Review Article

The Role of Homocysteine in Multisystem Age-Related Problems: A Systematic Review

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Homocysteine is a sulfur-containing amino acid that is involved in one-carbon metabolism. Hyperhomocysteinemia is a common phenomenon among elderly people. There is growing evidence of an association between hyperhomocysteinemia and geriatric multisystem problems, including coronary artery disease, stroke, peripheral vascular disease, cognitive impairment, dementia, depression, osteoporotic fractures, and functional decline. The proposed mechanisms of the association include angiotoxicity, neurotoxicity, and inhibition of collagen cross-linking. A homocysteine-lowering strategy may prevent or slow the development of these age-related problems. Vitamin supplementation and folic acid fortification of grain foods have been shown to decrease plasma homocysteine concentrations. More research is needed to investigate whether lifelong homocysteine lowering can prevent the development of late-life morbidity.

Hyperhomocysteinemia and homocystinuria due to abnormal homocysteine metabolism were first described by Carson and Neill in 1962 (1). Patients with this inborn error of metabolism usually manifest mental retardation, lens dislocation, skeletal abnormalities, and early thrombotic events (2). In 1969, McCully proposed that hyperhomocysteinemia may be a vascular risk factor. This proposition was based on autopsy evidence in two children with hyperhomocysteinemia and homocystinuria who had widespread arteriosclerotic changes (3). McCully’s hypothesis was supported by subsequent studies (4,5) linking hyperhomocysteinemia to peripheral vascular, cerebrovascular, and coronary artery disease (CAD). Recently, elevations in plasma homocysteine have also been shown to be associated with common problems seen with aging, such as cognitive impairment, dementia, depression, osteoporotic fractures, and functional decline. In this article we will review this evidence, and argue that public attention to lowering plasma homocysteine throughout life may reduce much of the morbidity and mortality associated with aging.

The normal range of plasma homocysteine level is 5–15 μmol/L. Hyperhomocysteinemia is defined as a plasma homocysteine level >15 μmol/L and is classified as moderate (15–30 μmol/L), intermediate (30–100 μmol/L), or severe (>100 μmol/L) (4). The prevalence of hyperhomocysteinemia in the general population is between 5% and 10% (6). However, the rate may be as high as 30% in the elderly population (older than 65 years), according to the Framingham Study (7). The prevalence of hyperhomocysteinemia may have declined in the United States since dietary fortification with folic acid began in 1996. Data from the Framingham Offspring Study cohort showed that the prevalence of hyperhomocysteinemia in individuals evaluated after the widespread institution of folate fortification has decreased by approximately 50% (8).

Homocysteine Metabolism and Determinants of Homocysteine Levels

Homocysteine is a sulfur-containing amino acid derived from the metabolism of methionine, an essential amino acid. Homocysteine is metabolized by one of two pathways: remethylation or transulfuration (Figure 1). Plasma homocysteine levels are determined by several factors described below.

Lifestyle and Physiologic Determinants

Homocysteine levels increase with age, are higher in men than in women (9), and are influenced by renal function (10). Renal impairment raises plasma homocysteine levels by reducing homocysteine clearance (11). The Nordland Homocysteine Study was the first population-based study to reveal homocysteine-determining lifestyle factors. The study showed that male sex, smoking status, high coffee consumption, lack of exercise, and older age are associated with elevated homocysteine levels (12). Alcohol intake and serum creatinine levels were two additional determinants according to the Framingham Offspring Study (13).
explaining 67% of the cases of hyperhomocysteinemia. Determinants of plasma homocysteine levels in older adults, vitamin B12, and vitamin B6 (as well as their intake) were primary and concluded that plasma concentrations of folate, vitamin B12, and regular use of vitamin B supplements were inversely associated with homocysteine levels (13). Selhub and colleagues (7) examined the Framingham Study cohort associated with homocysteine levels (12). The Framingham Offspring Study further examined the correlation between homocysteine levels and intake of different vitamin nutrients by using nutrition questionnaires. They demonstrated that intake of folate was a strong negative determinant of homocysteine metabolism, such as folate, vitamin B12, and vitamin B6, may lead to hyperhomocysteinemia (Figure 1).

**Figure 1.** Homocysteine metabolism. In the remethylation pathway, methionine synthase (MS), a vitamin B12-dependent enzyme, catalyzes the transfer of a methyl group from N5-methyl-tetrahydrofolate to homocysteine, forming methionine and tetrahydrofolate. Tetrahydrofolate accepts single carbon units from serine to form N5,N10-methylene-tetrahydrofolate and glycine. N5,N10-methylene-tetrahydrofolate reductase (MTHFR) catalyzes N5,N10-methylene-tetrahydrofolate to form N5-methyl-tetrahydrofolate, the methyl donor in the remethylation cycle. In the transulfuration pathway, homocysteine reacts with serine, under action of vitamin B6-dependent enzyme cystathionase β-synthase (CBS), to form cystathionine. Cystathionine is then catalyzed by cystathionase to form cysteine, a rate-limiting precursor for glutathione synthesis. MS = methionine synthase.

