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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

Background: Exposure to groundwater arsenic via drinking water is common in certain geographies, such as parts of India, and causes a range of negative health effects, potentially including adverse reproductive health outcomes.
Methods: We conducted an ecological analysis of self-reported rates of stillbirth, recurrent pregnancy loss, and infertility in relation to groundwater arsenic levels in India. We used a gridded, modeled dataset of the probability of groundwater arsenic exceeding 10 μg/L (World Health Organization drinking water limit) to calculate mean probabilities at the district level ($n = 599$ districts). A spatial integration approach was used to merge these estimates with the third India District-Level Health Survey (DLHS-3) conducted in 2007-08 ($n = 643,944$ women of reproductive age). Maps of district level arsenic levels and rates of each of the three outcomes were created to visualize the patterns across India. To adjust for significant spatial autocorrelation, spatial error models were fit.
Findings: District-level analysis showed that the average level of stillbirth was 4.3%, recurrent pregnancy loss was 3.3%, and infertility was 8.1%. The average district-level probability of groundwater arsenic levels exceeding 10 μg/L was 42%. After adjustment for sociodemographic factors, and accounting for spatial dependence, at the district level, for each percentage point increase in predicted arsenic levels exceeding 10 μg/L increased, the rates of stillbirths was 4.5% higher (95% confidence interval (CI) 2.4–6.6, $p < 0.0001$), the rates of RPL are 4.2% higher (95% CI 2.5–5.9, $p < 0.0001$), and the rates of infertility are 4.4% higher (95% CI 1.2–7.7, p=<0.0001).).
Conclusions: While arsenic exposure has been implicated with a range of adverse health outcomes, this is one of the first population-level studies to document an association between arsenic and three adverse reproductive pregnancy outcomes. The high levels of spatial correlation suggest that further and targeted efforts to mitigate arsenic in groundwater are needed.

1. 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 mining, when metal is extracted from the ground using heat. The general population is exposed to inorganic arsenic via drinking water and diet (Kumar et al., 2016; Pizent et al., 2012; Yan-Ping et al., 2017). Currently, the World Health Organization (WHO) guidelines on the limit of arsenic in drinking water is held at 10 parts per billion (ppb)(equivalent to 10 μg/L), even though a much lower level has been shown to cause adverse health effects (Lynch et al., 2017; Xu et al., 2020). 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

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Table 1
District level summary characteristics of survey participants (n = 599).

	Percent or mean	Std Dev	Min	Max
Any stillbirth, %	4.3	2.0	0.3	16.7
2 or more miscarriages, %	3.3	1.4	0	12.1
Any infertility, %	8.2	3.5	0.7	20.7
Arsenic >10 μg/L,%	0.42	0.12	0.18	0.74
Age, years	32.09	1.34	28.87	36.23
Rural, %	77.0	2.0	0	100
Wealth quintile (range 1–5 with 1 = poorest and 5 = richest))	3.2	0.8	1.3	4.9
Educational Attainment (range 0–3 with 0 = none and 3 = more than secondary)	1.2	0.5	0.2	2.5

(Lynch et al., 2017; Mink et al., 2008; Xu et al., 2020).

South and Southeast Asia are considered the most arsenic-polluted areas, including regions of India and Bangladesh (Ravenscroft et al., 2011). Other areas known to have high levels of arsenic contamination in drinking water include Chile, Mexico, China, Argentina, Pakistan, Cambodia, Vietnam, and regions across the United States of America (USA), affecting more than 150 million people worldwide Recent estimates suggest up to 220 million people (Podgorski and Berg, 2020) have exposure to arsenic contamination, with almost all (up to 95%) of residing in Asia. 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 (Podgorski and Berg, 2020). While the presence of arsenic hazards in groundwater has been documented since the 1980s, it remains an understudied health issue in many regions.

