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Water Fluoridation and Birth Outcomes in California

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Background: There is a lack of research on the relationship between water fluoridation and pregnancy outcomes.

Objectives: We assessed whether hypothetical interventions to reduce fluoride levels would improve birth outcomes in California.

Methods: We linked California birth records from 2000 to 2018 to annual average fluoride levels by community water system. Fluoride levels were collected from consumer confidence reports using publicly available data and public record requests. We estimated the effects of a hypothetical intervention reducing water fluoride levels to 0.7 ppm (the current level recommended by the US Department of Health and Human Services) and 0.5 ppm (below the current recommendation) on birth weight, birth-weight-for-gestational age z-scores, gestational age, preterm birth, small-for-gestational age, large-for-gestational age, and macrosomia using linear regression with natural cubic splines and G-computation. Inference was calculated using a clustered bootstrap with Wald-type confidence intervals. We evaluated race/ethnicity, health insurance type, fetal sex, and arsenic levels as potential effect modifiers.

Results: Fluoride levels ranged from 0 to 2.5 ppm, with a median of 0.51 ppm. There was a small negative association on birth weight with the hypothetical intervention to reduce fluoride levels to 0.7 ppm [−2.2 g; 95% confidence interval (CI): −4.4, 0.0] and to 0.5 ppm (−5.8 g; 95% CI: −10.0, −1.6). There were small negative associations with birth-weight-for-gestational-age z-scores for both hypothetical interventions (0.7 ppm: −0.004; 95% CI: −0.007, 0.000 and 0.5 ppm: −0.006; 95% CI: −0.013, 0.000). We also observed small negative associations for risk of large-for-gestational age for both the hypothetical interventions to 0.7 ppm [risk difference (RD) = −0.001; 95% CI: −0.002, 0.000 and 0.5 ppm (−0.001; 95% CI: −0.003, 0.000)]. We did not observe any associations with preterm birth or with being small for gestational age for either hypothetical intervention. We did not observe any associations with risk of preterm birth or small-for-gestational age for either hypothetical intervention.

Conclusion: We estimated that a reduction in water fluoride levels would modestly decrease birth weight and birth-weight-for-gestational-age z-scores in California. https://doi.org/10.1289/EHP13732

Introduction

Fluoridation of community water systems in the United States began in 1945 in Grand Rapids, Michigan.[1] At this time, researchers initiated what was supposed to be a 15-y epidemiological study of water fluoridation and rates of dental decay in Grand Rapids and Muskegon, a nearby town, serving as a control community. Researchers observed that rates of dental decay declined in Grand Rapids after fluoridation but stayed the same in Muskegon. Based on these findings, city officials in Muskegon decided to fluoridate their water in 1951, ending the study 9 y early. Since then, many water systems across the world have fluoridated their water supplies. Fluoride is added to the water supply at the treatment plant, and a sodium fluoride saturator system, fluorosilicic acid system, or dry fluoride feed system can be used.[2] In the case excess fluoride is added, water systems shut down the equipment and flush out the water lines; they are also required to notify the public.[2] Individuals who wish to remove fluoride must use a reverse osmosis filter.

Although the dental health benefits are well substantiated,[3] evidence suggests fluoride consumption in early life may adversely affect child neurodevelopment,[4–9] although some recent studies have also found positive or null associations.[10,11] Given existing evidence, the National Toxicology Program has concluded that "fluoride is presumed to be a cognitive neurodevelopmental hazard to humans."[12] Because birth outcomes can also affect neurodevelopment,[13,14] adverse birth outcomes may be on the pathway between *in utero* fluoride exposure and potential effects on neurodevelopment. However, only recently has the impact of water fluoridation on pregnancy outcomes been considered in the United States,[15,16] and studies in the United States and elsewhere that do exist show mixed results. For instance, some studies found higher fluoride levels were associated with lower birth weight,[15] whereas others found associations with higher birth weight.[17,18] Some studies have found increased risk of preterm birth,[19] others have found the opposite,[16,20] and one study found no association with either gestational age or fetal growth.[21] To our knowledge, no studies have been done at the population level, which is an important next step for establishing risk in a general population.

Despite the paucity of evidence surrounding the effects of water fluoridation on reproductive health, some animal and epidemiological studies in places with naturally high levels of fluoride in ground water point to potential mechanisms and suggest there may be adverse effects. Evidence indicates fluoride exposure may affect endocrine systems via alterations in thyroid hormone levels.[22–25] Many other endocrine-disrupting chemicals have been linked to adverse birth outcomes because of the key role of hormones in regulating the normal processes of growth during gestation and parturition.[26,27] Drinking water fluoride levels exceeding the World Health Organization (WHO) guideline of 1.5 ppm have also been linked to anemia,[28] hypertension,[29] and other adverse cardiovascular outcomes,[30] which may increase risk of adverse birth outcomes due to systemic inflammation and oxidative stress.[31–33] Animal studies have shown fluoride can affect antioxidant enzyme activity, including reactive oxygen species and NADPH oxidase, mechanisms related to inflammation and oxidative stress.[34,35] These mechanisms related to inflammation and oxidative stress have also

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been implicated in the pathogenesis of adverse birth outcomes.[36] However, given the lack of research investigating effects of water fluoridation on human reproductive outcomes, specific mechanistic pathways are not yet known.

California passed Assembly Bill 733 in 1995 requiring all public water systems with at least 10,000 service connections to install a water fluoridation system once the funds became available.[37] Since then, water districts have complied at different times, resulting in spatial and temporal variability in water fluoridation practices. The Metropolitan Water District of South California, which provides surface water to 18 million Southern Californians, began fluoridating in 2007.[38] Furthermore, in 2015, the US Department of Health and Human Services reduced the recommended level of fluoride in drinking water to 0.7 ppm, a change from previous standards that were dependent on ambient temperature and ranged from 0.7 to 1.2 ppm.[39] This policy change introduced additional variability in levels of water fluoridation within water systems over time in California, especially among those water districts that have fluoridated their water for decades. Some water districts also vary the proportion of ground vs. imported surface water they use over time, which creates variability in the amount of fluoride in the blended water distributed to consumers. Our goal was to use this variability to examine the effects of water fluoridation on birth outcomes. To evaluate the potential impacts of policy change regarding community water fluoride levels on birth outcomes, we estimated the effects of two hypothetical interventions to reduce water fluoride levels to 0.7 ppm and 0.5 ppm on birth outcomes in California. We chose these thresholds to represent reduction to the current recommended level (0.7 ppm) and to a level below the current recommendation (0.5 ppm).

Data and Methods

Study Population

We used California birth records to capture births that occurred in areas served by community water systems during the period 2000–2018. Birth records were geocoded to the pregnant person's address at the time of delivery and linked to water system boundaries using the UC Berkeley Water Equity Science Shop Community Water System boundaries.[40] We began with $N = 9{,}805{,}694$ births and limited our analyses to live singleton births, where the birthing parent's address was able to be geocoded, the parent was living in an area served by a community water system, and the outcome variables, covariates, and fluoride levels had nonmissing values ($n = 5{,}008{,}915$) (Supplemental Figure 1).

This study was approved by the institutional review board of the University of California, San Francisco (IRB No. 21-34762 and CDPH IRB No. 13-05-1231).

Birth Outcomes

The outcomes we considered in this study were birth weight in grams, birth-weight-for-gestational-age z-scores, gestational age in completed weeks, preterm birth, small-for-gestational age, large-for-gestational age, and macrosomia. We used a population reference to calculate birth weight-for-gestational-age z-scores, small-for-gestational age, and large-for-gestational age.[41] Small-for-gestational age was defined as below the 10th percentile of sex-specific birth-weight-for-gestational age based on a population reference,[41] and large-for-gestational age was defined as above the 90th percentile. Gestational age was determined based on the obstetric estimate of gestational age from 2007 forward; before 2007 the obstetrical estimate was not recorded on birth records so last menstrual period was used to estimate gestational age. Preterm birth was defined as delivery before 37 completed weeks of gestation. Macrosomia was defined as birth weight >4,000 g.

