Developmental Impacts of Heavy Metals and Undernutrition on Children’s Intellectual Function:
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Recent Lancet Series

- Linked compromised development with modifiable biological and psychosocial risks encountered by children < 5 years old
Walker et al. (2007) identified

- Four urgent risks
  - Stunting
  - Inadequate cognitive stimulation
  - Iodine deficiency
  - Iron deficiency anemia

- Five factors clearly warranting intervention
  - Heavy metals
  - Malaria
  - Intrauterine growth retardation
  - Maternal depression
  - Exposure to violence

- Impact of exposure to co-occurring risks rarely studied in developing nations
Columbia group’s studies of developmental consequences of metals exposure

- Lead exposure via mining and smelter operation
  - Kosovo 1986-2004
  - Longitudinal, from pregnancy through age 12

- Arsenic and manganese exposure via well water
  - Araihazar, Bangladesh 2004 to present
  - Cross-sectional cohorts at ages 6 and 10 years

- Consider here new analyses of joint impact of undernutrition and exposure
Undernutrition

- In developing countries, a third of young children experience stunting (156 million!)
  - 2 SDs or more below height-for-age standards
  - Reflects chronic undernutrition and disease rather than genetics
- Patterns of early growth similar across countries
  - Problems begin before or soon after birth
  - Pronounced in first 1.5 years
  - If not ameliorated by \( \approx 40 \) months, persists to adulthood: no NEW incident cases after early childhood
Stunting consistently associated with poorer intellectual and school functioning

- Poorer school progress or cognitive development in studies in 17 developing nations
- In six national studies, stunting predicts future poorer school or cognitive function

Providing food supplements in randomized trials benefits growth and development
Developmental consequences of metals exposure: Lead

- Worldwide prevalence of elevated exposure 40% globally, higher in developing countries

  - In Kosovo, with adjustment for social confounders, modest deficits in intellectual, motor, visual-motor and behavioral development appeared 2-12 years

  - Similar results in recent pooled analysis of 7 prospective studies around the world (N=1333)
Performance on the McCarthy Scales of Children's Abilities as Related to Lead Exposure in Infancy (BPb AUC 0–24 months)

Adjusted MSOC Subscale Score

- Perceptual Performance
- Verbal
- Quantitative
- Memory
- Motor
- GCI

Adjusted GCI

p < .0001 .0290 .0003 .0012 .0154 < .0001
Performance on the WISC-R as Related to Prenatal Lead Exposure (BPb AUC_{Mid-pregnancy-Birth})

Adjusted WISC-R Score

- 2.50-5.65 μg/dl
- 5.65-12.35 μg/dl
- 12.35-21.49 μg/dl
- 21.49-42.23 μg/dl

Verbal IQ: p = .0695
Performance IQ: p = .0118
Full Scale IQ: p = .0106
Developmental consequences: arsenic

- In Bangladesh, 30-40 million people have been exposed to high concentrations of arsenic (As) from tube wells
- Known carcinogenic and vascular effects

- Clinical and industrial reports with adults documents cognitive impairments
  - Learning, memory, concentration
  - Peripheral and central neuropathy

- Before ours, few studies, with minimal control for social and demographic features, on developmental toxicity
  - Urinary As associated with children’s lower verbal intelligence in Mexico (Calderon et al., 2001)
  - Adolescents from regions of Taiwan without exposure did better in some aspects of intelligence than those from exposed regions (Tsai et al 2003)
Developmental consequences: manganese

- Adult occupational exposure linked with neuromotor consequences (Parkinsonism)
- In preschool children in Paris with high exposures, poorer functioning in attention, non-verbal memory and hand skill (Takser et al 2003)
- Among 11-13 year olds from Chinese region with high exposure (sewage) lower scores in memory, manual dexterity and visuo-motor processing (Peng, 1994)
Health Effects of Arsenic Longitudinal Study (HEALS)
The Columbia Araihzar cohort

- Beginning in 2000, we enrolled 11,749 adults living in a 25km² region of Bangladesh.
- Families have been and interviewed regularly since then, and have received care at our field clinic.
- Eighty percent of wells in our study region exceed WHO standard of 500 µg/L for Mn.
Tubewell Locations for Maternal and Children Studies
Children and families receive medical care and assessments at our field clinic.
Children are also exposed to arsenic prenatally, through maternal exposure. The graph shows a strong correlation between maternal blood arsenic (µg/L) and umbilical cord blood arsenic (µg/L), with a Pearson correlation coefficient (r) of 0.93 and a regression coefficient (b) of 0.94.
Well-standardized tests of intellectual function not normed for children in non-Western cultures

- Normed tests allow us to compare the number of items the child passes to large age-specified samples, to generate an “IQ”

- Cultural adaptations needed for test materials, beyond translation
  - Particular problems with “Verbal” items, since words have different subsidiary meanings in different languages
IQ tests are standardized to generate scores with mean of 100 and sd of 15.

