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HOMOCYSTEINE AND MOBILITY IN OLDER ADULTS

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Abstract

Objective—To determine the influence of homocysteine on mobility decline in older adults.

Design—Prospective cohort.

Setting—Einstein Aging Study, community based aging study

Participants—574 non-demented seniors (mean age 80.2 ± 5.4 years, 61% women)

Measurements—Mobility decline defined using gait velocity measurements at baseline and annual follow-up visits. We used linear mixed effects models to adjust for age, sex, education, and other potential confounders.

Results—Higher homocysteine levels were associated with slower gait velocity at baseline. Adjusted for age, gender and education, a one-unit increase in baseline log homocysteine levels was associated with a 2.95 cm/sec faster mobility decline per year ($p=0.01$) over a median follow-up of 1.4 years. Compared to the 434 subjects in the lowest three quartiles of homocysteine (≤ 15 $\mu\text{mol/liter}$), the 140 subjects in the highest quartile of homocysteine had faster rate of mobility decline (1.75 cm/sec per year faster, $p=0.01$). The association of homocysteine with mobility decline remained robust even after adjusting for multiple confounders and accounting for presence of clinical gait abnormalities.

Conclusions—Higher homocysteine levels are associated with increased risk of mobility decline in community residing older adults.

Keywords

mobility decline; gait; homocysteine

INTRODUCTION

Loss of mobility is common with advancing age and is a harbinger of adverse health outcomes¹. The ability to ambulate is central to maintaining a high quality of life, including retention of many activities that are needed to be fully independent in the community such as shopping, making clinic visits, or visiting friends and relatives¹. Identifying risk factors for mobility decline in seniors is, hence, of major public health importance.

Homocysteine is an amino acid intermediate formed during the metabolism of methionine. The prevalence of hyperhomocysteinemia has been reported to be between 5% and 10% in the general population² and in up to a third of older adults³. Recent studies have linked vascular risk factors such as elevated homocysteine levels to the risk of developing peripheral vascular disease⁴, cardiovascular disease⁵, stroke⁶, and dementia⁷. Homocysteine has effects on multiple organs which include vascular⁴⁻⁶, neurologic⁷ and skeletal systems⁸. These systems may impact mobility and gait, suggesting a role for homocysteine as a potentially modifiable risk factor for mobility decline. Homocysteine levels have been linked with mobility and gait in older adults at cross-section⁹. Limited longitudinal data suggests an effect of homocysteine on distal mobility outcomes such as falls¹⁰ or decline in overall physical function¹¹, though more direct mobility measures such as gait velocity have not been studied.

We undertook this cohort study to prospectively determine whether and to what extent homocysteine levels at baseline are associated with future risk of mobility decline in

community residing seniors. We defined mobility decline as change in gait velocity over follow-up. Gait velocity is a good proxy for mobility, and is recommended as a simple screen of functional status in seniors^{1, 12}. Decline in gait velocity predicts major adverse outcomes such as falls, dementia, and death^{1, 13}. On the other hand, improvement in gait velocity is associated with increased survival in seniors¹. Establishing the role of homocysteine in mobility decline may provide new insights into early biological stages of disablement, improve current risk assessment procedures, and facilitate development of novel preventive strategies for loss of mobility in seniors.

METHODS

Study population

We conducted a prospective cohort study based at the Einstein Aging Study^{14, 15}. The primary aim of the Einstein Aging Study is to identify risk factors for cognitive decline. Study design and methods have been previously reported^{15, 16}. In brief, potential subjects (age 70 years and over) identified from population lists of Bronx County were contacted by letter explaining the purpose and nature of the study, and then by telephone. The telephone interview included verbal consent, medical history questionnaire and cognitive screening tests¹⁵. Exclusion criteria included severe audiovisual loss, bed bound due to illness, and institutionalization. Following the interview, an age stratified sample of subjects who matched on a computerized randomization procedure was invited for further evaluation at our research center. Informed consent was obtained at enrollment according to protocols approved by the local institutional review board.

This mobility substudy began on September 2004 when we started systematically ascertaining gait and mobility in our cohort¹³, and ended in October 2008 when we closed enrollment for this substudy. Of the 815 Einstein Aging study subjects evaluated during this 49-month period, 638 subjects received blood tests for homocysteine and 595 of these subjects also received gait assessments. We excluded 21 subjects with prevalent dementia leaving 574 non-demented subjects with complete homocysteine and gait data. Subjects who were and were not included were similar in terms of age, sex, and educational status. Subjects returned annually for clinical, neuropsychological, and mobility assessments.

