The Prevalence of Chronic Obstructive Pulmonary Disease by the Global Lung Initiative Equations in North-Western Russia

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What Is the Key Question?

- What is the prevalence of airflow obstruction in adults aged 35–70 years in two north-western cities in Russia, a country where smoking rates are among the highest in the world?

What Is the Bottom Line?

- The spirometrically defined chronic obstructive pulmonary disease prevalence was 6.8% by a fixed (0.7) and 4.8% by the Global Lung Initiative 2012 lower limit of normal cut-off, which is lower than what was reported in neighbouring countries, and should be put in perspective of the high cardiovascular mortality rates in this part of Russia.

Why Read on?

- In this first population-based prevalence study in the Russian Federation, we also found that 22.5% of participants with airflow obstruction had findings of asthma-chronic obstructive pulmonary disease overlap syndrome, and 1% presented a paradoxical bronchodilator response.

Key Words

Epidemiology of chronic obstructive pulmonary disease and asthma · Chronic obstructive pulmonary disease · Tobacco · Spirometry reference values

Abstract

Background: The prevalence of chronic obstructive pulmonary disease (COPD) varies in different countries, while the cut-off for airflow obstruction (AO) is still contested. No COPD prevalence data based on the Global Lung Initiative (GLI) 2012 equations are available in Russia. **Objectives:** This

study aims to assess AO prevalence by the GLI lower limit of normal (GLI-LLN) and the fixed cut-off, to identify AO risk factors and to assess the diagnostic value of respiratory symptoms in north-western Russia. **Methods:** In a north-western Russian population-based sample of 2,974 adults aged 35–70 years, data on socio-demographics, smoking, occupational exposures and respiratory symptoms were collected, and spirometry was performed before and after bronchodilator (BD) administration. **Results:** The AO prevalence was 6.8% (95% CI 5.8–7.9) based on the fixed and 4.8% (95% CI 3.9–5.7) based on the GLI-LLN cut-off. 22.5% of the participants with post-BD AO had a positive bronchodilator test, and 1% showed a paradoxical BD response. Of the environmental factors studied, only smoking was independently associated with AO (odds ratio 2.47, 95% CI 1.60–3.82). The positive predictive value of respiratory symptoms for AO was 11% based on the fixed and 8% based on the GLI-LLN cut-off. **Conclusions:** In a sample of adults in north-western Russia, the AO prevalence by the GLI-LLN cut-off was lower than that by the fixed cut-off. The predictive value of respiratory symptoms was low.

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Introduction

Chronic obstructive pulmonary disease (COPD) remains a major public health problem in the 21st century [1]. There is a significant heterogeneity in COPD prevalence that might be explained by a diversity of methodological approaches to the definition and diagnosis of COPD in different studies as well as by the different age and sex distributions of sampled populations [2–4]. Most of the individuals with COPD (70–90%) are undiagnosed; therefore, they do not receive appropriate medical care and continue to smoke and/or be exposed to other COPD risk factors [5].

COPD diagnosis requires a comprehensive approach that considers clinical signs and symptoms, risk factors and spirometry [6]. COPD diagnoses based only on symptoms or patient-reported diagnoses underestimate its prevalence. The positive predictive value (PPV) of signs and symptoms for a diagnosis of chronic air-flow obstruction (AO) is low in unselected populations [7–9].

Spirometry provides better estimates of the AO prevalence, but it has some limitations [3]. Subjects with comparable AOs have different phenotypes, with marked differences in age, symptoms, comorbidities and predicted mortalities [10].

Also, the appropriate cut-off value of the ratio of forced expiratory volume in 1 s to forced vital capacity (FEV₁/FVC) used to define AO is still contested [11, 12]. Although both the fixed ratio (0.7) and the lower limit of normal (LLN) cut-offs are related to clinically relevant outcomes, there is no clear preference for one over the other [13].

Variable prevalence rates of COPD in Russia are reported, but there are no COPD or AO prevalence data using the Global Lung Initiative (GLI) 2012 reference equations [14].

The aims of this study are to assess the prevalence of AO in adults aged 35–70 years in two north-western cities in Russia based on the fixed (0.7) and the GLI-LLN cut-offs, to identify risk factors for AO using both cut-offs and to assess the diagnostic value of respiratory symptoms for AO.

Methods

Study Design and Population

The RESPECT (RESearch on the PrEvalence and diagnosis of COPD and its Tobacco-related aetiology) study is a population-based study set up in collaboration with the Université Catholique de Louvain (Belgium), the North-Western State Medical University (named after I.I. Mechnikov), St. Petersburg (Russia) and the Northern State Medical University, Arkhangelsk (Russia). The study was designed to attain a better understanding of the epidemiology of COPD in north-western Russia.

A description of the design and rationale of the RESPECT study has previously been published elsewhere [15]. Briefly, 15 primary care centres in two north-western Russian cities (St. Petersburg and Arkhangelsk) were invited to participate in the RESPECT study, and 15 investigators (10 from St. Petersburg and 5 from Arkhangelsk) were recruited.

