Subclinical carotid atherosclerosis and neurocognitive function in an urban population

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ABSTRACT

Background and aims: Examine age, sex, race, and socioeconomic status as modifiers of the association between carotid intimal medial thickness (IMT) and neurocognitive performance in a socioeconomically diverse, biracial, urban, adult population.
Methods: Participants were 1712 community-dwelling adults (45% men, 56% African-American, 38% below poverty threshold, aged 30–64 years) enrolled in the Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study. Participants underwent initial carotid ultrasonography followed by cognitive testing on up to two occasions over 4 years. Mixed-effects regression analyses were adjusted for demographic, behavioral, and biomedical covariates.
Results: Significant cross-sectional IMT × race × poverty interactions were identified for measures of delayed recall memory, auditory-verbal attention, and working memory. An IMT × race interaction also appeared for auditory-verbal learning. Higher IMT was generally associated with worse cognitive performance, but the disadvantage was most pronounced among those with higher socioeconomic status and white participants. No longitudinal associations were identified.
Conclusions: Carotid IMT-cognition associations differed as a function of race and socioeconomic status and were most compelling for measures of attention, executive function, and memory. These findings highlight the possibility that subclinical atherosclerosis may be differentially informative as a predictor of cognitive performance among varied demographic subgroups.

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1. Introduction

Subclinical carotid atherosclerosis has been linked with future cardiovascular events [1,2] and all-cause mortality [3]. A growing literature further demonstrates relations of subclinical atherosclerosis, estimated by carotid intimal medial thickness (IMT) [4], to brain health outcomes and cognitive functioning [5]. In cross-sectional studies, carotid IMT has been associated with lower levels of cognitive functioning among multiple populations, including community-dwelling adults [6], patients with cardiovascular disease [7], and survivors of stroke [8]. Individuals with amnestic mild cognitive impairment [9], Alzheimer's disease [10], and vascular dementia [11] also have been found to have thicker IMTs. Longitudinally, our group has shown carotid IMT and/or plaque to predict cognitive decline among adults without clinical vascular disease [12], as well as portend dementia diagnosis above and beyond the presence of other cardiovascular risk factors and diseases [13]. Other studies have identified similar longitudinal findings involving varied populations, including community-dwelling adults [14], cognitively normal elderly [15], and individuals with type 2 diabetes [16].

Although the bulk of the evidence supports an association between subclinical atherosclerosis and cognitive functioning, three limitations of the current literature bear mention. First, much of the research has focused on screening measures such as the Mini-Mental State Examination [17,18], rather than a full neurocognitive battery designed to provide domain-specific information.

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Second, null findings have been identified [19], suggesting that further research is necessary to identify the reasons for these inconsistencies. Third, very few, if any, studies have comprehensively addressed demographic modification of associations (e.g., age, sex, race, socioeconomic status), raising the possibility that subgroup-specific findings have been overlooked, particularly among vulnerable groups. For example, examination of socioeconomic status (SES) as a moderator has revealed carotid IMT-cognition associations to be most pronounced among lower SES participants in the Whitehall II study [20]. Young adults, women, whites, and individuals of higher SES generally have lower IMTs and slower IMT progression over time [21–23], although higher SES African-Americans may be uniquely susceptible to faster IMT progression [24]. Although these studies have documented sex-, race-, and SES-related differences in carotid IMT and IMT progression, to our knowledge, none have directly examined these differences (or interactions of these differences) in relation to cognition.

In the present study, we addressed these limitations using data from the Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study, which is uniquely designed to evaluate multiple demographic modifiers of health associations simultaneously because of its biracial, socioeconomically diverse sample of 30–64-year-old men and women. We used mixed-effects regression models to examine age, sex, race, and SES as effect modifiers of IMT in the prediction of neurocognitive performance. Because of the novelty of this study and associated lack of precedent in the literature, these analyses were exploratory, but we posited that select subgroups may show relative vulnerability to the effect of carotid IMT on cognition. We expected the domains of memory, attention, and executive function to be most affected, based on prior literature [12,25].

