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Prevalence, symptom burden and under-diagnosis of Chronic Obstructive Pulmonary Disease in Polish lung cancer screening population.

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Title:

Prevalence, symptom burden and under-diagnosis of Chronic Obstructive Pulmonary Disease in polish lung cancer screening population.

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Abstract:

Objectives:
Lung cancer screening using LDCT may be not effective without consideration the presence of comorbidities related to chronic smoking. The aim of the study was to establish the prevalence of COPD in group of patients participating in the largest Polish lung cancer screening programme MOLTEST BIS and attempt to confirm necessity of combine lung cancer and COPD screening

Design:
cohort, prospective study

Setting:
Medical University of Gdańsk, Poland

Participants:
The study included 754 participants of lung cancer screening trial from Pomeranian region, aged 50-70 years old, current and former smokers with a smoking history ≥30 pack-years.

Primary and secondary outcome measures:
questionnaire, physical examination, anthropometric measurements, spirometry test before and after taking bronchodilator druga (400µg of salbutamol)

Results:
Obstructive disorders were diagnosed in 186 cases (103 male and 83 female). In case of 144 participants (19,73%) COPD was diagnosed. Only 13,3% of participants with COPD were known about the disease earlier. According to classification of airflow limitation 55,6 % of diagnosed COPD were in GOLD 1 (mild), 38,9 % in GOLD 2 (moderate), 4,9 % in GOLD 3 (severe) and 0,7 % in GOLD 4 (very severe) stage. Women with recognition of COPD were younger than men (63.7 vs 66.3 age) and they smoked less cigarettes (41.1 vs 51.9 pack-years).

Conclusions:
Prevalence of COPD in polish lung cancer screening cohort is significant. The COPD in this group is remarkably under-diagnosed. Most of diagnosed COPD cases were in initial stage of advancement. This early detection of airflow limitation highlight the potential benefits arising from combined oncological-pulmonary screening.

Trial registration:
Independent Bioethics Committee for Scientific Research at the Medical University of Gdańsk (No NKBBN / 173/2016)

Strengths and limitations of this study

- This was the largest Polish lung cancer screening program in which we enclosed additional diagnostic procedures to assess prevalence of most common comorbidities to establish optimal criteria for patients considered for lung cancer screening and further diagnostic.
- This was only one of few LDCT trial in Europe in with we established prevalence of COPD according with all respiratory guidelines by perform full spirometry with the bronchodilator reversibility test.
- The limitations of our study include the lack of randomization resulting from the specificity of screening tests, which are design for volunteers.

Introduction

Screening for lung cancer became the standard of care in USA, being piloted in Europe increasingly.(1)(2) In many countries studies have been conducted to assess the benefits of screening for this cancer and to determine the optimal eligibility criteria for screening tests.(3) Based on the data obtained from multicenter studies covering the smoking population, it has been proven that lung cancer screening using low-dose computed tomography (LDCT) in

people at high risk of this cancer may significantly reduce mortality in this group of patients.(4)(5) Ten-year follow-up of people who had underwent lung cancer screening as part of the European NELSON study (Nederlands-Leuvens Longkanker Screenings Onderzoek) showed a reduction in cancer deaths by 26% in men and by 61% in women.(1) However, researchers agree that appropriate group selection, taking into account comorbidities that may reduce the effectiveness of tests, is crucial for lung cancer screening to become the standard of care, reduce mortality and be cost-effective.(6)(7)(8)

Smoking is not only responsible for the development of lung cancer, but is also involved in the etiology of over 80% of chronic obstructive pulmonary disease (COPD) cases.(9) The most recent analyzes of the World Health Organization (WHO) indicate that 251 million people worldwide suffer from COPD and it is the third cause of death.(10)(11)

Given the high prevalence of COPD in the general population, the ever increasing mortality from this disease, and its close relationship with smoking, the presence of COPD should be an important factor in qualifying patients for lung cancer screening. People with COPD have been shown to have twice the risk of developing lung cancer than smokers without COPD.(7)(8)(11)(12)(13)(14) Moreover, in this group of patients there are more complications related to the diagnostic procedures and treatment of the diagnosed lung cancer. These patients are more likely to develop complications after biopsy, such as pneumothorax and bleeding requiring transfusion of blood products.(15) In the perioperative period, patients with COPD are more likely to develop respiratory failure, stay in hospital longer after surgery, and have an increased risk of 30-day mortality.(7)(16)

Therefore, the aim of this study is to establish the prevalence and clinical characteristics of COPD in a cohort of adult Poles who underwent screening for lung cancer.

Materials and methods

Screening of patients for the diagnosis of COPD was carried out as part of the MOLTEST-BIS program, which is one of the first Polish screening programs dedicated to the early diagnosis of lung cancer in the group of long-term tobacco smokers.(17) The project was implemented in 2016–2018 by the Medical University of Gdańsk. People aged 50 to 79 years, inhabitants of the Pomeranian Voivodeship, with a smoking history of over 30 pack-years were eligible for the study. Both current smokers and those who quit smoking no later than 15 years prior to the study enrollment date were included in the study. The study was aimed at a comprehensive

health assessment of the population undergoing screening for comorbidities, and in particular COPD.

All participants in the study were interviewed using a standardized questionnaire. The questionnaire included questions about the patient's medical history, with particular emphasis on chronic diseases, medications, respiratory and cardiovascular symptoms, smoking history, socio-demographic data, healthy behaviors and physical activity. Then physical examination, anthropometric measurements, electrocardiographic examination, three measurements of blood pressure according to the ESH / ESC recommendations, and heart rate assessment were examined.(18)(19) Each participant underwent a spirometry test using a Jaeger Masterscreen Pneumo (Germany) spirometer. Pulmonary function tests were performed by an experienced spirometry technician. The results were analyzed by a pulmonologist. Spirometry was performed in accordance with the current ERS / ATS standards.(20) If obstructive disorders were found, spirometry was repeated 20 minutes after the administration of 400 µg of salbutamol from a pressurized inhaler (Fig. 1). The COPD Assessment Test (CAT) was performed in people diagnosed with COPD and the incidence of dyspnea was assessed according to the mMRC (modified Medical Research Council) scale. The spirometric assessment and classification of the disease severity were carried out based on the guidelines of the Global Initiative for Chronic Obstructive Lung Disease (GOLD).(21)

Before the spirometry test, when participants were contacted by phone to arrange the test date, everyone was instructed on how to properly prepare for the test. After a comprehensive cardiovascular and pulmonary assessment, participants received feedback on their health. People whose tests revealed significant abnormalities were referred to specialists in order to extend the diagnosis or initiate appropriate treatment (e.g. COPD).

In addition, each tobacco smoker underwent smoking cessation intervention (5 A's to help patients quit tobacco).(22)

All participants in the study gave informed consent to participate and underwent medical procedures, such as taking samples for laboratory tests and assessing respiratory function. The study was approved by the Independent Bioethics Committee for Scientific Research at the Medical University of Gdańsk (No NKBBN / 173/2016).

In the statistical analyzes carried out in the study, quantitative variables were described with mean values and medians, and qualitative variables were presented as percentages with counts. The assumption of distribution normality was verified with the Shapiro-Wilk test. The significance of differences between the qualitative variables was tested using the Fisher test. The hypotheses were verified with two-sided tests. The level of significance was $p = 0.05$.

Patient and Public Involvement:

No patient involved

Results

The inclusion criteria for the study were met by 754 people. The analysis included the results of 730 screened participants who had no contraindications to perform spirometry and whose test results were without technical errors (Figure 1). Among people who had a spirometry test, 335 women and 395 men. The mean age of men and women participating in the study did not differ significantly and was 63 and 63.5 years, respectively.

As shown in Table 1, obstructive disorders were found in 186 patients (103 men and 83 women). Bronchodilator test showed irreversible obstruction in 144 patients (86 men and 58 women). COPD was diagnosed in 19.7% of the study participants.

Table 1. Proportion of patients with pulmonary function abnormalities in spirometry.

	Overall (N=730)	Men (M) (N=395)	Women (W) (N=335)	P-value M vs W
Obstruction	25.5% (186)	26.1% (103)	24.8% (83)	0.752
Irreversible obstruction (COPD)	19.7% (144)	21.7% (86)	17.3 % (58)	0.157
Reversible obstruction (ASTHMA)	5.7% (42)	4.3% (17)	7.4% (25)	0.096

There was no difference in the incidence of COPD between women and men. Only 13.3% of the subjects diagnosed with COPD based on spirometry were aware of the disease – 11.6% of men and 15.8% of women; the difference was not statistically significant (p = 0.641).

The mean FEV1 (forced expiratory volume in 1 second) in the entire cohort was 97.8%. In people without COPD, FEV1 was 103%, and in those with diagnosed COPD, the value of this

parameter was 75.6%. The most important spirometric parameters before and after administration of a bronchodilator in case of group diagnosed with COPD are presented in Table 2.

Table 2. Spirometric parameters in group with COPD

	Overall (N=144)	Men (M) (N=86)	Women (W) (N=58)	P-value M vs W
SPIROMETRIC PARAMETERS BEFORE BRONCHODILATOR				
FEV1 (% predicted value)	75.6	78.8	73.3	0.048
VC (L)	3.6	2.9	4.1	<0.001
FEV1/VC (%)	56.4	57.4	55.8	0.269
SPIROMETRIC PARAMETERS AFTER BRONCHODILATOR				
FEV1 (% predicted value)	80.812	78.550	84.167	0.027
VC (L)	3.848	4.339	3.120	<0.001
FEV1%/VC (%)	57.694	56.793	59.030	0.024

Table 3 presents data on the severity of the diagnosed COPD cases. In our analysis, according to the GOLD criteria for airflow-limitation severity, 55.6% of patient had mild obstruction, 38.9% moderate, 4.9% severe and 1.7% had very severe airflow obstruction. After assigning the diagnosed COPD cases to the appropriate category according to GOLD "ABCD" classification, most patients were in group B (63.9%) with more symptoms and a low risk of disease exacerbation, 29% were in group A, 1.4% in group C and 5.5% in group D.