Fluoride Levels

Comprehensive historical data on fluoride levels for community water systems across California are not publicly available. However, since 1998, water systems have been required to test and report levels of several chemicals, including fluoride to consumers as part of the Consumer Confidence Report Rule amendment to the Safe Drinking Water Act. This requirement usually means a hard copy brochure of the consumer confidence report is mailed to customers. The data are not compiled into electronic databases, and record keeping among water system administrators varies substantially. The US EPA compiles consumer confidence reports in the Safe Drinking Water Information System (SDWIS) system; however, only the most recent years are available. To compile a database of historical water fluoride levels from 2000 to 2018, we used all publicly available data, and we filed Freedom of Information Act requests to individual water systems for the consumer confidence reports for years that were missing data.

Consumer confidence reports provide fluoride levels measured at specific water sources (e.g., a water intake or treatment plant) and/or system average concentrations. They also distinguish between naturally occurring and treatment-related fluoride levels. To determine the average level of fluoride in a given water system and year, we used the level of fluoride reported in the consumer confidence report if only one water source was reported. If only the treatment-related level of fluoride was provided, we used this level. If only the naturally occurring level of fluoride was provided, we used this level. If more than one water source was listed, but an average for the system was listed, we used the average level reported. If more than one water source was listed and no system average was reported, but there were percentages listed for each water source, we created weighted averages using the percentages reported. If more than one water source was listed, no system average was reported, and no percentages were listed for each water source, we created a simple average between the sources. If only a range was reported, we used the median of the range. If only a range or no data were available, but a value of average annual fluoride levels was listed on the data provided on the California Water Board website,[42] we used that level. If levels were missing for a year but prior year levels were available, we carried those levels forward. We assumed nondetected fluoride levels were the limit of detection for the purpose of reporting (0.1 ppm) divided by the square root of 2. Of the 5,861 water systems and years we included in the study, fluoride levels for 893 (15.3%) were nondetected or were an average of a detected and nondetected level, and 3,408 (58.1%) had fluoride levels directly from the consumer confidence report, 984 (16.8%) had a simple average of fluoride levels from two or more sources in the consumer confidence report, 835 (14.2%) had a weighted average of source levels from the consumer confidence report, 184 (3.1%) had consumer confidence reports that did not report a fluoride level (which, given the current regulations, we determined to be a nondetect), 96 (1.6%) used the California Water Board level, 79 (1.3%) used a median of a range reported on the consumer confidence report, 15 (0.3%) used a weighted average of sources from a personal communication with someone who worked at the water system, and 260 (4.4%) had some other method, which sometimes represented when a water system purchased data from another system or if the method was not recorded. Of the 546 unique water systems included in this analysis, there were 349 small or medium water systems (<10,000 connections) and 196 large water systems (10,000 or more connections). The median service area for small or medium water systems

was 9.3 km^2, and the median service area for large water systems was 57.5 km^2 (Supplemental Table 1).

Birth records were linked to the average level of fluoride that was present in the community water system that served the pregnant person at delivery. We assigned each pregnancy the fluoride level in the year of the pregnancy, and if the pregnancy spanned 2 y, we created a weighted average for which the weights were the proportions of the pregnancy spent in each year. We previously conducted a study linking community water system fluoride levels to maternal serum, urine, and amniotic fluid collected during midgestation and found modest but statistically significant correlations between the community water system fluoride and fluoride levels in biological samples.[43] For example, the correlations between community water fluoride and the fluoride measured in maternal serum and amniotic fluid were 0.39 and 0.41, respectively. This finding provides some confidence that water fluoride level is a decent proxy for actual exposure levels.

Arsenic Levels

To control for arsenic levels, which often covary with fluoride levels (either because of geology or industrial pollution) and thus may cause coexposure confounding,[44] we linked birth records to the Water Quality Database Files from California's State Water board,[45] which provide historical public water monitoring data for community water systems. These data represent testing levels by water systems for each water source but do not include comprehensive data on treatment-related fluoride. To estimate the contaminant levels in the distribution system, we connected each source to a receiving source to avoid double counting of testing levels and remove duplicates as described in previous work.[46] We then created yearly averages of arsenic levels for each water source. If levels were missing for a year, but prior year levels were available, we carried those levels forward.

Statistical Analyses

Our goal was to estimate the effects of two hypothetical interventions of reducing water fluoride levels to 0.7 ppm and 0.5 ppm on birth outcomes. To do this, we used G-computation[47] with a linear regression model that included a natural cubic spline to allow for nonlinearity in the effects of fluoride. G-computation is a standardization approach that allows the investigator to model the effects of a hypothetical intervention.[48,49] We selected the number of knots for each outcome regression separately using the Aikake Information Criteria. We then predicted the outcomes if fluoride levels that exceeded 0.7 ppm were reduced to 0.7 ppm and did the same for 0.5 ppm. For inference, we used a clustered bootstrap with 200 bootstrapped samples to calculate Wald-type CIs at the water system level. All analyses were conducted on the additive scale.

Furthermore, we wanted to assess whether small changes in fluoride levels were associated with differences in birth outcomes across the distribution. Thus, we evaluated the association of fluoride levels with birth outcomes using generalized additive models to identify potential nonlinearities.

We selected covariates based on the literature and a directed acyclic graph (Supplemental Figure 2). We adjusted for individual-level characteristics including continuous birthing parent age, race/ethnicity, health insurance type, educational attainment, and the month and year of conception. We included race/ethnicity as a confounder and potential effect modifier because of the way racialized access to wealth and racial residential segregation influences where people live in California, as well as how racism can affect birth outcomes. The categories of race on the birth record included White, Black, American Indian/Native American, Asian-Specified, Asian-Chinese, Asian-Japanese, Asian-Korean, Asian-Vietnamese, Asian-Cambodian, Asian-Thai, Asian-Hmong, Other-Specified, Indian (Excludes American Indian, Aleut, and Eskimo), Filipino, Hawaiian, Guamanian, Samoan, Eskimo, Aleut, Pacific Islander (Excludes Hawaiian, Guamanian, Samoan), Withheld, and Unknown. The categories of Hispanic ancestry or origin were Not Hispanic, Mexican, Puerto Rican, Cuban, Other Hispanic, or Unknown/Withheld. We summarized these into the following categories: White, Black, Asian, American Indian/Alaska Native, Hawaiian/Pacific Islander, multirace, other race/ethnicity, and Hispanic/Latinx. Any participant with Hispanic/Latinx ethnicity was coded as Hispanic/Latinx, except for the multirace group. Insurance categories were public, private, and other payment. Public health insurance included Medicaid, other government insurance, and Indian Health Service. Before 2005, public insurance also included Medicare, worker's compensation, and Title V. Private insurance included private insurance and CHAMPUS/TRICARE. Before 2005, private insurance also included categories for Blue Cross–Blue Shield and health maintenance organization (HMO). Other payment source includes a medically unattended delivery, self-pay, and other payment. Before 2005, other options included no charge, other nongovernmental insurance, and medically indigent. Educational attainment was categorized as less than high school attainment, high school graduate, some college, college graduate, and graduate school graduate, which included a master's degree, doctorate, or professional degree. All individual characteristics were collected from the birth record.

