Lower limit of normal based spirometric abnormalities associated with radiographic abnormality in an elderly cohort at low risk for exposure

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Background: Although the relation between radiographic abnormalities and spirometric impairment in people with asbestosis has been studied extensively, the extent of spirometric impairment associated with milder radiographic abnormalities is not established.

Objective: To test associations between mild radiographic abnormalities and Lower Limit of Normal (LLN)-based spirometry interpretation.

Methods: Spirometry and CXRs were collected for 1,026 at low risk of exposure to pneumoconiotic agents participants in a medical screening program.

Results: Individuals with each type of isolated or combined International Labour Organization (ILO) abnormalities had up to over sixfold statistically significant increase in odds of LLN-based restrictive pattern physiology (OR = 1.96, 95%CI 1.03–3.73 for parenchymal to OR = 6.09, 95%CI 1.94–19.10 for parenchymal and pleural) compared to those with normal films.

Conclusions: The findings from this study confirm the association of mild profusion abnormalities with clinically relevant, LLN-based lung function abnormalities.

Keywords: Pneumoconiosis, ILO, Spirometry, Spirometric abnormalities, Lower limit of normal

Introduction

The International Labour Organization's International Classification System of Radiographs of Pneumoconioses (ILO system) is an epidemiologic tool for systematic radiologic evaluation of diffuse, exposure-related injury to lung parenchyma and/or pleura. Assessment of its validity has historically been based on correlations with various measures of lung function and exposure among workforces at high risk for pneumoconiosis.^{1–8} Cumulative exposure has been associated with lung function decline and spirometric impairment in asbestos workers with abnormal ILO profusion scores, severe fibrosis, focal and diffuse pleural abnormalities, and functional evidence of airways disease.^{9–11} The correlation of categorical characterization of lung function abnormality in relatively unexposed workforces with subtle radiographic abnormalities,

corresponding to low grade ILO profusion scores has been less extensively studied.

Spirometric functions, such as forced vital capacity (FVC%Pred), correlate inversely with ILO profusion scores and pleural fibrosis in asbestos exposed workers.^{1–6,8} Characterizations of spirometry vary depending on the reference values and interpretation protocols used.^{12–15} Lower limit of normal (LLN) values have been proposed as an improvement to the previous spirometric gold-standard, %Pred protocol, to correct for “over-diagnosis” of obstruction in older subjects.¹⁶ Data are lacking on correlations between low grade fibrosis using the ILO scoring system and spirometric abnormalities defined by the LLN protocol.

This study was conducted to evaluate the physiologic and clinical significance of subtle abnormalities of parenchyma and pleura on screening chest x-rays (CXR) using LLN-based characterization of spirometry. Associations between ILO profusion scores and LLN spirometry results

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were compared with associations between ILO profusion scores and FVC%Pred values, in a cohort of former atomic weapons workers with minimal or bystander exposure to known fibrogenic agents.

Materials and methods

Recruitment and methods for the screenings were previously described.¹⁷ Former nuclear weapons' workers from an assembly plant and a federal research laboratory were invited for spirometry, posteroanterior chest X-ray, and non-fasting blood panels. Testing was offered on a three-to-five-year basis with most recent results used for analysis.

Written informed consent was collected from participants before screening. A modified American Thoracic Society (ATS) adult respiratory questionnaire¹⁸ was used to obtain basic demographic information, height, weight, and smoking history with body mass index (BMI) calculated according to published methods.¹⁹

Chest films were reviewed independently, by three experienced A-readers, independently, according to the most recent ILO guidelines²⁰ without knowledge of individual clinical status or exposures. A-readers were employed to interpret the films given no access to B-readings by this study. Multiple readings were reconciled using median profusion scores for small opacities and two out of three consensus for pleural abnormalities. The profusion scores were collapsed into six categories for statistical analyses: 0 = 0/0; 1 = 0/1; 2 = 1/0; 3 = 1/1; 4 = 1/2; 5 = 2/1+, similar to the scheme proposed by Miller et al.⁶ Abnormal profusion was defined as ILO score $\geq 1/0$. The ILO CXR categories used in the analysis in this study were mutually exclusive i.e. parenchymal vs. parenchymal with pleural vs. pleural.

