What can we expect from ending exposure to biomass smoke? The example of tobacco smoke

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Indicators and Biomarkers of NDCs: Evaluating the Health Benefits of Clean Cooking Adoption
Global Alliance for Clean Cookstoves
Washington DC, Dec 15-16, 2014
What I am going to talk about

• How fast disease rates change.
• Burden estimates and the concept of accountability.
• Lessons from active and passive smoking.
• Research implications.
HOW FAST DISEASE RATES CHANGE
Infectious disease trends: 1900 – 1996

FIGURE 1. Crude death rate* for infectious diseases — United States, 1900–1996†

- 40 States Have Health Departments
- Influenza Pandemic
- Last Human-to-Human Transmission of Plague
- First Continuous Municipal Use of Chlorine in Water in United States§
- First Use of Penicillin
- Salk Vaccine Introduced
- Passage of Vaccination Assistance Act

*Per 100,000 population per year.
Selected mortality rates in US, 1900-2005

Adult per-capita cigarette consumption and major smoking and health events, US, 1900-2012
BURDEN ESTIMATES AND THE CONCEPT OF ACCOUNTABILITY.
Morton Levin’s Attributable Risk Formula

- Estimate the Relative Risk (RR)
- Estimate the prevalence (P) of each risk factor.

\[
\text{PAR} = \frac{P \times (RR - 1)}{1 + P(\text{RR} - 1)}
\]

Johns Hopkins School of Hygiene and Public Health, Department of Epidemiology, c. 1935-36
Burden of Disease Attributable to 20 Leading Risk Factors in 2010, % DALYs, both sexes

- High blood pressure
- Tobacco smoking, including second-hand smoke
- Alcohol use
- Household air pollution from solid fuels
- Diet low in fruits
- High body-mass index
- High fasting plasma glucose
- Childhood underweight
- Ambient particulate matter pollution
- Physical inactivity and low physical activity
- Diet high in sodium
- Diet low in nuts and seeds
- Iron deficiency
- Suboptimal breastfeeding
- High total cholesterol
- Diet low in whole grains
- Diet low in vegetables
- Diet low in seafood omega-3 fatty acids
- Drug use
- Occupational risk factors for injuries

Disability-adjusted life-years (%)

Slide attributed to Stephen Lim, Global Burden of Disease Project, Institute for Health Metrics and Evaluation, University of Washington
Adjusted Total Household Air Pollution (HAP) Burden of Disease, 2010

**a) HAP DALYs**
- Total all ages: 119,000,000 DALYs
- Men: 46,000,000 DALYs
- Women: 33,000,000 DALYs
- Children <5 years: 40,100,000 DALYs

**b) HAP deaths**
- Total all ages: 3,890,000 deaths
- Men: 1,920,000 deaths
- Women: 1,500,000 deaths
- Children <5 years: 466,000 deaths

Legend:
- Lung cancer
- Ischemic heart disease
- Chronic obstructive pulmonary disease
- Stroke
- Cataracts
- Lower respiratory infections

Smith et al. 2014;35:185-206
Millions Dead: How Do We Know and What Does It Mean? Methods Used in the Comparative Risk Assessment of Household Air Pollution

Kirk R. Smith, Nigel Bruce, Kalpana Balakrishnan, Heather Adair-Izquierdo, Mukesh Dheran, Daniel Pope, E Risk Expert Group

Abstract

In the Comparative Risk Assessment (CRA) done as part of the Global Burden of Disease project (GBD-2010), the global and regional burdens of household air pollution (HAP) due to the use of solid cookfuels, were estimated along with 60+ other risk factors. This article describes how the HAP CRA was framed; how global HAP exposures were modeled; how diseases were judged to have sufficient evidence for inclusion; and how meta-analyses and exposure-response modeling were done to estimate relative risks. We explore relationships with the other air pollution risk factors: ambient air pollution, smoking, and secondhand smoke. We conclude with sensitivity analyses to illustrate some of the major uncertainties and recommendations for future work. We estimate that in 2010 HAP was responsible for 3.9 million premature deaths and ~4.8% of lost healthy life years (DALYs), ranking it highest among environmental risk factors examined and one of the major risk factors of any type globally.
Integrated exposure-response-based outcomes:

- **Solid fuel exposures**
  - **Children:** 285 μg/m³ (95% CI: 201, 405)
  - **Women:** 337 μg/m³ (95% CI: 238, 479)
  - **Men:** 204 μg/m³ (95% CI: 144, 290)

- **Exposure-response**
  - **ALRI** RR: 2.0–3.8
  - **IHD** RR: 1.4–2.2
  - **Stroke** RR: 1.4–2.4
  - **Lung cancer** RR: 1.9–3.4

