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Epigenetic Alterations in Response to Toxic Exposures—The Need to Determine Effect Modification by Nutrient Status

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The challenge and promise of utilizing epigenetic and biomarker data to explore the impact of prenatal exposures on offspring health are highlighted in the recent publication by Xu et al. [1], "Contrasting association of maternal plasma biomarkers of smoking and one-carbon micronutrients with offspring DNA methylation: Evidence of AHRR [aryl hydrocarbon receptor repressor] gene-smoking-folate interaction." The authors found that maternal smoking (indicated by measured blood hydroxycotinine and cotinine) was associated with AHRR hypomethylation in offspring (cord blood) and this effect was strongest among new mothers with low serum folate concentrations [1]. The link between AHRR hypomethylation as a marker of cigarette exposure (both among smokers and their newborns' cord blood) is well established; subsequent long-term risk of lung cancer, heart disease, and other illnesses is a substantial concern [2–4]. Achieving adequate folate status during pregnancy is already an established clinical and public health recommendation; the potential of a simple intervention to mitigate the risks associated with smoking (in addition to avoidance) or other toxic exposures [5] would be of substantial public health benefit.

Inadequate folate status is deleterious, increasing the risk of adverse outcomes across the lifespan from birth defects to cancers [6]. One-carbon metabolites, including folate, are critical for basic processes from detoxification to DNA and RNA replication and methylation [7]. Smoking introduces a number of harmful substances into the body, and many of these are metabolized and cleared in processes dependent on one-carbon metabolism [6,7]. Failure to account for nutrient status (specifically one-carbon pathway components, such as vitamin B12 and folate) may account for the lack of replication between studies across disciplines impacted by this pathway. Many studies may only find associations in settings or persons with low folate status. This could be because of a threshold effect of a simple lack of statistical power when the folate status is high; this was observed with homocysteine reduction and heart disease [8] and likely important studies

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Author contributions

The authors' responsibilities were as follows—KSC: drafted and approved the commentary; and AW: drafted the statistical components and approved the final document.

Disclaimers

The findings and conclusions of this report are those of the authors and do not represent the official position of the Centers for Disease Control and Prevention.

of smoking and clefts [9] among others. Folic acid intake at recommended levels has been shown in studies to mitigate autism risk associated with phthalates [10] and air pollution [11]. This suggests that there is biological plausibility to the mitigation of the impact of smoking on AHRR methylation through adequate maternal folate status.

Epigenetic data can be particularly difficult to analyze and interpret in nutritional and environmental epidemiological studies. Best practices in analyzing epigenetic data are evolving. Epigenetic data are often analyzed either using M-values (unbound measure of methylation with 0 being 50% methylation) or beta-values (values bound from 0 to 1 where 1 is 100% methylated) [12]. Running epigenetic analyses using M-values has been shown to be more statistically valid, performing better in Detection Rate and True Positive Rate, whereas beta-values can allow for easier interpretation [12]. Conducting both types of techniques and having similar results increases confidence in findings, as was done in the Xu et al. analysis.

In both nutritional and environmental epidemiology, exposure mixtures occur frequently. Nutrients do not act alone and are not consumed or metabolized in isolation. Robust techniques to assess these interactions are needed. The authors utilized 2 robust methods to analyze exposure mixture of folate and smoking biomarkers. Bayesian kernel machine regression (BKMR) is an established robust and flexible method of analyzing exposure mixtures [13]. BKMR plots showed an overall effect of vitamin B6, folate, vitamin B12, and hydroxycotinine/cotinine on methylation, with overall decreases in methylation as the exposure mixture increases. Stratification of BKMR analysis by either vitamin B6, folate, or vitamin B12 might help provide some limited information on the relative contributions of each individual component in the exposure mixture. The inclusion of quantile-based g-computation (QGC)—relatively recent method in examining exposure mixture and has been recently used in epigenetic analyses—allows for a deeper understanding on individual components within an exposure mixture [14]. Unlike BKMR, QGC provides information on the directionality of individual components with the exposure mixture. In this analysis, QGC highlights the potentially protective effects of folate and B6 in the exposure mixture while also validating the overall decrease in methylation as the exposure mixture increases from BKMR. Although individually, BKMR and QGC are powerful methods for analyzing exposure mixtures, using them in tandem not only provides cross-validation of 2 methodologies but also provides different aspects on how individual components contribute to the exposure mixture. Further improvements in analytic approaches to exposure mixtures will help elucidate the relative contributions of various nutrients.

Many robust data sources (epidemiologic studies of exposures and outcomes, basic science, statistical and clinical studies) are needed to understand the interactions of adverse exposures during pregnancy and long-term health risks across the lifespan. Although elimination of high-risk exposures is ideal, the possibility of mitigating strategies, such as optimized nutrient status, that may apply across a range of exposures is promising.

