Plasma Total Homocysteine and Hospitalizations for Cardiovascular Disease

The Hordaland Homocysteine Study

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Background: Elevated total plasma homocysteine (tHcy) level is a risk factor for occlusive disease in the coronary, cerebral, and peripheral vessels and is related to several lifestyle factors associated with cardiovascular disease (CVD).

Objective: To examine the association of a single tHcy measurement on subsequent hospitalizations due to CVD.

Methods: A population-based prospective cohort study was conducted from April 1, 1992, to May 31, 1998 (mean follow-up, 5.3 years) in western Norway. The study included 17,361 individuals aged 40 to 42 or 65 to 67 years at baseline. Main outcome measure was CVD as the main hospital discharge diagnosis or coronary revascularization procedures (denoted “CVD hospitalizations”) during follow-up (n = 1275).

Results: At baseline, participants with preexisting CVD had higher mean tHcy values than individuals without CVD. Risk of CVD hospitalizations increased significantly with increasing baseline tHcy only in the oldest age group. Here, multiple risk factor–adjusted hospitalization rate ratios in 5 tHcy categories (<9, 9-11.9, 12-14.9, 15-19.9, and ≥20 µmol/L [to convert tHcy to milligrams per liter, divide by 7.397]) were as follows: 1 (reference level), 1.00, 1.34, 1.67, and 1.94, respectively (P for trend <.001). The relation between tHcy level and CVD hospitalizations was significantly stronger among individuals with preexisting CVD than those without (hospitalization rate ratio per 5-µmol/L tHcy increment, 1.29 vs 1.10; P for interaction, .02).

Conclusions: Plasma tHcy level is a strong predictor of CVD hospitalizations only in elderly individuals, and especially among those with preexisting CVD. Our findings are compatible with the theory that tHcy interacts with conventional CVD risk factors to provoke the acute event of CVD.

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Elevated plasma total homocysteine (tHcy) concentration has been associated with cardiovascular disease (CVD) and has, during the past few years, gained acceptance as an independent and graded risk factor for arterial as well as venous occlusive disease.1-3 While many prospective and retrospective studies, including a total of more than 20,000 subjects, have shown such associations,1,4 other studies have not.4,9

Our group has previously reported10 that an elevated tHcy level is a strong predictor of all-cause and CVD mortality among patients with established coronary artery disease. Similar results have been obtained from studies of free-living populations,11-13 demonstrating that elevated tHcy level is related to overall and CVD mortality. The strongest dose-response effect of tHcy is usually observed during the first few years of follow-up,7,14-16 suggesting that tHcy may particularly be related to early acute events.

Elevation of tHcy is caused by several factors, among which deficiencies of the B vitamins folate and B12 and impaired renal function are the most common. In addition, elevated tHcy levels are associated with older age, male sex, postmenopausal status, and lifestyle factors including smoking, heavy coffee consumption, and lack of exercise.17 Weaker associations with other traditional CVD risk factors such as blood pressure and serum cholesterol level have also been reported.2,4,17

The Hordaland Homocysteine Study is the largest population-based cohort study of tHcy.17 Plasma tHcy was measured in about 18,000 men and women who in 1992 and 1993 participated in a CVD screening program, and the cohort has been followed up for mortality and cardiovascular hospitalization end points. In
Self-administered questionnaires provided information about CVD risk factors and lifestyle factors. Cigarette smokers were grouped in 5 categories: never, former, light (1-9 cigarettes per day), moderate (10-19 cigarettes per day), and heavy (≥20 cigarettes per day) smokers.

Information on preexisting CVD was obtained from a questionnaire completed by the participant and checked by a nurse on the day of examination. The data recorded included history of myocardial infarction, stroke, angina pectoris, hypertension (defined as antihypertensive treatment), and diabetes mellitus. In addition, ever having been diagnosed as having renal disease was reported. Hyperlipidemia was defined as total cholesterol level greater than 270 mg/dL (7.0 mmol/L). Data on baseline disease were missing for less than 0.5% of all participating subjects. These were not included in the analyses stratified by baseline CVD or hypertension.

