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Reply to RJ Berry et al

Dear Sir:

Berry et al suggest that the results of our study (1) may apply only to American seniors and should not be generalized to countries considering fortification. Indeed, only American seniors were included in our study, and we sought to shed light on concerns expressed specifically for them. American seniors have been of particular concern not only because their vitamin B-12 status is low, but also because their consumption of fortified breakfast cereals and supplements is high (2). Consequently, American seniors are at high risk of exceeding the selected limit of <1 mg folic acid/d, including that in supplements, enriched cereal-grain products fortified under the government's folate-fortification policy, and other fortified foods. Although we never suggested that our results had important implications for countries considering folic acid fortification, our findings are relevant to those countries to the extent that their populations resemble American seniors in folate-consumption habits, vitamin B-12 status, or both. The rate of supplement use in developing countries may be low, but dietary deficiency of vitamin B-12, which is found naturally only in animal products (3), is often high (4).

Berry et al are concerned that the comparison of subjects with very high serum folate concentrations with those with lower folate concentrations is equivalent to a comparison of supplement users with nonusers and that such comparisons could be confounded by differences between those groups not controlled by our multivariate adjustments. Because most of the characteristics Berry et al list correlate with good health, such residual confounding would not be expected to create associations between high folate status and adverse health consequences. To provide further assurance that the association between high folate status and cognitive impairment in seniors with low vitamin B-12 status was not caused by an unfair comparison, we restricted our analyses to supplement-using seniors with a low vitamin B-12 status. We found significant inverse continuous associations between serum folate and Digit-Symbol Coding scores in the 153 users of any dietary supplement (β coefficient = -0.09, $P = 0.007$) and in the 92 users of supplements that contained folic acid (β coefficient = -0.13, $P = 0.003$).

A related issue mentioned by Berry et al is their belief that our results, even if not spurious, have nothing to do with fortification. Although 32 of the 42 subjects with both a low vitamin B-12 status and a high serum folate concentration used supplements that contained folic acid, and another 8 reported eating a fortified breakfast cereal within 24 h of the interview, it is incorrect to conclude that fortification made no contribution to our results. Applying the same exclusion and inclusion rules as we applied in our study to data from the third National Health and Nutrition Examination Survey (NHANES III), we found that only 10% of 501 qualifying seniors who used supplements providing 400 μg folic acid had a serum folate concentration >59 nmol/L compared with 40% of 1999–2002 NHANES participants supplemented at the same level. Folic acid contributed by foods was calculated during the NHANES 2001–2002 survey, and the data showed that 100 μg folic acid from enriched cereal-grain products was often provided by single-meal portions of rice- or pasta-based dishes, pizza, tortilla-wrapped entrees, batter-fried chicken, hamburgers, bagels, muffins, and a variety of desserts. Folic acid from food boosted daily intakes of folic acid from enriched cereal-grain products to >100 μg for 40% of subjects with a serum folate concentration >59 nmol/L and low vitamin B-12 status. Cereal eaters typically obtained about another 100 μg/d from cereal, although some cereals were much more heavily fortified.

Berry et al wondered how low vitamin B-12 status and high serum folate coexisted in users of supplements that contained vitamin B-12. Although most of the supplements were conventional multivitamin-multimineral combinations, it is difficult to know how much vitamin B-12 they provided. Such supplements almost always contained 400 μg folic acid, and the amount of vitamin B-12 attributed to survey participants from this source varied between 6 and 25–30 μg. However, an exact match for the reported product was found for only 18 of the 32 products recorded for the subjects with low vitamin B-12 status and high serum folate. Even 6 μg/d exceeds current recommendations of $\approx$3 μg/d (2), and normal aging should not affect absorption of crystalline vitamin B-12 (5). However, actual amounts and label-declared amounts may differ (6), and factors such as fasting status affect bioavailability (7). More importantly, the use of multivitamin formulations containing 2–30 μg vitamin B-12 have been found to be ineffective at normalizing vitamin B-12 status in community-dwelling elderly people (8). Furthermore, even a 6-wk course of 100 μg vitamin B-12/d orally rarely normalized methylmalonic acid concentrations in a study of seniors attending a veterans' affairs clinic who were identified through screening as having

low serum vitamin B-12 and elevated methylmalonic acid concentrations (9).