Spirometry was done pre-bronchodilator in accordance with ATS guidelines.^{21,22} and calibration of testing equipment on a daily basis as recommended.^{21,22} An effort was made to obtain at least three acceptable and reproducible results, but no test was rejected based on the lack of three results.²³

The Third National Health and Nutrition Examination Survey (NHANES III) equations with race corrections were used to calculate FVC%Pred and LLN reference values for FVC, FEV1, and FEV1/FVC%.^{24,25} Categorization of LLN results was based on a published algorithm²⁶ with low FEV1/FVC% ($< \text{LLN}$), low FEV1 ($< \text{LLN}$), and normal FVC ($\geq \text{LLN}$) described as obstruction; normal FEV1/FVC%, low FVC and normal or low FEV1 interpreted as a restrictive pattern physiology; and low FEV1/FVC%, FVC, and FEV1 characterized as possible mixed obstructive airways and restrictive pattern physiology impairment. Individuals with low FEV1/FVC% but normal FEV1 were recommended for follow-up evaluation and their results were categorized as normal for the purposes of analyses.

Exposure to known fibrogenic agents such as asbestos, beryllium, and metal dusts was assessed qualitatively, by site and for the workers' population at large, and used the

previously described methods to inform this process.^{17,27} Industrial hygiene teams reviewed available industrial hygiene records, job titles, job descriptions, and area monitoring records to conclude that majority of screened workers were at low risk of exposure given their work in an assembly of pre-manufactured components and/or research and development. These worksites have been characterized as relatively clean by the workers with the greatest dust exposure among the weapons assembly workforce being to trinitrotoluene (TNT)-derived explosives dusts among a subset of production workers and to lanthanide metals dusts among a small subset of the research laboratory workforce. No individual exposure assessments were conducted for the purposes of this study.

Statistical analysis

SAS 9.2 statistical software was used to analyze de-identified data.²⁸ Continuously distributed variables such as age, BMI, and FVC%Pred were described using mean, standard deviation, and ranges. Differences in medians of these covariates by smoking history, (never versus current and ex-smokers combined), were tested using the Wilcoxon rank-sum test. The Cochran–Armitage chi-square test was used to test the hypothesis of no difference in trend of ILO profusion score groupings between never and ever-smokers. Differences in the distribution of abnormal CXR ILO readings were tested using Pearson's chi-square test, and Fisher's exact chi-square test was used to test differences in distribution by gender.

Multivariable generalized logistic regression was used to model associations between radiographic abnormalities and spirometry. Separate models were fit using the LLN and %Pred protocols as dependent variables. The LLN spirometry results were characterized into normal (reference), restrictive, obstructive, and mixed results categories. The FVC%Pred values were stratified into normal (reference) 80%+, mild 79–70%, moderate 69–50%, and severe impairment $< 50\%$ categories. ILO readings were evaluated for associations with abnormality by both spirometry protocols in two fashions: as normal, isolated parenchymal or pleural fibrosis, or both, and separately by six profusion score categories. Smoking status and BMI were controlled for in every model.

A P-value of < 0.05 was considered statistically significant in all analyses.

Human participant protection

The University of Iowa Institutional Review Board (ID 200008081 and 200509719) and the Department of Energy Central Beryllium Institutional Review Board (ID 209956) issued approvals for this study.

Results

Spirometry results and ILO CXR readings for 1,026 individuals were analyzed. Characteristics of this population

