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Relationship of Homocysteine Levels to Quadriceps Strength, Gait Speed, and Late-Life Disability in Older Adults

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Abstract

Background—Elevated homocysteine, causing tissue injury by such mechanisms as oxidative stress, endothelial damage, and protein homocysteinylation, is associated with multiple age-related problems including cardiovascular diseases, dementia, and osteoporotic fracture. Disability is one of the most common features in older adults. However, little is known about the role of homocysteine in physical disability among older adults.

Methods—Participants (>60 years, *N* = 1677) were from the National Health and Nutrition Examination Survey (NHANES) 1999–2002. Nineteen questionnaires in five major domains were administered to assess the level of difficulty in performing various tasks: activities of daily living (ADL), instrumental ADL (IADL), leisure and social activities (LSA), lower extremity mobility (LEM), and general physical activities (GPA). Peak quadriceps strength was obtained by using an isokinetic dynamometer. Habitual gait speed was obtained from a 20-foot timed walk. Homocysteine levels were measured by the Abbott homocysteine assay, an automated fluorescence polarization immunoassay (FPIA).

Results—Elevated homocysteine was associated with disability in ADL, IADL, LSA, and GPA after multivariate adjustment. The odds ratios (ORs) for disability in these domains comparing participants in the highest quartile of homocysteine to those in the lowest were 2.18 (95% confidence interval [CI], 1.32–3.59) for ADL; 1.62 (95% CI, 1.02–2.57) for IADL; 2.00 (95% CI, 1.14–3.51) for LSA; and 1.52 (95% CI, 1.05–2.21) for GPA. The strength of associations weakened somewhat after additional adjustment of quadriceps strength and/or gait speed, suggesting a mediating role of quadriceps strength and gait speed in the association between homocysteine and disability. Homocysteine had an inverse relationship to quadriceps strength and gait speed. Likewise, quadriceps strength seemed to mediate the inverse association between homocysteine and gait speed.

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Conclusions—Elevated homocysteine is associated with multiple domains of disability mediated in part by muscle strength and gait speed. The results suggest that homocysteine levels may be important indicators of performance status in older adults.

Homocysteine is a sulfur-containing amino acid that is derived from the metabolism of methionine, an essential amino acid. Before introduction of mandatory folic acid fortification of cereal-grain products, the prevalence of hyperhomocysteinemia had been reported to be between 5% and 10% in the general population (1) and as high as 33% in people aged 65 and older (2). In the postfortification era, elevated homocysteine levels remain a common feature among U.S. elderly adults. According the National Health and Nutrition Examination Survey (NHANES) 1999–2000, 5% of the U.S. population, 18% of elderly men, and 11% of elderly women had plasma homocysteine concentrations > 13 μmol/L (3). Elevated homocysteine, causing angiotoxicity and atherosclerosis by targeting endothelial cells, platelets, vascular smooth muscle cells, blood lipids, coagulation factors, and nitric oxide, has been demonstrated to be an important risk factor for various cardiovascular diseases (4,5).

Abundant data support the notion that elevated homocysteine levels are linked to several multisystem geriatric problems (6), including dementia and Alzheimer's disease (7), osteoporotic fracture (8,9), and decline in physical function (10). With life expectancy reaching its historic pinnacle, disability and loss of independence have become common features in an aging society (11). Although homocysteine is associated with several aging phenotypes, data examining the relationship of homocysteine to disability are very sparse and limited to acute hospitalized elderly persons (12).

Physical performance measures including muscle strength and gait speed have been demonstrated to be important predictors for the development of disability in elderly people (13–17). However, there are no existing data showing the roles of muscle strength and gait speed in the association between homocysteine and late-life disability. We hypothesized that higher levels of homocysteine are associated with disability in community-dwelling elderly persons and that muscle strength and gait speed may mediate the association between homocysteine and disability. We sought to test the hypotheses by analyzing data from the NHANES 1999–2002.

Methods

Data Source

The NHANES, a population-based survey, used a stratified, multistage, and cluster-sampling design to obtain a representative sample of the noninstitutionalized U.S. civilian population. NHANES consists of a detailed home interview and a health examination conducted in a mobile examination center (MEC). Data sets, survey operations manuals, consent documents, and brochures of the NHANES 1999–2002 are available on the NHANES Web site (18,19).

