Original Article

Lung function impairment in the German Lung Cancer Screening Intervention Study (LUSI): prevalence, symptoms, and associations with lung cancer risk, tumor histology and all-cause mortality

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Background: Lung cancer screening may provide a favorable opportunity for a spirometry examination, to diagnose participants with undiagnosed lung function impairments, or to improve targeting of computed tomography (CT) screening intensity in view of expected net benefit.

Methods: Spirometry was performed in the CT screening arm (n=2,029) of the German Lung Cancer Screening Intervention Study (LUSI)—a trial examining the effects of annual CT screening on lung cancer mortality, in 50–69-year-old long-term smokers. Participants were classified as having chronic obstructive pulmonary disease (COPD) [forced expiration in one second (FEV_1)/forced vital lung capacity (FVC) <0.7], preserved ratio impaired spirometry (PRISm; FEV_1/FVC ≥0.7 and FEV_1% predicted <80%), or normal spirometry. Descriptive statistics were used to examine associations of COPD or PRISm with respiratory symptoms, and self-reported medical diagnoses of respiratory and other morbidities. Logistic regression and proportional hazards regression were used to examine associations of COPD and PRISm, as well as their self-reported medical diagnoses, with risks of lung cancer and all-cause mortality.

Results: A total of 1,987 screening arm participants (98%) provided interpretable spirometry measurements; of these, 34.3% had spirometric patterns consistent with either COPD (18.6%) or PRISm (15.7%). Two thirds of participants with COPD or PRISm were asymptomatic, and only 23% reported a previous medical diagnosis concordant with COPD. Participants reporting a diagnosis tended to be more often current and heavier smokers, and more often had respiratory symptoms, cardiovascular comorbidities, or more severe lung function impairments. Independently of smoking history, moderate-to-severe (GOLD 2–4) COPD (OR =2.14; 95% CI: 1.54–2.98), and PRISm (OR =2.68; 95% CI: 1.61–4.40), were associated with increased lung cancer risk. Lung cancer patients with PRISm less frequently had adenocarcinomas, and more often squamous cell or small cell tumors, compared to those with normal spirometry (n=45), and both PRISm and COPD were associated with more advanced lung cancer tumor stage for screen-detected cancers. PRISm and COPD, depending on GOLD stage, were also associated with about 2- to 4-fold increases in risk of overall mortality, which to 87 percent had causes other than lung cancer.

Conclusions: About one third of smokers eligible for lung cancer screening in Germany have COPD or PRISm. As these conditions were associated with detection of lung cancer, spirometry may help identify populations at high risk for death of lung cancer or other causes, and who might particularly benefit from CT screening.

Keywords: Spirometry; chronic obstructive pulmonary disease (COPD); preserved ratio impaired spirometry (PRISm); lung cancer screening; mortality

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Introduction

Chronic pulmonary airflow impairment is a frequent and major contributing cause of morbidity and premature death worldwide (1,2). One frequent disorder is chronic obstructive pulmonary disease (COPD), which is diagnosed also through spirometric lung function tests that reveal a reduced 1-second expiration volume (FEV_1) relative to the individual's forced vital lung capacity (FVC). COPD severity is graded further by the reduction in FEV_1 expressed as percent of predicted norm values, following guidelines of the Global Initiative for chronic Obstructive Lung Disease (GOLD) (3). Chronic bronchitis and emphysema are frequent underlying conditions and historical subtypes of COPD, with shortness of breath and chronic cough, with or without mucus production, as main symptoms. A complementary category of patients with diminished lung function does not meet spirometric GOLD criteria for COPD: they have reductions in both FVC and FEV_1 but no major reduction in the FEV_1/FVC ratio—a condition referred to as "restrictive", or also preserved ratio impaired spirometry (PRISm) (4-8). PRISm is a heterogeneous, often also unstable (5-7) condition marked by restricted expansibility of the lungs and reduced total lung capacity, with various underlying causes ranging from pulmonary parenchymal disease to reduced chest wall expansion resulting from obesity (9).

COPD (10,11) and PRISm (8,12-14) share an elevated prevalence among long-term, heavy smokers, and an association with cardiovascular, respiratory and other comorbidities (15,16). Additionally, PRISm was found to be associated with of obesity [higher average body mass index (BMI)] and diabetes (5-8). Independently of smoking, obstructive (17) and restrictive (6,7,18) spirometry patterns are both associated with increased mortality due to cardiovascular disease, cancer, and other causes. In addition, COPD and reduced FEV_1 have been related to increased lung cancer risk (12,19-23), while only few studies have reported on the lung cancer risk in association with PRISm (12,21).

COPD (24-27) and PRISm (7,8) often remain undiagnosed, since their early symptoms may be only moderate. Population screening by spirometry could help detect lung disease in earlier stages of development, but earlier medical treatments of asymptomatic COPD have not convincingly improved health-related quality of life, morbidity, or mortality (3,28). None withstanding, as airflow obstruction is more prevalent among long-term smokers above age 50—a target group for lung cancer screening by computed tomography (CT) (29,30)—several recent studies have piloted a combination of general pulmonary health check with CT screening programs (25,31). In the latter context, it has also been proposed that lung function tests might help identify individuals at elevated lung cancer risk, for improved risk-based targeting of CT screening (32,33), although concerns exist that co-existing (e.g., cardiovascular) morbidities and increased overall mortality risk may diminish the benefit of CT screening among individuals with severe lung function impairments (32-35).

We here present findings from the German Lung Cancer Screening Intervention Study (LUSI), a randomized trial (n=4,052) to examine the effects of annual CT screening on lung cancer mortality among long-term smokers 50–69 years of age (36). We report the prevalence of participants presenting with either spirometric COPD or PRISm, and provide descriptive data to characterize these participants regarding smoking history, BMI, respiratory symptoms and previous medical diagnosis of pulmonary and other morbidities. In addition, we then report associations of COPD and PRISm with lung cancer risk and all-cause mortality, independently of individuals' detailed smoking histories, and discuss findings in view of the potential utility of spirometric tests for better targeting of CT screening, to those participants for whom it may bring greatest net benefit. We present our article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-63/rc).

Methods

Study design and participants

LUSI (36,37) is a registered randomized trial

(ISRCTN30604390) with a recruitment phase between October 2007 and April 2011 and active screening between October 2007 and April 2016, and with continuing prospective ascertainment of lung cancer incidence and overall mortality until to date. A sample of 292,000 men and women aged 50–69 years was drawn from population registers in the metropolitan area around Heidelberg and asked by mailed questionnaire about their past and current smoking habits. Eligibility was defined by a lifetime smoking history of minimally 15 cigarettes per day during 25 years, or 10 cigarettes per day during 30 years, excluding those who had stopped smoking more than 10 years before invitation to screening [similar to criteria of the Dutch-Belgian NELSON trial (38)]. Among 89,722 respondents who replied to the pre-baseline smoking questionnaire, 4,708 were eligible by these criteria and willing to participate in the study, and were invited to the German Cancer Research Center (DKFZ) in Heidelberg for CT screening. A total of 4,052 participants accepted and were randomized into a screening intervention arm (n=2,029) comprising five annual CT screenings, and a control arm (n=2,023) without screening; 2,007 participants in the CT arm were also offered a spirometry test to be performed on occasion of their baseline CT scan. Practically all participants are of Caucasian ethnic ancestry.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethical approval for the LUSI trial was given by the University of Heidelberg Medical Ethics Committee (No. 073/2001) and by the radiation protection authority (BfS, 22462/2, 2006-045). Written informed consent was provided by all study participants.