Table 1 Characteristics of the screened population by smoking status

	Never Smoker <i>n</i> = 428 (41.7)	Current and Ex-smoker <i>n</i> = 598 (58.3)	P-Value
Age, mean (SD), range	65 (13); 31–94	71 (9); 41–92	< 0.01 ¹
Sex, <i>n</i> (%)			
Male	253 (59.1)	509 (85.1)	< 0.01 ²
Female	175 (40.9)	89 (14.9)	
BMI, mean(SD), range	28 (5); 17–58	28 (5); 17–55	0.67 ¹
Race, <i>n</i> (%)			
White	412 (96.2)	580 (96.9)	0.72 ⁴
African-American	8 (1.9)	10 (1.7)	
Asian	5 (1.2)	1 (0.2)	
Hispanic	3 (0.7)	7 (1.2)	
FVC%Pred mean (SD), range	91 (18); 36–162	83 (19); 20–144	< 0.01 ¹
FEV1/FVC% mean (SD) range	77 (8); 35–99	71 (12); 28–98	< 0.01 ¹
LLN spirometry results			
Normal*	321 (75.0)	344 (57.5)	< 0.01 ³
Obstructive**	5 (1.2)	28 (4.7)	
Restrictive***	96 (22.4)	157 (26.2)	
Mixed****	6 (1.4)	69 (11.6)	
ILO CXR, <i>n</i> (%) ^a			
Not abnormal	394 (92.1)	516 (86.2)	0.03 ³
Parenchymal abnormalities (1/0+)	18 (4.2)	35 (5.8)	
Parenchymal (1/0+) and Pleural abnormalities	4 (0.9)	14 (2.3)	
Pleural abnormalities	12 (2.8)	33 (5.7)	
ILO profusion			
Category 0 (0/0)	386 (90.2)	503 (84.1)	0.02 ⁴
Category 1 (0/1)	20 (4.7)	46 (7.7)	
Category 2 (1/0)	10 (2.3)	30 (5.0)	
Category 3 (1/1)	8 (1.9)	6 (1.0)	
Category 4 (1/2)	3 (0.7)	6 (1.0)	
Category 5 (2/1+)	1 (0.2)	7 (1.2)	

*Normal spirometry defined as FEV1/FVC%, FVC ≥ LLN, and FEV1/FVC% < LLN and FEV1 ≥ LLN.

**Obstructive airways defined as FEV1/FVC%, FEV1 < LLN, and FVC ≥ LLN.

***Restrictive pattern physiology defined as FEV1/FVC% ≥ LLN, FVC < LLN.

****Mixed obstructive airways and restrictive pattern physiology defined as FEV1/FVC%, FEV1, and FVC < LLN.

^aILO CXR abnormalities are mutually exclusive.

¹Wilcoxon rank-sum test.

²Fisher exact chi-square test.

³Pearson's chi-square test.

⁴Cochran–Armitage chi-square test.

Abbreviations: ILO, International Labour Organization International Classification of Radiographs of Pneumoconioses; LLN, Lower Limit of Normal; FVC%Pred,***Forced Vital Capacity Percent Predicted.

with never smokers compared to ever-smokers are given in Table 1.

Gender was statistically significantly associated with smoking status with 85.1% of ever smokers being male compared to 59.1% never smokers. Current and ex-smokers were slightly older, on average, than never smokers. Positive smoking history was associated with lower mean FVC%Pred and FEV1/FVC%. Over 40% of ever-smokers had an abnormal LLN spirometry result with 4.7% having obstructive airways, when compared to 25% of overall abnormal LLN spirometry results and 1.2% of obstructive airways specifically among never smokers. Isolated parenchymal abnormalities were found in 5.2% (*n* = 53) subjects, 1.8% (*n* = 18) had concurrent parenchymal and pleural fibrosis, and 4.4% (*n* = 45) isolated pleural fibrosis.

The distributions of ILO abnormalities, profusion scores, and age by categorical spirometry results and mean FVC%Pred values are presented in Table 2.

There were 253 (24.6%) individuals with restrictive pattern physiology using the LLN protocol, 33 (3.2%) with

obstruction, and 75 (7.3%) with mixed impairment. LLN-based spirometric abnormalities were each statistically and significantly associated with abnormalities of parenchyma and/or pleura before adjusting for confounders. The majority (56%) of abnormal profusion scores were low grade 1/0, with 1/1 score being the second most common abnormal ILO profusion reading (20%).

Table 3 summarizes the generalized logistic regression modeling of associations between spirometry and radiographic abnormalities.

Isolated and combined pleural and parenchymal abnormalities were each associated with LLN-based restrictive pattern physiology controlling for smoking and BMI. Concurrent parenchymal and pleural fibrosis was associated with a sixfold increase in odds of restrictive spirometry compared to normal radiography. Concurrent parenchymal and pleural fibrosis was associated with a sevenfold increase in odds of mixed spirometric impairment compared with normal radiography. Individuals with concurrent parenchymal and pleural fibrosis had a statistically significant nearly ten-fold increase in odds of

Table 2 Distribution of ILO abnormalities and profusion scores by LLN categorical spirometry results and FVC%Pred

