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Treatable Traits in Misdiagnosed Chronic Obstructive Pulmonary Disease: Data from the Akershus Cardiac Examination 1950 Study

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is often misdiagnosed. We aimed to estimate the prevalence of misdiagnosed COPD in middle-aged Norwegians, and to assess potentially treatable clinical traits in over- and undiagnosed individuals.

Methods and Findings: The Akershus Cardiac Examination (ACE) 1950 Study is a population-based study of the 1950 birth cohort of Akershus county including 3706 participants aged 62-65 years at baseline. COPD was defined as a forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) ratio<lower limit of normal (LLN). Misdiagnosed COPD was defined according to self-reported COPD.

A total of 259 (7.1%) participants had spirometry confirmed COPD. Of these, only 72 (28%) reported having COPD, thus 187 (72%) were undiagnosed. A total of 92 (2.5%) of the 164 particpants who reported having COPD had an FEV_1/FVC ratio≥LLN and were overdiagnosed. They had lower lung function, and more respiratory symptoms, self-reported asthma, eosinophils, and sleep apnea than other non-COPD participants . The main predictor of being overdiagnosed was overweight. Spirometry in participants reporting wheezing or cough and current smokers or participants with ≥20 tobacco pack-year history would have identified 85% of the undiagnosed cases.

Conclusion: Both over- and underdiagnosis of COPD is frequent. Undiagnosed individuals have better lung function and less symptoms, but similar prevalence of comorbidities and systemic inflammation. Overdiagnosed individuals have treatable traits including asthma, eosinophilic inflammation, and sleep apnea. The main predictor of being overdiagnosed was being overweight.

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This article has an online data supplement

Introduction

Chronic obstructive pulmonary disease (COPD) is currently the fourth leading cause of death worldwide and a major cause of chronic morbidity.[1,2] The disease is preventable and treatable, but misdiagnosis is common.[3-5] Current guidelines advocate spirometry in individuals with respiratory symptoms, a history of risk factors for the disease, and/or recurrent lower respiratory tract infection.[2,6] The diagnostic criteria of COPD is irreversible airflow limitation defined as a forced expiratory volume during 1 second (FEV_1) to forced vital capacity (FVC) ratio<0.70 or below the lower limit of normal (LLN). However, population-based samples suggest that 60%-86% of COPD patients remain undiagnosed, while 30%-50% are overdiagnosed.[3,5]

The undiagnosed group is described as having better lung function and fewer respiratory symptoms than individuals with diagnosed COPD, but with an increased risk of death compared to individuals without airflow limitation.[3,7-11] Overdiagnosis in COPD has been less studied. A population-based study reported that 50% of participants with self-reported COPD did not have irreversible airflow limitations,[4] while studies from primary care suggest that one-third to one-half of patients with a COPD diagnosis have been overdiagnosed.[4,5] Overdiagnosed individuals may receive inappropriate medication and have increased use of health services.[4,5,8,12]

Beyond a reduced FEV_1/FVC, other clinical characterizations based on risk factors, symptoms, and imaging may increase precision in diagnostics and treatment of COPD.[13-15,16] Phenotyping misdiagnosed COPD patients by assessing their treatable traits may help to optimize case-finding strategies and improve knowledge to better address this large group.[17-21]

Accordingly, the aims of the present study were to estimate the prevalence of over- and undiagnosed COPD in a middle-aged Norwegian population and to assess treatable traits in these groups. We also assessed diagnostic strategies for case finding based on our data.

Materials and Methods

Design and Data Sources

The ACE 1950 Study is a longitudinal cohort study of the 1950 birth cohort residing in Akershus County, Norway.[22] The baseline visit was conducted between January 2012 and May 2015 with participants aged 62-65 years. It was designed to investigate the development of cardiovascular and other related diseases in the general population.[22] The 1950 birth cohort had previously participated in a national population-based health examination survey, the Age 40 Program, conducted by the National Health Screening Service.[23] The ACE 1950 study and linkage of data from the Age 40 Program was approved by the Regional Ethical Committee of Southeastern Norway (2011/1475). All participants gave written, informed consent.

Participants

All inhabitants of Akershus County registered as residents according to the Norwegian National Registry as of November 2011 and born in 1950 (n=5827) were eligible for participation in the ACE 1950 Study. The participant flow in the ACE 1950 Study and the spirometry examinations are shown in Figure 1. In total, 3706 individuals (64% of the eligible, 51.2% male) signed an informed consent and participated in the study. Extensive information regarding the recruitment of participants and the data collection in the baseline

Figure 1. Participant Flow and Spirometry Examinations in the Akershus Cardiac Examination 1950 Study
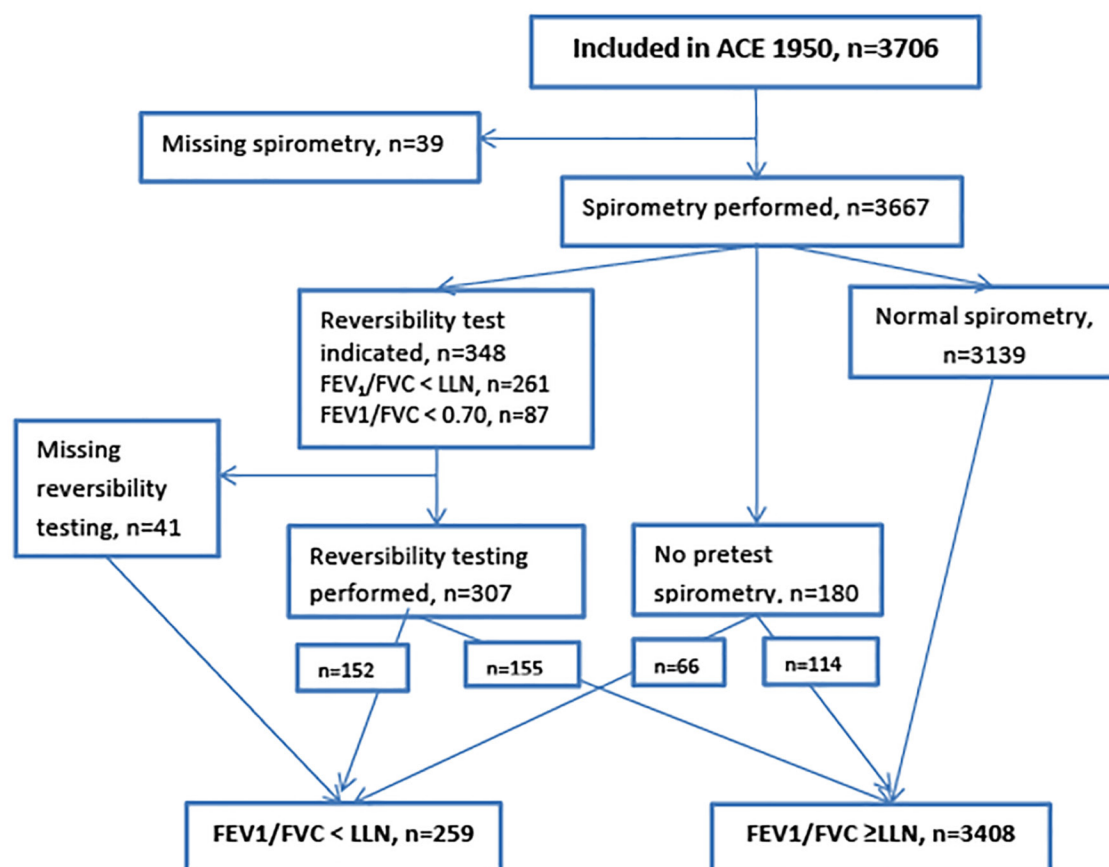
ACE=Akerhus Cardiac Examination; FEV$_1$=forced expiratory volume in 1 second; FVC= forced vital capacity; LLN=lower limit of normal

ACE 1950 Study visit has previously been reported.[22] In total, n=2742 (74%) of the participants in ACE 1950 had previously participated in the Age 40 Program.[24]

Data Collection in the ACE 1950 Study

The ACE 1950 Study was conducted at 2 hospitals located in Akershus County: Akershus University Hospital and Vestre Viken Hospital Trust, Bærum Hospital. The study personnel at both sites received the same training for the examination procedures.

