Plasma total homocysteine and cardiovascular and noncardiovascular mortality: the Hordaland Homocysteine Study[1–3]

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ABSTRACT

Background: Few population-based studies have assessed relations between plasma or serum total homocysteine (tHcy) and all-cause mortality.

Objective: Our goal was to study associations between plasma tHcy and all-cause, cardiovascular, and noncardiovascular mortality.

Design: This was a prospective cohort study of 2127 men and 2639 women aged 65–67 y in 1992–1993 when they were recruited as part of a population-based national cardiovascular screening program carried out in Hordaland County, Norway.

Results: During a median of 4.1 y of follow-up, 162 men and 97 women died. A strong relation was found between plasma tHcy and all-cause mortality. The association was highly significant for noncardiovascular and for cardiovascular causes of death. In a comparison of individuals having tHcy concentrations of 9.0–11.9, 12.0–14.9, 15.0–19.9, or ≥20 μmol/L with individuals having a tHcy concentration <9 μmol/L, adjusted mortality ratios were 1.4, 1.9, 2.3, and 3.6 (*P* for trend = 0.0002) for noncardiovascular and 1.3, 2.1, 2.6, and 3.5 (*P* for trend = 0.0002) for cardiovascular causes of death. A tHcy increment of 5 μmol/L was associated with a 49% (95% CI: 28%, 72%) increase in all-cause mortality, a 50% (95% CI: 21%, 85%) increase in cardiovascular mortality (121 deaths), a 26% (95% CI: –2%, 63%) increase in cancer mortality (103 deaths), and a 104% (95% CI: 44%, 289%) increase in noncancer, noncardiovascular mortality (33 deaths).

Conclusion: Plasma tHcy is a strong predictor of both cardiovascular and noncardiovascular mortality in a general population of 65–72-y-olds. These results should encourage studies of tHcy in a wider perspective than one confined to cardiovascular disease. *Am J Clin Nutr* 2001;74:130–6.

KEY WORDS Total homocysteine, cardiovascular mortality, noncardiovascular mortality, Hordaland Homocysteine Study, all-cause mortality, cardiovascular disease risk

INTRODUCTION

A causal role of moderately elevated concentrations of circulating total homocysteine (tHcy) in the pathogenesis of cardiovascular disease was proposed ≈30 y ago (1). Since then, the results of many clinical and epidemiologic studies have shown that tHcy measured in serum or plasma is a strong predictor of cardiovascular disease risk (2–4). The results of early cross-sectional and case-control studies strongly supported this hypothesis (5, 6). Since 1992, however, the results of several large, well-conducted prospective studies in which blood samples were collected before the cardiovascular event showed weaker relations and gave a less consistent picture (7, 8). Some prospective studies showed a strong association between tHcy and cardiovascular disease (9–13), some found weaker associations (14–17), and others, including the Multiple Risk Factor Intervention Trial and the Atherosclerosis Risk in Communities Study (18–20), failed to find any significant associations. The reasons for these conflicting results have not been fully explored, but may be related to differences in diet, lifestyle, and other cardiovascular disease risk factors, and to characteristics including length of follow-up and blood sample handling and storage. Notably, prospective studies of patient populations known to be at high risk of cardiovascular events consistently report strong positive associations between tHcy and cardiovascular morbidity or mortality or all-cause mortality (21–28). In follow-up studies of the Framingham cohort (29) and a cohort of Jerusalem residents (30), tHcy was shown to have strong and significant associations of similar strength with both all-cause and cardiovascular mortality.

Using follow-up data from a large population-based cohort, we assessed cause-specific associations between tHcy and mortality. On the basis of the participants' medical history at the time of inclusion, we divided the cohort into high- and low-risk groups with respect to future cardiovascular events. Our motivation for performing separate analyses in these 2 groups was to further investigate whether tHcy is more strongly associated with progno-

See corresponding editorial on page 3.

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[2] Supported by the Norwegian Research Council, the Norwegian Cancer Society, and EU Commission Demonstration Project contract BMH4-CT98-3549.

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Received November 8, 2001.

Accepted for publication January 26, 2001.

sis in clinical cohorts with elevated cardiovascular morbidity than it is to the risk of cardiovascular disease in the general population.

