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Biomarkers and indicators of COPD: Evidence of change

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Outline

- What is COPD?
- Summary of what we know (or think we know)
- Research needs
- Potential biomarkers
- Malawi Adult Lung Health Study

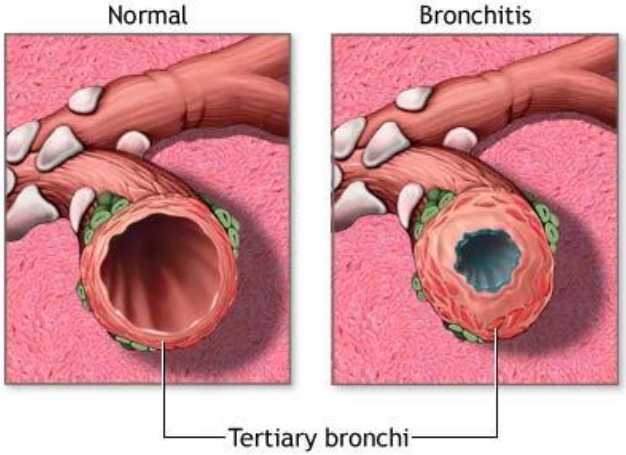
What is COPD?

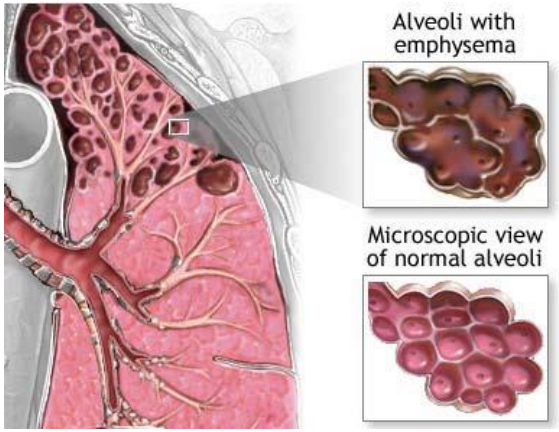
Chronic Obstructive Pulmonary Disease (COPD), a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients.

Global Strategy for the Diagnosis, Management, and Prevention of COPD (GOLD) 2011

What is COPD?

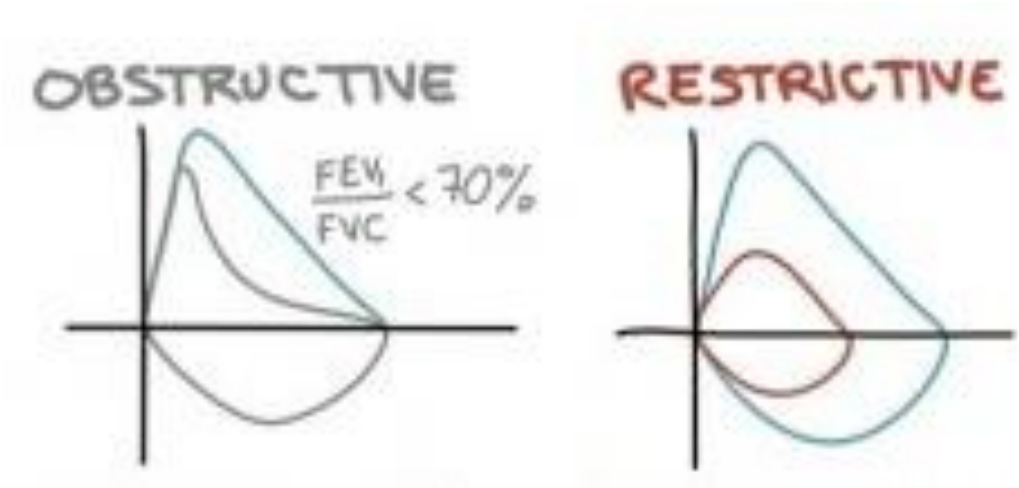
- Fixed obstruction
  - $FEV_1/FVC < 0.70$
  - Post-bronchodilator
- Chronic airway inflammation
- Airway remodeling
- Alveolar destruction





