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Total homocysteine and cognition in a tri-ethnic cohort:

The Northern Manhattan Study

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Abstract

Objective: Several studies implicate elevated homocysteine as a risk factor for dementia and cognitive decline, but most studies have involved subjects older than 55 years from homogeneous populations. The authors examined homocysteine and cognition in a tri-ethnic community sample 40 years and older.

Method: The Northern Manhattan Study includes 3,298 stroke-free subjects. Of these 2,871 had baseline fasting total homocysteine (tHcy) levels and Mini-Mental State Examination (MMSE) scores available. The authors used multiple linear regression to examine the cross-sectional association between baseline tHcy levels and mean MMSE scores adjusting for sociodemographic and vascular risk factors.

Results: Homocysteine levels were related to age, renal function, and B12 deficiency. Those with B12 deficiency had tHcy levels five points higher (9.4 vs 14.4 nmol/L). Mean MMSE scores differed by age, sex, and race-ethnic group. Those with hypertension, diabetes, cardiac disease, and B12 deficiency had lower MMSE scores. In multivariate analyses, elevated tHcy was associated with lower mean MMSE scores for those older than 65 but not for those 40 to 64. Adjusting for B12 deficiency and sociodemographic factors the mean MMSE was 2.2 points lower for each unit increase in the log tHcy level (95% CI –3.6, –0.9). Adding vascular risk factors to the model did not attenuate this effect (mean MMSE –2.2 points; 95% CI –3.5, –0.9).

Conclusions: Elevated homocysteine was independently associated with decreased cognition in subjects older than 65 in this tri-ethnic cohort, adjusting for sociodemographic and vascular risk factors.

There is increasing evidence that vascular risk factors play a role in the development of cognitive impairment and decline, raising the possibility that modification of these factors may slow its course. The amino acid homocysteine is a potentially modifiable¹ risk factor for heart disease and stroke.^{2,3} In addition, homocysteine may be an independent risk factor for cognitive impairment^{4–8} and decline,⁹ as well as dementia and Alzheimer disease (AD).^{10, 11} Several cross-sectional studies with small samples have found an inverse association between homocysteine level and cognitive status,^{6,12,13} but prospective studies have not all been in agreement. Incident dementia as well as AD were associated with elevated homocysteine in the Framingham cohort study,¹⁴ but homocysteine was not related to

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cognitive decline in the population based Rotterdam study.¹⁵ While large artery disease has been shown to be a mediator in some studies of the association between homocysteine and stroke,^{16,17} small vessel disease may be a more likely mechanism of cognitive impairment and dementia.^{18,19}

Most studies have focused on white subjects, but blacks and Hispanics may have greater rates of dementia than whites.²⁰ This may be due in part to a larger burden of cerebrovascular disease, as Hispanics and blacks have higher rates of diabetes, high blood pressure, as well as small vessel strokes and intracranial atherosclerosis than whites.²¹ However, little is known about the effect of vascular risk factors on cognition in these groups. This information is important for health care planners as dementia prevalence increases markedly in the aging US population. Hispanics are the largest growing segment of the US population, having increased by 58% in the last decade of the 20th century.²² To date few studies have examined the relationship between homocysteine and cognitive impairment in Hispanics, blacks, and whites drawn from the same community. In addition most studies of the relationship between homocysteine and cognition have been done in older subjects.^{15,23,24} We examined the independent effect of fasting total homocysteine (tHcy) level on cognition in the Northern Manhattan Study, which includes white, black, and Hispanic subjects older than 40 years of age.

Methods.

Subjects.

