Published in final edited form as:

Occup Environ Med. 2017 October ; 74(10): 756–761. doi:10.1136/oemed-2016-104178.

Pleural abnormalities in the Framingham Heart Study: prevalence and CT image features

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Abstract

Background—The prevalence of pleural abnormalities in the general population is an epidemiologically important index of asbestos exposure, which has not been investigated since a radiography-based study in 1980.

Methods—We examined 2633 chest CT scans (mean 59.2 years, 50% female) from the Framingham Heart Study (FHS) for the presence and image characteristics of pleural plaques and diffuse pleural thickening. Demographics and pulmonary function were stratified by the presence of pleural abnormalities in association with interstitial lung abnormalities (ILA).

Results—Pleural abnormalities were present in 1.5% (95% CI: 1.1–2.1%). Pleural lesions were most commonly bilateral (90.0%), multiple (77.5%), calcified (97.5%), and commonly involved posterior (lower: 92.5%, middle: 87.5%), anterior (upper: 77.5%, middle: 77.5%), and diaphragmatic areas (72.5%). Participants with pleural abnormalities were significantly older (75.7

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Conflicts of interest statement: MN reports consultancies or research grants with Bristol-Myers Aquibb Company, Canon Inc, and Merck & Co Inc. GW reports consultancies with GlaxoSmithKline and Genentech. HH reports research grants from Toshiba Corporation, AZE Ltd, Canon Inc, and Konica Minolta Group.

years, p<0.0001), male (92.5%, p<0.0001), former or current smokers (80.0%, p<0.001) with higher pack-years (33.3, p<0.0001). No significant reduction was noted in pulmonary function measures (p=0.07–0.94) when adjusted for the associated covariates, likely due to small number of cases with pleural abnormalities. Information about prior history of asbestos exposure and occupation was not available.

Conclusions—Pleural plaques and diffuse pleural thickening are present on CT in 1.5% of the FHS cohort. The current prevalence of the pleural abnormalities is smaller than that reported in the previous population-based study using chest radiography, likely representing lower asbestos exposure in recent decades. The posterior portion of the pleura is most frequently involved but the anterior portion is also commonly involved.

Introduction

Pleural plaques and diffuse pleural thickening are non-neoplastic pleural abnormalities typically caused by asbestos exposure. In addition to the asbestos-related pleural diseases, asbestos is known to induce a spectrum of pleuropulmonary diseases, such as malignant mesothelioma, lung cancer, and asbestosis.[1] Pleural plaques are the most common manifestations of asbestos exposure and usually arise from the parietal pleura. They may be an independent risk factor for death from lung cancer.[2] Diffuse pleural thickening is less specific for asbestos exposure and results from thickening and fibrosis of the visceral pleura.[3]

The clinical significance of pleural abnormalities has been investigated in previous studies.[4–8] Lilis et al investigated 1584 asbestos insulation workers between 1981 and 1983.[4] They reported that 75% (1185) of the participants had pleural fibrosis on chest X-ray and revealed a significant relationship of pleural fibrosis with decreased forced vital capacity (FVC). [4] In a recent meta-analysis in 2015, Kopylev et al reported that pleural plaques were associated with a small, but statistically significant impairment of pulmonary function.[7] Asbestos or dust exposure causes interstitial lung disease or pulmonary fibrosis, which plays the major role in the impairment of pulmonary function. Therefore, the impact of pleural abnormalities on pulmonary function has to be assessed in the context of asbestos-related pulmonary diseases.[910]

There are many studies investigating occupational cohorts with a known history of asbestos exposure.[1112] However, few studies investigate the prevalence of pleural plaques in the general population. One of the largest population-based studies is the second National Health and Nutrition Examination Survey (NHANES II), which was conducted between 1976 and 1980 including 8213 individuals aged 35–74 years. The study showed that the prevalence of asbestos-related pleural disease in the US population was 3.9% based on chest radiography findings, which was approximately two times higher than that of the prior corresponding study (1.6%) conducted between 1971 and 1975 (NHANES I).[13] In the United States, utilization of asbestos material increased in the 1940s, peaked in 1973, and then declined rapidly with increased awareness of the health issues related to asbestos and subsequent regulatory action to limit occupational exposure.[14] Regulation of asbestos usage varies depending on region and country, and the latent period of the asbestos-related disease

can be decades long, depending on the amount and duration of exposure.[12] Therefore, it is still not rare to encounter incidental findings of pleural plaques on imaging studies. There is increased concern about environmentally acquired asbestos-related disease; however, the current prevalence of pleural plaques in the general population is unknown.