What COPD is NOT

- Symptoms of “chronic bronchitis” alone
- Low FEV_1 and FVC with normal FEV_1/FVC (i.e., suggests restriction with no obstruction)



Biomass Smoke and COPD

- Four systematic reviews/meta-analyses
  - (Ho et al., Kurmi et al., Po et al., ***Smith et al.***)
- Strengths of evidence
  - Multiple studies from multiple countries
    - Consistency
    - Coherence
  - Biological plausibility
- Limitations
  - Exposure usually not measured
  - Few studies measured lung function
    - Only one has measured lung function post-bronchodilator

RESPIRE – Randomized Exposure Study of Pollution Indoors and Respiratory Effects

Opportunity to study respiratory health outcomes in mothers of the study children using the RCT platform

RESPIRE Stove Intervention Results (adult women)

- Measured difference in personal exposure of mothers to CO (a surrogate for PM) only 30% lower in *plancha* homes
- Incidence of eye irritation and wheezing among mothers also ~30% lower in *plancha* homes

Diaz E, et al. *Int J Tuberc Lung Dis 2007;*11:1372–1379

RESPIRE CO Exposure-Symptom Response (adult women)

Table 4 ORs* with 95%CIs for each respiratory symptom, per 1 unit increase in CO in exhaled breath and CO tubes, ppm

	CO breath OR† (95%CI)	CO tubes OR† (95%CI)
Cough	1.07 (1.01–1.15)	1.11 (1.02–1.20)
Chronic cough	1.10 (1.02–1.18)	1.13 (1.04–1.24)
Phlegm	1.10 (1.02–1.19)	1.05 (0.95–1.17)
Chronic phlegm	1.10 (1.01–1.19)	1.00 (0.88–1.15)
Wheeze	1.04 (0.98–1.11)	1.05 (0.97–1.14)
Tightness in the chest	1.08 (1.01–1.15)	1.04 (0.96–1.13)
Chronic cough and phlegm	1.15 (1.05–1.26)	1.04 (0.92–1.17)

* For women using open fires at baseline.
† Adjusted for age, pregnancy, mean temperature and mean rainfall.
OR = odds ratio; CI = confidence interval; CO = carbon monoxide; ppm = parts per million.

Diaz E, et al. *Int J Tuberc Lung Dis 2007;*11:1372–1379

RESPIRE Stove Intervention Results (adult women)

- Intention-to-treat analysis showed no effect on decline in lung function (18 months)
- Exposure-response analysis showed an association between exhaled CO and FEV_1

Measure of lung function	Coeff[1]	95% CI
FEV1 (unadjusted)	-0.031	-0.056, -0.006
FEV1 (adjusted)*	-0.035	-0.061, -0.009

[1] Beta coefficient represents the change in lung function associated with a 1 unit increase in CO (ln transformed);

