Air pollution as a preventable cause of adverse birth outcomes

Perspectives from the field in India

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Ubiquitous exposure environments
Comparative Risk Assessment (GBD 2016) for India

Dandona et al 2017
Air Pollution attributable DALY rates across states in India

India SLBI Report 2017
## Trends in attributable burdens (1990-2016)

<table>
<thead>
<tr>
<th></th>
<th>Leading causes 1990</th>
<th>Leading causes 2016</th>
<th>Mean % change number of DALYs 1990-2016</th>
<th>Mean % change DALY rate 1990-2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malnutrition [35.5%]</td>
<td>1 Malnutrition [14.6%]</td>
<td>-64.3%</td>
<td>-76.6%</td>
<td></td>
</tr>
<tr>
<td>WaSH* [12.8%]</td>
<td>2 Air pollution [9.8%]</td>
<td>-23.6%</td>
<td>-49.9%</td>
<td></td>
</tr>
<tr>
<td>Air pollution [11.1%]</td>
<td>3 Dietary risks [8.9%]</td>
<td>70.8%</td>
<td>12.1%</td>
<td></td>
</tr>
<tr>
<td>Dietary risks [4.5%]</td>
<td>4 High blood pressure [8.5%]</td>
<td>89.3%</td>
<td>24.2%</td>
<td></td>
</tr>
<tr>
<td>Tobacco use [4.4%]</td>
<td>5 High fasting plasma glucose [6.0%]</td>
<td>127.9%</td>
<td>49.6%</td>
<td></td>
</tr>
<tr>
<td>High blood pressure [3.9%]</td>
<td>6 Tobacco use [5.9%]</td>
<td>14.7%</td>
<td>-24.7%</td>
<td></td>
</tr>
<tr>
<td>High fasting plasma glucose [2.3%]</td>
<td>7 WaSH* [4.6%]</td>
<td>-69.0%</td>
<td>-79.6%</td>
<td></td>
</tr>
<tr>
<td>Occupational risks [2.0%]</td>
<td>8 High total cholesterol [4.1%]</td>
<td>106.2%</td>
<td>35.3%</td>
<td></td>
</tr>
<tr>
<td>High total cholesterol [1.7%]</td>
<td>9 High body mass index [3.6%]</td>
<td>281.6%</td>
<td>150.5%</td>
<td></td>
</tr>
<tr>
<td>Alcohol &amp; drug use [1.7%]</td>
<td>10 Alcohol &amp; drug use [3.6%]</td>
<td>80.6%</td>
<td>18.5%</td>
<td></td>
</tr>
<tr>
<td>Impaired kidney function [1.4%]</td>
<td>11 Occupational risks [3.0%]</td>
<td>32.4%</td>
<td>-13.1%</td>
<td></td>
</tr>
<tr>
<td>High body mass index [0.8%]</td>
<td>12 Impaired kidney function [2.8%]</td>
<td>76.4%</td>
<td>15.8%</td>
<td></td>
</tr>
<tr>
<td>Other environmental [0.5%]</td>
<td>13 Unsafe sex [1.1%]</td>
<td>214.4%</td>
<td>106.4%</td>
<td></td>
</tr>
<tr>
<td>Low physical activity [0.4%]</td>
<td>14 Other environmental [1.0%]</td>
<td>63.4%</td>
<td>7.2%</td>
<td></td>
</tr>
<tr>
<td>Unsafe sex [0.3%]</td>
<td>15 Low physical activity [0.9%]</td>
<td>109.6%</td>
<td>37.6%</td>
<td></td>
</tr>
<tr>
<td>Low bone mineral density [0.2%]</td>
<td>16 Low bone mineral density [0.6%]</td>
<td>127.4%</td>
<td>49.3%</td>
<td></td>
</tr>
<tr>
<td>Sexual abuse &amp; violence [0.2%]</td>
<td>17 Sexual abuse &amp; violence [0.3%]</td>
<td>48.0%</td>
<td>-2.9%</td>
<td></td>
</tr>
</tbody>
</table>

The percent figure in bracket next to each risk factor is DALYs attributable to that risk factor out of the total DALYs.