The aim of the present study was to reveal the current prevalence and CT image characteristics of pleural abnormalities in a large population-based cohort and investigate the association with demographic features, pulmonary function, and underlying interstitial lung abnormalities (ILA).

Materials and Methods

Study Population

The Framingham Heart Study (FHS) is a longitudinal population-based study initiated in 1948 in Framingham, Massachusetts, USA, including basically middle class white and originally designed to investigate the risk factors of cardiovascular diseases. Subsequently, the Offspring cohort (children of the original cohort members and their spouses) and the Third Generation cohort (grandchildren of the original cohort members) have been recruited in 1971 and 2002, respectively. From 2009 to 2011, 2764 participants from the Offspring and Third Generation cohorts underwent a non-contrast enhanced chest CT study (MDCT2). Female participants who were pregnant and/or breastfeeding within six months were excluded from the study before the scan. CT image data were missing in 131 cases. As a result, 2633 participants with chest CT scans from the FHS cohorts (mean age, 59.2 years; 50% male) were included in the present study. The current study was approved by the institutional review boards at Brigham and Women's Hospital and Boston University. Informed consent was obtained from all participants upon enrollment.

Chest CT image evaluation

CT images were obtained in the supine position at full inspiration using a 64-detector-row scanner (Discovery, GE Healthcare, Waukesha, WI). The scan parameters were 120 kV, 300–350 mA, gantry rotation time of 0.35 seconds, and slice thickness of 0.625 mm. Chest CT images were visually evaluated on a Picture Archiving and Communication System (PACS) workstation (VirtualPlace Raijin, AZE Ltd., Tokyo, Japan) with an appropriate mediastinal window setting (WL=50 HU, WW=350 HU).

First, the scans were assessed up to three times by a panel of board-certified radiologists (TA, MY, MN, HH) for the presence of pleural abnormalities using a modified sequential reading method as described previously.[15,16] CT scans were classified into three groups: 1) no pleural abnormalities (normal); 2) minor pleural changes; and 3) pleural abnormalities (pleural plaques and/or diffuse pleural thickening). Minor pleural changes are defined as non-specific, slight, focal thickenings or irregularities of the pleura that are identifiable on CT. Pleural plaques are defined as well-demarcated areas of pleural thickening, seen as elevated flat or nodular lesions that often contain calcification (Figure 1).[17] Diffuse pleural thickening is defined as a continuous sheet of pleural thickening with tapering margins.[18] The first reader reviewed all CT scans for the pleural abnormalities. The second reader

evaluated cases with minor pleural changes or pleural abnormalities, and approximately 10% of those with no pleural abnormalities diagnosed by the first reader. Lastly, the third reader reviewed discordant cases between the first and second readers. Final results were determined by the majority opinion of all three readers.

Cases diagnosed with pleural abnormalities as a result of modified sequential reading were further evaluated by consensus of two radiologists (TA and HH) for the detailed image features including: a) subtype of pleural abnormalities (pleural plaques, diffuse pleural thickening, mixed); b) bilateral or unilateral (right or left) involvement; c) number of pleural plaques (solitary, sporadic, multiple, not applicable if only diffuse pleural thickening exists); d) severity (mild, moderate, extensive); e) presence of calcification; f) locations involved (upper/middle/lower, anterior/posterior, mediastinal, diaphragmatic). Severity is defined as 1) mild: single plaque, unilateral plaques, or thin and sparsely distributed bilateral plaques, and/or unilateral diffuse pleural thickening (involvement of less than 25% of the arc of the thoracic cavity); 2) moderate: bilateral but localized plaques, and/or unilateral diffuse pleural thickening (25% to 50% of the arc of the thoracic cavity); 3) extensive: bilateral and diffusely distributed plaques, and/or bilateral diffuse pleural thickening (more than 50% of the arc of the thoracic cavity).[19,20] Locations are defined as 1) upper zone: above the level of the carina; 2) middle zone: between the level of the carina and the level of the right inferior pulmonary vein; and 3) lower zone: below the right inferior pulmonary vein. Anterior and posterior portions of the pleura are defined respectively as the half of the thoracic cavity above and below the mid-horizontal line. Separated from these zones, medial and caudal portions of the pleura are defined as mediastinal and diaphragmatic portions, abutting the mediastinum and the diaphragm, respectively.