- **Disease burdens**
  - **ALRI**
    - DALYs: 39,100,000
    - Deaths: 455,000
    - PAF: 52%
  - **IHD**
    - DALYs: 8,600,000
    - Deaths: 391,000
    - PAF: 17%
  - **Stroke**
    - DALYs: 11,100,000
    - Deaths: 546,000
    - PAF: 24%
  - **Lung cancer**
    - DALYs: 2,100,000
    - Deaths: 94,600
    - PAF: 22%

- **Burden from HAP**
  - **Children:** 39,100,000 DALYs, 455,000 deaths
  - **Women:** 21,800,000 DALYs, 1,030,000 deaths
  - **Men:** 33,700,000 DALYs, 1,380,000 deaths
  - **Total:** 94,600,000 DALYs, 2,860,000 deaths

**Inputs**
- India exposure model
- IER models TMRED
- Background disease rates, % solid fuel use
Selecting Counterfactuals

• Principles:
  – Theoretically achievable: “aspirational”
  – Technically achievable: “realistic”
  – Based on regulation: “regulatory”

• GBD for HAP
  – Dichotomous based on epidemiology
  – Based on guidelines (WHO)
  – Aspirational (7 μg/m³ PM$_{2.5}$)
**Regulatory Action**

**Compliance, effectiveness**

**Emissions**

**Atmospheric transport chemical transformation and deposition**

**Human time activity in relation to indoor and outdoor air quality**

**Ambient Air Quality**

**Exposure/Dose**

**Uptake, deposition, clearance, retention**

**Susceptibility factors; mechanisms of damage and repair, health outcomes**

**Human Health Response**

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**Chain of Accountability**
Increasing Exposure vs Decreasing Exposure

\[ \beta^+ \]

\[ \beta^- \]
LESSONS FROM ACTIVE AND PASSIVE SMOKING
Constituents of Tobacco Smoke

- Poison gases
  - Toluene
  - Butane
  - Carbon monoxide

- Cancer causing chemicals
  - Ammonia
  - Vinyl chloride
  - Benzene
  - Formaldehyde

- Toxic metals
  - Arsenic
  - Cadmium
  - Chromium
  - Polonium-210
  - Lead
Some Compounds Found in Smokers’ Blood

- Carbon monoxide
- Benzene
- Nicotine
- Cyanide (thiocyanate)
- Toluene
- Tobacco-specific nitrosamines
- N-hexane
- Ethylbenzene
- Xylenes
- Elevated concentrations of PAH and DNA adducts
Adult per-capita cigarette consumption and major smoking and health events, US, 1900-2012

- 1883: Great Depression begins
- 1917-1918: U.S. entry into WWI
- 1929: Great Depression begins
- 1941-1945: U.S. entry into WWII
- 1964: Surgeon General’s report on smoking and health
- 1965: Broadcast ad ban
- 2010: Federal Cigarette
- 2011: Synar Amendment enacted
- 2012: Nicotine medications available over-the-counter
- 2013: Master Settlement Agreement
- 2014: Family Smoking Prevention and Tobacco Control Act
- 2015: FDA proposed rule
- 2016: Surgeon General’s report on smoke (an update)
How smoking causes disease

- Mainstream smoke
  - Active smoking
    - Tar phase
      - Contained in lung
    - Gas phase
      - Circulated systemically
      - Metabolized in lung and systemically
  - Passive smoking

- Sidestream smoke

Effects:
- Carcinogenesis
- Cardiovascular Effects
- Oxidative Injury
- Proteolytic Changes
- Immune Function / Host Defense Changes

Adapted from the Surgeon General’s report 2010
How smoking causes disease

- Mainstream smoke
  - Active smoking
    - Tar phase
      - Contained in lung
    - Gas phase
      - Circulated systemically
      - Metabolized in lung and systemically
  - Passive smoking

Carcinogenesis

- Cardiovascular Effects
- Oxidative Injury
- Proteolytic Changes
- Immune Function / Host Defense Changes

Adapted from the Surgeon General’s report 2010
Figure 5.1  Link between cigarette smoking and cancer through carcinogens in tobacco smoke
How smoking causes disease

Adapted from the Surgeon General’s report 2010
Figure 8.3  Overview of mechanisms by which cigarette smoking causes an acute cardiovascular event

- Oxidant chemicals
  - Particulates
  - Other combustion products
  - Inflammation

- Carbon monoxide
  - Reduced oxygen availability
  - Sympathetic nervous system activation
  - Increased heart rate
  - Increased blood pressure
  - Increased myocardial contractility

