The Shanghai Textile Workers Study

- A 37-year collaborative research experience

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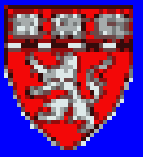


Old Problem, New Challenge

- Defined over a half of century ago
- A large exposed working population globally
- Acute symptom response to cotton dust: “Byssinosis”
- Adverse chronic effects – unclear
- Causal agent (s) – indefinite
- Major public health implications: other “organic” dusts in work/community settings

Byssinosis

- Described centuries ago by Ramazzini
- Defined by Schilling in 1950's in Lancashire:
- Onset of chest tightness/SOB on first day of working week after absence of 2 days.
- Grade ½ - occasional Mondays
- Grade 1 – most Mondays
- Grade 2 – first and other days.

Organic Dust

Definition: dust of vegetable, animal or microbial origin

Major sources: agricultural and textile settings

Organic dust	Types of disease
Mouldy hay, straw and grain	Farmer’s lung
Droppings and feathers	Bird Francier's lung
Mouldy sugar cane	Bagassosis
Compose dust	Mushroom worker's lung
Dust or mist	Humidifier fever
Dust of heat-treated sludge	Sewage sludge disease
Mould dust	Cheese washers' lung
Dust of dander, hair particles and dried urine of rats	Animal handlers' lung
Raw cotton fiber	Byssinosis

Organic Dust /Endotoxin Related Symptom / Syndrome

Acute responses

Flu-like symptoms: fever, cough, headache

Irritation (nose and throat) **"Mill Fever".**

Respiratory symptoms (chest tightness towards end of first day of work-week after several years of exposure) **"Byssinosis"**

Acute broncho-constriction (drop in FEV_1 over a work-shift) **"Asthma-like Syndrome"**

Organic Dust /Endotoxin Related Symptom / Syndrome (Cont.)

Chronic responses

Chronic bronchitis (cough and sputum)

Chronic dry cough (cough without sputum)

Airway hyperreactivity (usually after long-term exposure:>10 years)

?Chronic airflow obstruction (after chronic exposure)

Byssinosis: Mechanisms of Disease

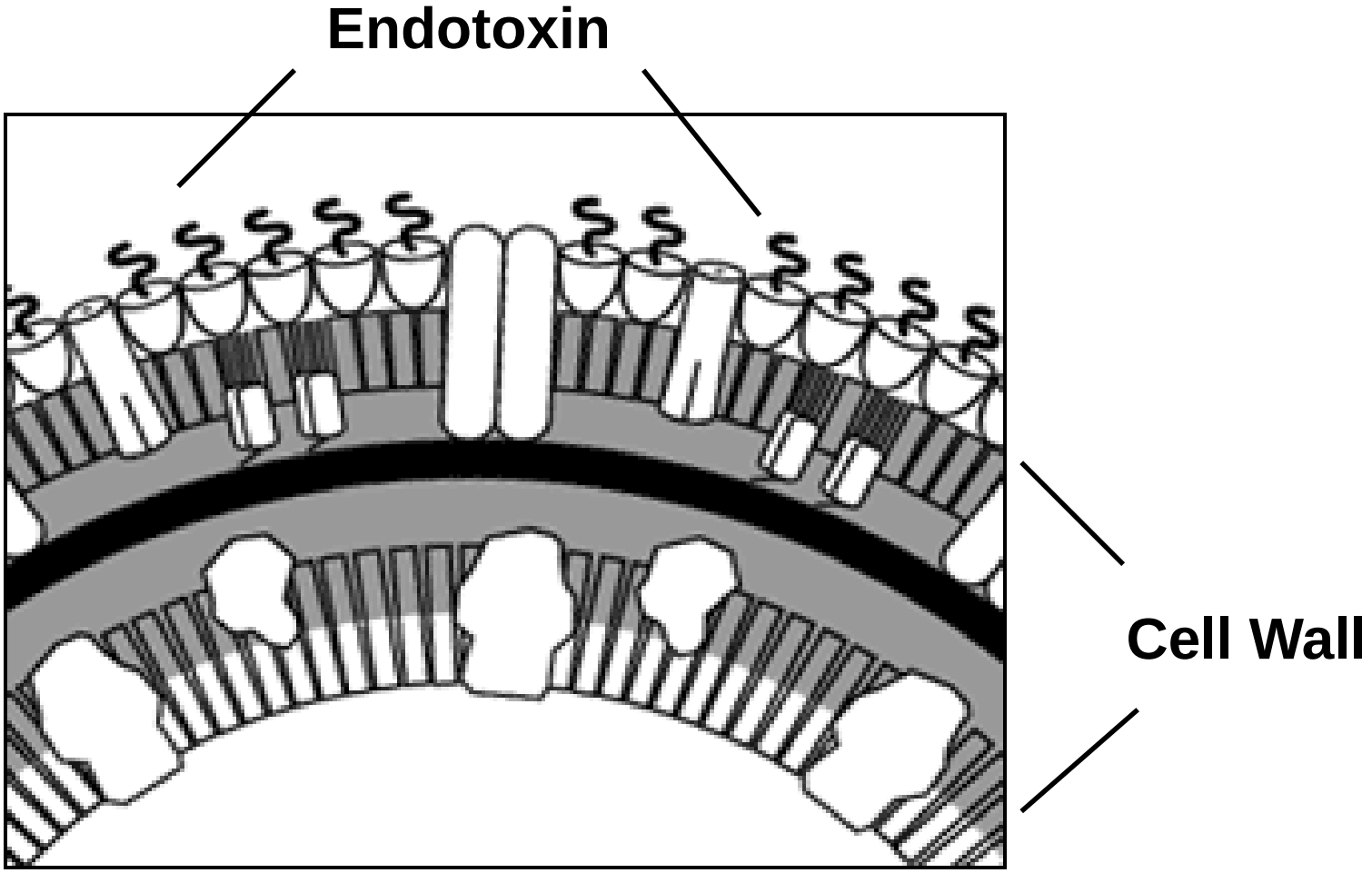
Pathogenesis still unclear. Three proposed mechanisms:

1. Direct release of histamine triggered by cotton dust components
2. Immunological responses (principally antibody mediated) to cotton dust antigens
3. Inflammatory responses triggered by endotoxin. ***
4. Direct (neuro/reflex) broncho-constriction

Etiology

Dust itself ?

Endotoxin?



Long, jagged molecules of a poison called endotoxin just out from the cell walls of Gram-negative bacteria.

