Environmental Quality and its linkages with age at menarche and menopause: New evidence from India

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Introduction:

India's air and water quality are facing challenges. Almost all of the country's 1.4 billion people live in areas where the annual average levels of Particulate Matter ($PM_{2.5}$) pollution level exceed the WHO guideline; about two-thirds of the population live in areas exceeding the country's national air quality standard of $PM_{2.5}$ (AQLI, 2023). Well-documented negative health effects from air pollution exposure include infertility, metabolic syndrome, hypertension and polycystic ovary syndrome. In Asia, especially in countries such as Bangladesh, India, Indonesia, Iran, Pakistan, and Turkey, groundwater abstraction rates are the highest, extracting over 60 % of groundwater (UNESCO, 2022). Excessive groundwater usage leads to water contamination with heavy metals, nitrates, pesticides, and pathogens that can harm human health (Madhav et al., 2020). Water contaminants can cause infectious diseases and hinder nutrient absorption (WHO, 2022). Evidence worldwide has shown that age at menarche and menopause can be affected by genetic and non-genetic factors (Li et al., 2024). Non-genetic modifiable factors, such as socioeconomic and nutrition status, are well explored in this context (Duan et al., 2020; Jung et al., 2018; Karim et al., 2021; Xu et al., 2023). However, exploring air and water quality in the framework of women's reproductive health, especially menstruation, is emerging. Many air and water components above permissible limits may impact human health and influence the age at first menstruation (Karapanou & Papadimitriou, 2010). Long-term exposure to ambient air pollution was associated with the risk of early menopause. However, those issues were analysed in only a few published studies, mainly from developed nations (Klis & Wronka, 2020; Salgueiro-González et al., 2013; Schell et al., 2009).

No such study has been published in India exploring the association between air and water pollution and age at menarche-menopause using large-scale data. Menstruation is a major public health and human rights issue that is linked to a series of Sustainable Development Goals (SDG). These concerns and gaps make this study, whose objective is to shed light on the linkages between air and water pollution and menstruation, all the more timely and relevant for policies and programmes. We hypothesise that exposure to air and water quality components above the Indian standard is associated with delayed menarche and early menopause among Indian women.

Data and Methods:

We use data from multiple sources.

Air: We used global estimates of annual surface $PM_{2.5}$, averaged from 2019 to 2021, provided by the Atmospheric Composition Analysis Group at Washington University. These estimates were based on Aerosol Optical Depth (AOD) measurements from various satellite sources, including NASA's MODIS C6.1, MISR v23, MAIAC C6, and SeaWiFS satellite data. The satellite data were combined and linked to surface $PM_{2.5}$ levels using geographically weighted regression (GWR). The final estimates were made at a fine resolution of 0.01° × 0.01° (about 1 km × 1 km) to assess exposure. The National Ambient Air Quality Standard (NAAQS) for $PM_{2.5}$ in India is 40 micrograms per cubic meter (µg/m3) as the annual mean.

Ground Water: The study relies on secondary data from diverse sources by the Government of India. Groundwater data (2019–21), encompassing information from 29,065 sites across India, was acquired from the Central Groundwater Board (CGWB). CGWB collected samples from 29,065 sites once during the summer, rainy, and winter seasons, respectively, in 2019–21, providing average data. The cut-off for water-related parameters was based on the specifications of the Bureau of Indian Standards (BIS). A comparative standard of India and other countries in the selected parameters is given in Table 1.

Socio-demographic and health data: Menarche, menopause and different socio-demographic data were derived from the Demographic and Health Survey (DHS), or National Family Health Survey (NFHS-5) in India, conducted between 2019 and 2021.

Table 1: Maximum permissible limits of different parameters for drinking water concentrations: A Comparison of parametric values across the European Union, United States, China, Canada, WHO, and India

Parameters	EU	US	China	Canada	WHO	India (BIS)
Water pH				6.5 - 8.5	6.5–9.2	6.5 - 8.5
Calcium (Ca) – mg/L				200	75	75
Magnesium (Mg) – mg/L				50.0	30	30
Sulphate (SO_4) – mg/L		250			250	200
Chloride (Cl^-) – mg/L	250	250			250	250
Nitrate (NO_3^-) – mg/L	50	10	10		50	45
Fluoride (F^-) – mg/L	1.5	0.7	1.0		1.5	1.0
Total Hardness (TH)				0–75		300
Total dissolved solids (TDS)					1000	500
Electrical Conductivity (EC) – μS/cm	2500				1500	300
Arsenic (As) – mg/L	0.01	0.01		0.01	0.01	0.01

