2006

The association of head circumference with selected cognitive outcomes in older adults in Charlotte County, Florida

Cathleen Copenhaver
University of South Florida

The Association of Head Circumference With Selected Cognitive Outcomes in Older Adults in Charlotte County, Florida

by

Cathleen Copenhaver

A thesis submitted in partial fulfillment
of the requirements for the degree of
Master of Science in Public Health
Department of Epidemiology and Biostatistics
College of Public Health
University of South Florida

Co-Major Professor: Amy R. Borenstein, Ph.D.
Co-Major Professor: James A. Mortimer, Ph.D.
Yougui Wu, Ph.D.

Date of Approval:
November 17, 2006

Keywords: brain reserve, alzheimer's disease, aging, 3ms, apolipoprotein e

Acknowledgements

I would like to extend special appreciation toward the members of my thesis committee. Their support, friendly advice and professional opinions inspired motivation, enthusiasm, and practicality when they were needed most. I would also like to thank members of the Department of Epidemiology and Biostatistics, professors and students, who provided moral support throughout all stages of this project.

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ABSTRACT

OBJECTIVE: The brain reserve hypothesis was examined in a secondary analysis of cross-sectional data from a community-based sample of 468 older adults residing in Charlotte County, Florida. The objective of the analysis was to determine the association between head circumference and eight cognitive outcomes and to assess any potential effect modification of existing associations by Apolipoprotein E (APOE) genotype. METHODS: Cognitive outcomes include scores from the Modified Mini-Mental State Exam (3MS), the Hopkins Verbal Learning Test-Revised (HVLT-R), Stroop Color-Word Test, Trail-Making Test A and B, and a word-stem completion task measuring implicit memory. Descriptive statistics were calculated for each variable. Head circumference and dependent cognitive outcomes were modeled as dichotomous variables using logistic regression, adjusting for gender, age, education, income, height, and Spot The Word test score, a measure of pre-morbid IQ. For dichotomized test scores, poor outcomes (cases) were defined as having scores in the lowest quintile; the remaining top four quintiles were considered non-cases. RESULTS: Small head circumference was significantly associated with low 3MS scores [OR(95%CI): 2.97 (1.12, 7.89), p=0.03], after adjustment for age, income and pre-morbid IQ. The association remained statistically

significant after adjustment for gender and education as well. After adjustment, head circumference was not found to be statistically significantly associated with any other cognitive outcome. No effect modification was found by APOE genotype or years of education. CONCLUSION: This analysis confirms previous findings that exposure to low head circumference significantly impacts cognition in late life.

Chapter 1

Introduction

This thesis offers an analysis of data from a community-based survey of older adults in Charlotte County, Florida. The purpose of the Charlotte County Healthy Aging Study (CCHAS) is to identify risk factors for cognitive function, and to understand life satisfaction and quality of life among an elder population. The objective of the current analysis is to study head circumference as a risk factor for cognitive function under the brain reserve hypothesis, and to examine any existing association for modification by genetic predisposition to Alzheimer's disease.

Head circumference has been studied previously as a risk factor for dementia and for neuropsychological outcomes. However, many of the cognitive outcomes examined in this analysis have not yet been adequately addressed within the literature on head size and cognition under the brain reserve hypothesis. This thesis seeks to address that gap by analyzing the risk due to smaller head circumference of poor outcomes among eight well-known neuropsychological tests. These tests are often used within a standard battery for identifying dementia and cognitive impairment among the elderly. While it is unlikely that head circumference will become part of a standard clinical risk profile for dementia, the etiological knowledge gained from discovery of its influence on these tests will be invaluable. Through this knowledge, a better understanding of the determinants of clinical presentation of dementia can be achieved, leading to potential new prevention

therapies that capitalize on modifiable components of individual reserve capacity against cognitive decline.

In the following pages, a detailed explanation of the brain reserve hypothesis will be presented, along with thorough coverage of the existing literature on the subject of head size and cognition. This background will be found in chapter two, followed by a description of the population of CCHAS and the methods used in that study and in this analysis in chapter three. Description of the eight cognitive tests under study will also be provided in chapter three. In chapter four, the results of this analysis will be presented, and a detailed discussion of the results and their interpretation will follow in chapter five.

Chapter 2

Background

Dementia and cognitive impairment among the elderly cause considerable public health concern, particularly in populations that have growing numbers of older adults. In North America, the prevalence of dementia has been estimated between 6 and 10 percent of adults aged 65 years and older, with nearly two-thirds of all dementia cases diagnosed as Alzheimer's disease (AD).[1-5] The prevalence of both all-cause dementia and AD rise dramatically with age, increasing from below an estimated 3 percent for those aged 65-74, to approximately 11 percent between ages 75-84, to over an estimated 30 percent in persons aged 85 years and older.[1-3] Mild cognitive impairment, considered a state of risk for dementia and Alzheimer's disease, has also been measured in the community using different diagnostic criteria at a prevalence between 3 and 19 percent, with an estimated conversion rate to dementia of 11-33 percent over two years.[6, 7] Etiologic factors that could be targeted for primary prevention, or that could aid in an understanding of the etiology of clinical presentation, are being widely studied. Among them, the study of individual capacity to avoid the symptoms of dementia or cognitive impairment during life has gained significant attention in the literature, largely in the field of Alzheimer's disease.

The concept of individual brain reserve originated from autopsy studies of Alzheimer's disease, where it was observed that individuals may meet the criteria for

neuropathologic AD at autopsy, even at very old ages, without having manifested symptoms of cognitive decline.[8-12] These observations led to hypotheses regarding the individual differences in apparent tolerance for the pathology resulting in the maintenance of relatively normal functioning.

The specific idea of brain reserve was posed following one such autopsy study, in which the observed differences between the demented and cognitively normal included a higher brain weight and greater number of large neurons at autopsy of the non-demented individuals.[8] A hypothesis of brain reserve was formalized,[13] stating that individuals may possess more neural substrate (larger brains) and redundant neural networks that allow for normal cognition in the presence of neuropathology. Conversely, those with small head sizes and therefore smaller brains may be at greater risk for cognitive decline given the same pathology.

The brain reserve hypothesis and its role in a threshold model of dementia were further specified by Mortimer.[14, 15] In this model, clinical expression of dementia in the individual is dependent both upon a propensity to accumulate pathological lesions and upon the attainment of a critical threshold of neural reserve below which normal cognition can no longer be maintained.[14] Risk factors for neuropathology and for clinical expression may therefore be considered separately. In Alzheimer's disease, for example, risk factors for neuropathology include genetic predisposition, Down's syndrome, head injury, diabetes, and cardiovascular and cerebrovascular conditions. Clinical expression, on the other hand, may be dependent upon brain development, body growth, early-life socioeconomic conditions, income, education and IQ.[16, 17]

The risk factors for clinical expression, as opposed to those for neuropathology, are contributors to the unified concept of brain reserve. In clarifying this concept, Mortimer stipulated that reserve could assume any of three forms: the number or density of neurons attained in adolescence, the collection of cognitive strategies and test-taking abilities (akin to cognitive reserve, discussed below), and the amount of functional brain tissue at any age.[15] Individual differences in these three subtypes of brain reserve, combined with individually-determined rates of pathological accumulation, influence the trajectory of descent toward the threshold, resulting in earlier clinical presentation of abnormal cognition for those with smaller maximal attained brain size, fewer cognitive strategies, and faster rates of accumulation. The current study aims to identify whether smaller attained brain size increases the risk of poor cognitive performance in an analysis that controls for both individual cognitive ability and a predictor of the rate of accumulation of Alzheimer pathology in a community sample. This analysis will use head circumference, pre-morbid IQ and genetic predisposition to Alzheimer's disease as proxy measures, respectively, for the three conditions under which cognitive decline is hypothesized to clinically manifest. There is also an interest as to whether the predisposition toward faster rates of accumulation interacts with smaller attained brain size to modify the association between head size and cognitive performance.

Prior to reviewing the literature investigating the associations between head size and cognition, it may be informative to discuss the determinants of head size measurements. The growth of the cranium is driven by brain growth achieved during childhood.[16] It is known that both brain weight and intracranial volume achieve at least 75% of their maximum size by the age of three and achieve adult size by age 15.[18, 19]

Brain growth is largely dependent upon genetic and environmental factors, although the extent of separate influence from these factors is unclear. For example, it has been observed that poor nutrition leads to delayed or abnormal brain development not amenable to catch-up growth[17, 20]. It has also been found in animal studies that an enriched environment increases brain weight and dendritic branching.[21] Additionally, secular increases in brain size have been noted in developed countries,[14, 22] furthering the case for the role of environment in brain growth. On the other hand, twin and family studies indicate a potentially large role for genetic, as compared to environmental, contribution. Estimates of the genetic influence on head size have placed heritability of intracranial volume at roughly 80%[23] and of head circumference at close to 60%.[24] Nevertheless, the authors caution against the possibility that these heritability estimates may be inflated, citing the difficulty in the separation of environmental and genetic factors of influence. It is possible, therefore, that both environmental and genetic factors play substantial roles in the growth of the brain, and thus attained head size.

