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Associations of lipid levels and cognition: Findings from the Hispanic Community Health Study/Study of Latinos

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Abstract

Objective: Hispanics/Latinos in the US are less aware of their cholesterol levels and have a higher burden of associated adverse cardiovascular and cerebrovascular outcomes than non-Latino Whites. Investigations of the associations between cholesterol levels and cognition in this population have often occurred within the context of metabolic syndrome or limited to select lipids despite the fact that triglycerides (TG) may be more relevant to Hispanic/Latino health.

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Methods: Baseline data from the Hispanic Community Health Study/Study of Latinos, collected from 2008-2011, was used to investigate the associations of lipid levels (i.e., TG, total cholesterol, TC; low-density and high-density lipoprotein cholesterol, LDL-C and HDL-C) on cognition (i.e, learning, memory, verbal fluency, and digit symbol substitution, DSS) adjusting for relevant confounders.

Results: In 7,413 participants 45-74 years old from Central American, Cuban, Dominican, Mexican, Puerto Rican, or South American backgrounds, separate fully-adjusted linear regression models revealed that TG levels were inversely associated with DSS performance; however, this relationship was no longer significant once additional cardiovascular disease risk factors were added to the model ($p=0.06$). TC and LDL-C (separately) were positively associated with learning and verbal fluency regardless of adjustments (p-values<0.05). Separate analyses investigating effect modification by background and by sex revealed a particularly robust association between TC and DSS for Puerto Ricans and Central Americans (albeit in opposite directions), and an inverse relationship between TG and DSS performance for women (p-values<0.02).

Conclusions: It is important to consider individual lipid levels and demographic characteristics when investigating associations between cholesterol and cognition in Hispanics/Latinos.

Keywords

cholesterol; triglycerides; cognition; Latinos; learning; memory

Introduction

The majority of directed studies of lipid levels and cognition, especially total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C), have been done in non-Latino White participants (Anstey, Lipnicki, & Low, 2008; Lv et al., 2016; Ma et al., 2017; Wardle et al., 2000). This is despite the fact that Hispanics/Latinos are less aware of their cholesterol levels (Rodriguez et al., 2015) and have consistently elevated triglyceride (TG) levels compared to other minority groups (Rodriguez & Brenes, 2008). Furthermore, Hispanics/Latinos have a high burden of dyslipidemia (Rodriguez et al., 2014) and associated adverse cardiovascular (Daviglus et al., 2012; Willey et al., 2011) and select cerebrovascular (Gezmu et al., 2014) outcomes. Thus, more work is needed studying lipid levels and cognition in Hispanic/Latinos.

Work to date in Hispanics/Latinos has often been done within the context of metabolic syndrome (e.g., Gonzalez et al., 2018) with fewer studies focused on a complete lipid panel. The majority of studies suggest that metabolic syndrome and/or global cardiovascular disease risk factor burden is associated with cognition including declarative memory, working memory, and information processing speed in cohorts either including or exclusively composed of Hispanics/Latinos (Del Brutto, Mera, & Zambrano, 2016; Lamar et al., 2019; Levin et al., 2014; Warsch et al., 2013; Yaffe et al., 2007; Zeki Al Hazzouri et al., 2013). All but one (Del Brutto et al., 2016) found that individual lipid levels contributed to these cognitive profiles. More directed studies either including (Reitz et al., 2008) or exclusively composed of Hispanics/Latinos (Ihle et al., 2017; Parthasarathy et al., 2017) reported differing results based on the lipid level and/or background studied. For example,

while TC and LDL-C did not contribute to cognitive impairment for Hispanics/Latinos of Caribbean background (Reitz et al., 2008), a Brazilian study reported associations between lower HDL-C and lower declarative and working memory (Ihle et al., 2017). A study of a heterogeneous group of older adults fluent in English reported a negative association between TG levels and executive functioning but not memory (Parthasarathy et al., 2017). These studies lay the foundation for a comprehensive investigation of the relationship between lipid levels (i.e., TC, LDL-C, HDL-C, and TG) and cognition within a large cohort study of Hispanics/Latinos from multiple backgrounds.

The Hispanic Community Health Study/Study of Latinos (HCHS/SOL) provides the opportunity to systematically examine associations between individual lipid levels and cognition in mid- to late-life Hispanics/Latinos of different backgrounds (e.g., Mexican, Puerto Rican, Cuban, Central American, Dominican). Given the outsized importance TG levels may play in burden of disease in this population (Martinez-Larrad et al., 2012; Rodriguez & Brenes, 2008; Vega-Lopez et al., 2013), and based on previous studies of TG and cognition incorporating Hispanics/Latinos, we hypothesized that TG levels would be associated with working memory and executive functioning (but not memory) performance after adjusting for relevant confounders. We also explored associations between TC and cognition with follow-up analyses investigating the contributions of LDL-C versus HDL-C on significant results. Given conflicting results of the association between lipid levels and cognition in distinct Hispanic/Latino backgrounds (Reitz et al., 2008), and the fact that Hispanic/Latino background contributes to differential levels of cholesterol and dyslipidemia (Daviglus, Pirzada, & Talavera, 2014; Daviglus et al., 2012; Rodriguez et al., 2015), and cognition (Gonzalez et al., 2015), we also investigated whether background was an effect modifier of the association between lipid levels and cognition. Lastly, Hispanics/Latinos with dyslipidemia in HCHS/SOL more likely to be female (Rodriguez et al., 2014); thus, we investigated whether sex was an independent effect modifier of the association between lipid levels and cognition. Investigating profiles of lipids and cognition in Hispanics/Latinos by background and sex may point toward biomarkers related to cognition in specific individuals.

Methods

The HCHS/SOL is a population-based prospective cohort study of 16,415 Hispanics/Latinos aged 18-74 years from four U.S. cities (Chicago, IL; Miami, FL; Bronx, NY; San Diego, CA) that oversampled persons ages 45-74 to facilitate examination of target outcomes based on a multi-stage stratified probability sampling design (Lavange et al., 2010). The baseline examination (2008 to 2011) consisted of comprehensive biological, behavioral, and socio-demographic assessments (Sorlie et al., 2010). Cognitive testing was also conducted during this baseline examination, but only for individuals 45 years and older. The cohort includes participants who self-identified as having a Central American, Cuban, Dominican, Mexican, Puerto Rican, or South American background regardless of race or genetic ancestral markers. The sample design and cohort selection have been described in detail elsewhere (Lavange et al., 2010). This HCHS/SOL was approved by the IRB at each site, all participants gave written informed consent, and the research was completed in accordance with the Helsinki Declaration.

