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Lipids, Lipoproteins, and Cardiovascular Risk Factors

Plasma Total Cysteine, Mortality, and Cardiovascular Disease Hospitalizations: The Hordaland Homocysteine Study

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Background: **We have previously reported a positive association between tHcy and mortality and cardiovascular disease (CVD) hospitalizations in the Hordaland Homocysteine Study cohort. Using the same data set, we assessed the relationship between plasma total cysteine (tCys) and mortality from all causes and from cardiovascular and noncardiovascular conditions, and the association between tCys and the risk of hospitalizations from CVD.**

Methods: **We measured plasma tCys in blood samples from 12 595 men and women 40–42 years of age and from 4766 men and women 65–67 years of age, collected as part of the Hordaland Homocysteine Study in the year 1992–1993. Follow-up data on mortality were collected through 1999. Data on CVD hospitalizations were collected from hospital records up to May 31, 1998.**

Results: **After a follow-up time of 6.6–7.6 years, there were a total of 610 deaths, of which 243 were cardiovascular deaths and 367 were noncardiovascular deaths. There was no association between tCys and all-cause, cardiovascular, or noncardiovascular mortality. When we used tCys values <247.6 μmol/L (lowest quartile) as the reference category, the adjusted mortality ratio (MR) for all-cause mortality at tCys concentrations of 247.6–270.79, 270.8–295.79, and ≥295.8 μmol/L (highest quartile) were 1.0, 0.9, and 1.0, respectively. The adjusted MRs for cardiovascular mortality were 1.0, 1.1, and 1.1, respectively. There were no associations between tCys and 1275 CVD hospitalizations, except that tCys was significantly associated with hospitalizations from coronary artery bypass grafting.**

Conclusion: **Plasma tCys is not associated with mortality or CVD hospitalizations.**

Increased plasma total homocysteine (tHcy)[4] is regarded as an independent risk factor for occlusive disease in coronary, cerebral, and peripheral arterial vessels and in the veins *(1, 2)*, and has been associated with all-cause and cardiovascular disease (CVD) mortality *(3–6)*. Case-control studies have shown stronger associations than prospective studies *(7–9)*.

Cysteine is another sulfhydryl-containing amino acid that is structurally similar to homocysteine. Furthermore, experimental studies indicate that cysteine could be atherogenic *(10, 11)*. Cysteine supports superoxide modification of LDL and has a cytotoxic effect in vitro against several cell types *(12, 13)*.

Few studies have evaluated the association between plasma total cysteine (tCys) and CVD *(14–18)*. These studies found higher concentrations of tCys in cases than in controls. In contrast, van den Brandhof et al. *(19)* found no relationship between tCys and the risk of coronary heart disease. We have previously evaluated the association between tCys and the risk of CVD, using the European Concerted Action Project data. In this case-control study, tCys had a U-shaped relationship with peripheral and cerebrovascular disease and a weak positive relationship with coronary heart disease *(20)*.

Using baseline data from the Hordaland Homocysteine Study, we have previously evaluated the relationship between tCys and several lifestyle and CVD risk factors. The strongest determinants of tCys were age, sex, body

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[4] Nonstandard abbreviations: tHcy, total homocysteine; CVD, cardiovascular disease; tCys, total cysteine; BMI, body mass index; ICD, International Classification of Disease; MR, mortality ratio; CI, confidence interval; and CABG, coronary artery bypass grafting.

mass index (BMI), cholesterol, and diastolic blood pressure *(21)*. In the present work, we investigated the relationship between tCys measured at baseline and the risk of mortality and CVD hospitalizations in this population.

Participants and Methods

STUDY POPULATION

In 1992–1993, the baseline data for the Hordaland Homocysteine cohort were collected by the National Health Screening Service in cooperation with the University of Bergen, Norway. A total of 18 043 individuals 40–67 years of age participated in the study. The participants belonged to three different age groups: 40–42 years (all participants living in the county of Hordaland were invited), 43–64 years (a 2% random sample of the residents in the city of Bergen were invited), and 65–67 years (all participants living in Bergen and three neighboring suburban municipalities were invited). Data collected included information about age, height, weight, blood pressure, serum total cholesterol, serum triglycerides, tCys, and tHcy. Plasma tCys and tHcy were measured by HPLC with fluorescence detection *(22, 23)*. Serum total cholesterol and triglycerides were measured with enzymatic methods. Questionnaires provided information about previous illness, symptoms, and dietary and other lifestyle habits. More detailed reports on the data collection, blood sample handling, and biochemical analyses have been published previously *(24)*.

