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
  - $\text{FEV}_1/\text{FVC} < 0.70$
  - 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
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

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

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

* 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.

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$_1$

<table>
<thead>
<tr>
<th>Measure of lung function</th>
<th>Coeff$^1$</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 (unadjusted)</td>
<td>-0.031</td>
<td>-0.056, -0.006</td>
</tr>
<tr>
<td>FEV1 (adjusted)*</td>
<td>-0.035</td>
<td>-0.061, -0.009</td>
</tr>
</tbody>
</table>

$^1$ 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

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

Risk of COPD: Vented vs. unvented coal stoves

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

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

Tobacco Smoke vs. Wood Smoke

ELASTOLYTIC ACTIVITY

µg of degraded elastin

<table>
<thead>
<tr>
<th></th>
<th>CONTROL</th>
<th>TS</th>
<th>WS</th>
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</thead>
<tbody>
<tr>
<td>Tobacco</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wood</td>
<td></td>
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</table>

Small Airways Fibrosis

Wood smoke

Tobacco smoke

Courtesy of Rogelio Perez-Padilla
Fibronectin Release from Fibroblasts

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.

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.

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

What Does Low FEV₁ 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.

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!