Table 3. Classification of severity of diagnosed COPD cases.

	Overall (N=144)	Men (M) (N=86)	Women (W) (N=58)	P-value (M vs W)
GOLD CLASSIFICATION OF SEVERITY OF AIRFLOW OBSTRUCTION				
Mild **GOLD 1** [FEV1 ≥80%]	55.6% (80)	50.0% (43)	63.8% (37)	
Moderate **GOLD 2** [FEV1 50–79%]	38.9% (56)	45.3% (39)	29.3% (17)	0.137
Severe **GOLD 3** [FEV1 30–49%]	4.9% (7)	4.7% (4)	5.2% (3)	
Very severe **GOLD 4**	1.7% (1)	0% (0)	0.7% (1)	

[FEV1 <30%]				
GOLD CLASSIFICATION OF COPD SEVERITY				
A (less symptoms and low risk of exacerbations)	29.2% (42)	27.9% (24)	31% (18)	0.959
B (more symptoms; low risk of exacerbations)	63.9% (92)	66.3% (57)	60.3% (35)	
C (less symptoms, but high risk of exacerbations)	1.4% (2)	1.2% (1)	1.7% (1)	
D (more symptoms; high risk of exacerbations)	5.5% (8)	5.8%(5)	5.1% (3)	

Screened patients with and without COPD were compared in terms of age, symptoms, and hospitalization rates (Table 4). The mean age of people diagnosed with COPD was 65.2 years and was significantly higher than that of people without the disease, 62.7 years. The mean age of men was 66.3 years in those with COPD and 62.5 years in those without COPD ($p < 0.001$). For women, it was 63.8 years and 62.7 years, respectively ($p = 0.212$).

People with COPD significantly more often reported chronic cough, defined as a cough lasting more than 8 weeks, (39% vs 29.9%) and dyspnea (51% vs 33.7%). There was no difference in the reporting rate of dyspnea between women without COPD and women with COPD.

The subjects were asked about hospitalization for coughing, breathlessness or shortness of breath. Respondents diagnosed with COPD reported it more often than people without the disease (6.9% vs 1.7%).

In the CAT test assessing the impact of COPD on the quality of life of patients, the mean score achieved by people diagnosed with COPD was 13.7 points out of maximum achievable score of 40 and it did not differ significantly by gender.

Table 4. Symptomatology

	Men (N=395)			Women (N=335)			Overall (N=730)		
	COPD (N=86)	Non-COPD (N=309)	P-value	COPD (N=58)	Non-COPD (N=277)	P-value	COPD (N=144)	Non-COPD (N=586)	P-value
Age	66.3	62.6	<0.001	63.7	62.7	0.212	65.2	62.7	<0.001
Cough	37.2% (32)	24.9% (77)	0.034	43.1% (25)	28.5% (79)	0.042	39% (57)	29.9% (175)	0.032

Dyspnea	50.6% (43)	26.3% (81)	<0.001	51.7% (30)	42% (116)	0.176	51% (73)	33.7% (197)	<0.001
Dyspnea severity according to the mMRC scale			0.08			0.159			0.022
0	14% (6)	33.8% (27)		6.7% (2)	23.3% (27)		11% (8)	27.6% (54)	0.033
1	53.5% (23)	46.2% (37)		53.3% (16)	49.1% (57)		53.4% (39)	48% (94)	0.49
2	25.6% (11)	15% (12)		26.7% (8)	20.7% (24)		26% (19)	18.4% (36)	0.17
3	7% (3)	5% (4)		13.3% (4)	6% (7)		9.6% (7)	5.6% (11)	0.06
4	0% (0)	0% (0)		0 (0%)	0.9% (1)		0% (0)	0.5% (1)	<1
Hospitalizations	7% (6)	1.3% (4)	0.003	6.9% (4)	2.2% (6)	0.054	6.9% (10)	1.7% (10)	<0.001

Data on smoking, education and type of work are presented in Table 5. The number of cigarettes smoked was significantly higher in people with COPD compared to those without COPD. Among men with COPD, the average number of pack-years was 51.9 and was significantly higher than in women diagnosed with COPD (41.1 pack-years). People diagnosed with COPD were significantly more often blue-collar than white-collar workers. There were also statistically significant differences in education between men diagnosed with COPD and men without the disease. Among men diagnosed with COPD, 39.5% had primary education, 39.5% had secondary education, and only 20.9% had higher education. In men without COPD, secondary education was the most frequent – 42.4%, and only 26.9% had primary education. No significant differences in the level of education between the groups were found in women.

Table 5. Sociodemographic data and smoking history.

	Men (N=395)			Women (N=335)		
	COPD (N=86)	Non-COPD (N=309)	P-value	COPD (N=58)	Non-COPD (N=277)	P-value
SMOKING STATUS						
Pack-years (mean)	51.9	45.4	0.002	41.155	31.91	<0.001
Current smoker	69.8% (60)	60.5% (187)	0.149	72.5% (42)	70.1% (194)	0.839

Former smokers	30.2% (26)	39.5% (122)		27.5% (16)	29.9% (83)	
TYPE OF JOB						
Blue-collar workers	63.9% (53)	58.2% (166)	0.36	46.6% (27)	34.1% (88)	0.075
White-collar workers	36.1% (30)	41.8% (119)		53.4% (31)	65.9% (170)	
EDUCATION LEVEL						
Primary	39.5% (34)	26.9% (83)	0.49	22.4% (13)	21.3% (59)	0.85
Secondary	39.5% (34)	42.4% (131)		46.6% (27)	50.5% (140)	
Higher	20.9% (18)	30.7% (95)		31.0% (18)	28.2% (78)	

There were no differences in the mean values of height, weight, waist circumference and BMI in the groups of women and men with and without COPD. There was a difference in the distribution of BMI between patients with COPD and those without COPD (Table 6).

Table 6. Anthropometric data

	Men (N=395)			Women (N=335)		
	COPD (N=86)	Non-COPD (N=309)	P-value	COPD (N=58)	Non-COPD (N=277)	P-value
Body weight, kg (mean)	86.26	89.15	0.116	70.2	71.7	0.437
BMI, kg/m^2 (mean)	28.43	29.2	0.170	27.2	27.8	0.499
BMI category			0.05			0.442
Underweight (BMI <18.5)	0 (0%)	1 (0.3%)	<1	0% (0)	0,4%(1)	
Normal weight (BMI 18.5–24.99)	26.7% (23)	14.6% (45)	0.0259	37.9% (22)	31.8% (88)	
Overweight (BMI 25.0–29.99)	33.7% (29)	47.7% (147)	0.061	32.8% (19)	38.6% (107)	
Obesity (BMI >=30)	39.5% (34)	37.2% (115)	<1	20.3% (17)	29.2% (81)	

Discussion

Our study shows the prevalence and characteristics of chronic obstructive pulmonary disease in the group of people participating in one of the first lung cancer screening studies in Poland. In our study, almost one-fifth (19.73%) of the participants were diagnosed with COPD.

According to epidemiological studies conducted both in Europe and around the world, the prevalence of COPD in people subjected to lung cancer screening is high; this disease was detected in up to two-thirds of the examined subjects. However, there is a large discrepancy in the results, which may suggest significant differences in the populations participating in the screening, and may result from different eligibility criteria for the study and adopted diagnostic criteria. It is noteworthy that in many of the studies conducted, only basic spirometry was assessed, without the bronchodilator reversibility test, which raises methodological doubts and might cause the obtained results to be overestimated. In one of the largest American lung cancer screening studies, the National Lung Screening Trial (NLST), the prevalence of COPD was 34.4%.(2) However, the bronchodilator test was not performed in this study, which could have an impact on the final result. In the British Lung Screen Uptake Trial (LSUT), the prevalence of COPD among people participating in lung cancer screening was as high as 57%; however, also in this study, analyzes included only basic spirometry without the bronchodilator test.(23) In addition, people aged 60–75 were eligible for the study, which means that the participants were older than in most lung cancer screening tests. The prevalence of COPD found in our study may appear lower than in most countries; however, the diagnosis of this disorder was carried out in accordance with the GOLD and the Polish Society of Lung Diseases guidelines ,(9)(21) using a complete diagnostic scheme including the bronchodilator reversibility test in every person with airflow obstruction. Additionally, the severity of COPD symptoms was assessed using the tools recommended in the guidelines: CAT test and mMRC scale. Such analyzes reliably refine the diagnosis of COPD. Unfortunately, it seems that the prevalence of COPD, as assessed in our study, may be underestimated. It should be emphasized that it was the second stage of the pilot screening study carried out in a big city, which was attended by people who were more interested in their health condition, with a higher socio-economic status, better education and higher awareness of diseases. It is a characteristic feature of the population participating in each screening test, but nevertheless this effect in the Polish population seems to be particularly pronounced. Compared to the above-mentioned multicenter studies, this could have resulted in the a lower accessibility of the study for volunteers from more distant parts of the voivodeship, especially from small towns and villages, where the prevalence of COPD may be higher than in large cities.

Another important aspect that should be highlighted is the number of newly diagnosed COPD cases. Analyzing the respondents' answers regarding their knowledge about the earlier diagnosis of COPD and considering the medications taken by the respondents, only 13.3% of people diagnosed with COPD during the visit knew about the disease beforehand. For example,

in the previously mentioned British study,(23) 33% participants were aware of COPD, and in the American study this proportion was almost 60%.(2) These data highlights how underdiagnosed the Polish population is in terms of lung diseases. Considering the importance of the presence of COPD in the diagnostic and therapeutic process and in the stratification of the benefits and risks of lung cancer screening, as well as the low awareness of the disease, it should be considered that the diagnosis of this disorder during screening should become a standard of care.