Self-Reported Disability

Nineteen questions in five major domains, shown in Table 1, were administered to assess the level of difficulty in performing various tasks: activities of daily living (ADL), instrumental ADL (IADL), leisure and social activities (LSA), lower extremity mobility (LEM), and general physical activities (GPA). Response options for each disability item were “no difficulty,” “some difficulty,” “much difficulty,” or “unable to do.” Disability was defined as any difficulty in performing one or more activities in a given domain.

Measures of Isokinetic Quadriceps Strength and Habitual Gait Speed

A Kinetic Communicator (Kin Com) isokinetic dynamometer (Chattecx Corp., Chattanooga, TN) was used to evaluate right quadriceps strength. The participant was asked to sit on the dynamometer chair with the back supported and to keep hands in the lap during the examination. A stabilizing strap was attached across the chest and the pelvis to help stabilize the participant in the chair. A thigh strap and shin pad were attached after the participant was positioned in the dynamometer chair. A goniometer (instrument used to measure joint angles) was used to measure the angle of the knee joint when the participant was positioned in the dynamometer chair. The start and stop angles of the isokinetic quadriceps strength test were set at 90° and 150°, respectively. The participant was asked to push the shin pad forward through the full range of motion of the right leg. Strength of the knee extensor muscles was tested by measuring peak torque of the quadriceps at one angular velocity speed (60°/s). Ideally, each participant would have a total of 6 trials during the strength test: 3 practice warm-ups and 3 trials for maximal voluntary effort. Highest peak force (PF) in Newtons was obtained according to the following algorithm: for examinees with > 4 trials, the highest PF was selected from Trials 4–6 (trials for maximal voluntary effort); for examinees with < 4 trials, a highest PF was selected from the completed trials (warm-up trials). Peak force velocity (PFVel) refers to the peak angular velocity (degrees [°]/s) recorded when peak quadriceps strength was measured. Most participants would have the PFVel closely approximating the chosen testing velocity (60°/s). Further details regarding this component of the NHANES assessment can be found in the NHANES Muscle Strength Procedures Manual (20).

The 20-foot timed walk test was performed at the participant's usual pace. Participants were allowed to use a walker or cane if needed. Habitual gait speed (m/s) was calculated as walking distance (20 feet = 6.15 m) divided by time in seconds.

Measurements of Homocysteine

Blood specimens were collected at the MECs and were frozen before analysis. Plasma homocysteine was measured by the Abbott homocysteine assay, a fully automated fluorescence polarization immunoassay (FPIA). Plasma total homocysteine concentrations were calculated by the Abbott IMx Immunoassay Analyzer using a machine-stored calibration curve. The FPIA method, used by the NHANES as a primary tool to determine homocysteine levels, was fully equivalent to other frequently used methods such as high performance liquid chromatography (HPLC) (21).

Selection of Study Population

The 20-foot timed walk test along with the isokinetic quadriceps strength test were completed in 2107 participants 60 years old or older without safety concerns (recent chest or abdominal surgery, heart attack in the past 6 weeks, brain aneurysm or stroke, current neck or back pain, difficulty in bending or straightening right knee, or right knee or right hip replacement) or any administrative, communicative, or technical problems. The NHANES isokinetic muscle testing was measured at an angular velocity of 60°/s. Participants (n = 370) with PFVel that varied >5°/s from the chosen testing velocity (60°/s), i.e., greater than 65°/s or less than 55°/s, might not have worked well with the isokinetic dynamometer and were thus excluded, leaving 1753 participants with reliable measures of quadriceps peak torque. Compared to participants with PFVel varied >5°/s from 60°/s when taking the muscle strength test (370 participants), participants with reliable measures of muscle strength (1737 participants) tended to be younger (mean age 70.2 years vs 72.3 years; $p < .001$), male (64.6% vs 46.2%; $p < .001$), and less disabled ($p < .01$) in all disability domains. Sixty of the 1737 participants were excluded because of missing values in homocysteine (59 participants) or self-report functional status (1 participant), leaving 1677 participants in the final analytic sample.

