LETTER

B vitamins and pollution, an interesting, emerging, yet incomplete picture of folate and the exposome

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We read the interesting article by Zhong et al. (1) describing how B-vitamin supplementation reduces the adverse epigenetic response to fine particles associated with air pollution. However, we feel it is extremely premature to suggest, as the authors do, that "individual-level prevention" via vitamin supplements "might be used as prevention to complement [environmental] regulations to attenuate the impact of air pollution" (1).

First, atmospheric pollution is a symptom of detrimental anthropogenic change to the Earth, and prevention, rather than a temporary Band-Aid fix, is the only sane approach.

Second, the pharmacology applied by Zhong et al. (1) is flawed. The level of B-vitamin intervention is excessive because it has already been established that 400 μg of pteroylmonoglutamic acid (PteGlu), the synthetic form of the vitamin, is optimal for conversion to the natural 5-methyltetrahydrofolate (5-CH3-H4PteGlu) form of folate (2). As used in the Zhong et al. (1) article, 2.5 mg of PteGlu will lead to an excessive accumulation of systemic PteGlu with attendant potential health risks (3), and is an inappropriate choice of dose, not in the least because it is 6× higher than is necessary for optimal methyl group formation (2). The possible health risks of excessive PteGlu are well documented (4–6), and need to be considered carefully in any intervention to mitigate cellular effects of air pollution (1). Indeed, one highly significant study has even reported that B vitamins increase the risk of myocardial infarction (7). It's important to note that unmetabolized PteGlu per se will not increase genomic methylation (only 5-CH3-H4PteGlu can achieve this). Unlike PteGlu, no negative health attributes are associated with 5-CH3-H4PteGlu. Vitamin B_6 is also given at supraphysiological levels that are potentially harmful. The recommended daily intake is 1.3 mg/d for a 31- to 50-y-old. At almost 40× this level, as used in the Zhong et al. (1) study, long-term use might be unsafe and has been linked to neurologic effects. Additionally, B_6 has more relevance in the transsulphuration of homocysteine than the remethylation of this thiol to methionine/s-adenosylmethionine (8).

Third, the Zhong et al. (1) study reflects a small cohort ($n = 10$), and as such cannot take account of the profound influence that a large number of folate-related genotypes will have on the production of de novo methyl groups for genomic methylation, let alone the effect of even a single gene variant. Key SNPs include MTHFR, MTR, MTRR, CBS, SHMT, DHFR, SHMT, TS, RFC, and BHMT variants. In addition, it would not take account of seasonal changes in folate status (8).

Fourth, the age range in the Zhong et al. (1) study is large (18–60 y), and takes no account of recognized age-related effects on homocysteine and the methionine cycle, and hence methyl group metabolism (9).

As an aside, we assume that in the Methods section of Zhong et al. (1), the text should read that HPLC was used to measure vitamin B_6 and not vitamin B_{12}.

Despite these comments, we feel the Zhong et al. (1) report is an important piece of work, and one that draws attention to the role of exposomal factors in B-vitamin biology. We recently published just such an exposomal association between UV exposure and folate involving the key C677T-MTHFR gene variant (8), and hope others will follow suite with similar studies that take account of natural and anthropogenic environmental factors.

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