ORIGINAL INVESTIGATION

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 reported[10] 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 B_{12} 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

SUBJECTS AND METHODS

STUDY PARTICIPANTS

The Hordaland Homocysteine Study is a collaboration between the National Health Screening Service, local health services, and the University of Bergen, Bergen, Norway. The source population included all individuals in Hordaland County, in western Norway, aged 40 to 42 years; all individuals aged 65 to 67 years residing in Bergen and 3 neighboring suburban municipalities; and a 2% random sample of 43- to 64-year-old residents in Bergen. The overall baseline attendance rate was 72.7%. The analyses presented in this report are based on the age groups 40 to 42 years and 65 to 67 years, a total of 17 361 individuals. All participating subjects gave their written informed consent. The study protocol was approved by the Norwegian Board of Health, the Data Inspectorate, and the Regional Committee for Medical Research Ethics of Western Norway.

BASELINE DATA COLLECTION

Data collection procedures have previously been reported in detail[17] and are only summarized here. Baseline measurements included height, weight, blood pressure, and heart rate. Nonfasting levels of serum total cholesterol, serum triglycerides, and plasma tHcy were determined. Plasma tHcy, which includes both the free and protein-bound fractions of homocysteine (Hcy), was determined by means of a fully automated high-performance liquid chromatography assay.[18,19] 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

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this article, we report on the relationship between baseline tHcy levels and subsequent hospitalizations with CVD as the main discharge diagnosis or with coronary revascularization procedures (denoted as "CVD hospitalizations").

RESULTS

Baseline characteristics according to tHcy levels are presented in **Table 1**. The proportion of participants with preexisting CVD, hypertension, or hyperlipidemia generally increased with increasing tHcy levels. Inverse and significant associations between tHcy level and prevalence of diabetes mellitus were observed in both younger and older men, but not in women. Smoking was strongly positively related to tHcy level in all groups.

Individuals with baseline CVD or hypertension had significantly higher tHcy levels than those without (10.6 µmol/L [95% CI, 10.2-11.0 µmol/L] vs 9.9 µmol/L [95% CI, 9.9-10.0 µmol/L], $P=.001$ in the youngest age group; and 12.0 µmol/L [95% CI, 11.9-12.2 µmol/L] vs 11.5 µmol/L [95% CI, 11.4-11.6 µmol/L], $P<.001$ in the oldest age group). The highest mean tHcy level (12.8 µmol/L [95% CI, 12.5-13.2 µmol/L]) in the oldest participants was seen among those with preexisting CVD or hypertension and who were hospitalized with CVD during follow-up, whereas in the youngest participants those who had preexisting CVD or hypertension, but were not subsequently hospitalized, had the highest mean tHcy level (10.7 µmol/L [95% CI, 10.2-11.2 µmol/L]). Those who did not report baseline CVD or hypertension and were not hospitalized during follow-up had the lowest mean tHcy level (11.4 µmol/L [95% CI, 11.3-11.5 µmol/L] in the elderly and 9.9 µmol/L [95% CI, 9.9-10.0 µmol/L] in middle-aged individuals).

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,[20] 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 ≥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

	Plasma Total Homocysteine, µmol/L*											
	Age 40-42 y						Age 65-67 y					
	All	<9	9-11.9	12-14.9	≥15	*P* for Trend	All	<9	9-11.9	12-14.9	≥15	*P* for Trend
Men												
No.	**6110**	1322	3032	1203	553		**2127**	196	832	674	425	
CVD, %†	0.9	0.8	1.0	0.8	1.4	.30	19.1	17.4	16.4	21.6	21.9	.01
Hypertension, %‡	1.8	1.2	2.1	1.3	2.4	.36	19.4	19.4	17.3	20.1	22.5	.06
Hyperlipidemia, %§	11.3	9.8	10.8	13.1	13.4	.003	25.4	25.5	25.4	24.2	27.3	.67
Diabetes mellitus, %	0.8	1.1	0.9	0.3	0.2	.005	5.5	11.7	4.9	5.5	3.8	.004
Current smokers, %	40.9	32.5	39.5	47.1	55.8	<.001	29.0	23.0	25.1	30.1	37.4	<.001
Women												
No.	**6485**	3308	2238	623	316		**2639**	569	1144	600	326	
CVD, %†	0.4	0.4	0.4	0.6	0.6	.38	9.6	9.1	8.7	11.0	11.1	.13
Hypertension, %‡	1.4	0.8	2.0	1.1	2.9	.001	19.6	14.9	19.1	25.9	17.8	.005
Hyperlipidemia, %§	5.8	4.9	6.3	7.5	8.5	<.001	50.4	47.5	49.6	52.5	54.6	.02
Diabetes mellitus, %	0.4	0.5	0.2	0.2	0.6	.26	3.8	4.9	3.6	3.2	3.4	.16
Current smokers, %	38.4	29.3	44.9	51.5	62.3	<.001	21.4	14.6	18.3	25.0	37.4	<.001