SUBJECTS AND METHODS

The baseline data for the population-based Hordaland Homocysteine Study were collected in 1992–1993 by the National Health Screening Service in cooperation with the University of Bergen, Norway (31). Men and women aged 40–67 y were invited to a cardiovascular health screening. The investigation included measurements of height, weight, blood pressure, heart rate, serum total cholesterol, serum triacylglycerol, and plasma tHcy. Self-administered questionnaires provided information on previous cardiovascular morbidity, symptoms, cardiovascular disease risk factors, lifestyle, diet, and reproductive history. Further details on data collection were published previously (31). The study protocol was approved by the Regional Ethics Committee of Western Norway, whose directives are based on the Declaration of Helsinki. The cohort considered in the present study was restricted to the 4766 participants who were aged 65–67 y at entry.

Information on causes of death, coded centrally by Statistics Norway (Oslo), was obtained from death certificates for 257 of the 259 deaths that occurred in the cohort until February 1997. The underlying cause of death according to the 9th revision of the *International Classification of Diseases* (32) was used to construct cause-of-death categories. The 121 deaths classified as cardiovascular included 84 due to ischemic heart disease (including 50 deaths due to acute myocardial infarction), 16 due to cerebrovascular disease, 17 due to other circulatory disease, and 4 sudden deaths. Of the 103 deaths attributed to malignant disease were 34 lung cancers, 12 colorectal cancers, 11 malignancies of lymphatic or blood-forming tissue, 8 pancreatic cancers, 8 cancers of the female reproductive system, and 7 stomach cancers. The 29 remaining cancer deaths belonged to 1 of 9 less frequent cancer types, and 6 were unspecified malignancies. The violent deaths included 4 fatal accidents and 4 deaths classified as suicides. Among the 25 deaths due to other causes, 10 were diseases of the respiratory system, 7 were diseases of the gastrointestinal system, and 4 were diseases of the central nervous system. The most common respiratory and gastrointestinal conditions were chronic obstructive lung disease and chronic liver disease, which accounted for 8 and 5 deaths, respectively. Two deaths remained unclassified.

Plasma tHcy, which includes both the free and protein-bound fractions of homocysteine, was measured by using a fully automated assay based on precolumn derivatization with monobromobimane followed by reversed-phase HPLC (33, 34). Our analyses included 20 participants who had a tHcy concentration ≥40 μmol/L. As described previously (35), these individuals were notified of their high concentrations and offered a clinical examination; appropriate B-vitamin supplementation was started at some stage during the follow-up period. Exclusion of these 20 individuals (including 2 who died) did not materially change the reported results.

On the basis of the subjects' self-reported medical history at baseline, we divided the cohort into groups at high and low risk of cardiovascular disease (high- and low-risk groups). The high-risk group included the subjects who reported a history of myocardial infarction (n = 327), stroke (n = 102), angina pectoris (n = 442), or diabetes mellitus (n = 216) or who were treated for hypertension (n = 926) at the time of the baseline examination. Analyses were carried out separately for these 1448 high-risk subjects and for the remaining 3318 subjects in the low-risk group.

Relations of tHcy to mortality were studied with Kaplan-Meier estimation and the Cox proportional hazards model. Covariates were grouped and are represented in the model as indicator variables to assess nonlinearity in the dose-response relation. If the effect of adjustment was similar for the indicator and the linear representation of the grouped covariate, we used the latter to achieve a more parsimonious model. Trend tests and trend coefficients were computed by using the categorized tHcy variable weighted by the median tHcy concentration of each category (8.2, 10.5, 13.1, 16.5, and 23.9 μmol/L, respectively) as recommended by Greenland (36).

Dose-response relations were also studied with generalized additive logistic regression (37) as implemented in S-PLUS (version 4.0 for WINDOWS; Mathsoft, Seattle). This method generates a graph of the relation between tHcy and the outcome in question on a logit scale, and allows adjustment for other variables. Pointwise 95% confidence curves are also given. The statistical analyses were carried out with the statistical packages SAS (release 6.12 for WINDOWS; SAS Institute Inc, Cary, NC) and S-PLUS. A 2-sided significance level of 0.05 was used.

RESULTS

Predictors of baseline plasma tHcy concentrations

Characteristics of the study population at baseline by 4 plasma tHcy categories (5.1–8.9, 9.0–11.9, 12.0–14.9, and 15.0–137 μmol/L) are presented in **Table 1**. As previously reported (31, 38), we observed strong and significant relations between tHcy and lifestyle characteristics including cigarette smoking, coffee drinking, vitamin supplement use, and physical activity. Additionally, tHcy was positively associated with a medical history of cardiovascular disease and negatively with diabetes mellitus, the latter particularly among men.