Abbreviations:

AHRR	aryl hydrocarbon receptor repressor

BKMR	Bayesian kernel machine regression
QGC	Quantile-based g-computation

References

[1]. Xu R, Hong X, Ladd-Acosta C, Buckley JP, Choi G, Wang G, et al. , Contrasting association of maternal plasma biomarkers of smoking and one-carbon micronutrients with offspring DNA methylation: evidence of AHRR gene-smoking-folate interaction, J. Nutr. 153 (2023) 2339–2351, 10.1016/j.tjnut.2023.05.002. [PubMed: 37156443]

[2]. Kupers LK, Xu X, Jankipersadsing SA, Vaez A, la Bastide-van Gemert S, Scholtens S, et al. , DNA methylation mediates the effect of maternal smoking during pregnancy on birthweight of the offspring, Int. J. Epidemiol. 44 (2015) 1224–1237, 10.1093/ije/dyv048. [PubMed: 25862628]

[3]. Nielsen CH, Larsen A, Nielsen AL, DNA methylation alterations in response to prenatal exposure of maternal cigarette smoking: a persistent epigenetic impact on health from maternal lifestyle? Arch. Toxicol. 90 (2016) 231–245, 10.1007/s00204-014-1426-0. [PubMed: 25480659]

[4]. van Otterdijk SD, Binder AM, Michels KB, Locus-specific DNA methylation in the placenta is associated with levels of pro-inflammatory proteins in cord blood and they are both independently affected by maternal smoking during pregnancy, Epigenetics 12 (2017) 875–885, 10.1080/15592294.2017.1361592. [PubMed: 28820654]

[5]. Tantoh DM, Lee KJ, Nfor ON, Liaw YC, Lin C, Chu HW, et al. , Methylation at cg05575921 of a smoking-related gene (AHRR) in non-smoking Taiwanese adults residing in areas with different PM(2.5) concentrations, Clin. Epigenetics. 11 (2019) 69, 10.1186/s13148-019-0662-9. [PubMed: 31060609]

[6]. Crider KS, Qi YP, Yeung LF, Mai CT, Head Zauche L, Wang A, et al. , Folic acid and the prevention of birth defects: 30 years of opportunity and controversies, Annu. Rev. Nutr. 42 (2022) 423–452, 10.1146/annurev-nutr-043020-091647. [PubMed: 35995050]

[7]. Fernandez-Ramos D, Lopitz-Otsoa F, Millet O, Alonso C, Lu SC, Mato JM, One carbon metabolism and S-adenosylmethionine in non-alcoholic fatty liver disease pathogenesis and subtypes, Livers 2 (2022) 243–257, 10.3390/livers2040020. [PubMed: 37123053]

[8]. Holmes MV, Newcombe P, Hubacek JA, Sofat R, Ricketts SL, Cooper J, et al. , Effect modification by population dietary folate on the association between MTHFR genotype, homocysteine, and stroke risk: a meta-analysis of genetic studies and randomised trials, Lancet 378 (2011) 584–594, 10.1016/S0140-6736(11)60872-6. [PubMed: 21803414]

[9]. Fell M, Dack K, Chummun S, Sandy J, Wren Y, Lewis S, Maternal cigarette smoking and cleft lip and palate: a systematic review and meta-analysis, Cleft Palate Craniofac. J. 59 (2022) 1185–1200, 10.1177/10556656211040015. [PubMed: 34569861]

[10]. Oulhote Y, Lanphear B, Braun JM, Webster GM, Arbuckle TE, Etzel T, et al. , Gestational exposures to phthalates and folic acid, and autistic traits in Canadian children, Environ. Health Perspect. 128 (2020) 27004, 10.1289/EHP5621. [PubMed: 32073305]

[11]. Goodrich AJ, Volk HE, Tancredi DJ, McConnell R, Lurmann FW, Hansen RL, et al. , Joint effects of prenatal air pollutant exposure and maternal folic acid supplementation on risk of autism spectrum disorder, Autism Res 11 (2018) 69–80, 10.1002/aur.1885. [PubMed: 29120534]

[12]. Du P, Zhang X, Huang CC, Jafari N, Kibbe WA, Hou L, et al. , Comparison of Beta-value and M-value methods for quantifying methylation levels by microarray analysis, BMC Bioinformatics 11 (2010) 587, 10.1186/1471-2105-11-587. [PubMed: 21118553]

[13]. Bobb JF, Valeri L, Claus Henn B, Christiani DC, Wright RO, Mazumdar M, et al. , Bayesian kernel machine regression for estimating the health effects of multi-pollutant mixtures, Biostatistics 16 (2015) 493–508, 10.1093/biostatistics/kxu058. [PubMed: 25532525]

[14]. Keil AP, Buckley JP, O'Brien KM, Ferguson KK, Zhao S, White AJ, A quantile-based g-computation approach to addressing the effects of exposure mixtures, Environ. Health Perspect. 128 (2020) 47004, 10.1289/EHP5838. [PubMed: 32255670]