The study population was randomly selected from lists (organized based on territories) provided by the 15 participating centres. Adults 35–70 years of age were selected from each centre using a random number generator and were subsequently invited to participate in the study. The participating sites agreed to recruit a population-based random sample of at least 200 adults who were not institutionalized, were aged 35–70 years and were living in a well-defined administrative area [15]. The research investigators administered questionnaires regarding the participants' background characteristics, including sociodemographic data, smoking status, occupational exposures and respiratory symptoms. All participants were invited to have spirometry. The local medical ethics review boards approved the study protocol [North-West State Medical University (named after I.I. Mechnikov), St. Petersburg, protocol No. 11 from December 7, 2011, and Northern State Medical University, Arkhangelsk, protocol No. 01/1-12 from January 11, 2012]. All participants provided informed consent. Patients were enrolled between June 8, 2012, and December 27, 2013.

Background Characteristics and Other Variables

The background characteristics included variables such as sex, age and sociodemographic status. Smoking status was specified as 'never smoked', 'former smoker' (quit smoking 6 months or more previously), or 'current smoker'.

The American Thoracic Society (ATS) 1978 Adult Questionnaire (ATS-DLD-78) was used to assess the exposure to occupational hazards [16]. The participants were asked about their use of personal gas or wood stoves to estimate their indoor exposure to biomass fuels [17]. The gas stove utilization ratings were as follows: 'none', 'low use' (1–6 times/week) or 'high use' (>7 times/week). Similar ratings were used for wood stove utilization: 'none', 'low use' (1–4 times/week) or 'high use' (>5 times/week).

Information regarding each individual's history of obstructive airway disease (asthma, chronic bronchitis, emphysema, chronic cough and allergic rhinitis), tuberculosis anamnesis and comorbidities was collected in a systematic manner.

The participants were asked about the presence of chronic cough, sputum production (defined as lasting longer than 3 months) and dyspnoea as chronic respiratory symptoms [18].

Spirometry

Spirometry was performed with a portable turbine Micro Spirometer (MIR Spirobank, Rome, Italy) and a personal computer equipped with the WiPam program to facilitate the uploading of data to a central database. The accuracy of the spirometry, which was performed by trained investigators, has been previously reported [19].

All investigators were invited to participate in a 3-week distance-learning course on spirometry with a 1-day face-to-face session (SpiroCourse) [20]. All investigators completed the course successfully and agreed to receive continuous quality feedback on the examinations.

The ATS/European Respiratory Society (ERS) quality criteria were used to assess the acceptability and repeatability of the results [21]. After the assessment, all spirometry results were evaluated by 2 independent judges and classified according to 4 categories: ATS1, all ATS/ERS criteria, including reproducibility, were satisfied; ATS2, all criteria, except for duration of expiration >6 s, were satisfied; ATS3, the test was 'usable' for the interpretation of the peak expiratory flow and FEV₁, and the spirograms displayed good starts and no cough was noted during the 1st second of the manoeuvre; ATS4, none of the ATS/ERS criteria were satisfied, and the spirograms were not usable. Spirograms scored as ATS1 or ATS2 were considered to be of acceptable quality.

Winspiro Pro software (MIR) was used to compare the measured values with those in reference tables and to automatically calculate the reproducibility of the performed spirometry, in accordance with the ERS guidelines. Pre- and post-bronchodilator (BD) spirometry test results were recorded. Using 400 µg of salbutamol or 160 µg of ipratropium bromide [for the patients older than 60 years of age or with comorbid cardiovascular disease (CVD)], reversibility testing was offered to all participants. The second spirometry test was performed 15 (for salbutamol) or 45 min (for ipratropium bromide) after the first spirometry test. Reversible AO was defined according to the ATS/ERS criteria (>12% and 200 ml increase in FEV₁ after BD administration). The ATS/ERS quality criteria were used to assess the acceptability and repeatability of the results [21].

The predictive values for the spirometry parameters were calculated based on the GLI 2012 reference data using GLI 2012

Data Conversion software [22]. COPD was defined as FEV₁/FVC <0.7 (fixed cut-off) and FEV₁/FVC < GLI-LLN (5th percentile of the Z scores of the GLI 2012 reference values) on the post-BD values.

Sensitivity Analysis

In order to test the robustness of our prevalence figures, we additionally performed a sensitivity analysis. Three different adjustment methods were used to assess the potential non-participation bias: (1) transformation of the observed prevalence in each age group using an index that is proportional to the relative weight of the age group in the general population in order to recalculate overall prevalence; (2) adaptation of the sample by 'at random' elimination of cases in the strata that are overrepresented (55–64 and 65–70 years old), and (3) simulation of the impact on the overall prevalence (or on the prevalence in different strata) starting from two hypotheses: (a) all of the non-responders are smokers, and (b) none of the non-responders are smokers, by using the average number of diagnosis of AO in smokers and non-smokers to adjust the prevalence. The age and sex distribution in the RESPECT study and in the general population were compared in detail earlier [15].