Lungs were also evaluated visually with a lung window setting (WL=−700 HU, WW=1500 HU) for ILA, as published previously.[21] In short, ILA was defined as nondependent changes affecting more than 5% of any lung zone, including ground glass or reticular abnormalities, diffuse centrilobular nodularity, nonemphysematous cysts, honeycombing, or traction bronchiectasis.

Clinical characteristics

The demographic features of participants, including age, sex, body mass index (BMI), smoking status with pack-years, and the results of pulmonary function tests (FEV_1, FVC, DLCO, TLC) were obtained from the exams performed closest to the CT scan date and were compared between the groups stratified with pleural abnormalities and ILA.

Statistical analysis

Inter-reader agreement of visual evaluation for the presence of the pleural abnormalities was indicated with κ values calculated using MedCalc (version 14.12.0, MedCalc Software, Ostend, Belgium).

Participant demographics were investigated using mixed effect models for quantitative variables (age, BMI, pack-years, pulmonary function) and generalized estimating equations for categorical variables (sex, smoking status, ILA status) to account for familial correlations

in the FHS cohorts, using R (version 3.1.1, The R Foundation for Statistical Computing, Vienna, Austria).[22]

Results

Inter-reader agreement regarding the diagnosis for the pleural abnormalities between the first and second readers in the sequential readings was substantial (κ=0.66; 95%CI, 0.60–0.72).[23] Of the cases diagnosed by the first reader as having no pleural abnormalities and subsequently reviewed by the second reader, the agreement rate between first and second readers was 93.4%. Of the discordantly read cases, none of those diagnosed as no pleural abnormalities by the first reader escalated to a final diagnosis of pleural abnormalities as a result of sequential readings.

Pleural plaques and/or diffuse pleural thickening were identified in 1.5% (95%CI: 1.1–2.1%, 40/2633) of the FHS cohort. CT image characteristics are shown in Table 1. Of the 40 cases with the pleural abnormalities, 13 cases had pleural plaques (32.5%) and 22 cases (55%) were mixed with both plaques and diffuse pleural thickening. Isolated diffuse pleural thickening with no pleural plaques was seen in 5 cases (12.5%). The pleural plaques/thickening were most commonly bilateral (90.0%), multiple (five or more, 77.5%), moderate severity (50.0%), and almost always calcified somewhere in the pleural lesions (97.5%). The most common locations of the pleural abnormalities were lower posterior (92.5% of all cases with pleural plaques/thickening), middle posterior (87.5%), upper anterior (77.5%), middle anterior (77.5%), and diaphragmatic areas (72.5%).

Clinical characteristics of participants are summarized in Table 2. In contrast to those with no pleural abnormalities, participants with pleural plaques/thickening were more likely to be older (75.7 years vs. 58.6 years, $p<0.0001$), male (92.5% vs. 48.6%, $p<0.0001$), former or current smokers (80.0% vs. 50.5%, $p<0.001$), and had a greater amount of tobacco smoke exposure (33.3 pack-years vs. 8.9, $p<0.0001$). Participants with pleural abnormalities tended to have ILA more frequently (17.5%) than those without pleural abnormalities (6.1%). However, in the model adjusted for age, sex, smoking status, and pack-years, the association between pleural abnormalities and ILA was not significant (p=0.11). Participants with pleural abnormalities showed slight reductions in FEV_1 and DLCO (p=0.04 and 0.02, respectively) in the unadjusted model (Table 2), whereas they showed no significant reduction in any pulmonary function measure (p=0.42 and 0.07, respectively) in the model adjusted for age, sex, smoking status, pack-years, and ILA status (Table 3). Participants with minor pleural changes showed a slight, but statistically significant decrease in DLCO in both unadjusted (p=0.01) and adjusted models (−3%, 95%CI −5.6, −0.4, p=0.02) for covariates (Tables 2 and 3).

