

Direct potable reuse and birth defects prevalence in Texas

An augmented synthetic control method analysis of data from a population-based birth defects registry

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Background: Direct potable reuse (DPR) involves adding purified wastewater that has not passed through an environmental buffer into a water distribution system. DPR may help address water shortages and is approved or is under consideration as a source of drinking water for several water-stressed population centers in the United States, however, there are no studies of health outcomes in populations who receive DPR drinking water. Our objective was to determine whether the introduction of DPR for certain public water systems in Texas was associated with changes in birth defect prevalence.

Methods: We obtained data on maternal characteristics for all live births and birth defects cases regardless of pregnancy outcome in Texas from 2003 to 2017 from the Texas Birth Defects Registry and birth and fetal death records. The ridge augmented synthetic control method was used to model changes in birth defect prevalence (per 10,000 live births) following the adoption of DPR by four Texas counties in mid-2013, with county-level data on maternal age, percent women without a high school diploma, percent who identified as Hispanic/Latina or non-Hispanic/Latina Black, and rural-urban continuum code as covariates.

Results: There were nonstatistically significant increases in prevalence of all birth defects collectively (average treatment effect in the treated = 53.6) and congenital heart disease (average treatment effect in the treated = 287.3) since June 2013. The estimated prevalence of neural tube defects was unchanged.

Conclusions: We estimated nonstatistically significant increases in birth defect prevalence following the implementation of DPR in four West Texas counties. Further research is warranted to inform water policy decisions.

Keywords: Birth defects; Congenital anomalies; Congenital heart disease; Neural tube defects; Direct potable reuse; Augmented synthetic control method; Prevalence; Pregnancy; Drinking water

Introduction

Direct potable reuse (DPR) involves the addition of purified wastewater that has not passed through an environmental

buffer into a water distribution system.^{1,2} DPR differs from de facto reuse or indirect potable reuse, in which treated wastewater is mixed with water from other sources in an environmental buffer before reentering the water supply. The first operational DPR plant in the United States began operating in Big Spring, Texas in 2013.³ While DPR systems remain relatively uncommon, their importance in water-stressed regions such as the Western United States is expected to increase in the coming years.² California, Colorado, and Texas agencies have finalized policies for DPR.⁴⁻⁶ El Paso, Texas is developing a “direct to distribution” Advanced Water Purification Facility with capacity to treat 10 million gallons of wastewater effluent from the Roberto R. Bustamante Wastewater Treatment Plant per day⁷ and Los Angeles, California is considering adopting DPR as an additional drinking water resource.⁸ Since biodegradation occurring in environmental buffers may play an important role in the removal of some drinking water contaminants, it is conceivable that teratogenic compounds could persist in DPR drinking

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The data that were used for this analysis are subject to data sharing limitations and may be obtained by application to the Texas Department of State Health Services and Texas Birth Defects Registry. The computing code written for this analysis is available at: https://github.com/schrawj/DPR_scripts_public.

SDC Supplemental digital content is available through direct URL citations in the HTML and PDF versions of this article (www.enviroepidem.com).

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What this study adds:

Direct potable reuse (DPR) involves adding purified wastewater that has not passed through an environmental buffer into a water distribution system. While DPR reduces environmental water loss, there may be concern regarding contaminants in these systems given the absence of an environmental buffer. Congenital anomalies have been linked to drinking water contaminants, but no epidemiological studies have evaluated whether DPR is associated with these conditions. We demonstrate that implementation of DPR in Texas was associated with a nonstatistically significant increase in the prevalence of congenital anomalies. Our work has important implications for water policy.

water.^{9–11} On the other hand, it has been noted that DPR can produce drinking water that is of superior microbiological quality relative to that from other sources.^{1,2} In general, public support has been high for DPR initiatives in specific communities where this drinking water source has been proposed,³ although in the San Gabriel Valley there has been some opposition.⁸