**Nutrition**

Nutritional deficiencies in vitamin cofactors required for homocysteine metabolism, such as folate, vitamin B12, and vitamin B6, may lead to hyperhomocysteinemia (Figure 1). The Hordaland Homocysteine Study assessed nutrient intake in 11,941 healthy participants aged 40–67 years by using nutrition questionnaires. They demonstrated that intake of folate was a strong negative determinant of homocysteine levels (12). The Framingham Offspring Study further examined the correlation between homocysteine levels and intake of different vitamin nutrients by using a validated food-frequency questionnaire. Dietary intake of B vitamins (including folate, vitamin B6, and riboflavin) and regular use of vitamin B supplements were inversely associated with homocysteine levels (13). Selhub and colleagues (7) examined the Framingham Study cohort and concluded that plasma concentrations of folate, vitamin B12, and vitamin B6 (as well as their intake) were primary determinants of plasma homocysteine levels in older adults, explaining 67% of the cases of hyperhomocysteinemia.

**Genetic Determinants**

A thermolabile variant of N5,N10-methylene-tetrahydrofolate reductase (MTHFR), caused by a cytosine (C) to thymine (T) point mutation at nucleotide 677 (C677T), leads to the substitution of valine for alanine (14). This mutation reduces MTHFR activity by 50%, predisposing to hyperhomocysteinemia. Homozygosity for MTHFR C677T has been found in 8% of Caucasian, 1.5% of African-American, and 13% of Hispanic people (15). Individuals homozygous for the T allele with folate levels above the median do not demonstrate hyperhomocysteinemia (16). Under conditions of folate deficiency, this mutation causes mild-to-moderate hyperhomocysteinemia (17), indicating a gene–nutrient interaction. Other genetic defects, including cystathionine β-synthase deficiency and MTHFR deficiency, will result in severe hyperhomocysteinemia and homocystinuria. Their occurrences are extremely rare.

**Other Associations**

Hypothyroidism raises plasma homocysteine levels, which may be attributed in part to reduced renal function in hypothyroidism (18). Hyperhomocysteinemia has been described in patients with rheumatoid arthritis (19), psoriasis (20), and cancer, including breast, ovarian, and pancreatic cancer, and acute lymphoblastic leukemia (21). The underlying mechanisms are not clear. Numerous drugs can increase homocysteine levels through interference with the vitamin cofactors in homocysteine metabolism. Methotrexate depletes folate, causing hyperhomocysteinemia (22). Anticonvulsants, such as phenytoin, carbamazepine, and valproic acid, also impair folate metabolism and lead to hyperhomocysteinemia (23). Several other drugs, such as theophylline, isoniazid, and hydralazine, may increase plasma homocysteine by inhibiting the synthesis of vitamin B6 (24). Nitrous oxide, an anesthetic agent, inhibits methionine synthase activity and raises homocysteine levels (20).

**METHODS OF ARTICLE IDENTIFICATION FOR RELATIONSHIP BETWEEN HOMOCYSTEINE AND AGE-RELATED PROBLEMS**

We searched the MEDLINE (January 1966 through March 2004) databases by using combinations of the following terms: “cardiovascular diseases,” “peripheral vascular diseases,” “dementia,” “cognitive impairment,” “cognition disorders,” “depression,” “falls,” “physical function,” “functional decline,” “musculoskeletal equilbrium,” “osteoarthritis fracture,” and “homocysteine,” both as key words and mapped to relevant Medical Subject Headings (MeSH) terms when possible. Only English-language journals were examined. Additional references were found by reviewing bibliographies from identified articles. Individual articles had to meet the following criteria to be included: (1) articles examining the relationship between homocysteine and age-related problems, including CAD, stroke, carotid artery disease, peripheral arterial disease, cognitive impairment, depression, functional decline, and osteoporotic fracture; and (2) studies or reviews based on older adults (age 55 years of older). Information of relevant articles was retrieved according to a standardized format.

**HOMOCYSTEINE AND AGE-RELATED PROBLEMS**

The various systems affected by homocysteine elevation and the proposed mechanisms underlying these effects are summarized in Figure 2 and discussed below.
Vascular Diseases

Traditional cardiovascular risk factors explain about 50%–60% of the variation in vascular disease occurrence (25). Hyperhomocysteinemia is an independent risk factor for CAD (26) and myocardial infarction (MI) (27). Elevated homocysteine level is a strong independent predictor of cardiac events and mortality in patients with angiographically confirmed CAD (28,29) and acute coronary syndromes (30). Hyperhomocysteinemia plays an important role in development of cerebrovascular disease (31) and cerebral small-vessel disease or leukoaraiosis (32,33). In addition, several meta-analyses concluded that homocysteine is an independent risk factor for CAD (34,35), cerebrovascular disease (34–36), and peripheral arterial disease (34). However, the majority of these studies were conducted in middle-aged individuals. Data from older people are relatively sparse. The major longitudinal studies examining the association between homocysteine and vascular disease in older adults are summarized in Table 1.

