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Ankle brachial index and cognitive function among Hispanics/Latinos: Results from the Hispanic Community Health Study/Study of Latinos

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Abstract

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Author contributions

Drs. Tarraf and González conceptualized the study. Dr. Tarraf conducted the analyses and drafted the manuscript. Drs. González, Allison, Criqui, Wright, Fornage, Daviglus, Kaplan, Davis, and Mr. Conceicao contributed to the manuscript and provided comments on the analyses and revised the draft.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.atherosclerosis.2018.02.016>.

Background and aims: The Ankle-Brachial index (ABI) is a well-accepted measure of peripheral artery disease (arterial stenosis and stiffness) and has been shown to be associated with cognitive function and disorders; however, these associations have not been examined in Hispanics/Latinos. Therefore, we sought to examine relationships between ABI and cognitive function among diverse middle-age and older Hispanics/Latinos.

Methods: We used cross-sectional data on $n = 7991$ participants aged 45–74 years, without stroke or coronary heart disease, from the Hispanic Community Health Study/Study of Latinos. Our primary outcome, global cognition (GC), was a continuous composite score of four cognitive domains (verbal learning and memory, verbal fluency, executive function, and mental status). Secondary outcomes were the individual tests representing these domains. The ABI was analyzed continuously and categorically with standard clinical cut-points. We tested associations using generalized survey regression models incrementally adjusting for confounding factors. Age, sex, hypertension, diabetes, and dyslipidemia moderations were examined through interactions with the primary exposure.

Results: In age, sex, and education adjusted models, continuous ABI had an inverse u-shape association with worse GC. We found similar associations with measures of verbal learning and memory, verbal fluency, executive function, but not with low mental status. The associations were attenuated, but not completely explained, by accounting for the confounders and not modified by age, sex, education, and vascular disease risks.

Conclusions: In addition to being a robust indicator of arterial compromise, our study suggests that abnormal ABI readings may also be useful for early signaling of subtle cognitive deficits.

Keywords

Cognition; Ankle-brachial index; Atherosclerosis; ABI; Peripheral arterial disease; Cardiovascular health; Hispanics; Latinos; Epidemiology

1. Introduction

Several studies have reported population-level associations between peripheral artery disease (PAD) and cardiovascular disease (CVD), including heart disease and stroke [1]. Additionally, PAD has been associated with cognitive impairment, Alzheimer's disease, and dementia [2]. However, evidence from large population-based studies examining the links between ABI and cognitive function remains scant, and non-existent for Hispanics/Latinos who have a higher risk for clinically undetected and uncontrolled CVD risks [3,4]. Early detection of CV risk through ABI measurement, and initiation of control regimen can be critical for slowing the cascades known to trigger vascular and heart disease, stroke and concomitant cognitive impairment [1].

The ankle brachial index (ABI) is a non-invasive and well-tolerated measure to evaluate arterial stenosis and stiffness [5]. Low ABI levels (≤ 0.9) are indicative of significant obstructive disease (i.e. PAD) and prognostic for atherosclerosis [5]. However, this threshold may not be appropriate for diverse populations where ABI shows lower sensitivity to disease detection at this level [5,6]. Higher ABI values (≥ 1.40) are considered indicative of arterial

stiffness, likely due to medial calcification [5,7]. Notably, the prognostic sensitivity of different thresholds for a high ABI also varies [8,9].

Most studies on the relationship between ABI and cognitive function have focused on older non-Hispanic White cohorts, used a restrictive set of cognitive measures, and controlled for relatively few confounding factors [2]. Cross sectional work from these data suggest that ABI is linearly and positively associated with better cognitive performance particularly in executive function [8,10], which is usually implicated in vascular disease induced cognitive dysfunction. Longitudinal data from mostly Caucasian cohort studies have also provided evidence that compromised ABI, in general, and PAD, in particular, is associated with cognitive impairment and dementia [2].

Early detection of cognitive disorders in middle age before further disease progression is a major public health priority, especially for Hispanics/Latinos who are at increased risk. Hispanics/Latinos are the largest ethnic group in the United States and are projected to account for a third of the population by 2050. Hispanics/Latinos are at higher risk for diseases secondary to CVD and have higher disease burden due to suboptimal levels of treatment and control for CV risk factors (e.g. hypertension) [3,11]; although differences between Hispanic/Latino backgrounds have been reported. Additionally, Hispanics/Latinos are reportedly at higher risk for age-related cognitive problems, again with reported differences in disease prevalence and incidence between subgroups [12]. Recent studies have shown consistent links between cardiovascular disease and risk factors and lower cognitive performance among diverse Latinos evident in middle age [13–16]. However, no previous work, to our knowledge, has comprehensively examined cognitive function and ABI in middle-aged and older diverse Latinos. Asymptomatic and untreated arterial disease presents long-term risks for adverse cerebrovascular events and vascular cognitive health particularly given known disparities and inequities in access to health and healthcare enabling resources among US Latinos. In the absence of pharmacological treatment for cognitive dysfunctions and dementias, identifying low-cost and well-tolerated means for detecting early vascular-related cognitive decline affords opportunities for mitigating cognitive decline.