Plasma tHcy and mortality

During a median of 4.1 y of follow-up, 162 men (7.6%) and 97 women (3.7%) died. We observed a strong and graded relation between plasma tHcy and all-cause mortality. The Kaplan-Meier estimates of 4-y total mortality were 2.2%, 3.8%, 6.6%, 8.0%, and 13.0% in the 5 tHcy categories of 5.1–8.9, 9.0–11.9, 12.0–14.9, 15.0–19.9, and 20.0–137 μmol/L (**Figure 1**).

As expected, both all-cause and cardiovascular mortality were higher in the high-risk group than in the low-risk group (**Table 2**, Figure 1). The tHcy mortality gradient was strongly present in both risk groups (Figure 1), but differences in absolute mortality risk were greater in the high-risk group. The difference in mortality between the extreme tHcy categories was 18.1% in the high-risk group and 6.4% in the low-risk group. When we further subdivided the endpoint into cardiovascular and noncardiovascular mortality, significant tHcy gradients were seen in all subgroups except for cardiovascular mortality in the low-risk group (Figure 1). For noncardiovascular mortality, the tHcy-mortality relation was of similar magnitude both in relative and absolute terms regardless of cardiovascular disease risk status.

TABLE 1
Baseline characteristics of the Hordaland Homocysteine Study cohort[1]

Characteristic	Women						Men					
		tHcy category (μmol/L)						tHcy category (μmol/L)				
	All (n = 2639)	5.1–8.9 (n = 569)	9.0–11.9 (n = 1144)	12.0–14.9 (n = 600)	15.0–137 (n = 326)	P for trend[2]	All (n = 2127)	5.1–8.9 (n = 196)	9.0–11.9 (n = 832)	12.0–14.9 (n = 674)	15.0–137 (n = 425)	P for trend[2]
	%						%					
Current smoker	21.4	14.6	18.3	25.0	37.4	<0.001	29.0	23.0	25.1	30.1	37.4	<0.001
Coffee consumption >5 cups/d	15.6	11.3	15.2	19.2	18.4	<0.001	27.0	17.4	25.0	31.0	29.2	<0.001
University or college education	10.1	11.9	10.7	7.4	9.4	0.05	23.3	26.3	25.4	22.3	19.1	0.01
No use of vitamin supplements	20.9	16.5	20.7	22.5	27.1	0.002	42.1	31.8	39.9	44.1	49.3	<0.001
Sedentary lifestyle	22.3	15.5	21.4	25.2	32.2	<0.001	15.7	12.8	13.1	17.2	19.5	0.001
Baseline cardiovascular disease	24.7	20.7	23.6	30.8	24.5	0.005	32.4	29.6	28.5	35.3	36.5	0.002
Treatment of hypertension	19.6	14.9	19.1	25.9	17.9	0.005	19.4	19.4	17.3	20.1	22.5	0.06
Prior myocardial infarction	3.3	1.9	3.1	4.7	4.3	0.01	11.3	9.7	9.4	13.1	12.7	0.03
Prior stroke	1.4	0.9	1.7	1.0	2.2	0.34	3.1	0.5	2.5	3.7	4.2	0.007
Angina pectoris	7.0	7.6	6.0	8.2	7.1	0.72	12.2	12.8	10.1	12.6	15.1	0.05
Diabetes mellitus	3.8	4.9	3.6	3.2	3.4	0.16	5.5	11.7	4.9	5.5	3.8	0.005
Cholesterol >8 mmol/L	20.7	18.3	20.6	21.0	24.5	0.04	6.1	3.6	7.0	4.6	8.0	0.28
Diastolic blood pressure >100 mm Hg	11.7	9.9	12.6	11.4	12.3	0.43	14.3	12.2	13.5	14.3	16.9	0.07
BMI (kg/m^2) ≥30	15.5	14.9	14.1	17.2	18.6	0.06	9.1	7.7	9.2	9.7	9.0	0.68

[1] Cohort members aged 65–67 y in 1992–1993. tHcy, total homocysteine.
[2] Cochran-Armitage test for trend in proportions.

