent—or even necessary—to combine LLN with fixed ratio among younger individuals, as some individuals with clinically relevant respiratory disease would be overlooked using fixed ratio alone.[8]

GOLD criteria yielded slightly lower risk estimates for COPD exacerbations and mortality compared with the four LLN criteria.

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Table 2 Baseline characteristics according to discordant clinical groups of airflow limitation by using GOLD relative to the four LLN criteria in individuals in the general population*

		GOLD				Not GOLD			
	No AFL n=88 793	Not GLI n=9006	Not NHANES n=7546	Not ECSC n=9366	Not CCHS/CGPS n=3750	GLI n=203	NHANES n=656	ECSC n=110	CCHS/CGPS n=1168
General characteristics									
Age – years	56.5 (47.2–65.8)	69.8 (63.0–76.5)	70.3 (63.7–77.0)	68.5 (61.2–75.7)	73.2 (67.2–79.3)	34.6 (27.0–40.5)	41.8 (34.7–45.1)	35.1 (27.0–40.3)	45.3 (41.1–49.9)
Men – no. (%)	39 531 (45)	4823 (54)	4394 (58)	5228 (56)	1481 (39)	52 (26)	68 (10)	11 (10)	485 (42)
Body mass index – kg/m^2	25.7 (23.3–28.5)	25.4 (23.2–28.1)	25.5 (23.3–28.1)	25.4 (23.2–28.1)	25.2 (23.0–27.8)	24.0 (21.9–26.4)	23.7 (21.7–26.2)	23.4 (21.8–26.1)	24.6 (22.5–27.3)
FEV_1 – L	3.04 (2.51–3.67)	2.38 (1.91–2.95)	2.41 (1.92–3.00)	2.45 (1.95–3.04)	2.23 (1.81–2.75)	3.06 (2.75–3.58)	2.99 (2.71–3.35)	3.00 (2.72–3.36)	2.98 (2.58–3.53)
FVC – L	3.84 (3.19–4.62)	3.54 (2.85–4.39)	3.57 (2.85–4.44)	3.62 (2.90–4.50)	3.25 (2.66–4.02)	4.33 (3.87–5.02)	4.18 (3.77–4.67)	4.25 (3.83–4.74)	4.19 (3.61–4.98)
FEV_1/FVC	0.79 (0.75–0.83)	0.68 (0.66–0.69)	0.68 (0.67–0.69)	0.68 (0.66–0.69)	0.69 (0.68–0.69)	0.71 (0.70–0.72)	0.71 (0.70–0.72)	0.71 (0.70–0.71)	0.71 (0.70–0.71)
Current smokers – no. (%)	13 148 (15)	1966 (22)	1613 (21)	2131 (23)	622 (17)	41 (20)	143 (22)	23 (21)	319 (27)
Former smokers – no (%)	35 287 (40)	4463 (50)	3781 (50)	4543 (49)	1893 (50)	55 (27)	211 (32)	28 (25)	378 (32)
Tobacco consumption – pack-years†	14.0 (5.0–27.0)	24.0 (10.5–40.0)	24.0 (10.5–40.0)	23.6 (10.7–40.0)	20.0 (8.5–36.4)	8.1 (4.0–16.3)	10.5 (4.0–19.5)	7.0 (4.0–12.8)	15.7 (6.0–27.0)
Clinical characteristics									
Airway medication use – no. (%)	3632 (4)	806 (9)	646 (9)	850 (9)	270 (7)	17 (8)	47 (7)	9 (8)	95 (8)
Asthma – no. (%)	4689 (5)	783 (9)	630 (8)	847 (9)	254 (7)	33 (16)	86 (13)	18 (16)	146 (13)
Symptoms									
Dyspnoea – no. (%)	25 817 (29)	3614 (40)	2984 (40)	3676 (39)	1546 (41)	61 (30)	216 (33)	32 (29)	373 (32)
mMRC ≥2 – no. (%)	5954 (7)	1179 (13)	994 (13)	1165 (12)	544 (15)	7 (3)	27 (4)	4 (4)	58 (5)
Chronic mucus hypersecretion – no. (%)	6347 (7)	1257 (14)	1073 (14)	1305 (14)	464 (12)	19 (9)	47 (7)	8 (7)	120 (10)
Wheezing – no. (%)	12 680 (14)	1897 (21)	1570 (21)	2044 (22)	647 (17)	57 (28)	162 (25)	30 (27)	308 (26)
Cough – no. (%)	9375 (11)	1205 (13)	977 (13)	1289 (14)	413 (11)	43 (21)	126 (19)	23 (21)	231 (20)
Any symptom – no. (%)	34 952 (39)	4671 (52)	3893 (52)	4837 (52)	1898 (51)	106 (52)	331 (50)	56 (51)	579 (50)
Number of acute bronchitis/pneumonia episodes in the last 10 years									
None – no. (%)	69 895 (79)	6608 (73)	5582 (74)	6900 (74)	2737 (73)	153 (75)	477 (73)	82 (75)	869 (74)
1–5 – no. (%)	17 613 (20)	2150 (24)	1777 (24)	2217 (24)	931 (25)	47 (23)	164 (25)	26 (24)	281 (24)
≥6 – no. (%)	1285 (1)	248 (3)	187 (2)	249 (3)	82 (2)	3 (1)	15 (2)	2 (2)	18 (2)
Number of GP visits in the last 12 months									
None – no. (%)	19 132 (22)	1500 (17)	1282 (17)	1635 (17)	608 (16)	37 (18)	122 (19)	22 (20)	267 (23)
Once – no. (%)	20 404 (23)	1645 (18)	1364 (18)	1758 (19)	617 (16)	46 (23)	151 (23)	27 (25)	294 (25)
Twice or more – no. (%)	49 257 (55)	5861 (65)	4900 (65)	5973 (64)	2525 (67)	120 (59)	383 (58)	61 (55)	607 (52)

