Developmental Impacts of Heavy Metals and Undernutrition on Children's Intellectual Function:

International Conference on Fetal Programming and Developmental Toxicity
Torshavn, Faroe Islands
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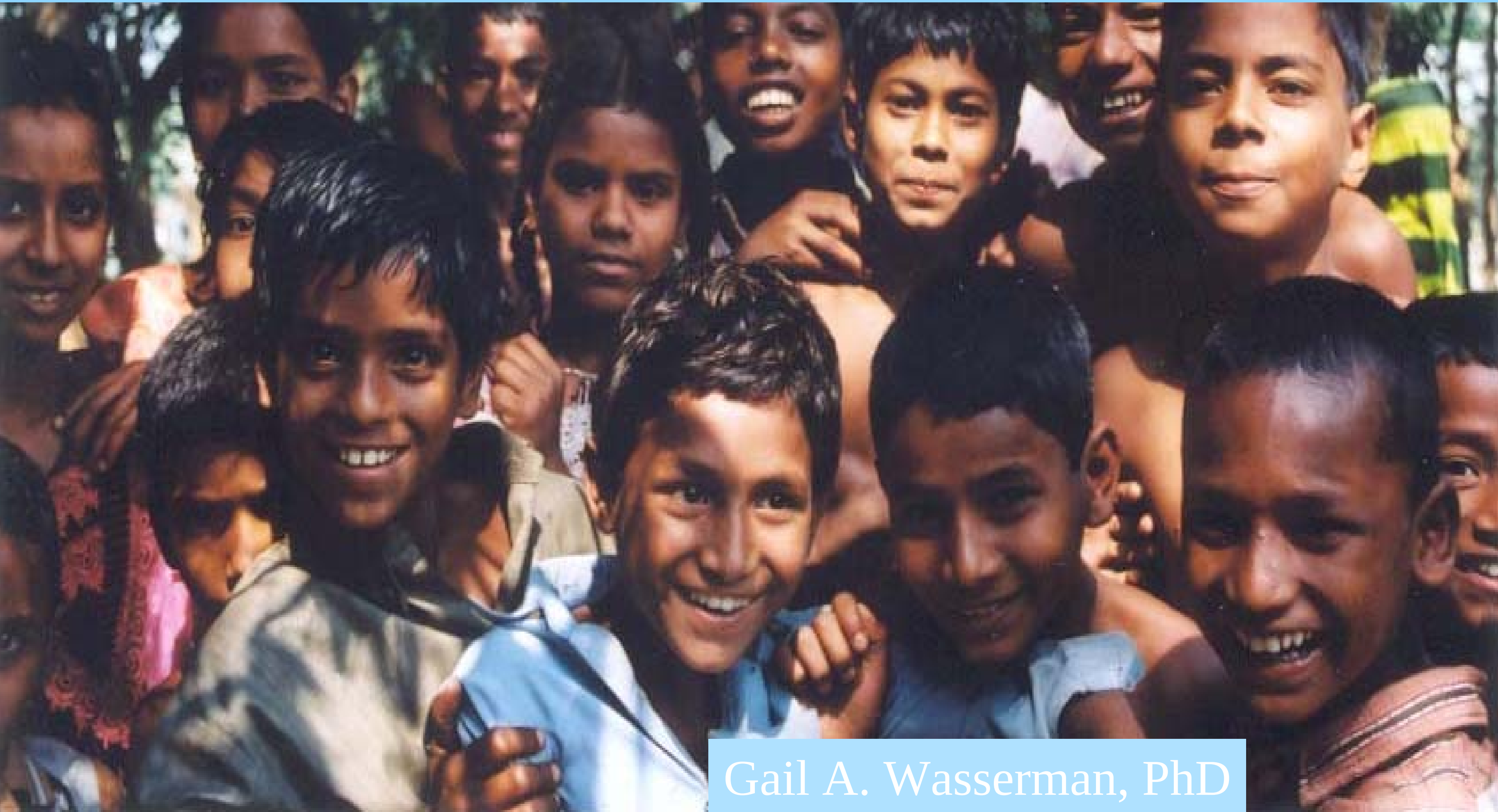

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Recent Lancet Series

- Linked compromised development with modifiable biological and psychosocial risks encountered by children < 5 years old
  - Grantham-McGregor, S., et al. (2007). Child development in developing countries 1: Developmental potential in the first 5 years for children in developing countries. Lancet, 369, 60-70.
  - Walker, S.P., et al. (2007). Child development in developing countries 2: Risk factors for adverse outcomes in developing countries. Lancet, 369, 145-157.
  - Engle, P.L., et al. (2007). Child development in developing countries 3: Strategies to avoid the loss of developmental potential in more than 200 million children in the developing world. Lancet, 369, 229-242.