Bureau of Indian Standards (BIS) values are considered for categorising the parameters as 'normal' and 'beyond permissible limits', used in the study

[Note: Categories used in the analysis: Water pH (6.5 - 8.5 as normal and >8.5 beyond permissible limits), Calcium (≤75 normal and >75 mg/l beyond permissible limits), Magnesium (≤30 normal and >30 mg/l beyond permissible limits), Sulphate (≤200 normal and >200 mg/l beyond permissible limits), Chloride (≤250 normal and >250 mg/l beyond permissible limits), Nitrate (≤45 normal and >45 mg/l beyond permissible limits), Fluoride (≤1 normal and >1 mg/l beyond permissible limits), Total Hardness (≤300 normal and >300 mg/l beyond permissible limits), Total Dissolved Solids (≤500 normal and >500 mg/l beyond permissible limits), Electrical Conductivity (≤300 normal and >300 µS/cm beyond permissible limits) and Arsenic (≤0.01 mg/l normal and >0.01 beyond permissible limits)]

Outcome indicators *Outcome indicators:* In this study, two key outcome variables - menarche and menopause - were derived from the NFHS-5 (2019-21) dataset. For menarche, data were collected from women aged 15-24 years. Age at menarche was categorized into two groups: women who reported having their first menstrual period at age 14 or younger were classified as having normal menarche (coded as 0), while those who had their first menstrual period at age 15 or older were classified as having late menarche (coded as 1). The sample for menarche at or before 10 years of age was 415 and hence merged with normal menarche. The menopause variable was created according to the Demographic Health Survey (DHS) guidelines for women aged 30-49 years. Women were considered menopausal if their last menstruation occurred six or more months before the survey, if they had a hysterectomy, if they declared they were menopausal, or if they had never menstruated. Women who were currently pregnant or experiencing postpartum amenorrhea were excluded from the analysis. Menopause was then categorized into two groups: women who experienced menopause before the age of 45 were classified as having early menopause (coded as 1), while those who experienced menopause at the age of 45 years and above were classified as having normal menopause (coded as 0).

***Confounding factors**:* Our analyses controlled for several variables that may influence menopause and menarche. These included marital status (never married, currently married, widowed, others), parity (0,1-2,>2), social group (scheduled tribe, scheduled caste, other backward classes, others), religion (Hindu, Muslim, Christian, others), education (no, primary, secondary, higher), wealth (poorest, poorer, middle, richer, richest), body mass index (BMI as underweight, normal, overweight and obese), region (north, central, east, northeast, west, south).

***Merging environmental data with NFHS-5 data**:* To merge groundwater contamination and $PM_{2.5}$ data with NFHS-5 data, we used the shape file of the NFHS-5 database. We matched the cluster IDs of NFHS-5 data with the groundwater and $PM_{2.5}$ data using GPS coordinates to extract environmental data.

Using Zonal Statistics, we estimated the mean value of air and water quality parameters at district levels in India. Hill states (mentioned below Fig 1) do not have groundwater sites; hence, they are excluded from the analysis of water pollution.

Analysis

Bivariate analysis (using Chi-square) was conducted in order to explore the relationships between menarche and menopause and various socio-environmental factors. Bivariate Local Moran's I statistics and LISA cluster maps were used to examine the spatial association between menarche and menopause and environmental predictor variables at the district level. Adjusted logistic regression (n=179972) and hazard model (n=268699) were then applied to investigate the influence of environmental factors on menarche and menopause further, controlling for a series of confounding factors.

Preliminary findings:

Extent of air and ground water pollution in India: The maps (Fig 1 and Appendix 1) describe the extent of air and water quality across India. $PM_{2.5}$ above 50 µg/m³ (Indian standard cut-off is 40 µg/m³) is largely found in the northern belt of the country. Significant variation in groundwater quality was observed across India, with numerous regions displaying poor quality. Based on a composite index (not shown here), approximately 27% of estimated geographical areas were deemed unfit for consuming groundwater, relied upon by about 85% of rural households and half of the urban households. Clearly, most of the Indian population breathes air with high $PM_{2.5}$ concentration and uses groundwater that is largely polluted in one or the other components analysed in the study.