MORTALITY DATA

Follow-up data on mortality were collected for the three age groups, but we included only the youngest age group (40–42 years) and the oldest age group (65–67 years) in this study. Causes of death were coded by Statistics Norway (Oslo) and were obtained from the death certificates of the 610 deaths that had occurred through 1999. Categories were constructed using the underlying cause of death according to the ninth revision of the International Classification of Disease (ICD-9; for deaths from 1992 through 1995) and ICD-10 (for deaths from 1996 through 1999).

HOSPITALIZATION DATA

No follow-up data on hospitalizations were collected for the 43–64 years group; therefore, these individuals were not included in the study. Data on hospitalizations were obtained from computerized records containing discharge diagnoses from six hospitals in Hordaland County between the time of baseline data collection and May 31, 1998. These records were searched for CVD codes or surgical procedures. Disease categories were constructed according to ICD-9. More details on the data collection have been published previously *(25)*.

STATISTICAL METHODS

The relationship between tCys and mortality/CVD hospitalizations was studied with the Cox proportional hazards model. For the total study population, tCys quartiles were used, and tCys concentrations <247.6 μmol/L (lowest quartile) were used as the reference category.

To have a more balanced distribution of individuals in each tCys category, we used age-specific tCys quartiles in each age group. All associations were adjusted for sex and age and then were further adjusted for CVD risk factors and factors associated with the tCys concentration, including tHcy, BMI, cholesterol, smoking, and diastolic blood pressure.

The analyses were also performed for different combinations of tCys and tHcy. Plasma tCys tertiles were used to define the low, medium, and high tCys concentrations, and tHcy concentrations <12 μmol/L and ≥12 μmol/L were used to define low and high tHcy. All statistical analyses were performed with SAS software (release 8.2 for Windows).

Results

BASELINE CHARACTERISTICS

The baseline characteristics of the population by tCys concentrations (quartiles) are shown in Table 1. The results are presented for older and younger men and women separately. The percentage of individuals with high BMI, high diastolic blood pressure, high cholesterol, and baseline CVD increased significantly with increasing tCys concentrations in all age and sex groups.

There was a significant correlation between tCys and tHcy in this population ($r = 0.22$; $P < 0.0001$).

tCys AND MORTALITY

After a follow-up time of 6.6–7.6 years, there were a total of 610 deaths, of which 243 were cardiovascular and 367 were noncardiovascular.

We investigated all-cause mortality, cardiovascular and noncardiovascular mortality, cancer mortality, and noncardiovascular noncancer mortality according to tCys quartiles. All associations were adjusted for sex and age and further adjusted for BMI, cholesterol, tHcy, smoking, and diastolic blood pressure.

In the total population, the crude relationship between tCys and all-cause mortality was strong [mortality ratios (MRs) with 95% confidence intervals (95% CIs) across the tCys quartiles were 1.5 (1.2–2.2), 2.5 (1.8–3.3), and 4.8 (3.7–6.3), respectively; $P < 0.0001$ for trend]. However, adjusting for age abolished this effect. After adjustment, there was no relationship between tCys and all-cause mortality or CVD mortality (Table 2). When we used the lowest quartile of tCys as the reference, there was no association between tCys and noncardiovascular mortality across the tCys quartiles ($P = 0.71$ for trend) or cancer mortality ($P = 0.38$ for trend). However, there was a weak and statistically nonsignificant association between tCys and noncardiovascular noncancer mortality [Adjusted MRs (95% CIs), 1.3 (0.6–2.5), 1.0 (0.5–2.0), and 1.8 (0.9–3.5); $P = 0.07$ for trend]. All relationships were evaluated

Table 1. Baseline characteristics by tCys concentrations.

