UNIVERSITY OF CALIFORNIA, MERCED

Exposure to environmental chemicals and infertility among US reproductive-aged women

A Thesis submitted in partial satisfaction of the requirements for the degree of Master of Science

in

Public Health

by

Valerie Martinez

Committee in charge:

Assistant Professor Sandie Ha, Chair
Assistant Professor Camila Alvarez
Professor Irene Yen

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The Thesis of Valerie Martinez is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

Professor Irene Yen

Assistant Professor Camila Alvarez

Assistant Professor Sandie Ha, Chair

University of California, Merced

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Abstract

Exposure to environmental chemicals and infertility among US reproductive-aged women

Valerie Martinez

A thesis submitted by Valerie Martinez in partial satisfaction of the requirements for the degree of Master of Science in Public Health (MSPH) at University of California, Merced in 2022. Committee chair: Dr. Sandie Ha

Background: Global environmental chemical exposure is expected to grow but its impacts on fertility is unclear.
Objectives: We characterized exposures to 23 common chemicals across socioeconomic characteristics and examined their relationship with self-reported infertility.
Methods: Non-pregnant women ages 18–49 years without history of hysterectomy or oophorectomy (n = 2,579) were identified from the National Health and Nutrition Examination Survey (2013–2016). Sociodemographic factors and infertility were self-reported. Environmental chemicals were analyzed from biospecimens and dichotomized as high and low based on the median. Logistic regression models estimated the odds ratio (OR) and 95% confidence intervals (CI) for the association between high exposures and infertility.
Results: Women who were older, of other/multi-race, and less educated had higher exposures to chemicals such as pesticides, heavy metals, and flame retardants. There were associations between infertility with cadmium (aOR: 1.83 95% CI: 1.00 – 3.63) and arsenic (aOR: 1.92 95% CI: 1.07-3.44), and two pesticides including hexachlorobenzene (OR: 2.04 95% CI: 1.05-3.98) and oxychlordane (OR: 2.04 (1.12-3.69). Only cadmium and arsenic remain statistically significant in adjusted models. We also found negative associations with two Per- and Polyfluoroalkyl substances.
Conclusions: Chemical exposures varied by sociodemographic characteristics. Associations were mixed and unstable due to small sample, but cadmium and arsenic were associated with infertility.

1. Introduction

Infertility is defined as not being able to achieve pregnancy after 12 months of regular unprotected sex for women ≤ 35 years of age and six months for women over >35 years of age.[1] About one in five (19%) of heterosexual women ages 15 to 49 with no prior births are not able to get pregnant after one year of trying in the United States (US).[1] Among women with one or more prior births, infertility is less common but affects 6% of women ages 15 to 49.[1] The rise in infertility is reflected in the increased rates of assisted reproductive technology (ART), which has increased from 0.7% in 1998 to 2.1% in 2019 in the US.[2,3] In addition, from 1990 to 2017, there was a .37% increase in age-adjusted prevalence of infertility per year.[4] Studies have also suggested that global female reproduction have been on the decline over the last several decades.[5,6] Specifically, from 1960 to 2002, the general fertility rate and total fertility rate per 1000 women declined by about 44%.[6]

The etiology of infertility is unclear but is likely a combination of individual and environmental risk factors. Individual-level risk factors of female infertility are diverse and include genetic disorders, chromosomal abnormalities, lifestyle factors, ovulatory disorders, tubal factors, endometriosis, and older age.[7–12] Among women with infertility issues, 40% experience anovulation, the most common overall cause of female infertility.[13] Polycystic ovary syndrome is another common cause of female infertility that affects 5 to 10% of women in the US and is also associated with anovulation.[1,14] Another possible cause of infertility is fallopian tube obstruction which prevents the sperm from reaching the egg for fertilization.[1] Structural problems in the uterus such as uterine fibroids have also been found to contribute to infertility and affect 5 to 10% of infertile women.[15] Lifestyle risk factors include older age, malnutrition, too much exercise, being obese, having psychological stress, smoking, and alcohol use also contribute to infertility.[9] Occupational factors such as shift work and stress are also known risk factors.[9] However, approximately 8 to 28% of infertility cases worldwide are considered unexplained, which necessitates further research into novel risk factors for the opportunity to intervene.[16]

Infertility has health implications even beyond a timely pregnancy. If a woman is not getting pregnant after one year, studies suggest that a time to pregnancy (TTP) of more than a year can increase the risk of adverse pregnancy outcomes including having a baby with lower Apgar score, low umbilical vein PH, and a need for neonatal intensive care. Longer TTP has also been linked with complications such as preeclampsia, which can then affect the progression of later-onset adult diseases, as explained through the ovarian dysgenesis syndrome (ODS) paradigm.[17,18] The ODS posits that changes in the ovarian function or structure or important and vulnerable stages of human development can later influence risk of gynecologic disorders, fecundity impairments, and later adult onset diseases.[19] Furthermore, the concept of the ODS also states that female fecundity starts at conception or *in-utero* and can be exposed to early damage or impairments occurring at the early stages of reproductive development.[19] Infertility can lead to detrimental psychological and social effects, including experiences of exclusion and divorce and social stigma that may turn into isolation and psychological distress.[20] Although one-third of infertility cases are caused by male factors and one third by female factors, much of the blame for infertility is attributed to women even if the cause of infertility is not related to them.[21,22] In turn, this can lead to having feelings of guilt and

insecurity, and therefore infertile women feel greater psychological stress than infertile men and can be significantly more stigmatized.[23] Although it is generally thought that stigma related to infertility occurs more often in developing countries, it has been found that both industrialized and developing countries stigmatize infertility.[24,25] Infertility has also been linked with marital problems and conflicts, which can cause serious mental and social well-being implications, which can become troublesome as marital relationship is an important factor of support when it comes to infertility treatment.[26,27] More generally, feelings of guilt, anxiety, frustration, turmoil, hopelessness, depression, and feeling worthless in life are common feelings that infertile women experience.[28–32] In fact, compared to the general population, the risk of psychological distress among infertile women is 60% higher.[33] Moreover, infertility treatment can be quite costly, which ranges from $5,000 to $73,000.[34] Each patient, on average, goes through two *in-vitro* fertilization (IVF) cycles (the most common form of infertility treatment), which can bring the total cost (including procedures and medications) to between $40,000 to $60,000.[35] Most of the IVF costs (85%) are often paid out of pocket.[34] Infertility treatments are typically not covered by public or private insurers except for 15 states that require private insurers to at least partially cover fertility treatment.[35] Thus, significant gaps in treatment access remain a concern for families impacted by infertility.