Parts of India and Bangladesh have some of the highest levels of groundwater arsenic detected in drinking water, and a large population residing in these areas (Rahman et al., 2001). Communities rely on tube wells and hand pumps that access groundwater used for drinking and cooking. In India, more than 85% of drinking water comes from groundwater (Shrivastava, 2016). India's National Drinking Water Program aims to provide safe water to rural households by 2024; the program aims to improve quality in the long-term through piped water supply as well as technological interventions for potable water ("Jal Jeevan Mission," n.d.). In the short-term, central guidelines recommend installation of community water purification plants in arsenic-affected habitats for safe basic drinking and cooking water (National Water Quality Sub-Mission Revised Guidelines, n.d.). For example, West Bengal has invested in several water treatment plants over the past fifteen years, resulting in gradual improvements in the proportion of the population covered by piped water supply ("Public Health Engineering Department," n.d.).

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 (Milton et al., 2017; Quansah et al., 2015). Documented adverse RH outcomes such as spontaneous abortion (<20 weeks gestational age), stillbirth (≥28 weeks gestational age, per WHO definition), low birthweight (<2500 g), and infant mortality suggesting multifactorial insults to the reproductive system (Milton et al., 2017; Mohammed Abdul et al., 2015; Quansah et al., 2015). For stillbirth, studies have found that even after adjustment for many socioeconomic characteristics, the risk of stillbirth is raised and increases with increasing levels of groundwater arsenic (Cherry et al., 2008; von Ehrenstein et al., 2006). Recurrent pregnancy loss (RPL), defined as two or more spontaneous abortions, affects ~5% of the population; however, clinical workups only uncovers a cause in about half of cases. Environmental exposures such as arsenic with its known association with any spontaneous abortion may have a causal role in cases of unknown etiology. 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 (Shen et al., 2013; Susko et al., 2017; Wang et al., 2016). Overall however the mechanisms for arsenic-induced adverse RH outcomes are not well known. In addition, most research on population-level variation in adverse RH outcomes has largely focused on demographic characteristics, with more recent recognition of the potential role of factors such as pollution, climate change, and other related environmental causes (Sorensen et al., 2018).

For this analysis, we examine adverse RH outcomes using data from the female respondents in India's nationally representative District Level Health Survey, Round 3 (DLHS=3). Modeled, gridded groundwater arsenic dataset to 1 km 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.

2. Methods

2.1. Surveys and populations

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) (District Level Household and Facility Survey (DLHS-3) under Reproductive and Child Health Project (2007-08), n.d.). The DLHS collects data from households, ever married women as well as from villages (availability of services) and health facilities. The DLHS uses a multi-stage stratified sampling design, with 1000-1500 households per district (for more details on survey methodology, see the full report (International Institute for Population Sciences (IIPS), 2010). In the third wave (DLHS-3), from 2007 to 2008, the household response rate was 93% overall, and the ever-married woman response rate was 89%. All waves of the DLHS include a women's questionnaire that includes self-reported information on reproductive health, and maternal and child health, while only round 3 includes a module of questions regarding infertility.

2.2. Key measures

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 ≥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. Each measure, when aggregated to the district level, is the proportion of women surveyed in that district that reported experiencing each outcome.

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 recently published global 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(Podgorski and Berg, n.d.) The prediction groundwater arsenic dataset is available at 1 km^2 grid cell resolution and freely available with the final dataset published in 2020. For India specifically, a total of 145,099 geographically distinct arsenic concentration measurements in groundwater were assembled from over