CAD and MI.—Cross-sectionally, elevated homocysteine level has been shown to be associated with increased baseline prevalence of CAD in a group of long-term care patients (37) and community-dwelling elderly people (38). The Zutphen Elderly Study (39) showed that an elevated homocysteine level was associated with an increased prevalence of MI. Several prospective studies suggested that hyperhomocysteinemia has a causal role in the development of CAD (40) and MI (41,42). Additionally, elevated homocysteine levels predicted cardiovascular hospitalization (43) and both cardiovascular death and all-cause mortality among elderly people (44–46).

Stroke.—In several cross-sectional studies, an elevated homocysteine level was associated with the prevalence of stroke (39,47), silent brain infarcts (48,49), cerebral white matter lesions (leukoaraiosis) (48,50), and cerebrovascular disease risk including history of stroke or MI (51,52). Several longitudinal follow-up studies suggested a causal role of hyperhomocysteinemia in stroke. The Framingham Study (53), the Rotterdam Study (41), and Aronow and colleagues (54) showed that elevated homocysteine level was an independent risk factor for incident stroke. In the longitudinal Zutphen Elderly Study, hyperhomocysteinemia was found to be a strong predictor for fatal cerebrovascular disease in normotensive men. The Rotterdam Scan Study showed that an elevated homocysteine level was marginally associated with new silent brain infarcts in persons without prevalent infarcts (55). In another study of 1039 stroke patients, plasma homocysteine measured within 24 hours of acute stroke independently predicted recurrent stroke within 15 months (56).

Carotid artery disease and peripheral arterial disease.—A significant cross-sectional association between elevated homocysteine levels and extracranial carotid artery disease has been established by several western studies (52,57–59). Two studies conducted in Japanese elderly people also supported this notion (60,61). Two cross-sectional studies, Aronow and Ahn (62) and Darius and colleagues (63), found that elevated homocysteine plasma levels were related to peripheral arterial disease in older adults. The Rotterdam Study found that persons with elevated homocysteine levels had a lower ankle–arm index (52), indicating peripheral atherosclerosis. No prospective studies have been conducted to examine the potential causal relationship between hyperhomocysteinemia and either carotid artery disease or peripheral arterial disease.

Pathophysiologic mechanisms of vascular disease in hyperhomocysteinemia.—Several mechanisms have been proposed for the development of vascular disease in patients with hyperhomocysteinemia. These arise from observations in patients with homocystinuria, animal experiments, and in vitro studies. Targets of homocysteine include endothelial cells, platelets, vascular smooth muscle cells, blood lipids, coagulation factors, and nitric oxide. Hyperhomocysteinemia-induced arteriosclerosis is characterized by endothelial injury followed by significant platelet activation and thrombus formation (64). Homocysteine is rapidly auto-oxidized in plasma, and potent oxidative products including superoxide and hydrogen peroxide are generated (65). These oxidative products promote endothelial damage (65) and oxidative modification of low-density lipoprotein (66), resulting in the formation of foam cells. Homocysteine promotes proliferation of vascular smooth muscle cells by inducing cyclin A gene expression (67) and hence contributes to atherosclerosis. Homocysteine also creates a prothrombotic environment by activating factor V (68), reducing protein C activation (69), inactivating expression of thrombomodulin.
Table 1. Major Longitudinal Studies of Homocysteine as a Risk Factor for Vascular Diseases in Older Adults

