Incidence of Coronary Heart Disease in Relation to Lifetime Exposure to Inorganic Arsenic in Drinking Water in Colorado

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Presenter Disclosures

- No relationships to disclose

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Objectives

- Characterize the spatial distribution of inorganic arsenic in groundwater in the San Luis Valley.
- Estimate exposure to inorganic arsenic in drinking water based on residential and occupational history and water consumption combined with predicted inorganic arsenic levels in drinking water.
- Validate predicted exposure to inorganic arsenic in drinking water with speciated arsenic concentrations in concurrently collected urine samples.
- Investigate the association between inorganic arsenic exposure in drinking water and CHD

Background

- Research in areas with high (>1000µg/L) inorganic arsenic levels in drinking water (Taiwan, Bangladesh, Mongolia) have found a positive association with CHD.*
- Research in areas with low-level inorganic arsenic levels in drinking water (MI, NH, NV) have been inconclusive.**
- Limitations of past research
  - Study design (ecologic and cross-sectional)
  - Geographic, grouped or ecologic exposure assessments
  - Non-standardized outcome definition (self-report, death certificate)

*Chen, 1996; Rahman, 1999; Wang, 2002; Tseng 2003

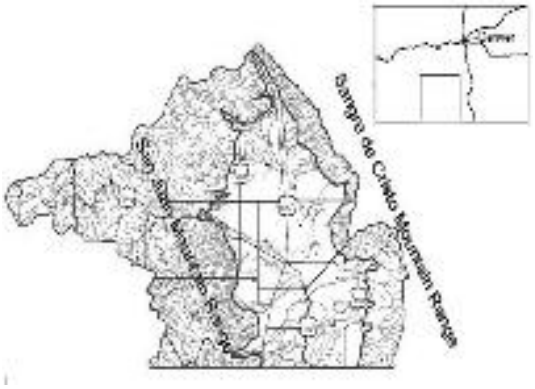
**Engle, 1994; Lewis, 1999; Zierold, 2004; Meliker, 2007

Strengths of this Study

- Large cohort (n=1351) with longitudinal clinical data
- Established presence of research in community
- Variable levels of arsenic in drinking water
- Little out migration
- Standardized criteria disease diagnosis

San Luis Valley, Colorado

- Largest mountain desert with deep aquifer ~3500ft
- Arsenic levels range from non-detected to 300 µg/L
- Drinking Water
  - 100% from groundwater
  - ~46,000 residents
    - 45% private wells
    - 55% public supply



Study Population-San Luis Valley Diabetes Study

- Population-based study of risk factors for diabetes in Hispanic and non-Hispanic Whites
- Residents of Alamosa and Conejos counties
- Aged 20-74
- Baseline clinic visit (1984-1988)
  - clinical, behavioral, and demographic data
- 2 or 3 follow-up clinic visits through 1992
- Vital status thru 1998

Study Design

- Case-Cohort Design
- Cohort (n=555)
  - Sample size based on preliminary data collected to estimate effect size of 1.4 with a power of 80 percent
- Case: any new CHD event from baseline visit thru 1998 (n=96)
  - CHD event defined as any of the following: myocardial infarction, cerebrovascular surgery, angioplasty, ischemic heart disease , or an ECG MN code 1.1-1.2
  - Confirmation by a three-member physician committee

Data Collection

- SLVDS data
  - Longitudinal demographic, behavioral, and clinical data
  - Residential history back to 1975
  - Birth city and state
  - Occupation
  - Average water intake
- Interview (n=357 participants)
  - Residential and occupational location history prior to 1975
  - Historical water consumption patterns
- Secondary data sources (n=198)
  - Residential history – county clerk records
  - Water consumption rates -- EPA estimated ingestion rates by age

Arsenic Data

- Private Wells (n=595 locations, 4126 samples)
  - 1961-2008
  - Arsenic range was non detectable to 300 µg/l; mean=15.5 µg/l
  - Primary water data (n=247 locations, n=247 samples)
    - Collected from kitchen tap during interview
    - Analyzed at chemistry laboratory of CO Dept. Public Health and Environment
  - Secondary water data (n=348 locations, n=3879 samples)
    - Federal agencies; USGS, EPA, and BoR
    - Past research in SLV; Drinking Water Exposures Rocky Mountain States
- Public Water (n=10 water supply districts, n=188 samples)