Participants

Only men and women 45 years and older with baseline examination data related to lipid levels and cognition were considered for this cross-sectional analysis (N=9,714). We excluded 1,696 participants who self-reported acute stroke, or substance abuse, and/or were found to have psychotropic medication use including anti-anxiolytics, antidepressants, and antipsychotics based on medication review at study visit. Stroke (Mijajlovic et al., 2017) and substance abuse (George & Koob, 2017) can negatively impact cognitive health. Psychotropic medication use suggests the presence of anxiety, depression, and/or psychotic disorders serious enough to warrant pharmacological intervention. These conditions, and at times the medications used to treat them (Barker, Greenwood, Jackson, & Crowe, 2004; Yeo, Lim, Mao, & Yau, 2017), may negatively impact cognition. Including these conditions and/or individuals using such medications in our analyses would confound our interpretation of results within the conceptual framework of lipid levels and cognition. We also excluded participants who were missing data on any cognitive variable (n=428) or key covariate (n=177). This resulted in 7,413 participants.

Determination of Lipid levels

Participants fasted for 12 hours prior to a blood draw by trained and certified clinic staff. Fasting blood samples were collected soon after participant arrival for their baseline visit, stored at −20°C, and shipped every week for analysis to the Lipoprotein Analytical Laboratory at the HCHS/SOL Central Lab at the University of Minnesota Medical Center. The Lipoprotein Analytical Laboratory participates in the Lipid Standardization Program of the CDC. TG levels were measured in EDTA plasma with the use of TG GB reagent (Roche Diagnostics) on a centrifugal analyzer. TC was measured using cholesterol oxidase enzymatic method. LDL-C was calculated using the Friedewald equation (Friedewald, Levy, & Fredrickson, 1972), and HDL-C was measured with an enzymatic method after precipitation of non–HDL cholesterol with heparin and magnesium dextran sulfate. All field center procedures and laboratory protocols are available online: http://www2.cscc.unc.edu/hchs/manuals-forms.

Cognitive Testing

Test measures were administered in the participants' preferred language during face-to-face interviews by study staff trained and supervised by doctorate-level, licensed, clinical neuropsychologists. Our brief neuropsychological assessment was designed to limit participant burden during the 6-hour clinic visit and structured to include important outcomes associated with aging. The Brief Spanish English Verbal Learning Test (B-SEVLT) (Gonzalez et al., 2015) asked participants to recall items from a 15-item list presented for three consecutive 'learning' trials followed by a 15-item distractor list and a free recall trial immediately following the distractor trial (Gonzalez, Mungas, & Haan, 2002; Gonzalez, Mungas, Reed, Marshall, & Haan, 2001). Variables of interest included total learning across all 3 trials (range=0-45) and recall post-interference (memory; range=0-15). Verbal Fluency required participants to generate as many words as possible within 60 seconds that began with a specific letter, i.e., 'F' and 'A' (Benton & Hamsher, 1989; Lezak, Howieson, & Loring, 2004). The total number of correctly generated words was summed

across both trials and represents the executive ability of establishing and maintaining mental set and word retrieval flexibility. Digit Symbol Substitution (DSS) from the Wechsler Adult Intelligence Scale-Revised measured working memory and information processing speed (Wechsler, 1981) by requiring the rapid copying and encoding of symbols to numbers within 90 seconds. The variable of interest was the total number of correctly transcribed symbols during the time allotted. A brief Six-Item Screener measured orientation and mental status (SIS; higher=better performance) (Callahan, Unverzagt, Hui, Perkins, & Hendrie, 2002), with scores of 4 or lower suggestive of low mental status (Callahan et al., 2002; Gonzalez et al., 2015).

Relevant Covariates

In addition to age, sex, education, and Hispanic/Latino background, we adjusted for language of test administration, health insurance status, physical activity, diet, body mass index (BMI), diabetes and hypertension. Language of administration may be an important consideration for cognitive testing in Hispanics/Latinos, thus, language preference for testing (Spanish/English) was used as a covariate in all analyses. Health insurance status (yes/no) was also queried given that this may impact access to care, overall health, and wellbeing.

Physical activity levels, known to affect lipid levels (Lin et al., 2015) and cognitive health (Gonzalez et al., 2016), and highly associated with functional status in older adults (Paterson & Warburton, 2010; Steeves, Shiroma, Conger, Van Domelen, & Harris, 2019), were evaluated using the WHO Global Physical Activity Questionnaire (Surveillance, 2008) and determined per the 2008 physical activity guidelines available at the time of the HCHS/SOL Visit 1. Five mutually exclusive levels of physical activity were determined: inactive (no activity beyond baseline activities of daily living), low (activity beyond baseline but fewer than 150 minutes of moderate-intensity physical activity a week or the equivalent amount of vigorous-intensity activity or the equivalent combination of moderate and vigorous activity), medium (150 minutes to 300 minutes of moderate-intensity activity a week, or 75 to 150 minutes of vigorous-intensity physical activity a week, or the equivalent combination of moderate and vigorous activity), high (more than the equivalent of 300 minutes of moderate-intensity physical activity a week, or more than 150 minutes of vigorous activity, or an equivalent combination of both) activity, and not reported. Activity had to be performed in episodes of at least 10 minutes.

Nutritional differences are known to influence cholesterol levels (Howell, McNamara, Tosca, Smith, & Gaines, 1997; Jin & Nicodemus-Johnson, 2018). We assessed diet intake via the 2010 Alternative Healthy Eating Index (AHEI-2010), a measure of diet quality based on 11 foods and nutrient components predictive of chronic disease risk (Chiuve et al., 2012). AHEI-2010 scores (range=0 to 110 with higher scores representing healthier eating habits) were derived from available 24-hour dietary recall data (one to two recalls per participant). BMI, a known contributor to both lipid levels (Fall et al., 2015) and a sometime associate of cognition (e.g., Dahl & Hassing, 2013; Han et al., 2009), was quantified via weight (kg)/height (m^2).

Diabetes and hypertension were also measured given that they combine with lipid levels to contribute to metabolic syndrome. Diabetes status (presence/absence) was determined using the criteria set forth by the American Diabetes Association (ADA, 2018) which included at least one of the following: random glucose of ≥200 mg/dL, fasting glucose≥126 mg/dL, hemoglobin A1C ≥6.5%, or, if available, 2-hour post load glucose≥200 mg/dL during an oral glucose tolerance test. Diabetes was also defined based on anti-diabetic medication use determined by medication review at the study visit. Hypertension status (presence/absence) was determined using the definition implemented in the NHANES. Thus, three blood pressure (BP) readings were obtained (and averaged) at 1-minute intervals following a 5-minute rest period on the right arm with the participant in a seated position and the arm resting. If systolic or diastolic BP was greater than or equal to 140/90 or if antihypertensive medications were provided during the medication review, the participant was deemed hypertensive. We chose to adjust for diabetes and hypertension status as opposed to continuous measures of glucose and/or BP, respectively, so that we could incorporate the presence/absence of medications for these conditions which have been shown to affect cognition in older adults (Lamar et al., 2017; Ryan et al., 2006). Additionally, values of BP tend to be "censored" due to treatment; occurring in over 30% of participants. Thus, continuous BP adjustment will not capture the entire effect of an individual's BP. Additionally, adjusting for both continuous BP and hypertension treatment has been demonstrated in the context of modeling BP as a function of covariates to yield biased estimates of regression coefficients. Thus, we opted to use hypertension and diabetes status as confounding variables to adjust for the effect of a health condition that reflects both levels and treatment.