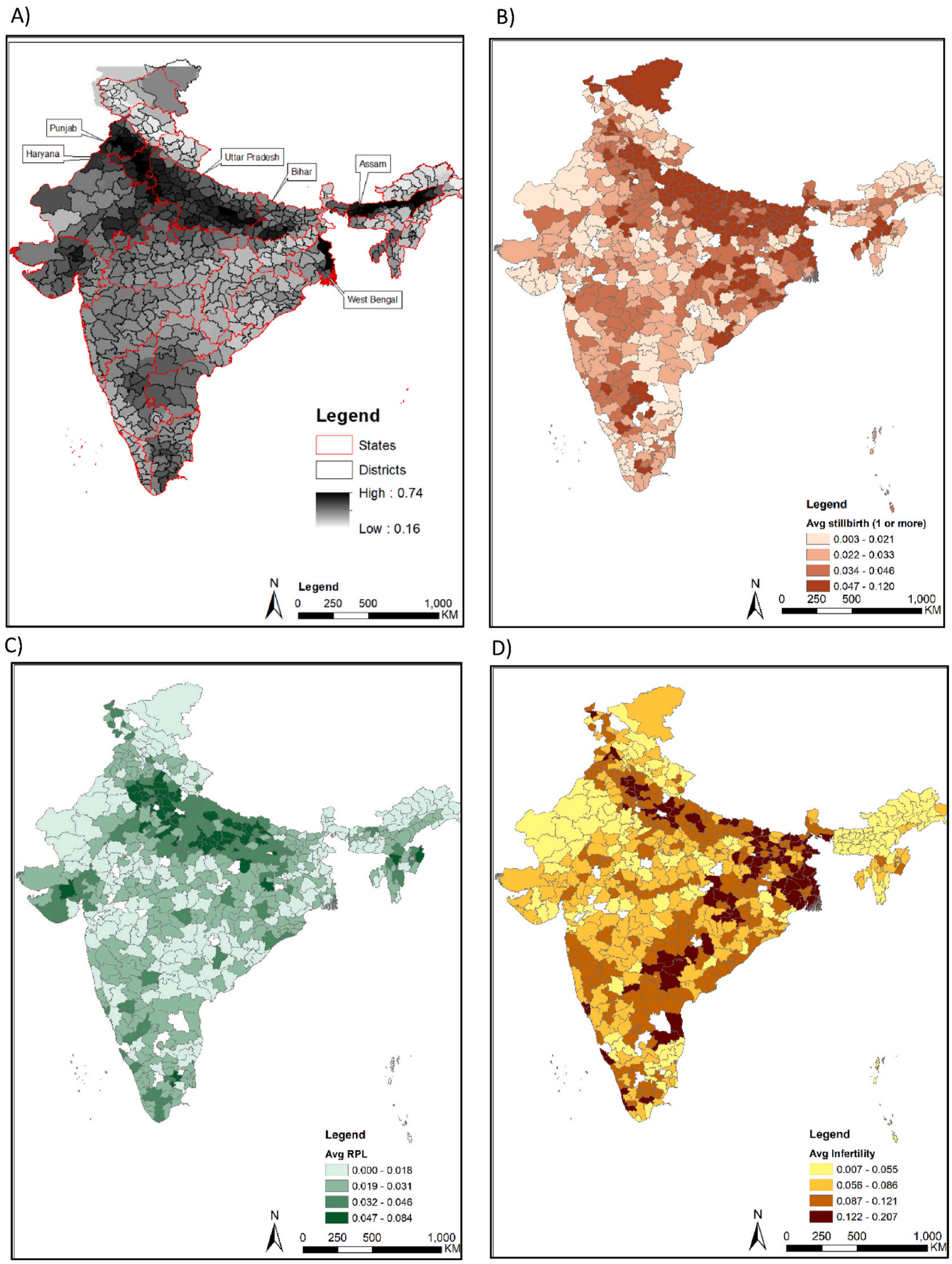

Fig. 1. Four panels showing district level: A) predicted probability groundwater arsenic levels>10 μg/L; B) average stillbirths (one or more); C) average RPL; and D) average infertility.

30 sources, mainly from India but also nearby Bangladesh, Nepal, and Pakistan (Podgorski et al., 2020). The underlying datasets for India range from 2005 to 2018. The arsenic modeled dataset is gridded, so these grid cells were overlaid with Indian 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).

2.3. *Data analysis*

First, we ran linear OLS regression models to explore the relationship between arsenic and the three RH outcomes, adjusting for sociodemographic variables. We adjusted models for covariates that were available in the DLHS-3, and known to be associated with adverse RH outcomes. These included age in years, educational attainment (0 = no formal schooling, 1 = some primary to completed primary, 2 = some secondary to completed secondary, 3 = greater than secondary), household wealth (categorized into quintiles from poorest to richest), and a variable for proportion rural (vs urban). We explored the data at the district level