*Data presented as median (25th and 75th percentiles), or number (%). Number of individuals are relative to GOLD. Numbers may not sum to 100% due to rounding. No AFL consists of individuals without AFL according to GOLD and four LLN criteria.
†Only for current and former smokers.
AFL, airflow limitation; CCHS, Copenhagen City Heart Study; CGPS, Copenhagen General Population Study; ECSC, European Coal and Steel Community; GLI, Global Lung Initiative; GOLD, Global Initiative for Chronic Obstructive Lung Disease; GP, general practitioner; LLN, lower limit of normal; mMRC, modified Medical Research Council Dyspnoea Scale; NHANES, National Health and Nutrition Examination Survey.;

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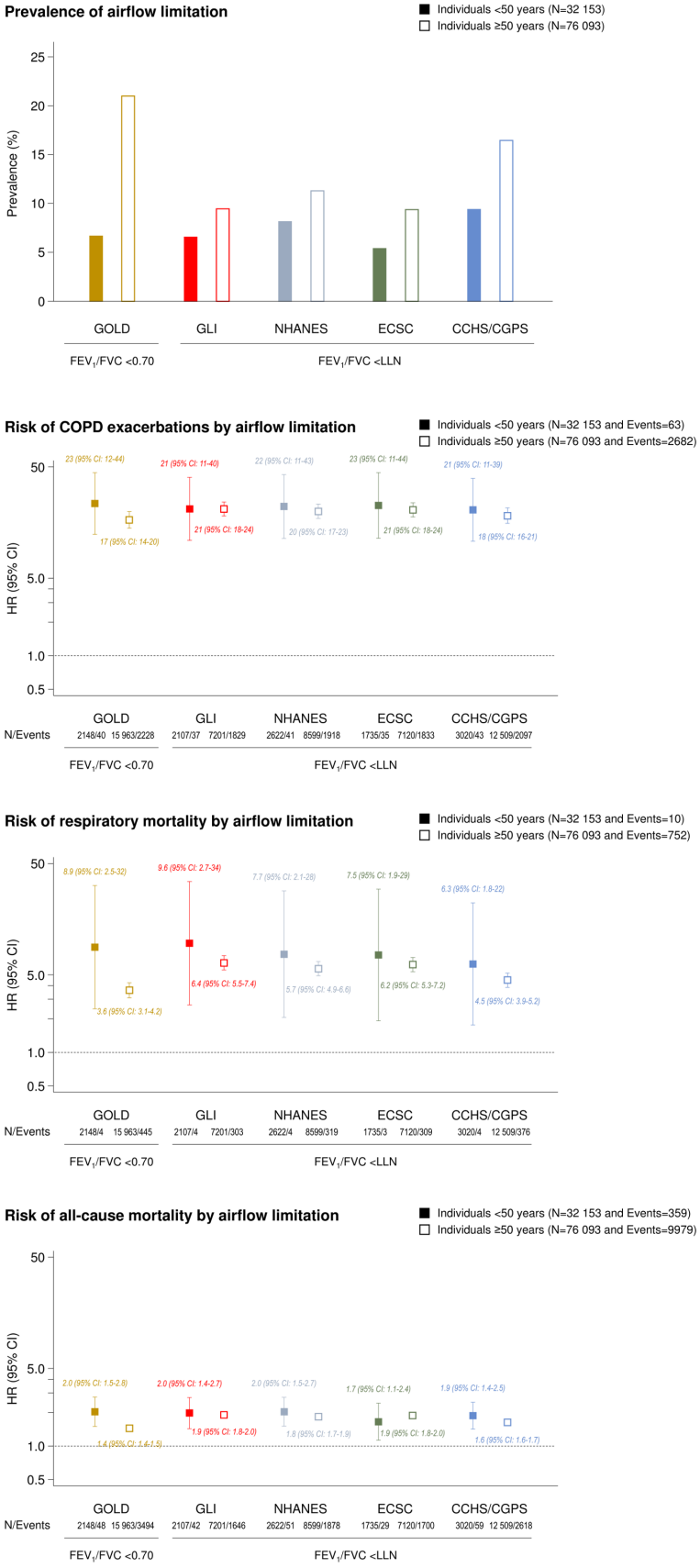

Figure 5 Age-stratified prevalence of airflow limitation and risk of COPD exacerbations and mortality by airflow limitation using different criteria in individuals in the general population. Risk estimates obtained from Cox proportional regression models adjusted for age and sex. Based on 108 246 individuals from the CGPS. CCHS, Copenhagen City Heart Study; CGPS, Copenhagen General Population Study; ECSC, European Coal and Steel Community; GLI, Global Lung Initiative; GOLD, Global Initiative for Chronic Obstructive Lung Disease; LLN, lower limit of normal; NHANES, National Health and Nutrition Examination Survey.

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A potential explanation may be that the difference in lung function impairment and symptoms between those with and without airflow limitation is less pronounced by using GOLD instead of the LLN criteria; that is, GOLD may include more individuals with mild disease especially in older individuals compared with LLN. However, comparison