ASSESSING THE RELATIONSHIP BETWEEN TOXIC METAL ENVIRONMENTAL JUSTICE INDICES FOR ARSENIC, CADMIUM, LEAD, AND MANGANESE AND PRETERM BIRTH IN NORTH CAROLINA

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A thesis submitted to the faculty at the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Master's of Science in the Department of Environmental Sciences and Engineering in the Gillings School of Global Public Health.

Chapel Hill
2023

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ABSTRACT

Noemi Gavino-Lopez: Assessing the Relationship Between Toxic Metal Environmental Justice Indices for Arsenic, Cadmium, Lead, and Manganese and Preterm Birth In North Carolina
(Under the direction of Rebecca C. Fry)

Prenatal metal exposure has been associated with an increased risk of preterm birth (PTB). In North Carolina (NC), metal exposure may occur via unregulated private wells. Low-income and people of color populations disproportionately exposed to well water metal contamination can be identified via Toxic Metal Environmental Justice Indices (TM-EJI). Four unique TM-EJIs have been previously determined for inorganic arsenic (iAs), cadmium (Cd), lead (Pb), and manganese (Mn). The aim of this study was to assess the relationship between the TM-EJIs and PTB prevalence in NC, at a census tract level. Linear regression models were employed to analyze the relationship between the TM-EJI indicator variables and PTB prevalence. Notably, census tracts with positive Mn TM-EJIs had a significant PTB prevalence on average 0.31% higher than census tracts with Mn TM-EJIs equal to zero. This finding highlights the impact of joint exposure to chemical and non-chemical stressors on PTB risk.

To my family, you all made this possible.

ACKNOWLEDGEMENTS

I would like to sincerely thank my advisor, Dr. Rebecca Fry, for introducing me to the field of environmental health and allowing me to grow as a researcher under her guidance. Dr. Fry's passion and leadership have continuously motivated me to pursue my own interests. It has been a gratifying experience to work alongside Dr. Fry, who has always cheered me on and believed in my potential as a researcher. Additionally, this endeavor would not have been possible without the close mentorship of Dr. Lauren A. Eaves. Her willingness to share her knowledge and patience have greatly contributed to my success. I would also like to thank Dr. Courtney G. Woods, for serving on my committee and sharing her expertise and feedback as I finalized my research project. Lastly, I would like to thank my parents and sister, Leticia, Omar, and Tania, whose endless support has encouraged me to pursue academic endeavors I could not have imagined.

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LIST OF ABBREVIATIONS

Cd	Cadmium
EPA	Environmental Protection Agency
iAs	Inorganic arsenic
MCL	Maximum Contaminant Level
Mn	Manganese
NHANES	National Health and Nutritional Examination Survey
NCBDMP	North Carolina Birth Defects Monitoring Program
Pb	Lead
POC	People of color
PTB	Preterm birth
TM-EJI	Toxic Metal Environmental Justice Indices
US	United States

INTRODUCTION

Preterm birth (PTB), defined as a live birth before 37 completed weeks of gestation, is a significant public health issue. Subcategories of PTB include, moderate to late preterm, very preterm, and extreme preterm defined by gestational ages of 32-37 weeks, 28-32 weeks, and less than 28 weeks, respectively, each carry increasing severity.[1] Every year, approximately 15 million infants are born prematurely, which is the global leading cause of death in children less than five years old.[1] In 2021, the PTB rate in the United States (US) was 10.5%, while individual states had varying rates.[2] For example, North Carolina (NC) had a PTB rate of 10.8% in 2021, 0.3% higher than the national rate.[3]

Multiple risk factors for PTB exist, including maternal sociodemographic factors. In the US, women 40 years or older had the highest rate of PTB (14.4%) during 2018-2020.[4] Lower individual and community level socioeconomic status, measured by income, job status, and education, are also associated with an increased risk of PTB.[4] Moreover, acial and ethnic disparities in PTB are stark in the US and are linked to instances of systemic racism and discrimination.[5, 6] Notably, Black mothers have the highest rate of PTB (14.2%) in the US, followed by American Indian/Alaska Natives (11.6%), Hispanics (9.8%), and Whites (9.2%).[3] These racial disparities in PTB are not explained by the small genetic differences between racial and ethnic groups nor by differences in behavioral and dietary factors.[6] Instead, different social and physical environmental exposures by racial and ethnic groups may be the primary contributor to the PTB racial disparity.[6] In the US, differences in exposures to environmental stressors are the result of continuous residential, educational, and economic racial segregation.[6]