According to the above analyzes, it seems that women are the group that should receive special attention when diagnosing COPD. Our results show that not only do women suffer from COPD at a younger age than men, but also with significantly less exposure to tobacco smoke. The frequency of the individual symptoms reported by the women was the same, regardless of whether they had COPD or not. In this group, the inclusion of early screening for COPD in lung cancer diagnostic testing may be particularly important.

Although the benefits of lung cancer screening have been proven in long-term observational studies, the financial burden on healthcare systems due to the high cost of the study remains under discussion. Research is ongoing in many countries on the potential introduction of a combined lung cancer screening and comorbidities, which could contribute to greater cost-effectiveness of the study and lower mortality associated with comorbidities in long-term smokers.(1)(4)(24) Most of the COPD cases diagnosed in our study were classified as low-stage disease (the most common were mild obstruction and COPD stages A and B). Studies show that in the early stages of the disease, patients die more often from lung cancer than from respiratory failure, the latter predominating at higher disease severity categories.(25) Therefore, people with early-stage COPD are optimal candidates for lung cancer screening, as the benefits of potential diagnosis and treatment for this cancer may outweigh the risk of possible adverse effects. Currently, analyzes are also conducted on the feasibility and cost-effectiveness of a combined screening for lung cancer and COPD by assessing the presence of emphysema in low-dose computed tomography.(6)(26)(27) Determining the prevalence of COPD by means of spirometry in the Polish population undergoing screening for lung cancer and the possible correlation of our results with the assessment of the severity of emphysema and symptoms of chronic bronchitis in LDCT, may contribute in the future to broadening the scope of diagnostic imaging examinations to assess the functioning of the respiratory system, which would make the screening applied cost-effective.

The limitations of our study include the lack of randomization resulting from the specificity of screening tests, which are aimed at people willing to participate. Moreover, the study, due to

time constraints, did not include the entire cohort of lung cancer screening participants, but only a part of the group. Due to easier access to the study of people from a big city, this group constituted the majority of participants, which could also have influenced the results obtained.

Conclusions

Our study showed a significant prevalence of COPD in a cohort of Polish smokers participating in the lung cancer screening test. Awareness of the disease in this group is very low and amounts to approx. 13%. Most people diagnosed with COPD are in the early clinical stage, which allows for effective prevention and means that they may be potential beneficiaries of lung cancer screening. Further studies are needed to assess the effectiveness of COPD diagnosis and prevention in this group in order to assess the effectiveness of combined oncological-pulmonary screening.

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Competing Interests: The authors have no conflicts of interest to declare

Contributorship statement: AU, KK, WR, TZ designed the study. AU, PK, AR performed literature search and conduct the study, AU and KK analyse spirometry results, AU, KK, TZ, WR, PK contributed to data analysis. AU wrote first draft and all authors contributed to producing the final text of the manuscript.

Ethics approval statement: Independent Bioethics Committee for Scientific Research at the Medical University of Gdańsk (No NKBBN / 173/2016). The participants were informed about the all procedures and signed the agreement to participate in the trial. The researchers informed participants about the results by mail or phone.

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Figure 1. Diagnostic diagram.

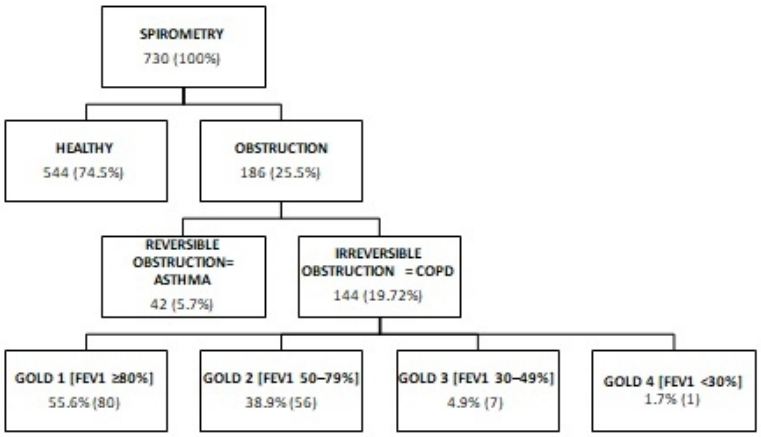

Figure 1. Diagnostic diagram

Diagnostic diagram

100x58mm (144 x 144 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3.4
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	3
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4-5
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	4-9
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	4-5

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	4-9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	4-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10,11,12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Prevalence, symptom burden and under-diagnosis of Chronic Obstructive Pulmonary Disease in Polish lung cancer screening population: a cohort observational study.

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Title:

Prevalence, symptom burden and under-diagnosis of chronic obstructive pulmonary disease in Polish lung cancer screening population: a cohort observational study.

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Abstract:

Objectives:
Lung cancer screening using LDCT may be not effective without consideration the presence of comorbidities related to chronic smoking. The aim of the study was to establish the prevalence of COPD in group of patients participating in the largest Polish lung cancer screening programme MOLTEST BIS and attempt to confirm necessity of combined lung cancer and COPD screening

Design:
cohort, prospective study

Setting:
Medical University of Gdańsk, Poland

Participants:
The study included 754 participants of lung cancer screening trial from Pomeranian region, aged 50-70 years old, current and former smokers with a smoking history ≥30 pack-years.

Primary and secondary outcome measures:
questionnaire, physical examination, anthropometric measurements, spirometry test before and after inhaled bronchodilator (400µg of salbutamol)

Results:
Obstructive disorders were diagnosed in 186 cases (103 male and 83 female). In case of 144 participants (19.73%) COPD was diagnosed. Only 13.3% of participants with COPD were known about the disease earlier. According to classification of airflow limitation 55.6 % of diagnosed COPD were in GOLD 1 (mild), 38.9 % in GOLD 2 (moderate), 4.9 % in GOLD 3 (severe) and 0.7 % in GOLD 4 (very severe) stage. Women with recognition of COPD were younger than men (63.7 vs 66.3 age) and they smoked less cigarettes (41.1 vs 51.9 pack-years).

Conclusions:
Prevalence of COPD in Polish lung cancer screening cohort is significant. The COPD in this group is remarkably under-diagnosed. Most of diagnosed COPD cases were in initial stage of advancement. This early detection of airflow limitation highlight the potential benefits arising from combined oncological-pulmonary screening.

Trial registration:
Independent Bioethics Committee for Scientific Research at the Medical University of Gdańsk (No NKBBN / 173/2016)

Strengths and limitations of this study

- the largest Polish lung cancer screening program with additional diagnostic procedures to assess prevalence of most common comorbidities
- one of few LDCT trials in Europe in which the prevalence of COPD was established according to all respiratory guidelines by performing full spirometry with the bronchodilator reversibility test
- the lack of randomization resulting from the specificity of screening tests, which are design for volunteers.

Introduction

Screening for lung cancer became the standard of care in USA, being piloted in Europe increasingly.(1)(2) In many countries studies have been conducted to assess the benefits of screening for this cancer and to determine the optimal eligibility criteria for screening tests.(3) Based on the data obtained from multicenter studies covering the smoking population, it has been proven that lung cancer screening using low-dose computed tomography (LDCT) in

people at high risk of this cancer may significantly reduce mortality in this group of patients.(4)(5) Ten-year follow-up of people who had underwent lung cancer screening as part of the European NELSON study (Nederlands-Leuvens Longkanker Screenings Onderzoek) showed a reduction in cancer deaths by 26% in men and by 61% in women.(1) However, researchers agree that appropriate group selection, taking into account comorbidities that may reduce the effectiveness of tests, is crucial for lung cancer screening to become the standard of care, reduce mortality and be cost-effective.(6)(7)(8)

Smoking is not only responsible for the development of lung cancer, but is also involved in the etiology of over 80% of chronic obstructive pulmonary disease (COPD) cases.(9) The most recent analyzes of the World Health Organization (WHO) indicate that 251 million people worldwide suffer from COPD and it is the third cause of death.(10)(11)

Given the high prevalence of COPD in the general population, the ever increasing mortality from this disease, and its close relationship with smoking, the presence of COPD should be an important factor in qualifying patients for lung cancer screening. People with COPD have been shown to have twice the risk of developing lung cancer than smokers without COPD.(7)(8)(11)(12)(13)(14) Moreover, in this group of patients there are more complications related to the diagnostic procedures and treatment of the diagnosed lung cancer. These patients are more likely to develop complications after biopsy, such as pneumothorax and bleeding requiring transfusion of blood products.(15) In the perioperative period, patients with COPD are more likely to develop respiratory failure, stay in hospital longer after surgery, and have an increased risk of 30-day mortality.(7)(16)

Therefore, the aim of this study is to establish the prevalence and clinical characteristics of COPD in a cohort of adult Poles who underwent screening for lung cancer.

Materials and methods

Screening of patients for the diagnosis of COPD was carried out as part of the MOLTEST-BIS program, which is one of the first Polish screening programs dedicated to the early diagnosis of lung cancer in the group of long-term tobacco smokers.(17) The project was implemented in 2016–2018 by the Medical University of Gdańsk. People aged 50 to 79 years, inhabitants of the Pomeranian Voivodeship, with a smoking history of over 30 pack-years were eligible for the study. Both current smokers and those who quit smoking no later than 15 years prior to the study enrollment date were included in the study. The study was aimed at a comprehensive

health assessment of the population undergoing screening for comorbidities, and in particular COPD.

