

Homocysteine and cognitive function in the Sacramento Area Latino Study on Aging¹⁻⁴

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ABSTRACT

Background: Elevated plasma homocysteine (hyperhomocysteinemia), an independent risk factor for vascular disease, has been reported to be inversely correlated with objective measures of cognitive function in patients with Alzheimer disease and in community-dwelling older adults.

Objective: We evaluated the cross-sectional relation between total plasma homocysteine concentration and cognitive function in elderly Latinos (aged ≥ 60 y; $n = 1789$) participating in the Sacramento Area Latino Study on Aging.

Design: Global cognitive function was assessed by using the Modified Mini-Mental State Examination, and specific cognitive functions were assessed by using 6 instruments developed for cross-cultural and multilingual neuropsychological evaluation of older persons. Associations between the cognitive function scores and total plasma homocysteine concentrations were then measured by multiple regression analysis with control for potential confounding by nutrient status (red blood cell folate, plasma vitamin B-12), kidney function (serum creatinine), demographic variables (age, sex, education, acculturation), and depressive symptoms.

Results: Modest inverse associations were found between homocysteine concentrations and several indexes of cognitive function, including the global Modified Mini-Mental State Examination assessment and the picture-association, verbal attention-span, and pattern-recognition tests ($P \leq 0.05$). Demographic variables, particularly age and education, were more strongly associated with cognitive function scores than was homocysteine.

Conclusions: Homocysteine is a modest independent predictor of cognitive function in community-dwelling elderly Latinos. Reducing plasma homocysteine concentrations by administering B-vitamin supplements may provide some protection against cognitive decline in this and other elderly populations, but the effect may be limited. *Am J Clin Nutr* 2003;78:441-7.

KEY WORDS Homocysteine, cognitive function, Modified Mini-Mental State Examination, folate, vitamin B-12, creatinine, elderly, aging, Latinos

INTRODUCTION

Vascular disease and its risk factors are receiving increasing attention as potentially modifiable causes of cognitive decline and dementia in older adults. Stroke, cardiovascular disease, peripheral vascular disease, hypertension, and diabetes mellitus have each been associated with cognitive deficits or dementia, or both, in various elderly populations (1-5).

An elevated plasma concentration of the sulfur amino acid homocysteine (hyperhomocysteinemia) is now recognized as an independent risk factor for cardiovascular, peripheral vascular, and cerebrovascular disease (6). Accordingly, a potential influence of hyperhomocysteinemia on cognitive functioning and dementia has been postulated. Clarke et al (7) compared patients with histologically confirmed Alzheimer disease with age-matched healthy control subjects. They found that individuals who had elevated serum homocysteine concentrations ($> 14 \mu\text{mol/L}$) were 4.5 times as likely to have had Alzheimer disease (as confirmed by post-mortem histologic analysis) as were those with low serum homocysteine ($\leq 11 \mu\text{mol/L}$). Similar observations have been made in other studies (8, 9), including the recent finding that baseline homocysteine concentrations predicted the risk of incident Alzheimer disease and dementia over an 8-y period in the Framingham Heart Study population (10). According to findings we published recently, however, it remains unclear whether elevated homocysteine is a causative factor or simply a marker of coexistent vascular disease in Alzheimer disease patients (11). Nonetheless, in addition to correlations with Alzheimer disease and dementia, significant correlations have been observed between homocysteine concentrations and indexes of cognitive function in case-control studies of patients with psychogeriatric conditions (12-15) and in cross-sectional, population-based studies of community-dwelling older adults (16-19). Two studies, however, found no significant associations between homocysteine concentrations and cognitive function in either cross-sectional (20, 21) or longitudinal (20) analyses.

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The purpose of the present study was to investigate the association between homocysteine concentrations and cognitive function in the Sacramento Area Latino Study on Aging (SALSA), a community-based cohort study of elderly Latinos (aged ≥ 60 y).

