Total Plasma Homocysteine and Depressive Symptoms in Older Hispanics

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Abstract.

Background: Very few studies have investigated the association between total plasma homocysteine (tHcy) and depressive symptoms in older Hispanics.

Objective: To test the hypothesis that high tHcy associates with depressive symptoms in older Hispanics.

Methods: A total of 1,418 participants ≥ 55 years old from the Maracaibo Aging Study (MAS) underwent standardized neurological, neuropsychiatric, and cardiovascular assessments. The Neuropsychiatric Inventory Depression Subscale (NPId) was used to assess the burden of depressive symptoms. The tHcy levels and other biochemical parameters in blood samples were measured. Univariate and multivariate logistic regression models were applied.

Results: Participants with depressive symptoms had higher levels of tHcy than those without (15.1 versus 13.9 µmol/L; $p = 0.009$). Elevated tHcy levels were associated with depressive symptoms after adjusting for age, sex, education, smoking, diabetes, hypertension, alcohol intake, stroke, and dementia (OR = 1.58; 95% CI, 1.18–2.12).

Conclusion: Elevated levels of tHcy were associated with depressive symptoms in older Hispanics living under the nutritional and environmental conditions of a developing country.

Keywords: Aging, cohort studies, depressive symptoms, elderly, Hispanics, homocysteine, Latinos

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INTRODUCTION

Depressive symptoms are very common among older adults and are associated with disability and poorer health outcomes [1, 2]. High blood concentrations of homocysteine have been found to be associated with depressive symptoms in some studies [3–6] but not all [7, 8]. Homocysteine is an amino acid derived from methionine and is a key component of two major metabolic pathways: remethylation to methionine and transsulfuration to cystathionine. The first of these pathways, remethylation to methionine, is vitamin B-12 dependent [9]. Once methionine is formed, the majority of it is activated to form S-adenosylmethionine (SAM) in a folate-dependent reaction, which serves as a methyl donor in neurological reactions such as the synthesis of neurotransmitters, the formation of membrane phospholipids, and the metabolism of nucleic acids [10]. Decreased SAM leads to impaired synthesis of serotonin [11, 12], which is an important factor in the genesis of depression [13] potentially explaining why individuals with depression have higher levels of total plasma homocysteine (tHcy).

Most studies examining the association between depression and tHcy have been performed in developed countries [4, 8]. The impact of the differences in nutritional contexts across low, middle, and high-income countries in the association between tHcy and depressive symptoms needs to be better understood. Ethnic differences might also play an important role in this association as studies in US populations had a 30% lower folate intake in Hispanics in contrast to White Americans [14]. We conducted this study to test the hypothesis that high levels of tHcy are associated with depressive symptoms in elderly Hispanics residing in Venezuela—a middle-income to developing country.

MATERIALS AND METHODS

Participants

This study examined a subset of participants from the Maracaibo Aging Study (MAS)—a population-based cohort study investigating age-related diseases among elderly residents of Santa Lucía, Maracaibo, Venezuela [15]. The study design and methods were described in detail elsewhere [16]. Briefly, the MAS enrolled approximately 2,438 participants from 1998 until 2001 in a catchment area known as "Santa Lucía". The clinical evaluation of each participant included a neuropsychiatric examination that integrated medical and family history with history of risk factors for dementia and depressive symptoms. The present study is restricted to a subset of 1,418 MAS participants who had a tHcy measurement and an assessment of mood and other evaluations as measured by the NPI (see below). The tHcy and neuropsychiatric assessments were measured the same day or the next day; in a small proportion of participants, these assessments were performed within one week. The 1,418 participants included here did not differ significantly from those who were excluded except for age, prevalence of diabetes, and hypertension (see Supplementary Table 1). Among 1,418 study participants, the proportion of missing values did not differ significantly between those with versus without depressive symptoms.

Ethical statement

The University of Zulia Institutional Ethical Review Board approved the MAS and informed consent was obtained from all participants.

