MedicalXpress

High blood homocysteine levels are not linked with coronary heart disease

February 21 2012

A comprehensive study in this week's *PLoS Medicine* shows levels of the amino acid, homocysteine, have no meaningful effect on the risk of developing coronary heart disease, closing the door on the previously suggested benefits of lowering homocysteine with folate acid once and for all.

Previous studies have suggested that high blood levels of homocysteine might be a modifiable risk factor for coronary heart disease, but in a detailed analysis of data from 19 unpublished and 86 published studies, led by Robert Clarke from the Clinical Trial Service Unit and Epidemiological Studies Unit at the University of Oxford, the researchers found that lifelong moderate elevation of homocysteine levels had no significant effect on the risk of developing coronary heart disease. The study findings suggest that extensive publication bias, together with methodological problems, has played a role in previous suggestions linking homocysteine with coronary heart disease risk.

In their analysis, the authors found that in almost 50 000 individuals with coronary heart disease and 68 000 controls, people who had a variant of the MTHFR gene that is associated with 20% higher blood homocysteine did not have an increased risk of developing coronary heart disease. (The MTHFR gene is responsible for methylene tetrahydofolate reductase, which uses folate to break down and remove homocysteine.)

The authors say: "The discrepancy between the overall results in the unpublished and the published datasets is too extreme to be plausibly

dismissed as a chance finding. Some studies, particularly if small, might have been prioritised for publication by investigators, referees, or editors according to the positivity of their results and some may have been liable to other methodological problems that bias the average of all results. To avoid such biases, we chiefly emphasise the new results from the previously unpublished datasets."

The authors conclude: "The magnitude of the effect of publication bias is substantial and in addition to distorting the association of MTHFR with CHD [coronary heart disease] in published studies, publication bias may also help explain the discrepant findings recently reported for MTHFR and stroke." Importantly, the lack of any link of disease with high homocysteine levels in the 50,000 unpublished heart disease cases with the MTHFR genetic variant is consistent with the null results from 10 large trials testing the effect on coronary heart disease of 5 years of folic acid treatment in 50,000 participants. Hence, both the genetic studies and the trials argue against the use of folic acid supplements as a means of reducing coronary heart disease risk.

More information: Clarke R, Bennett DA, Parish S, Verhoef P, Dötsch-Klerk M, et al. (2012) Homocysteine and Coronary Heart Disease: Meta-analysis of MTHFR Case-Control Studies, Avoiding Publication Bias. *PLoS Med* 9(2): e1001177. doi:10.1371/journal.pmed.1001177