"Endotoxin" Physiochemical Properties

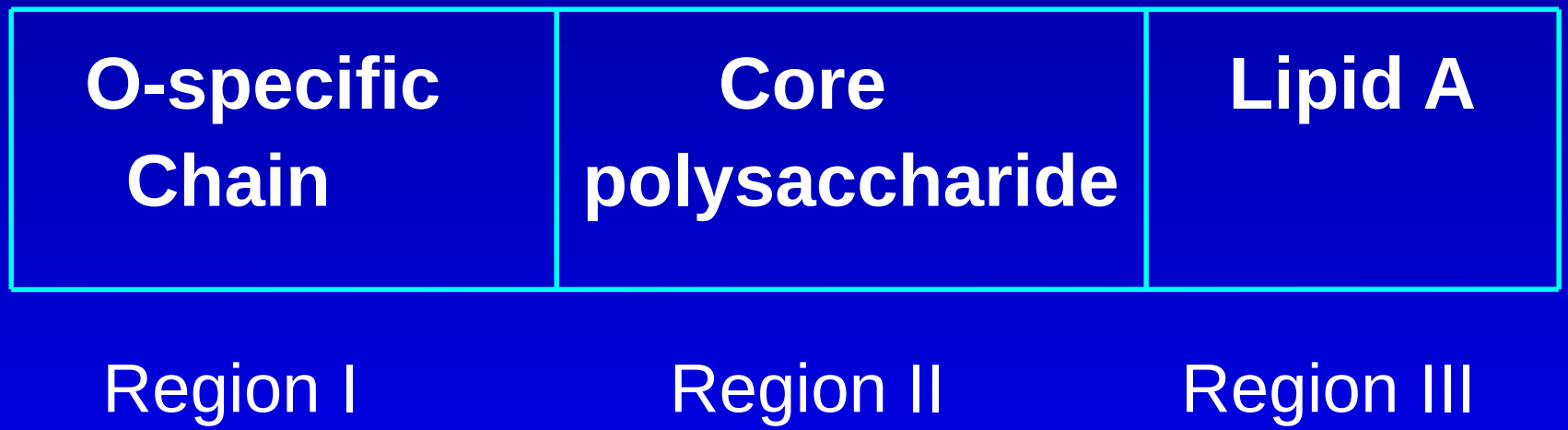
1. **Endotoxin** = part of cell envelope of gram-negative bacteria.
   - polysaccharide chain, core polysaccharide, lipid moiety.
   - most of its toxicity associated with lipid A
2. **Lipopolyssaccharide** (LPS) = Endotoxin = purified lipid A + core polysaccharide

3. Operating Definition

Endotoxin = LPS + other wall parts

(e.g., Lipid A protein)

- "Endotoxin", more accurately reflects environmental exposure
- Endotoxin activity does not depend on bacteria viability; is a highly refractory molecule



Structural diagram of bacterial lipopolysaccharide

Shanghai Textile Worker Study:

A prospective cohort

Why Study Cotton Textile Workers?

- Cotton is representative of organic dusts
- Share similar clinical manifestations, with other types of workers with a likely common mechanism of disease development
- Cotton dust causes an asthma-like syndrome in exposed workers
- Cotton dust exposure causes chronic bronchitis

Why Study Cotton Textile Workers? (Cont.)

- It is unclear whether long-term exposure causes chronic obstructive lung disease
- Cotton dust is contaminated with gram negative bacteria – Is it the bacterial endotoxin or the dust itself that causes respiratory disease?
- Model to study exposures *other than smoking* that result in COPD.

Unique Features of Shanghai

- Textile center of China
- Large, stable workforce
- Large, non-smoking female population

- Exchange program between HSPH and Shanghai First Medical College (now Shanghai First Medical University) established in 1979
- Excellent collaborators from First Textile Hospital (now Putuo District People's Hospital)

Cotton Textile Production

- Opening
- Cleaning
- Carding
- Drawing
- Combing
- Roving
- Spinning
- Weaving


Continental
Continental


LOWELL

Research Questions

1. Does long-term exposure to cotton dust result in excess annual decline in lung function and in chronic symptoms?
2. Is there a relationship between persistence of respiratory symptom and chronic changes in lung function in cotton dust exposed workers?
3. Is it the dust itself, or the associated endotoxin that results in chronic airways disease in exposed workers?

Study Design and Methods

- Prospective cohort study from 1981
- 447 cotton textile workers and 472 silk yarn workers as comparison group
- Environmental exposure assessment with analysis of dust and bacterial endotoxin
- Sampling repeated every 5 years.

Study Design and Methods

- Complete job history and smoking history
- Detailed health assessments from questionnaire and lung function tests
- Assessment of candidate gene-environment interactions
- Data today presented on first 20-25 years of study (1981-2001).

Dust and Endotoxin Levels (median)

	Dust (mg/m^3)		Endotoxin ($\mu g/m^3$)	
	Plant 1	Plant 2	Plant 1	Plant 2
Opening	1.83	1.15	0.24	0.11
Blowing	1.06	1.15	0.50	0.11
Carding	1.17	1.83	0.53	0.22
Drawing	0.49	1.58	0.10	–
Combing	0.31	0.66	–	0.07
Roving	0.43	0.46	0.23	–
Spinning	–	0.59	–	0.02

1981 measurements

Persistence of Respiratory Symptoms (%, 95%CI)

	1 time	2 times	3 or 4 times
Byssinosis			
Cotton	23.1 (18.4–27.9)	9.9 (6.5–13.3)	1.3 (0.3– 2.6)
Silk	0.0	0.0	0.0
P value			< 0.0001
Chest tightness			
Cotton	20.8 (16.2–25.4)	7.3 (4.3–10.2)	1.3 (0.3–2.6)
Silk	8.9 (5.7–12.2)	1.7 (2.3–3.2)	0.0
P value			< 0.0001
Chronic bronchitis			
Cotton	14.2 (10.3–18.1)	5.9 (3.3–8.6)	5.9 (3.8– 8.6)
Silk	10.7 (7.1–14.2)	3.1 (1.1–5.1)	1.7 (0.2–3.2)
P value			< 0.01
Chronic cough			
Cotton	14.5 (10.6–18.5)	5.0 (2.5–7.4)	5.3 (2.8–7.8)
Silk	9.3 (5.9–12.6)	4.5 (2.1–6.8)	1.7 (0.2– 3.2)
P value			< 0.01
Dyspnea (+2)			
Cotton	24.1 (19.3–28.9)	9.2 (6.0–12.5)	7.3 (4.3–10.2)
Silk	23.4 (18.5–28.2)	5.8 (3.2–8.5)	1.4 (0.4–2.7)
P value			< 0.001

Adjusted Odds Ratios for Byssinosis in Relation to Cumulative Exposure Levels in Cotton Workers

	Exposure to endotoxin	Exposure to dust
Whole group (n = 429)		
Low	0.6 (0.29 – 1.32)	1.6 (0.70 – 3.46)
Middle	1.4 (0.54 – 3.35)	1.0 (0.44 – 2.15)
High	1.9 (1.02 – 3.51)	1.8 (1.03 – 3.32)

Cumulative Incidence of Byssinosis.

The odds ratios were adjusted by age, years worked, smoking status and gender (for whole group) in GEE models. The lowest levels of cumulative exposure were as reference. Statistically significant odds ratios are underlined.