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<th>Reference</th>
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<tr>
<td>Stehouwer et al. (39)</td>
<td>CS and Pros</td>
<td>878 elderly men (mean age 71.5 years, range 64–84) from the Zutphen Elderly Study followed for 10 y</td>
<td>CAD, MI, stroke, and vascular mortality</td>
<td>Age, BMI, systolic blood pressure, total and HDL Chol, DM, and smoking status</td>
<td>CS analysis: Elevated Hcy (≥17 μmol/L) was associated with increased prevalence of MI (OR 1.81; CI, 1.07–3.08) and stroke (OR 4.61; CI, 1.79–11.89). Longitudinal analysis: Elevated Hcy (≥17 μmol/L) predicted fatal cerebrovascular disease in normotensive men (RR 6.18; CI, 2.28–16.76).</td>
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<tr>
<td>Aronow et al. (40)</td>
<td>Pros</td>
<td>500 elderly patients (age 81 ± 8 y, range 60–99) in a long-term care facility followed for 31 mo</td>
<td>New coronary events</td>
<td>Age, smoking status, HTN, DM, triglycerides, total and HDL Chol</td>
<td>RRs for new coronary events were 1.07 (CI, 1.03–1.11) and 1.11 (CI, 1.05–1.17) for each 1 μmol/L increase in Hcy level in persons with prior CAD and without CAD, respectively.</td>
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<tr>
<td>Nurk et al. (43)</td>
<td>Pros</td>
<td>2127 persons 65–67 y from the Hordaland Homocysteine Study with mean follow-up 5.3 y</td>
<td>Cardiovascular disease hospitalization</td>
<td>Age, sex, smoking status, DM, Chol, BMI, and systolic blood pressure</td>
<td>Hospitalization RRs in five Hcy categories (&lt;9, 9–11.9, 12–14.9, 15–19.9, and ≥20 μmol/L) were 1 (reference), 1.34, 1.67, and 1.94 (p for trend &lt;.001).</td>
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<tr>
<td>Boston et al. (44)</td>
<td>Pros</td>
<td>1933 elderly persons (age 70 ± 7 y, range 59–91 y) from the Framingham Study cohort followed for &gt;10 y</td>
<td>Cardiovascular and all-cause mortality</td>
<td>Age, sex, DM, smoking status, systolic blood pressure, total and HDL Chol</td>
<td>Elevated Hcy (≥14.26 μmol/L) predicted both cardiovascular death (RR 1.52; CI, 1.16–1.98) and all-cause mortality (RR 1.54; CI, 1.31–1.82).</td>
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<tr>
<td>Kark et al. (45)</td>
<td>Pros</td>
<td>1788 residents of Jerusalem (≥50 y of age) followed for &gt;9 y</td>
<td>Cardiovascular and all-cause mortality</td>
<td>Age, smoking status, systolic blood pressure, Chol, HDL, glucose</td>
<td>Hazard ratios for cardiovascular mortality and all-cause mortality were 1.81 (CI, 1.19–2.76) and 1.70 (CI, 1.28–2.25) with 1 unit increase in the natural logarithm of Hcy.</td>
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<tr>
<td>Vollset et al. (46)</td>
<td>Pros</td>
<td>4766 persons age 65–72 y from the Hordaland Homocysteine Study with a median follow-up of 4.1 y</td>
<td>Cardiovascular and all-cause mortality</td>
<td>Age, sex, Chol, systolic and diastolic blood pressure, smoking status, BMI, and physical activity</td>
<td>An Hcy increment of 5 μmol/L was associated with a 50% (CI, 21% to 85%) increase in cardiovascular mortality and a 49% (CI, 28% to 72%) increase in all-cause mortality</td>
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<td>Bostom et al. (53)</td>
<td>Pros</td>
<td>1941 Framingham Study participants (age 70 ± 7 y) followed for 9.9 y</td>
<td>Stroke</td>
<td>Age, sex, DM, smoking status, systolic blood pressure, history of CAD or atrial fibrillation</td>
<td>RR for incident stroke was 1.82 (CI, 1.14–2.91) comparing persons in the highest quartile of homocysteine levels to those in the lowest quartile. Linear trend across the quartiles was significant (p &lt; .001).</td>
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<tr>
<td>Aronow et al. (54)</td>
<td>Pros</td>
<td>500 elderly patients (age 81 ± 9 y, range 60–99 y) in a long-term care facility followed for 31 mo</td>
<td>Stroke</td>
<td>Age, smoking status, prior ischemic stroke, HTN, and DM</td>
<td>RR of new brain infarction was 1.08 (CI, 1.04–1.12) with each 1 μmol/L increase in Hcy levels.</td>
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<tr>
<td>Vermeer et al. (55)</td>
<td>Pros</td>
<td>1077 persons from the Rotterdam Scan Study (age 72.2 ± 7.4 y, range 60–90 y)</td>
<td>Silent brain infarct</td>
<td>Age, sex</td>
<td>Homocysteine levels were marginally associated with new silent brain infarcts in persons without prevalent infarcts. OR of new silent brain infarct was 1.31 (CI, 0.95–1.82) with each 1 standard deviation increase in Hcy levels.</td>
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<tr>
<td>Boysen et al. (56)</td>
<td>Pros</td>
<td>1039 elderly patients (mean age 75 y) with acute stroke followed for 15 mo</td>
<td>Recurrent stroke</td>
<td>Age, sex, smoking status, prior stroke or TIA, DM, CAD, HTN, and severity of neurological deficit</td>
<td>OR of recurrent stroke was 1.3 (CI, 1.1–1.5) with each 10 μmol/L increase in Hcy levels.</td>
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<td>Bots et al. (41)</td>
<td>Nested CC with incident case sampling</td>
<td>104 MI cases (age 71.8 ± 8.0 y), 120 stroke cases (age 76.5 ± 8.4 y), and 533 controls (age 67.9 ± 7.2 y) from the Rotterdam Study</td>
<td>MI and stroke</td>
<td>Age, sex, and smoking status</td>
<td>RRs for MI and stroke were 2.46 (CI, 1.11–5.42) and 2.30 (CI, 1.08–4.9) comparing persons in 5th quintile of homocysteine levels to those in 1st quintile. Adjustment for other cardiovascular factors (previous MI and stroke, DM, HTN, and Chol) attenuated the significance level.</td>
</tr>
<tr>
<td>Ridker et al. (42)</td>
<td>Nested CC with incident case sampling</td>
<td>122 postmenopausal cases (mean age 59.3 y) and 244 age-matched postmenopausal controls from the Women's Health Study with a mean 3 y of follow-up</td>
<td>Cardiovascular death, nonfatal MI, stroke, coronary angioplasty, or coronary bypass graft</td>
<td>Self-reported multivitamin supplement, BMI, exercise frequency, HTN, hyperlipidemia, DM, and family history of premature MI</td>
<td>RRs for any cardiovascular event and MI or stroke were 2.3 (CI, 1.2–4.3) and 2.4 (CI, 1.2–5.0) comparing persons in highest quartile of homocysteine levels to those in lowest quartile.</td>
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Notes: *Plus-minus values are means ± standard deviation.