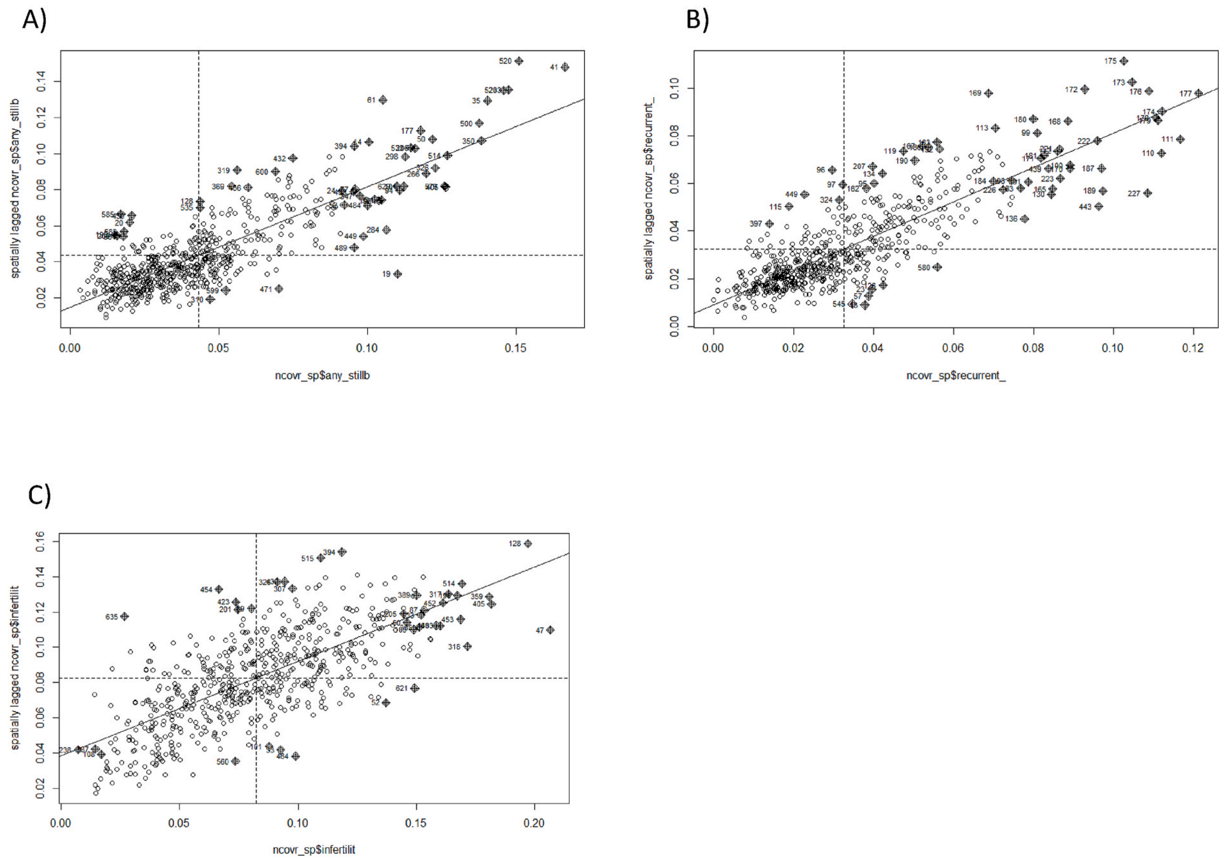

Fig. 2. Local Morans I scatterplots for each outcome: A) average stillbirths (one or more); B) average RPL, C) average infertility (primary or secondary).

across these characteristics.

Second, we took steps to determine the degree of spatial autocorrelation in the data. The dataset was exported to R for spatial analysis. Moran's I statistics were calculated to determine the degree of spatial autocorrelation in the outcomes of interest. A high degree of autocorrelation was detected, implying that neighboring districts are more similar to nearby districts, than would be expected at random. It is critical to account for spatial autocorrelation otherwise standard errors can be underestimated leading to inaccurate results due to underestimation of standard errors. Bivariate and adjusted models were constructed, and the global Moran's I implemented to detect the overall spatial clustering of the models (Moran, 1950). The local Moran's I statistics were then calculated, providing a clustering value for each individual district, by comparing each district to its neighboring districts. The results were plotted and mapped 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). SEMs are a linear regression model with a spatial autoregressive error term. The final models also adjust for all sociodemographic variables. We fit three separate SEMs for self-reported stillbirth, RPL and infertility as the outcomes and present both unadjusted and adjusted estimates.