Most of the research on estimates of maximal attained brain size with cognition has generated consistent support for the brain reserve hypothesis. Several studies have found a consistent association between head circumference and measures of cognition among those diagnosed with dementia.[25-27] In one of the earliest studies examining a large (n=1985) population-based sample of Japanese-Americans in King County, Washington for prevalent dementia (*Kame* Project), a significant association (p=0.006) between head circumference and Cognitive Abilities Screening Instrument (CASI) scores was found among those diagnosed with AD.[25] It was found that scores among those patients with lower HC were worse than those among patients with higher HC, an

association that was not seen among non-demented individuals. Another study examining a hospital-based sample of AD patients in Japan found that intracranial volume (ICV), a measure of maximal brain size, was correlated between 0.289 and 0.396 ($p<0.05$) with several measures of intelligence, including the Wechsler Adult Intelligence Scale-Revised (WAIS-R) and Raven's Colored Progressive Matrices (RPM).[26] A third and more recent study identified a statistically significant correlation of 0.33 ($p=0.01$) between ICV and MMSE scores among those with AD and VaD.[27] The same study, using linear regression, found that a 66.7 cm^3 increase in ICV was associated with a 1-point change in MMSE, adjusted for age and gender.

Compelling evidence in support of the brain reserve hypothesis has come from studies that compare cognitively impaired subjects with normal controls. Schofield et al. found, for example, that head circumference in the lowest gender-specific quintile, compared with the other four quintiles, was associated with increased prevalence of probable and possible AD with an OR (95%CI) of 2.9 (1.4, 6.1) in women and 2.3 (0.6, 9.8) in men.[28] Wolf et al. examined ICV across normal controls and patients with prevalent mild cognitive impairment (MCI), AD and vascular dementia (VaD).[29] The authors found a decreasing prevalence of cognitive impairment among increasing quartiles of ICV (chi-square statistic for linear trend = 8.5, df=1, $p=0.003$). Later work by Wolf et al. on a different population demonstrated an increased risk of cognitive impairment [OR: 2.8 (1.3, 6.0)], including MCI, and of dementia [OR: 2.5 (1.2, 5.1)] for ICV in the lowest quartile compared to the top three quartiles.[27] Additionally, Mortimer et al. found in a study of 294 Catholic sisters that head circumference in the lower two

tertiles and low education (<16 years) interacted to substantially increase the risk of prevalent dementia [OR: 4.3 (1.9, 9.6)].[30]

A third line of research on the role of brain reserve in the timing of clinical presentation has generated slightly less consistent results. Several studies have found strong inverse associations between time to onset of cognitive impairment and head size. Schofield et al., in a study of 28 female AD patients from a New York clinic, found that age at first symptom onset was significantly correlated ($r=0.64$, $p=0.01$) with a cross-sectional measure of intracranial area.[31] In the follow-up phase of the *Kame* Project, mentioned previously, two subsequent analyses revealed head circumference as an important risk factor for incident AD among those at genetic risk for the disease, defined as possession of one or more APOE ε4 alleles.[32, 33] The first analysis found that head circumference in the lowest tertile (<21.4 inches) combined with positive ε4 status predicted earlier onset of incident AD at a hazard ratio (HR) of 14.1 (3.0-65.0), adjusted for gender and education.[32] The second analysis found that developmental variables including small head circumference (≤ 54.4 cm, or 21.4 inches) and having four or more children in the household at age 2-3 years were independently predictive of earlier onset of AD among ε4-positive subjects, while vascular risk factors were more important among ε4-negative individuals.[33] These findings illustrates the importance of reserve factors (e.g. HC) in delaying clinical presentation of disease among those individuals who may be at genetic risk for faster accumulation of pathology.

There have been a few studies that have not found evidence that pre-morbid brain size protects against cognitive decline. In one case-control examination of familial (early onset) and sporadic (late onset) AD, no difference was found in mean ICV across groups,

controlling for age, education and gender.[34] The author also found that ICV, the dependent variable in a linear regression, did not differ by age or age at onset of symptoms, although the approach of adding an indicator of dementia type (familial or sporadic) to the model may have offered less than ideal control for this factor without stratified analysis. Furthermore, it is possible that findings may have varied had the authors examined the range of risk (lowest quantile) instead of continuous ICV.

A second analysis by Edland et al. with more thorough control of potential confounders and examination of both tertiles and continuous ICV in a case-control study of 166 subjects with and 184 subjects without AD found no significant difference in mean ICV between patients and controls, accounting for age, education, APOE ε4 status, and birth year.[35] ICV in the lowest tertile did not predict AD for men or women, and age at onset was not correlated with ICV. Although the study appears well-controlled, the population in which this study was conducted tended to be a well-educated sample[36] and the author cited the limitation that adverse developmental conditions (leading to reduced adult brain size) probably were not common among the sample. It is possible, therefore, that there were insufficient numbers of individuals with small ICV. Additionally, it was unclear whether the authors specified the lowest tertile in a gender-specific manner, as did Wolf et al. and Schofield et al. mentioned above.[27-29] Analyses from the *Kame* Project, which similarly found no mean difference of HC between cases and non-cases, also did not specify HC in a gender-specific fashion.[25, 32, 33] Given likely differences in brain structure and function in men and women,[37] specification of the gender-specific range of risk in head size may be subject to less bias from misclassification and may result in more valid measures of risk. Gender-specific quantiles also help to overcome

problems of collinearity between gender and head size in modeling, such as those encountered in the *Kame* analysis.[33] It is unknown as to the extent to which these issues may have contributed to the null finding in the results presented in Edland et al.[35]

The most recent study to produce null findings provided both a large-scale case-control analysis and a longitudinal follow-up of 450 non-demented controls examining head circumference and time to conversion to AD.[38] This study found no mean difference in HC across case-status in the case-control analysis and no association between either continuous HC or the lower gender-specific quartile of HC and time to conversion to AD, although the sample size and relatively few conversion events may have limited the prospective analysis. The analyses were adjusted for age, APOE ε4 status, family history of AD, gender and education. While there are many strengths to this study in addressing some of the analytic concerns, findings in previous analyses of time-to-AD with head size as a predictor[33] indicate the importance of stratifying results by APOE ε4 status to examine reserve while 'controlling' for genetic predisposition toward faster decline.

Examining the reserve hypothesis more generally, several studies have found associations between head size and cognitive outcomes, particularly cognitive decline, among non-demented and community-living individuals. Among the first to do so, Reynolds et al. examined head size and MMSE scores in a community-based survey of the MoVIES cohort (n=852), which followed initially non-demented subjects of mostly Caucasian background with relatively low socioeconomic status from 1993 until 1996.[39] In a baseline analysis, and using gender-stratified logistic regression with low MMSE ($\leq 10^{th}$ percentile) as the dependent variable, each 1-centimeter increase in HC was

inversely associated with low MMSE scores [OR (95%CI) women: 0.83 (0.69, 0.99); OR men: 0.79 (0.63, 0.98)]. A similar finding was observed by Tisserand et al. in a baseline examination of multiple cognitive outcomes with HC among initially non-demented adults.[40] In that study, increasing continuous HC adjusted for age and gender was significantly and positively associated with continuous MMSE scores and several measures of intelligence using the Groningen Intelligence Test, adjusted for gender, sex, and either height, socioeconomic background or educational level. The authors also found significantly increased time to completion of the Stroop Color-Word task, scored so that longer times indicate slower processing speeds, with lower HC.[40]

A third study also confirmed the association between adult head size and cognition, finding that mean intelligence scores as measured by the AH4 test at two test periods 3.5 years apart in a sample with a mean age of 70 years increased with increasing quartile of HC (p for trend <0.01 at both trials, adjusted for age, sex, education, social class at birth, history of cerebrovascular disease, and health profile emotional scores).[41] Conversely, no such trend was observed for cross-sectional measures of immediate and delayed memory measured by the Logical Memory Test, an observation replicated by Tisserand et al., though there was a trend toward decline in immediate recall (p=0.03) and delayed recall (p=0.07) over time for those with smaller head circumferences.[40, 41]

Finally, two studies examined the association between ICV and cognition with inconsistent results. One study comprehensively measured both ICV and regional brain volumes in 97 healthy, non-medicated men with a mean of 68 years of age.[42] ICV correlated with measures of pre-morbid intelligence (National Adult Reading Test, r=0.304, p<0.005; Raven's Standard Progressive Matrices (RPM), r=0.39, p<0.000) and

visual memory, but not immediate or delayed verbal memory (from the Auditory Verbal Learning Test, or AVLT, among others). The second study measured ICV and cognitive functioning also using RPM and AVLT in a sample of healthy men born in 1921, aged 79 years, finding no association between the 'passive' reserve represented by ICV.[43] The measure was adjusted for intelligence scores measured at age 11, measures of brain burden by number of white-matter hyperintensities, age and sex. A comparison between the studies is made very difficult by the differences in adjustment and subject age: whereas the former study did not make adjustments for other factors, the latter study more rigorously explored the reserve hypothesis by controlling for pathological burden and childhood intellectual function, which may provide a "cognitive reserve" in terms of more flexible or efficient networks that may protect against decline in lieu of brain reserve.[43, 44] However, the statistical adjustment and inclusion of childhood IQ in the study by Staff et al. may have weakened the association to the extent that it was undetectable in that sample. Additionally, the much older subjects in that study may have been selected by survival to have slower rates of accumulated pathology and less effect of head circumference, as was suggested in the *Kame* Project analyses above. Unfortunately, no data on APOE ε4 status was available for either study, rendering further speculation about the effect of genetic risk for AD pathological accumulation impractical.

