
Paediatric and Perinatal Epidemiology

doi: 10.1111/ppe.12428

Commentary

Considerations for Studying Folate Beyond the Typical Range of Exposure

Julie L. Daniels

Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC

Folate availability in the first days of pregnancy is critical for neural tube closure. Evidence strongly supports that folic acid supplementation around conception elevates circulating folate and prevents neural tube defects (NTD),[1,2] especially for women who have particular variants of genes involved in the one-carbon/folate metabolism pathway.[3] Thus, the United States adopted widespread folic acid fortification of grains in 1998, and the prevalence of NTDs precipitously has dropped since.[4] The US Preventive Services Task Force, in a recent review of its 2009 recommendations, assessed the benefits and harms of folic acid supplementation for women of childbearing age and concluded that substantial benefits outweighed the potential small harms for supplements intake at regular doses. The recommendation that all women should take 400–800 μg of folic acid daily supplement during pregnancy was strengthened.[5]

The folate-dependent one-carbon transport pathway regulates the availability of methyl groups for DNA synthesis and DNA methylation, impacting gene expression and differentiation. Folate deficiency, in combination with genetic or enzymatic variability, can disrupt the one-carbon transport/folate metabolism pathway, interrupting typical methylation during embryogenesis and altering natural patterning of neuron differentiation, migration, and ultimately apoptosis in mid-late gestation.[6,7] Accordingly, there is a growing body of literature focused on potential for folate deficiency to adversely impact neurodevelopment. But to date, few have reported on the potential for risk associated with excess folate.

In this issue of *Paediatric and Perinatal Epidemiology*, Raghavan and colleagues conscientiously examined potential associations amongst prenatal multivitamin use, circulating folate and B_{12}, and autism spectrum disorder (ASD).[8] They replicated prior reports that regular intake of prenatal multivitamins was inversely associated with ASD risk in the child. However, they also report a new finding: an association between *excess* maternal plasma folate and B_{12} around delivery and increased risk of ASD. The association was not apparent when conventional standards were used to categorise folate adequacy (13.5–45.3 nmol/L).[9] But, women with folate above 60.3 nmol/L (the 90th percentile in this cohort) were nearly three times as likely to have a child with ASD as those in middle 80%.[8] Notably, exploring the extreme tails of the folate exposure distribution revealed associations that were not apparent when evaluating more traditional cut-points for adequacy.

These findings do not challenge the WHO adequacy standards for folate or that fortification and supplementation with folic acid has been highly successful in preventing neural tube defects.[1–3] Raghavan *et al.* carefully noted that they observed no risk for ASD at folate levels within recommended adequacy standards. But, nearly 25% of the cohort had serum folate levels in excess of WHO recommendations (>45.3 nmol/L). The reasons for the very high folate were unclear, but they found no evidence of doctors prescribing mega-doses of vitamins that contained folate. This raises the possibility that the collective efforts towards reaching folate sufficiency for all women (based primarily on NTD prevention) may have had unintended consequence, resulting in some women with very high folate levels. Thus, exploring the potential for excessively high folate and vitamin B_{12} to have adverse effects remains critical.

Following the example of this study, future aetiologic investigations should take care to explore the entire distribution of folate and vitamin B_{12} exposure. Though using clinically relevant cut-points for exposure classification in epidemiologic studies remains important, because clinical cut-points are often based on optimising the benefit or reducing risk relevant to a single outcome (such as the recommendations for

Correspondence: Julie L. Daniels, Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.
E-mail: julie_daniels@unc.edu

folate to prevent NTD), sole dependence on a single standard may mask important risks or benefits associated with alternate outcomes. When studying exposures such as essential nutrients, which can have different impact on human development depending on the dose and timing of exposure, it is prudent to (i) investigate the full range of exposures represented by the population; (ii) investigate how differences in the timing of exposure may impact multiple outcomes; and (iii) investigate differences in associations across susceptible sub-groups of the population.

Folic acid fortification is arguably one of the greatest successes in contemporary public health.[1,2] The study by Raghavan and colleagues[8] observed no increased risks among those within the range of daily folate recommended by WHO. Yet, there is a growing literature suggesting that extremely high levels of folate in late pregnancy may increase risk for asthma[10] and now autism spectrum disorder,[8] which warrants investigation. Should future rigorous studies identify risks associated with "excess" folate or vitamin B_{12}, we can consider exploring whether routine screening for folate deficiency and folate excess could be efficacious in maximising benefits and minimising harm across a range of adverse perinatal outcomes.

About the author

Julie Daniels is Professor of Epidemiology, and Maternal and Child Health at the Gillings School of Global Public Health at the University of North Carolina at Chapel Hill where she directs the Reproductive and Paediatric Epidemiology Training Program. Her research focuses on nutrition and environmental exposures during pregnancy and early life that can impact children's growth and neurodevelopment.

References

1 Obican SG, Finnell RH, Mills JL, Shaw GM, Scialli AR. Folic acid in early pregnancy: a public health success story. *FASEB Journal* 2010; 24:4167–4174.
2 Wolff T, Witkop CT, Miller T, Syed SB. Folic Acid Supplementation for the Prevention of Neural Tube Defects: An Update of the Evidence for the U.S. Preventive Services Task Force [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US), 2009.
3 Shaw GM, Rozen R, Finnell RH, Wasserman CR, Lammer EJ. Maternal vitamin use, genetic variation of infant methylenetetrahydrofolate reductase, and risk for spina bifida. *American Journal of Epidemiology* 1998; 148:30–37.
4 Castillo-Lancellotti C, Tur JA, Uauy R. Impact of folic acid fortification of flour on neural tube defects: a systematic review. *Public Health Nutrition* 2012; 31:1–11.
5 Bibbins-Domingo K, Grossman DC, Curry SJ, Davidson KW, Epling JW Jr, García FA, *et al.* US Preventive Services Task Force. Folic acid supplementation for the prevention of neural tube defects: US preventive services task force recommendation statement. *JAMA* 2017; 317:183–189.
6 Zeisel SH. Importance of methyl donors during reproduction. *American Journal of Clinical Nutrition* 2009; 89:673S–677S.
7 LaSalle JM. A genomic point-of-view on environmental factors influencing the human brain methylome. *Epigenetics* 2011; 6:862–869.
8 Raghavan R, Reily A, Volk J, Caruso D, Sices L, Hong X, *et al.* Maternal multivitamin intake, plasma folate and vitamin B12 levels and Autism Spectrum Disorder risk in offspring. *Paediatric and Perinatal Epidemiology* 2017; PMID: 28984369.
9 World Health Organization. Guidelines: Optimal serum and red blood cell folate concentrations in women of reproductive age for prevention of neural tube defects. ISBN: 978 92 4 154904 2; 2015 pdf accessed: http://apps.who.int/iris/bitstream/10665/161988/1/9789241549042_eng.pdf?ua=1.
10 Brown SB, Reeves KW, Bertone-Johnson ER. Maternal folate exposure in pregnancy and childhood astma and allergy: a systematic review. *Nutrition Reviews* 2014; 72:55–64.