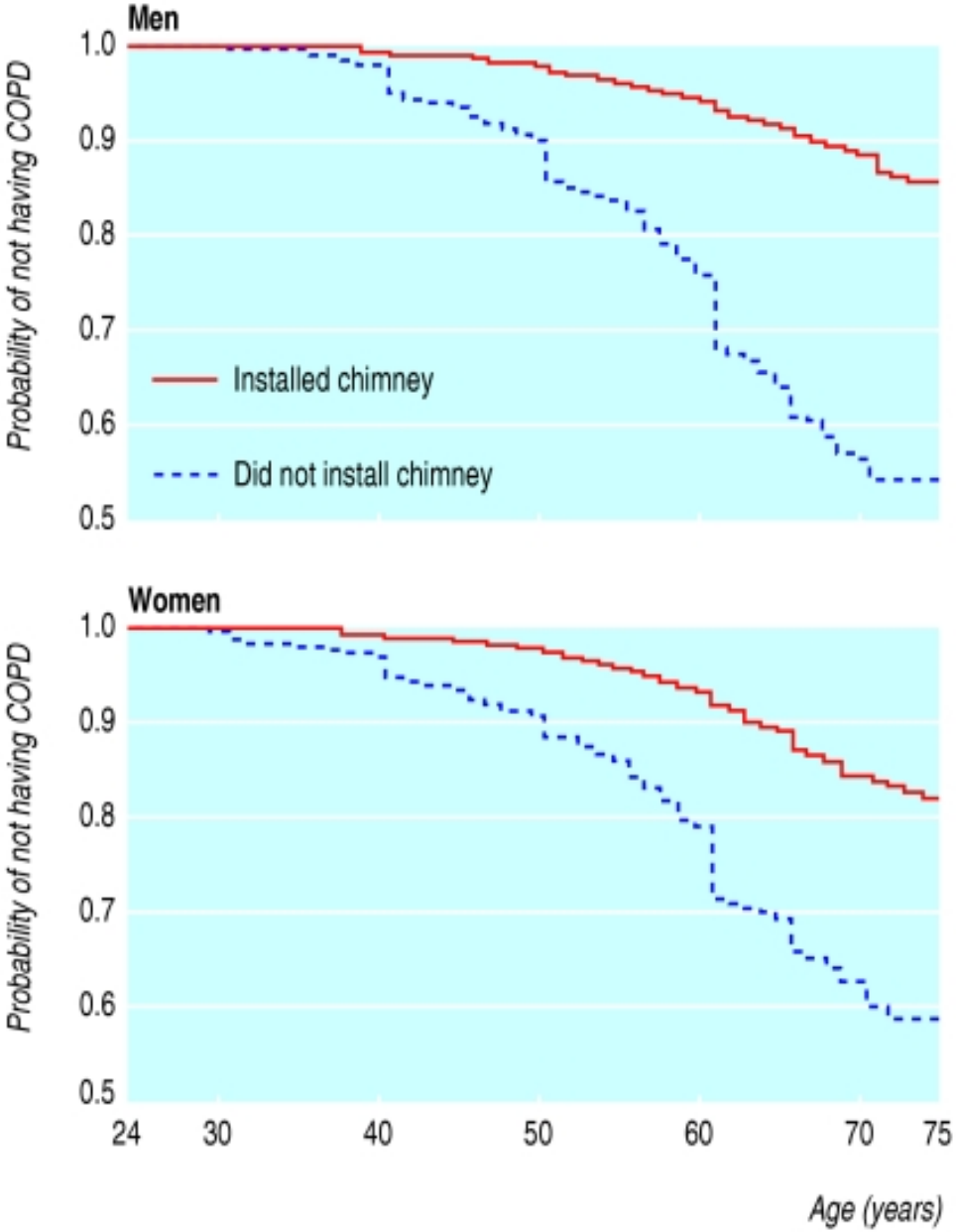
* adjusted for age, age-squared, weight, test round, and fieldworker, income, season, day of week

Pope D, et al. Environ Health Perspect 2014; Nov 14. [Epub ahead of print]

Mexico Stove Intervention Results (adult women)

- ITT analysis showed no effect of *Patsari* chimney stove on FEV_1
- Adherence with *Patsari* use was poor (~50%)
- In women who reported using the stove there was a lower decline in FEV_1 (-31 ml) vs open fire use (-61 ml) over 1-year follow-up

Romieu I, et al. Am J Respir Crit Care Med 2009;180:649-656



Risk of COPD:

Vented vs. unvented coal stoves

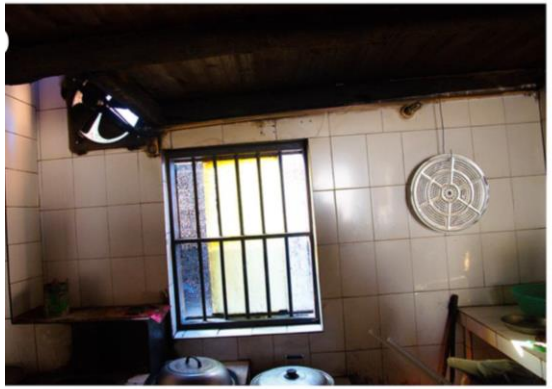
Xuan Wei County
China,
retrospective cohort,
1976-1992,
20,453 subjects
81% added chimneys