The Northern Manhattan Study (NOMAS) includes a community-based prospective cohort of 3,298 stroke-free Hispanic, black, and white subjects enrolled between 1993 and 2001 and was designed to evaluate the effects of socioeconomic, vascular, and race-ethnic factors on stroke risk and vascular outcomes. Northern Manhattan consists of the area north of 145th street, south of 218th street, and bounded on the east by the Harlem river and on the west by the Hudson river. The 1990 Census showed a population of nearly 260,000 with 40% older than 39 years and a race-ethnic mixture of 20% black, 63% Hispanic, and 15% white residents. Community subjects were identified using random-digit dialing with dual-frame sampling to include non-published numbers. Of 84,612 telephone numbers dialed, 22,868 households were contacted by Audits and Surveys, Inc. (New York, NY). Bilingual trained research assistants performed the telephone screening. The initial telephone response rate was 91% and 5,314 households were identified in which at least one member satisfied eligibility requirements. Overall, 3,298 had an in-person interview for an overall response rate of 68%. Subjects were enrolled if they were 1) >40 years of age, 2) had never been diagnosed with a stroke, and 3) had resided in Northern Manhattan for ≥ 3 months in a household with a telephone. The Institutional Review Board of Columbia-Presbyterian Medical Center approved the study.

Assessment of vascular risk factors and cognitive status.

Trained bilingual research assistants collected data directly from subjects. Interviews were performed in English or Spanish depending on the primary language of the participant and a proxy was necessary in less than 1% of subjects. Race-ethnicity was assessed based on self-identification through questions similar to those used in the US Census and conforming to standard definitions outlined by Directive 15.²⁵ Subjects were classified as Hispanic if they described themselves as such or as being of Spanish origin. Non-Hispanic subjects identifying themselves as white were classified as white non-Hispanic and those identifying themselves as black were classified as black non-Hispanic.

Cognitive status was assessed at baseline by bilingual trained research assistants using the 30-item Mini-Mental State Examination (MMSE) in English or Spanish depending on the

language spoken by the subject at home.²⁶ We chose to examine differences in mean MMSE score because we do not have specific age and education based cutoffs for cognitive impairment and dementia in this multiethnic cohort. Published cut points for dementia using the MMSE may not be appropriate in a cohort where a large percentage of subjects are of Caribbean Hispanic origin.

The interview questions adapted from the Behavioral Risk Factor Surveillance System by the Centers for Disease Control and Prevention were used to collect data on vascular risk factors, including a history of coronary artery disease, atrial fibrillation, and smoking status.

Alcohol use was assessed through a structured in-person interview using questions adapted from the National Cancer Institute Food Frequency Questionnaire²⁷ and another semi-quantitative food frequency questionnaire.²⁸ The questions were modified to provide a defined frequency response set. Inquiries were made about consumption of three different forms of alcohol (wine, beer, and liquor) both during the past year and on average during the subject's drinking lifetime. Alcohol consumption was divided into four categories: no drinks during the past year, at least one drink in the past month up to two drinks per day (moderate), more than two but less than five drinks per day (intermediate), and five or more drinks per day (heavy). We dichotomized, comparing moderate alcohol consumption to the other groups for two reasons. First, moderate alcohol consumption is associated with a protective effect against ischemic stroke in our cohort and second, moderate alcohol consumption was associated with higher MMSE scores than those who did not drink and those who drank intermediate and heavy amounts. Hypertension was defined as a systolic blood pressure ≥ 140 mm Hg or a diastolic blood pressure ≥ 90 mm Hg based on the mean of two blood pressure measurements, self-report of a diagnosis of hypertension, or medical treatment thereof. Diabetes was defined as a fasting blood glucose ≥ 127 mg/dL, subject self-report of a diagnosis of diabetes, or insulin or oral hypoglycemic use. Any cardiac disease was defined as a history of coronary artery disease, atrial fibrillation, or myocardial infarction.

Laboratory analyses.

Fasting total homocysteine levels (tHcy) were drawn into serum tubes and spun immediately at 3,000 g at 4°C for 20 minutes and then directly stored at -70° C, which has been shown to be stable for homocysteine assays. Serum was sent to the research laboratory at the University of Colorado Health Sciences Center where tHcy and methylmalonic acid (MMA) were assayed by stable isotope dilution gas chromatography-mass spectrometry (GC-MS) as previously described.²⁹⁻³¹ Most subjects with clinical B12 deficiency have elevated levels of MMA and this can be used to differentiate B12 from folate deficiency as a cause of elevated tHcy levels.^{32,33} Vitamin B12 and folate levels were assessed using SimulTRAC-S radioimmunoassay kits. The number of apolipoprotein epsilon 4 alleles carried by each subject was determined by *HhaI* digestion of PCR products amplified from genomic DNA as previously described.³⁴

Statistical analyses.