The consideration of APOE ε4 status as a proxy for accumulated pathology and of pre-morbid intelligence as a measure of *cognitive* reserve is important in the study of the reserve hypothesis. Cognitive reserve has been proposed as a complementary means of explaining the disparity between sufficient pathological accumulation and clinical

presentation of dementia under the reserve hypothesis.[44] It states that those individuals possessing more efficient and flexible cognitive networks may compensate for pathology more successfully during life than those who do not have such networks. Staff et al. and Mortimer et al., among others mentioned previously, have used measures of pre-morbid (i.e. pre-decline, whether age-related or pathological) intelligence and/or education level as a proxy for such reserve.[30, 43] Most commonly, the measure of adjustment is education, given a known association with head size[29, 35, 40] and with cognitive measures,[45, 46] although pre-morbid intelligence measures may be a more sensitive individual measure of cognitive reserve.[47, 48] Diverse measures of increasing *physical* reserve, such as physical activity in youth, height and limb length, which may indicate a type of robustness against decline in age, have also been demonstrated to have an inverse association with cognitive decline.[49-53] None of the studies of physical reserve, however, have accounted for the correlation between body measurements and head size.

Consistent adjustment for these measures of burden and reserve have been absent in studies of head size with cognitive impairment or decline. While measures of cognitive reserve are often controlled for in analyses with demented subjects, it has produced inconsistent results among the cognitively normal. Adjustment for height and APOE ε4 status has also been sporadic in the literature, even though the substantial findings involving these measures indicate a need to consider them as standard potential confounders in the study of cognitive decline. In the current analysis, head size as measured by HC is compared with eight cognitive outcomes in a sample of community-living older adults. Both APOE ε4 status and height, along with education and a measure of pre-morbid IQ,[54] are considered as potential confounders, and data are examined for

potential effect modification by APOE ε4 status. BMI is also included among the covariates as a convenient, though imprecise, proxy for potential risk from vascular, diabetic or metabolic syndrome factors.[55, 56]

The main hypothesis being tested is that small head circumference, determined in a manner that includes the gender-specific range of risk, is associated with a greater odds of poor cognitive outcome among subjects in the community. The secondary goal of the analysis is to test for effect-modification by APOE ε4 status in any association found between head circumference and cognitive outcome. Literature support and applicability of the hypothesis to the specific cognitive outcomes analyzed in this study will be discussed in further detail in the Discussion chapter.

Chapter 3

Methods

Design and Population

This study analyzes secondary data from the Charlotte County Healthy Aging Study (CCHAS), a cross-sectional study of primarily Caucasian community-living older adults in Charlotte County, Florida. Two census tracts from this region were selected for CCHAS based on information from the 1990 U.S. Census that indicated it contained the highest proportion of residents aged 65 and older in Florida. One tract contained 7,093 inhabitants in 1990 (45.2% aged over 65 years), and the other contained 6,233 inhabitants in 1990 (37.4% over 65 years). Census blocks were sampled consecutively from a randomly ordered list obtained for each of the two larger census tracts. Prior to recruitment, a large-scale publicity campaign generated support for the study through newspaper articles, presentations to community organizations, local television and radio appearances, and the formation of a Community Advisory Council of 12 community leaders.[57]

Eligible subjects were identified by canvassing all households, documenting all addresses within each block, and then revisiting the blocks at different times on different days to request household information on name, age and sex of all persons in residence. Unreachable households were those that did not answer the door after two attempts. A stratified sampling procedure was used within the selected census blocks until the desired

sample size was reached. The final sample was to contain approximately equal proportions of male and female participants, a total of 126 persons within each of two age strata: age 60-74 and 75-84.[57, 58] The sampling method was also modified slightly to facilitate obtaining as representative a sample as possible of the independently living elderly population of Charlotte County (for example, by including all members on each side of a street when a census block divided them).

Of 4017 households surveyed in the selected tracts, census data were obtained for 2164 (54%) in the first phase of the study. From these, 1394 subjects were identified as eligible and invited to participate via postal mail and follow-up telephone calls, including multiple eligible subjects per household. Of those eligible, 584 (42%) were unreachable, defined as no answer to up to nine telephone attempts at contact. Of those eligible and reachable, 468 participated in the study, 306 refused, and 36 accepted and later declined. From age, gender and education data on a portion of those who refused or did not complete all phases, it was determined that those who completed all phases were comparable to those who did not. Refusers were similar in age to completers, were more likely to be women and to have less education ($p<0.05$). Sampled participants were primarily Caucasian (>98%).[57, 58]

Measures

CCHAS Procedures

Exposure, outcomes, and potentially confounding and/or modifying variables for each subject were assessed during two personal, structured interviews conducted over approximately one week, both in the homes of the subjects or at a neutral location

according to subject preference.[58] Income and years of education were assessed during the first interview, in which trained personnel administered a risk factor questionnaire. Interviewers recorded physical measures, including head circumference (HC), weight and height, and assessed cognitive outcomes during the second interview one week later. Blood samples were collected by a phlebotomist during the week between the two interviews. The phlebotomist visited the subject's home, where blood samples were taken to measure cholesterol levels, A1C levels for diabetes, folate, and to obtain DNA for genotyping of APOE. All data were collected between November 1, 1997 and June 30, 1998. Procedures for CCHAS were approved by the University of South Florida Institutional Review Board and written informed consent collected for each participating subject.

Variables

Head Circumference. Head circumference (HC) is the primary exposure of interest in the current analysis. HC was measured by placing a non-distensible, flexible measuring tape at the line of the eyebrows and passing it snugly around the outermost occipital protuberance, returning to the eyebrows. HC was measured in inches for each subject and rounded to the nearest ¼ inch.[32]

Cognitive Outcomes. The following defines the eight cognitive outcomes of interest. All outcomes were dichotomized as described in the section on Bivariate Statistics in the Methods.

a. The Modified Mini-Mental State Examination: The 3MS is a standardized measure of general cognitive ability in which the subject is asked a series of

questions. It samples a range of cognitive functions and the total score, used for this analysis, is scaled from 0 to 100.[59]

b. Memory subscales of the Hopkins Verbal Learning Test-Revised (HVLT),[60] including Immediate Recall (ImR), Delayed Recall (DeR), Cued Recall (CuR) and Recognition (Cite Small here): For each of the four measures, a word list of 12 words was used. For ImR, there are three learning trials, and the number of words remembered immediately after each trial is recorded and the three totals summed. For DeR, the subject is asked to remember the list in the three trials of free recall after an interference test; the total number of words recalled for each trial are summed. In the CuR subsection, administered directly after the DeR subsection, the subject is asked to recall the words according to the category they belong to. There are three categories, and the numbers of words recalled in each category are summed for a total cued score. The score used in this analysis is the *gain* from cues, measured as the DeR score subtracted from the summed total cued score. Finally, the subject is read a list of 24 words including the 12 they were asked to remember, and is asked to respond as to whether or not the word read was on the original list of 12. The correct and incorrect positive responses are summed, and the incorrect positive responses are subtracted from the correct positive responses to yield a *discrimination index* score representing Recognition.

c. Stroop Color-Word Test[61] (Stroop): In this test, the subject is asked to read from three panels containing, respectively, words referring to colors (e.g. Blue), only colors with no words, and mismatched color-word combinations.

The score used in this analysis is the number of words completed on the color-word task within a time limit.

d. Trail-Making Test, Parts A and B[62] (Trails): In these tests, subjects are asked to draw a line trail through randomly scattered bubbles containing numbers only (Part A) or numbers and letters (Part B) in sequential and sequential/alphabetical order, respectively. The score used for this analysis is the difference between the amount of time it took for the subject to correctly finish Parts A and B.

e. Implicit Memory[63] (Implicit): For this test, the subject was asked to read a word list containing nonsense and real words and to identify the real words. After an interference test (Trails), the subject was asked to complete word stems. Half of the stems were from real words they had seen on the previous task. The score used for this analysis, the *priming* score, is the total number of stems completed with words subjects had seen before minus the total number of stems completed with words not seen before.

Other Variables of Interest. Age was measured as the age at examination and calculated using SAS variables for the unique dates of examination and birth. Education was measured as the number of formal years of regular school completed, as reported by the subject. Income was scored as an ordinal variable representing nine levels of annual household income from "below $10,000 per year" (Level 1) to "above $150,000 per year" (Level 9). Scales to measure height were calibrated to one another and taken into the field. Height was measured against a wall and was in inches, rounded to the nearest ¼ inch. BMI was calculated as the weight in kilograms of the subject divided by the

squared height in meters. Pre-morbid intelligence was assessed using a standard measure, Spot The Word Test 1.[54] In this test, participants are asked to identify the real words in a list of 60 word pairs containing one real and one nonsense word. Each correctly identified word earns one point, with a maximum score of 60. Higher scores indicate higher crystallized intelligence, an indication of higher pre-morbid intelligence.