Statistical Analysis

Descriptive statistics were calculated for all variables, with the continuous variables presented as the mean ± standard deviation (SD) and the categorical variables presented as numbers and frequencies. The baseline variables were compared across the three groups with one-way ANOVA, and Pearson's χ^2 test was carried out for the categorical variables. Multivariable logistic regression was used to estimate the association between AO and predictors (adjusted in three consecutive steps for potential confounders). Statistical significance was set at <0.05 (a two-tailed probability value).

Based on the two FEV₁/FVC cut-offs, the study population was divided into three AO categories: (1) participants with FEV₁/FVC ≥0.70 and ≥GLI-LLN (no AO according to either cut-off); (2) participants with FEV₁/FVC <0.7 and ≥GLI-LLN (the discordant group; AO according to the fixed cut-off only), and (3) participants with FEV₁/FVC <0.70 and <GLI-LLN (AO according to both cut-offs). The only 2 participants with FEV₁/FVC ≥0.70 and <GLI-LLN were excluded from this analysis.

SPSS version 20.0 (SPSS Inc., Chicago, Ill., USA) was used for the statistical analysis.

Results

Out of the 4,419 individuals who were invited to participate in the RESPECT study, 3,133 agreed to participate and met the inclusion criteria. Satisfactory quality of spirometry (after comprehensive assessments for reproducibility and acceptability) was achieved by 2,974 participants before and by 2,388 after the BD test (fig. 1, 2). The mean age of the RESPECT study population was 54 years (SD, 9.25); 31.8% were male, and 47.8% were current or ex-smokers. The background characteristics of the

Fig. 1. RESPECT flow diagram (obstruction based on the fixed ratio FEV₁/FVC <0.7).

Fig. 2. RESPECT flow diagram (obstruction based on the ratio FEV₁/FVC < GLI-LLN).

Table 1. Baseline characteristics of the total population after BD testing and across categories based on the two cut-offs

	Total population with high-quality post-BD tests (n = 2,386) ^c	FEV ₁ /FVC >0.7 and ≥GLI-LLN (n = 2,224)	FEV ₁ /FVC <0.7 (n = 162)		p
			≥GLI-LLN (n = 50)	<GLI-LLN (n = 112)	
Age, years	54.0±9.23	53.64±9.27	61.6±4.26	57.1±7.89	<0.000 ^a
Men, n (%)	757 (31.7)	657 (29.5)	36 (72.0)	64 (57.1)	<0.001 ^b
Educational level ^d	2,380	2,219	50	111	0.198 ^b
Primary, n (%)	70 (2.9)	61 (2.7)	3 (6.0)	6 (5.4)	
Secondary, n (%)	1,441 (61.8)	1,370 (61.7)	26 (52.0)	75 (67.6)	
Higher, n (%)	839 (35.3)	788 (35.5)	21 (42.0)	30 (27.0)	
Smoking status	2,380	2,219	50	111	
Smoker/ex-smoker, n (%)	1,142 (48.0)	1,018 (45.9)	41 (82.0)	83 (71.8)	<0.001 ^b
Dusty job ^e	2,274	2,121	47	106	
≥10 years, n (%)	409 (18.0)	366 (17.3)	14 (29.8)	29 (27.4)	0.008 ^b
Symptoms ^f	1,112 (46.6)	990 (44.5)	34 (68.0)	88 (78.6)	<0.001 ^b
Current respiratory diseases (means by patient)	2,371	2,212	50	109	
COPD, n (%)	34 (0.7)	16 (0.7)	3 (6.0)	15 (13.8)	<0.001 ^b
Asthma, n (%)	161 (6.8)	129 (5.8)	9 (18.0)	23 (21.1)	<0.001 ^b
Emphysema, n (%)	9 (4.6)	6 (0.3)	1 (2.0)	2 (1.8)	0.006 ^b
Chronic bronchitis, n (%)	256 (10.8)	222 (10.0)	7 (14.0)	27 (24.8)	<0.001 ^b
No respiratory diseases, n (%)	1,978 (83.4)	1,990 (90.0)	43 (86.0)	82 (75.2)	
BMI	28.1±5.04	28.14±5.41	27.33±4.84	27.51±5.62	0.285 ^a
FEV ₁ , litres	2.92±0.78	2.96±0.77	2.66±0.64	2.21±0.70	<0.000 ^a
FVC, litres	3.63±0.97	3.63±0.96	3.96±0.99	3.62±1.09	0.053 ^a
FEV ₁ /FVC	0.80±0.07	0.82±0.52	0.68±0.01	0.60±0.08	<0.000 ^a

Figures are means ± SD unless indicated otherwise. ^a p value based on one-way ANOVA. ^b p value based on Pearson's χ^2 test (p values adjusted using the Bonferroni method). ^c Participants with FEV₁/FVC ≥0.70 and <GLI-LLN were excluded due to the small number of persons (n = 2). ^d Educational level: primary (primary school or none or unfinished secondary education), secondary (secondary education or secondary vocational education), higher (unfinished higher education or higher education). ^e Working in a dusty job for more than 1 year. ^f Chronic respiratory symptoms were defined as the presence of chronic cough and chronic phlegm (on most days for as long as 3 months each year), together with chronic dyspnoea.