Statistical analyses

All summary statistics and formal statistical analyses were conducted in STATA 15.1 and accounted for the HCHS/SOL sample design including sampling weights, cluster sampling, and stratification to allow appropriate generalization to the target population (Lavange et al., 2017). Separate multivariable linear regressions were used to adjust for potential confounders. Statistical significance was assessed via p-values≤0.05 and 95% confidence intervals (CIs).

All lipid levels, i.e., TC, HDL-C, LDL-C, and TG, were $\log_2$ transformed, e.g., $\log_2$(TG) for triglyceride levels, not only to approximate normality but because our application of fractional polynomials to our data revealed that the log transform proved the best fit for the data. Thus, beta weights reflect the effect of doubling a given lipid level on cognition. While individual lipid levels are often converted into ratios, e.g., a ratio of TG to HDL-C, we chose to analyze each variable separately given the fact that ratios may increase variability in our metrics and cause spurious correlations, making it difficult to interpret the exact contributing factors for resulting associations. Cognitive outcomes were normally distributed based on Q-Q plots and Kolmogorov-Smirnov testing (Razali & Wah, 2011).

For each cognitive outcome (B-SEVLT learning and memory, Verbal Fluency, and DSS performance) we fit two survey linear regression models using $\log_2$(TG) and $\log_2$(TC) separately as continuous variables. Model 1 adjusted for age, sex, education, Hispanic/

Latino background, language of test administration, health insurance status, physical activity, diet, and BMI. In order to determine whether other cardiovascular disease risk factors of diabetes and hypertension contributed to our results, we ran a second model (Model 2) adding these terms. If $\log_2$(TC) was statistically significant in Model 2, we substituted it with $\log_2$(HDL-C) and $\log_2$(LDL-C) as the predictor variables to determine whether good or bad cholesterol levels were driving results. We investigated whether background or sex were effect modifiers of the association between lipid levels and cognition by running a series of models that added either the interaction term $\log_2$(lipid)*background or $\log_2$(lipid)*sex to both Model 1 and Model 2. To aid in the interpretation of significant interaction terms (as appropriate given our corrected p-value of 0.01), we followed up with overall survey-adjusted Wald tests.

Results

Key characteristics and cognitive test performance data for our target population may be found in Table 1. Levels of fasting TC were, on average, elevated above published Cholesterol Clinical Practice Guidelines (Grundy et al., 2018). Key characteristics and cognitive test performance data by Hispanic/Latino background may be found in Supplemental Table 1.

Triglyceride Levels and Cognitive Test Performance

As seen in Table 2, $\log_2$(TG) levels were not associated with any cognitive test score, regardless of adjustments.

When we investigated whether background was an effect modifier, $\log_2$(TG) levels were inversely associated with DSS performance only but the $\log_2$(TG)*background interaction term did not meet threshold for significance, regardless of adjustments (p-values≥0.56). Thus, a doubling of TG levels resulted in a significant reduction in DSS performance by slightly over 1 point (beta=−1.40, SE=0.67, t=−2.08, 95% CI=−2.72 -- −0.08, p=0.03) when adjusting for age, sex, education, Hispanic/Latino background, language of test administration, health insurance status, physical activity, diet, and BMI. While the magnitude of the effect did not change with the additional adjustments for hypertension and diabetes (Model A, Table 2), results did not meet the threshold for significance (p=0.06).

When we investigated whether sex was an effect modifier of $\log_2$(TG) and cognitive test scores, the $\log_2$(TG)*sex interaction term was significant for fluency regardless of adjustments (p≤0.008; Table 2); follow-up analyses did not reach the threshold for significance in the fully adjusted model (p-values≤0.07). The $\log_2$(TG)*sex interaction term was significant for DSS regardless of adjustments (p≤0.005). A doubling of TG levels was associated with a significant reduction in DSS performance for women (beta=−0.83, SE=0.31, t=−2.65, 95% CI=−1.45 -- −0.21, p=0.008) in the fully adjusted model (Table 2). Sex was not a significant effect modifier for either B-SEVLT test score regardless of adjustments (fully adjusted models outlined in Table 2).

Total Cholesterol and Cognitive Test Performance

Several significant positive associations between $\log_2$(TC) and cognitive test variables were noted such that a doubling of TC levels were associated with an increase in performance across learning and verbal fluency, regardless of adjustments (all p-values<0.05; Table 3). Follow-up analyses replacing $\log_2$(TC) with $\log_2$(HDL-C) and $\log_2$(LDL-C) levels as predictors to these cognitive test variables in fully adjusted models (Supplemental Table 2) revealed that $\log_2$(LDL-C) was driving the positive association between $\log_2$(TC) and both learning and verbal fluency. Thus, a doubling of 'bad' cholesterol was associated with an increase in performance across both test scores, but only verbal fluency (p=0.04) reached our threshold for significance (learning p-value=0.06).

Results revealed effect modification of Hispanic/Latino background between $\log_2$(TC) and DSS only (Model A p=0.01; Table 3). Follow-up survey-adjusted Wald testing revealed that individuals reporting either a Puerto Rican or a Central American background showed a significant association between $\log_2$(TC) and DSS. More specifically, a doubling of total cholesterol was associated with a decrease in DSS performance for Central Americans (beta=−3.11, SE=1.39, t=−2.24, 95% CI=−5.85 -- −0.38, p=0.02), but resulted in an increase in DSS performance for Puerto Ricans (beta=2.95, SE=1.16, t=2.53, 95% CI=0.66 -- 5.25, p=0.01) (Supplemental Table 3). When we replaced $\log_2$(TC) with $\log_2$(HDL-C) and $\log_2$(LDL-C) levels as predictors, there was a significant effect modification of Hispanic/Latino background and $\log_2$(LDL-C) on DSS performance in fully adjusted models similar to that outlined for $\log_2$(TC): Central Americans (beta=−2.07, SE=0.98, t=−2.10, 95% CI=−4.01 -- −0.13, p=0.03); Puerto Ricans (beta=1.75, SE=0.80, t=2.17, 95% CI=0.16 – 3.30, p=0.03).

Sex was not an effect modifier of $\log_2$(TC) for any cognitive test score in fully adjusted models (Model B p-values≥0.15; Table 3). Thus, we did not conduct follow up analyses replacing $\log_2$(TC) with $\log_2$(HDL-C) and $\log_2$(LDL-C) levels as predictors.

Post-hoc analyses of cholesterol-lowering medication use

Medication information gleaned from review and scanning at baseline visit was used to determine cholesterol-lowering medication use for hypercholesterolemia (Table 1). Results reported above did not change when considering the presence/absence of cholesterol-lowering medication use (data not shown).