Until recently, most epidemiologic work on Hispanic/Latino populations has been limited to specific subgroups (e.g. Mexicans). This has limited generalization to the larger diverse Hispanic/Latino population. The Hispanic Community Health Study/Study of Latinos is the largest study of diverse Hispanics/Latinos in the US designed to characterize chronic disease (e.g. CVD) and their putative antecedents [17]. In this study, we investigate associations between cognitive function and ABI among middle-aged and older Hispanics/Latinos of diverse backgrounds. We hypothesize that high and low ABI would both be associated with lower cognitive scores, especially for executive function which is considered vulnerable to CVD [18–20].

2. Materials and methods

2.1. Study sample

HCHS/SOL is a multiethnic, multisite, prospective cohort study of 16,415 community-dwelling Hispanic/Latino adults (18–74-years old). The HCHS/SOL design was formulated

to estimate representative baseline risk factors for overall Hispanics/Latinos as well as for specific backgrounds, including Central Americans, Cubans, Dominicans, Mexicans, Puerto Ricans, and South Americans. Data were collected from field centers in four U.S. cities with substantial Hispanic/Latino population concentrations (Bronx, NY; Chicago, IL; Miami, FL; and San Diego, CA). Each field center recruited about 4000 eligible, self-identified Hispanic/Latino adults. Detailed HCHS/SOL sampling methods are available elsewhere [17]. Written informed consent was obtained from all included participants, and the study was reviewed and approved by the Institutional Review Boards of all participating institutions. We focused on the oversampled, middle-aged and older adults (45–74-years) with baseline cognitive assessment data (n = 9623). We excluded participants reporting prevalent stroke or transient ischemic attack (TIA) diagnoses, and those reporting prevalent coronary heart disease (CHD; n = 1184). We also excluded (n = 448) participants with missing values for ABI (n = 30) or on the model covariates (n = 418) for an unweighted analytic n = 7991.

2.2. Cognitive tests

We used confirmatory factor analyses to estimate a factor score for a latent global cognition measure using four available cognitive tests, representing multiple cognitive domains, and the Six-Item Screener (SIS). We also examined, independently, the four domain specific tests: 1) Brief Spanish English Verbal Fluency Test (B-SEVLT) sum over 3 trials, 2) B-SEVLT recall, 3) Word Fluency (WF), and 4) Digit Symbol Substitution (DSS) test. The B-SEVLT is an episodic learning and memory test with two scores: 1) the summed total of correctly learned items across three learning trials (B-SEVLT-sum; range 0–45), and 2) total correctly recalled items (B-SEVLT recall; range 0–15) following an interference trial. WF is a verbal fluency test scored as the total number of correctly generated words (beginning with letters F and A) within 1 min. DSS is a mental processing speed and executive function exam (range 0–90). These cognitive tests and scoring procedures have been previously described [21]. We also examined a dichotomized SIS [22] coded to distinguish between respondents with and without probable low mental status scores (SIS ≤ 4 vs. SIS > 4). Briefly, the SIS (range 0–6) is a mental status test that was scored dichotomously with a value of 4 or lower representing “low mental status.” The cutpoint reflects previous validation work in patients with dementia [22]. All cognitive tests were administered in the participants’ preferred language during face-to-face interviews by trained, bilingual research assistants. To facilitate cross-test results comparisons, we generated and analyzed standardized (z-transformed; using population-specific means and standard deviations ((Score – Mean)/SD) indicators of all five continuous cognitive outcomes.

2.3. Primary exposure

ABI measurements were conducted using standard Doppler procedures using a Nicolet Doppler Elite 100R probe (Natus, Golden, CO). Briefly, first, the participant’s upper arm circumference was measured to determine appropriate cuff size for placement on each ankle and upper arm. Following a 5-min rest period, systolic BP was measured once in the bilateral brachial, anterior tibial, and posterior tibial arteries in a counterclockwise pattern starting with the right arm while the participant was in supine position and after ensuring that head and heel were level. The higher value of the ankle artery pressures was divided by

the higher of the two brachial artery pressures to compute the limb-specific index and the final indexed ABI was the lower of the two limb indices (more details on the ABI measurement are provided in supplemental text). In secondary analyses, we also considered a categorical ABI classification reflective of clinically significant thresholds. An index value 0.90 or lower, on either left or right limb, was considered indicative of PAD. A value 1.40 was coded as indicative of arterial stiffness, a value between 0.9 and < 1.0 was considered borderline PAD, and all others were coded as normal.