Association of menarche and menopause with pollution exposure:
Among women aged 15-24 years, 15% had experienced late menarche (ages 15 and beyond). Nearly 17% of women aged 30-49 years experienced menopause. Among those who experienced menopause, 39% had menopause before age 45.

<u>*Bivariate associations*</u>: Bivariate associations (table not shown here) indicate that environmental factors are significantly associated with late menarche and early menopause. For instance, 16% of women exposed to high $PM_{2.5}$ levels experienced late menarche, compared to 12% of those living in areas with $PM_{2.5}$ exposure within permissible limits. Moreover, 39% of women with high exposure to $PM_{2.5}$ reported early menopause, compared to 37% with $PM_{2.5}$ exposure within Indian standard. Similarly, 18% and 39% of women consuming ground water with higher pH (>8.5) experienced late menarche and early menopause, respectively, compared to 15% and 36%, respectively, among those living in areas with pH between 6.5 and 8.5. Furthermore, 17% of women with late menarche and 41% with early menopause experienced water with high calcium levels (>75 mg/l), compared to 15% and 38%, respectively, of women residing in areas reporting normal calcium water levels. Spatial analysis reveals a high spatial association of $PM_{2.5}$ (above 40 µg/m³) with late menarche and early menopause in northern plains. Calcium, EC, fluoride, arsenic and nitrate in water significantly reduce age at menopause, mainly in the west, south-central part of India (Nitrate and EC shown in Fig 2).

<u>*Multivariable associations*</u>: Table 2 indicates the adjusted odds ratios (AOR) and hazard ratios (HR) of late menarche and early menopause. It discloses a strong link between air and water quality and late menarche and early menopause, even after adjusting for confounding factors (Table 2). For example, the odds of late menarche were far greater among those residing in areas with high water pH (AOR: 1.48, CI: 1.39-1.57), higher EC (AOR: 1.15, CI: 1.10: 1.20), and elevated $PM_{2.5}$ levels (AOR: 1.24, CI: 1.17:1.32). Other significant factors included higher TDS (AOR: 1.06, CI: 1.02- 1.10), elevated Arsenic levels (AOR: 1.06, CI: 1.01-1.11), and higher magnesium (AOR: 1.04, CI: 1.00-1.07). For early menopause, the most significant predictors were higher EC levels (HR: 1.25, CI: 1.18-1.32), higher $PM_{2.5}$ levels (HR: 1.13, CI:1.09-1.18), elevated fluoride levels (HR: 1.04, CI: 1.00-1.08), higher calcium levels (HR: 1.10, CI: 1.07-1.14), and higher arsenic levels (HR: 1.05,CI: 1.02-1.18), higher magnesium levels (HR: 1.09, CI: 1.03-1.15), higher water pH (HR: 1.09, CI: 1.02-1.07), as well as higher nitrate

levels (AOR: 1.04, CI: 1.00-1.08). Alkaline water has strong effects in delaying menarche, while water with high electrical conductivity (high dissolved ions) is unfavourable for normal menopause.

Discussions:

The age at menarche in India has declined marginally over the last four decades (13.8 to13.3 years) (Meher & Sahoo, 2024). The average age at menopause in India is 47 years, lower than most other countries where data were available (Prasad et al., 2021). Emerging studies indicate a higher susceptibility of women to toxicological hazards. Women may have different susceptibility to the impacts of toxic exposure, due to differences in physiology in connection with their reproductive phase. Limited studies ascertain environmental exposures in shaping reproductive development in India, a country that stands in the high rung in air and water pollution globally (PIB, 2018**;** CPCB, 2024)**.**

