Title: Is living in a region with high groundwater arsenic contamination associated with adverse reproductive health outcomes? An analysis using nationally representative data from India

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Abstract:

Exposure to groundwater arsenic via drinking water is common in certain geographies, and causes a range of negative health effects, potentially including adverse reproductive health outcomes. We conducted an ecological analysis of rates of stillbirth, recurrent pregnancy loss (RPL), and infertility in relation to groundwater arsenic in India. A gridded, modeled dataset of the probability of groundwater arsenic exceeding 10 µg/L (World Health Organization drinking water limit) was spatially integrated with the India District Level Health Survey (DLHS-3) wave 3 conducted in 2007-08 (n = 643,944 women of reproductive age; 599 districts). Maps were generated for each outcome. To adjust for significant spatial autocorrelation, spatial error models were fit for each outcome. As the probability of groundwater arsenic levels exceeding 10 µg/L increased, there was a significant 3.8 percentage point (pp) increase in stillbirths (β=0.038; 95% confidence interval 0.017, 0.059), 3.6pp in RPL (β=0.036; 95% CI 0.20, 0.053), and 3.7 pp increase in infertility (β=0.037, 95% CI 0.001, 0.066) at the district level. All models adjusted for urban/rural setting and demographic characteristics. Living in districts with high probability of groundwater arsenic contamination was significantly associated with adverse reproductive health outcomes including stillbirth, RPL, and infertility.

Background

Arsenic is a naturally occurring chemical element known to be highly toxic in its inorganic form. Natural arsenic contamination of water comes from rocks and sediments in the earth, and manmade contamination comes from industrial activities such as copper smelting, when metal is extracted from the ground using heat.(1) The general population is exposed to inorganic arsenic via drinking water and diet. Currently, the World Health Organization (WHO) guidelines on the limit of arsenic in drinking water is held at 10 ppb (equivalent to 10 µg/L), even though a level much lower than that has been shown to cause acute exposure symptoms and arsenic-inducing tumors.(2) Acute arsenic exposure and poisoning symptoms are well documented and include dermatological lesions, gastrointestinal effects, abdominal pain, dehydration, and hypotension.(3) It is now known that chronic arsenic exposure affects multiple organ systems and can be the cause of disorders of the skin and peripheral blood vessels, diabetes, hypertension and a variety of cancers: including skin, bladder, kidney, and lung cancers. Groundwater arsenic may affect over 150 million people worldwide; recent estimates suggest up to 220 million people. (4,5) Almost all (up to 95%) of these reside in Asia.(5) However, arsenic is not routinely included in water quality testing parameters and is not detected by human senses, making it challenging to understand the scale of the problem.

Studies have suggested arsenic exposure is associated with a range of adverse reproductive health (RH) outcomes, and birth outcomes as inorganic arsenic can cross the placenta.(6,7) Documented adverse pregnancy-related outcomes such as spontaneous abortion, low birthweight (< 2,500 g), and infant mortality suggesting multifactorial insults to the reproductive system. More recently, some work has suggested arsenic exposure may be linked with infertility. Several small case control studies, particularly from China, have suggested an association between exposure to groundwater arsenic and infertility, potentially through oxidative stress and reported decreased sperm quality after arsenic exposure.(8–11) Overall however the mechanisms for arsenic-induced adverse RH outcomes are not well known.

To measure adverse RH outcomes, we use nationally representative data from the female respondents in India's District Level Health Survey (DLHS) round 3 (2007-2008). Modeled, gridded groundwater arsenic dataset to 1km spatial resolution were joined with the DLHS-3 data to assess district level associations. We hypothesized that we would find evidence in support of known associations between arsenic exposure and stillbirths, as well as with the more novel outcomes of RPL and infertility.

Methods

The District Level Household and Facility Survey (DLHS) is a nationally representative survey and one of the largest sources of health data in India. To date, there have been four 'waves' of data collection (first collected in 1998-99). The DLHS collected data from households, ever married women as well as from villages (availability of services) and health facilities. The DLHS-3 used a multi-stage stratified sampling design, with 1000-1,500 households per district (n=599 districts) and includes survey questions regarding RH outcomes and infertility.

Three outcome variables comprise our analysis of "adverse reproductive health outcomes". From women's reports of their pregnancy histories, we created a variable indicating having had one or more stillbirth (defined as pregnancy ending at $\geq$28 weeks gestation), or recurrent pregnancy loss (RPL) (defined as two or more spontaneous abortions), and women's reports of experiencing any infertility, based on the question "In every place there are couples who want children but some women do not get pregnant. Did you face any such problem in getting pregnant?". Women who answered yes to this question were considered to have had experienced infertility.