BMI = body mass index; CAD = coronary artery disease; CC = case–control study; Chol = cholesterol; CI = 95% confidence interval; CS = cross-sectional study; Pros = prospective study; DM = diabetes mellitus; Hcy = homocysteine; HDL = high-density lipoprotein; HTN = hypertension; MI = myocardial infarction; OR = odds ratio; RR = risk ratio.
(70), inducing expression of tissue factor (71), suppressing anticoagulant heparin sulfate expression (72), and blocking tissue plasminogen activator binding to endothelial cells (73). Finally, homocysteine depletes endothelium-derived nitric oxide and reduces its production (74), further impairing endothelial function.

In conclusion, hyperhomocysteinemia is a risk indicator for vascular diseases in older adults. A causal association between hyperhomocysteinemia and carotid and/or peripheral artery disease in elderly people remains to be established.

Cognitive Impairment

Progressive cognitive decline and dementia are common in old age. The prevalence of dementia in those aged 65 or older is estimated to range from 6% to 10% (75). Alzheimer’s disease (AD) and vascular dementia (VaD) are the two most common forms of dementia, comprising approximately 70% and 20%, respectively, of all dementia cases (75,76). Homocysteine has been proposed as a neurotoxin (77), and the notion that homocysteine may be an important risk factor for cognitive impairment has recently attracted research interest. Follow-up studies of the association between homocysteine and cognition in older adults are summarized in Table 2.

Dementia.—Hyperhomocysteinemia is a common finding in psychogeriatric patients (78). In case–control studies by Joosten and colleagues (79) and McCaddon and colleagues (80), patients with AD had significantly higher homocysteine levels than did controls. More convincing evidence for the association was reported by Clarke and colleagues (81), who found that patients in the upper third of the serum homocysteine distribution had a 5-fold elevated risk of histologically confirmed AD compared with patients in the bottom third of the distribution.

In addition to AD, many case–control studies have demonstrated that elevated homocysteine levels are associated with VaD. Leblhuber (82), Bottiglieri (83), Nagga (84) and their colleagues showed that homocysteine levels were significantly higher in patients with VaD and AD than in controls. However, these studies were criticized because they did not adjust for cardiovascular risk factors and determinants of homocysteine levels. McIlroy and colleagues (85), by appropriately controlling for potential confounders, concluded that moderately high homocysteine levels are independently associated with VaD and AD.

Although there is a cross-sectional association between hyperhomocysteinemia and dementia (78–85), this association does not indicate causation. Seshadri and colleagues (86) followed the Framingham Study cohort over a median of 8 years and concluded that an increased plasma homocysteine level is a strong, independent risk factor for the development of dementia and AD.

Global cognition and individual cognitive domains.—Elevation of plasma homocysteine has been reported to affect global cognition as well as specific cognitive domains. Many population-based cross-sectional studies (87–92) have shown that plasma homocysteine levels are inversely related to global cognitive function. Certain cognitive domains, such as executive function, are selectively impaired by cardiovascular risk factors (93,94). Budge and colleagues (89) and Morris and colleagues (95) reported a cross-sectional association between elevated homocysteine levels and memory impairment. More studies have reported a negative relationship between homocysteine levels and executive function (including psychomotor speed and attention, abstract thinking, mental flexibility, and multitasking) or visuospatial performance (such as spatial copying skill, spatial organization ability, and pattern recognition ability), both of which require intact frontal–subcortical circuits and are sensitive to increased loads of cardiovascular risk. The Sacramento Area Latino Study on Aging (SALSA) (91) suggested that homocysteine levels were inversely related to both executive functions and visuospatial performance. Another population-based study by Duthie and colleagues (96) supported this finding by examining a group of individuals born in 1921. The Normative Aging Study (97) found a negative association between homocysteine levels and visuospatial performance, while the Rotterdam Scan Study (90) suggested that homocysteine was inversely related to executive function.