Questionnaire information, at baseline and during prospective follow-up

At their first screening visit, participants completed a baseline questionnaire, and then follow-up questionnaires on occasion of their annual follow-up screens, about (recent changes in) smoking habits, use of radiologic (X-ray, CT, MRI) or other (e.g., endoscopic) examinations of the lungs independently of annual CT screening, surgical chest procedures, and possible occurrence of cancer (lung or other organs) or past major cardiovascular incidents and diagnoses. In addition, they reported about respiratory symptoms and pulmonary and other comorbidities. After the five screening rounds, annual follow-up questionnaires continued to be sent to participants in both study arms. Participants who did not respond immediately were contacted by telephone and also offered assistance with the completion of questionnaires during the call.

Questions about respiratory symptoms and morbidities covered chronic cough (≥3 months a year), chronic sputum production, shortness of breath during physical exertion, shortness of breath at rest (dyspnea), recurrent respiratory tract infections, and use of bronchodilators. Regarding pulmonary morbidities, participants were asked at their first screening visit (baseline questionnaire) to report whether their physician had ever diagnosed chronic bronchitis, or non-allergic or allergic asthma. At annual follow-up visits, participants provided further, complementary self-reports on medical diagnoses of any pulmonary disease, including asthma, chronic bronchitis, emphysema, COPD, interstitial lung disease, pulmonary edema, or pneumonia. Other morbidities covered past or current physician-based diagnoses of circulatory disease (myocardial infarction, coronary heart disease, angina pectoris, stroke), diabetes mellitus, and hypertension.

Spirometry

Pre-bronchodilator spirometry was performed using a MasterScreen IOS (VIASYS Healthcare) spirometer. FEV_1/FVC ratios were calculated from the largest FEV_1 and FVC values recorded in any 1 of 2 repeated assessments, and individuals' predicted FEV_1 and FVC values for given age, sex and body height and race (FEV_1% predicted, FVC% predicted) were calculated by equations provided in (39). Participants with FEV_1/FVC <0.70 were classified as having COPD, the severity of their airflow impairment was further classified into stages 1 (FEV_1 ≥80% predicted), 2 (50% ≤ FEV_1 < 80% predicted), or 3–4 (FEV_1 <50% predicted) following the GOLD criteria (3). Participants with FEV_1/FVC ≥0.70 but with FEV_1% <80% were classified as having PRISm (5,7).

Prospective ascertainment of incident lung cancer, and overall and cause-specific mortality

Till April 2021, 99 cases of lung cancer were diagnosed among the CT-arm participants. Of these, 63 were screen-detected, 6 were "interval" cases missed by CT screening, and 30 were diagnosed after the screening period (i.e., 12 or more months after a participant's last screening participation). Besides screen-detection, cases were identified through annual follow-up questionnaires, reports

from treating hospitals, and systematic record linkages to cancer and mortality registers. For all patients, detailed medical information (pathology reports, medical letters on diagnosis and treatment, radiology reports) was obtained and coded to ICD-O-3 for tumor histology and stage.

Mortality and causes of death were ascertained through record linkages with municipal population registers and regional health offices. Up to July 2021, 239 deaths were observed in the CT arm. Based on death certificate data and clinical data records, all cases of death were classified by leading cause (ICD-10).

Further details on ascertainment of lung cancer incidence and overall and cause-specific mortality have been published previously (36).

Statistical analyses

Of the 2,007 trial participants for which a spirometry test was available, 20 were excluded from statistical analyses because of missing values for FEV_1 (n=12, 0.6%) or FVC (n=14, 0.7%) or because of having FEV_1/FVC ratio >1.0 (n=5), leaving a final study set of 1,987 participants (Figure S1).

Descriptive statistics were used to calculate the population prevalence of spirometrically diagnosed COPD or PRISm, and to describe the frequency of self-reported symptoms and comorbidities across categories of participants with COPD, PRISm or normal spirometry. Potential significance of risk factor differences between the three lung function status groups, and between participants with or without medical diagnosis concordant with the presence of COPD, was assessed through independent *t*-tests for continuous data, or Fisher's exact tests for categorical data, as well as by logistic regression models. Information on smoking duration, the time since quitting, and the average daily cigarettes was originally collected and coded in form of categorical variables [6 categories for lifetime smoking duration; 6 for time since quitting; 12 for average smoking intensity (cigarettes/day)]. To obtain quantitatively scored variables for smoking duration (years), the time since quitting (years), and average daily cigarettes category indicator values were replaced with their class midpoints.

Numbers of prevalent plus incident lung cancer cases, and numbers of deaths, were tabulated by lung function status (COPD, by GOLD stage; PRISm; normal spirometry). Logistic regression was used for evaluation of features that may independently predict lung cancer diagnosis, combining all prevalent plus incident lung cancer cases. Cox proportional hazards models were used to evaluate these same features in relation to overall or cause-specific mortality rates. Further to age and sex, key features examined were lifetime smoking duration, time since smoking cessation, average cigarettes/day and spirometric COPD (by GOLD stage) or PRISm *vs.* normal spirometry, as well as self-reported medical diagnosis of COPD-related lung disease. FEV_1/FVC, FEV_1% predicted and FVC% predicted were also examined as continuous risk factors.

Results

Spirometric COPD and PRISm: prevalence and associations with education, smoking, and BMI

In a total of 1,987 of the 2,029 participants in the CT screening arm, spirometry yielded interpretable data (*Table 1*); of these, 369 (18.6%) had spirometry patterns consistent with COPD, 311 (15.7%) had patterns consistent with PRISm, and 1,307 (65.8%) had normal spirometry. Of the 369 participants with COPD, 92 (4.6%) were classified as mild (GOLD 1), 236 as moderate (GOLD 2; 11.9%), and 41 as severe or very severe COPD (GOLD 3–4; 2.1%). Compared to participants with normal spirometry, those with COPD or PRISm more often had lower levels of formal education, and included higher proportions of current, as opposed to ex-smokers. Participants with PRISm had slightly higher, and those with COPD slightly lower median BMI compared to those with normal spirometry. COPD, but not PRISm, showed a higher male-to-female ratio compared to those with normal spirometry (*Table 1*).