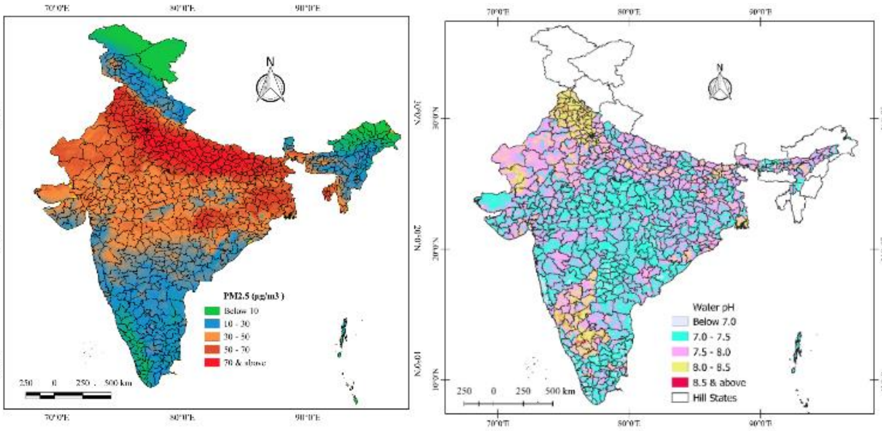
This study explored multiple forms of pollution exposure to age at menstrual and menopause by triangulating data from multiple sources. The study reveals strong spatial and individual-level associations between delayed menarche and early menopause, respectively, with high $PM_{2.5}$ exposure, mainly in the northern plains of India. The possible pathway of particulate matter exposure leading to disturbances in reproductive hormones is complex: PM emitted into the air from multiple sources can be absorbed into the human body and may exert adverse effects on various systems, including reproductive systems (Rudel & Perovich, 2009). Additionally, in PM, heavy metals can interfere with the estrogen receptor, resulting in disturbed biosynthesis of hormones and altered hormone levels. After accumulating various compounds from anthropogenic sources, PM may exhibit endocrine-disrupting properties, which account for the unusual ages at menarche and menopause. Literature suggests that exposure to air pollution during the menopausal transition may contribute to hormonal changes and possibly imbalances in midlife women by decreasing their estradiol levels. This decrease and accelerated rate of estradiol decline, primarily driven by $PM_{2.5}$, could potentially intensify menopausal symptoms (Wang, et al., 2024).

The study reveals multiple parameters of groundwater quality above permissible limits, leading to late menarche and early menopause. Groundwater and surface water are closely linked and interact in many ways. High exposure to groundwater pollutants and late menarche- early menopause clusters are particularly visible in India's western and south-central regions. Literature supports the prevalence of high water pollution levels in the abovementioned regions (Biswas et al., 2024). A study in Bangladesh estimated a 2-year reduction in menopausal age among women who have been exposed to arsenic (Yunus et al., 2014). Groundwater contamination in India is mostly geogenic in nature. However, nitrate contamination is mostly anthropogenic, and its spread can be caused by excessive use of fertilisers and urbanization (GOI-MJS, 2021). Several studies conducted in developed countries have found positive associations between exposure to certain environmental contaminants leading to disruption of endocrinal hormones and reproductive ageing and earlier onset of menopause (Neff et al., 2022). The multi-pollutant models of this study provide preliminary evidence of the impact of groundwater pollution exposure on the reproductive span in India.

Conclusion: Most research in India has focused on changes in the ages of menarche and menopause, but exploring it in the context of the environment remains largely ignored. Our study, the first of its kind in India, has documented that exposure to unacceptable levels of $PM_{2.5}$ and water pollutants is associated with such reproductive health outcomes as delayed menarche and premature menopause. Findings call on programmes and policies to pay attention to the ways in which poor air and water quality affect reproductive health outcomes, notably the ages at onset and cessation of the reproductive span. India is undergoing a pollution-related crisis, and measures to reduce $PM_{2.5}$ and provide safer groundwater are essential, both for general wellbeing and for better reproductive health.