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

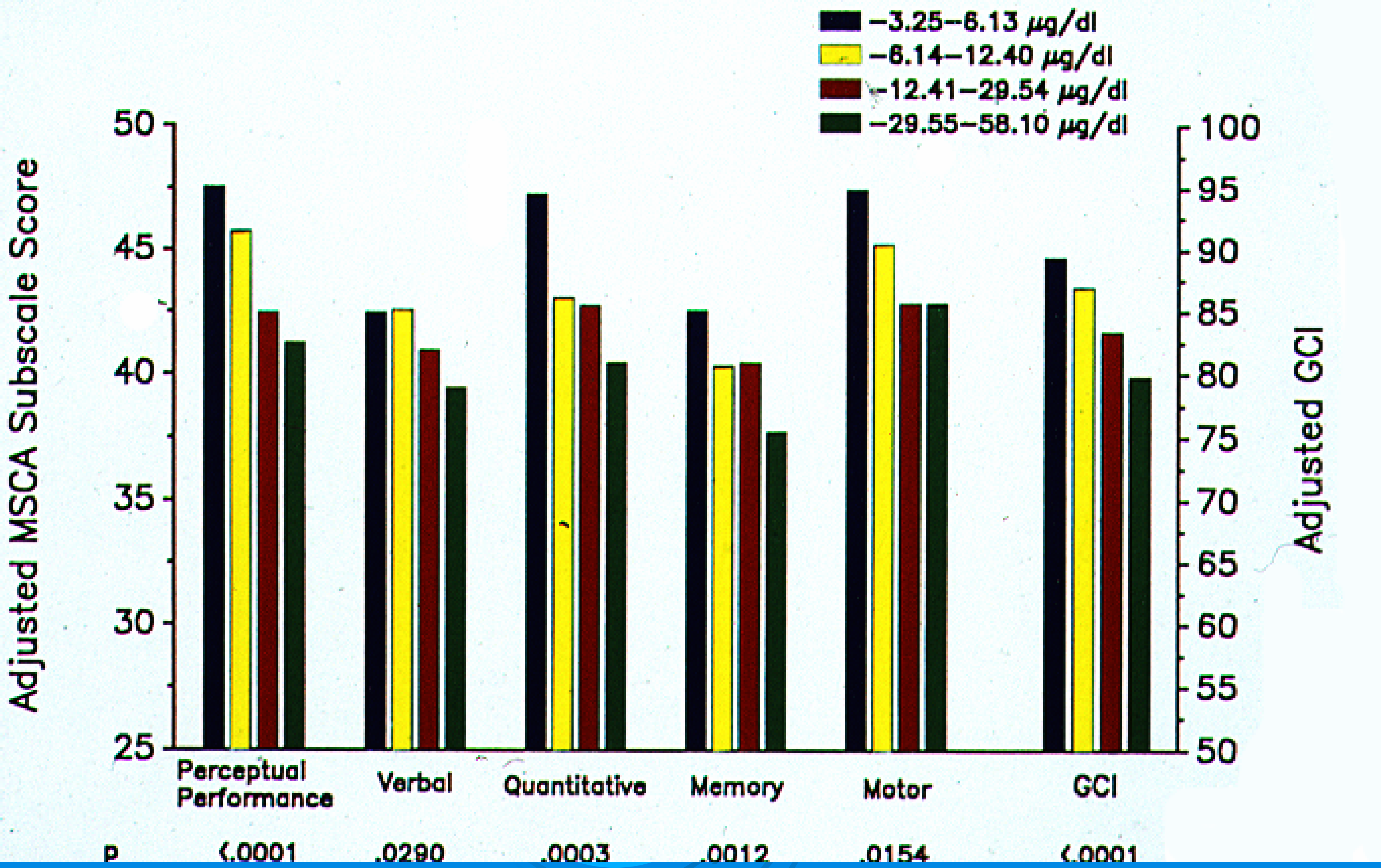
- In developing countries, a third of young children experience stunting (156 million!)
  - 2 SDs or more below height-for-age standards
  - Reflects chronic undernutrition and disease rather than genetics
- Patterns of early growth similar across countries
  - Problems begin before or soon after birth
  - Pronounced in first 1.5 years
  - If not ameliorated by $\cong$ 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

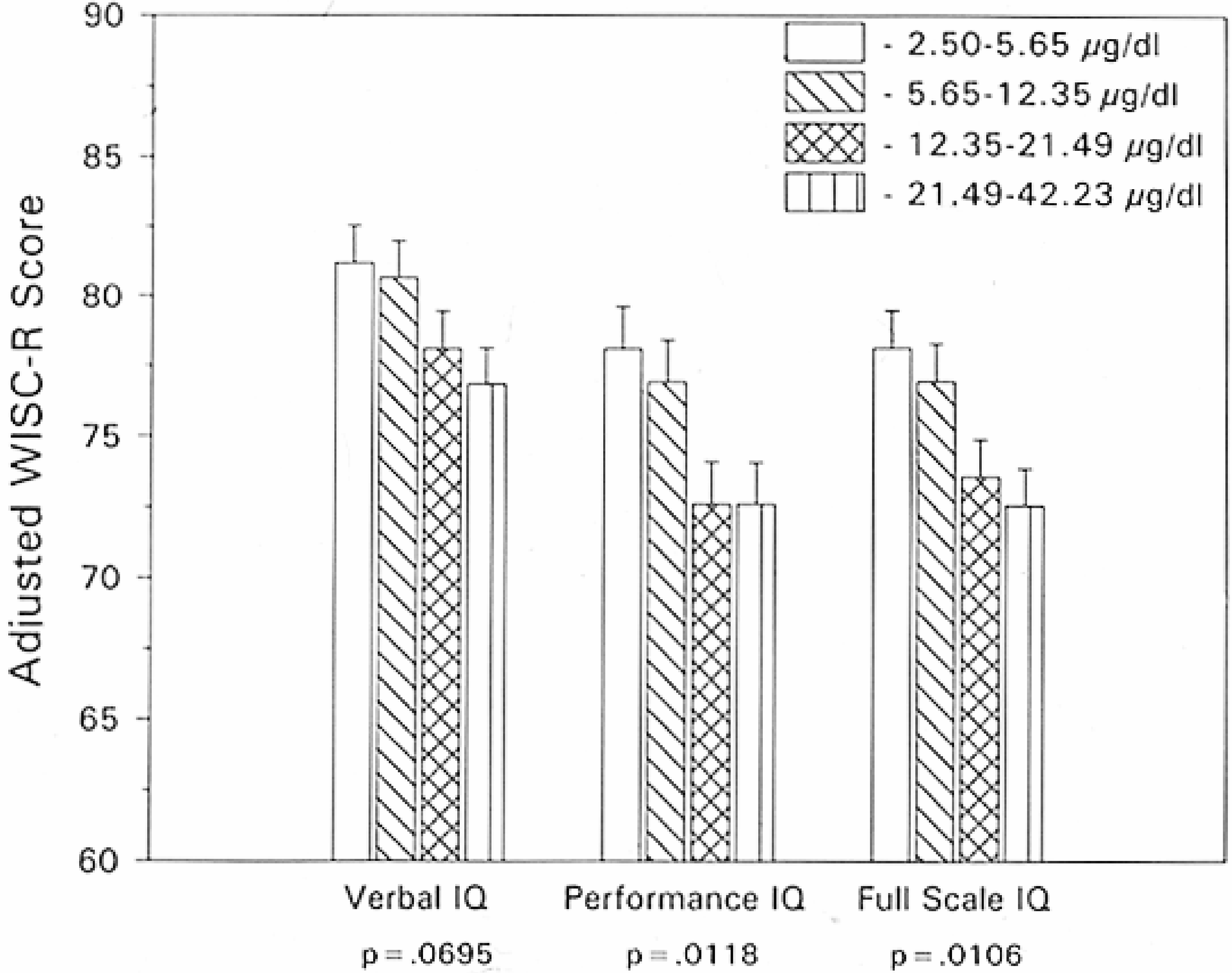
Developmental consequences of metals exposure: Lead