Associations with respiratory symptoms

Compared to those with normal spirometry, participants with spirometric COPD, and also those with PRISm, more frequently reported respiratory symptoms typical of COPD, notably chronic cough, sputum production, shortness of breath, physical stress when inhaling poor-quality air, and persistent lower airway infections, and more often reported the use of bronchodilators (*Table 2*). Among those with COPD, the proportion of persons with at least one symptom increased with increasing GOLD stage, from 33.7% of participants with mild (GOLD 1) COPD up to 61% of participants with severe (GOLD 3–4) COPD. Severe dyspnea at rest was reported only rarely (Table S1). Likewise, use of bronchodilators varied from 8.7% for participants with mild (GOLD 1) to 36.6% for those

Table 1 Basic characteristics of LUSI screening arm participants (n=1,987) with spirometry patterns consistent with COPD, PRISm or absence of respiratory impairments (normal spirometry)

Characteristics	PRISm (n=311)	P value	COPD all GOLD stages (n=369)	P value	Normal spirometry (n=1,307)
FEV_1/FVC	0.78 (0.79); [0.74–0.83]	<0.01*	0.65 (0.62); [0.59–0.68]	<0.01*	0.81 (0.81); [0.76–0.86]
FEV_1 (L)	2.30 (2.34); [1.98–2.71]	<0.01*	2.36 (2.32); [1.78–2.82]	<0.01*	3.17 (3.19); [2.70–3.67]
FEV_1% predicted	74.26 (71.87); [68.20–76.86]	<0.01*	71.61 (69.52); [58.86–80.00]	<0.01*	94.83 (96.59); [87.85–103.98]
FVC (L)	2.89 (2.99); [2.48–3.47]	<0.01*	3.67 (3.81); [3.07–4.38]	<0.01*	3.91 (3.94); [3.31–4.52]
FVC% predicted	72.47 (71.50); [66.18–78.21]	<0.01*	86.66 (88.97); [78.04–96.87]	<0.01*	92.54 (93.29); [85.08–100.55]
Age (years)	56.6 (57.7); [52.6–61.5]	0.04*	59.0 (59.2); [54.3–64.2]	<0.01*	55.6 (57.0); [52.3–60.5]
Sex		0.09*		0.03*	
Male	184 (59.2%)		261 (70.7%)		844 (64.6%)
Female	127 (40.8%)		108 (29.3%)		463 (35.4%)
BMI (kg/m^2)	26.9 (27.6); [24.6–30.1]	<0.01*	25.4 (26.1); [23.0–28.3]	0.28*	26.3 (26.6); [23.9–29.0]
Smoking status		0.11*		0.06*	
Current	201 (64.6%)		240 (65.0%)		778 (59.5%)
Former	110 (35.4%)		129 (35.0%)		529 (40.5%)
Smoking duration (years)		0.02*		<0.01*	
26–30	48 (15.4%)		33 (11.9%)		253 (19.4%)
31–35	93 (29.9%)		64 (23.1%)		417 (31.9%)
36–40	104 (33.4%)		71 (25.6%)		402 (30.8%)
41–45	44 (14.1%)		71 (25.6%)		161 (12.3%)
46–50	14 (4.5%)		30 (10.8%)		66 (5.0%)
>50	8 (2.6%)		8 (2.9%)		8 (0.6%)
Time since quitting		0.16*		0.04*	
<1 month	1 (0.9%)		3 (3.2%)		8 (1.5%)
1–6 months	8 (7.3%)		6 (6.4%)		32 (6.0%)
7 months–1 year	11 (10.0%)		6 (6.4%)		25 (4.7%)
1–2 years	12 (10.9%)		14 (14.9%)		88 (16.6%)
3–5 years	38 (34.5%)		38 (40.4%)		159 (30.1%)
6–10 years	40 (36.4%)		27 (28.7%)		217 (41.0%)
Average daily cigarettes		0.22*		<0.01*	
11–15	56 (18.0%)		41 (14.8%)		225 (17.2%)
16–20	77 (24.8%)		76 (27.4%)		438 (33.5%)
21–25	91 (29.3%)		61 (22.0%)		312 (23.9%)
26–30	34 (10.9%)		40 (14.4%)		133 (10.2%)
31–35	15 (4.8%)		21 (7.6%)		60 (4.6%)
36–40	19 (6.1%)		17 (6.1%)		64 (4.9%)
41–45	7 (2.3%)		5 (1.8%)		24 (1.8%)

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	PRISm (n=311)	P value	COPD all GOLD stages (n=369)	P value	Normal spirometry (n=1,307)
46–50	2 (0.6%)		8 (2.9%)		19 (1.5%)
51–55	2 (0.6%)		6 (2.2%)		4 (0.3%)
56–60	4 (1.3%)		1 (0.4%)		18 (1.4%)
>60	4 (1.3%)		1 (0.4%)		10 (0.8%)
Education[a]		0.07*		0.43*	
Primary/lower secondary [ISCED 1–2]	161 (51.8%)		174 (47.1%)		574 (43.9%)
Secondary [ISCED 3]	74 (23.8%)		90 (24.4%)		314 (24.0%)
Post secondary/non tertiary [ISCED 4]	24 (7.7%)		29 (7.9%)		125 (9.6%)
Tertiary (university level) [ISCED 5/6]	50 (16.1%)		71 (19.2%)		283 (21.7%)
Other/unknown	2 (0.6%)		5 (1.3%)		11 (0.8%)
Higher education [ISCED 5/6]	50 (16.1%)	0.01*	53 (19.1%)	0.80*	290 (22.2%)

Median (mean) values and IQR ranges [in square brackets] are reported for continuous variables, while n (%) are reported for categorical variables. *, P values for the comparisons between the PRISm and COPD groups respectively *vs.* the normal spirometry group. For continuous variables these are derived using independent *t*-test, while for the categorical ones, the Fisher's exact test has been implemented; [a], Volks/Hauptschulabschluss (ISCED 1–2), Mittlere Reife (ISCED 3), Fachhochschule (ISCED 4), Hochschule (ISCED 5/6). LUSI, the German Lung Cancer Screening Intervention Study; COPD, chronic obstructive pulmonary disease; PRISm, preserved ratio impaired spirometry; FEV_1, forced expiration in one second; FVC, forced vital lung capacity; BMI, body mass index; ISCED, International Standard Classification of Education; IQR, interquartile range.

with severe (GOLD 3–4) COPD, *vs.* 12.9% among those with PRISm and 4.4% for those with normal spirometry (Table S1).

Associations with previous medical diagnoses of respiratory and other morbidities

About twenty-eight percent (27.9%) of participants with COPD and 19% of those with PRISm reported a past or recent physician's diagnosis of chronic bronchitis, COPD or emphysema, against 9% of those with normal spirometry, and compared to those with normal spirometry participants with COPD or PRISm more frequently also reported a diagnosis of asthma (*Table 2*). Among COPD patients, the prevalence of each of these self-reported diagnoses increased with increasing GOLD stage (Table S1). Among participants with spirometry-based COPD or PRISm, participants reporting a corresponding physician's diagnosis more often were current smokers, more often had respiratory symptoms, more often had lower formal levels of education (PRISm) and on average had more severe lung function impairments than those without a diagnosis of airway-related disease (Tables S2,S3). Regarding other morbidities, especially PRISm was associated with increased prevalence of diabetes, and previous stroke or heart attacks, whereas both PRISm and COPD were associated with increased prevalence of hypertension as well as coronary heart disease.