RESPECT population are presented in the online supplementary appendix 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000442887). The RESPECT population includes more women than the average population in the north-west region (68.2 vs. 55.3%; p < 0.05) as well as more participants aged 55–70 years (53.7 vs. 35.3%; p < 0.05) [15].

The baseline characteristics of the total study population with the BD test and three AO categories based on fixed and GLI-LLN cut-offs are presented in table 1.

AO prevalence was 6.8% according to the fixed cut-off and 4.8% according to GLI-LLN. Participants with AO by both cut-offs tended to be male, older, and smokers/ex-smokers, were more frequently exposed to dusty jobs and reported chronic respiratory symptoms compared to the participants with no AO. There was no statistically sig-

nificant difference between the AO categories in terms of educational level and body mass index (BMI).

The prevalence of AO (based on pre- and post-BD spirometry) was higher with the fixed cut-off than with the GLI-LLN (table 2a). The overall prevalence of AO (after BD administration) for men was higher than for women for both cut-offs (table 2a).

Generally, the prevalence of post-BD AO according to both cut-offs increased with age (table 2a), i.e. it was less than 5% in patients aged 35–44 years, while in those aged 65–70 years, the prevalence for the fixed and GLI-LLN cut-offs was 26.9 and 15.7% for men and 4.1 and 2.6% for women, respectively.

The prevalence of AO, according to the smoking status, is presented in table 2b. Generally, the prevalence of post-BD AO increased with an increasing number of

Table 2. AO before and after BD tests**a** Based on the two cut-off values by sex and age groups

	FEV ₁ /FVC <0.7		FEV ₁ /FVC <GLI-LLN	
	before the BD test	after the BD test	before the BD test	after the BD test
Men ^a	935 (140)	758 (100)	935 (90)	758 (65)
Overall prevalence ^b , %	14.9 (12.6–17.7)	13.2 (10.7–16.1)	9.6 (7.7–11.8)	8.6 (6.6–10.9)
Prevalence by age groups ^b , %				
35–44 years	7.0 (3.8–11.8)	2.6 (0.7–6.7)	7.0 (3.8–11.8)	3.3 (1.1–7.7)
45–54 years	12.1 (8.1–17.4)	8.7 (5.2–13.7)	9.2 (5.8–13.9)	8.2 (4.8–13.1)
55–64 years	17.1 (13.2–21.9)	16.8 (12.5–22.3)	9.8 (6.8–13.5)	8.9 (5.8–13.1)
65–70 years	26.4 (18.3–36.8)	26.9 (18.0–38.6)	14.0 (8.3–22.1)	15.7 (9.2–25.2)
Women ^a	2,039 (107)	1,630 (62)	2,039 (84)	1,630 (49)
Overall prevalence ^b , %	5.2 (4.3–6.3)	3.8 (2.9–4.9)	4.1 (3.9–5.1)	3.0 (2.2–4.0)
Prevalence by age groups ^b , %				
35–44 years	2.0 (0.9–4.0)	0.6 (7.2–6.7)	4.1 (2.3–6.6)	0.9 (0.2–2.8)
45–54 years	4.3 (2.9–6.5)	3.6 (2.1–5.9)	4.2 (2.6–6.2)	3.6 (2.1–5.9)
55–64 years	6.6 (5.0–8.5)	5.3 (3.7–7.3)	4.2 (3.0–5.9)	3.7 (2.4–5.4)
65–70 years	7.8 (4.7–12.2)	4.1 (1.8–8.1)	3.7 (1.7–7.0)	2.6 (0.8–6.0)
RESPECT ^a	2,974 (247)	2,388 (162)	2,974 (174)	2,388 (114)
Overall prevalence ^b , %	8.3 (7.3–9.4)	6.8 (5.8–7.9)	5.9 (5.0–6.8)	4.8 (3.9–5.7)
Prevalence by age groups ^b , %				
35–44 years	3.7 (2.3–5.6)	1.3 (0.5–2.8)	5.1 (3.4–7.2)	1.7 (0.7–3.4)
45–54 years	6.6 (5.0–8.7)	5.3 (3.6–7.3)	5.7 (4.1–7.6)	5.1 (3.5–7.2)
55–64 years	9.8 (8.1–11.7)	8.8 (7.0–10.8)	5.9 (4.6–7.4)	5.3 (3.9–6.9)
65–70 years	14.3 (10.7–18.6)	12.3 (8.6–16.9)	7.3 (4.8–10.6)	7.3 (4.6–11.0)

^a Total number with number of obstructions in parentheses. ^b Figures in parentheses indicate 95% CI.