To assess the effect of homocysteine on cognitive function, we constructed multiple linear regression models using MMSE score as an outcome. Homocysteine and other potential confounders were used as covariates. Fasting tHcy levels were examined as both continuous and categorical variables to see if there was an association with mean MMSE score. When used as a continuous variable, tHcy levels were log-transformed to create a normal distribution, and the mean MMSE score per one unit increase in the log fasting tHcy level was computed. For the analysis in which tHcy was examined as a categorical variable we trichotomized, with fasting total homocysteine levels above the 90th percentile (>15 $\mu\text{mol/L}$), those with levels between the 50th and 90th percentiles (>10 and ≤ 15 $\mu\text{mol/L}$), and those below the 50th percentile (reference group). These groups were chosen because they have been shown to be

associated with vascular death and ischemic stroke in this cohort.³⁵ In addition, analysis of the relationship between homocysteine deciles and MMSE scores did not support the use of more than three categories. We used multiple linear regression models to examine differences in the mean MMSE score. We examined the relationship between homocysteine and MMSE score adjusting for potential confounders. We noted that the interaction between tHcy and creatinine (a measure of renal function) was significant, implying that the effect of homocysteine differed depending on creatinine. We centered creatinine levels by subtracting the mean from each value to avoid colinearity, and the centered creatinine was used in all models. Model 1 included age in years, creatinine, tHcy, and the interaction between tHcy and creatinine. In Model 2, we added sex, race-ethnicity (white subjects as the reference), education, Medicaid status, and B12 deficiency (defined as MMA level >271 nmol/L) in addition to the variables in Model 1. In Model 3 we assessed the contribution of vascular risk factors by adding hypertension, diabetes, heart disease (including a history of coronary disease, myocardial infarction, or atrial fibrillation), current smoking, amount of alcohol consumed, and body mass index. We did not control for folate deficiency as less than 1% of subjects had levels below normal.

Since the relationship between tHcy and mean MMSE score differed in older and younger age groups, we examined Models 1 through 3 stratified by age 65, while keeping age in years as a continuous variable as well. In a supplementary analysis, we adjusted for the number of apolipoprotein epsilon 4 alleles carried by each subject. All analyses were carried out using SAS software (SAS Institute, Cary, NC).

Results.

Data on 2,871 stroke-free subjects with both MMSE scores and fasting tHcy levels out of 3,298 enrolled subjects were available for analysis. Their baseline characteristics did not differ from the overall cohort. Variables that were associated with homocysteine, MMSE score, or both in univariate analysis are shown in table 1. Subjects older than 65 had lower scores than younger subjects and women had lower scores than men. Subjects describing themselves as Hispanic and black had lower scores compared to those self-identified as white.

The mean fasting total homocysteine level was 10.2 $\mu\text{mol/L}$ and a level of 15.0 $\mu\text{mol/L}$ approximated the 90th percentile in the overall sample and differed by race-ethnic group. Hispanics (mean 9.8 ± 5.2 ; 90th %ile 14.2 $\mu\text{mol/L}$) and whites had similar values (mean 10.2 ± 4.5 ; 90th %ile 14.4 $\mu\text{mol/L}$), and black subjects had higher values (mean 11.3 ± 5.1 ; 90th %ile 17.0 $\mu\text{mol/L}$). The mean MMA level was 214 nmol/L and 17% of subjects had levels above 271 nmol/L and thus were considered B12 deficient. The MMA values ranged to 5,966 nmol/L with 9% greater than 1,000 nmol/L.

In analyses treating tHcy as a continuous variable, fasting tHcy level was associated with lower mean MMSE scores even after adjusting for age and creatinine with a drop of 3.5 points among those over 65 and almost 2.0 for those under 65 (Model 1, table 2). When we adjusted for B12 deficiency and other vascular risk factors the relationship remained significant only for those older than 65 (Models 2 and 3, see table 2). In the older group the effect was attenuated after adjusting for B12 deficiency and sociodemographic factors but after adjusting for vascular risk factors no further attenuation occurred (see table 2).

