

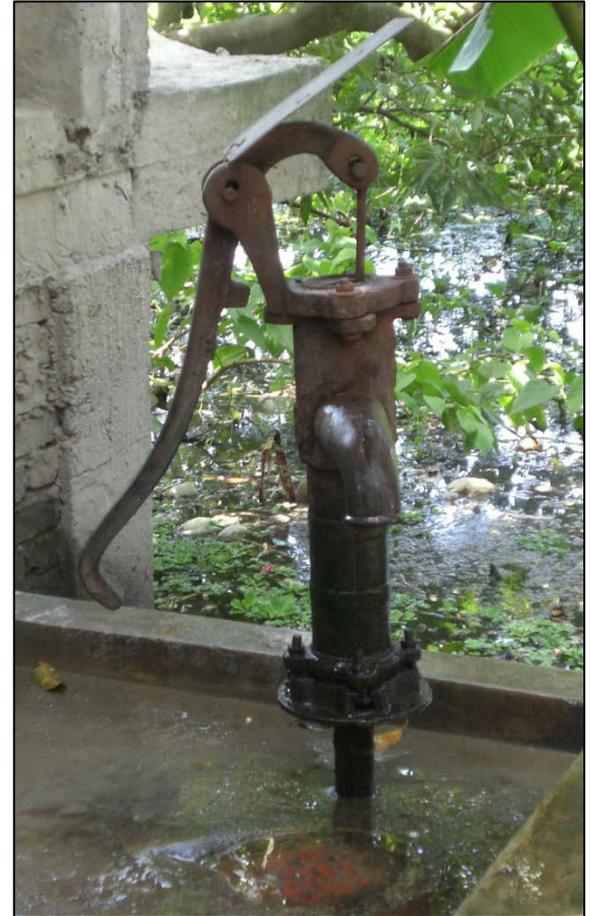
Arsenic Exposure and Mortality in Bangladesh: Findings from the Health Effects of Arsenic Longitudinal Study

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Background

- Hand-pumped tubewells installed to provide pathogen-free groundwater beginning in 1970s
- Groundwater in Bangladesh naturally contaminated with high levels of arsenic
- Arsenic in groundwater discovered only after decades of exposure and an epidemic of skin lesions, a hallmark characteristic of arsenic toxicity
- Arsenic is an established human carcinogen



Magnitude of Arsenic Public Health Issue Globally and in Bangladesh

- Countries where arsenic in drinking water has been detected at concentration $>10 \mu\text{g/L}$ or the prevailing national standard
 - Argentina, Australia, Bangladesh, Chile, China, Hungary, India, Mexico, Peru, Thailand, and the United States of America
- British Geological Survey study of wells in Bangladesh
 - 27% of well samples $>50 \mu\text{g/L}$ → 28-35 million individuals
 - 46% of well samples $>10 \mu\text{g/L}$ → 46-57 million individuals
(est. 2000)

