CHEST

Characterization of Occupational Endotoxin-Related Small Airway Disease With Longitudinal Paired Inspiratory/Expiratory CT Scans

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BACKGROUND: Although small airway disease (SAD) has been recognized as a major contributor to obstructive respiratory diseases, the association between occupational endotoxin exposure and SAD, as characterized by CT scans, requires further investigation.

RESEARCH QUESTION: What is the association between occupational endotoxin exposure and SAD, and which CT imaging biomarkers effectively detect preclinical airway dysfunction?

STUDY DESIGN AND METHODS: This study included 404 patients from the Shanghai Textile Workers Cohort. We collected longitudinal inspiratory/expiratory CT scans, spirometry data, and endotoxin levels in 2011 and 2016. We evaluated the marginal association among endotoxin, small airway measures, and spirometry by Pearson correlation coefficient. We applied linear mixed models and linear regression models to understand the adjusted association among endotoxin, small airway measures, and spirometry.

RESULTS: We found significant association between endotoxin and SAD and airflow obstruction, as quantified by small airway measures and spirometry, respectively. All small airway measures were marginally correlated with endotoxin, among which relative volume change in voxels with attenuation between −856 Hounsfield units (HU) and −950 HU ($RVC_{-856\ to\ -950}$) and residuals from the linear regression of Exp_{-856} on the percentage of voxels with attenuation less than −950 HU ($Residual_{-856}$) showed the strongest positive correlations. Percent predicted FEV_1 (pp FEV_1) showed the strongest negative correlation with endotoxin. After adjusting for confounders, the expiratory-to-inspiratory ratio of mean lung attenuation (E/I MLA), $RVC_{-856\ to\ -950}$, $Residual_{-856}$, FEV_1, and pp FEV_1 yielded a significant association with endotoxin. Workers who were exposed to 1,500 to 2,300 EU/m^3 endotoxin showed a significantly higher $RVC_{-856\ to\ -950}$ by 0.071 ($P = .006$) and a 8.57% lower pp FEV_1 ($P = .007$) compared with workers exposed to less than 50 EU/m^3 endotoxin.

INTERPRETATION: We found that occupational endotoxin exposure was significantly associated with SAD and lower FEV_1. We identified $Residual_{-856}$ and E/I MLA as the imaging biomarkers for early detection of small airway dysfunction in preclinical individuals (FEV_1/FVC $\geq$ 0.70). These findings have important implications for identifying early-stage SAD and airflow obstruction with CT imaging biomarkers. CHEST 2025; 168(1):43-55

KEY WORDS: imaging biomarkers; occupational endotoxin exposure; paired CT scans; small airway disease

Take-Home Points

Study Question: What is the association between occupational endotoxin exposure and small airway disease (SAD), and which CT imaging biomarkers effectively detect preclinical airway dysfunction?
Results: We found significant association between endotoxin and SAD and airflow obstruction, as quantified by small airway measures and spirometry, respectively.
Interpretation: The results suggest that quantitative small airway measures are important tools in the detection of small airway remodeling and lung function decline for preclinical individuals.

The textile and clothing industry is the most labor-intensive manufacturing sector in the world, employing more than 60 million people worldwide.[1] A study on the global burden of chronic respiratory disease reported 519,000 deaths in 2016 due to occupational airborne exposures.[2] Occupational exposure to textile dust is associated with increased risks of byssinosis, COPD, and other respiratory diseases.[3] Endotoxin is generated from gram-negative bacterial membranes in textile dust.[4] It is the major contributor to occupational respiratory diseases.[5] Furthermore, many studies have reported stronger correlations between chronic lung function loss and endotoxin exposure than dust exposure.[6-8] However, whether occupational exposure to endotoxin can cause small airway disease (SAD) remains controversial.[9,10]

Small airways, usually defined as those with an internal diameter $\leq$ 2 mm,[11] are the predominant sites of airflow resistance in obstructive pulmonary diseases, such as asthma[12,13] and COPD.[12,14] The airflow obstruction in small airways often occurs at an early stage of obstructive pulmonary disease, making SAD an early indicator of lung damage.[15,16] Although spirometry has been the reference standard for diagnosing and assessing airflow obstruction in lung diseases, it is more sensitive to large airway dysfunction and therefore is not an effective biomarker for SAD (Fig 1).[17,18] Furthermore, pathological changes in small airways can occur before the spirometric impairment of pulmonary functions, making the detection of SAD by spirometry even more challenging.[19,20]

To overcome these challenges, researchers have used high-resolution CT at inspiration and expiration to detect and evaluate damage to small airways.[21-23] Specifically, researchers have assessed SAD using CT images by measuring the density of air trapping and quantifying voxels with attenuation less than −856 Hounsfield units (HU) in expiratory CT scans.[24,25] More recently, researchers have developed other quantitative measures based on paired inspiratory/expiratory CT scans, including the ratio of expiratory-to-inspiratory mean lung attenuation,[26,27] relative volume change between inspiratory and expiratory CT scans,[24] and other quantitative measures adjusting for the air trapping due to large airway damage.[28] However, there is no consensus about the best quantitative measures of SAD, and further investigation is still required.[29]

The Shanghai Textile Worker Study is a longitudinal cohort study for respiratory disease among textile workers established in 1981.[30] The unique strength of this study lies in the measurement of endotoxin exposure throughout the patients' working lifetime and the longitudinal collection of paired inspiratory/expiratory CT scans from the cohort. In this study, our primary goal was to investigate the association between endotoxin exposure and SAD, characterized by quantitative small airway measures from CT scans and spirometry. In addition, we aimed to identify CT imaging biomarkers of small airway dysfunction for preclinical individuals who exhibit no airway obstruction ($FEV_1/FVC \geq 0.70$).[31,32]