SUBJECTS AND METHODS

Subjects

Subject recruitment and study procedures were approved by the Human Subjects Review Committee at the University of California, Davis, and written informed consent was obtained from all study participants. The study population consisted of community-dwelling older adults (aged ≥ 60 y; $n = 1789$) of Latino ancestry residing in Sacramento, CA, and the surrounding Northern California communities. Subjects were considered "Latino" if they, their parents, or their grandparents were born in Central or South America. Subjects were recruited over a period of 18 mo beginning in February 1998. The details of sampling and recruitment were described elsewhere (22). Briefly, 1990 census tracts and more recent sampling lists from other sources were used to identify localities in which $\geq 5\%$ of the population was potentially eligible for the study on the basis of Latino ancestry and age. Subjects were recruited by a variety of means, including mailings, telephone calls, and door-to-door canvassing, and 82% of those contacted agreed to participate. The age and sex distributions of the final sample compared favorably with data collected during a 1998 Sacramento-area dress rehearsal for the Year 2000 United States Census, and thus the final sample was generally representative of the target population. Subject recruitment and study procedures were approved by the Human Subjects Review Committee at the University of California, Davis, and written informed consent was obtained from all study participants.

Sample collection and analysis

Fasting blood was collected from each participant by standard venipuncture into evacuated tubes with and without EDTA. The blood was transported on ice to the Medical Center Clinical Laboratory at the University of California, Davis, for processing within 4 h of collection. Plasma and serum were isolated and stored at -80°C until they were analyzed. Plasma homocysteine concentrations were measured by using HPLC with post-column fluorescence detection (23). Red blood cell (RBC) folate was measured by using an automated chemiluminescence assay [ACS 180; Chiron Diagnostics (now Bayer Diagnostics), Tarrytown, NY). Plasma vitamin B-12 concentrations were measured by using a radioassay (Quantaphase II; BioRad Diagnostics, Hercules, CA). Serum creatinine was analyzed by using a standard spectrophotometric assay. Because the present study was a sub-study of the larger SALSA, there was significant demand for blood samples to be used for a variety of other biochemical assays, and sufficient volumes of blood were not available from all subjects for each assay. The sample sizes for the study of each of the biochemical variables were $n = 1642$, 1501, 1545, and 1640 for plasma homocysteine, RBC folate, plasma vitamin B-12, and serum creatinine, respectively.

Neuropsychological assessment instruments

Neuropsychological assessments were made with the use of several instruments. The Modified Mini-Mental State Examination (3MSE; 24), which evaluates memory, orientation, attention,

and language on a scale of 0–100, was used to determine global cognitive ability. Specific subdomains of cognitive function were assessed by using a battery of 6 instruments developed for cross-cultural and multilingual neuropsychological assessment of older persons (25). These instruments are summarized here.

Delayed recall

The delayed-recall scale is an assessment of the ability to learn and recall verbal information. This test follows a standard word-list learning-task format using an inventory of 15 common items that can be purchased in a grocery store. The list contains words from 5 semantic categories with various numbers of exemplars. Subjects are put through 5 learning trials and a delayed-recall trial, with the order of presentation fixed across the trials. Scores are based on a 15-point scale.

Object naming

The object-naming scale is an assessment of the ability to retrieve verbal information from semantic memory. Subjects are shown color pictures and are asked to name specific objects. Scores are based on a 20-point scale.

Picture association

The picture-association scale is an assessment of the ability to access and use semantic memory of nonverbal information. Subjects are shown color pictures of stimulus objects along with 6–12 potentially associated images, and they are asked to point to the one image that is most related to the stimulus. Scores are based on a 20-point scale.

Verbal conceptual thinking

The verbal conceptual-thinking scale is an assessment of the capacity for abstract or conceptual thinking. The subject is presented with 6 words, 5 of which belong to a common category, and is asked to identify the outlier. Scores are based on a 20-point scale.