Annual Changes in Lung Function (ml/yr) Over 20-Years

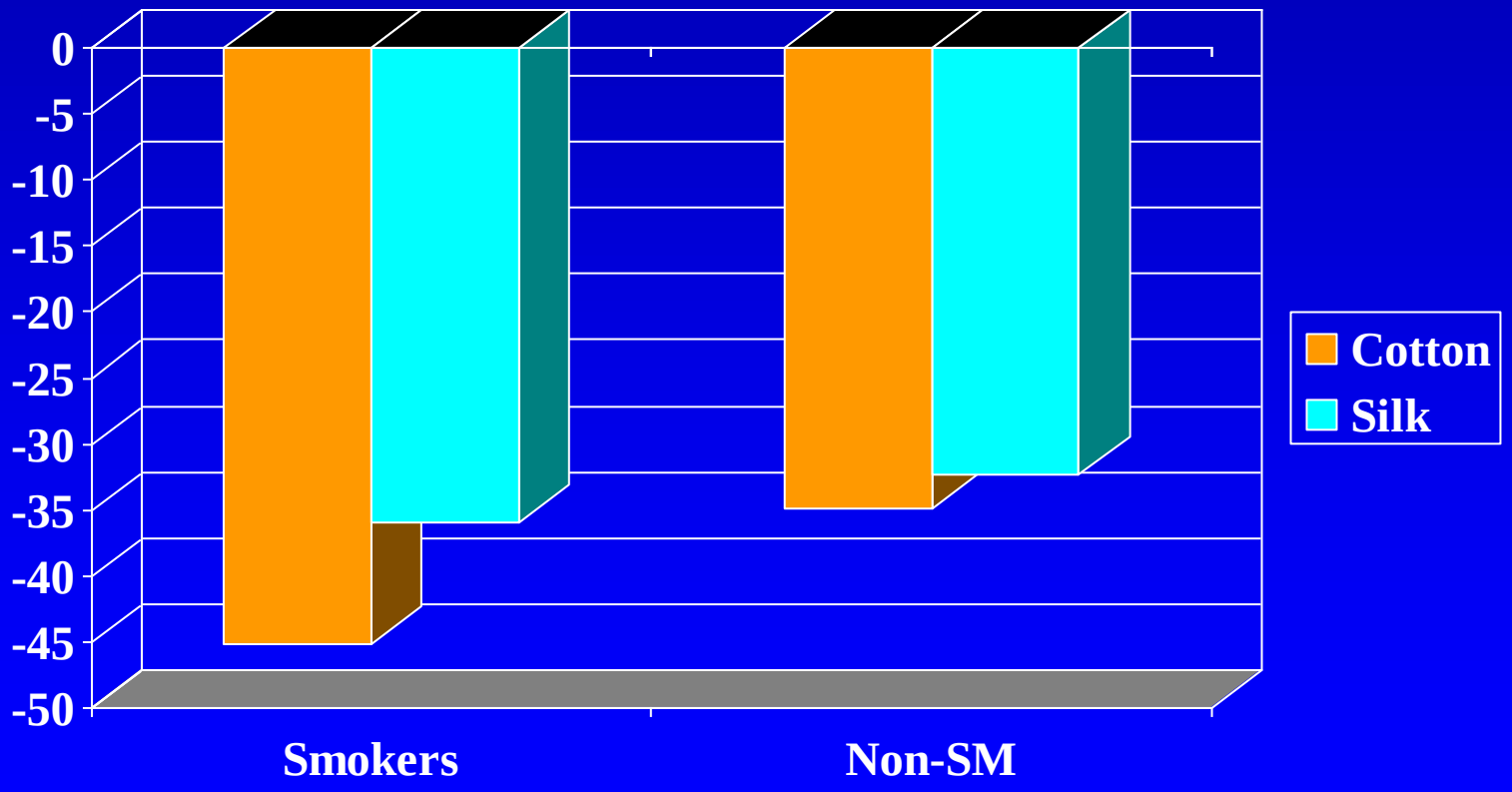
	FEV_1		FVC	
	Cotton	Silk	Cotton	Silk
Total	- 32.4 (1.0)**	- 27.3 (0.9)	- 29.2 (1.3)*	- 25.0 (1.3)
Male	- 42.3 (1.5)**	- 35.0 (1.3)	- 36.8 (2.0)	- 33.6 (2.1)
Female	- 24.6 (1.0)*	- 21.5 (1.0)	- 23.1 (1.5)*	- 18.6 (1.4)
Smokers¶	- 45.2 (1.6)**	- 36.0 (1.6)	- 38.1 (2.4)	- 33.4 (2.6)
Non-smokers	- 34.9 (2.8)	- 32.3 (2.3)	- 33.5 (3.9)	- 34.1 (3.4)

Standard error shown in parentheses.

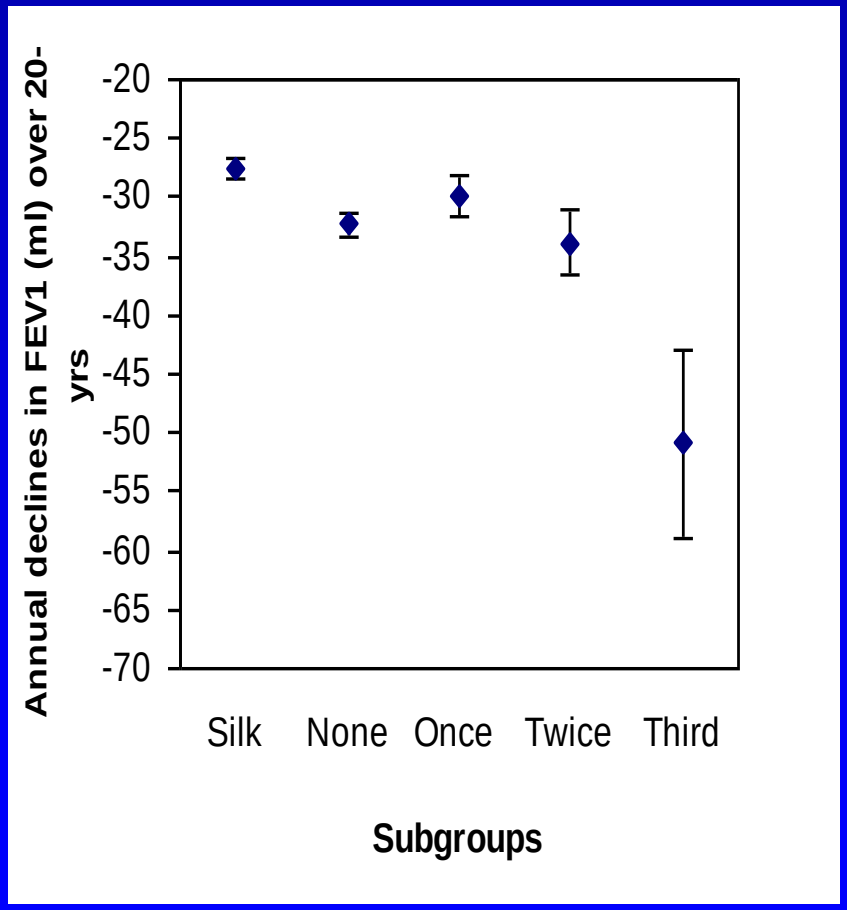
¶ Calculations from smokers and nonsmokers were restricted to male workers.

