Homocysteine and Risk of Ischemic Heart Disease and Stroke

A Meta-analysis

The Homocysteine Studies Collaboration

Context It has been suggested that total blood homocysteine concentrations are associated with the risk of ischemic heart disease (IHD) and stroke.

Objective To assess the relationship of homocysteine concentrations with vascular disease risk.

Data Sources MEDLINE was searched for articles published from January 1966 to January 1999. Relevant studies were identified by systematic searches of the literature for all reported observational studies of associations between IHD or stroke risk and homocysteine concentrations. Additional studies were identified by a hand search of references of original articles or review articles and by personal communication with relevant investigators.

Study Selection Studies were included if they had data available by January 1999 on total blood homocysteine concentrations, sex, and age at event. Studies were excluded if they measured only blood concentrations of free homocysteine or of homocysteine after a methionine-loading test or if relevant clinical data were unavailable or incomplete.

Data Extraction Data from 30 prospective or retrospective studies involving a total of 5073 IHD events and 1113 stroke events were included in a meta-analysis of individual participant data, with allowance made for differences between studies, for confounding by known cardiovascular risk factors, and for regression dilution bias. Combined odds ratios (ORs) for the association of IHD and stroke with blood homocysteine concentrations were obtained by using conditional logistic regression.

Data Synthesis Stronger associations were observed in retrospective studies of homocysteine measured in blood collected after the onset of disease than in prospective studies among individuals who had no history of cardiovascular disease when blood was collected. After adjustment for known cardiovascular risk factors and regression dilution bias in the prospective studies, a 25% lower usual (corrected for regression dilution bias) homocysteine level (about 3 μmol/L [0.41 mg/L]) was associated with an 11% (OR, 0.89; 95% confidence interval [CI], 0.83-0.96) lower IHD risk and 19% (OR, 0.81; 95% CI, 0.69-0.95) lower stroke risk.

Conclusions This meta-analysis of observational studies suggests that elevated homocysteine is at most a modest independent predictor of IHD and stroke risk in healthy populations. Studies of the impact on disease risk of genetic variants that affect blood homocysteine concentrations will help determine whether homocysteine is causally related to vascular disease, as may large randomized trials of the effects on IHD and stroke of vitamin supplementation to lower blood homocysteine concentrations.

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THE HYPOTHESIS THAT ELevated blood concentrations of the sulfur-containing amino acid homocysteine may be a risk factor for cardiovascular disease was suggested by the observation that children with homozygous homocystinuria, a rare inborn error of metabolism causing markedly elevated blood total homocysteine concentrations, had a high incidence of premature occlusive vascular disease.[1] The initial epidemiological evidence in support of this hypothesis came from retrospective case-control studies.[2-4] More recently, however, inconsistent results have been reported from prospective observational studies, including cohort and nested case-control studies, with some showing highly significant associations but others showing none.[5]

The aim of this collaborative meta-analysis was to combine individual participant data from all relevant observational studies to produce reliable estimates of the associations of total plasma homocysteine with ischemic heart disease (IHD) and stroke, with adjustment for confounding caused by known cardiovascular risk factors and correction for regression dilution caused by random variation in homocysteine measurements.[6,7] The chief emphasis in this report is on combined

See also pp 2023 and 2042.

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analyses of the prospective studies (which involve the measurement of homocysteine in blood collected before the onset of disease) rather than on the retrospective studies, since the former should be less prone to artifacts produced by any effects of preexisting vascular disease on homocysteine levels (referred to as *reverse causality*).

METHODS

Study Populations

Relevant studies were identified by systematic searches of the scientific literature for all reported observational studies of associations between IHD or stroke risk and homocysteine concentrations (using the terms *coronary heart disease*, *myocardial infarction*, *cerebrovascular disease*, *stroke*, *cardiovascular disease*, *homocysteine* or *homocyst(e)ine*, and *hyperhomocystinemia*). We searched the MEDLINE database for articles published from January 1966 to January 1999 and identified additional studies by hand-searching references of original articles or review articles on this topic and by personal contact with relevant investigators in that period. Studies were included if they had data available by January 1999 on total blood homocysteine concentrations, sex, age at entry (for prospective studies), and age at event (G. S. Omenn, unpublished data, September 2002).[8-37] Studies were excluded if they measured only blood concentrations of free homocysteine or of total homocysteine only after a methionine-loading test[3,38-40] or if relevant data were unavailable[41-48] or incomplete.[49-51] To avoid confounding by disease, prospective studies of participants selected on the basis of existing cardiovascular disease, diabetes mellitus, renal impairment, or some other disease were also excluded,[52-56] as were participants with preexisting cardiovascular disease in prospective studies of apparently healthy populations.