Spirometry

For measurement of lung function, a dry bellow spirometer (Vitalograph Alpha III) was used in accordance with the

European Respiratory Society/American Thoracic Society recommendations.[25] Calibrations were performed daily, including registration of temperature and atmospheric pressure in the laboratory. A supervising pulmonologist (VS) performed the theoretical and practical training of all personnel conducting spirometry. The quality of the spirometry efforts was assessed consecutively by readings of the printed volume/time curve by the personnel conducting the spirometry.

Participants were seated, wore nose clips, and completed 3 consecutive performances of full inspiration followed by forced expiration for a minimum of 6 seconds while receiving instructions from the technician. The FEV$_1$ and FVC were registered by manual readings on the printed time-volume curves, as the best of the 3 performances. If the 2 best performances varied by

>150ml or 5%, further performances were attempted until the 2 best performances varied by <150ml or 5%. Lung volumes were converted to body temperature and pressure saturated volumes.[26,27]

By protocol, there were no exclusion criteria for spirometry. Registered explanations for not performing spirometry (n=39, 1.1%) included technical difficulties (equipment or patient related, n=6), medical reasons (including cough, facial paralysis, rib fracture, epistaxis, jaw surgery, Alzheimer's disease, syncope, n=13), refusal to perform (n=2), or unknown (n=18). All current analysis included only participants with valid spirometry (n=3667).

Administration of inhaled medication on the day of examination was registered. If any short-acting or long-acting beta-adrenergic or muscarine receptor blockers had been inhaled within 4 hours, lung function measurements were considered post-bronchodilatory (bronchodilation [BD]).

All participants with pre-BD FEV_1/FVC<lower limit of normal (LLN) according to the European Coal and Steel Company (ECSC) reference values were offered reversibility test by 0.4mg salbutamol on an inhalation chamber. New spirometries were performed within 30 minutes following drug administration and the best of the repeated performances was registered as post-BD lung function.

We performed a double reading of the spirometry results on a randomized sample of 125 participants. Cohen's κ was run to determine if there was agreement between the 2 readings in categorizing FEV_1/FVC<LLN. We found an acceptable agreement between the 2 rater judgements (κ=0.873, 95% confidence interval [CI] 0.77–0.98, p<0.001).

Demographic and Medical History and Clinical Examination

The participants answered a questionnaire, either electronically or as a printed version. The questions that participants received were previously used in other Norwegian population-based cohorts, i.e., the Age 40 Program[23] and the Trøndelag Health Study.[28] Self-reported obstructive pulmonary disease was assessed by the question "Have you ever been diagnosed with asthma, chronic bronchitis, or COPD/emphysema?" and "If yes, which diagnosis" with asthma, chronic bronchitis, and COPD/emphysema as alternative answers. Chronic bronchitis and COPD/emphysema were both interpreted as COPD. Respiratory symptoms were assessed by unique questions regarding regular cough, expectorate, and/or wheezing. Self-reported dyspnea was evaluated by the modified Medical Research Council dyspnea scale (mMRC). Coronary artery disease was defined as self-reported history of myocardial infarction or revascularization procedure. Atrial fibrillation was defined as self-reported disease or atrial fibrillation on electrocardiogram (ECG) at inclusion and was validated by re-evaluation of ECG and investigation of patient records.[29] History of heart failure and obstructive sleep apnea was self-reported. Diabetes was defined as self-reported diagnosis, use of anti-diabetic medication, or both elevated fasting blood glucose (≥7.0mmol/L) and a hemoglobinA1c (≥6.5%).[29] We measured arterial blood pressure, weight, and height, and calculated body mass index (BMI). Hypertension was defined as blood pressure ≥140mmHg systolic and/or ≥90mmHg diastolic and/or use of antihypertensive medication. Self-reported physical activity level was evaluated by a previously validated physical activity index (PAI) and deconditioning was defined as PAI 0 (no physical activity) or 1 (low physical activity).[28] All current medication was registered, and participants were asked if they had been treated with antibiotics for bronchitis or pneumonia during the last 3 years.

Tobacco History

Tobacco consumption was registered in both ACE 1950 and in the Age 40 Program as current daily, former, or never smoking. Current or previous daily number of cigarettes (or cigarillos), and time point for start and quitting was registered. For former smokers in ACE 1950 who reported a lower cumulative tobacco exposure in ACE 1950 than in the Age 40 Program, their report from the Age 40 Program was used in the present analyses. For current smokers in ACE 1950 who reported a lower cumulative tobacco exposure in ACE 1950 than in the Age 40 Program, their report from the Age 40 Program was added to estimated pack years between the Age 40 Program and ACE 1950 based on their report from ACE 1950. Finally, participants in ACE 1950 claiming to be never smokers who responded as current or former smokers in the Age 40 Program were recoded as former smokers in ACE 1950.

Blood Sampling and Laboratory Analyses

Fasting venous blood samples were obtained during the examination day. Hematological analyses were performed by standard automatic cell counts on the same day, and the number of eosinophil cells/µl was registered. Systemic inflammation was assessed by C-reactive protein (CRP) (Vitros 5.1 FS, Ortho Clinical Diagnostics, Raritan, New Jersey,). Detection limits for CRP were changed during the conduct of the study (3mg/L, 2.9mg/L, and 1mg/L). We used a cutoff of CRP≥3mg/L (the highest detection limit throughout the study) to address the issue of elevated CRP as a marker of systemic inflammation.

Defining COPD and Treatable Traits

We defined COPD as post-BD FEV_1/FVC ratio below the LLN according to ECSC reference values; FEV_1/FVC ratio <0.64 for men and <0.66 for women.[27] We did not include respiratory symptoms as obligatory for the COPD diagnosis. Many patients with established respiratory disease had already taken their medication on the day of examination and their spirometries were considered post-BD. Undiagnosed COPD was defined as spirometry-confirmed COPD at the ACE 1950 visit without self-reported history of COPD. Overdiagnosed COPD was defined as self-reported COPD and a spirometry within normal limits at the ACE 1950 visit. During the conduction of ACE 1950, a new set of reference values from the Global Lung Initiative (GLI) 2012 was established. Accordingly, we performed sensitivity analyses applying the GLI 2012 reference values.[30]

We assessed clinical characteristics as traits relevant to evaluation and treatment of chronic airway disease.[16,17,31] Pulmonary traits included lung function, eosinophilic inflammation (blood eosinophil cell count≥300/µL), respiratory symptoms (dyspnea, cough, sputum, and wheezing), and prevalence of exacerbations (lower airway infections requiring treatment with antibiotics the last 3 years). Extrapulmonary traits included inactivity/low physical activity (PAI 0 or 0.05–1.50), obesity (BMI≥30 kg/m^2), underweight (BMI<18kg/m^2),[32] systemic inflammation (CRP≥3mg/L), and comorbidities including coronary artery disease, heart failure, atrial fibrillation, hypertension, obstructive sleep apnea, and diabetes mellitus. Among modifiable life-style factors, we assessed current and cumulative tobacco exposure.

