

A. COVER PAGE

Project Title: Lung Disease in Chinese Textile Workers	
Grant Number: 5R01OH002421-26	Project/Grant Period: 09/01/2018 - 08/31/2022
Reporting Period: 09/01/2021 - 08/31/2022	Requested Budget Period: 09/01/2021 - 08/31/2022
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Human Subjects: NA	Vertebrate Animals: NA
hESC: No	Inventions/Patents: No

B. ACCOMPLISHMENTS

B.1 WHAT ARE THE MAJOR GOALS OF THE PROJECT?

At least 5 million workers in the United States are potentially exposed to airborne endotoxin. Acute endotoxin exposure produces features of dynamic airflow obstruction. However, the health effects of long-term exposure remain unclear. A few studies of chronic endotoxin exposure have identified an accelerated decline in forced expiratory volume at 1 second (FEV1), a hallmark of chronic obstructive pulmonary disease (COPD). Even studies of chronic exposure, though, tend to span less than a decade, and little is known about the trajectory of lung disease after exposure cessation, the mechanisms underlying disease severity, and the extra-pulmonary effects of chronic exposure.

The goal of this competing continuation was to complete a longitudinal study of a closed cohort of 919 textile workers living in the same geographical region in Shanghai, China. This unique cohort comprises cotton workers exposed to high levels of workplace endotoxin with matched control silk workers exposed to non-detectable levels of endotoxin, both with a high proportion of lifetime non-smokers. Since 1981, they have been evaluated for dust and endotoxin exposure as well as pulmonary effects. All workers are retired, but 74.2% of those still alive participated in the 30th-year survey, with comparable follow-up participation expected at 36 years. The previous continuation cycle of this study enabled us to describe the persistent deleterious effects of workplace endotoxin even after worker retirement. The adverse respiratory effects include impaired lung function recovery with accelerated FEV1 decline, increased airway narrowing, and increased lung mass and lung density on chest computed tomography (CT), which likely represents persistent lung inflammation. These findings raise new questions: whether persistent inflammation plays a role in disease progression, whether disease is reversible after exposure cessation, and whether long-term endotoxin exposure leads to extra-pulmonary disease. Our overarching hypothesis is that prior cumulative workplace endotoxin exposure leads to persistent lung disease after exposure cessation due to systemic, lung parenchymal, and airway inflammation, and has extra-pulmonary health effects. We plan to test this hypothesis with the following specific aims.

Project Specific Aims

Aim 1: Characterize the reversibility and extent of functional respiratory impairment due to prior cumulative workplace endotoxin exposure using lung function testing. Since current data suggest that ongoing inflammation is present and is associated with chronic obstruction, we hypothesize that endotoxin exposure is associated also with a reversible component of airflow obstruction.

Aim 2: Quantify the progression of anatomic lung disease due to prior cumulative workplace endotoxin with repeat quantitative chest CT. We hypothesize that, compared to 2011 measures, repeat CT in 2017-19 will demonstrate that prior cumulative endotoxin exposure is associated with an interval increase in lung parenchymal inflammation (measured with lung mass) and airway narrowing (measured with wall area %).

Aim 3: Determine the extent to which pulmonary and systemic inflammation (as measured by lung diffusing capacity/DLCO, exhaled nitric oxide, and a comprehensive panel of biomarkers using serum proteomics) mediates endotoxin-associated disease. We hypothesize that cumulative workplace endotoxin exposure is associated with increased inflammation, and that persistent inflammation mediates the association between endotoxin and longitudinal FEV1 decline.

Aim 4: Determine the effects of cumulative workplace endotoxin exposure on mortality and extra-pulmonary disease. We hypothesize that endotoxin increases mortality for most chronic conditions except for lung cancer. To test this hypothesis, we will estimate the exposure-response in a follow-up mortality study (done at years 38-9). We will also assess the association between endotoxin exposure and the burden of coronary artery disease using coronary calcium scores on chest CT.

We anticipate that completion of these aims will allow us to identify the role that ongoing inflammation plays in workplace endotoxin exposure and disease after worker retirement, leading to new preventive insights. Additionally, we will identify important extra-pulmonary health effects of workplace endotoxin exposure. This proposal will yield new insights into health effects of a common workplace exposure.

B.1.a Have the major goals changed since the initial competing award or previous report?