All participants in the study were interviewed using a standardized questionnaire. The questionnaire included questions about the patient's medical history, with particular emphasis on chronic diseases, medications, respiratory and cardiovascular symptoms, smoking history, socio-demographic data, healthy behaviors and physical activity. Then physical examination, anthropometric measurements, electrocardiographic examination, three measurements of blood pressure according to the ESH/ESC recommendations, and heart rate assessment were examined.(18)(19) Each participant underwent a spirometry test using a Jaeger Masterscreen Pneumo (Germany) spirometer. Pulmonary function tests were performed by an experienced spirometry technician. The results were analyzed by a pulmonologist. Spirometry was performed in accordance with the current ERS / ATS standards.(20). Both static (VC, IC, IRV, ERV) and dynamic (FVC, FEV_1) lung volumes were measured. If obstructive disorders were found, spirometry was repeated 20 minutes after the administration of 400 µg of salbutamol from a pressurized inhaler (Fig. 1). The COPD Assessment Test (CAT) was performed in people diagnosed with COPD and the incidence of dyspnea was assessed according to the mMRC (modified Medical Research Council) scale. The spirometric assessment and classification of the disease severity were carried out based on the guidelines of the Global Initiative for Chronic Obstructive Lung Disease (GOLD).(21) Primarily the diagnosis of obturation was evaluated using the absolute value of FEV_1/FVC ratio. The FEV_1 / FVC cut-off point was considered to be less than 0.7. Furthermore, in case of uncertain results, we assessed if this value was lower than LLN (lower limit of normal – LLN). In the study besides from GOLD criterion, reference values from Global Lungs Initiative were used.(22)(23). Before the spirometry test, when participants were contacted by phone to arrange the test date, everyone was instructed on how to properly prepare for the test. After a comprehensive cardiovascular and pulmonary assessment, participants received feedback on their health. People whose tests revealed significant abnormalities were referred to specialists in order to extend the diagnosis or initiate appropriate treatment (e.g. COPD).

In addition, each tobacco smoker underwent smoking cessation intervention (5 A's to help patients quit tobacco).(24)

All participants in the study gave informed consent to participate and underwent medical procedures, such as taking samples for laboratory tests and assessing respiratory function. The study was approved by the Independent Bioethics Committee for Scientific Research at the Medical University of Gdańsk (No NKBBN / 173/2016).

The whole results from MOLTES-BIS about lung cancer prevalence will be presented in

	Overall (N=730)	Men (M) (N=395)	Women (W) (N=335)	P-value M vs W
Obstruction	25.5% (186)	26.1% (103)	24.8% (83)	0.752
Irreversible obstruction (COPD)	19.7% (144)	21.7% (86)	17.3 % (58)	0.157

separate publication. Predicted incidence of lung cancer screening in our study varies between 1-2%, the data are still under revision.

In the statistical analyses carried out in the study, quantitative variables were described with mean values, standard deviations and medians, and qualitative variables were presented as percentages with counts. The assumption of distribution normality was verified with the Shapiro-Wilk test. The quantitative variables of the two groups were compared using the Mann-Whitney test. The significance of differences between the qualitative variables was tested using the Fisher test. The hypotheses were verified with two-sided tests. The level of significance was taken as $p < 0.05$.

Patient and Public Involvement:

No patient involved

Results

The inclusion criteria for the study were met by 754 people. The analysis included the results of 730 screened participants (335 women and 396 men) who had no contraindications to perform spirometry and whose test results were without technical errors (Figure 1). The mean age of men and women participating in the study did not differ significantly and was 63 and 63.5 years, respectively.

As shown in Table 1, obstructive disorders were found in 186 patients (103 men and 83 women). Bronchodilator test showed irreversible obstruction in 144 patients (86 men and 58 women). COPD was diagnosed in 19.7% of the study participants.

Table 1. Proportion of patients with pulmonary function abnormalities in spirometry.

Reversible obstruction (ASTHMA)	5.7% (42)	4.3% (17)	7.4% (25)	0.096

There was no difference in the incidence of COPD between women and men. Only 13.3% of the subjects diagnosed with COPD based on spirometry were aware of the disease – 11.6% of men and 15.8% of women; the difference was not statistically significant (p = 0.641).

14 from 144 responders with COPD reported having asthma in their medical history. The age of first asthma diagnosis in this cases ranged from 40 to 70 years.

The mean FEV_1 (forced expiratory volume in 1 second) in the entire cohort was 97.8% [mean SD 37.527, median (Q1,Q3) 97.500 (86.300, 109.100)]. In people without COPD, FEV_1 was 103% [mean SD 39.215, median (Q1,Q3) 100.900 (92.300, 112.000)], and in those with diagnosed COPD, the value of this parameter was 75.6% [mean SD 16.342, median (Q1,Q3) 75.350 (67.075, 85.800)]. The most important spirometric parameters before and after administration of a bronchodilator in case of group diagnosed with COPD are presented in Table 2.

Table 2. Spirometric parameters in group with COPD

	Overall (N=144)	Men (M) (N=86)	Women (W) (N=58)	P-value M vs W
SPIROMETRIC PARAMETERS BEFORE BRONCHODILATOR				
FEV_1(% predicted value) – Mean (SD) – Median (Q1,Q3)	75.6 (16.342) 75.350 (67.075, 85.800)	73.4 (14.672) 72.650 (64.650, 82.000)	78.8 (18.185) 79.750 (70.025, 89.675)	0.048
FVC (L) – Mean (SD) – Median (Q1,Q3)	3.6 (0.913) 3.505 (3.098, 4.272)	4.1(0.826) 4.095 (3.433, 4.637)	2.9 (0.588) 3.025 (2.547, 3.415)	<0.001
FEV_1/FVC (%) – Mean (SD) – Median (Q1,Q3)	56.4 (8.479) 58.755 (53.830, 62.398)	55.8 (8.320) 57.745 (53.445, 61.865)	57.4 (8.695) 59.770 (55.215, 63.227)	0.269
SPIROMETRIC PARAMETERS AFTER BRONCHODILATOR				
FEV_1(% predicted value) – Mean (SD) – Median (Q1,Q3)	80.81 (17.049) 81.000 (71.000, 90.925)	78.55 (15.354) 79.950 (69.200, 89.275)	84.17 18.935) 86.650 (74.975, 96.625)	0.027

FVC (L) – Mean (SD) – Median (Q1,Q3)	3.85 (1.001) 3.705 (3.147, 4.458)	4.34 (0.919) 4.310 (3.683, 4.918)	3.12 (0.591) 3.070 (2.688, 3.530)	<0.001
FEV1%/FVC (%) – Mean (SD) – Median (Q1,Q3)	57.69 (8.824) 59.650 (54.130, 64.207)	56.79 (8.474) 59.055 (53.900, 62.378)	59.03 (9.232) 60.995 (54.945, 65.707)	0.024

Table 3 presents data on the severity of the diagnosed COPD cases. In our analysis, according to the GOLD criteria for airflow-limitation severity, 55.6% of patient had mild obstruction, 38.9% moderate, 4.9% severe and 1.7% had very severe airflow obstruction. After assigning the diagnosed COPD cases to the appropriate category according to GOLD "ABCD" classification, most patients were in group B (63.9%) with more symptoms and a low risk of disease exacerbation, 29% were in group A, 1.4% in group C and 5.5% in group D.

Table 3. Classification of severity of diagnosed COPD cases.

	Overall (N=144)	Men (M) (N=86)	Women (W) (N=58)	P-value (M vs W)
GOLD CLASSIFICATION OF SEVERITY OF AIRFLOW OBSTRUCTION				
Mild **GOLD 1** [FEV1 ≥80%]	55.6% (80)	50.0% (43)	63.8% (37)	
Moderate **GOLD 2** [FEV1 50–79%]	38.9% (56)	45.3% (39)	29.3% (17)	0.137
Severe **GOLD 3** [FEV1 30–49%]	4.9% (7)	4.7% (4)	5.2% (3)	
Very severe **GOLD 4** [FEV1 <30%]	1.7% (1)	0% (0)	0.7% (1)	
GOLD CLASSIFICATION OF COPD SEVERITY				
A (less symptoms and low risk of exacerbations)	29.2% (42)	27.9% (24)	31% (18)	0.959
B (more symptoms; low risk of exacerbations)	63.9% (92)	66.3% (57)	60.3% (35)	

C (less symptoms, but high risk of exacerbations)	1.4% (2)	1.2% (1)	1.7% (1)	
D (more symptoms; high risk of exacerbations)	5.5% (8)	5.8%(5)	5.1% (3)	

Screened patients with and without COPD were compared in terms of age, symptoms, and hospitalization rates (Table 4). The mean age of people diagnosed with COPD was 65.2 years and was significantly higher than that of people without the disease, 62.7 years. The mean age of men was 66.3 years in those with COPD and 62.5 years in those without COPD ($p < 0.001$). For women, it was 63.8 years and 62.7 years, respectively ($p = 0.212$).

People with COPD significantly more often reported chronic cough, defined as a cough lasting more than 8 weeks, (39% vs 29.9%) and dyspnea (51% vs 33.7%). There was no difference in the reporting rate of dyspnea between women without COPD and women with COPD.

The subjects were asked about hospitalization for coughing, breathlessness or shortness of breath. Respondents diagnosed with COPD reported it more often than people without the disease (6.9% vs 1.7%).

In the CAT test assessing the impact of COPD on the quality of life of patients, the mean score achieved by people diagnosed with COPD was 13.7 points out of maximum achievable score of 40 and it did not differ significantly by gender.