b Based on the two cut-off values by smoking status

	FEV ₁ /FVC <0.7		FEV ₁ /FVC <GLI-LLN	
	before the BD test	after the BD test	before the BD test	after the BD test
Men ^a	935 (140)	758 (100)	935 (90)	758 (65)
Overall prevalence ^b , %	14.9 (12.6–17.7)	13.2 (10.7–16.1)	9.6 (7.7–11.8)	8.6 (6.6–10.9)
Prevalence by smoking status ^b , %				
Never	4.8 (2.5–8.4)	4.6 (2.1–8.7)	2.8 (1.9–3.6)	3.6 (1.4–7.4)
Current smoker	22.5 (18.3–27.5)	19.2 (14.9–24.3)	14.6 (11.2–18.7)	12.5 (9.1–16.7)
Ex-smoker	12.1 (8.2–17.3)	10.6 (6.5–16.1)	7.7 (4.6–12.0)	6.0 (3.1–10.5)
Prevalence by smoking exposure ^c				
<10 pack-years	10.2 (5.4–17.4)	10.6 (5.1–19.6)	5.5 (2.2–11.3)	4.3 (1.2–10.9)
≥10 and <20 pack-years	8.7 (4.6–14.9)	6.3 (2.5–13.0)	6.7 (3.3–12.3)	5.4 (2.0–11.8)
≥20 pack-years	25.4 (20.46–30.9)	21.4 (16.6–26.7)	16.7 (12.6–21.0)	13.7 (10.0–18.2)
Women ^a	2,039 (107)	1,630 (62)	2,039 (84)	1,630 (49)
Overall prevalence ^b , %	5.2 (4.3–6.3)	3.8 (2.9–4.9)	4.1 (3.9–5.1)	3.0 (2.2–4.0)
Prevalence by smoking status ^b , %				
Never	3.9 (2.9–5.2)	2.7 (1.8–3.9)	2.6 (1.8–3.6)	2.0 (1.3–3.1)
Current smoker	8.9 (6.3–12.2)	6.2 (3.9–9.3)	7.3 (5.0–10.3)	5.6 (3.4–8.7)
Ex-smoker	5.9 (3.4–9.5)	5.3 (2.7–9.2)	6.3 (3.7–10.0)	3.5 (1.5–6.9)
Prevalence by smoking exposure ^c				
<10 pack-years	5.2 (3.2–8.1)	3.6 (1.8–6.5)	5.0 (3.0–7.7)	3.3 (1.6–6.0)
≥10 and <20 pack-years	8.4 (4.6–14.1)	7.1 (3.4–13.1)	9.6 (5.5–15.6)	6.4 (3.0–12.2)
≥20 pack-years	13.2 (8.3–20.0)	9.6 (5.1–16.3)	9.0 (5.0–14.8)	6.6 (3.0–12.6)

Table 2 (continued)

	FEV ₁ /FVC <0.7		FEV ₁ /FVC <GLI-LLN	
	before the BD test	after the BD test	before the BD test	after the BD test
RESPECT ^a	2,974 (247)	2,388 (162)	2,974 (174)	2,388 (114)
Overall prevalence ^b , %	8.3 (7.3–9.4)	6.8 (5.8–7.9)	5.9 (5.0–6.8)	4.8 (3.9–5.7)
Prevalence by smoking status ^b , %				
Never	4.1 (3.1–5.2)	3.0 (2.1–4.1)	2.6 (1.9–3.6)	2.3 (1.5–3.3)
Current smoker	15.7 (13.2–18.5)	12.7 (10.2–15.6)	10.9 (8.9–13.4)	9.1 (7.0–11.6)
Ex-smoker	8.8 (6.5–11.7)	7.7 (5.3–10.9)	6.9 (4.9–9.6)	4.7 (2.9–7.2)
Prevalence by smoking exposure ^c				
<10 pack-years	6.5 (4.4–9.1)	5.3 (3.3–8.1)	5.1 (3.3–7.4)	3.5 (1.9–5.9)
≥10 and <20 pack-years	8.5 (5.6–12.4)	6.8 (4.0–10.8)	8.2 (5.4–12.0)	6.0 (3.3–9.9)
≥20 pack-years	21.7 (18.0–26.0)	17.9 (14.3–22.1)	14.2 (11.2–17.7)	11.7 (8.8–15.2)

^a Total number with number of obstructions in parentheses. ^b Figures in parentheses indicate 95% CI. ^c One pack-year of smoking indicates that an individual smoked one package of cigarettes (20 cigarettes) daily for 1 year.

Table 3. Multivariable analysis of risk factors for AO by the two cut-offs after BD testing

	AO hazard ratio (95% CI)					
	FEV ₁ /FVC <0.7			FEV ₁ /FVC <GLI-LLN		
	model 1	model 2	model 3	model 1	model 2	model 3
Age	1.08 (1.06–1.10)*	1.08 (1.05–1.10)*	1.07 (1.05–1.10)*	1.05 (1.02–1.07)*	1.05 (1.02–1.08)*	1.04 (1.01–1.075)**
Sex (male)	2.63 (1.84–3.76)*	2.59 (1.78–3.76)*	3.06 (2.07–4.53)*	2.09 (1.39–3.15)*	2.10 (1.36–2.23)**	2.51 (1.60–3.95)*
Smoker/ex-smoker	3.08 (2.05–4.62)*	2.98 (1.95–4.53)*	2.47 (1.60–3.82)*	2.79 (1.75–4.44)*	2.60 (1.61–4.20)*	2.06 (1.25–3.39)**
Dusty work, >10 years		1.17 (0.75–1.82)	1.05 (0.67–1.64)		1.27 (0.76–2.12)	1.14 (0.66–1.87)
Gas/chemical fumes at work, >10 years		1.47 (0.95–2.27)	1.40 (0.90–2.18)		1.16 (0.69–2.00)	1.09 (0.65–1.84)
Highly exposed to biomass fuel		1.61 (0.81–3.19)	1.65 (0.83–3.30)		1.04 (0.53–2.05)	1.05 (0.52–2.09)
Chronic cough			1.76 (1.22–2.53)**			2.10 (1.36–3.24)**
Chronic dyspnoea			2.23 (1.55–3.22)*			2.44 (1.59–3.76)*