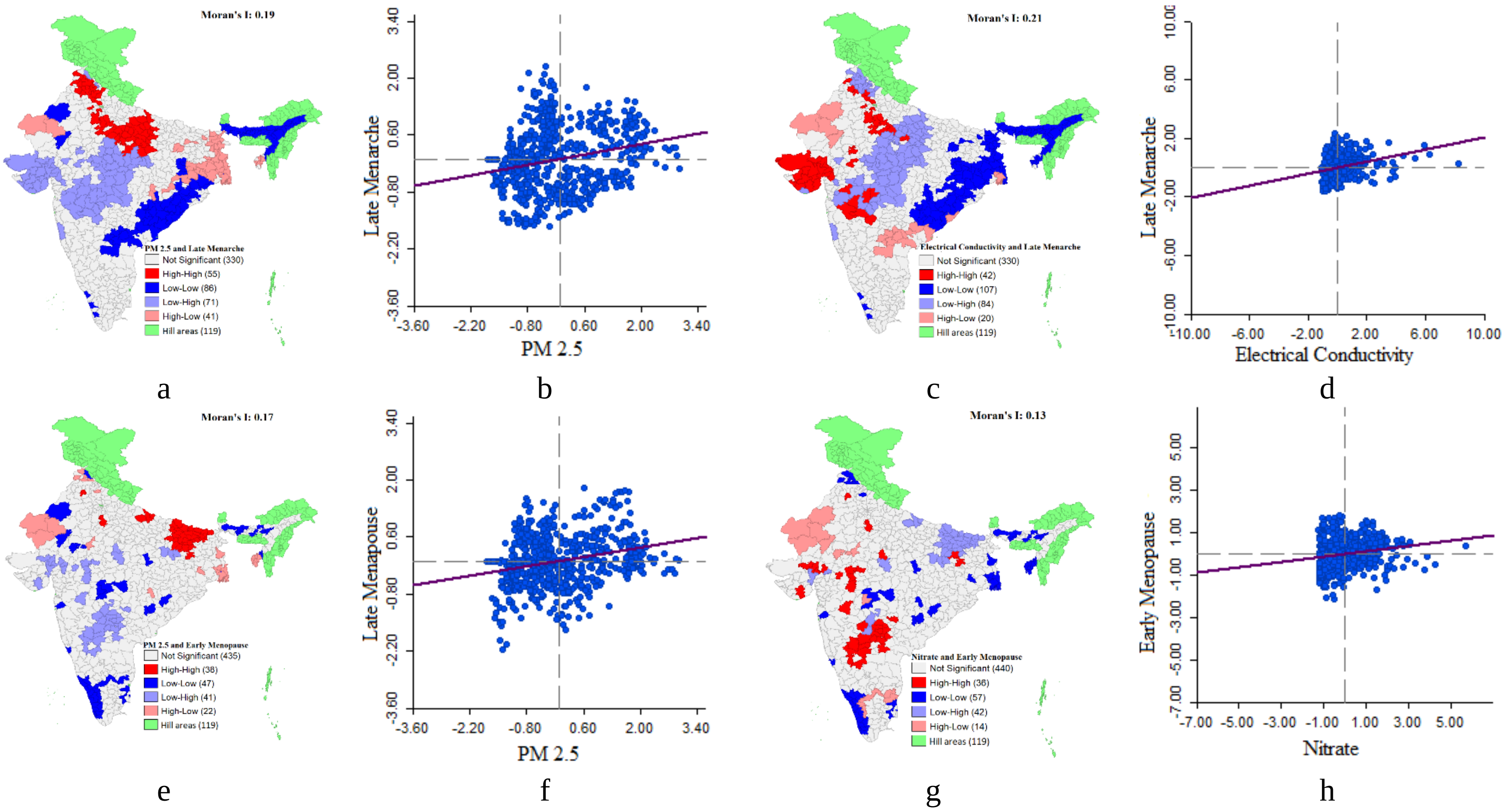
(statistical analysis is still ongoing, exploring separately the effect of air and water quality on the outcome variables, and we anticipate expanding this analysis and discussion further and corroborating the findings with the existing limited literature).

Fig: 1: Spatial distribution PM $_{2.5}$ and pH across India, 2019-21



Note: Hill states, i.e. Jammu- Kashmir, Ladakh, Himachal Pradesh, Uttaranchal, Sikkim, Meghalaya, Manipur, Mizoram, Tripura Arunachal Pradesh are excluded for ground water analysis for 'no data' availability (7 parameters are analysed to understand ground water quality- all maps are not shown here)

Figure 2 (a-h): Bivariate LISA cluster maps and scatter plots showing the geographic clustering of (a-b) PM $_{2.5}$ and late menarche, (c-d) electrical conductivity and late menarche, (e-f) PM $_{2.5}$ and early menopause, (g-h) nitrate and early menopause patterns at district level in India.



Note: Spatial analysis is applied to all parameters considered for water, few maps are shown here

Table 2: Adjusted Odds Ratios (AOR) and Hazard Ratios (HR) (and 95% confidence intervals) from logistic regression analyses assessing the relationship between Air and Water quality and onset of Menarche and Menopause: India 2019-21