- 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 $_{0-24\ months}$)



Performance on the WISC-R as Related to Prenatal Lead Exposure (BPb $AUC_{Mid\text{-}pregnancy\text{-}Birth}$)



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

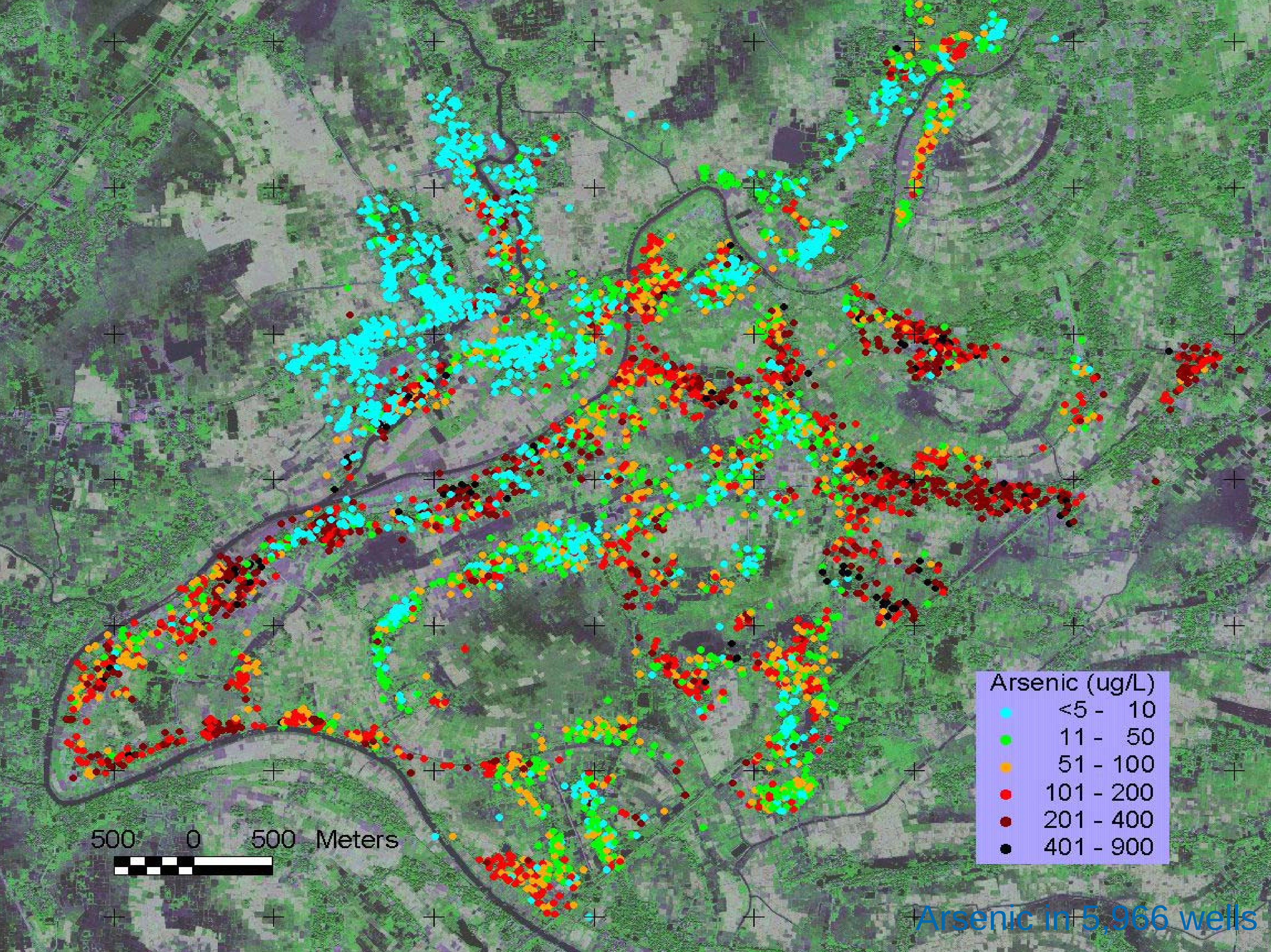
- Before ours, few studies, with minimal control for social and demographic features, on developmental toxicity
  - Urinary As associated with children's lower verbal intelligence in Mexico (Calderon et al., 2001)
  - Adolescents from regions of Taiwan without exposure did better in some aspects of intelligence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