ABBREVIATIONS: E/I MLA = expiratory-to-inspiratory ratio of mean lung attenuation; Exp_{-856} = percentage of voxels with attenuation less than −856 HU on expiratory CT scans; GOLD = Global Initiative for Chronic Obstructive Lung Disease; HU = Hounsfield unit; PRISm = preserved ratio impaired spirometry; pp FEV_1 = percent predicted FEV_1; $Residual_{-856}$ = residuals from the linear regression of Exp_{-856} on the percentage of voxels with attenuation less than −950 HU; $RVC_{-856\ to\ -950}$ = relative volume change in voxels with attenuation between −856 HU and −950 HU; SAD = small airway disease; TWA = time-weighted average

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DOI: https://doi.org/10.1016/j.chest.2024.12.037

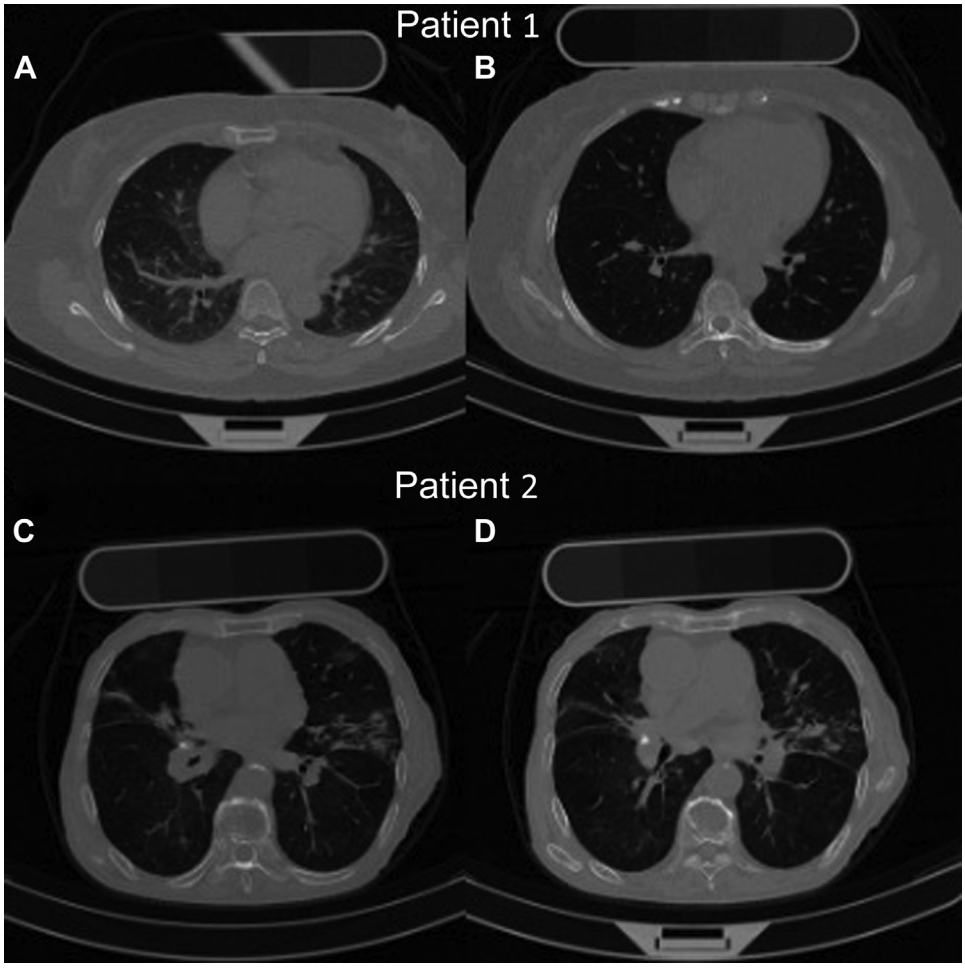

Figure 1 – *Inspiratory (A, C) and expiratory (B, D) CT scans from 2 patients of different occupations at GOLD stage 1 with similar spirometry but different small airway measures. Patient 1 (silk worker): 8-h TWA endotoxin = 0 EU/m^3; spirometry: pp FEV_1 = 0.808; small airway measures: Exp_{-856} = 0.057, E/I MLA = 0.759, $RVC_{-856\ to\ -950}$ = –0.477, $Residual_{-856}$ = –0.164. Patient 2 (cotton worker): 8-h TWA endotoxin = 4,890 EU/m^3; spirometry: pp FEV_1 = 0.803; small airway measures: Exp_{-856} = 0.422, E/I MLA = 1.001, $RVC_{-856\ to\ -950}$ = 0.006, $Residual_{-856}$ = 0.266. E/I MLA = expiratory-to-inspiratory ratio of mean lung attenuation; Exp_{-856} = percentage of voxels with attenuation less than –856 HU on expiratory CT scans; GOLD = Global Initiative for Chronic Obstructive Lung Disease; pp FEV_1 = percent predicted FEV_1; HU = Hounsfield unit; $Residual_{-856}$ = residuals from the linear regression of Exp_{-856} on the percentage of voxels with attenuation less than –950 HU; $RVC_{-856\ to\ -950}$ = relative volume change in voxels with attenuation between –856 HU and –950 HU; TWA = time-weighted average.*

The institutional review boards of the Harvard School of Public Health (# IRB22-0933), the Putuo District People's Hospital, and the Human Resources Administration of China approved the study protocols.

Study Design and Methods

Study Population

The Shanghai Textile Workers Cohort, starting from 1981, includes cotton textile workers exposed to high levels of endotoxin and demographically similar, unexposed silk textile workers. In this study, we focused on the surveys conducted in 2011 and 2016 when the paired inspiratory/expiratory CT scans were collected. The initial population included 480 textile workers, of whom 76 were excluded due to the lack of paired CT scans. Thus, 404 textile workers were analyzed in this study, comprising 178 cotton workers and 226 silk workers (Fig 2). We calculated the minimum detectable difference[33] for the spirometry and quantitative small airway measures based on the current sample size, using a significance level of .05 and a power level of 80% (e-Table 1).