OUTCOME VARIABLES

Computerized records containing discharge diagnoses for all hospitalizations occurring between the baseline screening and May 31, 1998, at the 6 hospitals serving Hordaland County were searched for CVD codes or procedures. Although the exact figures are unknown, most hospitalizations among the study participants took place within these 6 hospitals. The main hospital discharge diagnosis (fatal and nonfatal events) according to the International Classification of Diseases, Ninth Revision (ICD-9), was used to construct the following disease categories: coronary heart disease, peripheral vascular disease, other cardiovascular disease, and other noncardiovascular disease.

During the mean follow-up period of 5.3 years, 1275 individuals (7.3%) were hospitalized either with CVD as the main discharge diagnosis or for coronary revascularization procedures. The proportion hospitalized was about 5 times higher in the oldest (22.0%) than the youngest (4.3%) men and about 4 times higher in the oldest (12.7%) than the youngest (3.2%) women.

Kaplan-Meier plots of hospitalizations for CVD (‘hospitalization-free survival”) according to baseline tHcy are shown in the Figure. Although men had higher tHcy levels than women, the patterns of associations between tHcy and hospitalizations were similar for both sexes, and their data were combined in the analysis.

Baseline tHcy levels were not associated with subsequent hospitalizations among the youngest participants. In contrast, the risk of CVD hospitalization increased significantly with increasing baseline tHcy level in the oldest age group, with the strongest association among those with baseline CVD or hypertension. In the latter group, about 30% had been hospitalized because of CVD at the end of the 5-year follow-up period (Table 2). To examine whether the risk differed for those with particularly high tHcy levels, we divided the high-
disease (ICD-9 codes 410-414; n=452); acute myocardial infarction (ICD-9 code 410; n=220); cerebrovascular disease (ICD-9 codes 430-438; n=202); aortic and peripheral arterial disease (ICD-9 codes 440-442 and 443.9-444; n=67); pulmonary emboli and venous thrombosis (ICD-9 codes 415, 437.6, and 451.1-453; n=58); and miscellaneous CVD (ICD-9 codes 390-398, 401-405, 416-429, 443.0-443.8, 446-448, 454-459, 780.2, 781.4, 782.3, 785.5-785.9, 786.0, 786.5, 794.3, 798-799, 996.0-996.1, 996.7, 997.0-997.2, V12.5, V15.1, V42.1-V42.2, V43.2-V43.4, V45.0, V47.2, V53.3, and V71.7; n=783). Coronary revascularization procedures were grouped according to the Norwegian classification of surgery, including percutaneous coronary intervention (n=70) and coronary artery bypass grafting (n=104).

Information on causes of death, coded centrally by Statistics Norway (Oslo), was obtained from death certificates for 310 deaths that occurred in the cohort until February 28, 1997 (the latest date for which data on cause of death were available to us). The underlying cause of death according to ICD-9 was used to identify deaths due to CVD. Altogether, 133 deaths were classified as cardiovascular, including 95 deaths due to coronary heart disease (55 of these due to acute myocardial infarction), 21 due to cerebrovascular disease, 5 due to aortic and peripheral arterial disease, 1 due to venous thrombosis, and 11 due to miscellaneous CVD.