Assessment of depressive symptoms and cognitive functions

Depressive symptoms were evaluated using the validated Spanish version of the Neuropsychiatric Inventory (NPI) [17, 18], the NPI depression subscale (NPId). The NPId rates each symptom according to frequency (0–4 points) and severity (1–3 points), and the total score is calculated by multiplying the frequency x severity. The possible scores from the NPId range from 0 to 12 points. The interpretation of the results is as follows: 0 points = There are no depressive symptoms; 1–3 points = mild depressive symptoms; and 4–12 points = clinically significant depressive symptoms. While most NPI scores were self-reported, the family provided the information for NPI scores for participants with dementia. Methods are described in detail elsewhere [16]. A diagnosis of dementia was determined by consensus in a diagnostic conference of physicians, psychologists, and social workers based on the criteria in the *Diagnostic and Statistical Manual of Mental Disorders* (4th edition) [19]. The Clinical Dementia Rating (CDR) was used to assess the dementia severity [20, 21].

Other measures

Sociodemographic variables included age, sex, and years of formal education. Potentially confounding

medical conditions were also studied including hypertension, diabetes, stroke, and hyperhomocysteinemia. Hypertension was defined as having systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or current treatment with antihypertensive drugs. Diabetes was defined as a serum glucose level ≥ 126 mg/dL, current pharmacological treatment of diabetes, or a self-reported history of diabetes. Stroke was defined through self-reported diagnosis. Hyperhomocysteinemia or elevated tHcy levels were defined as tHcy ≥ 14 μmol/L [22]. Depressive symptoms were defined as having a cut-off point of ≥ 4 in the NPId subscale (clinically significant depressive symptoms).

Laboratory analysis

Plasma tHcy, folate, serum glucose, cholesterol, and triglycerides were measured using blood samples obtained between and 7:00 and 8:00 AM after overnight fasting. All blood samples were obtained and processed at the Cardiovascular Center of the University of Zulia (CCUZ) in Maracaibo. Samples were immediately placed in crushed ice and protected from light and were processed within 1 h of collection. The biochemical assays for all samples were performed at the CCUZ, and a subset was validated at two external laboratories: The University of Texas Southwestern Medical School and the Instituto Venezolano de Investigaciones Científicas in Caracas. The values obtained by the three laboratories were highly comparable—the Pearson's correlation coefficient (r2) between absolute values from MAS analyses and the HPLC results from Caracas and Texas was 0.99 in each case. Details of sample collection and analyses have been published previously [22].

Statistical analysis

Quantitative traits between individuals with versus without depressive symptoms were tested using Student's *t*-test. The distribution of cardiovascular risk factors was compared using the Pearson χ^2 test. To test whether hyperhomocysteinemia (defined as tHcy ≥ 14 μmol/L) was associated with depressive symptoms, we applied multivariable logistic regression models. Because the relationships between depressive symptoms and tHcy levels could be altered by the presence of chronic conditions, we present three logistic multivariate models with two potentially confounding medical conditions, namely stroke

and dementia. Model 1 adjusted for age, sex, level of education, smoking history, diabetes, folate, hypertension, and alcohol intake. Model 2 adjusted for a history of stroke as well as the covariates in Model 1. Model 3 adjusted for a history of dementia as well as the covariates in Model 2. We first performed the analysis using the entire set of 1,418 individuals; we then performed an additional analysis stratified by age (55–66 versus >66 years). All statistical analyses were performed using SPSS software version 22 (SPSS, IBM Corporation, Armonk, NY, USA).

RESULTS

Cohort characteristics

Table 1 shows the mean age of the study participants to be 66.8 years. The proportion of women was higher (69.3%) than that of men. Men were slightly younger than women and had higher levels of education. This study includes a subset of MAS study participants who had both levels of tHcy and NPId measured at one time point, differences with MAS participants excluded from this analysis are presented in Supplementary Table 1.