Long-term Health Effects

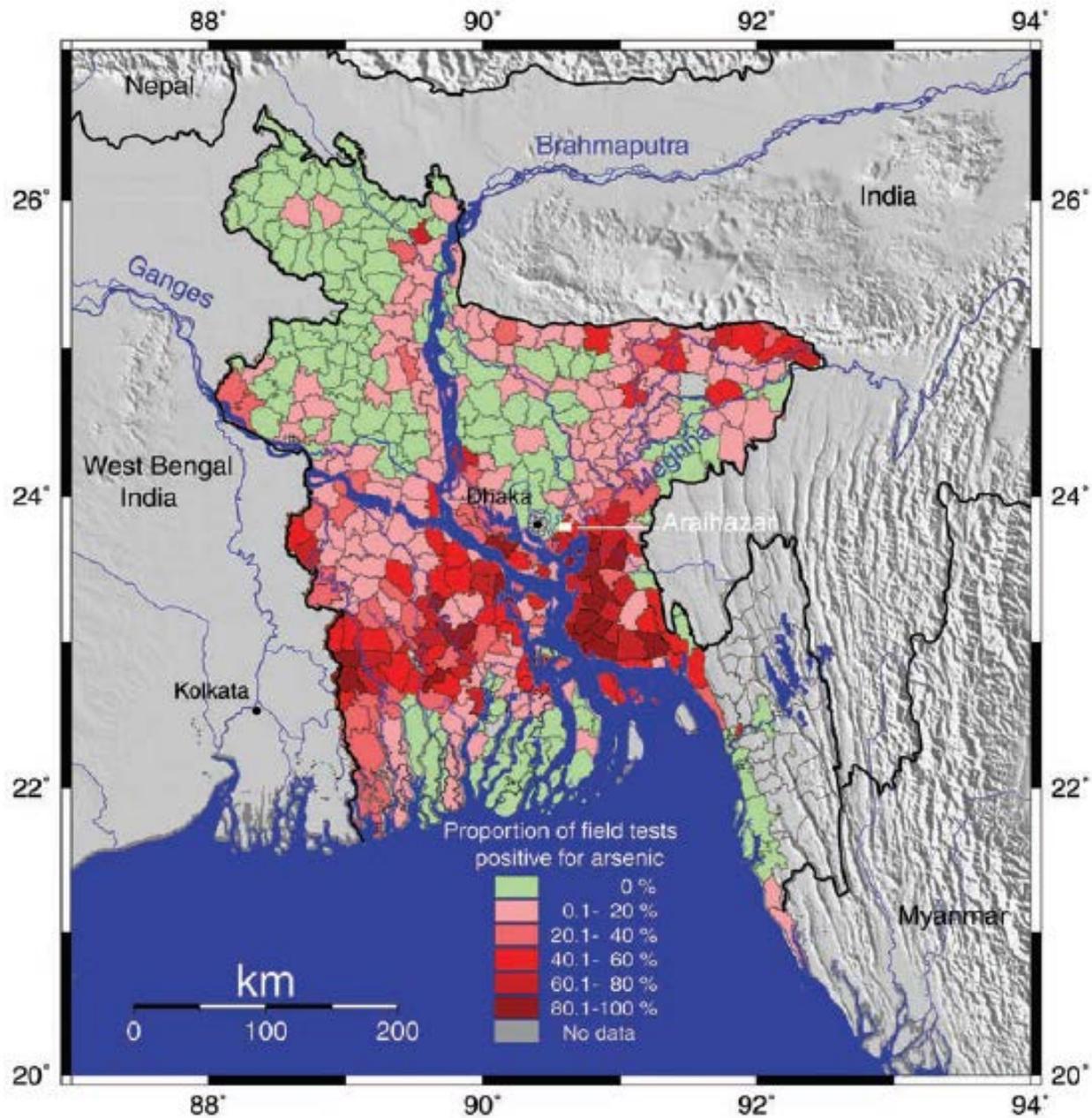
- Skin lesions
- Non-melanoma skin cancers
- Internal cancers:
 - Urinary tract
 - Lung
 - Liver
- Developmental effects
- Neurological effects
- Hypertension
- Cardiovascular disease
- Pulmonary disease
- Peripheral vascular disease
- Mortality
- Reproductive effects

Epidemiologic Evidence at Low-to-Moderate Exposure Levels

- Epidemiologic evidence of these health effects not well-established at low-to-moderate exposure levels (<300 µg/L)
- Limitations of prior studies
 - Small sample sizes
 - Unreliable measures of arsenic exposure
 - Ecologic or cross-sectional measures of exposure
- Difficult to assess associations in many populations due to heterogeneity of drinking water sources and high migration rates