Data Collection

Investigators who agreed to collaborate were asked to provide data for each participant on date of birth, sex, blood homocysteine concentration (with the date of blood collection), any nonfatal or fatal myocardial infarction or occlusive coronary artery disease, and any nonfatal or fatal stroke or transient cerebral ischemic attack (with the dates of all such events). If available, data were also collected on history of heart disease event, prior cerebrovascular disease event, diabetes mellitus, smoking (current vs not), alcohol consumption, blood concentrations of total and high-density lipoprotein cholesterol and of creatinine, systolic and diastolic blood pressure, weight, and height. Studies were classified as prospective if the blood sample used to measure homocysteine was collected before the IHD or stroke event (whether homocysteine was measured in all individuals or in a nested manner among cases and matched controls) and as retrospective if the blood sample was collected after the event in cases. Retrospective studies were further classified as population-based if the controls were selected randomly from the same source population as the cases or as other if the controls were spouse controls or patients with some other illness.

Statistical Analyses

Cases and controls were restricted to people who were at least 40 years of age at baseline (ie, when the blood sample for homocysteine measurement was taken) and had measured homocysteine concentrations between 3 and 40 µmol/L (0.41 and 5.41 mg/L). Analyses were conducted for all ages together and for 3 age-at-event bands (40-54, 55-64, and ≥65 years), with prospective and retrospective studies considered separately to assess the possible impact of reverse causality and of any bias caused by control selection or participation.[57] Results from prospective studies in which all participants had had homocysteine measured in a baseline sample were combined with those from prospective studies in which only the cases and a matched random sample of controls had had homocysteine measured in a baseline sample (ie, nested case-control studies). For prospective studies that provided data as nested case-control studies, the controls originally used for each case were retained in this study. For the other prospective studies, up to 8 controls per case were selected in each age-at-event band (matched for sex and age at baseline in 5-year bands), with age at last follow-up having to be greater than the lower limit of the age-at-event band. Controls could be selected only once within an age-at-event band but could be selected again for a later age-at-event band. For anyone experiencing multiple vascular events, only the first event was considered.

All analyses were based on logarithmically transformed homocysteine values because homocysteine values are positively skewed, with $\log_2$ used so that a unit increase in $\log_2$ of homocysteine is equivalent to a doubling in homocysteine. Conditional logistic regression analyses stratified for study were used 2 ways to describe the dose-response relationships. First, to investigate the shape of the association, the odds ratios (ORs) for groups defined by quintiles of baseline values of homocysteine within each study were calculated, with 95% confidence intervals (CIs) estimated from floated variances reflecting the amount of information underlying each group (including the reference group).[58] Second, assuming a log-linear association, regression coefficients were calculated for the percentage of difference in risk associated with a 25% lower homocysteine concentration (which is equivalent to the average change in plasma total homocysteine concentration achieved by folic acid supplementation).[59] Heterogeneity between the results of prospective and retrospective study designs and between studies within each type of design was assessed by a χ^2 statistic. Heterogeneity between the results of prospective studies was investigated with respect to mean age at baseline, percentage of men, percentage of current smokers, mean homocysteine concentrations in controls, and mean time between blood collection and vascular events. Analyses of the prospective studies were

adjusted for the effects of smoking (tobacco use vs not), total cholesterol level, and systolic blood pressure by using multivariable logistic regression, with the stepwise change in the χ^2 statistic after making these adjustments providing a quantitative indication of the potential confounding effects of these factors. All analyses were performed with SAS version 8.1 (SAS Institute Inc, Cary, NC).