It is widely believed that the low fertility rates in industrialized countries like the US are caused by various factors, such as the increasing number of women working outside the home, postponement of the desire to have a child, and the decreasing ideal family size, but there has been increasing evidence that point to environmental chemicals as a contributor to the increasing patterns and trends of infertility. Of specific concern is the potential influence of ubiquitous environmental chemicals on infertility. According to the Centers for Disease Control and Prevention (CDC), environmental chemicals consist of chemical compounds or elements that are present in the air, water, food, soil, dust, or any other environmental medium, such as consumer products.[36] Globally, the use of chemicals other than pharmaceuticals is expected to grow by 70% in 2030.[37] The US is the second largest producer in the chemical business, contributing to about 13% of the world's total chemical production.[38] In 2021, chemical production increased by 1.6% and according to industry experts, the production of chemicals is expected to increase by 4.1% in 2022 and expand to 2.4% in 2023.[39,40] Over the past 40 years, the global chemical manufacturing industry has been growing significantly and is expected to continue growing at a rate of 3.4% annually until 2030.[41,42] Currently, approximately 70,000 to 100,000 chemicals in the global commerce and 48,000 "high production volume chemicals" make up the majority of the global chemical production.[42,43] The US National Toxicology Program has registered over 80,000 chemicals and almost 2,000 new chemicals are being circulated every year.[44] While many of these chemicals such as phthalates have been banned or extremely restricted in other countries due to their reproductive toxicity, many are still produced and used in the US.[36] In addition, increased industrial activities have contributed to increased exposure to heavy metals such as cadmium and arsenic found either in air, soil, food, or water.[45–47] Such chemicals are considered priority metals for environmental health efforts because of their high degree of toxicity and ability to cause human poisonings.[46,48,49] Meanwhile, increased use of flame retardants, plastics, personal care products, household cleaning products, paint, and non-stick surface, has led to increasing population exposure to potentially dangerous

chemicals, especially for people of color, pregnant women and low-income individuals.[50,51]

Numerous classes of environmental chemicals that are considered racially/ethnically disparate are commonly used in personal care products, suggesting that there are cultural factors that influence the use of these products and, by extension, exposures to these chemicals.[52] The increasing number of women participating in the work sectors due to industrialization has increased the exposure of women to various chemicals, and the effects of occupational exposure to these chemicals may result in a range or adverse reproductive outcomes.[53] As a result, there are concerns that ubiquitous environmental chemicals may contribute to infertility through multiple routes of exposure including digestion, inhalation, and/or absorption through dermal contact. Along with the increased population exposures, there is limited understanding regarding potential differences in chemical exposures across socioeconomic groups. Few studies to date have identified sub-populations of reproductive-aged women who may have a particularly high risk of exposure to environmental chemicals. This is an important knowledge gap for health equity efforts as disparities in exposures may contribute to known reproductive health disparities.[54] This is especially important when ethnic minorities such as Black and American Indian/Alaskan Native women are disproportionately affected by maternal mortality, preterm birth, and other adverse reproductive outcomes.[55,56]As such, to understand further the effects of environmental chemicals on reproductive health, racial and ethnic disparities in exposures remain a critical knowledge gap because environmental chemicals can be found in a wide range of sources including occupation, personal products, diet, and the built environment, all of which are socially patterned.[57–68]

Studies suggest that the biological mechanisms linking environmental chemicals and adverse health outcomes include endocrine disruption, oxidative stress, and systemic inflammation.[69–71] For example, bisphenol-A (BPA), commonly found in shatterproof windows, eyewear, water bottles, and epoxy resins that cover metal food cans, bottle tops, and water supply pipes, is detected in about 89% of US women ages 16 to 49 years of age from 2011 to 2012.[72] BPA has been shown to have estrogenic activities in the hypothalamus, which interrupts the proper functioning of the gonadotropin-releasing hormone (GnRH), a hormone responsible for its key role in human reproduction by regulating puberty onset, sexual development, and ovulatory cycles in females. [69,72,73] Similarly, per- and polyfluoroalkyl substances (PFAs), which can be found in food packages, cleaning products, paint, varnishes, and sealants, has been detected in drinking water in more than 16 million Americans in 33 states.[74,75] PFAs are unique chemicals due to their persistence in the environment and their capacity to bioaccumulate.[76,77] PFAs can induce oxidative stress that ultimately influences the risk of infertility by affecting progesterone production, increasing reactive oxygen species (ROS) production, and disrupting progesterone hormonal activity.[78] Furthermore, more mature literature on the health impacts of heavy metals (from smoking exposure) has also suggested that oxidative stress and systemic inflammation processes induced shortly after exposure may ultimately influence risks of multiple adverse health outcomes such as heart disease and cancer.[79,80]

Consistent with the biological plausibility discussed above, several epidemiological studies have reported elevated BPA levels among infertile women compared to fertile women.[81,82] Nevertheless, the literature on health impacts of

environmental chemicals is relatively scarce and include very few large human studies. More specifically, the effects of environmental chemicals on infertility that have been explored more through *in-vitro* and animal studies.[83,84] While animal studies suggest significant negative impacts on fertility outcomes (e.g. infertility) as a result of exposure to environmental chemicals, the overall evidence regarding this relationship remains limited and inconclusive.[85–89] As such, the potential impact of environmental chemicals on human fertility needs further investigation.

