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Bringing clarity to the role of MTHFR variants in neural tube defect prevention[1–3]

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The WHO recently released an evidence-informed guideline, "Optimal serum and red blood cell folate concentrations in women of reproductive age for prevention of neural tube defects" (1), for use in the implementation, monitoring, and impact evaluation of interventions for preventing neural tube defects (NTDs). The guideline reports the threshold values of red blood cell folate concentrations required for NTD prevention and the factors that make meaningful contributions to blood folate concentrations at the population level. Because primary data directly addressing the primary question of interest were scant, the WHO's recommendation was informed by a Bayesian model that estimated dose-response relations between maternal red blood cell folate concentrations at the time of neural tube closure with risk of NTDs, with the use of published data from a community intervention project and a randomized clinical trial of folic acid supplementation in China (2). Remarkably, the dose-response estimates for red blood cell folate concentrations and risk of NTDs generated from the model were consistent with the only available case-control data linking red blood cell folate and NTDs, previously reported by Daly et al. (3) in an Irish population. In addition, the WHO's guideline places a spotlight on the primary factors that interact to determine folate status in human populations, which include dietary intake of folate and a common gene polymorphism, the 677C>T (rs1801133) single nucleotide polymorphism in the gene encoding the enzyme methylenetetrahydrofolate reductase (MTHFR).

As is well established for numerous nutrition-associated diseases, NTDs are complex in their etiology and involve interactions between environmental exposures (e.g., nutrients and nutrient status indicators) on one hand, and the physiologic systems that sense and respond to the environmental factor (e.g., metabolic pathways) on the other. Importantly, the 677C>T *MTHFR* polymorphism has biologically meaningful impacts on both the functioning of folate-mediated one-carbon metabolism ("the system") as well as folate status (1). The dual effects of the *MTHFR* polymorphism on both folate status and the functional capacity of one-carbon metabolism have challenged our ability to determine the mechanism underlying the association between the 677C>T *MTHFR* polymorphism and NTD risk (4). The association could be caused by the impact of the polymorphism on folate status or its impact on MTHFR catalysis, including its role in providing 5-methyltetrahydrofolate for the homocysteine remethylation pathway and subsequent effects on cellular methylation (5).

In this issue of the Journal, Tsang et al. (6) present a systematic review of trials and observational studies and apply Bayesian meta-analytic techniques to assess the association between the 677C>T *MTHFR* polymorphism and blood folate concentrations in women of child-bearing age. The results show a consistent effect of the 677C>T *MTHFR* allele on lowering plasma and red blood cell folate concentration as a function of *MTHFR* genotype (CC>CT>TT). Given the stark differences in the prevalence of the 677C>T *MTHFR* polymorphism across ethnic groups and geographic regions, and its established role in influencing NTD risk, this study emphasizes the increasing importance of identifying genetically susceptible subgroups and optimizing the dose and duration of the nutrient intervention. This is consistent with another study recently published online in the Journal that identifies gene variants in the folate pathway that are associated with diminished folate status in a folic acid–fortified Canadian population (7). The study by Tsang et al. also provides increasing evidence that the primary contribution of the *MTHFR* variant on risk of NTDs is likely due to its impact on folate status, as opposed to its effect on homocysteine remethylation and subsequently cellular methylation capacity.

Understanding the mechanism by which the *MTHFR* 677C>T polymorphism influences both folate status and folate metabolism will help guide future interventions for the prevention of folate-associated pathologies, including NTDs, cancers associated with folate deficiency, and neurodegeneration. Because MTHFR functions to generate 5-methyltetrahydrofolate, and knowledge that the 677C>T *MTHFR* polymorphism can decrease MTHFR functional capacity in generating 5-methyltetrahydrofolate, it has been suggested in both the popular media and the scientific literature that dietary folic acid should be replaced by the more "natural" 5-methyltetrahydrofolate for NTD prevention. These suggestions should be interpreted with caution because there is currently no evidence that 5-methyltetrahydrofolate can prevent NTDs, whereas it has been shown conclusively that folic acid supplementation reduces the risk of NTDs across diverse

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[2] Supported by Health Canada (AJM) and NIH grant HD059120 (PJS).

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First published online May 13, 2015; doi: 10.3945/ajcn.115.111088.

populations (8). Importantly, folic acid supplementation in women with the *TT MTHFR* genotype has been shown to increase folate status above that which is considered maximally protective for NTDs (9). Furthermore, women with vitamin B-12 deficiency have diminished ability to metabolize 5-methyltetrahydrofolate, which may make it less effective in preventing NTDs than folic acid. Public health nutrition will be increasingly challenged by the complexity that underpins biological differences in responses to interventions among individuals and subgroups within populations, but this study by Tsang et al. provides strong evidence that these challenges can be addressed.

The authors had no conflicts of interest related to this editorial.

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