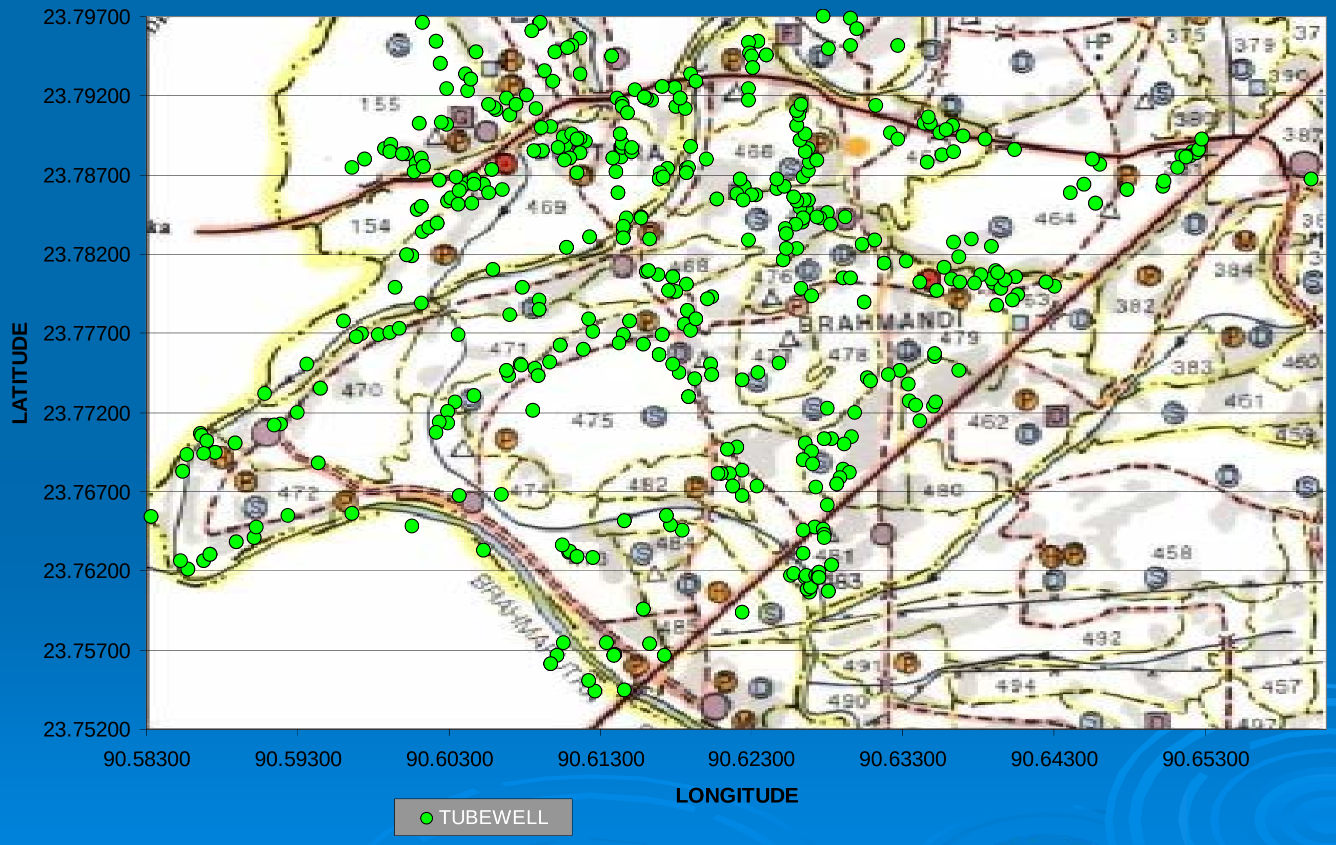
Health Effects of Arsenic Longitudinal Study (HEALS) The Columbia Araihzar cohort

- Beginning in 2000, we enrolled 11,749 adults living in a 25km^2 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