Correction for Regression Dilution Bias

The analyses of the prospective studies relate vascular disease risk to the estimated usual concentrations of homocysteine at approximately the time of the event by using remeasurements of homocysteine in samples collected at an appropriate interval after baseline to correct for regression dilution.[6,7] Random fluctuations in a measured value of homocysteine will underestimate the strength of the real association between the usual (ie, long-term average) level of homocysteine during a particular exposure period and disease. This so-called regression dilution effect may be caused by measurement error or transient fluctuations in homocysteine levels caused by treatment, disease, age, or changes in diet. Information from repeated homocysteine

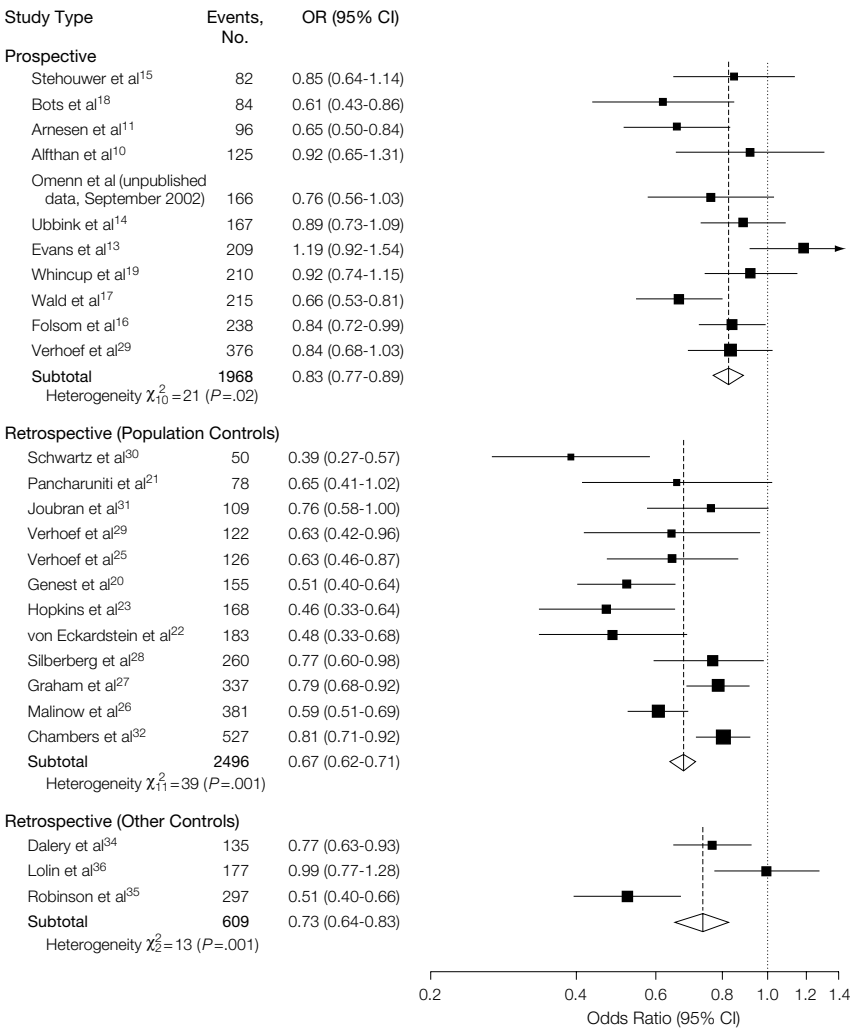
Table 1. Characteristics of Included Studies*