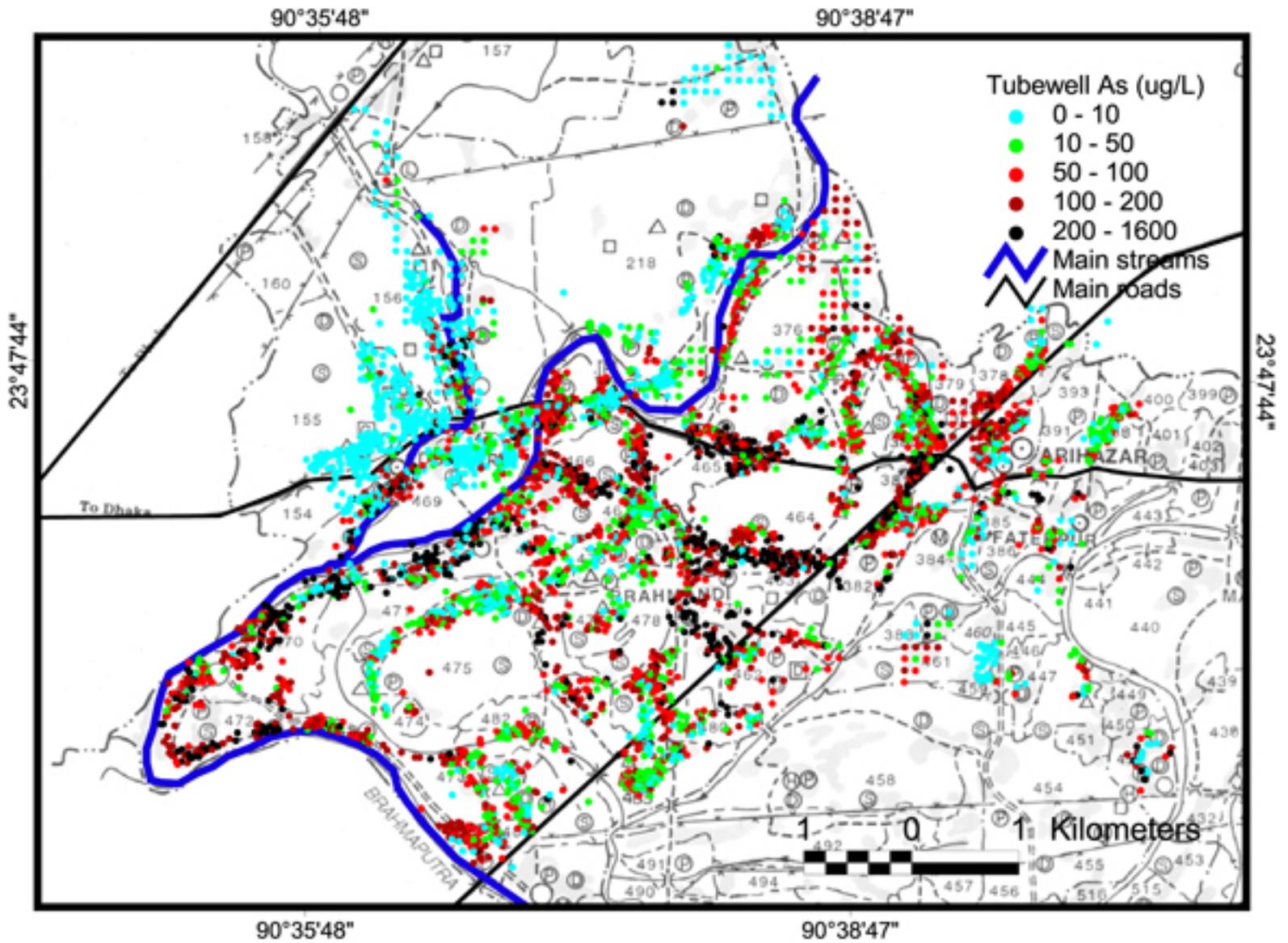
Study Population

- The Health Effects of Arsenic Longitudinal Study (HEALS) cohort was established in Araidhazar, Bangladesh, in 2000-2002 as part of Columbia University's Superfund Research Program
 - 11,746 adults enrolled
- Study cohort expanded in 2006-2008
 - 20,033 adults total
- The cohort consists of adults chronically exposed to arsenic through drinking water
- Inclusion criteria
 - Married adults
 - Aged 18-75 years
 - Resided in study area for at least 5 years
 - 97.5% response rate among those approached for enrollment