	LLN restrictive* <i>n</i> = 253 (24.6) ^a	LLN obstructive <i>n</i> = 33 (3.2) ^b	LLN mixed** <i>n</i> = 75 (7.3) ^c	LLN normal <i>n</i> = 665 (64.9) ^d	FVC%Pred mean (SD); range ^e
<i>Age</i>					
< 60	46 (22.1)	3 (1.4)	1 (0.6)	158 (75.9)	92 (15); 51–137
60–69	71 (24.4)	10 (3.4)	19 (6.5)	192 (65.7)	86 (16); 20–131
70–79	101 (29.2)	9 (2.6)	35 (10.1)	201 (58.1)	83 (22); 29–162
80+	35 (19.4)	11 (6.1)	20 (11.1)	114 (63.4)	84 (19); 36–155
P ¹	0.24	0.02	< 0.01		N/A
<i>ILO CXR</i>					
Not abnormal	208 (22.8)	25 (2.7)	60 (6.6)	617 (67.9)	87 (18); 20–162
Parenchymal (1/0+)	18 (34.0)	4 (7.5)	6 (11.3)	25 (47.2)	80 (21); 36–127
Parenchymal (1/0+) and pleural	8 (44.4)	1 (5.5)	4 (22.2)	5 (27.9)	68 (20); 39–100
Pleural	19 (42.2)	3 (6.7)	5 (11.1)	18 (40.0)	76 (18); 39–127
P ²	< 0.01	< 0.01	< 0.01		N/A
<i>ILO profusion score</i>					
Category 0 (0/0)	201 (22.6)	25 (2.8)	59 (6.6)	604 (68.0)	87 (18); 20–162
Category 1 (0/1)	26 (39.4)	3 (4.5)	6 (9.1)	31 (47.0)	80 (20); 29–129
Category 2 (1/0)	12 (30.0)	5 (12.5)	5 (12.5)	18 (45.0)	80 (21); 36–127
Category 3 (1/1)	5 (35.7)	–	2 (14.3)	7 (50.0)	79 (21); 43–113
Category 4 (1/2)	4 (44.5)	–	3 (33.3)	2 (22.2)	70 (17); 52–100
Category 5 (2/1+)	5 (62.5)	–	–	3 (37.5)	71 (27); 39–120
P ¹	< 0.01	0.04	< 0.01		N/A

*Restrictive pattern physiology.

**Mixed obstructive airways and restrictive pattern physiology.

^{a,b,c,d}Total number *n* (%).^eMean (SD); range.¹Cochran–Armitage chi-square test.²Pearson's chi-square test.**Table 3** Logistic regression modeling of association between spirometry results and ILO abnormalities*

	Spirometry					
	LLN**				FVC%Pred***	
	Restrictive OR (95% CI)	Obstructive OR (95% CI)	Mixed OR (95% CI)	79–70 OR (95% CI)	69–50 OR (95% CI)	<50 OR (95% CI)
<i>ILO CXR</i>						
Not abnormal	1.0	1.0	1.0	1.0	1.0	1.0
Parenchymal (1/0+)	1.96 (1.03–3.73)	3.50 (1.10–11.12)	2.11 (0.80–5.56)	0.64 (0.24–1.68)	2.34 (1.17–4.68)	3.06 (0.99–9.47)
Parenchymal (1/0+) and pleural	6.09 (1.94–19.10)	3.82 (0.42–35.21)	6.80 (1.68–27.57)	0.75 (0.09–6.32)	9.92 (3.28–30.00)	9.82 (2.25–42.95)
Pleural	3.03 (1.54–5.97)	4.15 (1.12–15.41)	2.77 (0.96–7.97)	1.88 (0.83–4.26)	3.86 (1.83–8.14)	3.75 (1.03–13.68)
P		< 0.01				< 0.01

*Controlled for smoking and BMI.

**Reference value – participants with normal spirometry by LLN protocol.

***Reference value – participants with normal spirometry (FVC 80%Pred+) by %Pred protocol.

FVC between 50 and 69% of predicted, while those with isolated pleural disease had a nearly fourfold increase in odds of FVC between 50 and 69% of predicted, compared to those with normal films.

Results of generalized logistic regression modeling of associations between spirometric abnormalities and fibrosis profusion scores are summarized in Table 4.

