ARIC Manuscript Proposal #4160

PC Reviewed: 11/8/22	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association of birth weight with incident dementia and PET-amyloid burden: The Atherosclerosis Risk in Communities (ARIC) Neurocognitive Study

b. Abbreviated Title (Length 26 characters): Birth weight and dementia/PET-amyloid

2. Writing Group:

Writing group members: Olivia Emanuel (first author); Mark Lee; Pam Lutsey; Kevin Sullivan; Renee Groechel; Thomas Mosley; Andrea L.C. Schneider; Dean Wong; Rebecca Gottesman (last and corresponding author); Others welcome

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

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3. Timeline: 3-9 months; abstract and manuscript submission spring-summer 2023

4. Rationale:

Alzheimer's disease and other forms of dementia deploy significant disability and burden at the individual and population levels. The estimated number of people globally with dementia is

predicted to increase from 57.4 million cases in 2019 to 152.8 million in 2050 (1). These numbers underscore the urgent need for the identification of risk factors to better guide efforts towards disease delay and prevention. Early life factors, such as birth weight, may be an avenue towards this identification. Birth weight is frequently used as a proxy measure for impaired fetal growth to supplement more precise data on fetal growth trajectory. There is evidence that low birth weight is related to an increased tendency towards the development of cardiovascular disease in later life (2). The development of later life cardiovascular disease may be attributed to fetal undernutrition, as represented by low birth weight. Additionally, there is evidence that low birth weight is associated with hypertension (3) and type 2 diabetes mellitus (4, 5) in midlife. Furthermore, these vascular risk factors in midlife are associated with mild cognitive impairment and incident dementia in later-life (6), suggesting a possible relationship with early life factors, such as birth weight, and later life cognitive disorders.

If birth weight is associated with dementia, there are multiple potential mechanisms by which this association may occur. There are a number of important social factors that co-occur with low birth weight, which could influence the subsequent development of dementia (lack of access to good health care, poor access to healthy food, and other environmental or social factors), or birth weight might contribute to chronic risk factors as described above. Understanding if a relationship is present and, if so, if birth weight is associated with neuropathologic evidence of dementia (such as through amyloid deposition) would help confirm any observed association. Birth weight may be especially important to consider in association with these changes since brain pathology is present decades before clinical symptoms of dementia develop. Amyloid deposition has been established as a biomarker for dementia and is an independent predictor of dementia progression (7). Investigating amyloid deposition identified on PET scans in this population will provide quantitative measures to evaluate specific dementia mechanisms related to birth weight.

The existing large studies on birth characteristics and incident dementia are predominantly registry studies (8) or retrospective surveys (9) conducted on relatively homogeneous populations. Furthermore, investigations into birth weight in particular have focused on cardiovascular abnormalities (10), brain tissue volumes (11), and age-related cognitive impairment (8). There is a need for a large, longitudinal study that prospectively examines and characterizes birth weight, cognition, dementia incidence, and amyloid burden over the years of mid- to late-adulthood. It is necessary to better understand these associations to identify potential risk factors and focus early-life and reproductive health interventions for disease delay and prevention.

The ARIC Neurocognitive Study (NCS) has employed dementia surveillance methods that allow for the evaluation of dementia incidence as it relates to birth weight over nearly thirty years from mid- to late-life. The ancillary ARIC-PET study allowed for the collection of PET imaging data to relate amyloid burden in later-life to birth weight. Using this large, biracial community sample, the current study will investigate the association of birth weight during ARIC study follow-up with incident dementia and amyloid burden. We are particularly interested in differences between individuals who reported low birth weight and individuals who reported high birth weight, as well as those who were born prematurely and those who were not, to better characterize early life factors and their connections with dementia. Given the potential

moderating effects of birth year on the association between birth weight and dementia and amyloid burden (as many ARIC participants were born during the Great Depression, a time of severe economic depression affecting access to healthy food and medical care, for example, which likely would impact birth weight(12)), we will explore the potentially moderating role of this factor. Specifically, we will consider those born before the Great Depression (about 25% of our population), during the Great Depression (about 55% of our population), and after the Great Depression (about 20% of our population).

5. Main Hypothesis/Study Questions:

H1. Participants who report lower birth weight experience a greater rate of incident dementia compared to participants who report higher birth weight.

H2. Participants who report lower birth weight will experience greater odds of elevated amyloid deposition on PET compared to those who report higher birth weight.

H3. Participants who report premature birth experience a higher rate of incident dementia compared to those who report non-premature birth.

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).

Inclusion criteria:

H1. All participants who report birth weight at Visit 4 and have dementia surveillance data at any point during follow-up.

H2. All participants who report birth weight at Visit 4 and underwent β-amyloid (Aβ) PET imaging at Visit 5.

H3. All participants who report premature birth status at Visit 4 and have dementia surveillance data at any point during follow-up.

Exclusion criteria: Participants who do not report birth weight **(H1-2).** Participants who have dementia diagnosis prior to study baseline. Participants who did not undergo Aβ PET imaging (**H2**). Participants who do not report premature birth status (**H3**).