APOE Genotype

Blood samples were prepared by separating leukocytes from whole blood and lysing the cells using prepared stock solutions. The DNA was extracted by centrifugation and washed with ethanol before resuspension in tris-EDTA acid buffer solution. APOE genotyping was performed using standard digestion and PCR amplification.[57, 58] From the dual-allele genotype, APOE status was dichotomized as an ε4 allele being present or absent, defined in the methods of analysis below.

Analysis

All analyses were performed using the SAS Statistical Software package, version 9.3.

Univariate Statistics

Histograms were generated to visually assess the distribution of each continuous variable, and the mean and standard deviation of each was calculated to describe central tendency and dispersion. Means and standard deviation for the exposure measure, HC, were also stratified by gender, and tested for difference in means using a t-test for independent means.[64] For categorical variables, frequency and relative frequency were calculated to describe distribution across levels.

Defining the Variables for Analysis

The exposure variable, HC, was first stratified by gender and then frequency, relative and cumulative relative frequencies for each ¼-inch interval were examined across the entire range. This was done to identify an acceptable dichotomization point that would accurately reflect the range of risk by gender in this sample. Once an appropriate point was identified, male and female subjects were classified by their exposure status separately then combined within a single dichotomous variable. Outcomes were also dichotomized. Those subjects with scores falling at or below the bottom 20th percentile were classified as having a poor outcome, as compared with normal outcomes above the bottom 20th percentile. (Note: For Trails, the absolute value of the difference was scored, where larger differences indicated a poor outcome, therefore scores falling at or above the top 20th percentile were classified as a poor outcome.) Two exceptions, CuR and Implicit memory, were dichotomized at the interval directly below that in which the 20th percentile resided due to a small range and tight clustering about the mean. Body Mass Index was dichotomized as obese and non-obese, using a BMI of ≥ 30 to indicate obesity.[65] All other covariates, except gender and APOE, were kept as continuous variables. APOE status was described as either possessing one or more APOE ε4 alleles (ε4-positive) or possessing no ε4 alleles (ε4-negative).

Bivariate Analysis

Logistic regression was performed and crude odds ratios, 95% confidence intervals, and p-values were generated for each outcome with exposure, and for each outcome with each covariate. For each outcome with the exposure, the crude association was also analyzed stratified by gender. Logistic regression was then performed for the

exposure with each covariate. Those variables having associations reaching a significance of $p \leq 0.10$ with both the exposure and outcome were considered as potential confounders. Concomitant predictors of outcome also were identified. All odds ratios are reported for the odds of low head circumference (exposed), poor outcome, increasing value (continuous covariates), being female (Gender), obese (BMI) and ε4-positive (APOE).

Multivariate Analysis and Modeling

The main objective of the multivariate analysis was to identify the most parsimonious model that described the odds ratios for the eight outcomes as they related to head circumference. The approach taken was to illustrate the crude, standard-adjusted, fully-adjusted, and trimmed models. The standard-adjusted model contained those variables most consistently identified as potential confounders and used as model variables in the literature: age, gender and years of education. The fully-adjusted model contained all confounding variables and concomitant predictors identified for each outcome at the specified significance within this sample. The trimmed model, accepted as the final model for each outcome, was identified by a manual backwards selection procedure for those HC-Outcome associations reaching significance at $p<0.05$ in the full model. In this procedure, variables were removed singly from the full model and the effect of their removal was ranked in terms of percent change in the point estimate of the exposure. The least change earned a value of one, the next largest change two, and so on. Variables were then removed sequentially from the full model in order of rank until a noticeable (10%) difference in the point estimate from the full model was observed. The model analyzed just prior to the noted change in estimate was selected for analysis of

potential joint confounders, which were added if found, completing the final model.[66] In the instance that no statistically significant association was observed between head circumference and the outcome, the fully adjusted model was accepted over the crude as the final model. Although no inference can be drawn from either model, the fully adjusted model was chosen as final over the crude in these non-statistically-significant instances primarily so that the final model could reflect the best-fitting model as indicated by the Likelihood Ratio statistic.

All model summaries list odds ratios, 95% confidence intervals, and p-values for the models as calculated both with the total sample and stratified by gender. Final models were analyzed for fit using the Hosmer-Lemeshow Goodness of Fit test.[67]

Interactions

All final models were analyzed for interaction using logistic regression by reintroducing the main effect term for APOE where necessary and adding a term for the interaction between the exposure variable and APOE status to each final model. Interactions were accepted as potentially inferential at a significance of $p \leq 0.1$. A *post hoc* analysis of model fit was completed separately for the addition of APOE and the interaction term, and the data were also examined further for potential interaction by analyzing the two-by-two tables for outcome and HC stratified by APOE status.

Chapter 4

Results

Descriptive Analysis

A histogram (not shown) for each continuous variable of interest was generated in order to characterize their distributions in this sample. All continuous variables displayed a roughly normal distribution with little skew, implicating the mean and standard deviation as acceptable measures of central tendency and dispersion. Results of the univariate analysis of continuous variables are found in Table 1a and 1b. The frequencies and relative frequencies of gender and APOE status are found in Table 1c. There was a significant difference in the mean head circumference by gender (t-test $p<0.0001$), indicating the need to examine the range of risk stratified by gender.

Table 1. Descriptive Measures for HC, Covariates and Outcomes

Table 1a. Mean and Standard Deviation for Continous HC and Covariates

		HC	**Age**	**Education**	**Income**
Mean (SD)	M	22.7 (0.7)	73.5 (6.2)	14.6 (3.2)	4.4 (1.5)
	F	21.6 (0.6)	72.6 (6.3)	13.2 (2.7)	3.9 (1.6)
	All	22.2 (0.8)	73.0 (6.2)	13.9 (3.0)	4.2 (1.6)

		IQ	**Height**	**BMI**
Mean (SD)	M	49.7 (6.2)	68.9 (3.4)	28.4 (4.6)
	F	49.3 (5.9)	62.9 (2.8)	26.9 (5.8)
	All	49.5 (6.0)	65.8 (4.3)	27.6 (5.3)

Table 1b. Mean and Standard Deviation for Continous Outcomes

	3MS	ImR	DeR	CuR
Mean (SD)	91.6 (7.6)	20.1 (5.5)	7.5 (2.8)	1.0 (1.6)

	Recog.	Stroop	Trails	Implicit
Mean (SD)	9.5 (2.0)	28.1 (9.6)	74.8 (57.6)	2.1 (2.7)

Table 1c. Frequency and Relative Frequency for Gender and APOE Status

	Gender		APOE	
	Male	Female	ε4 Neg	ε4 Pos
N (%)	228 (49)	240 (51)	360 (78)	102 (22)

Bivariate Analysis

After stratifying by gender and examining the frequencies across the range of HC for each stratum, it was determined that using the interval in which fell the exact bottom tertile, quartile or quintile (standard levels of comparison in the literature) would not allow sufficient diversity between the dichotomized levels to ensure that the "low" classification was capturing risk. Therefore, the interval directly below that which contained the bottom 20th percentile was chosen as the appropriate point at which to dichotomize the variable. As Table 2 illustrates, this created an exposed group containing 5.8 percent of the sample. Table 2 also shows the relative frequency across levels for outcomes and BMI after dichotomizing in the interval of the bottom 20th percentile for outcome and at or above 30 (obese) for BMI. CuR and Implicit outcomes show that slightly less of the sample, 12.6 and 19.2 percent respectively, was classified as a poor outcome for those variables.

Table 2. Frequencies and Relative Frequencies of Dichotomized Variables

	HC		**3MS**		**ImR**		**DeR**		**CuR**	
	L	H	L	H	L	H	L	H	L	H
N	27	441	101	367	99	369	103	365	59	409
%	*5.8*	*94.2*	*21.6*	*78.4*	*21.2*	*78.9*	*22.0*	*78.0*	*12.6*	*87.4*
* L: Low H: High/Normal O: Obese NO: Non-obese										
	Recog.		**Stroop**		**Trails**		**Implicit**		**BMI**	
	L	H	L	H	L	H	L	H	O	NO
N	128	340	98	370	101	367	90	378	121	347
%	*27.4*	*72.7*	*20.9*	*79.1*	*21.6*	*78.4*	*19.2*	*80.8*	*25.9*	*74.2*

Appendix A shows the results of all crude logistic analysis for the exposure with outcomes (Table A1), and for covariates with both exposure and outcome (Tables A2 and A3). In crude analysis, HC was significantly associated at $p \leq 0.001$ with 3MS [OR(95%CI): 4.38 (1.99, 9.66)], an association that persisted for both sexes when stratified by gender [Male OR: 3.09 (1.07, 8.96); Female OR: 6.58 (1.99, 21.8)]. HC did not approach statistical significance for any other outcome. Larger HC also was statistically significantly associated with more years of education [OR for low HC with increasing number of years of education: 0.86 (0.76, 0.98); p=0.02], increasing height [OR: 0.91 (0.83, 1.00); p=0.05] and most significantly increasing IQ [OR: 0.92 (0.87, 0.98); p=0.004]. There were also non-significant associations (p=0.09) of HC with the possession of an APOE ε4 allele [OR: 0.28 (0.07, 1.21)], which may suggest that individuals with higher HC were more likely to possess an APOE-e4 allele in this sample, and with increasing age [OR: 1.06 (0.99, 1.13)], suggesting that individuals with smaller HC tended to be somewhat older than those with larger HC.