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

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B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

For this reporting period, is there one or more Revision/Supplement associated with this award for which reporting is required?

No

B.4 WHAT OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT HAS THE PROJECT PROVIDED?

NOTHING TO REPORT

B.5 HOW HAVE THE RESULTS BEEN DISSEMINATED TO COMMUNITIES OF INTEREST?

NOTHING TO REPORT

B.6 WHAT DO YOU PLAN TO DO DURING THE NEXT REPORTING PERIOD TO ACCOMPLISH THE GOALS?

Not Applicable

Results:

Aim 1: We have recruited 413 participants from the original cohort of 919 thus far. On these, we have completed questionnaire, blood draw, FeNO measurements, Spirometry, and HRCT of the lung. We have 384 good quality scans of the 413.

As shown in the **tables 1 and 2 below**, cotton/ endotoxin exposed workers had a larger annual decline in lung function. Multivariable regression models are now being constructed to adjust for potential confounders. Overall symptoms at year 35 did not appear different between cotton and silk workers, but a sensitivity model (table 2) clearly shows that from baseline survey in 1981, cotton workers developed more symptoms, had greater lung function losses and left the workplace earlier than did silk workers. Such a phenomenon would result in a healthy worker effect confounding bias if the population were surveyed cross-sectionally at the last survey, but our longitudinal cohort allows us to detect and account for it.

Assessment of potential healthy worker effect confounding bias:

Rationale: Estimates of the long-term effects of endotoxin on lung function change may be biased if potential sources of selection bias are not adjusted for adequately.

Objectives: This study aimed to evaluate and adjust for bias due to loss to follow-up, intermittent participation, and healthy worker survivor effect when estimating the long-term and intermediate-term effect of endotoxin on lung function changes among textile workers in Shanghai.

Methods: A total of 447 cotton and 472 silk workers were followed up every 5 years since 1981, with repeated spirometry measurements and symptom questionnaires. On-site sampling for cotton dust and endotoxin was conducted prior to 2001. Potential sources of bias, including censoring, intermittent participation, and healthy worker survivor effect were evaluated. The long-term (greater than 5 year) and intermediate-term (5-year) effect of endotoxin on lung function change were evaluated in marginal structural models adjusting for potential sources of bias.

Measurement and Main Results: After adjusting for censoring and intermittent participation, workers with low and high cumulative endotoxin exposures were associated with a -8.17 ml/year (95% CI: [-10.11, -6.23]) and a -5.03 ml/year (95% CI: [-7.19, -2.87]) annual declines in FEV-1 since baseline respectively when compared to never exposed silk workers. After adjusting intermittent participation and censoring, each 1000 EU/m³-year increase in endotoxin exposure between two successive surveys was associated with an annual change of 0.1 ml/year (95% CI: [-1.73, 1.93]). After further adjustments of HWSE, each 1000 EU/m³-year increase resulted in an annual change of -1.07 ml/year (95% CI: [-3.60, 1.47]) in FEV-1 in cotton workers.

Conclusions: This study provides evidence that long-term endotoxin exposure can lead to declines in lung function. Endotoxin exposure may also result in intermediate-term declines in lung function. Proper adjustment for potential sources of selection bias in occupational cohort studies is necessary to obtain reliable estimates of the effects of endotoxin exposure on respiratory health

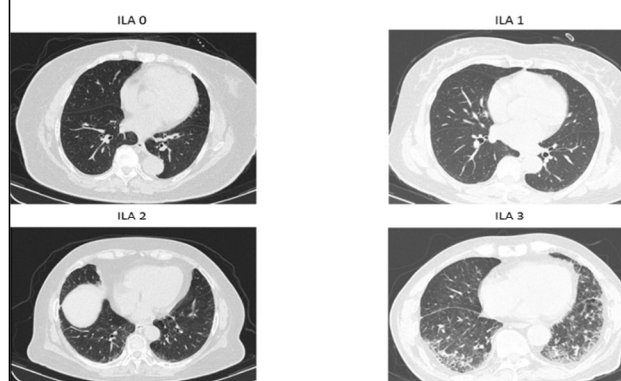
Table 1.

