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Folic Acid Supplementation and Cardiovascular Diseases

To the Editor: In their meta-analysis of randomized controlled trials of folic acid supplementation and risk of cardiovascular disease, Dr Bazzano and colleagues[1] provided a clear description of their inclusion criteria and study selection process. Using multiple databases when searching for studies that meet meta-analysis inclusion criteria may help avoid selection bias.[2] Failure to search multiple health databases can result in missing up to half of the relevant literature.[3]

EMBASE and MEDLINE are the 2 most comprehensive databases used in meta-analyses. EMBASE focuses on drugs and pharmacology and contains more than 18 million records, including an index of more than 7000 journals from 70 countries. It may be a relevant source of negative studies, because European and non–English-language journals may be more likely to publish negative findings. However, Bazzano et al limited their literature search to MEDLINE. In addition, an important source for obtaining negative studies is hand searching of "grey literature" (such as abstracts from major meetings and symposiums, newsletters, and theses). Omitting gray literature from meta-analyses can affect analysis outcome by as much as 15%.[4]

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To the Editor: Several large prospective observational studies and a recent meta-analysis[1] suggested an association between elevated levels of homocysteine and risk of cardiovascular diseases. A population-based cohort study found that folate supplementation is effective in decreasing total homocysteine concentration.[2] However, the meta-analysis of randomized controlled trials by Dr Bazzano and colleagues[3] did not find any effect of folic acid supplementation on the risk of cardiovascular diseases or all-cause mortality among patients with a prior history of vascular disease.

The authors suggested possible factors that may have contributed to the discrepancy between the results of their meta-analysis and those of observational studies, including the presence of confounding factors in observational studies, the lack of efficacy of folic acid supplementation in secondary preven-

tion, and the beneficial effect of folic acid supplementation only in populations with specific genetic backgrounds or with folate deficiency. However, the inefficacy of folate supplementation in reducing the risk of cardiovascular diseases may be dependent on other mechanisms that should be explored.

First, since implementation of a 1996 US Food and Drug Administration regulation, flour, rice, pasta, and other grain products have been fortified with folic acid.[4] Because all 12 studies included in this meta-analysis enrolled patients after 1996, the number of patients with increased homocysteine levels at the time of the enrollment may be small. Fortification of grain in the country of origin of the studies was used in only 4 of the 12 studies. However, these studies included more than 10 000 of the 16 000 patients, and mean homocysteine levels were higher than 15 µmol/L in only 4 studies. Furthermore, the difference in homocysteine concentration achieved between the vitamin supplementation group and the placebo or usual-care groups may be very small. Appropriate sensitivity analyses should explore the validity of these hypotheses.

Second, recent data suggest that homocysteine levels are related to other established cardiovascular risk factors such as smoking, elevated blood pressure, and presence of the metabolic syndrome.[5] Therefore, hyperhomocysteinemia could be a marker and not an independent risk factor for cardiovascular disease.

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In Reply: In response to Dr Mahid and colleagues, although we did not have access to EMBASE, we did conduct bibliographic searches of review articles and included abstracts from the "grey literature" through these searches. For example, the results of Baker et al were published only in abstract form.[1] We agree that searching this type of literature is particularly important for finding negative studies, because positive findings are more likely to be published in peer-reviewed journals indexed by MEDLINE. In the case of our pooled analysis, we identified no association between folic acid supplementation and the risk of cardiovascular diseases or all-cause mortality.

We have searched the EMBASE database using identical terms and limits and identified 240 references that were screened; only 1 additional study met our inclusion criteria.[2] This study found no difference between the folic acid supplementation group and control group in rate of in-stent restenosis after percutaneous coronary intervention.[2] Addition of this negative study to our pooled estimate would not have affected our results.

Dr Dentali and colleagues suggest that fortification of grains with folic acid could have been responsible for the lack of association in our study. Of the included trials, 4 (10 027 participants) were conducted in countries with folic acid fortification of grains, while 8 (6931 participants) were conducted in countries without folic acid fortification of grains. We conducted a sensitivity analysis to determine if fortification in the country of study origin affected our results. The confidence intervals of all pooled estimates crossed 1, so none of the results changed.

Dentali et al also suggest that lower baseline homocysteine levels may have affected our results. However, in sensitivity analyses, no significant effect of folic acid supplementation was found in pooled estimates among the 5 studies (4876 participants) with baseline homocysteine levels greater than the median value of 13.1 µmol/L. We agree that the possibility exists for hyperhomocysteinemia to be a marker, rather than an independent risk factor, for cardiovascular disease.

We want to highlight the importance of the planned pooled analysis by the B-Vitamin Treatment Trialists' Collaboration.[3] Their analysis will include approximately 52000 participants and will have sufficient power to determine whether lowering homocysteine levels by approximately 25% reduces the risk of coronary heart disease by 10% or more.

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