Verbal attention span

The verbal attention-span scale is an assessment of fixed attention span. Subjects are asked to repeat a string of digits read at a rate of 1/s. Some items contain nonrandom sequences of digits, which are included to facilitate grouping of information and produce subtle gradients of item difficulty. Scores are based on a 20-point scale.

Pattern recognition

The pattern-recognition scale is an assessment of the ability to discriminate between black and white designs. A stimulus design is presented with 6 target alternatives, one of which is identical to the stimulus, and the subject must indicate which target is the same as the stimulus. Scores are based on a 20-point scale.

Demographic data

The 3MSE and delayed-recall instruments were administered to all but 10 subjects ($n = 1779$). The other 5 neuropsychological instruments were administered to a subgroup of the total population ($n = 537$) consisting of all subjects who scored below the 20th percentile on either the 3MSE or delayed-recall instruments and a random sample of 20% of the total population.

Subjects were given the choice of taking the neuropsychological tests in English or Spanish. Age, sex, and the number of years of education were recorded for each subject as potential



determinants of cognitive function scores. In addition, an acculturation score was determined by using the Acculturation Rating Scale for Mexican Americans–II (26). This is a self-reported measure of how well an individual is assimilated into American culture as determined by such factors as language preference, food choices, entertainment choices, and social group preference. Individuals were scored on a scale of 0–37; a score of 0 indicated no acculturation, and a score of 37 indicated complete acculturation. Depressive symptoms were assessed with the use of the Center for Epidemiologic Studies Depression scale (CES-D; 27).

Statistical analysis

Associations between plasma homocysteine concentrations (dependent variable) and each of the demographic (ie, age, sex, education, and acculturation), biochemical (ie, RBC folate, plasma vitamin B-12, and serum creatinine), and depressive symptom (CES-D) variables were evaluated by multiple linear regression analysis. Multiple linear regression analyses were also used to build statistical models describing the relations between homocysteine concentration (independent variable) and each of the cognitive-function test instruments (dependent variables) before and after adjustment for confounding by the demographic, biochemical, and depressive symptom variables. A general linear model procedure and the Tukey-Kramer multiple-comparisons test were used to compare mean \pm SEM cognitive function scores among subjects grouped by quintiles of homocysteine concentrations, by age, and by education. Because the values for plasma homocysteine, RBC folate, plasma vitamin B-12, and serum creatinine were not normally distributed (ie, there was tailing toward higher values), these variables were natural log-transformed before analysis. Statistical significance was defined for all analyses as $P < 0.05$. The statistical analyses were carried out by using STATVIEW for MACINTOSH and WINDOWS (version 5.0.1; Abacus Concept, Berkeley, CA) and SAS for WINDOWS (version 7; SAS Institute Inc, Cary, NC).

RESULTS

Summary data for the SALSA population are presented in **Table 1**. A significant proportion (17%) of the population had plasma homocysteine concentrations above the cutoff value for hyperhomocysteinemia defined in a report from the Framingham Heart Study, ie, ≥ 13 $\mu\text{mol/L}$ (28). In the present study, hyperhomocysteinemia had a high prevalence despite the fact that $< 1\%$ of the population had RBC folate values below the cutoff for deficiency (ie, ≤ 160 ng/mL). Low vitamin B-12 status (plasma vitamin B-12: ≤ 200 pg/mL in 6.5% of subjects, 200–300 pg/mL in 16.4%) and impaired renal function (serum creatinine: > 1.4 mg/dL in 5.4% of men and > 1.1 mg/dL in 6.5% of women) were highly prevalent, findings that are consistent with the advanced age of the population. Approximately one-fifth of the population had cognitive function scores indicative of cognitive impairment (3MSE ≤ 78 , delayed recall ≤ 6 , or both). One-quarter of the population had elevated depressive symptoms (CES-D: ≥ 16), as previously reported (27). With the use of multiple regression analysis (**Table 2**), the primary determinants of plasma homocysteine were creatinine, vitamin B-12, and RBC folate; age, sex, education, and acculturation were statistically significant but comparatively minor correlates. The CES-D score was not associated with plasma homocysteine (data not shown).