- Nicotine
  - Increased myocardial demand for oxygen and nutrients

- Platelet activation/thrombosis

- Endothelial dysfunction

- Coronary vasoconstriction
  - Reduced myocardial blood, oxygen, and nutrient supply
  - Coronary occlusion

- Myocardial ischemia
  - Myocardial infarction

- Sudden death
How smoking causes disease

Mainstream smoke

含ixed in lung

Circulated systemically

Metabolized in lung and systemically

Sidestream smoke

Active smoking

Passive smoking

Tar phase

Gas phase

Carcinogenesis

Cardiovascular Effects

Proteolytic Changes

Immune Function / Host Defense Changes

Oxidative Injury

Adapted from the Surgeon General’s report 2010
Figure 7.17 Oxidant and antioxidant systems in the lungs

Enzyme antioxidants
Superoxide dismutase
Catalase
Glutathione peroxidase
Ceruloplasmin

Inhaled oxidants
$O_2^{-}, H_2O_2$

Oxidants released from leukocytes
Metal binding proteins
Transferrin
Ferritin
Lactoferrin

Chain-breaking antioxidants
Directly scavenge free radicals
Consumed during scavenging process
Lipid phase
Tocopherols
Ubiquinol
Carotinoids
Flavonoids

Aqueous phase
Ascorbate
Urate
Glutathione and other thiols

Transition metals
$Fe^{2+}, Cu^{+}$

$\cdot OH$

Tissue damage

Note: $Cu^{+}$ = copper ion; $Fe^{2+}$ = iron ion; $H_2O_2$ = hydrogen peroxide; $O_2^{-}$ = superoxide anion; $\cdot OH$ = hydroxyl radical.
How smoking causes disease

Mainstream smoke

Active smoking

Tar phase
- Contained in lung
- Circulated systemically

Gas phase
- Metabolized in lung and systemically

Sidestream smoke

Passive smoking

Carcinogenesis
Cardiovascular Effects
Oxidative Injury

Proteolytic Changes

Immune Function / Host Defense Changes

Adapted from the Surgeon General’s report 2010
Figure 7.18  Pathogenesis of smoking-induced pulmonary emphysema

Cigarette smoke

Activate resident inflammatory cells and structural cells

Injury, necrosis, and apoptosis of structural cells

Cell recruitment (lymphocytes, PMNs, macrophages)

Cleavage

Oxidation

AAT

Expose/degrade extracellular matrix

EMPHYSEMA
How smoking causes disease

- Carcinogenesis
- Cardiovascular Effects
- Oxidative Injury
- Proteolytic Changes

Immune Function / Host Defense Changes

Adapted from the Surgeon General’s report 2010
Figure 10.4 Overview of immune defects caused by smoking in the lungs

Early exposure
Airways

Infection and colonization
- Impaired killing
- Virus
- Bacteria
- Secondary necrosis products

Established and late smoking-associated disease
- Bacteria colonization and biofilm formation
- Dysplastic epithelium
- Carcinoma
- CTL
- Impaired mucosal defences

Inflammatory cell recruitment
- NK cell
- Neutrophil
- Microcirculation

Tissue
- Lung
- DC
- CD8+ T cell
- T<sub>H</sub>17 cell
- T<sub>Reg</sub> cell

Chemical modification
- Degradation
- Extracellular matrix
- Autoimmune loop?
Active Smoking

Cancers
- Oropharynx
- Larynx
- Esophagus
- Trachea, bronchus, and lung
- Acute myeloid leukemia
- Stomach
- Liver

Chronic Diseases
- Stroke
- Blindness, cataracts, age-related macular degeneration
- Congenital defects—maternal smoking: orofacial clefts
- Periodontitis
- Aortic aneurysm, early abdominal aortic atherosclerosis in young adults
- Coronary heart disease
- Pneumonia
- Atherosclerotic peripheral vascular disease
- Chronic obstructive pulmonary disease, tuberculosis, asthma, and other respiratory effects
- Diabetes
- Reproductive effects in women (including reduced fertility)
- Hip fractures
- Ectopic pregnancy
- Male sexual function—erectile dysfunction
- Rheumatoid arthritis
- Immune function
  - Overall diminished health

Source: USDHHS 2014
Passive Smoking

**Children**
- Middle ear disease
- Respiratory symptoms, impaired lung function
- Lower respiratory illness
- Sudden infant death syndrome

**Adults**
- Stroke
- Nasal irritation
- Lung cancer
- Coronary heart disease
- Reproductive effects in women: low birth weight