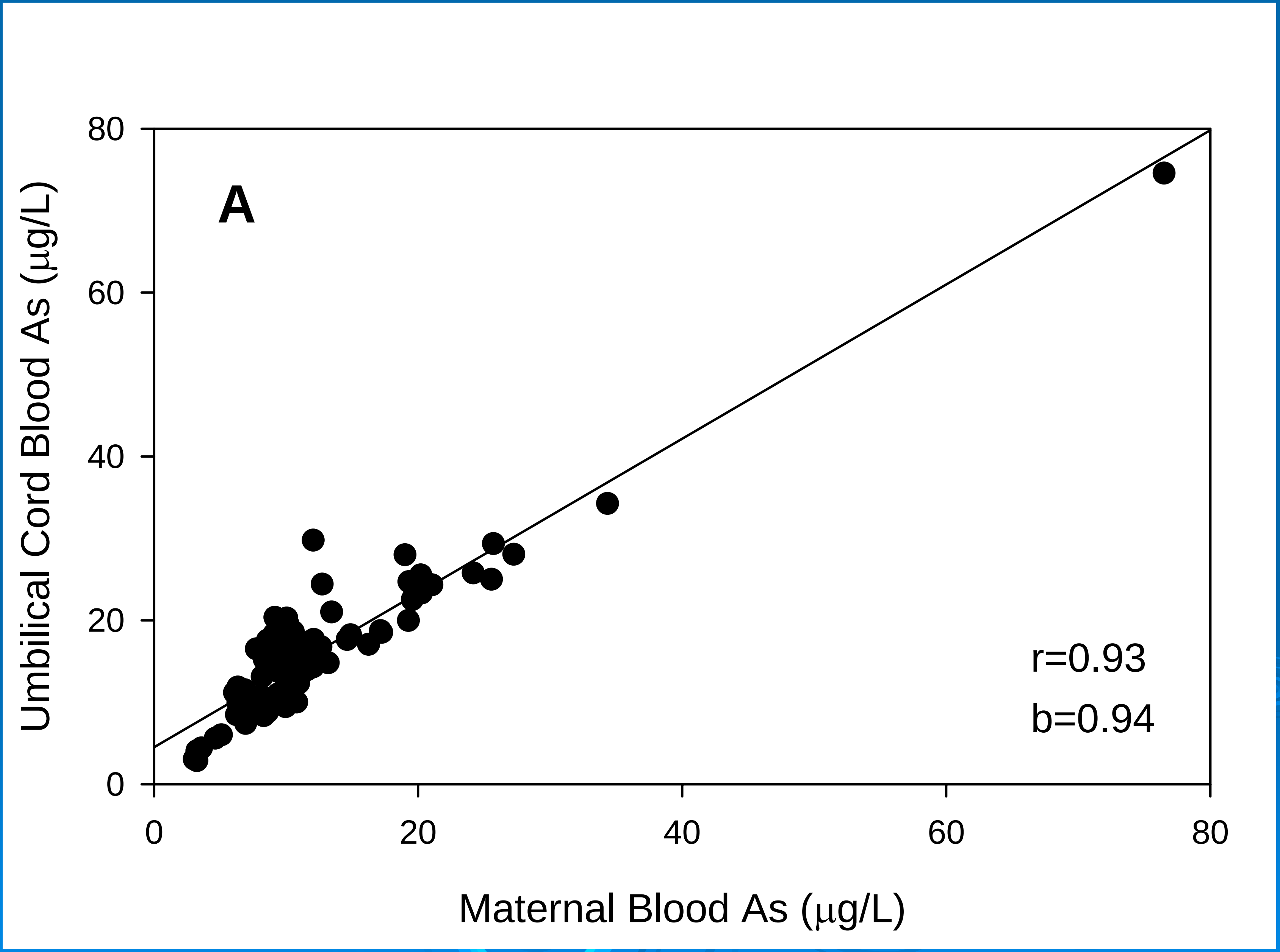
Arsenic in 5,966 wells

Tubw Well 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



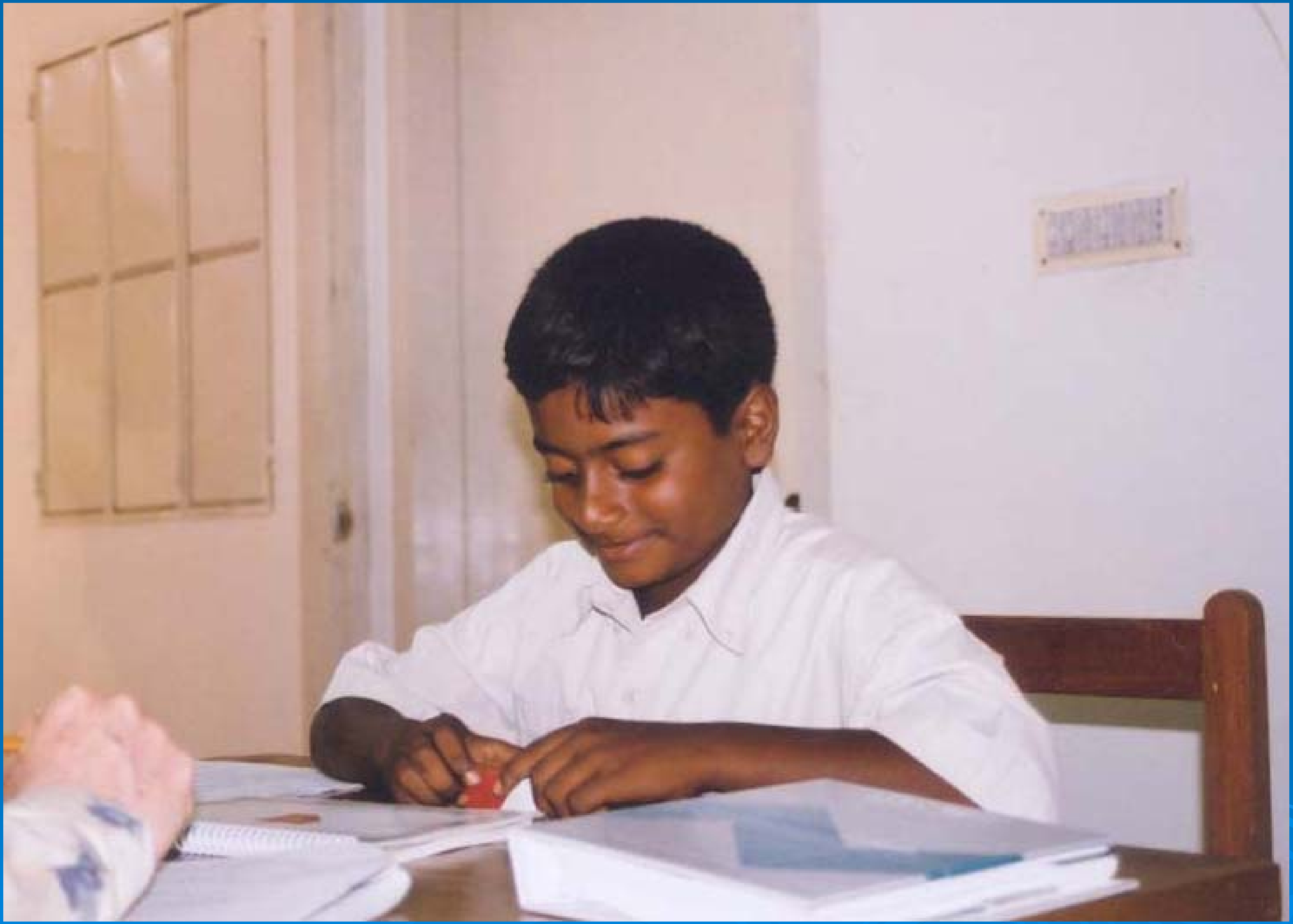
Well-standardized tests of intellectual function not normed for children in non-Western cultures