Source	Total Population†	Age at Screening, Mean (SD), y	Homocysteine Level in Controls, Mean (SD), µmol/L‡	Ischemic Heart Disease Events, No.	Stroke Events, No.	Study Type
Prospective (12 studies)						
Stampfer et al[8] and Verhoef et al[9]	985	60 (9)	10.7 (3.6)	376	121	I
Alfthan et al[10]	407	54 (7)	9.5 (3.0)	125	51	F
Arnesen et al[11]	527	53 (6)	11.4 (3.7)	96	. . .	I
Perry et al[12]	212	54 (5)	12.3 (3.8)	. . .	95	F
Evans et al[13]	646	48 (5)	12.9 (4.7)	209	5	I
Ubbink et al[14]	1778	57 (5)	12.1 (4.1)	167	12	P
Stehouwer et al[15]	643	71 (5)	14.5 (4.7)	82	67	P
Folsom et al[16]	758	56 (5)	9.6 (3.9)	238	. . .	F
Wald et al[17]	1268	54 (6)	11.8 (3.6)	215	. . .	I
Bots et al[18]	746	69 (8)	14.9 (3.8)	84	93	F
Whincup et al[19]	540	51 (6)	13.4 (4.3)	210	. . .	F
Omenn et al (unpublished data, September 2002)	515	62 (5)	11.5 (4.2)	166	19	I
Subtotal	**9025**	58 (9)	12.1 (4.2)	**1968**	**463**	
Retrospective: population controls (13 studies)						
Genest et al[20]	408	50 (6)	10.8 (4.3)	155	. . .	
Pancharunti et al[21]	157	46 (4)	12.3 (3.4)	78	. . .	
von Eckardstein et al[22]	320	51 (5)	8.1 (1.7)	183	. . .	
Hopkins et al[23]	317	53 (7)	10.3 (3.0)	168	. . .	
Lindgren et al[24]	211	74 (11)	14.3 (4.6)	. . .	164	
Verhoef et al[25]	241	58 (9)	9.5 (3.3)	126	. . .	
Malinow et al[26]	855	55 (7)	13.0 (4.6)	381	. . .	
Graham et al[27]	1169	50 (5)	10.9 (3.9)	337	144	
Silberberg et al[28]	455	55 (11)	13.1 (5.2)	260	. . .	
Verhoef et al[29]	219	53 (7)	12.0 (3.1)	122	. . .	
Schwartz et al[30]	265	42 (1)	10.9 (3.4)	50	36	
Joubran et al[31]	219	53 (9)	12.9 (5.3)	109	. . .	
Chambers et al[32]	1501	51 (7)	10.9 (3.6)	527	. . .	
Subtotal	**6337**	52 (9)	11.3 (4.1)	**2496**	**344**	
Retrospective: other controls (5 studies)						
Coull et al[33]	225	66 (8)	10.3 (2.7)	. . .	189	
Dalery et al[34]	350	48 (5)	9.7 (4.8)	135	. . .	
Robinson et al[35]	503	59 (11)	11.0 (3.5)	297	. . .	
Lolin et al[36]	200	61 (8)	13.3 (7.9)	177	. . .	
Evers et al[37]	146	57 (9)	11.3 (3.0)	. . .	177	
Subtotal	**1424**	57 (11)	10.5 (4.3)	**609**	**306**	
Total	**16 786**	56 (9)	11.8 (4.2)	**5073**	**1113**	

*Ellipses indicate data not computed; I, individually matched nested case-control study; F, frequency-matched nested case-control study; and P, prospective study.
†Total population includes participants who had homocysteine values between 3.0 and 40.0 µmol/L (0.41 and 5.41 mg/L), were 40 years or older when screened, and had no history of vascular disease.
‡To convert µmol/L to mg/L, divide by 7.397.

measurements in a representative sample of individuals can be used to correct for the effects of regression dilution. Most of the studies did not have such repeat measurements of homocysteine, but 3 studies involving a total of 2318 individuals had remeasured participants at 3 to 8 years after baseline,[60-62] and 1 other study had done so in 500 individuals at 3, 6, 9, and 12 years.[63] Baseline measurements of homocysteine were used to divide people into quintiles, and the ratio of the range between the mean values of the repeat measurements in the top vs the bottom quintile to the range of the baseline measurements was used to estimate regression dilution ratios for various intervals. The regression dilution ratio declined with increasing intervals between measurements,[6] with a value of 0.75 for the mean interval of 5 years from the initial homocysteine measurement to IHD events in prospective studies and of 0.77 for the mean interval of 4 years to stroke events. In the retrospective studies, homocysteine was measured at or shortly after the event, so a regression dilution ratio of 0.83 (which makes allowance for short-term variability only) was used for IHD and stroke analyses. The regression coefficient (and its SE) relating risk to usual concentrations of homocysteine was then estimated as the uncorrected regression coefficient (and its SE) that related risk to single measurements of baseline homocysteine concentrations (1 divided by the regression dilution ratio).