Model 1: adjusted for age, gender and smoking status; model 2: model 1 adjusted for exposure to dust, gas or chemical fuels at work and exposure to biomass fuels (firewood used >5 days per week); model 3: model 2 adjusted for chronic cough or chronic dyspnoea. Reference categories: FEV₁/FVC ≥0.7 and FEV₁/FVC ≥GLI-LLN. * p < 0.001, ** p < 0.05. Highly exposed to biomass fuels was defined as higher wood/coal stove use (>5 times/week). Chronic cough was defined as the presence of any cough first thing in the morning or during the day or on most days for as long as 3 months each year. Chronic dyspnoea was defined as the presence of any dyspnoea (shortness of breath when hurrying on level ground or walking up a slight hill or walking with other people of his/her own age on level ground or having to stop for breath when walking at his/her pace on level ground).

pack-years, and among never-smokers it tended to be similar to the prevalence in those with <10 pack-years of smoking exposure.

The prevalence of reversible AO for the fixed and GLI-LLN cut-offs (FEV₁ ≥12% and 200 ml after BD) was 1.3% (95% CI 0.9–1.9) and 1.1% (95% CI 0.7–1.6), respectively (fig. 1, 2).

The results of our sensitivity analysis using three different adjustment methods for modelling non-participation are reported in online supplementary appendix 2. We found no relevant difference between the global and sex-specific prevalence observed in the RESPECT population, and the estimates after adjustments.

Age, sex and smoking status were risk factors for AO according to both cut-offs, even after adjusting for occupation (dusty jobs ≥10 years, gas/chemical fume exposure

≥10 years), indoor pollution (significant exposure to biomass fuels) and existing respiratory symptoms (chronic cough and dyspnoea; table 3). Dyspnoea was more strongly associated with AO than cough for both cut-offs. There was no association between AO and any kind of exposure (e.g. occupational hazards and indoor pollution), except for tobacco.

Using the ATS/ERS criteria (FEV₁ >12% and 200 ml), approximately 3% of the participants without AO according to both cut-offs had a 'significant' response to a BD (fig. 1, 2).

At least 0.97% (95% CI 0.60–1.49) of the participants without pre-BD AO according to the fixed cut-off and 0.76% (95% CI 0.4–1.2) of those according to GLI-LLN demonstrated a negative response after the administration of BD (FEV₁/FVC <0.7 or GLI-LLN; fig. 1, 2).

Table 4. Predictive value of chronic respiratory symptoms for AO by the two cut-offs after BD testing

	FEV ₁ /FVC <0.70		FEV ₁ /FVC <GLI-LLN	
	positive	negative	positive	negative
<i>Chronic respiratory symptoms</i>				
With symptoms (n = 1,113)	122	991	89	1,024
No symptoms (n = 1,275)	40	1,235	25	1,250
Total (n = 2,388)	162	2,226	114	2,274
Sensitivity (95% CI), %	75.31 (67.93–81.74)		78.07 (69.35–85.28)	
Specificity (95% CI), %	55.48 (53.39–57.56)		54.97 (52.90–57.03)	
AUC (95% CI)	0.65 (0.61–0.69)		0.66 (0.62–0.71)	
PPV (95% CI), %	10.96 (9.19–12.95)		8.00 (6.47–9.75)	
Negative predictive value (95% CI), %	96.86 (95.75–97.75)		98.04 (97.12–98.73)	
<i>Chronic cough</i>				
With cough (n = 890)	100	790	74	816
No cough (n = 1,487)	61	1,426	39	1,448
Sensitivity(95% CI), %	62.11 (54.14–79.63)		65.49 (55.96–74.18)	
Specificity (95% CI), %	64.35 (62.32–66.35)		63.96 (61.94–65.94)	
AUC (95% CI)	0.63 (0.59–0.68)		0.65 (0.59–0.70)	
PPV (95% CI), %	11.24 (9.24–13.50)		8.31 (6.58–10.33)	
Negative predictive value (95% CI), %	95.90 (94.76–96.85)		97.38 (96.43–98.13)	
<i>Chronic dyspnoea</i>				
With dyspnoea (n = 879)	93	786	69	810
No dyspnoea (n = 1,498)	68	1,430	44	1,454
Sensitivity (95% CI), %	57.76 (49.74–65.50)		61.06 (51.44–70.09)	
Specificity (95% CI), %	64.53 (62.50–66.52)		64.22 (62.21–66.20)	
AUC (95% CI)	0.61 (0.57–0.66)		0.63 (0.57–0.68)	
PPV (95% CI), %	10.58 (8.62–12.80)		7.85 (6.16–9.83)	
Negative predictive value (95% CI), %	95.46 (94.28–96.46)		97.06 (96.08–97.86)	

Chronic respiratory symptoms were defined as the presence of chronic cough and chronic phlegm on most days for as long as 3 months each year, together with chronic dyspnoea. Chronic cough was defined as the presence of any cough first thing in the morning or during the day or on most days for as long as 3 months each year. Chronic dyspnoea was defined as the presence of any dyspnoea (shortness of breath when hurrying on level ground or walking up a slight hill or walking with other people of his/her own age on level ground or having to stop for breath when walking at his/her pace on level ground).