2.4. Covariates

We adjusted for age (years), sex, and education (less than high school (HS); HS or more). We also accounted for confounding CVD measures including hypertension (no/yes), diabetes (no/yes), dyslipidemia (no/yes), and self-reported atrial fibrillation (no/yes). Additionally, we controlled for cardiovascular risk factors including alcohol consumption (no current use; low risk; and high risk), self-reported smoking (never; former/current), body mass index (<18.5; 18.5 BMI < 25; 25 BMI < 30; and ≥ 30), and waist circumference to hip ratio. Finally, we controlled for depressive symptoms (Center for Epidemiologic Studies Depression-10) and anxiety (10-item Spielberger Trait Anxiety Scale). Details on covariates measurement are provided in supplemental text.

2.5. Analytic procedures

We used statistical procedures specific to complex survey sample designs in the Stata software package (14.1) for all study analyses, and accounted for the probability weighting, clustering and stratification underlying the HCHS/SOL design [17]. We used a Taylor Series Linearization approach to compute appropriate variance estimates and derive correct standard errors for statistical inferences, and implemented recommended procedures for sub-population analyses [23].

Our analytic plan included four steps. First, we generated descriptive statistics to characterize the study's population on the variables of interest (Table 1). ABI groups were compared using survey-adjusted Wald tests for categorical variables and *t*-tests for continuous variables. To facilitate the visualization of the modeled cognitive outcomes (*z*-scores) relative to ABI we provide weighted scatterplots and quadratic fit lines in Supplemental Fig. 1. Second, we used survey generalized linear regression models to examine the hypothesized associations between ABI (linear) and ABI [2] (quadratic) and the cognitive outcomes, as well as the attenuation in these associations in models adjusted for our proposed confounders. We used linear regression models for the continuous *z*-score outcomes, and logistic regression for the dichotomous SIS (Table 2). For all tested models we report observed *p*-values for the estimated parameters from all primary analyses in Supplemental Table 1. Furthermore, we conducted sensitivity analyses to adjust the *p*-values of the estimates generated in sex, age, and education adjusted models using Simes-Benjamini-Hochberg methods [24]. Inferences (for linear and quadratic terms) were robust to multiple (*n* = 42) testing. To assess the U-shaped relationship in both the unadjusted and adjusted models we estimated and tested outcome specific inflection points (Supplemental Table 2) and used a Wald test to test the significance of linear and quadratic terms. Third, to facilitate the interpretation of our results we plotted the adjusted and unadjusted estimated

cognitive z-scores and their 95% confidence bounds over the ABI continuum for the overall sample in Fig. 1. To enable the reader to assess these associations using the metric of the tests, we reproduce the plots in the original metric of the cognitive scores in Supplemental Fig. 2. Fourth, we examined whether the associations between ABI and cognitive function were moderated by age, sex, and educational attainment as well as by hypertension, diabetes status, and dyslipidemia (Supplemental Table 3). To do so, we refit the fully adjusted models to account independently for interactions between ABI and age group (45–64; and 65–74), sex, education (less than HS; HS or more), hypertension (No/Yes), diabetes (No/Yes), and dyslipidemia (No/Yes). In secondary analyses, we repeated steps 2 and 3 using the categorical operationalization of ABI and setting the reference to the “clinically normal” category. These results are provided in Supplemental Table 4, and plotted in Fig. 2 for the z-scored cognitive outcomes and Supplemental Fig. 3 using the original metrics.

3. Results

3.1. Descriptive statistics

Survey weighted descriptives to characterize the HCHS/SOL target population are included in Table 1. Slightly more than half of the target population was female (56%), and the mean age was 56-years. Two-fifths of the target population (39%) had less than HS education. Slightly more than a quarter (25.5%) were diabetic, 45% were hypertensive, 44% dyslipidemic, and about 1% self-reported atrial fibrillation. High risk alcohol use was relatively low (4.4%), more than two-fifth of the target population were current or former smokers, and 41% were obese. Finally, the average waist to hip ratio was 0.9 (SD = 0.1) and the mean scores on the CESD-10 and STAI-10 were 7.3 and 16.8, respectively.

The overall ABI mean was 1.06 (SD = 0.15). Women were more likely to have PAD (69.1%) whereas men more likely to satisfy criteria for arterial stiffness (65.3%). Individuals satisfying criteria for PAD or arterial stiffness were more likely to be diabetic and hypertensive. Individuals with low ABI were much more likely to be former or current smokers (60.6%), whereas those satisfying criteria for arterial stiffness were more likely to be high risk alcohol consumers (7.6%), to be obese (56%), and to have a higher average waist to hip ratio. The ABI groups did not statistically differ by education level, dyslipidemia status, CESD-10, and STAI-10 scores.