Covariates

Age, gender, race/ethnicity, and educational level were obtained by self-report. Diabetes was defined by self-report of a physician's diagnosis, the presence of a random plasma glucose level > 200 mg/dL, or use of diabetic medications (including insulin injection and/or oral hypoglycemic agents). Three and sometimes four blood pressure (BP) determinations were taken using a mercury sphygmomanometer by a NHANES physician. BP was measured in the right arm unless specific conditions prohibited the use of the right arm. Averaged systolic and diastolic BPs were obtained. The presence of hypertension was defined by self-reported doctor's diagnosis, use of antihypertensive medications, or averaged BP > 140/90 mmHg. In addition to diabetes mellitus and hypertension, other medical comorbidities including myocardial infarction (>6 weeks), coronary heart disease, congestive heart failure, chronic bronchitis, emphysema, and arthritis were ascertained by self-report. Body mass index (BMI), calculated as weight in kilograms divided by the square of height in meters, was categorized according to the National Institutes of Health obesity standards: <18.5 = underweight, 18.5–24.9 = normal weight, 25.0–29.9 = overweight, and >30 = obese (22). A 2-minute timed Digit Symbol Substitution test was administered to determine cognitive function. Cognitive impairment was defined as a score of 45 (median) or lower on the Digit Symbol Substitution test. Current smoker was defined by an affirmative response to the question “Do you now smoke cigarettes, pipes, or cigars?” Alcohol intake was determined by an affirmative response to the question “In any one year, have you had at least 12 drinks of any type of alcohol beverage?” and was dichotomized. Serum vitamin B_{12} and folate levels were measured by using the Bio-Rad Laboratories “Quantaphase II Folate/vitamin B_{12}” radioimmunoassay kit. Serum creatinine was measured using a standard biochemistry method.

Analysis

We divided homocysteine levels into quartiles, and participants in the lowest quartile were the reference group. Multiple logistic regression was used to examine the relationship between homocysteine and disability in ADL, IADL, LSA, LEM, or GPA. We used an extended-model approach for covariate adjustment: Model 1 = age, sex, race, BMI category, educational level, smoking status, alcohol intake, presence of comorbidities (diabetes, hypertension, myocardial infarction, congestive heart failure, coronary heart disease, chronic bronchitis, emphysema, arthritis, and cognitive impairment), as well as levels of folate, vitamin B_{12}, and serum creatinine; Model 2 = Model 1 + peak quadriceps strength; Model 3 = Model 1 + habitual gait speed; Model 4 = Model 1 + peak quadriceps strength + habitual gait speed.

We also assessed the relationship of homocysteine levels and performance-based physical measures, specifically quadriceps strength and habitual gait speed, by using multiple linear regression while adjusting for covariates in Model 1. Given the fact that muscle strength is a proximal pathway component in the impairment–disability pathway, we additionally adjusted for quadriceps strength in the association between homocysteine and habitual gait speed to observe possible change of association. Effect modification of sex was examined by testing the Sex × Homocysteine interaction.

Because the NHANES population weights are only applicable to analyses that use the entire population and we limited our analyses to a special subset of participants, we did not use the NHANES 1999–2002 population weights for the purposes of this study. Data management and analysis were performed using STATA 8.0 software (STATA Corporation, College Station, TX).

Results

Characteristics of Study Population

Selected baseline characteristics of the study participants as a whole (N = 1677, mean age 70.2 years) and by quartiles of homocysteine levels are summarized in Table 2. The quartile-based homocysteine levels among the study population were: <7.42 μmol/L, 7.42–9.06 μmol/L, 9.07–11.25 μmol/L, and >11.25 μmol/L, respectively. Participants in the upper quartile of homocysteine seemed more likely to be male and hypertensive. They tended to have higher levels of creatinine and lower levels of vitamin B_{12} and folate. Participants with higher levels of homocysteine tended to walk slower and had a higher prevalence of disability.

Homocysteine and Self-Reported Disability

We observed positive associations between homocysteine levels and multiple domains of disability. In Model 1, the odds ratios (ORs) for disability in ADL, IADL, LSA, and GPA comparing participants in the highest quartile of homocysteine to the lowest were 2.18 (95% confidence interval [CI], 1.32–3.59), 1.62 (95% CI, 1.02–2.57), 2.00 (95% CI, 1.14–3.51), and 1.52 (95% CI, 1.05–2.21), respectively (Table 3). The trends of disability in these domains were all statistically significant across homocysteine quartiles. When quadriceps strength, habitual gait speed, or both were additionally introduced in the homocysteine–disability models, the magnitude of the association was attenuated (Model 2 to Model 4). However, the association between homocysteine and ADL disability remained statistically significant even after full adjustment (Model 4). There was no effect modification of sex in the association between homocysteine and disability.