3. Results

A total of 643,944 women ages 15–49 were included in the analysis, aggregated to the district level ($n = 599$). Table 1 shows the district-level range of key characteristics in the analysis. The average district proportion of women experiencing at least one stillbirth was 4.3% (range 0.3–16.7%), the average district proportion of women experiencing RPL was 3.3% (range 0.0–12.1%), and any infertility was 8.1% (range 0.7–20.7%). The predicted probability of arsenic >10 μg/L at the district level was 0.43, ranging from 0.18 to 74.0. Most of the women sampled in each district were rural (77%), the average district-level wealth was 3.2 (just over neither rich or poor), and the level of educational attainment was 1.2 (slightly more than some primary education).

The maps in Fig. 1 show the spatial distribution of the independent variable, the probability of arsenic in the groundwater above the WHO 10 μg/L cutoff (Panel A) and the average district-level rate of stillbirth (Panel B), RPL (Panel C), and infertility (Panel D). Panel A highlights the regions with the highest probability of groundwater arsenic above the 10 μg/L cutoff including in eastern (Bihar, Jharkand and West Bengal) and northern states (Uttar Pradesh, Haryana and Punjab). Panels B–D show the average district-level rates of any stillbirth, RPL, and infertility presented in quartiles. Any stillbirth and RPL follow a very similar pattern, with the highest district level rates reported in Bihar, Uttar Pradesh, and districts in Rajasthan. For infertility, rates were highest in West Bengal Bihar, Uttar Pradesh and Chhattisgarh, along with southern states of Andhra Pradesh and Telangana. The maps suggest a spatial pattern for both the RH outcomes and for arsenic.

To assess whether there was significant spatial autocorrelation of the outcomes, global and local Moran's I estimates were calculated. The global Moran's I value for stillbirth was 0.670 ($p < 0.0001$), for RPL was 0.719 ($p < 0.0001$), and for infertility was 0.536 ($p < 0.0001$) suggesting spatial autocorrelation. Fig. 2 presents local Moran's I scatterplots for stillbirth (Panel A), RPL (panel B), and infertility (panel C). While the global Moran's I shows significant spatial autocorrelation, it does not identify the location of clusters. Fig. 3 presents local indicator of spatial association (LISA) maps, depicting the degree of spatial clustering of local Moran's I values for each district. The LISA maps highlight the locations of clusters of districts that have higher or lower than expected rates of each outcome (compared to what would be expected at