- 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

Sub Test	Actual item	Eliminated/Substituted item
Picture Completion		
	Telephone	Eliminated
	Bathtub	Eliminated
Similarities		
	Apple and Banana	Mango and Banana
	Piano and Guitar	Flute and Drum
	Cat and Mouse	Dog and Cow
	Tire and Ball	Wheel and Ball

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

From our cohort's12,000 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 μ g/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

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

Exposure characteristics in 3 samples

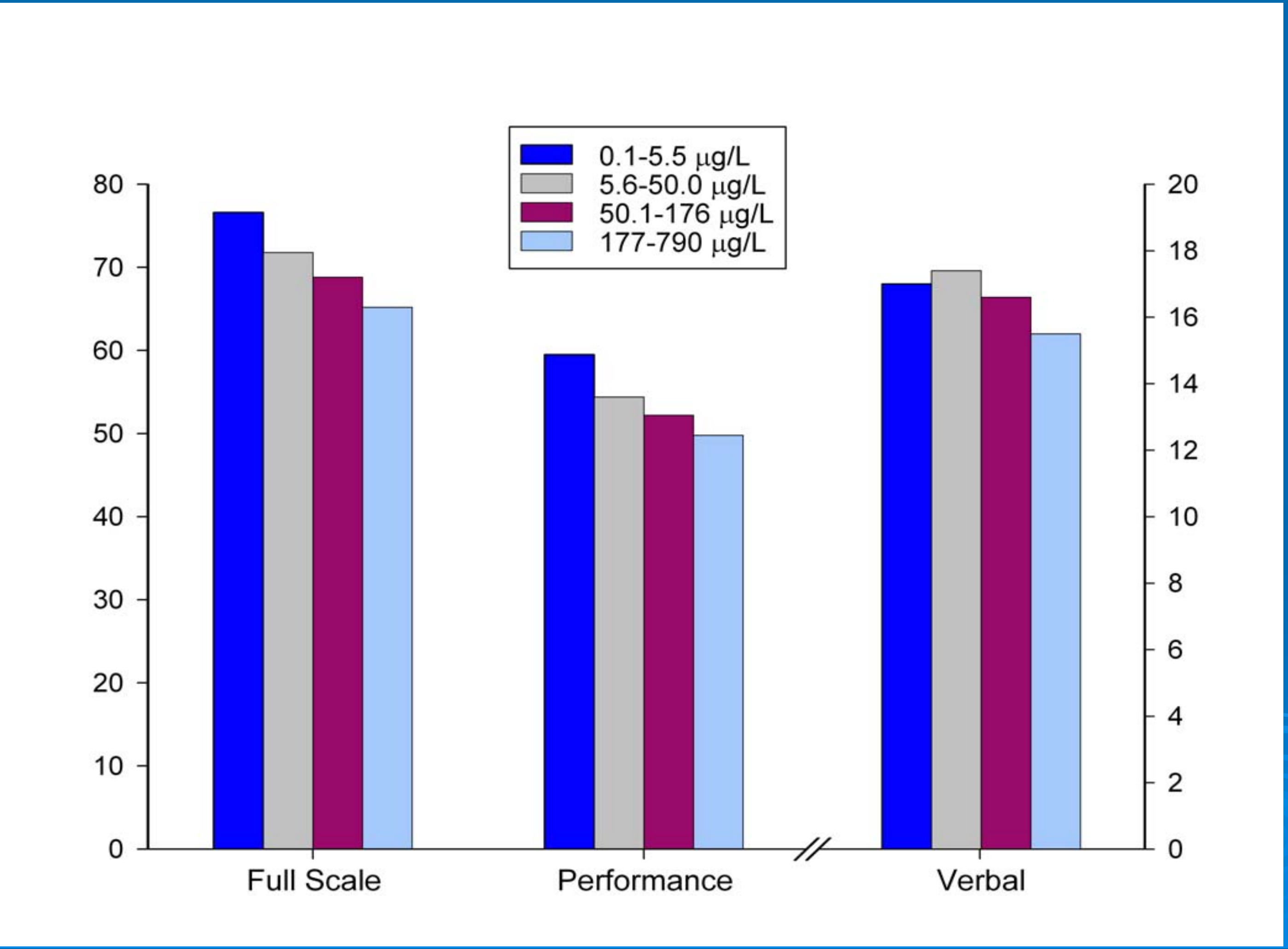
Measure	As age 10	Mn age 10	As age 6
N	201	142	301
Water As ⌘	117.8 μg/L	3 μg/L§	120.1 μg/L
Water Mn⌘	1386 μg/L	795 μg/L✷	1302 μg/L
Urinary As	116.6 μg/L	57.5 μg/L	110.7 μg/L

