1.a. Full Title: The Relationship of Central Adiposity and Cognitive Decline: The Atherosclerosis Neurocognitive Study

b. Abbreviated Title (Length 26 characters): Central Adiposity and Cognitive Decline

2. Writing Group:

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. **SL [please confirm with your initials electronically or in writing]**

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3. Timeline:

Analysis and manuscript will be completed within a year of receiving approval.
4. **Rationale:**

The societal burden of dementia is high due to its high prevalence and associated disability. An estimated 47 million individuals worldwide have dementia in 2015 [1], and this number is projected to triple in 2050 due to the increasing number of elderly individuals in industrialized countries [2]. In the absence of disease-modifying treatments or cure, the importance of identifying and intervening upon modifiable factors that contribute to the pathogenesis of disease are of great interest and importance to prevent, or delay, the progression of cognitive decline and dementia.

Obesity, a worldwide epidemic, is a well-established risk factor for many chronic diseases, such as metabolic syndrome, type 2 diabetes, heart disease, stroke, and certain types of cancers [3]. A growing body of evidence suggests that mid-life adiposity/obesity is associated with cognitive performance or decline. However, most existing studies are cross-sectional and used body mass index (BMI) as the sole marker of adiposity [4-8]. Longitudinal studies provide strong support that midlife obesity has a detrimental effect on subsequent cognitive performance [9-14], with the exception of the Atherosclerosis Risk in Communities (ARIC) study which found no association between BMI and cognitive decline [15]. This null finding in ARIC may be attributable to BMI not being a good measure of obesity. Researchers have argued that BMI measurement neglects the original distribution of lean and fat tissues masses in evaluating adiposity and suggested that measures of central adiposity (i.e., waist circumference (WC) or waist hip-ratio (WHR)) are better suited measure to assess obesity [16]. Central adiposity is closely related to cardio-metabolic risk [17] and may be more consistently associated with the negative effects of cognitive function in older age [18]. Longitudinal studies that assess the association of cognitive function and markers of central adiposity (i.e., WC and WHR) are lacking [14, 19]. In the ARIC study, metabolic syndrome (MetS) (defined as elevated blood pressure, increased waist circumference (WC), elevated triglycerides (TG), low high-density lipoprotein (HDL), and impaired fasting glucose) was found to be associated with increased odds of low cognitive performance in the domains of executive function and word fluency, but not with 6-year cognitive decline [20].

The mechanisms by which obesity adversely affects the brain are not well understood. A high-fat diet is associated with hyperglycemia which has been shown to damage the vascular system and may indirectly affect brain shrinkage through decreases in neurons or impaired neurogenesis [21]. Recent evidence suggests obesity is associated with increased production of triglycerides and fatty free acids which may cause a chronic inflammatory response in the central nervous system, which may also affect the brain [22].

Methodologic weaknesses of existing studies include inadequate adjustment for cardio-metabolic parameters or modifiable lifestyle factors (i.e., physical activity and diet) preventing interpretation of the findings in terms of a direct and/or indirect role of adiposity in cognitive age. Directly assessing the effect of adiposity on cognitive function warrants the inclusion of covariates (i.e., hypertension, Type 2 diabetes, cerebral vascular disease, and metabolic abnormalities) that may modify the relationship of adiposity on cognitive decline [4, 23, 24]. A recent study found an independent association between central adiposity (i.e., WC) and lower executive function scores, after adjustment for cardio-metabolic risk factors, physical activity and dietary parameters [24]. However, a
A major limitation of this study is the lack of baseline cognitive evaluation which prevented the assessment of cognitive decline over time.

Several longitudinal studies have shown that weight loss, up to 10 years precedes dementia in both men and women [25-28]. This phenomenon is believed to contribute to findings such as lower/normal BMI associations with dementia or lack of association between obesity measures and dementia or cognition. To date, few studies have addressed this complex issue [27, 29]. As a result, in the ARIC cohort we will also investigate the relationship between central adiposity and cognitive performance in men and women whose weight remained stable or gained weight in older age.

The rich data source of the ARIC study which includes repeated measurements of central adiposity and of cognitive function, measurements of established cardio-metabolic risk factors, and modifiable lifestyle factors collected on black and white men and women from mid- to-late life is well-suited to address these current research need.

5. Main Hypothesis/Study Questions:

**Aim 1:** Estimate the relationship between measures of central adiposity (i.e., WC and WHR) assessed at visit 2 and 20-year cognitive decline in black and white men and women from mid-to-late life.

**Hypothesis 1a:** High waist circumference will be associated with greater 20-year cognitive decline.

**Hypothesis 1b:** High waist hip ratio will be associated with greater 20-year cognitive decline.

**Aim 2:** Estimate the relationship between measures of central adiposity (i.e., WC and WHR) assessed at visit 2 and subsequent cognitive performance in men and women with stable weight or gained weight in older age.

**Hypothesis 2a:** Measures of central adiposity will be associated with cognitive performance in men and women with stable weight in older age.

**Hypothesis 2b:** Measures of central adiposity will be associated with cognitive performance in men and women who have gained weight in older age.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

**Study population and design:** The primary analysis will include all ARIC participants with at least two measurements of cognitive function. Excluded from the study population will be participants who did not self-identify as black or white, blacks residing in Washington County or Minneapolis (due to low numbers), and participants who had missing cognitive data at visit 2.