Among the environmental exposures that may contribute to racial disparities in PTB, there is an important consideration for the potential role of chemical contaminants as an etiologic factor. Several studies have detected an association between PTB and toxic metals and metalloids, including arsenic (iAs), cadmium (Cd), and lead (Pb).[7-9] For example, multiple studies in China have detected a positive association between Cd levels in maternal urine and blood, and PTB.[7] Furthermore, a study conducted by Jeliffe Pawlowski et al. in California determined that women with higher blood Pb levels had increased risk for PTB compared to those with lower blood Pb levels.[8] Moreover, one study in Bangladesh, conducted with a prospective birth cohort during 2008-2011, found a positive association between arsenic exposure, measured through tube wells and PTB risk.[9] It is also important to note that racial disparities have been documented for metal concentrations in US women. Statistical analysis using data from the National Health and Nutritional Examination Survey (NHANES) on chemical biomarkers and demographics demonstrated that heavy metals, including Pb, were significantly higher in non-Hispanic Black women than those in non-Hispanic White women.[10] Levels of other heavy metals, such as Cd and As biomarkers, among Hispanic women were significantly higher relative to Non-Hispanic White Women.[10] Another study assessing NHANES data similarly identified that blood Cd concentrations were higher in non-smoking minority women of childbearing age than in non-Hispanic Whites.[11]

Private well water is a potential source of exposure to metals and metalloids, as they are not federally regulated nor protected by the Safe Drinking Water Act.[12] In NC about 2.4 million individuals rely on private drinking wells as their water source. As a result, the potential for an association between metal exposures via private well water and PTB is a concern.[13] The NCWELL database highlights private well contamination in NC, detecting thousands of private well water tests exceeding the Environmental Protection Agency (EPA) standards for iAs and Pb.[14] Notably, racial disparities in contaminants exposure via private wells exist in NC due its history of municipal underbounding.[15] Underbounded regions are located in municipal extraterritorial jurisdictions, neighborhoods located just outside of municipal limits, but without access to essential services, including public sewage and water systems. Historically, underbounded communities were predominately Black, purposefully excluded from municipal boundaries to limit their political involvement.[15, 16] Consequently, these communities may rely on other water sources such as unregulated private wells.[16] Providing evidence for differential exposure in communities, it has been documented that children residing in unincorporated areas in Wake County, NC had significantly higher blood Pb concentrations compared to children living within municipal boundaries or rural areas.[17] Moreover, children's blood Pb concentration was inversely associated with the median household income of the census block where they resided.[17] The costs associated with testing private wells and installing and maintaining water treatment systems, if needed, often compounded socioeconomic vulnerability.[15, 18]

Based on documented evidence of associations between metal exposure and PTB, and an understanding that race and income influence the extent to which one is exposed to metals via private well water, we set out to determine if there was an association between Toxic Metal Environmental Justice Indices (TM-EJIs) and PTB in NC. TM-EJIs are index values that summarize how private well contamination with one of four metals and demographics (race and income) intersect in a single location. Currently, there are four individual TM-EJIs for iAs, Cd, Pb, and manganese (Mn); their development has been detailed elsewhere.[19] In this analysis, we planned to assess the differences in PTB prevalence between census tracts with contaminated well water above EPA standards and higher or lower averages of people of color (POC) and low-income populations than the state and census tracts with no private well contamination above EPA standards. Given the legacy and continued practice of municipal underbounding, which affects predominantly Black and low-income communities, and that POC and low-income populations have higher baseline rates of PTB, driven by socioeconomic and environmental exposures, we hypothesized that PTB would be higher in census tracts that experience private well contamination above EPA standards and have higher averages of low-income and POC populations than the state when compared to census tracts that did not experience private well contamination.[6, 15, 16, 20]

MATERIALS AND METHODS

PTB Prevalence Data

An ecological analysis was performed to assess the relationship between individual TM-EJIs and PTB. Census tract-level PTB prevalence was calculated from 1.3 million birth certificates inclusive of all singleton non-anomalous livebirths in NC from 2003-2015. Birth certificates were obtained from the North Carolina Birth Defects Monitoring Program (NCBDMP), organized by the State Center for Health Statistics. As a surveillance program, NCBDMP collects information about medically diagnosed birth defects and maintains birth certificate records for live births across the state.[21] The percentage of PTB prevalence was determined for census tracts with an existing population and documented well water tests, n=1,944.