Discussion

This study investigated the associations of lipid levels (i.e., TG, TC, LDL-C, and HDL-C) with cognition in the largest study of mid- to late-life Hispanics/Latinos in the US to date. Consistent with our hypothesis, TG levels were inversely associated with working memory performance as measured by DSS; however, only when considering effect modification of TG by background. Further, although the magnitude of the association did not change substantially, it did not remain significant after additional adjustment for hypertension and diabetes. In contrast, sex was a significant effect modifier of the association between TG and DSS, such that women with higher TG levels had lower test performance. We found positive

associations of TC and LDL-C (separately) with learning and verbal fluency. Lastly, we found significant effect modification of the DSS association by background, such that individuals reporting a Puerto Rican or Central American background showed a significantly stronger association between TC (and LDL-C) and DSS performance, albeit in opposite directions. Taken together, these results suggest differential associations of individual lipid levels on cognitive test performance that may depend on select demographic variables (i.e., sex, Hispanic/Latino background) in Hispanics/Latinos.

Our work in Hispanics/Latinos adds to the existing literature in non-Latino Whites in several ways. The negative association between TG and working memory reported in our study extends previous reports of a negative association between TG and declarative memory in non-Latino Whites and Blacks (Leritz, McGlinchey, Salat, & Milberg, 2016) suggesting this association exist in other populations as well as our own. Likewise, our results related to TC and LDL-C support previous studies suggesting higher levels of these lipids are associated with higher declarative memory and attentional processes (Aine et al., 2014; Elias, Elias, D'Agostino, Sullivan, & Wolf, 2005; Henderson, Guthrie, & Dennerstein, 2003; Leritz et al., 2016; Lv et al., 2016) and extend it to include learning and working memory in a large cohort of mid- to late-life Hispanics/Latinos. While findings exist in the non-Latino literature suggesting that higher TC and LDL-C levels are associated with lower cognition (Lu et al., 2017; Meusel et al., 2017; Smit et al., 2016; Solomon et al., 2009; Stough et al., 2019; van den Kommer et al., 2009; van den Kommer, Dik, Comijs, Jonker, & Deeg, 2012), the majority of these studies were conducted either in older adults (Lu et al., 2017; Stough et al., 2019), significantly smaller sample sizes (Meusel et al., 2017), embedded within a longitudinal treatment study (Smit et al., 2016), or leveraged mid-life lipid levels to predict late-life cognition (Solomon et al., 2009). Any one of these study differences would make direct comparisons difficult regardless of race or ethnicity. Taken within this larger context, our results point toward the importance of considering alternative metrics available in a lipid panel, e.g., TG, when investigating the relationship between cholesterol and cognition in Hispanics/Latinos.

While the underlying mechanisms to explain these associations are beyond the scope of this cross-sectional study, potential underpinnings may be found in the literature. For example, the fact that our TG results did not withstand additional adjustments for hypertension and diabetes suggests that the negative association of TG levels on working memory scores in Hispanics/Latinos of this study may reflect the combined role of TG in the metabolic syndrome and overall cardiovascular disease risk factor burden as previously reported (Gonzalez et al., 2018; Levin et al., 2014; Warsch et al., 2013; Yaffe et al., 2007; Zeki Al Hazzouri et al., 2013). The fact that female sex modified the negative association of TG levels on working memory, withstanding all adjustments, including those for hypertension and diabetes further suggests that the higher overall cardiovascular disease risk factor burden known to exist in Hispanic/Latino men compared to women (Daviglus et al., 2016; Daviglus et al., 2012) may have diluted the effect of TG in the main analyses. Lastly, the fact that TG levels, the lipid that may play an outsized role in disease burden for Hispanics/Latinos (Martinez-Larrad et al., 2012; Rodriguez & Brenes, 2008; Vega-Lopez et al., 2013) showed a negative association with cognition suggesting it may also play an outsized role in cognitive burden as well.

Select positive associations between TC and LDL-C levels and cognition showed an effect modification by background. Thus, while higher TC and LDL-C levels associated with higher learning and verbal fluency performance overall, the association between TC and DSS was particularly robust for individuals of Puerto Rican and Central American background. Within HCHS/SOL, Puerto Ricans have the highest levels of awareness and treatment-related control of their cholesterol levels (Rodriguez et al., 2015). Within this analytic sample, Puerto Ricans reported the lowest levels of uninsured individuals while Central Americans reported the highest (Supplemental Table 1); additionally, Central Americans had some of the highest levels of TC and LDL-C and some of the lowest levels of lipid-lowering medication use. While the presence of lipid lowering medications did not alter our results, it may be that within the Puerto Rican background, optimal TC levels (and health status more generally secondary to available health insurance) associate more robustly with higher levels of working memory, or, alternatively, higher levels of working memory associate more robustly with optimal TC levels. The cross-sectional nature of our work does not allow us to explore the directionality of this particular outcome; however, it is clear that Central Americans show a differential relationship between TC and cognition than Puerto Ricans that may be due, in part, to their more precarious health situation.

In addition to its cross-sectional nature, this study possesses other limitations. Most obviously, the direction and causal nature of the reported associations cannot be explicitly known without longitudinal follow up. As with any study, not all potential exclusionary conditions or confounds were considered. For example, while we excluded individuals with self-reported stroke, we did not consider self-reported myocardial infarctions. Likewise, while we excluded individuals based on psychotropic medication use to ensure the interpretation of our results as it relates to lipid levels and cognition, this approach may limit generalizability. Information on APOE status thought to exacerbate TG levels (van den Kommer et al., 2009) was not adjusted for in the current project and may represent an additional contributor to our reported results. Given that the focus of the HCHS/SOL study was cardiovascular in nature (Sorlie et al., 2010), our cognitive testing was limited; however, it incorporated important outcomes (and several identical test measures) documented to be associated with TG, TC, LDL-C, and HDL-C including learning and memory, as well as verbal fluency and DSS thought to involve attention, working memory, and executive functioning.

Despite these limitations, this study represents one of the largest studies within the Hispanic/Latino ethnicity on the associations between lipids (i.e., TG, TC, LDL-C, and HDL-C) and cognition in mid- to late-life. Recent studies suggest that variability in lipid levels (Smit et al., 2016) as well as steeper declines in select cholesterol levels (Ma et al., 2017) may influence cognitive decline. While the test point alterations reported in this study may not equate to clinically significant cross-sectional implications, they may represent baseline levels of functioning that portend either slowed or accelerated cognitive decline in later life given the relatively young age of our cohort. For example, while a 1-3 point decrement in cognitive testing may not meet standard cut-points for at-risk states for dementia including mild cognitive or vascular cognitive impairment currently, it may place Hispanic/Latino individuals with higher lipid levels at increased risk for accelerated aging given their scores are closer to these cut-points to begin with when compared to an individual with lower lipid

levels. Taken together, more work is needed within the Hispanic/Latino population generally, and by background specifically, to fully understand the long-term consequences of our reported associations on cognitive health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

Aine CJ, Sanfratello L, Adair JC, Knoefel JE, Qualls C, Lundy SL, … Stephen JM (2014). Characterization of a normal control group: are they healthy? Neuroimage, 84, 796–809. doi:10.1016/j.neuroimage.2013.09.025 [PubMed: 24060318]

American Diabetes, Association. (2018). Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2018. Diabetes Care, 41(Supplement 1), S13–S27. [PubMed: 29222373]

Anstey KJ, Lipnicki DM, & Low LF (2008). Cholesterol as a risk factor for dementia and cognitive decline: a systematic review of prospective studies with meta-analysis. Am J Geriatr Psychiatry, 16(5), 343–354. doi:10.1097/JGP.0b013e31816b72d4 [PubMed: 18448847]

Barker MJ, Greenwood KM, Jackson M, & Crowe SF (2004). Cognitive effects of long-term benzodiazepine use: a meta-analysis. CNS Drugs, 18(1), 37–48. doi:10.2165/00023210-200418010-00004 [PubMed: 14731058]

Benton AL, & Hamsher K (1989). Multilingual Aphasia Examination (2 ed.). Iowa City: AJA Associates.