Baseline Characteristic of Participants in 2016 Survey			
	Silk (N=217)	Cotton (N=234)	Total (N=451)
Sex			
Female	152 (70.0%)	154 (65.8%)	306 (67.8%)
Male	65 (30.0%)	80 (34.2%)	145 (32.2%)
Age			
Mean(SD)	71.0(9.00)	70.1(8.79)	70.6(8.89)
Smoker			
Never	163 (75.1%)	163 (69.7%)	326 (72.3%)
Current	25 (11.5%)	36 (15.4%)	61 (13.5%)
Former	29 (13.4%)	35 (15.0%)	64 (14.2%)
Pack-year			
Mean(SD)	7.08(15.8)	10.3(22.2)	8.76(19.4)
Cumulative Endotoxin (1000 EU/m3)			
Mean (SD)	0 (0)	46.6 (41.0)	24.2 (37.6)
FEV-1 (ml)			
Mean(SD)	2070(549)	2090(618)	2080(586)
FEV-1 change Since 1981 (ml)			
Mean(SD)	-812(351)	-923(400)	-871(381)
Annualized FEV-1 Change (%)			
Mean(SD)	-22.4(9.58)	-25.4(11.0)	-24.0(10.5)
Chronic Bronchitis			
No	18 (8.3%)	17 (7.3%)	35 (7.8%)
Yes	16 (7.4%)	15 (6.4%)	31 (6.9%)
Chronic Cough			
No	184 (84.8%)	210 (89.7%)	394 (87.4%)
Yes	0 (0%)	0 (0%)	0 (0%)
Dyspnea			
No	131 (60.4%)	153 (65.4%)	284 (63.0%)
Yes	78 (35.9%)	72 (30.8%)	150 (33.3%)

Table 2

Summary Statistics at latest FEV-1 Measurement			
	Silk (N=442)	Cotton (N=418)	Total (N=860)
Sex			
Female	253 (57.2%)	219 (52.4%)	472 (54.9%)
Male	189 (42.8%)	199 (47.6%)	388 (45.1%)
Person-time (Year)			
Mean (SD)	26.7 (10.7)	28.1 (10.3)	27.4 (10.5)
Years worked			
Mean (SD)	26.5(9.83)	26.7(8.55)	26.6(9.23)
Years since cessation			
Mean (SD)	16.7(9.86)	17.4(9.29)	17.0(9.59)
Cumulative Endotoxin (1000 EU/m3)			
Mean (SD)	0(0)	1.00(0)	0.486(0.500)
Pack-year			
Mean (SD)	8.13(16.3)	11.0(20.3)	9.52(18.4)
FEV-1 in 1981 (ml)			
Mean (SD)	2840(671)	2910(715)	2870(693)
FEV-1 (ml)			
Mean (SD)	2220(638)	2140(670)	2180(654)
FEV-1 change Since 1981 (ml)			
Mean (SD)	-620(389)	-769(440)	-692(421)
Annualized FEV-1 Change (ml/year)			
Mean (SD)	-24.0(16.6)	-28.7(18.0)	-26.3(17.5)
% Predicted (GLI) (%)			
Mean(SD)	100(18.8)	96.9(20.7)	98.7(19.8)

Aim 2: All scans underwent densitometric and airway analysis. Results were stratified by smoking and silk vs. cotton worker status and, internal to cotton workers, by cumulative dust and endotoxin levels. In additional analyses we read the CT scans for the presence of interstitial lung abnormalities (ILA). All CT readings use a validated method to identify interstitial lung abnormalities (ILA), where scans are read independently by two trained radiologist, with a third adjudicating any disagreements. Scans are graded on a zero to three scale (see **Figure 1**).



Aim 2: CT analysis of gas trapping

This study aims to investigate the relationships between gas trapping measures of small airway disease from Chest CT scans and pulmonary function and explore how these relationships vary between occupations and time points. We focused on 343 patients with inspiratory/expiratory Chest CT scans taken in 2011 and 2016. We extracted the following gas trapping measures from the paired inspiratory/expiratory Chest CT scans.