Figure 1. Odds Ratios of Ischemic Heart Disease for a 25% Lower Usual Homocysteine Level in Individual Studies



Data were adjusted for study, sex, and age at enrollment and were corrected for regression dilution. The size of the square is inversely proportional to the variance of the log odds ratio (OR). The horizontal lines represent the 95% confidence intervals (CIs). The combined ORs in the subtotals for each study design and their 95% CIs are indicated by the diamonds.

RESULTS

Study Populations

Individual participant data were obtained for 30 studies, which include 18 of 28 eligible retrospective studies and 12 of 13 eligible prospective studies (TABLE 1). Of 5073 IHD events, 1968 came from prospective studies, 2496 from retrospective studies with population controls, and 609 from retrospective studies with other controls. Of 1113 stroke events, 463 came from prospective studies, 344 from retrospective studies with population controls, and 306 from retrospective studies with other controls. The median (and interquartile range [IQR]) (SD) homocysteine level among controls in the different studies varied from 7.8 µmol/L (1.05 mg/L; IQR, 7.0-8.9) to 14.3 µmol/L (1.93 mg/L; IQR, 12.3-17.0), with an overall median of 11.0 µmol/L (1.49 mg/L; IQR, 9.0-13.6) (SD, 4.2 µmol/L [0.57 mg/L]). Eighty-five percent of the participants were men (88% in prospective studies, 83% in retrospective studies with population controls, and 73% in retrospective studies with other controls), and 36% were current smokers (41%, 31%, and 24%, respectively). In the prospective studies, the mean age at IHD was 62 years (SD, 8 years), and these events occurred at an average of 5 years (range, 2-9 years) after baseline. The mean age at stroke was 68 years (SD, 11 years) in prospective studies, and these events occurred at an average of 4 years (range, 2-11 years) after baseline. The mean age of IHD cases in retrospective studies with population controls was 53 years (SD,

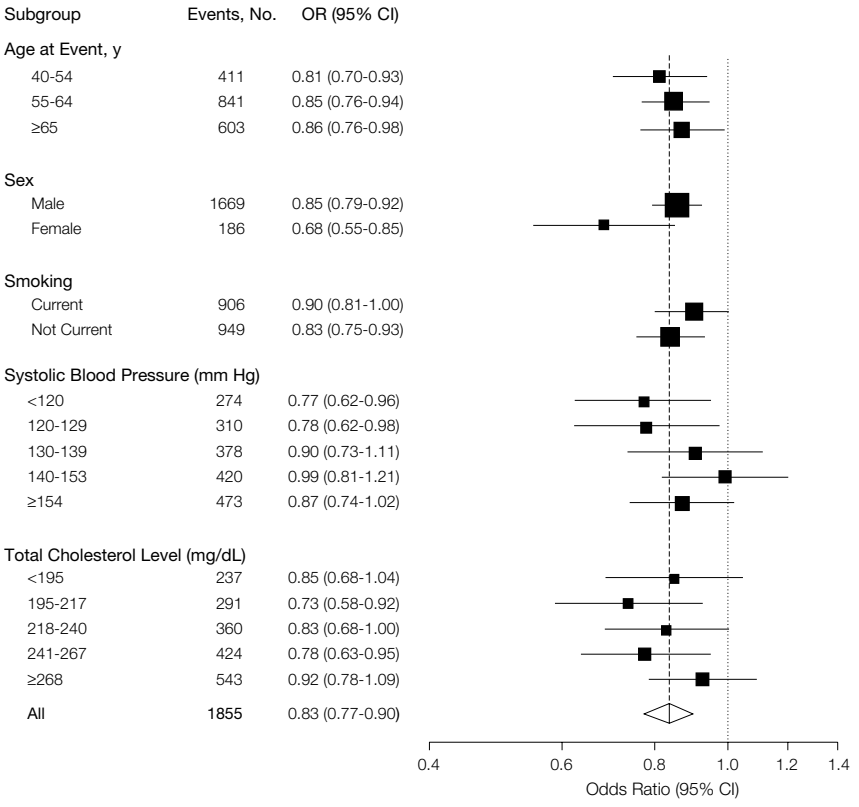
7 years); in retrospective studies with other controls, 59 years (SD, 10 years); and of stroke cases, 61 years (SD, 16 years) and 63 years (SD, 9 years), respectively.