Discussion

Our study reveals that the prevalence of pleural plaques and thickening is 1.5% in the FHS cohort (2009–2011) on CT. This is less than half of the prevalence (3.9%) previously reported from NHANES II (1976–1980) based on the evidence of chest radiography.[13] Given that CT scan has a better capacity to detect and characterize pleural plaques and

thickening than chest radiography,[24–26] the decrease in prevalence over several decades could be more substantial. However, The difference between the cohorts should be taken into account. NHANES II includes male and female, white and non-white individuals aged from 35–74 years. The current study from the FHS has similar age range (mean 59.2 years, range 34–92 years) with almost equal number of male and female. However, it should be noted the FHS includes mostly middle class, white individuals, which may confound the results. In our study, no participants younger than 50 years appeared to have pleural abnormalities. This is explained by less exposure to asbestos in younger generations due to the restriction of asbestosis use in the USA. However, we should be aware that absence of pleural plaques at this time point does not necessarily mean a complete ban on asbestos use, and still, longitudinal observation of the population is necessary because of a long latent period for the pleural abnormalities.

The classic distribution of pleural plaques seen on chest radiographs is in the posterolateral chest wall between the seventh and tenth ribs, lateral chest wall between the sixth and ninth ribs, the dome of the diaphragm, and the mediastinal pleura.[325] Diaphragmatic plaques are virtually pathognomonic to asbestos exposure.[27] Our results support the previous reports but also reveal that pleural plaques in the anterior portion, which could be underestimated on chest radiography,[25] are also common on chest CT. Since the lymphatic pathway of asbestos fibers is a possible pathogenesis of pleural plaques,[3] anterior involvements could be explained by an association with the internal mammary (parasternal) lymph node chain. Understanding the CT image characteristics of pleural abnormalities and their associated demographic features may help improve the accuracy of their assessment.

The impact of pleural abnormalities should be assessed considering underlying pulmonary parenchymal diseases because, in addition to pleural abnormalities, asbestos exposure causes interstitial lung diseases and fibrosis (asbestosis), which affect pulmonary function significantly by the direct destruction of lung parenchyma. Asbestosis manifests as ILA, including HRCT findings of interlobular septal thickening, subpleural dot-like opacities, ground-glass opacity, subpleural lines, parenchymal bands, and honeycombing.[128] Participants with pleural abnormalities showed a slight decrease in FEV_1 and DLCO. However, with adjustment for covariates such as smoking and ILA, the decrement turned out to be insignificant. As the current study investigated a population-based cohort rather than an occupational cohort with asbestos exposure, we only had a small number of cases with pleural abnormalities. Therefore, assessment of the impact of pleural abnormalities in pulmonary function is limited. However, it is still important to identify pleural abnormalities on CT because pleural plaques are the relatively early manifestations of asbestos-related diseases and could be used as a biomarker of asbestos exposure and useful to predict an associated risk for pulmonary fibrosis and lung cancer.[11] Pairon et al reported that pleural plaques may be an independent risk factor for lung cancer and could be used as an additional criterion for lung cancer CT screening of high-risk population.[2] In a study evaluating asbestos-induced CT findings by Copley et al, pleural plaques showed the best inter-reader agreement (κ=0.88) compared to other findings in the lungs such as traction bronchiectasis, parenchymal bands, coarseness of fibrosis, subpleural lines, and interstitial lines.[18] Therefore, identification of pleural abnormalities on CT may affect risk stratification and clinical management of patients.