Associations of spirometric COPD and PRISm with lung cancer risk and histology

From baseline screen up to a median follow-up of 12.1 years, 26 prevalent plus incident cases of lung cancer were diagnosed among participants with COPD (cumulative diagnosis of 7.0%), 28 among participants with PRISm (7.7%) and 45 among participants with normal spirometry (3.4%). Regarding histologic subtypes, lung cancer patients with PRISM showed a significantly lower percentage of adenocarcinomas and a higher percentage of squamous cell or small-cell tumors, compared to patients with normal baseline spirometry (*Table 3*). A suggestion towards a similar

Table 2 Medically diagnosed comorbidities (self-reported), respiratory symptoms and use of bronchodilators among LUSI participants classified as having COPD (GOLD-all stages), PRISm or normal spirometry

Symptoms and comorbidities	PRISm (n=311)	P value	COPD All GOLD stages (n=369)	P value	Normal spirometry (n=1,307)
Frequent pulmonary symptoms					
Chronic cough	73 (23.5%)	<0.01	113 (30.6%)	<0.01	197 (15.1%)
Chronic sputum production	57 (18.3%)	0.06	97 (26.3%)	<0.01	157 (12.0%)
Dyspnea (at rest)	12 (3.9%)	<0.01	9 (2.4%)	0.28	15 (1.1%)
Avoiding physical efforts because of breathlessness	22 (7.1%)	<0.01	33 (8.9%)	<0.01	39 (3.0%)
Persistent bronchial infections	41 (13.2%)	<0.01	53 (14.4%)	<0.01	91 (7.0%)
Any of the above symptoms	108 (34.7%)	<0.01	161 (43.6%)	<0.01	288 (22.0%)
Use of medications					
Bronchodilators (inhalers)	40 (12.9%)	<0.01	68 (18.4%)	<0.01	57 (4.4%)
Medically diagnosed respiratory disease, self-reported					
Chronic bronchitis (ever)*	55 (17.7%)	<0.01	89 (24.1%)	<0.01	119 (9.1%)
Chronic bronchitis (past 12 months)**	4 (1.3%)	0.09	5 (1.4%)	0.05	5 (0.4%)
COPD (past 12 months)**	5 (1.6%)	0.03	11 (3.0%)	<0.01	5 (0.4%)
Emphysema (past 12 months)**	0	1.00	4 (1.1%)	<0.01	1 (0.1%)
Any of the four diagnoses above	59 (19.0%)	<0.01	103 (27.9%)	<0.01	118 (9.0%)
Asthma (ever)*	22 (7.1%)	<0.01	29 (7.9%)	<0.01	37 (2.8%)
Prior (ever) diagnosis of other (non-pulmonary) disease or major health events, self-reported					
Diabetes	50 (16.1%)	<0.01	29 (7.9%)	0.97	101 (7.7%)
Stroke	24 (7.7%)	0.01	20 (5.4%)	0.31	54 (4.1%)
Heart attack	48 (15.4%)	<0.01	38 (10.3%)	0.48	118 (9.0%)
Coronary heart disease	27 (8.7%)	<0.01	24 (6.5%)	0.06	73 (5.2%)
Hypertension	139 (44.7%)	<0.01	141 (38.2%)	0.05	403 (30.8%)

n (%) are reported for categorical variables. *, questionnaire at baseline visit (1st screening round); **, questionnaire at 1st follow-up visit (2nd screening round). LUSI, the German Lung Cancer Screening Intervention Study; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for chronic Obstructive Lung Disease; PRISm, preserved ratio impaired spirometry.

histology shift was observed for lung cancer patients with severe (GOLD 3–4) COPD (Table S4), although numbers of observations were small. In addition, lung cancer patients with COPD or PRISm showed a lower proportion of cases with stage-1 tumors, and higher proportions of stage 3–4 tumors, especially when lung cancer was diagnosed during the screening period.

Adjusting for age, sex and smoking history, logistic regression showed significant associations of lung cancer risk with PRISm (OR =2.68; 95% CI: 1.61–4.40) and moderate-to-severe (GOLD 2–4) COPD (OR =2.05; 95% CI: 1.20–3.42); however, the association was not statistically for all-stage COPD (GOLD 1–4: OR =1.54; 95% CI: 0.91–2.55) (*Table 4*), as no lung cancer cases were observed among the 92 participants with mild (GOLD 1) COPD. Lung cancer risk was significantly inversely related to FEV_1 percent predicted (for 10% absolute difference: OR =0.82; 95% CI: 0.73–0.91), FVC percent predicted (10% difference: OR =0.73; 95% CI: 0.63–0.85), and FEV_1/FVC ratio (percent) (10% difference: OR =0.94; 95% CI: 0.79–1.13) modelled as continuous variables. Odds ratio estimates obtained from models adjusting only for age and sex differed little

Table 3 Lung cancer cases, overall and by histologic subtype, by spirometry classifications (PRISm, COPD stratified by GOLD grade, or neither)

Patient characteristics	PRISm (n=311)	COPD (all stages) (n=369)	Normal spirometry (n=1,307)
Total detection/diagnosed during screening period*	17	19	33
1st screening round* ("prevalence screening")	5	8	11
2nd–5th screening round* ("incidence screenings")	8	10	21
Interval cases	4	1	1
Lung cancer cases diagnosed after the end of screening	11	7	12
Cumulative prevalence plus incidence, n (%)	28 (7.7)	26 (7.0)	45 (3.4)
P value	<0.01	<0.01	
Histology distribution, n (%)			
Adenocarcinomas	12 (42.9)	16 (61.5)	33 (73.3)
Squamous-cell	8 (28.6)	4 (15.4)	4 (8.9)
Small-cell	6 (21.4)	2 (7.7)	4 (8.9)
Other	2 (7.1)	4 (15.4)	4 (8.9)
P value	0.03	0.66	
Stage distribution—screen-detected cases, n (%)			
Stage 1	8 (28.6)	9 (34.6)	25 (55.6)
Stage 2	5 (17.9)	7 (26.9)	5 (11.1)
Stage 3	2 (7.1)	3 (11.5)	2 (4.4)
Stage 4	2 (7.1)	0	0
Unknown	0	0	1 (2.2)
P value	0.22	<0.01	
Stage distribution—screen-detected plus further incident (all) cases, n (%)			
Stage 1	9 (31.1)	12 (46.1)	27 (60.0)
Stage 2	7 (25.0)	7 (26.9)	9 (20.0)
Stage 3	3 (10.7)	4 (15.4)	4 (8.9)
Stage 4	8 (28.6)	3 (11.5)	3 (6.7)
Unknown	1 (3.6)	0	2 (4.4)
P value	0.28	0.22	

*, P values are based on Fischer's exact test. PRISm, preserved ratio impaired spirometry; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for chronic Obstructive Lung Disease.

from those of models additionally adjusting for smoking history, suggesting little confounding by smoking in this population. Beyond spirometry and smoking history, self-reported diagnoses of COPD-related pulmonary disease or symptoms showed no further association with lung cancer risk (results not shown).

Associations of spirometric COPD and PRISm with mortality

The cumulative incidence of deaths of all causes combined was increased among participants with COPD (cumulative incidence of 21.1%) as well as PRISm (17.4%), compared

Table 4 Odds ratios for lung cancer in relation to spirometry-based conditions and measurements

Spirometry categories	Statistical model	Odds ratio (95% CI)	P value, comparison with normal spirometry
COPD (all GOLD stages) *vs.* normal	Model 1	1.72 (1.03–2.84)	0.04
	Model 2	1.54 (0.91–2.55)	0.10
COPD (GOLD 2 *vs.* normal)*	Model 1	2.43 (1.40–4.12)	<0.01
	Model 2	2.18 (1.24–3.72)	<0.01
COPD (GOLD 3–4 *vs.* normal)*	Model 1	1.82 (0.52–4.92)	0.28
	Model 2	1.50 (0.42–4.11)	0.47
COPD (GOLD 2–4 *vs.* normal)*	Model 1	2.32 (1.37–3.84)	<0.01
	Model 2	2.05 (1.20–3.42)	<0.01
PRISm *vs.* normal*	Model 1	2.64 (1.59–4.30)	<0.01
	Model 2	2.68 (1.61–4.40)	<0.01
FEV_1/FVC (%)**	Model 1	0.90 (0.77–1.08)	0.25
	Model 2	0.94 (0.79–1.13)	0.47
FEV_1% predicted**	Model 1	0.80 (0.72–0.89)	<0.01
	Model 2	0.82 (0.73–0.91)	<0.01
FVC% predicted **	Model 1	0.73 (0.63–0.84)	<0.01
	Model 2	0.73 (0.63–0.85)	<0.01
Known respiratory disease***	Model 1	1.13 (0.60–1.97)	0.68
	Model 2	1.01 (0.54–1.77)	0.97