LLN-based results were associated with fibrosis, with individuals with 0/1 profusion score having an over two times increase in odds and those with a 1/2 score an up to eight times increase in odds of restrictive pattern physiology, respectively, compared to those with a 0/0 reading; however there were only four (*n* = 4) subjects with restrictive pattern spirometry and 1/2 profusion score reading and

the confidence interval was wide (95% CI 1.36–43.27). In addition, individuals with a 1/2 profusion score had a nearly fifteen-fold increase in odds of mixed impairment on spirometry compared to participants with normal films adjusting for smoking and BMI and all confidence intervals differing from one, but again there were only three subjects (*n* = 3) identified with these readings (95% CI 2.09–100.89). Low-grade fibrosis scores of 0/1 were associated with an over twofold increase in odds of mild and moderate restriction, (FVC%Pred 79–70% and 69–50%), scores of 1/0 associated with an over threefold increased odds of severe restriction (FVC%Pred < 50%), scores of 1/1 (*n* = 1) associated with a nearly fivefold increase in odds of moderate restriction (FVC%Pred 69–50%), and profusions scores of 1/2 (*n* = 3)

Table 4 Logistic regression modeling of association between spirometry results and ILO profusion scores*

	Spirometry					
	LLN			FVC%Pred		
	Restrictive OR (95% CI)	Obstructive OR (95% CI)	Mixed OR (95% CI)	79–70 OR (95% CI)	69–50 OR (95% CI)	<50 OR (95% CI)
<i>Profusion score</i>						
0/0	1.0	1.0	1.0	1.0	1.0	1.0
0/1	2.23 (1.28–3.90)	1.94 (0.54–6.94)	1.54 (0.60–3.99)	2.04 (1.10–3.80)	2.03 (1.03–4.01)	2.15 (0.61–7.60)
1/0	2.02 (0.94–4.34)	5.39 (1.80–16.18)	2.25 (0.78–6.50)	0.34 (0.08–1.47)	2.21 (1.00–4.88)	3.31 (1.05–10.43)
1/1	2.23 (0.69–7.26)	–	3.19 (0.55–18.58)	0.63 (0.08–5.20)	4.81 (1.45–15.99)	3.78 (0.43–33.20)
1/2	7.67 (1.36–43.27)	–	14.54 (2.09–100.89)	4.72 (0.65–34.25)	18.42 (3.32–102.30)	–
2/1+	3.42 (0.78–15.06)	–	–	1.04 (0.11–10.21)	1.94 (0.31–12.34)	15.40 (2.32–102.30)
P		0.01			< 0.01	

*Controlled for smoking and BMI.

associated with an over eighteen-fold increase in odds of moderate restriction (FVC%Pred 69–50%).

Discussion

The association of radiographic evidence of pulmonary fibrosis with lung function abnormalities has been reported in populations highly exposed to asbestos.^{1–8} These studies found ILO abnormalities on CXR to be negatively correlated with spirometric parameters, specifically FVC%Pred, and this correlation was found for pleural disease alone and more pronounced for pleural coincident with interstitial changes. Our study confirmed these findings for all types of ILO abnormalities in a population with minimal to negligible exposures to asbestos, and other fibrogenic dusts and comparatively low-grade radiographic changes. Parenchymal, isolated pleural and parenchymal coincident with pleural fibrosis were each associated with lower FVC%Pred values and with restrictive physiology using the LLN protocol.

These results are significant for both clinicians and epidemiologists. The association of decrement in pulmonary function with pleural abnormalities could reflect occult interstitial changes too subtle to be detected with conventional chest films. The increase in the risk of parenchymal coincident with pleural abnormalities was up to three times as high compared to isolated parenchymal or pleural disease, but only for moderate to severe FVC%Pred impairment. The ILO profusion score is at present the most consistently agreed upon system for characterizing type and severity of pneumoconiosis, and may have relevance to pulmonary fibrosis in general. The study population was an elderly group of former weapons assembly and research and development workers who, for the most part, based on the qualitative IH assessment were not heavily exposed to beryllium, asbestos, or silica.^{17,27} The etiology of observed fibrotic changes is likely to represent a mix of age and undetermined exposures. These findings confirm ILO system as a valid tool in the detection of clinically relevant pulmonary abnormalities resulting from exposures at work.