	40–42 years					65–67 years				
	<241 μmol/L	241–260.9 μmol/L	261–282.79 μmol/L	≥282.8 μmol/L	All	<276.2 μmol/L	276.2–297.69 μmol/L	297.7–320.49 μmol/L	≥320.5 μmol/L	All
Men										
n	879	1355	1723	2153	6110	515	565	514	533	2127
Baseline CVD, %	0.6	1.3	0.9	1.0	1.0	17.3	18.8	20.2	21.4	19.4
Cholesterol >8 mmol/L, %	1.4	2.1	2.1	3.3	2.4	5.6	5.3	6.8	6.8	6.1
Diastolic blood pressure >100 mmHg, %	2.2	2.2	2.8	3.8	2.9	7.6	8.3	12.5	14.3	10.6
BMI >30 kg/m^2, %	3.1	3.5	6.3	10.8	6.8	5.8	7.1	9.9	13.7	9.1
Women										
n	2266	1797	1438	984	6485	673	629	678	659	2639
Baseline CVD, %	0.3	0.5	0.7	0.4	0.5	9.4	8.6	9.0	11.7	9.7
Cholesterol >8 mmol/L, %	1.0	0.5	2.0	2.6	1.3	19.2	22.3	20.5	21.4	20.8
Diastolic blood pressure >100 mmHg, %	1.3	1.1	1.5	1.9	1.4	4.3	7.0	9.1	12.4	8.2
BMI >30 kg/m^2, %	4.0	6.2	8.6	14.2	7.2	8.5	10.7	18.7	24.0	15.5

in the younger and older groups separately, and similar results were obtained for both groups (Table 2). All relationships were further evaluated at high tCys concentrations (>95th percentile) compared with lower tCys concentrations, and similar results were obtained (results not shown).

The relationship between tCys and specific CVD mortality was evaluated, and there was no association between tCys and cerebrovascular or coronary heart disease mortality (results not shown).

To test whether tCys might be involved in the promotion of existing disease, we evaluated the relationship between tCys and all-cause, CVD, and noncardiovascular mortality in individuals with baseline CVD or hypertension or diabetes and in those free of CVD at baseline. We observed stronger but statistically nonsignificant associations in those with preexisting CVD, whereas there was no association between tCys and CVD risk among those free of CVD at baseline. Furthermore, to evaluate whether the association between tCys and mortality is influenced by the length of follow-up time, we evaluated the associations for those who died during the first 4 years of follow-up but found no association between tCys and mortality (results not shown).

Table 2. Cox regression of plasma tCys and mortality during follow-up from 1992 through 1999.

			All-cause mortality			Cardiovascular mortality		
Group	tCys, μmol/L	No. at risk	Events, n (%)	MR[a] (95% CI)	MR[b] (95% CI)	Events, n (%)	MR[a] (95% CI)	MR[b] (95% CI)
All	Total	17 361	610 (3.5)			243 (1.4)		
	<247.6	4381	64 (1.5)	1	1	19 (0.4)	1	1
	247.6–270.79	4365	100 (2.3)	0.9 (0.7–1.2)	1.0 (0.7–1.3)	34 (0.7)	0.9 (0.5–1.6)	1.0 (0.5–1.7)
	270.8–295.79	4294	152 (3.4)	0.8 (0.6–1.1)	0.9 (0.6–1.2)	68 (1.6)	1.1 (0.6–1.8)	1.1 (0.6–1.8)
	≥295.8	4321	294 (6.7)	1.0 (0.7–1.3)	1.0 (0.8–1.4)	122 (2.8)	1.1 (0.7–1.8)	1.1 (0.6–1.8)
P for trend				0.77	0.67		0.41	0.67
Young (40–42 years)	Total	12 595	112 (0.9)			30 (0.2)		
	<241	3145	27 (0.9)	1	1	9 (0.3)	1	1
	241–260.9	3152	26 (0.8)	0.9 (0.5–1.5)	0.9 (0.5–1.5)	6 (0.2)	0.6 (0.2–1.6)	0.6 (0.2–1.7)
	261–282.79	3161	25 (0.8)	0.8 (0.4–1.3)	0.7 (0.4–1.3)	6 (0.2)	0.5 (0.2–1.4)	0.5 (0.2–1.3)
	≥282.8	3137	34 (1.1)	0.9 (0.6–1.6)	0.8 (0.5–1.4)	9 (0.3)	0.6 (0.2–1.7)	0.5 (0.2–1.3)
P for trend				0.81	0.37		0.38	0.17
Old (65–67 years)	Total	4766	498 (10.4)			213 (4.5)		
	<276.2	1188	125 (10.5)	1	1	46 (3.9)	1	1
	276.2–297.69	1194	119 (10.0)	0.9 (0.7–1.2)	1.0 (0.7–1.2)	59 (4.9)	1.2 (0.8–1.8)	1.2 (0.8–1.8)
	297.7–320.49	1192	122 (10.2)	1.0 (0.8–1.3)	1.0 (0.8–1.3)	47 (3.9)	1.0 (0.7–1.6)	1.0 (0.7–1.5)
	≥320.5	1192	132 (11.1)	1.0 (0.8–1.3)	1.1 (0.8–1.4)	61 (5.1)	1.3 (0.9–1.9)	1.2 (0.8–1.8)
P for trend				0.91	0.85		0.88	0.91

[a] Adjusted for sex and age.