Risks of IHD in Relation to Differences in Homocysteine Levels

Before correction for regression dilution, the ORs for IHD associated with a 25% lower baseline homocysteine level after adjustment for study, age, and sex were 0.87 (95% CI, 0.82-0.92) in prospective studies, 0.71 (95% CI, 0.68-0.75) in retrospective studies with population controls, and 0.77 (95% CI, 0.69-0.86) in retrospective studies with other controls. There was significant heterogeneity between the results from these study designs (χ^2_2=27; P<.001), which was attenuated only slightly by correction for regression dilution (χ^2_2=21; P<.001). After correction for regression dilution (separately within each study), the adjusted ORs for IHD associated with a 25% lower usual homocysteine level were 0.83 (95% CI, 0.77-0.89) in prospective studies, 0.67 (95% CI, 0.62-0.71) in retrospective studies with population controls, and 0.73 (95% CI, 0.64-0.83) in retrospective studies with other controls (FIGURE 1). Among the prospective studies, there was only marginally significant heterogeneity between the adjusted ORs for IHD (χ^2_{10}=21; P=.02) after correction for regression dilution, with a slight trend toward attenuation of the ORs with increasing mean time to event in the studies (test for trend, χ^2_1=4.1; P=.04). In contrast with previous suggestions,[27] however, there was no evidence that the association of homocysteine level with IHD was influenced by age, sex, smoking, levels of blood pressure or blood cholesterol (FIGURE 2), or mean homocysteine concentrations in controls (or size of study, which might have reflected a tendency not to report small studies with less extreme findings).

Homocysteine concentrations were correlated with current smoking, total cholesterol levels, and systolic blood pressure, and the study-, age-, and sex-adjusted ORs for IHD in prospective studies were attenuated after further adjustment for these risk factors in individuals with all relevant data (to 0.89 [95% CI, 0.83-0.96]) (TABLE 2). The substantial change in the χ^2 statistic with these adjustments (from 24 to 9) suggests that a large part of the asso-

Figure 2. Odds Ratios of Ischemic Heart Disease for a 25% Lower Usual Homocysteine Level Among People in Prospective Studies



Data were adjusted for study, sex, and age at enrollment. Studies are grouped by age at event, sex, smoking, and quintiles of systolic blood pressure and total cholesterol level. A global test for heterogeneity between all of these subgroups was not significant (χ^2_{16}=14; P=.60). Symbols and conventions are as for Figure 1. To convert cholesterol to mmol/L, multiply by 0.02586. OR indicates odds ratio; CI, confidence interval.

Table 2. Odds Ratios for Ischemic Heart Disease (IHD) and for Stroke Associated With 25% Lower Usual Homocysteine Levels in Prospective Studies

	Events, No.*	Adjusted Odds Ratio (95% Confidence Interval)			
		Age and Sex	Age, Sex, and Smoking	Age, Sex, Smoking, and Systolic Blood Pressure	Age, Sex, Smoking, Systolic Blood Pressure, and Total Cholesterol Level
IHD	1855	0.83 (0.77-0.90) χ^2_1 = 24	0.85 (0.78-0.91) χ^2_1 = 20	0.89 (0.82-0.96) χ^2_1 = 10	0.89 (0.83-0.96) χ^2_1 = 9
Stroke	435	0.77 (0.66-0.90) χ^2_1 = 11	0.78 (0.67-0.91) χ^2_1 = 10	0.81 (0.69-0.96) χ^2_1 = 6	0.81 (0.69-0.95) χ^2_1 = 6

