ARIC Manuscript Proposal # 3091 (amended)

PC Reviewed: 6/9/20	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:

The Effects of Gravidity and Parity on Risk of Cognitive Impairment

b. Abbreviated Title (Length 26 characters): Gravidity, Parity, and Neurologic Outcomes

2. Writing Group:

Rebecca DiBiase, BA (first author); Aozhou Wu; David Knopman; Keenan Walker; Thomas Mosley; Pamela L. Lutsey; Rebecca Gottesman, MD, PhD; Sarah Tom PhD; Eliza Miller MD (corresponding/ senior author)

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

First author: Rebecca DiBiase, BA
Address: 1729 Gough Street
Baltimore, MD 21231
Phone: 781-956-0809
E-mail: rdibias1@jhmi.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

Name: Rebecca Gottesman, MD, PhD
Address: Johns Hopkins University Department of Neurology
600 North Wolfe Street
Baltimore, MD 21228
Phone: 410-614-2381
E-mail: rgottesm@jhmi.edu

3. Timeline: Data to be used in this proposal are already available. Analyses and manuscript preparation will be performed over the next 6 months.

4. Rationale:

Recently, the association between female hormonal changes and dementia has become a topic of interest. While men initially have a higher risk of developing early-onset Alzheimer's Disease (AD) than women, women become two times more likely to acquire the disease after the age of 75. This sex difference is so pronounced that women with only one copy of the apolipoprotein E

ε4 allele have a higher likelihood of AD diagnosis than men with two copies.[1] At a pathologic level, Barnes et al. found that after this sex risk reversal occurs, one can observe a nearly 3-fold increase in the odds of clinical AD in men compared to more than 22-fold in women with each additional unit of AD pathology.[2] Clinically, women with mild cognitive impairment (MCI) experience cognitive decline at a faster rate than men, and a synergistic effect can be seen when examining women who are apolipoprotein E ε4 carriers. In addition, Weber et al. found that postmenopausal women tend to perform worse on phonemic verbal fluency and delayed verbal memory tests, and perimenopausal and postmenopausal women are more likely to experience depressive symptoms and to be diagnosed with Major Depressive Disorder than premenopausal women.[3]

The data indicate that a complex interplay between the physiological effects of estrogen and apolipoprotein E ε4 drives these results for women in the perimenopausal and postmenopausal states. Specifically, it has been shown in rat models that estrogen can upregulate apolipoprotein E ε4 expression by increasing production of mRNA coding for apolipoprotein E ε4. However, despite the significant research findings thus far, apolipoprotein E ε4 genotype and sex factors are still insufficient to explain many findings, and therefore unknown system interactions are likely at play.[1]

Many of the hypothesized effects of estrogen on cognition can be extrapolated from findings involving hormone replacement therapy. In general, the main consensus, largely drawn from the Women's Health Initiative and offshoot studies, is that hormone therapy in the "critical window" at the onset of menopause may have protective cognitive effects, while later use of HRT may actually accelerate cognitive decline[4]. The work of Brinton et al. further supports this hypothesis with the finding that during the perimenopausal transition, there is an induced hypometabolic physiologic state associated with neurologic dysfunction.[5]

In addition, basic science research has corroborated these findings, and specifically suggested that elevated concentrations of estradiol and progesterone can affect the concentration of hippocampal dendritic spines in animal models. The physiologic effect is that the increased exposure to estrogen during pregnancy decreases hippocampal volume in the short-term, but enhances long-term hippocampal learning plasticity and potentiation through a mechanism of dendritic remodeling[6,7,8].

Thus, it is clear that estrogen exposure has an effect on cognitive function, likely through a complex interplay of multiple physiologic systems. Our study seeks to expand the research in this area by examining gravidity and parity as important factors in lifetime estrogen exposure within the ARIC cohort as they relate to mild cognitive impairment and dementia.

5. Main Hypotheses/Study Questions:

Our study seeks to answer the following questions:

1. To determine whether higher numbers of gravidity and parity are associated with a) a lower risk of dementia, and b) a decreased risk of mild cognitive impairment or dementia.

We hypothesize that increased gravidity and parity will have either no effect or a protective effect against MCI and dementia.

2. To determine whether race and/ or APOE status modifies the relationship described in #1.

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:

We plan to use recorded gravidity and parity at visit 1 as our exposure. Data from the ARIC-NCS study will be used to examine time-to-event for incident dementia through visit 6, as well as, in separate secondary analyses, diagnoses of MCI and dementia at visit 6.

Study Population:

Inclusion Criteria:

All female ARIC study participants will be included in the analysis. For the analysis of MCI and dementia (1b), participants will need to have attended or been evaluated at visit 6 (ARIC-NCS[9]), and for time-to-event incident dementia diagnoses (hypothesis 1a), we will include level 3 diagnoses, so only need to be without prevalent dementia at ARIC visit 1.