Mobility Assessment

Subjects received both clinical and quantitative assessments at baseline and at each annual follow-up visit. Mobility was measured using a computerized walkway (180.0 × 35.5 × 0.25 inches) with embedded pressure sensors (GAITRite; CIR systems. Havertown, PA). Subjects were asked to walk on the instrumented mat by research assistants at their “normal pace” for two trials in a quiet well-lit hallway wearing comfortable footwear and without any attached monitoring devices. Start and stop points were marked by white lines on the floor, and included three feet from the walkway edge for initial acceleration and terminal deceleration. Based on footfalls recorded on the walkway, the software automatically computes gait velocity (cm/sec) as the mean of two trials. The GAITRite system is widely used in clinical research settings, and excellent reliability has been reported in our and other centers^{12, 13, 16}.

Gait was evaluated clinically at each yearly follow-up visit by study clinicians as part of the standard neurological examination^{14, 16}. Gait was determined to be normal or abnormal (due to neurological or non-neurological causes) after visual inspection of walking patterns. The clinical gait assessment has established test-retest reliability and predictive validity in our studies^{14, 16}.

Homocysteine levels

Serum aliquots from the fasting blood draw were processed and stored at -70°C . Serum homocysteine was measured using an enzymatic assay with reagents and calibrators from Equal Diagnostics Inc. (Exton, PA). Inter and intra-assay coefficients of variation according to the manufacturer are $< 3\%$. Other measurements done from the same fasting blood samples, and included as covariates to adjust for possible confounding effects as in previous studies^{9, 11}, were serum levels of triglycerides (mg/dL), glucose (mg/dL), creatinine (mg/dL) and blood urea nitrogen (mg/dL).

Covariates

Presence or absence of depression, diabetes, heart failure, hypertension, angina, myocardial infarction, strokes, Parkinson's disease, chronic obstructive lung disease, and severe arthritis reported by subjects at entry into this mobility substudy or at any previous Einstein Aging study visits was used to calculate a summary illness index (range 0-10) as previously described^{13,17}. We consulted medical records and contacted family members when available or physicians to verify or obtain further details of illnesses and medications¹⁷. Blood pressure, height, and weight were recorded by research assistants using standard protocols¹⁸. Mean arterial pressure was calculated as sum of the diastolic blood pressure and one-third pulse pressure (systolic – diastolic blood pressure). General cognitive status was assessed by the Blessed-Information-Memory concentration test¹⁹. Depressive symptoms were assessed by the 15-item Geriatric depression scale²⁰.

Data Analysis

The distribution of homocysteine levels were skewed to the right, and were log-transformed for all analyses. The transformed homocysteine levels were divided into quartiles. The corresponding non-transformed quartile ranges were ≤ 10.8 , 10.9 to 12.5, 12.6 to 15, and > 15 $\mu\text{mol/liter}$. In our preliminary linear regression analysis, there were no significant associations ($p > 0.10$) with mobility decline for comparisons of subjects in the lowest homocysteine quartile with those in the second or third quartiles. Hence, we examined possible threshold effects of homocysteine on mobility by comparing the fourth quartile (highest values) versus the other three quartiles combined (reference group). For baseline comparisons, the high homocysteine group represents subjects with homocysteine values in the highest quartile (> 15 $\mu\text{mol/liter}$) and the low represents subjects in the other three combined quartiles (≤ 15 $\mu\text{mol/liter}$).

To determine the longitudinal association of homocysteine (per unit increase in log homocysteine levels) with risk of developing mobility decline, linear mixed effects models controlled for age, sex, and education were applied to the 574 eligible subjects (Model 1)²¹. A random intercept was included in the model to allow entry point to vary across individuals. 'Time' represents average rate of change in mobility over time. An interaction between 'homocysteine' and 'time' was included to model the effect of baseline homocysteine on rate of change in mobility. Associations are reported as parameter estimates with 95% CI.

In additional analyses (Model 2), we added the following covariates to account for possible confounding: self-reported medical illnesses index, clinical gait abnormalities, self-reported low physical activity, Blessed test score, Geriatric depression scale score, mean arterial pressure, body mass index (BMI), and biomarkers (triglyceride, glucose, blood urea nitrogen, and creatinine). Including log transformed values for covariates with skewed distributions in Model 2 did not materially change results. Hence, untransformed values for covariates other than homocysteine were used in the analysis. The linear mixed effects model can accommodate unbalanced data resulting from missing data points, unequal

numbers of follow up visits and unequal intervals between visits. The assumption on missing data on repeated measures of velocity is missing at random (MAR)²². Though the proportion of missing data on individual covariates adjusted in Model 2 was low (5% on BMI, 6% on blood pressure, glucose, creatinine and BUN, and 7% clinical gait abnormalities), 20% (112) of the sample were missing at least one covariate. There was no significant differences on baseline homocysteine level, age, gender, education, gait velocity, and the rate of mobility decline between those with and without missing covariates. Hence, the occurrence of missing values among the covariates seems to be at random. Thus our main analysis for Model 2 is based on the 462 subjects without missing data on the covariates adjusted. We repeated Model 2 using multiple imputations for missing data, and results were similar.