A series of 4 regression models describing the relations between homocysteine and cognitive function scores are presented

TABLE 1
Description of the SALSA population¹

	Value ²	Percentage abnormal ³
Sex (% female)	58 [1789]	—
Age (y)	70 (60–101) ⁴ [1789]	—
Education (y)	6 (0–32) [1778]	—
Acculturation score (0–100)	18 (0–37) [1789]	—
Homocysteine ($\mu\text{mol/L}$)	9.8 (4.2–129) [1642]	17 (≥ 13)
RBC folate (ng/mL)	488 (50–900) [1501]	0.9 (≤ 160)
Vitamin B-12 (pg/mL)	416 (22–1968) [1545]	6.5 (≤ 200)
Creatinine (mg/dL)	[1640]	
Men	0.9 (0.4–10.2)	5.4 (> 1.4)
Women	0.7 (0.3–7.7)	6.5 (> 1.1)
3MSE score (0–100)	86 (0–100) [1779]	22 (≤ 78)
Delayed-recall score (0–15)	9 (0–15) [1779]	22 (≤ 6)
CES-D score (0–60)	6 (0–54) [1663]	25 (≥ 16) ⁵

¹ $n = 1789$. SALSA, Sacramento Area Latino Study on Aging; RBC, red blood cell; 3MSE, Modified Mini-Mental State Examination (24); CES-D, Center for Epidemiologic Studies Depression scale (27).

² n in brackets.

³ Cutoff value in parentheses.

⁴ Median; range in parentheses.

⁵ Data reported previously (27).

in **Table 3**. Before adjustment for confounding by demographic and biochemical variables (model 1), homocysteine was inversely correlated with all 7 cognitive function tests ($P < 0.001$). The R^2 values for these simple regressions indicate that homocysteine explains 2.2%–5.1% ($R^2 = 0.022$ – 0.051) of the variance in cognitive function scores within the sample. Homocysteine remained inversely correlated with all 7 cognitive function tests after the addition of folate, vitamin B-12, and creatinine to the model (in all cases, $P < 0.001$) (model 2). The inclusion of the demographic variables (ie, age, sex, education, and acculturation) in the model, however, significantly attenuated the relations between homocysteine and the cognitive function tests (models 3 and 4). Correlation coefficients for homocysteine were largely reduced in these models compared with model 1, whereas R^2 values were 5-fold–20-fold those in model 1. These R^2 values indicate that the demographic variables explain a much higher proportion of the variance in cognitive function scores than do the biochemical variables homocysteine, folate, vitamin B-12, or creatinine. Of the demographic variables, education was the most strongly associated, age and

TABLE 2
Predictors of plasma homocysteine in the SALSA population¹

	Coefficient	P
RBC folate	-0.134 ± 0.020	< 0.001
Plasma vitamin B-12	-0.249 ± 0.014	< 0.001
Serum creatinine	0.483 ± 0.025	< 0.001
Age	0.009 ± 0.001	< 0.001
Sex	0.031 ± 0.015	0.036
Education	-0.004 ± 0.001	0.004
Acculturation	-0.003 ± 0.001	0.006

¹ $\bar{x} \pm \text{SEM}$; $n = 1424$. Values for homocysteine, folate, vitamin B-12, and creatinine were natural log-transformed before analysis. Coefficients and P values were determined by multiple linear regression and adjusted for all other variables listed. The score on the Center for Epidemiologic Studies Depression scale was not significantly correlated with homocysteine. SALSA, Sacramento Area Latino Study on Aging; RBC, red blood cell.