Chapman R, et al. Br Med J 2005; 331: 1050

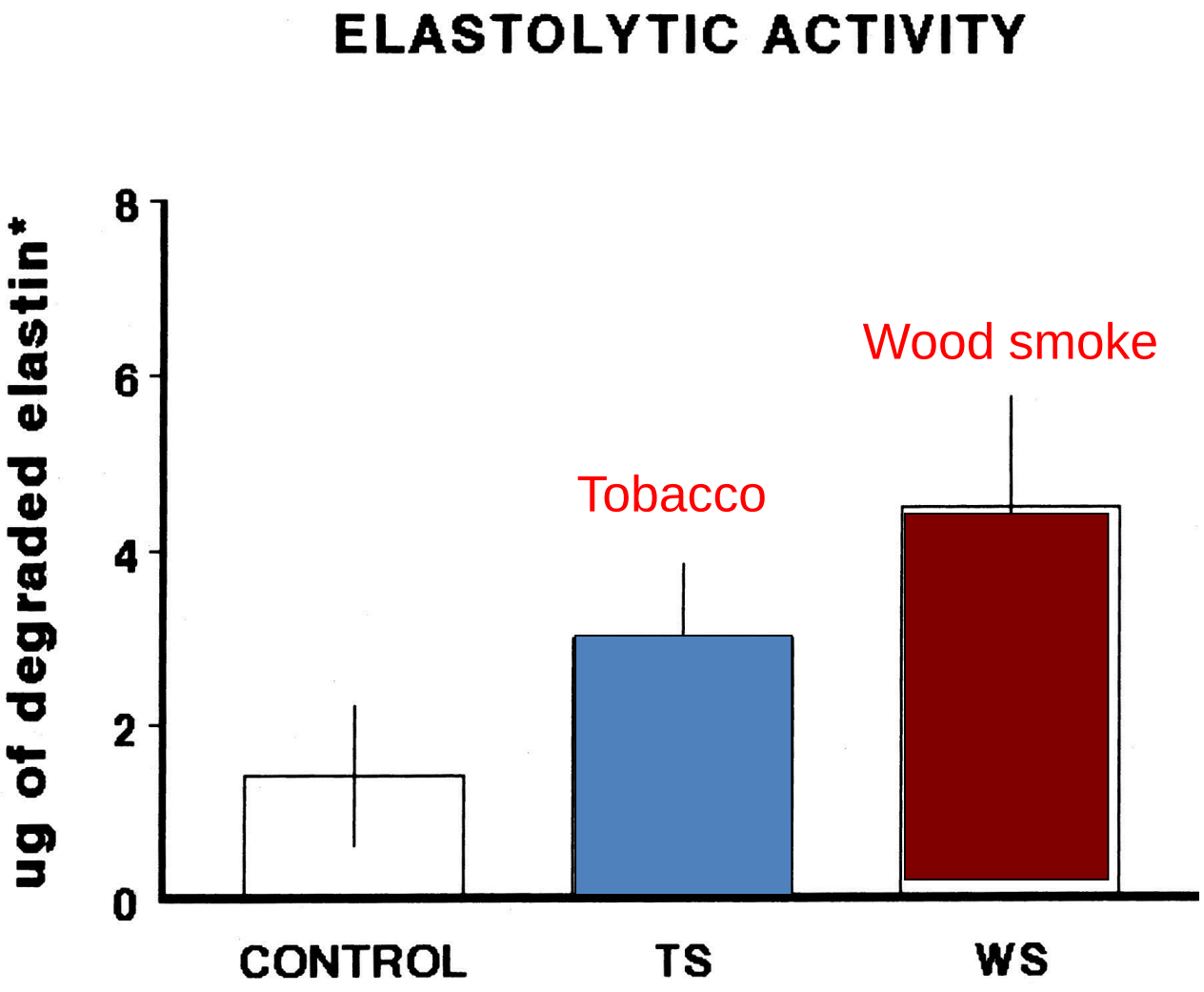
Chinese Stove Intervention Study

- A 9-y prospective cohort study (n=996 men and women)
- Interventions
  - improved kitchen ventilation (chimney stoves or exhaust fans)
  - biogas instead of biomass
- Decreased rate of decline in FEV_1
  - 12 ml/yr with either intervention
  - 16 ml/yr with both
- Decreased risk of COPD
  - OR 0.28 with both interventions