Several prospective studies have suggested a causal relation between hyperhomocysteinemia and impairment in global and selective cognitive functions. McCaddon and colleagues (98) found that homocysteine independently predicted global cognition, word recall, orientation, and constructional praxis scores over a 5-year period. The Epidemiology of Vascular Aging Study (92) found that elevated plasma homocysteine was a significant predictor for decline in both global cognition and executive function for over 4 years. The Rotterdam Study by Kalmijn and colleagues (99), however, did not show a significant association between elevated homocysteine levels and cognitive decline, but their follow-up period of 2.7 years was relatively short.

Mechanism of hyperhomocysteinemia-related cognitive impairment.—Homocysteine exhibits angioxicity that may lead to large- or small-vessel disease in the brain, eventually causing cognitive impairment. Additionally, hyperhomocysteinemia may cause cognitive impairment via direct neurotoxicity. Recent studies have shown that homocysteine can be directly toxic to cultured human and murine neuronal cells (77,100). Homocysteine stimulates N-methyl-D-aspartate (NMDA) receptors, resulting in calcium influx and excitotoxicity (100). Excitotoxicity may also be enhanced via homocysteine-related potentiation of glutamate neurotoxicity (100). Homocysteine also enhances β-amyloid toxicity (101) and causes tau hyperphosphorylation (102). It has also been reported to impair DNA repair in hippocampal neurons (103) and induce apoptosis by eliciting DNA damage (77). Anatomically, hyperhomocysteinemia is associated with cerebral cortical and hippocampal atrophy (104,105), potentially resulting in cognitive decline.

In conclusion, hyperhomocysteinemia is associated with cognitive decline and increased risk of dementia in elderly people. Although most of the studies have controlled for
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<th>Results</th>
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</thead>
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<tr>
<td>Seshadri et al. (86)</td>
<td>Pros</td>
<td>1097 elderly persons from the Framingham Study cohort (mean 76 y) followed for a median period of 8 y</td>
<td>NINDS-ADRDA (AD diagnosis) DSM-IV (dementia diagnosis)</td>
<td>AD and any dementia</td>
<td>Age, sex APOE genotype, vitamin B6/B12, folate, education, history of stroke, smoking status, alcohol intake, diabetes mellitus, BMI, and systolic blood pressure</td>
<td>RRs for AD and any dementia were 1.8 (CI 1.3–2.5) and 1.4 (CI 1.1–1.9) per increment of 1 standard deviation in the log-transformed Hcy value.</td>
</tr>
<tr>
<td>McCaddon et al. (98)</td>
<td>Pros</td>
<td>32 healthy elderly persons (aged 69–80 y) followed for 5 y</td>
<td>MMSE, ADAS-Cog</td>
<td>Global cognition and individual domains</td>
<td>Age, sex, HTN, smoking status, education, vitamin B12, folate, and serum creatinine</td>
<td>Hcy predicted global cognitive decline. Hcy also predicted word recall (p = .01), orientation (p = .02), and constructional praxis scores (p &lt; .0001)</td>
</tr>
<tr>
<td>Kalmijn et al. (99)</td>
<td>CS and Pros</td>
<td>702 community-dwelling persons (age ≥ 55 y) from the Rotterdam Study followed for a mean duration of 2.7 y</td>
<td>MMSE</td>
<td>Global cognition</td>
<td>Age, sex, and education</td>
<td>CS analysis: There was no association between Hcy and cognitive impairment.</td>
</tr>
<tr>
<td>Dufouil et al. (92)</td>
<td>CS and Pros</td>
<td>1241 healthy elderly persons (67.0 ± 3.0 y) from the Epidemiology of Vascular Aging Study followed-up over 4 y</td>
<td>MMSE, TMT-B, DS, FTT</td>
<td>Global cognition and individual domains</td>
<td>Age, sex, education, BMI, alcohol, smoking status, HTN, Chol, glucose, history of vascular disease, folate, and vitamin B12</td>
<td>CS analysis: Hcy was inversely associated with global cognition (MMSE) and executive function (DS and FTT). Longitudinal analysis: Elevated Hcy predicted decline in global cognition (MMSE) and executive function (DS and FTT).</td>
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Notes: *Plus-minus values are means ± standard deviation.
AD = Alzheimer’s disease; ADAS-Cog = Alzheimer’s Disease Assessment Scale; ADRDA = Alzheimer’s Disease and Related Disorders Association; APOE = apolipoprotein E; BMI = body mass index; Chol = cholesterol; CI = 95% confidence interval; CS = cross-sectional study; DS = digit symbol test; FTT = Finger Tapping Test; Hcy = homocysteine; HTN = hypertension; MMSE = Mini-Mental State Examination; NINDS = National Institute of Neurological Disorders and Stroke; Pros = prospective study; RR = risk ratio; TMT-B = Trail Making Test part B.
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nutritional markers, including folate and vitamin B status, elevated homocysteine levels could be a consequence of deficiencies in other nutritional factors associated with cognitive disorders.

