Commentary: An updated review of the published studies of homocysteine and cardiovascular disease

Robert Clarke

Over the last decade, evidence has accumulated that elevated plasma total homocysteine concentrations are associated with an increased risk of atherosclerotic and thromboembolic events. Plasma homocysteine concentrations reflect genetic and environmental factors including diet. Vitamin supplementation with folic acid and vitamin B-12 achieves substantial reductions in blood homocysteine concentrations. Several large-scale clinical trials are currently under way to assess whether vitamin supplementation to lower homocysteine concentrations can reduce vascular risk. Accurate estimates of the likely strength of association of homocysteine with cardiovascular disease are necessary for the rational design and interpretation of the results of such trials. There have been several qualitative and quantitative reviews on homocysteine and risk of cardiovascular disease and each has been informative at the time of their separate publication. Such systematic reviews can avoid selective biases, minimize random error and provide summary measures of effect based on the totality of available published data. The review by Ford et al. in this issue of the International Journal of Epidemiology set out to provide an updated summary of the published evidence from observational studies on plasma total homocysteine and risk of cardiovascular disease. They abstracted from each publication either the reported odds ratio or relative risk for a change in homocysteine concentration; or the odds ratio or relative risk for more than four levels of homocysteine concentration; or the mean and standard deviation of homocysteine concentrations in cases and controls. They used these data to calculate the log odds ratio for a 5-µmol/l increase in homocysteine concentration and a pooled variance from the case and control group variance weighted by their sample sizes. One important study (COMAC case-control study) has been excluded, but the results of this review are unlikely to be materially altered by this exclusion. The most striking finding of the meta-analysis is the marked heterogeneity between the results of studies of different designs. The odds ratio of coronary heart disease for a 5-µmol/l increase in homocysteine concentration was 1.06 (95% CI: 0.99–1.13) for 2 cohort studies, 1.23 (95% CI: 1.07–1.41) for 10 nested case-control studies and 1.70 (95% CI: 1.50–1.93) for 26 case-control studies (Figure 1).

Figure 1 Association of a 5-µmol/l increase in homocysteine concentration with the probability of coronary heart disease and stroke. Meta-analysis of observational studies stratified by study design. Adapted from Ford et al.6
The strength of association and heterogeneity between the results of studies of homocysteine and risk of stroke was even more extreme than for coronary heart disease. The odds ratio for a 5-µmol/l increase in homocysteine concentration for stroke was 1.10 (95% CI : 0.94–1.28) for 2 cohort studies, 1.58 (95% CI : 1.35–1.85) for 5 nested case-control studies and 2.16 (95% CI :1.65–2.82) for 17 case-control studies (Figure 1). This updated summary of a large number of published studies illustrates the strength and limitations of systematic reviews of published data from observational studies. This review highlighted the heterogeneity between the results of individual studies, but was unable to explain the reasons for such heterogeneity. The review was unable to distinguish the extent to which the discrepant results of individual studies were due to confounding (due to differences in other aspects of lifestyle or cardiovascular risk factors) or bias (due to the effects of underlying disease or effects of other systematic differences) on homocysteine concentrations.

An individual patient data meta-analysis of the observational studies of homocysteine and cardiovascular disease is currently being co-ordinated by the Clinical Trial Service Unit to address these and other related questions on the age- and sex-specific relevance of homocysteine with risk of heart disease and stroke. Individual patient data overviews, which involve central data collection, validation and re-analysis of the data from individual studies on behalf of the collaborative group, can address issues in a way that it is not possible to do in a meta-analysis of published studies. Individual patient data meta-analysis can explore reasons for heterogeneity such as differential effects of prior vascular disease, age at screening, age at event and interval between screening and event. Moreover, individual patient data overviews can assess the effects of confounding by known risk factors. Individual patient overviews often involve collection of additional information to address particular questions such as the impact of bias, which is required to interpret the results of the overview. The present review illustrates that both types of systematic reviews may be informative in particular circumstances. The unexplained heterogeneity between the results of different study types suggests the results of the present review should be interpreted with caution.

Accurate assessment of the true strength of risk associations for differences in homocysteine concentrations after controlling for bias and confounding are necessary for prediction of the likely treatment effects in clinical trials. The results of clinical trials of homocysteine lowering therapy are necessary to assess treatment effects particularly where causal associations are uncertain and where residual confounding cannot be fully excluded and where risk associations are not likely to be fully reversible. The results of these large-scale trials (and possibly a further meta-analysis of post-publication results of individual trials) are required before formulating public health recommendations on screening for homocysteine concentrations or advocating fortification of foods with folic acid to reduce cardiovascular risk.

References


