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REFERENCES

1. Brouwer I, Verhoef P. Folic acid fortification: is masking of vitamin B-12 deficiency what we should really worry about? Am J Clin Nutr 2007;86:897–8 (editorial).
2. Wyckoff KF, Ganji V. Proportion of individuals with low serum vitamin B-12 concentrations without macrocytosis is higher in the post–folic acid fortification period than in the pre–folic acid fortification period. Am J Clin Nutr 2007;86:1187–92.
3. Carmel R. Macrocytosis, mild anemia and delay in diagnosis of pernicious anemia. Arch Intern Med 1979;1979;139:47–50.
4. Carmel R. Pernicious anemia: the expected findings of very low serum cobalamin levels, anemia and macrocytosis are often lacking. Arch Intern Med 1988;148:1712–4.
5. Carmel R, Sarrai M. Diagnosis and management of clinical and subclinical cobalamin deficiency: advances and controversies. Curr Hematol Reports 2006;5:23–33.
6. Lindenbaum J. Aspects of vitamin B12 and folate metabolism in malabsorption syndromes. Am J Med 1979;67:1037–48.
7. Lindenbaum J, Rosenberg IH, Wilson PWF, Stabler S, Allen RH. Prevalence of cobalamin deficiency in the Framingham elderly population. Am J Clin Nutr 1994;60:2–11.
8. Carmel R, Green R, Jacobsen DW, Rasmussen K, Florea M, Azen C. Serum cobalamin, homocysteine and methylmalonic acid concentrations in a multiethnic elderly population: ethnic and sex differences in cobalamin and metabolite abnormalities. Am J Clin Nutr 1999;70:904–10.
9. Carmel R. Cobalamin (vitamin B_{12}). In: Shils ME, Ross AC, Caballero B, Cousins RJ, eds. Modern nutrition in health and disease. 10th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2006: 482–97.
10. Elwood PC, Shinton NK, Wilson CI, Sweetnam P, Frazer EC. Hemoglobin, vitamin B12 and folate levels in the elderly. Br J Hematol 1971; 21:557–63.
11. Hvas AM, Ellegaard J, Lous J, Nexo E. Health technology assessment in clinical biochemistry. Methylmalonic acid: a Danish showcase. Scand J Clin Lab Invest 2003;63:319–30.

Reply to R Carmel

Dear Sir:

Dr Carmel states that mean corpuscular volume (MCV) is an important marker of serious vitamin B-12 deficiency. He also argues that it is important to distinguish clinical vitamin B-12 deficiency from subclinical deficiency when discussing possible adverse effects of supplemental folic acid. Furthermore, he makes the case that patients with severe vitamin B-12 deficiency are unlikely to benefit from fortification with vitamin B-12.

In our editorial, which ended with the suggestion that folic acid fortification be combined with vitamin B-12 fortification, we took the position that, despite a normal MCV, a person may still have vitamin B-12 deficiency. We do not contest the relevance of a high MCV value for diagnosis of vitamin B-12 deficiency, and we should have expressed ourselves more carefully. It would have been clearer had we said that every physician should know by now that a normal MCV does not mean that the person has no vitamin B-12 deficiency. We clearly recognize the value of an MCV measurement for diagnosis of vitamin B-12 deficiency and do consider it a valuable parameter for the detection of anemia in general.

We also agree with Carmel that the controversy surrounding the effects of folic acid in vitamin B-12–deficient persons may never be resolved. It is indeed not known whether the neurologic progression seen at folic acid supplementation in clinical deficiency also occurs in subclinical vitamin B-12 deficiency. However, it is not impossible that folic acid may also have detrimental health effects in persons with mild vitamin B-12 deficiency.

Carmel further states that patients who have progressive vitamin B-12 deficiency, including neurological deterioration, are unlikely to benefit from vitamin B-12 fortification because of malabsorption. We agree with him if this situation concerns patients who have reduced absorption due to lack of intrinsic factor, because these patients can passively absorb only ≈1% of crystalline vitamin B-12 (1). Therefore, they will still require intramuscular injections with vitamin B-12. Fortunately, this possibility affects only a relatively small group of patients. However, in most older persons, the absorption problem is caused by age-related gastric atrophy (2–4), which will lead to a reduced ability to extract vitamin B-12 from food protein. There is no reason to expect absorption problems for crystalline vitamin B-12 in this group.

We therefore expect that most older persons with low vitamin B-12 status will benefit from food fortification with vitamin B-12. When a food is already fortified with folic acid, additional vitamin B fortification may correct the otherwise unnoticed low vitamin B-12 status in elderly. Moreover, it may have other positive health effects, eg, on cognitive performance. Recent research shows that low vitamin B-12 status is associated with more rapid cognitive decline (5). However, randomized controlled clinical trials will have to show whether vitamin B-12 supplementation can indeed delay cognitive decline. In conclusion, although it is not a solution for patients who lack intrinsic factor, fortification with vitamin B-12 along with folic acid may have important health effects for a large group of elderly.

Petra Verhoef is an employee of Unilever, which markets food products, some of which are enriched with B vitamins. Neither of the authors had any personal or financial conflict of interest.

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REFERENCES

1. Baik HW, Russell RM. Vitamin B12 deficiency in the elderly. Annu Rev Nutr 1999;19:357–77.
2. Hvas AM, Nexo E. Diagnosis and treatment of vitamin B12 deficiency—an update. Hematologica 2006;91:1506–12.