The estimated means for the cognitive tests were: B-SEVLT Sum, 22.7 (SD = 7.0), B-SEVLT Recall, 8.2 (SD = 3.5), WF, 18.5 (SD = 9.0), DSS, 34.5 (SD = 16.5). Additionally, 14.6% of the target population satisfied criteria for low mental status on the SIS (4). Individuals satisfying criteria for PAD and arterial stiffness had lower average scores on the continuous cognitive tests (Table 1). Individuals satisfying criteria for arterial stiffness were more likely to be classified as having a low mental status (SIS 4).

3.2. Crude associations

We found that ABI had a consistent curvilinear (inverted u-shape) association with all the considered cognitive (z-scores) measures (Table 2). The estimated marginal means for the cognitive measures over the continuum of ABI values are presented in Fig. 1. The inversion

points characterizing the u-shape associations – presented in Supplemental Table 1 – for ABI were estimated at 1.24 (SE = 0.06), 1.22 (SE = 0.07), 1.23 (SE = 0.07), 1.38 (SE = 0.09), 1.33 (SE = 0.05), for cognition, B-SEVLT-sum, B-SEVLT-recall, WF, and DSS, respectively (Supplemental Table 2).

3.3. Adjusted associations

Adjusting for age, sex, and education attenuated by half the reported quadratic association between ABI and global cognition ($\beta_{ABI} = 1.45$ [SE = 0.39], $p < 0.001$; $\beta_{ABI2} = -0.51$ [SE = 0.15], $p = 0.001$). The inverted u-shaped associations of ABI with all cognitive tests, except for low mental status, remained statistically significant. The magnitudes of the beta coefficients for the quadratic polynomial (ABI [2]) were reduced to 55%, 56%, 55%, 75% of the crude estimates for B-SEVLT-sum ($\beta_{ABI} = 1.27$ [SE = 0.41], $p = 0.002$; $\beta_{ABI2} = -0.44$ [SE = 0.16], $p = 0.005$), B-SEVLT-recall ($\beta_{ABI} = 1.18$ [SE = 0.40], $p = 0.003$; $\beta_{ABI2} = -0.40$ [SE = 0.16], $p = 0.01$), WF ($\beta_{ABI} = 1.35$ [SE = 0.37], $p < 0.001$; $\beta_{ABI2} = -0.46$ [SE = 0.13], $p = 0.001$), and DSS ($\beta_{ABI} = 1.76$ [SE = 0.33], $p < 0.001$; $\beta_{ABI2} = -0.61$ [SE = 0.13], $p < 0.001$), respectively.

Full adjustment for CVD, metabolic, and behavioral confounders further attenuated, but only modestly so, the linear and quadratic coefficients of ABI for global cognition ($\beta_{ABI} = 1.09$ [SE = 0.39], $p = 0.006$; $\beta_{ABI2} = 0.37$ [SE = 0.16], $p = 0.017$), SEVLT-sum ($\beta_{ABI} = 0.95$ [SE = 0.42], $p = 0.023$; $\beta_{ABI2} = -0.32$ [SE = 0.16], $p = 0.048$), WF ($\beta_{ABI2} = 1.11$ [SE = 0.36], $p = 0.002$; $\beta_{ABI2} = -0.35$ [SE = 0.13], $p = 0.007$) and DSS ($\beta_{ABI} = 1.58$ [SE = 0.31], $p < 0.001$; $\beta_{ABI2} = -0.53$ [SE = 0.11], $p < 0.001$) and explained the association with SEVLT-recall (Table 2; p -values presented in Supplemental Table 1). Fig. 1 provides a visual representation of the adjusted associations (and incremental attenuations) between cognitive performance and ABI.

3.4. Interaction effects

Tests of interactions for ABI with age-groups, sex, education, hypertension, diabetes, and dyslipidemia indicated that none of these indicators modified the ABI effects on the cognitive outcomes detailed in our regression results above. The survey adjusted F-tests and p -values for the interactions are presented in Supplemental Table 2.

3.5. Secondary analyses

Our results using the categorical ABI classifications indicated that PAD was consistently associated with lower cognitive performance (*cf* clinically “normal”) in crude and age, sex, and education-adjusted models (Fig. 2; Supplemental Table 4). We also found negative crude associations between arterial stiffness and lower cognitive performance (*cf* clinically “normal”), but these associations were explained by sex, age, and education adjustment. In fully adjusted models, PAD (*cf* clinically “normal”) remained associated with lower performance on global cognition ($\beta = -0.13$ [SE 0.05], $p = 0.012$), SEVLT-Sum ($\beta = -0.13$ [SE = 0.06], $p = 0.02$), SEVLT-Recall ($\beta = -0.11$ [SE = 0.05], $p = 0.044$), WF ($\beta = -0.12$ [SE = 0.05], $p = 0.017$), and DSS ($\beta = -0.14$ [SE = 0.04], $p = 0.001$).