Birth defects, which are structural or functional abnormalities present at birth, are diagnosed in approximately 3% of deliveries in the United States.¹² These diagnoses, which include a wide array of phenotypes, have enormous health and economic impacts: according to 2022 estimates from the Centers for Disease Control and Prevention, 20% of infant mortality in the United States was attributable to birth defects, and inpatient expenditures alone exceeded \$23 billion.¹³ The majority of cases are believed to have complex, multifactorial etiologies, potentially involving both genetic and social/environmental factors. Established risk factors for birth defects include maternal age, alcohol or tobacco consumption, pregestational diabetes, and folate deficiency.¹⁴

Additionally, a number of studies have evaluated associations between drinking water contamination and risk for birth defects. Compounds of concern include metals such as arsenic and lithium, industrial and agricultural chemicals (e.g., di-, tri-, and tetra-chloroethylene, atrazine, and nitrates), and water disinfection byproducts including haloacetonitriles and iodoacetic acids.^{15–17} While findings from observational studies in humans are equivocal, some evidence of association has emerged. Maternal consumption of ≥ 4 glasses of tap water (vs. none) in an area with a recent history of 1,1,1-trichloroethane and 1,1-dichloroethylene contamination was associated with a 10-fold increase in the prevalence of congenital heart disease (CHD), and an assessment of drinking water nitrate exposure in the National Birth Defects Prevention Study found evidence of association with neural tube defects (NTDs), orofacial clefts, and limb deficiencies.^{18,19} Large cohort studies from Denmark and Missouri found associations between modeled drinking water nitrate exposure during pregnancy and defects of the eye, ear, face or neck, nervous system, and limbs.^{20,21} Developmental toxicity studies have characterized mechanisms of action linking drinking water disinfection byproducts¹⁷ and organophosphorus pesticides²² to adverse pregnancy outcomes. Contrariwise, neither total water consumption (including tap and bottled) nor maternal exposure to disinfection byproducts from 1-month preconception through 3 months of pregnancy were consistently associated with birth defects in the National Birth Defects Prevention Study,^{23,24} and the Danish study found evidence of an inverse relationship between maternal drinking water nitrate exposure and defects of the digestive system and genitourinary systems.²⁰ In addition, some animal studies of specific contaminants failed to produce deleterious effects.^{25,26}

Because of the lack of clarity regarding the relationship between drinking water quality and birth defects prevalence, and because DPR has been approved or is under consideration as a source of drinking water for additional population centers, we performed the first assessment of birth defects prevalence in relation to DPR. Our objective was to inform future policy decisions by determining whether the implementation of DPR was associated with a change in birth defects prevalence at the population level. We hypothesized that an increase in birth defects prevalence might be observed in regions that implemented DPR, due to the absence of an environmental buffer.

Methods

Study population and birth defects ascertainment

The present study includes all cases with birth defects ascertained by the Texas Birth Defects Registry (TBDR) for delivery years 2003 (10 years before DPR implementation) to 2017 (the most recent year in which case ascertainment was complete). Registry practices have been described in detail before.²⁷ Briefly,

TBDR is a population-based, active birth defects surveillance system; during the study period, it ascertained cases from all pregnancies among Texas women, regardless of gestational age or outcome. Staff reviewed birth and fetal death records, hospital discharge records, and procedural records from hospitals, birthing centers, and other facilities offering labor and delivery or postnatal care services to identify possible cases. These data were abstracted and entered into a web-based system for review by registry staff, and, for approximately half of cases, by a medical geneticist affiliated with the registry. Birth defects were classified using the Centers for Disease Control modification to the British Paediatric Association six-digit codes (referred to as “BPA” codes). While phenotypes ascertained by TBDR must be congenital, diagnoses made within 1 year of the date of delivery are accepted. This study included only those cases with definite birth defect diagnoses; possible or probable cases (~4%) were excluded.