We also adjusted for the total population served by the water system, drinking water arsenic levels, county-level annual average temperature from the National Oceanic and Atmospheric Administration,[50] and urbanicity from the National Center for Health Statistics.[51] The urbanicity measure is based on the Office of Management and Budget's classification of metropolitan and micropolitan statistical areas and is designed to characterize health differences across urban and rural areas. Ambient temperature has historically been considered in fluoride recommendations, because it was assumed that people living in warmer climates drink more water, and therefore fluoride levels should be lower to prevent excess consumption.[52,53] We included county-level unemployment from the Bureau of Labor Statistics[54] and income inequality, represented as the ratio of the 80th to the 20th percentiles of household income, from the County Health Rankings[55] as proxies for public finances and area-level socioeconomic status.

Effect Modification

We performed various stratified analyses to assess whether there were any populations for whom fluoride exposure was particularly harmful. We were particularly interested in identifying whether socially or economically marginalized groups experience larger impacts that may raise environmental justice concerns. Thus, we estimated associations within each subgroup of race/ethnicity and health insurance status and assessed differences in associations with each hypothetical intervention across groups. Given the effects of *in-utero* exposure to chemicals including fluoride can differ by fetal sex,[6–8,56,57] we also evaluated stratified by sex. Finally, given the potential for synergistic effects with arsenic,[44] we stratified analyses by whether the water system had arsenic levels that exceeded the maximum contaminant level (MCL) of 10 ppb or exceeded the 75th percentile of arsenic levels (2.53 ppb) observed across California births during the study period. To evaluate whether associations differed meaningfully across groups, we used a Wald test for heterogeneity.[58]

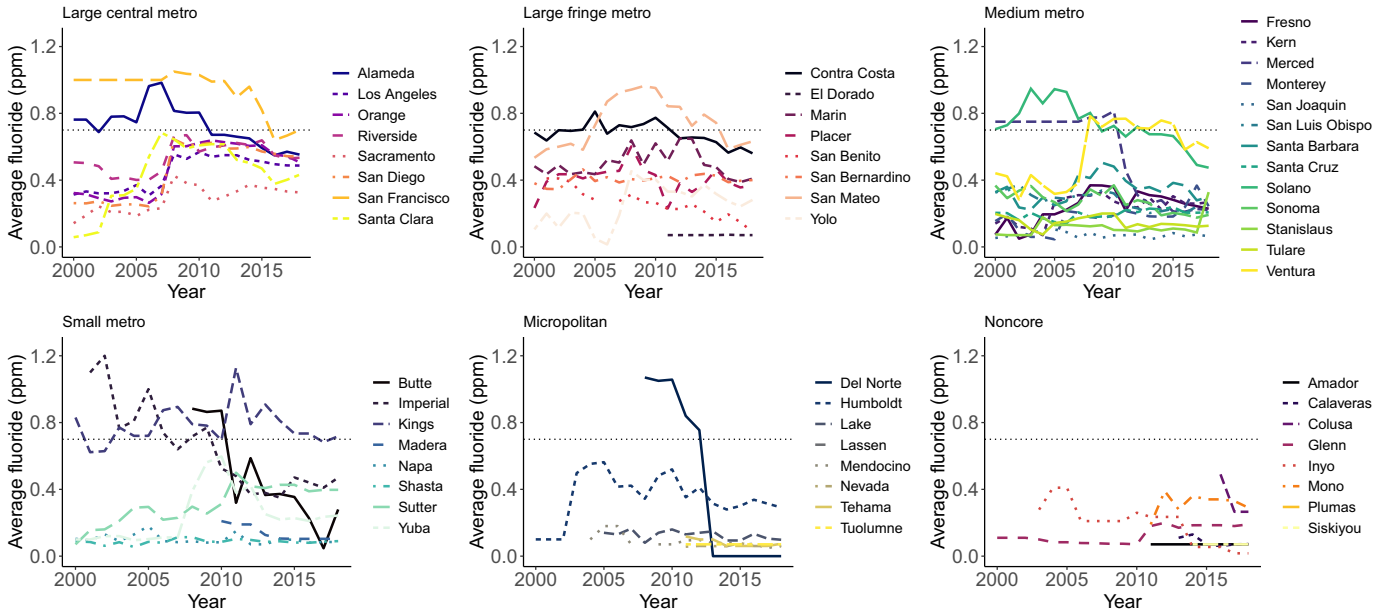

Figure 1. Average drinking water fluoride levels in California community water systems from 2000 to 2018 by county urbanicity. Note: These county urbanicity categories are defined using the National Center for Health Statistics Urban-Rural Classification Scheme.

Sensitivity Analyses

As a sensitivity analysis, we identified any birth weight and gestational age combination as implausible if the birth-weight-for-gestational-age z-score was < -5 or more than 5 for term births and < -4 or more than 3 for preterm births, following the algorithm of Basso and Wilcox.[59] We excluded births with implausible combinations of gestational age and birth weight to assess the impact of this on our results.

We conducted a matched sibling analysis to better control for potentially unobserved confounders across birth parents. Our sibling approach analyzes differences in fluoride levels between pregnancies for the same birth parent. Matched sibling information was only available from 2001 to 2018, so births in 2000 were excluded. We compared siblings by differencing all variables from the birthing parent-specific mean, which is equivalent to including a fixed effect for each birthing parent in the analysis.[60] The fixed effect model estimated for the within-sibling analysis is:

$$Y_{imsct} = \beta_0 + \beta_1 fluoride_{st} + \alpha_j X_{imst} + \gamma_k Z_{ct} + \phi_m + \epsilon_{imsct},$$

where i indexes the baby born to parent m in water system s in county c for conception year t. Y_{imsct} is the birth outcome, X_{imst} is the vector of individual-level control variables, Z_{ct} is the vector of county-level control variables, ϕ_m is the birthing parent fixed effect, and ϵ_{imsct} is the residual. The individual-level control variables that could vary between births were age, educational attainment, and health insurance type. For this analysis, we estimated the difference in the outcome for a 0.1-ppm change in fluoride levels between siblings. To help understand whether any differences between the sibling analysis and the overall analysis were due to unmeasured confounding or population composition, we also estimated the associations of a 0.1-ppm change in fluoride among all births in California, and among the unmatched sibling data. To further examine the differences between the main analytic cohort and the sibling cohort, we compared the demographic characteristics and distribution of fluoride levels for each group.

The database of water fluoride levels by water system and the statistical analysis scripts are available at https://github.com/degoin/fluoridation-birth-outcomes.

Results

The fluoride levels varied within and across water systems over the study period, 2000–2018, and patterns differed based on the urbanicity of the water system (Figure 1). There is a large increase in water fluoridation levels around 2007, which is when the Metropolitan Water District started fluoridating water it delivered to Southern California districts.[38] There is also a decrease starting in 2015, which is when the recommended level of fluoride changed to 0.7 ppm for all districts, whereas previously it ranged from 0.7–1.2 ppm, depending on the ambient temperature.

After limiting to our inclusion criteria, we had a sample size of 5,008,915 births (Supplemental Figure 1). The demographics of all births compared with those included in the study during the 2000–2018 period are shown in Supplemental Table 2. The median fluoride level among participants in our study was 0.51 ppm (Table 1). Black, Asian, and Hawaiian/Pacific Islander participants had higher median fluoride levels (0.61, 0.59, and 0.60 ppm, respectively) in comparison with White (0.52 ppm) and Hispanic/Latinx participants (0.49 ppm). Those with college or graduate level education had higher median exposure levels (0.59 and 0.61 ppm, respectively) in comparison with those with a high school education or less (0.49 ppm).