STATISTICAL ANALYSES

The tHcy distribution was markedly skewed, and geometric means with 95% confidence intervals (CIs) are therefore presented. Relationships between tHcy and CVD hospitalizations were studied by Kaplan-Meier estimation and Cox proportional hazards model. Covariates were grouped and represented in the model as indicator variables to assess nonlinearity in dose-response relationships. Consistent with a previous report from the Hordaland Homocysteine Study, cutoff levels for tHcy of 9, 12, and 15 µmol/L (to convert tHcy to milligrams per liter, divide by 7.397) were chosen. For the analyses of hospitalization rate ratio (HRR) by Cox regression, the highest baseline tHcy group was divided in 2 (15.0-19.9 and \(\geq 20\) µmol/L), to examine the effect of the highest tHcy levels. Analyses were carried out for the total study population and separately for the 1587 individuals with baseline CVD and/or hypertension (referred to as baseline CVD and based on self-reported data about previous myocardial infarction [n=354], stroke [n=125], angina pectoris [n=491], and antihypertensive treatment [n=1125]), and for the 15691 individuals without baseline CVD or hypertension. Individuals who died (n=427) or emigrated from Norway (n=80) during the follow-up period were censored in the main analyses.

To estimate the HRR per 5-µmol/L tHcy increment, tHcy groups were weighted by the median tHcy level in each group. Analyses were repeated with hospitalizations for various cardiovascular diseases or coronary revascularization procedures as end points and with testing for possible effect modification of the tHcy-hospitalization relationship by different risk factors. A 2-sided P value less than .05 was considered significant.

| Table 1. Baseline Characteristics by Plasma Total Homocysteine Levels at the Beginning of the Study |
|---------------------------------|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|
hypertension, the relative risk of a CVD event was 13% to 30% higher than the relative risk obtained when CVD deaths outside hospitals were not included. The event rate ratios in 5 tHcy categories (<9, 9-11.9, 12-14.9, 15-19.9, and ≥20 µmol/L) were as follows: 1.0 (reference level), 1.21, 1.90, 1.80, and 3.02 (P for trend, <.001). Among the oldest individuals without baseline CVD or hypertension, the relative risk of a CVD event was lower (except the group of tHcy levels from 15-19.9 µmol/L) when the fatal CVD cases were included: rate ratios in the same 5 tHcy categories were 1.0 (reference level), 1.04, 0.97, 1.78, and 1.13, respectively (P for trend, <.02). No significant associations between baseline tHcy levels and subsequent CVD events were found in the youngest age group either among those with or those without baseline CVD or hypertension.

We also found that subjects with fatal CVD had higher mean tHcy values at baseline than those with non-fatal CVD (youngest age group: 11.0 µmol/L [95% CI, 9.5-12.7 µmol/L] vs 10.3 µmol/L [95% CI, 9.9-10.6 µmol/L] [P=.36]; oldest age group: 13.4 µmol/L [95% CI, 12.7-14.1 µmol/L] vs 12.4 µmol/L [95% CI, 12.2-12.7 µmol/L] [P=.009]).

Inclusion of self-reported renal disease (339 subjects [3.4%] in the youngest and 215 [6.0%] in the oldest age group) in the Cox regression model did not alter the relative risk of hospitalization in the youngest group. In the oldest age group, the HRR increased by approximately 10% in the 3 highest tHcy categories.

The HRRs for several CVD discharge diagnoses per 5-µmol/L increment in tHcy are shown in Table 3. For the youngest age group, the numbers of events in the various subgroups were low, and there were no significant trends of increasing hospitalization risk with increasing baseline tHcy level in any subgroup. In the oldest age group with baseline CVD or hypertension, a 5-µmol/L increment in tHcy was associated with 53% higher risk of all CVD compared with 21% among those without CVD or hypertension. In addition, whereas elderly persons with preexisting CVD or hypertension were at particular high risk for new CVD events (66%-144% increase per 5-µmol/L tHcy increment), elderly persons without previously known clinical vascular disease were at highest risk for coronary revascularization procedures (60%-106% increase).

Because elevated tHcy level was associated with a particularly high risk in elderly persons with baseline CVD or hypertension, we evaluated whether the association between tHcy level and hospitalization differed according to various CVD risk factors. To attain optimal statistical power in these analyses, the 2 age groups were combined. The effect of tHcy was modified by baseline CVD or hypertension (P = .02) and by hypertension without CVD (P = .03) (Table 4). Among those with 2 or more baseline risk factors (high risk), the interaction between tHcy and CVD outcomes was borderline significant (P = .07).