TM-EJIs

TM-EJIs data were previously constructed in another study.[19] Currently, four unique TM-EJIs exist for iAs, Cd, Pb, and Mn. TM-EJIs, calculated at a census tract level, are the product of three variables, including an environmental indicator, demographic data, and a population variable (**Figure 1**). The environmental indicator, for toxic metal contamination in private wells, is defined as the number of well water tests with concentrations exceeding EPA standards for the metal of interest within a single census tract. These standards include a maximum contaminant level (MCL) for iAs and Cd, a secondary MCL for Mn, and a health action level for Pb. The demographic variable takes into account the difference between the average percentage of low-income and POC populations between the census tract and the state. Lastly, the population variable is the percentage that a census tract contributes to the state's overall population. Data used to determine the environmental indicators values for iAs, Cd, Pb, and Mn were obtained from the NCWELL Database, a collection of n=117,960 of well water tests obtained between 1998 and 2019 representative of all counties in NC and 89% of census tracts[14] Estimates for low-income and POC populations at the census tract and state level were obtained from the 2019 American Community Survey demographic data.[22] For each of the four metals, n=2,038 TM-EJIs were calculated, each corresponding to a unique census tract, representative of 92.85% of all census tracts in NC.

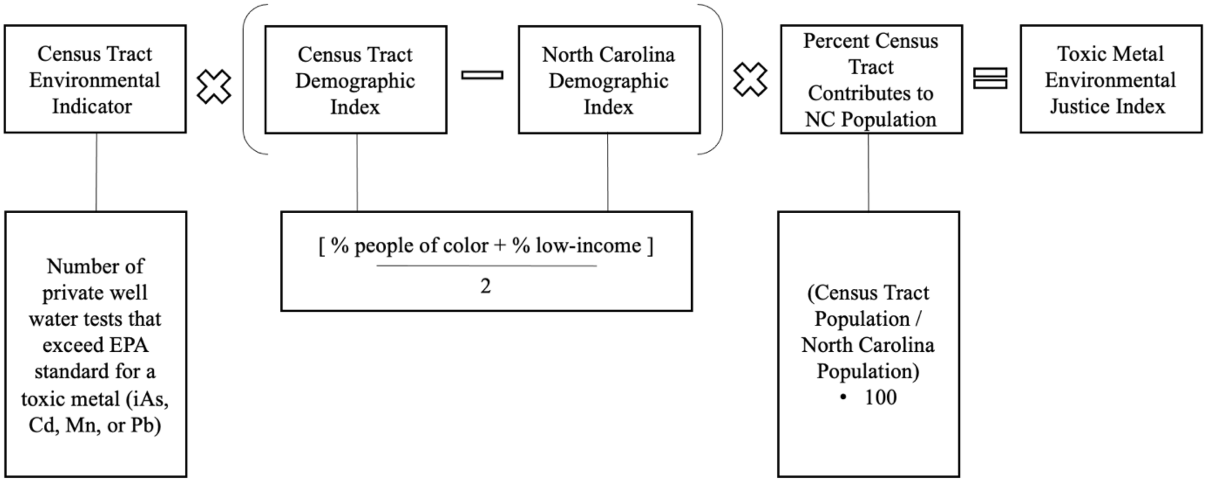


Figure 1. TM-EJI Formula and breakdown of variables. Adapted from Gavino-Lopez 2022.[19]

Statistical Analysis

Due to the demographic variable used to construct TM-EJIs, these indices could either take on a positive or negative value. Positive TM-EJIs are representative of census tracts that experience private well contamination with a given metal above its EPA standard and have a higher average of low-income and POC populations than the NC average. Conversely, negative TM-EJIs are representative of census tracts that experience private well contamination, but have a lower average of low-income and POC populations than the state. TM-EJIs are equal to zero if the census tract did not have any documented well water tests exceeding the standard for the metal of interest.