3. Hin H, Clarke R, Sherliker P, et al. Clinical relevance of low serum vitamin B12 concentrations in older people: the Banbury B12 study. Age Aging 2006;35:416–22.
4. Stabler SP, Allen RH. Vitamin B12 deficiency as a worldwide problem. Annu Rev Nutr 2004;24:299–326.
5. Clarke R, Sherliker P, Hin H, et al. Detection of vitamin B12 deficiency in older people by measuring vitamin B12 or the active fraction of vitamin B12, holotranscobalamin. Clin Chem 2007;53:963–70.

Effects of breastfeeding on health outcomes in childhood: beyond dose-response relations

Dear Sir:

Kramer et al (1), whose report was published recently in the Journal, should be congratulated for their 6.5-y follow-up of nearly 14 000 participants in the Promotion of Breastfeeding Intervention Trial (PROBIT), the first randomized trial of a breastfeeding promotion intervention in healthy, full-term infants. Whereas they acknowledge that their findings may not apply to comparisons of breastfed and formula-fed children, they nevertheless conclude, "Previously reported beneficial effects [of breastfeeding] on these outcomes [measures of adiposity, stature, or blood pressure] may be the result of uncontrolled bias due to confounding and selection." In our view, Kramer et al cannot draw this conclusion, because their study addresses only the effect of prolonging the duration of exclusive breastfeeding on anthropometric and blood pressure outcomes at 6.5 y of age.

It has been stated that evidence of a dose-dependent association between breastfeeding and health outcomes would be required to support the biological causality of the assumed beneficial effects (2). The potential consequences of prolonging the duration of breastfeeding, addressed by Kramer et al, therefore are certainly of relevance for the debate on the long-term health benefits of breastfeeding. A recent meta-analysis suggests that, for each additional month of breastfeeding, the risk of overweight would be reduced by 4% (2). Unfortunately, Kramer et al did not provide information on the mean number of weeks for which children in the intervention and control groups had been breastfed; that information would have allowed an estimation of the magnitude of the differences in outcomes that could have been expected. In addition, their attempt to reproduce the results of other observational studies by comparing infants completely weaned within the first month with those exclusively breastfed for >6 mo, to further illustrate the absence of an effect of extended breastfeeding, is misleading. Infants who have been exclusively breastfed for >6 mo often represent a relatively selected group (eg, in this case, only 1.5% of the PROBIT cohort), which is characterized by particular behaviors. Any consequences of this practice are likely to be associated with these behaviors rather than with breastfeeding per se. It has even been argued that these infants may receive nutritional intakes below requirements at this age (3), and the "catch-up" or accelerated growth that may follow such early undernutrition could result in unfavorable body-composition development in the long term.

Current evidence suggests that even the substantial extension of breastfeeding duration achieved in the PROBIT cohort could be expected to yield only modest effects on adiposity and blood pressure (2, 4). Therefore, the limited precision of the outcome measurements in the PROBIT cohort is of particular concern. The correlation coefficients presented to illustrate the validity and reproducibility of the data are of questionable value because they compare measurements made an average of 18 mo apart; the range is an astonishing 5.3–32.6 mo. They do not allow one to distinguish the quality of the measurements from the biological tracking of anthropometric variables or plausible deviations that may be expected over the course of 18 mo in growing children (5). Thus, imprecise measurements may well have masked the likely modest effects of breastfeeding prolongation on the health outcomes assessed.

Despite the importance of potential benefits associated with prolonging the duration of breastfeeding, it appears more relevant from a public health perspective to focus on the differences between formula-fed and breastfed children—ie, whether children who have been offered formula in place of human milk may experience adverse health effects in the longer term. The intervention study by Kramer et al does not, however, add any new evidence to this debate, although nonscientists and the general public could erroneously assume, from their overly general conclusion, that it does. Even if prolonging the duration of breastfeeding has only a limited (or no) benefit for health outcomes, breastfeeding per se—as opposed to formula feeding—could still be beneficial for these outcomes for the following 2 reasons.

First, benefits could stem primarily from breastfeeding in the first weeks of life, which is a potentially critical window for programming long-term health (6). Support for this proposal comes from a study investigating the offspring of diabetic mothers, in whom adjustment for the volume of breast milk ingested during the first week of life largely accounted for the associations between breastfeeding in the 2nd to 4th week (or its duration) and relative body weight or risk of overweight (7). Accordingly, a recent analysis by our group (8), using data from the Dortmund Nutritional and Anthropometric Longitudinally Designed Study, showed a protective effect of full breastfeeding on the development of percentage body fat throughout childhood, irrespective of whether full breastfeeding was defined as full breastfeeding for ≥2 wk or as full breastfeeding for ≥4 mo. In addition to this main finding, a modest dose-response relation between breastfeeding and adiposity was observed.

Second, breastfeeding could still be of relevance for subgroups of infants. In our recent analysis, only boys whose mothers were overweight profited from being fully breastfed for the development of their percentage body fat between 0.5 and 7 y of age (8). Additive interactions of maternal prepregnancy BMI and breastfeeding for childhood overweight between 2 and 14 y of age were also seen in the 1996 National Longitudinal Survey of Youth (9). Changes in maternal weight after a pregnancy are common, and maternal overweight in later childhood, which was the variable used in these PROBIT analyses, will more likely be a marker of the child's current behavioral environment than an indication of the fetal environment. Thus, it is perhaps not surprising that studies assessing maternal weight in later childhood could not corroborate an interaction between maternal overweight and breastfeeding (1, 10).

Admittedly, the study by Kramer et al contributes to the accumulating evidence that the overall effects of breastfeeding on later health outcomes are likely to be modest. The prolongation of exclusive breastfeeding may confer limited benefit for adiposity, stature, and blood pressure in later childhood. Future studies should, however, address whether breastfeeding per se, particularly in the first weeks of life, may nonetheless entail long-term health benefits for specific subgroups.

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