Model 1: adjusted for age and sex; Model 2: adjusted for age, sex, lifetime smoking duration, average cigarettes/day, time since quitting (for ex-smokers). *, compared to reference group of normal spirometry (n=1,307). No lung cancer cases were observed among screening participants with GOLD stage-1 COPD; **, continuous variable (the odds ratios correspond to a unit of 10% increase); ***, known respiratory disease = self-report of previous physician's diagnosis of chronic bronchitis, emphysema or COPD. COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for chronic Obstructive Lung Disease; PRISm, preserved ratio impaired spirometry; FEV_1, forced expiration in one second; FVC, forced vital lung capacity.

to participants with normal spirometry (8.2%) (*Table 5*). A total of 41 lung cancer deaths occurred, thereof 16 in the PRISm group (cumulative incidence of 16/311=5.1%), 9 in the group with COPD (9/369=2.4%), and 16 among participants with normal spirometry (16/1,307=1.2%). For PRISm, as well as for COPD, increased cumulative mortality was also observed for deaths caused by malignancies other than lung cancer (ICD-10, C00–D48), or caused by circulatory diseases (ICD-10, I00–I99) (*Table 5*). Overall, 87% of the deaths were due to other causes than lung cancer.

Proportional hazards models adjusting for age, sex, smoking history and pre-existing diabetes mellitus showed significant associations for overall mortality risk for screening participants classified with PRISm [hazard ratio (HR) =2.29; 95% CI: 1.65–3.19] or with all-stage COPD (GOLD 1–4, HR =1.98; 95% CI: 1.47–2.66), and increasing HRs with increasing severity of COPD (GOLD 1: HR =1.40, 95% CI: 0.77–2.55); GOLD 2: HR =1.74, 95% CI: 1.22–2.49; GOLD 3–4: HR =4.33, 95% CI: 2.68–6.99) (*Table 6*). Overall and cause-specific mortality were inversely related to FEV_1% predicted (HR =0.82; 95% CI: 0.76–0.86 for a 10% increase), percent FVC% predicted (HR =0.75; 95% CI: 0.69–0.82 for a 10% increase), as well as to FEV_1/FVC ratio (HR =0.86; 95% CI: 0.78–0.94, for a 10% increase), analyzed as continuous variables. HR estimates remained essentially unaffected by adjustments for smoking history (*Table 6*). Beyond spirometry and smoking history, self-reported diagnoses of COPD-related pulmonary disease or symptoms showed no further association with all-cause mortality (results not shown).

Table 5 Total cases of death, overall and by major principal causes, for participants with spirometric COPD, PRISm, or normal spirometry

Deaths, overall and by cause	PRISm (n=311)	COPD (GOLD 1–4) (n=369)	Normal spirometry (n=1,307)
Total, n (%)	54 (17.4)	78 (21.1)	107 (8.2)
P value	<0.01	<0.01	
By frequent cause, n (%)			
Cancer			
Total	29 (9.3)	26 (7.0)	52 (4.0)
Lung	16 (5.1)	9 (2.4)	16 (1.2)
Other	13 (4.2)	17 (4.6)	36 (2.8)
P value	0.04	0.66	
Circulatory diseases	11 (3.5)	21 (5.7)	22 (1.7)
Respiratory diseases	3 (1.0)	15 (4.0)	4 (0.3)
Other	11 (3.5)	16 (4.3)	29 (2.2)

COPD, chronic obstructive pulmonary disease; PRISm, preserved ratio impaired spirometry; GOLD, Global Initiative for chronic Obstructive Lung Disease.

Discussion

In this population-based lung cancer screening trial, we observed a prevalence of spirometric COPD (18.6%) clearly above that reported for general population samples un-selected for smoking history (40-43), but less elevated than in several other lung cancer screening studies, notably the American College of Radiology Imaging Network (ACRIN) component of the US National Lung Screening Trial (NLST-ACRIN) (34%) (21), the UK the Lung Screen Uptake Trial (LSUT) (57%) (25), or the Manchester Lung Health Check (MLHC) study (34.7%) (31). For severe (GOLD 3–4) COPD, NLST-ACRIN reported a prevalence of 7.0% (21) *vs.* only 2.1% in LUSI. The higher prevalence of COPD in NLST-ACRIN, LSUT and MLHC, relative to LUSI, may be explained by the higher age range and higher cumulative smoking exposures used as eligibility requirement for each of these former studies. Furthermore, the prevalence of PRISm (15.7%) was also higher than in general population studies unselected for smoking habits (7,12-14,16), but again lower than in NLST-ACRIN (19.5%) (21,32).

As in NLST-ACRIN (32,33), the Lung Screening Uptake Trial (25) and the Manchester Lung Health Check (31) study, we found that increasing severity of COPD-related abnormal spirometry was associated with an increasing proportion of participants reporting classical COPD symptoms, up to about 60 percent in GOLD stages 3–4. PRISm was associated with a moderate increase of these symptoms, relative to normal spirometry. Overall, however, about two thirds of participants with COPD or PRISm were asymptomatic. Furthermore, only about 40% of LUSI participants with COPD or PRISm reported a past or current medical diagnosis of airway disease (chronic bronchitis, COPD or emphysema). In keeping with recent reports from NLST-ACRIN (33), Manchester Lung Health Check (31) and Lung Screening Uptake Trial (25), we found that participants with prior medical diagnoses of lung disease concordant with COPD were more likely to also report respiratory symptoms and be a current and more intense smoker, while more often also having cardiovascular comorbidities or more severe lung function impairments.

Adjusting for smoking history, we observed an approximate 2-fold increase in lung cancer risk for screening participants with moderate or severe (GOLD 2–4) COPD, relative to individuals with normal spirometry, in keeping with previous studies (12,20,21,23). Interestingly, we found that PRISm was also associated with an even 2.6-fold increase in lung cancer risk. Overall, it is worth highlighting that 55% of the lung cancer cases observed in the LUSI screening arm had either COPD or PRISm according to the baseline spirometry examination. Only two previous studies previously reported lung cancer risks in association with PRISm, with relative risk estimates of 1.6 and 1.5, respectively: NLST-ACRIN (n=18,466; 757 lung cancer cases over 6.4 years' average follow-up;

Table 6 Mortality HRs for screening participants with spirometric PRISm or COPD compared to normal spirometry, and in relation to FEV_1/FVC ratio, FEV_1% predicted, FVC% predicted as continuous covariates