Data Collection

- **Baseline and Biennial Follow-up Interviews**
 - Physician-administered interview in Bangla using structured questionnaire
 - Patterns and history of well use
 - Demographic and lifestyle characteristics
 - Validated food frequency questionnaire
 - Comprehensive clinical and skin examination
 - Spot urine sample collection
 - Measurement of urinary total arsenic concentration
- **Pre-cohort Well Survey**
 - Measure of well water arsenic concentration of all wells in study region



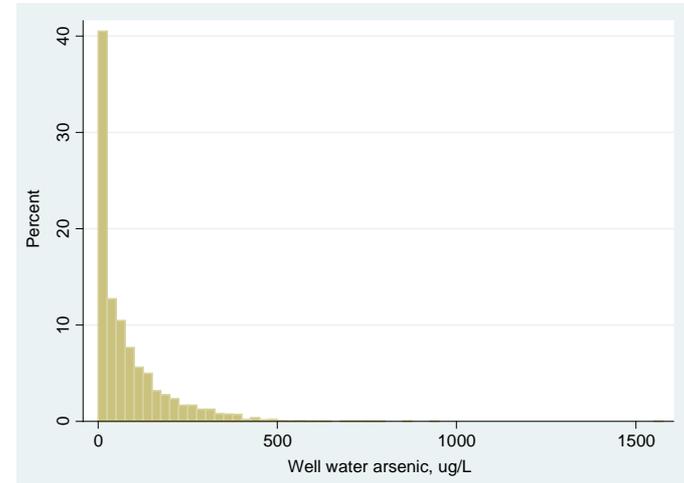
Exposure Assessment

- **Well water arsenic concentration**
 - Measured by graphite-furnace atomic absorption (LD 5 $\mu\text{g/L}$)
 - Inductively coupled plasma-mass spectrometry (LD 0.1 $\mu\text{g/L}$)
- **Urinary total arsenic concentration**
 - Measured by graphite-furnace atomic absorption in spot urine samples (LD 2 $\mu\text{g/L}$)
 - Standardized by urinary creatinine and subsequently expressed as $\mu\text{g/g}$ creatinine

Baseline Exposure Distribution

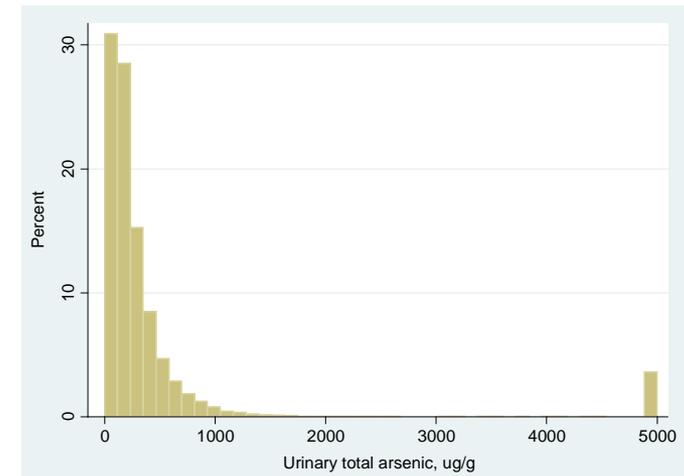
Well water arsenic exposure, $\mu\text{g}/\text{L}$

0.1-10:	30.5%
10.1-50:	22.7%
50.1-100:	18.1%
100.1-200:	16.6%
200.1-1500:	12.1%



Urinary total arsenic exposure, $\mu\text{g}/\text{g}$

2-100:	26.6%
100.1-150:	15.7%
150.1-250:	22.4%
250.1-400:	17.3%
400.1-5000:	17.9%



Mortality

- Increased cancer and chronic disease mortalities have been reported in arsenic-exposed populations in the USA, Chile, Argentina, Taiwan, and Bangladesh
- Evidence for the dose-response relationship between low-to-moderate level exposure and mortality has not been well established
- ***Study objective:*** To evaluate the effects of low-to-moderate levels of arsenic on the risk of all-cause, chronic disease, cardiovascular disease, and lung disease mortalities in the HEALS cohort