of the discriminative accuracy for risk of COPD exacerbations and mortality between GOLD and the four LLN criteria showed small and no clinically important difference. Also, as already mentioned, using LLN criteria in older individuals may lead to potential underdiagnosis.

Interestingly, the prevalence of airflow limitation varied from 8% to 14% between the different LLN criteria. During follow-up, individuals diagnosed with airflow limitation according to CCHS/CGPS but not from GLI, NHANES and ECSC had an increased risk of COPD exacerbations, respiratory mortality and all-cause mortality compared with those with normal lung function according to all four LLN criteria, suggesting presence of clinically important COPD. In contrast, individuals diagnosed with airflow limitation according to GLI, NHANES or ECSC and independent from CCHS/CGPS did not differ prognostically compared with those with normal lung function. Thus, the locally derived LLN criteria seem to be better at identifying high-risk individuals with COPD compared with the other three LLN criteria. It is also noteworthy that the largest overlap with GOLD of those with airflow limitation was for CCHS/CGPS with 74%, as opposed to the other three LLN criteria with 48%–56% overlap. This suggests that the locally derived LLN criteria approximate more nearly to GOLD, which can also be observed both when determining prevalence of airflow limitation and risk of COPD exacerbations and mortality. Increase in prevalence of airflow limitation with age can be physiologically explained by the normal age-related decline of FEV_1. Since GOLD uses a fixed ratio as a cut-off for airflow limitation for all age groups, we witness a higher increase in the prevalence using GOLD as opposed to the four LLN criteria.