- **Emphysema measures**
 - *Inspiratory*₋₉₅ (*Insp*₋₉₅₀): Percent of the lung voxels on inspiratory CT scan with attenuation <-950 HU.^[1]
- **Small airway disease measures**
 - *Expiratory*₋₈₅₆ (*Exp*₋₈₅₆): Percent of the lung voxels with attenuation < -856 HU on the expiratory CT images.^[2]
 - *Expiratory to Inspiratory Ratio of Mean Lung Attenuation (E/I MLA)*: Ratio of mean lung attenuation from the density histograms on expiratory and inspiratory scans.^[3]
 - *Relative Volume Change*_{-856 to -950} (*RVC*₈₅₆₋₉₅₀): The difference between the expiratory and inspiratory values for relative lung volumes, which is the limited lung volume with attenuation between -856 to -950HU divided by the lung volume without emphysema.^[4]
 - *Residual*: The residuals from the linear regression of *Exp*₋₈₅ on *Insp*₋₉₅₀.^[5]

Table 3. shows the distribution of pulmonary function scores and extracted numerical measures of gas trapping for cotton/silk workers in 2011 and 2016. There is no cumulative endotoxin or cumulative dust for silk workers. We did not find a significant difference in pulmonary function scores between cotton workers and silk workers. However, the pulmonary function scores decreased from 2011 to 2016. For example, the median of FEV-1 decreased from 2,376 (IQR: 1,966, 2,740) in 2011 to 2,070 (IQR: 1,760, 2,450) in 2016 for cotton workers. For silk workers, the median FEV-1 decreased from 2,324 (IQR: 2,005, 2,657) in 2011 to 2,095 (IQR: 1,820, 2,408) in 2016. Similar to the pulmonary function scores, there is no significant difference in the gas trapping measures between cotton workers and silk workers, but the median of *Exp*₋₈₅₆ increases from 0.29 (IQR: 0.24, 0.35) in 2011 to 0.32 (IQR: 0.28, 0.36) in 2016 for cotton workers and from 0.27 (IQR: 0.23, 0.33) to 0.31 (IQR: 0.27, 0.35) for silk workers.

To study the relationships between the gas trapping measures of small airway disease and pulmonary function, we constructed partial correlation networks to connect small airway disease measures with pulmonary function scores, endotoxin levels, and dust exposure for various occupations at different time points. The partial correlation between variables y_i and y_j is the correlation between the two variables conditioning on all other variables in y , $y_{-(i,j)}$.^[6] Table 4 and Figure 2 show that the correlations differ significantly between cotton workers and silk workers. Among all the small airway disease measures, *RVC*₈₅₆₋₉ is the most highly correlated with pulmonary functions for cotton workers, with the partial correlation of -0.09, 0.05, 0.18, and -0.09 with FEV-1, FVC, Percentage Predicted FEV-1, cumulative dust and cumulative endotoxin in 2011. However, for silk workers, *Exp*₋₈₅₆ is the most highly correlated small airway disease measure. The partial correlations between *Exp*₋₈₅₆ and FVC and Percentage Predicted FEV-1 were 0.12 and -0.03 in 2011. Additionally, the correlation between small airway disease measures and pulmonary function scores changes with time. For cotton workers, the partial correlation between *RVC*₈₅ and cumulative endotoxin decreased to 0.04 in 2016, while the partial correlation between *RVC*₈₅₆₋₉₅₀ and cumulative dust increased to 0.05 in 2016. For silk workers, the partial correlation between *Exp*₋₈₅₆ and FEV-1 decreased from 0 in 2011 to -0.16 in 2016, and the partial correlation between *Exp*₋₈₅ and FVC increased to 0.24 in 2016.