4. Discussion

We examined cross-sectional associations between ABI, a measure of significant obstructive subclinical atherosclerosis, as well as arterial stiffness, and cognition in a large group of diverse community-dwelling, middle-aged and older Hispanic/Latino cohort without stroke or CHD. Two main findings emerged. First, we found evidence for a curvilinear inverted u-shaped association between ABI and global cognition. We anticipated that ABI abnormalities would be more strongly associated with lower executive function but the results indicate that the associations are consistent across the four cognitive domains covered in this study. Second, the associations between ABI and cognitive performance were not moderated by age, sex, or other considered CVD risks.

Our results show that, in our Hispanic/Latino population, ABI clinical cut-points for arterial stiffness, were less consistent than continuous ABI scores in relation to cognition. This suggests that clinical thresholds for high ABI might be less informative in relation to cognitive problems, particularly at younger age. We modeled continuous ABI to take advantage of the full spectrum rather than just focus on the clinical cutpoints and provided estimates for inversion points associates with optimal cognitive function. Our findings contribute to the debate on variations in optimal clinical cutpoints for ABI across populations. The results suggest that the determination of protective ranges for ABI in relation to cognitive health might also be population specific. More data from cross race/ethnic population cohorts, however, are needed to directly test variations and overlap in these ranges.

Overall, our study contributes to the continuing debate on the links between ABI and cognitive function [2], and complements emerging findings from studies using non-Hispanic white populations. Wang and colleagues recently reported a linear positive association between ABI and Mini Mental State scores among middle-age and older (40y+) community-dwelling Chinese adults that were independent of age, CVD and other risk factors similar to those used in our study [25]. Similarly, Hilal and colleagues reported significant associations between ABI and verbal memory and executive function independent of demographic and vascular risk factors among Singaporeans [26]. However, in more recent analyses of these data, Shaik and colleagues showed that associations with ABI were limited to verbal fluency [27]. Guerchet and colleagues, using data from a Central African sample 65-years and older, reported a significant association between prevalent PAD and dementia [28]. These findings were recently affirmed by another study examining the association between low ABI and cognitive impairment using an expanded sample from this population [29].

Our first finding is consistent with previous studies reporting that subacute vascular disease, PAD and arterial stiffening, may be a useful midlife markers of cognitive problems and impending disorders [2]. Recently, Espeland and colleagues reported evidence for a curvilinear association between ABI and cognitive function but mostly driven by low ABI values [30]. Our results provide further evidence that low ABI is linked to lower cognitive function that is evident even in middle-age. We also found that high ABI values (below clinical classification i.e. ≥ 1.40) were associated with lower cognitive performance even after adjusting for diabetes status; a major confounder for valid PAD classification at high ABI

levels. This is consistent with arguments on the vascular pathway to degenerative cognitive dysfunction [31]. Current evidence indicate that high ABI increases the risk for CV events [32], disease morbidity [7], and mortality [33]. Work linking high ABI to cerebrovascular events (e.g. stroke) is less clear, however; for example, some work shows no evidence [34] or crude only associations [35] whereas others report higher risk and hazards for cerebrovascular events [36,37].

The ABI-cognition relationships we found were not moderated by age, suggesting that midlife cognition may already be jeopardized by subacute and acute ABI. This is in line with evidence that pathological modifications due to vascular risk are likely to occur years before clinical indicators of cognitive impairment show up [31,38]. This also points to the possibility that age and vascular risk are independent pathological pathways to cognitive dysfunction. Recent work suggests that vascular neurodegenerative pathologies affect cognitive performance but have limited roles in explaining variations in age/time related cognitive decline [39]. Similar strains of work that specifically examine how atherosclerosis affects cognitive change found only an initial hit on cognitive function but time stable effects in terms of cognitive trajectories [40]. In context, our findings suggest that while vascular neurodegenerative processes might be important to triggering cognitive deficits starting in midlife, other age-related neurodegenerative processes might be responsible for the variance and severity of cognitive decline into older age.