[b] Adjusted for age, sex, BMI, cholesterol, tHcy, smoking, and diastolic blood pressure.

Table 3. Mortality in different tCys-tHcy combinations.

			All-cause mortality			Cardiovascular mortality		
tCys[a]	tHcy[b]	No. at risk	n (%)	MR[c] (95% CI)	MR[d] (95% CI)	n (%)	MR[c] (95% CI)	MR[d] (95% CI)
L	L	5037	65 (1.3)	1	1	18 (0.4)	1	1
M	L	4423	87 (2.0)	0.7 (0.5–1.0)	0.8 (0.5–1.1)	30 (0.7)	0.8 (0.5–1.5)	0.8 (0.4–1.5)
H	L	3181	128 (4.0)	0.8 (0.6–1.1)	0.9 (0.6–1.2)	50 (1.6)	1.0 (0.6–1.7)	1.0 (0.6–1.8)
L	H	712	25 (3.5)	1.7 (1.1–2.8)	1.5 (0.9–2.3)	10 (1.4)	2.2 (1.0–4.7)	2.0 (0.9–4.3)
M	H	1362	70 (5.1)	1.5 (1.1–2.2)	1.4 (1.0–1.8)	30 (2.2)	1.9 (1.1–3.5)	1.8 (1.0–3.3)
H	H	2646	235 (8.9)	1.4 (1.0–1.9)	1.3 (1.0–1.8)	105 (4.0)	1.8 (1.1–3.0)	1.6 (0.9–2.7)

[a] L, low tCys (<255 μmol/L); M, medium tCys (255.1–286.09 μmol/L); H, high tCys (≥ 286.1 μmol/L).
[b] L, low tHcy (<12 μmol/L); H, high tHcy (≥ 12 μmol/L).
[c] Adjusted for sex and age.
[d] Adjusted for sex, age, BMI, cholesterol, tHcy, smoking, and diastolic blood pressure.

MORTALITY RISK AT VARIOUS COMBINATIONS OF tCys AND tHcy

We investigated the risk of all-cause and CVD mortality in various combinations of tCys and tHcy concentrations (Table 3). A combination of low tCys (<255.1 μmol/L) and low tHcy (<12 μmol/L) was used as the reference. There was no association with mortality at low tHcy combined with medium (255.1–286.09 μmol/L) or high tCys (≥286.1 μmol/L), but there was an association with all-cause and CVD mortality at high tHcy (≥12 μmol/L) combined with low, medium, or high tCys. The results indicate a pattern suggestive of higher all-cause and cardiovascular mortality for the combination of high tHcy and low tCys (Table 3). In addition, we evaluated the association between tCys and mortality separately in those with high tHcy. There was a statistically nonsignificant inverse trend toward lower risk as tCys increased (results not shown).

tCys AND CVD HOSPITALIZATIONS

We assessed the relationship between tCys and the risk of hospitalizations for CVD for the whole study population and for the younger and older age groups separately (Table 4). There was a trend of increasing sex- and age-adjusted hospitalization rate with increasing tCys in the total study population and in the young age group. This weak association disappeared after adjustment for BMI, cholesterol, tHcy, smoking, and diastolic blood pressure.

We evaluated the association between tCys and the risk of hospitalization for different disease categories (acute myocardial infarction, coronary heart disease, arterial occlusive disease, cerebrovascular disease, and venous thrombosis) and surgical procedures [percutaneous coronary intervention and coronary artery bypass grafting (CABG)] separately. There were no associations between tCys and specific CVD hospitalizations, but there was a positive association between tCys and hospitalizations for CABG. When we used tCys concentrations <247.6 μmol/L (lowest quartile) as the reference category, the adjusted hospitalization ratio for CABG at tCys concentrations of 247.6–270.79, 270.8–295.79, and ≥295.8 μmol/L (highest quartile) were 0.9 (0.3–2.6), 1.6 (0.6–4.2); and 2.0 (0.8–5.1); $P = 0.02$ for trend. The associations

Table 4. Cox regression for plasma tCys and CVD hospitalizations.

