ARIC Manuscript Proposal #4294

PC Reviewed: 07/11/23 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Measures of adiposity in late life and their associations with incident dementia

b. Abbreviated Title (Length 26 characters): Adiposity and dementia

2. Writing Group: Ethan Cannon, Sanaz Sedaghat, B. Gwen Windham, Michael Griswold, Priya Palta (invited), Pamela Lutsey; other interested investigators welcome.

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

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3. Timeline: Data analysis to being immediately, anticipated draft completion fall 2023

4. Rationale:

As the US population ages, the prevalence of dementia and the substantial public health burden it imposes will continue to rise. Alzheimer's disease, the predominant cause of dementia,

is estimated to affect approximately 14 million Americans by 2050, a nearly three-fold increase from 2010.[1] Nevertheless, the etiology of dementia is not well understood. Midlife vascular risk factors have been examined as potential predictors of dementia.[2] While results for obesity have been mixed,[3-5] they tend towards an association with an increased risk of dementia.[6,7]

However, when measured in later life, significant evidence has accrued that greater adiposity is inversely associated with dementia risk.[6,8,9] For example, a retrospective analysis of 2 million individuals found that the risk of dementia decreased as body mass index (BMI) increased, with the lowest risk found in those with BMI>40.[5] Additionally, analyses of multiple longitudinal cohorts have observed that high BMI in middle age was associated with increased risk of dementia, but the reverse was true in later life.[10,11] Other studies have reported contrasting results, particularly when quantifying adiposity via other anthropometric measures such as waist circumference (WC).[12-14] Still, results of analyses using BMI have been consistent enough that in older adults, high BMI is among the factors to have shown the strongest associations with a decreased risk of dementia.[15,16] Consequently, the term "obesity paradox" has been frequently employed in research literature discussing this topic.

Most researchers have ascribed these surprising findings to bias, although explanations for a causal, protective effect of late-life overweight and obesity have been proposed.[9,15] Because studies have found that weight loss not only follows but also precedes the clinical diagnosis of dementia,[17,18] reverse causation is the primary reason postulated for the obesity paradox.[19,20] Additionally, many studies have utilized BMI as an exposure. However, the use of BMI, which measures both fat and lean mass as a proxy for adiposity, is problematic as it may result in confounding, especially in analyses of older adults.[21]

While reasonable in theory, there is a dearth of studies published to support the hypotheses that previous results were affected by reverse causality or poor measurement of adiposity. Therefore, we propose to assess these relationships in ARIC using two unique strategies: first, we will use fat mass index (FMI) from measurements made by bioelectrical impedance analysis (BIA) as our primary exposure. BIA measures adiposity more directly than BMI by identifying fat mass (FM) and fat free mass (FFM) separately, thereby avoiding confounding due to the contribution of low FFM (an indicator of chronic disease and poor general health) to low BMI. In validation studies, moderate individual-level errors of BIA compared to gold-standard DEXA measurements were reported, but are less important for the purposes of this analysis than the high correlations (e.g., r ~ 0.82-0.95) between the two methods that were also documented.[22-24]

Second, we will carefully consider exclusion criteria, interactions, and covariates. For example, we will assess for interactions with weight change, and adjust for variables such as frailty status that are indicative of overall health. We will also perform a sensitivity analysis excluding participants who were diagnosed with dementia <5 years after late-life adiposity assessment (visit 5).

5. Main Hypothesis/Study Questions:

We hypothesize that among individuals who did not experience major weight loss between visit 4 and visit 5, greater late-life adiposity as measured by FMI will be marginally associated with increased risk of dementia. We further hypothesize that this relationship will be reversed

among individuals who experienced major weight loss, and when using BMI as a measure of adiposity.

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 Design

Prospective cohort from Visit 5 to most recent follow-up.

Inclusion/Exclusion

Individuals who identify as neither Black nor white, as well as Black participants from the MN and MD centers, will be excluded due to low numbers. We will also exclude participants with missing exposure or covariate values, and those with prevalent dementia. We will further exclude individuals with BMI<18.5.

Variables

Exposures: the primary exposure will be BIA-derived FMI, obtained by dividing FM (kg) by the square of height (m). We will also assess relationships using BMI (calculated from height and weight) and WC.

Outcome: incident level 3 dementia diagnosis.

Potential effect modifiers and/or mediators: Age, sex, race, sarcopenia status (determined by fat free mass index [FFMI] and grip strength),[25,26] and Visit 4-Visit 5 BMI change category (significant decrease [< -2 units], minor increase/decrease [> -2 units and < 2 units], or significant increase [> 2 units]).

Other potential confounders: Age, sex, education, APOE, race/center, alcohol status, smoking status, frailty status, hypertension, diabetes, CRP, and depressive symptoms.

Data analysis

Baseline characteristics of participants will be described using means and proportions stratified by quartiles of the exposure. We will use Cox proportional hazards regression to assess the relationship between FMI and incident dementia. We plan to analyze FMI both in quartiles, and as a continuous variable. Restricted cubic splines will be used to assess non-linear associations of continuous FMI. We will also perform analyses using BMI and WC as exposures instead of FMI.

We will use a series of nested models. Model 1 will adjust for age, sex, education, APOE, and race/center. Model 2 will also include alcohol and smoking. Model 3 will further adjust for frailty status. Finally, model 4 will additionally include hypertension, diabetes, CRP, and depressive symptoms. Cross-product terms will be used to evaluate whether age, sex, race,

sarcopenia status, and/or BMI change category modify the associations of FMI with risk of incident dementia on the multiplicative scale. Stratified results will be presented, as appropriate.

As a sensitivity analysis, we will test our hypotheses after excluding participants diagnosed with dementia <5 years after visit 5 date. We will perform an additional sensitivity analysis by excluding current smokers and those with evidence of active cancer within the past year. Finally, we will perform an analysis using Fine and Gray's proportional subdistribution hazards model to account for the competing risk of death.

Methodologic Limitations or Challenges: Previous research has demonstrated that individuals who go on to develop dementia exhibit patterns of excess weight loss beginning years and even decades prior to diagnosis.[17,18] The preclinical stage of dementia can indeed be long-lasting.[27] Stratifying by weight loss category may address this issue to a degree by distinguishing the association between incident dementia and low adiposity versus adiposity decline.[20,28] Still, this analysis will be unable to differentiate weight loss due to the effects of prodromal dementia (i.e., reverse causation) from that due to other factors that may legitimately expedite cognitive decline.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes __X__ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The 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 current derived consent file ICTDER05 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.cscc.unc.edu/aricproposals/dtSearch.html

__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)?

PUBLISHED

#1365 Alvaro Alonso…Josef Coresh. Midlife cardiovascular risk factors and risk of dementia hospitalization in a biracial cohort: the ARIC study.

#3589 Emmanuel Quaye…Deborah Levine. Obesity and Cognitive Decline in Black and White Americans: A Pooled Cohort Analysis of ARIC, CARDIA, CHS, FOS, MESA, and NOMAS.

NOT YET PUBLISHED

#3965 Paulo Chaves… B. Gwen Windham. Dynamics of Risk Factors for 32-Year Incident Dementia Across Mid And Late-Life in ARIC: Implications for Dementia Prevention.

#2628 Shelly-Ann Love…B. Gwen Windham. The Relationship of Central Adiposity and Cognitive Decline: The Atherosclerosis Neurocognitive Study.

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 https://sites.cscc.unc.edu/aric/approved-ancillary-studies

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.cscc.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.

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