Statistical Analyses

Comparisons of clinical characteristics between groups were performed by chi-square tests, Fisher's exact test, t-tests or Mann-Whitney U tests and one-way analysis of variance analysis as appropriate. A significance level of 0.01 was used due to multiple comparisons. Univariate logistic regression was applied to determine associations between clinical characteristics and the presence of undiagnosed COPD. Variables that were significantly associated with undiagnosed COPD in univariate analyses were included in the multivariable logistic regression model. Sex was predetermined to be included in the multivariable analysis, but age was not included as all participants were from the same birth cohort. The diagnostic accuracy for undiagnosed COPD was assessed by receiver operating statistics' area under the curve (ROC-AUC). Separate AUCs were made for respiratory symptoms (dyspnea, cough, wheezing, sputum), current smoking, ≥20 pack-year history of tobacco use, and the use of antibiotics for respiratory infection during the last 3 years. Combinations of the individual variables with the highest AUCs were also examined and compared to a best-fit curve provided from the logit probabilities (optimal statistical model) from the final multivariable analysis. Finally, to assess the clinical utilities of early case finding strategies, 2x2 tables with previously undiagnosed COPD as the outcome were made to calculate the sensitivity, specificity, spirometries needed to detect 1 case (proportion of cases in screening positive), and the number of cases not detected. All statistical analyses in the present study have been performed in Statistical Package of Social Science 22 or STATA/SE 14.2.

Results

Baseline Characteristics

A total of 259 participants (7.1%) had a post-BD FEV_1/FVC ratio below LLN. Only 72 of these 259 participants (28.0%) reported a previously recognized COPD diagnosis, while 187 (72.2%) were undiagnosed. A total of 164 participants (4.5%) reported a history of COPD, of which 92 participants (56.1%) did not have post-BD $FEV_1/FVC<LLN$. Demographic and clinical characteristics of the study population according to the presence of correctly diagnosed, undiagnosed, and overdiagnosed COPD are presented in Table 1. All 3 groups had more current smokers, a higher cumulative tobacco exposure, lower lung function, more respiratory symptoms,

Table 1. Clinical Characteristics of The Akershus Cardiac Examination 1950 Population in Total and According to the Presence of Correctly Diagnosed, Over-, and Undiagnosed COPD

	Total n=3667	No COPD ($FEV_1/FVC \geq LLN$ and No Self-reported COPD) n=3316	Correctly Diagnosed COPD ($FEV_1/FVC < LLN$ and Self-reported COPD) n=72	Undiagnosed COPD ($FEV_1/FVC < LLN$ and No Self-reported COPD) n=187	Overdiagnosed COPD ($FEV_1/FVC \geq LLN$ but Self-reported COPD) n=92
Sex, %					
Male	51.3	51.6	51.4	48.1	46.7
Activity					
Inactive	682 (18.6)	589 (18.1)	26 (37.1)[a]	49 (26.5)[a]	18 (20.2)
Low	706 (19.3)	638 (19.7)	12 (17.1)	36 (19.5)	20 (22.5)
Medium	1445 (39.4)	1318 (40.6)	24 (34.3)	75 (40.5)	28 (31.5)
High	757 (20.6)	701 (21.6)	8 (11.4)	25 (13.5)[a]	23 (25.8)
Anthropometric Data					
BMI, kg/m^2, mean (SD)	27.2 (4.4)	27.2 (4.4)	26.3 (5.2)	25.6 (4.6)[a]	27.9 (4.02)
<25 (n=1187)	1187 (32.4)	1056 (31.8)	28 (38.9)	84 (44.9)[a]	19 (20.7)
25–29.9 (n=1650)	1650 (45.0)	1498 (45.2)	27 (37.5)	77 (41.2)	48 (52.2)
≥30 (n=830)	830 (22.6)	762 (23.0)	17 (23.6)	26 (13.9)[a]	25 (27.2)
WHR	0.92 (0.10)	0.91 (0.10)	0.95 (0.10)[a]	0.92 (0.10)	0.93 (0.09)
Smoking History, (%)					
Never	1279 (33.7)	1245 (37.5)	2 (2.8)[a]	13 (7.0)[a]	19 (20.7)[a]
Current	526 (14.3)	391 (11.8)	27 (37.5)[a]	90 (48.1)[a]	18 (19.6)
Former	1683 (45.9)	1518 (45.8)	39 (54.2)	75 (40.1)	51 (55.4)
≥20 pack years	917 (25.6)	713 (22.1)	59 (81.9)[a]	99 (55.0)[a]	46 (50.0)[a]
Lung Function, mean (SD)					
FEV_1, L	3.10 (0.79)	3.18 (0.75)	1.94 (0.74)[a]	2.34 (0.75)[a]	2.78 (0.76)[a]
FVC, L	4.20 (1.02)	4.23 (1.01)	3.64 (1.08)[a]	4.04 (1.16)	3.89 (1.09)[a]
FEV_1/FVC	0.74 (0.07)	0.75 (0.05)	0.53 (0.10)[a]	0.58 (0.06)[a]	0.72 (0.06)[a]
FEV_1, % of Predicted	108.5 (19)	111.2 (16.6)	70.0 (21.5)[a]	82.5 (19.6)[a]	97.3 (16.4)[a]
FVC, % of Predicted	119.1 (18.3)	119.9 (17.8)	104.9 (20.3)[a]	115.5 (21.5)[a]	110.3 (17.6)[a]
Symptoms of Respiratory Disease, %					
mMRC≥2	214 (6.0)	152 (4.8)	29 (41.4)[a]	16 (8.6)	17 (19.1)[a]
Cough	795 (21.4)	621 (19.3)	40 (56.3)[a]	79 (43.2)[a]	45 (50.6)[a]
Sputum	519 (14.2)	383 (12.0)	43 (60.6)[a]	52 (29.2)[a]	41 (46.6)[a]
Wheezing	400 (10.9)	265 (8.3)	40 (56.3)[a]	59 (32.6)[a]	36 (41.1)[a]
One or More Respiratory Symptoms	1163 (31.7)	930 (29.1)	61 (85.9)[a]	111 (60.0)[a]	61 (68.5)[a]
Respiratory Infections, n (%)					
Antibiotics for Lower Respiratory Tract Infection in Last 3 Years	656 (17.9)	504 (15.6)	42 (59.2)[a]	68 (37.0)[a]	42 (46.7)[a]
Medical History, %					
Self-reported Asthma	396 (10.8)	293 (8.8)	16 (22.2)[a]	55 (29.4)[a]	32 (34.8)[a]
Coronary Artery Disease	259 (7.1)	226 (6.8)	10 (13.9)	14 (7.5)	9 (9.8)
Heart Failure	59 (1.6)	48 (1.4)	3 (4.2)	4 (2.1)	4 (4.3)

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Atrial Fibrillation	164 (4.5)	148 (4.5)	5 (6.9)	8 (4.3)	3 (3.3)
Hypertension	2276 (62.1)	2061 (62.2)	47 (65.3)	107 (57.2)	61 (66.3)
Sleep Apnea	228 (6.2)	191 (5.8)	7 (9.7)	15 (8.1)	15 (16.3)[a]
Diabetes	311 (8.5)	280 (8.4)	7 (9.7)	12 (6.4)	12 (13.0)
Current Medication, n (%)					
SABA	68 (1.9)	34 (1.0)	14 (19.4)[a]	9 (4.8)[a]	11 (12.0)[a]
LABA	198 (7.9)	100 (3.0)	39 (54.2)[a]	13 (16.2)[a]	29 (31.5)[a]
LAMA	42 (1.1)	4 (0.1)	26 (36.1)[a]	5 (2.7)[a]	7 (7.6)[a]
ICS Including Combinations	212 (8.4)	119 (3.6)	35 (48.6)[a]	31 (16.6)[a]	27 (29.3)[a]
Antihistamines	249 (6.8)	216 (6.5)	10 (13.9)	12 (6.4)	11 (12.0)
Laboratory Tests, n (%)					
CRP≥3	768 (20.9)	648 (19.6)	31 (43.1)[a]	56 (30.3)[a]	33 (35.9)[a]
Blood Eosinophil Cell Count≥300	524 (14.3)	448 (13.6)	14 (19.4)	41 (21.9)[a]	21 (23.3)

[a]Significant group differences

Inactivity/low activity (physical activity index [PAI] 0 or 0.05–1.5

The correctly diagnosed, over- and undiagnosed groups were compared with the no COPD group using chi square tests to compare categorical variables and T-test analysis for group comparison on continuous variables. Differences in lung function between groups were not tested as groups were defined based on spirometry values. A significance level of 0.01 was used due to multiple comparison.