The prevalence of individuals diagnosed with clinically significant depressive symptoms by NPId was 16.7% (Table 1). The group with depressive symptoms had a significantly higher mean age, higher percentage of women, lower average years of education, and higher illiteracy rate than the group without depressive symptoms (Table 1). The individuals with depressive symptoms had a significantly higher prevalence of diabetes (15.0 versus 10.7%), stroke (10.1 versus 5.0%), and dementia (15.2 versus 5.1%). Individuals with depressive symptoms were less likely to be currently exposed to smoking and alcohol than those without depressive symptoms.

Homocysteine and depressive symptoms

Individuals with depressive symptoms were more likely to have hyperhomocysteinemia than those without depressive symptoms (49.8 versus 36.8%, $\chi^2 = 13,927$; $p < 0.0001$). In addition to having significantly higher mean tHcy levels (15.1 versus 13.9 μmol/; $p = 0.009$), individuals with depressive symptoms had higher levels of cholesterol and triglycerides but had lower levels of folate than those without depressive symptoms.

Table 1
Comparison of Characteristics between Participants With versus Without Depressive Symptoms

Characteristics	Study Sample ($n = 1,418$)	With Depressive Symptoms ($n = 237$)	Without Depressive Symptoms ($n = 1,181$)	p^*
Demographics				
Age, y	66.8 (8.6)	69.1 (9.3)	66.3 (8.3)	<0.001
Female, n (%)	982 (69.3)	187 (78.9)	795 (67.3)	<0.001
Illiteracy, n (%)	153 (10.8)	45 (18.9)	108 (9.1)	<0.001
Education, y	5.4 (5.7)	4.3 (3.6)	5.8 (4.1)	<0.001
Clinical Information				
Diabetes mellitus, n (%)	161 (11.4)	35 (14.8)	126 (10.7)	0.058
Hypertension, n (%)	1,171 (82.6)	198 (83.5)	973 (82.4)	0.668
Current smoker, n (%)	204 (14.4)	23 (9.7)	181 (15.3)	0.029
Alcohol intake, n (%)	455 (32.1)	56 (23.6)	399 (33.8)	0.002
Stroke, n (%)	84 (5.9)	24 (10.1)	60 (5.1)	0.003
Clinical dementia rating ≥ 1, n (%)	97 (6.8)	36 (15.2)	61 (5.2)	<0.001
Vitamins intake, n (%)	646 (45.6)	117 (49.4)	529 (44.8)	0.139
Hyperhomocysteinemia, n (%)	553 (39.0)	118 (49.8)	435 (36.8)	<0.001
Biochemistry				
Cholesterol, mg/dl	196.6 (57.7)	201.4 (57.1)	195.6 (57.9)	0.210
Triglycerides, mg/dl	163.2 (126.4)	171.5 (163.3)	161.5 (117.2)	0.332
Total plasma homocysteine, μmol/L	14.1 (6.5)	15.1 (7.2)	13.9 (6.3)	0.009
Folate, ng/ml	5.2 (3.1)	4.8 (2.4)	5.3 (3.2)	0.160

Frequency and proportions (%) are presented for categorical variables, mean and standard deviation are presented for continuous variables. $^*p$ value for the comparison of characteristics between participants with *vs.* without depressive symptoms.

Table 2
Odds Ratio for Depressive Symptoms Associated with Hyperhomocysteinemia by Age Groups

Age Group	Cases (%)	Univariate		Model 1		Model 2		Model 3	
		OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Study Sample ($n = 1,418$)	237 (16.7)	1.73 (1.33–2.25)	<0.001	1.71 (1.30–2.28)	<0.001	1.68 (1.26–2.25)	<0.001	1.58 (1.18–2.12)	0.002
By Age Group									
55–66 y ($n = 767$)	105 (13.7)	1.62 (1.06–2.47)	0.026	1.89 (1.21–2.96)	0.005	1.84 (1.17–2.88)	0.008	1.81 (1.15–2.84)	0.011
>66 y ($n = 651$)	132 (20.3)	1.58 (1.12–2.22)	0.010	1.62 (1.12–2.35)	0.010	1.62 (1.11–2.35)	0.012	1.46 (0.99–2.14)	0.052

OR, odds ratio; CI, confidence intervals. Model 1 adjusts for age, sex, education, current smoking, diabetes, hypertension and alcohol intake. Model 2 adds a covariate stroke to Model 1. Model 3 adds a covariate dementia to Model 2.