The key independent variable was a measure of groundwater arsenic. Groundwater arsenic measures are challenging particularly for a population-based study, since this would require many water samples over a very large geographic area. A new analysis used data from over 80 previous studies (comprised of over 50,000 aggregated data points of measured groundwater arsenic concentration) and additional environmental variables (e.g., soil pH) to train a machine learning model using the random forest method to predict where groundwater arsenic exceeds 10 µg/L.(5) The prediction groundwater arsenic dataset is available at 1km^2 grid cell resolution and freely available. The data were published in 2020, and underlying datasets for India range from 2005 to 2018. The arsenic dataset is gridded, so these grid cells were overlaid with district administrative boundaries from 2008 to match the DLHS-3 districts. The arsenic dataset was aggregated to the district level using the Zonal Statistics tool (extracting the average, minimum, maximum pixel values that cross each district polygon) in ArcGIS version 10.4.1 (ESRI, Redlands, CA).

First, we will explore linear OLS regression models then take steps to determine the degree of spatial autocorrelation in the data. Moran's I statistics will be calculated. It is critical to account for spatial autocorrelation otherwise standard errors can be underestimated leading to inaccurate results. Bivariate and adjusted models will be constructed. We will plot local Moran's I and map them in local indicators of spatial association (LISA) maps to identify districts with clustering of high or low value districts for each outcome (high-high suggests the district has a higher than expected value, and its neighboring districts do also). Based on the significant spatial autocorrelation detected, the third and final step of data analysis was to fit spatial error models (SEM).

Preliminary Results

A total of 643,944 women ages 15-49 were included in the analysis. About 4% reported having one or more stillbirth, 3% reported RPL, and 8% experienced any infertility. Maps of the spatial distribution at the district level of the probability of arsenic in the ground water above the WHO 10 µg/L cutoff (Panel A) and the average district-level rate of infertility (Panel B) are presented in Figure 1. Figure 2 presents the local indicator of spatial association (LISA) map, depicting the degree of spatial clustering of local Moran's I values for each district for infertility.

Next Steps

We will replicate this analysis for three outcomes, infertility, RPL and stillbirth and present the results including the adjusted SEM models in the final paper.

This is the first national level analysis of adverse RH outcomes including infertility in relation to arsenic levels in India. We use a novel spatial integration approach to extract predicted groundwater arsenic levels and link these with the District Level Health Survey (DLHS) round 3 (2007-08) a nationally representative survey of women of reproductive age. The DLHS-3 is one of the few nationally representative surveys to include women's direct reports of difficulties conceiving, timing of these difficulties, treatment sought and resolution. Preliminary findings show that women residing in districts with higher predicted groundwater arsenic concentrations are more likely to report stillbirth, recurrent pregnancy loss, and infertility.

References

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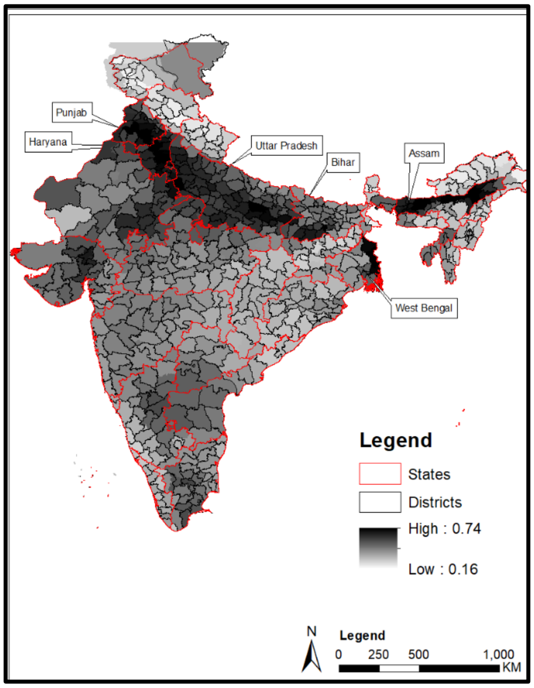
Figures

Figure 1: Four panels showing district level: A) predicted probability groundwater arsenic levels>10 µg/L; B) average infertility



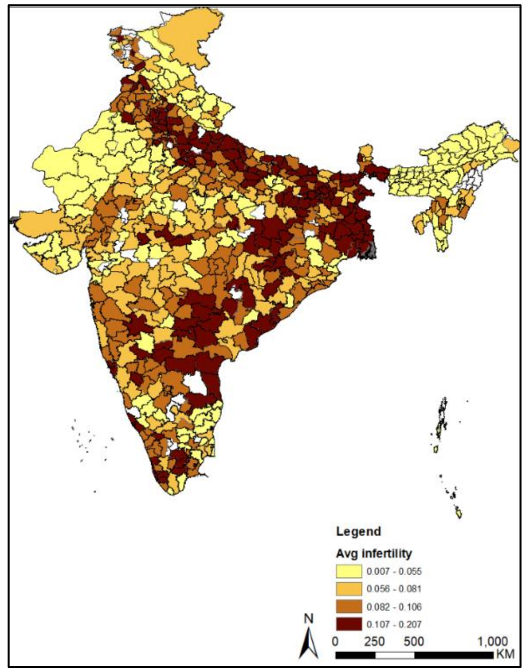


Figure 2: local indicators of spatial association (LISA) maps for average district infertility