Homocysteine and Performance-Based Physical Measures

Homocysteine levels were inversely associated with quadriceps strength and habitual gait speed. Participants in the highest quartile of homocysteine had lower peak quadriceps strength ($\beta = -26.52$, $p < .001$) and slower gait speed ($\beta = -0.036$, $p = .039$) compared to those in the lowest quartile (Model 1). Moreover, the decreasing trends of quadriceps strength and habitual gait speed across increasing quartiles of homocysteine levels were significant ($p < .001$ and $p = .013$, respectively) (Table 4). Additional adjustment of quadriceps strength diminished the association between homocysteine and gait speed (Model 2, Table 4), meaning that the inverse association of homocysteine and habitual gait speed, to a large extent, could be explained by the magnitude of quadriceps muscle strength. There was no interactive effect of sex and homocysteine on quadriceps strength and habitual gait speed.

Discussion

Among older adults in the United States, homocysteine was associated with disability in ADL, IADL, LSA, and GPA. These homocysteine–disability associations were independent of age, sex, race, BMI category, educational level, smoking status, alcohol intake, presence of comorbidities, as well as levels of folate, vitamin B_{12}, and serum creatinine. Moreover, the association between homocysteine and disability was partially mediated by quadriceps strength and habitual gait speed.

Our study supports and extends previous investigations examining the relationship between homocysteine and functional status. Kado and colleagues from the MacArthur Studies of Successful Aging followed 499 highly functioning older adults for an average of 28 months. They suggested that elevated plasma homocysteine levels were predictive of decline in summary measure of physical performance which included balance, gait, lower body strength and coordination, and manual dexterity (10). Marengoni and colleagues (12) cross-sectionally examined 214 acutely hospitalized geriatric patients and demonstrated that homocysteine

levels were inversely related to both ADL and IADL (12). However, both studies had limitations in terms of external validity because Kado and colleagues studied only high functioning community-dwelling elderly people, and Marengoni and colleagues investigated hospitalized geriatric patients. To the best of our knowledge, this is the first report to present the relationship of homocysteine to self-reported disability while considering the roles of performance-based physical measures by using a national population–based sample of elderly persons living in the United States.

Our results suggest an explanation for the association of homocysteine and disability. We found that the magnitude of the association diminished after additional adjustment of quadriceps strength, gait speed, or both, meaning that both measures, to a large extent, may mediate the association between homocysteine and disability. Likewise, quadriceps strength seemed to mediate the association between homocysteine and gait speed. Homocysteine is metabolized to homocysteine thiolactone by methionyl-transfer RNA (tRNA) synthetase. Homocysteine thiolactone acylates lysine residues of cellular and extracellular proteins, a process called protein homocysteinylation (23). The protein homocysteinylation is a possible mechanism of homocysteine-related protein damage (23) and may thus affect muscle strength, resulting in slow gait speed and subsequent functional dependence. Moreover, as an independent risk factor for vascular diseases (4,5), elevated homocysteine predicts stroke (24), silent brain infarction (25,26), and cerebral white matter lesions (leukoaraiosis) (26). These cerebrovascular changes may interrupt the descending motor fibers arising from the medial cortical area which is important for lower extremity motor control and may debilitate the frontal–subcortical circuit responsible for normal gait and balance (27). Impairment or limitation in balance, gait, or muscle strength has been linked to incident disability among older adults (13). Our study sheds new light on possible consequences of homocysteine-related tissue injury.

The study findings have several implications. In addition to being a marker for poor nutritional status and high cardiovascular risk, high homocysteine may be useful in screening elderly individuals for physical disability. Second, pharmacological therapies such as B vitamins have been shown to lower homocysteine levels (28). Although homocysteine-lowering therapy with B vitamins has not been shown to have cardiovascular benefits (29,30), clinical trials of B vitamins with physical function and disability as outcomes are needed.

