Effect of a randomized controlled clean stove intervention study on inflammatory biomarkers in pregnant women in Ibadan, Nigeria

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Scope of the HAP problem

- Over 3 Billion people cook with solid fuels and other polluting fuels
- 4 million premature deaths each year are attributable to household air pollution
- Most deaths occur in women and children
- Systemic inflammation is suspected as etiology for cerebrovascular diseases, pneumonia in children, diabetes and COPD
CleanCook stove and bioethanol fuel use will reduce pregnant women’s personal exposures to PM$_{2.5}$ (particulate matter), PAH (polycyclic aromatic hydrocarbon), and CO and reduce adverse pregnancy outcomes.
Important Questions

• Can ethanol stove intervention reduce personal exposure to PM$_{2.5}$, CO and PAH?
• What is the relationship between HAP exposure birth-weight and other pregnancy outcomes?
• Does HAP exposure lead to intrauterine growth restriction, impaired pulmonary function and changes in BP?
• Will participants use and adopt the ethanol stoves?
• Can ethanol stove intervention reduce systemic inflammation?
Objective of biomarker sub-study

• To determine if clean cookstove intervention will reduce serum levels of biomarkers of systemic inflammation and oxidative stress between 2\textsuperscript{nd} and 3\textsuperscript{rd} trimesters of pregnancy.
Pathway

HAP/Ambient PM

Pulmonary Reflexes

Autonomic Nervous System

Automaticity Conduction Repolarization

Heart Rate Rhythm

Arrhythmia

Pulmonary Inflammation

Oxidative Stress

Endothelial Dysfunction

Leukocyte/Platelet Activation

Atherosclerosis Progression And Plaque Instability

Plaque Rupture

Thrombosis

Acute Phase Response/Activation of Coagulation

Direct effect on the Heart

Myocardial Infarction
A randomized controlled stove intervention and pregnancy outcome

Randomized Controlled Intervention Trial

324

162 CleanCook stove/ethanol

162 Kerosene (104) or Firewood (58)

Exclusion

• Smoker in home
• Cooking profession
• HIV infection
• Diabetes
• High risk pregnancy

Last delivery end of October 2015
The CleanCook Tier 4 Stove*
Biomarker Determination

- Serum biomarkers determined by ELISA in 2\textsuperscript{nd} and 3\textsuperscript{rd} Trimesters of pregnancy

- Pro-inflammatory markers
  - IL-6
  - IL-8
  - TNF-\alpha

- Oxidative stress marker
  - Malondialdehyde (MDA)
Exposure and cookstove monitoring

- 72 hour exposure monitoring for PM2.5 was performed during 2nd and 3rd trimesters of pregnancy
- SUMs placed on all stoves in study homes
- SUMs recorded temperature every 10 minutes

*SUMs = Stove Use Monitors
SUMs monitoring confirms use and absence of stove stacking
Biomarker levels similar between Ethanol users and Controls

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Ethanol Intervention</th>
<th>Control (Firewood OR Kerosene)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean Change</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>116</td>
<td>0.46</td>
</tr>
<tr>
<td>IL-8 (pg/ml)</td>
<td>112</td>
<td>16.2</td>
</tr>
<tr>
<td>TNF-α (pg/ml)</td>
<td>114</td>
<td>3.43</td>
</tr>
<tr>
<td>MDA (pmol/ml)</td>
<td>118</td>
<td>-19.7</td>
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</table>
Change from Kerosene to ethanol did not reduce inflammation

<table>
<thead>
<tr>
<th>Ethanol (From Kerosene)</th>
<th>Control (Kerosene)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean Change</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>1.42</td>
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<tr>
<td>IL-8 (pg/ml)</td>
<td>35.5</td>
</tr>
<tr>
<td>TNF-α (pg/ml)</td>
<td>8.25</td>
</tr>
<tr>
<td>MDA (pmol/ml)</td>
<td>-20.3</td>
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Transition from firewood to ethanol stove reduced TNF-α levels

<table>
<thead>
<tr>
<th></th>
<th>Ethanol (From Firewood)</th>
<th>Control (Firewood)</th>
<th>n</th>
<th>Mean Change</th>
<th>SE</th>
<th>n</th>
<th>Mean Change</th>
<th>SE</th>
<th>P-Value</th>
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<tbody>
<tr>
<td>IL-6 (pg/ml)</td>
<td>38</td>
<td>-1.51</td>
<td>1.73</td>
<td>34</td>
<td>2.03</td>
<td>2.51</td>
<td>0.43</td>
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<tr>
<td>IL-8 (pg/ml)</td>
<td>37</td>
<td>-23.1</td>
<td>15.2</td>
<td>35</td>
<td>-25.7</td>
<td>6.1</td>
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<tr>
<td>TNF-α (pg/ml)</td>
<td>38</td>
<td>-6.20</td>
<td>5.24</td>
<td>35</td>
<td>14.03</td>
<td>5.89</td>
<td>0.011*</td>
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<tr>
<td>MDA (pmol/ml)</td>
<td>38</td>
<td>-18.4</td>
<td>5.0</td>
<td>35</td>
<td>-10.0</td>
<td>6.2</td>
<td>0.16</td>
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</table>
Biomarker levels as a function of PM2.5 levels