We collected data on demographics, work history, smoking status, and respiratory symptoms, including

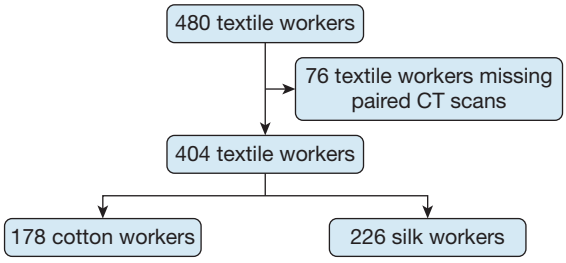

Figure 2 – *Flow diagram for the inclusion of textile workers in the analysis.*

chronic bronchitis, chronic cough, and dyspnea. We performed prebronchodilator spirometry to collect FEV_1, percent predicted FEV_1 (pp FEV_1), and FVC data. $FEV_1/FVC < 0.70$ was used as the indicator of airway obstruction.[34,35] For workers with airway obstruction, we defined the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages 1 through 4 for airway obstruction by pp FEV_1.[36] Among workers without airway obstruction, preserved ratio impaired spirometry (PRISm) was defined as pp $FEV_1 < 80\%$.[37]

Exposure Assessment

Details of the exposure assessment were previously described.[38] Briefly, the exposure of interest was the 8-hour time-weighted average (TWA) area endotoxin concentration. We collected dust samples in 6 work areas of 2 cotton textile mills with a vertical elutriator (General Metalworks), following National Institute for Occupational Safety and Health guidelines. We measured the endotoxin exposure from collected cotton dust sample filters using the Limulus amebocyte lysate assay, chromogenic method (Kinetic-QCL; BioWhittaker).[39] The lower detection limit for endotoxin is 0.001 endotoxin unit (EU/m^3). Samples collected from the silk mill provided nondetectable levels of endotoxin exposure (below 0.001 EU/m^3), so silk workers were considered unexposed to endotoxin.

Paired Chest CT Scans

Chest CT scans were obtained at full inspiration and expiration from patients who consented to volumetric chest CT scans using a single Siemens Emotion-16 CT scanner. Images were reconstructed using a B65s kernel with slice thickness and intervals of 1 mm. The other parameters of the CT scanner were as follows: X-ray voltage, 130 kilovoltage peak (kVp); tube current, 100 milliampere-seconds (mAs) for inspiratory CT scans and 50 mAs for expiratory CT scans; table speed, 13.2 mm/rotation; rotation time, 0.6 s; and pitch value, 1.1. The scanner and scanning protocol were the same in 2011 and 2016.

Quantitative Small Airway Measures

We used 3D Slicer software to perform lung segmentation before extracting the quantitative small airway measures from paired CT scans.[40] We used *PyRadiomics* to extract the quantitative small airway measures,[41] including Exp_{-856}, E/I MLA, $RVC_{-856\ to\ -950}$, and $Residual_{-856}$. Exp_{-856} indicates the percentage of gas trapping, measured as the percentage of voxels with attenuation less than –856 HU on expiratory CT scans.[26] E/I MLA represents the ratio of mean voxel attenuation between expiratory and inspiratory CT scans.[42,43] $RVC_{-856\ to\ -950}$ measures the difference in relative lung volume between the expiratory and inspiratory CT scans, where the relative lung volume is the volume of voxels with attenuation between –856 HU and –950 HU divided by that with attenuation greater than –950 HU.[24] $Residual_{-856}$ represents the residuals from the linear regression of Exp_{-856} on $Inspiratory_{-950}$. $Inspiratory_{-950}$ is the percentage of voxels with attenuation less than –950 HU.[28]

To evaluate the reproducibility of lung segmentation and feature extraction, we conducted internal validation for 30 patients who were randomly selected from the 2011 and 2016 follow-ups, respectively. We performed the lung segmentation and feature extraction twice for the same CT scans of the selected patients with a 2-month interval. We used the intraclass correlation coefficient to evaluate the agreement between the small airway measures collected in the 2 sessions.

Statistical Analysis

In the descriptive analysis, we used mean ± SD to describe continuous variables and frequency (%) to display categorical variables. Missing data in spirometry were addressed by imputing values from the closest survey year available, thereby maintaining data continuity and minimizing the impact of missing data on the analysis. We evaluated the unadjusted correlation between 8-hour TWA endotoxin and small airway measures/spirometry in 2011 and 2016 using Pearson correlation coefficients. In the multivariate analysis, we classified 8-hour TWA endotoxin into quintiles. We replaced the reference group of the first quintile by 0 to 50 EU/m^3. We used the linear mixed model with a random intercept to evaluate the effect of endotoxin exposure on small airway measures and spirometry, adjusting for age, sex, height, smoking intensity, survey time, and the interaction between 8-hour TWA endotoxin and survey

year (8-hour TWA endotoxin × survey year). We also performed all the multivariate analyses restricted to cotton workers. We conducted similar analyses to investigate the relationships between small airway measures and spirometry. The statistical analysis was conducted with R version 4.3.2.

Results

There were a total of 404 patients in the study population, including 178 cotton workers and 226 silk workers. Table 1 presents the baseline characteristics of the study population. The population consisted of more female workers (66%) than male workers. Fifty-five workers (13.6%) had airway obstruction (FEV_1/FVC < 0.70), among which 42 workers (76.4%) were in GOLD stage 1, 11 workers (20%) were in GOLD stage 2, 1 worker (1.8%) was in GOLD stage 3, and 1 worker (1.8%) was in GOLD stage 4. For the workers without airway obstruction, there were 10 individuals (2.5%) with reported PRISm. The BMI of silk workers (23.7 ± 3.1) was significantly lower than that of cotton workers (24.7 ± 3.6; $P = .008$). There was no significant difference between cotton workers and silk workers in terms of other demographic characteristics. Silk workers reported longer work history (26 years) than cotton workers (24 years). The 8-hour TWA endotoxin for cotton workers was 2,302 ± 1,678 EU/m^3. Silk workers were unexposed to endotoxin. Specifically, all 226 silk workers and 11 cotton workers were exposed to endotoxin levels ≤ 50 EU/m^3. Among the cotton workers, 61 were exposed to levels between 50 and 1,500 EU/m^3, 35 to levels between 1,500 and 2,300 EU/m^3, 37 to levels between 2,300 and 3,900 EU/m^3, and 34 to levels exceeding 3,900 EU/m^3. Silk workers reported slightly better lung function than cotton workers did. The mean FEV_1 was 2,321 mL for silk workers, which was higher than the FEV_1 of 2,305 mL for cotton workers. The pp FEV_1 for silk workers (109% ± 18%) was higher than that for cotton workers (105% ± 18%). The FEV_1-to-FVC ratio of cotton workers was similar to that of silk workers with a mean of about 0.77. In the current sample, we did not find significant differences between cotton workers and silk workers regarding other spirometry, quantitative small airway measures, or symptom burden, including chronic bronchitis, chronic cough, and dyspnea, which aligns with the small minimum detectable differences reported in e-Table 1.