We were surprised that sex did not moderate the relationships between ABI and cognitive function. This is particularly interesting given that Latino populations present intriguing sex differences in the distributions of CV risk factors and disease prevalence. On one hand, Hispanic/Latino women have better biological risk profiles (e.g. blood pressure, and fasting glucose), are more likely to satisfy overall American Heart Association criteria for heart health compared to men [16], and have lower prevalence of CHD and stroke [4]. However, our data shows that middle-age and older Hispanic/Latino women (45-years and older) are less likely to satisfy criteria for clinically normal ABI, and particularly more likely to fall below clinical threshold for low ABI PAD. They are also much more likely to have abdominal obesity (45% more so than men), and more likely to satisfy criteria for the metabolic syndrome [11]. The role of sex in the relationship between CVD and cognition is complex. Competing risks in males and females, including genetic predispositions, that influence disease onset, course, complexity, and severity could have played a role in masking modification effects in a community based study. It is also possible that moderation effects do not emerge until later in life, an epoch that is not currently captured by the relative younger age spectrum of our sample.

Other CV (e.g. hypertension) and metabolic (e.g. diabetes) factors, that coexist with PAD, are also implicated in the atherosclerotic pathway to cerebrovascular disease and cognitive dysfunction [38]. We showed that controlling for these factors partially, but only slightly, explained the detected associations. However, hypertension, diabetes, and dyslipidemia did not modify the associations with cognitive function; which counters findings from studies focused on other populations [25]. This suggests that in a relatively young community cohort these risk factors (e.g. diabetes) point to a shared common etiology, but do not amplify the effect, in the link between PAD and lower cognition. More detailed analyses,

particularly in longitudinal settings, can disentangle the effects of these risk clusters and the mediating roles that vascular risks play, yielding a clearer understanding of the underlying relationship. This data would be particularly informative if MRI markers of macro- and microvascular diseases are accounted for, as they would allow for explicit accounting of degenerative changes in the brain.

4.1. Perspectives

The direct individual level clinical implications of this work are modest and limited by the study's cross-sectional design and the associational nature of the findings. However, our results suggest that the population-level gains from improving ABI can be substantial. Based on our models, for example, the association between PAD (ABI<0.9) and global cognition was 8 times the magnitude of the age-specific association and 3 times the magnitudes of diabetes and hypertension associations, respectively. As such, two important points could be emphasized. First, our results support the argument that abnormal ABI values (whether high or low) can serve as a risk warning for insidious development of cognitive deficits. While not currently adopted as a clinical indicator for risk of cognitive dysfunction, the ABI can serve as a tool, among others, in the clinical toolbox of practitioners to help build more precise patient risk profiles. They can also inform patient provider discussions about steps to be undertaken to modify and improve risk factors and conditions that can prevent cerebrovascular events and cognitive problems. Second, although the direct benefits at the patient-level might be modest, shifting the population distribution of ABI through pharmacological and behavioral management can lead to important population level savings in years of cognitive aging.

4.2. Limitations

This study has several limitations. First, our findings are based on cross-sectional data. As such, we can not infer a causal direction for the reported associations. Secondly, we were unable to contrast the findings to other ethnic/racial groups, which limits our inferences to Hispanic/Latino only. Future work would benefit from examining the moderating effects of race and ethnic backgrounds on these associations. Additionally, we did not ascertain cognitive decline or disorders (e.g., dementias) and did not examine other biomarkers of brain disorders and dysfunction (e.g., MRI), which limits our inferences to brain function. Future studies should incorporate these markers in order to better understand the mechanistic pathways between preclinical and early stage diseases, cerebrovascular change, and cognitive function and decline. The evidenced associations, however, have the potential to inform public health given the global health priority status of Alzheimer's disease and dementias [41], and shifting or delaying cognitive disease onset in the absence of successful pharmacological interventions that target disease course and onset.

4.3. Conclusion

We found that abnormal ABI levels (both low and high) were related to lower cognitive performance in a large sample of diverse, middle-age and older Hispanic/Latino. Prevention and treatment of arterial disease may be a feasible avenue for maintaining cognitive function, particularly among Hispanics/Latinos who are a high-risk population. Prevention and treatment in middle-age, a vulnerable period for developing CVD and cognitive decline,

may delay longitudinal declines. From a population health perspective, such delays could yield sizeable public health benefits, particularly in Hispanics/Latinos.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Estimated marginal means (z-scores)/probabilities for cognitive outcomes across the ABI continuum.

Results are derived from survey generalized linear regression models. Results for Hispanic/Latino adults aged 45–74 years, without prevalent stroke or transient ischemic attack (TIA), and without prevalent coronary heart disease from the HCHS/SOL (2008–2011).

a Crude (short dash). Model 2 (dash-dot) = adjusted for age, sex, and education. Model 3 (long dash) = additional adjustment for diabetes, hypertension, dyslipidemia, and self-reported atrial fibrillation. Model 4 (solid with 95% confidence interval) = additional adjustment for alcohol consumption, smoking status, body mass index, waist to hip ratio, Center for Epidemiologic Studies Depression Scale (CESD-10), and Spielberger Trait Anxiety Scale (STAI-10). The 95% CIs are not shown for the marginal probability estimates (SIS ≤ 4).

b SEVLT=Spanish English verbal learning test; WF = word fluency, DSS = digit symbol substitution; Global Cognition = composite factor score; ABI = Ankle-Brachial Index; SIS= Six-Item Screener.