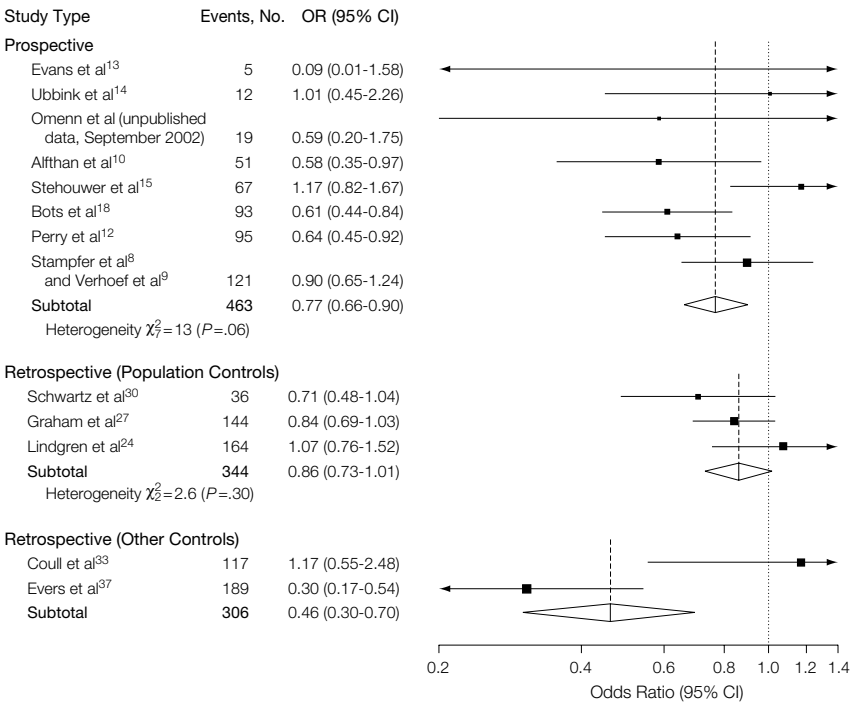
*Among people with all available data used for adjustment for known cardiovascular risk factors.

Table 3. Odds Ratio (95% Confidence Interval) of Ischemic Heart Disease for Quintiles of Baseline Homocysteine Levels in Prospective Studies*

	Quintiles				
	1	2	3	4	5
Adjusted for age, sex, and study	1.00 (0.87-1.15)	1.05 (0.92-1.19)	1.05 (0.92-1.20)	1.20 (1.06-1.36)	1.44 (1.28-1.62)
Adjusted for age, sex, study, smoking, systolic blood pressure, and cholesterol level	1.00 (0.86-1.16)	1.05 (0.92-1.21)	0.91 (0.79-1.04)	1.10 (0.97-1.26)	1.16 (1.02-1.32)

*Based on 1855 cases of ischemic heart disease for whom data on each of homocysteine level, systolic blood pressure, total cholesterol level, and current smoking were available.

Figure 3. Odds Ratios of Stroke for a 25% Lower Homocysteine Level in Individual Studies



Data were adjusted for study, sex, and age at enrollment and were corrected for regression dilution. Symbols and conventions are as for Figure 1. OR indicates odds ratio; CI, confidence interval.

ciation was due to confounding. Moreover, because these confounding factors will necessarily have been measured with some error, substantial residual confounding will remain.

TABLE 3 compares ORs of IHD in quintiles of homocysteine levels determined separately within each study before combined analyses. The study-, age-, and sex-adjusted ORs of IHD appeared to increase with increasing homocysteine concentrations in a graded relationship, but this pattern was attenuated after further adjustment for current smoking, systolic blood pressure, and total cholesterol levels.

Risk of Stroke in Relation to Differences in Homocysteine Concentrations

After adjustment for study, age, and sex and correction for regression dilution, the ORs for stroke were 0.77 (95% CI, 0.66-0.90) in prospective studies, 0.86 (95% CI, 0.73-1.01) in retrospective studies with population controls, and 0.46 (95% CI, 0.30-0.70) in retrospective studies with other controls (FIGURE 3). The heterogeneity between the results from these designs for stroke (χ^2_2=7.4; P=.02) was less extreme than that observed for IHD. Among the prospective studies, there was no significant heterogeneity between the adjusted ORs for stroke (χ^2_7=13; P=.06), and there was no good evidence that the association of homocysteine level with stroke was influenced by age or sex. As for IHD, there was a substantial reduction in the χ^2 statistic (from 11 to 6) for the association of homocysteine level with stroke risk after further adjustment for current smoking, systolic blood pressure, and cholesterol level (OR, 0.81; 95% CI, 0.69-0.95) (Table 2), suggesting that confounding may have inflated the estimated strength of this association.