Table 4. Symptomatology

	Men (N=395)			Women (N=335)			Overall (N=730)		
	COPD (N=86)	Non-COPD (N=309)	P-value	COPD (N=58)	Non-COPD (N=277)	P-value	COPD (N=144)	Non-COPD (N=586)	P-value
Age – Mean (SD) – Median (Q1,Q3)	66.3 (6.978) 66.000 (62.250, 72.000)	62.6 (6.444) 62.000 (58.000, 67.000)	<0.001	63.7 (6.230) 63.500 (60.000, 68.000)	62.7 (5.768) 62.000 (58.000, 67.000)	0.212	65.2 (6.78) 66.000 (60.000, 70.000)	62.7 (6.129) 62.000 (58.000, 67.000)	<0.001
Cough	37.2% (32)	24.9% (77)	0.034	43.1% (25)	28.5% (79)	0.042	39% (57)	29.9% (175)	0.032
Dyspnea	50.6% (43)	26.3% (81)	<0.001	51.7% (30)	42% (116)	0.176	51% (73)	33.7% (197)	<0.001

Dyspnea severity according to the mMRC scale			0.08			0.159			0.022
0	14% (6)	33.8% (27)		6.7% (2)	23.3% (27)		11% (8)	27.6% (54)	0.033
1	53.5% (23)	46.2% (37)		53.3% (16)	49.1% (57)		53.4% (39)	48% (94)	0.49
2	25.6% (11)	15% (12)		26.7% (8)	20.7% (24)		26% (19)	18.4% (36)	0.17
3	7% (3)	5% (4)		13.3% (4)	6% (7)		9.6% (7)	5.6% (11)	0.06
4	0% (0)	0% (0)		0 (0%)	0.9% (1)		0% (0)	0.5% (1)	<1
Hospitalizations	7% (6)	1.3% (4)	0.003	6.9% (4)	2.2% (6)	0.054	6.9% (10)	1.7% (10)	<0.001

Data on smoking, education and type of work are presented in Table 5. The number of cigarettes smoked was significantly higher in people with COPD compared to those without COPD. Among men with COPD, the average number of pack-years was 51.9 and was significantly higher than in women diagnosed with COPD (41.1 pack-years). People diagnosed with COPD were significantly more often blue-collar than white-collar workers. There were also statistically significant differences in education between men diagnosed with COPD and men without the disease. Among men diagnosed with COPD, 39.5% had primary education, 39.5% had secondary education, and only 20.9% had higher education. In men without COPD, secondary education was the most frequent – 42.4%, and only 26.9% had primary education. No significant differences in the level of education between the groups were found in women.

Table 5. Sociodemographic data and smoking history.

	Men (N=395)			Women (N=335)		
	COPD (N=86)	Non-COPD (N=309)	P-value	COPD (N=58)	Non-COPD (N=277)	P-value
SMOKING STATUS						
Pack-years – Mean (SD) – Median (Q1, Q3)	51.9 (17.306) 3.070 (2.688, 3.530)	45.4 (17.350) 40.000 (34.000, 50.000)	0.002	41.15 (11.055) 40.000 (34.250, 45.750)	31.91 (12.509) 36.000 (30.000, 42.000)	<0.001
Current smoker	69.8% (60)	60.5% (187)	0.149	72.5% (42)	70.1% (194)	0.839

Former smokers	30.2% (26)	39.5% (122)		27.5% (16)	29.9% (83)	
TYPE OF JOB						
Blue-collar workers	63.9% (53)	58.2% (166)	0.36	46.6% (27)	34.1% (88)	0.075
White-collar workers	36.1% (30)	41.8% (119)		53.4% (31)	65.9% (170)	
EDUCATION LEVEL						
Primary	39.5% (34)	26.9% (83)	0.49	22.4% (13)	21.3% (59)	0.85
Secondary	39.5% (34)	42.4% (131)		46.6% (27)	50.5% (140)	
Higher	20.9% (18)	30.7% (95)		31.0% (18)	28.2% (78)	

There were no differences in the mean values of height, weight, waist circumference and BMI in the groups of women and men with and without COPD. There was a difference in the distribution of BMI between patients with COPD and those without COPD (Table 6).

Table 6. Anthropometric data

	Men (N=395)			Women (N=335)		
	COPD (N=86)	Non-COPD (N=309)	P-value	COPD (N=58)	Non-COPD (N=277)	P-value
Body weight, kg – Mean (SD) – Median (Q1,Q3)	86.26 (15.171) 84.300 (75.375, 98.500)	89.15 (14.978) 87.500 (77.700, 98.150)	0.116	70.2 (12.380) 69.000 (60.950, 75.900)	71.7 (14.045) 69.500 (61.400, 79.500)	0.437
BMI, kg/m^2 – Mean (SD) – Median (Q1,Q3)	28.43(4.538) 28.569 (24.724, 31.392)	29.2 (4.813) 28.550 (26.108, 31.540)	0.170	27.2 (4.297) 26.732 (23.926, 30.181)	27.8(7.457) 26.780 (23.914, 30.860)	0.499
BMI category			0.05			0.442
Underweight (BMI <18.5)	0 (0%)	1 (0.3%)	<1	0% (0)	0,4%(1)	
Normal weight (BMI 18.5–24.99)	26.7% (23)	14.6% (45)	0.0259	37.9% (22)	31.8% (88)	
Overweight (BMI 25.0–29.99)	33.7% (29)	47.7% (147)	0.061	32.8% (19)	38.6% (107)	
Obesity (BMI >=30)	39.5% (34)	37.2% (115)	<1	20.3% (17)	29.2% (81)	

Discussion

Our study shows the prevalence and characteristics of chronic obstructive pulmonary disease in the group of people participating in one of the first lung cancer screening studies in Poland. In our study, almost one-fifth (19.73%) of the participants were diagnosed with COPD.

According to epidemiological studies conducted both in Europe and around the world, the prevalence of COPD in people subjected to lung cancer screening is high; this disease was detected in up to two-thirds of the examined subjects.(2)(25) However, there is a large discrepancy in the results, which may suggest significant differences in the populations participating in the screening, and may result from different eligibility criteria for the study and adopted diagnostic criteria. It is noteworthy that in many of the studies conducted, only basic spirometry was assessed, without the bronchodilator reversibility test, which raises methodological doubts and might cause the obtained results to be overestimated. In one of the largest American lung cancer screening studies, the National Lung Screening Trial (NLST), the prevalence of COPD was 34.4%.(2) However, the bronchodilator test was not performed in this study, which could have an impact on the final result. In the British Lung Screen Uptake Trial (LSUT), the prevalence of COPD among people participating in lung cancer screening was as high as 57%; however, also in this study, analyzes included only basic spirometry without the bronchodilator test.(26) In addition, people aged 60–75 were eligible for the LSUT study, which means that the participants were older than in most other lung cancer screening tests. The prevalence of COPD found in our study may appear lower than in most countries; however, the diagnosis of this disorder was carried out in accordance with the GOLD and the Polish Society of Lung Diseases guidelines (9)(21), using a complete diagnostic scheme including the bronchodilator reversibility test in every person with airflow obstruction. Additionally, the severity of COPD symptoms was assessed using the tools recommended in the guidelines: CAT test and mMRC scale. Such analyzes reliably refine the diagnosis of COPD. Unfortunately, it seems that the prevalence of COPD, as assessed in our study, may be underestimated. It should be emphasized that it was the second stage of the pilot screening study carried out in a big city, which was attended by people who were more interested in their health condition, with a higher socio-economic status, better education and higher awareness of diseases. It is a characteristic feature of the population participating in each screening test, but nevertheless this effect in the Polish population seems to be particularly pronounced. Compared to the above-mentioned multicenter studies, this could have resulted in the a lower accessibility of the study for volunteers from more distant parts of the voivodeship, especially from small towns and villages, where the prevalence of COPD may be higher than in large cities.

Another important aspect that should be highlighted is the number of newly diagnosed COPD cases. Analyzing the respondents' answers regarding their knowledge about the earlier diagnosis of COPD and considering the medications taken by the respondents, only 13.3% of people diagnosed with COPD during the visit knew about the disease beforehand. For example, in the previously mentioned British study,(26) 33% participants were aware of COPD, and in the American study this proportion was almost 60%.(2) These data highlights how underdiagnosed the Polish population is in terms of lung diseases. Considering the importance of the presence of COPD in the diagnostic and therapeutic process and in the stratification of the benefits and risks of lung cancer screening, as well as the low awareness of the disease, it should be considered that the diagnosis of this disorder during screening should become a standard of care.

According to the above analyzes, it seems that women are the group that should receive special attention when diagnosing COPD. Our results show that not only do women suffer from COPD at a younger age than men, but also with significantly less exposure to tobacco smoke. The frequency of the individual symptoms reported by the women was the same, regardless of whether they had COPD or not. In this group, the inclusion of early screening for COPD in lung cancer diagnostic testing may be particularly important.

Although the benefits of lung cancer screening have been proven in long-term observational studies, the financial burden on healthcare systems due to the high cost of the study remains under discussion. Research is ongoing in many countries on the potential introduction of a combined lung cancer screening and comorbidities, which could contribute to greater cost-effectiveness of the study and lower mortality associated with comorbidities in long-term smokers.(1)(4)(27) Most of the COPD cases diagnosed in our study were classified as low-stage disease (the most common were mild obstruction and COPD stages A and B). Studies show that in the early stages of the disease, patients die more often from lung cancer than from respiratory failure, the latter predominating at higher disease severity categories.(28) Therefore, people with early-stage COPD are optimal candidates for lung cancer screening, as the benefits of potential diagnosis and treatment for this cancer may outweigh the risk of possible adverse effects. Currently, analyzes are also conducted on the feasibility and cost-effectiveness of a combined screening for lung cancer and COPD by assessing the presence of emphysema in low-dose computed tomography.(6)(29)(30) Determining the prevalence of COPD by means of spirometry in the Polish population undergoing screening for lung cancer and the possible correlation of our results with the assessment of the severity of emphysema and symptoms of chronic bronchitis in LDCT, may contribute in the future to broadening the scope of diagnostic

imaging examinations to assess the functioning of the respiratory system, which would make the screening applied cost-effective.

The limitations of our study include the lack of randomization resulting from the specificity of screening tests, which are aimed at people willing to participate. Moreover, the study, due to time constraints, did not include the entire cohort of lung cancer screening participants, but only a part of the group. Due to easier access to the study of people from a big city, this group constituted the majority of participants, which could also have influenced the results obtained.

Conclusions

Our study showed a significant prevalence of COPD in a cohort of Polish smokers participating in the lung cancer screening test. Awareness of the disease in this group is very low and amounts to approx. 13%. Most people diagnosed with COPD are in the early clinical stage, which allows for effective prevention and means that they may be potential beneficiaries of lung cancer screening. Further studies are needed to assess the effectiveness of COPD diagnosis and prevention in this group in order to assess the effectiveness of combined oncological-pulmonary screening.