Incident mobility disability (gait velocity ≤ 70 cm/sec) was examined as a secondary outcome. This velocity cut score has been used to define slow gait and predicts risk of adverse outcomes such as falls, and functional decline^{1, 23}. Cox proportional-hazards models²⁴ were used to compute hazard ratios (HR) with 95% CI for developing incident mobility disability based on baseline homocysteine levels in the 357 subjects without prevalent mobility disability¹⁶. All analyses are adjusted for age, sex, and education. Time to event was from baseline to incident mobility disability or to final study contact, whichever came first. Proportional hazards assumptions of models were examined analytically and graphically and were adequately met. In additional analysis we adjusted for the following covariates: medical illnesses index, mean arterial pressure, body mass index (BMI), clinical gait abnormalities, physical activity, serum triglyceride, glucose, BUN, and creatinine levels.

RESULTS

Table 1 shows the characteristics of the cohort at entry into this mobility substudy as well comparisons by homocysteine status. The 574 eligible subjects included 221 men (39%) and 353 women (61%). Mean age at entry was 80.2 ± 5.4 years. The median follow-up time was 1.4 years (814 person years follow-up). The mean number of follow-up visits was 2.3 (range 0 to 4). Among the 435 subjects with one or more annual follow-up assessments, 78 had prevalent mobility disability.

The mean homocysteine level at baseline was 13.3 ± 4.1 $\mu\text{mol/liter}$. There were 140 subjects with high homocysteine levels (>15 $\mu\text{mol/liter}$) and 434 subjects with low or normal levels (≤ 15 $\mu\text{mol/liter}$). Subjects in the high homocysteine quartile were older (81.7 vs. 79.7y) and walked more slowly (89.2 vs. 96.1 cm/sec) compared to the remaining subjects. Subjects in the high homocysteine quartile had a higher prevalence of diabetes ($p = 0.03$), heart failure ($p=0.01$), hypertension ($p<0.001$), stroke ($p=0.03$), and myocardial infarctions ($p = 0.002$) (Table 1).

Mobility decline

Adjusted for age, gender and education (Model 1), each one-unit increase in log homocysteine levels were associated with a 2.95 cm/sec increased rate of decline per year in gait velocity (Table 2). The association was strengthened after adjustments for additional covariates in Model 2.

Table 1 shows that clinical gait abnormalities were more prevalent among subjects with high homocysteine values (57% vs. 31%, $p<0.001$). Model 2 analyses were adjusted for presence of clinical gait abnormalities. Moreover, when the analysis was restricted to subjects without clinical gait abnormalities ($n=335$), the longitudinal mobility effect of log homocysteine remained significant after adjustments for all covariates other than clinical gait abnormalities

in Model 2 (4.63 cm/sec increased rate of decline per year, $p = 0.004$). Subjects who developed clinical gait abnormalities during follow-up were not excluded since such an event could be part of the causal chain between elevated homocysteine levels and mobility decline.

There were fewer men (53% vs. 44%) in the highest homocysteine quartile compared to the lowest three quartiles (Table 1). All models reported were adjusted for gender, and the interaction between gender and homocysteine was not significant in our models. Moreover, results for analysis stratified by gender were similar (data not shown).

Subjects in the highest quartile of homocysteine had faster decline in gait velocity (1.75 cm/sec per year faster, $p=0.01$) in the Model 1 compared to subjects in the other three quartiles. The results were similar after adjustments for additional covariates in Model 2; the difference in rate of mobility decline between groups was 1.79 cm/sec per year ($p=0.02$).

Figure 1 contrasts relationship between homocysteine levels and mobility decline for typical study participants (80 year old male, 12 years education) with homocysteine levels in the highest ($>15 \mu\text{mol/liter}$, 75th percentile) versus remaining three quartiles ($\leq 15 \mu\text{mol/liter}$). Adjusted for age, sex, and education, the estimated difference in rate of mobility decline in the high homocysteine group compared to the lower homocysteine group was 1.75 cm/sec per year.