The associations of fluoride with birth weight, gestational age, and birth-weight-for-gestational-age z-scores were nonlinear (Supplemental Figures 3–5). Hypothetical interventions to reduce fluoride levels were not associated with changes in the risk of preterm birth or small-for-gestational age (Figure 2; Supplemental Excel Table S1). We estimated small reductions in birth weight associated with the hypothetical intervention to 0.5 ppm (−5.8 g; 95% CI: −10.0, −1.6) and for the hypothetical intervention to 0.7 ppm (−2.2 g; 95% CI: −4.4, 0.0). We also estimated small reductions in birth-weight-for-gestational-age z-scores; the association was slightly larger for the hypothetical intervention to 0.5 ppm (−0.006; 95% CI: −0.013, 0.000) in comparison with the hypothetical intervention to 0.7 ppm (−0.004; 95% CI: −0.007, 0.000). Differences in fetal growth may have

Table 1. Descriptive statistics of drinking water fluoride levels (in ppm) among California births from 2000 to 2018 by individual-level and area-level covariates.

Births	*n*	%	Min	Max	Mean	Median	SD
All	5,008,915	100.0%	0.00	2.50	0.49	0.51	0.28
Race/ethnicity							
White	1,243,166	24.8%	0.00	2.50	0.49	0.52	0.29
Black	290,392	5.8%	0.00	1.95	0.57	0.61	0.28
Asian	657,290	13.1%	0.00	2.50	0.54	0.59	0.29
American Indian/Alaska Native	12,411	0.2%	0.00	2.50	0.42	0.38	0.31
Hawaiian or Pacific Islander	21,828	0.4%	0.00	1.52	0.56	0.60	0.30
Other	3,832	0.1%	0.00	1.80	0.54	0.60	0.28
Multirace	143,044	2.9%	0.00	2.50	0.51	0.55	0.30
Hispanic/Latinx	2,636,952	52.6%	0.00	2.50	0.47	0.49	0.27
Education							
Less than high school	1,187,518	23.7%	0.00	2.50	0.47	0.49	0.28
High school graduate	1,450,109	29.0%	0.00	2.50	0.47	0.47	0.28
Some college	1,122,950	22.4%	0.00	2.50	0.48	0.50	0.29
College graduate	799,154	16.0%	0.00	2.50	0.53	0.59	0.28
Graduate school	449,184	9.0%	0.00	2.28	0.56	0.61	0.27
Insurance type							
Public insurance	2,505,737	50.0%	0.00	2.50	0.48	0.49	0.28
Private insurance	2,306,198	46.0%	0.00	2.50	0.51	0.54	0.29
Other payment	190,877	3.8%	0.00	2.50	0.52	0.56	0.25
Birthing parent age							
<25	1,427,768	28.5%	0.00	2.50	0.47	0.47	0.28
25–34	2,651,528	52.9%	0.00	2.50	0.49	0.51	0.28
>35	929,619	18.6%	0.00	2.50	0.53	0.58	0.28
Month of conception							
January	437,130	8.7%	0.00	2.50	0.49	0.51	0.28
February	398,438	8.0%	0.00	2.50	0.49	0.51	0.28
March	421,137	8.4%	0.00	2.50	0.49	0.51	0.28
April	399,449	8.0%	0.00	2.50	0.49	0.50	0.28
May	415,146	8.3%	0.00	2.50	0.49	0.50	0.28
June	401,076	8.0%	0.00	2.50	0.49	0.50	0.28
July	402,113	8.0%	0.00	2.50	0.49	0.51	0.28
August	408,741	8.2%	0.00	2.50	0.49	0.51	0.28
September	401,093	8.0%	0.00	2.50	0.49	0.51	0.28
October	431,542	8.6%	0.00	2.50	0.49	0.51	0.28
November	433,389	8.7%	0.00	2.50	0.49	0.51	0.28
December	459,661	9.2%	0.00	2.50	0.49	0.51	0.28
Year of conception							
2000	89,053	1.8%	0.00	1.50	0.39	0.30	0.27
2001	97,473	1.9%	0.00	1.50	0.39	0.30	0.27
2002	102,387	2.0%	0.00	1.50	0.40	0.30	0.28
2003	125,512	2.5%	0.00	1.50	0.44	0.32	0.28
2004	143,420	2.9%	0.00	1.80	0.45	0.35	0.28
2005	239,799	4.8%	0.00	1.80	0.43	0.35	0.28
2006	306,139	6.1%	0.00	1.80	0.43	0.39	0.28
2007	335,161	6.7%	0.00	1.94	0.49	0.50	0.27
2008	338,484	6.8%	0.01	1.95	0.55	0.58	0.27
2009	328,656	6.6%	0.01	1.95	0.55	0.56	0.29
2010	342,261	6.8%	0.00	1.96	0.54	0.55	0.29
2011	346,236	6.9%	0.00	1.90	0.52	0.56	0.29
2012	351,588	7.0%	0.00	1.85	0.52	0.58	0.29
2013	358,933	7.2%	0.00	1.85	0.51	0.59	0.29
2014	358,997	7.2%	0.00	2.50	0.51	0.59	0.28
2015	359,640	7.2%	0.00	2.50	0.49	0.56	0.28
2016	355,186	7.1%	0.00	2.50	0.47	0.53	0.26
2017	342,152	6.8%	0.00	2.00	0.48	0.51	0.26
2018	87,838	1.8%	0.00	1.94	0.47	0.51	0.26
Total population served by the water system							
<10,000	102,860	2.1%	0.00	2.50	0.30	0.20	0.29
10,000 or more	4,906,055	97.9%	0.00	1.94	0.50	0.52	0.28
Annual average temperature							
Less than or equal to 12.1°C (53.7°F)	23,000	0.5%	0.01	0.90	0.31	0.21	0.27
More than 12.1°C (53.7°F)–14.6°C (58.3°F)	601,582	12.0%	0.00	2.50	0.35	0.17	0.35
More than 14.6°C (58.3°F)–17.7°C (63.8°F)	2,797,716	55.9%	0.00	2.50	0.52	0.58	0.29
More than 17.7°C (63.8°F)–21.4°C (70.6°F)	1,525,026	30.4%	0.00	1.85	0.50	0.50	0.23
More than 21.4°C (70.6°F)	61,591	1.2%	0.04	1.38	0.48	0.49	0.21
Urbanicity							
Large central metro	3,551,807	70.9%	0.00	1.96	0.55	0.59	0.25
Large fringe metro	542,521	10.8%	0.00	1.53	0.47	0.46	0.29
Medium metro	777,224	15.5%	0.00	2.50	0.27	0.15	0.29
Small metro	113,477	2.3%	0.00	1.85	0.36	0.14	0.41
Micropolitan	17,944	0.4%	0.00	0.93	0.16	0.10	0.17
Noncore	5,942	0.1%	0.02	0.49	0.17	0.09	0.12
Unemployment							
<5%	1,119,058	22.3%	0.00	1.80	0.49	0.49	0.26
5% to <10%	2,573,112	51.4%	0.00	2.50	0.50	0.54	0.28
10% or more	1,316,745	26.3%	0.00	2.50	0.47	0.49	0.31
Income inequality							
<5	2,907,873	58.1%	0.00	2.00	0.42	0.41	0.28
5 or more	2,101,042	41.9%	0.00	2.50	0.58	0.65	0.26
Drinking water arsenic							
Below MCL	4,932,121	98.5%	0.00	2.50	0.49	0.51	0.28
At or above MCL	76,794	1.5%	0.02	1.85	0.55	0.68	0.32

Note: We have created categories of birthing parent age, total population served by the water system, annual average temperature, unemployment, income inequality, and drinking water arsenic for this table but they are included as continuous covariates in the models. The categories for annual average temperature are based on the recommended control limits for fluoridation from the 1962 Drinking Water Standards. The MCL for arsenic is 10 ppb. MCL, maximum contaminant level; ppb, parts per billion; ppm, parts per million; SD, standard deviation.

occurred by changes toward the right side of the distribution, because we estimated small reductions in the risk of large-for-gestational-age for both the hypothetical intervention to 0.5 ppm (RD = −0.001; 95% CI: −0.003, 0.000) and to 0.7 ppm (RD = −0.001; −0.002, 0.000). We also estimated reductions in the risk of macrosomia for the hypothetical intervention to 0.5 ppm (RD = −0.002; 95% CI: −0.004, −0.001) and to 0.7 ppm (RD = −0.001; 95% CI: −0.002, 0.000). We estimated small reductions in gestational age associated with the hypothetical intervention to 0.5 ppm (−0.01 wk; 95% CI: −0.03, 0.00) and 0.7 ppm (−0.01 wk; 95% CI: −0.02, 0.00). For each outcome, the direction of the association changed (lower birth weight, birth-weight-for-gestational-age *z*-scores, and gestational age) when fluoride levels were above 1.0 ppm (Supplemental Figures 3–5), although CIs were wide. When removing implausible combinations of birth weight and gestational age, we saw minimal differences in the findings (Supplemental Table 3).