COPD=chronic obstructive pulmonary disease; FEV$_1$=forced expiratory volume in 1 second; FVC= forced vital capacity; LLN=lower limit of normal; BMI=body mass index; SD=standard deviation; WHR=waist-hip ratio; mMRC=modified Medical Research Council; SABA=shorting-acting beta2-agonist; LABA=long-acting beta2-agonist; LAMA=long-acting muscarinic antagonist; inhaled corticosteroids=ICS; CRP=C-reactive protein

a higher prevalence of respiratory tract infections treated with antibiotics in the last 3 years, and more systemic inflammation than the group with no COPD. The correctly and undiagnosed COPD groups also had a significantly higher prevalence of inactivity when compared to the group with no COPD. The prevalence of obesity (BMI≥30) was lower in the undiagnosed COPD group compared to the group with no COPD.

The overdiagnosed group had a lower prevalence of BMI<25kg/m^2, more obstructive sleep apnea, more self-reported asthma, and a higher prevalence of eosinophilic inflammation than participants with no COPD. There were no differences in the physical activity level between the overdiagnosed and the no COPD group.

Clinical Characteristics of Participants with Undiagnosed COPD

The group with undiagnosed COPD had lower prevalence of cumulative tobacco consumption of ≥20 pack years, less respiratory symptoms, and better lung function compared to the group with correctly diagnosed COPD (Supplementary Table 1 in the online supplement). However, there was no significant difference in the prevalence of current smoking, deconditioning, obesity, underweight, cardiovascular comorbidities, systemic inflammation, or eosinophilia between the groups. Notably, the prevalence of current smoking was numerically higher in participants with undiagnosed COPD (48.1 %) than in participants with diagnosed COPD (37.5 %), although not significant. The proportion of individuals with FEV$_1$<50% of predicted was higher in the diagnosed group than among undiagnosed, but the prevalence of moderate disease, defined as FEV$_1$ between 50% and 80% of predicted, did not differ significantly between the groups.

In order to assess determinants of undiagnosed COPD, participants with correctly diagnosed COPD (FEV$_1$/FVC<LLN and self-reported COPD, n=72) were excluded from analysis. The remaining 3595 participants included 187 participants with undiagnosed COPD. We found the prevalence of current smoking, dyspnea, cough, expectorate, wheezing, and respiratory infections to be higher in participants with spirometry results consistent with undiagnosed COPD (Table 2). Participants with undiagnosed COPD were also more underweight and deconditioned and had more systemic inflammation compared to participants not

Table 2. Determinants of Undiagnosed COPDᵃ in a General Population-Based Sample, Multivariable Logistic Regression Model

	Univariable OR (95 % CI)	P	Multivariable OR (CI)	P
Demographic Data				
Male Gender	0.88 (0.65, 1.18)	0.374	0.91 (0.64, 1.27)	0.565
Inactivity/Low Activity	1.39 (1.03, 1.87)	0.030	0.94 (0.67, 1.33)	0.737
Anthropometric Data				
Underweight (BMI<18.5)	4.49 (1.82, 11.07)	0.001	1.09 (0.34, 3.56)	0.884
Obesity (BMI≥30)	0.54 (0.35, 0.82)	0.004	0.53 (0.33, 0.85)	0.008
Smoking History				
Current Smoking	6.80 (5.02, 9.23)	<0.001	3.42 (2.30, 5.09)	<0.001
≥20 Pack Years	4.13 (3.05, 5.60)	<0.001	2.06 (1.41, 3.03)	<0.001
Respiratory Symptoms				
mMRC≥2	1.75 (1.02, 2.98)	0.041	0.64 (0.34, 1.20)	0.165
Regular Cough	3.02 (2.23, 4.09)	<0.001	1.36 (0.90, 2.05)	0.148
Regular Expectorate	2.78 (1.98, 3.89)	<0.001	0.83 (0.53, 1.33)	0.439
Regular Wheezing	4.77 (3.42, 6.65)	<0.001	2.24 (1.44, 3.48)	<0.001
Respiratory Infections				
Antibiotics for Lower Respiratory Infection in the Last 3 years	2.99 (2.18, 4.09)	<0.001	2.06 (1.44, 2.96)	<0.001
Comorbidities				
Coronary Artery Disease	1.09 (0.62, 1.91)	0.757		
Heart Failure	1.41 (0.51, 3.94)	0.512		
Atrial Fibrillation	0.96 (0.47, 1.99)	0.921		
Hypertension	0.81 (0.60, 1.09)	0.165		
Sleep Apnea	1.36 (0.79, 2.35)	0.268		
Diabetes	0.73 (0.40, 1.33)	0.304		
Laboratory Tests				
CRP≥3	1.73 (1.25, 2.39)	0.001	1.37 (0.94, 2.00)	0.098
Blood Esinophil Cell Count≥300	1.75 (1.22, 2.51)	0.002	1.20 (0.79, 1.84)	0.391

ᵃN=187

Inactivity /low activity (physical activity index (PAI) 0 or 0.05-1.5)

COPD=chronic obstructive pulmonary disease; OR=odds ratio; CI=confidence interval; BMI=body mass index; mMRC=modified Medical Research Council dyspnea scale; CRP=C-reactive protein

meeting the spirometry criteria for COPD. In contrast, comorbidities did not differ between the groups.

In multivariable analyses, obesity reduced the odds of having undiagnosed COPD while the presence of current smoking, cumulative smoking of ≥20 pack years, wheezing, and treatment with antibiotics for lower respiratory tract infections during the last 3 years were all independently associated with undiagnosed COPD (Table 2).

Clinical Characteristics of Participants with Overdiagnosed COPD

In Table 3 we assessed predictors of overdiagnosed COPD in the population with self-reported COPD (n=164) and found that overdiagnosed participants were more often overweight (BMI≥25), had a lower prevalence of current smoking and tobacco consumption ≥20 pack years, and were more inactive and dyspneic compared to correctly diagnosed individuals.