Eighty-six percent of the participants with AO according to the fixed cut-off only, as well as 72.5% of the participants with AO according to both cut-offs, did not report a diagnosis of any chronic respiratory disease (table 4).

The PPV for the diagnosis of chronic AO according to both cut-off values was low for all chronic respiratory symptoms together, as well as for chronic cough and dyspnoea separately (table 4). The PPV for chronic dyspnoea and cough for AO according to the fixed cut-off was significantly higher for men than for women (22.9 and 6.3% for chronic dyspnoea and 19.4 and 6.5% for chronic cough, respectively). The PPV was significantly lower for the younger (35–54 years old) than the older age group (55–70 years old; 5.9 and 14.2% for any respiratory symp-

toms; 5.1 and 16.2% for chronic cough; 5.36 and 13.52% for chronic dyspnoea, respectively).

Discussion

Main Findings and Comparison with Previous Research

In our population-based cross-sectional sample of adults aged 35–70 years in two north-western cities in Russia, post-BD AO according to the GLI-LLN was lower than for the fixed cut-off. AO based on both cut-offs was significantly associated with tobacco exposure, but not with occupational or indoor pollution. The PPV of all chronic respiratory symptoms for AO by both cut-off values (adjusted by sex and age) was low.

AO Prevalence Using the Fixed and GLI-LLN Cut-Offs for FEV₁/FVC

The prevalence of COPD varies significantly across countries, ranging from 15.3 to 28.7% in men and from 7.6 to 25.7% in women (based on the fixed cut-off), and these differences are primarily due to the differences in smoking prevalence between the sexes [4].

A different prevalence for AO is reported in the literature based on the fixed or GLI-LLN cut-off [22, 23]. The prevalence of AO in persons aged 40–95 years in England and Wales is 2.8, 22.2 and 13.1% for diagnosed COPD, fixed-ratio and GLI-LLN values, respectively [23]. The gap in the prevalence between values based on the fixed and GLI-LLN cut-offs is higher in the older age groups. Among adults aged 40–79 years in the USA, the COPD prevalence using the fixed cut-off was 20.9% for pre-BD and 14.0% for post-BD values, while for the LLN it was 15.4 and 10.2%, respectively [24].

In line with these previous studies, we observed that in north-western Russia, the AO prevalence by GLI-LLN was lower than by the fixed cut-off. Previous studies have reported a higher AO prevalence using both fixed and GLI-LLN cut-offs compared to our RESPECT study population, but their populations included more older adults (up to 79 or 95 years old) [23–25]. We also found that our participants with AO were more likely to be older, current smokers, and with more pack-years of smoking, and the gap in the prevalence between the fixed and LLN cut-offs increased in older age groups (0.4% for younger and 5.0% for older age groups, $p < 0.0001$).

Finding a relatively low prevalence of AO in the RESPECT population was unexpected but was supported by a sensitivity analysis. Additional research is needed in order to understand this. One possible explanation could be the huge cardiovascular mortality rate.

Similar to most developed countries, CVD is a leading cause of mortality in Russia, but the levels of CVD mortality in working-age Russian men and women are the highest in Europe. The CVD mortality is 38.8 and 36.8% for men and women aged 25–64 years, respectively. In St. Petersburg, the rate of deaths from CVD among men in this age category is 47.0%, i.e. significantly higher than the average Russian mortality rate [26]. In the Arkhangelsk region, CVDs are the main cause of death at ages <70 years, and were responsible for 35% of all deaths in men and women. Both the absolute number of cardiovascular deaths and the age-standardized rates in men were more than twice those in women [27]. However, our findings should also be put in perspective of our population characteristics. In online supplementary appen-

dix 3, we tried to make an age- and sex-stratified comparison with data available from other northern countries.

Risk Factors for AO

Tobacco smoking and outdoor, occupational or indoor pollution are major COPD risk factors [4, 6, 28]. In our population, only smoking was a risk factor for AO. Although cigarette smoke is widely acknowledged as the single most important risk factor for COPD, never-smokers may account for 25–33% of all COPD cases, with women being a substantial proportion of AO cases [4, 29]. The predictors of COPD in never-smokers include age, education, exposure to occupational hazards, childhood respiratory diseases and BMI.

Our study demonstrated heterogeneity in the prevalence of AO between men and women, and this difference can be at least partly explained by sex differences in the prevalence of cigarette smoking. We observed a fairly high prevalence of AO in never-smokers, particularly in men (4.6% AO in male never-smokers and 2.7% in females, $p < 0.05$). It is still contested whether women are at greater risk for COPD than men if they are equally exposed to smoking and other pollutants [30, 31]. The current understanding of risk factors for COPD is in many aspects still incomplete; a better understanding of relations and interactions between risk factors as well as their contribution to COPD is crucial for developing the best prevention policies including smoking cessation [4, 6].