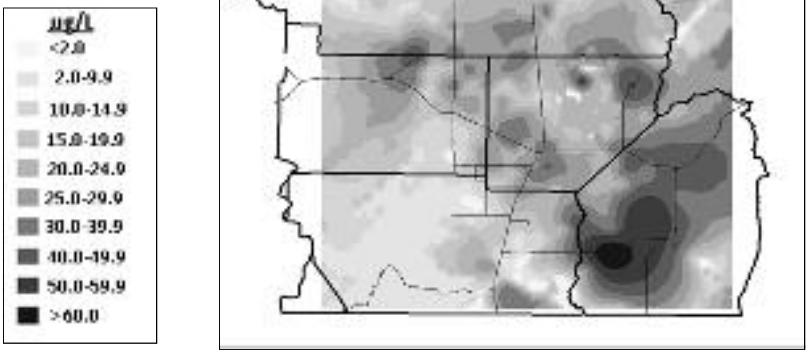
Predicting Inorganic Arsenic Concentrations in Drinking Water

- Temporal Stability
  - Naturally occurring arsenic is stable over long periods of time (Steinmaus, 2004; Focazio, 2000)
  - Replicated analysis in SLV
    - 170 wells with 4 to 25 samples collected over 20 years
    - Results found a significant correlation of arsenic concentrations over 5 and 10 year periods (r=0.88, r=0.87 respectively)
  - Conclude that inorganic arsenic concentrations are stable over long periods of time in the SLV
- Spatial Variation
  - Complex geospatial modeling
  - Mean arsenic concentration at each well location (n=595)

Geospatial Modeling

- Ordinary Kriging in GS+® Software
  - Predicts arsenic concentrations over the entire study area
  - A 10% random sample of wells were withheld from the model as a validation dataset (n=56)
- Predicted arsenic concentrations were significantly correlated with observed values (r=0.740) in the validation dataset

Predicted Inorganic Arsenic Concentrations in Groundwater



Exposure Matrix

- Record for each year of life per subject (n=41,639)
- Arsenic concentration at home (predicted or observed)
- Water intake in liters
- Arsenic concentration at employment/school (predicted)
- Water intake in liters at employment/school
- Locations out of the valley
  - Mean arsenic concentrations for city and state (NRC, 2000)
  - Outside of US 3.0 µg/L (Meliker, 2007)
  - Unknown city or state national average of 3.0 µg/L (Meliker, 2007)
- Calculated Doses
  - Residential Dose = arsenic conc µg/L x Water intake L
  - Total Dose = residential dose + employment dose

Identifying the Most Accurate Exposure Estimate

- Three estimates of exposure in the matrix
  - Residential arsenic concentration
  - Residential arsenic dose
  - Total Dose
- Urine is a biomarker for recent arsenic exposure
- Spot urine samples collected at baseline clinic visit and frozen at –80 ºC for 25 years
- Analyzed for total arsenic and metabolic species
  - Laboratory method: Inductively Coupled Plasma Mass Spectrometry
  - All species concentrations were creatinine corrected.

Arsenic Exposure Estimate

- Residential arsenic concentrations explained the most variability in urinary arsenic concentrations adjusted for creatinine levels.
  - Observed arsenic concentrations (R^2=0.34)
  - Predicted arsenic concentrations (R^2=0.40)

- Exposure was defined as time weighted average (TWA):

$$TWA = \Sigma(C) / T$$

$\Sigma(C)$ = Cumulative arsenic concentration at residence(μg/L)

T = Total time (years)

TWA = (μg/L-year)

Association Statistical Methods

- Cox proportional hazards model (modified for case-cohort design with robust variance estimator)

- Adjusted for known risk factors
  - Water consumption level
  - Age, Race, Gender, income
  - Family history, BMI, diabetes status
  - Alcohol consumption, smoking, physical activity
  - Lipid levels (LDL, HDL, triglycerides)

Table 1 Baseline demographic, clinical, and behavioral characteristics of study participants with and without incident CHD during follow-up (n = 555).