Confounders and concomitant predictors were identified for each outcome using Tables A2 and A3. Table A2 shows the confounders and their associations for each

outcome, associated with both outcome and HC at $p \leq 0.1$. Concomitant predictors (T) and confounders (C) for each outcome are summarized in Table 3 in the Full Model (F). No confounders or predictors were identified for CuR.

Multivariate Analysis

The resulting odds ratios and corresponding confidence intervals for poor outcome with exposure to low HC can be seen in Table 3 for the crude, standard-adjusted, full and trimmed models. All final models demonstrated good fit with the Hosmer-Lemeshow test for goodness of fit. These results, as well as the results of the final model selection process, are presented below by outcome:

3MS (Table 3a)

After adjustment for standard and full-model variables, the estimate of the OR was reduced slightly from 4.38 to 2.96, but remained significant (p=0.03). From the stratified results of the full model we see that while the OR for men remained consistently above 2, the OR for women was higher [4.35 (1.00, 18.9)], reaching significance at p=0.05. Model selection procedures (MSP) revealed education and income as variables with little impact on the exposure-outcome association in the model. Removal of both resulted in a slightly higher odds ratio for all three estimates, and greater significance in the total sample and male subsample (Model 5). The change in estimate for the total sample was less than 10% of the unstratified full model, the previously identified criterion for allowing removal of the variable, but considerably changed the estimate in males. Income was identified as the variable responsible for the large change, a predictor variable that showed more potential as a confounder in men than women

(Appendix A, Table A3). Income was therefore reintroduced to produce a more conservative final model (Model 4). The final estimate, adjusted for age, education and income, was nearly identical to the full model and had a slightly smaller confidence interval [OR: 2.97 (1.12, 7.89)]. Given that only education was removed during the MSP, assessment for joint confounding was not necessary for this outcome.

Table 3. Model Selection for Main Effect of Head Circumference and APOE Interaction

Table 3a. Model Selection for HC with 3MS

		HC									
		OVERALL		Age	Education	Gender	Income	IQ	Height	APOE	APOE*HC
Model	N	OR (95% CI)	*p*								
1	468	4.38 (1.99 , 9.66)	*<0.0001*								
2	462	3.37 (1.40 , 8.11)	*0.01*	X	X	X					
3 F	421	2.90 (1.09 , 7.71)	*0.03*	C	C		T	C			
4 *	421	2.97 (1.12 , 7.89)	*0.03*	C			T	C			
5	463	3.11 (1.18 , 8.25)	*0.02*	C				C			
I	417	*No interaction observed***		C			T	C		R	I

*Final Model F: Full Model X: Standard Adjustment Variable C: Confounder T: Concomitant I: Interaction R: Required

**Term for interaction not statistically significant (p=0.99)

		HC *(Stratified by Gender)*			
		M		F	
Model	N	OR (95% CI)	*p*	OR (95% CI)	*p*
1	468	3.09 (1.07 , 8.96)	*0.04*	6.58 (1.99 , 21.8)	*0.002*
2	462	2.36 (0.69 , 8.07)	*0.17*	5.25 (1.40 , 19.6)	*0.01*
3 F	421	2.00 (0.51 , 7.84)	*0.39*	4.29 (1.00 , 18.4)	*0.05*
4 *	421	2.04 (0.52 , 7.94)	*0.31*	4.51 (1.03 , 19.7)	*0.05*
5	463	2.46 (0.64 , 9.01)	*0.17*	4.60 (1.02 , 20.8)	*0.05*

*Final Model F: Full Model

ImR (Table 3b)

The crude association between low HC and poor outcome showed an initially positive direction [OR (95%CI): 1.62 (0.69, 3.82); p=0.27; Model 1], but after both standard and full adjustment the OR moved toward the null and showed no significant association between exposure and poor outcome (Model 3).

Table 3b. Model Selection for HC with ImR

		HC										
		OVERALL		Age	Education	Gender	Income	IQ	Height	APOE	APOE*HC
Model	N	OR (95% CI)	*p*								
1	468	1.62 (0.69 , 3.82)	*0.27*								
2	462	1.05 (0.40 , 2.76)	*0.92*	X	X	X					
3 *F	419	1.09 (0.37 , 2.94)	*0.94*	C	C	T	T	C	C		
I	456	*No interaction observed***		C	C	T	T	C	C	R	I

*Final Model F: Full Model X: Standard Adjustment Variable C: Confounder T: Concomitant I: Interaction R: Required

**Term for interaction not statistically significant (p=0.50)

		HC *(Stratified by Gender)*			
		M		F	
Model	N	OR (95% CI)	*p*	OR (95% CI)	*p*
1	468	1.37 (0.45 , 4.18)	*0.58*	1.90 (0.49 , 7.39)	*0.35*
2	462	0.83 (0.22 , 3.06)	*0.78*	1.33 (0.33 , 5.44)	*0.69*
3 *F	419	0.73 (0.17 , 3.13)	*0.67*	1.51 (0.33 , 6.88)	*0.60*

*Final Model F: Full Model

DeR (Table 3c)

Though the crude OR for delayed recall showed a positive direction initially, standard and full adjustment changed the direction of the association for the total sample (Models 2 and 3). No associations were found to be statistically significant, therefore no

selection procedures were performed. The male subsample showed a consistently positive direction in all adjusted models, but also highly insignificant (p=0.68). In women, the crude direction of association was negative and continued to drop and gain significance with adjustment, resulting in an OR (95%CI) = 0.37 (0.06, 2.19) at p=0.28 in the final model.

Table 3c. Model Selection for HC with DeR

		HC										
		OVERALL		Age	Education	Gender	Income	IQ	Height	APOE	APOE*HC
Model	N	OR (95% CI)	*p*								
1	468	1.53 (0.65 , 3.61)	*0.33*								
2	462	0.96 (0.36 , 2.52)	*0.93*	X	X	X					
3 *F	416	0.80 (0.28 , 2.29)	*0.67*	C	C	T	T	C		C	
I	416	*No interaction observed***		C	C	T	T	C		R	I

*Final Model F: Full Model X: Standard Adjustment Variable C: Confounder T: Concomitant I: Interaction R: Required

**Term for interaction not statistically significant (p=0.64)

		HC *(Stratified by Gender)*			
		M		F	
Model	N	OR (95% CI)	*p*	OR (95% CI)	*p*
1	468	2.01 (0.68 , 5.92)	*0.20*	0.89 (0.19 , 4.19)	*0.88*
2	462	1.32 (0.39 , 4.54)	*0.66*	0.55 (0.11 , 2.77)	*0.47*
3 *F	416	1.34 (0.34 , 5.32)	*0.68*	0.37 (0.06 , 2.19)	*0.28*

*Final Model F: Full Model

CuR (Table 3d)

Since there were no confounders identified for CuR, the full model used standard adjustment variables (Model 2) and resulted in no substantial change. Therefore the standard-adjusted model was chosen as the final one (Model 1). In both models, no significant association was observed. The direction of association for the total sample

was positive (p=0.60), was positive in men [OR: 2.12 (0.53, 8.46); p=0.29], and inverse in women [OR: 0.61 (0.07, 4.97); p=0.64].

Table 3d. Model Selection for HC with CuR

		HC										
		OVERALL										
Model	N	OR (95% CI)	*p*	Age	Education	Gender	Income	IQ	Height	APOE	APOE*HC
1	468	1.22 (0.41 , 3.66)	*0.72*								
2 *	462	1.35 (0.44 , 4.11)	*0.60*	X	X	X					
I	462	*No interaction observed***								R	I

*Final Model F: Full Model X: Standard Adjustment Variable C: Confounder T: Concomitant I: Interaction R: Required

**Term for interaction not statistically significant (p=0.99)

		HC *(Stratified by Gender)*			
		M		F	
Model	N	OR (95% CI)	*p*	OR (95% CI)	*p*
1	468	2.17 (0.57 , 8.29)	*0.26*	0.54 (0.07 , 4.30)	*0.56*
2 *	462	2.12 (0.53 , 8.46)	*0.29*	0.61 (0.07 , 4.97)	*0.64*

*Final Model F: Full Model

Recognition (Table 3e)

Crude and adjusted models agreed in the total sample and in both gender strata for Recognition, showing an inverse association that strengthened and gained significance with adjustment. However, no significance was observed in any model, therefore no model selection procedures were performed. In the final model, the OR (95%CI) for the total sample was 0.38 (0.12, 1.15) (p=0.09)(Model 3). In males, the point estimate for OR was 0.51 (0.13, 2.02), non-significant p=0.34, and in females it dropped substantially to 0.18 (0.02, 1.58), also non-significant at p=0.12.