- RBP
- IL-6
- IL-8
- TNF-α
- MDA

Rainy Season
Dry Season
Biomarker levels as a function of Minutes above 100μg/m³

- Log RBP
- Log IL-6
- Log IL-8
- Log TNF-α
- Log MDA

Rainy Season

Dry Season
Biomarker levels as a function of PM2.5 levels: TNF-α

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Slope estimate</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>Log RBP</td>
<td>0.0090</td>
<td>0.811</td>
</tr>
<tr>
<td>Log IL-6</td>
<td>0.0293</td>
<td>0.768</td>
</tr>
<tr>
<td>Log IL-8</td>
<td>0.2363</td>
<td>0.028*</td>
</tr>
<tr>
<td>Log TNF-α</td>
<td>0.1863</td>
<td>0.022*</td>
</tr>
<tr>
<td>Log MDA</td>
<td>-0.0686</td>
<td>0.060</td>
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Biomarker levels as a function of PM2.5 levels: IL-8

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<th>Slope Estimate</th>
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<td>-0.0686</td>
<td>0.060</td>
</tr>
</tbody>
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Conclusions

• Shifting to cleaner fuel and improved stoves reduces TNF-α during pregnancy
• There is linear correlation between PM2.5 and serum levels of TNF-α and IL-6
• There was wide adoption of the CleanCook stove
• CleanCook stove with ethanol as fuel resulted in lower exposure to PM2.5
• Sustained use and reduction in HAP may lead to reduction in systematic inflammation and thromboembolic risks
Limitations

• Relatively small sample size especially in the baseline firewood subgroup

• Inability to control for the effect of ambient air pollution and automobile-related pollution is an important confounder

• Lack of nutritional marker data to determine level of anti-oxidant defense
Appendix 1: Stove and Fuel Type

Control

- Kerosene Stove
- Firewood stove (Three-Stone)

Intervention

- Ethanol-fueled Stove Intervention
Appendix 2: Study Design

324 Pregnant Women

Randomized at 16-18 weeks

162 Control
- Firewood (n=58)
- Kerosene (n=104)

162 Intervention
- Firewood (n=51)
- Kerosene (n=111)

Kerosene

Firewood (three-stone)

Ethanol (CleanCook)
Appendix 3A: Participants

Inclusion Criteria:

- Apparently healthy women
- Non-smokers and non-chewers of tobacco
- Cooked regularly with firewood or kerosene
- Less than 18 weeks gestational age (determined by self-reported first day of last menstrual period (LMP) and/or ultrasound biometry

324 Pregnant Women

162 Control
- Firewood (n=58)
- Kerosene (n=104)

162 Intervention
- Firewood (n=51)
- Kerosene (n=111)
Appendix 3B: Participants

Exclusion Criteria:

- Smoker
- Lived with a smoker
- Cooked for a living
- HIV positive
- High-risk pregnancy (multiple gestations)
- Uncontrolled material hypertension
- Maternal age greater than 35 for first delivery
- Three or more prior miscarriages
- Prior C-section

324 Pregnant Women

162 Control
- Firewood (n=58)
- Kerosene (n=104)

162 Intervention
- Firewood (n=51)
- Kerosene (n=111)
Appendix 4: Clinic

8 Clinic Visits

Measurements:
• Ultrasound- intrauterine growth rate
• Birth weight and length
• Blood Draw for Biomarker analysis
• Blood Pressure
• **Spirometry** assesses lung function by measuring the amount of air that can be maximally inhaled and exhaled
### Appendix 5: Characteristics of PM

<table>
<thead>
<tr>
<th></th>
<th>Düsseldorf PM</th>
<th>Washington DC PM</th>
<th>ROFA</th>
<th>Mt St Helen’s dust</th>
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<tbody>
<tr>
<td>Carbon</td>
<td>19.7</td>
<td>17.7</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Ash</td>
<td>63.2</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<td>Cobalt</td>
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<td>44</td>
<td>10</td>
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<tr>
<td>Copper</td>
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<td>223</td>
<td>107</td>
<td>164</td>
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<tr>
<td>Chromium</td>
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<td>211</td>
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<td>Iron</td>
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<td>Manganese</td>
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<td>Vanadium</td>
<td>2767</td>
<td>345</td>
<td>2611</td>
<td>1.2</td>
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Appendix 6A: Pathway

HAP/Ambient PM

- Pulmonary Inflammation
  - Oxidative Stress
  - Endothelial Dysfunction
  - Leukocyte/Platelet Activation
  - Acute Phase Response/Activation of Coagulation

- Atherosclerosis Progression And Plaque Instability
- Plaque Rupture
- Thrombosis

Direct effect on the Heart

Myocardial Infarction

- Heart Rate Rhythm

Arrhythmia

- Automaticity Conduction Repolarization

Autonomic Nervous System

Pulmonary Reflexes
Appendix 6B: Pathway