Table 3. Descriptive Analysis of Pulmonary Function and Gas Trapping Measures

Characteristics	2011			2016		
	Cotton Worker (N=185) ¹	Silk Worker (N=158) ¹	p-value	Cotton Worker (N=185) ¹	Silk Worker (N=158) ¹	p-value
Cumulative Endotoxin	38 (18, 64)	0 (0, 0)	<0.001	38 (18, 64)	0 (0, 0)	<0.001
Cumulative Dust	13 (9, 20)	0 (0, 0)	<0.001	13 (9, 20)	0 (0, 0)	<0.001
FEV-1	2,376 (1,966, 2,740)	2,324 (2,005, 2,657)	0.5	2,070 (1,760, 2,450)	2,095 (1,820, 2,408)	0.8
FVC	3,016 (2,604, 3,488)	2,990 (2,549, 3,439)	0.5	2,710 (2,380, 3,210)	2,760 (2,302, 3,128)	0.8
Percentage Predicted FEV-1 (PP FEV1)	1.08 (0.96, 1.18)	1.09 (0.99, 1.19)	0.6	1.04 (0.91, 1.15)	1.05 (0.93, 1.16)	0.4
<i>Insp</i> ₋₉₅₀	0.20 (0.17, 0.23)	0.19 (0.16, 0.22)	0.062	0.22 (0.19, 0.24)	0.21 (0.18, 0.24)	0.3
<i>Exp</i> ₋₈₅₆	0.29 (0.24, 0.35)	0.27 (0.23, 0.33)	0.11	0.32 (0.28, 0.36)	0.31 (0.27, 0.35)	0.14
E/I MLA	0.96 (0.93, 0.98)	0.95 (0.93, 0.97)	0.2	0.973 (0.956, 0.987)	0.974 (0.960, 0.987)	0.6
<i>RVC</i> ₈₅₆₋₉₅₀	-0.06 (-0.09, -0.02)	-0.06 (-0.09, -0.03)	0.2	-0.08 (-0.10, -0.05)	-0.08 (-0.10, -0.05)	>0.9
Residual	0.00 (-0.03, 0.02)	0.00 (-0.02, 0.02)	0.3	-0.01 (-0.02, 0.01)	0.00 (-0.02, 0.02)	0.2

¹ Median (IQR)² Wilcoxon rank sum test**Table 4. Partial Correlation Between Small Airway Disease Measures and Pulmonary Function**

	<i>Exp</i> ₋₈₅₆	2011			2016			
		E/I MLA	<i>RVC</i> ₈₅₆₋₉₅₀	Residual	<i>Exp</i> ₋₈₅₆	E/I MLA	<i>RVC</i> ₈₅₆₋₉₅₀	Residual
Cotton Worker								
FEV-1	0.09	0.00	-0.09	-0.03	0.00	-	-0.05	0.00
FVC	0.00	-	0.00	0.01	0.07	0.04	-0.04	0.00
PP FEV-1	0.00	0.05	0.05	0.04	-0.02	-	0.00	0.00
Dust Endotoxin	-0.12	0.13	0.18	-0.08	0.06	0.00	0.04	0.00
	0.03	0.00	-0.09	0.00	0.00	-	0.05	0.00
						0.02		
Silk Worker								
FEV-1	0.00	0.00	0.00	-0.02	-0.16	0.03	-0.02	-0.05
FVC	0.12	-	-0.02	0.00	0.24	0.00	-0.06	0.00
PP FEV-1	-0.03	0.00	0.00	0.00	-0.04	0.00	0.00	0.00