Mobility disability

Of the 357 subjects without mobility disability (gait velocity $<70 \text{ cm/sec}$) at baseline, 47 (13.2%) developed incident mobility disability over a mean follow-up of 18 months. Adjusting for age, gender and education, baseline homocysteine was associated with increased risk of incident mobility disability (HR per one-unit increase in log homocysteine 3.83, 95% CI 1.04 -14.16). The association was not significant after adjusting for additional covariates though the direction was unchanged (HR 3.42, 95% CI 0.79 – 14.78). When examined as a categorical variable, the association of homocysteine (highest versus remaining three quartiles) with risk of mobility disability was not significant (HR 1.67, 95% CI 0.81-3.42).

DISCUSSION

In this cohort of community-dwelling older adults, elevated homocysteine levels at baseline were associated with increased risk of mobility decline; each one-unit increase in log homocysteine (which corresponds to a 1.7 times increase in untransformed homocysteine levels) was associated with a 2.95 cm/sec increased rate of mobility decline. In comparison, the rate of mobility decline in the overall cohort was 1.48 cm/sec per year. This association remained robust even after adjustments for potential confounders such as age, gender, education, clinical gait abnormalities, physical activity, depressive symptoms, cognition, chronic medical illnesses, BMI, blood pressure, and other biomarkers. The association with mobility decline was stronger in subjects with highest homocysteine levels (worst quartile), suggesting a possible threshold effect of homocysteine in increasing risk for mobility decline. Similar threshold effects (and at similar homocysteine cutscores) have been reported for homocysteine and risk of other adverse outcomes such as dementia or hip fractures^{7, 10}.

Our findings are supported by previous studies which have shown that elevated homocysteine levels were correlated at cross-section with gait velocity, quadriceps strength, frailty and disability in older adults^{9, 11}. Observational studies have linked homocysteine levels with increased risk of developing distal mobility related outcomes such as hip

fractures and functional impairment^{8, 10, 11}. A previous study in a cohort of successfully aging adults aged 70 to 79 years reported that high homocysteine levels predicted risk of decline in physical function, defined using a summary measure that included gait velocity, muscle strength, balance, and manual dexterity¹¹. Given the restricted age range, high functional status, and composite physical function measure used in this previous study¹¹, the specificity of the association of homocysteine with mobility decline in community residing seniors was not established. Our study complements findings from these prior studies to provide prospective evidence about the inverse relationship between homocysteine levels and risk of mobility decline in older adults.

There are various mechanisms by which homocysteine may be related to mobility decline. Baseline comparisons showed a higher prevalence of vascular diseases in subjects in the highest homocysteine quartile, suggesting that vascular mechanisms may be an important link between homocysteine and mobility decline. Elevated homocysteine levels are an independent risk factor for cerebrovascular disease⁶, which in turn is a risk factor for cognitive and mobility decline^{25,26}. However, our findings remained significant when adjusted for clinical and biological vascular risk factors. We also accounted for clinical gait abnormalities, which include hemiparetic, frontal or unsteady subtypes that were associated with risk of vascular dementia in our cohort¹⁴. Hence, non-vascular pathways may also contribute to the mobility effects of homocysteine. Other possible mechanisms by which homocysteine levels may influence mobility include direct effects on nerve and muscle²⁷, osteoporosis²⁸, and oxidative injury²⁹.

The strengths of our study include the large cohort size and standardized clinical and mobility protocols. Our results are supported by our analyses with mobility disability as a secondary outcome. Each one-unit increase in log homocysteine was associated with a three-fold increased risk of developing incident mobility disability. Given the low number of incident cases, the association between homocysteine and mobility disability was not significant after adjustments for additional covariates, though the direction of the association was unchanged.

Our quantitative gait assessment yields multiple gait variables^{1, 12}, but the value of gait variables other than velocity to track mobility decline have not been well established.

This study was necessarily restricted to subjects in our cohort who received gait and homocysteine assessments, but subjects seen previously were not differentially excluded. Because our cohort was recruited from the community and we excluded subjects with dementia or inability to ambulate at baseline, caution should be applied when attempting to generalize our findings to clinic or nursing home based samples. However, the observed associations may be stronger in less healthy populations. Medical illnesses were based on self-report, so we may have underestimated effects. The homocysteine levels were based on a single measurement. Cutscores for elevated homocysteine may vary in other populations or age groups³⁰. A limitation was that we did not have dietary accounts or serum measurements of B vitamins, which may influence homocysteine levels. We did include BMI as a covariate to partially control for nutritional status. Thus, while our analyses were adjusted for multiple confounders, we cannot exclude the possibility of residual or unmeasured confounding.