We considered all monitored birth defects collectively, then evaluated two prevalent categories of birth defects specifically: CHD and NTDs. Due to the small number of cases for most other birth defects phenotypes in exposed counties and some unexposed counties in the synthetic control donor pool, which led to unstable or imprecise prevalence estimates, we felt we were unable to evaluate additional birth defect phenotypes.

Data on maternal demographic characteristics were obtained for cases and a reference population of all live births in Texas to Texas women during the study period from the Texas Center for Health Statistics, by linkage to birth and fetal death records. Demographic information included offspring’s year and month of delivery, and mother’s age, educational attainment, race, ethnicity, and county of residence. Education was categorized as less than high school, high school or equivalent, or post-high school; race and ethnicity were categorized as Hispanic/Latina, non-Hispanic/Latina Black, non-Hispanic/Latina White, other non-Hispanic/Latina, or unknown. Rural-urban continuum codes (RUCC or “Beale” codes) were obtained from the United States Department of Agriculture Economic Research Service and used to describe urbanization at the county-level. Possible values ranged from one (large, urban center) to nine (completely rural); 2003 RUCC classifications were used for deliveries occurring January 2003–June 2008, whereas 2013 RUCC classifications were used for deliveries occurring July 2008–December 2017. Information on year and month of birth were obtained to determine exposure status and estimate birth defects prevalence for each period; demographic variables were included as potential confounders, as these may vary geographically and have been associated with birth defects prevalence (Supplemental Figure S1; <http://links.lww.com/EE/A269>).

Exposure assessment

Cases and live births were considered exposed to DPR-treated drinking water if the birth or fetal death record indicated they were delivered between July 2013 and December 2017 by a woman who resided in Ector, Howard, Midland, or Scurry counties at the time of delivery. These counties and dates were chosen based on the dates of operation and service area for the big spring water treatment plant, a DPR treatment facility utilizing microfiltration, reverse osmosis, and ultraviolet light-hydrogen peroxide disinfection technologies. These counties had previously operated an indirect potable reuse facility. Of note, certain counties not exposed to DPR drinking water recorded < 25 live births during some of the study years and birth defects prevalence estimates in these counties were highly variable. To produce more valid and precise estimates of birth defects prevalence, these were pooled with the contiguous county that recorded the fewest births in the same year, and this process was repeated until all observational units included ≥ 25 live births in all study years. Supplemental Figure S2; <http://links.lww.com/EE/A269> and Supplemental

Table S1; <http://links.lww.com/EE/A269> provide additional detail regarding the aggregation of these data. RUCC values for the new units were assigned by taking the median among the pooled counties.

The city of Wichita Falls, Texas operated a DPR facility from July 2014 to July 2015 in response to prolonged drought. During this time, up to half of the city's water demands were met by DPR-treated water. Because this exposure was transient and impacted a subset of the residents, and because the ridge augmented synthetic control method (ASCM; described below) requires balanced panel data, we considered Wichita County unexposed to DPR in our primary analysis. We compared these results to those from a sensitivity analysis in which Wichita County was excluded from the synthetic control donor pool to assess whether this impacted our results.

Statistical analysis

The ridge ASCM²⁸ was used to estimate the effect of DPR implementation on the prevalence of birth defects, expressed as the number of cases per 10,000 live births. In this analysis, synthetic “control” counties were constructed as weighted combinations of unexposed counties or sets of counties such that, in the pre-exposure period, birth defects prevalence and demographic characteristics of the exposed counties closely resembled those of the synthetic controls. We chose this method because DPR was implemented at the county-level and there were few county units exposed to DPR but multiple pre-DPR periods. In such a setting, with panel data including many pretreatment periods and few exposed units, common estimation approaches include: (1) two-way fixed effects linear regression; (2) differences-in-differences (DID); and (3) synthetic control methods (SCM).^{29–31} Two-way fixed effects linear regression has been criticized for not estimating the average treatment effect on the treated (ATT) consistently in the presence of treatment effect heterogeneity, which we believed was plausible in this case.³¹ DID and SCM approaches are similar, but SCM generally relaxes the parallel-trends assumption invoked in most DID methods by allowing for time-varying confounding and may make fewer parametric modeling assumptions.²⁸ Given that we wanted to estimate the ATT while making the fewest assumptions, we chose SCM for our estimator.