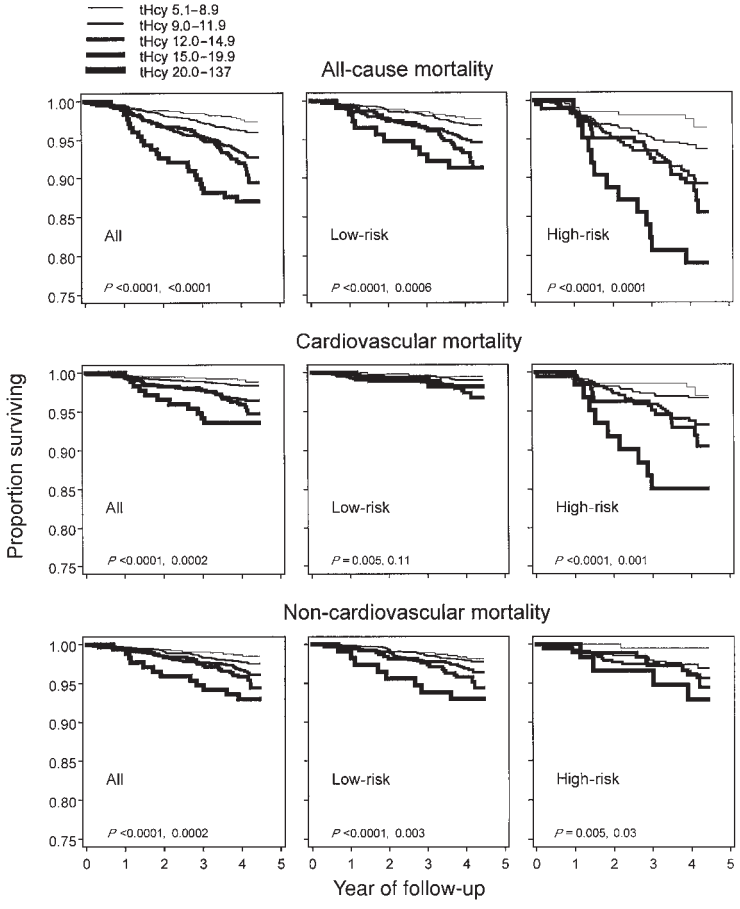

FIGURE 1. Kaplan-Meier survival curves by plasma total homocysteine (tHcy) concentration. The curves are given for all cohort members and for the groups with low and high cardiovascular disease risk. The high-risk group included the individuals who at inclusion reported a history of myocardial infarction, stroke, angina pectoris, diabetes mellitus, or ongoing treatment for hypertension (n = 1448). The remaining 3318 individuals were included in the low-risk group. All-cause, cardiovascular, and noncardiovascular mortality were considered separately. Two P values are given in each plot: a log-rank test for trend and the Cox-adjusted test for trend.

TABLE 2
Cox regression of plasma total homocysteine (tHcy) and mortality during follow-up from 1992 to 1997 in the Hordaland Homocysteine Study cohort[1]