Figure 3 shows the correlation network of small airway measures, spirometry, and 8-hour TWA endotoxin. There are strong positive correlations within small airway measures and spirometry. Table 2 reports the correlations between small airway measures/spirometry and endotoxin. At the significance level of .05, significant negative correlations existed only between pp FEV_1 (correlation coefficient, –0.187; $P < .001$), FEV_1/FVC (correlation coefficient, –0.145; $P = .004$), and 8-hour TWA endotoxin in 2011. We found similar correlation between pp FEV_1 (correlation coefficient, –0.184; $P < .001$), FEV_1/FVC (correlation coefficient, –0.118; $P = .017$), and 8-hour TWA endotoxin in 2016. Concerning small airway measures, all the measures were significantly and positively correlated with 8-hour TWA endotoxin ($P < .05$) in 2016, with the strongest correlation of 0.135 for $Residual_{-856}$. e-Table 2 shows the correlation between the quantitative small airway measures and spirometry.

Tables 3, 4 and 5 report the effect of endotoxin on small airway dysfunction in 2011 and 2016, as well as the difference between 2 years. Specifically, Table 4 reports the association between SAD measured by quantitative small airway measures and 8-hour TWA endotoxin in the entire population and restricted to cotton workers. In the entire population, we found significant association between endotoxin exposure and E/I MLA and $RVC_{-856\ to\ -950}$ in both 2011 and 2016 at the significance level of .05. Comparing patients who were exposed to 1,500 to 2,300 EU/m^3 8-hour TWA endotoxin with those exposed to less than or equal to 50 EU/m^3 8-hour TWA endotoxin, E/I MLA was 0.022 higher ($P = .04$) in 2011 and 0.023 higher ($P = .035$) in 2016, and $RVC_{-856\ to\ -950}$ was 0.066 higher ($P = .011$) in 2011 and 0.071 higher ($P = .006$) in 2016. The effect of endotoxin on small airway measures was generally larger in 2016 than in 2011, but the difference was not statistically significant. Restricted to cotton workers, we found that 8-hour TWA endotoxin was significantly associated with $Residual_{-856}$, E/I MLA, and $RVC_{-856\ to\ -950}$. Table 5 reports effect of endotoxin on pulmonary function. In the entire population, we found a significant association between pp FEV_1 and 8-hour TWA endotoxin. pp FEV_1 was 7.022% lower ($P = .027$) for workers exposed to 1,500 to 2,300 EU/m^3 and 6.717% lower ($P = .043$) for workers exposed to more than 3,900 EU/m^3 compared with those exposed to less than or equal to 50 EU/m^3 endotoxin in 2011. In 2016, pp FEV_1 was 8.570% lower

for workers exposed to 1,500 to 2,300 EU/m^3 endotoxin and 6.634% lower for workers exposed to more than 3,900 EU/m^3. We found a significant difference in the effects of endotoxin on FEV_1 between 2011 and 2016. Comparing workers exposed to 50 to 1,500 EU/m^3 with those exposed to less than 50 EU/m^3, FEV_1 was an additional 72.093 mL lower in 2016 than in 2011. In the cotton workers, there was no significant association between endotoxin and spirometry. Similar results were found using occupation as the exposure variable (e-Tables 3, 4).

TABLE 1] Baseline Characteristics of Study Population

Characteristic	All[a] (n = 404)	Cotton Workers[a] (n = 178)	Silk Workers[a] (n = 226)	*P* Value[b]
8-h TWA endotoxin, EU/m^3[c]				< .001
≤ 50	237 (58.7%)	11 (6.2%)	226 (100%)	
50-1,500	61 (15.1%)	61 (34.3%)	0 (0%)	
1,500-2,300	35 (8.7%)	35 (19.7%)	0 (0%)	
2,300-3,900	37 (9.2%)	37 (20.8%)	0 (0%)	
> 3,900	34 (8.4%)	34 (19.1%)	0 (0%)	
Age, y	64 ± 9	63 ± 9	64 ± 9	.6
Sex				.8
Female	267 (66.1%)	119 (66.9%)	148 (65.5%)	
Male	137 (33.9%)	59 (33.1%)	78 (34.5%)	
BMI	24.2 ± 3.4	24.7 ± 3.6	23.7 ± 3.1	.008
Smoking status				.7
Current	83 (20.5%)	40 (22.5%)	43 (19.0%)	
Former	30 (7.4%)	12 (6.7%)	18 (8.0%)	
Never	291 (72.0%)	126 (70.8%)	165 (73.0%)	
Work history, y	25 ± 8	24 ± 7	26 ± 9	.086
Chronic bronchitis	35 (8.7%)	18 (10.1%)	17 (7.5%)	.4
Chronic cough	11 (2.7%)	4 (2.2%)	7 (3.1%)	.8
Dyspnea	94 (23.3%)	40 (22.5%)	54 (23.9%)	.7
PRISm	10 (2.5%)	5 (2.8%)	5 (2.8%)	.8
Airway obstruction	55 (13.6%)	23 (12.9%)	32 (14.2%)	.7
GOLD stage[d]				.8
1	42 (76.4%)	17 (73.9%)	25 (78.1%)	
2	11 (20.0%)	5 (21.7%)	6 (18.8%)	
3	1 (1.8%)	0 (0%)	1 (3.1%)	
4	1 (1.8%)	1 (4.3%)	0 (0%)	
Spirometry				
FEV_1, mL	2,314 ± 601	2,305 ± 639	2,321 ± 570	.4
≤ 2,756.88	323 (80.0%)	141 (79.2%)	182 (80.5%)	.7
pp FEV_1, %	107 ± 18	105 ± 18	109 ± 18	.066
≤ 1.22	323 (80.0%)	147 (82.6%)	176 (77.9%)	.2
FEV_1/FVC	0.77 ± 0.07	0.77 ± 0.07	0.77 ± 0.08	.5
Small airway measures				
Exp_{-856}	0.22 ± 0.13	0.21 ± 0.12	0.23 ± 0.14	.5
≤ 0.31	323 (80.0%)	148 (83.1%)	178 (78.8%)	.2
E/I MLA	0.86 ± 0.07	0.86 ± 0.06	0.86 ± 0.07	.9
≤ 0.90	323 (80.0%)	145 (81.5%)	178 (78.8%)	.5