TABLE 3
Multiple linear regression models for homocysteine (independent variable) versus cognitive function score (dependent variable)^{1/}

Assessment Instrument	Model 1			Model 2			Model 3			Model 4		
	R ²	Coefficient	P	R ²	Coefficient	P	R ²	Coefficient	P	R ²	Coefficient	P
3MSE	0.033	-7.56 ± 1.02 ²	<0.001	0.069	-10.8 ± 1.39	<0.001	0.320	-2.37 ± 0.92	0.01	0.324	-2.97 ± 1.25	0.02
Delayed recall	0.051	-2.08 ± 0.22	<0.001	0.076	-1.73 ± 0.31	<0.001	0.290	-0.52 ± 0.21	0.01	0.306	-0.32 ± 0.28	NS
Object naming	0.027	-1.95 ± 0.51	<0.001	0.111	-4.30 ± 0.76	<0.001	0.491	-0.29 ± 0.41	NS	0.518	-1.00 ± 0.60	NS
Picture association	0.040	-2.54 ± 0.55	<0.001	0.114	-5.18 ± 0.84	<0.001	0.563	-0.91 ± 0.41	0.03	0.567	-1.27 ± 0.63	0.05
Verbal conceptual thinking	0.036	-2.23 ± 0.51	<0.001	0.102	-4.04 ± 0.77	<0.001	0.452	-0.84 ± 0.42	0.05	0.468	-1.16 ± 0.64	NS
Verbal attention span	0.022	-1.75 ± 0.51	<0.001	0.077	-3.50 ± 0.78	<0.001	0.326	-0.94 ± 0.46	0.04	0.357	-1.42 ± 0.70	0.04
Pattern recognition	0.039	-2.67 ± 0.59	<0.001	0.121	-5.86 ± 0.88	<0.001	0.439	-1.20 ± 0.49	0.02	0.467	-2.41 ± 0.74	0.001

^{1/}Multiple linear regression models are as follows: Model 1 = ln(homocysteine) alone; model 2 = model 1 + ln(creatine); model 3 = model 1 + age + sex + education + acculturation; and model 4 = model 2 + model 3. R² values are those for the entire model including ln(homocysteine) and covariates. Coefficients and P values are for ln(homocysteine) within each model. Sample sizes for the Modified Mini-Mental State Examination (3MSE) and delayed-recall tests varied from n = 1614 (model 1) to n = 1406 (model 4). Sample sizes for the object-naming, picture-association, verbal conceptual-thinking, verbal attention-span, and pattern-recognition tests varied from n = 517 (model 1) to n = 436 (model 4). The score on the Center for Epidemiologic Studies Depression scale did not significantly affect the associations between homocysteine and cognitive function scores and therefore was not included in the models.

² $\bar{x} \pm \text{SEM}$.

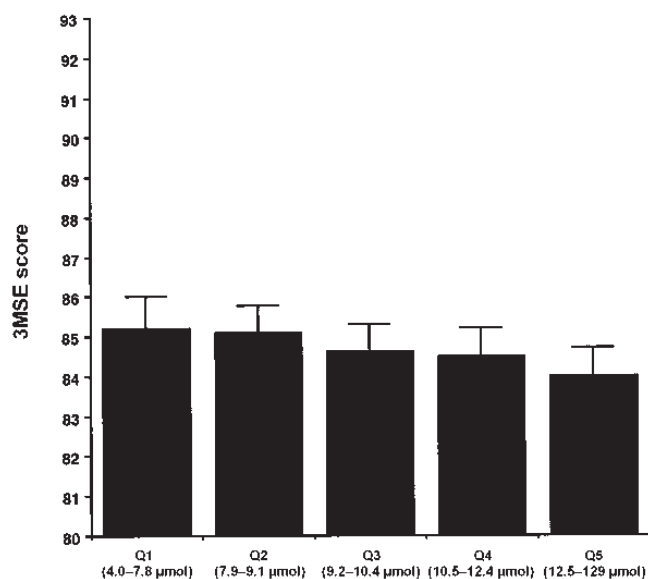


FIGURE 1. Mean (\pm SEM) scores (0–100) on the Modified Mini-Mental State Examination (3MSE) for subjects in the homocysteine concentration quintiles (Qs), showing the relation between global cognitive function score and homocysteine concentration. The scores were adjusted for folate, vitamin B-12, creatinine, age, sex, education, and acculturation of subjects. $n = 1406$ (281 or 282 per quintile). There were no significant differences between the quintiles (Tukey-Kramer multiple-comparisons test).