	All-cause mortality				Cardiovascular mortality		Noncardiovascular mortality	
			MR (95% CI)					
tHcy concentration	No. at risk	Events	Age and sex adjusted	Multiple adjustment[2]	Events	MR (95% CI): multiple adjustment[2]	Events	MR (95% CI): multiple adjustment[2]
		n (%)			*n* (%)		*n* (%)	
All	4766	259 (5.4)			121 (2.5)		136 (2.9)	
tHcy (μmol/L)								
5.1–8.9	765	19 (2.5)	1	1	8 (1.1)	1	11 (1.4)	1
9.0–11.9	1976	77 (3.9)	1.40 (0.85, 2.32)	1.33 (0.81, 2.21)	32 (1.6)	1.25 (0.58, 2.73)	44 (2.2)	1.38 (0.71, 2.69)
12.0–14.9	1274	88 (6.9)	2.36 (1.43, 3.90)	2.02 (1.22, 3.34)	44 (3.5)	2.13 (0.99, 4.56)	44 (3.5)	1.94 (0.99, 3.81)
15.0–19.9	574	52 (9.1)	3.02 (1.77, 5.13)	2.48 (1.45, 4.23)	26 (4.5)	2.60 (1.16, 5.84)	25 (4.4)	2.28 (1.10, 4.71)
20.0–137	177	23 (13.0)	4.51 (2.44, 8.32)	3.56 (1.92, 6.60)	11 (6.2)	3.48 (1.38, 8.79)	12 (6.8)	3.60 (1.57, 8.27)
P for trend			<0.0001	<0.0001		0.0002		0.0002
Low-risk group	3318	139 (4.2)			46 (1.4)		92 (2.8)	
tHcy (μmol/L)								
5.1–8.9	560	13 (2.3)	1	1	3 (0.5)	1	10 (1.8)	1
9.0–11.9	1424	44 (3.1)	1.18 (0.63, 2.19)	1.09 (0.58, 2.04)	14 (1.0)	1.35 (0.39, 4.75)	30 (2.1)	1.02 (0.49, 2.10)
12.0–14.9	831	43 (5.2)	1.87 (0.99, 3.50)	1.63 (0.87, 3.08)	16 (1.9)	2.17 (0.62, 7.60)	27 (3.3)	1.45 (0.69, 3.05)
15.0–19.9	388	29 (7.5)	2.64 (1.36, 5.13)	2.10 (1.07, 4.12)	11 (2.8)	2.91 (0.79, 10.71)	17 (4.4)	1.70 (0.75, 3.81)
20.0–137	115	10 (8.7)	3.35 (1.46, 7.67)	2.64 (1.14, 6.08)	2 (1.7)	1.85 (0.30, 11.33)	8 (7.0)	2.96 (1.15, 7.60)
P for trend			<0.0001	0.0006		0.11		0.003
High-risk group	1448	120 (8.3)			75 (5.2)		44 (3.0)	
tHcy (μmol/L)								
5.1–8.9	205	6 (2.9)	1	1	5 (2.4)	1	1 (0.5)	1
9.0–11.9	552	33 (6.0)	1.93 (0.81, 4.60)	1.83 (0.77, 4.38)	18 (3.3)	1.15 (0.43, 3.12)	14 (2.5)	
12.0–14.9	443	45 (10.2)	3.19 (1.35, 7.50)	2.79 (1.18, 6.59)	28 (6.3)	2.02 (0.77, 5.29)	17 (3.8)	1.67 (0.82, 3.43)
15.0–19.9	186	23 (12.4)	3.75 (1.52, 9.26)	3.17 (1.27, 7.89)	15 (8.1)	2.27 (0.80, 6.42)	8 (4.3)	1.92 (0.81, 4.57)
20.0–137	62	13 (21.0)	6.17 (2.32, 16.45)	5.00 (1.87, 13.41)	9 (14.5)	3.96 (1.29, 12.16)	4 (6.5)	2.51 (0.81, 7.78)
P for trend			<0.0001	0.0001		0.001		0.03

[1] MR, mortality ratio.
[2] Adjusted for total cholesterol, systolic and diastolic blood pressure, pack-years of smoking, BMI, physical activity, age, and sex. The overall analysis was also adjusted for cardiovascular disease risk status at baseline.

These results were upheld in the Cox regression analysis (Table 2), which included adjustment for age, sex, pack-years of cigarette smoking (ie, the average number of packs of cigarettes smoked/d × the number of years smoked), total cholesterol, blood pressure, body mass index, physical activity, and an indicator of cardiovascular disease risk status. Multiple adjustment somewhat weakened the tHcy relations, but they remained strong and significant in all subgroups considered except for cardiovascular mortality in the low-risk group. Thus, when subjects having tHcy concentrations of 9.0–11.9, 12.0–14.9, 15.0–19.9, and ≥20 μmol/L were compared with those having a tHcy concentration <9 μmol/L, adjusted mortality ratios were 1.4, 1.9, 2.3, and 3.6 (*P* for trend = 0.0002) for noncardiovascular causes of death and 1.3, 2.1, 2.6, and 3.5 (*P* for trend = 0.0002) for cardiovascular causes of death. The estimated dose-response curve of the relation between plasma tHcy and all-cause mortality is shown in **Figure 2**. On the logit scale, the increase in mortality was close to linear within the tHcy range of ≈7–20 μmol/L. The dose-response relation was steeper and present over a wider range in the high-risk group.