*WaSH is unsafe water, sanitation, and handwashing.
Air Pollution in Indian Cities

WHO (2011)

Cities in Top 100 with the worst air quality

27

WHO (2014)

Cities in Top 100 with the worst air quality

37

Source: Guttikunda et al., Atmospheric Environment, 2014
Ambient Air Pollution Exposures

Ghosh, Balakrishnan et al 2014

Brauer et al 2016

Population weighted PM$_{2.5}$ Exposures
Household Air Pollution Exposures in India

PM$_{2.5}$ Estimates in solid fuel using households in India (also used as the basis for global exposures in the Global Burden of Disease 2010 estimate)

HH Concentrations
- Kitchen: $450\mu g/m^3$ (95% CI: 318,640)
- Living: $113\mu g/m^3$ (95% CI: 102,127)

Exposures
- Children: $285\mu g/m^3$ (95% CI: 201,405)
- Women: $337\mu g/m^3$ (95% CI: 238,479)
- Men: $204\mu g/m^3$ (95% CI: 144,290)

For reference:
WHO AQG 10 $\mu g/m^3$ annual average (no public microenvironment should be more than 35 $\mu g/m^3$)
National Standards: USA(12 $\mu g/m^3$); China(35 $\mu g/m^3$) India (40 $\mu g/m^3$);
Diseases for which we have epidemiological studies:

- ALRI/Pneumonia
- COPD
- Lung cancer (coal)
- Lung cancer (biomass)
- Cataracts
- Ischemic heart disease
- Stroke

Diseases included in the GBD Assessments:

- Ischemic heart disease
- Stroke

Courtesy: Dr. Kirk R Smith
PICs- The common enemy

Smoking, ETS, HAP, AAP

- Small particles PM 2.5, CO, NO$_2$
- Hydrocarbons
  - 25+ saturated hydrocarbons such as $n$-hexane
  - 40+ unsaturated hydrocarbons such as 1,3 butadiene
  - 28+ mono-aromatics such as benzene & styrene
  - 20+ polycyclic aromatics such as benzo($\alpha$)pyrene
- Oxygenated organics
  - 20+ aldehydes including formaldehyde & acrolein
  - 25+ alcohols and acids such as methanol
  - 33+ phenols such as catechol & cresol
  - Many quinones such as hydroquinone
  - Semi-quinone-type and other radicals
- Chlorinated organics such as methylene chloride and dioxin

Typical chulha releases 400 cigarettes per hour worth of smoke
Illustration of an Integrated Exposure-Response: Outdoor Air, SHS, and Smoking and Heart Disease
PM$_{2.5}$ Integrated Exposure Response Functions

Burnett et al. 2014; Forouzanfar et al. 2015; Cohen et al. 2017

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Percent Risk Factor Attributions (India Case Study)

A. Male IHD: 17,100,000 DALYs

B. Female IHD: 9,090,000 DALYs

C. Child ALRI: 17,100,000 DALYs

Smith-Bruce, Balakrishnan et al. 2014
Why Study Air Pollution and Pregnancy?

- Developing organism is uniquely sensitive to environmental toxins within a short time window

- Adverse outcomes are common; in India:
  - ~10% are preterm
  - ~27% are low birth weight (amongst the highest in the world)

- Immediate and long term health effects
  - Infant morbidity and mortality
  - Child Cognitive Function
  - Adverse effects on adult health?
Existing Epidemiologic Studies

- Most completed in last 10 years (<50 published studies)
  - China, U.S., Brazil, Czech Republic, Canada, S. Korea, Taiwan, Lithuania, Croatia, Sweden, Mexico

- Recent SRs/MA
  - Glinianaia et al. 2003, Epidemiology, 15:36-45
  - Vrijheid et al 2011, EHP, 119:598–606
  - Li et al 2011, Am.J.Epid. Vol. 174, No. 4
  - Amegah et al 2014, PLOS One
Outcome Events Studied

- Deaths
  - Intrauterine (28 weeks of gestation to birth)
  - Neonatal (<28 days)
  - Infant (<1 year)

- Low birth weight (LBW)
  - Weight at birth <2500g
  - Born LBW at term vs. preterm
  - Reduction in mean weight
  - Small for gestational age (SGA; <10th percentile of weight for gestational age)

- Preterm births (<37 weeks of gestation) or
  - Reduction of mean gestational age