Death Ascertainment

- Deaths were ascertained from the biennial follow-up interviews
 - Vital status and date of death was determined from relative or neighbor if the participant was not available
- Verbal autopsies were conducted to determine the cause of death
 - Validated questionnaire administered to death informant
 - Supplemental documents regarding disease condition prior to death collected
 - All documents reviewed by an expert panel of physicians to assign a cause of death coded using the WHO's ICD-10

Characteristic	Baseline cohort %	Deaths %	Sex- and age-adjusted HR (95% CI)
Sex			
Female	59.3	30.9	1.0
Male	40.7	69.1	1.6 (1.4, 1.9)
Age, years			
18-30	33.8	7.7	1.0
31-40	31.9	17.9	2.0 (1.5, 2.7)
41-50	23.2	31.7	5.0 (3.8, 6.7)
51-60	10.6	37.0	13.3 (10.0, 17.6)
61-75	0.5	5.7	30.9 (20.8, 45.9)
Body mass index, kg/m²			
<18.5	39.5	54.7	1.0
18.5-24.9	53.4	39.9	0.7 (0.6, 0.8)
≥25.0	7.1	5.4	0.7 (0.5, 0.9)
Education, years			
0	43.6	52.8	1.0
1-5	30.5	25.0	0.8 (0.6, 0.9)
6-16	25.9	22.2	0.8 (0.7, 0.9)
Cigarette smoking			
Never	67.5	32.6	1.0
Ever	32.5	67.4	1.8 (1.4, 2.2)

	All-cause mortality*		Chronic-disease mortality*	
	Deaths	HR (95% CI)	Deaths	HR (95% CI)
Arsenic ($\mu\text{g/L}$) in well water				
0-1-10-0	74	1-00	58	1-00
10-1-50-0	90	1-34 (0-99-1-82)	69	1-33 (0-94-1-87)
50-1-150-0	98	1-09 (0-81-1-47)	83	1-22 (0-87-1-70)
150-1-864-0	131	1-68 (1-26-2-23)	101	1-68 (1-21-2-33)
Arsenic dose (μg per day)				
0-041-35-0	87	1-00	66	1-00
35-1-163-0	97	1-10 (0-83-1-47)	80	1-21 (0-88-1-67)
163-1-401-0	91	1-09 (0-81-1-46)	76	1-22 (0-88-1-71)
401-1-4898-0	118	1-54 (1-17-2-04)	89	1-58 (1-15-2-18)
Total arsenic in urine ($\mu\text{g/g}$)				
7-0-105-0	83	1-00	64	1-00
105-1-199-0	96	1-07 (0-80-1-43)	80	1-17 (0-84-1-62)
199-1-352-0	100	1-22 (0-91-1-63)	83	1-37 (0-98-1-90)
352-1-5000-0	105	1-45 (1-09-1-94)	77	1-47 (1-05-2-06)
Data are number or HR (95% CI). * Multivariate estimates were adjusted for age, sex, body-mass index, systolic blood pressure, education, and smoking status.				
Table 2: Hazard ratio (HR) for mortality in participants in relation to baseline arsenic exposure				

Change in Arsenic Exposure

	Follow-up exposure	Events	Patients at risk	All-cause mortality*
Baseline and follow-up 1				
Low	Low	103	4453	1.00
Low	High	13	765	0.88 (0.49-1.57) [†]
High	Low	70	1937	1.56 (1.14-2.13)
High	High	82	3373	1.33 (0.99-1.80) [‡]
Baseline and follow-up 2				
Low	Low	61	4226	1.00
Low	High	12	833	1.37 (0.75-2.50) [§]
High	Low	47	2072	1.67 (1.14-2.44)
High	High	38	3064	1.17 (0.77-1.77) [¶]