Spirometry categories	Statistical model	HR (95% CI)	P value, comparison with normal spirometry
COPD (all GOLD stages) *vs.* normal	Model 1	2.19 (1.63–2.94)	<0.01
	Model 2	1.98 (1.47–2.66)	<0.01
COPD (GOLD 1 *vs.* normal)*	Model 1	1.38 (0.76–2.50)	0.30
	Model 2	1.40 (0.77–2.55)	0.28
COPD (GOLD 2 *vs.* normal)*	Model 1	2.00 (1.40–2.84)	<0.01
	Model 2	1.74 (1.22–2.49)	<0.01
COPD (GOLD 3–4 *vs.* normal)*	Model 1	4.81 (2.99–7.73)	<0.01
	Model 2	4.33 (2.68–6.99)	<0.01
COPD (GOLD 2–4 *vs.* normal)*	Model 1	2.45 (1.80–3.35)	<0.01
	Model 2	2.15 (1.57–2.94)	<0.01
PRISm *vs.* normal*	Model 1	2.27 (1.63–3.15)	<0.01
	Model 2	2.29 (1.65–3.19)	<0.01
FEV_1/FVC (%)**	Model 1	0.84 (0.76–0.92)	<0.01
	Model 2	0.86 (0.78–0.94)	<0.01
FEV_1% predicted**	Model 1	0.80 (0.75–0.85)	<0.01
	Model 2	0.82 (0.76–0.86)	<0.01
FVC% predicted **	Model 1	0.75 (0.68–0.82)	<0.01
	Model 2	0.75 (0.69–0.82)	<0.01
Known respiratory disease***	Model 1	1.57 (1.13–2.18)	<0.01
	Model 2	1.38 (0.99–1.04)	0.06

Model 1: adjusted for age and sex; Model 2: adjusted for age, sex, lifetime smoking duration, average cigarettes/day, time since quitting (for ex-smokers), diabetes. *, compared to reference group of normal spirometry (n=1,307); **, continuous variable (the odds ratios correspond to a unit of 10% increase); ***, known respiratory disease = self-report of previous physician's diagnosis of chronic bronchitis, emphysema or COPD. PRISm, preserved ratio impaired spirometry; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiration in one second; FVC, forced vital lung capacity; HR, hazard ratio; GOLD, Global Initiative for chronic Obstructive Lung Disease.

baseline PRISm prevalence 19.5%) (21,32) and one in the first National Health and Nutrition Examination Survey (NHANES-I; n=5,402, 113 cases over 17.9 years' average follow-up; PRISm prevalence 5.6%) (12). Further studies may be needed to understand the reasons for the association of PRISm with lung cancer risk in further detail, and to identify more specific underlying phenotypes related to lung cancer development. In the COPDGene study, a positive association was found between spirometry patterns analogous to PRISm and reduced total lung capacity with interstitial lung abnormalities (44), and further studies in COPDGene, as well as in NLST (45) and other lung cancer screening cohorts (46), have also shown an association of interstitial lobular abnormalities (ILA) with increased lung cancer risk. In our data, unlike spirometric assessments, self-reported diagnoses of chronic bronchitis, COPD or emphysema showed no association with lung cancer risk.

In NLST-ACRIN, lung cancer cases among participants with spirometrically determined COPD included a lower proportion of patients with adenocarcinomas and early-stage tumors, and higher proportions of squamous-cell, small-cell, and advanced-stage tumors, relative compared with patients who had normal spirometry (21,32,47). In further analyses of NLST-ACRIN data, Young and Hopkins found that reductions in lung cancer deaths for those randomized to the CT arm were mainly obtained among screening

participants who had either no, or only mild or undiagnosed COPD, whereas no reduction was observed for those with severe (GOLD 3–4) or already previously diagnosed COPD (32,33). A possible explanation of this could be that patients without major lung function impairments or only mild COPD more often had adenocarcinomas that were detected in earlier stages in the CT screening arm, whereas advanced COPD was frequently associated with squamous-cell or small-cell carcinoma. The latter is notoriously incurable even in early stages, and both are frequently centrally located, where they escape early detection by unenhanced CT. Unfortunately, the lack of spirometry data in the control arm of LUSI precluded a similar comparison as performed by Young and Hopkins of lung cancer mortality in the CT-screening and control arms, stratified by presence or absence of COPD or also PRISm. However, similar to NLST-ACRIN findings, our data did suggest histology and stage shifts for lung cancer patients who had abnormal spirometry, notably so in the COPD and PRISm groups. Several screening studies (48-51), including LUSI (36), found an increased proportion of adenocarcinomas among early-stage lung tumors detected by CT screening, likely because these are more slowly growing tumors, detectable over a longer period prior to clinical manifestation (52,53), and because of their more peripheral location in the lungs, where small nodules are detected more easily. Analyses of the full NLST trial data by sex and by tumor histology (48) showed that non-small cell and non-squamous cell tumors, notably adenocarcinomas, likely are the tumor subtypes most associated with reduced mortality upon early detection by CT screening. This may also explain why, as e.g., in LUSI, a lung cancer mortality reduction by CT screening was found to be more pronounced in women rather than in men: female lung cancer patients tend to include a higher proportion of cases with adenocarcinomas, and fewer with squamous- and small-cell carcinomas, compared to male patients (36,38,48).

Parallel to lung cancer risk we found that, additionally to smoking, PRISm and COPD (all GOLD stages combined) were each associated with an approximately 2-fold increase in overall mortality. Notably, 87% of deaths were not due to lung cancer; circulatory diseases and non-pulmonary neoplasms combined were the most frequent causes of death. With increasing severity lung function impairment, HRs increased to more than four-fold for severe (GOLD 3–4) COPD, and to 2.7-fold for PRISm combined with FEV_1 below 70% of predicted values. Using a multivariable, flexible parametric model for overall survival that includes baseline variables as age, BMI, and smoking information, we further estimate that, in this population, individuals with PRISm or severe COPD have considerably reduced median life expectancy, with approximately 3.6 to 4.4 and life years lost due to either PRISm or COPD for both men and women, independently of the other risk factors (Table S5). Similar estimates for life years lost in association with airflow restriction (COPD) were made in the NHANES-III study (54). These estimates suggest that for older individuals, e.g., 75 years or older, who continue to smoke and additionally show spirometric lung function impairments the benefit from CT screening may be very limited: there remain few life years to be gained even if lung cancer death is avoided, whereas the risk of being over-diagnosed cannot be neglected. Beyond spirometry, we did not find further improvement of mortality prediction when integrating self-reports of medical diagnosis of COPD-related lung disease (chronic bronchitis, COPD, emphysema).

The question remains how spirometry measurements might best be used to improve targeting of CT screening, to optimize screening benefits (life years gained) against monetary costs, risks of over-diagnosis or possible consequences of false-positive screening tests. PRISm and COPD predict higher lung cancer risk independently of age and smoking history, and individuals at higher lung cancer risk may be more likely to benefit from lung cancer screening than those with lower risk (55). However, both COPD and PRISm appear to be associated with increased rates of those cancers that are aggressive and difficult to detect in early and still curable stages. Screening benefits will be additionally limited by reduced overall life expectancy.