Our study has potential limitations deserving comment. First, a causal relationship between homocysteine, physical performance, and late-life disability cannot be established based on the cross-sectional design. The relationship should be confirmed prospectively. Second, although late-life disability was evaluated beyond the traditional scope of ADL, IADL, or mobility, measures of physical performance were confined to quadriceps strength and gait speed. Other suitable physical performance measures, such as maximal gait speed or transfer ability, were not available in the NHANES and may mediate the homocysteine–disability association in a different way. Finally, although the data were drawn from a national population–based sample, we limited the sample to participants 60 years old or older who had reliable measures of isokinetic quadriceps strength without technical, physical, administrative, or safety reasons. Therefore, our results were not generalizable to the entire U.S. elderly population.

Conclusion

Homocysteine levels were associated with multiple domains of physical disability. The association between homocysteine and disability was mediated somewhat by quadriceps strength and usual gait speed. We provide new information about the association of homocysteine on physical functioning in older adults living in the community. Further research

in this important area is needed to determine whether clinical or public health interventions are warranted.

References

1. Booth GL, Wang EE. Preventive health care, 2000 update: screening and management of hyperhomocysteinemia for the prevention of coronary artery disease events. The Canadian Task Force on Preventive Health Care. CMAJ 2000;163:21–29. [PubMed: 10920726]
2. Selhub J, Jacques PF, Wilson PW, Rush D, Rosenberg IH. Vitamin status and intake as primary determinants of homocysteinemia in an elderly population. JAMA 1993;270:2693–2698. [PubMed: 8133587]
3. Pfeiffer CM, Caudill SP, Gunter EW, Osterloh J, Sampson EJ. Biochemical indicators of B vitamin status in the US population after folic acid fortification: results from the National Health and Nutrition Examination Survey 1999–2000. Am J Clin Nutr 2005;82:442–450. [PubMed: 16087991]
4. Refsum H, Ueland PM, Nygard O, Vollset SE. Homocysteine and cardiovascular disease. Annu Rev Med 1998;49:31–62. [PubMed: 9509248]
5. Welch GN, Loscalzo J. Homocysteine and atherothrombosis. N Engl J Med 1998;338:1042–1050. [PubMed: 9535670]
6. Kuo HK, Sorond FA, Chen JH, Hashmi A, Milberg WP, Lipsitz LA. The role of homocysteine in multisystem age-related problems: a systematic review. J Gerontol A Biol Sci Med Sci 2005;60:1190–1201. [PubMed: 16183962]
7. Seshadri S, Beiser A, Selhub J, et al. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. N Engl J Med 2002;346:476–483. [PubMed: 11844848]
8. van Meurs JB, Dhonukshe-Rutten RA, Pluijm SM, et al. Homocysteine levels and the risk of osteoporotic fracture. N Engl J Med 2004;350:2033–2041. [PubMed: 15141041]
9. McLean RR, Jacques PF, Selhub J, et al. Homocysteine as a predictive factor for hip fracture in older persons. N Engl J Med 2004;350:2042–2049. [PubMed: 15141042]
10. Kado DM, Bucur A, Selhub J, Rowe JW, Seeman T. Homocysteine levels and decline in physical function: MacArthur Studies of Successful Aging. Am J Med 2002;113:537–542. [PubMed: 12459398]
11. Manton KG, Corder LS, Stallard E. Estimates of change in chronic disability and institutional incidence and prevalence rates in the U.S. elderly population from the 1982, 1984, and 1989 National Long Term Care Survey. J Gerontol 1993;48:S153–S66. [PubMed: 8315240]
12. Marengoni A, Cossi S, De Martinis M, Calabrese PA, Orini S, Grassi V. Homocysteine and disability in hospitalized geriatric patients. Metabolism 2004;53:1016–1020. [PubMed: 15281011]
13. Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. N Engl J Med 1995;332:556–561. [PubMed: 7838189]
14. Ostir GV, Markides KS, Black SA, Goodwin JS. Lower body functioning as a predictor of subsequent disability among older Mexican Americans. J Gerontol Med Sci 1998;53A:M491–M495.
15. Giampaoli S, Ferrucci L, Cecchi F, et al. Hand-grip strength predicts incident disability in non-disabled older men. Age Ageing 1999;28:283–288. [PubMed: 10475865]
16. Shinkai S, Watanabe S, Kumagai S, et al. Walking speed as a good predictor for the onset of functional dependence in a Japanese rural community population. Age Ageing 2000;29:441–446. [PubMed: 11108417]
17. Rantanen T, Avlund K, Suominen H, Schroll M, Frandin K, Pertti E. Muscle strength as a predictor of onset of ADL dependence in people aged 75 years. Aging Clin Exp Res 2002;14:10–15. [PubMed: 12475129]
18. Bethesda, MD: National Center for Health Statistics; [February 12, 2007]. 1999–2000 National Health and Nutrition Examination Survey (NHANES). Available at http://www.cdc.gov/nchs/about/major/nhanes/currentnhanes.htm
19. Bethesda, MD: National Center for Health Statistics; [February 12, 2007]. 2001–2002 National Health and Nutrition Examination Survey (NHANES). Available at http://www.cdc.gov/nchs/about/major/nhanes/current_nhanes_01_02.htm

