Homocysteine as a Cause of Ischemic Heart Disease: The Door Remains Open

To the Editor:

Clarke et al. conclude that serum homocysteine does not cause ischemic heart disease (IHD) (1), an assessment they based on 19 new studies that showed no increased IHD risk in individuals with the MTHFR1 [methyleneetetrahydrofolate reductase (NAD(P)H)] polymorphism, compared with those without. In excluding results from 86 earlier publications that collectively did show an increased risk, they claimed that the reports of increased risk were due to publication bias (1). The studies were incorrectly described as “unpublished,” the implication being that they caused the publication bias (preferential reporting of small studies with positive results over small studies with negative results), but that outcome could not have arisen, because until Clarke et al. did the analyses, there was nothing to publish.

MTHFR polymorphism studies are used to investigate whether homocysteine and IHD are causally linked, because moderately increased homocysteine concentrations can be caused by, in certain environments (e.g., low folate), the C-to-T mutation in the MTHFR gene. The study of IHD risk in people with the mutation (TT) and without it (CC) provides a natural randomized experiment of the relationship of homocysteine to IHD (2).

We performed 2 analyses to address the issue: (a) an overall metaanalysis of the 19 new studies and the 86 earlier publications to determine whether any effect was apparent when all available data were used, and (b) a “dose–response analysis” comparing IHD risk (TT vs CC) according to the differences between TT and CC individuals with respect to homocysteine concentration in each study.

The metaanalysis of the 107 MTHFR studies (86 previous publications reporting on 88 studies (1) and the 19 new ones) that compared IHD risk in TT and CC individuals (76 792 individuals with IHD and 109 818 unaffected controls) yielded an odds ratio of 1.07 (95% CI, 1.02–1.13), which is lower than previously reported for the 86 published studies (odds ratio, 1.15; 95% CI, 1.09–1.21) (1), but the difference was still significant (P = 0.006). References and the metaanalysis plot are available at http://www.wolfson.qmul.ac.uk/mthfr/.

Publication bias was previously considered (2–4), and this possibility was judged as extremely unlikely to have led to a negative result appearing positive, because the number of unpublished studies needed to produce such a result is implausibly large (4). Even with 50 additional negative studies, each with an odds ratio of 0.95 (95% CI, 0.5–1.9), the overall odds ratio would be reduced from 1.07 to only 1.04 and would remain statistically significantly different from 1. There is no reason to accept the 19 “new” studies, which collectively show no effect, and reject the 88 “older” ones that do. The results from an overall metaanalysis of all 107 studies remain positive.

The overall metaanalysis cannot allow for the variable effect between studies of the MTHFR mutation on homocysteine concentrations, because the homocysteine concentration is not usually measured. Including studies with little or no difference in homocysteine between TT and CC individuals reduces the magnitude of the estimated effect. A “dose–response analysis” of results of studies reporting both a difference in risk and a difference in homocysteine concentration between TT and CC individuals overcomes the problem.

Fig. 1 shows the IHD relative risk between TT and CC individuals for each of the 26 studies reporting homocysteine differences (TT minus CC) among control individuals (no history or angiographic evidence of IHD). Studies are ranked according to homocysteine differences into tertile groups specified before the analysis. IHD risk increases across tertile groups: an odds ratio of 0.86 (95% CI, 0.70–1.06) in the lowest group (no homocysteine difference between TT and CC individuals) and 1.52 (95% CI, 1.09–2.08) in the highest tertile (homocysteine, 3.8 μmol/L higher in TT individuals than in CC individuals). The trend is significant (odds ratio, 1.1 per 1-μmol/L increase in the homocysteine concentration; P = 0.017) and is due mainly to the highest group (homocysteine differences ≥3 μmol/L, representing population concentrations ≥15 μmol/L). This result suggests a possible threshold effect. Therefore, folic acid would be expected to have a greater effect in preventing IHD in populations with low folate intake than in those with higher folate intake.

Publication bias is unlikely to explain the dose–response analysis, because to do so would require (a) a failure to publish studies with negative results involving large homocysteine differences and (b) positive results for studies with small homocysteine differences. Furthermore, both of these requirements would have to be satisfied in small studies but not in large studies.

A metaanalysis of randomized trials of homocysteine lowering with folic acid showed no reduction in IHD events (4), possibly because most patients in the trials took aspirin, which negates the antiplatelet effect of lowering the homocysteine concentration.

1 Human genes: MTHFR, methylenetetrahydrofolate reductase (NAD(P)H).
mocysteine concentration (4). On this basis, folic acid would have a role in the primary prevention of IHD, when aspirin is not taken routinely, but not in secondary prevention, when it is.

Our analysis of all 107 MTHFR studies, together with the dose–response analysis of 26 studies also reporting homocysteine concentrations, suggests a causal effect of homocysteine on IHD, perhaps limited to people with homocysteine concentrations >15 µmol/L. The result is not reasonably explained by publication bias, but chance cannot be confidently excluded. A role for homocysteine in causing IHD therefore remains open, as does a role for folic acid in preventing IHD. It would be a mistake, on the present evidence, to exclude homocysteine as a cause of IHD.

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**Fig. 1.** Plot of the odds ratios (OR) of ischemic heart disease (IHD) between TT and CC homozygotes in different studies. Studies are ranked according to the difference in homocysteine (Hcy) concentration between TT and CC. Also presented are summary estimates of effect in each tertile group of Hcy difference. Study references (w1, w2, . . .) are available at http://www.wolfson.qmul.ac.uk/mthfr/.
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References


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