The analyses by Young and Hopkins of NLST-ACRIN data (32,33) indeed suggest that CT screening in the NLST study would have had greater benefit, had it been focused exclusively on participants without severe lung function impairments. The relationship of screening benefits to lung function impairments, however, is likely to be complex, as simultaneously it also depends on a participant's age, sex, detailed smoking history, BMI and presence of further comorbidities, whereas the relationships of these various predictors to the risks of lung cancer vary with regard to subtypes of various aggressiveness, and with regard to risk of death by competing causes. More comprehensive models are being developed that predict an individual's expected gain in life years by participation in CT screening, based on these multiple risk factors (56). Predictions from such models could be used to determine an individual's general eligibility for CT screening, or whether he or she is not

expected to receive sufficient clinical benefit, weighed against the financial costs of screening or also risks of false-positive screening tests or overdiagnosis. Conceivably, in organized screening programs such model predictions could be further improved by the inclusion of spirometry lung function tests. Likewise, ascertainments of spirometric abnormality may also be integrated in models predicting lung cancer risk, in view of determining personally optimized screening intervals (56-58), modulating screening frequency according to risk of having lung cancer detected upon a next screening visit.

In summary, the Lung Screening Uptake Trial and the Manchester Lung Health Check studies in the UK, the NLST-ARCIN trial as well as the LUSI trial have demonstrated that spirometry tests can be successfully integrated into a population-based lung cancer screening program, and all studies showed a high prevalence of previously undiagnosed, symptomatic as well as asymptomatic lung function impairment among screening participants. LUSI and previous studies also showed substantial concordance with regards to factors associated with previously undiagnosed, as compared to diagnosed, lung function impairment. A limitation of the LUSI study is that airflow measurements were based on pre-bronchodilator spirometry, on only a single study visit. Thus, abnormal spirometry indications may have included a proportion of participants with asthma or other reversible airflow conditions, and may have resulted in some overestimation of the prevalence of undiagnosed COPD and PRISm. This same limitation was also acknowledged for the previous reports from NLST, Lung Screening Uptake Trial and the Manchester Lung Health Check study. Nonetheless, as indicated also by these latter studies, pre-bronchodilator spirometry can be usefully applied to find potential COPD cases, to be further diagnostically verified and treated by a specialized pulmonology practice. For PRISm, however, previous studies have shown this is a more unstable, often transient phenotype that frequently transitioned either into, or away from other lung function categories (COPD, normal spirometry) and with highly variable rates of longitudinal decline in FEV_1% (5-7). Furthermore, our data suggest that pre-bronchodilator spirometry readings indicating PRISm or more severe COPD may be associated with higher risk especially of having more aggressive forms of lung cancer (small cell and squamous cell tumors, as opposed to adenocarcinomas), similar to previous observations in NLST-ACRIN, and that both PRISm and COPD are also important predictors for increased overall mortality due to causes competing with lung cancer. Thus, our findings confirm that spirometry measurements may be useful predictors for lung cancer screening outcomes, which could be incorporated into models for the prediction of, both, screening benefits or harms and into optimized guidelines for screening eligibility and frequency.

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Footnote

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References

1. GBD Chronic Respiratory Disease Collaborators. Prevalence and attributable health burden of chronic respiratory diseases, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Respir Med 2020;8:585-96.
2. Burney PG, Patel J, Newson R, et al. Global and regional trends in COPD mortality, 1990-2010. Eur Respir J 2015;45:1239-47.
3. Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease: GOLD. 2021. Available online: https://goldcopd.org/wp-content/uploads/2020/11/GOLD-REPORT-2021-v1.1-25Nov20_WMV.pdf
4. Clay RD, Iyer VN, Reddy DR, et al. The "Complex Restrictive" Pulmonary Function Pattern: Clinical and Radiologic Analysis of a Common but Previously Undescribed Restrictive Pattern. Chest 2017;152:1258-65.
5. Wan ES, Castaldi PJ, Cho MH, et al. Epidemiology, genetics, and subtyping of preserved ratio impaired spirometry (PRISm) in COPDGene. Respir Res 2014;15:89.
6. Wan ES, Fortis S, Regan EA, et al. Longitudinal Phenotypes and Mortality in Preserved Ratio Impaired Spirometry in the COPDGene Study. Am J Respir Crit Care Med 2018;198:1397-405.
7. Wijnant SRA, De Roos E, Kavousi M, et al. Trajectory and mortality of preserved ratio impaired spirometry: the Rotterdam Study. Eur Respir J 2020;55:1901217.
8. Kaise T, Sakihara E, Tamaki K, et al. Prevalence and Characteristics of Individuals with Preserved Ratio Impaired Spirometry (PRISm) and/or Impaired Lung Function in Japan: The OCEAN Study. Int J Chron Obstruct Pulmon Dis 2021;16:2665-75.
9. Martinez-Pitre PJ, Sabbula BR, Cascella M. Restrictive Lung Disease. Treasure Island, FL, USA: StatPearls Publishing, 2022.
10. Forey BA, Thornton AJ, Lee PN. Systematic review with meta-analysis of the epidemiological evidence relating smoking to COPD, chronic bronchitis and emphysema. BMC Pulm Med 2011;11:36.
11. Burney P, Jithoo A, Kato B, et al. Chronic obstructive pulmonary disease mortality and prevalence: the associations with smoking and poverty--a BOLD analysis.