Causes of death

The relations of plasma tHcy to cause-specific mortality are shown in **Table 3**. After multivariate adjustment, a 5-μmol/L increase in tHcy was associated with an increase in all-cause mortality of 49% (95% CI: 28%, 72%). The corresponding values were 50% for cardiovascular, 26% for cancer, and 104% for noncancer, noncardiovascular deaths. With full adjustment, no significant associations were seen between any specific type of cancer and tHcy. Within the cardiovascular mortality group, the

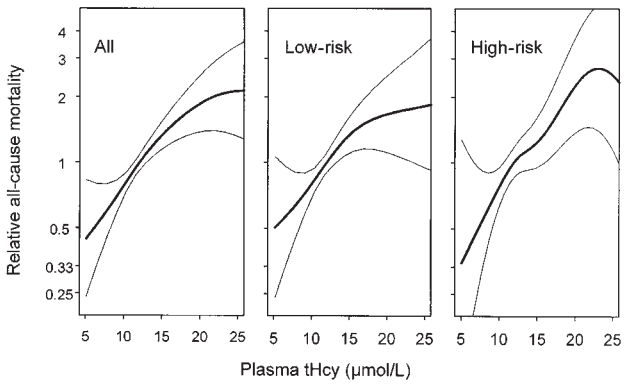

FIGURE 2. Dose-response curves of the relation between plasma total homocysteine (tHcy) and all-cause mortality. The relation is shown for all cohort members and for the groups with low and high cardiovascular disease risk. The curves were constructed by using generalized additive logistic regression with adjustment for age, sex, pack-years of cigarette smoking, total cholesterol, blood pressure, BMI, and physical activity. Thin lines indicate 95% pointwise confidence limits.

TABLE 3
Cause-specific mortality and plasma total homocysteine (tHcy) in the Hordaland Homocysteine Study cohort[1]

		MR per 5-μmol/L plasma tHcy increment			
		Age and sex adjusted		Multiple adjustment[2]	
Cause of death	No. of deaths	MR (95% CI)	*P* for trend	MR (95% CI)	*P* for trend
All causes	259	1.61 (1.40, 1.85)	<0.0001	1.49 (1.28, 1.72)	<0.0001
Cardiovascular	121	1.65 (1.35, 2.02)	<0.0001	1.50 (1.21, 1.85)	0.0002
Ischemic heart disease	88	1.60 (1.26, 2.04)	0.0001	1.46 (1.14, 1.87)	0.003
Acute myocardial infarction	50	1.60 (1.16, 2.21)	0.004	1.49 (1.06, 2.08)	0.02
Cerebrovascular disease	16	1.99 (1.20, 3.32)	0.008	1.76 (1.04, 2.98)	0.04
Noncardiovascular	136	1.57 (1.29, 1.91)	<0.0001	1.47 (1.20, 1.80)	0.0002
Cancer	103	1.32 (1.03, 1.70)	0.03	1.26 (0.98, 1.63)	0.07
Lung cancer	34	1.53 (1.03, 2.27)	0.04	1.37 (0.91, 2.07)	0.13
Colorectal cancer	12	0.64 (0.22, 1.85)	0.41	0.64 (0.22, 1.91)	0.43
Other causes	33	2.33 (1.67, 3.26)	<0.0001	2.04 (1.44, 2.89)	<0.0001
Accidents or violent deaths	8	2.07 (1.02, 4.17)	0.04	2.06 (0.96, 4.45)	0.07
Other specific causes	25	2.42 (1.66, 3.53)	<0.0001	2.05 (1.39, 3.03)	0.0003

[1] MR, mortality ratio.
[2] Adjusted for total cholesterol, systolic and diastolic blood pressure, pack-years of smoking, BMI, physical activity, cardiovascular disease risk status at baseline, age, and sex by using a Cox regression model.

strongest association with tHcy was seen for cerebrovascular disease. After subarachnoidal hemorrhage from the cerebrovascular deaths was excluded, however, the association became of similar strength to that between tHcy and ischemic heart disease and was no longer significant. The strongest association of tHcy to mortality was observed in the heterogeneous group of 33 deaths for which neither cancer nor cardiovascular disease was the underlying cause of death. A strong positive association was observed in the small subgroup that included accidental and violent deaths and for deaths due to diseases of other organ systems.

The association between all-cause mortality and tHcy was somewhat stronger in women than in men and was stronger in subjects who had never smoked than in former or current smokers. Exclusion of the deaths that occurred during the first year of follow-up did not materially alter the results.