Zhou Y, et al. PLoS Med 2014; 11(3): e1001621

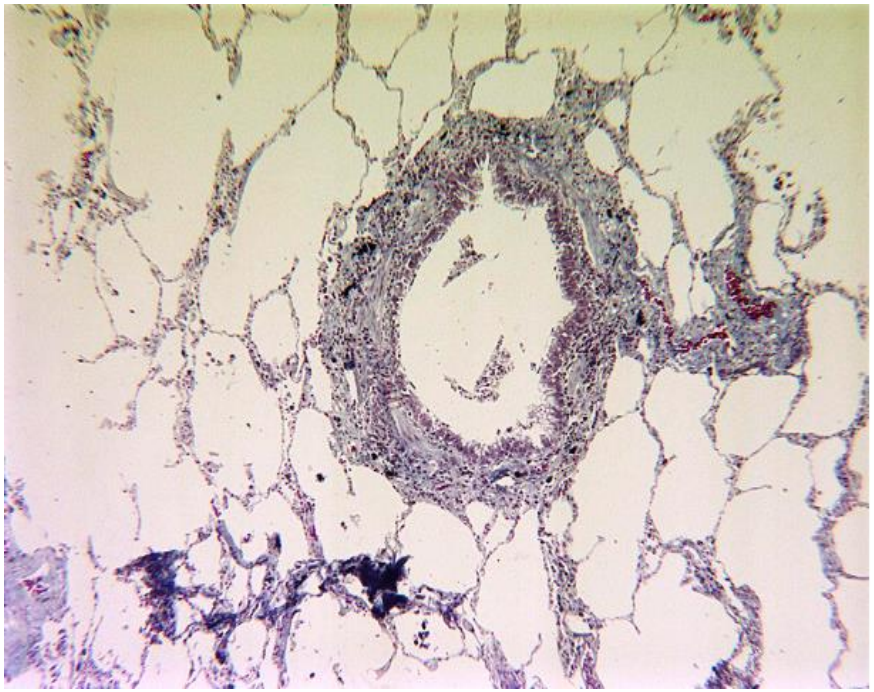


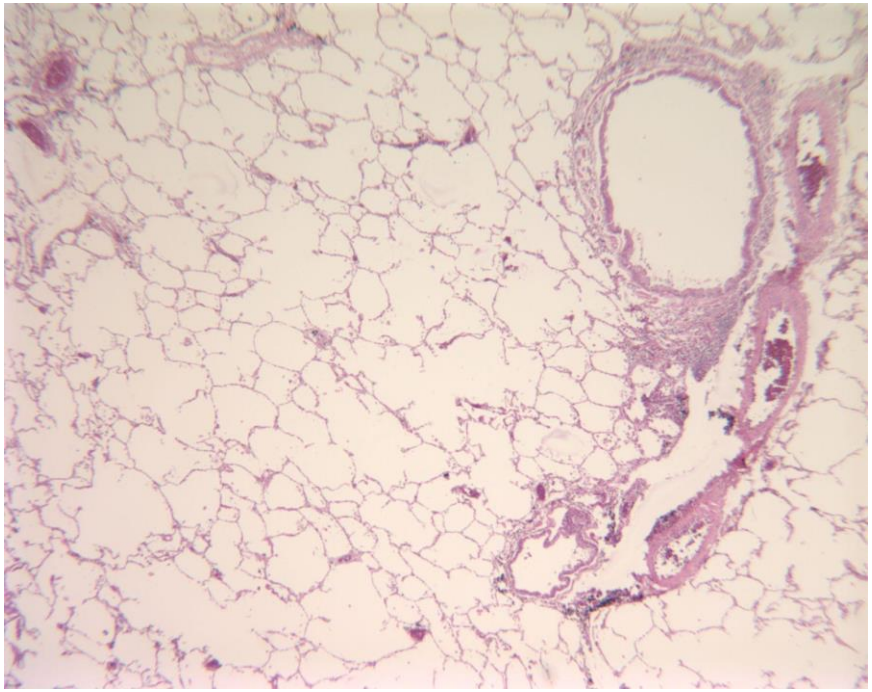
Tobacco Smoke vs. Wood Smoke



Montano M, et al. Chest 2004;125:466-472

Small Airways Fibrosis