Selected Characteristics	AOR [95 % CI]	Hazard Ratio [95 % CI]
	Late Menarche	Early Menopause
	n= 179,972	n= 268699
$PM_{2.5}$ level (µg/m3)		
≤40®	ref	Ref
>40	1.24***[1.17,1.32]	1.13***[1.09,1.18]
pH		
≤8.5®	ref	Ref
>8.5	1.48***[1.39,1.57]	1.04*[1.00,1.08]
Calcium (Ca)		
≤75 mg/l®	ref	Ref
>75 mg/l	1.02[0.98,1.06]	1.10***[1.07,1.14]
Magnesium (Mg)		
≤30 mg/l®	ref	Ref
>30 mg/l	1.04*[1.00,1.07]	1.07***[1.04,1.10]
Sulphate (SO_4)		
≤200 mg/l®	ref	Ref
>200 mg/l	1.04[0.98,1.10]	1.02[0.96,1.08]
Chloride (Cl^-)		
≤250 mg/l®	ref	Ref
>250 mg/l	1.01[0.95,1.07]	0.90[0.76,1.04]
Nitrate (NO_3^-)		
≤45 mg/l®	ref	Ref
>45 mg/l	0.96[0.93,1.00]	1.04*[1.00,1.08]
Fluoride (F^-)		
≤1 mg/l®	ref	Ref
>1 mg/l	1.01[0.94,1.08]	1.02***[1.01,1.03]
Total Hardness (TH)		
≤300 mg/l®	ref	Ref
>300 mg/l	1.05*[1.00,1.10]	1.04*[1.00,1.07]
Total Dissolved Solids (TDS)		
≤500 mg/l®	ref	Ref
>500 mg/l	1.06**[1.02,1.10]	1.02[0.95,1.09]
Electrical Conductivity (EC)		
≤300 µS/cm®	ref	Ref
>300 µS/cm	1.15**[1.10,1.20]	1.25***[1.18,1.32]
Arsenic (As)		
≤0.01 mg/l®	ref	Ref
>0.01 mg/l	1.06**[1.01,1.11]	1.05***[1.02,1.07]
Landcover & Landuse		
Cultivated & Managed Areas®	ref	Ref
Vegetation Cover	0.88***[0.84,0.92]	0.90***[0.87,0.93]
Sub Canopy Cover	0.97[0.93,1.02]	0.96*[0.93,0.99]
Bare Land	0.87***[0.82,0.91]	0.93***[0.90,0.97]
Water Bodies	0.98[0.87,1.12]	1.03[0.94,1.12]

*Controlling for level of schooling completed, wealth quintiles, religion, social castes, marital status, parity, body mass index, and region. *** significant at 1%; ** significant at 5% and * significant at 10%.*

Menarche: 0 = menarche at age 14 or younger (normal) 1= menarche at age 15-24 (late menarche);
Menopause: 0=menopause at age 45-49 years (normal) 1= menopause below 45 years (early menopause)

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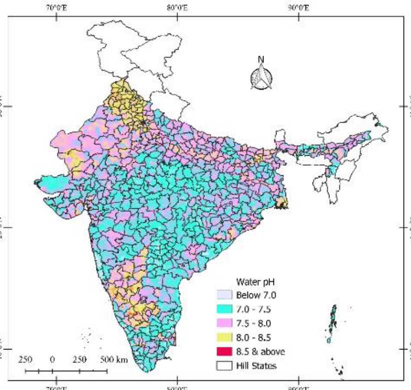
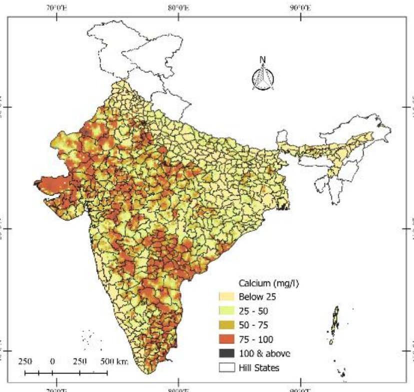
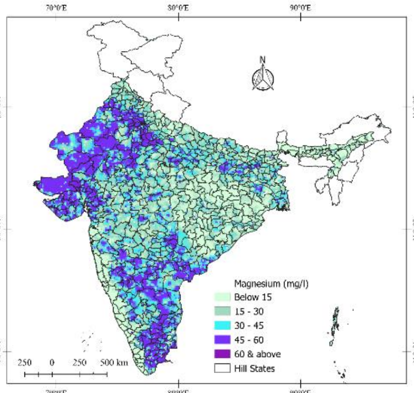
Appendix 1: Spatial distribution of various groundwater components across India