Callahan CM, Unverzagt FW, Hui SL, Perkins AJ, & Hendrie HC (2002). Six-item screener to identify cognitive impairment among potential subjects for clinical research. Med Care, 40(9), 771–781. doi:10.1097/01.MLR.0000024610.33213.C8 [PubMed: 12218768]

Chiuve SE, Fung TT, Rimm EB, Hu FB, McCullough ML, Wang M, … Willett WC (2012). Alternative dietary indices both strongly predict risk of chronic disease. J Nutr, 142(6), 1009–1018. doi:10.3945/jn.111.157222 [PubMed: 22513989]

Dahl AK, & Hassing LB (2013). Obesity and cognitive aging. Epidemiol Rev, 35, 22–32. doi:10.1093/epirev/mxs002 [PubMed: 23258415]

Daviglus ML, Pirzada A, Durazo-Arvizu R, Chen J, Allison M, Aviles-Santa L, … Stamler J (2016). Prevalence of Low Cardiovascular Risk Profile Among Diverse Hispanic/Latino Adults in the United States by Age, Sex, and Level of Acculturation: The Hispanic Community Health Study/Study of Latinos. J Am Heart Assoc, 5(8). doi:10.1161/JAHA.116.003929

Daviglus ML, Pirzada A, & Talavera GA (2014). Cardiovascular disease risk factors in the Hispanic/Latino population: lessons from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). Prog Cardiovasc Dis, 57(3), 230–236. doi:10.1016/j.pcad.2014.07.006 [PubMed: 25242694]

Daviglus ML, Talavera GA, Aviles-Santa ML, Allison M, Cai J, Criqui MH, … Stamler J (2012). Prevalence of major cardiovascular risk factors and cardiovascular diseases among Hispanic/Latino individuals of diverse backgrounds in the United States. JAMA, 308(17), 1775–1784. doi:10.1001/jama.2012.14517 [PubMed: 23117778]

Del Brutto OH, Mera RM, & Zambrano M (2016). Metabolic syndrome correlates poorly with cognitive performance in stroke-free community-dwelling older adults: a population-based, cross-sectional study in rural Ecuador. Aging Clin Exp Res, 28(2), 321–325. doi:10.1007/s40520-015-0404-6 [PubMed: 26142624]

Elias PK, Elias MF, D'Agostino RB, Sullivan LM, & Wolf PA (2005). Serum cholesterol and cognitive performance in the Framingham Heart Study. Psychosom Med, 67(1), 24–30. doi:10.1097/01.psy.0000151745.67285.c2 [PubMed: 15673620]

Fall T, Hagg S, Ploner A, Magi R, Fischer K, Draisma HH, … Consortium, E. (2015). Age- and sex-specific causal effects of adiposity on cardiovascular risk factors. Diabetes, 64(5), 1841–1852. doi:10.2337/db14-0988 [PubMed: 25712996]

Friedewald WT, Levy RI, & Fredrickson DS (1972). Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem, 18(6), 499–502. [PubMed: 4337382]

George O, & Koob GF (2017). Individual differences in the neuropsychopathology of addiction. Dialogues Clin Neurosci, 19(3), 217–229. [PubMed: 29302219]

Gezmu T, Schneider D, Demissie K, Lin Y, Giordano C, & Gizzi MS (2014). Lipid profiles and ischemic stroke risk: variations by sex within racial/ethnic groups. Int J Womens Health, 6, 585–595. doi:10.2147/IJWH.S61274 [PubMed: 24940081]

Gonzalez HM, Mungas D, & Haan MN (2002). A verbal learning and memory test for English- and Spanish-speaking older Mexican-American adults. Clin Neuropsychol, 16(4), 439–451. doi:10.1076/clin.16.4.439.13908 [PubMed: 12822053]

Gonzalez HM, Mungas D, Reed BR, Marshall S, & Haan MN (2001). A new verbal learning and memory test for English- and Spanish-speaking older people. J Int Neuropsychol Soc, 7(5), 544–555. [PubMed: 11459106]

Gonzalez HM, Tarraf W, Gouskova N, Gallo LC, Penedo FJ, Davis SM, … Mosley TH (2015). Neurocognitive function among middle-aged and older Hispanic/Latinos: results from the Hispanic Community Health Study/Study of Latinos. Arch Clin Neuropsychol, 30(1), 68–77. doi:10.1093/arclin/acu066 [PubMed: 25451561]

Gonzalez HM, Tarraf W, Gouskova N, Rodriguez CJ, Rundek T, Grober E, … Mosley TH (2016). Life's Simple 7's Cardiovascular Health Metrics are Associated with Hispanic/Latino Neurocognitive Function: HCHS/SOL Results. J Alzheimers Dis, 53(3), 955–965. doi:10.3233/JAD-151125 [PubMed: 27340845]

Gonzalez HM, Tarraf W, Vasquez P, Sanderlin AH, Rosenberg NI, Davis S, … Schneiderman N (2018). Metabolic Syndrome and Neurocognition Among Diverse Middle-Aged and Older Hispanics/Latinos: HCHS/SOL Results. Diabetes Care, 41(7), 1501–1509. doi:10.2337/dc17-1896 [PubMed: 29716895]

Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, … Yeboah J (2018). 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. doi:10.1016/j.jacc.2018.11.003

Han C, Jo SA, Seo JA, Kim BG, Kim NH, Jo I, … Park KW (2009). Adiposity parameters and cognitive function in the elderly: application of "Jolly Fat" hypothesis to cognition. Arch Gerontol Geriatr, 49(2), e133–138. doi:10.1016/j.archger.2008.11.005 [PubMed: 19108905]

Henderson VW, Guthrie JR, & Dennerstein L (2003). Serum lipids and memory in a population based cohort of middle age women. J Neurol Neurosurg Psychiatry, 74(11), 1530–1535. [PubMed: 14617710]

Howell WH, McNamara DJ, Tosca MA, Smith BT, & Gaines JA (1997). Plasma lipid and lipoprotein responses to dietary fat and cholesterol: a meta-analysis. Am J Clin Nutr, 65(6), 1747–1764. doi:10.1093/ajcn/65.6.1747 [PubMed: 9174470]

Ihle A, Gouveia ER, Gouveia BR, Freitas DL, Jurema J, Tinoco MA, & Kliegel M (2017). High-Density Lipoprotein Cholesterol Level Relates to Working Memory, Immediate and Delayed Cued Recall in Brazilian Older Adults: The Role of Cognitive Reserve. Dement Geriatr Cogn Disord, 44(1–2), 84–91. doi:10.1159/000477846 [PubMed: 28743108]