(Continued)

TABLE 1] *(Continued)*

Characteristic	All[a] (n = 404)	Cotton Workers[a] (n = 178)	Silk Workers[a] (n = 226)	*P* Value[b]
$RVC_{-856\ to\ -950}$	−0.36 ± 0.16	−0.36 ± 0.16	−0.36 ± 0.16	.7
≤ −0.22	323 (80.0%)	144 (80.9%)	179 (79.2%)	.7
$Residual_{-856}$	0.00 ± 0.12	0.00 ± 0.11	0.00 ± 0.12	> .9
≤ 0.08	323 (80.0%)	148 (83.1%)	175 (77.4%)	.2

No. (%) and mean ± SD are reported for categorical variables and continuous variables, respectively. E/I MLA = expiratory-to-inspiratory ratio of mean lung attenuation; Exp_{-856} = percentage of voxels with attenuation less than −856 HU on expiratory CT scans; GOLD = Global Initiative for Chronic Obstructive Lung Disease; HU = Hounsfield unit; pp FEV_1 = percent predicted FEV_1; $Residual_{-856}$ = residuals from the linear regression of Exp_{-856} on the percentage of voxels with attenuation less than −950 HU; $RVC_{-856\ to\ -950}$ = relative volume change in voxels with attenuation between −856 HU and −950 HU; TWA = time-weighted average.

[a]Characteristics of 404 textile workers who had inspiratory/expiratory CT scans were collected in 2011 or 2016, including 178 cotton textile workers and 226 silk textile workers.

[b]Wilcoxon rank-sum test; Pearson χ^2 test; Fisher exact test.

[c]50 EU/m^3 represents the reference level. 1,500 EU/m^3 is the 40th percentile, 2,300 EU/m^3 is the 60th percentile, and 3,900 EU/m^3 is the 80th percentile.

[d]The GOLD stage is reported for the subset of 55 workers with COPD (FEV_1/FVC < 0.7).

The adjusted association between small airway measures and spirometry and the association between small airway measures in 2011 and spirometry in 2016 can be found in e-Table 5 and e-Table 6, respectively.

Discussion

In this longitudinal study of textile workers, we evaluated the impact of occupational exposure to endotoxin on SAD. Exposure to endotoxin was significantly associated with the higher quantitative small airway measures of SAD and lower pulmonary function. We also identified imaging biomarkers for detecting preclinical small airway dysfunction. All the small airway measures were significantly associated with a decline in pulmonary function. Among all the small airway measures, E/I MLA and $RVC_{-856\ to\ -950}$ were the 2 CT imaging biomarkers that showed the strongest association with, and were the most predictive of, pulmonary function decline due to small airway damage. The quantitative measures showed high reproducibility in terms of lung segmentation and feature extraction (e-Table 7).

To our knowledge, this is the first study to examine the association between occupational exposure and SAD using longitudinal paired CT scans. The association between SAD and occupational exposure found in this study has also been reported in other studies. Paulin and