Table 3e. Model Selection for HC with Recognition

		HC		Age	Education	Gender	Income	IQ	Height	APOE	APOE*HC
		OVERALL									
Model	N	OR (95% CI)	*p*								
1	468	0.75 (0.30 , 1.90)	*0.54*								
2	462	0.45 (0.16 , 1.30)	*0.14*	X	X	X					
3 *F	419	0.38 (0.12 , 1.15)	*0.09*	C	C	T	T	C	C		
I	415	*No interaction observed***		C	C	T	T	C	C	R	I

*Final Model F: Full Model X: Standard Adjustment Variable C: Confounder T: Concomitant I: Interaction R: Required

**Term for interaction not statistically significant (p=0.98)

		HC *(Stratified by Gender)*			
		M		F	
Model	N	OR (95% CI)	*p*	OR (95% CI)	*p*
1	468	0.98 (0.32 , 2.97)	*0.97*	0.32 (0.04 , 2.57)	*0.29*
2	462	0.58 (0.16 , 2.11)	*0.41*	0.25 (0.03 , 2.01)	*0.19*
3 *F	419	0.51 (0.13 , 2.02)	*0.34*	0.18 (0.02 , 1.58)	*0.12*

*Final Model F: Full Model

Stroop (Table 3f)

The crude OR for low HC with poor outcome was initially positive at 1.64 (0.70, 3.87) (p=0.26) in the total sample (Model 1), but after adjustment for standard variables dropped to unity (p=0.98) (Model 2). After full adjustment (Model 3), the point estimate dropped somewhat further, leaving an OR of 0.81 (0.29, 2.25) p=0.68. The male subsample exhibited positive associations in all models [final OR: 1.73 (0.43, 6.95); p=0.44], and the females exhibited inverse point estimates [final OR: 0.42 (0.08, 2.18); p=0.30]. No significant associations were observed.

Table 3f. Model Selection for HC with Stroop

		HC		Age	Education	Gender	Income	IQ	Height	APOE	APOE*HC
		OVERALL									
Model	N	OR (95% CI)	*p*								
1	468	1.64 (0.70 , 3.87)	*0.26*								
2	462	0.99 (0.37 , 2.64)	*0.98*	X	X	X					
3 *F	419	0.81 (0.29 , 2.25)	*0.68*	C	C		T	C	C		
I	415	*No interaction observed***		C	C		T	C	C	R	I

*Final Model F: Full Model X: Standard Adjustment Variable C: Confounder T: Concomitant I: Interaction R: Required

**Term for interaction not statistically significant (p=0.30)

		HC *(Stratified by Gender)*			
		M		F	
Model	N	OR (95% CI)	*p*	OR (95% CI)	*p*
1	468	2.88 (0.97 , 8.57)	*0.06*	0.71 (0.15 , 3.36)	*0.67*
2	462	2.06 (0.56 , 7.59)	*0.28*	0.45 (0.09 , 2.23)	*0.33*
3 *F	419	1.73 (0.43 , 6.95)	*0.44*	0.42 (0.08 , 2.18)	*0.30*

*Final Model F: Full Model

Trails (Table 3g)

This analysis also showed a reversed direction from a positive crude estimate toward an increasingly inverse estimate throughout adjustment. The total sample estimate dropped from a crude OR (95%CI) of 1.58 (0.67, 3.71) (p=0.30) to an OR of 0.78 (0.28-2.19) (p=0.63) in the final model (Model 3). The trend was the same in males and females, though the drop was more precipitous in males throughout adjustment [final Male OR: 0.40 (0.06, 2.52); p=0.33] whereas the female estimates approached unity [final Female OR: 1.12 (0.30, 4.21); p=0.87]. No associations were found to be significant, and no selection procedures were performed.

Table 3g. Model Selection for HC with Trails

		HC										
		OVERALL										
Model	N	OR (95% CI)	*p*	Age	Education	Gender	Income	IQ	Height	APOE	APOE*HC
1	468	1.58 (0.67 , 3.71)	*0.30*								
2	462	0.91 (0.34 , 2.47)	*0.85*	X	X	X					
3 *F	420	0.78 (0.28 , 2.19)	*0.63*	C	C		T	C			
I	416	*No interaction observed***		C	C		T	C		R	I

*Final Model F: Full Model X: Standard Adjustment Variable C: Confounder T: Concomitant I: Interaction R: Required

**Term for interaction not statistically significant (p=0.47)

		HC *(Stratified by Gender)*			
		M		F	
Model	N	OR (95% CI)	*p*	OR (95% CI)	*p*
1	468	1.44 (0.44 , 4.74)	*0.55*	1.78 (0.52 , 6.15)	*0.36*
2	462	0.62 (0.12 , 3.32)	*0.57*	1.28 (0.35 , 4.60)	*0.71*
3 *F	420	0.40 (0.06 , 2.52)	*0.33*	1.12 (0.30 , 4.21)	*0.87*

*Final Model F: Full Model

Implicit (Table 3h)

Only one potential confounder, IQ, was identified for this outcome. Though IQ has consistently remained a substantial confounder for most outcomes, it was found that its addition did not produce estimates that were substantially different from the crude estimates. An additional model was run (not shown), including the standard adjustment variables and IQ, but the results were not substantially different from the standard adjusted model (Model 2). The variable of impact in that model and Model 2 was determined to be education. Since the model with education (Model 2) offered a noticeably more conservative estimate, and since it is in line with standard adjustment practices, Model 2 was adopted as final. Nevertheless, no associations were significant.

The direction of the estimate in all models was positive for both the total and gender stratified samples.

Table 3h. Model Selection for HC with Implicit

		HC		Age	Education	Gender	Income	IQ	Height	APOE	APOE*HC
		OVERALL									
Model	N	OR (95% CI)	*p*								
1	468	1.51 (0.62 , 3.69)	*0.37*								
2 *	462	1.22 (0.47 , 3.18)	*0.69*	X	X	X					
3 F	464	1.43 (0.58 , 3.55)	*0.44*					C			
I	458	*No interaction observed***		X	X	X				R	I

*Final Model F: Full Model X: Standard Adjustment Variable C: Confounder T: Concomitant I: Interaction R: Required

**Term for interaction not statistically significant (p=0.99)

		HC *(Stratified by Gender)*			
		M		F	
Model	N	OR (95% CI)	*p*	OR (95% CI)	*p*
1	468	1.79 (0.54 , 5.93)	*0.34*	1.28 (0.33 , 4.93)	*0.72*
2 *	462	1.30 (0.33 , 5.09)	*0.71*	1.28 (0.33 , 5.01)	*0.73*
3 F	464	1.65 (0.48 , 5.66)	*0.39*	1.27 (0.33 , 4.91)	*0.73*

*Final Model F: Full Model

Interaction With APOE

No significant interactions were found by adding an interaction term for APOE and HC (and APOE itself in models that lacked this term). P-values for the interaction term can be found in Model I in Tables 3a-h. All p-values were above p=0.3 and did not meet the criteria for potential inference.

Post hoc analysis of model fit with the inclusion of APOE revealed that model fit was significantly improved for ImR, CuR, Recognition, and Trails, though APOE did not

reach significance as a predictor for either of these models [ImR OR: 1.71 (0.93, 3.13), p=0.08; CuR OR: 0.92 (0.47, 1.82) p=0.81; Recogn. OR: 1.44 (0.83, 2.47), p=0.19; Trails OR: 0.92 (0.47, 1.82), p=0.39]. Neither term changed the measure of the association between HC and outcome. The interaction term was found to improve the fit of the model beyond that observed for APOE singly for Recognition, however the parameter estimate and standard error were prohibitively large (β=15.56, SE=692.2) and indicated against interpretation.

Given the lack of significance or model improvement with the addition of APOE or the interaction term, a two-by-two analysis was completed for HC with each outcome, stratified by APOE. Examination of the tables showed that only two subjects possessed both low HC and at least one APOE ε4 allele, making impossible any meaningful interpretation of effect modification by APOE status.

Chapter 5

Discussion

For the majority of cognitive outcomes assessed in this study, head circumference was not associated with poor cognitive outcomes. Of eight cognitive outcomes, one clear result, consistent with the brain reserve hypothesis and existing literature, emerged along with one suggestive but not statistically significant result that contradicted the *a priori* hypothesis.

The statistically significant finding for the association between low head circumference and poor 3MS outcome is consistent with the published literature. While the 3MS has not previously been directly studied in relation to head size, results for the MMSE from which the 3MS was created have consistently shown a significant positive association with increasing head circumference in non-demented subjects[39, 40] and with increasing intracranial volume in cognitively impaired subjects.[29] The association between head size and outcome has also been observed for other measures of global cognition, such as a positive correlation between mean CASI scores, a measure very similar to the 3MS, and HC in a community sample of Japanese-Americans in the *Kame* Project,[25] for several measures of general and specific intelligence scores with HC,[40, 41] intracranial area,[42] and intracranial volume,[26, 43] and for a modified Clinical Dementia Rating with intracranial area in a sample of female dementia patients.[31] In all of the studies, these measures of association reached statistical significance.