When stratifying by race/ethnicity, we saw no consistent differences in birth weight, gestational age, or birth weight-for-gestational age *z*-scores across racial/ethnic groups for either of the hypothetical interventions (Figure 3). We also did not observe differences across racial/ethnic groups for preterm birth (Supplemental Figure 6), small-for-gestational age (Supplemental Figure 7), or large-for-gestational age (Supplemental Figure 8). We did observe some differences in the estimated effect of hypothetical fluoride interventions by insurance status. For example, the association of birth weight with the hypothetical intervention to 0.7 ppm was in the opposite direction for those with private insurance (−2.6 g; 95% CI: −5.1, −0.2) and public insurance (−2.3 g; 95% CI: −4.3, −0.3) in comparison with those with another source of payment (2.6 g; 95% CI: −0.6, 5.8) (Figure 4). The association for the hypothetical intervention to 0.5 ppm was −5.5 g (95% CI: −9.9, −1.1) for those with private insurance, −6.3 g (95% CI: −11.0, −1.5) for those with public insurance, and −1.7 g (95% CI: −8.8, 5.4) for those with other insurance. The patterns were similar for gestational age and birth-weight-for-gestational-age *z*-scores (Supplemental Figures 9 and 10). We did not see consistent differences across insurance status for preterm birth (Supplemental Figure 11), small-for-gestational age (Supplemental Figure 12), or large-for-gestational age (Supplemental Figure 13). We did not find any differences in the estimated effects of the hypothetical interventions by fetal sex for

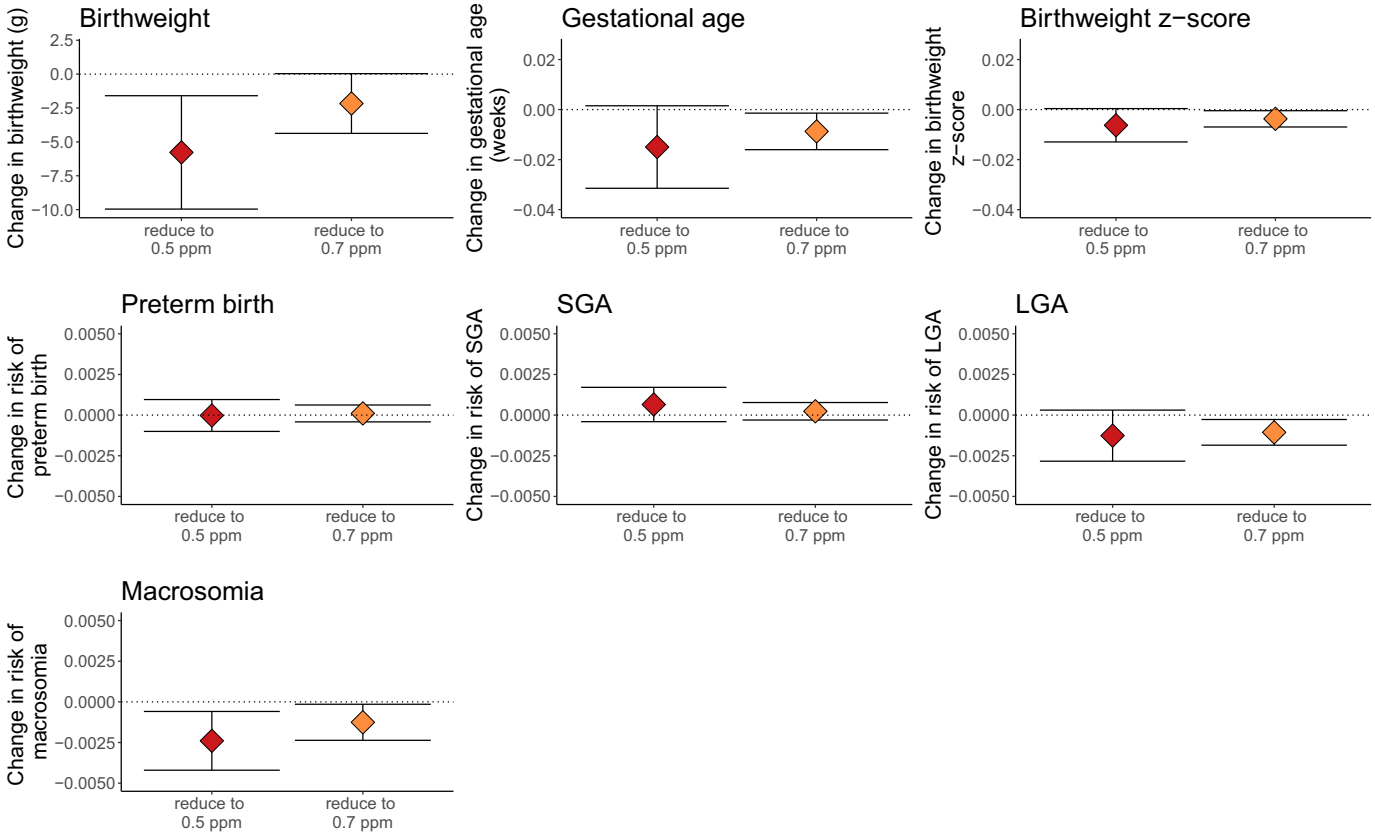

Figure 2. Associations of hypothetical interventions to reduce drinking water fluoride among California births from 2000 to 2018 with birth weight, gestational age, birth-weight-for-gestational-age *z*-scores, and risk of preterm birth, small-for-gestational age, large-for-gestational age, and macrosomia ($n = 5{,}008{,}915$). Note: To estimate the effects of the hypothetical interventions, we used G-computation with linear regression and a spline for the fluoride levels with a nonparametric bootstrap clustered by water system for inference. All models were adjusted for birthing parent age, race/ethnicity, health insurance type, educational attainment, month and year of conception, total population served by the water system, county-level annual average temperature, urbanicity, unemployment, income inequality, and drinking water arsenic levels. The point estimates are represented by diamond shapes, and the 95% CIs are represented by the error bars. These results are available in Excel Table S1. CI, confidence level.

any of the pregnancy outcomes studied (Supplemental Figures 14–19).