Table 3. Predictors of Overdiagnosed COPD in the Group with Self-reported COPD

	Univariable OR (95 % CI)	P	Multivariable OR (CI)	P
Demographic Data				
Male Gender	1.21 (0.65, 2.23)	0.555	1.17 (0.57, 2.41)	0.674
Inactivity/Low Activity	0.43 (0.21, 0.87)	0.019	0.66 (0.20, 1.47)	0.312
Anthropometric Data				
BMI≥25	2.45 (1.22, 4.89)	0.011	3.18 (1.43, 7.08)	0.005
WHR	0.14 (0.01, 3.32)	0.220		
Smoking History				
Current Smoking	0.41 (0.20, 0.82)	0.012		0.001
≥20 Pack Years	0.22 (0.11, 0.46)	<0.001	0.27 (0.12, 0.60)	
Respiratory Symptoms				
mMRC≥2	0.33 (0.16, 0.68)	0.002	0.44 (0.20, 0.97)	0.041
Cough	0.79 (0.42, 1.48)	0.467		
Pleghm	0.57 (0.30, 1.07)	0.080		
Wheezing	0.55 (0.29, 1.03)	0.062		
Respiratory Infections				
Antibiotics for Lower Respiratory Infection in the Last 3 years	0.60 (0.32, 1.13)	0.116		
Comorbidities				
Self-reported Asthma	1.87 (0.93, 3.77)	0.081		
Coronary Artery Disease	0.67 (0.16, 1.75)	0.417		
Heart Failure	1.05 (0.23, 4.83)	0.955		
Atrial Fibrillation	0.45 (0.10, 1.96)	0.288		
Hypertension	1.05 (0.55, 2.01)	0.891		
Sleep Apnea	1.81 (0.70, 4.71)	0.224		
Diabetes	1.39 (0.52, 3.74)	0.511		
Laboratory Tests				
CRP≥3[c]mg/L	0.74 (0.39, 1.39)	0.350		
Blood Esinophil Cell count≥300 cells/μL	1.26 (0.59, 2.70)	0.551		

[a]FEV_1/FVC ≥ LLN, n=92
[b]n=164

Inactivity/low activity (physical activity index [PAI] 0 or 0.05-1.5).

The multivariable model was adjusted for gender, inactivity, BMI≥25, mMRC≥ 2 and cumulative tobacco exposure >20 pack years. To avoid collinearity, current smoking was not included in the model as it was highly correlated with cumulative tobacco consumption >20 pack years (chi-square=5.95, p=0.015, phi=0.205).

COPD=chronic obstructive pulmonary disease; OR=odds ratio; BMI=body mass index; WHR=waist- hip ratio mMRC= modified Medical Research Council dyspnea scale; CRP=C-reactive protein

Diagnostic Strategies to Detect Undiagnosed COPD

The diagnostic accuracy of clinical variables to detect participants currently unaware of their COPD diagnosis is demonstrated in Figure 2. Coughing and wheezing had the highest ROC-AUCs among respiratory symptoms, significantly higher than dyspnea (Figure 2a and Supplementary Table 2 in the online supplement). We also explored the diagnostic accuracy of the combination of variables. Both the combination of current smoking or ≥20 pack years and the combination cough or wheezing had significantly higher ROC-AUCs than individual

Figure 2a. Respiratory Symptoms and Exacerbations
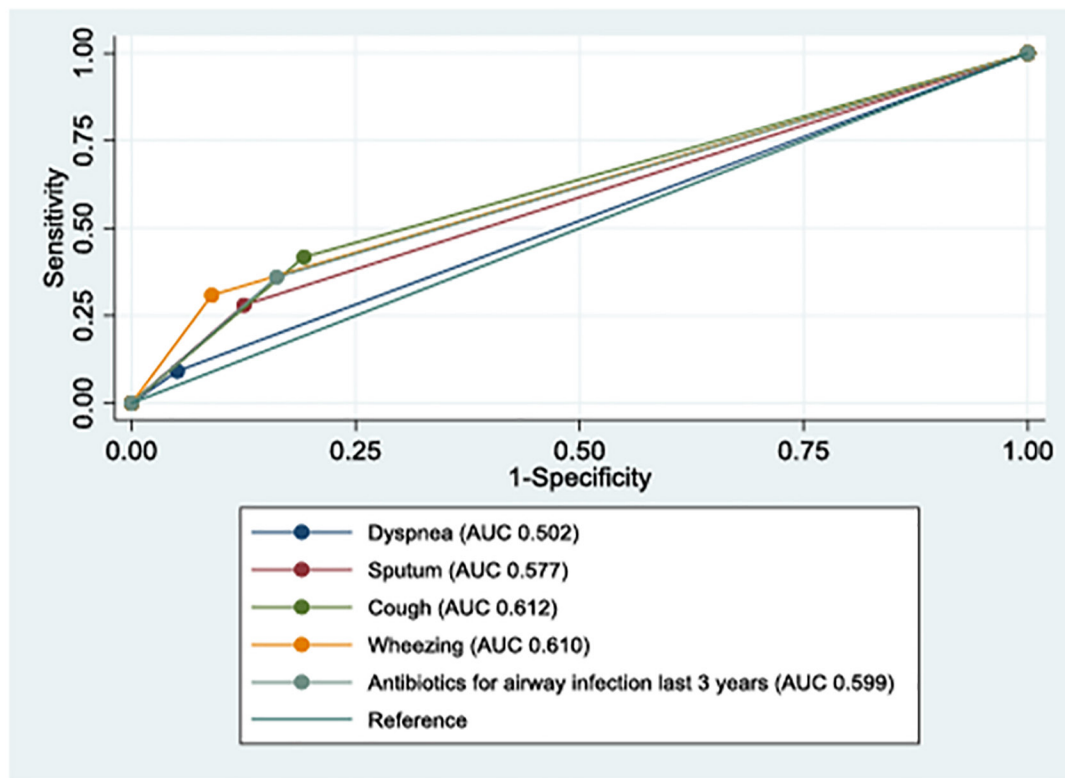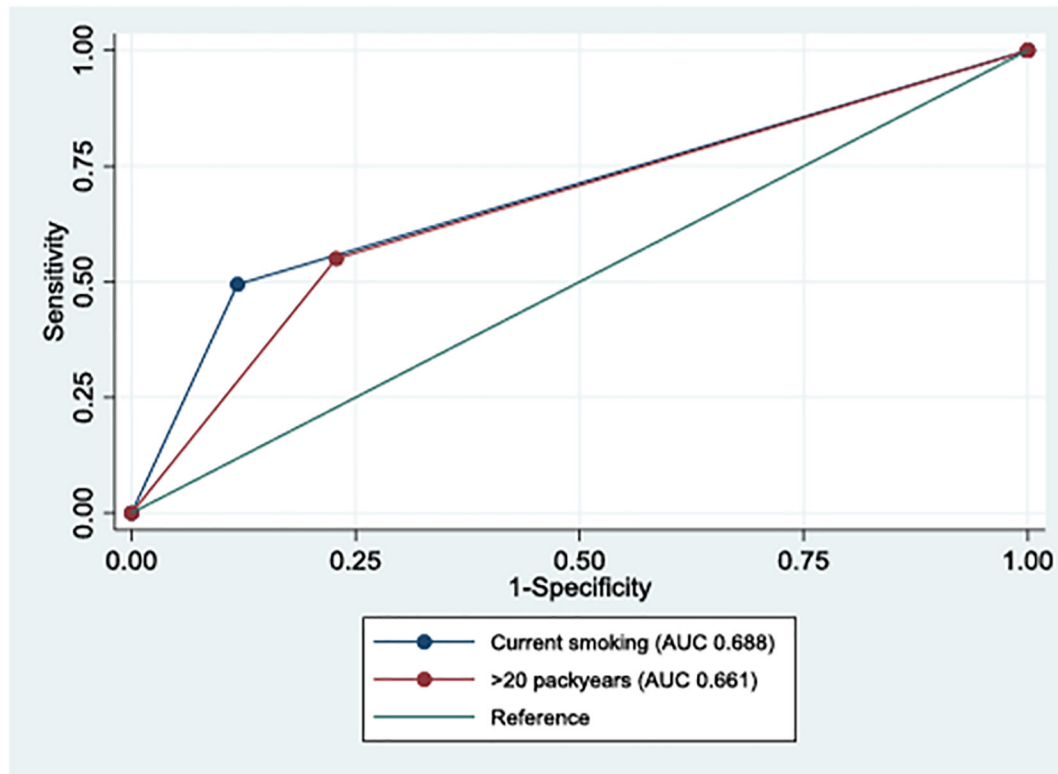

AUC=area under the curve

variables (Figure 2b and Supplementary Table 2 in the online supplement). Current smoking or >20 pack years had higher accuracy than cough or wheezing. Figure 2c presents combined variables. Adding wheezing or cough to current smoking or >20 pack years did not increase diagnostic accuracy (*p*=0.72). A model including wheezing or cough, current smoking or >20 pack years, or exacerbations in the last 3 years did not improve diagnostic accuracy compared to current smoking or >20 pack years alone (*p*=0.42). However, a statistical optimal model consisting of predicted individual probabilities based on the multivariable model in Table 3 had higher diagnostic accuracy than the clinical approach focusing on smoking history and symptoms (*p*<0.001).