The validity of the SCM approach hinges on the pretreatment outcome trend of the weighted controls being a close match to the pretreatment outcome trend of the exposed units, the

assumption being that if it is a close match to the exposed units before the DPR policy, it will be a good match for the counterfactual exposed units after the DPR policy.²⁸ In other words, the weighted controls can be assumed to be a good representation of the expected outcome trends of the exposed units had they not been exposed (contrary to fact, hence the name “counterfactual”). Specifically, we used a recent implementation of SCM, called the ridge ASCM that extends the classic SCM to improve pretreatment fit by: (1) incorporating an outcome model and (2) allowing for negative weights if a treated unit lies outside the area support of the control units.²⁸ This was necessary for our analysis of all birth defects combined, as pretreatment fit without these extensions was not sufficiently close in this instance. Ridge ASCM assumes: (1) the units (counties in this case) are independent and identically distributed; (2) no anticipation, meaning that the outcomes in exposed counties would not be affected before DPR implementation; (3) one of several assumptions about how the outcomes were generated (detailed in Ben-Michael et al²⁸); and (4) there is a well-fitting synthetic control for the treated unit (as discussed above). Under these assumptions, any differences in the post-exposure period may be attributed to the causal effect of the exposure on the outcome.

Ridge ASCM models using two different hyperparameter (λ) values were constructed: one in which λ was chosen to minimize the cross-validation mean squared error (MSE), and one in which the maximal value of λ with MSE within one standard deviation of the minimum MSE was chosen. This hyperparameter controls the level of extrapolation/improvement in pretreatment fit due to the use of the ridge outcome regression (discussed above). We performed in-space placebo tests,³⁰ where the exposure was assumed to have occurred in a different set of randomly selected observational units, to derive an empirical estimate of the statistical significance of our findings. Two-sided pointwise $P < 0.05$ (estimated using conformal inference) were considered statistically significant. We used the `augynth` package in R; all statistical analyses were performed in R v3.6.3 (R Core Team, Vienna, Austria).

Ethical considerations

This study was approved by the institutional review boards of the Texas Department of State Health Services and Baylor College of Medicine and performed in accordance with the Declaration of Helsinki. The staff of the TBDR has legislative authority to

Table 1. Preintervention (2003–2013) characteristics of counties that did and did not adopt direct potable reuse during the study period

	Counties that adopted DPR (N = 4)	Counties that did not adopt DPR (N = 250)
Live births, N	57,108	4,041,785
Cases with birth defects, N	2,702	184,147
Birth defects prevalence (per 10,000 live births)	473.1	455.6
Maternal age at delivery (years), mean (SD)	24.8 (5.6)	26.7 (6.1)
Maternal educational attainment, N (%)		
No high school diploma	16,615 (29.1)	1,123,879 (27.8)
High school diploma	19,530 (34.2)	1,110,890 (27.5)
Any post-high school education	20,842 (36.5)	1,791,999 (44.3)
Missing or unknown	121 (0.2)	15,017 (0.4)
Maternal race and ethnicity, N (%)		
Hispanic/Latina	31,934 (55.9)	1,985,320 (49.1)
Non-Hispanic Black	2,806 (4.9)	458,554 (11.3)
Non-Hispanic White	21,474 (37.6)	1,407,902 (34.8)
Other non-Hispanic	879 (1.5)	185,571 (4.6)
Missing or unknown	15 (0.0)	4,438 (0.1)
County-level RUCC classification ^a , N (%)		
Metropolitan urbanized	49,654 (86.9)	3,615,160 (89.4)
Nonmetropolitan urbanized	4,831 (8.5)	151,329 (3.7)
Rural	2,623 (4.6)	275,296 (6.8)

^aCounty-level rural-urban continuum code (RUCC): metropolitan urbanized, 1–3; nonmetropolitan urbanized, 4–5; rural, 6–9. 2003 RUCC values were used for births from January 1999 to June 2013; 2013 RUCC values were used from births July 2013–December 2017.