In a previous study by Clin et al, individuals with diffuse pleural thickening showed a more evident decrease in pulmonary function (FVC, FEV_1, TLC) than those with pleural plaques.[10] However, the definitions of pleural plaques and diffuse pleural thickening often vary in the literature, potentially leading to confusion.[1029] In our study, although we subclassified pleural abnormalities as pleural plaques, diffuse pleural thickening, and a mixed pattern, we realized that differentiation between pleural plaques and diffuse pleural thickening is often ambiguous. In fact, more than half of cases with pleural abnormalities are diagnosed as a mixed pattern. Also, it should be noted that diffuse pleural thickening is not a finding specific to asbestos-related pleural disease. Acute pleuritis of any cause can result in diffuse pleural thickening; empyema, tuberculosis, and trauma are the most likely causes.[1]

Our study has several limitations. First, the current study was conducted retrospectively and clinical and occupational history of participants was not sufficiently obtained. Therefore, the possible cause of pleural abnormalities was not necessarily due to asbestosis exposure but may include other medical conditions that are associated with pleural changes such as pneumonia, empyema, and thoracic surgeries. Second, because the FHS cohort participants are not selected for particular diseases, the statistical power could be diluted compared to an investigation of an occupational cohort study. However, the FHS provided a unique opportunity to investigate participants with pleural abnormalities in the general population with a variety of demographic features, such as wide age range, smokers and non-smokers, and an almost equal male/female ratio. Lastly, our results rely mostly on visual evaluation of CT scans and no pathological confirmation was available. The possibility that subpleural lung parenchymal lesions or intercostal vessels could mimic minor pleural changes or diffuse pleural thickening may not be entirely excluded.[30] However, we categorized unclear pleural changes separate from pleural abnormalities, and inter-reader analysis showed substantial concordance rate, which suggests that the results from visual evaluation are reliable.

In conclusion, pleural plaques and diffuse pleural thickening are present on CT in 1.5% of the FHS cohort. The current prevalence of the pleural abnormalities appears smaller compared to those reported in the previous population-based study based on chest radiography findings, likely representing lower asbestos exposure in recent decades. The posterior portion of the pleura is most frequently involved, although involvement of the anterior portion is also common. Older age, male sex, and cigarette smoking are associated with the presence of pleural abnormalities. Identification of pleural abnormalities is important because of associated risk of malignancy, which needs to be further investigated.

Acknowledgments

Funding: Dr. Nishino is supported by NIH Grant Number: K23 CA157631. Dr. Washko is supported by NIH Grant Number: R01 HL122464, R01 HL116473 and R01 HL107246. Dr. Hunninghake and this work were supported by NIH Grant Numbers: P01 HL114501, and R01 HL111024. This work was partially supported by the NHLBI's Framingham Heart Study contract: N01 HC25195.

Authors are deeply grateful to Alba Cid M.S. for editorial work on the manuscript.

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What this paper adds

- The prevalence of pleural abnormalities in the general population has not been investigated since 1980, and is an important index of asbestos exposure on the population and regarded as a risk factor for associated malignancy.
- Pleural abnormalities were seen in 1.5% of the Framingham Heart Study cohort. CT evaluation of pleural lesions revealed involvement of posterior portion is common, but anterior portion is also commonly involved.
- The current prevalence of the pleural abnormalities is smaller than that reported in the previous study, likely representing lower asbestos exposure in recent decades.