Source: USDHHS 2014
Adult per-capita cigarette consumption and major smoking and health events, US, 1900-2012

- U.S. entry into WWI
- Great Depression begins
- U.S. entry into WWII
- Confluence of evidence linking smoking and illness
- Reassurance campaign begins
- Nonsmokers' rights movement begins
- Broadcast ad ban
- 1964 Surgeon General's report on smoking and health
- Federal cigarette tax doubles
- Federal $1.01 tax increase
- Master Settlement Agreement
- Family Smoking Prevention and Tobacco Control Act
- Nicotine medications available over-the-counter
- Synar Amendment enacted
- 1986 Surgeon General's report on secondhand smoke
- Cigarette price drop
- FDA proposed rule
- 2006 Surgeon General's report on secondhand smoke (an update)
Benefits of Cessation

**Stroke** risk is reduced to that of a person who never smoked after 5 to 10 years of not smoking

**Cancers of the mouth, throat, and esophagus** risks are halved 5 years after quitting

**Cancer of the larynx** risk is reduced after quitting

**Coronary heart disease** risk is cut by half 1 year after quitting and is nearly the same as someone who never smoked 15 years after quitting

**COPD** risk of death is reduced after you quit

**Lung cancer** risk drops by as much as half 10 years after quitting

**Ulcer** risk drops after quitting

**Bladder cancer** risk is halved a few years after quitting

**Peripheral artery disease** goes down after quitting

**Cervical cancer** risk is reduced a few years after quitting

**Low birth weight baby** risk drops to normal if you quit before pregnancy or during your first trimester.
Smoking and the Lung

- Increased rates of chronic respiratory symptoms.
- Diminished host defenses and increased risk for pneumonia and influenza.
- Accelerated decline of lung function.
- Greatly increased risk for COPD (underlying airways changes and emphysema)
The 1990 Surgeon General’s Report: Health Benefits of Smoking Cessation

FIGURE 4.—Symptom ratio (number of observed symptoms to number of possible symptoms) in nonmodifiers, modifiers, and quitters at each test period: symptoms are cough, sputum production, wheezing, and shortness of breath.

SOURCE: Barn et al. (1976).
FIGURE 24.—Risks for men with varying susceptibility to cigarette smoke and consequences of smoking cessation

NOTE: + = death
FIGURE 25.—Distribution of 8-year FEV₁ slope in 792 London men

SOURCE: Fletcher et al. (1978).
FIGURE 11.—Mean $\Delta FEV_1$ values in never smokers (NN), consistent ex-smokers (XX), subjects who quit smoking during follow-up (SQ), and consistent smokers (SS) in several age groups.

NOTE: Numbers of subjects in each category are shown in parentheses. $FEV_1$ = 1-sec forced expiratory volume.

SOURCE: Camilli et al. (1987)
Chapter 7 Conclusions: Nonmalignant Respiratory Diseases

1. Smoking cessation reduces rates of respiratory symptoms such as cough, sputum production, and wheezing, and respiratory infections such as bronchitis and pneumonia, compared with continued smoking.

2. For persons without overt chronic obstructive pulmonary disease (COPD). Smoking cessation improves pulmonary function about 5 percent within a few months after cessation.

3. Cigarette smoking accelerates the age-related decline in lung function that occurs among never smokers. With sustained abstinence from smoking, the rate of decline in pulmonary function among former smokers returns to that of never smokers.

4. With sustained abstinence, the COPD mortality rates among former smokers decline in comparison with continuing smokers.
Smoking and CVD

• Multiple mechanisms
  – Inflammation
  – Endothelial cell functioning
  – Increased clotting
  – Atherosclerosis
  – Sympathetic nervous system

• Immediate and long-term changes in risk in active smokers

• Immediate effects of SHS exposure and benefits of ending exposure
The 1990 Surgeon General’s Report: Health Benefits of Smoking Cessation

FIGURE 2.—Estimated relative risk of MI after quitting smoking among men under age 55, adjusted for age; 95% CIs are indicated by vertical line; relative risk for men who never smoked is 1.0
The 1990 Surgeon General’s Report: Health Benefits of Smoking Cessation

FIGURE 6.—Effect of smoking cessation on survival among men with documented coronary atherosclerosis; pooled survival among quitters (○) (N=1,490) and continuers (△) (N=2,675)
Chapter 6 Conclusions: Cardiovascular Disease