Exposure variables: Birth weight is ascertained from standardized interviews at Visit 4 (1996 through 1998). Participants are asked to report their exact birth weight (in pounds and ounces). If unable to do so, participants can inform whether their birth weight was low (<5.5 lbs.), medium (5.5-9.0 lbs.), or high (>9.0 lbs.). Additionally, premature birth status is ascertained from standardized interviews at Visit 4. Participants are asked to recall if they were a premature baby, that is if they were born a month or more early. There are relatively few (1.2%) missing data at least for the category of birth weight.

Outcome variables:

Dementia incidence: Dementia incidence and date of onset will be defined using expert committee diagnosis from in-person testing and informant interviews assessing cognitive performance, neurologic signs and symptoms, and functional status from Visit 5 onwards, as well as hospitalization codes for dementia from Visit 1. Level 3 dementia diagnoses will be used. Dementia cases over the entire duration of follow-up will be used.

β-amyloid burden: Amyloid burden will be assessed in the participants recruited to the ARIC-PET ancillary study from the ARIC-Neurocognitive Study (ARIC-NCS) (Visit 5). Florbetapir PET scans were performed and images were transferred to the PET image analysis center (Johns Hopkins). Images were quantified for standardized uptake value ratios (SUVRs), which will be dichotomized at the sample median of SUVR >1.2. Primary analysis will use a global cortical SUVR measure of β-amyloid (Aβ).

Covariates:

Covariates will include the following for all analyses: baseline age, sex, race-center (Washington County white; Minneapolis white; Forsyth County white; Forsyth County African-American; Jackson African-American), education (less than high school; high school/GED/vocational school; or any college), parental education, parental occupation, birth year, cigarette smoking and alcohol use status (never/former/current), BMI (kg/m^2), hypertension, total cholesterol, diabetes, coronary heart disease, stroke, and *APOE* ε4 status. All variables will be considered from the baseline visit.

For H1-2 analyses, we will also consider premature birth status.

Statistical analysis:

We will use Cox proportional hazards models to examine the association between self-reported birth weight and time to dementia onset among participants who do not have dementia at ARIC baseline. Dementia onset will be defined using the earliest date of dementia classification based on the comprehensive neurocognitive assessment (Visits 5-7), the SIS or AD8 administered as part of the AFU, or hospitalization discharge or death certificate code, starting when overall cohort followup began (after Visit 1). We acknowledge that the majority of the covariates of interest are potentially on a causal pathway between birth weight and dementia, so will build our models accordingly: Model 1 (with no potential mediators) will adjust for age, sex, race-center, and APOE; Model 2 will add education; and Model 3 will add the vascular risk factors described above (hypertension, total cholesterol, diabetes, coronary heart disease, and stroke).

We will examine the association between reported birth weight at Visit 4 and amyloid burden in participants who received Aβ-PET imaging at Visit 5 (2011-2013). We will conduct a logistic regression model with a binary outcome of amyloid present or amyloid absent using the global cortical SUVR>1.2 cutoff as described above.

Separate analyses will be repeated for self-reported prematurity yes/no; and for actual continuous birth weight for those individuals who provided this information, as well as for category of birth weight for the larger sample of individuals who provided this information (with the continuous values placed into categories for ease of analysis and larger sample size). In a sensitivity analysis, we will also consider the combination of prematurity status and birth weight (for instance: premature birth and low birth weight, premature birth and high birth weight, non-premature birth and low birth weight, and non-premature birth and high birth weight), as numbers allow.

Anticipated Limitations:

In the ARIC study, information regarding early life factors, including birth weight, are ascertained through self-report measures. Bias in self-reporting will be considered in the present analysis. Prior investigations have reported good agreement between recalled and recorded birth weight to support the validity of self-reported birth weight in investigations (13-15), however this is still anticipated as a possible limitation.

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? __X__ Yes ____ 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"? __X__ 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)?

MSP 1174: Association Between Birthweight and Cognitive Function in Middle Age: The Atherosclerosis Risk in Communities Study (Costa)

MSP 2288: Midlife vascular risk factors and midlife cognitive status in relation to prevalence of mild cognitive impairment and dementia in later life: The Atherosclerosis Risk in Communities Study (Knopman)

MSP 1772: Birth weight and the risk of atrial fibrillation in whites and African Americans: the Atherosclerosis Risk in Communities (ARIC) study (Lawani)

MSP 1062r: Association of Birth Weight And Leg Length With Retinal Microvascular Signs and Age-related Maculopathy (Wong)

MSP 685: The association between Weight at birth and prevalence of cardiovascular disease in middle-age: the ARIC Study (Rose)

MSP 746: Association between birth weight and extent of adult periodontal disease (Slade)

MSP 686: The association between weight at birth and risk factors in middle-age associated with the multiple metabolic syndrome: the ARIC Study (Rose)

MSP 1174: Association between birthweight and cognitive function in middle age: the ARIC study (Szklo)

MSP 835: The relationship between birthweight and intima-media thickness in middle-age. (Tilling)

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

11.b. If yes, is the proposal

__X_ A. primarily the result of an ancillary study (list number* 2008.06 (ARIC-NCS))

___ 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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