Hyperhomocysteinemia associated with depressive symptoms

Hyperhomocysteinemia was associated with a 1.71-fold (CI, 1.30–2.28; $p < 0.001$) increase in the probability of having depressive symptoms after controlling for potential confounders, namely, age, sex, education, smoking and alcohol exposure, presence of hypertension and diabetes, and folate levels (Model 1, Table 2). When a history of stroke was added to the model (Model 2), the odds ratio declined slightly to 1.68 (CI, 1.26–2.25); $p = 0.001$. With the further addition of dementia (Model 3), the odds ratio further reduced to 1.57 (CI, 1.17–2.09; $p = 0.002$).

To account for the fact that levels of tHcy increase with age, we performed a stratified analysis by age using the same three models above (Table 2). The effect of hyperhomocysteinemia was slightly stronger in the younger age group (55–66 years) than in the older group (>66 years) after controlling for potential confounders: age, sex, education, smoking and alcohol exposure, presence of hypertension and diabetes, and folate levels (Model 1, Table 2). When a history of stroke was added to the model, the odds ratio declined slightly in both groups (Model 2). With further addition of dementia, the odds ratio for depressive symptoms was relatively constant in the younger group (Model 3); however, the odds ratio for the older group was reduced and was no longer statistically significant.

Model performance

The inclusion of hyperhomocysteinemia significantly improved the model performance in a basic model accounting for sex, age, education, current

Table 3
Nested Logistic Regression Models Relating Depressive Symptoms with Hyperhomocysteinemia

Models	χ^2 Statistic	p	R^2 (%)[‡]
Study sample			
Base model*	86.5	<0.001	5.92
+Hyperhomocysteinemia	96.0	0.002	0.68%
Subjects 55–66 years			
Base model*	35.2	<0.001	4.91%
+Hyperhomocysteinemia	46.6	0.001	1.61%
Subjects>66 years			
Base model*	44.0	<0.001	5.95%
+Hyperhomocysteinemia	47.8	0.052	0.53%

*Base model accounted for age, sex, education, current smoking, diabetes, hypertension, alcohol intake, stroke, and dementia. [‡]R^2 is an estimate of the additional variance explained (https://apha.confex.com/apha/134am/techprogram/paper_135906.htm).

smoking, diabetes, hypertension, alcohol intake, stroke, and dementia in the study sample, and in subjects 55–66 years old (Table 3). The basic model accounted for 4.91% to 5.95% of the model performance ($p < 0.001$) in the study sample and stratified by age groups. When hyperhomocysteinemia was included, the model performance improved 0.68% ($p = 0.002$) in the study sample, and 1.61% ($p = 0.001$) and 0.53% ($p = 0.052$) among subjects 55–66 and >66 years old, respectively.

DISCUSSION

The present study of the MAS cohort showed that individuals with depressive symptoms had significantly higher mean tHcy levels and a higher proportion of hyperhomocysteinemia than individuals without depressive symptoms. This study provides the first evidence that elevated tHcy is associated with depressive symptoms in Hispanics living under the nutritional and environmental conditions of Latin America. Our findings agree with previous studies of older adults residing in developed countries [23, 24]. The relationship between elevated tHcy levels and depressive symptoms is complex because there are health conditions associated with depression such as stroke [25], dementia [26], and diabetes [27]. The tHcy levels vary with sex and age [28] and are influenced by diet (including supplementation of folate and others vitamins), lifestyle, health status, and genetic factors [29]. Furthermore, late-life depression or depressive symptoms in the elderly are associated with cerebrovascular disease, poor health status, diabetes, dementia, and genetic factors [29] as well as psychosocial risk factors including personality disorders and personality attributes [30]. Here, we

accounted for those potential factors in the adjusted logistic regression models. When the sample was stratified by age groups (Model 1), hyperhomocysteinemia only remained significantly associated to depressive symptoms in subjects 55–66 years old.