		Non-Cases	CHD cases
		N=459	N=96
Age (baseline) (median, IQR)		57 (46, 64)	64 (57.0, 69.0)
Race	White	262 (53%)	53 (55%)
	Hispanic	231 (47%)	41 (45%)
Gender	Male	226 (46%)	63 (66%)
	Female	266 (54%)	31 (34%)*
Income	Low	230 (47%)	36 (38%)
	High	263 (53%)	58 (62%)
First Degree Family History of CHD	No	307 (81%)	66 (69%)
	Yes	96 (19%)	28 (31%)*
BMI (median, IQR)		26.0 (23.7, 29.4)	26.1 (23.7, 29.0)
Diabetic	No	485 (98%)	93 (99%)
	Yes	8 (2%)	2 (1%)
Current Smoker	Yes	234 (48%)	44 (46%)
	No	258 (52%)	50 (54%)
Alcohol	Average	466 (95%)	89 (93%)
	High	27 (5%)	5 (7%)
Water Consumption	Low	185 (39%)	26 (27%)
	High	290 (61%)	68 (73%)
Physical Activity	Sedentary	334 (69%)	49 (51%)
	Active	151 (31%)	45 (49%)*
TDI (median, IQR)		134.0 (108.0, 163.0)	146.0 (118.0, 178.8)*
HDL (median, IQR)		46.0 (38.0, 56.0)	44.0 (38.0,49.0)
Triglycerides (median, IQR)		145.0 (102.0, 197.0)	142.0 (113.0, 227.0)

Figure 1 The distribution of CHD cases and non-cases across time-weighted average arsenic exposure.

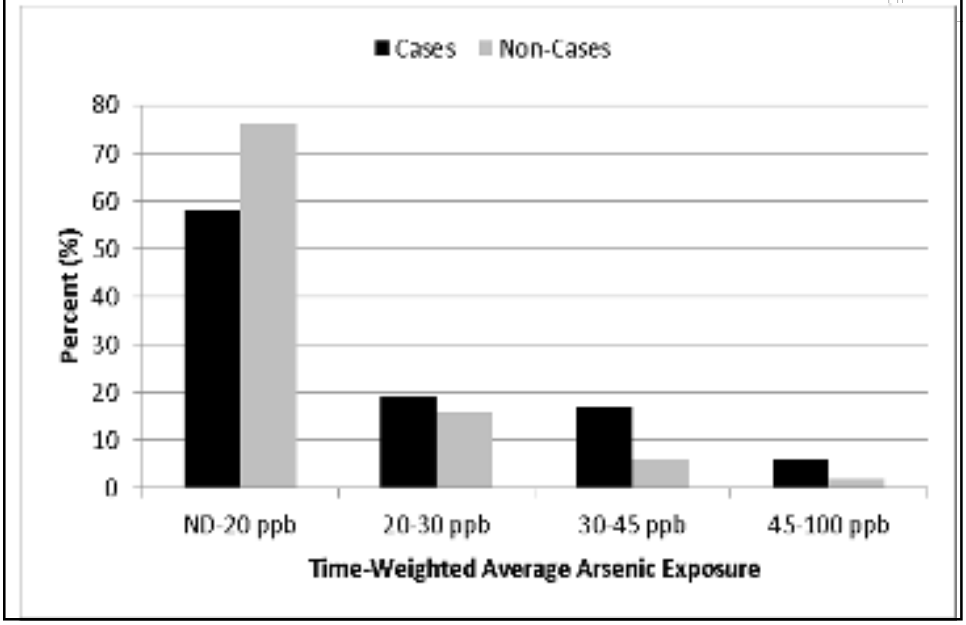
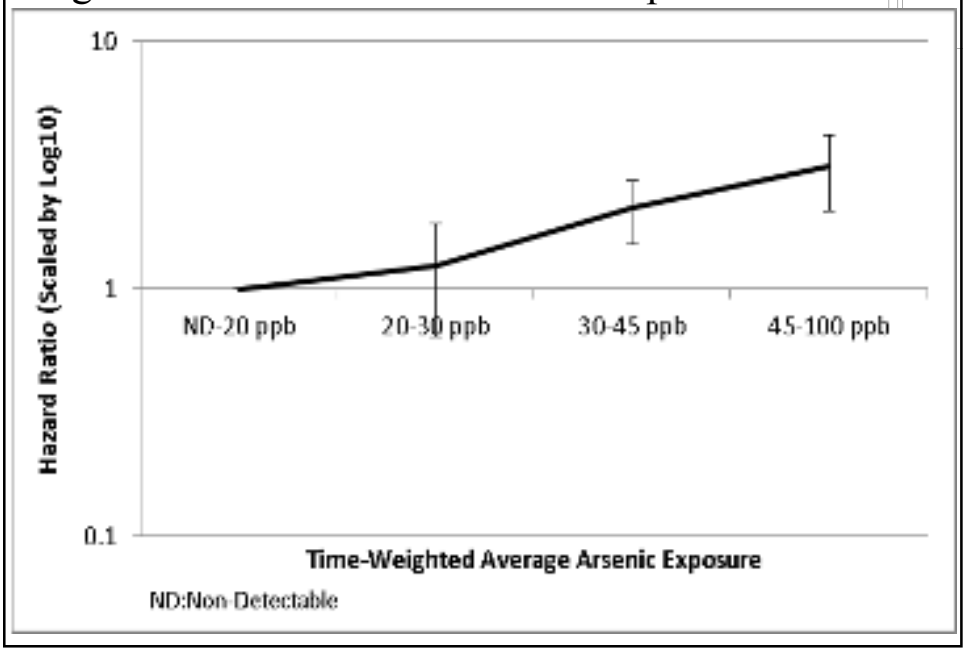