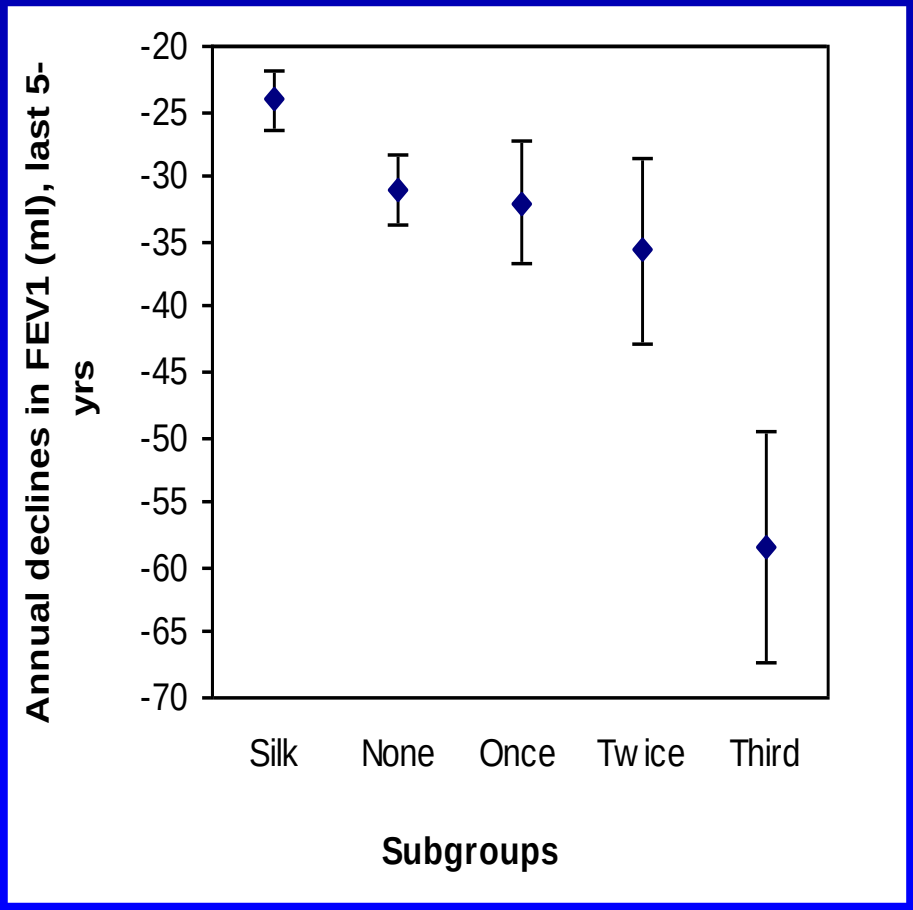
* $p < 0.05$, **$p < 0.01$.

Annual Changes in FEV_1 (ml/yr)
over 20-years



Adjusted Annual Declines in FEV_1 Over 20-years and Last 5-years by Byssinosis Reporting



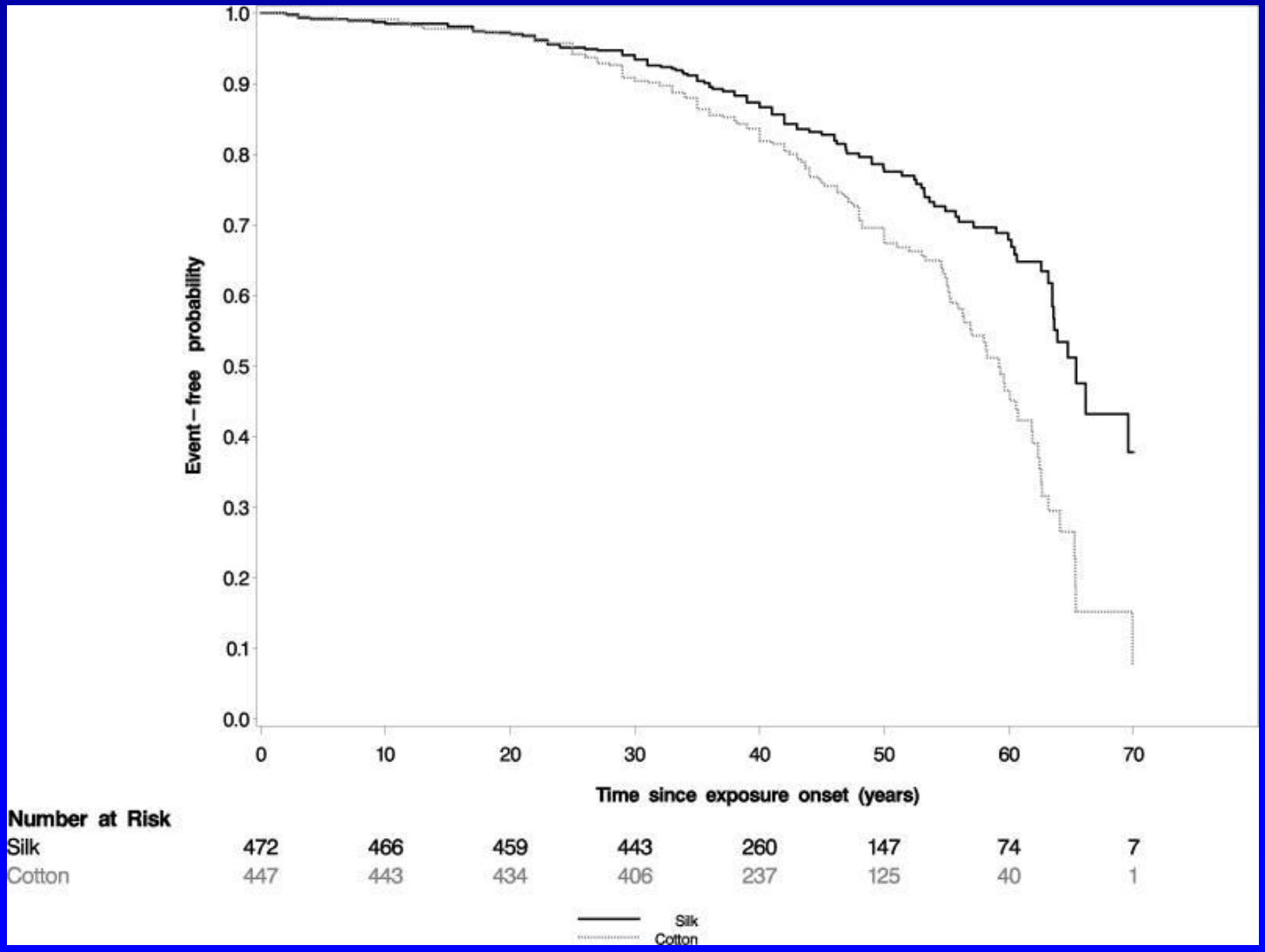


Annual Changes in Lung Function (ml) over 20-years in Relation to Cumulative Exposure

	FEV_1	FVC
	Estimate (SE)	Estimate (SE)
Endotoxin		
Low	- 48.0 (115.7)	83.6 (208.7)
High	- 49.4 (116.5)	79.5 (202.8)
Highest	-187.7 (115.7)	- 92.2 (203.4)