Multiple authors reported finding no clear distinction in physiological measurements between ILO 0/1 and 1/0 profusion scores, the conventional cut-off for normal versus abnormal parenchymal findings.^{1,4,8,29} Our study did not find any significant difference in odds of abnormal lung function in individuals across these profusion scores; the odds of restrictive airways or lower FVC%Pred values in those with 0/1 and 1/0 readings were, however, consistently twice as high, though 1/0 and FVC 69–50%Pred not significant, as those with completely negative, (0/– and 0/0), readings but the numbers of individuals with these readings were low resulting possibly in inability to detect the difference. The significance of this finding may be, as other authors suggest, related to minimal and radiographically non-distinguishable abnormalities associated with fibrogenic dust exposures.⁶ This is also consistent with a lack of an objective or absolute cut-off point for discrimination of normal and abnormal lungs using conventional chest radiography. These findings imply the need for more rigorous radiographic evaluation of individuals with 0/1 and 1/0 scores, especially when associated with physiologic impairment.

The biggest increase in odds of abnormal lung function result in our study was noted for individuals with 1/2 ILO profusion scores, with a subsequent sharp decrease noted in scores of 2/1 and greater. The 1/2 score is considered by some to be the most clinically specific cut-score for normal vs. abnormal parenchymal readings.⁸ This finding is consistent with other studies.⁶ It should be noted that this increase in odds of association of lung function abnormality with abnormal vs. normal films (i.e. 0/– and 0/0) was found not only for lower FVC%Pred values but also for categorical spirometry results, specifically restrictive physiology and mixed obstructive airways and restrictive pattern physiology, using the LLN. To our knowledge, this is the first study examining correlations between abnormal ILO profusion score and LLN-based categorical spirometry results.

Previous reports have shown correlation between smoking and ILO profusion readings, considered the “dirty

chest" issue.^{30–32} While questions have been raised regarding the methodology used in some of these studies^{33,34}, our study showed a statistically significant increase in rates of abnormal ILO readings, both for parenchymal abnormalities and profusion scores with the exception of category 1/1, in former and current smokers compared to never smokers. Detailed smoking history was not available to further explore this association, but these findings certainly warrant the need for further studies and recommendations for ILO readers with regards to the significance of the smoking history. As described by other authors chest computed tomography (CT) scans likely provide both greater sensitivity and specificity for lung pathology, including fibrosis and airways disease, in subjects with lower profusion scores.^{35–37} At present, there is no accepted ordinal scale for degree of abnormality on CT scan, there are few large population studies assessing the significance of CT findings and ILO scores in these populations, and inter-reader variability in chest CT readings continues to be problematic.³⁸ Further study with more advanced imaging techniques is warranted to explore the significance of smoking and clinically relevant pulmonary function abnormalities in subjects with low-grade ILO abnormalities on CXR.

Over one-third of spirometries in this study were characterized as abnormal using the NHANES III LLN-based reference values and spirometry interpretation protocol, with 3% of subjects demonstrating obstructive airways, 25% restrictive pattern physiology, and 7% mixed obstructive and restrictive impairment results. This finding is consistent with the 12.5% prevalence estimates of obstructive airways impairment in the NHANES III 2007–2008 population testing,³⁹ based on the <FEV1/FVC LLN ratio as the only criterion to characterize obstruction and inclusive of mixed impairment.²⁶ Using the same %Pred protocol to characterize abnormal spirometry showed differences in the estimates of restrictive pattern physiology between the two studies, the mean age of workers included in this study was, however, 68.7 (± 11.4) years with 10% of individuals over the age of 80 compared to 44.8 (± 0.4) years and 20 to 79 years old individuals included in the NHANES III study. As lung volumes were not available for either study, the correct interpretation of these results remains unknown.

This study employed three experienced ILO NIOSH A-readers with an inter-reader agreement in ILO categorical results ranging from moderate to substantial, as reported previously in the study of the subset of this population.²⁷ The agreement in profusion scoring was also substantial between all three readers. Such high degree of agreement is certainly helpful in any type of validation studies involving ILO-guided interpretation of screening radiographs, it is however unknown, without the detailed exposure information or gold standard radiographic testing, whether this may have

led to under- or overestimate of lung disease rates in this population.

Conclusions

The findings from our study confirm the utility of ILO scale, specifically in the range of minimal category 1 profusion abnormalities, in detection of clinically relevant abnormalities using the LLN-based spirometry interpretation.