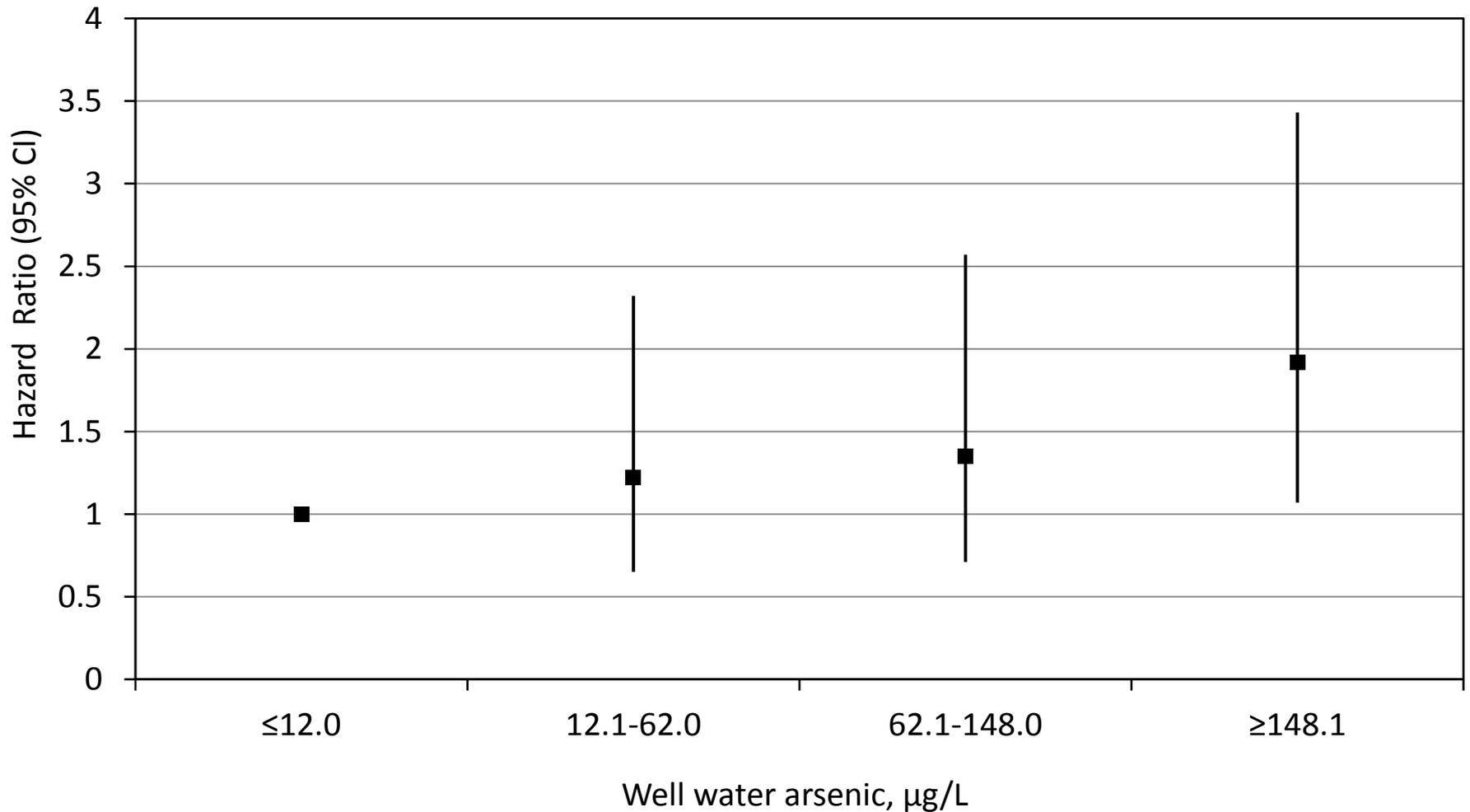
Data are number or HR (95% CI). * Multivariate estimates were adjusted for age, sex, body mass-index, systolic blood pressure, education, and smoking status. [†]p=0.67 versus low-low category. [‡]p=0.34 versus high-low category. [§]p=0.30 versus low-low category. [¶]p=0.11 versus high-low category.