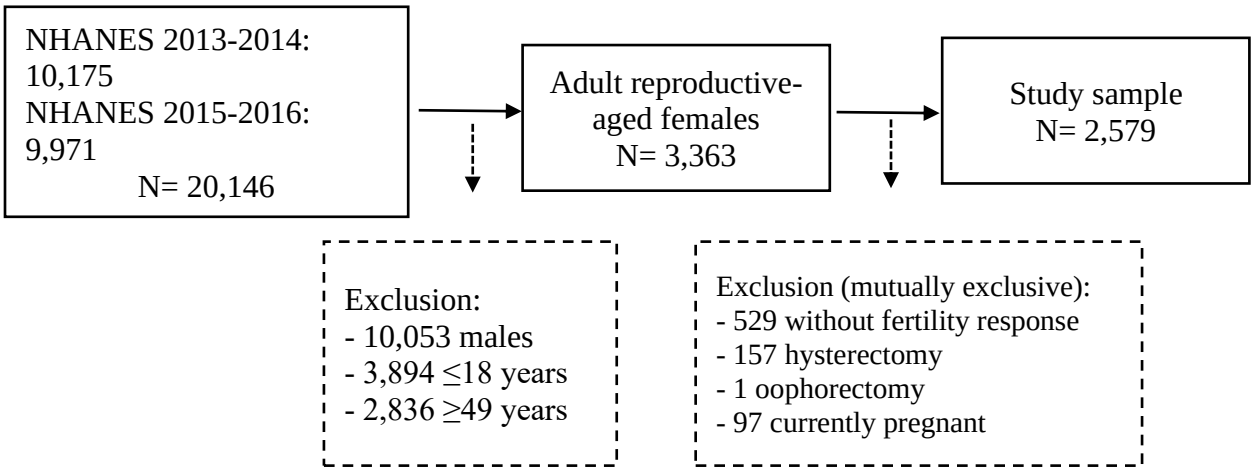
Epidemiological studies regarding environmental chemicals and fertility have been limited and inconsistent because of high heterogeneity in the study populations, sample size, measurement approach for the exposure, and ascertainment of infertility outcome. Furthermore, there is limited understanding regarding potential differences in chemical exposures across socioeconomic groups. Given the increased diversity of our population and differences in behavior and awareness, it is critical to identify potentially high-risk population(s) for targeted intervention. Such knowledge will also shed light on potential contributors to sociodemographic disparities in infertility rate. To address the gaps identified above, the purpose of this cross-sectional study is two-fold. First, we characterized the exposures to environmental chemicals in US reproductive-aged women and explored whether exposures vary by sociodemographic factors. Second, we assessed the relationship between exposure to environmental chemicals and self-reported infertility. We hypothesize that exposure to environmental chemicals vary by socioeconomic indicators and is positively associated with the odds of self-report infertility in US reproductive-aged women.

2. Materials and Methods

2.1 Data and participants

Conducted by the CDC and the National Center for Health Statistics, the National Health and Nutrition Examination Survey (NHANES) is a cross-sectional, nationally representative survey designed to assess the health and nutritional status of adults and children in the US.[90] NHANES utilizes a complex, multistage, probability sampling design to select participants representative of the civilian, non-institutionalized US population. The study collects comprehensive data from self-reports; medical, dental, and physiological assessment; as well as laboratory tests, all of which are administered by centrally trained professionals. NHANES data are released in 2-year cycles, and for the purpose of this study, we utilized cycles 2013-2014 and 2015-2016 (N= 20,146). After excluding males (n= 10,053); children below 18 (n= 3,894) and older adults over 49 years of age (n= 2,836); women who were pregnant at the time of survey (n= 97) or had a history of oophorectomy or hysterectomy (n=157, n= 1, respectively); and those who did not answer the infertility question (n= 529), the final analytic sample includes 2,579 women. Figure 1 illustrates how participants were selected. Given the anonymous nature of the data, no informed consent was necessary.

Figure 1. Study sample selection, NHANES (2013-2016).



2.2 Exposure Assessment

The primary exposures of interest were 23 ubiquitous environmental chemicals belonging to six chemical classes assessed in the NHANES (Table S1). Most chemicals were measured in subsets which include about one-third of our sample of 2,579 individuals. Additionally, in the NHANES, not all classes of chemicals were measured in each data cycle. Thus, we examined the 2013-2014 and 2015-2016 cycles as they represent the most recent data at the time of analysis and encompass a wider variety of chemicals. The chemicals were assessed using urinary, blood or serum samples as indicated in Table S1. Details regarding the methods of data collection for these chemicals has been previously published.[91,92] Briefly, for chemicals that were based on blood plasma, the samples were vortexed, diluted, and then were measured by inductively coupled plasma mass spectrometry. Urinary samples (24-hour) were analyzed using on-line solid phase extraction (SPE) coupled to high performance liquid chromatography (HPLC)-isotope dilution tandem mass spectrometry. Blood serum samples were collected in non–anticoagulant-containing (red top) vacuum tubes and prepared by a standard protocol.[93] Regardless of specimen type, concentrations of chemicals were available as continuous variables. NHANES also captured the limit of detection (LOD) or maximum limit of detection (MLOD) depending on the environmental chemical and the type of biospecimen each of the environmental chemicals was collected in (Table S1). For the second aim, due to the non-normal distribution and the low prevalence of infertility, we dichotomized each chemical based upon the median: a) high exposure, defined as above the median of the chemical-specific distribution, and b) low exposure, defined as at or below the median of the distribution.

2.3 Outcome Assessment

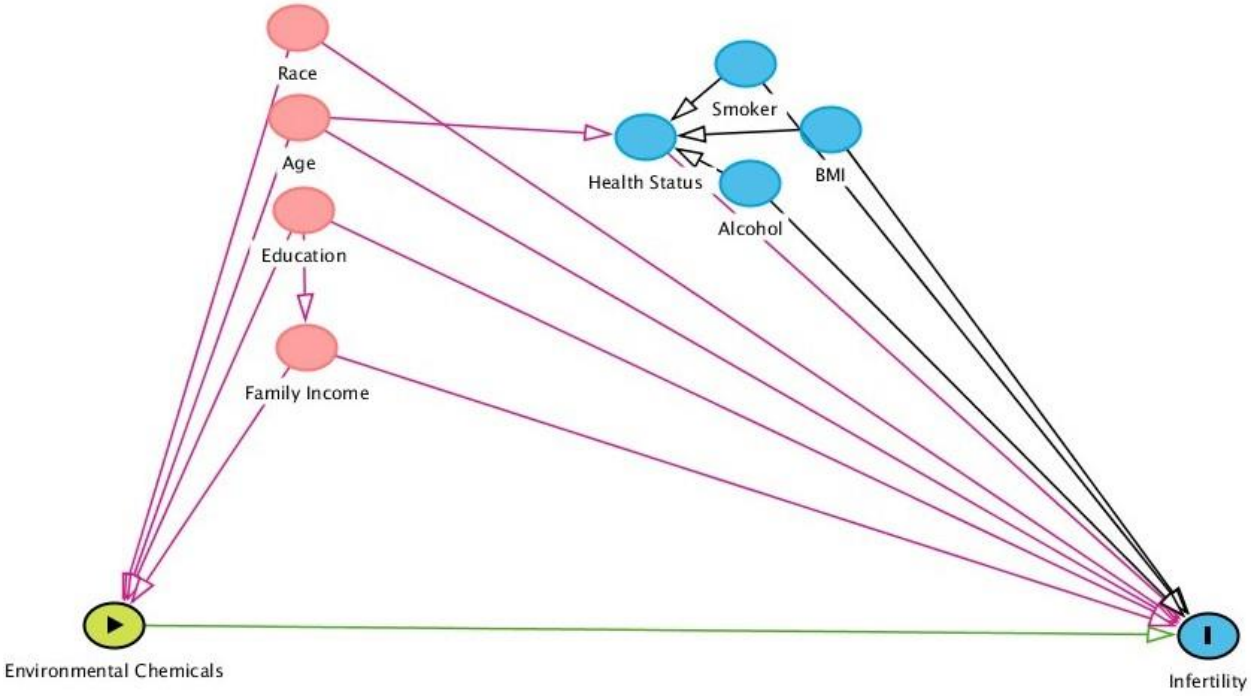
The primary outcome was self-reported infertility, which was assessed in the reproductive health questionnaire of the NHANES. The question used to assess infertility was “Have you ever attempted to become pregnant over a period of at least a year without becoming pregnant.” If a participant responded “Yes” then they were categorized as “ever infertile”, if a participant responded “No” then they were categorized as

"fertile." The questionnaire was conducted via computer-assisted personal interviews administered by qualified interviewers in participant's residence. Participants that did not speak English or Spanish had interpreters used.