- Because no currently used test of child IQ has been standardized for Bangladesh, we adapted WPPSI-III, WISC-III
  - Eliminated some subscales
  - Eliminated or substituted some items

- Instead of examining Full Scale, Performance, and Verbal IQ as primary measures, we created Raw item scales, totalling Performance, Verbal, and all items
## Test Items Eliminated/Substituted from WPPSI-III

<table>
<thead>
<tr>
<th>Sub Test</th>
<th>Actual item</th>
<th>Eliminated/Substituted item</th>
</tr>
</thead>
<tbody>
<tr>
<td>Picture Completion</td>
<td>Telephone</td>
<td>Eliminated</td>
</tr>
<tr>
<td></td>
<td>Bathtub</td>
<td>Eliminated</td>
</tr>
<tr>
<td>Similarities</td>
<td>Apple and Banana</td>
<td>Mango and Banana</td>
</tr>
<tr>
<td></td>
<td>Piano and Guitar</td>
<td>Flute and Drum</td>
</tr>
<tr>
<td></td>
<td>Cat and Mouse</td>
<td>Dog and Cow</td>
</tr>
<tr>
<td></td>
<td>Tire and Ball</td>
<td>Wheel and Ball</td>
</tr>
</tbody>
</table>
Many factors that undermine children’s intellectual function are also more common in more disadvantaged families

- More advantaged families live further from sources of pollution
- More intelligent parents restrict children’s exposure
  - To accurately understand the risk of exposure, we must measure and adjust for such socio-demographic confounders

Diagram:
- Parent IQ
- Parent Education
- Family resources
- Exposure
- Children’s Intelligence
From our cohort’s 12,000 adult participants, we selected 3 age- and exposure-groups of children.

- **Study I:** Arsenic: random sample of 201 10 year olds (2002)
- **Study II:** Manganese: 54 from Study I with well water As < 10 µg/L, plus 88 randomly sampled, newly recruited 10-year-olds with well water As < 10 µg/dL (2002 and 2004)
- **Study III:** Arsenic: random sample of 301 6-year-olds (2004)
Measuring exposure

- Water samples via graphite furnace atomic absorption or mass spectrometry (ICP-MS)
- Urine samples via GFAA
- All samples analyzed at Columbia University’s Lamont Doherty Earth Observatory
In 3 overlapping groups of children, social characteristics were similar.

<table>
<thead>
<tr>
<th>Measure</th>
<th>As age 10</th>
<th>Mn age 10</th>
<th>As age 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>201</td>
<td>141</td>
<td>301</td>
</tr>
<tr>
<td>Male (%)</td>
<td>48.8</td>
<td>50.3</td>
<td>49.8</td>
</tr>
<tr>
<td>Father Ed</td>
<td>3.7 yr</td>
<td>3.9 yr</td>
<td>3.7 yr</td>
</tr>
<tr>
<td>Mother Ed</td>
<td>2.9 yr</td>
<td>3.1 yr</td>
<td>3.3 yr</td>
</tr>
<tr>
<td>Father Laborer/Farmer</td>
<td>23.5%</td>
<td>34.5%</td>
<td>18.3%</td>
</tr>
<tr>
<td>Father Factory</td>
<td>33.3%</td>
<td>34.5%</td>
<td>35.6%</td>
</tr>
<tr>
<td>House thatched roof or poorer</td>
<td>10.0%</td>
<td>13.5%</td>
<td>13.6%</td>
</tr>
<tr>
<td>House corrugated tin</td>
<td>74.1%</td>
<td>71.6%</td>
<td>78.1%</td>
</tr>
<tr>
<td>Maternal Raven</td>
<td>14.4</td>
<td>14.1</td>
<td>14.2</td>
</tr>
</tbody>
</table>
Exposure characteristics in 3 samples

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<th>Mn age 10</th>
<th>As age 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>201</td>
<td>142</td>
<td>301</td>
</tr>
<tr>
<td>Water As</td>
<td>117.8 µg/L</td>
<td>3 µg/L</td>
<td>120.1 µg/L</td>
</tr>
<tr>
<td>Water Mn</td>
<td>1386 µg/L</td>
<td>795 µg/L</td>
<td>1302 µg/L</td>
</tr>
<tr>
<td>Urinary As</td>
<td>116.6 µg/L</td>
<td>57.5 µg/L</td>
<td>110.7 µg/L</td>
</tr>
</tbody>
</table>

§ By design
WHO allowable standard for As/Mn in drinking water: 10.0 and 500 µg/L
* Varies with As levels
Study 1: As results at age 10 years

- After adjusting for maternal education and intelligence, quality of house construction (as a marker for socio-economic status: concrete, tin, thatched roof), child height and head circumference and TV access (as a marker of stimulation)
- Well-water arsenic was significantly associated with poorer Performance and Full Scale measures of intellectual function
  - Water As explained 4.33 and 3.88% of the variance in Performance and Full Scale scores
Dose-Response Relationship Between Water Arsenic Concentrations and Intellectual Function in 10-yr-olds (adjusted)
Study 2: Mn results at age 10 years

- Well-water Mn was negatively associated with children’s Verbal, Performance and Full Scale scores, even after adjustment for maternal education and intelligence, house type, TV access, height and head circumference, and water As.

