

Homocysteine, B Vitamins, and the Risk of Cardiovascular Disease

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Featured Article: Clarke R, Daly L, Robinson K, Naughton E, Cahalane S, Fowler B, Graham I. Hyperhomocysteinemia: an independent risk factor for vascular disease. *N Engl J Med* 1991;324:1149–55.²

Our report, published in the *New England Journal of Medicine* in 1991, demonstrated that hyperhomocysteinemia was present in about one-third of cases with early-onset coronary heart disease, cerebral vascular disease, and peripheral vascular disease, compared with none in the age- and sex-matched controls. The results were striking and suggested that hyperhomocysteinemia was associated with at least a 3-fold excess risk of vascular disease, after adjustment for established risk factors in this population. We defined hyperhomocysteinemia on the basis of the peak homocysteine concentrations after methionine loading in 25 obligate heterozygotes (i.e., parents of children with homozygous homocystinuria), compared with 28 age- and sex-matched controls. Using assays for cystathionine β -synthase activity in a small number of cases and controls, we erroneously attributed most of the hyperhomocysteinemia to heterozygosity for cystathionine β -synthase deficiency. Nevertheless, the report attracted considerable interest because homocysteine concentrations are easily lowered with folic acid, raising the prospect that such treatment might lower the risk of cardiovascular disease.

The development of assays for total homocysteine in the early 1990s replaced the methionine-loading test and led to an exponential increase in the evidence on this topic. Our main findings were subsequently tested in tens of thousands of vascular disease cases and controls in many diverse settings and populations (1–4). Our report was careful to state that it remained to be seen whether lowering homocysteine would reduce the risk of cardiovascular disease.

After completing my doctoral thesis on this topic at the National University of Ireland, I started work

with Sir Rory Collins and Sir Richard Peto in the Clinical Trial Service Unit (CTSU) at the University of Oxford in 1991. I then spent the greater part of the subsequent 2 decades seeking to establish the causal relevance and clinical significance of the associations defined in our original report (1–4). CTSU specializes in the conduct of large-scale trials, observational studies, and metaanalyses of such studies. We carried out 4 large-scale collaborative metaanalyses, mostly based on individual participant data, from the (a) dose-finding trials of folic acid assessing the effects on homocysteine concentrations, (b) the observational studies of homocysteine and cardiovascular disease, (c) the genetic studies of *MTHFR* [methyltetrahydrofolate reductase (NAD(P)H)] variants and coronary disease, and (d) the large-scale homocysteine-lowering trials for the prevention of cardiovascular disease (4).

The chief credit for these metaanalyses is to the many investigators worldwide who agreed to collaborate and provide individual participant data from their studies to these collaborative metaanalyses. With data on about 2000 individuals in the Homocysteine Lowering Trialists' Collaboration, 20 000 individuals in the Homocysteine Studies Collaboration, 50 000 cases in the B-Vitamin Treatment Trialists' Collaboration, and 120 000 individuals in the *MTHFR* Studies Collaboration, we were able to influence both the design of homocysteine-lowering trials worldwide and the interpretation of the observational studies and randomized trials (1–4). The SEARCH trial carried out by CTSU in Oxford tested the effects of almost 7 years of treatment with 2 mg folic acid and 1 mg vitamin B₁₂, compared with placebo, in 12 064 patients with a prior myocardial infarction. Despite a 28% reduction in homocysteine concentrations in the SEARCH trial, B vitamins had no significant effects on vascular outcomes (3). Taken together with 7 other trials in the first cycle of the B-Vitamin Treatment Trialists' Collaboration, we examined the effect of allocation to folic acid or placebo for 5 years (on average) on 9326 major vascular events, 3010 cancers, and 5125 deaths (4). Allocation to folic acid yielded a mean 25% reduction in homocysteine concentrations but had no significant effect on major vascular events in >37 500 participants, overall or in any of the prespecified subgroups. Folic acid was also not associated with any significant excess risk of cancer or cause-specific mortality. Although the lack of any

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² This article has been cited more than 1450 times since publication.

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beneficial effects was disappointing, the lack of any significant adverse effect on vascular events, cancer incidence, cancer mortality, and overall mortality provides some reassurance about the safety of folic acid fortification for the prevention of neural tube defects (4). Mandatory folic acid fortification has led to substantial changes in mean population folate concentrations, but after 2 decades of research, we have clarified that lowering mildly increased homocysteine concentrations with folic acid has no clinical or public health relevance for the prevention of cardiovascular disease.

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