				Hospitalization ratio (95% CI)	
Groups	tCys, μmol/L	No. at risk	Events, %	Adjusted for sex and age	Multiple adjustment[a]
All	<247.6	4381	180	1	1
	247.6–270.79	4366	223	0.9 (0.8–1.1)	0.9 (0.7–1.1)
	270.8–295.79	4293	338	1.0 (0.9–1.3)	0.9 (0.8–1.1)
	≥295.8	4321	534	1.2 (1.0–1.4)	1.0 (0.8–1.2)
P for trend				0.02	0.71
Young (40–42 years)	<241	3145	105	1	1
	241–260.9	3154	106	1.0 (0.7–1.3)	0.9 (0.7–1.2)
	261–282.79	3159	111	1.0 (0.7–1.3)	0.8 (0.6–1.1)
	≥282.8	3137	150	1.3 (1.0–1.7)	1.0 (0.8–1.3)
P for trend				0.06	0.94
Old (65–67 years)	<276.2	1188	181	1	1
	276.2–297.69	1194	196	1.1 (0.9–1.3)	1.0 (0.8–1.2)
	297.7–320.49	1192	188	1.0 (0.8–1.3)	1.0 (0.8–1.2)
	≥320.5	1192	238	1.3 (1.1–1.6)	1.2 (1.0–1.5)
P for trend				0.004	0.08

[a] Adjusted for age, sex, BMI, cholesterol, tHcy, smoking, and diastolic blood pressure.

between tCys and the different CVD hospitalizations were slightly strengthened when the analysis was confined to the older age group and to individuals with baseline CVD or hypertension.

Discussion

We investigated the relationship between tCys and the risk of mortality and CVD hospitalizations in the Hordaland Homocysteine Study cohort, using follow-up data on 17 361 men and women. This is the first prospective study to evaluate the association between tCys and mortality and tCys and CVD hospitalizations. We found no association between tCys and all-cause, cardiovascular, or non-CVD mortality after a follow-up time of 6.6–7.6 years. Furthermore, there was no relationship between tCys and CVD hospitalizations, except that tCys was significantly associated with hospitalizations for CABG.

The relationship between tHcy and CVD and non-CVD mortality and CVD morbidity was studied recently in this population *(4, 25)*. The results showed that tHcy is a strong predictor of both CVD and non-CVD mortality and of CVD morbidity in elderly individuals. The median follow-up time for the mortality study was 4.1 years, and only individuals belonging to the oldest age group (65–67 years of age at baseline) were included. In the present study, individuals were followed up for >7 years; therefore, the lack of association between tCys and mortality might be attributable to the longer follow-up time. In fact, a few studies have shown that associations between tHcy and risk of disease/mortality are weakened by a longer follow-up time *(3, 26)*. However, when analyses of the tCys-mortality relationship were confined to those who died during the first 4 years of follow-up, similar results were obtained. Therefore, the longer follow-up time could not explain our findings.

To study the interaction between tCys and tHcy in relation to mortality, we investigated the risk of all-cause and CVD mortality in various combinations of tCys and tHcy concentrations. The highest MR was for the combination of low tCys and high tHcy. In agreement with this, using data from the European Concerted Action Project, we have previously found that the highest risk for CVD was for the combination of low tCys and high tHcy *(20)*.

In the present study we found no association between tCys and CVD mortality or CVD hospitalizations. Few case-control studies have evaluated the relationship between tCys and the risk of CVD *(14, 15, 17, 19, 20)*. Two of these studies reported higher tCys concentrations in cardiovascular patients than in controls *(14, 15)*. After adjusting for several factors, including age, sex, smoking status, and creatinine, Jacob et al. *(17)* found a positive association between tCys and the risk of CVD. However, the authors did not adjust for tHcy, so the possibility remains that tCys merely reflected the association between tHcy and disease. Alternatively, the positive associations between tCys and the risk of CVD in these case-control studies might be attributable to the effect of the disease itself on tCys concentrations because tCys was measured in these patients after the occurrence of disease. A renal mechanism should be considered because there are preliminary data showing increased tCys in renal patients *(27)*.

We have previously found in a case-control study a U-shaped relationship with cerebrovascular and peripheral vascular disease and a weak positive association between tCys and coronary heart disease *(20)*. The lack of association in the present study should carry weight. Our study was prospective and included a large number of events that have been shown to be related to tHcy.