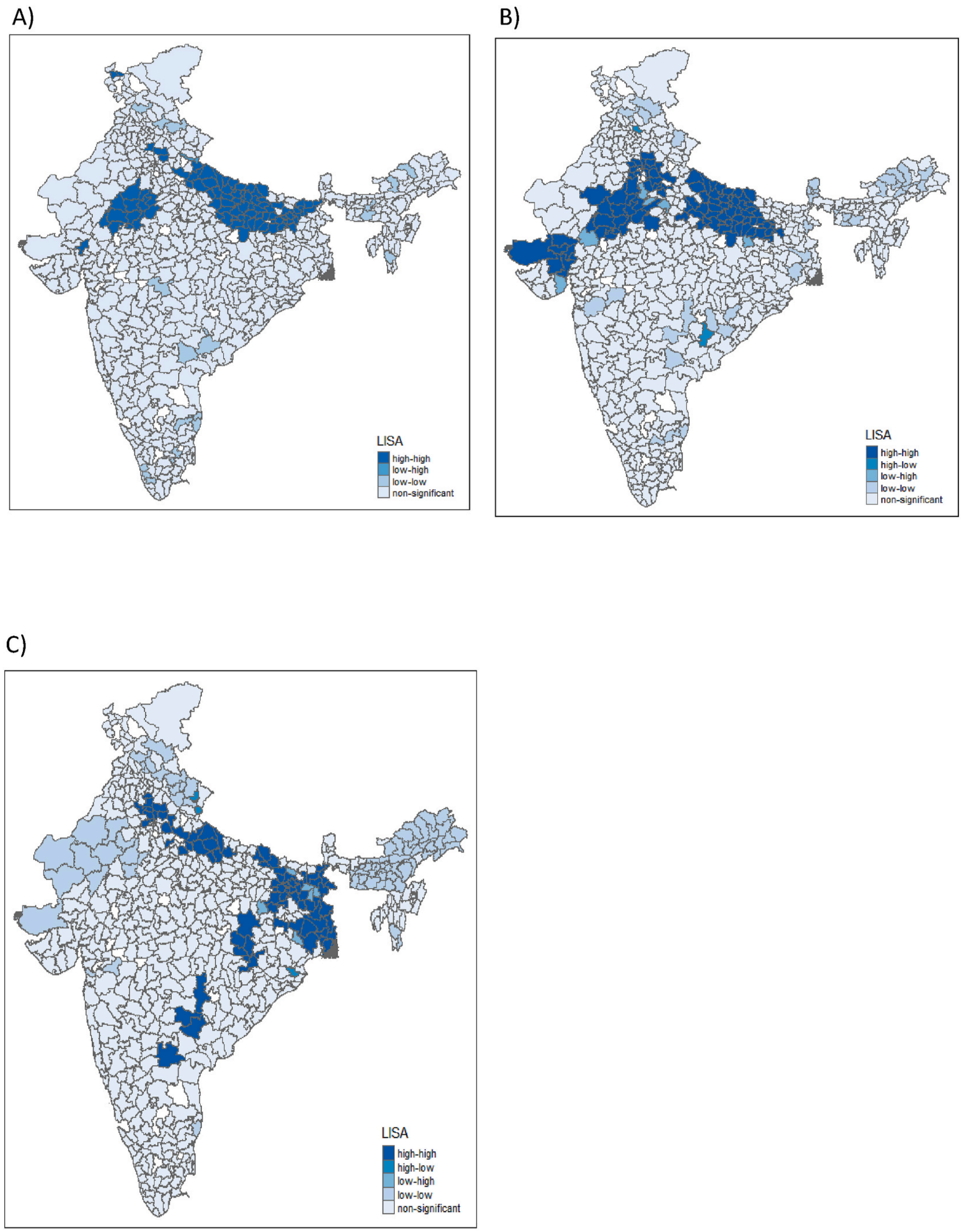

Fig. 3. Local indicators of spatial association (LISA) maps for each outcome highlighting clusters of higher than expected or lower than expected rates of the following outcomes: A) average stillbirths (one or more); B) average RPL, C) average infertility (primary or secondary).

random) to show regions with high or low values that are of interest.

Table 2 shows the unadjusted and adjusted spatial error model results which present the association between arsenic and each of the three adverse reproductive health outcomes. Adjusted models were adjusted for age, wealth quintile, educational attainment, and urban or rural residence. As there is no evidence of substantial attenuation or interactions, we focus on the adjusted models. We find that for all outcomes, in districts with a higher predicted level of arsenic in the groundwater, the average rate of adverse RH outcomes is statistically significantly higher. At the district level, for each percentage point increase in the predicted probability of arsenic in groundwater being greater than 10 μg/L, of the rates of stillbirths are 4.5% higher (95% confidence interval 2.4–6.6, $p < 0.0001$), the rates of RPL are 4.2% higher (95% CI 2.5–5.9, $p < 0.0001$), and the rates of infertility are 4.4% higher (95% CI 1.2–7.7, p=<0.0001). We also find that wealthier districts had a higher proportion of women reporting infertility (1.1%, 95% CI 0.4–1.8, $p = 0.002$) and that districts higher levels of educational attainment had significantly lower rates of stillbirth (−2.6%, 95 CI -4.1 to −1.2, $p < 0.0001$) and infertility (−3.8%, 95% CI -6.2 to −1.5, $p = 0.001$) (Table 2). The spatial autocorrelation coefficient (λ) for all three adjusted SEM models highlight the significant spatial variation in the models.