acculturation ranked next, and sex was mostly insignificant (data not shown). In model 4, which included all demographic and biochemical variables, homocysteine remained significantly correlated with 4 of the 7 cognitive function tests (3MSE, picture association, verbal attention, and pattern recognition). Inclusion of the biochemical measures added very little to the variance explained by the demographic factors. The CES-D score did not significantly affect the observed associations between homocysteine and cognitive function scores (data not shown), and therefore it was not included in any of the models.

The coefficients listed in Table 3 indicate the magnitude of the change in cognitive function score associated with a 1-unit change in the natural log of homocysteine. Such a small change in a natural log of a variable, however, is difficult to interpret. To obtain additional information about the magnitude of the relation, we compared mean \pm SEM cognitive function scores, adjusted for the demographic and biochemical variables, among subjects by quintiles of homocysteine concentrations within the sample (Figure 1). The adjusted mean 3MSE score was 1.2 points lower in the highest homocysteine quintile than in the lowest quintile. This difference is not statistically significant by general linear model analysis. Similarly small, nonsignificant differences in adjusted mean scores were observed between the lowest and highest homocysteine quintiles for the 6 other cognitive function tests (data not shown). These data are contrasted with the results shown in Figures 2 and 3, in which adjusted mean 3MSE scores are compared among subjects grouped by age and education within the study sample. The adjusted mean 3MSE score was 5.3 points lower in the oldest subjects (aged ≥ 80 y) than in the youngest subjects (aged 60–69 y) and was 10.8 points higher in those subjects with the greatest number of years of education (> 12 y, ie, beyond high school) than in those with the fewest

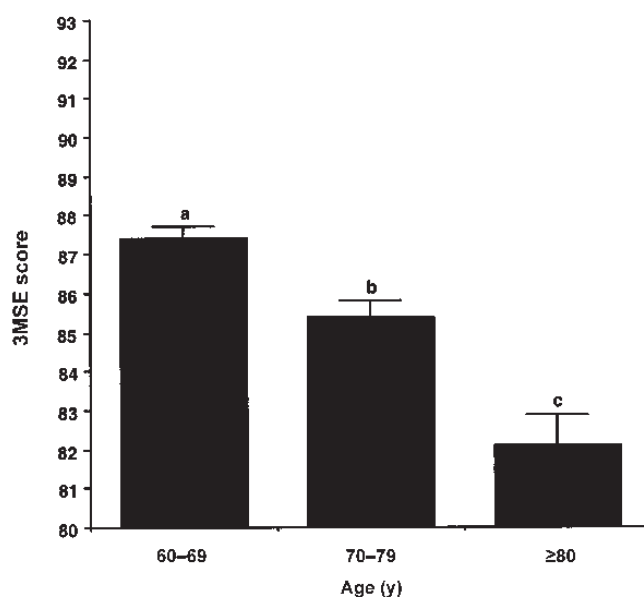


FIGURE 2. Mean (\pm SEM) scores (0–100) on the Modified Mini-Mental State Examination (3MSE) for subjects in 3 age groups, showing the relation between global cognitive function score and age. The scores were adjusted for folate, vitamin B-12, homocysteine, creatinine, sex, education, and acculturation of subjects. $n = 693$, 565, and 148 in the 60–69-y-old, 70–79-y-old, and ≥ 80 -y-old groups, respectively. Bars with different letters are significantly different, $P < 0.001$ (Tukey-Kramer multiple-comparisons test).