We also examined different strategies to detect undiagnosed COPD (Table 4). Using individual clinical variables as selection criteria for spirometry was generally associated with high specificities and low sensitivities. Performing spirometry in all current smokers would require spirometry testing in 6 persons to detect 1 person currently unaware of having COPD but would imply a large fraction of individuals remaining undiagnosed. By combining several individual clinical variables, the sensitivity in diagnosing COPD increased at the cost of lower specificity and a larger number of spirometries to be performed per diagnosed person. Table 4 shows that combining information on wheezing and cough with current smoking and ≥20 pack years has a sensitivity of 85% and specificity of 59%, thus requiring 10 spirometries to detect 1 undiagnosed case of COPD, with 28 of 185 individuals (15%) potentially remaining undiagnosed.

Applying the new reference values of GLI 2012 to define COPD increased the total prevalence of COPD to 307 (8.4%), with a fraction of 75% undiagnosed cases. In the sensitivity analyses similar results as in the main analyses were found, except that the diagnosed group also reported more cough and systemic inflammation than the undiagnosed group (Supplementary Tables 2 and 3 in the online supplement).

Figure 2b. Tobacco Consumption

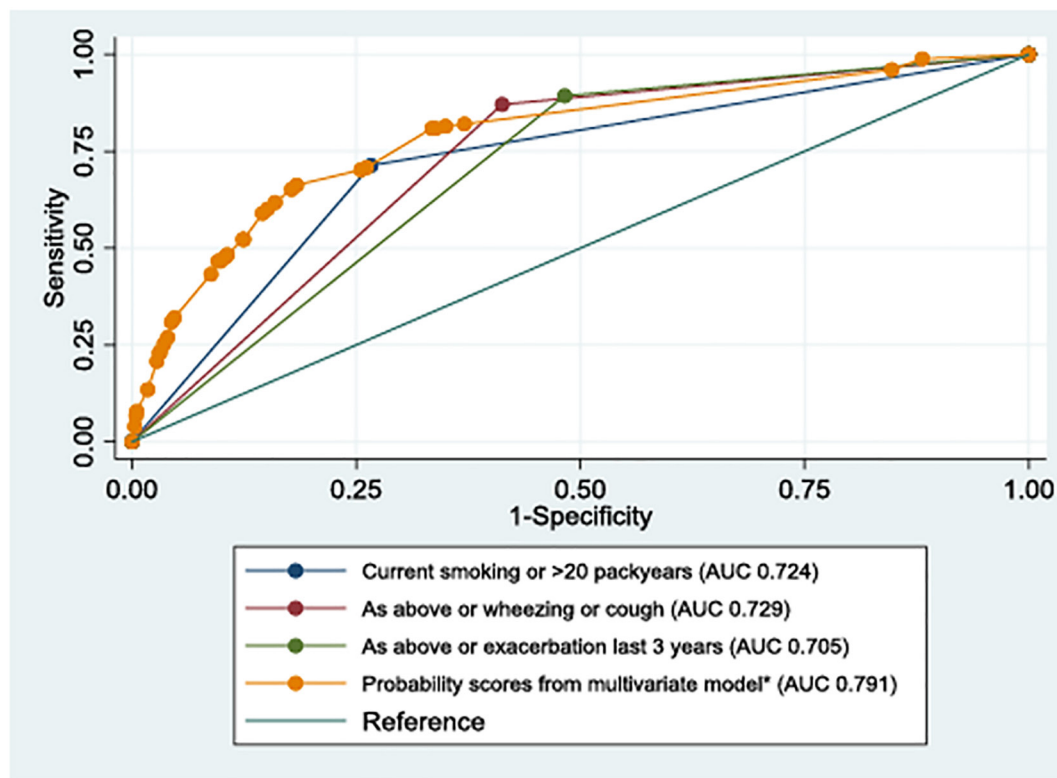AUC=area under the curve

Discussion

In the present population-based study consisting of 3667 individuals aged 62-65 years, we found a prevalence of COPD of 7.1%. Moreover, 72.2% of the participants with an $FEV_1/FVC<LLN$ were not aware of having reduced lung function consistent with a COPD diagnosis, while 56% of participants with self-reported COPD did not have an $FEV_1/FVC<LLN$. The undiagnosed group had better lung function and less respiratory symptoms, but similar rates of extrapulmonary clinical traits as diagnosed individuals. BMI≥25 was the main predictor of overdiagnosed COPD among the self-reported. We found that restricting spirometry to participants with current or past substantial tobacco consumption and self-reported wheezing or cough would have identified most undiagnosed COPD cases.

A Danish study analyzing data from the Copenhagen General Population Study found that 78% of participants with COPD were undiagnosed,[9] while a multinational study with data from 27 countries and a total of 30,874 participants found that 81.4% of participants with COPD were undiagnosed.[33] Although the overall prevalence of COPD varies in these and other similar studies, the prevalence of undiagnosed disease is universally high.[9,11,33-35]

In line with other studies, we find that the undiagnosed group has better lung function and fewer respiratory symptoms compared to individuals without COPD.[3,8,9] A few findings and novel contributions in the current study merit mentioning. We have studied clinical characteristics in accordance with a recent focus on treatable traits, information relevant for prognosis, and treatment selections.[16] First, despite a higher average pulmonary function in the undiagnosed group, the prevalence of moderate severity of COPD (FEV_1 50%-70% of predicted) did not differ between the diagnosed and undiagnosed, and 7% of the undiagnosed participants had airflow limitation consistent with Global Initiative for Chronic Obstructive Lung Disease[2] stages 3 or 4, likely to affect prognosis.[36,37] Second, extrapulmonary traits such as deconditioning and systemic inflammation

Figure 2c. Composite Assessment

AUC=area under the curve

were more prevalent in the undiagnosed COPD group. The association between inflammatory markers, such as CRP or eosinophilia, and undiagnosed COPD has, to our knowledge, not been studied previously, and may describe a clinically relevant trait. Third, the undiagnosed group reported more frequent lower respiratory tract infections, compared to individuals without COPD. Unfortunately, we did not have data on short-term oral steroid use. However, we believe that more frequent use of treatment with antibiotics for lower respiratory tract infections in the undiagnosed group may indicate exacerbations. Fourth, persons with overlapping asthma/COPD may be prone to misdiagnosis. In our data, 29% of individuals in the undiagnosed group reported a previous diagnosis of asthma suggesting that some of the undiagnosed individuals may have progressed to chronic obstruction from asthma or represent an overlapping phenotype.

In summary, these findings indicate that patients unaware of having COPD have similar clinical traits affecting prognosis as those diagnosed with COPD.

More than 50% of participants with self-reported

COPD did not have irreversible airway limitation. This group was recognized by intermediate level symptoms, and the main predictor of being overdiagnosed was a BMI≥25. Two explanations are relevant for this finding: the difference between diagnostic cut-offs in the 2012 guidelines ($FEV_1/FVC<0.70$) and $FEV_1/FVC<LLN$ explains 39% of the participants in this group. Second, overdiagnosis in overweight and obese individuals may reflect a clinical evaluation based on respiratory symptoms and/or risk exposure, but with preserved FEV_1/FVC ratio caused by significant, but disproportionate reductions in FEV_1 and FVC.[12,38]

The clinical relevance of increasing the proportion of individuals aware of having COPD depends on the potential for intervention and possible changes in outcomes. The rationale for early and active case-finding by physicians in primary care is strong.[18,19,39,40] First and foremost, the undiagnosed group probably has the most to gain by early smoking cessation.