4. Discussion

Our study supports recent literature that has reported an association

Table 2
Unadjusted (bivariate) and adjusted spatial error model results for effects of district level groundwater arsenic probability of exceeding 10 μg/L on three RH outcomes of interest.

	Stillbirth		RPL		Infertility	
	Unadjusted SEM	Adjusted SEM	Unadjusted SEM	Adjusted SEM	Unadjusted SEM	Adjusted SEM
	β/(95% CI)	β/(95% CI)	β/(95% CI)	β/(95% CI)	β/(95% CI)	β/(95% CI)
Arsenic >10 μg/L	0.044*** (0.023, 0.066)	0.045*** (0.024, 0.066)	0.042*** (0.026, 0.059)	0.042*** (0.025, 0.059)	0.051** (0.019, 0.083)	0.044** (0.012, 0.077)
Age	−0.003** (−0.005, −0.002)	−0.001 (−0.003, 0.001)	0.001 (−0.001, 0.001)	0.001 (−0.002, 0.001)	−0.003* (−0.006, 0.000)	−0.003 (−0.006, 0.000)
Rural (vs Urban)	0.011* (0.003, 0.019)	−0.006 (−0.017, 0.006)	−0.001 (−0.007, 0.005)	0.001 (−0.008, 0.010)	0.005 (−0.008, 0.018)	0.004 (−0.014, 0.022)
Wealth	−0.005*** (−0.008, −0.002)	−0.001 (−0.006, 0.003)	0.002 (−0.001, 0.004)	0.002 (−0.001, 0.006)	0.011*** (0.004, 0.018)	0.011** (0.004, 0.018)
Educational attainment	−0.028*** (−0.038, −0.017)	−0.026** (−0.041, −0.012)	0.001 (−0.007, 0.009)	−0.003 (−0.014, 0.008)	−0.02* (−0.036, −0.003)	−0.038** (−0.062, −0.015)
Spatial Autocorrelation (λ)		0.81		0.81		0.71

Note: Adjusted models include all covariates shown in the table.
*p < 0.05; **p < 0.01; ***p < 0.001.

between arsenic exposure and stillbirth. Further, we identified a strong relationship between arsenic and RPL and infertility. While the link between arsenic and infertility has been suggested in rodent models and small case studies, this is the first documentation of this potential association using nationally representative data of women's reports of difficulty conceiving. Our findings highlight the strong spatial association in the adverse RH outcomes, aligned closely with the spatial distribution of arsenic at the district-level.

Our study is one of the first national and district-level analyses of the association between living in an area with high levels of groundwater arsenic contamination, and adverse RH outcomes. Our study is strengthened by a very large, nationally representative survey that measures multiple outcomes. While the DLHS-3 data was collected in 2007-08, it is one of the only large-scale surveys that asks women to directly report on their experiences in having had difficulty conceiving. This study also leverages a newly published model that predicts fine-scale geographic arsenic contamination in groundwater (Podgorski and Berg, n.d.). Our spatial integration approach is a unique approach to link datasets that capture silo-ed health or environment information. This spatial approach can be replicated in other settings, with available survey data using either GPS coordinates or matched administrative areas (e.g., districts).

Our findings suggest one possible explanation for previously established, yet puzzling geographic variation in infertility concentrated along parts of the Gangetic basin (Patra and Unisa, 2017). Geographic variation in adverse reproductive health outcomes warrants deeper examination of a wider range of environmental determinants at both the state and district level. Treatment for infertility, particularly assisted reproductive technology, is growing rapidly in India's private sector. In addition to policy efforts to regulate such services, heightened focus on identifying and addressing potential underlying determinants, such as arsenic, will be critical for prevention. Similarly, the uneven burden of adverse reproductive health outcomes requires targeted state-level public health responses, particularly strengthening resources in the district public health system (Patra and Unisa, 2017).