A similar relationship was seen when the fasting tHcy level was examined as a categorical variable. In those older than 65 but not in younger subjects, levels from subjects above the 90th percentile (>15 $\mu\text{mol/L}$), but not between the 50th and 90th percentiles (10 to 15 $\mu\text{mol/L}$), had significantly lower scores compared to those with homocysteine levels below the 50th percentile. Black and Hispanic subjects had significantly lower MMSE scores than white

subjects in all models, as did those with less than a high school education, and those with Medicaid. Interestingly, subjects consuming moderate amounts of alcohol were significantly more likely to have higher scores on the MMSE compared to non-drinkers, intermediate, and heavy drinkers. Hypertension, diabetes, and cardiac disease were not significantly associated with lower mean MMSE scores when controlling for other factors.

In stratified analyses by race-ethnicity in those older than 65 using Model 3, the relationship between homocysteine and MMSE score differed by race-ethnic group. Each unit increase in the log tHcy level was associated with lower MMSE scores for Hispanic subjects older than 65 ($p = 0.01$) but levels above the 90th percentile were not ($p = 0.1$). For white subjects homocysteine levels above the 90th percentile were associated with lower MMSE scores compared to those below the 50th percentile (-3.0 points lower; $p = 0.04$), but there was only a trend toward such a relationship examining tHcy as a continuous variable (-2.4 points lower; $p = 0.06$). There was no association between homocysteine and MMSE score among black subjects over 65.

We performed several separate analyses to examine potential confounders. *APOE-4* allele status was not available in all subjects, however older subjects with this allele would be expected to have lower MMSE scores in this cohort. Indeed, *APOE-4* was associated with mean MMSE scores about one point lower in 747 subjects older than 65 (-0.8 points; 95% CI: $-0.2, -1.3$). However, adjusting for *APOE-4* allele status in addition to sociodemographic factors, B12 deficiency, and vascular risk factors included in Model 3, the log tHcy level was still associated with mean MMSE scores more than 3.5 points lower. Thus, adjusting for *APOE-4* status did not attenuate the relationship between homocysteine and MMSE score.

Poor renal function can raise homocysteine levels and affect cognitive function. We handled this by adjusting for creatinine level and including an interaction term for the relationship between tHcy and creatinine in all models. Data points with very high creatinine levels could be influential in determining the fit of the model. To examine robustness of the finding, we re-fitted Model 3 excluding those with creatinine levels above 1.5 mg/dL. The relationship between tHcy and lower mean MMSE scores remained significant.

It is difficult to interpret differences in mean MMSE scores, but an appropriate cutoff score for cognitive impairment and dementia is not available in this cohort. We examined Model 3 using a traditional cutoff for the MMSE of less than 24 points and found there was still a significant inverse association with higher homocysteine levels.

Discussion.

We found that elevated fasting homocysteine levels were associated with lower mean MMSE scores in this tri-ethnic cohort. Although the association was significant in the overall analysis, stratification revealed that the association was driven by older subjects, specifically those older than 65. In this older group, those with a homocysteine value above 15 $\mu\text{mol/L}$ —that is, above the 90th percentile—had average MMSE scores that were one and one half points lower than those with a level less than 10 $\mu\text{mol/L}$ (the 50th percentile; 95% CI: -2.0 to -1.0). By contrast, this effect was not seen in those younger than 65 years ($n = 1,049$), suggesting that the length of exposure to high homocysteine levels may be an important factor in its effect on cognition.

There is limited information on the effect of homocysteine on cognition in Hispanic and black subjects. One recent cross-sectional community-based study was performed among Mexican-Americans. The authors found that higher homocysteine values were associated with lower cognitive function scores on several tests.²³ However, they did not control for vascular risk factors and this may have affected their ability to evaluate the independence of an association. Our study is the first cohort study to examine the effects of vascular risk factors on cognition