Another novel approach in the current study was to explore case-finding strategies based on these clinical

Table 4. Screening Approaches in General Practice to Detect Individuals with Undiagnosed COPD

Individuals Tested	Sensitivity (%)	Specificity (%)	Spirometries Needed to Detect a Case (n)	COPD Not Detected (n)
All Persons	N/A	N/A	19	0
Individual Factors Assessed				
Current Smoking	48%	88%	6	97
Cumulative Consumption ≥20 pack years	55%	77%	9	84
Dyspnea	9%	95%	12	171
Cough	43%	80%	9	106
Sputum	29%	87%	9	132
Wheezing	32%	91%	6	128
Exacerbation in Last 3 Years	37%	84%	9	118
Combination of Factors Assessed				
Wheezing or Cough	53%	76%	9	88
Any Clinical Symptom	58%	71%	10	79
Current Smokers or ≥20 Pack Years	70%	74%	8	57
Current Smokers or ≥20 Pack Years or Wheezing or Cough	85%	59%	10	28
Current Smokers or ≥20 Pack Years or Wheezing or Cough or Exacerbation in Last 3 Years	89%	51%	11	21

COPD=chronic obstructive pulmonary disease

characteristics in the undiagnosed population. We assessed how any of these clinical characteristics, easily obtained in primary care, could contribute to detecting individuals with undiagnosed COPD in our population-based cohort. When modeling the optimal case-finding strategy to detect those currently unaware of COPD, the highest diagnostic accuracy was found by including the 2 questions of current smoking and/or history of ≥20 pack years. With those 2 questions, 30% of the participants would still remain undiagnosed, while adding questions of wheezing or cough would reduce this fraction to 15% at the cost of performing 2 more negative spirometries for each positive case.

We also report that the statistical optimal approach to detect previously undiagnosed COPD would include taking into consideration BMI and CRP in addition to tobacco consumption and symptoms. Obesity was the only factor that remained associated with lower probability of having undiagnosed COPD in multivariable analysis. It is commonly observed that patients with severe COPD have a lower BMI compared to the general population[19] and we also now extend such observations to a cohort with mainly mild COPD. However, as the prevalence

of obesity was comparable among diagnosed and undiagnosed COPD, this observation may have limited clinical implication for case-finding strategies in COPD.

Compared to previous epidemiological studies, a strength of the current study is the use of post-BD values in defining COPD, thereby, reducing the misclassification of asthmatic individuals. Furthermore, we expect no significant participation bias with regard to respiratory symptoms, as pulmonary disease was not a focus in the study invitations.

The participation rate of 64% from a general population is reasonably high, compared to other general population cohorts of today.[41,42]

A limitation is the cross-sectional study design with a very limited age range. Hence, our results may not be valid for other age groups. The study was initiated prior to the publication of the GLI 2012 reference values, and the main analysis is, thus, reported according to the ECSC reference set. Yet, the similar results of the sensitivity analyses using the GLI 2012 reference set suggest that our data are valid also for populations diagnosed from 2012 to the present day. Our data may also support that

those few extra persons diagnosed with COPD by GLI 2012 compared to ECSC do not have highly symptomatic disease but share some traits with the more symptomatic group.

Factors that lead to miscommunication of a COPD diagnosis include different cutoffs defining chronic obstruction clinically and epidemiologically, spirometries performed without reversibility testing, or stigmas surrounding COPD. Medical health records were not available, and the use of self-reported COPD as an indicator of diagnosed COPD may not have been consistent with the diagnoses provided by each individual's primary physician. This is most relevant for persons having overlapping asthma/COPD. Additionally, COPD and emphysema were combined in the questionnaire identifying previous respiratory disease. This may have led to misclassification of some participants with emphysema, but no COPD.

Conclusion

In the present study of a Norwegian general population sample, we found a COPD prevalence of 7.1%, of which 72.2 % were undiagnosed. Individuals with undiagnosed COPD have better lung function, and fewer symptoms and exacerbations than individuals with an established COPD diagnosis, but similar extrapulmonary traits including physical inactivity, comorbidities, and systemic inflammation. We recommend that current smokers and smokers with cumulative tobacco consumption ≥20 pack years, cough, and wheezing should be offered spirometry with BD-test to uncover undiagnosed COPD.

The prevalence of overdiagnosed COPD was 2.5%. Individuals with overdiagnosed COPD have lower lung function, more respiratory symptoms, more self-reported asthma, more eosinophilic inflammation, and more sleep apnea than other individuals without COPD. The main predictor of being overdiagnosed was being overweight.

References

1. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet.* 2012;380(9859):2095-2128. doi: https://doi.org/10.1016/S0140-6736(12)61728-0

2. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of COPD, 2020 report. GOLD website. Published 2020. Accessed October 2021 https://goldcopd.org/wp-content/uploads/2019/11/GOLD-2020-REPORT-ver1.0wms.pdf

3. Martinez CH, Mannino DM, Jaimes FA, et al. Undiagnosed obstructive lung disease in the United States. Associated factors and long-term mortality. *Ann Am Thorac Soc.* 2015;12(12):1788-1795. doi: https://doi.org/10.1513/AnnalsATS.201506-388OC

4. Sator L, Horner A, Studnicka M, et al. Overdiagnosis of COPD in subjects with unobstructed spirometry: a BOLD analysis. *Chest.* 2019;156(2):277-288. doi: https://doi.org/10.1016/j.chest.2019.01.015

5. Diab N, Gershon AS, Sin DD, et al. Underdiagnosis and overdiagnosis of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2018;198(9):1130-1139. doi: https://doi.org/10.1164/rccm.201804-0621CI

6. Csikesz NG, Gartman EJ. New developments in the assessment of COPD: early diagnosis is key. *Int J Chron Obstruct Pulmon Dis.* 2014;9:277-286. doi: https://10.2147/COPD.S46198

7. Lamprecht B, Soriano JB, Studnicka M, et al. Determinants of underdiagnosis of COPD in national and international surveys. *Chest.* 2015;148(4):971-985. doi: https://doi.org/10.1378/chest.14-2535

8. Hangaard S, Kronborg T, Hejlesen OK. Characteristics of subjects with undiagnosed COPD based on post-bronchodilator spirometry data. *Respir Care.* 2019;64(1):63-70. doi: https://doi.org/10.4187/respcare.06296

9. Colak Y, Afzal S, Nordestgaard BG, Vestbo J, Lange P. Prognosis of asymptomatic and symptomatic, undiagnosed COPD in the general population in Denmark: a prospective cohort study. *Lancet Respir Med.* 2017;5(5):426-434. doi: https://doi.org/10.1016/S2213-2600(17)30119-4

10. Hvidsten SC, Storesund L, Wentzel-Larsen T, Gulsvik A, Lehmann S. Prevalence and predictors of undiagnosed chronic obstructive pulmonary disease in a Norwegian adult general population. *Clin Respir J.* 2010;4(1):13-21. doi: https://doi.org/10.1111/j.1752-699X.2009.00137.x

11. Waatevik M, Skorge TD, Omenaas E, Bakke PS, Gulsvik A, Johannessen A. Increased prevalence of chronic obstructive pulmonary disease in a general population. *Respir Med.* 2013;107(7):1037-1045. doi: https://doi.org/10.1016/j.rmed.2013.04.008