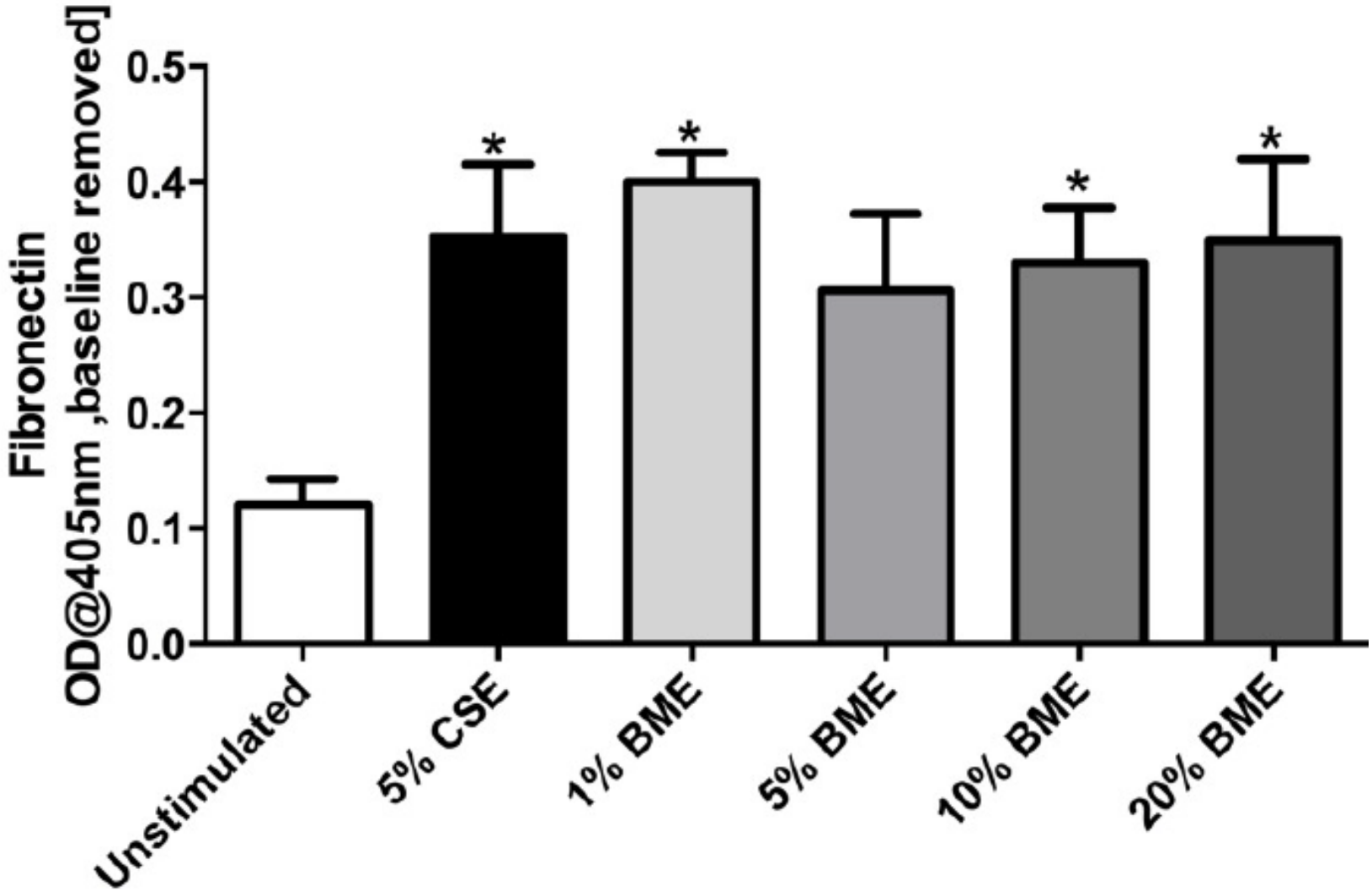


Wood smoke

Tobacco smoke

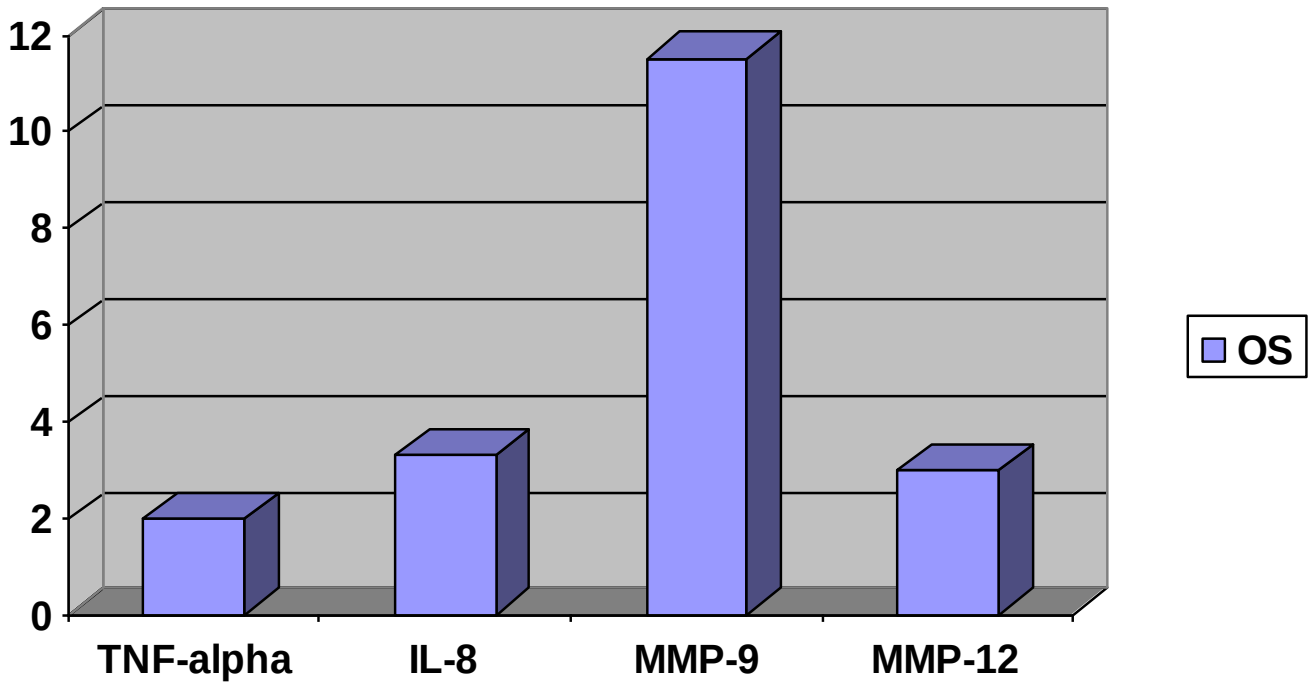
Courtesy of Rogelio Perez-Padilla

Fibronectin Release from Fibroblasts



Krimmer D, et al. Plos One 2013;8(12):e83938.

RESPIRE Sputum Gene Expression



Higher 48-hr personal CO concentrations were associated with higher gene expression of IL-8, TNF- α, MMP-9 and MMP-12; reaching statistical significance for MMP-9 and MMP-12.