2.4 Sociodemographic and health characteristics

For sociodemographic factors we explored age (in years): 18-29,30-39,40-49; race/ethnicity: Non-Hispanic Whites, NH Blacks, Hispanic, NH Asians, Other/Multiple race groups; educational levels: less than high school, high-school graduates, some college or Associates in Arts (AA) degree, college graduate or more; annual family income levels: less than $45k, $46-$99k, more than $100k. Other confounders that were considered included health status: very good/excellent, good, and fair/poor; body mass index (BMI): underweight, normal, overweight, obese; smoking status: never smoker, former smoker, current smoker; alcohol use: yes, no. These confounders were identified using a directed acyclic graph, and were all self-reported, except for BMI, which was measured through physical examinations at the mobile examination center (DAG, Figure 2).

Figure 2. Direct acyclic graph to identify potential confounders.



2.5 Statistical Analysis

The data cycles from 2013 to 2014 and 2015 to 2016 were combined using appropriate sampling weights determined by the NHANES criteria and documentation.[90] Kruskal Wallis tests were conducted to compare the difference in exposure to environmental chemicals across the different demographic factors. Logistic regression models estimated the odds ratio and 95% confidence intervals for the association between

environmental chemicals and self-reported infertility, comparing those in the high exposed to those in the low exposed group. Models adjusted for potential confounders and complex probability sampling. We used three different models. The first model is an unadjusted model that only accounts for complex probability weighting. The second model adjusts for complex sampling and potential confounders identified by the DAG (Figure 2). In the third model, we included all covariates that were both associated with the exposures and the outcome of interest based on exploratory analyses. Alpha was set at 0.05 for statistical significance.

To examine whether the impact of various chemicals on infertility differed by socioeconomic factors, we tested interaction terms between each chemical and age, race, education, and family income. Interactions with p-value <0.10 were considered statistically significant and further investigated. Since the exposure definition cut-off at the median is somewhat arbitrary, we also considered a different cut-off at the 75th percentile in a sensitivity analysis.

3. Results

The final analyses included a total of 2,579 non-pregnant women ages 18 to 49 who did not have a history of hysterectomy or oophorectomy. Table 1 presents the characteristics of the study participants overall and by self-reported infertility status. The estimated prevalence of self-reported infertility in the study population was 12.6% (95% CI: 11.0-14.2). The majority of study participants were between the ages of 18 to 29, NH White, had an educational level of some college, had an annual family income of less than $45,000, drink alcohol, reported having a good health status, were never smokers, were underweight or had normal weight, and reported a good to excellent diet. Compared to their counterparts', self-reported infertility was significantly more prevalent among women who were ages 40 to 49 years (19.8% vs. 5.6% in women 18-29), had an income of over $100,000 (16.7% vs. 9.9% among those who had <45K) and women who were married or cohabiting (17.0 vs. 7.7% among single/divorced/widowed women) or were obese (17.9% vs 10.1% among those with normal weight).

Table 1. Individual characteristics of reproductive-aged women from the 2013-2016 National Health and Nutrition Examination Survey (NHANES) by infertility status (unweighted *n* = 2,579).

Characteristics	All N (% CI) [a]		Infertility[a]		No Infertility		*p*-value[b]
	n = 2,579	% and CI[c]	n = 293	% and CI[d]	n = 2,286	% and CI[d]	
Age (years)							**<.0001**
18-29	1,049	39.17(36.34-42.00)	64	5.63(4.03-7.22)	985	94.36(92.77-95.96)	
30-39	751	30.13(27.64-32.62)	98	14.57(11.60-17.53)	653	85.42(82.46-88.39)	
40-49	779	30.68(28.32-33.04)	131	19.75(16.09-23.42)	648	80.24(76.57-83.90)	
Race/Ethnicity							0.2227
NH White	842	57.34(51.04-63.64)	111	13.89(11.08-16.71)	731	86.10(83.28-88.91)	

Characteristics	All N (% CI) [a]		Infertility[a]		No Infertility		*p*-value[b]
	n = 2,579	**% and CI[c]**	**n = 293**	**% and CI[d]**	**n = 2,286**	**% and CI[d]**	
NH Black	551	13.06(9.54-16.58)	64	12.22(9.36-15.07)	487	87.77(84.92-90.63)	
Hispanics	767	19.68(15.05-24.31)	74	10.43(8.26-12.59)	693	89.56(87.40-91.73)	
NH Asians	310	6.19(4.85-7.52)	30	9.69(6.74-12.64)	280	90.30(87.35-93.25)	
Other/Multi	109	3.71(2.88-4.54)	14	11.80(5.03-18.58)	95	88.19(81.41-94.96)	
Education Level							0.2580
Less than High School	467	13.32(10.97-15.68)	40	9.23(5.69-12.77)	427	90.76(87.22-94.30)	
High School graduate/GED	557	18.93(16.24-21.63)	56	11.51(8.27-14.75)	501	88.48(85.24-91.72)	
Some College/AA Degree	875	34.79(32.04-37.54)	112	12.99(10.55-15.43)	763	87.00(84.56-89.44)	
College Graduate or more	676	32.87(28.69-37.05)	84	14.33(10.99-17.67)	592	85.66(82.32-89.00)	
Missing	4	0.06(0.00-0.14)	1	21.80(0.00-63.33)	3	78.19(36.66-100.00)	
Marital Status							**<.0001**
Married/Cohabiting	1,343	57.63(54.12-61.14)	211	16.97(14.22-19.71)	1,132	83.02(80.28-85.77)	
Single/Divorced/Widow	956	36.50(33.05-39.95)	78	7.69(5.92-9.47)	878	92.30(90.52-94.07)	
Missing	280	5.86(4.74-6.97)	4	1.13(0.00-2.43)	276	98.86(97.56-100.00)	
Annual Family Income							**0.0003**
< $45k	1,242	40.97(37.58-44.35)	127	9.94(7.68-12.20)	1,115	90.05(87.79-92.31)	
$45k - $100k	713	29.38(26.84-31.92)	86	14.51(11.17-17.85)	627	85.48(82.14-88.82)	
≥ $100k	434	23.69(19.75-27.63)	67	16.67(11.84-21.49)	367	83.32(78.50-88.15)	
Missing	190	5.94(4.55-7.33)	13	6.19(3.29-9.08)	177	93.80(90.91-96.70)	
Alcohol Use							0.2367
Yes	1,595	70.55(66.64-74.46)	204	13.27(11.31-15.24)	1391	86.72(84.75-88.68)	
No	89	29.44(25.53-33.35)	89	11.17(8.29-14.05)	895	88.82(85.94-91.70)	
General Health Status							0.3592
Excellent/Very Good	992	44.96(41.53-48.39)	104	11.99(9.18-14.80)	888	88.00(85.19-90.81)	
Good	1,059	39.12(36.40-41.83)	117	12.34(9.88-14.80)	942	87.65(85.19-90.11)	