Therefore, TM-EJI data were transformed into indicator variables, to allow for the assessment of changes in PTB prevalence as a result of TM-EJIs ranging from zero to either positive or negative values (**Table 1**). Four linear regression models were employed to analyze the relationship between the iAs TM-EJI and PTB, Cd TM-EJI and PTB, Pb TM-EJI and PTB, and lastly Mn TM-EJI and PTB. In total, n=1,935 census tracts had PTB prevalence and TM-EJI data available and were therefore included in the regression models. While there are n=2,195 census tracts in NC, n=159 were removed due to a lack of well water tests and/or demographic data and n=103 were removed due to no birth certificate records. Maternal age and education were selected as confounders using a directed acyclic graph approach and analyzed utilizing Dagitty (v3.0); these data were also derived from NC birth certificates **(Supplementary Figure 1)**. Models were adjusted for the census tract percentage of mothers with less than high school education and the percentage of mothers greater than age 40 at delivery due the associated risk of PTB.[23-25]

Table 1. Indicator variable assignment based on raw TM-EJI value.

Raw TM-EJI	$X_{Negative}$	$X_{Positive}$
0	0	0
+	0	1
−	1	0

RESULTS

PTB Prevalence in NC

PTB is a widespread occurrence in NC (**Figure 2**). Based on birth certificates from 2003 to 2015, the highest census tract prevalence of PTB in the state was 15.97%, located in Beaufort County (**Table 2**). Multiple census tracts had the lowest prevalence of PTB observed in the state of 0%, located in Brunswick, New Hanover, Orange, Swain, and Wake counties (**Table 2**). A total of n=84 census tracts had a PTB prevalence less than 5%, while n=328 tracts had a PTB prevalence greater than 10% (**Table 2**).

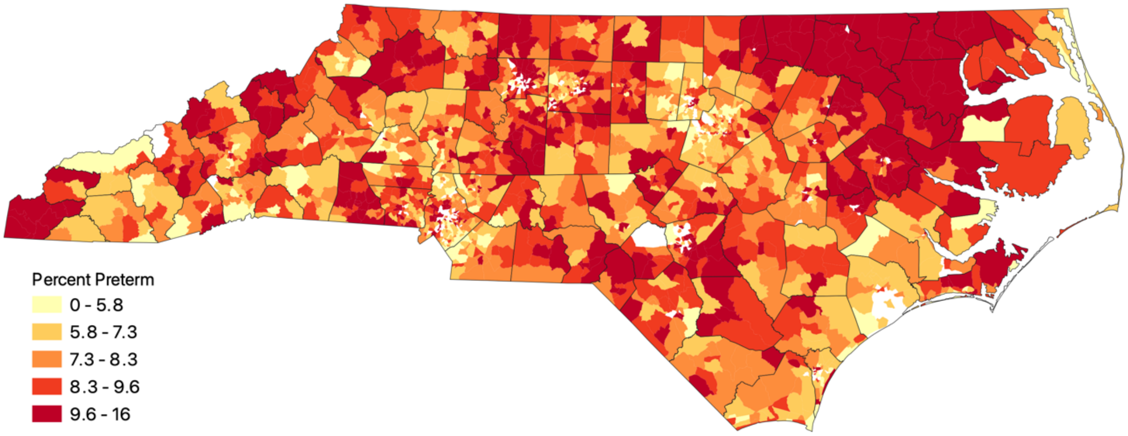


Figure 2. PTB prevalence in NC census tracts.

Table 2. Descriptive statistics of PTB in NC census tracts.

Minimum (%)	Median (%)	Maximum (%)	Below 5% (N (%))	Above 10% (N (%))
0	8.13	15.97	84 (4.32)	328 (16.87)

iAs TM-EJIs and PTB

Overall, non-statistically and statistically significant results were identified through the linear regression model of iAs TM-EJIs and PTB (**Figure 3**). The mean difference in PTB prevalence between positive iAs TM-EJIs and zero iAs TM-EJIs was -0.103% (95% CI: -0.520, 0.315, p-value: 0.630) (**Table 3**). The mean difference in PTB prevalence between negative iAs TM-EJIs and zero iAs TM-EJIs was -0.294% (95% CI: -0.523, -0.066, p-value: 0.012) (**Table 3**).