*To convert to milligrams per liter, divide by 7.397.
†Baseline cardiovascular disease (CVD) includes myocardial infarction, stroke, and angina pectoris.
‡Hypertension defined as antihypertensive treatment.
§Total cholesterol level greater than 270 mg/dL (7.0 mmol/L).

est tHcy group in 2 (15-19.9 and ≥20 µmol/L). This showed further risk enhancement at tHcy levels above 20 µmol/L among the oldest participants, except for the group without baseline CVD or hypertension.

We repeated the same analyses with a shorter follow-up period (mean, 4.2 years), including also individuals who suffered a fatal CVD event without hospitalization. In the oldest age group with baseline CVD or

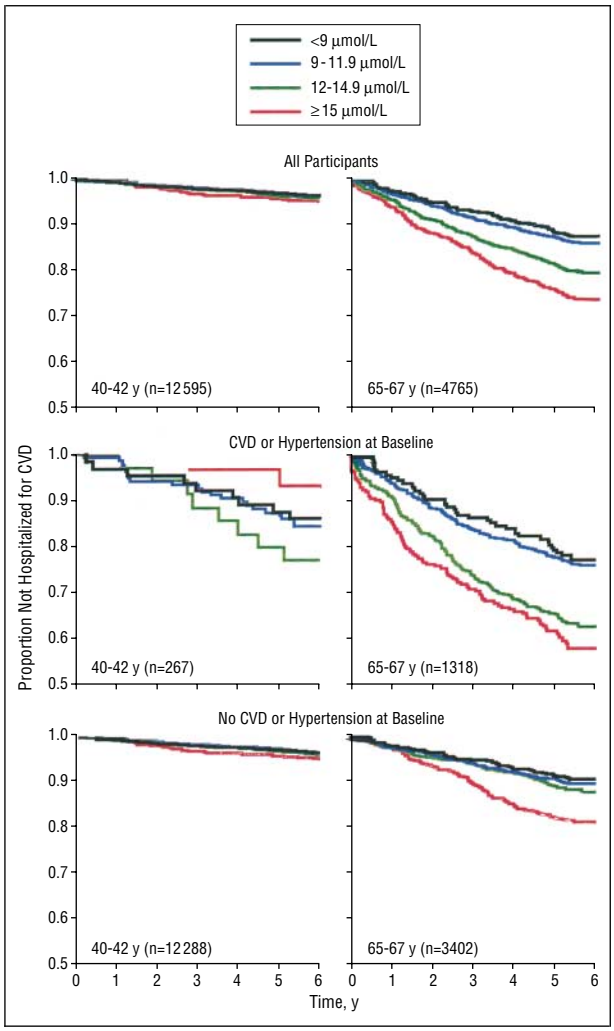
hypertension, the relative risk of a CVD event was 13% to 30% higher than the relative risk obtained when CVD deaths outside hospitals were not included. The event rate ratios in 5 tHcy categories (<9, 9-11.9, 12-14.9, 15-19.9, and ≥20 µmol/L) were as follows: 1.0 (reference level), 1.21, 1.90, 1.80, 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 nonfatal 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 particularly 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).



Time to first hospitalization with cardiovascular disease (CVD) as the main discharge diagnosis by baseline plasma total homocysteine levels: Hordaland Homocysteine Study, 1992-1998. For all participants: 40 to 42 years old: *P*=.20 (Kaplan-Meier log-rank test for differences between homocysteine groups), *P*=.27 (Cox trend test adjusted for age and sex), *P*=.79 (Cox trend test adjusted for sex, baseline age, smoking status, diabetes mellitus, serum cholesterol level, body mass index, and systolic blood pressure); 65 to 67 years old: *P*<.001, *P*<.001, *P*<.001, respectively. For CVD or hypertension at baseline: 40 to 42 years old: *P*=.34, *P*=.45, *P*=.63, respectively; 65 to 67 years old: *P*<.001, *P*<.001, *P*<.001, respectively. For no CVD or hypertension at baseline: 40 to 42 years old: *P*=.20, *P*=.31, *P*=.87, respectively; 65 to 67 years old: *P*<.001, *P*<.001, *P*=.007, respectively. To convert total homocysteine to milligrams per liter, divide by 7.397.