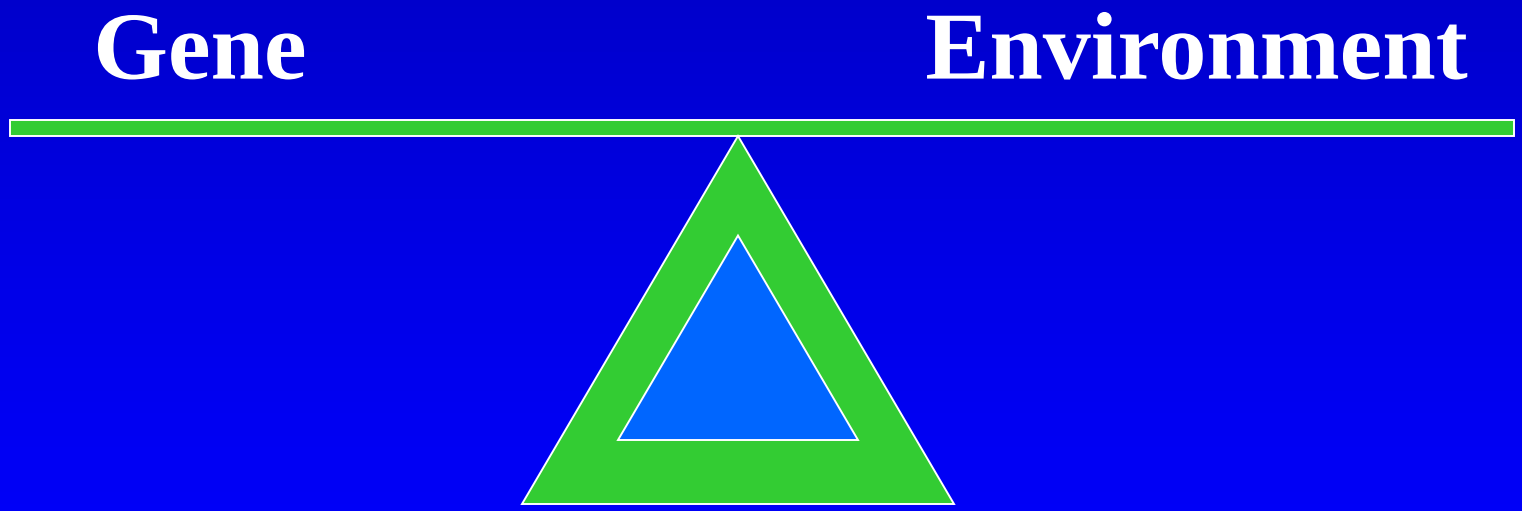
† Estimated from Genmod, in which gender, age and height at last survey, smoking habit and smoking amount over 20-years were adjusted. The lowest levels served as reference in the models.

Pulmonary function (<5th percentile predicted) and all cause mortality in Shanghai cotton vs. silk factory workers*



*Lai PS, et al. (2014) Occup Environ Med 71:118-25

Gene-Environment Interactions in Common Diseases

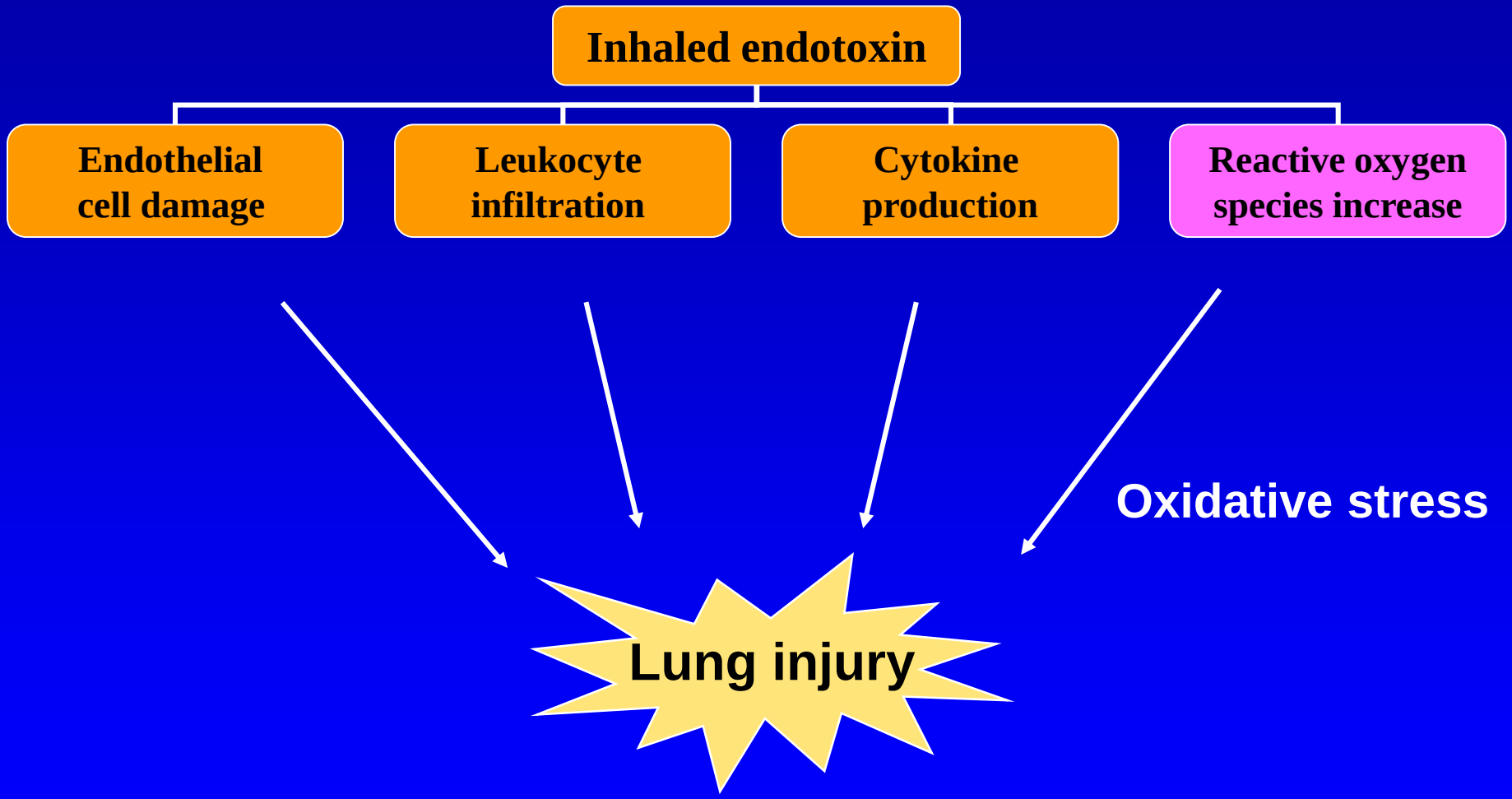


Epoxide Hydrolases

- A family of enzymes that hydrate simple epoxides to diols and arene oxides to transdihydrodiols
- Microsomal epoxide hydrolase (mEHx) detoxifies ROS and reactive epoxide intermediates
- In the coding region of the *mEH* gene are two common polymorphisms in exons 3 and 4.
- In exon 3, the *C113T (Tyr113His)* polymorphism results in 30-40 % decrease in enzyme activity (*His* allele = “slow allele”)