- Congenital abnormalities (cardiac anomalies and orofacial clefts)
Biological Plausibility

Figure 1. Proposed biologic framework for exploring possible effect modification of PM–birth outcomes by maternal nutrition.
Rationale for a Rural-Urban Cohort

- Exposures are seamless across rural-urban boundaries
- Virtually no experience with environmental health cohorts in India
- AP and birth-weight the least well explored in terms of E-R relationships
- Impacts on birth outcomes would have tremendous implications in India (NFHS 2010 estimate of low birth weight prevalence at 24.5%)
- E-R relationships for chronic adult outcomes need to be informed by developing country studies
- Opportunity to link with secondary datasets through newly introduced (Pregnancy and Infant Cohort Monitoring and Evaluation System – PICME in Tamil Nadu), The National maternal and child cohort tracking system (MCTS) and IDSP

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The TAPHE Cohort Study in Southern India

ADULT COHORT

Respiratory symptoms

PFT

EXPOSURE ASSESSMENT

EXPOSURE MODELING

Bio-repository + SNPs

Birth Weight

ARI

MOTHER-CHILD COHORT

INDOOR

Primarily Rural & HH fuel use related

OUTDOOR

Primarily Urban & Fossil fuel use related

Balakrishnan et al 2015, Balakrishnan et al 2018
Recruitment of Participants (N=1285)
Directed acyclic graph for variable selection in multivariate models
# Health and Exposure Data Collection

<table>
<thead>
<tr>
<th>Activity</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number active in cohort</td>
<td>1285</td>
</tr>
<tr>
<td><strong>Health</strong></td>
<td></td>
</tr>
<tr>
<td>Antenatal records</td>
<td>1066</td>
</tr>
<tr>
<td>Sonogram data</td>
<td>1057</td>
</tr>
<tr>
<td>Birth outcome assessment including birth weight</td>
<td>1242</td>
</tr>
<tr>
<td><strong>Exposure</strong></td>
<td></td>
</tr>
<tr>
<td>24-hr Micro-environmental (kitchen, living and near outdoor) PM 2.5 measurements across trimesters</td>
<td>1121</td>
</tr>
<tr>
<td>24-hr personal exposure measurements</td>
<td>65</td>
</tr>
</tbody>
</table>

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Distribution of PM$_{2.5}$ Exposures and Birthweight in the TAPHE cohort

- Prevalence of LBW (%)
  - Rural: 16.8
  - Urban: 15.2

- Birth Weight (kg)
  - Rural: N 602, Mean 2.81, Median 2.75, SD 0.46
  - Urban: N 519, Mean 2.88, Median 2.83, SD 0.47

- Pre-natal PM$_{2.5}$ exposure
  - Rural:
    - N 508, Mean 104.76, Median 69.11, IQR 69.62, Min 2, Max 800
  - Urban:
    - N 421, Mean 69.35, Median 83.09, IQR 40, Min 2, Max 797.5

- % below WHO Guideline
  - Rural: 1.4, Urban: 1.2
  - Annual Guideline: 1.4, Annual ITG: 17.7, 27.1
Results from multi-variate modeling in the TAPHE Cohort

<table>
<thead>
<tr>
<th></th>
<th>Change in birth weight (gm) per 10 μg/m^3 change in PM2.5 concentration</th>
<th>OR (for Low birth weight) per 10 μg/m^3 change in PM2.5 concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>All births</td>
<td>-3.922 (−6.761, −1.083)</td>
<td>1.0232 (1.0054, 1.0413)</td>
</tr>
<tr>
<td>Male births</td>
<td>-3.141 (−7.14, 0.858)</td>
<td>1.0212 (0.9947, 1.0484)</td>
</tr>
<tr>
<td>Female births</td>
<td>-4.709 (−8.724, −0.695)</td>
<td>1.0248 (1.0009, 1.0493)</td>
</tr>
<tr>
<td>Term Births</td>
<td>-3.252 (−6.113, −0.392)</td>
<td>1.0223 (1.0042, 1.0407)</td>
</tr>
<tr>
<td>Pre-term Births</td>
<td>-28.211 (−45.274, −11.148)</td>
<td>3.8595 (0.8321, 17.9018)</td>
</tr>
</tbody>
</table>