Previous studies have observed discrepancies between different lung function reference equations when comparing predicted values and prevalence of airflow limitation according to LLN.[29–34] In a clinical setting, Quanjer and colleagues observed that NHANES overestimated the LLN lung function in adults aged 20–90 years compared with GLI and ECSC, while ECSC underestimated compared with GLI and NHANES until age 70 years.[34] In addition, GLI had the steepest decline in FEV_1/FVC compared with NHANES and ECSC.[30 34] Interestingly, similar results could be observed in the present study in a general population setting, suggesting that calibration issues need to be considered before implementing lung function reference equations for defining airflow limitation according to LLN.

Strengths of the present study include a large contemporary population-based cohort with 108 246 randomly selected individuals without any losses to follow-up, and with information on clinically relevant prognostic outcomes of COPD.

A limitation of the present study is the lack of postbronchodilator spirometry preventing us from classifying the subtype of airflow limitation.[35] Thus, some may have reversible airflow limitation suggesting asthma, and some may have irreversible airflow limitation suggesting COPD or asthma-COPD overlap. Nonetheless, in sensitivity analyses, results were similar in a more clinically defined study population where the majority would be expected to have COPD or asthma-COPD overlap.[36] In addition, acute emergency department visit and/or hospitalisation with a primary diagnosis of COPD in the national Danish Patient Registry has previously been shown to have a high positive predictive value of 92% for the diagnosis of COPD.[37] It is also reassuring to know that even prebronchodilator airflow limitation was associated with important COPD-related outcomes irrespective of the applied criterion. However, a single spirometric assessment may not be reliable for diagnosing COPD in individuals with mild to moderate airflow obstruction.[38]

Another potential limitation is that we have only investigated severe exacerbations of COPD that require emergency department visits and/or hospitalisations. Thus, mild to moderate exacerbations of COPD that are only treated at home with use of reliever medications and/or at the general practitioner's office will be undetected.

Furthermore, since an exacerbation is a clinical diagnosis very much relying on the treating medical doctor, and the criteria used for the diagnosis and treatment in individual patient cases are unknown, we cannot exclude potential misclassification. To reduce potential misclassification, we have deliberately only chosen primary discharge diagnoses with COPD as events. However, as the majority of individuals with COPD is undiagnosed, as previously reported in the Copenhagen General Population Study,[11] we believe that such a misclassification likely will be non-differential and therefore bias towards the null-hypothesis.

Another potential limitation is that we only studied white individuals and may be limited in generalisability to other ethnicities. Lastly, we had a response rate of 43%, and since responders compared with non-responders were younger, we have likely underestimated the prevalence of airflow limitation and risk of clinical outcomes of COPD.

Clinical implications of the present study relate to diagnosis of airflow limitation. Airflow limitation according to LLN in early adulthood has been suggested to identify susceptible individuals at risk of developing COPD later in life.[3] Choosing inappropriate lung function reference equations could misclassify individuals with early airflow limitation and close a window of opportunity for preventive measures.

In conclusion, prevalence of airflow limitation ranged from 8% to 17% using GOLD and four different LLN criteria; however, identified individuals with the five different criteria had similar risk of COPD exacerbations and mortality. Among LLN criteria, locally derived criteria seem optimal for identifying high-risk individuals.

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Contributors YÇ and SA had full access to all data in the study and had final responsibility for the decision to submit for publication. YÇ, BGN, JV, PL and SA contributed to the study concept and design. YÇ, BGN, JV, PL and SA collected, analysed or interpreted the data. YÇ did the statistical analyses and wrote the draft manuscript. YÇ, BGN, JV, PL and SA revised the manuscript for important intellectual content. BGN obtained funding. BGN provided administrative, technical or material support. BGN and SA supervised the study. All authors have read and approved the final manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Patient consent for publication Not required.

Ethics approval The study was approved by Herlev and Gentofte Hospital and a regional ethics committee (approval number: H-KF-01-144/01) and was conducted according to the Declaration of Helsinki.

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Data availability statement Data are available upon reasonable request. Summarised data and scripts for analyses are available according Danish law.

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