It is worth noting that the association between head circumference and 3MS in the current study remained statistically significant after adjustment for a measure of pre-morbid IQ. Measures of IQ provide an important control in the investigation of brain reserve, since it is itself hypothesized to be a form of reserve against cognitive decline independent of brain size.[44] In our analysis, it was also one of the strongest confounders of association, not surprisingly given the well-known correlation between head size and measures of intelligence.[26, 40-43, 68] Nevertheless, after adjustment for IQ, head circumference remained a strong independent predictor of 3MS scores in this sample.

The non-statistically significant trend of an inverse association of HC with recognition memory, which is contrary to our hypothesis, has no support from the existing literature. Though AD patients are known to answer more positively in yes/no recognition trials, studies have shown that the discrimination scores on recognition subtests generally do not differ across groups with varying cognitive pathologies,[69] and that the verbal recognition component of the HVLT, similar to recognition components on other verbal tests, does not improve the sensitivity and specificity of the HVLT scores in predicting later clinical decline into dementia.[70, 71] Given its poor discrimination ability, one would not expect any significant deviation away from unity.

In our sample, poor recognition outcome showed the expected associations with all confounders except height, in which there was a significant and slightly elevated association of poor outcome with increasing height that likely was a reflection of the association between height and HC. It was positively correlated with intelligence, and remained so after adjustment in the full model, suggesting its similarity to other outcomes in terms of potential confounders. Given this, it appears unlikely that some unknown

confounder could have generated the finding. Nevertheless, the association indicated in this analysis merits further investigation in samples with perhaps a larger cognitively-impaired subpopulation to more accurately study the effects of low head circumference on poor outcome.

The findings for HC with the remaining outcomes did not reach any inferential level of statistical significance in our sample. Upon close inspection of the literature, particularly for immediate and delayed verbal recall, we find that this is not at odds with previously published investigations. In several of the studies mentioned above with significant findings for measures of head size with global cognition and intelligence outcomes there has consistently been no association found between these measures and immediate or delayed recall tests similar in nature to that on the HVLT,[40-43] despite the excellent early predictive value these tests have demonstrated for cognitive decline.[70-74]

To date, there has been no research to support an association or lack thereof between HC and cued recall, the gain from cues that is particularly useful in predicting AD, other than generalized associations of this outcome with clinical disease.[75, 76] Logically, one could argue that accurate discriminators for AD or amnestic mild cognitive impairment would be poor candidates for associative analysis with a measure, such as HC, that is hypothesized to be protective of clinical manifestation for many types of progressive pathological insult, especially in a population that is likely demonstrating mixed pathologies through low cognitive outcomes. Therefore, it is unsurprising that no association was observed for cued recall in this community sample with undefined pathologies.

Among the Stroop interference test, Trails difference score (see Methods), and the implicit memory test, only the Stroop test has been reported as having an association with head size. Tisserand et al. found an inverse association with between *time* to complete the interference task and head circumference in least-squares regression (β from –1.18 to –1.48, depending on adjustment for age and sex alone, or with SES, height or education).[40] In the current study, no significant association was observed between HC and *number* of words completed in a set time period (a *direct* association would be expected based on the reserve hypothesis and literature). It is possible that the sample size, nearly twice as large in Tisserand et al. as compared to the current study, contributed to the difference in findings.

By contrast, no findings have been reported for an association between HC and the Trails difference score or implicit memory, although Trails was among the cognitive tests performed by Wolf et al. in her comparison of HC and cognition among normal, MCI and demented subjects.[27] As a measure of executive function,[62, 77] poor outcome on the difference score is hypothesized to be associated with lower HC under the reserve hypothesis. However, it is again possible that magnitude of the measure of association is too small to detect among a population of this size.

It is worth discussing in more detail the difference in findings for an association between HC and the outcomes 3MS, Stroop and Trails, given that all three tests are measures of executive function and that their scores strongly correlate with each other (Pearson correlation coefficients in this sample range between 0.40 and 0.46, $p<0.0001$, data not shown). The most likely explanation given the data in this sample is that the tests, measuring executive function by different means, demonstrate disparate true

associations with HC. Crude analysis of the association between HC and these outcomes, given in Appendix A (Table A1), shows the initial difference in the effect sizes for HC on 3MS and both Stroop and Trails, where for 3MS the OR>4.0 and for the latter two crude OR≈1.6. In a retrospective power analysis under the assumption of an unmatched case control study with the given proportion of cases to controls and proportion of exposure to low HC among the controls, it was found that the power to detect an association at α=0.05 in this sample would fall dramatically for the three outcomes as the hypothetical association drops below an OR of about 3. Given this and the initial differences in effect size, it seems entirely possible that the association between HC and both Stroop and Trails scores is low to moderate in this sample, and that there is likely insufficient power to detect a statistically significantly elevated risk of poor outcome.

The eighth outcome in this analysis, implicit memory scores from a word-stem completion task, also failed to demonstrate a statistically significant association with dichotomous HC. While there is no known literature on this association, existing literature on the association between Alzheimer's disease case status and performance on word-stem completion tasks has generated mixed results.[78-81] A meta-analysis attempting to overcome the limitations of smaller studies suggested a weak but statistically significant correlation between case status and word-stem completion scores.[82] However, the authors cautioned that null findings should be interpreted carefully given the apparent need for large sample sizes and adequate power to detect the small association. Therefore, while the current analysis detected no statistically significant association between head size and cognitive outcome, the conclusion that there is no biological impact of head size on implicit memory scores can likely not be drawn from our data.

Apart from outcome-specific interpretations of these results, there are several points to consider in the analysis and interpretation of the overall findings. First, the sample in the Charlotte County Healthy Aging Study was drawn from a population in a popular retirement location in Florida, subject to substantial migration. It is likely that those migrating to the region might on average have higher income and better education, which would correlate with higher IQ scores, than those who do not. This self-selection may explain the relatively high mean years of education and level of income among our sample. These characteristics impart two possible implications for interpretation of the results. First, higher education is known to be inversely associated with poor cognitive performance and dementia,[83, 84] indicating that poor cognition may be less prevalent in this community sample than in other populations studied in North America or Europe. Since poor cognition was defined relatively (as a quantile) for analysis, this may have contributed to fewer findings among the eight outcomes. Second, if the relative classification of poor cognition in this highly educated sample led to misclassification of truly poor cognition, it would indicate that the statistically significant finding that small head size predicted low 3MS scores might underestimate the true association with the same bottom quantile of scores among the general population.

Another point of consideration is the use of multiple comparisons in this analysis. No corrections for multiple comparisons were used, which generally raises the possibility of finding a statistically significant association by chance. This is of less concern in this analysis given that the eight endpoints were dependent (the correlation between them, data not shown, was observed to be between 0.3 and 0.7, excepting cued recall and implicit memory scores). Nevertheless, since correction accounting for these correlations

may still place the required per-comparison allowable error below the observed p-value of 0.03 for a familywise error rate of α=0.05,[85] the possibility should be considered that a Type I error may have occurred. There are two reasons why it is unlikely that the single significant finding in this study is the result of Type I error. First, the finding is substantially supported by similar results in previously published studies. Second, the observations, consistent in male and female subjects, are supported by a biologically plausible hypothesis. Therefore, it is concluded that in this sample the statistically significant association identified between head size and 3MS scores is likely valid.

Finally, it was found that the interactive effects of APOE ε4 status could not be examined in this sample due to a very small number of subjects who had both low HC and possessed one or more APOE ε4 alleles (n=2). Crude analysis indicated that APOE ε4-positive subjects performed less well on cognitive measures. *Post hoc* analyses of model fit after failure to detect interaction also showed that inclusion of APOE statistically significantly improved the fit of the final models with immediate recall, recognition and trails. The estimates of effect were generally too unstable to infer much from this information, although it was suggested that possession of an ε4 allele independently increased risk of poor outcome in the Trails test (p=0.08).

In examining effect modification by APOE ε4 status, this analysis attempted to replicate the results found in the *Kame* Project, in which it was seen that the effect of head circumference on incident AD was restricted to those with one or more ε4 alleles.[32, 33] Had the data permitted, it was hypothesized that possession of an ε4 allele may have modified the association between HC and poor outcome such that the effect would have been stronger in ε4-positive subjects. Given the significance of the findings from the

Kame Project, however, it is important that other large and well-designed studies with sufficient exposed individuals analyze these associations further so that risk of impairment can be accurately described with respect to head size and genetic risk of AD.