When stratifying by arsenic concentrations in drinking water, we did not observe any differences in the effects of a hypothetical intervention to 0.5 ppm for people with arsenic above or below the MCL (Supplemental Figure 20). However, when we analyze the effects for the hypothetical intervention to 0.7 ppm, there are some potential differences by arsenic levels (Supplemental Figure 21). For example, we did not observe an association for small-for-gestational age in the group below the arsenic MCL (RD = 0.000; 95% CI: 0.000, 0.001), but we saw a negative association for those above the arsenic MCL (RD = −0.002; 95% CI: −0.005, 0.000). Among those below the arsenic MCL, we also saw a small negative association with large-for-gestational age (RD = −0.001; 95% CI: −0.002, 0.000), whereas the association was in the opposite direction for those above the arsenic MCL (RD = 0.005; 95% CI: −0.002, 0.011). Similarly, among those below the arsenic MCL, there was no association with preterm birth (RD = 0.000; 95% CI: 0.000, 0.001), but we observed a positive association for those above the MCL (RD = 0.005; 95% CI: −0.002, 0.011). However, these differences were not consistent with the results of the hypothetical intervention to 0.5 ppm, nor with the results that stratified above and below the 75th percentile of arsenic levels, rather than the MCL (Supplemental Figures 22 and 23).

Finally, we analyzed the associations of a 0.1-ppm change in fluoride levels on each of the perinatal outcomes among siblings in California. Due to exclusion of the year 2000 data, single children, and missing data among any of the siblings, our sample size was reduced to 1,386,826 (Supplemental Table 4). We also compared the results of a 0.1-ppm change in fluoride among all births in California and among the unmatched sibling data (Table 2). For both the overall analysis and the unmatched sibling analysis, we found that higher fluoride levels of 0.1 ppm were associated with an increase in birth weight (all births RD = 1.51 g; 95% CI: 1.32, 1.71 and unmatched siblings RD = 1.68 g; 95% CI: 1.32, 2.05). However, when we analyzed the matched siblings, we did not see an association (RD = −0.03; 95% CI: −0.38, 0.33). We observed a similar pattern for birth-weight-for-gestational-age *z*-scores. We did observe small consistent positive associations with gestational age and negative associations with risk of preterm birth across all births, the matched sibling, and unmatched sibling populations. For instance, a 0.1-ppm increase in fluoride was associated with a reduction in risk of preterm birth of −0.0002 (95% CI: −0.0003, −0.0001) among all births, −0.0007 (95% CI: −0.0009, −0.0006) among the matched siblings, and −0.0004 (95% CI: −0.0005, −0.0002) among the unmatched siblings. Associations for small-for-gestational age and large-for-gestational age were inconsistent across the study populations. However, we did observe positive associations of a 0.1-ppm increase in fluoride levels with the risk of macrosomia.

To further assess whether a difference in population composition or confounding is driving the differences in results, we compared the demographic characteristics and distribution of fluoride levels for each group between the siblings and the main analysis (Supplemental Table 4). Despite the reduction in sample size

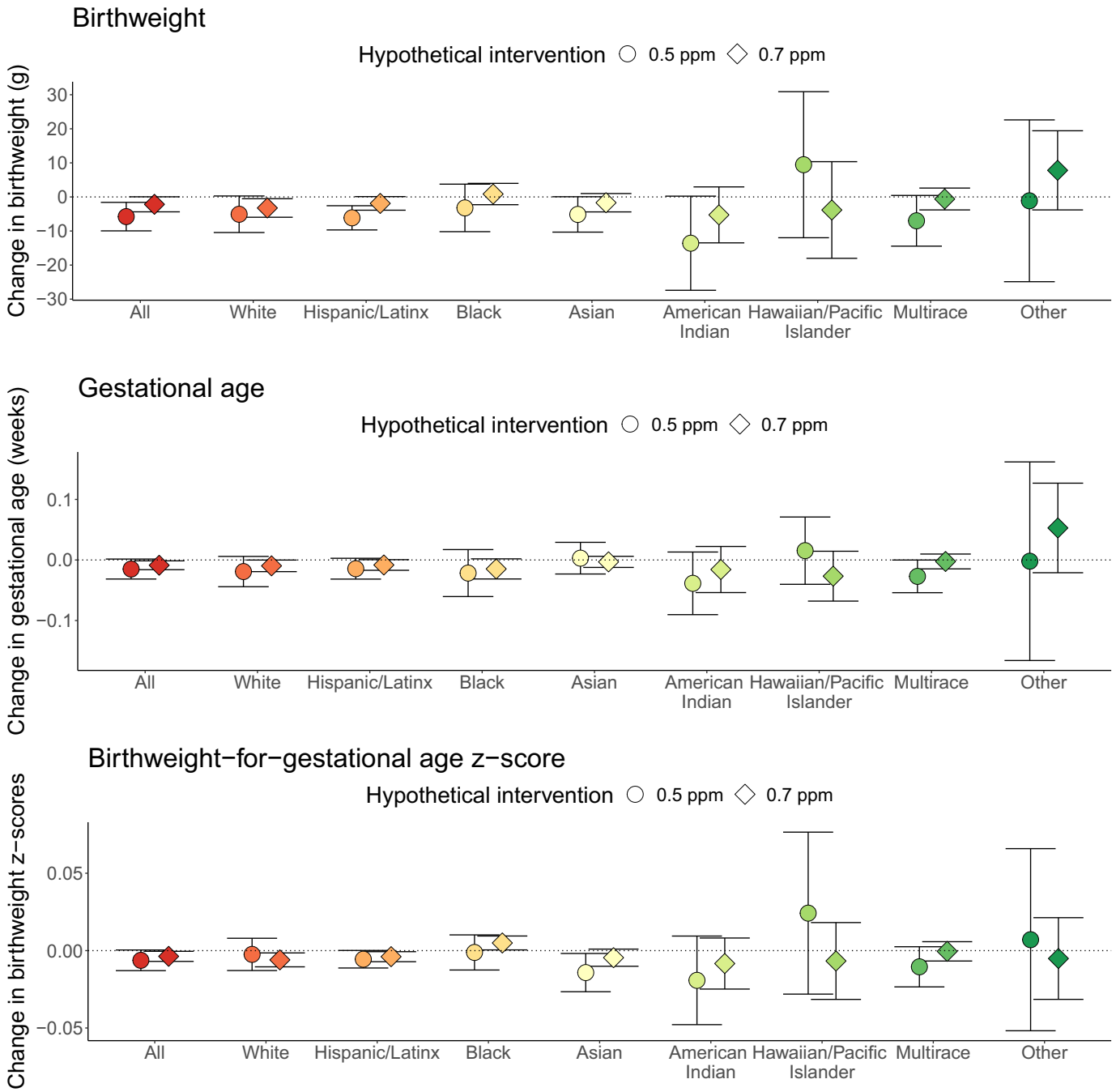

Figure 3. Associations of hypothetical interventions to reduce drinking water fluoride among California births from 2000 to 2018 with birth weight, gestational age, and birth-weight-for-gestational age *z*-scores by racial/ethnic groups. Note: To estimate the effects of the hypothetical interventions, we used G-computation with linear regression and a spline for the fluoride levels with a non-parametric bootstrap clustered by water system for inference. All models were adjusted for birthing parent age, race/ethnicity, health insurance type, educational attainment, month and year of conception, total population served by the water system, county-level annual average temperature, urbanicity, unemployment, income inequality, and drinking water arsenic levels. Race-specific models did not include race/ethnicity as a covariate. The point estimates are represented by diamond shapes, and the 95% CIs are represented by the error bars. The Wald test for heterogeneity across racial groups showed no difference for birth weight ($p = 0.77$ for intervention to 0.5 ppm, $p = 0.27$ for intervention to 0.7 ppm), no difference for gestational age ($p = 0.69$ for intervention to 0.5 ppm, $p = 0.48$ for intervention to 0.7 ppm), and no difference for birth-weight-for-gestational age *z*-scores ($p = 0.58$ for intervention to 0.5 ppm), but there was a potential difference for the intervention to 0.7 ppm ($p = 0.02$). These results are available in Excel Table S1. The sample sizes for each group are as follows: All $n = 5{,}008{,}915$; White $n = 1{,}243{,}166$; Hispanic/Latinx $n = 2{,}636{,}952$; Black $n = 290{,}392$; Asian $n = 657{,}290$; American Indian $n = 12{,}411$; Hawaiian/Pacific Islander $n = 21{,}828$; Multirace $n = 143{,}044$; Other race $n = 3{,}832$. CI, confidence interval.

from 5,008,915 to 1,386,826, we did not observe many demographic differences between the populations, although the sibling group was slightly more likely to be Hispanic or Latinx, have less than a high school education, and receive public insurance. The distribution of fluoride levels was also similar between the main analysis and the sibling group.