Jin H, & Nicodemus-Johnson J (2018). Gender and Age Stratified Analyses of Nutrient and Dietary Pattern Associations with Circulating Lipid Levels Identify Novel Gender and Age-Specific Correlations. Nutrients, 10(11). doi:10.3390/nu10111760

Lamar M, Durazo-Arvizu RA, Sachdeva S, Pirzada A, Perreira KM, Rundek T, … Daviglus ML (2019). Cardiovascular disease risk factor burden and cognition: Implications of ethnic diversity within the Hispanic Community Health Study/Study of Latinos. PLoS One, 14(4), e0215378. doi:10.1371/journal.pone.0215378 [PubMed: 31009492]

Lamar M, Wu D, Durazo-Arvizu RA, Brickman AM, Gonzalez HM, Tarraf W, & Daviglus ML (2017). Cognitive Associates of Current and More Intensive Control of Hypertension: Findings From the Hispanic Community Health Study/Study of Latinos. Am J Hypertens, 30(6), 624–631. doi:10.1093/ajh/hpx023 [PubMed: 28402388]

Lavange LM, Davis SM, Hankinson J, Enright P, Wilson R, Barr RG, … Talavera GA (2017). Spirometry Reference Equations from the HCHS/SOL (Hispanic Community Health Study/Study of Latinos). Am J Respir Crit Care Med, 196(8), 993–1003. doi:10.1164/rccm.201610-1987OC [PubMed: 28613924]

Lavange LM, Kalsbeek WD, Sorlie PD, Aviles-Santa LM, Kaplan RC, Barnhart J, … Elder JP (2010). Sample design and cohort selection in the Hispanic Community Health Study/Study of Latinos. Ann Epidemiol, 20(8), 642–649. doi:10.1016/j.annepidem.2010.05.006 [PubMed: 20609344]

Leritz EC, McGlinchey RE, Salat DH, & Milberg WP (2016). Elevated levels of serum cholesterol are associated with better performance on tasks of episodic memory. Metab Brain Dis, 31(2), 465–473. doi:10.1007/s11011-016-9797-y [PubMed: 26873100]

Levin BE, Llabre MM, Dong C, Elkind MS, Stern Y, Rundek T, … Wright CB (2014). Modeling metabolic syndrome and its association with cognition: the Northern Manhattan study. J Int Neuropsychol Soc, 20(10), 951–960. doi:10.1017/S1355617714000861 [PubMed: 25382144]

Lezak M, Howieson DB, & Loring DW (2004). Neuropsychological Assessment. New York: Oxford University Press.

Lin X, Zhang X, Guo J, Roberts CK, McKenzie S, Wu WC, … Song Y (2015). Effects of Exercise Training on Cardiorespiratory Fitness and Biomarkers of Cardiometabolic Health: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Am Heart Assoc, 4(7). doi:10.1161/JAHA.115.002014

Lu Y, An Y, Yu H, Che F, Zhang X, Rong H, … Xiao R (2017). Sex-specific nonlinear associations between serum lipids and different domains of cognitive function in middle to older age individuals. Metab Brain Dis, 32(4), 1089–1097. doi:10.1007/s11011-017-9999-y [PubMed: 28374237]

Lv YB, Yin ZX, Chei CL, Brasher MS, Zhang J, Kraus VB, … Zeng Y (2016). Serum Cholesterol Levels within the High Normal Range Are Associated with Better Cognitive Performance among Chinese Elderly. J Nutr Health Aging, 20(3), 280–287. doi:10.1007/s12603-016-0701-6. [PubMed: 26892577]

Ma C, Yin Z, Zhu P, Luo J, Shi X, & Gao X (2017). Blood cholesterol in late-life and cognitive decline: a longitudinal study of the Chinese elderly. Mol Neurodegener, 12(1), 24. doi:10.1186/s13024-017-0167-y [PubMed: 28270179]

Martinez-Larrad MT, Lorenzo C, Gonzalez-Villalpando C, Gabriel R, Haffner SM, & Serrano-Rios M (2012). Associations between surrogate measures of insulin resistance and waist circumference, cardiovascular risk and the metabolic syndrome across Hispanic and non-Hispanic white populations. Diabet Med, 29(11), 1390–1394. doi:10.1111/j.1464-5491.2012.03723.x [PubMed: 22681498]

Meusel LC, Anderson ND, Parrott MD, Yuen W, Tchistiakova E, MacIntosh BJ, … Greenwood CE (2017). Brain Function Is Linked to LDL Cholesterol in Older Adults with Cardiovascular Risk. J Am Geriatr Soc, 65(2), e51–e55. doi:10.1111/jgs.14663 [PubMed: 27869302]

Mijajlovic MD, Pavlovic A, Brainin M, Heiss WD, Quinn TJ, Ihle-Hansen HB, … Bornstein NM (2017). Post-stroke dementia - a comprehensive review. BMC Med, 15(1), 11. doi:10.1186/s12916-017-0779-7 [PubMed: 28095900]

Parthasarathy V, Frazier DT, Bettcher BM, Jastrzab L, Chao L, Reed B, … Kramer JH (2017). Triglycerides are negatively correlated with cognitive function in nondemented aging adults. Neuropsychology, 31(6), 682–688. doi:10.1037/neu0000335 [PubMed: 28604016]

Paterson DH, & Warburton DE (2010). Physical activity and functional limitations in older adults: a systematic review related to Canada's Physical Activity Guidelines. Int J Behav Nutr Phys Act, 7, 38. doi:10.1186/1479-5868-7-38 [PubMed: 20459782]

Surveillance and Population-Based Prevention. (2008). Global Physical Activity Questionnaire (GPAQ): Analysis Guide. Geneva, Switzerland: World Health Organization.

Razali NM, & Wah YB (2011). Power comparisons of Shapiro-Wilk, Kolmogorov-Smirnov, Lilliefors, and Anderson-Darling tests. Journal of Statistical Modeling and analytics, 2(1), 21–33.

Reitz C, Tang MX, Manly J, Schupf N, Mayeux R, & Luchsinger JA (2008). Plasma lipid levels in the elderly are not associated with the risk of mild cognitive impairment. Dement Geriatr Cogn Disord, 25(3), 232–237. doi:10.1159/000115847 [PubMed: 18264008]

Rodriguez CJ, & Brenes JC (2008). Hypercholesterolemia in minorities In Chavez-Tapia NC & Uriba M (Eds.), Topics in Prevalent Diseases: A Minority's Perspective (pp. 125–136). New York: Nova Science Publishers.