Epoxide Hydrolase Gene

- In exon 4, the *G139A (His139Arg)* is associated with a 25% increase in enzyme activity, hence *Arg* is termed the “fast allele”
- Slow activity genotypes have been associated with COPD (emphysema)

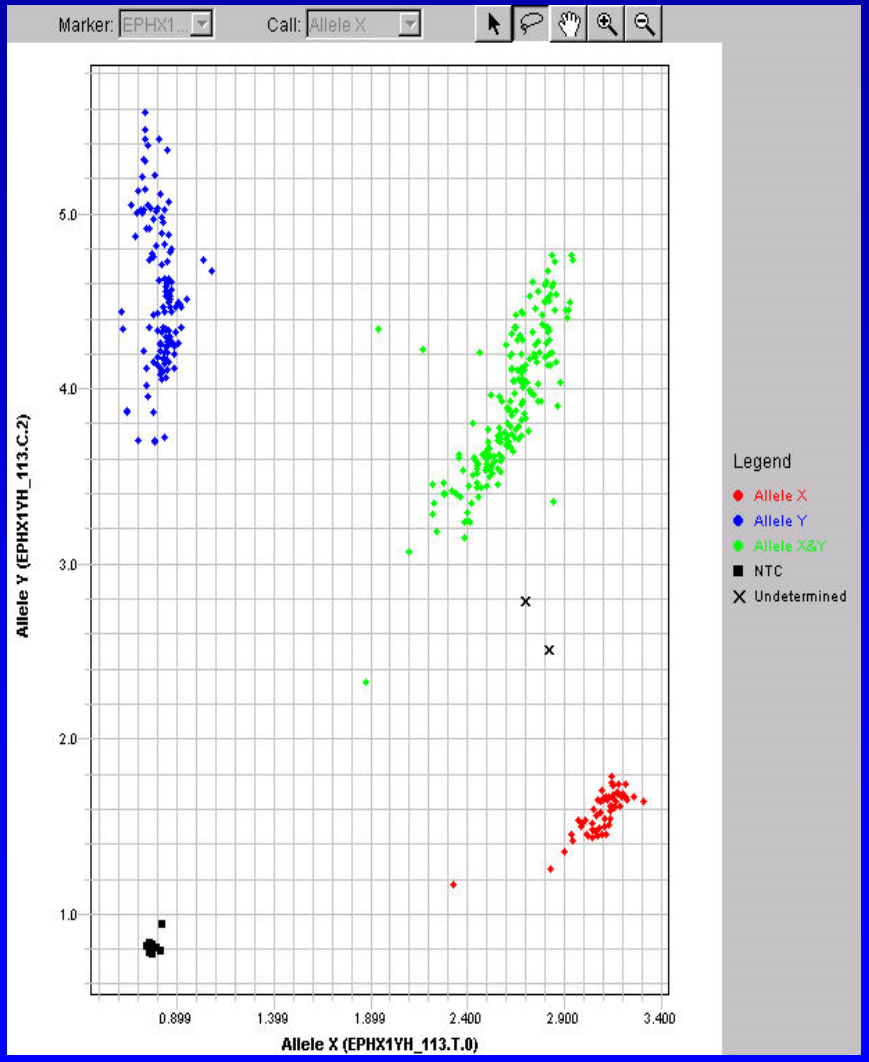

Inhaled endotoxin
Endothelial cell damage
Leukocyte infiltration
Cytokine production
Reactive oxygen species increase
Oxidative stress
Lung injury

Epoxide Hydrolase Gene

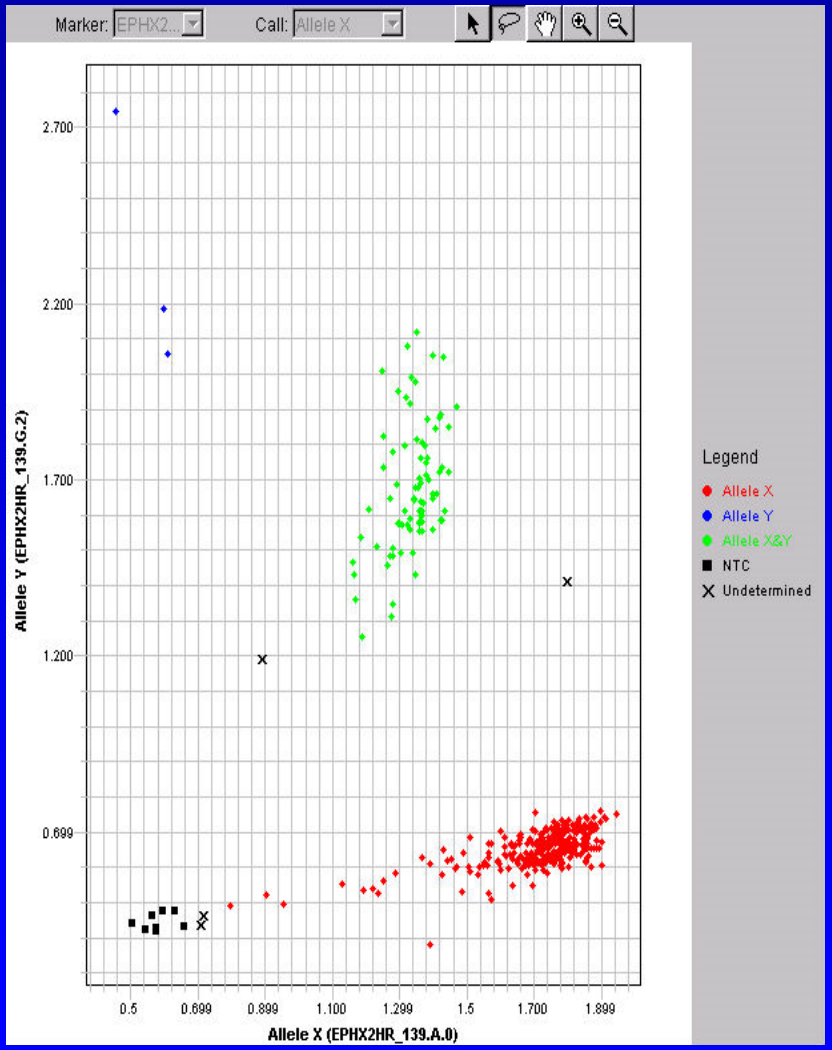
- Epoxide hydrolase enzyme metabolizes ROS generated by gram negative endotoxin exposure, possibly modifying the association between endotoxin exposure and airway disease
- We hypothesized that *mEH* polymorphisms modify the relationship between endotoxin exposure and airway disease in textile workers

Genotypes Results by TaqMan

Tyr113His



His139Arg



Joint Effects of m*EH* Polymorphisms and Exposure to Endotoxin on Annual Decline of FEV_1 (ml) Over 20-yr

