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

Direct potable reuse (DPR) is the process of reintroducing highly purified wastewater, often blended with water from other sources, into the drinking water supply.¹ DPR can help meet potable water demand in arid regions and represents a significant step toward sustainable water resource management.² The first DPR system in the United States opened in Big Spring, Texas in May 2013. Additional jurisdictions have since approved DPR, indicative of a trend toward its wider adoption across Western states. As noted by Dr. Gerrity and colleagues, microbiological and toxicological assessments indicate that this reclaimed wastewater can satisfy current regulatory standards, and, indeed, is often less polluted than other source waters.^{1,3} That said, there have not been epidemiological assessments of health outcomes in populations whose water supplies are supplemented by DPR.

In the present study, we evaluated congenital anomalies, common adverse pregnancy outcomes that have been associated with drinking water contaminants including arsenic, nitrates, and disinfection byproducts.^{4,5} Our primary analysis indicated no statistically significant increase or decrease in the birth prevalence of congenital anomalies following the implementation of DPR. Though encouraging, our finding is subject to important caveats, which we discuss here.

First, though we found no change in the prevalence of all monitored congenital anomalies combined, readers should bear in mind that this analysis combined many phenotypes with distinct etiologies. To address this heterogeneity, we conducted secondary analyses evaluating two prevalent categories of anomalies: congenital heart disease (CHD) and neural tube defects. Of potential concern, we observed consistently positive point estimates in our analysis of CHD. Permutation tests in which other, randomly chosen counties were treated as exposed indicated that such a change was unlikely to occur by chance, being observed in <2% of simulations. This finding, not addressed in

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the correspondence by Dr. Gerrity and colleagues, is insufficient to establish a link between DPR and CHD but is suggestive of the need for further research.

Second, as noted, we did not measure individual water use, though this will be important in future, prospective assessments as public response to DPR has been mixed.⁶ It is unknown whether or how community members who find DPR unacceptable may change their water consumption patterns upon its implementation, but there is anecdotal evidence that this occurred in Texas.⁷ Such behavior change represents an alternative mechanism by which DPR may impact public health because replacing or supplementing tap water with water from sources that are not subject to the same monitoring and reporting requirements, such as private wells, could increase exposure to contaminants of (emerging) concern. We argue that characterizing the public response to DPR is necessary to understand its health effects at the population level.

Finally, we note that our failure to reject the null hypothesis (no change in prevalence of congenital anomalies) does not imply that it is true,8 and caution against the representation of findings from this single study as a "persuasively null result." While our study does not provide evidence that DPR is harmful, neither is it sufficient to demonstrate its safety. We cannot draw general conclusions from a single study; rather, we would need a distribution of studies providing consistent estimates across diverse populations that may exhibit heterogeneity in the effects of DPR on CHD. Indeed, future studies may demonstrate that DPR is associated with improved health outcomes-a plausible outcome given the available microbiological and toxicological data. At the time of this writing, however, the paucity of real-world data in combination with our finding concerning CHD argues strongly for additional epidemiologic studies. As gestation represents a vulnerable window for exposure to environmental toxicants, we advocate particularly for the evaluation of pregnancy and birth outcomes.

Conflicts of interest statement

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

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