Fig. 2.

Estimated marginal means (z-scores)/probabilities for cognitive outcomes and 95% confidence intervals across the ABI groups.

Results are derived from survey generalized linear regression models. Results for Hispanic/Latino adults aged 45–74 years, without prevalent stroke or transient ischemic attack (TIA) diagnoses, and without prevalent coronary heart disease from the HCHS/SOL (2008–2011). a An index value 0.90, on either left or right limb, was considered to be indicative of PAD, a value 1.40 was coded as indicative of arterial stiffness, a value between 0.9 and < 1.0 was considered borderline, and all others were coded as normal.

b Crude (hollow circle). Model 2 (hollow diamond) = adjusted for age, sex, and education. Model 3 (hollow square) = additional adjustment for diabetes, hypertension, dyslipidemia, and self-reported atrial fibrillation. Model 4 (hollow triangle) = additional adjustment for alcohol consumption, smoking status, body mass index, waist to hip ratio, Center for Epidemiologic Studies Depression Scale (CESD-10), and Spielberger Trait Anxiety Scale (STAI-10). The vertical lines represent 95% confidence intervals.

c SEVLT = Spanish English verbal learning test; WF = word fluency, DSS = digit symbol substitution; Global Cognition = composite factor score; ABI = Ankle-Brachial Index; SIS= Six-Item Screener.

Table 1

Descriptive statistics to characterize the outcomes, and covariates of the HCHS/SOL target population by Ankle-Brachial Index categories.

	Low (PAD) ^a	Borderline	Normal	High ^a	Total	p-value
	0.9	0.9–1	1–1.39	1.4+		
	(5.0%; n = 346) ^b	(19.3%; n = 1428) ^b	(73.6%; n = 6064) ^b	(2.2%; n = 153) ^b		
Cognitive Outcomes^c						
Global cognition [mean (SD)]	47.8 (11.7)	50.7 (10.5)	50.9 (11.5)	47.6 (10.6)	50.7 (11.4)	<0.001
SEVLT sum [mean (SD)]	21.1 (7.2)	22.7 (6.4)	22.8 (7.1)	20.9 (6.3)	22.7 (7)	<0.001
SEVLT recall [mean (SD)]	7.5 (3.6)	8.3 (3.3)	8.3 (3.6)	7.5 (3.3)	8.2 (3.5)	<0.001
WF [mean (SD)]	17 (7.9)	18.3 (8.8)	18.7 (9.1)	18.2 (7.6)	18.5 (9.0)	<0.001
DSS [mean (SD)]	30 (15.7)	33.3 (15.6)	35.3 (16.7)	31.4 (15.2)	34.5 (16.5)	<0.001
Low mental status (SIS 4; %)	13.3	15.4	14.2	25.0	14.6	0.0890
Model covariates						
Age [mean (SD)]	60(9.9)	57.4(9.6)	55.1(9.6)	60.1(10.2)	55.9 (9.8)	<0.001
Sex						
Female (%)	69.1	73.8	51.0	34.7	55.9	<0.001
Education						
High school or more (%)	54.6	61.4	61.8	61.3	61.3	0.3301
Diabetes						
Yes (%)	37.7	23.9	24.3	45.8	25.4	<0.001
Hypertension						
Yes (%)	65.8	54.0	40.6	59.4	44.9	<0.001
Dyslipidemia						
Yes (%)	44.4	42.3	44.7	43.2	44.2	0.7323
Atrial Fibrillation						
Yes (%)	0.3	1.5	0.7	3.4	0.9	0.0825
Alcohol use (%)						
No current use	68.3	60.6	51.9	50.7	54.4	0.001
Low risk	29.5	36.1	43.4	41.6	41.2	
High risk	2.2	3.3	4.7	7.6	4.4	
Smoking status (%)						

