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Invited Commentary

Invited Commentary: Interaction Between Diet and Chemical Exposures

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A growing literature indicates that changes in modifiable factors, including diet, can counteract the toxic developmental and reproductive health effects of chemical exposures. In this issue of the *Journal*, Gaskins et al. (*Am J Epidemiol*. 2019;188(9):1595–1604) present data supporting this hypothesis. Specifically, using data on a cohort of 304 women seeking fertility treatment in Boston, Massachusetts, they found that women with higher exposure to ambient air pollutants had lower fertility treatment success but only when they also consumed <800 μg/day of supplemental folate. No association was observed among women consuming ≥800 μg/day of supplemental folate. The public health importance of this interaction is high: Diet and dietary supplement intake are modifiable factors, whereas exposure to air pollution is less so. While this research question is grounded in a strong biological hypothesis related to epigenetic modifications, oxidative stress, and inflammation, this study raises several key questions. In this commentary, we discuss the inconsistency of the interaction across exposure metrics, the possibility of unmeasured confounding by folate intake, and the importance of examining this association in populations with lower folate intake and/or higher exposure to air pollution.

air pollution; diet; effect modification; fertility; folate

Abbreviations: $PM_{2.5}$, particulate matter with an aerodynamic diameter equal to or less than 2.5 μm; NO_2, nitrogen dioxide; O_3, ozone.

In this issue of the *Journal*, Gaskins et al. (1) used data from an infertility cohort to evaluate the extent to which folate intake modifies the association between ambient air pollution and fertility treatment outcomes. The analysis included 513 in vitro fertilization cycles from 304 women residing in the Boston, Massachusetts, region. The authors used spatiotemporal models to estimate residence-based daily average nitrogen dioxide (NO_2), ozone (O_3), fine particulate matter ($PM_{2.5}$), and black carbon concentrations, averaged over the 3 months before fertility treatment. They also assessed distance of residence from major roadways as a proxy for traffic-related air pollution. Data on dietary and supplemental folate intake and potential confounders were assessed via self-report. The authors reported that total folate intake modified the association between NO_2, but not other exposures, and the probability of livebirth. These findings appeared to be driven by supplemental folate intake (rather than dietary). Among women with supplemental folate intake of <800 μg/day, the odds of livebirth were 24% (95% confidence interval: 2, 42) lower for every 20-parts-per-billion increase in NO_2 exposure; however, no appreciable association was seen among women with supplemental folate intake ≥800 μg/day (1). Results were strongest when examining pregnancy loss as the outcome, rather than implantation or clinical pregnancy.

This study adds to a growing literature on the interaction between chemical exposures and diet (2), which indicates that changes in modifiable factors might counteract the toxic reproductive and developmental effects of chemical exposures (3–9). This is, to our knowledge, the first study to focus on dietary modifiers of the association between air pollution and fertility. The findings are biologically plausible, given that both traffic-related air pollution and folic acid intake are potentially related to epigenetic modifications (10, 11), oxidative stress, and inflammation (12, 13), all of which could play a role in the etiology of infertility.

The public health implications of this body of research are large, because diet and dietary supplement intake are personally modifiable exposures, whereas air pollution and other chemical exposures are substantially less so. This study has

several strengths, including its prospective study design, ability to measure individual events in the reproductive process (e.g., implantation), and use of validated spatiotemporal models to measure exposure to individual air pollutants. Nevertheless, before we can promote supplemental folate to prevent adverse health effects of air pollution, we need to consider a few key questions that this intriguing study raises.

WHY WAS THE INTERACTION INCONSISTENT ACROSS INDIVIDUAL EXPOSURE METRICS?

The strongest interaction was observed for NO_2, with some evidence of a similar interaction for O_3 and distance to roadways. There was little evidence of interaction for black carbon, and the interaction was reversed for $PM_{2.5}$: Higher $PM_{2.5}$ levels were associated with higher odds of livebirth among women with low supplemental folate intake and with lower odds of livebirth among women with high supplemental folate intake (1). This discrepancy is inconsistent with the general biologic hypotheses prompting this research, which posit that the interaction exists because folate intake counteracts either the hypomethylating effect or the increase in oxidative stress and inflammation caused by air pollution. Interactions going in opposite directions would require $PM_{2.5}$ and NO_2 to act in opposing directions on DNA methylation, oxidative stress, and/or inflammation, which seems implausible. On the other hand, this is a small study, and chance alone might explain the overall pattern better than an overarching biologic hypothesis.

IS THE OBSERVED INTERACTION ACTUALLY DUE TO FOLATE, OR IS IT DUE TO ANOTHER FACTOR ASSOCIATED WITH FOLATE INTAKE?

The observed interaction was stronger for supplemental folate than for dietary folate. Intake of supplements might be a proxy for healthy lifestyle or higher socioeconomic status. Individuals who are healthier or of higher socioeconomic status might be less susceptible to toxic effects of chemical exposures for a variety of reasons that have little to do with folate. It is difficult to say that the lack of adverse association between air pollution exposure and livebirth at the highest levels of supplemental folate intake reflects a causal interaction between air pollution and folate rather than an effect of healthy lifestyle or socioeconomic status. However, the population studied by Gaskins et al. was relatively homogeneous with respect to education, and over 92% of participants took prenatal vitamins (1). In fact, the authors did not observe strong associations between supplemental folate intake and other measures of a healthy lifestyle. However, residual confounding is still possible.

CAN THE FINDINGS BE REPLICATED IN A MORE FOLATE-DEFICIENT POPULATION?

The average supplemental folate intake in this study population was high (median, 571 μg/day), and only 16% of women consumed less folate than the amount recommended for supplementation (400 μg/day) (1), possibly reflecting a study population with high income and education. Because Gaskins et al. had limited data for assessing interaction at the 400 μg/day cut point, they selected twice the recommended daily value as a cutpoint (although they also examined the interaction using continuous measures) (1). It would be interesting to evaluate this relationship in other populations with lower folate consumption, and using lower cutpoints.

IS THIS INTERACTION RELEVANT IN A SETTING WITH HIGHER AIR POLLUTION LEVELS?

Although there was some variability in the estimated air pollutant concentrations in this study, pollutant levels were generally below the National Ambient Air Quality Standards (14) and were markedly lower than pollutant levels in many other parts of the world. Given the relatively low range of exposure, we might not be able to extrapolate findings to regions with higher air pollution exposure. In addition, Gaskins et al. restricted their analysis to assessment of linear effects of exposures. It would be interesting to assess nonlinear effects, such as a threshold. Is there a level of air pollution high enough so that folic acid is no longer protective against diminished fertility? This question is of particular interest in more highly polluted regions.

FUTURE DIRECTIONS

This study by Gaskins et al. (1) was restricted to infertile women attending a fertility clinic. It will be interesting to see if these intriguing findings can be replicated in reproductive-aged women without fertility problems. Like most promising science, this study raises several important questions that researchers should consider in future investigations into the roles of diet, chemical exposures, and their interaction in reproduction.

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