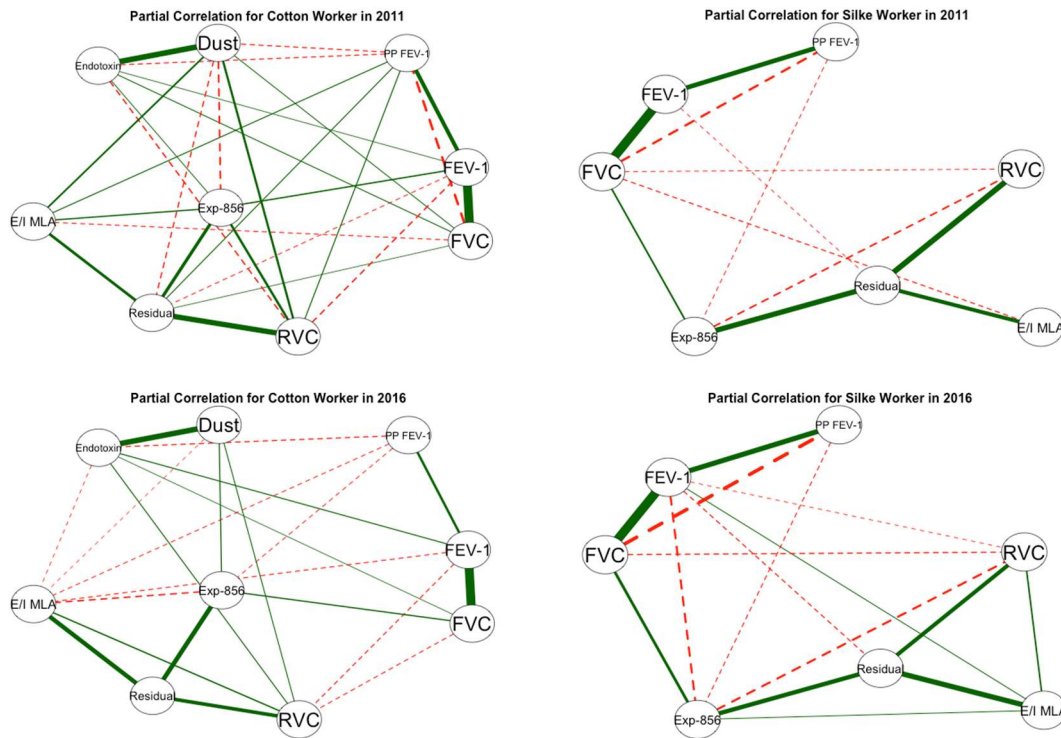


Figure 2. Partial Correlation Between Small Airway Disease Measures and Pulmonary Function: The green edges represent positive partial correlation, and the red edges represent negative partial correlation.

Aim 3: Biomarker analysis using high-dimensional proteomics:

Proteomics

Protein quantifications are obtained by sample normalization and log₂ transformation according to *DIA Quantification Proteomics Report (2020/7/1)* provided by BGI. After standard quality control process, there are 1234 (accounting for 41.66%) proteins with missing rate less than 50% among the study population (Table 5).

Table 5 Missingness of one or more proteins

Missing rate	Number of proteins	Proportion
< 50%	1234	41.66%
<20%	938	31.67%
<10%	836	28.22%
=0	346	11.68%

Analysis Model

We used mixed model for repeated measures (MMRM) to analyze the association between proteins and repeated FEV1 measures, with first-order autocorrelation matrix (AR1). The model is as follows:

$$FEV1_{ij} \sim \alpha + \beta_1 \cdot protein_i + \beta_2 \cdot protein_i \cdot age_{ij} + \beta_3 \cdot protein_i \cdot cotton_i + \beta_4 \cdot age_{ij} + \beta_5 \cdot cotton_i + \beta_6 \cdot sex_i + \beta_7 \cdot smoking_status_{ij} + \beta_8 \cdot working_status_{ij} + \beta_9 \cdot baseline_FEV1_i + u_{ij} + \epsilon_{ij} \quad (1),$$

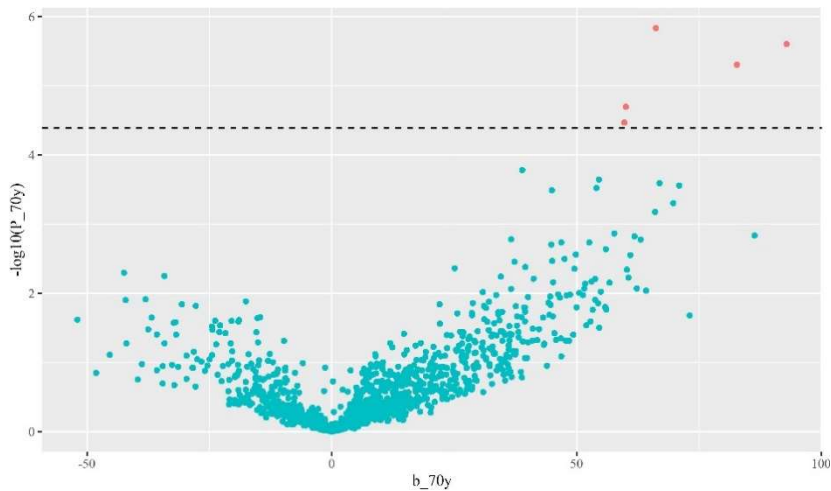
of which, u_{ij} is random effect for age at follow up.

After Bonferroni correction ($P = 0.05/1234 = 4.05 \cdot 10^{-5}$), there were **5** proteins that showed a main effect on FEV1 at 70 years old, and **11** proteins showed significant interaction with age at follow up on FEV1 alterations.

Meanwhile, there were **54** additional proteins showed potential interactions, by FDR adjustment for multiple comparison, with age at follow up.