2. Materials and methods

2.1. Participants

Participants were recruited via field interview and enrolled in the baseline (August 2004–March 2009) and first examination follow-up (June 2009–July 2013) waves of the Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study. HANDLS is a prospective, population-based, longitudinal study examining the influences and interaction of race and SES on the development of health disparities. Comprehensive information regarding study design and procedures has been published elsewhere [26]. Briefly, a fixed cohort of community-dwelling adults was recruited from an area probability sample of 13 Baltimore City neighborhoods chosen to span diverse levels of income and socioeconomic status. Approximately equal numbers of participants were recruited from separate clusters of contiguous census tracts — neighborhoods — containing sufficient numbers of residents to fill a factorial cross of sex, race (African-American or white), 5-year age groups (ranging from 30 to 64 years), and poverty status (above or below 125% of the federal poverty lines). Households were selected randomly for potential participation, as were individuals within households. Participants were eligible if they self-identified as either Black/African-American or White/Caucasian. Recruiters visited 32,959 dwellings in which they found 14,799 potentially eligible individuals in 9904 households among whom 8150 individuals actually met initial screening criteria. Of these potentially eligible individuals, 3720 participants met all study inclusion criteria and none of the exclusion criteria listed below. Study inclusion criteria at baseline were 1) age of 30–64 years, 2) able to give informed consent, 3) able to perform at least five data measures on the medical research vehicle (MRV), and 4) able to provide valid picture identification. Study exclusion criteria at baseline

were 1) pregnancy and 2) being within 6 months of receiving chemotherapy, radiation, or biological treatments for cancer. If the participant was too ill to participate due to AIDS or blood pressure >160/100 at the first MRV visit, the visit was delayed until their health improved. Seventy-eight percent of all eligible and non-excluded individuals agreed to participate in the first wave of the HANDLS study. HANDLS was approved by the MedStar Institutional Review Board and the National Institute of Environmental Health Science, NIH. All participants provided informed consent.

Among individuals who completed both phases of the HANDLS protocol (n = 2707, described below), 1993 participants completed carotid ultrasonography. Exclusions for carotid ultrasonography included 1) elevated blood pressure at time of ultrasound (>200/100), 2) presence of carotid bruit, 3) weight exceeding or equal to 295 pounds, and 4) inability to lie in a completely supine position for 15 min. For the present analysis, we additionally excluded individuals with stroke (n = 32), dementia (n = 2), ongoing dialysis treatment (n = 1), history of carotid endarterectomy (n = 2), heart failure (n = 36), HIV/AIDS (n = 45), epilepsy (n = 63), Parkinson's disease (n = 1), multiple sclerosis (n = 7), schizophrenia (n = 17), bipolar disorder (n = 74), or missing data on all cognitive measures (n = 1). The final sample thus included 1712 participants, 1258 of whom participated at both Waves 1 and 3.

2.2. General procedures

The HANDLS protocol was administered in two phases during the first wave. Phase I was conducted in participants' homes and involved screening, recruitment, informed consent, and administration of an interview regarding sociodemographic characteristics, neighborhood characteristics, and similar information. Phase II, conducted at Waves 1 and 3, took place in mobile MRVs that visited each neighborhood. Data collected in the MRVs included medical history, physical examination, laboratory measurements, cognitive testing, and other physiological diagnostic procedures.

2.3. Carotid IMT assessment

High resolution B-mode ultrasonography of the left common carotid artery was performed with a standard transducer (5.0L45) and equipment (Acuson CV 70, Siemens) at the Wave 1 MRV visit. A region 1.5 cm proximal to the carotid bifurcation was identified, and the IMT of the far arterial wall was evaluated as the distance between the intimal-luminal interface and the medial-adventitial interface. Specific care was taken to measure IMT in areas devoid of plaque. IMT was measured on a frozen-frame image, magnified to achieve higher resolution of detail. The IMT measurement was obtained from five contiguous sites at approximate 1-mm intervals; the mean of these values was used in statistical analyses. Measurements were performed by a single sonographer. Intraobserver correlation between repeated carotid IMT measurements on 10 participants was 0.96 ($p < 0.001$) [27].

2.4. Neurocognitive assessment

During both Waves 1 and 3, cognitive measures were administered by highly trained psychometrists. The numbers that follow each test indicate respective sample sizes because of test-specific missing data. The Mini-Mental State Examination (MMSE; n = 1696) is a 30-item cognitive screening measure [28]. The Benton Visual Retention Test (BVRT, 5th edition, form D, administration A; n = 1710) evaluated immediate visuospatial memory [29]. Total number of errors served as the outcome measure. A modified version of the California Verbal Learning Test (CVLT; n = 1707) assessed auditory-verbal learning and memory [30].