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Appendix A: Additional Tables

Table A. Unadjusted Logistic Regression of Head Circumference, Outcomes and Covariates

Table A1. Dichotomized Outcomes Modeled With Dichotomous Head Circumference (Crude)

Dichotomized Outcome	**HC**								
	OVERALL N=468			Male N=228			Female N=240		
	OR	(95% CI)	*p*	OR	(95% CI)	*p*	OR	(95% CI)	*p*
3MS	**4.38**	(1.99 , 9.66)	*<0.001*	**3.09**	(1.07 , 8.96)	*0.04*	**6.58**	(1.99 , 21.8)	*0.002*
ImR	1.62	(0.69 , 3.82)	*0.27*	1.37	(0.45 , 4.18)	*0.58*	1.90	(0.49 , 7.4)	*0.35*
DeR	1.54	(0.65 , 3.61)	*0.33*	2.01	(0.68 , 5.92)	*0.21*	0.89	(0.19 , 4.2)	*0.88*
CuR	1.22	(0.41 , 3.66)	*0.72*	2.17	(0.57 , 8.29)	*0.26*	0.54	(0.07 , 4.3)	*0.56*
Discrim.	0.75	(0.30 , 1.90)	*0.54*	0.98	(0.32 , 2.97)	*0.97*	0.32	(0.04 , 2.6)	*0.29*
Stroop	1.64	(0.70 , 3.87)	*0.26*	**2.88**	(0.97 , 8.57)	*0.06*	0.71	(0.15 , 3.4)	*0.67*
Trails	1.58	(0.67 , 3.17)	*0.30*	1.44	(0.44 , 4.74)	*0.55*	1.78	(0.52 , 6.2)	*0.36*
Implicit	1.51	(0.62 , 3.69)	*0.37*	1.79	(0.54 , 5.93)	*0.34*	1.28	(0.33 , 4.9)	*0.72*

*Continous covariates. Crude OR is for probability of event (Low HC; Poor Outcome) with each increasing unit of the covariate: Age and Educ in yrs; Income in levels 1(<10k)-9(>150k); IQ in points; Height in inches.

**Categorical covariates. Crude OR is for probability of event with: Gender (female); BMI (obese); APOE (ε4+).

Potential confounders assoc. with outcome and total-sample exposure at p<0.1

Table A2*. Dichotomized Outcomes Modeled With Covariates (Crude)

Dichotomized Outcome	**Age** N=467**		**Education** N=463**		**Gender*** N=468**	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
3MS	**1.11** (1.07 , 1.16)	*<0.001*	**0.79** (0.73 , 0.87)	*<0.001*	0.79 (0.51 , 1.22)	*0.28*
ImR	**1.09** (1.05 , 1.13)	*<0.001*	**0.88** (0.82 , 0.95)	*0.001*	**0.49** (0.31 , 0.77)	*0.002*
DeR	**1.09** (1.05 , 1.13)	*<0.001*	**0.85** (0.78 , 0.92)	*<0.001*	**0.64** (0.41 , 1.00)	*0.05*
CuR	0.99 (0.95 , 1.04)	*0.75*	0.98 (0.89 , 1.07)	*0.62*	1.34 (0.77 , 2.33)	*0.30*
Discrim.	**1.06** (1.02 , 1.09)	*0.0012*	**0.91** (0.85 , 0.97)	*0.0067*	**0.53** (0.35 , 0.80)	*0.0026*
Stroop	**1.11** (1.06 , 1.15)	*<0.001*	**0.82** (0.75 , 0.89)	*<0.001*	1.09 (0.70 , 1.71)	*0.69*
Trails	**1.11** (1.07 , 1.16)	*<0.001*	**0.80** (0.73 , 0.87)	*<0.001*	1.12 (0.72 , 1.74)	*0.62*
Implicit	1.02 (0.99 , 1.06)	*0.24*	0.95 (0.88 , 1.02)	*0.16*	1.24 (0.78 , 1.96)	*0.37*

Dichotomized Outcome	**Income** N=424**		**IQ** N=464**		**Height** N=465**	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
3MS	**0.69** (0.58 , 0.83)	*<0.001*	**0.84** (0.81 , 0.88)	*<0.001*	0.96 (0.91 , 1.01)	*0.13*
ImR	**0.76** (0.64 , 0.91)	*0.002*	**0.91** (0.88 , 0.95)	*<0.001*	**1.06** (1.00 , 1.11)	*0.05*
DeR	**0.72** (0.60 , 0.85)	*<0.001*	**0.89** (0.86 , 0.92)	*<0.001*	1.01 (0.96 , 1.06)	*0.80*
CuR	1.01 (0.84 , 1.21)	*0.94*	0.97 (0.93 , 1.02)	*0.25*	0.99 (0.93 , 1.06)	*0.78*
Discrim.	**0.89** (0.77 , 1.02)	*0.10*	**0.92** (0.89 , 0.95)	*<0.001*	**1.05** (1.00 , 1.10)	*0.05*
Stroop	**0.72** (0.60 , 0.85)	*<0.001*	**0.92** (0.89 , 0.95)	*<0.001*	**0.94** (0.89 , 0.99)	*0.03*
Trails	**0.65** (0.55 , 0.78)	*<0.001*	**0.90** (0.87 , 0.94)	*<0.001*	0.98 (0.93 , 1.03)	*0.36*
Implicit	0.88 (0.75 , 1.04)	*0.13*	**0.97** (0.93 , 1.01)	*0.10*	0.97 (0.92 , 1.02)	*0.22*

***TABLE A2 CONTINED ON THE NEXT PAGE**

**Continous covariates. Crude OR is for probability of event (Low HC; Poor Outcome) with each increasing unit of the covariate: Age and Educ in yrs; Income in levels 1(<10k)-9(>150k); IQ in points; Height in inches.

***Categorical covariates. Crude OR is for probability of event with: Gender (female); BMI (obese); APOE (ε4+).

Potential confounders assoc. with outcome and total-sample exposure at p<0.1

Table A2. Dichotomized Outcomes Modeled With Covariates (Crude) - Continued

Dichotomized Outcome	**BMI** N=468**		**APOE** N=468**	
	OR (95% CI)	*p*	OR (95% CI)	*p*
3MS	0.81 (0.48 , 1.36)	*0.42*	1.15 (0.67 , 1.95)	*0.62*
ImR	0.67 (0.39 , 1.15)	*0.15*	1.30 (0.77 , 2.18)	*0.32*
DeR	1.02 (0.62 , 1.69)	*0.92*	**1.62** (0.98 , 2.67)	*0.06*
CuR	0.97 (0.52 , 1.82)	*0.94*	0.91 (0.46 , 1.79)	*0.79*
Discrim.	1.11 (0.70 , 1.76)	*0.65*	1.39 (0.86 , 2.25)	*0.17*
Stroop	0.79 (0.47 , 1.34)	*0.39*	0.94 (0.54 , 1.64)	*0.83*
Trails	0.93 (0.56 , 1.54)	*0.78*	1.65 (1.00 , 2.72)	*0.52*
Implicit	1.21 (0.73 , 2.02)	*0.46*	1.13 (0.66 , 1.96)	*0.65*

*Continous covariates. Crude OR is for probability of event (Low HC; Poor Outcome) with each increasing unit of the covariate: Age and Educ in yrs; Income in levels 1(<10k)-9(>150k); IQ in points; Height in inches.

**Categorical covariates. Crude OR is for probability of event with: Gender (female); BMI (obese); APOE (ε4+).

Potential confounders assoc. with outcome and total-sample exposure at p<0.1

Table A3 Dichotomized Head Circumference Modeled With Covariates (Crude)

Continous Covariates	**HC**								
	OVERALL			M			F		
	OR	(95% CI)	*p*	OR	(95% CI)	*p*	OR	(95% CI)	*p*
Age*	**1.06**	(0.99 , 1.13)	*0.09*	1.01	(0.93 , 1.10)	*0.85*	1.13	(1.01 , 1.26)	*0.03*
Education*	**0.86**	(0.76 , 0.98)	*0.02*	0.83	(0.71 , 0.98)	*0.02*	0.90	(0.73 , 1.10)	*0.30*
Gender**	0.75	(0.34 , 1.63)	*0.47*	---			---		
Income*	0.92	(0.70 , 1.20)	*0.52*	0.79	(0.53 , 1.18)	*0.25*	1.03	(0.71 , 1.49)	*0.88*
IQ*	**0.92**	(0.87 , 0.98)	*0.004*	0.91	(0.84 , 0.98)	*0.01*	0.94	(0.86 , 1.02)	*0.14*
Height*	**0.91**	(0.83 , 1.00)	*0.05*	0.83	(0.73 , 0.94)	*0.0047*	0.83	(0.67 , 1.03)	*0.09*
BMI**	0.67	(0.24 , 1.72)	*0.37*	0.87	(0.27 , 2.82)	*0.8111*	0.30	(0.04 , 2.38)	*0.25*
APOE**	**0.28**	(0.07 , 1.21)	*0.09*	0.32	(0.04 , 2.54)	*0.28*	0.25	(0.03 , 2.00)	*0.19*

*Continous covariates. Crude OR is for probability of event (Low HC; Poor Outcome) with each increasing unit of the covariate: Age and Educ in yrs; Income in levels 1(<10k)-9(>150k); IQ in points; Height in inches.

**Categorical covariates. Crude OR is for probability of event with: Gender (female); BMI (obese); APOE (ε4+).

Potential confounders assoc. with outcome and total-sample exposure at p<0.1