

# Review: Elevated homocysteine levels are modestly associated with increased ischemic heart disease and stroke risk

The Homocysteine Studies Collaboration. **Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis.** *JAMA.* 2002;288:2015-22.

## QUESTION

Are elevated homocysteine levels associated with increased ischemic heart disease (IHD) and stroke risk?

## DATA SOURCES

Studies were identified by searching MEDLINE (1966 to January 1999), reviewing references of studies and reviews, and contacting investigators in the field.

## STUDY SELECTION

Studies were selected if they were observational studies of associations between homocysteine levels and IHD or stroke risk and included data on sex, age at entry (for prospective studies), and age at event. Studies were excluded if they measured only blood levels of free homocysteine or of total homocysteine after a methionine-loading test.

## DATA EXTRACTION

Collaborating investigators provided individual patient data on date of birth, sex, blood homocysteine level (at date of blood collection), any fatal or nonfatal myocardial infarction or occlusive coronary artery disease, and any fatal or nonfatal stroke or transient ischemic attack. If available, data were also collected on previous heart disease events,

cerebrovascular disease events, diabetes mellitus, smoking status, alcohol consumption, cholesterol and creatinine levels, blood pressure, weight, and height.

## MAIN RESULTS

Individual patient data were obtained for 30 studies meeting the inclusion criteria (12 prospective studies and 18 retrospective studies [13 with population control groups and 5 with other control groups]). The reasons for heterogeneity between the results of individual studies were explored, and analyses were corrected for regression-dilution bias. Risk for IHD or stroke was assessed for a 25% lower homocysteine level. This level was associated with lower risk for IHD; the association was stronger in retrospective than in

prospective studies (Table). Homocysteine levels were correlated with smoking, total cholesterol level, and systolic blood pressure; after adjusting for these factors, the strength of the association with IHD and stroke was further reduced (Table).

## CONCLUSION

Elevated homocysteine levels are modestly associated with increased risk for ischemic heart disease and stroke.

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*For correspondence:* Dr. R. Clarke, Clinical Trial Service Unit, Radcliffe Infirmary, Oxford, England, UK. E-mail robert.clarke@ctsu.ox.ac.uk. ■

### Odds ratios (ORs) for ischemic heart disease (IHD) or stroke associated with a 25% lower homocysteine level\*

Adjustment	Study type	OR (95% CI) for IHD	OR (CI) for stroke
Sex and age at enrollment	Prospective	0.83 (0.77 to 0.89)	0.77 (0.66 to 0.90)
	Retrospective with population controls	0.67 (0.62 to 0.71)	0.86 (0.73 to 1.01)
	Retrospective with other controls	0.73 (0.64 to 0.83)	0.46 (0.30 to 0.70)
Sex, age, smoking, systolic blood pressure, and total cholesterol	Prospective	0.89 (0.83 to 0.96)	0.81 (0.69 to 0.95)

\*Corrected for regression dilution.

## COMMENTARY

In the meta-analysis from the Homocysteine Studies Collaboration, lower plasma homocysteine levels are associated with a modest reduction in cardiovascular disease (CVD) risk, but a true causal association cannot be concluded. No studies adjusted for the presence of renal impairment, a condition known to increase both plasma homocysteine and risk for CVD (1). More important, genetic studies and large intervention trials are needed to establish causation.

Plasma homocysteine can be reduced in most patients using 1 mg/d oral folic acid, with or without vitamins B12 and B6 (2). In a randomized placebo-controlled trial of patients who had successful coronary angioplasty, triple vitamin therapy produced a relative risk reduction of 38% (95% CI 3 to 60) in the need for target lesion revascularization, after a mean follow-up of 11 months (3).

In North America and Chile, food fortification with 0.2 mg/d synthetic folic acid was associated with a dramatic increase in blood folate levels and a substantial decline in plasma homocysteine levels (4–6). Whether this has had an effect on the incidence of CVD remains unknown.

Until completion of ongoing primary and secondary prevention trials of homocysteine reduction and CVD, measurement of plasma homocysteine should be restricted to those with unexplained premature CVD.

Joel G. Ray, MD, MSc  
Sunnybrook and Women's College Health Sciences Centre  
Toronto, Ontario, Canada

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