20. Muscle Strength Procedures Manual. Bethesda, MD: National Center for Health Statistics; [February 12, 2007]. National Health and Nutrition Examination Survey. Available at http://www.cdc.gov/nchs/data/nhanes/ms.pdf
21. Pfeiffer CM, Huff DL, Smith SJ, Miller DT, Gunter EW. Comparison of plasma total homocysteine measurements in 14 laboratories: an international study. Clin Chem 1999;45(8 pt 1):1261–1268. [PubMed: 10430793]
22. National Heart, Lung, and Blood Institute. Obesity Education Initiative: The Evidence Report. Bethesda, MD: National Institutes of Health; 1998.
23. Jakubowski H. Homocysteine thiolactone: metabolic origin and protein homocysteinylation in humans. J Nutr 2000;130:377S–381S. [PubMed: 10721911]
24. Bostom AG, Rosenberg IH, Silbershatz H, et al. Nonfasting plasma total homocysteine levels and stroke incidence in elderly persons: the Framingham Study. Ann Intern Med 1999;131:352–355. [PubMed: 10475888]
25. Vermeer SE, Den Heijer T, Koudstaal PJ, Oudkerk M, Hofman A, Breteler MM. Incidence and risk factors of silent brain infarcts in the population-based Rotterdam Scan Study. Stroke 2003;34:392–396. [PubMed: 12574548]
26. Vermeer SE, van Dijk EJ, Koudstaal PJ, et al. Homocysteine, silent brain infarcts, and white matter lesions: the Rotterdam Scan Study. Ann Neurol 2002;51:285–289. [PubMed: 11891822]
27. Masdeu JC, Wolfson L, Lantos G, et al. Brain white-matter changes in the elderly prone to falling. Arch Neurol 1989;46:1292–1296. [PubMed: 2590013]
28. Lowering blood homocysteine with folic acid based supplements: meta-analysis of randomised trials. Homocysteine Lowering Trialists' Collaboration. BMJ 1998;316:894–898. [PubMed: 9569395]
29. Lonn E, Yusuf S, Arnold MJ, et al. Homocysteine lowering with folic acid and B vitamins in vascular disease. N Engl J Med 2006;354:1567–1577. [PubMed: 16531613]
30. Bonaa KH, Njolstad I, Ueland PM, et al. Homocysteine lowering and cardiovascular events after acute myocardial infarction. N Engl J Med 2006;354:1578–1588. [PubMed: 16531614]

Table 1

Self-Report Functional Status

Domains	Components
Activities of daily living	Eating difficulty: using fork and knife, and drinking from cup
	Dressing yourself difficulty
	Walking between rooms on same floor difficulty
	Getting in and out of bed difficulty
Instrumental activities of daily living	Managing money difficulty
	Housework difficulty
	Preparing meals difficulty
Leisure and social activities	Going out to movies and events difficulty
	Attending social events difficulty
	Leisure activity at home difficulty
Lower extremity mobility	Walking for a quarter mile difficulty
	Walking up 10 steps difficulty
General physical activities	Stooping, crouching, kneeling difficulty
	Lifting or carrying difficulty
	Standing up from armless chair difficulty
	Standing for long periods difficulty
	Sitting for long periods difficulty
	Reaching up over head difficulty
	Grasping/holding small objects difficulty

Note: Participant was asked about the abilities to perform a series of activities without using any special equipment.