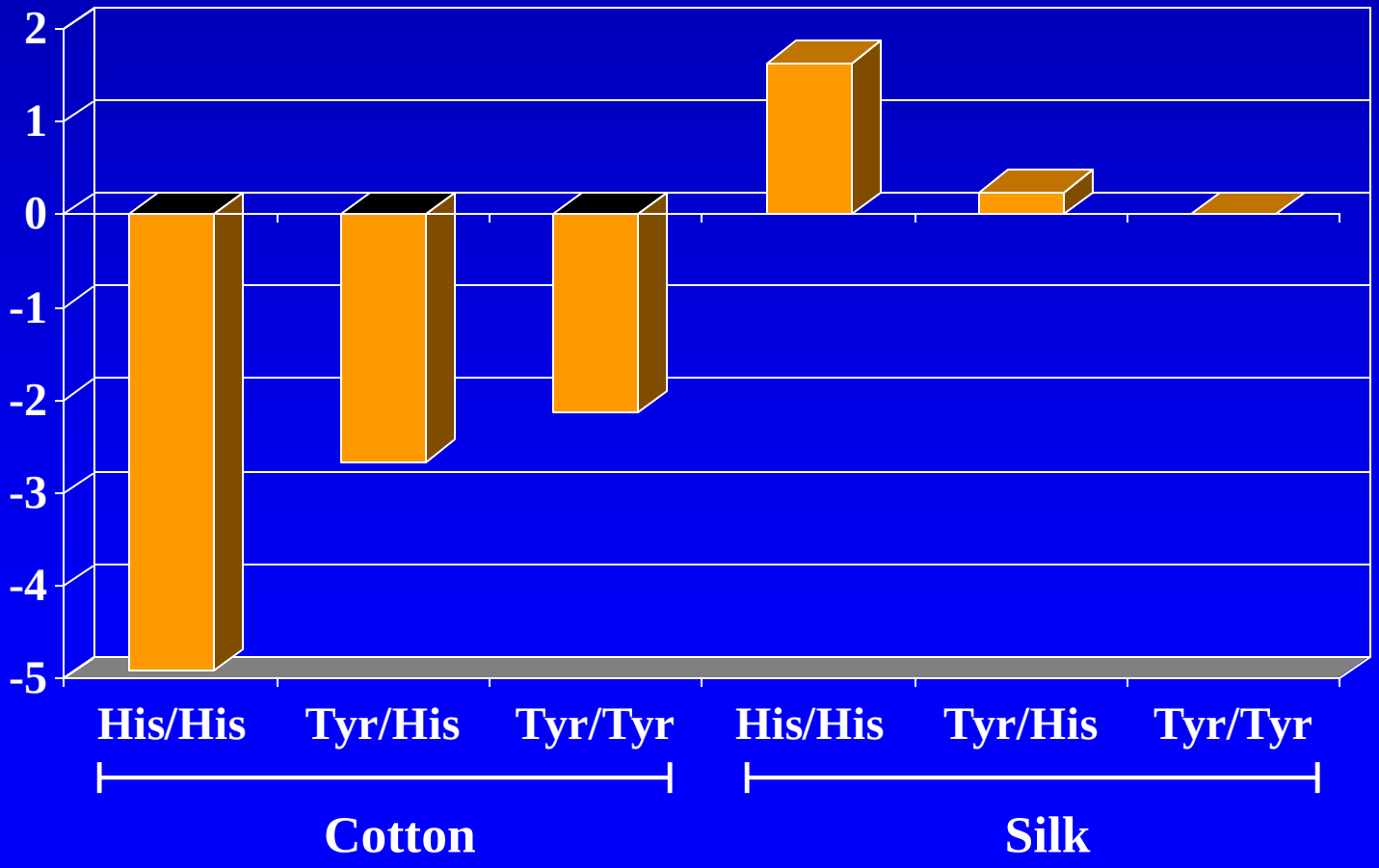
Genotype	Endotoxin non-exposed	Endotoxin exposed
Tyr113His polymorphism		
Tyr/Tyr	*Ref.*†	*-2.13 (2.02)*
Tyr/His	*0.24 (1.86)*	*-2.66 (1.82)*
His/His	1.63 (2.51)	-4.91 (2.26)‡
His139Arg polymorphism		
Arg/Arg + His/Arg	*Ref.*†	*-1.04 (2.35)*
His/His	-0.40 (1.94)	-4.37 (1.91)‡

Using multivariate liner regression models, adjusting for age, smoker status (ever smokers and never smokers), pack-years of smoking, and baseline FEV1.

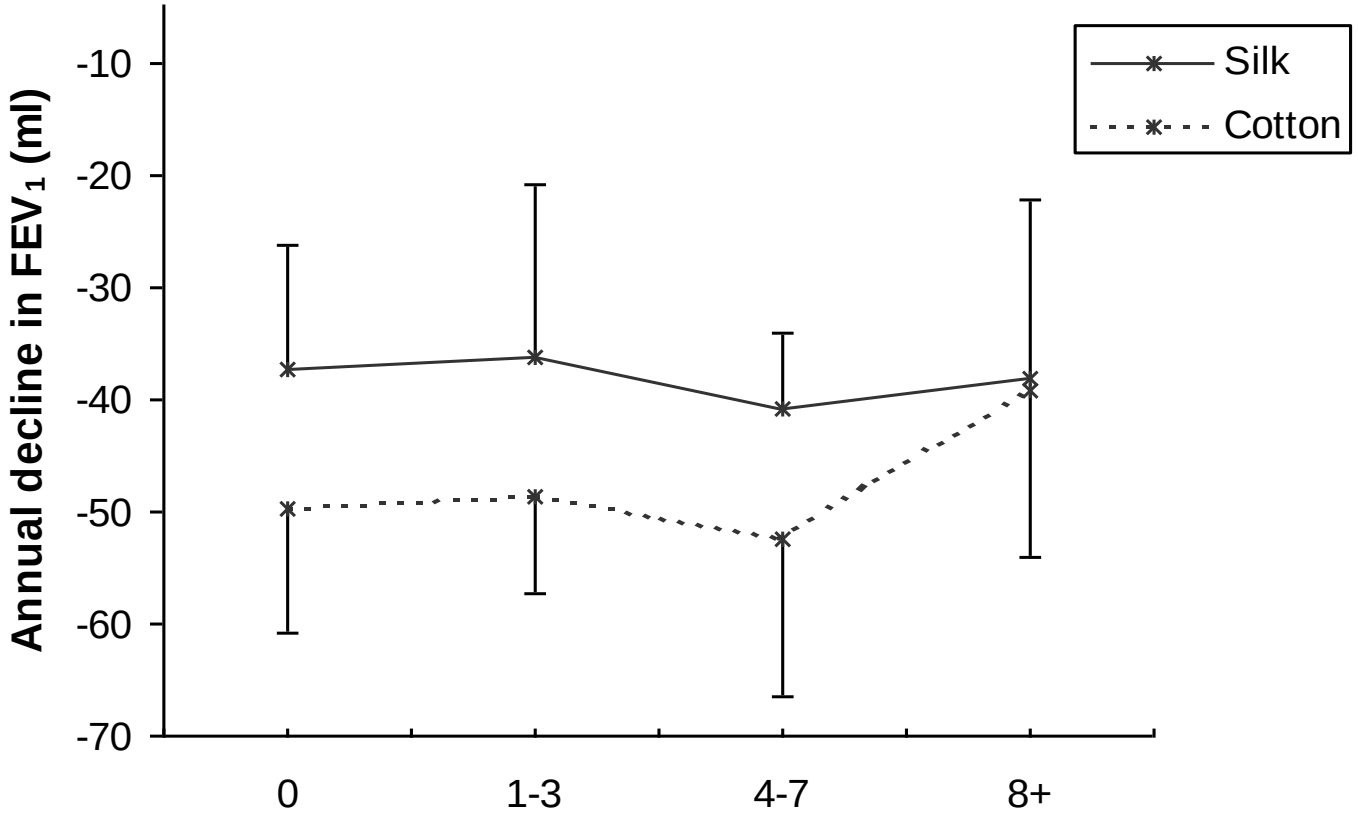
†*Tyr/Tyr* genotype of *Tyr113His* polymorphism and *Arg/Arg+ His/Arg* genotype of *His139Arg* polymorphism in endotoxin non-exposed groups serve as reference

‡$P<0.05$ (compared with reference).