years of education (0–5 y, ie, elementary school or less). General linear model analyses with post hoc comparisons by the Tukey-Kramer procedure indicate that these differences are statistically significant ($P < 0.001$). Statistically significant differences in adjusted mean scores also were observed between the lowest and highest age and education groups for the 6 other cognitive function tests (data not shown). In secondary multiple regression analyses, we assessed whether the relative strengths of the relations between homocysteine and cognitive function scores varied among the defined age and education groups. The question was whether homocysteine was more strongly correlated with cognitive function scores in one age or education group [eg, the oldest (aged ≥ 80 y) or the least educated (0–5 y of school) subjects] than with those in another group [eg, the youngest (aged 60–79 y) or the most educated (> 12 y of school) subjects]. No clear differences among the 3 age groups or among the 4 education groups were detected in the strengths of the associations between homocysteine and the cognitive function tests (data not shown). The sample size and power of the study may not have been sufficient to allow us adequately to address this question, however.

DISCUSSION

The primary observation of this study is that there are statistically significant associations between homocysteine and several quantifiable measures of cognitive function in a community-dwelling, elderly, Latino population. Notably, these associations are independent of folate and vitamin B-12 status and of kidney function, as reflected in the serum creatinine concentrations. The associations are modest, however: homocysteine predicted $\leq 5\%$ of the variance in cognitive function scores in this study sample. In contrast, demographic variables,

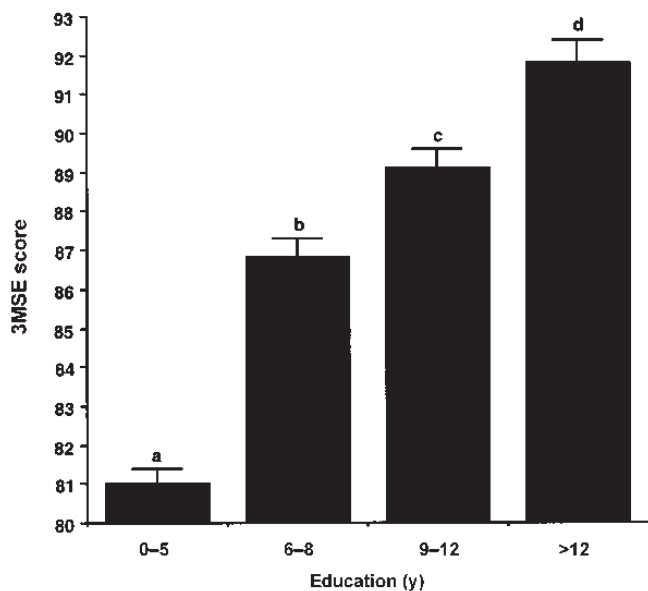



FIGURE 3. Mean (\pm SEM) scores (0–100) on the Modified Mini-Mental State Examination (3MSE) for subjects in 4 education groups, showing the relation between global cognitive function score and education. The scores were adjusted for folate, vitamin B-12, homocysteine, creatinine, age, sex, and acculturation of subjects. $n = 543, 282, 334,$ and 247 in the 0–5-y, 6–8-y, 9–12-y, and >12-y groups, respectively. Bars with different letters are significantly different, $P \leq 0.01$ (Tukey-Kramer multiple-comparisons test).

particularly age and education, were found to be much stronger determinants of cognitive function scores.

These findings are generally consistent with previous assessments of the relations between homocysteine and cognitive function in various at-risk populations, including patients with dementia and other psychogeriatric conditions (12–15), and community-dwelling older adults (16–21). There are, however, some discrepancies. Morris et al (18) recently examined the relation between homocysteine and cognitive function in a subset of the third National Health and Nutrition Examination Survey (NHANES III). Elderly participants in that study (aged ≥ 60 y) with hyperhomocysteinemia (defined as homocysteine concentration $> 13.7 \mu\text{mol/L}$) were more likely to score poorly on tests of word recall and story idea recall than were their counterparts without hyperhomocysteinemia. In the present study, however, no significant association was observed between homocysteine concentrations and delayed recall. The reason for this difference from the NHANES III data is unclear, but it may be related to significant demographic differences between the studies, including the ethnicity, education levels, and range of cognitive abilities of the study subjects. In another study with discrepant results, carried out in Rotterdam, Netherlands, Kalmijn et al (20) reported that homocysteine did not correlate with Mini-Mental State Examination (MMSE) scores in a cross-sectional analysis of 702 community-dwelling older adults (aged ≥ 55 y), nor did homocysteine correlate with a decline in MMSE score over time. The present study used a modified version of the MMSE, the 3MSE, which is considered to have a somewhat better capacity for discrimination than does the MMSE (24). The use of this modified test may explain why a modest association between homocysteine and global cognitive function was observed in the