Rodriguez CJ, Cai J, Swett K, Gonzalez HM, Talavera GA, Wruck LM, … Daviglus ML (2015). High Cholesterol Awareness, Treatment, and Control Among Hispanic/Latinos: Results From the Hispanic Community Health Study/Study of Latinos. J Am Heart Assoc, 4(7). doi:10.1161/JAHA.115.001867

Rodriguez CJ, Daviglus ML, Swett K, Gonzalez HM, Gallo LC, Wassertheil-Smoller S, … Kaplan R (2014). Dyslipidemia Patterns among Hispanics/Latinos in the United States of Diverse Background. Am J Med. doi:10.1016/j.amjmed.2014.07.026

Ryan CM, Freed MI, Rood JA, Cobitz AR, Waterhouse BR, & Strachan MW (2006). Improving metabolic control leads to better working memory in adults with type 2 diabetes. Diabetes Care, 29(2), 345–351. [PubMed: 16443885]

Smit RA, Trompet S, Sabayan B, le Cessie S, van der Grond J, van Buchem MA, … Jukema JW (2016). Higher Visit-to-Visit Low-Density Lipoprotein Cholesterol Variability Is Associated With Lower Cognitive Performance, Lower Cerebral Blood Flow, and Greater White Matter Hyperintensity Load in Older Subjects. Circulation, 134(3), 212–221. doi:10.1161/CIRCULATIONAHA.115.020627 [PubMed: 27436880]

Solomon A, Kareholt I, Ngandu T, Wolozin B, Macdonald SW, Winblad B, … Kivipelto M (2009). Serum total cholesterol, statins and cognition in non-demented elderly. Neurobiol Aging, 30(6), 1006–1009. doi:10.1016/j.neurobiolaging.2007.09.012 [PubMed: 18022292]

Sorlie PD, Aviles-Santa LM, Wassertheil-Smoller S, Kaplan RC, Daviglus ML, Giachello AL, … Heiss G (2010). Design and implementation of the Hispanic Community Health Study/Study of Latinos. Ann Epidemiol, 20(8), 629–641. doi:10.1016/j.annepidem.2010.03.015 [PubMed: 20609343]

Steeves JA, Shiroma EJ, Conger SA, Van Domelen D, & Harris TB (2019). Physical activity patterns and multimorbidity burden of older adults with different levels of functional status: NHANES 2003–2006. Disabil Health J, 12(3), 495–502. doi:10.1016/j.dhjo.2019.02.005 [PubMed: 30871954]

Stough C, Pipingas A, Camfield D, Nolidin K, Savage K, Deleuil S, & Scholey A (2019). Increases in total cholesterol and low density lipoprotein associated with decreased cognitive performance in healthy elderly adults. Metab Brain Dis, 34(2), 477–484. doi:10.1007/s11011-018-0373-5 [PubMed: 30649667]

van den Kommer TN, Dik MG, Comijs HC, Fassbender K, Lutjohann D, & Jonker C (2009). Total cholesterol and oxysterols: early markers for cognitive decline in elderly? Neurobiol Aging, 30(4), 534–545. doi:10.1016/j.neurobiolaging.2007.08.005 [PubMed: 17888546]

van den Kommer TN, Dik MG, Comijs HC, Jonker C, & Deeg DJ (2012). Role of lipoproteins and inflammation in cognitive decline: do they interact? Neurobiol Aging, 33(1), 196 e191–112. doi:10.1016/j.neurobiolaging.2010.05.024

Vega-Lopez S, Calle MC, Fernandez ML, Kollannoor-Samuel G, Chhabra J, Todd M, … Perez-Escamilla R (2013). Triglyceride screening may improve cardiometabolic disease risk assessment in Latinos with poorly controlled type 2 diabetes. J Health Care Poor Underserved, 24(4), 1739–1755. doi:10.1353/hpu.2013.0171 [PubMed: 24185167]

Wardle J, Rogers P, Judd P, Taylor MA, Rapoport L, Green M, & Nicholson Perry K (2000). Randomized trial of the effects of cholesterol-lowering dietary treatment on psychological function. Am J Med, 108(7), 547–553. [PubMed: 10806283]

Warsch JR, Rundek T, Paik MC, Elkind MS, Sacco RL, & Wright CB (2013). Association between northern Manhattan study global vascular risk score and successful aging. J Am Geriatr Soc, 61(4), 519–524. doi:10.1111/jgs.12166 [PubMed: 23527874]

Wechsler D (1981). WAIS-R Manual. San Antonio, TX: Psychological Corporation.

Willey JZ, Rodriguez CJ, Carlino RF, Moon YP, Paik MC, Boden-Albala B, … Elkind MS (2011). Race-ethnic differences in the association between lipid profile components and risk of myocardial infarction: The Northern Manhattan Study. Am Heart J, 161(5), 886–892. doi:10.1016/j.ahj.2011.01.018 [PubMed: 21570518]

Yaffe K, Haan M, Blackwell T, Cherkasova E, Whitmer RA, & West N (2007). Metabolic syndrome and cognitive decline in elderly Latinos: findings from the Sacramento Area Latino Study of Aging study. J Am Geriatr Soc, 55(5), 758–762. doi:10.1111/j.1532-5415.2007.01139.x [PubMed: 17493197]

Yeo SH, Lim ZI, Mao J, & Yau WP (2017). Effects of Central Nervous System Drugs on Recovery After Stroke: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Clin Drug Investig, 37(10), 901–928. doi:10.1007/s40261-017-0558-4

Zeki Al Hazzouri A, Haan MN, Neuhaus JM, Pletcher M, Peralta CA, Lopez L, & Perez Stable EJ (2013). Cardiovascular risk score, cognitive decline, and dementia in older Mexican Americans: the role of sex and education. J Am Heart Assoc, 2(2), e004978. doi:10.1161/JAHA.113.004978 [PubMed: 23608609]

Table 1.

Summary Statistics for the Target Population

	N=7413
Descriptive Characteristics	
Age in years, mean	55.86 (55.56--56.16)
Female (%)	54.61 (52.99--56.23)
Education (%)	
< High School	38.36 (36.29--40.44)
High School graduate	21.98 (20.29--23.67)
Some college	39.66 (37.74--41.58)
Background (%)	
Mexican	33.59 (29.92--37.26)
Cuban	25.25 (21.33--29.16)
Puerto Rican	16.83 (14.68--18.98)
Dominican	8.85 (7.48--10.23)
Central American	6.90 (5.94--7.86)
South American	6.23 (5.41--7.04)
% Spanish language preference	86.37 (84.62--88.12)
% No Health Insurance	46.11 (43.53--48.69)
% Diabetic	26.18 (24.43--27.93)
% Hypertensive	45.14 (43.29--46.99)
HbA1c	6.11 (6.06--6.15)
% on Anti-diabetes medication	14.71 (13.21--16.21)
Systolic Blood Pressure	128.32 (127.70--128.94)
Diastolic Blood Pressure	75.08 (74.68--75.49)
% on Anti-hypertensive medication	25.19 (23.47--26.92)
Physical Activity Level (%)	
Inactive	26.09 (24.30--27.87)
Low	14.45 (13.1--15.72)
Medium	11.09 (10.08--12.10)
High	48.21 (46.41--50.01)
Not reported	0.17 (0.06--0.28)
Diet Quality	50.50 (50.06--50.93)
Body Mass Index	29.82 (29.62--30.02)
Annual Family Income (%)	
<$20,000	43.21 (40.96--45.47)
$20,000-50,000	36.62 (34.77--38.47)
>50,000	11.82 (10.01--13.63)
Not reported	8.34 (7.37--9.31)
% Low Mental Status	13.95 (12.55--15.35)

