

## Reply to Quinlivan: Postfortification, folate intake in vitamin B12 deficiency is positively related to homocysteine and methylmalonic acid

With cross-sectional data, causes and effects are difficult to distinguish, and Quinlivan suggests that high circulating concentrations of homocysteine (Hcy), methylmalonic acid (MMA), and folate observed among vitamin B12-deficient survey participants all resulted from a lack of vitamin B12 (1). However, we observed the interaction between vitamin B12 status and folate status in the current, postfortification era, when high folic acid intake is common (2).

Because folic acid can be directly converted to tetrahydrofolate (3), polyglutamation should have occurred even in the vitamin B12-deficient subjects. Furthermore, dietary data from the survey support the hypothesis that high folate intake is associated with high metabolite levels in vitamin B12-deficient people. We defined higher folate intake as dietary intake  $531 \mu\text{g}/\text{d}$  (the 80th percentile) or use of folic acid supplements and found that this variable also interacted significantly with vitamin B12 status in relation to circulating metabolite levels ( $P < 0.01$ ). Specifically, among those with serum vitamin B12  $>148 \text{ pmol}/\text{liter}$ ,

multivariate-adjusted geometric mean Hcy for those with lower and higher folate intakes were  $8.1 \mu\text{mol}/\text{liter}$  and  $7.3 \mu\text{mol}/\text{liter}$  ( $P < 0.001$ ), respectively, as compared with  $10.2 \mu\text{mol}/\text{liter}$  and  $12.3 \mu\text{mol}/\text{liter}$  for those with serum vitamin B12  $P < 0.05$ ). Corresponding MMA values were  $137 \text{ nmol}/\text{liter}$  and  $128 \text{ nmol}/\text{liter}$  ( $P < 0.001$ ) for subjects with normal serum vitamin B12, and  $224 \text{ nmol}/\text{liter}$  and  $337 \text{ nmol}/\text{liter}$  ( $P = 0.021$ ) for the vitamin B12-deficient subjects. Vitamin B12 deficiency should not increase folate intakes; consequently, these results likely reflect different effects of high folate intakes on circulating metabolite levels in people with normal and low vitamin B12 status.

**Jacob Selhub\***, **Martha S. Morris<sup>†‡</sup>**, and **Paul F. Jacques<sup>†</sup>**

*\*Vitamin Metabolism Laboratory and <sup>†</sup>Nutritional Epidemiology Program, Jean Mayer United States Department of Agriculture Human Nutrition Research Center on Aging, Tufts University, Boston, MA 02111*

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The authors declare no conflict of interest.

<sup>†</sup>E-mail: martha.morris@tufts.edu.

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