COMMENT

This meta-analysis indicates that homocysteine level is less strongly related to IHD and stroke risk in healthy populations than has been suggested.[4] The chief strength of this study is that inclusion of data from individual participants has allowed adjustment for possible confounding caused by known cardiovascular risk factors and appropriate correction for regression dilution bias. Data from 1 prospective study of homocysteine and cardiovascular disease (involving 244 cases)[48] that fulfilled the inclusion criteria were unavailable, as were data from 5 relevant prospective studies that were completed after January 1999 (involving about 600 IHD cases and 50 stroke cases).[64-68] These prospective studies reported results similar to those of the prospective studies that were included in this study (based on 1968 IHD cases and 463 strokes), suggesting that our findings were probably not materially altered by their exclusion.

The risks of IHD and stroke associated with homocysteine level were significantly weaker in the prospective studies than the retrospective studies,

which may reflect bias in retrospective studies because of the difficulties of selecting appropriate controls or the effects of changes in treatment, renal function, or other factors after the onset of disease that produce increases in homocysteine concentrations among the cases. To minimize such bias, the chief emphasis in this study was on the results from prospective studies (in which blood for homocysteine measurements had been collected before the clinical onset of disease) among individuals with no recorded history of cardiovascular disease at enrollment. The risks of IHD associated with given differences in homocysteine level observed in the prospective studies of such individuals were remarkably consistent, with the exception of the Multiple Risk Factor Intervention Trial.[13] The reasons for the apparent discrepancy in that study are unclear, although the mean time from baseline homocysteine measurement to IHD events was about twice that of the other prospective studies.[13] Homocysteine concentrations were strongly correlated with current smoking and systolic blood pressure, and the strength of the association of homocysteine with vascular disease was reduced substantially after adjustment for these known cardiovascular risk factors. Moreover, because these confounding factors will necessarily have been measured with some error, substantial residual confounding may well remain. Indeed, because systolic blood pressure (on remeasurement a few years later) has a self-correlation of only about two-thirds,[7] adjustment of the relationship between homocysteine and vascular disease should reduce the χ^2 value by about two thirds, as full adjustment for usual blood pressure would have done. Hence, the results in Table 2 are also consistent with the suggestion that the relationship of homocysteine to disease is largely due to confounding by the usual blood pressure. Thus, among prospective studies of individuals with no history of cardiovascular disease, and after appropriate adjustment for known cardiovascular risk factors and correction for regression dilution bias, a 25% lower usual homocysteine level was associated with about an 11% lower IHD risk and about a 19% lower stroke risk.

If the modest associations observed in this study are causal, then the implications for public health of decreasing the population mean levels of homocysteine could still be substantial. Studies of genetic variants affecting blood homocysteine concentrations and risk of IHD may well help to assess the nature of this association.[69,70] Individuals who have a C-to-T substitution at base 677 (amino acid change alanine 222 valine) of the gene that encodes the methylenetetrahydrofolate reductase enzyme have reduced enzyme activity and, as a consequence, have homocysteine levels that are about 25% higher than those with the *CC* genotype.[70,71] An accompanying article in THE JOURNAL (2002;288: 2023-2031) describes a meta-analysis of 40 studies of this genetic polymorphism in which individuals with the *TT* polymorphism have a 16% (95% CI, 5%-28%) higher risk of IHD than those with the *CC* polymorphism.[72] The concordance of the IHD risks associated with genetically determined differences in homocysteine and of those observed in the population studies of such homocysteine differences provides support for these associations being causal.[69] Results from large randomized trials of the effects on vascular disease of lowering homocysteine with folic acid–based vitamin supplementation should provide further information about the relevance of homocysteine levels to the risks of IHD and stroke.[73]

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