Characteristics	All N (% CI) [a]		Infertility[a]		No Infertility		*p*-value[b]
	n = 2,579	% and CI[c]	n = 293	% and CI[d]	n = 2,286	% and CI[d]	
Fair/Poor	528	15.91(13.60-18.21)	72	15.30(11.23-19.37)	456	84.69(80.62-88.76)	
Smoking Status							0.6979
Current	425	18.22(16.38-20.05)	56	12.54(8.93-16.16)	369	87.45(83.83-91.06)	
Former	261	13.04(10.53-15.55)	41	14.51(9.96-19.05)	220	85.48(80.94-90.03)	
Never	1,893	68.73(65.56-71.90)	196	12.33(10.31-14.36)	1,697	87.66(85.63-89.68)	
Body Mass Index							**0.0018**
Underweight/Normal (0 – 24.99)	980	39.70(36.44-42.97)	91	10.05(7.83-12.27)	889	89.94(87.72-92.16)	
Overweight (25.0 – 29.99)	611	23.69(21.58-25.81)	50	8.95(5.65-12.25)	561	91.04(87.74-94.34)	
Obese (30.0+)	988	36.59(34.11-39.06)	152	17.88(14.07-21.70)	836	82.11(78.29-85.92)	
Healthy Diet							0.2225
Excellent/Very Good/Good	1,680	70.14(67.57-72.71)	183	11.80(9.80-13.80)	1,497	88.19(86.19-90.19)	
Fair/Poor	899	29.85(27.28-32.42)	110	14.66(10.81-18.52)	789	85.33(81.47-89.18)	

[a] The sample size (*n*) is unweighted but the percentage (%) accounted for the complex sampling design.
[b] *p*-values were obtained using Kruskal-Wallis tests and were accounted for the complex sampling design.
[c] Column percent
[d] Row percent

Tables S2-S11 describes the distributions of environmental chemical exposures by participant characteristics including age, race/ethnicity, education, household income, marital status, health status, BMI levels, smoking status, alcohol use, and infertility status. Generally, the median concentration of brominated fire retardants (BFRs) was higher among women who were older, of multiple and or other races, and had less than high school education. For example, one BFR chemical 2,2',4,4',5,5'-Hexabromobiphenyl (PBB-153) was significantly higher among women who were married or cohabiting or had normal BMI weight, current smokers, or self-reported infertility. Broadly, the median concentration of volatile organic chemicals (VOCs) was greater among women NH Blacks, had less than high school education, had an annual family income of $100k or greater, current smokers, and drink alcohol (independent of each other). Cotinine was elevated among women who were younger, NH Blacks, less educated, had an annual family income of less than $45k, were single/divorced/widowed, had a general health status of fair or poor, had a BMI level of underweight, were current smokers or drank alcohol. Median concentrations of metals were more pronounced in women who were older between the ages of 40 to 49, and NH Asians. For example, lead and mercury concentrations were higher in women with more education, had a higher annual family income, or who drank alcohol. Additionally, median concentration of lead and cadmium

were higher in women who were overweight or current smokers. Pesticides concentrations were larger among women who were the oldest, more educated, had higher annual family income, were married or cohabiting, were current smokers, drank alcohol, and reported infertility. Environmental phenols such as Bisphenol A (BPA) had a higher median concentration among women who were the youngest, NH Black, had some college education, had an annual family income of less than $45k, were single, divorced, or widowed, had general health status of fair or poor, classified as having a BMI level of obese, current smokers, and drink alcohol. Lastly, Per- and polyfluoroalkyl substances (PFAs) were found in higher median concentrations equally among those who were the youngest and oldest, higher among NH Asians, most educated, had more than an income of $45k, women who were singled, divorced, or widowed, had excellent, very good, or good general health status, were overweight, were former smokers, or drank alcohol. Table 2 presents results from logistic regression models estimating the association between environmental chemicals and the odds of self-reported infertility. The unadjusted model indicates that women who were highly exposed to 2,2',4,4',5,5'-Hexabromobiphenyl (PBB-153), a common chemical among flame retardants, had 2.09 times the odds of reporting infertility [OR:2.09, 95% CI: 1.24-3.53] in comparison to women who were exposed to low PBB-153. Similarly, in the unadjusted model, women who were highly exposed to the metal cadmium, commonly found in tobacco smoke or eating cadmium-contaminated foods, had 2.09 times the odds of reporting infertility [OR:2.09, 95% CI: 1.20 – 3.61] compared to those who had low exposure. The DAG-based model showed consistent, but findings were attenuated for all chemicals except cadmium, where after adjusting for confounders women who were highly exposed to cadmium had 1.83 times the odds of reporting infertility [aOR:1.83, 95% CI: 1.00 – 3.63] compared to those who had low exposure. Pesticide exposures were positively associated with the odds of self-reported infertility. More specifically, women who were highly exposed to hexachlorobenzene [OR: 2.04, 95% CI: 1.05 - 3.98] and oxychlordane [OR: 2.04, 95% CI: 1.12 - 3.61] had 2.04 times the odds of reporting infertility compared to those who had low exposure. After adjustment for potential confounders, these associations were no longer statistically significant despite slightly elevated magnitude of association ([DAG-based model, aOR: 1.05, 95% CI: 0.46 – 0.2.39] and full-model [aOR: 1.04, 95% CI: 0.48-2.27]). On the other hand, we also observed an inverse association between Per- and Polyfluoroalkyl substances (PFAs) and self-reported infertility in all three models. For example, in the fully adjusted model, women who were highly exposed to n-perfluorooctanoic acid (n-PFOA) had 0.52 times the odds of reporting infertility [OR: 0.52, 95% CI: 0.31- 0.86] compared to women who were less exposed to n-PFOA. Similar results were found for PFAs chemical n-perfluorooctane sulfonic acid (n-PFOS) [OR: 0.51, 95% CI: 0.26-0.92).