Many case-control and prospective studies have shown that homocysteine is associated with CVD *(1, 2)*. The absence of a relationship between tCys and CVD mortality/morbidity in the present study may be regarded as supportive of the homocysteine theory of CVD *(28–30)*. It has been suggested that confounding by renal function might explain the tHcy-CVD relationship *(31)*. Renal failure has been shown to cause increased concentrations of both tHcy and tCys *(32)*. In contrast to tCys, tHcy showed a strong association with CVD mortality/morbidity in the same population *(4, 25)*, which suggests that the renal mechanism does not fully explain the relationship between tHcy and CVD because one would then expect an artificial relationship with tCys and later morbidity/mortality. Furthermore, Demuth et al. *(33)* have recently shown that tHcy is independently and positively associated with carotid artery internal diameter and intima media thickness, both of which are measures of preclinical vascular disease, but that tCys was not. This adds credence to tHcy as an independent cardiovascular risk factor.

Some authors have reported a strong association between tHcy and noncardiovascular noncancer mortality *(3, 4)*. In the present study, tCys was weakly associated with noncardiovascular noncancer mortality. This is a diverse group, with the underlying cause of death ranging from respiratory diseases to accidents. It is therefore difficult to speculate on the nature of the borderline significant association between tCys and mortality in this group.

In conclusion, unlike tHcy, tCys was not associated with all-cause mortality, CVD or non-CVD mortality, and CVD morbidity. These findings indicate that although cysteine shares some of the determinants of tHcy and is metabolically and structurally linked to homocysteine in plasma, tCys is not a predictor of mortality or morbidity in the general population.