Table 2

Characteristics of Study Population According to Quartiles of Homocysteine Levels (N = 1677)

Characteristics	Quartiles of Homocysteine (μmol/L) Q1 (<7.42) N = 421	Q2 (7.42–9.06) N = 420	Q3 (9.07–11.25) N = 418	Q4 (>11.25) N = 418	Total	p Value
Continuous variables*						
Age, y	67.2 (6.4)	69.0 (6.7)	71.2 (7.4)	73.4 (8.0)	70.2 (7.5)	<.001
Body mass index, kg/m^2	27.9 (5.2)	28.4 (5.1)	27.9 (4.8)	27.6 (4.7)	28.0 (5.0)	.245
Vitamin B_{12}, pg/mL†	574 (302)	513 (280)	447 (264)	374 (245)	477 (287)	<.001
Folate, ng/mL†	18.8 (11.3)	16.1 (9.4)	15.4 (11.7)	13.3 (10.7)	16.1 (11.3)	<.001
Serum creatinine, mg/dL	0.7 (0.2)	0.8 (0.2)	0.9 (0.2)	1.2 (0.9)	0.9 (0.5)	<.001
Isokinetic peak quadriceps strength, Newtons	330 (107)	347 (111)	339 (104)	320 (106)	334 (108)	.094
Habitual gait speed, m/s	1.028 (0.257)	1.016 (0.216)	0.960 (0.219)	0.918 (0.238)	0.980 (0.237)	<.001
Categorical variables‡						
Female	272 (64.6)	209 (49.8)	162 (38.8)	138 (33.0)	781 (46.6)	<.001
Non-Hispanic white	229 (54.4)	243 (57.9)	240 (57.4)	278 (66.5)	990 (59.0)	.001
Education more than high school	180 (42.8)	154 (36.7)	166 (39.7)	124 (29.7)	624 (37.2)	<.001
Hypertension	257 (61.1)	271 (64.5)	285 (68.2)	309 (73.9)	1122 (66.9)	.001
Diabetes mellitus	70 (16.6)	57 (13.6)	58 (13.9)	74 (17.7)	259 (15.4)	.261
Current smoker	54 (12.8)	48 (11.4)	57 (13.6)	63 (15.1)	222 (13.2)	.468
Alcohol intake > 12 drinks per year	240 (57.0)	266 (63.3)	271 (64.8)	276 (66.0)	1053 (62.8)	.082
Self-reported functional disability						
Activities of daily living	47 (11.2)	56 (13.3)	68 (16.3)	90 (21.5)	261 (15.6)	<.001
Instrumental activities of daily living	75 (17.8)	65 (15.5)	77 (18.4)	107 (25.6)	324 (19.3)	.002
Leisure and social activities	44 (10.5)	45 (10.7)	52 (12.4)	75 (17.9)	216 (12.9)	.004
Lower extremity mobility	108 (25.7)	101 (24.1)	112 (26.8)	151 (36.1)	472 (28.2)	<.001
General physical activities	203 (48.2)	209 (49.8)	228 (54.6)	245 (58.6)	885 (52.8)	.01

*Values in the continuous variables were expressed as mean (standard deviation) unless otherwise specified.

†Values were expressed as median (interquartile range) due to right skewness.

‡Values in the categorical variables were expressed as number (percentage).

Table 3

Logistic Regression Models Testing the Association Between Quartiles of Homocysteine and Functional Status