We found a significantly higher prevalence of stroke in subjects with depressive symptoms than in those without depressive symptoms corroborating the results of previous studies that showed that cerebrovascular disease and stroke are associated with depression or depressive symptoms [25]. After adjustment by stroke (Model 2), hyperhomocysteinemia remained significantly related to depressive symptoms. These results suggest that the effects of hyperhomocysteinemia on depressive symptoms are independent of stroke especially in the younger group. Further studies need to address the effectiveness of monitoring and reducing tHCY levels in middle age as a preventive measure of depressive symptoms in populations at high risk of depression such as Hispanics.

The prevalence of dementia was significantly higher in subjects with depressive symptoms than in those without depressive symptoms in agreement with previous findings [31]. Elevated tHcy was associated with depressive symptoms after adjustment for dementia (Model 3) in all subjects and in the group of subjects aged 55–66 years old suggesting that the effects of hyperhomocysteinemia on depressive symptoms are independent of dementia—especially in the younger group. Our findings of the association of hyperhomocysteinemia with a 1.58-fold increase in the probability of having depressive symptoms after controlling for confounding factors is similar to the findings of some previous studies where the odds ratio ranged from a 1.26 to 1.90-fold increase [4, 5]. The significant but relatively modest associations between depressive symptoms and elevated Hcy levels in these studies might explain the discrepancies between other previous studies that are smaller than the MAS.

The incremental value of hyperhomocysteinemia as a marker for depressive symptoms is significant in this population, particularly among those participants in the younger group (55–66 years). Even if the effect size of high levels of tHcy is small (Table 3) and clinical relevance uncertain, adding a marker related to depressive symptoms to the prediction models containing standard risk factors might lead to improved quantification of true future risk of developing depression. Longitudinal studies are needed to test the implications of this study.

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Limitations and strengths

Some limitations in our study are recognized and need to be discussed. First, this study used cross-sectional data; therefore, it was not possible to determine if the elevated levels of homocysteine preceded the depressive symptoms or other medical conditions including stroke, dementia, and diabetes. Second, given the participants excluded from the analysis (that were older and with more chronic illness), our results are likely to underestimate the degree of association between depressive symptoms and tHcy. Another potential limitation in our study was that our clinical definition of stroke was based on self-reports not accounting for "silent" cerebrovascular disease only detectable by brain imaging; therefore, the prevalence of cerebrovascular disease was likely underestimated [32]. Finally, the NPId does not diagnose depressive disorders according the DSM-5. The main strength of our study is the inclusion of older Hispanics residing in their country of origin in Latin America, because these subjects live under unfavorable nutritional and environmental conditions that might contribute to increased Hcy levels in contrast to other older adults residing in developed countries [22, 32]. A previous study of tHcy and depressive symptoms in older Latinas residing in Sacramento, California, focused on the relationship between folate levels and depressive symptoms [33], and tHcy was not associated with depressive symptoms. Earlier studies of the relationship between tHcy and depressive symptoms included diverse ethnic groups with varying environmental exposures and had inconsistent results [6, 34].

CONCLUSIONS

This study suggests that elevated tHCY independently associates with depressive symptoms in elderly Latin Americans. Although longitudinal data are needed to assess causality, the demonstrated relationship between tHcy and depressive symptoms in this Latin American population provides new insights into the relevance of hyperhomocysteinemia throughout life and particularly for depressive symptoms in populations from developing countries where hyperhomocysteinemia is common.

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SUPPLEMENTARY MATERIAL

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