In asking whether the cognitive deficits of the cognitively impaired seniors with both low vitamin B-12 status and high serum folate could have been due to their low vitamin B-12 status, Berry et al seem to miss the point that the prevalence of cognitive impairment in this group exceeded that in the group with low vitamin B-12 status and lower serum folate (odds ratio: 2.6; 95% CI: 1.6, 6.6).

We never attributed the presence of unmetabolized folic acid in blood to folic acid fortification, as Berry et al claim, nor did we state that our findings support the theory that folic acid directly exacerbates the neurologic and neuropsychiatric effects of low vitamin B-12 status. In fact, we cautioned that our study could not address hypotheses specifically related to the effects of unmetabolized folic acid and noted consistencies and inconsistencies between our results and predictions of harm to seniors with a high folic acid intake. For example, contrary to expectations, we found more, not less, anemia in association with high serum folate when vitamin B-12 status was low.

Finally, we strongly agree with Berry et al's support of continuing vigilance in examining potential positive and negative effects of public health intervention programs in an effort to make decisions that are safe for the entire population. In fact, this sentiment closely resembles that expressed by one of us in an editorial recently published in this Journal (10).

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Reply to RJ Berry et al

Dear Sir:

The information presented by Berry et al is of considerable interest, but perhaps not very surprising in that it shows that 92% of the elderly with the highest blood folate concentrations are consuming supplements containing folic acid. I did point out in my editorial that high blood folate concentrations, particularly unmetabolized folic acid, are not only a consequence of fortification but also of supplement use (1). What is irrefutable is that blood concentrations of folate increased dramatically in the United States after mandatory fortification was introduced, with the concentration of serum folate increasing from a median of 12.5 nmol/L to a median of 32.2 nmol/L (2). Furthermore, the skewness toward higher levels apparent before fortification is just as marked as after fortification (2); this skewness might be due in part to the use of supplements (3).

Whereas Berry et al focus on the elderly, these changes also relate to young children. The data reported by Pfeiffer et al (2) show that the section of the US population with the highest blood folate concentrations after fortification was children aged ≤5 y, 43% of whom had serum folate concentrations >45.3 nmol/L. Ten percent of these children had concentrations >77.3 nmol/L. Using the formula provided by Quinlivan and Gregory (4), we can estimate the dietary folate intake in folic acid equivalents: 43% of children aged <5 y are consuming the equivalent of >780 μg folic acid/d, ie, double the Institute of Medicine's proposed tolerable upper limit (300–400 μg/d) for children of that age. What is of greater concern is that 10% are consuming the equivalent of >1320 μg folic acid/d, which is well above the tolerable upper limit of 1000 μg/d for adults. The next highest blood concentrations were found in children aged 6–11 y. It is plausible, as Berry et al suggest for the elderly, that such high concentrations are in part the result of supplement use in young children (5). However, it is perhaps more likely that the high concentrations in children are the consequence of 2 factors: the consumption of large amounts of bread and a diet rich in fortified ready-to-eat breakfast cereals. We simply do not know whether these high blood concentrations cause harm, but it must be of concern that such concentrations occur in children during a rapid stage of development. The study by Morris et al (6) highlights the potential importance of the correct balance between folate and vitamin B-12 in the elderly and we should consider whether a similar balance is important in young children, especially in parts of the world where many children have a low vitamin B-12 status.

Berry et al believe that a delay in implementing folic acid fortification in other countries would be detrimental to public health. This is likely to be the case in relation to neural tube defects, but should millions of people have to eat food fortified with folic acid without choice? The point that I was trying to make in my editorial is that fortification might potentially harm more people than it would benefit. The benefit of fortification in relation to neural tube defects