**COMMENT**

In a large population-based cohort study of men and women, 40 to 42 and 65 to 67 years old, we have shown that tHcy is a predictor of being hospitalized for CVD during 5-year follow-up in the older but not the younger age group. The relationship observed among the elderly was graded, independent of other measured CVD risk factors, and applied to all of the major categories of CVD. The association was strongest among those with preexisting CVD and/or antihypertensive treatment, which is consistent with the study by Knekt et al. They found an elevated risk of major coronary heart disease events among women with higher serum Hcy levels and preexisting CVD, but not among women free of CVD at baseline.

In contrast to our findings, some earlier studies among middle-aged individuals have found that el-
evated tHcy level confers independent risk of occlusive vascular disease. Our study may lack statistical power to detect a possible weak association between tHcy level and CVD morbidity in the age group 40 to 42 years; only 3.7% were hospitalized, and more than 75% of the end points were classified as neither arterial nor venous occlusive disease in this age group.

Smaller studies including about 20 subjects have reported an intra-individual coefficient of variation for tHcy ranging from 7% to 11%,24-27 and the 2 largest studies28,29 in-cluded 96 healthy subjects with a mean age of 69 years, 54 healthy subjects with a mean age of 33 years, and 12 outpatients in a lipid clinic with a mean age of 47 years; the intra-individual coefficients of variation were 9.0%, 9.4%, and 9.3%, respectively. Thus, the intra-individual variation does not seem to vary by age and cannot explain the lack of effect in the youngest subjects.

The lack of association in the youngest age group may be real. There is evidence that tHcy may be a short-term risk factor,7 and the length of follow-up in the present study (5.3 years) should be sufficient to detect a major effect of tHcy at least on combined end points of arterial occlusive disease or coronary heart disease. Atherosclerosis is usually responsible for about 80% of myocardial infarctions among patients younger than 45 years,30 and our results may therefore indicate that Hcy is not a major etiologic component of atherosclerosis.

This conclusion is also supported by our previous finding among patients with angiographically verified coronary artery disease, namely, that tHcy is more strongly related to subsequent mortality than to the extent of coronary atherosclerosis at baseline.10 The role of tHcy in the progression of coronary atherosclerosis has been evaluated angiographically in 2 recent prospective studies,31,32 and an effect of tHcy was demonstrated in only 1 study.31

Current available data indicate that tHcy is related to acute or thrombotic events,33 and the contribution of thrombosis to atherothrombotic vascular disease may be particularly important at a young age.34 Prothrombotic factors are, however, not associated with CVD risk in the absence of other risk factors,34 and multiple factors are usually required to provoke a CVD event early in life.35 Our study may lack statistical power to detect such effect modification in the young group, and the negative finding does not exclude that elevated tHcy is clinically important in this subgroup. In fact, data from the total study population indicated that the tHcy effect is modified by other risk factors. In particular, the association between tHcy and hospitalization was stronger among individuals with preexisting CVD or hypertension. Furthermore, high risk was observed in diabetic patients. Although the association was not statistically significantly different from nondiabetic patients, it supports previ-

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**Table 2. Risk of Hospitalizations Due to Cardiovascular Disease* According to Baseline Plasma Total Homocysteine Concentration**

<table>
<thead>
<tr>
<th>tHcy, µmol/L†</th>
<th>Age 40-42 y</th>
<th>Age 65-67 y</th>
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</thead>
<tbody>
<tr>
<td>At Risk</td>
<td>Events</td>
<td>Survival, %‡</td>
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<tr>
<td>All participants</td>
<td>12,955</td>
<td>472</td>
</tr>
<tr>
<td>&lt;9</td>
<td>4629</td>
<td>160</td>
</tr>
<tr>
<td>9-11.9</td>
<td>5271</td>
<td>194</td>
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<tr>
<td>12-14.9</td>
<td>1826</td>
<td>74</td>
</tr>
<tr>
<td>15-19.9</td>
<td>581</td>
<td>31</td>
</tr>
<tr>
<td>≥20</td>
<td>288</td>
<td>13</td>
</tr>
</tbody>
</table>