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Competing Interests: The authors have no conflicts of interest to declare

Contributorship statement: AU, KK, WR, TZ designed the study. AU, PK, AR performed literature search and conduct the study, AU and KK analyse spirometry results, AU, KK, TZ, WR, PK contributed to data analysis. AU wrote first draft and all authors contributed to producing the final text of the manuscript.

Ethics approval statement: Independent Bioethics Committee for Scientific Research at the Medical University of Gdańsk (No NKBBN / 173/2016). The participants were informed about the all procedures and signed the agreement to participate in the trial. The researchers informed participants about the results by mail or phone.

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Data available: Extra data is available by emailing Piotr Kasprzyk: kasprzyk@gumed.edu.pl

List of abbreviations:

BMI- Body mass index

CAT- COPD Assessment Test

COPD- chronic obstructive pulmonary disease

ERS / ATS- European Respiratory Society/ American Thoracic Society

ESH/ ECS- European Society of Hypertension/ European Society of Cardiology

FEV_1- forced expiratory volume in one second

FVC- forced vital capacity

GOLD- Global Initiative for Chronic Obstructive Lung Disease

LDCT- low-dose computed tomography

mMRC- modified Medical Research Council

NELSON study- Nederlands-Leuvens Longkanker Screenings Onderzoek study

VC- vital capacity

WHO- World Health Organization

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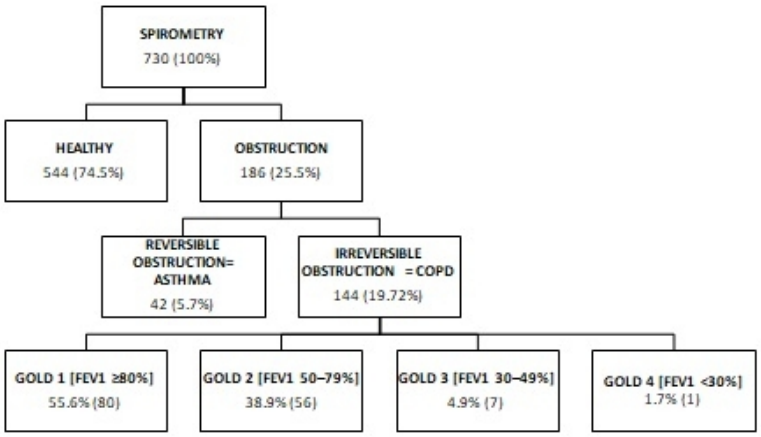

Figure 1. Diagnostic diagram

Diagnostic diagram

100x58mm (144 x 144 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3.4
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	3
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4-5
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	4-9
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	4-5

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	4-9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	4-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10,11,12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Prevalence, symptom burden and under-diagnosis of Chronic Obstructive Pulmonary Disease in Polish lung cancer screening population: a cohort observational study.

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Prevalence, symptom burden and under-diagnosis of chronic obstructive pulmonary disease in Polish lung cancer screening population: a cohort observational study.

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Abstract:

Objectives:
Lung cancer screening using LDCT may be not effective without consideration the presence of comorbidities related to chronic smoking. The aim of the study was to establish the prevalence of COPD in group of patients participating in the largest Polish lung cancer screening programme MOLTEST BIS and attempt to confirm necessity of combined lung cancer and COPD screening

Design:
cohort, prospective study

Setting:
Medical University of Gdańsk, Poland

Participants:
The study included 754 participants of lung cancer screening trial from Pomeranian region, aged 50-70 years old, current and former smokers with a smoking history ≥30 pack-years.

Primary and secondary outcome measures:
questionnaire, physical examination, anthropometric measurements, spirometry test before and after inhaled bronchodilator (400µg of salbutamol)

Results:
Obstructive disorders were diagnosed in 186 cases (103 male and 83 female). In case of 144 participants (19.73%) COPD was diagnosed. Only 13.3% of participants with COPD were known about the disease earlier. According to classification of airflow limitation 55.6 % of diagnosed COPD were in GOLD 1 (mild), 38.9 % in GOLD 2 (moderate), 4.9 % in GOLD 3 (severe) and 0.7 % in GOLD 4 (very severe) stage. Women with recognition of COPD were younger than men (63.7 vs 66.3 age) and they smoked less cigarettes (41.1 vs 51.9 pack-years).

Conclusions:
Prevalence of COPD in Polish lung cancer screening cohort is significant. The COPD in this group is remarkably under-diagnosed. Most of diagnosed COPD cases were in initial stage of advancement. This early detection of airflow limitation highlight the potential benefits arising from combined oncological-pulmonary screening.

Trial registration:
Independent Bioethics Committee for Scientific Research at the Medical University of Gdańsk (No NKBBN / 173/2016)

Strengths and limitations of this study

- the largest Polish lung cancer screening program with additional diagnostic procedures to assess prevalence of most common comorbidities
- one of few LDCT trials in Europe in which the prevalence of COPD was established according to all respiratory guidelines by performing full spirometry with the bronchodilator reversibility test
- the lack of randomization resulting from the specificity of screening tests, which are design for volunteers.

Introduction

Screening for lung cancer became the standard of care in USA, being piloted in Europe increasingly.(1)(2) In many countries studies have been conducted to assess the benefits of screening for this cancer and to determine the optimal eligibility criteria for screening tests.(3) Based on the data obtained from multicenter studies covering the smoking population, it has been proven that lung cancer screening using low-dose computed tomography (LDCT) in

people at high risk of this cancer may significantly reduce mortality in this group of patients.(4)(5) Ten-year follow-up of people who had underwent lung cancer screening as part of the European NELSON study (Nederlands-Leuvens Longkanker Screenings Onderzoek) showed a reduction in cancer deaths by 26% in men and by 61% in women.(1) However, researchers agree that appropriate group selection, taking into account comorbidities that may reduce the effectiveness of tests, is crucial for lung cancer screening to become the standard of care, reduce mortality and be cost-effective.(6)(7)(8)

Smoking is not only responsible for the development of lung cancer, but is also involved in the etiology of over 80% of chronic obstructive pulmonary disease (COPD) cases.(9) The most recent analyzes of the World Health Organization (WHO) indicate that 251 million people worldwide suffer from COPD and it is the third cause of death.(10)(11)

Given the high prevalence of COPD in the general population, the ever increasing mortality from this disease, and its close relationship with smoking, the presence of COPD should be an important factor in qualifying patients for lung cancer screening. People with COPD have been shown to have twice the risk of developing lung cancer than smokers without COPD.(7)(8)(11)(12)(13)(14) Moreover, in this group of patients there are more complications related to the diagnostic procedures and treatment of the diagnosed lung cancer. These patients are more likely to develop complications after biopsy, such as pneumothorax and bleeding requiring transfusion of blood products.(15) In the perioperative period, patients with COPD are more likely to develop respiratory failure, stay in hospital longer after surgery, and have an increased risk of 30-day mortality.(7)(16)

Therefore, the aim of this study is to establish the prevalence and clinical characteristics of COPD in a cohort of adult Poles who underwent screening for lung cancer.

Materials and methods

Screening of patients for the diagnosis of COPD was carried out as part of the MOLTEST-BIS program, which is one of the first Polish screening programs dedicated to the early diagnosis of lung cancer in the group of long-term tobacco smokers.(17) The project was implemented in 2016–2018 by the Medical University of Gdańsk. People aged 50 to 79 years, inhabitants of the Pomeranian Voivodeship, with a smoking history of over 30 pack-years were eligible for the study. Both current smokers and those who quit smoking no later than 15 years prior to the study enrollment date were included in the study. The study was aimed at a comprehensive

health assessment of the population undergoing screening for comorbidities, and in particular COPD.

All participants in the study were interviewed using a standardized questionnaire. The questionnaire included questions about the patient's medical history, with particular emphasis on chronic diseases, medications, respiratory and cardiovascular symptoms, smoking history, socio-demographic data, healthy behaviors and physical activity. Then physical examination, anthropometric measurements, electrocardiographic examination, three measurements of blood pressure according to the ESH/ESC recommendations, and heart rate assessment were examined.(18)(19) Each participant underwent a spirometry test using a Jaeger Masterscreen Pneumo (Germany) spirometer. Pulmonary function tests were performed by an experienced spirometry technician. The results were analyzed by a pulmonologist. Spirometry was performed in accordance with the current ERS / ATS standards.(20). Both static (VC, IC, IRV, ERV) and dynamic (FVC, FEV_1) lung volumes were measured. If obstructive disorders were found, spirometry was repeated 20 minutes after the administration of 400 µg of salbutamol from a pressurized inhaler (Fig. 1). The COPD Assessment Test (CAT) was performed in people diagnosed with COPD and the incidence of dyspnea was assessed according to the mMRC (modified Medical Research Council) scale. The spirometric assessment and classification of the disease severity were carried out based on the guidelines of the Global Initiative for Chronic Obstructive Lung Disease (GOLD).(21) Primarily the diagnosis of obturation was evaluated using the absolute value of FEV_1/FVC ratio. The FEV_1 / FVC cut-off point was considered to be less than 0.7. Furthermore, in case of uncertain results, we assessed if this value was lower than LLN (lower limit of normal – LLN). In the study besides from GOLD criterion, reference values from Global Lungs Initiative were used.(22)(23). Before the spirometry test, when participants were contacted by phone to arrange the test date, everyone was instructed on how to properly prepare for the test. After a comprehensive cardiovascular and pulmonary assessment, participants received feedback on their health. People whose tests revealed significant abnormalities were referred to specialists in order to extend the diagnosis or initiate appropriate treatment (e.g. COPD).

In addition, each tobacco smoker underwent smoking cessation intervention (5 A's to help patients quit tobacco).(24)

All participants in the study gave informed consent to participate and underwent medical procedures, such as taking samples for laboratory tests and assessing respiratory function. The study was approved by the Independent Bioethics Committee for Scientific Research at the Medical University of Gdańsk (No NKBBN / 173/2016).