Table 3: Hazard ratio (HR) of all-cause mortality in participants in relation to change in total arsenic concentration in urine

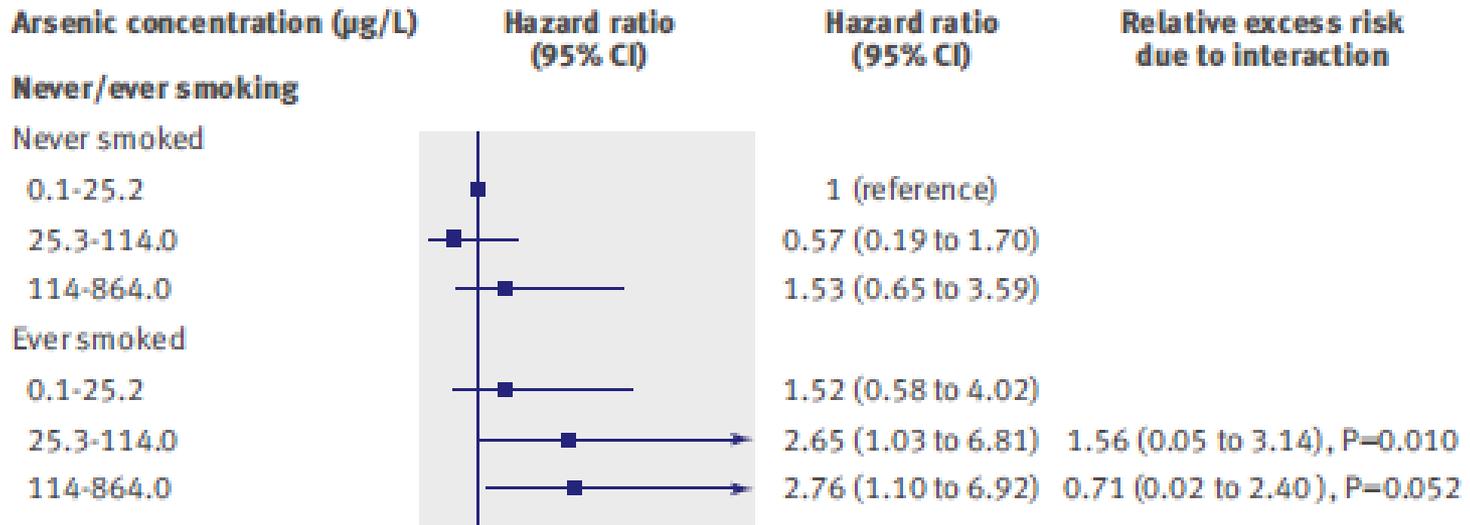
Attributable Proportion

- All-cause mortality
 - 21% could be attributed to arsenic exposure from drinking water at concentrations $>10 \mu\text{g/L}$
- Chronic disease mortality
 - 24% could be attributed to arsenic exposure from drinking water at concentrations $>10 \mu\text{g/L}$