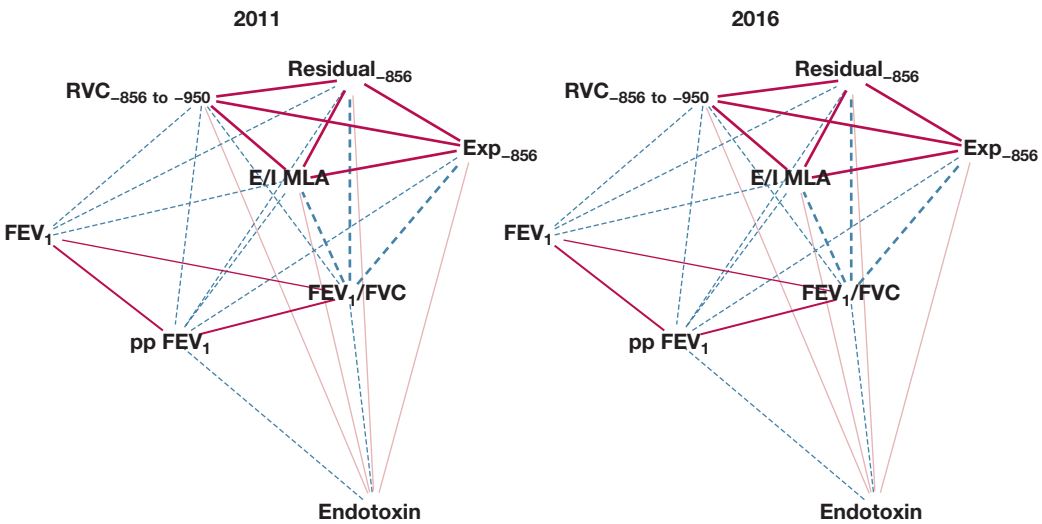

Figure 3 – *Correlation networks of quantitative small airway measures, spirometry, and endotoxin exposures in 2011 and 2016. Edge colors and types indicate the directions of the Pearson correlation coefficients. Solid red edges represent positive correlations and dashed blue edges represent negative correlations. Edge widths represent the magnitude of Pearson correlation coefficients. There were 404 textile workers in 2011 and 2016, respectively. E/I MLA = expiratory-to-inspiratory ratio of mean lung attenuation; Exp_{-856} = percentage of voxels with attenuation less than −856 HU on expiratory CT scans; pp FEV_1 = percent predicted FEV_1; $Residual_{-856}$ = residuals from the linear regression of Exp_{-856} on the percentage of voxels with attenuation less than −950 HU; $RVC_{-856\ to\ -950}$ = relative volume change in voxels with attenuation between −856 HU and −950 HU.*

TABLE 2] Unadjusted Correlations Between Quantitative Small Airway Measures, Spirometry, and 8-Hour TWA Endotoxin

	8-Hour TWA Endotoxin			
	2011 (n = 404)	*P* Value	2016 (n = 404)	*P* Value
Small airway measures				
Exp_{-856}	0.053	.288	0.113	.023
E/I MLA	0.060	.229	0.117	.019
$RVC_{-856\ to\ -950}$	0.065	.191	0.127	.011
$Residual_{-856}$	0.066	.187	0.135	.007
Spirometry				
FEV_1	0.044	.380	0.027	.583
pp FEV_1	−0.187	< .001	−0.184	< .001
FEV_1/FVC	−0.145	.004	−0.118	.017

Pearson correlation coefficients are reported. $P < .05$ was considered significantly different from zero. E/I MLA = expiratory-to-inspiratory ratio of mean lung attenuation; Exp_{-856} = percentage of voxels with attenuation less than -856 HU on expiratory CT scans; HU = Hounsfield unit; pp FEV_1 = percent predicted FEV_1; $Residual_{-856}$ = residuals from the linear regression of Exp_{-856} on the percentage of voxels with attenuation less than −950 HU; $RVC_{-856\ to\ -950}$ = relative volume change in voxels with attenuation between −856 HU and −950 HU; TWA = time-weighted average.

colleagues[44] reported a significant association between occupational exposure to vapors, gas, dust, or fumes and SAD measured by air trapping. Marchetti and colleagues[45] conducted a study on patients from the COPDGene cohort and found a similar association between occupational exposure to dust/fumes and air trapping. Mendelson and colleagues[46] found significant association between dust exposure and CT scan-measured air trapping in workers exposed to World Trade Center disaster dust. These findings are consistent with the results of this study. However, this study provides more comprehensive evaluation of quantitative small airway measures other than air trapping.

We observed the largest effect at 8-hour TWA endotoxin exposure levels between 1,500 and 2,300 EU/m^3. This could partly be due to the unequal sample sizes across exposure categories (Table 1). Alternatively, the observed effect may suggest a threshold effect rather than a linear dose-response relationship, a pattern that has also been reported in previous studies.[47,48] We also found differences in the correlation between spirometry and imaging-based small airway measures with endotoxin exposure. These may be due to nuances in the types of airway changes each biomarker detects. Although standard spirometry reflects broader airway involvement, it does not consistently capture small airway changes that

TABLE 3] Unadjusted Correlations Between Quantitative Small Airway Measures and Spirometry

Small Airway Measures	FEV_1	*P* Value	pp FEV_1	*P* Value	FEV_1/FVC	*P* Value
2011 (n = 404)						
Exp_{-856}	0.011	.831	−0.112	.024	−0.446	< .001
E/I MLA	−0.210	< .001	−0.232	< .001	−0.354	< .001
$RVC_{-856\ to\ -950}$	−0.292	< .001	−0.240	< .001	−0.232	< .001
$Residual_{-856}$	−0.149	.003	−0.189	< .001	−0.410	< .001
2016 (n = 404)						
Exp_{-856}	−0.072	.149	−0.126	.011	−0.486	< .001
E/I MLA	−0.292	< .001	−0.233	< .001	−0.385	< .001
$RVC_{-856\ to\ -950}$	−0.324	< .001	−0.220	< .001	−0.223	< .001
$Residual_{-856}$	−0.216	< .001	−0.181	< .001	−0.413	< .001

Data are presetned as Pearson correlation coefficients unless otherwise indicated. $P < .05$ was considered significantly different from zero. E/I MLA = expiratory-to-inspiratory ratio of mean lung attenuation; Exp_{-856} = percentage of voxels with attenuation less than -856 HU on expiratory CT scans; HU = Hounsfield unit; pp FEV_1 = percent predicted FEV_1; $Residual_{-856}$ = residuals from the linear regression of Exp_{-856} on the percentage of voxels with attenuation less than −950 HU; $RVC_{-856\ to\ -950}$ = relative volume change in voxels with attenuation between −856 HU and −950 HU.

TABLE 4] Multivariate Analysis of Association Between 8-Hour Time-Weighted Average Endotoxin and Quantitative Small Airway Measures