The whole results from MOLTES-BIS about lung cancer prevalence will be presented in

	Overall (N=730)	Men (M) (N=395)	Women (W) (N=335)	P-value M vs W
Obstruction	25.5% (186)	26.1% (103)	24.8% (83)	0.752
Irreversible obstruction (COPD)	19.7% (144)	21.7% (86)	17.3 % (58)	0.157

separate publication. Predicted incidence of lung cancer screening in our study varies between 1-2%, the data are still under revision.

In the statistical analyses carried out in the study, quantitative variables were described with mean values, standard deviations and medians, and qualitative variables were presented as percentages with counts. The assumption of distribution normality was verified with the Shapiro-Wilk test. The quantitative variables of the two groups were compared using the Mann-Whitney test. The significance of differences between the qualitative variables was tested using the Fisher test. The hypotheses were verified with two-sided tests. The level of significance was taken as $p < 0.05$.

Patient and Public Involvement:

No patient involved

Results

The inclusion criteria for the study were met by 754 people. The analysis included the results of 730 screened participants (335 women and 396 men) who had no contraindications to perform spirometry and whose test results were without technical errors (Figure 1). The mean age of men and women participating in the study did not differ significantly and was 63 and 63.5 years, respectively.

As shown in Table 1, obstructive disorders were found in 186 patients (103 men and 83 women). Bronchodilator test showed irreversible obstruction in 144 patients (86 men and 58 women). COPD was diagnosed in 19.7% of the study participants.

Table 1. Proportion of patients with pulmonary function abnormalities in spirometry.

Reversible obstruction (ASTHMA)	5.7% (42)	4.3% (17)	7.4% (25)	0.096

There was no difference in the incidence of COPD between women and men. Only 13.3% of the subjects diagnosed with COPD based on spirometry were aware of the disease – 11.6% of men and 15.8% of women; the difference was not statistically significant (p = 0.641).

14 from 144 responders with COPD reported having asthma in their medical history. The age of first asthma diagnosis in this cases ranged from 40 to 70 years.

The mean FEV_1 (forced expiratory volume in 1 second) in the entire cohort was 97.8% [mean SD 37.527, median (Q1,Q3) 97.500 (86.300, 109.100)]. In people without COPD, FEV_1 was 103% [mean SD 39.215, median (Q1,Q3) 100.900 (92.300, 112.000)], and in those with diagnosed COPD, the value of this parameter was 75.6% [mean SD 16.342, median (Q1,Q3) 75.350 (67.075, 85.800)]. The most important spirometric parameters before and after administration of a bronchodilator in case of group diagnosed with COPD are presented in Table 2.

Table 2. Spirometric parameters in group with COPD

	Overall (N=144)	Men (M) (N=86)	Women (W) (N=58)	P-value M vs W
SPIROMETRIC PARAMETERS BEFORE BRONCHODILATOR				
FEV_1(% predicted value) – Mean (SD)	75.60 (16.34)	73.40 (14.67)	78.80 (18.19)	0.048
FVC (L) – Mean (SD)	3.60 (0.91)	4.10 (0.83)	2.90 (0.59)	<0.001
FEV_1/FVC (%) – Mean (SD)	56.40 (8.48)	55.80 (8.32)	57.40 (8.70)	0.269
SPIROMETRIC PARAMETERS AFTER BRONCHODILATOR				
FEV_1(% predicted value) – Mean (SD)	80.81 (17.05)	78.55 (15.35)	84.17 18.94)	0.027

FVC (L) – Mean (SD)	3.85 (1.00)	4.34 (0.92)	3.12 (0.59)	<0.001
FEV1%/FVC (%) – Mean (SD)	57.69 (8.82)	56.79 (8.47)	59.03 (9.23)	0.024

Table 3 presents data on the severity of the diagnosed COPD cases. In our analysis, according to the GOLD criteria for airflow-limitation severity, 55.6% of patient had mild obstruction, 38.9% moderate, 4.9% severe and 1.7% had very severe airflow obstruction. After assigning the diagnosed COPD cases to the appropriate category according to GOLD "ABCD" classification, most patients were in group B (63.9%) with more symptoms and a low risk of disease exacerbation, 29% were in group A, 1.4% in group C and 5.5% in group D.

Table 3. Classification of severity of diagnosed COPD cases.

	Overall (N=144)	Men (M) (N=86)	Women (W) (N=58)	P-value (M vs W)
GOLD CLASSIFICATION OF SEVERITY OF AIRFLOW OBSTRUCTION				
Mild **GOLD 1** [FEV1 ≥80%]	55.6% (80)	50.0% (43)	63.8% (37)	
Moderate **GOLD 2** [FEV1 50–79%]	38.9% (56)	45.3% (39)	29.3% (17)	0.137
Severe **GOLD 3** [FEV1 30–49%]	4.9% (7)	4.7% (4)	5.2% (3)	
Very severe **GOLD 4** [FEV1 <30%]	1.7% (1)	0% (0)	0.7% (1)	
GOLD CLASSIFICATION OF COPD SEVERITY				
A (less symptoms and low risk of exacerbations)	29.2% (42)	27.9% (24)	31% (18)	
B (more symptoms; low risk of exacerbations)	63.9% (92)	66.3% (57)	60.3% (35)	0.959
C (less symptoms, but high risk of exacerbations)	1.4% (2)	1.2% (1)	1.7% (1)	

D (more symptoms; high risk of exacerbations)	5.5% (8)	5.8%(5)	5.1% (3)	

Screened patients with and without COPD were compared in terms of age, symptoms, and hospitalization rates (Table 4). The mean age of people diagnosed with COPD was 65.2 years and was significantly higher than that of people without the disease, 62.7 years. The mean age of men was 66.3 years in those with COPD and 62.5 years in those without COPD (p <0.001). For women, it was 63.8 years and 62.7 years, respectively (p = 0.212).

People with COPD significantly more often reported chronic cough, defined as a cough lasting more than 8 weeks, (39% vs 29.9%) and dyspnea (51% vs 33.7%). There was no difference in the reporting rate of dyspnea between women without COPD and women with COPD.

The subjects were asked about hospitalization for coughing, breathlessness or shortness of breath. Respondents diagnosed with COPD reported it more often than people without the disease (6.9% vs 1.7%).

In the CAT test assessing the impact of COPD on the quality of life of patients, the mean score achieved by people diagnosed with COPD was 13.7 points out of maximum achievable score of 40 and it did not differ significantly by gender.

Table 4. Symptomatology

	Men (N=395)			Women (N=335)			Overall (N=730)		
	COPD (N=86)	Non-COPD (N=309)	P-value	COPD (N=58)	Non-COPD (N=277)	P-value	COPD (N=144)	Non-COPD (N=586)	P-value
Age – Mean (SD)	66.3 (6.98)	62.6 (6.44)	<0.001	63.7 (6.23)	62.7 (5.77)	0.212	65.2 (6.78)	62.7 (6.13)	<0.001
Cough	37.2% (32)	24.9% (77)	0.034	43.1% (25)	28.5% (79)	0.042	39% (57)	29.9% (175)	0.032
Dyspnea	50.6% (43)	26.3% (81)	<0.001	51.7% (30)	42% (116)	0.176	51% (73)	33.7% (197)	<0.001
Dyspnea severity according to the mMRC scale			0.08			0.159			0.022
0	14% (6)	33.8% (27)		6.7% (2)	23.3% (27)		11% (8)	27.6% (54)	0.033

1	53.5% (23)	46.2% (37)		53.3% (16)	49.1% (57)		53.4% (39)	48% (94)	0.49
2	25.6% (11)	15% (12)		26.7% (8)	20.7% (24)		26% (19)	18.4% (36)	0.17
3	7% (3)	5% (4)		13.3% (4)	6% (7)		9.6% (7)	5.6% (11)	0.06
4	0% (0)	0% (0)		0 (0%)	0.9% (1)		0% (0)	0.5% (1)	<1
Hospitalizations	7% (6)	1.3% (4)	0.003	6.9% (4)	2.2% (6)	0.054	6.9% (10)	1.7% (10)	<0.001

Data on smoking, education and type of work are presented in Table 5. The number of cigarettes smoked was significantly higher in people with COPD compared to those without COPD. Among men with COPD, the average number of pack-years was 51.9 and was significantly higher than in women diagnosed with COPD (41.1 pack-years). People diagnosed with COPD were significantly more often blue-collar than white-collar workers. There were also statistically significant differences in education between men diagnosed with COPD and men without the disease. Among men diagnosed with COPD, 39.5% had primary education, 39.5% had secondary education, and only 20.9% had higher education. In men without COPD, secondary education was the most frequent – 42.4%, and only 26.9% had primary education. No significant differences in the level of education between the groups were found in women.

Table 5. Sociodemographic data and smoking history.

	Men (N=395)			Women (N=335)		
	COPD (N=86)	Non-COPD (N=309)	P-value	COPD (N=58)	Non-COPD (N=277)	P-value
SMOKING STATUS						
Pack-years – Mean (SD)	51.9 (17.31)	45.40 (17.35)	0.002	41.15 (11.06)	31.91 (12.51)	<0.001
Current smoker	69.8% (60)	60.5% (187)	0.149	72.5% (42)	70.1% (194)	0.839
Former smokers	30.2% (26)	39.5% (122)		27.5% (16)	29.9% (83)	
TYPE OF JOB						
Blue-collar workers	63.9% (53)	58.2% (166)	0.36	46.6% (27)	34.1% (88)	0.075
White-collar workers	36.1% (30)	41.8% (119)		53.4% (31)	65.9% (170)	
EDUCATION LEVEL						

Primary	39.5% (34)	26.9% (83)	0.49	22.4% (13)	21.3% (59)	0.85
Secondary	39.5% (34)	42.4% (131)		46.6% (27)	50.5% (140)	
Higher	20.9% (18)	30.7% (95)		31.0% (18)	28.2% (78)	

There were no differences in the mean values of height, weight, waist circumference and BMI in the groups of women and men with and without COPD. There was a difference in the distribution of BMI between patients with COPD and those without COPD (Table 6).