§ 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

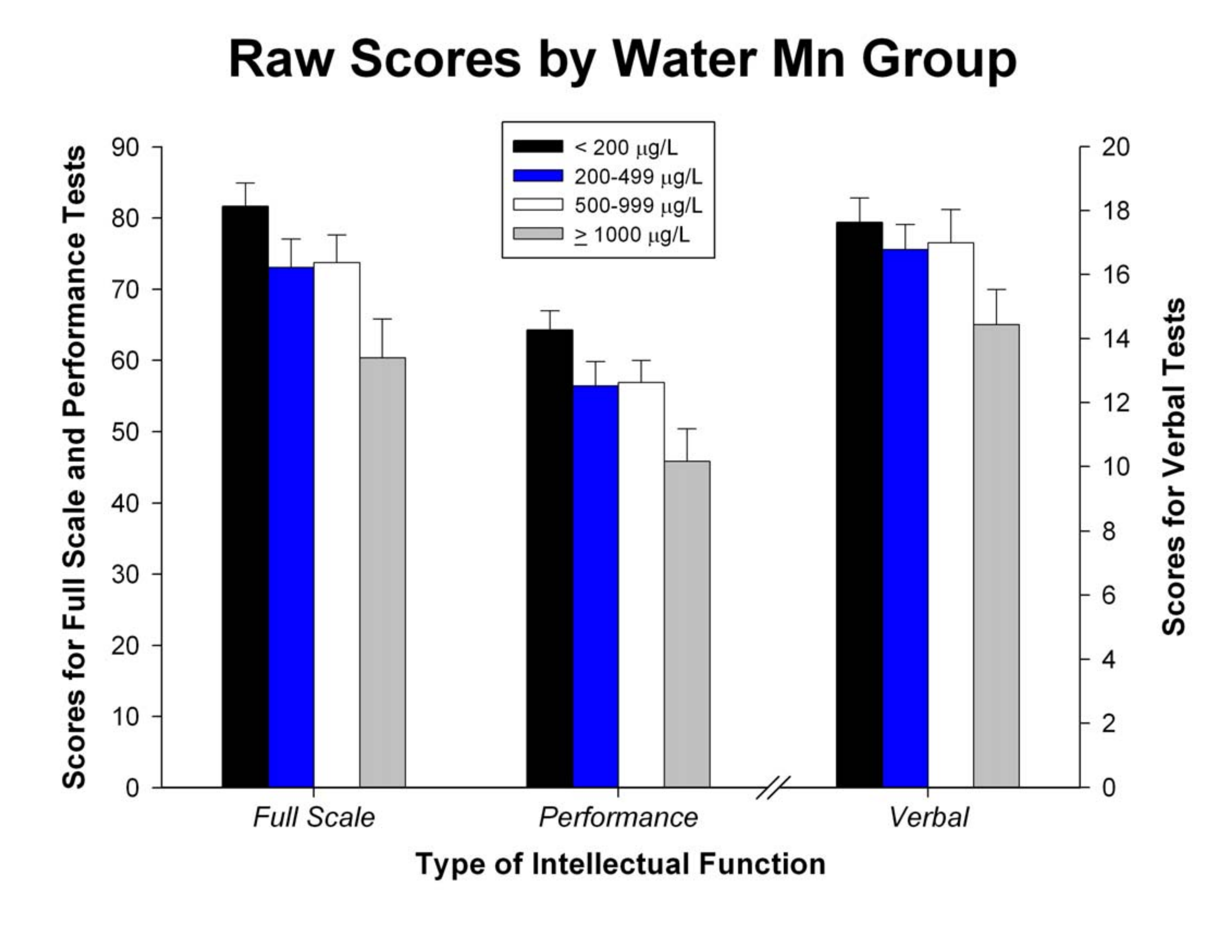
Dose-Response Relationship Between Water Arsenic Concentrations and Intellectual Function in 10-yr-olds (adjusted)



Study 2: Mn results at age10 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 acess, 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



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*

	Full Scale B	Performance B	Verbal B
Well water As (Log)	-1.79***	-1.57***	-0.22
Stunting	-7.79*	-6.67*	-1.12

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

Study 2*

	Full Scale B	Performance B	Verbal B
Well water Mn (Log)	-4.26**	-3.70***	-0.60^{m}
Stunting	-16.20***	-13.72***	-2.36*