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References

1. Wald DS, Law M, Morris JK. Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis. BMJ 2002; 325:1202–8.
2. Kelly PJ, Rosand J, Kistler JP, Shih VE, Silveira BA, Plomaritoglou A, et al. Homocysteine, MTHFR 677C→T polymorphism, and risk of ischemic stroke: results of a meta-analysis. Neurology 2002; 59:529–36.
3. Kark JD, Selhub J, Adler B, Gofin J, Abramson JH, Friedman G, et al. Nonfasting plasma total homocysteine level and mortality in middle-aged and elderly men and women in Jerusalem. Ann Intern Med 1999;131:321–30.
4. Vollset SE, Refsum H, Tverdal A, Nygård O, Nordrehaug JE, Tell GS, et al. Plasma total homocysteine and cardiovascular and noncardiovascular mortality: the Hordaland Homocysteine Study. Am J Clin Nutr 2001;74:130–6.
5. Bostom AG, Silbershatz H, Rosenberg IH, Selhub J, D'Agostino RB, Wolf PA, et al. Nonfasting plasma total homocysteine levels and all-cause and cardiovascular disease mortality in elderly Framingham men and women. Arch Intern Med 1999;159:1077–80.
6. Nygård O, Nordrehaug JE, Refsum H, Farstad M, Ueland PM, Vollset SE. Plasma homocysteine levels and mortality in patients with coronary artery disease. N Engl J Med 1997;337:230–6.
7. Ford ES, Smith SJ, Stroup DF, Steinberg KK, Mueller PW, Thacker SB. Homocysteine and cardiovascular disease: a systematic review of the evidence with special emphasis on case-control studies and nested case-control studies. Int J Epidemiol 2002; 31:59–70.
8. Clarke R, Collins R, Lewington S, Donald A, Alfthan G, Tuomilehto J, et al. Homocysteine and risk of ischemic heart disease and stroke—a meta analysis. JAMA 2002;288:2015–22.
9. Bautista LE, Arenas IA, Penuela A, Martinez LX. Total plasma homocysteine level and risk of cardiovascular disease: a meta-analysis of prospective cohort studies. J Clin Epidemiol 2002;55: 882–7.
10. Heinecke JW, Rosen H, Suzuki LA, Chait A. The role of sulfur-containing amino acids in superoxide production and modification of low density lipoprotein by arterial smooth muscle cells. J Biol Chem 1987;262:10098–103.
11. Hogg N. The effect of cysteine on the auto-oxidation of homocysteine. Free Radic Biol Med 1999;27:28–33.
12. Parthasarathy S. Oxidation of low-density lipoprotein by thiol compounds leads to its recognition by the acetyl LDL receptor. Biochim Biophys Acta 1987;917:337–40.
13. Nishiuch Y, Sasaki M, Nakayasu M, Oikawa A. Cytotoxicity of cysteine in culture media. In Vitro 1976;12:635–8.
14. Araki A, Sako Y, Fukushima Y, Matsumoto M, Asada T, Kita T. Plasma sulfhydryl-containing amino acids in patients with cerebral infarction and in hypertensive subjects. Atherosclerosis 1989;79: 139–46.
15. Mansoor MA, Bergmark C, Svardal AM, Lønning PE, Ueland PM. Redox status and protein binding of plasma homocysteine and other aminothiols in patients with early-onset peripheral vascular disease. Arterioscler Thromb Vasc Biol 1995;15:232–40.
16. Verhoef P, Stampfer MJ, Buring JE, Gaziano JM, Allen RH, Stabler SP, et al. Homocysteine metabolism and risk of myocardial infarction: relation with vitamins B_6, B_{12}, and folate. Am J Epidemiol 1996;143:845–59.
17. Jacob N, Bruckert E, Giral P, Foglietti M, Turpin G. Cysteine is a cardiovascular risk factor in hyperlipidemic patients. Atherosclerosis 1999;146:53–9.
18. Mills BJ, Weiss MM, Lang CA, Liu MC, Ziegler C. Blood glutathione and cysteine changes in cardiovascular disease. J Lab Clin Med 2000;135:396–401.
19. van den Brandhof WE, Haks K, Schouten EG, Verhoef P. The relation between plasma cysteine, plasma homocysteine and coronary atherosclerosis. Atherosclerosis 2001;157:403–9.
20. El-Khairy L, Ueland PM, Refsum H, Graham IM, Vollset SE. Plasma total cysteine as a risk factor for vascular disease: The European Concerted Action Project. Circulation 2001;103:2544–9.
21. El-Khairy L, Ueland PM, Nygård O, Refsum H, Vollset SE. Lifestyle and cardiovascular disease risk factors as determinants of total cysteine in plasma: The Hordaland Homocysteine Study. Am J Clin Nutr 1999;70:1016–24.
22. Refsum H, Ueland PM, Svardal AM. Fully automated fluorescence assay for determining total homocysteine in plasma. Clin Chem 1989;35:1921–7.
23. Fiskerstrand T, Refsum H, Kvalheim G, Ueland PM. Homocysteine and other thiols in plasma and urine: automated determination and sample stability. Clin Chem 1993;39:263–71.
24. Nygård O, Vollset SE, Refsum H, Stensvold I, Tverdal A, Nordrehaug JE, et al. Total plasma homocysteine and cardiovascular risk profile. The Hordaland Homocysteine Study. JAMA 1995;274: 1526–33.
25. Nurk E, Tell GS, Vollset SE, Nygård O, Refsum H, Ueland PM. Plasma total homocysteine and hospitalizations for cardiovascular disease. Arch Intern Med 2002;162:1374–81.
26. Chasan-Taber L, Selhub J, Rosenberg IH, Malinow MR, Terry P, Tishler PV, et al. A prospective study of folate and vitamin B_6 and risk of myocardial infarction in US physicians. J Am Coll Nutr 1996;15:136–43.
27. Marcucci R, Fedi S, Brunelli T, Pepe G, Prisco D, Rosati A, et al. High cysteine levels in renal transplant recipients: relationship with hyperhomocysteinemia and 5,10-MTHFR polymorphism. Transplantation 2001;71:713–5.
28. McCully KS. Vascular pathology of homocysteinemia: implications for the pathogenesis of arteriosclerosis. Am J Pathol 1969;56: 111–28.
29. McCully KS, Wilson RB. Homocysteine theory of arteriosclerosis. Atherosclerosis 1975;22:215–27.
30. Ueland PM, Refsum H, Beresford SAA, Vollset SE. The controversy over homocysteine and cardiovascular risk. Am J Clin Nutr 2000; 72:324–32.
31. Brattström L, Wilcken DE. Homocysteine and cardiovascular disease: cause or effect? Am J Clin Nutr 2000;72:315–23.
32. Hultberg B, Andersson A, Arnadottir M. Reduced, free and total fractions of homocysteine and other thiol compounds in plasma from patients with renal failure. Nephron 1995;70:62–7.
33. Demuth K, Drunat S, Girerd X, Moatti N, Paul JL, Safar M, et al. Homocysteine is the only plasma thiol associated with carotid artery remodeling. Atherosclerosis 2002;165:167–74.