**Depression**

Depression is a common disorder in elderly people with a major impact on public health. Between 1% and 2% of elderly persons carry a diagnosis of major depression (106). However, the prevalence of depressive symptoms not meeting criteria for a major depression is high in elderly people (average prevalence 13.5%) (107). When a depressive episode occurs in late life, a cerebrovascular cause may be more common than genetic or psychological causes. Some studies (108,109) have demonstrated an association between cardiovascular conditions (such as hypertension or transient ischemic attacks) and depression. Homocysteine, by acting as a cardiovascular risk factor, may be associated with, or even lead to, depressive symptoms in old age.

Several studies examined the association between homocysteine and depression in older adults. Investigators in the Women’s Health and Aging Study (110) enrolled 700 physically disabled women (mean age 77.3 years, range 65–100 years) and found that women with higher grades of depression tended to have higher homocysteine levels, although this observation did not achieve statistical significance. However, this study was restricted to physically disabled women, raising the issue of generalizability. The population-based Rotterdam Study (111) screened 3884 elderly people (mean age 72.9 years) and did not find any association between elevated homocysteine levels and depression after multivariable adjustment. Another population-based study, the Hordaland Homocysteine Study (112), cross-sectionally examined the association between homocysteine and depression in 5948 persons aged 46–49 years (mean 47.4 years) and 70–74 years (mean 71.9 years) and found that homocysteine was significantly associated with depression in 4338 elderly persons (70–74 years) after controlling for age and sex.

Depression may be accompanied by anorexia, which may lead to poor nutrition and hyperhomocysteinemia. Hence, the importance of adequate adjustment for possible confounders to pursue an independent association cannot be overemphasized. Because the association between homocysteine and depression is not consistent across all cross-sectional studies in older adults, additional prospective studies are needed.

**Osteoporotic Fracture**

Osteoporosis is characterized by low bone mineral density, or deterioration of bone microarchitectures, resulting in increased risk of fracture. Osteoporotic fracture is becoming a major public health issue as the population ages, and is associated with increased morbidity, mortality, and economic costs. Elevated homocysteine level has been proposed as a potential risk factor for osteoporosis based on the observation that there is an increased prevalence of skeletal deformities, including generalized osteoporosis, in patients with autosomal recessive homocystinuria (113).

Two recent population-based prospective studies support the notion that homocysteine is an important risk factor for osteoporotic fractures in older persons. In the study from The Netherlands, van Meurs and colleagues (114) examined 2406 individuals aged 55 years or older, and found that the risk of osteoporotic fracture increased by 40% for each increase of 1 standard deviation in the homocysteine level after multivariable adjustment. Additionally, a serum homocysteine level in the highest quartile doubled the risk of fracture (114). McLean and colleagues followed 1999 elderly persons in the Framingham Study cohort for more than 10 years, and suggested that plasma homocysteine concentrations were associated with the risk of hip fracture in both men and women. After controlling for potential confounders, the risk ratios for hip fractures in men and women were 3.84 (95% confidence interval [CI], 1.38–10.70) and 1.9 (95% CI, 1.18–3.10), respectively, comparing persons in the highest quartile of homocysteine levels to those in the lowest quartile (115). In the study from The Netherlands, moreover, the effect of high homocysteine levels on the risk of fractures was comparable in magnitude to some well established risk factors of fractures, including low bone mineral density, cognitive impairment, and recent falls (114). These findings can be attributed to the fact that increased homocysteine levels could interfere with collagen cross-linking (116,117), important for the stability and strength of the collagen network, and thus could lead to an increased risk of fracture.

**Physical Function**

Decline in physical function is a common geriatric problem. The incidence of walking difficulty is as high as 40% in noninstitutionalized adults aged 85 and older; among older nursing home residents, it reaches 60% or higher (118). Given the fact that homocysteine is associated with many age-related illnesses, it is reasonable to hypothesize that there is an association between hyperhomocysteinemia and functional decline.

There is one study supporting this notion. The MacArthur Study of Successful Aging was a longitudinal study of successful aging (119) that followed 499 healthy and highly functional community-dwelling people (aged 70–79 years) over 3 years (120). Physical performance was based on gait, balance, lower body strength and coordination, and manual dexterity. People with elevated plasma homocysteine levels had an increased risk of functional decline over 3 years. With each standard deviation increase in homocysteine levels, there was a 50% higher risk of being in the worst quartile of physical function (odds ratio = 1.5; 95% CI, 1.2–1.9) after multivariable adjustment. The mechanism of this relationship is thought to be linked to oxidative damage of endothelial cells, protein, and deoxyribonucleic acid, and accelerated telomere loss (120). Another explanation is that hyperhomocysteinemia is a risk factor for leukoaraiosis (32), which may (a) interrupt frontal lobe circuits responsible for normal gait and balance (121) and (b) interfere with descending motor fibers arising from medial cortical areas, which are important for lower extremity motor control (122).