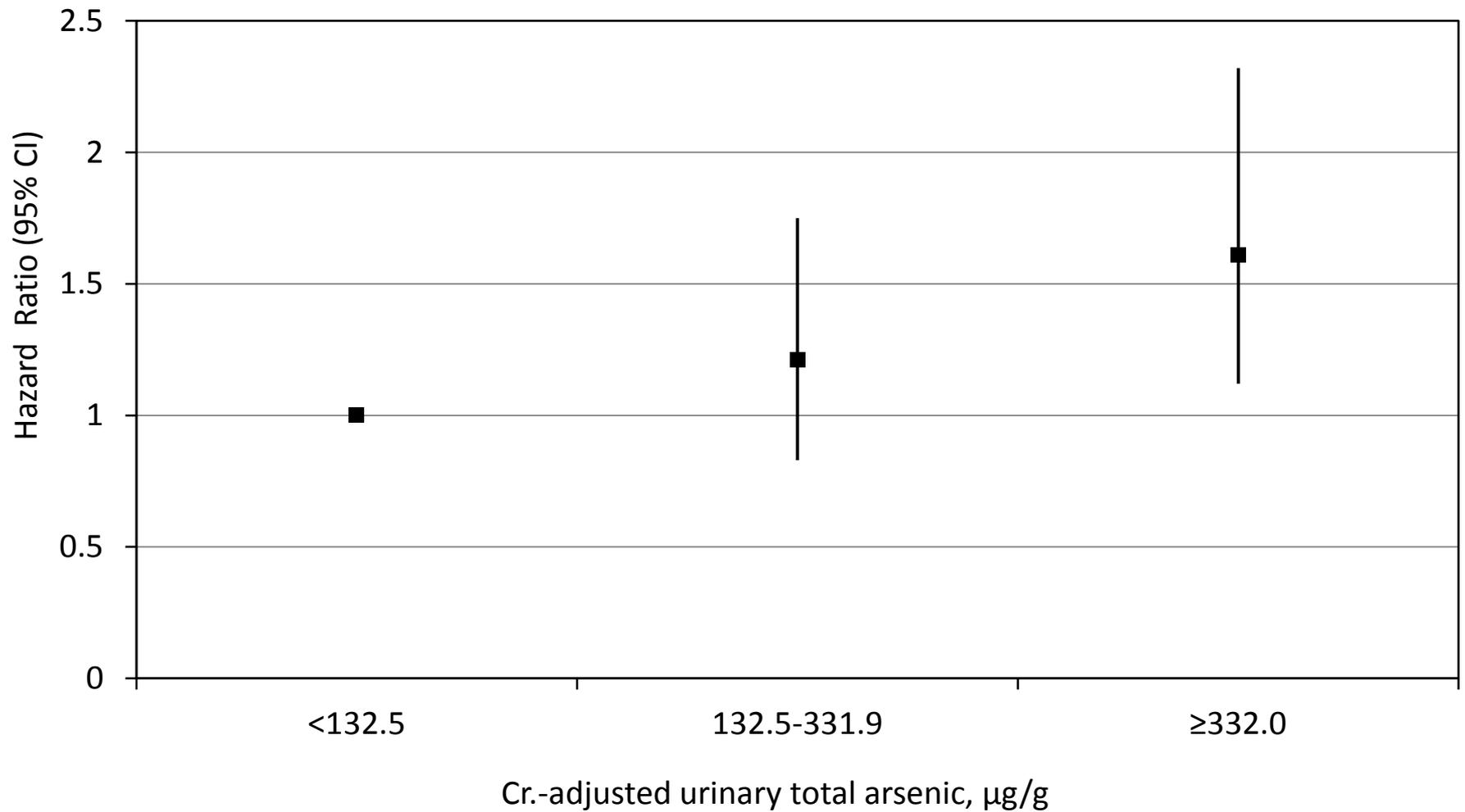
Well Water Arsenic and Ischemic and Other Heart Disease Mortalities



Effect Modification by Smoking



Urinary Total Arsenic and Lung Disease Mortality



Effect Modification by Smoking

Outcome	Cr-adjusted urinary total arsenic tertiles ($\mu\text{g/g}$)			P for trend	RERI
	<132.5	132.5-331.9	≥ 332.0		
All lung disease mortality	1.00	1.21 (0.83, 1.75)	1.61 (1.12, 2.32)	0.01	
Never smoker	1.00	1.12 (0.52, 2.39)	1.23 (0.59, 2.57)	0.65	0.39 (-0.03, 0.82)
Ever smoker	1.00	1.25 (0.82, 1.92)	1.78 (1.17, 2.70)	0.01	

Public Health Implications and Future Directions

- Cross-sectional and prospective analyses from the HEALS cohort have demonstrated increased risk of various health outcomes associated with arsenic in a dose-dependent manner
 - Including effects observed in the low-to-moderate dose range (<300 µg/L)
- Limitations include complete historical assessment of arsenic exposure
- Future analyses will explore effects of arsenic remediation on health outcomes

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