Discussion

We conducted a population-level study to characterize drinking water fluoride exposure among pregnant people and to evaluate the association between water fluoridation and pregnancy outcomes in the United States. We found small negative associations with birth weight, gestational age, birth-weight-for-gestational-

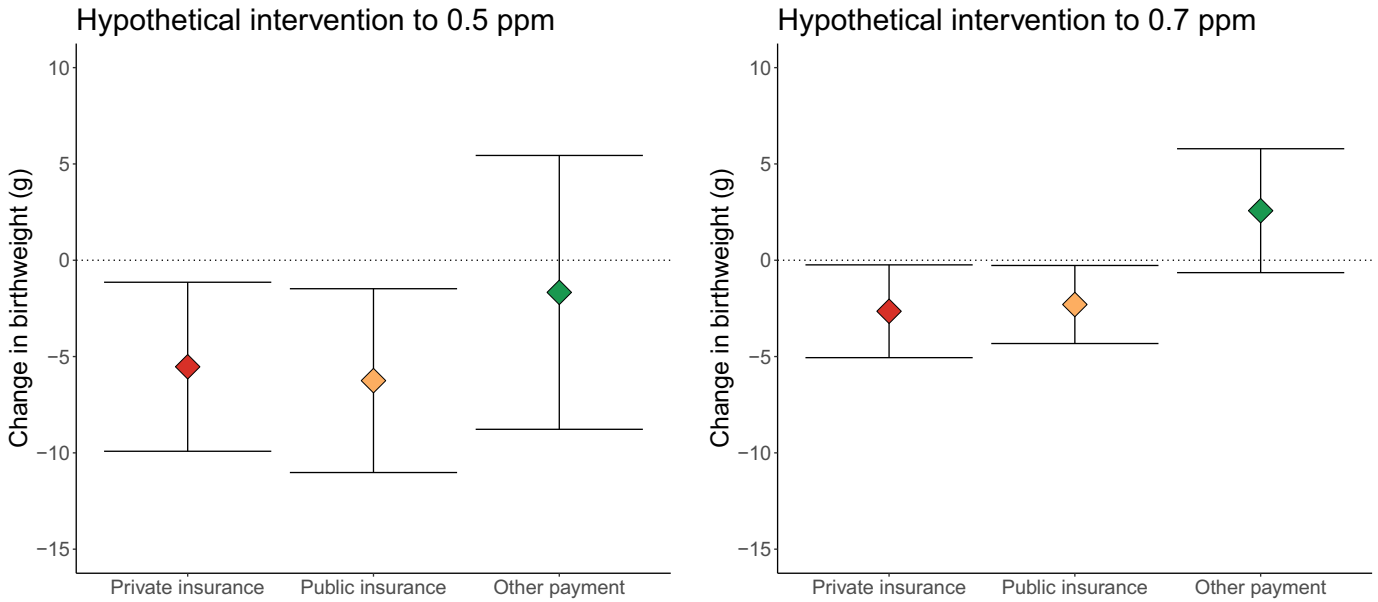

Figure 4. Associations of hypothetical interventions to reduce drinking water fluoride among California births from 2000 to 2018 with birth weight by insurance status. Note: To estimate the effects of the hypothetical interventions, we used G-computation with linear regression and a spline for the fluoride levels with a non-parametric bootstrap clustered by water system for inference. Models were adjusted for birthing parent age, race/ethnicity, educational attainment, month and year of conception, total population served by the water system, county-level annual average temperature, urbanicity, unemployment, income inequality, and drinking water arsenic levels. The point estimates are represented by diamond shapes, and the 95% CIs are represented by the error bars. The Wald test for heterogeneity across insurance groups showed no difference for the intervention to 0.5 ppm ($p = 0.51$), whereas there was a potential difference between groups for the intervention to 0.7 ppm ($p = 0.01$). These results are available in Excel Table S1. The sample sizes for each group are as follows: Private insurance $n = 2{,}306{,}198$; Public insurance $n = 2{,}505{,}737$; Other payment $n = 190{,}877$. CI, confidence interval.

age *z*-scores, risk for large-for-gestational age, and macrosomia associated with hypothetical interventions to reduce fluoride levels to 0.5 and 0.7 ppm, but no associations with risk of preterm birth or small-for-gestational age. This finding suggests that higher fluoride levels as observed in our study are unlikely to increase risk for the most severe adverse birth outcomes, like preterm birth and small-for-gestational age, but levels above may slightly increase fetal growth beyond what is ideal. Large-for-gestational-age babies are at greater risk for birth injury, including fracture, shoulder dystocia, and Erb's palsy.[61,62] Very macrosomic babies with birth weights over 4,500 g are at higher risk for birth complications and death.[63] Large-for-gestational-age and macrosomic babies can also have increased risk for cardiometabolic disorders later in life.[64–66] However, the risk differences we observed were very small, and although the findings contribute to data on etiological investigations of adverse birth outcomes in relation to fluoride on a population level, the results were not strong enough to impact changes in clinical guidance or practice. Furthermore, we observed only increased risk of macrosomia but not large-for-gestational age, with higher levels of fluoride in the sibling-matched analysis. Nevertheless, gestational diabetes is an important risk factor

Table 2. Associations of a 0.1-ppm increase in drinking water fluoride with birth weight, gestational age, birth-weight-for-gestational-age *z*-scores, preterm birth, small for gestational age, large for gestational age, and macrosomia among the full sample of births from 2000 to 2018 and matched and unmatched sibling births from 2001 to 2018 in California.

	All births $n = 5{,}008{,}915$	Matched siblings $n = 1{,}386{,}826$	Unmatched siblings $n = 1{,}386{,}826$
Outcome	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)
Birth weight (grams)	1.51 (1.32, 1.71)	−0.03 (−0.38, 0.33)	1.68 (1.32, 2.05)
Gestational age (wk)	0.006 (0.006, 0.007)	0.007 (0.006, 0.008)	0.007 (0.006, 0.009)
Birth-weight-for-gestational-age *z*-scores	0.002 (0.002, 0.002)	−0.003 (−0.003, −0.002)	0.002 (0.001, 0.003)
Preterm birth	−0.0002 (−0.0003, −0.0001)	−0.0007 (−0.0009, −0.0006)	−0.0004 (−0.0005, −0.0002)
Small for gestational age	−0.0001 (−0.0002, 0.0000)	0.0001 (−0.0001, 0.0003)	−0.0001 (−0.0003, 0.0001)
Large for gestational age	0.0005 (0.0004, 0.0006)	−0.0006 (−0.0008, −0.0004)	0.0006 (0.0004, 0.0008)
Macrosomia	0.0006 (0.0005, 0.0007)	0.0003 (0.0001, 0.0005)	0.0007 (0.0005, 0.0009)

Note: The overall analysis uses a linear regression model to estimate the effect of a 0.1-ppm increase in water fluoride levels across all births in California from 2000 to 2018. The matched sibling analysis estimates the effect of a 0.1-ppm change in fluoride levels within siblings from 2001 to 2018. The unmatched sibling analysis estimates the effect of a 0.1-ppm increase in fluoride across all sibling births in California from 2001 to 2018, without taking into account the sibling relationships. The estimates for preterm birth, small-for-gestational age, large-for-gestational age, and macrosomia represent risk differences. CI, confidence level; ppm, parts per million.

for large-for-gestational age and has been increasing in prevalence since 2016.[67] Water fluoridation has been linked to alterations in thyroid hormone levels,[68] and thyroid disease and diabetes are physiologically related,[69] which suggest potential mechanisms linking fluoride levels with neonate size. Examining the relationship of fluoride with pregnancy health complications, including gestational diabetes, preeclampsia, and pregnancy-related hypertensive disorders may be important for future inquiry.