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 level 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.[21] 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[22,23] among middle-aged individuals have found that el-

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

	Age 40-42 y					Age 65-67 y				
tHcy, µmol/L†	At Risk	Events	Survival, %‡	HRR§ (95% CI)	HRR‖ (95% CI)	At Risk	Events	Survival, %‡	HRR§ (95% CI)	HRR‖ (95% CI)
All participants	12 595	472				4766	803			
<9	4629	160	96.5	1.00	1.00	765	94	87.7	1.00	1.00
9-11.9	5271	194	96.3	0.97 (0.77-1.20)	0.89 (0.72-1.11)	1976	269	86.4	1.02 (0.80-1.29)	1.00 (0.79-1.27)
12-14.9	1826	74	96.0	1.04 (0.77-1.37)	0.94 (0.70-1.25)	1274	252	80.2	1.46 (1.14-1.85)	1.34 (1.05-1.71)
15-19.9	581	31	94.7	1.40 (0.92-2.04)	1.15 (0.77-1.72)	574	141	75.4	1.84 (1.41-2.39)	1.67 (1.28-2.19)
≥20	288	13	95.5	1.18 (0.61-2.00)	0.93 (0.52-1.65)	177	47	73.5	2.07 (1.45-2.94)	1.94 (1.35-2.78)
P for trend			.19¶	.19	.94			<.001¶	<.001	<.001
Baseline CVD/hypertension#	268	41				1319	394			
<9	65	9	86.2	1.00	1.00	173	38	78.3	1.00	1.00
9-11.9	137	22	83.9	1.01 (0.43-2.12)	1.03 (0.45-2.27)	501	115	77.1	1.02 (0.71-1.48)	1.05 (0.72-1.53)
12-14.9	35	8	77.1	1.32 (0.51-3.53)	1.55 (0.58-4.23)	412	147	64.3	1.70 (1.18-2.44)	1.66 (1.15-2.40)
15-19.9	16	2	87.5	0.71 (0.15-3.34)	0.79 (0.16-3.98)	176	65	63.1	1.75 (1.17-2.63)	1.67 (1.10-2.52)
≥20	15	0	100.0	. . .	. . .	57	29	49.1	2.60 (1.59-4.25)	2.69 (1.63-4.44)
P for trend			.39¶	.28	.44			<.001¶	<.001	<.001
No baseline CVD/hypertension	12 288	430				3402	398			
<9	4552	151	96.7	1.00	1.00	585	55	90.6	1.00	1.00
9-11.9	5118	172	96.6	0.94 (0.74-1.17)	0.87 (0.68-1.08)	1463	151	89.7	0.99 (0.72-1.35)	0.98 (0.71-1.35)
12-14.9	1782	66	96.3	1.01 (0.73-1.34)	0.89 (0.65-1.19)	843	99	88.3	1.07 (0.76-1.49)	0.99 (0.70-1.40)
15-19.9	563	28	95.0	1.38 (0.89-2.05)	1.16 (0.74-1.72)	392	76	80.6	1.83 (1.29-2.61)	1.64 (1.14-2.36)
≥20	273	13	95.2	1.32 (0.68-2.24)	1.08 (0.56-1.85)	119	17	85.7	1.39 (0.80-2.40)	1.19 (0.68-2.10)
P for trend			.21¶	.19	.81			<.001¶	.001	.01

*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.

¶Kaplan-Meier log-rank test.

#Baseline CVD/hypertension includes myocardial infarction, stroke, angina pectoris, or antihypertensive treatment.

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 intraindividual coefficient of variation for tHcy ranging from 7% to 11%.[24-27] The 2 largest studies[28,29] included 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 intraindividual coefficients of variation were 9.0%, 9.4%, and 9.3%, respectively. Thus, the intraindividual 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-

Table 3. Risk of Hospitalizations Due to Various Cardiovascular Diseases During a Mean Follow-up of 5.3 Years*