present study, but not in the Rotterdam study. Another possible contributor to this difference may be the larger sample size of the SALSA cohort.

A potential confounding factor that must be considered in the present study is folic acid fortification. The participants in SALSA were recruited after the institution of folic acid fortification in the United States (fully implemented by January 1998). The efficacy of this program in lowering the prevalence of folate deficiency was previously documented in a report on the Framingham Study (28) and is reflected by the very low prevalence of folate deficiency in the SALSA sample ($< 1\%$ defined as RBC folate $\leq 160 \text{ ng/mL}$). Folic acid is the most important modifiable determinant of plasma homocysteine concentrations (29), and, consequently, folic acid fortification may have attenuated the relation between homocysteine and cognitive function. This could have occurred as a consequence of reduced homocysteine concentrations or through a homocysteine-independent mechanism. Alternatively, folic acid fortification may have obscured the hyperhomocysteinemia that existed in some study participants before fortification. Sheshadri et al (10) showed that incident dementia over an 8-y period was higher in individuals with the highest baseline concentrations of homocysteine. It is possible that post-folic acid–fortification homocysteine concentrations are less predictive of cognitive function scores than are prefortification homocysteine concentrations. This hypothesis cannot be tested in the SALSA population because prefortification blood samples are not available. However, it should be noted that, despite a low prevalence of folate deficiency, 17% of the SALSA participants had hyperhomocysteinemia (defined as total plasma homocysteine $\geq 13 \mu\text{mol/L}$). On the basis of the findings of Sheshadri et al (10), it may be predicted that these subjects with current hyperhomocysteinemia are at increased risk of accelerated cognitive decline and dementia over the next decade.

This raises the important question of whether interventions designed to lower plasma homocysteine concentrations will prevent cognitive decline in older adults. The most effective means of lowering homocysteine concentrations is B-vitamin supplementation, and intervention trials are currently underway to determine whether B vitamins reduce the risk of vascular disease (30). It will be interesting to see if the risk of dementia is also reduced in these studies. However, the modest association between homocysteine concentration and cognitive function observed in the present study leads to the conclusion that the effect of B vitamins may be limited. 

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JWM participated in the concept and design of the study, supervised blood processing and biochemical analyses, participated in the statistical analysis and interpretation of the data, and was responsible for drafting the article. RG participated in the concept and design of the study, participated in the interpretation of the data, and provided input on the final draft of the article. MIR participated in the statistical analysis and interpretation of the data and provided input on the final draft of the article. LHA (Principal Investigator of US Department of Agriculture grant 5456) participated in the concept and design of the study, participated in the interpretation of the data, and provided input on the final draft of the article. DMM was responsible for development of several of the cognitive function tests used in the study, participated in the statistical analysis and interpretation of the data, and provided input on the

final draft of the article. WJJ (Principal Investigator of NIH grant R01 AG10129) participated in the concept and design of the study, participated in the interpretation of the data, and provided input on the final draft of the article. MNH (Principal Investigator of the Sacramento Area Latino Study on Aging, NIH grant R01 AG12975) participated in the concept and design of the study; was responsible for the recruitment of study subjects, the acquisition of blood samples, data collection, and data management; participated in the statistical analysis and interpretation of the data; and provided input on the final draft of the article. None of the authors had a personal or financial conflict of interest with respect to this study.

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