12. Collins BF, Ramenofsky D, Au DH, Ma J, Uman JE, Feemster LC. The association of weight with the detection of airflow obstruction and inhaled treatment among patients with a clinical diagnosis of COPD. *Chest.* 2014;146(6):1513-1520. doi: https://doi.org/10.1378/chest.13-2759

13. Celli BR, Wedzicha JA. Update on clinical aspects of chronic obstructive pulmonary disease. *N Engl J Med.* 2019;381(13):1257-1266. doi: https://doi.org/10.1056/NEJMra1900500

14. Agustí A, Hogg JC. Update on the pathogenesis of chronic obstructive pulmonary disease. *N Engl J Med.* 2019;381(13):1248-1256. doi: https://doi.org/10.1056/NEJMra1900475

15. Agusti A, Sin DD. Biomarkers in COPD. *Clin Chest Med.* 2014;35(1):131-141. doi: https://doi.org/10.1016/j.ccm.2013.09.006

16. Agusti A, Bel E, Thomas M, et al. Treatable traits: toward precision medicine of chronic airway diseases. *Eur Respir J.* 2016;47(2):410-419. doi: https://doi.org/10.1183/13993003.01359-2015

17. McDonald VM, Fingleton J, Agusti A, et al. Treatable traits: a new paradigm for 21st century management of chronic airway diseases: Treatable traits down under international workshop report. *Eur Respir J.* 2019;53(5):1802058. doi: https://doi.org/10.1183/13993003.02058-2018

18. Decramer M, Miravitlles M, Price D, et al. New horizons in early stage COPD-improving knowledge, detection and treatment. *Respir Med.* 2011;105(11):1576-1587. doi: https://doi.org/10.1016/j.rmed.2010.12.015

19. Rossi A, Butorac-Petanjek B, Chilosi M, et al. Chronic obstructive pulmonary disease with mild airflow limitation: current knowledge and proposal for future research - a consensus document from six scientific societies. *Int J Chron Obstruct Pulmon Dis.* 2017;12:2593-2610. doi: https://doi.org/10.2147/COPD.S132236

20. Han MK, Agusti A, Calverley PM, et al. Chronic obstructive pulmonary disease phenotypes: the future of COPD. *Am J Respir Crit Care Med.* 2010;182(5):598-604. doi: https://doi.org/10.1164/rccm.200912-1843CC

21. Han MK, Agusti A, Celli BR, et al. From Gold 0 to Pre-COPD. *Am J Respir Crit Care Med.* 2021;203(4):414-423. doi: https://doi.org/10.1164/rccm.202008-3328PP

22. Berge T, Vigen T, Pervez MO, et al. Heart and brain interactions-the Akershus Cardiac Examination (ACE) 1950 study design. *Scand Cardiovasc J*. 2015;49(6):308-315.
doi: https://www.tandfonline.com/doi/full/10.3109/14017431.2015.1086813

23. Tverdal A, Hjellvik V, Selmer R. Heart rate and mortality from cardiovascular causes: a 12 year follow-up study of 379,843 men and women aged 40-45 years. *Eur Heart J*. 2008;29(22):2772-2781. doi: https://doi.org/10.1093/eurheartj/ehn435

24. Vigen T, Ihle-Hansen H, Lyngbakken MN, et al. Blood pressure at age 40 predicts carotid atherosclerosis two decades later: data from the Akershus Cardiac Examination 1950 Study. *J Hypertens*. 2019;37(10):1982-1990.
doi: https://doi.org/10.1097/HJH.0000000000002131

25. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26(2):319-338.
doi: https://doi.org/10.1183/09031936.05.00034805

26. Hankinson JL, Viola JO. Dynamic BTPS correction factors for spirometric data. *J Appl Physiol Respir Environ Exerc Physiol*. 1983;55(4):1354-1360.
doi: https://doi.org/10.1152/jappl.1983.55.4.1354

27. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report working party standardization of lung function tests, European community for steel and coal. Official statement of the European Respiratory Society. *Eur Respir J*. 1993;6(Suppl 16):5-40.
doi: https://doi.org/10.1183/09041950.005s1693

28. Aspenes ST, Nauman J, Nilsen TI, Vatten LJ, Wisloff U. Physical activity as a long-term predictor of peak oxygen uptake: the HUNT Study. *Med Sci Sports Exerc*. 2011;43(9):1675-1679.
doi: https://doi.org/10.1249/MSS.0b013e318216ea50

29. Berge T, Lyngbakken MN, Ihle-Hansen H, et al. Prevalence of atrial fibrillation and cardiovascular risk factors in a 63-65 years old general population cohort: the Akershus Cardiac Examination (ACE) 1950 Study. *BMJ open*. 2018;8(7):e021704.
doi: https://doi.org/10.1136/bmjopen-2018-021704

30. Langhammer A, Johannessen A, Holmen TL, et al. Global Lung Function Initiative 2012 reference equations for spirometry in the Norwegian population. *Eur Respir J*. 2016;48(6):1602-1611.
doi: https://doi.org/10.1183/13993003.00443-2016

31. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of COPD, 2019 report. GOLD website. Published 2019. Accessed October 2021. https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-POCKET-GUIDE-FINAL_WMS.pdf

32. World Health Organization (WHO). Body mass index – BMI. WHO website. Published 2020. Updated 2022. Accessed October 2021. http://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi

33. Bernd L, Joan BS, Michael S, et al. Determinants of underdiagnosis of COPD in national and international surveys. *Chest*. 2015;148(4):971-985.
doi: https://doi.org/10.1378/chest.14-2535

34. Borlee F, Yzermans CJ, Krop E, et al. Spirometry, questionnaire and electronic medical record based COPD in a population survey: comparing prevalence, level of agreement and associations with potential risk factors. *PLoS One*. 2017;12(3):e0171494.
doi: https://doi.org/10.1371/journal.pone.0171494

35. Miravitlles M, Soriano JB, García-Río F, et al. Prevalence of COPD in Spain: impact of undiagnosed COPD on quality of life and daily life activities. *Thorax*. 2009;64(10):863-868.
doi: https://doi.org/10.1136/thx.2009.115725

36. Stavem K, Aaser E, Sandvik L, et al. Lung function, smoking and mortality in a 26-year follow-up of healthy middle-aged males. *Eur Respir J*. 2005;25(4):618-625.
doi: https://doi.org/10.1183/09031936.05.00008504

37. Hole DJ, Watt GC, Davey-Smith G, Hart CL, Gillis CR, Hawthorne VM. Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. *In Br Med J*. 1996;313:711.
doi: https://doi.org/10.1136/bmj.313.7059.711

38. Colak Y, Marott JL, Vestbo J, Lange P. Overweight and obesity may lead to under-diagnosis of airflow limitation: findings from the Copenhagen City Heart Study. *COPD*. 2015;12(1):5-13.
doi: https://doi.org/10.3109/15412555.2014.933955

39. Zhou Y, Zhong NS, Li X, et al. Tiotropium in early-stage chronic obstructive pulmonary disease. *N Engl J Med*. 2017;377(10):923-935. doi: https://doi.org/10.1056/NEJMoa1700228

40. Anthonisen NR, Connett JE, Kiley JP, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The lung health study. *JAMA*. 1994;272(19):1497-1505.
doi: https://doi.org/10.1001/jama.1994.03520190043033

41. Krokstad S, Langhammer A, Hveem K, et al. Cohort profile: the HUNT study, Norway. *Int J Epidemiol*. 2013;42(4):968-977.
doi: https://doi.org/10.1093/ije/dys095

42. Jacobsen BK, Eggen AE, Mathiesen EB, Wilsgaard T, Njolstad I. Cohort profile: the Tromso study. *Int J Epidemiol*. 2012;41(4):961-967. doi: https://doi.org/10.1093/ije/dyr049