Table 6. Anthropometric data

	Men (N=395)			Women (N=335)		
	COPD (N=86)	Non-COPD (N=309)	P-value	COPD (N=58)	Non-COPD (N=277)	P-value
Body weight, kg – Mean (SD) – Median (Q1,Q3)	86.26 (15.17) 84.30 (75.38, 98.50)	89.15 (14.99) 87.50 (77.70, 98.15)	0.116	70.2 (12.38) 69.00 (60.95, 75.90)	71.7 (14.05) 69.50 (61.40, 79.50)	0.437
BMI, kg/m^2 – Mean (SD)	28.43 (4.54)	29.2 (4.81)	0.170	27.2 (4.3)	27.8 (7 .45)	0.499
BMI category			0.05			0.442
Underweight (BMI <18.5)	0 (0%)	1 (0.3%)	<1	0% (0)	0,4%(1)	
Normal weight (BMI 18.5–24.99)	26.7% (23)	14.6% (45)	0.0259	37.9% (22)	31.8% (88)	
Overweight (BMI 25.0–29.99)	33.7% (29)	47.7% (147)	0.061	32.8% (19)	38.6% (107)	
Obesity (BMI >=30)	39.5% (34)	37.2% (115)	<1	20.3% (17)	29.2% (81)	

Discussion

Our study shows the prevalence and characteristics of chronic obstructive pulmonary disease in the group of people participating in one of the first lung cancer screening studies in Poland. In our study, almost one-fifth (19.73%) of the participants were diagnosed with COPD.

According to epidemiological studies conducted both in Europe and around the world, the prevalence of COPD in people subjected to lung cancer screening is high; this disease was detected in up to two-thirds of the examined subjects.(2)(25) However, there is a large

discrepancy in the results, which may suggest significant differences in the populations participating in the screening, and may result from different eligibility criteria for the study and adopted diagnostic criteria. It is noteworthy that in many of the studies conducted, only basic spirometry was assessed, without the bronchodilator reversibility test, which raises methodological doubts and might cause the obtained results to be overestimated. In one of the largest American lung cancer screening studies, the National Lung Screening Trial (NLST), the prevalence of COPD was 34.4%.(2) However, the bronchodilator test was not performed in this study, which could have an impact on the final result. In the British Lung Screen Uptake Trial (LSUT), the prevalence of COPD among people participating in lung cancer screening was as high as 57%; however, also in this study, analyzes included only basic spirometry without the bronchodilator test.(26) In addition, people aged 60–75 were eligible for the LSUT study, which means that the participants were older than in most other lung cancer screening tests. The prevalence of COPD found in our study may appear lower than in most countries; however, the diagnosis of this disorder was carried out in accordance with the GOLD and the Polish Society of Lung Diseases guidelines (9)(21), using a complete diagnostic scheme including the bronchodilator reversibility test in every person with airflow obstruction. Additionally, the severity of COPD symptoms was assessed using the tools recommended in the guidelines: CAT test and mMRC scale. Such analyzes reliably refine the diagnosis of COPD. Unfortunately, it seems that the prevalence of COPD, as assessed in our study, may be underestimated. It should be emphasized that it was the second stage of the pilot screening study carried out in a big city, which was attended by people who were more interested in their health condition, with a higher socio-economic status, better education and higher awareness of diseases. It is a characteristic feature of the population participating in each screening test, but nevertheless this effect in the Polish population seems to be particularly pronounced. Compared to the above-mentioned multicenter studies, this could have resulted in the a lower accessibility of the study for volunteers from more distant parts of the voivodeship, especially from small towns and villages, where the prevalence of COPD may be higher than in large cities.

Another important aspect that should be highlighted is the number of newly diagnosed COPD cases. Analyzing the respondents' answers regarding their knowledge about the earlier diagnosis of COPD and considering the medications taken by the respondents, only 13.3% of people diagnosed with COPD during the visit knew about the disease beforehand. For example, in the previously mentioned British study,(26) 33% participants were aware of COPD, and in the American study this proportion was almost 60%.(2) These data highlights how underdiagnosed the Polish population is in terms of lung diseases. Considering the importance

of the presence of COPD in the diagnostic and therapeutic process and in the stratification of the benefits and risks of lung cancer screening, as well as the low awareness of the disease, it should be considered that the diagnosis of this disorder during screening should become a standard of care.

According to the above analyzes, it seems that women are the group that should receive special attention when diagnosing COPD. Our results show that not only do women suffer from COPD at a younger age than men, but also with significantly less exposure to tobacco smoke. The frequency of the individual symptoms reported by the women was the same, regardless of whether they had COPD or not. In this group, the inclusion of early screening for COPD in lung cancer diagnostic testing may be particularly important.

Although the benefits of lung cancer screening have been proven in long-term observational studies, the financial burden on healthcare systems due to the high cost of the study remains under discussion. Research is ongoing in many countries on the potential introduction of a combined lung cancer screening and comorbidities, which could contribute to greater cost-effectiveness of the study and lower mortality associated with comorbidities in long-term smokers.(1)(4)(27) Most of the COPD cases diagnosed in our study were classified as low-stage disease (the most common were mild obstruction and COPD stages A and B). Studies show that in the early stages of the disease, patients die more often from lung cancer than from respiratory failure, the latter predominating at higher disease severity categories.(28) Therefore, people with early-stage COPD are optimal candidates for lung cancer screening, as the benefits of potential diagnosis and treatment for this cancer may outweigh the risk of possible adverse effects. Currently, analyzes are also conducted on the feasibility and cost-effectiveness of a combined screening for lung cancer and COPD by assessing the presence of emphysema in low-dose computed tomography.(6)(29)(30) Determining the prevalence of COPD by means of spirometry in the Polish population undergoing screening for lung cancer and the possible correlation of our results with the assessment of the severity of emphysema and symptoms of chronic bronchitis in LDCT, may contribute in the future to broadening the scope of diagnostic imaging examinations to assess the functioning of the respiratory system, which would make the screening applied cost-effective.

The limitations of our study include the lack of randomization resulting from the specificity of screening tests, which are aimed at people willing to participate. Moreover, the study, due to time constraints, did not include the entire cohort of lung cancer screening participants, but only a part of the group. Due to easier access to the study of people from a big city, this group constituted the majority of participants, which could also have influenced the results obtained.

Conclusions

Our study showed a significant prevalence of COPD in a cohort of Polish smokers participating in the lung cancer screening test. Awareness of the disease in this group is very low and amounts to approx. 13%. Most people diagnosed with COPD are in the early clinical stage, which allows for effective prevention and means that they may be potential beneficiaries of lung cancer screening. Further studies are needed to assess the effectiveness of COPD diagnosis and prevention in this group in order to assess the effectiveness of combined oncological-pulmonary screening.

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Competing Interests: The authors have no conflicts of interest to declare

Contributorship statement: AU, KK, WR, TZ designed the study. AU, PK, AR performed literature search and conduct the study, AU and KK analyse spirometry results, AU, KK, TZ, WR, PK contributed to data analysis. AU wrote first draft and all authors contributed to producing the final text of the manuscript.

Ethics approval statement: Independent Bioethics Committee for Scientific Research at the Medical University of Gdańsk (No NKBBN / 173/2016). The participants were informed about the all procedures and signed the agreement to participate in the trial. The researchers informed participants about the results by mail or phone.

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List of abbreviations:

BMI- Body mass index

CAT- COPD Assessment Test

COPD- chronic obstructive pulmonary disease

ERS / ATS- European Respiratory Society/ American Thoracic Society

ESH/ ECS- European Society of Hypertension/ European Society of Cardiology

FEV_1- forced expiratory volume in one second

FVC- forced vital capacity

GOLD- Global Initiative for Chronic Obstructive Lung Disease

LDCT- low-dose computed tomography

mMRC- modified Medical Research Council

NELSON study- Nederlands-Leuvens Longkanker Screenings Onderzoek study

VC- vital capacity

WHO- World Health Organization

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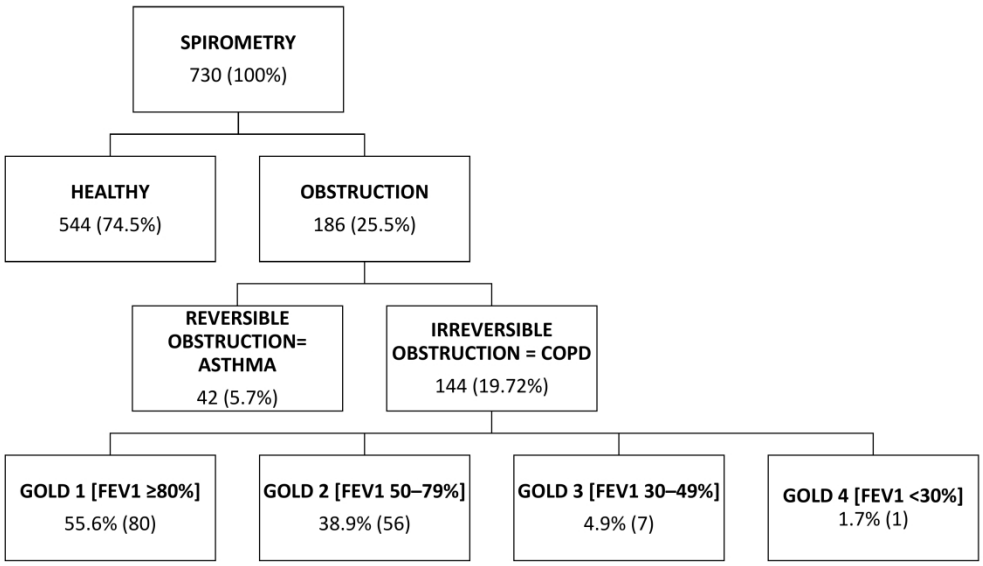
Figure 1. Diagnostic diagram



Diagnostic diagram

297x210mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3.4
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	3
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4-5
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	4-9
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	4-5

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	4-9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	4-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10,11,12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.