Table 2.

Estimated effect of direct potable reuse adoption on birth defects prevalence per 10,000 live births in synthetic control method models, Texas, 2003–2017

Model	Scaled L2 imbalance	ATT estimate	P (conformal inference)
SCM			
Any monitored anomaly	0.15	64.5	0.19
Congenital heart disease	0.29	198.5	0.20
Neural tube defects	0.07	-3.5	0.43
Ridge ASCM			
Any monitored anomaly	0.01	53.6	0.16
Congenital heart disease	0.004	287.3	0.43
Neural tube defects	0.01	-3.6	0.18

ASCM indicates augmented synthetic control method; ATT, average treatment effect on the treated, defined as the average change in birth defects prevalence per 10,000 live births in treated units; SCM, synthetic control method.

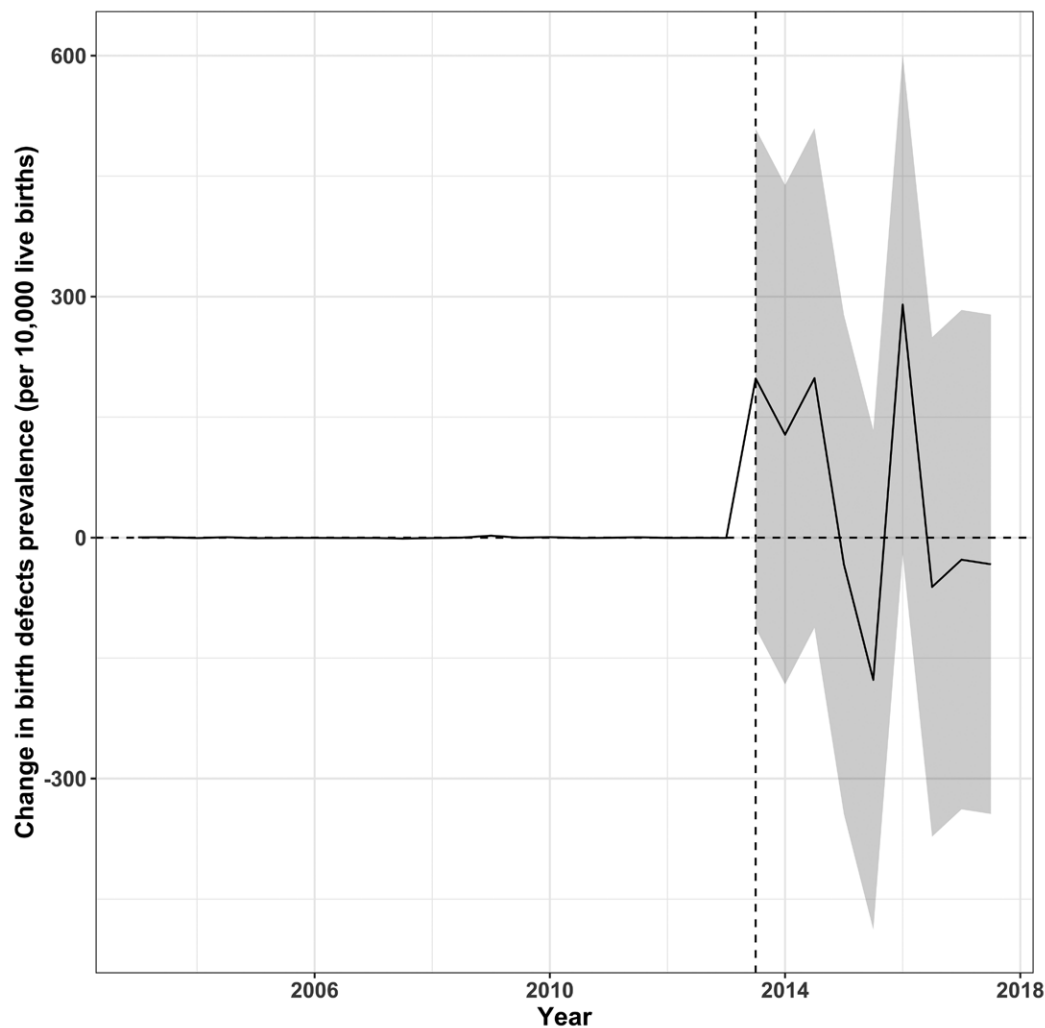


Figure 1. Estimated change in birth defects prevalence for four West Texas counties that adopted direct potable reuse in 2013 in a ridge augmented synthetic control method analysis, with 95% confidence intervals.

collect the TBDR data on all deliveries in Texas without individual consent (Texas Health and Safety Code, Chapter 87; Texas Administrative Code, Title 25, Part 1, Chapter 37, Subchapter P, Rules 37.301–37.306). Therefore, the requirement for written informed consent was waived.

Results

During the study period, there were 5,872,319 live births in Texas and 291,823 cases with birth defects were delivered. Table 1

summarizes the demographic characteristics of people who delivered during the pre-exposure period in counties that subsequently adopted DPR and counties that did not. During this period, the prevalence of all monitored birth defects combined was 473.1 per 10,000 live births in counties that adopted DPR compared with 455.6 per 10,000 in counties that did not, and differences were observed with respect to maternal age, educational attainment, and race/ethnicity. Additionally, there were between-group differences in the proportion of births that occurred in metropolitan, nonmetropolitan, and rural areas. In contrast, ridge augmented