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References

- 1 Rosenstock L, Barnhart S, Heyer NJ, Pierson DJ, Hudson LD. The relation among pulmonary function, chest roentgenographic abnormalities, and smoking status in an asbestos-exposed cohort. *Am Rev Respir Dis*. 1988;138:272–7.
- 2 Schwartz DA, Fuortes LJ, Galvin JR, Burmeister LF, Schmidt LE, Leistikow BN. Asbestos-induced pleural fibrosis and impaired lung function. *Am Rev Respir Dis*. 1990;141(2):321–6.
- 3 Lilis R, Miller A, Godbold J, Chan E, Selikoff IJ. Pulmonary function and pleural fibrosis: quantitative relationships with an integrative index of pleural abnormalities. *Am J Ind Med*. 1991;20(2):145–61.
- 4 Miller A, Lilis R, Godbold J, Chan E, Selikoff IJ. Relationship of pulmonary function to radiographic interstitial fibrosis in 2,611 long-term asbestos insulators: an assessment of the international labour office profusion score. *Am Rev Respir Dis*. 1992;145:263–70.
- 5 Miller A, Lilis R, Godbold J, Chan E, Wu X, Selikoff IJ. Spirometric impairments in long-term insulators. Relationships to duration of exposure, smoking and radiographic abnormalities. *Chest*. 1994;105(1):175–82.
- 6 Miller A, Lilis R, Godbold J, Wu X. Relation of spirometric function to radiographic interstitial fibrosis in two large workforces exposed