**HOMOCYSTEINE-LOWERING THERAPY: OPPORTUNITIES FOR PREVENTION?**

Ample evidence indicates that hyperhomocysteinemia is associated with several common age-related syndromes, but
proof of causality can only be established by showing that lowering homocysteine can prevent these problems. Plasma homocysteine levels can be lowered by therapy with B vitamins, such as vitamin B12 and folate, or by folic acid fortification of grain foods. A previous meta-analysis (123) indicated that daily supplementation with both 0.5–5.0 mg of folic acid and 0.5 mg of vitamin B12 could be expected to reduce homocysteine concentrations by about one-quarter to one-third. Folic acid fortification of grain foods, fully implemented since January 1, 1998, has been shown to improve folate status and reduce mean homocysteine levels by 7% in the Framingham Heart Study cohort (8). This policy has been advocated as a cost-effective public health strategy for the prevention of CAD (124). Although homocysteine levels can be lowered effectively, more studies are required to determine whether multivitamin therapy or the folic acid fortification policy can prevent the development of vascular disease, cognitive impairment, dementia, depression, or functional decline in old age.

Homocysteine-lowering therapy has been shown to improve arterial endothelial function. Woo and colleagues (125) found that folic acid supplementation significantly improved endothelium-dependent flow-mediated dilation in asymptomatic hyperhomocysteinemic adults. Chambers and colleagues (126) found that supplementation with folic acid and vitamin B12 improved vascular endothelial function in male CAD patients. By improving arterial endothelial function in humans, folic acid-based vitamin therapy may have therapeutic potential for vascular protection. Observational studies (127–129) have shown that an increase in folic acid intake by vitamin supplementation and fruit and vegetable intake can reduce the risk of stroke and CAD. A randomized, controlled trial (130) showed that multivitamin combination therapy (folate, vitamin B12, and pyridoxine) for 6 months was effective in reducing the rate of cardiovascular events and coronary restenosis in 205 patients after successful percutaneous angioplasty. A recent homocysteine-lowering trial, known as the Vitamin Intervention for Stroke Prevention (VISP) (117), showed no reduction in cardiovascular events in patients with ischemic stroke. The results of the Vitamins to Prevent Stroke (VITATOPS) (131) trial, another ongoing international homocysteine-lowering trial enrolling patients at high risk for cardiovascular and stroke events, are eagerly awaited.

The effect of a folic acid-based supplement on cognitive function was examined by Nilsson and colleagues (132) in an open label trial. They found that patients with mild-to-moderate dementia and hyperhomocysteinemia improved clinically on the Mini-Mental Status Examination and the Short Performance Test, a short cognitive test for assessing memory and attention, after vitamin substitution. Bryan and colleagues (133) conducted a randomized, controlled trial showing that folate, vitamin B12, or vitamin B6 supplementation had a positive effect on memory measures in a group of healthy women aged 20–94 years. Two other randomized, controlled trials (134,135) studying patients with dementia or cognitive impairment did not find cognitive benefit after folic acid supplementation; however, the sample sizes in the two studies were small, and large-scale trials are required to investigate the effect of homocysteine-lowering therapy on cognition. No evidence was found regarding folic acid-based supplementation in the prevention of depression. However, folic acid has been shown to enhance antidepressant action (136) and hasten recovery from episodes of major depression (137). With regard to the association between homocysteine and risk of osteoporosis, fracture or functional decline, a causal relationship cannot easily be ascertained because interventional homocysteine-lowering studies with functional decline or fracture as outcomes are still lacking. In summary, the evidence discussed so far has not yet supported a role for homocysteine-lowering therapy in the prevention of functional decline, osteoporotic fractures, and neuropsychiatric disorders.

Conclusion

Homocysteine has been found to have multisystem effects in older adults, and elevated levels may play a pathophysiologic role in vascular diseases, cognitive decline, dementia, depression, osteoporotic fracture, and functional decline. The proposed mechanisms of these associations include angiototoxicity, neurotoxicity, and inhibition of collagen cross-linking. Hence, homocysteine-lowering agents, such as folic acid and vitamin B12, seem reasonable choices for the prevention and management of these problems. Currently, there is no consensus regarding regular screening for homocysteine levels in the asymptomatic, elderly population. Folic acid supplements and folic acid fortification in food products seem to show promise for the prevention of cardiovascular disease. More studies are needed to document the role of our folic acid fortification policy and vitamin supplementation in primary and secondary prevention of age-related illnesses.

Acknowledgments

Dr. Kuo is supported by the Men’s Associates Fellowship from the Hebrew Rehabilitation Center for Aged, Boston, MA. Dr. Lipsitz holds the Irving and Edyth S. Usen and Family Chair in Geriatric Medicine at the Hebrew Rehabilitation Center for Aged, Boston, MA. The work was supported in part by the National Institutes of Health Grants A604390 and A608812, the National Institute on Aging K12 Grant AG00294, and the Department of Veterans Affairs Medical Research Service. The authors thank Dr. Yau-Hua Yu for editorial assistance and support. Address correspondence to Lewis A. Lipsitz, MD, Hebrew Rehabilitation Center for Aged, 1200 Centre Street, Boston, MA 02131. E-mail: lipsitz@mail.hrca.harvard.edu

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