8-Hour TWA Endotoxin[a] (EU/m^3)	Exp_{-856}	*P* Value	E/I MLA	*P* Value	$RVC_{-856\ to\ -950}$	*P* Value	$Residual_{-856}$	*P* Value
All (N = 404)								
Survey year 2011								
≤ 50								
50-1,500	−0.014	.431	0.002	.787	0.006	.778	−0.002	.901
1,500-2,300	0.009	.691	0.022	.040	0.066	.011	0.028	.159
2,300-3,900	−0.013	.535	−0.010	.333	−0.010	.693	−0.016	.421
> 3,900	−0.007	.765	0.009	.411	0.024	.380	0.013	.538
Survey year 2016								
≤ 50								
50-1,500	−0.001	.972	0.008	.354	0.023	.255	0.010	.547
1,500-2,300	0.019	.390	0.023	.035	0.071	.006	0.033	.100
2,300-3,900	0.014	.525	−0.003	.754	0.009	.719	0.012	.532
> 3,900	0.001	.972	0.021	.070	0.051	.060	0.028	.181
Difference								
≤ 50								
50-1,500	0.013	.435	0.006	.507	0.018	.385	0.012	.487
1,500-2,300	0.010	.634	0.001	.948	0.005	.842	0.005	.823
2,300-3,900	0.027	.193	0.007	.508	0.019	.444	0.028	.171
> 3,900	0.008	.723	0.011	.298	0.028	.289	0.015	.472
Cotton workers (n = 178)								
Survey year 2011								
≤ 50								
50-1,500	0.033	.412	0.039	.036	0.087	.060	0.055	.126
1,500-2,300	0.057	.179	0.059	.003	0.144	.003	0.087	.023
2,300-3,900	0.033	.453	0.030	.143	0.080	.107	0.042	.276
> 3,900	0.046	.302	0.052	.013	0.113	.027	0.075	.063
Survey year 2016								
≤ 50								
50-1,500	0.052	.202	0.050	.008	0.114	.014	0.075	.038
1,500-2,300	0.072	.091	0.064	.001	0.159	.001	0.099	.010
2,300-3,900	0.065	.137	0.041	.041	0.109	.028	0.079	.044
> 3,900	0.057	.208	0.067	.001	0.149	.004	0.097	.018
Difference								
≤ 50								
50-1,500	0.019	.602	0.010	.520	0.028	.492	0.020	.560
1,500-2,300	0.015	.692	0.005	.756	0.015	.728	0.012	.732
2,300-3,900	0.032	.386	0.012	.484	0.030	.484	0.036	.312
> 3,900	0.011	.773	0.016	.363	0.036	.393	0.022	.545

Coefficients and *P* values from the linear mixed model with a random intercept are reported. $P < .05$ was considered significantly different from zero. Small airway disease quantified by small airway measures was the outcome, and 8-h TWA endotoxin was the exposure variable in the model. The linear mixed models were adjusted for age, sex, height, smoking intensity, survey year, and the interaction between 8-h TWA endotoxin and survey year (8-h TWA endotoxin × survey year). E/I MLA = expiratory-to-inspiratory ratio of mean lung attenuation; Exp_{-856} = percentage of voxels with attenuation less than -856 HU on expiratory CT scans; HU = Hounsfield unit; pp FEV_1 = percent predicted FEV_1; $Residual_{-856}$ = residuals from the linear regression of Exp_{-856} on the percentage of voxels with attenuation less than −950 HU; $RVC_{-856\ to\ -950}$ = relative volume change in voxels with attenuation between −856 HU and −950 HU; TWA = time-weighted average.

[a]50 EU/m^3 represents the reference level. 1,500 EU/m^3 is the 40th percentile, 2,300 EU/m^3 is the 60th percentile, and 3,900 EU/m^3 is the 80th percentile. There are 237 textile workers exposed to ≤ 50 EU/m^3 endotoxin, 61 workers exposed to 50 to 1,500 EU/m^3 endotoxin, 35 workers exposed to 1,500 to 2,300 EU/m^3 endotoxin, 37 workers exposed to 2,300 to 3,900 EU/m^3 endotoxin, and 34 workers exposed to more than 3,900 EU/m^3.

TABLE 5] Multivariate Analysis of Association Between 8-Hour Time-Weighted Average Endotoxin and Spirometry

8-Hour TWA Endotoxin[a] (EU/m^3)	FEV_1	*P* Value	pp FEV_1	*P* Value	FEV_1/FVC	*P* Value
All (N = 404)						
Survey year 2011						
≤ 50						
50-1,500	17.546	.759	0.090	.972	−0.003	.717
1,500-2,300	−121.286	.091	−7.022	.027	0.008	.484
2,300-3,900	−9.607	.892	−0.553	.859	−0.012	.314
> 3,900	−135.806	.071	−6.717	.043	−0.014	.274
Survey year 2016						
≤ 50						
50-1,500	−54.546	.341	−2.386	.345	−0.009	.364
1,500-2,300	−164.020	.023	−8.570	.007	−0.003	.774
2,300-3,900	−50.986	.472	−1.253	.688	−0.008	.495
> 3,900	−155.622	.041	−6.634	.048	0.003	.788
Difference						
≤ 50						
50-1,500	−72.093	.013	−2.477	.065	−0.005	.455
1,500-2,300	−42.734	.245	−1.549	.361	−0.012	.181
2,300-3,900	−41.379	.248	−0.700	.671	0.004	.656
> 3,900	−19.816	.598	0.083	.962	0.017	.058
Cotton workers (n = 178)						
Survey year 2011						
≤ 50						
50-1,500	−17.182	.901	−0.922	.871	−0.006	.786
1,500-2,300	−148.325	.303	−7.517	.208	0.006	.778
2,300-3,900	−51.750	.728	−1.928	.754	−0.015	.508
> 3,900	−161.792	.290	−7.134	.260	−0.018	.429
Survey year 2016						
≤ 50						
50-1,500	−71.708	.603	−3.451	.546	−0.028	.185
1,500-2,300	−175.111	.225	−9.170	.126	−0.023	.308
2,300-3,900	−76.496	.608	−2.747	.657	−0.028	.213
> 3,900	−166.739	.280	−7.070	.268	−0.018	.439
Difference						
≤ 50						
50-1,500	−54.526	.408	−2.529	.394	−0.022	.150
1,500-2,300	−26.786	.701	−1.653	.598	−0.029	.070
2,300-3,900	−24.745	.720	−0.819	.792	−0.013	.407
> 3,900	−4.947	.944	0.063	.984	<0.001	.990

Coefficients and *P* values from the linear mixed model with a random intercept are reported. $P < .05$ was considered significantly different from zero. Spirometry was the outcome, and 8-h TWA endotoxin was the exposure variable in the model. The linear mixed models were adjusted for age, sex, height, smoking intensity, survey year, and the interaction between 8-h TWA endotoxin and survey year (8-h TWA endotoxin × survey year). E/I MLA = expiratory-to-inspiratory ratio of mean lung attenuation; Exp_{-856} = percentage of voxels with attenuation less than -856 HU on expiratory CT scans; HU = Hounsfield unit; pp FEV_1 = percent predicted FEV_1; $Residual_{-856}$ = residuals from the linear regression of Exp_{-856} on the percentage of voxels with attenuation less than −950 HU; $RVC_{-856\ to\ -950}$ = relative volume change in voxels with attenuation between −856 HU and −950 HU; TWA = time-weighted average.