Table 2. Logistic regression analysis estimating the associations between environmental chemicals and self-reported infertility, NHANES 2013-2016.

Environmental Classes	Environmental Chemicals	N	Odds Ratio (95% CI)		
			Unadjusted Model	DAG-based Model[a]	Full Model[b]
Brominated Fire Retardants (BFRs)	2,2',4,4',5,5'-Hexabromobiphenyl (PBB-153) (pg/g)	798	**2.09(1.24-3.53)**	1.17(0.57-2.38)	1.11(0.51-2.40)
	2,4,4'-Tribromodiphenyl ether (PBDE-28) (pg/g)	798	1.12(0.71-1.77)	0.96(0.61-1.50)	1.10(0.71-1.72)
	2,2',4,4'-Tetrabromodiphenyl ether (PBDE-47) (pg/g)	798	1.15(0.64-2.05)	1.10(0.58-2.07)	1.20(0.64-2.24)
	2,2',4,4',5-Pentabromodiphnyl ether (PBDE-99) (pg/g)	798	1.02(0.63-1.64)	0.92(0.53-1.61)	0.95(0.54-1.65)
	2,2',4,4',6-Pentabromodiphyl ether (PBDE-100) (pg/g)	798	0.94(0.51-1.77)	1.02(0.55-1.88)	1.05(0.56-1.96)
	2,2',4,4',5,5'-Hxbromodiphnyl ether (PBDE-153) (pg/g)	798	1.16(0.60-2.24)	0.76(0.33-1.78)	0.81(0.36-1.83)
Volatile Organic Compounds (VOCs)	1,4-Dichlorobenzene (ng/mL)	1,214	1.03(0.68-1.54)	1.18(0.84-1.67)	1.17(0.83-1.64)
	Benzene (ng/mL)	1,192	0.92(0.58-1.45)	1.00(0.59-1.67)	1.09(0.61-1.94)
	Toluene (ng/mL)	1,199	0.79(0.51-1.23)	0.85(0.51-1.42)	0.87(0.49-1.53)
	Methyl-tert-butyl ether (MTBE) (ng/mL)	1,153	0.73(0.13-3.95)	0.71(0.14-3.53)	0.69(0.14-3.42)
	Cotinine (ng/mL)	2,476	0.83(0.60-1.13)	0.96(0.70-1.32)	0.98(0.67-1.45)
Metals	Arsenic, total (ug/L)	880	1.28(0.73-2.23)	1.28(0.71-2.31)	1.37(0.78-2.40)
	Cadmium (ug/L)	880	**2.09(1.20-3.61)**	**1.83(1.00-3.63)**	1.76(0.96-3.20)
	Lead (ug/dL)	1,263	1.02(0.68-1.54)	0.83(0.52-1.33)	0.89(0.53-1.50)
	Mercury, total (ug/L)	1,263	1.05(0.67-1.65)	0.96(0.58-1.60)	1.01(0.57-1.79)
Pesticides	3-(Ethlycarbamoyl) benzoic acid (DEET acid) (ng/mL)	806	1.15(0.69-1.91)	1.32(0.76-2.27)	1.21(0.71-2.06)
	Hexachlorobenzene (HCB) (pg/g)	798	**2.04(1.05-3.98)**	1.46(0.48-4.46)	1.43(0.52-3.93)
	Oxychlordane (OXYCHLOR) (pg/g)	798	**2.04(1.12-3.69)**	1.05(0.46-2.39)	1.04(0.48-2.27)
Environmental Phenols	Bisphenol A (ng/mL)	789	0.82(0.45-1.50)	1.08(0.54-2.18)	1.10(0.54-2.23)

Environmental Classes	Environmental Chemicals	N	Odds Ratio (95% CI)		
			Unadjusted Model	**DAG-based Model[a]**	**Full Model[b]**
	n-perfluorooctanoic acid (n-PFOA) (ng/mL)	752	**0.52(0.31-0.86)**	**0.44(0.25-0.78)**	**0.46(0.25-0.82)**
	n-perfluorooctane sulfonic acid (n-PFOS) (ng/mL)	752	**0.51(0.28-0.95)**	**0.48(0.25-0.92)**	**0.48(0.25-0.89)**
	Perfluorohexane sulfonic acid (PFHxS) (ng/mL)	795	0.93(0.54-1.63)	0.98(0.55-1.75)	1.01(0.54-1.90)
	Perfluorononanoic acid (PFNA) (ng/mL)	795	0.63-0.31-1.29)	0.50(0.24-1.08)	0.52(0.25-1.09)

[a] Models adjusted for confounder defined by the direct acyclic graph including age, race, education level, and annual family income.
[b] Models were fully adjusted for covariates including age, race, education level, and annual family income, body mass index, general health status, smoking status, and alcohol use.
[c] Boldface indicates p-value <0.05.

Table S12 presents the association between environmental chemicals and self-reported infertility for the sensitivity analysis, where the 75th percentile was used as a cut-off for high/low exposure definition instead of the median. The sensitivity analysis estimated the odds ratio and 95% confidence intervals for the association between environmental chemicals and self-reported infertility, comparing those in the 75th percentile and those under the 75th percentile. The results were generally consistent but an association between environmental chemical arsenic and self-reported infertility became significant. In the unadjusted model, high arsenic exposure increases odds of infertility by 83% compared to low exposure [OR:1.83, 95% CI: 1.04-3.22]. The results were consistent after adjusting for confounders based on the DAG model and the full model ([aOR: 1.87, 95% CI: 1.04-3.38, aOR: 1.92, 95% CI: 1.07-3.44], respectively). Results from the sensitivity analysis on pesticides were similar to the main analyses based on the median. The sensitivity analysis showed that the inverse associations with PFAs mostly disappeared except for the associations with n-PFOS in the DAG-based model [OR: 0.51, 95% CI: 0.29-0.90].

We also tested for a potential interaction between the environmental chemicals and sociodemographic characteristics including some sociodemographic variables such as age, race, education, income, marital status, and health variables such as general health status, BMI, smoking status, and alcohol use. Although our analyses showed some statistically significant effect modifiers for specific chemicals, given the small sample size the odds ratio estimates were unstable and did not show a meaningful pattern of observation (not shown).