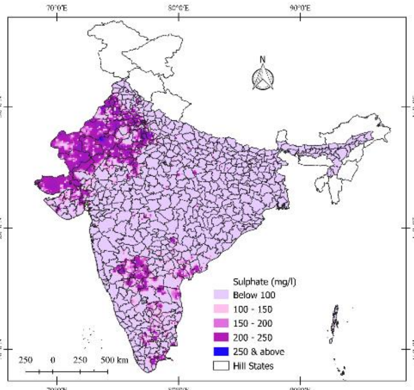
A: pH



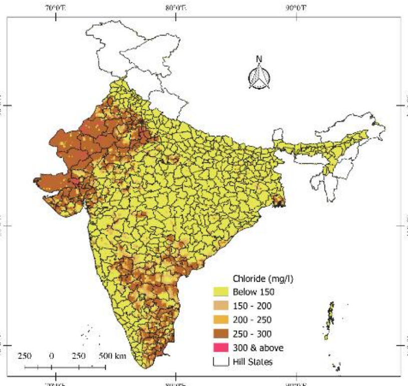
B: Calcium



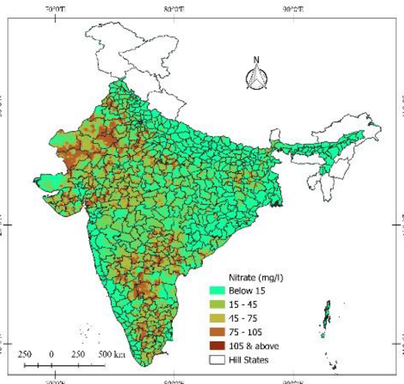
C: Magnesium



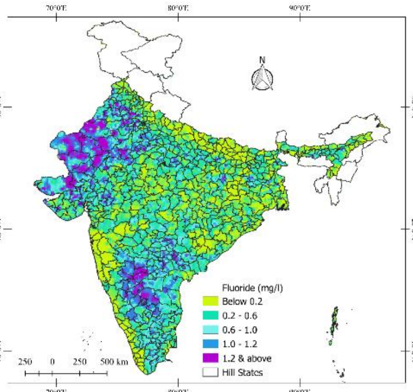
D: Sulphate



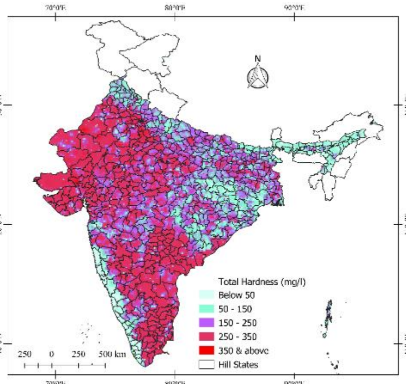
E: Chloride



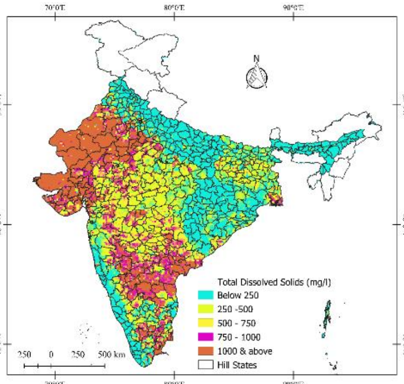
F: Nitrate



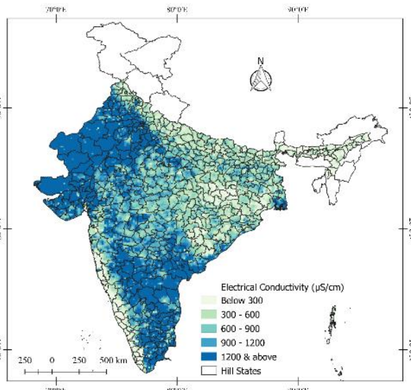
G: Fluoride



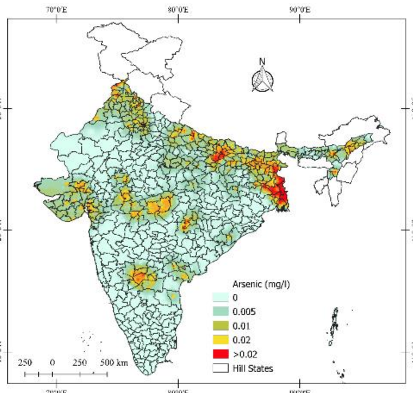
H: Total Hardness



I: Total Dissolved Solids



J: Electrical Conductivity



K: Arsenic