Guarnieri M, et al. PLoS One 2014; 9(3):e88455

Potential Blood Biomarkers of Effect

- Plasma levels of MMP-1, MMP-7, MMP-9, and MMP-9/TIMP-1 and CRP were higher in biomass smoke-exposed women and tobacco smokers compared to non-smokers
- Inverse correlations between MMP-1, MMP-7, MMP-9, MMP-9/TIMP-1 and CRP plasma concentrations and FEV_1 were observed

Montano M, et al. Respir Res. 2014;15:74

FEV_1 Rate of Decline

- Annual spirometry in a Mexican cohort of patients with COPD associated with biomass or tobacco over a 15-year follow-up period
- Mean rate of decline was significantly lower for the biomass exposure group than for the tobacco smoke group
  - 23 vs. 42 ml, respectively
  - More rapid decliners in the TS group

Ramirez-Venegas A, et al. Am J Respir Crit Care Med 2014;190:996-1002

What Does Low FEV_1 Mean? BOLD Data

- National COPD mortality rates were more strongly associated with spirometric restriction than obstruction
- Obstruction increased with mean pack years smoked, but COPD mortality fell with increased cigarette consumption and rose rapidly as GNI fell below US $15,000
- Prevalence of restriction also increased rapidly as GNI fell below US $15,000

Burney P, et al. Thorax 2014;69:465–473

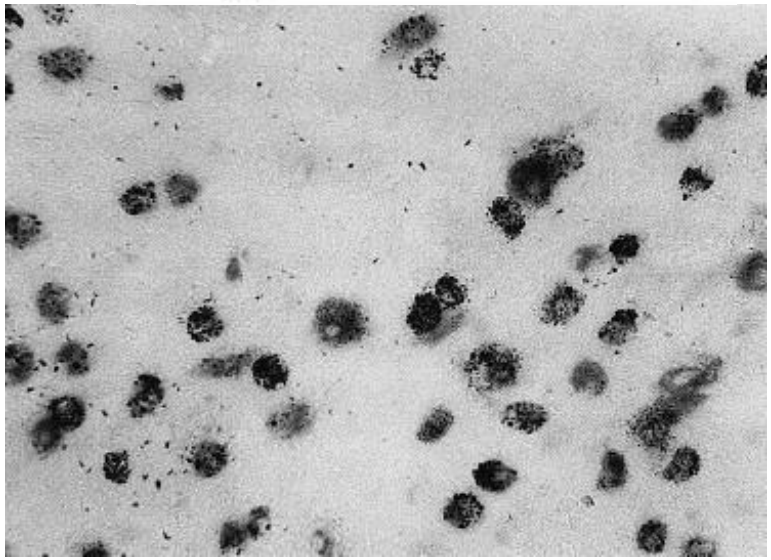
What Does Low FEV_1 Mean?

- Recent cross-sectional study from India (681 women cooking with biomass, 438 cooking with LPG)
- Biomass group had greater prevalence of lower respiratory symptoms (72 versus 31%) and dyspnea (58 versus 20%)
- 30% of biomass group and 16% of LPG users had low lung function, and a *restrictive* deficit was predominant
- COPD was diagnosed in 4.6% of biomass group and 0.9% of LPG group

Mukherjee S, et al. Inhal Tox 2014;26:866-72

Research Needs

- Better RCTs of “clean” stoves
  - longer duration studies for lung function effect
  - pre-clinical outcomes
- Exposure-response data
- Mechanisms
- Biomarkers
  - exposure (analogous to cotinine)
  - susceptibility/early effect



Potential Biomarkers of Early Effect

- Accelerated decline of lung function
- Airway inflammation and oxidative stress
  - Induced sputum
  - Exhaled breath condensate
  - Exhaled nitric oxide
- Peripheral blood markers of systemic inflammation and oxidative stress
- Genetic variants/epigenetic modification

Malawi Adult Lung Health Study

- The 2,000 men and women enrolled in the Chikhwawa BOLD study followed annually with respiratory symptom questionnaire and spirometry for 2 years
- Annual exposure assessment with 48-hr personal CO and $PM_{2.5}$ monitoring using the Aprovecho device
- Will be adding $PM_{2.5}$ monitoring using the Micro PEMS device

Adult Lung Health Study

- ITT analysis of effect of Philips stove on rate of decline in lung function over 2 years in CAPS sub-cohort (Mortimer NIRG funding)
  - ~600 in intervention homes, ~600 in control homes
- Extended longitudinal follow-up (6 years total) of entire cohort to determine exposure-response (seeking NIEHS funds)
  - Will do interim E-R analysis of 2-year follow-up data

Thank You!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