No significant interactions for protein and remote cotton dust exposure were identified. However, it should be noted that the analysis was done in the current grant period on samples drawn between 2017-2019. Hence, the finding suggests that the systemic effects of past cotton dust/ endotoxin exposure on FEV1 are no longer significant after workers retire for more than 15 years, and reach 70 years of age or older (Figure 3):

Figure 3: Participants over 70 years of age.



Aim 4: Determine the effects of cumulative workplace endotoxin exposure on mortality and extra-pulmonary disease. We hypothesize that endotoxin increases mortality for most chronic conditions except for lung cancer. To test this hypothesis, we will estimate the exposure-response in a follow-up mortality study (done at years 38-9). We assessed the association between endotoxin exposure and the burden of coronary artery disease using coronary artery calcium (CAC) scores on chest CT.

Results of the CAC analysis on CT scans showed a generally low prevalence (%) of high CAC score compared to published results from USA populations. Moreover, the severity of CAC was low in this population. Moreover, there were no differences in the distribution of CAC scores between the cotton vs. silk populations. These results suggest that cotton dust and associated gram negative bacterial endotoxin exposure does not result in the type of systemic inflammation that is associated with coronary artery calcification, and, by extension, with increase coronary artery disease in occupationally-exposed populations.

C. PRODUCTS**C.1 PUBLICATIONS**

Are there publications or manuscripts accepted for publication in a journal or other publication (e.g., book, one-time publication, monograph) during the reporting period resulting directly from this award?

No

C.2 WEBSITE(S) OR OTHER INTERNET SITE(S)

NOTHING TO REPORT

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

C.4 INVENTIONS, PATENT APPLICATIONS, AND/OR LICENSES

Have inventions, patent applications and/or licenses resulted from the award during the reporting period? No

If yes, has this information been previously provided to the PHS or to the official responsible for patent matters at the grantee organization? No

C.5 OTHER PRODUCTS AND RESOURCE SHARING

NOTHING TO REPORT

D. PARTICIPANTS

D.1 WHAT INDIVIDUALS HAVE WORKED ON THE PROJECT?

Commons ID	S/K	Name	Degree(s)	Role	Cal	Aca	Sum	Foreign Org	Country	SS
DCHRISTIANI	Y	Christiani, David C	BS,MPH,MS,MD	PD/PI	1.9	0.0	0.0			NA
PSLAI1	N	Lai, Peggy Sue	AB,MD,MPH	Co-Investigator	1.3	0.0	0.0			NA
	N	Principe, LucyAnn		Non-Student Research Assistant	5.2	0.0	0.0			NA
	N	Su, Li		Lab Director	5.5	0.0	0.0			NA
	N	Donato, Daniel		Non-Student Research Assistant	1.2	0.0	0.0			NA

Glossary of acronyms:

S/K - Senior/Key
 Cal - Person Months (Calendar)
 Aca - Person Months (Academic)
 Sum - Person Months (Summer)

Foreign Org - Foreign Organization Affiliation
 SS - Supplement Support
 RS - Reentry Supplement
 DS - Diversity Supplement
 OT - Other
 NA - Not Applicable

D.2 PERSONNEL UPDATES

D.2.a Level of Effort

Not Applicable

D.2.b New Senior/Key Personnel

Not Applicable

D.2.c Changes in Other Support

Not Applicable

D.2.d New Other Significant Contributors

Not Applicable

D.2.e Multi-PI (MPI) Leadership Plan

Not Applicable

E. IMPACT**E.1 WHAT IS THE IMPACT ON THE DEVELOPMENT OF HUMAN RESOURCES?**

Not Applicable

E.2 WHAT IS THE IMPACT ON PHYSICAL, INSTITUTIONAL, OR INFORMATION RESOURCES THAT FORM INFRASTRUCTURE?

NOTHING TO REPORT

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

Not Applicable

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?

Dollar Amount	Country
\$48,000	CHINA

G. SPECIAL REPORTING REQUIREMENTS SPECIAL REPORTING REQUIREMENTS

G.1 SPECIAL NOTICE OF AWARD TERMS AND FUNDING OPPORTUNITIES ANNOUNCEMENT REPORTING REQUIREMENTS

NOTHING TO REPORT

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

G.4.a Does the project involve human subjects?