Paradoxical BD Response and Overlap Syndrome

In our study, we found that approximately 1% of the participants with normal pre-BD FEV₁/FVC using both cut-offs converted to AO after BD administration. This significant reduction in lung function after the administration of a BD is termed paradoxical bronchoconstriction [32], and it has been previously reported to range between 0.5 and 1.5% according to the fixed and GLI-LLN cut-offs, respectively [33, 34]. In another study, paradoxical responses were noted in 5% of the patients, and their frequency was similar in those with COPD and in smokers without AO [35]. This phenomenon was also independently associated with COPD intermediate end-points, including reduced exercise capacity, increased dyspnoea and a greater frequency of exacerbations, and the authors assume it is an enigmatic COPD phenotype [35].

A few possible explanations regarding a paradoxical (or negative) BD response can be forwarded, for example as an isolated increase in residual volume (a peripheral

AO) and a decrease in FEV₁ (a bronchoconstriction that might be triggered by repeated maximum respiratory manoeuvres during spirometry) [36–38]. Additional research is needed in order to investigate this phenomenon, which appeared to be more frequent than we suspected.

Recently, it has been reported that approximately 15–45% of the population with obstructive airway disease may have asthma-COPD overlap syndrome [39]. In our population, we found reversible AO in 1.3% of all participants. We also observed a positive reversibility test in 22.5% (32/142) of those with post-BD AO by the fixed cut-off, suggesting that these participants may have asthma-COPD overlap syndrome, but this finding should be put in perspective of an additional clinical assessment [40].

Predictive Value of Symptoms for AO

The diagnosis of COPD is complex, including spirometry-based AO as well as symptoms and risk factors. Thus far, spirometry has been the basis for COPD diagnosis using a fixed or LLN cut-off of FEV₁/FVC, but neither of these cut-offs is able to fully characterize the complex diagnostic features of this disease [41]. An assessment of COPD, particularly for milder AO, requires a comprehensive clinical and functional evaluation that cannot be limited to an FEV₁/FVC value [42].

In addition, in patients with similar degrees of AO, perceived symptoms and signs, such as dyspnoea and/or breathlessness, cough or mucus production, peripheral muscle weakness, exercise tolerance or physical capacity, can vary greatly [43].

The diagnostic value of clinical signs and symptoms for COPD is still contested [44, 45]. Price et al. [44] have reported on a simple self-administered patient questionnaire that could be used to identify patients exhibiting a high likelihood of COPD for whom spirometry testing would be important. Eight items in this questionnaire had significant relationships with COPD diagnosis, including age, pack-years, BMI, symptoms, wheezing frequency and history of allergies. Only one cough-related and one dyspnoea-related item significantly predicted COPD in a multivariate analysis [44]. Another study showed that the PPV was 12.2% when using only respiratory symptoms, but 43.5% when using symptoms with spirometry [45].

In our population-based study, we found a low PPV for symptoms regarding AO diagnosis (10.96% for chronic respiratory symptoms, 11.24% for cough and 10.58% for dyspnoea), thus supporting the need for a comprehensive COPD diagnosis that includes spirometry.

Strengths and Limitations

The protocol of the RESPECT study enabled the collection of information about several potential risk factors for COPD including smoking, occupational exposure to dust, indoor exposure to biomass fuels used for home heating and cooking, tuberculosis and socioeconomic status considering validated international questionnaires. Spirometry was performed before and after the BD test and followed the ATS/ERS standards of spirometry quality. Our study is the first to report the prevalence of AO in a cohort population in north-western Russia using the recently published GLI 2012 reference values and comparing it with the fixed cut-off, as well as analysing predictors of AO and the diagnostic value of respiratory symptoms.

Our study has also some limitations. We restricted our sample population to individuals aged 35–70 years, because COPD develops over several decades of exposure to inhaled particulates, and our aim was to identify the early stages of COPD and AO.

The RESPECT study population differs from the total population of the north-western region of Russia in terms of age and sex [46]. It includes more women than the average population in the north-western region of Russia (68.2 vs. 55.3%), as well as more participants aged 55–70 years (53.7 vs. 35.3%). It also includes fewer current and ex-smokers than the average Russian population [47] (47.8 vs. 53.9%). These differences might have led to a discrete underestimation of the AO prevalence.

Conclusion

In a representative sample of adults aged 35–70 years in north-western Russia, the prevalence of post-BD AO was higher when using the fixed rather than the GLI-LLN cut-off for FEV₁/FVC. Only tobacco smoking was an independent risk factor for AO, while there was no association between AO by both cut-offs and reported exposure to occupational or indoor pollution. The diagnostic value of respiratory symptoms for AO by both cut-offs was low, supporting a comprehensive approach to diagnosing COPD which includes spirometry and the assessment of symptoms and risk factors.

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The authors declare that they have no competing interests.

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