	N=7413
Lipid Level Predictor (mg/dL)	
Total cholesterol levels (mg/dL)	208.82 (207.10--210.53)
HDL-C levels (mg/dL)	49.64 (49.18--50.11)
LDL-C levels (mg/dL)	131.02 (129.53--132.50)
Triglyceride levels (mg/dL)	140.78 (138.07--143.50)
% on Lipid-lowering medication	17.05 (15.53--18.58)
Cognitive Outcomes	
Verbal Fluency	18.67 (18.36--18.98)
Digit Symbol Substitution Test	34.52 (33.91--35.13)
B-SEVLT total learning	22.81 (22.58--23.03)
B-SEVLT recall post-interference	8.26 (8.15--8.36)

Note: All values represent the mean percent and (95% confidence intervals) unless otherwise noted, and account for the HCHS/SOL sample design (including sampling weights, cluster sampling, and stratification) to allow appropriate generalization to the target population, cluster sampling, and stratification (Lavange et al., 2010); Low Mental Status= Six Item Screener ≤4; B-SEVLT=Brief Spanish English Verbal Learning test

Table 2.

The association of triglyceride levels, log_2(TG), with cognitive test performance

		Cognitive Test Performance			
		Learning Beta±SE (95% CI)	**Memory Beta±SE (95% CI)**	**Fluency Beta±SE (95% CI)**	**DSS Beta±SE (95% CI)**
Model 1	log_2(TG)	−0.06±0.11 (−0.29 -- 0.16)	−0.03±0.06 (−0.15 -- 0.08)	−0.04±0.15 (−0.34 -- 0.24)	−0.13±0.23 (−0.59 -- 0.33)
Model 2	log_2(TG)	−0.03±0.12 (−0.27 -- 0.20)	−0.03±0.06 (−0.15 -- 0.09)	0.04±0.15 (−0.26 -- 0.35)	−0.02±0.24 (−0.49 -- 0.45)
Effect Modification of Background					
Model A	log_2(TG)	0.11±0.32 (−0.52 -- 0.75)	−0.08±0.17 (−0.42 -- 0.25)	−0.27±0.39 (−1.04 -- 0.51)	−1.28±0.68 $^{+}$ (−2.62 -- 0.05)
	log_2(TG) *Background	F(6,639)=0.64, p=0.70	F(6,639)=0.49, p=0.82	F(6,639)=0.80, p=0.58	F(6,639)=1.03, p=0.40
Effect Modification of Sex					
Model B	log_2(TG)	−0.17±0.16 (−0.50 -- 0.15)	−0.08±0.08 (−0.24 -- 0.07)	−0.37±0.21 $^{+}$ (−0.79 -- −0.03)	−0.83±0.31 ** (−1.45 -- −0.21)
	log_2(TG) *Sex	F(1,644)=1.18 p=0.27	F(1,644)=0.79 p=0.37	F(1,644)=7.15 p=0.007 **	F(1,644)=12.15 p<0.005 $^{\wedge}$

Note: log_2(TG) = triglyceride levels log 2 transformed to approximate normality and improve model fit; thus, beta weights reflect the effect of doubling triglyceride levels on cognition.

Model 1: Adjusted for age, sex, education, Hispanic/Latino background, language of test administration, health insurance status, physical activity, diet, and body mass index (BMI)

Model 2: Adjusted for age, sex, education, Hispanic/Latino background, language of test administration, health insurance status, physical activity, diet, and BMI, as well as diabetes and hypertension

Effect Modification Model A: Adjusted for age, sex, education, Hispanic/Latino background, language of test administration, health insurance status, physical activity, diet, and BMI, as well as diabetes and hypertension, and included the interaction term of log_2(TG)*background

Effect Modification Model B: Adjusted for age, sex, education, Hispanic/Latino background, language of test administration, health insurance status, physical activity, diet, and BMI, as well as diabetes and hypertension, and included the interaction term of log_2(TG)*sex

$^{\wedge\wedge}$p<0.001,

$^{\wedge}$p<0.005,

**p<0.01,

*p<0.05,

$^{+}$p<0.10

Table 3.

The association of total cholesterol, log_2(TC), with cognitive test performance

		Cognitive Test Performance			
		Learning Beta±SE (95% CI)	**Memory Beta±SE (95% CI)**	**Fluency Beta±SE (95% CI)**	**DSS Beta±SE (95% CI)**
Model 1	log_2(TC)	0.79±0.29 ** (0.21 -- 1.36)	0.23±0.13 + (−0.04 -- 0.50)	1.45±0.40 ^^ (0.66 -- 2.25)	1.50±0.70 * (0.11 -- 2.87)
Model 2	log_2(TC)	0.53±0.27 * (0.00 -- 1.07)	0.13±0.13 (−0.13 -- 0.39)	1.01±0.38 ** (0.27 -- 1.76)	0.82±0.58 (−0.33 -- 1.97)
Effect Modification of Background					
Model A	log_2(TC)	0.19±0.67 (−1.12 -- 1.51)	0.16±0.33 (−0.49 -- 0.82)	−0.92±0.88 (−2.66 -- 0.82)	−0.07±1.31 (−2.66 -- 2.51)
	log_2(TC) *Background	F(6,639)=0.71, p=0.64	F(6,639)=0.11, p=0.99	F(6,639)=1.88, p=0.08 +	F(6,639)=2.59, p=0.01 **
Effect Modification of Sex					
Model B	log_2(TC)	0.11±0.41 (−0.69 -- 0.92)	−0.04±0.20 (−0.43 -- 0.35)	0.56±0.50 (−0.42 -- 1.55)	0.84±0.77 (−0.67 -- 2.35)
	log_2(TC) *Sex	F(1,644)=2.07 p=0.15	F(1,644)=1.56 p=0.21	F(1,644)=1.64 p=0.20	F(1,644)=0.00 p=0.97

Note: log_2(TC) = total cholesterol levels log 2 transformed to approximate normality and improve model fit; thus, beta weights reflect the effect of doubling total cholesterol levels on cognition.

Model 1: Adjusted for age, sex, education, Hispanic/Latino background, language of test administration, health insurance status, physical activity, diet, and BMI

Model 2: Adjusted for age, sex, Hispanic/Latino background, language of test administration, health insurance status, physical activity, diet, and BMI, as well as diabetes and hypertension

Effect Modification Model A: Adjusted for age, sex, education, Hispanic/Latino background, language of test administration, health insurance status, physical activity, diet, and BMI, as well as diabetes and hypertension, and included the interaction term of log_2(TC)*background

Effect Modification Model B: Adjusted for age, sex, education, Hispanic/Latino background, language of test administration, health insurance status, physical activity, diet, and BMI, as well as diabetes and hypertension, and included the interaction term of log_2(TC)*sex

^^ p<0.001,

^ p<0.005,

** p<0.01,

* p<0.05,

+ p<0.10