- to asbestos: an evaluation of the ILO profusion score. *Occup Environ Med.* 1996;53(12):808–12.
- 7 Larson TC, Lewin M, Gottschall EB, Antao VC, Kapil V, Rose CS. Associations between radiographic findings and spirometry in a community exposed to Libby amphibole. *Occup Environ Med.* 2012;69(5):361–6.
 - 8 Miller A, Warshaw R, Nezamis J. Diffusing capacity and forced vital capacity in 5,003 asbestos-exposed workers: relationships to interstitial fibrosis (ILO profusion score) and pleural thickening. *Am J Ind Med.* 2013;56:1383–93.
 - 9 Abejie BA, Wang X, Kales SN, Christiani DC. Patterns of pulmonary dysfunction in asbestos workers: a cross-sectional study. *J Occup Med Toxicol.* 2010;5:12.
 - 10 Dement JM, Welch L, Ringen K, Bingham E, Quinn P. Airways obstruction among older construction and trade workers at Department of Energy nuclear sites. *Am J Ind Med.* 2010;53:224–40.
 - 11 Algranti E, Mendonca EM, Hnizdo E, De Capitani EM, Freitas JB, Raile V, Bussacos MA. Longitudinal decline in lung function in former asbestos exposed workers. *Occup Environ Med.* 2013;70(1):15–21.
 - 12 Aggarwal AN, Gupta D, Behera D, Jindal SK. Comparison of fixed percentage method and lower confidence limits for defining limits of normality for interpretation of spirometry. *Respir Care.* 2006;51:737–43.
 - 13 Hnizdo E, Glindmeyer HW, Petsonk EL, Enright P, Buist AS. Case definitions for chronic obstructive pulmonary disease. *COPD.* 2006;3:95–100.
 - 14 Mannino DM, Buist AS, Vollmer WM. Chronic obstructive pulmonary disease in the older adult: what defines abnormal lung function? *Thorax.* 2007;62:237–41.
 - 15 Mikulski MA, Gerke AK, Lourens S, Czezok T, Sprince NL, Laney AS, Fuortes LJ. Agreement between fixed-ratio and lower limit of normal spirometry interpretation protocols decreases with age: Is there a need for a new GOLD standard. *J Occup Environ Med.* 2013;55(7):802–8.
 - 16 Swanney MP, Ruppel G, Enright PL, Pedersen OF, Crapo RO, Miller MR, Jensen RL, Falaschetti E, Schouten JP, Hankinson JL, Stocks J, Quanjer PH. Using the lower limit of normal for the FEV1/FVC ratio reduces the misclassification of airway obstruction. *Thorax.* 2008;63:1046–51.
 - 17 Mikulski MA, Leonard SA, Sanderson WT, Hartley PG, Sprince NL, Fuortes LJ. Risk of beryllium sensitization in a low-exposed former nuclear weapons cohort from the cold war era. *Am J Ind Med.* 2011a;54:194–204.
 - 18 Ferris BG. Epidemiology standardization project (American Thoracic Society). *Am Rev Respir Dis.* 1978;118:1–120.
 - 19 Keys A, Fidanza F, Karvonen MJ, Kimura N, Taylor HL. Indices of relative weight and obesity. *J Chronic Dis.* 1972;25:329–43.
 - 20 International Labour Organization (ILO). International Labour Office. Guidelines for the use of the ILO international classification of radiographs of pneumoconioses. Occupational Safety and Health Series No. 22, Rev 2000. Geneva: ILO; 2002.
 - 21 American Thoracic Society (ATS). Standardization of spirometry – 1994 Update. *Am J Respir Crit Care Med.* 1995;152:1107–36.
 - 22 Miller MR, Hankinson J, Pellegrino R, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J, ATS/ERS Task Force. Standardisation of spirometry. *Eur Respir J.* 2005;26:319–38.
 - 23 Eisen EA, Robins JM, Greaves IA, Wegman DH. Selection effects of repeatability criteria applied to lung spirometry. *Am J Epidemiol.* 1984;120(5):734–42.
 - 24 Hankinson JL, Kawut SM, Shahar E, Smith LJ, Stukovsky KH, Barr RG. Performance of American Thoracic Society-recommended spirometry reference values in a multiethnic sample of adults: the multi-ethnic study of atherosclerosis (MESA) lung study. *Chest.* 2010;137:138–45.
 - 25 Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med.* 1999;159:179–87.
 - 26 Townsend MC. Spirometry in the occupational health setting-2011 update. *J Occup Environ Med.* 2011;53(5):569–84.
 - 27 Mikulski MA, Hartley PG, Sprince NL, Sanderson WT, Lourens S, Worden NE, Wang K, Fuortes LJ. Risk and significance of chest radiograph and pulmonary function abnormalities in an elderly cohort of former nuclear weapons workers. *J Occup Environ Med.* 2011b;53(9):1046–53.
 - 28 SAS [computer program]. Version 9.2. Cary, NC: SAS Institute Inc.; 2002–2008.
 - 29 Ng TP, Chan SL. Lung function in relation to silicosis and silica exposure in granite workers. *Eur Respir J.* 1992;5:986–91.
 - 30 Castellán RM, Sanderson WT, Petersen MR. Prevalence of radiographic appearance of pneumoconiosis in an unexposed blue collar population. *Am Rev Respir Dis.* 1985;131:684–6.
 - 31 Weiss W. Cigarette smoking and small irregular opacities. *Br J Ind Med.* 1991;48:841–4.
 - 32 Kirchner J, Goltz JP, Lorenz F, Obermann A, Kirchner EM, Kickuth R. The, “dirty chest” – correlations between chest X-ray, multi-slice CT and tobacco burden. *Br J Radiol.* 2012;85:339–45.
 - 33 Frank AL. Cigarette smoking and small irregular opacities. *Br J Ind Med.* 1992;49(8):600.
 - 34 Laney AS, Tramma S, Petsonk EL, Attfield MD. The association between tobacco burden and “dirty chest” is unlikely to follow a linear dose-response pattern. *Br J Radiol.* 2012;85:470–1.
 - 35 Huuskonen O, Kivisaari L, Zitting A, Taskinen K, Tossavainen A, Vehmas T. High-resolution computed tomography classification of lung fibrosis for patients with asbestos-related disease. *Scand J Work Environ Health.* 2001;27(2):106–12.
 - 36 Bauer TT, Heyer CM, Duchna HW, Andreas K, Weber A, Schmidt EW, Ammenwerth W, Schultze-Werninghaus G. Radiological findings, pulmonary function and dyspnea in underground coal miners. *Respiration.* 2007;74(1):80–87.
 - 37 Meijer E, Tjoe NE, Kraus T, van der Zee JS, van Delden O, van Leeuwen M, Lammers JW, Heederik D. Pneumoconiosis and emphysema in construction workers: results of HRCT and lung function findings. *Occup Environ Med.* 2011;68(7):542–6.
 - 38 Ochsmann E, Carl T, Brand P, Raithel HJ, Kraus T. Inter-reader variability in chest radiography and HRCT for the early detection of asbestos-related lung and pleural abnormalities in a cohort of 636 asbestos-exposed subjects. *Int Arch Occup Environ Health.* 2010;83(1):39–46.
 - 39 Ford ES, Mannino DM, Wheaton AG, Giles WH, Presley-Cantrell L, Croft JB. Trends in the prevalence of obstructive and restrictive lung function among adults in the United States. Findings from the National Health and Nutrition Examination Surveys from 1988–1994 to 2007–2010. *Chest.* 2013;143(5):1395–406.