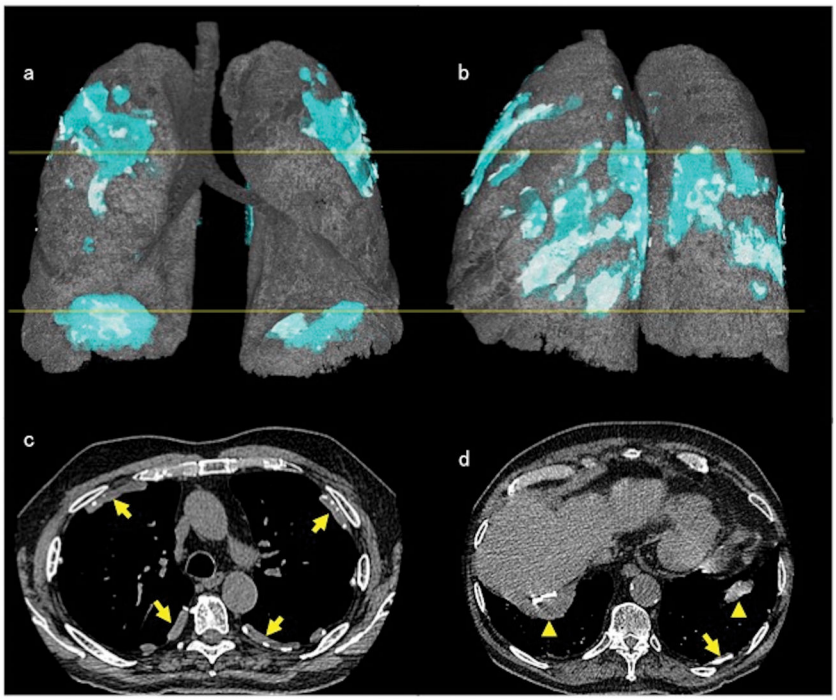

Figure 1.

Table 1

CT image characteristics of the pleural abnormalities

Subtype	N (%)
Pleural plaque	13 (32.5)
Diffuse pleural thickening	5 (12.5)
Mixed	22 (55)
Laterality	
Bilateral	36 (90)
Right	1 (2.5)
Left	3 (7.5)
Number of lesions	
Solitary	0 (0)
Sporadic (2–4)	4 (10)
Multiple (≥5)	31 (77.5)
NA	5 (12.5)
Severity	
Mild	6 (15)
Moderate	20 (50)
Extensive	14 (35)
Involved locations *	
Upper anterior	31 (77.5)
Upper posterior	18 (45)
Middle anterior	31 (77.5)
Middle posterior	35 (87.5)
Lower anterior	8 (20)
Lower posterior	37 (92.5)
Mediastinal	3 (7.5)
Diaphragmatic	29 (72.5)
Calcification	
Present	39 (97.5)
Absent	1 (2.5)

* Percentages for the involved locations do not add up to 100 because most cases involved multiple areas.

Occup Environ Med. Author manuscript; available in PMC 2017 November 24.

Table 2

Clinical characteristics of participants stratified with the presence of pleural abnormalities.

	Overall N = 2633	**No pleural abnormality (0) N = 2420**	**Minor pleural changes (1) N = 173**	**Pleural abnormalities (2) N = 40**	**P Value*1,2***		
					Three groups (0, 1, 2)	**0 vs. 1**	**0 vs. 2**
Age — year	59.21 ± 12.1 (range 34.0, 92.0)	58.6 ± 11.8 (range 34.0, 92.0)	63.4 ± 12.6 (range 38.1, 88.9)	75.7 ± 8.3 (range 51.8, 87.7)	<0.0001	<0.0001	<0.0001
Male sex — no. (%)	1308 (49.7)	1176 (48.6)	95 (54.9)	37 (92.5)	<0.0001	0.28	<0.0001
BMI*3	28.5 ± 5.4 (N=2619, range 16.3, 54.7)	28.5 ± 5.4 (N=2406, range 16.3, 54.7)	28.5 ± 5.4 (N=173, range 17.5, 46.4)	28.6 ± 4.6 (N=40, range 21.0, 44.6)	0.99	0.99	0.99
Smoking status —no. (%)							
Never	1262 (48.4)	1185 (49.5)	69 (39.9)	8 (20.0)	0.0003	0.03	0.003
Former	1184 (45.4)	1057 (44.1)	97 (56.1)	30 (75.0)	<0.0001	0.003	0.001
Current	162 (6.2)	153 (6.4)	7 (4.1)	2 (5.0)	0.46	0.49	0.94
Pack-years	9.5 ± 16.0 (N=2520)	8.9 ± 15.2 (N=2312)	12.3 ± 17.8 (N=168)	33.3 ± 28.7 (N=40)	<0.0001	0.04	<0.0001
Interstitial lung abnormalities (ILA) — no. (%)	177 (6.7)	148 (6.1)	22 (12.7)	7 (17.5)	0.0001	0.003	0.02
Pulmonary function							
FEV_1 — % of predicted value*4	98 ± 15 (N=2467, range 32, 168)	98 ± 15 (N=2268, range 32, 168)	97 ± 16 (N=161, range 45, 141)	93 ± 18 (N=38, range 33, 133)	0.01	0.26	0.04
FVC — % of predicted value*4	102 ± 13 (N=2467, range 47, 168)	102 ± 13 (N=2268, range 47, 168)	101 ± 14 (N=161, range 61, 143)	97 ± 16 (N=38, range 57, 132)	0.022	0.31	0.06
FEV_1 / FVC — % of predicted value*4	96 ± 9 (N=2468, Range 44, 119)	96 ± 9 (N=2269, range 44, 119)	95 ± 9 (N=161, range 58, 115)	94 ± 11 (N=38, range 59, 112)	0.37	0.74	0.48
DLCO — % of predicted value*5	97 ± 15 (N=2062, range 31, 184)	97 ± 15 (N=1906, range 42, 184)	94 ± 17 (N=124, range 31, 153)	90 ± 16 (N=32, range 59, 118)	0.0002	0.01	0.02
TLC*6— % of predicted value*7	84 ± 15 (N=2428, range 31, 132)	84 ± 15 (N=2236, range 31, 132)	84 ± 15 (N=159, range 51, 126)	81 ± 15 (N=33, range 56, 114)	0.33	0.99	0.35