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

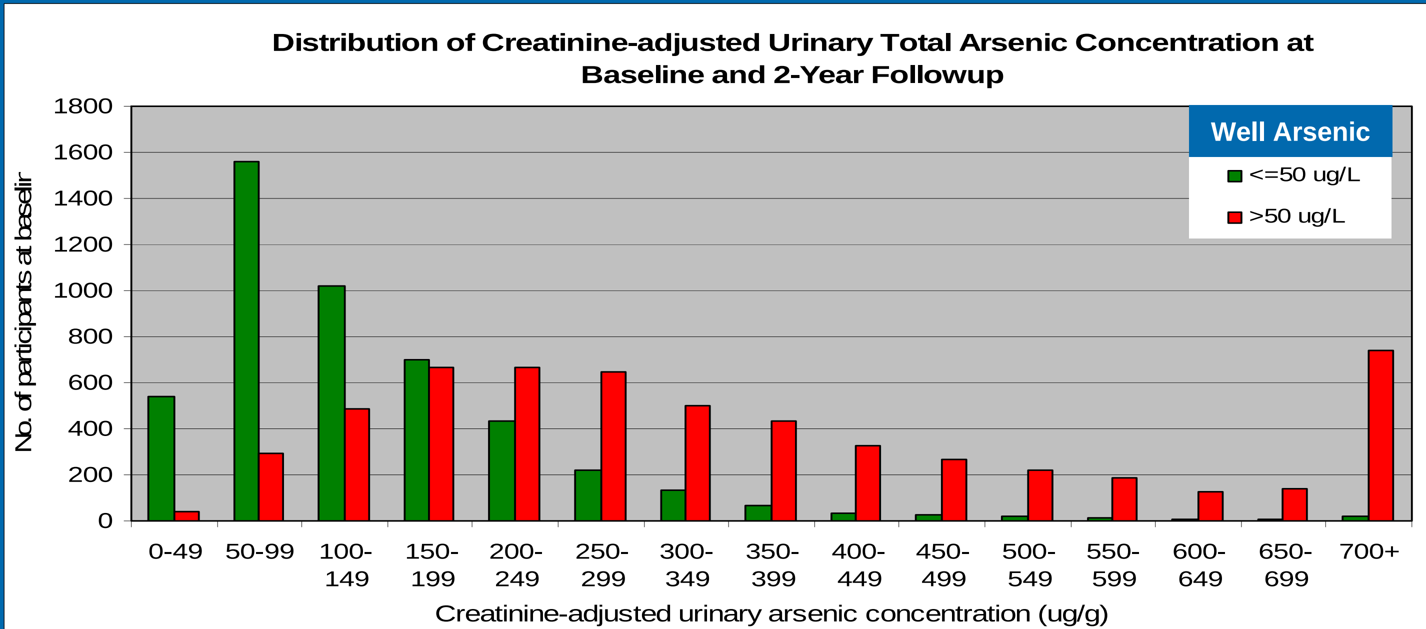
Gaps in studying environmental exposures in developing countries

- 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)

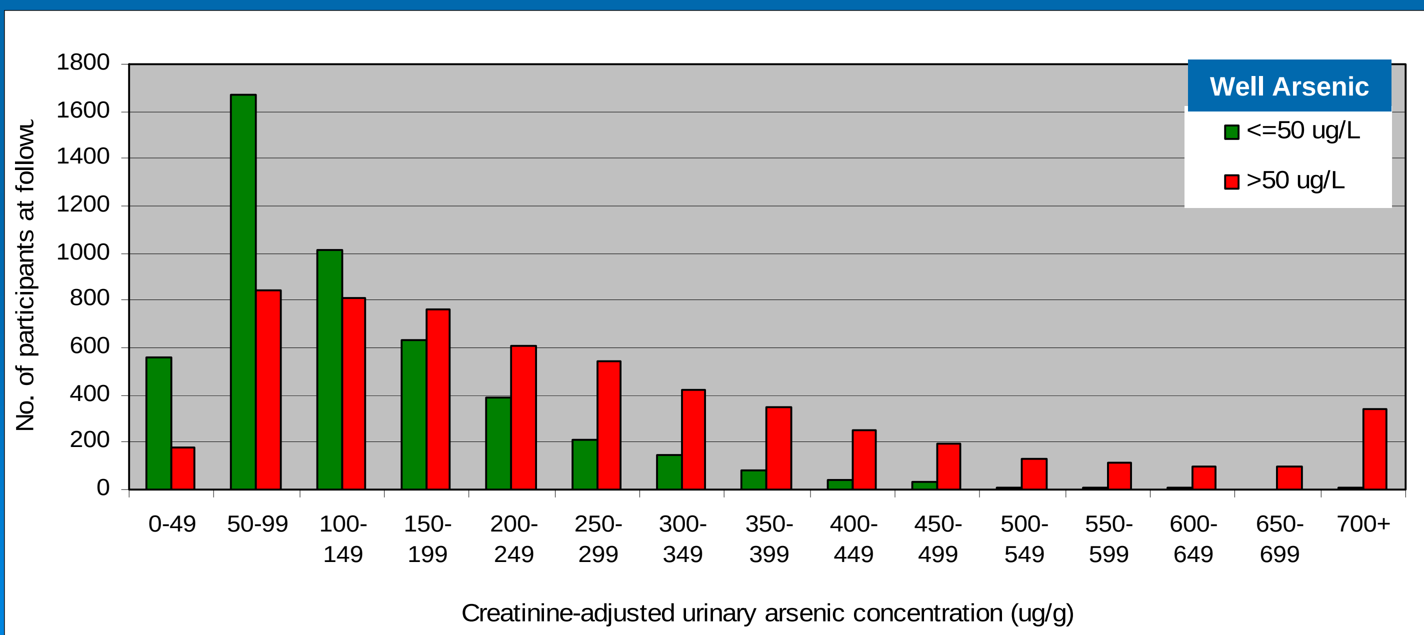


Baseline

N=10,546

Mean = 143.6 ug/g
SD=132.1

Mean = 400.1 ug/g
SD=373.4



2-Year Follow Up

N=10,546

Mean = 136.4 ug/g
SD=101.3

Mean = 289.0 ug/g
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