Cd TM-EJIs and PTB

Overall, no statistically significant results were identified through the linear regression model of Cd TM-EJIs and PTB (**Figure 3**). The mean difference in PTB prevalence between positive Cd TM-EJIs and zero Cd TM-EJIs was 0.105% (95% CI: -0.813,1.02, p-value: 0.823) (**Table 3**). The mean difference in PTB prevalence between negative Cd TM-EJIs and zero Cd TM-EJIs was 0.139 (95% CI: -0.346, 0.624, p-value: 0.574) (**Table 3**).

Mn TM-EJIs and PTB

Overall, statistically significant results were identified through the linear regression model Mn TM-EJIs and PTB (**Figure 3**). The mean difference in PTB prevalence between positive Mn TM-EJIs and zero Mn TM-EJIs was 0.308% (95% CI: 0.0815, 0.534, p-value: 0.008) (**Table 3**). The mean difference in PTB prevalence between negative Mn TM-EJIs and zero Mn TM-EJIs was -0.337 (95% CI: -0.538, -0.137, p-value: 0.001) (**Table 3**).

Pb TM-EJIs and PTB

Overall, borderline and non-statistically significant results were identified through the linear regression model examining the association between Pb TM-EJIs and PTB (**Figure 3**). The mean difference in PTB prevalence between positive Pb TM-EJIs and zero Pb TM-EJIs was 0.233% (95% CI: -0.008, 0.475, p-value: 0.059) (**Table 3**). The mean difference in PTB prevalence between negative Pb TM-EJIs and zero Pb TM-EJIs was -0.152 (95% CI: -0.324,0.021, p-value: 0.085) (**Table 3**).

Table 3. Beta estimates, p-values, and 95% confidence intervals for linear regression models comparing PTB prevalence between positive or negative TM-EJIs and TM-EJIs equal to zero.

	Beta Coefficient (β)	P–value	95% Confidence Interval (CI)
Positive iAs TM-EJIs	-0.103	0.630	-0.520, 0.315
Negative iAs TM-EJIs	-0.294	0.012	-0.523, -0.066
Positive Cd TM-EJIs	0.105	0.823	-0.813, 1.02
Negative Cd TM-EJIs	0.139	0.574	-0.346, 0.624
Positive Mn TM-EJIs	0.308	0.008	0.0815, 0.534
Negative Mn TM-EJIs	-0.337	0.001	-0.538, -0.137
Positive Pb TM-EJIs	0.233	0.059	-0.008, 0.475
Negative Pb TM-EJIs	-0.152	0.085	-0.324, 0.021