In the fully adjusted multivariate models, a 10-μg/m^3 increase in pregnancy period PM2.5 exposures was associated with a 4 g (95% CI: 1.08 g, 6.76 g) decrease in birthweight and 2% increase in prevalence of low birthweight [odds ratio (OR) = 1.02; 95% CI: 1.005, 1.041] after adjusting for gestational age, infant sex, maternal BMI, maternal age, history of previous low birth weight child, birth order and season of conception. Stratified analyses for term vs. pre-term births estimated 3.2 g (95% CI: 0.39 g, 6.1 g) decrease for term births and a 28.2 g (95% CI: 11.1 g, 45.2 g) decrease for preterm births, per 10-μg/m^3 increase in pregnancy period PM_{2.5} exposures.
Study Strengths

- Provides some of the first quantitative exposure-response functions centered on more proximal (household) measures of exposure for birthweight
- Provides some of the first integrated rural urban E-R estimates
- Large emphasis on reducing exposure misclassification and confounding
- Uses well validated study instruments/protocols while developing a parsimonious and yet reliable framework of data collection
Comparisons to previous studies: HAP and Birthweight/Low Birthweight

Exposure to HAP associated with 86 g (95%CI: 55.0, 117) reduction in birthweight and a 35% increased odds of low birthweight (OR: 1.35, 95%CI: 1.15, 1.5) (Amegah et al 2014)

Results from the TAPHE cohort estimate a 72 gm change associated with biomass use when compared to LPG (Balakrishnan et al 2018)
Comparisons to previous studies: AAP and Birth weight /Low birthweight

Exposure to AAP associated with 15.9 g (95%CI: 5.0, 26.8) reduction in birthweight and a 9% increased odds of low birthweight (OR: 1.09, 95%CI: 1.03, 1.15)
IER in the making for birthweight?

- Outdoor air pollution studies done in developed countries find about a 16 gram decline.
- Pregnant women living with a smoker have about 30-40 gram smaller babies.
- Household air pollution studies from low income countries find a 86 gm decline (new results from TAPHE study in Tamil Nadu estimates a 72 gm decline).
- Pregnant women who smoke themselves have babies that are over 200 grams lighter.
Follow Up Potential: HAP and Other adverse birth outcomes

- Cookfire smoke additionally associated with:
  - Still Birth
    - OR: 1.29 (95%CI: 1.18, 1.41)
  - Preterm birth (3 studies):
    - OR: 1.30 (95%CI: 1.06, 1.59)
  - Intrauterine growth retardation (IUGR) (2 studies):
    - OR: 1.23 (95%CI: 1.01, 1.49)
  - Neural tube defect (1 study):
    - OR: 1.9 (95%CI: 1.4, 2.6)
  - Miscarriage (2 studies):
    - OR: 1.65 (95%CI: 0.74, 3.67)
  - Moderate stunting (2 studies):
    - OR: 1.27 (95%CI: 1.12, 1.43)
  - Severe stunting (2 studies):
    - OR: 1.55 (95%CI: 1.04, 2.30)

(Amegah, *PLOS One*, 2014); Bruce, *BMC Pub Health*, 2013)
Follow Up Potential: AAP and congenital abnormalities

Vrijheid et al  EHP 2011
Continued evidence from smoking literature (Smoking and Birth Defects)

Hackshaw et al
Hum Reprod Update (2011) 17 (5): 589-604
Conclusions

- Adverse pregnancy outcomes are likely to account for a major proportion of attributable disease burden for air pollution globally and in India.
- The ubiquity of air pollution exposures and high prevalence of adverse pregnancy outcomes in India argue for a concerted effort to examine these linkages more thoroughly.
- Augmentation of surveillance registries for birth outcomes can provide fertile grounds to integrate newer methods of exposure reconstruction (including use of high resolution satellite data).

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Conclusions

- Several natural experiments including the massive LPG expansion programs and introduction of metros can provide fertile grounds for testing the role of air pollution as a risk factor for adverse pregnancy outcomes.

- Adverse pregnancy impacts may represent charismatic outcomes that can add momentum to air quality actions within poor communities.

- Finally, inter-disciplinary engagement can catalyze capacity building for addressing multiple public health issues surrounding maternal and child health.
Team EHE at SRU, Chennai, India

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