4. Discussion

The purpose of this study was to characterize environmental exposures to environmental chemicals and examine the association between exposures to environmental chemicals and self-reported infertility in a nationally representative sample of US reproductive-aged women ages 18 to 49 with no history of hysterectomy or

oophorectomy. Findings demonstrated that exposures to environmental chemicals varied by sociodemographic and lifestyle factors among US reproductive-aged women where concentrations were found higher among women who had lower educational status and belong to racialized minority groups. Our results also generally suggest that pesticides and metals such as arsenic and cadmium are associated with increased odds of infertility.

Our study found elevated levels for all polybrominated diphenyl ethers (PBDEs) or otherwise known as BFRs, among older women ages 40 to 49. To date, few studies have examined PBDE serum levels among older females.[94] A study examining PBDE serum levels, particularly 2,2',4,4'-Tetrabromodiphenyl ether (PBDE-47), among the NHANES population over the age of 12 from 2003 to 2004 found a two-fold increase of this PBDE in adults 60 years and older above the 95th percentile compared to adults 20 to 59 years of age.[95] Older women may bear exposure to PBDEs because they may have been exposed for an extended amount of time throughout the years compared to younger individuals. Moreover, the levels of these chemicals were above today's safety standards thus making older individuals more exposed. Another reason older individuals may bear higher exposure is because they may have a slower metabolism that may make it harder to excrete PBDEs.[95] In our study, metals such as cadmium were also found at higher concentrations in older reproductive-aged women, a trend similar to other studies.[96,97]

We found racial/ethnic differences across different chemical classes among reproductive-aged women. Consumer products such as electronics, textile products, and upholstered furniture are common products where PBDE flame retardants can be found.[68,98] Although PBDEs are no longer being used and alternative flame retardants have been created, PBDEs are persistent chemicals and are known to have long half-lives ranging from several months to more than 10 years being stored in adult human adipose tissue.[99] Moreover, PBDEs are lipophilic and can accrue in human body fat.[100] Our study's findings showed elevated levels of BFR chemicals, particularly among reproductive-aged women who were of other and multi-race, but most literature on PBDE and racial/ethnic disparities shows that there are increased levels among non-White women compared to White women.[101,102] One study found lower total PBDE concentrations among Whites in comparison to Hispanic women and others among adolescent girls in the US. Similarly, another study detected that NH Hispanic women (Native American, or Asian) had elevated levels in comparison to White women of certain PBDEs among Californian women.[101,102] Differences in racial/ethnic exposure of PBDEs could be due to the variability in housing stock and furniture quality because the main important exposures to PBDEs are household dust.[103]

VOCs are common components in consumer products such as personal care products like deodorants and nail varnish, household products like mother repellants, air freshers, caulks, and automotive products like fuel.[104,105] Our study found a significant amount of 1,4-Dichlorobenzene (DCB) among NH Black which is consistent with another study that found significantly higher concentrations of DCB among US Black women ages 20 to 49.[106]

Our findings depicted that reproductive-aged women who had both low and high levels of education and income had significant amount of several environmental chemicals including BFRs, VOCs and metals. It is believed that individuals with low education or low income are overburdened with environmental chemicals and, although that may be true, our study showed mixed results. Some findings were consistent with

evidence suggesting that low socioeconomic factors are not always associated with increased chemical burden.[107,108] In addition, high exposures among reproductive-aged women with high levels of education and income may be due to the differences in exposure from in comparison to reproductive-aged women from lower levels of education and income. Still, our study broadens the literature by examining a wider range of environmental chemicals and identifying subpopulations that may have elevated levels of environmental chemicals. Variations across sociodemographic groups may contribute to the widening racial and ethnic disparities in reproductive health outcomes. Future research should explore how there may be difference in exposures to environmental chemicals across different sociodemographic groups.

Our findings also show positive associations between cadmium exposure and self-reported infertility. Although there are some existing studies regarding the association between exposure to cadmium and infertility, the research on this relationship is limited.[109–111] A study in Znehe County of China examined the health effects of women residing near lead-zinc mine and found that women residing closer to the mine were exposed to higher urinary cadmium levels. the study also found that residing near the mine was associated with difficulties becoming pregnant and other pregnancy related issues (e.g. premature births and stillbirths).[109] Another study prospectively followed a cohort of 501 US couples to examine fecundability and results showed that there was a significant association between high levels of cadmium in the blood in the female partner and reduced fecundity.[110] Lastly, a study examining exposure to lead, mercury, and cadmium through occupational exposures in workplaces in Denmark found that exposed females were more likely to experience pregnancy-related issues such as conception delay and idiopathic infertility.[111]

The biologic mechanisms underlying the observed association between exposure to cadmium and infertility have been suggested in *in vivo* studies in laboratory animal models.[112–116] Early rat studies showed that the number of oocytes that made it to metaphase II reduced significantly in association with increased cadmium accumulation.[117] The hypothalamic-pituitary-gonadal axis can be affected at multiple levels by cadmium, as experimentally it has been demonstrated to take a part in the alteration of reproduction hormone levels.[118,119] Other biologic mechanisms may include oxidative stress and systemic inflammatory pathways.[120]

Despite cadmium being a ubiquitous environmental chemical, epidemiological studies on exposure to cadmium and female infertility are limited. Although our study found a positive association between cadmium and infertility, more research is needed on this environmental chemical. It is important for women who want to get pregnant to decrease their exposure to cadmium as it is an environmental chemical that is excreted minimally thus the body burden of cadmium builds up with age and its long half-life of 38 years.[121] The Agency of Toxic Substances and Disease Registry have offered several ways to minimize exposure to cadmium. These include reducing smoking exposure as tobacco smoke contains cadmium that can be absorbed through the lungs, take iron supplementation as individuals who are iron deficient can absorb cadmium orally more and bring it to their system, and lastly, avoid occupational exposure by practicing proper occupational precautions.[122]

The association between hexachlorobenzene (HCB) and self-reported infertility—although not significant after adjustment of confounders likely due to small size—can

still be of concern since HCB is a type of pesticide that is considered an organochlorine and is commonly utilized in pest and fungus control.[123] It is banned in the US since 1966, but is still being produced outside of the country, and is a byproduct of organic chemical production processes.[124] Humans are exposed to HCB mainly through dietary ingestion of meat, fish, and milk.[125–128] HCB is a persistent chemical that can remain in the body for years because of its ability to accumulate in adipose tissue.[129] Much of the research on the role of HCB on reproductive outcomes have been in women undergoing IVF success, but not infertility itself. Other studies are mostly based on *in vitro* animal studies.[124,130] An earlier study in Germany investigated chlorinated hydrocarbons such as HCB and found high concentrations of it among infertile women compared to fertile women.[131] Another prospective study following a cohort of 501 couples for a year found a significant association between HCB and reduced fecundity, the probability of achieving a pregnancy within one menstrual cycle in females, but the associations did not continue after adjustment for confounding factors.[132] This was similar to our finding when we adjusted based on the DAG model and full model. Given the increasing concern with fertility complications and environmental exposures, future research is needed to elucidate the mechanisms as to how HCB contributes to female infertility and although is banned, it is a chemical that is still worrisome as HCB is formed as a by-product of organic chemical manufacturing processes.[124] Moreover, the chemical is also being produced outside the US and because of its lipophilic properties, it can remain in a person's body fat for years causing further adverse effects.[124] It has been found that individuals who rapidly lose weight can have high exposures to environmental chemicals due to fat tissues being broken up within a short amount of time.[133,134]