in Hispanic, black, and white subjects that includes a large group between the ages of 40 and 65. Although the power was decreased we examined our models stratified by race-ethnicity and the findings remained significant for white and Hispanic subjects but not for blacks. Homocysteine levels were significantly higher in black subjects (compared to both Hispanics and whites) but the prevalence of B12 deficiency was lower in this group, suggesting that the effect of homocysteine on cognition may be specific to the cause of its elevation. For white subjects, a significant relationship with MMSE score was seen for homocysteine values above the 90th percentile but not when examined as a continuous variable. This may be due to the ceiling effect using the MMSE in white subjects, as the median score in this group was 28 compared to 27 for black and 26 for Hispanic subjects. Conversely, only the continuous analysis showed a significant relationship for Hispanic subjects. Perhaps this is explained by the fact that the prevalence of a low score on the MMSE (<24) was only 11% in Hispanic subjects with tHcy values above the 90th percentile, whereas it was 17% for white and 21% for black subjects with tHcy levels in this category. Prospective data on cognitive decline in this cohort using more sensitive measures of cognitive function may help clarify these race-ethnic differences.

Cross-sectional analyses such as this one may be problematic when applied to chronic conditions such as vascular disease and cognitive impairment because a measured association cannot be used to evaluate causality as the temporal relationship between the exposure of interest and the outcome is not clear. In studies involving older subjects with several vascular risk factors that may be associated with cognitive impairment, homocysteine may simply be a marker of vascular disease. However, this conclusion is not supported by our data because the strength of the inverse relationship between homocysteine and MMSE score did not attenuate after adjusting for known vascular risk factors. Thus, the estimates of the association between tHcy levels and MMSE scores did not vary substantially between Models 2 and 3 (see table 2), suggesting an independent relationship. On the other hand, deficiencies of B vitamins have been associated with dementia and AD and can increase homocysteine levels.¹¹ About 17% of subjects in our study had an elevated MMA in this cohort. The prevalence of elevated MMA differed among the age groups with a prevalence increasing to 20% in those older than 65, and mean tHcy levels were 5 $\mu\text{mol/L}$ greater for those with B12 deficiency than without, raising the possibility that lowering homocysteine using B12 supplementation might decrease the risk of cognitive impairment. Interestingly, there was only a weak effect of increased MMA on mean MMSE score in the models, while the association between tHcy and lower mean MMSE scores remained significant. Folate deficiency has also been associated with cognitive impairment, however less than 1% of subjects had low serum folate levels in a subsample in which this measure was available. Folic acid fortification of the diet was instituted in the United States in 1998 and may have led to lower homocysteine values in subjects enrolled after this time point and lessened the effect of homocysteine on cognition. This has been noted as a potential confounding factor in other studies.²³ However, we examined those who were enrolled before and after 1998 and found no effect modification (data not shown).

Impaired renal function can raise homocysteine and MMA levels, as well as potentially affect cognitive status, and some studies have excluded subjects with creatinine levels above specific values. We chose not to do this because elevated creatinine may be a consequence as well as a cause of hyperhomocysteinemia. Homocysteine may lead to vascular damage resulting in poor renal function. Hence, excluding these subjects may lead to bias since poor renal function and elevated creatinine may be on the causal pathway between elevated plasma homocysteine and cognitive impairment. In addition, excluding these subjects would also result in selective loss of older subjects with the highest risk because of length of exposure to vascular risk factors. There was a significant interaction between homocysteine and creatinine levels and we included a multiplicative term in all models to avoid mistaking the effects of poor renal function on cognition for those of homocysteine (see table 2). We also performed a separate analysis

excluding those with higher creatinine levels and the relationship between tHcy and MMSE score was still significant (data not shown). It is unlikely that elevated MMA as a marker of B12 deficiency was confounded by poor renal function because very few of these subjects had elevated methylcitrate levels, which would have been expected if impaired renal function were the cause.