- Water Mn explained 6.3%, 6.9% and 2.3% of the variances in Full Scale, Performance and Verbal scores.
Adjusted dose response relationship by well water Mn

![Bar chart showing raw scores by water Mn group for different types of intellectual function. The x-axis represents the type of intellectual function (Full Scale, Performance, Verbal), and the y-axis represents scores for full scale and performance tests. Different Mn concentration groups are indicated by various colors: < 200 µg/L (black), 200-499 µg/L (blue), 500-999 µg/L (white), and ≥ 1000 µg/L (gray).]
Study 3: As results at age 6 years

- Well-water As was negatively associated with children’s Performance and Processing Speed scores, even after adjustment for maternal education and intelligence, child school attendance, height and head circumference, water Mn and childrearing qualities of the home.

- Water As explained only approximately 1% of the variance in Performance and Processing Speed scores.

- In contrast, social factors explained 30%-40% of the respective variances.

- Associations for Full Scale scores were marginally significant after adjustment.
Re-analysis considers consequences of stunting in 10yr olds

- WHO Growth norms only through age 5
- Define children in Studies 1 and 2 as stunted if they were 2 SD or more below the CDC gender-specific height for age norms
  - Study 1: 45 children (22%)
  - Study 2: 48 children (34%)
- Replace terms for head circumference and height with one for stunting
- Consider metal-by-stunting interaction
Including stunting in models

- Stunting contributed unique variance
- Did not alter contributions of other variables
  - In each case where we had earlier found a metals effect, we retained that effect (slight reduction in significant for Manganese/Verbal score association)
- No significant metal-by-stunting interactions
  - Stunting by As interaction negative for all intelligence measures, suggesting stronger impact in stunted children, that might be significant with larger N
- Similar findings for lead and 4-year intelligence
## Study 1*

<table>
<thead>
<tr>
<th></th>
<th>Full Scale B</th>
<th>Performance B</th>
<th>Verbal B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well water As (Log)</td>
<td>-1.79***</td>
<td>-1.57***</td>
<td>-0.22</td>
</tr>
<tr>
<td>Stunting</td>
<td>-7.79*</td>
<td>-6.67*</td>
<td>-1.12</td>
</tr>
</tbody>
</table>

* Adjusted for Maternal education and intelligence, House type and TV access
## Study 2*

<table>
<thead>
<tr>
<th></th>
<th>Full Scale B</th>
<th>Performance B</th>
<th>Verbal B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well water Mn (Log)</td>
<td>-4.26**</td>
<td>-3.70***</td>
<td>-0.60\text{m}</td>
</tr>
<tr>
<td>Stunting</td>
<td>-16.20***</td>
<td>-13.72***</td>
<td>-2.36*</td>
</tr>
</tbody>
</table>

* Adjusted for Maternal education and intelligence, House type and TV access
Gaps in studying environmental exposures in developing countries

- Risks may operate differently in children in more marginalized environments
- Though metals may be well-studied
  - PCBs: psychomotor deficits, but not examined in developing countries
  - Pesticides not systematically examined
  - Methyl mercury: known developmental toxicity but not well-studied in developing countries (single? study)
New directions
Even before providing new wells, our mitigation program resulted in a 25% reduction in UAs in 2 years

- Identifying exposure characteristics and labelling wells (red and green)
- Psychoeducational program for participating villages
- Digging of 50 safer deep water wells
- Training for elementary school teachers (upcoming)
Distribution of Creatinine-adjusted Urinary Total Arsenic Concentration at Baseline and 2-Year Followup

**Baseline**
- N=10,546
- Mean = 143.6 ug/g
- Mean = 400.1 ug/g
  - SD=132.1
  - SD=373.4

**2-Year Follow Up**
- N=10,546
- Mean = 136.4 ug/g
- Mean = 289.0 ug/g
  - SD=101.3
  - SD=262.4
Planned study of consequences of well mitigation

- We have new resources to conduct well mitigation in an area adjacent to our previous study site, providing safe water to an additional 150,000 residents.
- Beginning in summer 2007 we will assess 7-9 yr-old children in 25 villages.
- 4 groups of children using wells high and low in arsenic and manganese.
- Assessments before, and at 12- and 24- months after, well mitigation.
- Measure intellectual function and motor skills.