Thorax 2014;69:465-73.
12. Mannino DM, Aguayo SM, Petty TL, et al. Low lung function and incident lung cancer in the United States: data From the First National Health and Nutrition Examination Survey follow-up. Arch Intern Med 2003;163:1475-80.
13. Kurth L, Hnizdo E. Change in prevalence of restrictive lung impairment in the U.S. population and associated risk factors: the National Health and Nutrition Examination Survey (NHANES) 1988-1994 and 2007-2010. Multidiscip Respir Med 2015;10:7.
14. Higbee DH, Granell R, Davey Smith G, et al. Prevalence, risk factors, and clinical implications of preserved ratio impaired spirometry: a UK Biobank cohort analysis. Lancet Respir Med 2022;10:149-57.
15. Soriano JB, Visick GT, Muellerova H, et al. Patterns of comorbidities in newly diagnosed COPD and asthma in primary care. Chest 2005;128:2099-107.
16. Wan ES, Balte P, Schwartz JE, et al. Association Between Preserved Ratio Impaired Spirometry and Clinical Outcomes in US Adults. JAMA 2021;326:2287-98.
17. Berry CE, Wise RA. Mortality in COPD: causes, risk factors, and prevention. COPD 2010;7:375-82.
18. Guerra S, Sherrill DL, Venker C, et al. Morbidity and mortality associated with the restrictive spirometric pattern: a longitudinal study. Thorax 2010;65:499-504.
19. Calabrò E, Randi G, La Vecchia C, et al. Lung function predicts lung cancer risk in smokers: a tool for targeting screening programmes. Eur Respir J 2010;35:146-51.
20. de-Torres JP, Wilson DO, Sanchez-Salcedo P, et al. Lung cancer in patients with chronic obstructive pulmonary disease. Development and validation of the COPD Lung Cancer Screening Score. Am J Respir Crit Care Med 2015;191:285-91.
21. Hopkins RJ, Duan F, Chiles C, et al. Reduced Expiratory Flow Rate among Heavy Smokers Increases Lung Cancer Risk. Results from the National Lung Screening Trial-American College of Radiology Imaging Network Cohort. Ann Am Thorac Soc 2017;14:392-402.
22. Opina MTD, Nicklas BJ, Lovato JF, et al. Association of Symptoms of Obstructive Lung Disease and All-Cause Mortality in Older Adult Smokers. J Am Geriatr Soc 2019;67:2116-22.
23. Fry JS, Hamling JS, Lee PN. Systematic review with meta-analysis of the epidemiological evidence relating FEV1 decline to lung cancer risk. BMC Cancer 2012;12:498.
24. Petrie K, Toelle BG, Wood-Baker R, et al. Undiagnosed and Misdiagnosed Chronic Obstructive Pulmonary Disease: Data from the BOLD Australia Study. Int J Chron Obstruct Pulmon Dis 2021;16:467-75.
25. Ruparel M, Quaife SL, Dickson JL, et al. Prevalence, Symptom Burden, and Underdiagnosis of Chronic Obstructive Pulmonary Disease in a Lung Cancer Screening Cohort. Ann Am Thorac Soc 2020;17:869-78.
26. Labaki WW, Han MK. Improving Detection of Early Chronic Obstructive Pulmonary Disease. Ann Am Thorac Soc 2018;15:S243-8.
27. Martinez CH, Mannino DM, Jaimes FA, et al. Undiagnosed Obstructive Lung Disease in the United States. Associated Factors and Long-term Mortality. Ann Am Thorac Soc 2015;12:1788-95.
28. US Preventive Services Task Force (USPSTF); Siu AL, Bibbins-Domingo K, et al. Screening for Chronic Obstructive Pulmonary Disease: US Preventive Services Task Force Recommendation Statement. JAMA 2016;315:1372-7.
29. US Preventive Services Task Force; Krist AH, Davidson KW, et al. Screening for Lung Cancer: US Preventive Services Task Force Recommendation Statement. JAMA 2021;325:962-70.
30. Kauczor HU, Baird AM, Blum TG, et al. ESR/ERS statement paper on lung cancer screening. Eur Radiol 2020;30:3277-94.
31. Balata H, Harvey J, Barber PV, et al. Spirometry performed as part of the Manchester community-based lung cancer screening programme detects a high prevalence of airflow obstruction in individuals without a prior diagnosis of COPD. Thorax 2020;75:655-60.
32. Young RP, Hopkins RJ. Chronic obstructive pulmonary disease (COPD) and lung cancer screening. Transl Lung Cancer Res 2018;7:347-60.
33. Young RP, Hopkins RJ, Gamble GD, et al. Incorporating Baseline Lung Function in Lung Cancer Screening: Does a "Lung Health Check" Help Predict Outcomes? Chest 2021;159:1664-9.
34. Young RP, Hopkins RJ. Mortality Reduction, Overdiagnosis, and the Benefit-to-Harm Ratio of Computed Tomography Screening. Am J Respir Crit Care Med 2015;192:398-9.
35. Rivera MP, Tanner NT, Silvestri GA, et al. Incorporating Coexisting Chronic Illness into Decisions about Patient Selection for Lung Cancer Screening. An Official American Thoracic Society Research Statement. Am J Respir Crit Care Med 2018;198:e3-13.
36. Becker N, Motsch E, Trotter A, et al. Lung cancer mortality reduction by LDCT screening-Results from

the randomized German LUSI trial. Int J Cancer 2020;146:1503-13.
37. Becker N, Motsch E, Gross ML, et al. Randomized study on early detection of lung cancer with MSCT in Germany: study design and results of the first screening round. J Cancer Res Clin Oncol 2012;138:1475-86.
38. de Koning HJ, van der Aalst CM, Oudkerk M. Lung-Cancer Screening and the NELSON Trial. Reply. N Engl J Med 2020;382:2165-6.
39. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J 2012;40:1324-43.
40. Petty TL. Scope of the COPD problem in North America: early studies of prevalence and NHANES III data: basis for early identification and intervention. Chest 2000;117:326S-31S.
41. Çolak Y, Afzal S, Nordestgaard BG, et al. Prognosis of asymptomatic and symptomatic, undiagnosed COPD in the general population in Denmark: a prospective cohort study. Lancet Respir Med 2017;5:426-34.
42. Terzikhan N, Verhamme KM, Hofman A, et al. Prevalence and incidence of COPD in smokers and non-smokers: the Rotterdam Study. Eur J Epidemiol 2016;31:785-92.
43. GBD 2015 Chronic Respiratory Disease Collaborators. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Respir Med 2017;5:691-706.
44. Washko GR, Hunninghake GM, Fernandez IE, et al. Lung volumes and emphysema in smokers with interstitial lung abnormalities. N Engl J Med 2011;364:897-906.
45. Whittaker Brown SA, Padilla M, Mhango G, et al. Interstitial Lung Abnormalities and Lung Cancer Risk in the National Lung Screening Trial. Chest 2019;156:1195-203.
46. Wille MM, Thomsen LH, Petersen J, et al. Visual assessment of early emphysema and interstitial abnormalities on CT is useful in lung cancer risk analysis. Eur Radiol 2016;26:487-94.
47. Young RP, Duan F, Chiles C, et al. Airflow Limitation and Histology Shift in the National Lung Screening Trial. The NLST-ACRIN Cohort Substudy. Am J Respir Crit Care Med 2015;192:1060-7.
48. Pinsky PF, Church TR, Izmirlian G, et al. The National Lung Screening Trial: results stratified by demographics, smoking history, and lung cancer histology. Cancer 2013;119:3976-83.
49. Wilson DO, Ryan A, Fuhrman C, et al. Doubling times and CT screen–detected lung cancers in the Pittsburgh Lung Screening Study. Am J Respir Crit Care Med 2012;185:85-9.
50. Thalanayar PM, Altintas N, Weissfeld JL, et al. Indolent, Potentially Inconsequential Lung Cancers in the Pittsburgh Lung Screening Study. Ann Am Thorac Soc 2015;12:1193-6.
51. Pastorino U. Lung cancer screening. Br J Cancer 2010;102:1681-6.
52. Patz EF Jr, Pinsky P, Gatsonis C, et al. Overdiagnosis in low-dose computed tomography screening for lung cancer. JAMA Intern Med 2014;174:269-74.
53. González Maldonado S, Motsch E, Trotter A, et al. Overdiagnosis in lung cancer screening: Estimates from the German Lung Cancer Screening Intervention Trial. Int J Cancer 2021;148:1097-105.
54. Shavelle RM, Paculdo DR, Kush SJ, et al. Life expectancy and years of life lost in chronic obstructive pulmonary disease: findings from the NHANES III Follow-up Study. Int J Chron Obstruct Pulmon Dis 2009;4:137-48.
55. Ten Haaf K, van der Aalst CM, de Koning HJ, et al. Personalising lung cancer screening: An overview of risk-stratification opportunities and challenges. Int J Cancer 2021;149:250-63.
56. Robbins HA, Berg CD, Cheung LC, et al. Identification of Candidates for Longer Lung Cancer Screening Intervals Following a Negative Low-Dose Computed Tomography Result. J Natl Cancer Inst 2019;111:996-9.
57. Robbins HA, Cheung LC, Chaturvedi AK, et al. Management of Lung Cancer Screening Results Based on Individual Prediction of Current and Future Lung Cancer Risks. J Thorac Oncol 2022;17:252-63.
58. González Maldonado S, Hynes LC, Motsch E, et al. Validation of multivariable lung cancer risk prediction models for the personalized assignment of optimal screening frequency: a retrospective analysis of data from the German Lung Cancer Screening Intervention Trial (LUSI). Transl Lung Cancer Res 2021;10:1305-17.

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