1. Compared with continued smoking, smoking cessation substantially reduces risk of coronary heart disease (CHD) among men and women of all ages.
2. The excess risk of CHD caused by smoking is reduced by about half after 1 year of smoking abstinence and then declines gradually. After 15 years of abstinence, the risk of CHD is similar to that of persons who have never smoked.
3. Among persons with diagnosed CHD, smoking cessation markedly reduces the risk of recurrent infarction and cardiovascular death. In many studies, this reduction in risk of recurrence or premature death has been 50 percent or more.
4. Smoking cessation substantially reduces the risk of peripheral artery occlusive disease compared with continued smoking.
5. Among patients with peripheral artery disease, smoking cessation improves exercise tolerance, reduces the risk of amputation after peripheral artery surgery, and increases overall survival.
6. Smoking cessation reduces the risk of both ischemic stroke and subarachnoid hemorrhage compared with continued smoking. After smoking cessation, the risk of stroke returns to the level of never smokers; in some studies this has occurred within 5 years, but in others as long as 15 years of abstinence were required.
Smokefree bans and coronary events: Pooled RR = 0.85 (95% CI, 0.82–0.88)
The 2014 Surgeon General’s Report

Causal Conclusions on Impact of Smokefree Laws on Acute Cardiovascular Events

1. The evidence is sufficient to infer a causal relationship between the implementation of a smokefree law or policy and a reduction in coronary events among people younger than 65 years of age.

2. The evidence is suggestive but not sufficient to infer a causal relationship between the implementation of a smokefree law or policy and a reduction in cerebro-vascular events.

3. The evidence is suggestive but not sufficient to infer a causal relationship between the implementation of a smokefree law or policy and a reduction in other heart disease outcomes, including angina and out-of-hospital sudden coronary death.
Changes in health risks from time since quitting

- ↓ CO levels
- ↓ Lung inflammation
- Reversal of clotting effects
- ↓ Respiratory symptom
- ↓ CVD risk
- ↑ Lung function
- ↓ Cancer risk
- ↓ Lung function loss
- ↓ CVD risk

Time since quitting

Days  Months  Years
Longitudinal Relation between Smoking and White Blood Cells

Jordi Sunyer,1,2 Alvaro Muñoz,1 Yun Peng,1 Joseph Margolick,1 Joan S. Chmiel,3 John Oishi,4 Lawrence Kingsley,5 and Jonathan M. Samet1

Higher white blood cell counts in smokers compared with nonsmokers have been well documented, but the longitudinal relation between changes in smoking and changes in white blood cells has not been well described. Since 1984, data have been collected semiannually by the Multicenter AIDS Cohort Study (MACS), a four-center prospective cohort study of acquired immunodeficiency syndrome (AIDS) in homosexual men. The study population includes 2,435 participants who were human immunodeficiency virus (HIV) seronegative as of September 1994 and who contributed 20,918 person-visits for this analysis. For individuals who modified their smoking behavior, changes in white blood cell counts occurred primarily during the first 6 months following changes in the amount of cigarettes smoked. Among former smokers who resumed smoking, the extent of the increase in white blood cell count depended on the number of cigarettes smoked. Specifically, increases of 241, 340, and 740 cells/µliter were observed for smokers who resumed smoking <1, 1 to <2, and ≥2 packs/day, respectively. Conversely, smokers who quit smoking had a decrease of white blood cell count: −32, −629, and −1,122 cells/µliter for men who previously smoked <1, 1 to <2, and ≥2 packs/day, respectively. Long-term ex-smokers, however, still had higher white blood cell counts than did never smokers. There was a high within-individual correlation of white blood cell count in persons who reported a consistent level of smoking (i.e., average correlations between two white blood cell counts 6 years apart were 0.51 for never smokers, 0.48 for ex-smokers, 0.56 for men who smoked <1 pack/day, and 0.43 for men who smoked ≥1 pack/day). These analyses indicate an acute effect of changes in smoking on changes in white blood cell count, a residual effect of having been a smoker, and high long-term tracking for white blood cell count. Am J Epidemiol 1996 144:734–41.

leukocytes; longitudinal studies; smoking
RESEARCH AND EVALUATION IMPLICATIONS
What research questions?

• Biomarker changes over time;
• Advancing mechanistic understanding;
• Further evidence for hazard identification;
• Refining exposure-response relationships;
• Accountability—degree of burden reduction.
Lessons Learned

• Temporal dynamics critical—tobacco cessation provides some insights.
• Biomarkers can be useful—tobacco story provides mechanistic insights.
• Long-term tracking of consequences needed.
• Removal of powerful risk factors should have measurable consequences.
ENOUGH IS ENOUGH!!!

Click for clip of press conference:
http://youtu.be/yr_HID2lUUU?t=31m38s
BIGGEST LESSON: ACTION CAN BE TAKEN WHILE KNOWLEDGE IS IMPERFECT