**Exposures:** The exposures of interest are baseline (visit 2) measures of central adiposity: WC and Waist-to-hip ratio (WHR). Anthropometric measurements were obtained with the participant wearing light-weight, non-constricting underwear without shoes. Waist
circumference (WC) was measured by wrapping a flexible measuring tape around the waist at the level of the umbilicus while the participant was standing and breathing quietly. Hip circumference was measured at the level of maximal protrusion of the gluteal muscles with the measuring tape kept in horizontal position. Waist-to-hip ratio (WHR) was calculated by WC divided by hip circumference. The inter-technician reliability coefficient for WC was $r > 0.94$ [30].

**Outcome:** Cognitive function was assessed at visit 2 (1990-1992), visit 4 (1996-1998), and the ARIC-Neurocognitive Study (ARIC-NCS) at visit 5 (2011-2013) using 3 standard cognitive tests that assessed different domains of cognition: 1) the Delayed Word Recall Test (DWRT) - a test of memory [31], 2) the Digit Symbol Substitution Test (DSST) - a test of language [32], and 3) the Word Fluency Test (WFT) - a test of executive function [33]. All three tests were administered by trained examiners using standardize protocols in a quiet room. Recordings were reviewed for quality control.

**Statistical analysis:** We will use linear mixed models to estimate the relationship between measures of central adiposity (i.e., WC and WHR) and cognitive decline. WC and WHR, measured across all study visits, will be modeled as continuous variables. The DWRT, DSST, WFT, and global cognition z-scores will be assessed as continuous measures of cognitive function. In this analysis three models will fitted. In the initial model, analyses will be adjusted for age, sex, race-center, education, and the Apo lipoprotein E ε4 polymorphism. In the second set of models, analyses will be further adjusted for modifiable lifestyle factors, such as smoking status, ethanol intake, and physical activity. To assess whether the potential association between measures of central adiposity (i.e., WC and WHR) and cognitive function are driven by obesity-related cardio-metabolic factors/conditions, a third set of models will be adjusted for diabetes mellitus (defined as a fasting glucose level > 126 mg/dL, a nonfasting glucose level >200 mg/dL), hypertension will be defined as systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or any use of antihypertensive medications in the previous 2 weeks), cholesterol level, lipid-lowering treatment and cardiovascular disease history (i.e., history of coronary heart disease (CHD), stroke, and heart failure (HF). We will also consider all models with and without adjustment for BMI, so that we can be sure to estimate an effect of central adiposity that is independent from overall adiposity. Linear mixed models will also be used to investigate the relationship between central adiposity and cognitive performance in men and women whose weight remained stable or gained weight in older age. Weight or WC change will be defined as the difference between this study’s baseline (visit 2) and last available measurement preceding ARIC-NCS.

Linear mix models utilizes all available data over follow-up, handle differences in length of follow-up, and account for the fact that repeated measures on the same individual are correlated. Both the intercept and slope will be fitted as random effects, allowing for differences in cognitive function at baseline and rate of cognitive decline. We will use unstructured correlation matrices and robust variance estimates. Time since baseline (visit 2) will be modeled using a linear spline with a knot at 6 years (the mean duration between visits 2 and 4). The spline term will allow for a nonlinear association between time and cognitive decline, more appropriately fit the study design than a quadratic term, and is supported by diagnostics. The primary coefficients of interest will be the
interactions between each measure of central adiposity and the time spline terms, which will address the hypothesis of greater decline among participants with higher central adiposity after adjustment of age and other covariates.

Twenty-five percent of ARIC participants died over the course of 22 years of follow-up, and 45% of those alive at the time of the exam 5 visit did not attend. As a result, attrition is a methodological concern. Multivariate imputation by chained equations (MICE) will be used to evaluate and correct for attrition due to missing cognitive data. MICE involves filling in the missing cognitive data values multiple times, creating multiple “complete” datasets. The missing values are imputed based on the observed values for a given individual and the relations observed in the data for other participants, assuming the observed variables are included in the imputation model [34]. Because multiple imputations involves creating multiple predictions for each missing value, the analyses of multiple imputed data take into account the uncertainty in the imputations and yield accurate standard errors [35].

Covariates: Potential confounder were identified through directed acyclic graphs and a priori knowledge from existing literature and include age, sex, education, smoking status, ethanol intake, physical activity, medication use (e.g., antidiabetic, antihypertensive and lipid-lowering drugs) and the Apo lipoprotein E ε4 polymorphism.

7.a. Will the data be used for non-CVD analysis in this manuscript?  
____ Yes  ____X__ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD Research” would be used?  
____ Yes  ____ No
(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript?  
____ Yes  ____X__ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = “No use/storage DNA”?  
____ Yes  ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscs.unc.edu/ARIC/search.php  
____X__ Yes  ____No
10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?


MS1092: The Metabolic Syndrome, MRI Volumetrics and Cognitive Outcomes: Brain Structure and Function in the ARIC cohort (Lead: J. Dearborn)

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  _____ Yes  _____X_____ No

11.b. If yes, is the proposal

_____ A. primarily the result of an ancillary study (list number* __________)

_____ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* __________  __________ __________)

*ancillary studies are listed by number at http://www.cscu.unc.edu/aric/forms/

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is your responsibility to upload manuscripts to PUBMED Central whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscu.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.
References

17. Klein, S., et al., Waist Circumference and Cardiometabolic Risk: a Consensus Statement from Shaping America's Health: Association for Weight Management and Obesity Prevention; NAASO, the Obesity Society; the American Society for