[a]50 EU/m^3 represents the reference level. 1,500 EU/m^3 is the 40th percentile, 2,300 EU/m^3 is the 60th percentile, and 3,900 EU/m^3 is the 80th percentile. There are 237 textile workers exposed to ≤ 50 EU/m^3 endotoxin, 61 workers exposed to 50 to 1,500 EU/m^3 endotoxin, 35 workers exposed to 1,500 to 2,300 EU/m^3 endotoxin, 37 workers exposed to 2,300 to 3,900 EU/m^3 endotoxin, and 34 workers exposed to more than 3,900 EU/m^3.

are detectable on imaging.[17,18] This suggests that imaging biomarkers for small airways may be more sensitive indicators of SAD than standard spirometry. The comparison between imaging biomarkers and other spirometric biomarkers for SAD, such as residual volume, total lung capacity, forced oscillation technique, lung clearance index, and forced expiratory flow at 25% to 75% of vital capacity requires further investigation. In addition, the absence of a significant correlation between imaging biomarkers and endotoxin exposure in the 2011 cohort could be related to sample size limitations. Future studies with larger samples and more comprehensive spirometry values are essential to clarify these findings.

In this study, we identified 2 imaging biomarkers, E/I MLA and $RVC_{-856\ to\ -950}$, that are indicative of endotoxin-related small airway dysfunction. SAD has been difficult to diagnose using traditional spirometric definitions mainly because the small airway abnormalities could occur for years before significant pulmonary function decline.[49] Mets and colleagues[50] conducted a study on lung cancer screening patients and identified E/I MLA as the most suitable quantitative measure from CT scans for early detection of SAD. Hersh and colleagues[28] assessed quantitative small airway measures, using 8,517 patients from the COPDGene study, and found results similar to our findings: that imaging biomarkers, such as E/I MLA and $RVC_{-856\ to\ -950}$, were a better way to describe spirometry, exercise capacity, and quality of life.

This study has several advantages. First, to our knowledge this is the first study on the association between occupational endotoxin and SAD, determined by small airway measures from longitudinal CT scans. The longitudinal CT scans allow us to model the long-term effects of exposure to endotoxin on small airways. Second, most of the patients (86.4%) in the study were at the preclinical stage with no airway obstruction (FEV_1/FVC $\geq$ 0.70), which helps to identify the imaging biomarkers for early detection of small airway abnormalities. Third, detailed work history and exposure data over the entire working lifetime were available in this study, providing a comprehensive evaluation of occupational exposure effects.

This study also has some limitations. The predominance of patients in the preclinical stages may result from selection bias, as only patients who were still alive in 2011 since 1981 were included. However, the sensitivity analysis in cotton workers yielded results similar to those in the entire cohort, reinforcing the confidence in our conclusion. Measurement bias may arise from variations in spirometry and CT scan equipment calibration or operator technique, potentially affecting the reliability of spirometry and small airway measurements. The environmental exposure to endotoxin was not measured after retirement of textile workers, which may be a confounder for the effect of occupational endotoxin on SAD. However, there has been research showing that prior occupational endotoxin has a long-term association with changes in the airways.[30] Although we found significant association between endotoxin exposure and spirometry/quantitative small airway measures, the dose-response relationship between endotoxin and indexes of small airway disease still requires further investigation in future study. In addition, as multiple metrics were analyzed in this study, there is a potential for chance associations between endotoxin exposure and spirometry or quantitative small airway measures due to multiple testing. Finally, other image-based measures, such as parametric response mapping to identify functional SAD, and disease probability measurement of functional SAD, were not included in this study. However, our findings demonstrated significant associations between endotoxin exposure and SAD as measured by E/I MLA, $RVC_{-856\ to\ -950}$, and $Residual_{-856}$. These findings indicate potential associations between endotoxin concentrations and other imaging-based measures, providing an important direction for future research.

Interpretation

In this longitudinal study of textile workers, we found significant association between occupational endotoxin exposure and SAD, described by small airway measures from paired inspiratory/expiratory CT scans and pulmonary function decline. The results suggest that quantitative small airway measures are important tools in the detection of small airway remodeling and lung function decline for preclinical individuals (FEV_1/FVC $\geq$ 0.70). Specifically, our study identifies E/I MLA and $RVC_{-856\ to\ -950}$ as potential imaging biomarkers for the detection of SAD in preclinical patients.

Funding/Support

This work was supported by National Institutes of Health (Grants R01CA249096 and R01CA269398), and National Institute for Occupational Safety and Health (Grants R01 OH002421 and T42OH008416).

Financial/Nonfinancial Disclosures

None declared.

Acknowledgments

Author contributions: Y. S. is the guarantor of the article, responsible for conducting data analysis and drafting the manuscript. J. K., Y. L., and D. C. C. conceptualized and designed the study. F.-y. Z. oversaw data collection. H. W., P. S. L., G. R. W., and R. S. J. E. significantly contributed to the imaging preprocessing and analysis. All authors participated in interpreting the results and revising the manuscript.

Role of sponsors: The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

Other contributions: The authors acknowledge the support of Jing-qing Hang, MD, Li Su, MD, the leaders and staff of the Shanghai Putuo District People's Hospital, and the workers and staff of the Shanghai Textile Bureau and the participating mills who made this study possible.

Additional information: The e-Tables are available online under "Supplementary Data."

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