Plus-minus values are mean ± standard deviation.

BMI: body-mass index, FEV: forced expiratory volume, FEV_1: forced expiratory volume in 1 second, FVC: forced vital capacity, DLCO: diffusing capacity of the lung for carbon monoxide, TLC: total lung capacity.

*1 P values were calculated with the use of mixed effect models or generalized estimation equations to account for familial relationships in the Framingham Heart Study.[22]

*2 P values were unadjusted with covariates.

*3 BMI is the weight in kilograms divided by square of the height in meters.

*4 Predicted values for FEV_1 and FVC are derived from Hankinson et al.[31]

*5 Predicted values for DLCO are derived from Miller et al.[32]

*6 Quantitative values for TLC were calculated using Airway Inspector (www.airwayinspector.org).

*7 Predicted values for total lung capacity are derived from the guidelines of the American Thoracic Society and European Respiratory Society.[33]

Table 3

Estimated change in pulmonary function based on the presence of pleural abnormalities and minor pleural changes.

	Minor pleural changes		Pleural abnormalities	
	Estimated change (95%CI)	**P value*1**	**Estimated change (95%CI)**	**P value*1,2**
FEV_1 — % of predicted value *3	−1.4 (−3.7, 0.9)	0.21	−1.9 (−6.7, 2.8)	0.42
FVC — % of predicted value *3	−1.3 (−3.4, 0.8)	0.16	−2.7 (−7.0, 1.5)	0.21
FEV_1 / FVC — % of predicted value *3	−0.3 (−1.6, 1.0)	0.75	0.1 (−2.7, 2.9)	0.94
DLCO — % of predicted value *4	−3.0 (−5.6, −0.4)	0.02	−4.8 (−9.9, 0.3)	0.07
TLC *5 — % of predicted value *6	2.0 (−0.3, 4.3)	0.09	−4.0 (−8.9, 0.9)	0.11

FEV: forced expiratory volume, FEV_1: forced expiratory volume in 1 second, FVC: forced vital capacity, DLCO: diffusing capacity of the lung for carbon monoxide, TLC: total lung capacity.

*1 P values were calculated with the use of mixed effect models to account for familial relationships in the Framingham Heart Study.[22]

*2 P values are the results of comparison with the group of “no pleural abnormality” adjusted for age, sex, smoking status, pack-years, and ILA status.

*3 Predicted values for FEV_1 and FVC are derived from Hankinson et al.[31]

*4 Predicted values for DLCO are derived from Miller et al.[32]

*5 Quantitative values for TLC were calculated using Airway Inspector (www.airwayinspector.org).

*6 Predicted values for total lung capacity are derived from the guidelines of the American Thoracic Society and European Respiratory Society.[33]