	Low (PAD) ^a	Borderline	Normal	High ^a	Total	p-value
	0.9	0.9-1	1-1.39	1.4+		
	(5.0%; n = 346) ^b	(19.3%; n = 1428) ^b	(73.6%; n = 6064) ^b	(2.2%; n = 153) ^b		
Former/current	60.6	47.5	44.2	34.6	45.5	<0.001
BMI groups (%)						
<18.5	2.3	0.8	0.4	0.3	0.6	<0.001
18.5-24.99	25.2	17.8	16.1	17.7	16.9	
25-29.99	31.8	40.3	42.7	26.0	41.4	
30+	40.7	41.1	40.8	56.0	41.2	
Waist-Hip ratio [mean (SD)]	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	1.0 (0.1)	0.9(0.1)	<0.001
Behavioral health^c						
CESD-10 [mean (SD)]	7.8 (7.3)	7.9 (7.9)	7.1 (7.7)	7.6 (6.9)	7.3 (7.8)	0.0712
STAI-10 [mean (SD)]	17.4 (7.1)	17.2 (7.1)	16.7 (7.2)	16.4 (5.8)	16.8 (7.2)	0.1539

^a An index value 0.90, on either left or right limb, was considered to be indicative of PAD, a value 1.40 was coded as indicative of arterial stiffness, a value between 0.9 and < 1.0 was considered borderline, and all others were coded as normal.

^b Unweighted n; weighted prevalence.

^c Global cognition = composite factor score; SEVLT=Spanish English verbal learning test; WF = word fluency, DSS = digit symbol substitution; BMI= Body Mass Index; Center for Epidemiologic Studies Depression Scale (CESD-10); Spielberger Trait Anxiety Scale (STAI-10).

Table 2

Associations between ABI and cognitive function (z-scores for continuous outcomes). Results are derived from survey generalized linear models. Results for Hispanic/Latino adults ages 45–74 years without prevalent stroke or transient ischemic attack (TIA), and without prevalent coronary heart disease from the HCHS/SOL (2008–2011).

	Model 1 ^{a,f} b (se) ^b	Model 2 ^{a,f} b (se) ^b	Model 3 ^{a,f} b (se) ^b	Model 4 ^{a,f} b (se) ^b
Global cognition^b				
ABI	2.28 (0.5) ^c	1.45 (0.39) ^c	1.34 (0.39) ^c	1.09 (0.39) ^d
ABI ²	−0.92 (0.2) ^c	−0.51 (0.15) ^c	−0.46 (0.15) ^d	−0.37 (0.16) ^e
SEVLT-Sum^b				
ABI	1.92(0.51) ^c	1.27 (0.41) ^d	1.18 (0.42) ^d	0.95 (0.42) ^e
ABI ²	−0.79 (0.21) ^c	−0.44 (0.16) ^d	−0.40 (0.16) ^e	−0.32 (0.16) ^e
SEVLT-Recall^b				
ABI	1.80 (0.47) ^c	1.18 (0.4) ^d	1.10 (0.4) ^d	0.83 (0.39) ^e
ABI ²	−0.73 (0.19) ^c	−0.40 (0.16) ^e	−0.37 (0.16) ^e	−0.28 (0.16)
WF^b				
ABI	1.69 (0.41) ^c	1.35 (0.37) ^c	1.15 (0.37) ^d	1.11 (0.36) ^d
ABI ²	−0.61 (0.15) ^c	−0.46 (0.13) ^c	−0.37 (0.13) ^d	−0.35 (0.13) ^d
DSS^b				
ABI	3.21 (0.47) ^c	1.76 (0.33) ^c	1.61 (0.33) ^c	1.58 (0.31) ^c
ABI ²	−1.20(0.19) ^c	−0.61 (0.13) ^c	−0.55 (0.12) ^c	−0.53 (0.11) ^c
	OR (95% CI)^b	OR (95% CI)^b	OR (95% CI)^b	OR (95% CI)^b
Low mental status (SIS 4)				
ABI	0.06 (0.00,3.65)	0.45 (0.01,29.95)	0.57 (0.01,39.05)	0.89 (0.01,64.38)
ABI ²	3.56 (0.77,16.47)	1.65 (0.33,8.15)	1.48 (0.30,7.36)	1.29 (0.26,6.54)

^aModel 1 = crude; Model 2 = adjusted for age, sex, and education. Model 3 = additional adjustment for diabetes, hypertension, dyslipidemia, and self-reported atrial fibrillation. Model 4 = additional adjustments for alcohol consumption levels, smoking status, body mass index, waist to hip ratio, and Center for Epidemiologic Studies Depression Scale (CESD-10), and Spielberger Trait Anxiety Scale (STAI-10).

^bGlobal Cognition = composite factor score; SEVLT=Spanish English verbal learning test; WF = word fluency, DSS = digit symbol substitution; ABI = Ankle-Brachial Index; SIS= Six-Item Screener; b = beta coefficient from survey linear regression; se = survey design adjusted standard error; OR = odds ratio; CI = confidence interval.

^c $p < 0.001$.

^d $p < 0.01$.

^e $p < 0.05$.

^f Detailed p -values are provided in Supplemental Table 3.