DISCUSSION

We observed a strong association between tHcy and all-cause mortality during 4 y of follow-up of 65–67-y-old men and women enrolled in the population-based Hordaland Homocysteine Study in 1992–1993. Our results agree with the report of tHcy as an equally strong predictor of both all-cause and cardiovascular mortality in elderly Framingham subjects (29) and in a follow-up of Jerusalem residents (30). The observation of stronger tHcy-mortality associations among cohort members considered to be at high risk of cardiovascular disease according to their medical history agrees with similar findings in a series of patient cohorts characterized by elevated risk of cardiovascular events (21–28). These observations, combined with increasing experimental evidence for an induction of acute vascular dysfunction by homocysteine (39, 40), further corroborate the hypothesis that elevated tHcy is more strongly associated with acute vascular events than with the slowly evolving atherosclerotic process (24).

In participants at low risk of cardiovascular disease, we found a slightly weaker but highly significant association between tHcy and all-cause mortality. In this subgroup, our study had insufficient power to establish significance for the observed increase in cardiovascular mortality of 35% per 5-μmol/L increase in tHcy. This estimate agrees remarkably well with the corresponding 33% increase in ischemic heart disease mortality reported in a British cohort (10). The results of several other (9, 11, 12, 14–17) but not all (18–20) prospective, population-based studies support our findings with respect to cardiovascular disease events. Although our results cannot fully explain the heterogeneity of results among the prospective studies, they show that weaker associations between tHcy and cardiovascular events may be expected after the exclusion of individuals with cardiovascular disease or conditions that increase cardiovascular risk, such as hypertension or diabetes.

An unexpected finding in our study was the strong relation between tHcy and deaths from noncardiovascular disease. The associations between tHcy and noncardiovascular mortality was of similar magnitude and statistically significant regardless of cardiovascular disease risk status. In the low-risk group, the tHcy-mortality association was stronger for noncardiovascular than for cardiovascular mortality. Conceivably, the ability of high tHcy to provoke vascular occlusion (39) may enhance mortality, even in subjects without overt cardiovascular disease.

The positive relation between tHcy and cancer mortality was significant before, but not after, adjustment for smoking and cardiovascular disease risk factors. This is not surprising because known cancer risk factors such as cigarette smoking and a low intake of fruit and vegetables (41) also are associated with elevated tHcy concentrations (38). However, because of low numbers of specific cancers, a short follow-up time, and a lack of information on cancer incidence, our data concerning the role of tHcy as a cancer marker should be regarded as preliminary.

Explanations for the strong relations between tHcy and the heterogeneous group of 33 deaths attributed to neither cancer nor cardiovascular disease are speculative. For instance, tHcy was shown to be a risk factor for Alzheimer disease (42) and is associated with declined cognitive function in the elderly (43, 44). Furthermore, vitamin B-12 deficiency is associated with both neuropsychiatric disorders (44) and hyperhomocysteinemia (45) in the elderly. These observations may explain the relation between tHcy and violent or accidental deaths and may provide a link to the association between tHcy and deaths due to central nervous system disease. Further understanding of the clinical significance of these strong associations will require in-depth

studies with larger numbers of cases. In the cohort of Jerusalem residents, a strong association was also noted between tHcy and noncancer, noncardiovascular deaths (30).

Associations between tHcy concentrations, lifestyle, and presence of cardiovascular disease have been observed (14, 24, 38). Such findings suggest that some of the unadjusted tHcy-mortality association may be due to confounding with known risk factors, eg, smoking. However, the tHcy-mortality relation was strongest in subjects who had never smoked, a finding also noted in one other study (12). Another possibility is that tHcy may reflect the severity of cardiovascular or renal disease. In this study, no such information is available, but we showed previously that in patients with coronary artery disease, adjustment for the severity of heart disease, ejection fraction, and creatinine only moderately weakens the tHcy-mortality association (24).

In conclusion, the main finding in this population-based follow-up study of elderly men and women is that plasma tHcy is strongly related to both noncardiovascular and cardiovascular mortality. These results should encourage further studies of tHcy as a prognostic marker or risk factor in a wider perspective than one confined to cardiovascular disease.

We are grateful to the staffs of the Department of Pharmacology, the Section for Medical Statistics, University of Bergen, and the National Health Screening Service, Oslo, for their valuable assistance in this work. We also thank Statistics Norway for providing the death certificate information. SEV is grateful to the Unit of Nutrition and Cancer, International Agency for Research on Cancer, Lyon, France, for sharing an excellent working environment during his stay there in 1998–1999.

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