Model*	Quartile Comparison	ADL Disability		IADL Disability		LSA Disability		LEM Disability		GPA Disability	
		OR (95% CI)†	*p* for Trend	OR (95% CI)†	*p* for Trend	OR (95% CI)†	*p* for Trend	OR (95% CI)†	*p* for Trend	OR (95% CI)†	*p* for Trend
1	Q2 vs Q1	1.24 (0.78–1.95)	.001	0.86 (0.57–1.31)	.032	1.07 (0.65–1.77)	.017	0.89 (0.62–1.27)	.074	1.11 (0.82–1.51)	.015
	Q3 vs Q1	1.59 (1.00–2.51)		1.06 (0.70–1.61)		1.21 (0.73–2.00)		0.99 (0.69–1.42)		1.35 (0.97–1.86)	
	Q4 vs Q1	2.18 (1.32–3.59)		1.62 (1.02–2.57)		2.00 (1.14–3.51)		1.46 (0.97–2.18)		1.52 (1.05–2.21)	
2	Q2 vs Q1	1.26 (0.80–2.00)	.005	0.88 (0.58–1.33)	.098	1.10 (0.66–1.82)	.064	0.90 (0.63–1.29)	.291	1.11 (0.82–1.52)	.059
	Q3 vs Q1	1.57 (0.99–2.49)		1.05 (0.69–1.59)		1.19 (0.72–1.98)		0.94 (0.65–1.37)		1.30 (0.94–1.81)	
	Q4 vs Q1	2.01 (1.21–3.32)		1.45 (0.91–2.32)		1.74 (0.98–3.08)		1.27 (0.84–1.91)		1.39 (0.96–2.02)	
3	Q2 vs Q1	1.27 (0.80–2.02)	.004	0.89 (0.58–1.36)	.091	1.12 (0.67–1.87)	.051	0.89 (0.62–1.28)	.244	1.13 (0.83–1.54)	.042
	Q3 vs Q1	1.55 (0.98–2.46)		1.02 (0.67–1.57)		1.17 (0.70–1.96)		0.92 (0.64–1.34)		1.30 (0.93–1.80)	
	Q4 vs Q1	2.07 (1.25–3.43)		1.50 (0.93–2.41)		1.84 (1.03–3.30)		1.31 (0.87–1.99)		1.44 (0.99–2.10)	
4	Q2 vs Q1	1.29 (0.81–2.05)	.009	0.90 (0.59–1.37)	.165	1.13 (0.68–1.89)	.106	0.90 (0.62–1.30)	.511	1.13 (0.83–1.55)	.094
	Q3 vs Q1	1.53 (0.97–2.44)		1.01 (0.66–1.55)		1.15 (0.69–1.93)		0.89 (0.62–1.31)		1.27 (0.91–1.76)	
	Q4 vs Q1	1.94 (1.17–3.23)		1.40 (0.87–2.25)		1.68 (0.94–3.02)		1.19 (0.78–1.81)		1.35 (0.93–1.98)	

*Adjusted covariates: Model 1 = age, sex, race, body mass index category, educational level, smoking status, alcohol intake, presence of comorbidities (diabetes, hypertension, myocardial infarction, congestive heart failure, coronary heart disease, chronic bronchitis, emphysema, arthritis, and cognitive impairment), as well as levels of folate, vitamin B_{12}, and serum creatinine. Model 2 = Model 1 + peak quadriceps strength. Model 3 = Model 1 + habitual gait speed. Model 4 = Model 1 + peak quadriceps strength + habitual gait speed.

†ORs were for disability in a specific domain comparing participants in the 2nd, 3rd, or 4th quartiles of homocysteine to those in the lowest quartile.

ADL = activities of daily living; IADL = instrumental activities of daily living; LSA = leisure and social activities; LEM = lower extremity mobility; GPA = general physical activities; OR = odds ratio; CI = confidence interval.

Table 4

Associations Between Quartiles of Homocysteine and Performance-Based Physical Measures

Dependent Variables	Model*	Quartile	β (*SE*)†	*p* Value	Adjusted Means	*p* for Trend
Peak quadriceps strength	1	Q1	Reference		343.57	<.001
		Q2	0.93 (5.34)	.861	344.52	
		Q3	−9.08 (5.60)	.105	334.49	
		Q4	−26.52 (6.37)	<.001	317.05	
Habitual gait speed	1	Q1	Reference		0.996	.013
		Q2	0.006 (0.015)	.672	1.002	
		Q3	−0.024 (0.015)	.110	0.971	
		Q4	−0.036 (0.017)	.039	0.960	
Habitual gait speed	2	Q1	Reference		0.991	.103
		Q2	0.006 (0.014)	.692	0.996	
		Q3	−0.019 (0.015)	.196	0.971	
		Q4	−0.021 (0.017)	.215	0.969	

Notes: Units of measure: quadriceps strength (Newtons) and habitual gait speed (m/s).

*Adjusted covariates: Model 1 = age, sex, race, body mass index category, educational level, smoking status, alcohol intake, presence of comorbidities (diabetes, hypertension, myocardial infarction, congestive heart failure, coronary heart disease, chronic bronchitis, emphysema, arthritis, and cognitive impairment), as well as levels of folate, vitamin B_{12}, and serum creatinine. Model 2 = Model 1 + peak quadriceps strength.

†Coefficients (β) can be interpreted as differences in mean quadriceps strength or gait speed comparing subjects in the 2nd, 3rd, or 4th quartiles of homocysteine levels to those in the lowest quartile.

SE = standard error.