Exclusion Criteria:

All males will be excluded from our study. Participants will be excluded if they had a previous diagnosis of dementia preceding visit 1.

Exposures:

The main exposures of interest are gravidity and parity, used as a partial representation of cumulative lifetime estrogen exposure. We will use the reported gravidity and parity from visit 1 for each woman. We will categorize these variables based on their distribution.

Outcomes:

Potential neurologic outcomes for hypothesis #1a will include time-to-event for level 3 dementia. For hypothesis 1b, cognitive status is the primary outcome (normal, MCI or dementia considered separately or together, in separate analyses).

Presence of these outcomes was assessed in the ARIC-NCS study[9] using in-person assessments or telephone interviews if participants were unwilling or unable to be examined in person, as well as informant interviews and hospitalization codes for level 3 dementia.

In-person assessments included the Centers for Epi Studies – Depression Scale, the delayed word recall task and digit symbol substitution from the Wechsler Adult Intelligence Scale- Revised (WAIS-R), a letter fluency task, MMSE, neuropsychologic test battery, logical memory immediate and delayed recall, incidental learning from the Wechsler Memory Scale-III, WAIS-R digits span backward, Boston naming test, and animal naming test. A more detailed test battery was then administered to participants with an MRI in 2004-2006 as part of the ARIC-MRI study and who had either a low MMSE or low constructed Z-score from the previous cognitive tests. A random sample of cognitively normal participants also received this more complex testing, which included MRI scans of the brain. An algorithm was then employed to diagnose cognitive normality, MCI, or dementia based on criteria from the National Institute on Aging-Alzheimer's Association workgroups and Statistical Manual of Mental Disorders, 5^{th} edition (DSM-5). Internal consistency was evaluated for the cognitive-functional profiles generated by the algorithm. These adjudicated diagnoses will be required for the MCI/ dementia analysis (1b), but for time-to-event for level 3 dementia we will also incorporate other dementia surveillance methods are previously described.

Covariates:

Potential covariates (assessed at visit 1) include age, race-field center, smoking status (current, former, never), alcohol consumption (current, former, and never), waist-to-hip ratio, apolipoprotein E ε4 genotype, total cholesterol, hypertension status, physical activity, highest education level (as a proxy for socioeconomic status) and diabetes status.

Statistical Analysis Plan:

For hypothesis #1a, we will use Cox proportional hazards regression to consider time-to-dementia diagnosis.

For hypothesis #1b, we will use logistic regression to evaluate the association of gravidity and parity as two separate ordinal variables using adjudicated MCI and dementia at visit 5. In a primary model, we will combine MCI and dementia and consider MCI/dementia versus normal cognition. In addition, depending on the available number of cases, we will consider ordinal or multinomial logistic regression to evaluate all three cognitive categories.

For hypothesis 2, we will stratify models and evaluate for interaction based on race and aPOE, each X parity or gravidity category.

Limitations:

Our sample size will be relatively small, for hypothesis 1b. Hypothesis 1a, with time-to-event, should capture more dementia cases. Because data has already been collected and recorded, there will likely be limitations in our ability to examine other questions and hypotheses that may arise.

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

8. Will the DNA data be used in this manuscript? ____ Yes __X__ 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/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)?

1.) *Menopause aging genes, cognition and frailty: The Atherosclerosis Risk in Communities Study* (proposal #2503)
Authors: Marina Bessel, Nora Franceschini, Gerardo Heiss, B. Gwen Windham, Thomas H. Mosley, Bruce B. Duncan, Maria Inês Schmidt, Álvaro Vigo, Ellen Demerath, Lisa Wruck

2.) *Associations Between Midlife Vascular Risk Factors and 25-Year Incidence Dementia in the Atherosclerosis Risk in Communities (ARIC) Cohort* (proposal #2551)
Authors: Rebecca Gottesman, Michael Griswold, Cliff Jack, Tom Mosley (senior), Melinda Power (first)

3.) *Associations of Brain Imaging with Cognitive Change over 20 years* (proposal #2288)
Authors: D Knopman, C Jack, J Graff-Radford, K Kantarci, T Mosley, R Gottesman, M Griswold, AR Sharrett, G Windham, M Albert, L Coker

4.) *Reproductive history and late life health status among older African American and White Women* (proposal #678)
Authors: S. Shreeniwas, C. Suchindran, E. Mutran

5.*) Parental history of cardiovascular disease and the risk of incident coronary heart disease and stroke in women with and without bilateral oophorectomy: the Atherosclerosis Risk in Communities (ARIC) study* (proposal #2424)
Authors: D. Appiah, P.J. Schreiner, A.R. Folsom, S.J. Winters, C.A. Hornung

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

This manuscript proposal uses data from ancillary studies #2009.29 (ARIC-PET) and #2008.06 (ARIC-NCS).

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.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes _X_ No.

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