In conclusion, these prospective data indicate that elevated homocysteine levels are strongly associated with increased risk of mobility decline in community residing older adults. Measurement of homocysteine levels may help improve current mobility and disability risk assessments. Given the major functional and health consequences of reduced mobility¹⁶,

homocysteine should also be further explored as a possible target for intervention to prevent mobility decline in older adults.

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Figure 1. Expected trajectory of gait velocity from Model 1 for two subjects (male, age 80, and with 12 years education) with different homocysteine categories. High homocysteine level (>15 μmol/liter) is represented by the dotted line and normal homocysteine level (≤15 μmol/liter) by the unbroken line in the figure.

Table 1

Baseline characteristics in overall cohort as well as by homocysteine quartiles. High homocysteine represents subjects with homocysteine values in the highest quartile (>15 $\mu\text{mol/liter}$) and low represents remaining subjects in the lowest three quartiles (≤ 15 $\mu\text{mol/liter}$)

	Overall (n = 574)	High homocysteine (n = 140)	Low Homocysteine (n = 434)	P-value *
Age, mean (SD), y	80.22 (0.40)	81.72 (5.50)	79.74 (5.29)	<.001
Education years, mean (SD), y	14.03 (3.49)	13.68 (3.41)	14.15 (3.51)	.098
Female, No. (%)	353 (61)	66 (47)	287 (66)	<.001
Clinical tests				
Blessed test score, mean ($\pm$ SD), range 0-32	1.91 (1.94)	2.09 (1.93)	1.86 (1.94)	.117
Geriatric depression scale (range 0-15)	2.18 (2.09)	2.34 (2.00)	2.13 (2.12)	.070
Clinical gait abnormality, %	37	57	31	<.001
Low physical activity, %	4	4	5	.399
Mean arterial pressure, mean ($\pm$ SD), mmHg	97.64 (10.00)	96.03 (10.66)	98.17 (9.72)	.131
Body mass index, mean ($\pm$ SD)	27.12 (4.81)	27.25 (4.96)	27.08 (4.77)	.674
Gait velocity, mean ($\pm$ SD), cm/sec	94.40 (22.91)	89.17 (22.73)	96.08 (22.74)	.002
Medical illnesses				
Diabetes, %	16	22	15	.034
Heart Failure, %	3	6	2	.014
Hypertension, %	63	78	58	<.001
Depression, %	11	8	12	.137
Stroke, %	10	15	9	.027
Parkinson's disease, %	1	1	0.5	.718
Chronic lung disease, %	6	6	6	.930
Angina, %	10	14	8	.065
Myocardial infarction, %	8	14	6	.002
Severe arthritis, %	5	8	4	.081
Illness index (range 0 -10)	1.32 (1.05)	1.71 (1.21)	1.20 (0.97)	<.001
Laboratory tests				
Homocysteine, mean ($\pm$ SD), $\mu\text{mol/liter}$	13.25 (4.09)	18.26 (4.95)	11.63 (1.89)	<.001
Triglycerides, mean ($\pm$ SD), mg/dL	116.27 (64.90)	124.46 (74.11)	113.65 (61.52)	.118
Glucose, mean ($\pm$ SD), mg/dL	101.24 (36.54)	106.90 (50.94)	99.38 (30.23)	.017
Creatinine, mean ($\pm$ SD), mg/dL	1.04 (0.40)	1.35 (0.62)	0.94 (0.22)	<.001
Blood Urea Nitrogen, mean ($\pm$ SD), mg/dL	20.85 (8.47)	27.17 (12.17)	18.78 (5.44)	<.001

* P-values are for comparison of subject with high homocysteine values versus rest, and derived from Chi square or Fisher's exact test for categorical variables and Wilcoxon rank-sum test for continuous variables.

Table 2

Association between baseline homocysteine levels and mobility decline (defined using gait velocity in cm/sec per year)

Model	Homocysteine level* Estimate (CI)	p-value	High vs. low homocysteine** Estimate (CI)	p-value
Model 1	-2.95 (-5.20 to -0.69)	0.01	-1.75 (-3.14 to -0.37)	0.01
Model 2	-3.99 (-6.58 to -1.39)	0.003	-1.79 (-3.33 to -0.26)	0.02

Model 1 is adjusted for baseline age, sex, and education.

Model 2 is in addition adjusted for medical illness index, presence of clinical gait abnormalities, Blessed test scores, Geriatric depression scale scores, mean arterial pressure, BMI, and blood variables (glucose, triglyceride, creatinine, and BUN).

* per one-unit increase in log homocysteine levels (adjusted for age, sex, and education).

** Highest quartile (>15 $\mu\text{mol/liter}$) versus the other three quartiles (≤ 15 $\mu\text{mol/liter}$).