Rigorous data and evidence on environmental determinants of reproductive health are generally challenging to identify in low- and middle-income country settings. A population-based, prospective cohort study of almost 3000 women in Matlab, Bangladesh evaluated urinary arsenic levels and several adverse RH outcomes. They found an increased risk of infant mortality, spontaneous abortion, and stillbirth with increasing exposure to arsenic (Rahman et al., 2010). Several other studies from the region have also reported an association of arsenic exposure with spontaneous abortion and stillbirth, with about 2–3 times higher risks among women with high arsenic concentrations in their drinking water (>50 μg/L) (Cherry et al., 2008; Milton et al., 2005; von Ehrenstein et al., 2006). A recent publication on infertility in India highlights several potential causes, such as demographic characteristics and obesity, but did not explore arsenic or environmental toxins, and used a different dataset to estimate infertility using indirect methods (Naina Purkayastha and Sharma, 2021). Overall, the region has a high awareness of groundwater arsenic contamination, and several government-funded programs in place to reduce exposure, including increasing access to piped water. Since the 2007-08 DLHS survey used here, there have been improvements; conducting a future analysis with up-to-date information on both RH outcomes, infertility, and arsenic exposure (including drinking water sources) would provide additional insight into this issue, and whether it has resolved somewhat due to improved conditions.

This study has several limitations. First, it is an ecological analysis, which allows for presentation of associations but not causality. Second, the nature of our data sources require the unit of analysis to be districts, preventing the reporting of data at the individual level. Additionally, the DLHS-3 did not collect water samples, so we rely on the gridded groundwater arsenic dataset to approximate exposure. With only the single time point survey for the adverse RH outcomes, we cannot show temporality. Relatedly, we did not have information on how long the woman had resided in the district at the time of the survey, so it is not possible to measure duration of exposure. Third, while the RH outcomes reported in the DLHS-3 survey are comprehensive they are self-reported. The sociodemographic variables in our analyses are also limited and some individual level risk factors that may be associated with the outcomes, such as tobacco use, were not collected. Lastly, the survey data are older, but unique in their direct assessment of difficulty conceiving in a region that has not historically assessed this metric. And while the arsenic dataset is newer, it is based on estimates of groundwater arsenic, and does not account for interventions to treat water or close high risk tube wells; data collected from in-use water sources may provide better estimates of exposure.

Despite these limitations, we provide evidence for a strong association between arsenic exposure and adverse RH outcomes using a unique combination of datasets. Based on our results, we suggest furthering efforts to mitigate arsenic exposure, which remains high despite awareness of the multitude of health problems arsenic in drinking water is likely cause. Exposure to toxic environmental agents is nearly ubiquitous, however, some areas and populations face heightened exposure and risk ("Exposure to Toxic Environmental Agents," n.d.). Overall, vulnerable and underserved populations remain disproportionately affected. Our results find that even adjusting for income, or educational attainment, the effects of arsenic are still significant. Professional organizations such as the International Federation of Gynecology and Obstetrics have released statements advocating for policy to prevent exposure to toxic environmental contaminants, and to ensure access to a healthy food system inclusive of drinking water free of toxic chemicals ("Exposure to Toxic Environmental Agents," n.d.). Numerous organizations in the field of reproductive medicine have called for action to achieve environmental justice by identifying and reducing exposure to environmental toxins while addressing the consequences of this exposure ("Exposure to Toxic Environmental Agents," n.d.). Climate change may exacerbate some of these exposures. Given the potential harm from environmental toxins, we hope this novel methodology will be replicated to explore associations between adverse health outcomes and environmental toxins broadly across the globe.

Declaration of interests

None declared.

Author contributions

JP conceptualized the study, designed and conducted the data analysis, and drafted the manuscript.

BM conceptualized the study, conducted review of the literature, and supported with drafting and revision of the manuscript.

KK conducted review of the literature and revision of the manuscript.

SD supported with review of the literature, study design, review of key literature, and supported with drafting and revision of the manuscript.

RA critically reviewed the drafting and revisions of the manuscript.

MJH conceptualized the study, informed the design and analysis of the data, and reviewed the manuscript.

JP and MJH verified the underlying data.

Data sharing

All data are publicly available; no primary data collection was collected for this analysis.

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