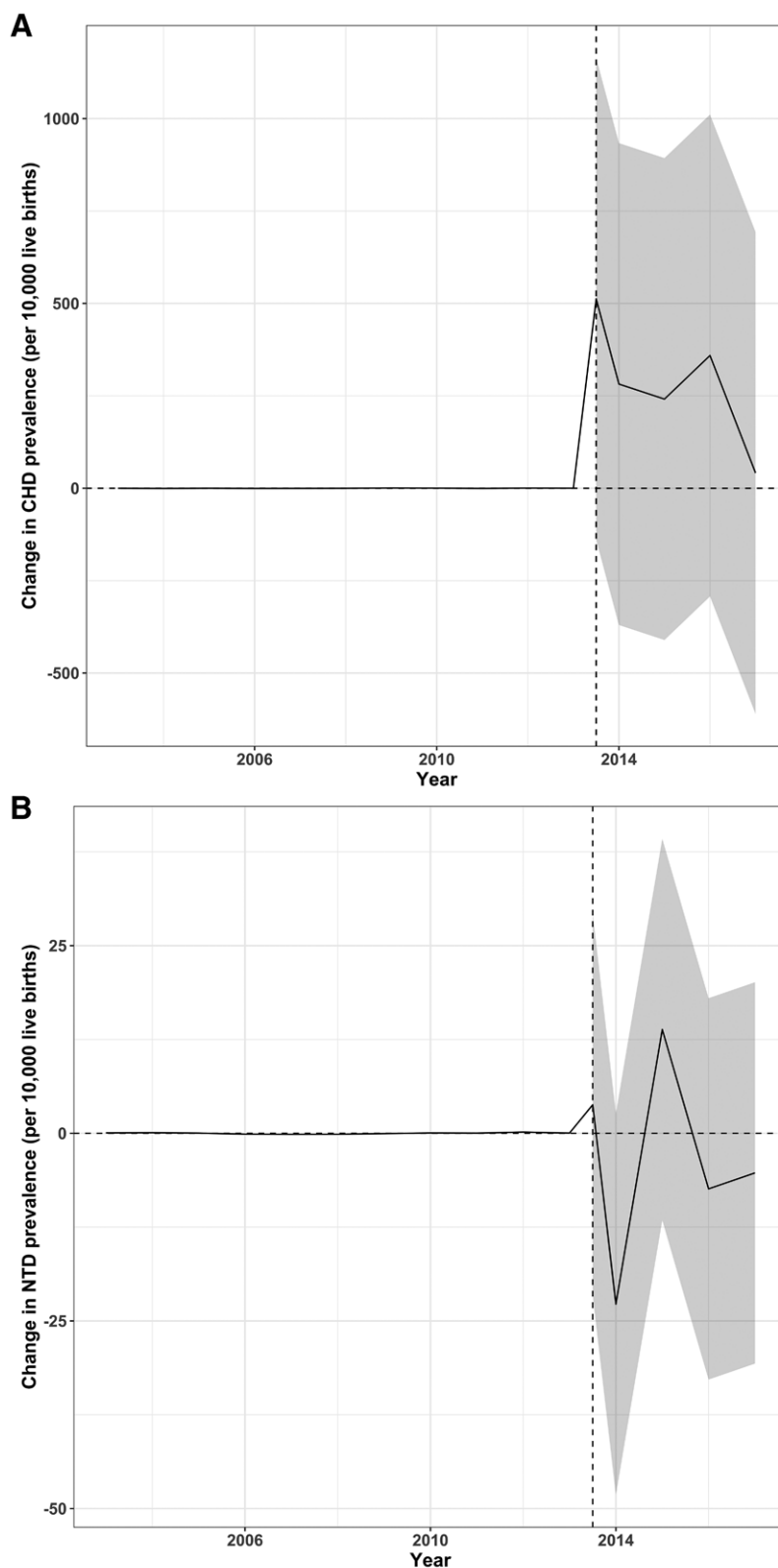


Figure 2. Estimated change in (A) congenital heart disease (CHD) prevalence; and (B) neural tube defects (NTD) prevalence for four West Texas counties that adopted direct potable reuse in 2013 in a ridge augmented synthetic control method analysis, with 95% confidence intervals.

synthetic controls were a good fit for exposed counties with respect to birth defects prevalence and pre-exposure covariates based on scaled L2 imbalances (Table 2).

Both the SCM model without auxiliary covariates and the ridge ASCM model indicated a small, statistically nonsignificant

in birth defects prevalence following DPR implementation. The estimated ATT, which described the change in birth defects prevalence per 10,000 live births estimated to have resulted from the introduction of DPR, was 64.5 ($P = 0.19$) in the SCM model and 53.6 ($P = 0.16$) in the ridge ASCM model (Figure 1 and Table 2).

Results were not substantively changed when an alternate version of the ridge hyperparameter chosen to minimize the cross-validation MSE was used, or when Wichita County was excluded from the donor pool (ATT estimate from the ASCM model 53.2, $P = 0.19$). Of 1,000 in-space placebo studies in which DPR was assumed to have been adopted at the same time in four randomly chosen untreated units, 398 produced an ATT estimate with an absolute value greater than that observed (Supplemental Figure S3; <http://links.lww.com/EE/A269>), suggesting that the likelihood of estimating a change in birth defects prevalence at least as large as that observed in this study due to chance alone is substantial.

We observed a nonsignificant increase in the prevalence of CHD following the implementation of DPR (ATT = 287.3; Figure 2A) whereas there appeared to be no change in the prevalence of NTDs (ATT = -3.6; Figure 2B). Of 1,000 in-space placebo studies for the outcome of CHD, only 14 (1.4%) produced an ATT estimate with an absolute value greater than that observed. None of these estimates changed appreciably when Wichita County was excluded from the synthetic control donor pool.