Oxychlordane is a metabolite of chlordane and functioned as a pesticide that was applied on agricultural crops, lawns, and gardens. Although it's not likely that current populations would be exposed to high levels of chlordane to cause adverse health effects because of its ban in 1988, it is interesting that our study found that people are still exposed to it, and an increased odds of self-reported infertility for those with high exposure. The association between exposure to oxychlordane and increased odds of self-reported infertility can be explained by the potential for exposure through inhalation or dermal contact by touching soil near a home that was treated with chlordane to control termites, or consuming contaminated crops or seafood.[135].[136] Research on chlordane and reproductive outcomes is limited. One animal study that examined the toxic effects of chlordane found reduced fertility in male and female rats that were given chlordane in their diet.[137] Other pharmacokinetic animal studies found that the residue of chlordane had a tendency to build up in the body fat and suggested that absorption can occur in any of the routes of exposure.[136] It is estimated that in the US, nearly 52 million people reside in chlordane-treated houses.[138] More generally, although chlordane is banned, it still persists in the environment and investigations on exposures to organo-pesticides like oxychlordane to female fertility remains scarce. Thus, epidemiological studies investigating the reproductive effects of women residing in homes that have been treated with chlordane would be helpful for future research.

In terms of health equity, our findings highlight the disproportionate exposures to environmental chemicals among racialized minority groups. These disproportionate exposures do not just influence infertility risk as our results suggest, but also many other reproductive health outcomes such as menstrual cycle length, miscarriage, and preterm

delivery[104–106]. The results of this study also remind us that the principles of environmental justice may not be upheld consistently across the population. Environmental Justice is defined as "all people and communities are entitled to equal protection of environmental and public health laws and regulation".[139] Yet, our findings demonstrate disparities in exposures to environmental chemicals across sociodemographic factors, and these chemicals may influence the risk of infertility, a growing public health concern. Efforts should be continued to take precautionary measures to control or minimize exposures to environmental chemicals, as every human being has the right to being able to enjoy the best possible health and to make their own decisions regarding their fertility (e.g. timing and spacing, and number of children).[140] Infertility induced by exposure to environmental chemicals, which people are often unaware about, can halt the realization of such an important human right. Thus, addressing the role of environmental chemicals and their effects on fertility functions is an important part of ensuring that all individuals realizing their right and having the opportunity to build a family and reach parenthood. Given the increasing diversity of the population, trend in infertility, and complexity of environmental threats, efforts to minimize exposures in an equitable and sustainable way are warranted.

For clinical and public health practice, clinicians and healthcare providers can inform women and advocate for safer chemical policies. It's been already noted that hardly any doctors caution expectant mothers about environmental hazards and this may be even fewer for women who want to become pregnant.[141] Some avoid counseling patients about risk due to concern of inducing anxiety in their patients and concerns regarding the fact that patients do not have a way to reduce exposure. However, healthcare providers can offer a concise list of economical alternatives or offer suggestions on how to reduce exposure to such chemicals.[142] A recent review offered mitigation strategies at the individual and at health policy level.[143] In short, at the individual level, there are three ways to minimize exposure via food and water, around the home, and taking considerations about air pollution.[143] In regards to food and water, women can consume fresh food and limit processed and canned food that incorporate plastic liners. Around the home, women can take off their shoes before entering their residence; and in regards to air pollution, women can check local air quality data if available.[143] At the environmental health policy level regulators can consider a more proactive approach by making manufacturer demonstrate safety to keep their chemicals in the marketplace, as opposed to taking a reactive stance where actions are taken only after evidence of harm has been suspected or demonstrated.[143] In public health practices, policymakers, clinicians/healthcare providers, industry organizations and community organizations should come together to create effective mitigations strategies against ubiquitous environmental chemicals. Furthermore, efforts to reduce outflow for existing sources of environmental chemicals should be continued. Studies have found that when there are strong agreements that environmental chemical are hazardous, individuals are willing to take some protective behaviors.[144] This means that people are more likely to take action to reduce their exposure of environmental chemicals if they are made informed of the likely risks associated with their exposure. However, they are less likely to follow recommendations when there is conflicting information.[144–146] Thus, consistent efforts to raise awareness about the health implications of environmental chemicals are crucial to improve public health.

This study has several limitations. First, the cross-sectional nature of this study limits the ability to infer temporality of the relationship between infertility and exposures to environmental chemicals. Second, infertility was based on a single question that was self-reported. It is possible that women who responded affirmatively to the question could have erroneously reported that they were experiencing difficulty becoming pregnant for a year while attempting to become pregnant, or vice versa. Despite this limitation, it has been suggested that self-reported infertility is an appropriate and valid measure of infertility to measure the population's level of fertility, with a high specificity at 95% and sensitivity at 70% when compared against medical records.[147] Furthermore, due to the lack of data, male factors were not considered although they do affect about one third of infertility cases.[21] Lastly, the sample size in our study was small which limited the ability to perform more detailed analyses to identify susceptible subgroups.

Despite the limitations, our study has notable strengths. First, the study is nationally representative and provides a generalizable analysis of the relationship between exposure to environmental chemicals and infertility. We also conducted a sensitivity analysis where we evaluated a different cut-off at the 75th percentile for the exposure, which allowed robustness in our results. Another strength of the study was the use of biomarker data which are more reliable and less subject to misclassification.

5. Conclusion

In a US nationally representative sample, reproductive-aged women with high exposures to pesticides and metals had significant higher odds of self-reported infertility. Furthermore, exposures to these chemicals varied across sociodemographic indicators (age, race/ethnicity, education levels, income, and marital status) as well as other factors such as general health status, BMI levels, smoking statuses, and alcohol use. While awaiting larger studies to improve our understanding of the impacts of environmental chemicals on infertility, it is important to raise awareness as these are ubiquitous chemicals that appear in high concentrations in the US populations.

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