Table 2 Cox proportional hazards modeling results for the association between time-weighted average (TWA) inorganic arsenic exposure and CHD

Primary Analysis Continuous Exposure Variable	Univariate Model HR(95%CI)	Full Model HR(95%CI)	Adjusted Model HR(95%CI)
Arsenic Exposure TWA (15 ug/l)*	1.36 (1.1,1.8)	1.43 (1.11,1.84)	1.38 (1.09,1.78)
High Water Consumption		1.20 (0.77, 2.12)	
Female Gender		0.38 (0.22,0.61)	0.35 (0.19,0.53)
Hispanic Ethnicity		1.11 (0.70,1.84)	
Low Income		1.25 (0.69,2.10)	
Diabetic		2.23 (0.48,9.84)	
BMI (per 5.5 kg/m2)		0.82 (0.61,1.22)	
Primary Family Member with CHD		1.60 (0.89,2.82)	1.75 (1.07,2.88)
Sedentary Physical Activity		1.12 (0.72,1.83)	
Smoker		1.04 (0.70,1.71)	
High Alcohol Consumption		1.71 (0.69,4.37)	
Triglycerides (90ug/ dl)*		0.99 (0.67,1.39)	
Low Density Cholesterol (53ug/dl)*		1.49 (1.12,2.10)	1.40 (1.04,1.88)
High Density Cholesterol (17ug/dl)*		0.65 (0.39,1.02)	

*** Interquartile range**

Figure 2 Hazard Ratio for CHD Exposure



Discussion

- For every 15 µg/L increase in arsenic concentration in drinking water, the risk for CHD increased by 36 percent and across increasing levels of exposure, risk increased in dose-dependent fashion.
- Consistent results to research from high arsenic areas
- Understanding for CHD risk at arsenic exposure < 100ug/L
- Presents an association based on a complex exposure assessment

Limitations

- Does not account for other sources of arsenic exposure
- Potential misclassification bias given that 57% of the cohort was interviewed
- Arsenic exposure estimates were included in the proportional hazards model under the assumption of no error associated with the estimate generated from the kriging model

Conclusions

- Low-level inorganic arsenic in drinking water is associated with an increased risk for CHD
- This increased risk could have large public health implications
- The use of a comprehensive exposure assessment is critical for assessing exposure in diseases with complex pathways
- Future Directions
  - Investigate the increased risk with pre-clinical phases of CHD
  - Incorporate genetic and altered gene expression factors
  - Assess the clinically relevant exposure period