Although the MMSE has been found to be both valid and reliable as a measure of cognitive function, it lacks sensitivity. This may have limited our ability to detect differences among those with milder forms of cognitive dysfunction. We did find a significant association between elevated tHcy and a low score on the MMSE using a cutoff of less than 24 that is often used for dementia. However, Hispanic and black subjects are less likely to reach a top score due to lower education and other factors. More than 20% of Hispanic and black subjects had a low score based on this measure, compared to 8% of whites. Further validation in this population is needed before meaningful cut points can be chosen. Another limitation is that the MMSE does not include a measure of executive function. This cognitive domain may be of particular relevance to cognitive impairment caused by vascular disease³⁶ and elevated homocysteine³⁷ and our ability to detect the effects of vascular risk factors on cognition may have been limited by the lack of an executive measure. A more complete neuropsychological test battery that includes measures of executive function and processing speed is currently being collected in a subsample from this cohort and may help clarify those cognitive domains most susceptible to elevated plasma homocysteine levels.

The mechanism by which homocysteine may affect cognition is unclear, but the finding in observational studies of an association between homocysteine and heart disease and stroke would suggest the mechanism is vascular.^{2,3} In addition, randomized controlled trials have shown that lowering homocysteine levels slows the progression of vascular disease such as carotid plaque.³⁸ Neuroimaging studies, however, suggest that homocysteine affects cognition through vascular and nonvascular mechanisms. The Rotterdam study found that elevated homocysteine levels were associated with silent infarcts and white matter lesions, but also hippocampal atrophy.^{18,39} Similarly, an association with white matter disease was also found in the French EVA study but homocysteine was associated with cognitive decline to the same extent in those with and without white matter disease.⁹ To date, no imaging studies involving homocysteine have been done in black and Hispanic subjects from the same community. We are currently performing brain MRI scans in a subsample of our cohort to examine white matter hyperintensities, silent infarcts and microbleeds, and brain atrophy as it relates to cognition. Homocysteine may have effects on cognition through nonvascular mechanisms such as by interacting with the neurodegenerative processes that cause AD. One study found high homocysteine levels in patients with pathologically confirmed AD with and without concomitant cerebrovascular disease.¹¹ In addition, an inverse relationship between homocysteine level and poor recall of the elements of a story was seen in the third National Health and Nutrition Examination, indicating that elevated homocysteine may be related to poor short term verbal memory,²⁴ and suggesting some of the subjects may have had mild cognitive impairment or early AD.

Basic science suggests plausible mechanisms by which homocysteine might interact with AD such as by enhancing the effects of beta-amyloid toxicity⁴⁰ or through neurotoxic effects via the NMDA receptor.⁴¹ Our study was not designed to separate the vascular effects of homocysteine on cognition from other mechanisms. However, if homocysteine were associated with AD in our sample, one might expect *APOE-4* allele status to modulate the association with MMSE scores. This did not occur in the smaller group for whom *APOE-4* allele status was available.

We have found an independent inverse association between fasting homocysteine levels and MMSE scores in older subjects adjusting for relevant metabolic, socioeconomic, and vascular risk factors in this tri-ethnic cohort. The importance of elevated MMA in this study supports the idea that vitamin B12 therapy might have the potential to modulate the effects of homocysteine on cognition. Prospective data in this cohort may help clarify race-ethnic differences in the effects of homocysteine on cognition and more sensitive neuropsychological tests that include measures of executive function may provide insight into the cognitive domains that are affected. In addition, brain imaging may add to our understanding about the pathogenesis of cognitive problems associated with elevated homocysteine levels as well as other vascular risk factors.

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Table 1

Relationship of selected covariates with tHcy and MMSE score among 2,871 baseline community subjects in northern Manhattan