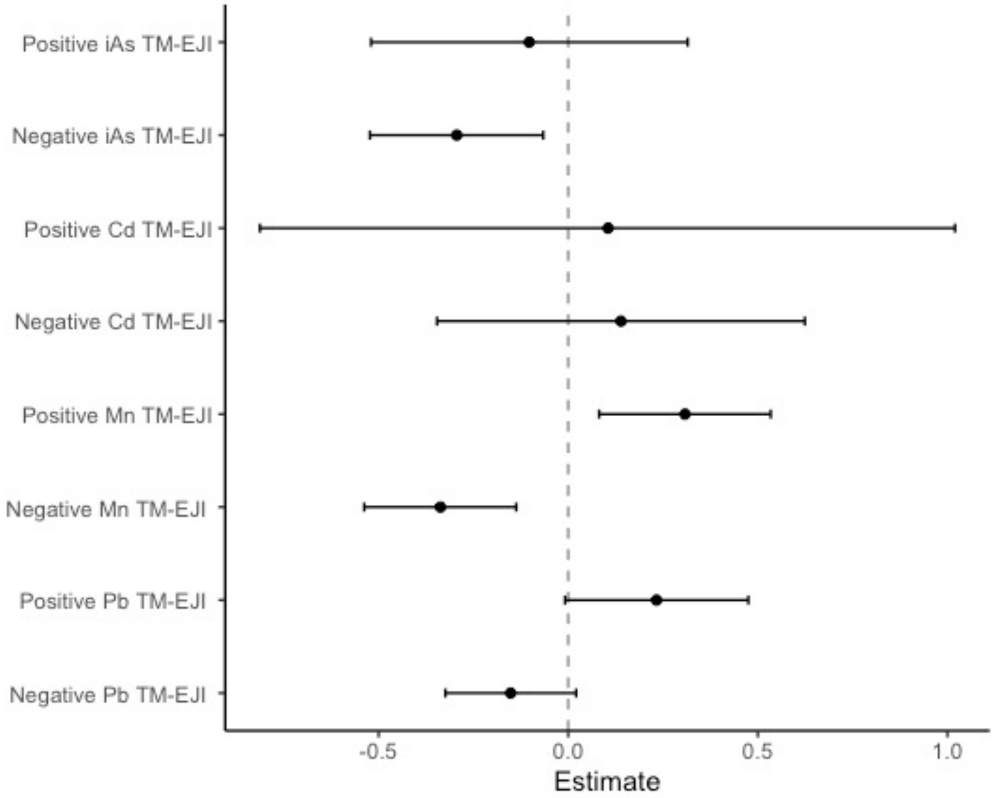


Figure 3. Beta estimates of average tract-level PTB prevalence difference between positive or negative TM-EJIs in comparison to reference group, tracts in which the TM-EJIs equal zero.

DISCUSSION

PTB is a well-documented public health concern and reducing the prevalence is a national priority.[26] While many risk factors are associated with PTB, exposure to metals during the prenatal period is of particular concern. In NC, TM-EJIs for iAs, Cd, Mn, and Pb summarize how private wells contaminated with one of these metals and demographics intersect within a single census tract. Positive TM-EJIs reveal census tracts with POC and low-income populations that are disproportionately exposed to contaminated drinking water. In contrast, negative TM-EJIs reveal census tracts that experience private well contamination with a specific metal above an EPA standard, but among communities with a lower average of low-income and POC populations than the state. Here we set out to assess if an association exists between the individual TM-EJIs for iAs, Cd, Mn, and Pb and PTB at a census tract level.

One notable finding of this present study is the statistically significant association identified between positive Mn TM-EJIs and PTB. These data are in line with prior studies. For example, in a pregnancy cohort in Puerto Rico, increased maternal blood concentrations of Mn were associated with higher odds (OR:1.32, 95% CI: 0.96, 1.8). of PTB.[27] Likewise, in a birth cohort from Boston, Massachusetts elevated maternal urinary Mn concentrations were associated with increased odds ratio of PTB of 1.08 (95% CI: 0.85, 1.37).[28] While these studies have confidence intervals that include the null values, and thus are not statistically significant, they provide estimates that suggest a positive association between Mn and PTB. Other adverse effects of high Mn exposure have also been well documented. For example, an ecologic analysis study in NC assessed the relationship between groundwater Mn concentrations and county-level infant mortality rates and low-birth weight. This study established that for every log increase in groundwater Mn concentration, there was a 2.074 increase in county-level infant deaths per 1,000 live births (p-value: 0.008).[29] These findings implied that increasing from lowest (0.003 mg/L) to highest Mn concentration (0.346 mg/L) in groundwater was associated with an increase of up to 4 infant deaths per 1,0000 live births.[29] No association was found between groundwater Mn concentrations and low-birth weight.[29] In the present study, well water tests used to develop the TM-EJIs documented a maximum Mn concentration of 46,300 ppb while 24.3% of Mn tests were at or exceeded the EPA secondary MCL standard of 50 ppb.[14]

Another significant finding of this study was that census tracts with documented Mn private well contamination above the EPA secondary MCL and a lower average of low-income and POC population than the state had a lower percentage of PTB in comparison to census tracts without documented Mn private well contamination above the standard. One possible explanation may be that while these communities experienced Mn private well contamination, it occurred mostly in a population that had greater access to finances and other resources required for identification and remediation of private well contamination.