Discussion

Compounds such as atrazine, lithium, and nitrate have been associated with birth defects and exposure may occur through drinking water.^{9,32} In addition, water treated by DPR or other means can contain complex mixtures that may be toxicologically distinct from individual constituents.^{10,33,34} To inform future policy decisions, we evaluated whether there was a change in birth defects prevalence in four West Texas counties following the implementation of DPR. We hypothesized that an increase in birth defects prevalence might be observed in regions that implemented DPR. Utilizing the ASCM, we observed an increase in total birth defects prevalence of 54 cases per 10,000 live births following DPR implementation in four West Texas counties, a somewhat larger increase in the prevalence of CHD, and no change in the prevalence of NTDs. These increases were not statistically significant, although placebo studies indicated that the observed difference in CHD prevalence was unlikely to have occurred due to chance. Our findings should be interpreted cautiously owing to the limitations discussed below, but our study suggests that further research into the association between water treatment modality and birth defects prevalence is warranted.

Our analysis included data from nearly 300,000 birth defects cases obtained from a large, population-based birth defects surveillance program with essentially complete ascertainment. In contrast to some previous assessments that employed case-control designs,^{18,23,24} our approach should also ensure that there was no differential reporting of exposure history according to birth defects status. For these reasons, the risk of selection or information bias in our study should be minimal. In addition, our use of the ASCM to investigate the effect of DPR on birth defects prevalence is novel, resulted in excellent fit between the exposed and control units on pre-exposure outcomes and covariates, and allowed for a causal interpretation of our results.

Our study is also subject to certain limitations. Our analysis does not incorporate direct assessment of drinking water source, quality, or consumption patterns at the individual level. Therefore, we are unable to estimate any individual's exposure to drinking water contaminants. Nonetheless, at the population level, we believe that our findings provide an unbiased estimate of the effect of this policy change on birth defects prevalence. The relatively small number of live births and cases with birth defects that occurred in some counties during the study period precluded us from evaluating individual birth defect phenotypes, which could potentially obscure associations, and necessitated that we pool data from some unexposed counties, which may have impacted the characteristics of the observational units

in our synthetic control donor pool. For rigor and reproducibility, we have included a detailed description of the pooling procedure in the online supplement. We assigned exposure status based on maternal residential address at delivery because this was the only information available. Thus, we were unable to account for address at conception or residential mobility during pregnancy. We previously demonstrated that residential mobility during pregnancy in Texas was low overall and similar when comparing mothers of infants with NTDs to mothers of infants without birth defects.³⁵ Therefore, we do not anticipate that this limitation resulted in substantial bias or misclassification in the present study. Finally, we did not investigate other adverse pregnancy outcomes that have been linked to drinking water contamination, such as prematurity and low birthweight.^{36,37}

DPR may increase efficiency and sustainability while reducing costs and wastewater discharge,³⁸ but concerns regarding the safety and acceptability of this approach remain. Importantly, the lack of an environmental buffer could conceivably result in increased concentrations of contaminants that have been linked to birth defects and adverse pregnancy outcomes in treated drinking water.^{9,39} In its Framework for Direct Potable Reuse,⁴⁰ the WateReuse Research Foundation identified a number of constituents of emerging concern, including perfluorooctanoic acid, sex hormones, pharmaceuticals (e.g., cotinine, atenolol), triclosan, and other chemicals. It is worth noting that the composition of a DPR-treated water mixture would depend on the composition of the wastewater input and may be variable across time and space. Therefore, further research into the composition of these water mixtures is warranted, and our results may or may not be directly applicable to other populations. Our study suggested a small increase in total birth defects prevalence following DPR implementation, which was not statistically significant, along with a potentially greater increase in CHD prevalence. Additional research into these and other adverse pregnancy outcomes such as preterm birth and low birthweight is warranted, as the population exposed to DPR programs increases.

Conflicts of interest statement

M.O.G. previously owned shares in a water sector mutual fund (FLOWX) that he has divested. The other authors declare that they have no conflicts of interest with regard to the content of this report.

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