	Baseline CVD† or Antihypertensive Treatment							
	Age 40-42 y				Age 65-67 y			
	No.‡	Yes (n = 268)	No.‡	No (n = 12 288)	No.‡	Yes (n = 1319)	No.‡	No (n = 3402)
All CVD§	41	0.76 (0.46-1.27)	426	1.03 (0.90-1.18)	387	1.53 (1.33-1.77)‖	390	1.21 (1.06-1.37)¶
Arterial occlusive disease	19	0.74 (0.36-1.54)	108	0.88 (0.66-1.17)	280	1.52 (1.28-1.80)‖	232	1.25 (1.06-1.47)#
Coronary heart disease	16	0.71 (0.31-1.59)	70	1.02 (0.75-1.38)	212	1.38 (1.13-1.69)¶	142	1.29 (1.05-1.58)**
Acute myocardial infarction	6	0.48 (0.10-2.30)	42	1.06 (0.73-1.54)	75	1.66 (1.20-2.28)¶	90	1.20 (0.92-1.57)
Coronary revascularization	10	0.49 (0.14-1.72)	26	1.19 (0.77-1.82)	79	1.33 (0.95-1.87)	46	1.63 (1.19-2.23)¶
PCI	4	0.92 (0.28-3.02)	22	1.10 (0.68-1.80)	28	1.55 (0.91-2.66)	16	2.06 (1.27-3.35)¶
CABG	6	0.14 (0.01-1.70)	9	1.34 (0.70-2.56)	54	1.19 (0.78-1.82)	33	1.60 (1.10-2.31)#
Cerebrovascular disease	6	0.80 (0.19-3.29)	37	0.53 (0.26-1.11)	68	1.85 (1.34-2.55)‖	85	1.21 (0.92-1.58)
Aortic and peripheral arterial disease	0	. . .	10	0.61 (0.19-1.99)	29	2.44 (1.53-3.89)‖	25	1.34 (0.85-2.11)
Venous thrombosis and pulmonary emboli	1	. . .	25	1.14 (0.68-1.91)	10	2.27 (0.98-5.24)	18	1.17 (0.63-2.17)
Miscellaneous CVD	29	0.65 (0.33-1.30)	323	1.08 (0.92-1.26)	209	1.67 (1.38-2.02)‖	205	1.15 (0.95-1.35)

*Hospitalization rate ratio and 95% confidence interval per 5 µmol/L (0.68 mg/L) of plasma total homocysteine, adjusted for sex, baseline age, smoking status, diabetes mellitus, body mass index, serum cholesterol level, and systolic blood pressure. Thus, the number may be lower than the total numbers of each category. CVD indicates cardiovascular disease; PCI, percutaneous coronary intervention; and CABG, coronary artery bypass grafting.

†Baseline CVD includes myocardial infarction, stroke, and angina pectoris.

‡Number of events.

§Some individuals had multiple hospitalizations, and thus they may be presented in different groups of discharge diagnosis, whereas for groups of all CVD they are counted only once.

‖*P* for trend <.001.

¶*P* for trend <.005.

#*P* for trend <.01.

**_P_ for trend <.05.

Table 4. Effect Modification of the Association Between Plasma Total Homocysteine and Cardiovascular Hospitalizations by Baseline CVD and Several Risk Factors*

	Absence		Presence		
Baseline Factor	Events	HRR† (95% CI)	Events	HRR† (95% CI)	*P* for Interaction
CVD/hypertension‡	816	1.10 (1.00-1.21)	428	1.29 (1.15-1.46)	.02
CVD	971	1.13 (1.04-1.23)	273	1.30 (1.12-1.51)	.38
Hypertension‡	979	1.12 (1.03-1.22)	265	1.32 (1.14-1.54)	.03
Hyperlipidemia§	842	1.14 (1.04-1.25)	407	1.24 (1.10-1.41)	.27
Diabetes mellitus	1187	1.16 (1.08-1.25)	57	1.45 (1.02-2.06)	.39
Current smoking	793	1.23 (1.12-1.36)	462	1.10 (0.98-1.23)	.18
High risk‖	331	1.07 (0.90-1.28)	347	1.23 (1.08-1.40)	.07

*Baseline cardiovascular disease (CVD) includes myocardial infarction, stroke, and angina pectoris. Data are events and hospitalization rate ratio (HRR) per 5-µmol/L (0.68-mg/L) plasma total homocysteine increment with 95% confidence interval (CI).

†HRR adjusted for multiple risk factors (sex, baseline age, CVD, antihypertensive treatment, smoking status, diabetes mellitus, serum cholesterol level, body mass index, and systolic blood pressure) except the factor-defining category.

‡Hypertension defined as antihypertensive treatment.

§Total cholesterol level greater than 270 mg/dL (7.0 mmol/L).

‖High risk includes 2 or more of the baseline risk factors.

ous findings of hyperhomocysteinemia being particularly harmful in diabetic patients.[36-38] Our results also concur with the observation in a large cross-sectional study showing that elevated tHcy level may be particularly detrimental in patients with hypertension.[22] In contrast to that study, we found the weakest tHcy effect among smokers, and we have recently made a similar observation according to total and cardiovascular mortality within the same cohort.[20] This may suggest that the association of tHcy with CVD is not due to confounding by smoking, and that Hcy is not a major mediator of the smoking effect. 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.[4,13,14,20,21,33] Although a number of mechanisms have been suggested

to explain the association,[39] there is experimental evidence of acute vascular effects of elevated tHcy level.[40] The available data therefore indicate that hyperhomocysteinemia is more strongly associated with acute vascular events than with the slowly evolving atherosclerotic process.[41]

Traditional CVD risk factors and renal function are established determinants of tHcy level,[2-4,17] and elevated tHcy levels in patients with CVD have been attributed to subclinical nephrosclerosis.[13] 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.[42] 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=17 361), 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.[43] 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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