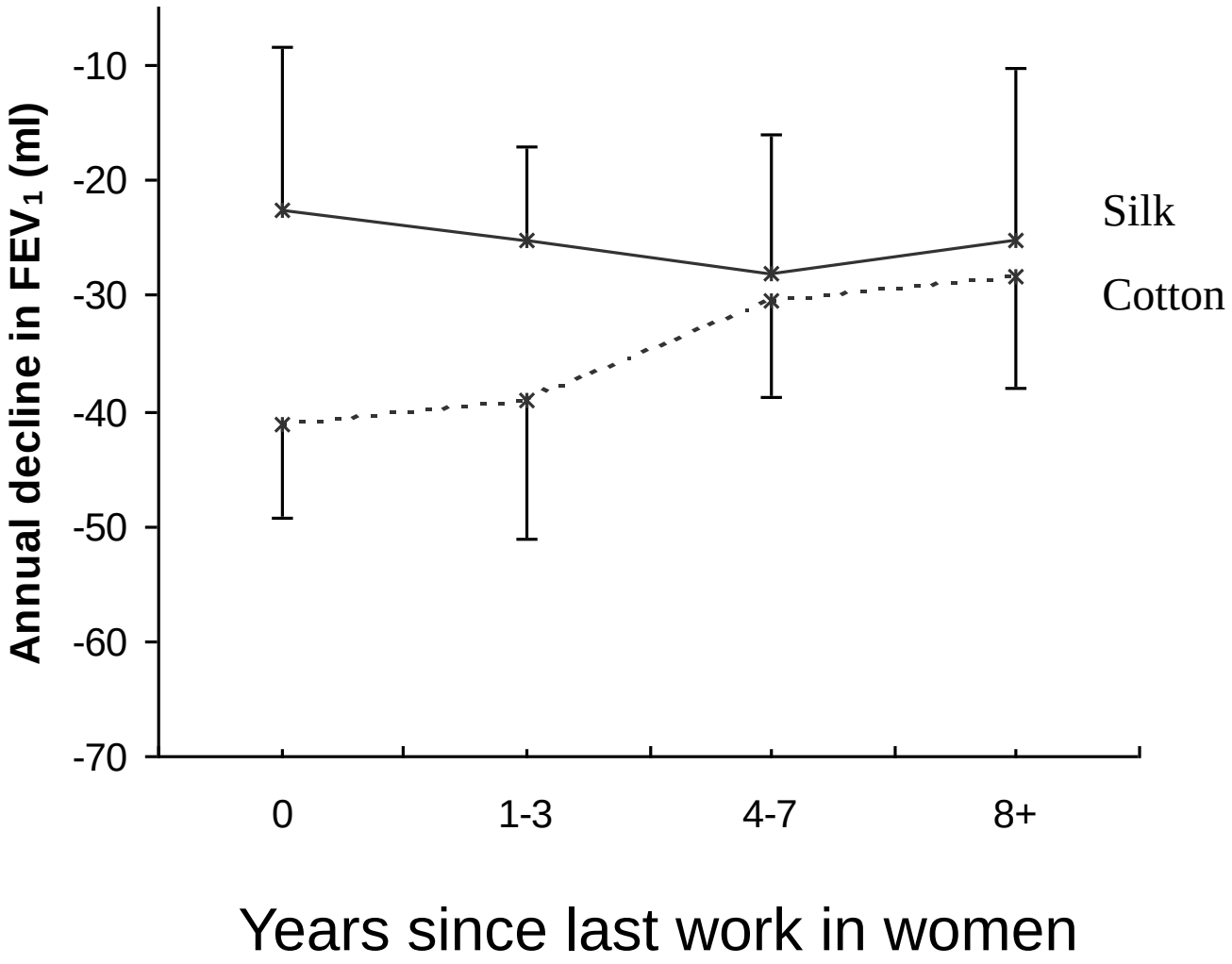
Effects of mEH Polymorphisms and Endotoxin Exposure on Annual Changes in FEV_1 (ml/yr)



Is Chronic Airway Obstruction Reversible After Exposure Ceases?



Years since last work in men


Annual decline in FEV1 (ml)
-10
-20
-30
-40
-50
-60
-70
0
1-3
4-7
8+
Silk
Cotton
Years since last work in women

Prevalence of COPD* by Retirement and Smoking Status† in Cotton Workers

	5-years	15-years	Remission‡
Total			
Active	34/201 (17)	12/154 (8)	18/201 (9)
Retired	76/228 (33)	51/184 (28)	32/228 (14)
Men			
Smokers	17/64 (27)	26/55 (47)	3/64 (5)
Non-SM	11/30 (37)	8/24 (33)	4/30 (13)

*COPD was defined as the ratio of FEV1/FVC being lower than 70%. Actual numbers and percentages (in parentheses) are represented.

† Calculation by smoking status was restricted to retired workers only.

‡ Remission indicates those with COPD at 5-years, and without at 15-years.

Summary

- Long-term exposure to cotton dust was associated with persistent respiratory symptoms and excess chronic loss of lung function, which was more evident in smokers.
- The occurrence and persistence of byssinosis symptoms predict the magnitude of chronic airway obstruction among cotton textile workers.
- *mEH* polymorphisms modify the association between exposure to cotton dust (endotoxin) and longitudinal lung function decline.

Summary (Cont.)

- Bacteria endotoxin contaminating in cotton dust may play a more important role than dust itself in cotton dust - related airway disease
- These findings from cotton textile workers imply that long-term exposure to other types of organic dust contaminated by endotoxin may be related to chronic airway disease
- Cessation of the exposure may slow lung function loss and reduce airway obstruction, but FEV1 is unlikely to return to the level seen in an unexposed population

The Shanghai Textile Study as a Case Study of Conducting Global Occupational Epidemiology Research in a Changing Socio-economic Climate

Changes in Housing

Changes in Work Environment

Changes in Transportation

Relevance of International Collaborations

- Take advantage of unique populations and research setting
- Stable population, good infrastructure
- Build upon long-term, well-established collaborations
- Feasible
- Mutual scientific interest; common problems to be addressed by research
- Builds friendships between our nations, our peoples

Grant Support

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Questions?