Characteristics	N (%)	tHcy	MMSE
Age, y			
>65	1,822 (65)	10.8 (5.5) *	25.8 (3.9) *
≤65	1,049	9.1 (3.9)	26.6 (3.4)
Sex			
Women	1,798 (63)	9.8 (4.9) *	25.8 (3.9) *
Men	1,070	10.9 (5.1)	26.5 (3.3)
Race ethnicity			
Hispanic	1,528 (53)	9.8 (5.2)	25.3 (3.9) *
Black	675 (24)	11.3 (5.1) *	26.3 (3.4) *
White	603 (21)	10.2 (4.5)	27.7 (2.7)
Education			
<High school	1,543 (54)	10.2 (5.5)	24.7 (4.0) *
≥High school	1,327	10.1 (4.5)	27.6 (4.5)
Insurance status			
Medicaid	957 (33)	10.1 (5.3)	24.5 (4.2) *
Medicare or private	1,914	10.2 (4.9)	26.9 (3.1)
Hypertension			
Yes	2,106 (73)	10.4 (5.3) *	25.9 (3.8) *
No	765	9.6 (4.3)	26.7 (3.4)
Diabetes			
Yes	607 (21)	9.9 (3.8)	25.6 (4.0) *
No	2,264	10.3 (5.3)	26.2 (3.6)
Cardiac disease [†]			
Yes	670 (23)	10.9 (5.6) *	25.8 (3.9) *
No	2,201	10.0 (4.8)	26.2 (3.6)
Current smoker			
Yes	446 (15)	10.5 (4.2)	26.5 (3.4) *
No	2,424	10.1 (5.2)	26.0 (3.8)
Moderate alcohol use			
Yes	953 (33)	9.8 (4.5) *	27.0 (3.1) *
No	1,914	10.4 (5.3)	25.6 (3.9)
MMA > 271 nmol/L [‡]			
Yes	476 (17)	14.4 (8.7) *	25.3 (4.1) *
No	2,395 (83)	9.4 (3.3)	26.2 (3.4)
Body mass index			
≥30	784 (27)	9.8 (4.9) *	26.1 (3.5)
≥25 <30	1,197 (42)	10.2 (5.0)	26.0 (3.8)
<25 (reference)	890 (31)	10.5 (5.2)	26.2 (3.8)

tHcy and MMSE values in columns 3 and 4 = mean (SD).

* $p < 0.05$.

[†] Cardiac disease = history of atrial fibrillation, myocardial infarction, or coronary artery disease.

[‡] MMA > 271 nmol/L is cutpoint for B-12 deficiency.

tHcy = fasting plasma total homocysteine level; MMSE = Mini Mental State Examination; MMA = methylmalonic acid.

Table 2
Multivariate linear regression models of the relationship between homocysteine and MMSE score

Model	Subjects <65, Δ in MMSE	p Value	Subjects ≥ 65 , Δ in MMSE	p Value
Model 1 [*]				
Continuous (log tHcy)	-1.95 (-3.74, -0.17)	0.032	-3.48 (-4.89, -2.07)	<0.001
Categorical tHcy				
50th to 90th %ile (10–15 $\mu\text{mol/L}$)	-0.23 (-2.86, 2.39)	0.861	-2.56 (-4.21, -0.90)	0.003
>90th %ile (>15 $\mu\text{mol/L}$)	-1.36 (-3.33, 0.60)	0.173	-3.32 (-4.82, -1.82)	<0.001
Model 2 [†]				
Continuous (log tHcy)	0.03 (-1.70, 1.76)	0.970	-2.24 (-3.58, -0.90)	0.001
Categorical tHcy				
50th to 90th %ile (10–15 $\mu\text{mol/L}$)	0.96 (-1.45, 3.37)	0.435	-1.16 (-2.67, 0.36)	0.134
>90th %ile (>15 $\mu\text{mol/L}$)	0.68 (-1.19, 2.55)	0.474	-1.66 (-3.09, -0.23)	0.023
Model 3 [‡]				
Continuous (log tHcy)	-0.0002 (-1.74, 1.74)	0.9998	-2.20 (-3.54, -0.86)	0.001
Categorical tHcy				
50th to 90th %ile (10–15 $\mu\text{mol/L}$)	0.99 (-1.44, 3.41)	0.424	-0.92 (-2.43, 0.59)	0.231
>90th %ile (>15 $\mu\text{mol/L}$)	0.66 (-1.21, 2.54)	0.489	-1.55 (-2.98, -0.13)	0.033

* Model 1: continuous = age, creatinine, log tHcy*creatinine; categorical = age, creatinine, categorical tHcy*creatinine.

† Model 2 = model 1, B-12 deficiency (MMA = 271 nmol/L), sex, race ethnicity, education, Medicaid status.

‡ Model 3 = model 2, hypertension, diabetes, cardiac disease, smoking, ethanol use, body mass index.

tHcy = fasting plasma total homocysteine level; MMSE = Mini Mental State Examination; MMA = methylmalonic acid.