In NC, the cost of testing well water for inorganic analytes, through local health departments, ranges between $35 and $250, with a median of $90.[30] Higher testing costs may be prohibitive for lower-income households and deter regular testing.[17, 20] Remediation efforts, in the case of identified contaminants in private wells, may be even more costly than testing. For example, a kitchen tap filter, capable of removing Pb from water costs approximately $200, not including installation fees, and an additional $100 for annual maintenance. The financial burdens associated with testing and maintenance of private well water safety offers insight as to why census tracts with Mn contamination above the MCL and higher averages of low-income and

POC populations, in comparison to the state, experience a higher prevalence of PTB. Although these communities may have the capacity to identify contamination, costs associated with remediation efforts may present an insurmountable barrier, thus providing an avenue for Mn exposure among pregnant women.

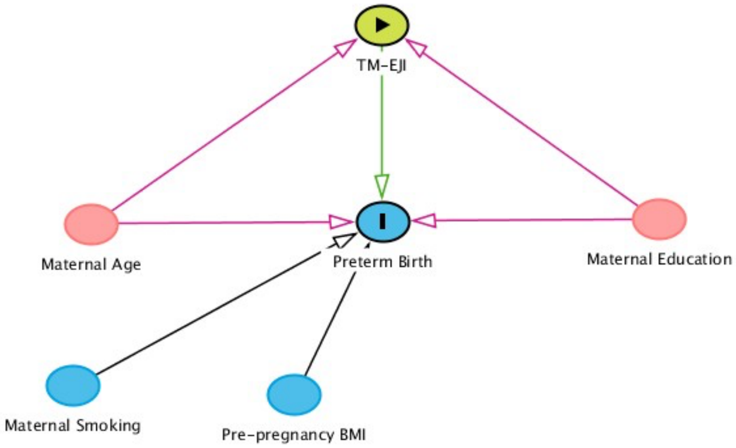
One last notable finding of this study is the borderline statistically significant association between positive Pb TM-EJIs and PTB. In comparison to census tracts that did not have documented Pb private well contamination above the EPA action level, census tracts with Pb private well contamination above the standard and a higher average of low-income and POC populations than the state, experienced a higher percentage of PTB. This finding is supported by literature that assesses the relationship between Pb and adverse pregnancy outcomes. In California, a study that examined deliveries between 1996-2002 observed that blood Pb levels ≥10 μg/dL during pregnancy were associated with a significantly higher risk of PTB.[8] Moreover, Pb exposure *in utero* has also been linked to other adverse effects, including increased risk for miscarriage, low birth weight, and damage to the brain, kidney, and nervous system. Since Pb can readily pass the placenta and is a neurotoxic metal, it can cause neurocognitive damage in developing fetuses due to an underdeveloped blood-brain barrier that facilitates its entry into the brain.[31]

The results of the study should be considered in the context of several factors. First, it is important to note that the TM-EJIs are not an exposure measurement but rather an assessment of an environmental factor (private well contamination with a metal) and demographic data in a single value. Second, the linear regression model employed assesses the relationship between TM-EJIs and PTB at an ecologic level, with the use of a reference group. Third, as an ecologic analysis, this study does not reflect individual experiences particularly those as nuanced as instances of racism and discrimination which we know to be drivers of racial disparities in PTB.[5,6] Lastly, the TM-EJIs used in this study were constructed based on the EPA's previous release version of EJScreen 2.0 which included three variables, an environmental indicator, a demographic index that considered the difference in demographics between the unit of analysis and the country, and a population variable. Currently, the EPA has updated to EJScreen 2.1, which includes an updated methodology for computing the EJ Index, including only two variables, a normalized indicator variable as a percentile and a demographic index for the unit of analysis. Potential next steps in this study include conducting a secondary analysis to elucidate what variables within the TM-EJIs are driving differences in PTB and reconstructing TM-EJIs to reflect the current method employed by the EPA.

Overall, the results from the present study show that PTB prevalence is higher in census tracts with positive Mn and Pb TM-EJIs. These findings highlight the impact of joint exposure of chemical and non-chemicals stressors on PTB risk; emphasizing the importance of public health action and prioritization in communities that are impacted by racial and/or economic disparities and experience private well contamination to help mitigate the prevalence of PTB.

SUPPLEMENTARY FIGURES

Supplementary Figure 1. Directed acyclic graph used to identify covariates.



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