Not Applicable

G.4.b Inclusion Enrollment Data

File(s) uploaded:
CumulativeInclusionEnrollmentReport.pdf

G.4.c ClinicalTrials.gov

Does this project include one or more applicable clinical trials that must be registered in ClinicalTrials.gov under FDAAA?

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

NOT APPLICABLE

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

Does this project involve human embryonic stem cells (only hESC lines listed as approved in the NIH Registry may be used in NIH funded research)?

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT

Organization Name: Shanghai Putuo District People's Hospital

Country: CHINA

Description of Foreign Component:

The hospital has relatively independent, well-equipped buildings for outpatient, emergency, inpatient, medical, logistics and administration functions. In addition, the hospital is equipped with a batch of advanced medical instruments and equipment, including double gradient magnetic resonance imaging equipment, multi-slice spiral CT, ECT, large hyperbaric oxygen chamber, large Digital splint C arm X-Ray machine, digital gastrointestinal X-ray machine, ultrasound machine, automatic biochemical analyzer, ultrasound emulsification instrument, ventilator, multi-function monitor , hemodialysis machine, providing strong material and technical supports for the expansion of medical services.

G.10 ESTIMATED UNOBLIGATED BALANCE

Not Applicable

G.11 PROGRAM INCOME

Not Applicable

G.12 F&A COSTS

Not Applicable

Cumulative Inclusion Enrollment Report

Study Title: Lung Disease in Chinese Textile Workers

Comments: This cohort study is a follow-up of a closed cohort begun in 1981. The population is 100% East Asian, and 58% female. Only those in the original cohort of 919 individuals were eligible for the 37 year follow up, begun in 2018. An Inclusion Enrollment Table is attached above. Children are not eligible, as this is an occupational study of an established close cohort.

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/ Alaska Native										0
Asian	306	145								451
Native Hawaiian or Other Pacific Islander										0
Black or African American										0
White										0
More Than One Race										0
Unknown or Not Reported										0
Total	306	145	0	0	0	0	0	0	0	451

I. OUTCOMES

I.1 What were the outcomes of the award?

OUTPUTS, OUTCOMES, and RESEARCH to PRACTICE (R2P)

Outputs: We conducted training sessions for workers, physicians, and public health specialists in Shanghai on research methods and on occupational respiratory disease prevention. Dr. Christiani gave lectures on methods of studying, identifying and controlling occupational lung disease in Nanjing, China as well as in Shanghai, and at the Harvard Medical School and Harvard School of Public Health.

Outcomes: Include citations of our work on the subject over a 38 year period. The early decades of this work resulted in a 10-fold reduction of the permissible exposure limit for cotton dust in China, and the endotoxin exposure-response results have been cited in US studies proposing an endotoxin standard.

R2P: Is the transfer and translation of knowledge, interventions, and technologies into highly effective prevention practices and products which are adopted into the workplace. This study has had impact on R2P for over 35 years. In addition to lowering the permissible exposure limit, the study has provided scientific basis for improved exhaust ventilation, and the textile industry in China has purchased state of the art exhaust controls for the newer mills from US and European companies. The study has also increased awareness of the importance of organic (vegetable) dust exposures in the workplace (beyond textiles) both in the US and abroad.

Significance: Findings from the study to date have improved our understanding of the chronic effects of long-term exposure to cotton dust on workers' respiratory health, particularly the influence of cessation of exposure on the chronic respiratory effects due to long-term exposure to cotton dust and endotoxin. With the advent of improved high-resolution computed tomography (HRCT) in 2002, as well as validated automated techniques to quantify the degree of emphysema and airways disease present in an individual, this proposal represents an unusual opportunity to settle the issue of whether organic dust such as cotton can cause COPD in non-smokers, and the additive or multiplicative effects of smoking in this well characterized cohort of cotton textile workers. Moreover, our analysis of physiologic and biologic markers in relation to cessation of work will provide insight into the reversibility of the effects of cotton dust and endotoxin on chronic respiratory disease.

Future Plans: We will publish a series of papers on the final results on the chronic health effects of long-term exposure to cotton vegetable dust, endotoxin in exposed workers. The final publications were delayed because of the outbreak and lock-downs associated with the COVID19 pandemic. However, we were able to collect the necessary data, and run the planned assays in the later part of the grant cycle and we have all we need to proceed with publications.