Our main findings are consistent with a cohort study in Sweden, which found that higher urinary fluoride levels during pregnancy were associated with higher birth weight, birth-weight-for-gestational-age *z*-scores, and risk of large-for-gestational age births.[17] In this study, median urinary fluoride levels were 0.71 mg/L, and an increase of 1 mg/L was associated with an increase in birth weight (RD = 84 g; 95% CI: 30, 138) and increased odds of large-for-gestational age (OR = 1.39; 95% CI: 1.03, 1.89). In addition, a study in Mexico found urinary fluoride levels were positively associated with birth-weight-for-gestational-age *z*-scores, but only in the first trimester,[18] where an increase of 1 mg/L in maternal urinary fluoride above 0.99 mg/L was associated with an increase in birth-weight *z*-scores (RD = 0.79; 95% CI: 0.10, 1.48). A study in Canada with median maternal urinary fluoride of 0.5 mg/L also found no associations of urinary fluoride levels with the risk of preterm birth or small-for-gestational age.[21] These studies used urinary fluoride concentrations to evaluate the reproductive impacts of exposure to fluoride from all sources, whereas our study estimated the impact of exposure to drinking water fluoride specifically.

Evidence evaluating associations with drinking water fluoride, rather than urinary fluoride, is less consistent. For instance, living in a ZIP code with fluoridated water was associated with increased risk of preterm birth in New York State,[19] and one study using National Health and Nutrition Examination Survey (NHANES) data found that higher fluoride levels in drinking water were associated with low birth weight, but only among Hispanic mothers.[15] One study in Massachusetts found community water fluoridation was protective for preterm birth, especially when combined with dental cleaning during pregnancy,[16] and another Massachusetts study found higher water fluoride levels were protective against major malformations and neonatal deaths.[20]

Studies in Africa and South Asia have tended to find associations between higher drinking water fluoride levels with adverse birth outcomes. For instance, a study in India found 8.7 higher odds of preterm birth and 10.6 higher odds of low birth weight among mothers with serum fluoride levels >1 ppm,[70] and a study in Senegal found increased risk of low birth weight among mothers with dental fluorosis and those who consumed well water during pregnancy in areas of endemic fluoride contamination.[71] Pregnant women in India with serum fluoride above 1 ppm were found to have high rates of anemia and congenital abnormalities in offspring.[28] Differences between these findings and the current study may be due to exposure levels, because mothers in India and Senegal were exposed to much higher fluoride levels on average in comparison with California mothers. In addition, these studies represent areas in which fluoride occurs naturally in high amounts, whereas in California there is a mix of naturally occurring and treatment-related fluoride.

This work had several important limitations. The water fluoride levels likely included measurement error because we used annual averages, which are the only estimates available from the consumer confidence reports from community water systems. In addition, these measures tend to round to one decimal place, which may reduce precision, especially for lower levels of exposure. We used the detection limit for the purpose of reporting (0.1 ppm) divided by the square root of 2 when fluoride levels were reported to be nondetected. Given the limited number of nondetects in the data (7.5% of water system-years), we expect this approach introduced only minimal bias.[72] The reports sometimes did not clarify the proportion of water used from different sources, and in this case, we used a simple average of the sources. We geocoded participants based on their address at delivery, but people may have moved during pregnancy, which we were not able to capture. We also excluded participants living outside of water boundary service areas from our analysis because we did not have estimates of fluoride levels for them. In addition, people relying on domestic wells who live within water system service boundaries may have been misclassified. Previous studies have shown some groups are less likely to drink tap water and thus may have different levels of exposure,[15,73] but we were not able to measure drinking water consumption behaviors in our study. However, our previous study evaluated the relationship between community water system annual fluoride levels and fluoride levels in maternal urine, serum, and amniotic fluid and found significant correlations,[43] suggesting the water system levels do capture variation in fluoride exposure and reflect prenatal exposures, including fetal exposures. Additional studies outside the United States also suggest water fluoride levels are an important predictor of fluoride measures in urine and plasma of pregnant people.[74] However, we did not measure fluoride within individuals and were unable to include sources of fluoride other than drinking water, including tea and dental products.[75]

There was also some missingness in the fluoride data. Many water systems did not keep records back to 2000, and several systems did not respond to our public records requests. Specifically, the California American Water Company and California Water Service Company did not respond to our multiple public records requests. Thus, we were able to include only data on their water systems for recent years, which were publicly available. We were also unable to assess whether there are critical windows of exposure during the prenatal period because the exposure information was only available annually. Previous studies in Mexico have suggested minimal changes in urinary and plasma fluoride levels over the course of pregnancy,[76] although there may be differential effects of fluoride on fetal growth depending on the trimester of exposure.[18] We were unable to evaluate whether associations differed by the type of chemical used for fluoridation due to lack of data. Previous studies have suggested potential effects of water fluoridation on fertility.[77] For instance, an ecological study of water fluoridation and birth rates found reduced fertility linked to water fluoride levels in the United States,[77] and toxicological evidence suggests fluoride exposure can inhibit both male[78,79] and female fertility.[80] It is also possible our results were biased downward due to live birth bias and the exclusion of miscarriages and stillbirths in the population.[81] Both reductions in fertility and higher risk of fetal loss can mask associations of chemicals with birth outcomes due to selection bias.

More than 200 million Americans receive fluoridated water, and no previous studies to our knowledge had evaluated the effect on birth outcomes at the population level. This study built a novel database of fluoride levels in California community water systems using consumer confidence reports collected using public records requests and linked those records to more than 5 million births. We did not find associations with either preterm birth or being small for gestational age, both birth outcomes that have the strongest associations with later morbidity and mortality. However, we did estimate small reductions in birth weight, gestational age, and risk for large-for-gestational age associated with hypothetical interventions to reduce fluoride levels. These results suggest that fluoride levels above 0.5 and 0.7 ppm are

associated with higher birth weights, longer gestational ages, and greater risk for large-for-gestational age and macrosomia. We did not observe differences in associations by race/ethnicity or insurance status, which in combination with our mostly null results suggests that water fluoridation does not contribute to inequities in adverse birth outcomes. Our hypothesis that water fluoride would be associated with birth outcomes was motivated by the associations of *in utero* and early-life fluoride consumption with lower IQ,[12] because birth outcomes like preterm birth and being small for gestational age are linked to later neurodevelopment. However, given we did not find associations with these perinatal health outcomes (and if anything found small protective effects for preterm birth in the sibling analyses), the effects of fluoride on neurodevelopment likely operate through alternate mechanistic pathways.

The US Environmental Protection Agency (US EPA) regulates the level of fluoride in drinking water, and the current maximum contaminant level goal is 4.0 ppm, which establishes the level to prevent adverse health effects in the general population. However, it is difficult to claim this standard protects maternal and infant health, because very limited evidence exists. In our study the maximum fluoride level was 2.5 ppm, and although the association of fluoride with each outcome was nonlinear, the directions of effect were largely negative for birth weight, birthweight-for-gestational-age z-scores, and gestational age when fluoride levels exceeded 1 ppm. Additional research to evaluate associations with other measures of reproductive health and child development will help ensure the benefits of fluoridation for caries prevention do not come at the cost of other adverse health outcomes.

Acknowledgments

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