*Cardiovascular disease (CVD) or coronary revascularization procedure as the main hospital discharge diagnosis. Mean follow-up, 5.3 years. tHcy indicates total homocysteine; HRR, hospitalization rate ratio; and CI, confidence interval.
†To convert to milligrams per liter, divide by 7.397.
‡Hospitalization-free survival.
§Hospitalization rate ratio adjusted for sex and baseline age.
¶Hospitalization rate ratio adjusted for sex, baseline age, smoking status, diabetes mellitus, serum cholesterol level, body mass index, and systolic blood pressure. In addition, hypertension (antihypertensive treatment) is included in the analyses for all participants.
#Baseline CVD/hypertension includes myocardial infarction, stroke, angina pectoris, or antihypertensive treatment.
The potential interaction of tHcy with CVD risk factors has been discussed in a recent review.13

We found that the relative risk for CVD events increased up to 30% when fatal CVD cases outside the hospitals were included in the model and that subjects with fatal CVD had higher baseline mean tHcy values than subjects with nonfatal CVD. These findings indicate that elevated tHcy level may reflect severity of disease at baseline.

A key finding in the present study is an association between tHcy level and hospitalization because of CVD, in particular among subjects with underlying vascular disease or risk factors. This is in accordance with previous studies on populations with high CVD risk.13,14,20,21,31 Although a number of mechanisms have been suggested...
to explain the association, there is experimental evidence of acute vascular effects of elevated tHcy level. The available data therefore indicate that hyperhomocysteinemia is more strongly associated with acute vascular events than with the slowly evolving atherosclerotic process.

Traditional CVD risk factors and renal function are established determinants of tHcy levels, and elevated tHcy levels in patients with CVD have been attributed to subclinical nephrosclerosis. The relative risk of hospitalization increased about 10% among elderly subjects with tHcy levels greater than 12 µmol/L, when the effect of baseline renal disease was controlled for. Because the reliability of self-reported renal disease may be questioned, these findings should be interpreted with caution. Markers of renal function were not determined in the present study, and residual confounding may therefore exist.

In the present study, individuals who had baseline tHcy levels greater than 40 µmol/L (n = 67) were offered treatment with cyanocobalamin and/or folic acid. About 2 to 3 years later, all 51 available subjects had tHcy levels less than 20 µmol/L. Conceivably, tHcy reduction by vitamin supplementation might have protected against CVD events in some individuals with high tHcy levels. In that case, the CVD risk conferred by elevated tHcy level might have been underestimated.

Strengths of our study included a cohort design, population-based samples, a large number of participants (N = 17361), and a relatively large number of hospitalizations (N = 1275). Concentration of tHcy was measured only once, but inferences based on a single exposure measurement usually underestimate risks in prospective studies. We included only hospitalizations with CVD as the main hospital discharge diagnosis or coronary revascularization procedures. Although the validity of hospital discharge diagnoses may be questioned, the use of only the main discharge diagnosis should reduce this potential weakness. It is possible that the use of computerized records containing discharge diagnosis may not be totally reliable with regard to the true cause of underlying disease. However, we do not believe this to have a major impact on our findings. Hospital records were retrieved from all 6 hospitals in the area. Although it is possible that a few participants could have been hospitalized for CVD elsewhere, failure to include these participants should tend to weaken rather than strengthen our findings.

In conclusion, in this community-based 5-year follow-up study of CVD hospitalizations among middle-aged and elderly adults, a strong association with tHcy levels was observed only in elderly individuals, and especially among those with baseline CVD. This suggests that tHcy primarily interacts with established risk factors to provoke the CVD event leading to hospitalization.

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