ARIC Manuscript Proposal #3489

PC Reviewed: 10/8/19	**Status: _____**	**Priority: 2**
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1.a. Full Title: Plasma Amyloid-Beta and Risk of MCI/Dementia in ARIC-NCS

b. Abbreviated Title (Length 26 characters): Plasma Aβ and Dementia Risk

2. Writing Group:

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

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3. Timeline: Manuscript submission 3-6 months following approval

4. Rationale:

The recently proposed National Institute on Aging – Alzheimer's Association research framework for defining Alzheimer's disease (AD) emphasizes a classification system based on three pathological processes: amyloid-beta (Aβ), tau, and neurodegeneration (ATN).[1,2] Regarding Aβ deposition, the currently validated biomarkers under the ATN criteria include positron emission tomography (PET) with an Aβ tracer, or measuring circulating Aβ peptides in cerebrospinal fluid (CSF) via lumbar puncture. While well validated, these measurement methods are restricted in application by expense and/or invasiveness. Concerning the research application for which the ATN framework was developed, restrictive biomarker assessment methods may be particularly problematic in older adult populations, contributing to greater selection bias by ensuring Aβ assessment is possible only in participants who can consent to and meet eligibility requirements for these high burden procedures. Therefore, the framework advocated for the investigation and validation of less invasive biomarkers that could be integrated into the ATN criteria. This remains a priority. Of relevance to this need, several recent reports have suggested utility in measuring Aβ in plasma. Specifically, two Aβ peptide variants, Aβ42 and Aβ40, the primary components of brain Aβ,[3] have emerged as candidate plasma biomarkers related to risk of AD.[4] If validated, plasma-based measurement of Aβ will not only prove less invasive and less expensive, but the increased accessibility may assist in earlier measurement and detection than existing methods, a key advantage considering the insidious decades-long pathological cascade of AD.[5]

Results from several small studies suggest plasma Aβ has the potential to be informative within the ATN framework. Plasma Aβ has been shown to be significantly associated with PET measures of Aβ,[6-8] and CSF measured Aβ.[8,9] In the largest, most comprehensive validation study to date, Aβ positivity classification by plasma measurement had 90% agreement with classification based on Pittsburgh Compound B(PiB) retention PET standard, which was equivalent to the agreement of CSF Aβ compared to PiB-PET standard.[8] However, the value of plasma-based Aβ measurement depends not only on validation with the gold standards of Aβ measurement, but association with risk of development of dementia or mild cognitive impairment (MCI).

An early meta-analysis by Koyama et al 2012 suggested a pattern in which a higher ratio of plasma Aβ42:Aβ40, but not Aβ42 or Aβ40 alone, was associated with lower risk of incident AD in 13 studies with follow-up times ranging from 2-11 years.[10] A recent update added evidence to support the observation that higher Aβ42:Aβ40 ratio was protective, but unlike the previous meta-analysis, also suggested higher Aβ42 alone was associated with lower risk, with continuing inconclusive results for Aβ40.[11] This updated meta-analysis was reported alongside results from the Framingham Heart Study, among the largest prospective studies of plasma-Aβ and dementia to date at over 2000 participants, which suggested a 21% AD risk reduction per standard deviation increase in Aβ42 and a 17% AD risk reduction per standard deviation increase in Aβ42:Aβ40 ratio. Considering these results, it has been posited that imbalance of plasma Aβ peptides is a better predictor of future neurocognitive disorder than either Aβ peptide alone.

In the proposed study, we aim to address several gaps in the literature associating plasma Aβ42 and Aβ40 levels with neurocognitive disorder. Of the studies associating Aβ42 and Aβ40 with dementia, most have measured these predictors in late-life, with the dementia outcome investigated either cross-sectionally or prospectively with limited follow-up time. Additionally, many studies have not considered MCI an outcome of interest. Therefore, the utility of these

plasma biomarkers for long-term prediction of dementia and early identification of preclinical AD has yet to be validated, particularly in a racially diverse community-based sample. The Atherosclerosis Risk in Communities Study is in a unique position to address this gap. During ARIC Visit 5, plasma Aβ40 and Aβ42 were measured in 2588 selected participants. In the same sample, plasma Aβ42 and Aβ40 were also measured at ARIC Visit 3 (1993-1995) using stored blood samples. By investigating Visit 3 plasma Aβ42 and Aβ40 levels with cognitive status through Visits 5 and 6, we will model 20+ year risk of dementia and MCI starting from midlife. Furthermore, while most studies have suggested that both Aβ42 and Aβ40 are relevant to dementia risk, it is possible that examining a ratio between the two may not fully capture the nuances of the interrelationship of these peptides and dementia risk. In this study we will achieve the following aims to address these gaps:

1.) Investigate the relationship between midlife plasma Aβ peptides including Aβ40, Aβ42, Aβ42:Aβ40 ratio and additional non-linear combinations of Aβ40 and Aβ42, with late-life MCI/dementia.

2.) Investigate the change in Aβ peptides from midlife to late-life and risk of MCI/dementia.

3.) Investigate the relationship between midlife and late-life Aβ peptides with incident MCI and dementia events.

5. Main Hypothesis/Study Questions:

H1: Midlife plasma Aβ (Visit 3, average age 59.4 years) will be associated with adjusted risk of MCI/dementia at Visits 5 and 6.

i. Higher Aβ40 will be associated with higher risk of MCI/dementia

ii. Higher Aβ42 will be associated with lower risk of MCI/dementia

iii. Higher Aβ42:40 ratio and/or other non-linear combinations will be associated with lower risk of MCI/dementia

iv. We will also investigate V5 and V6 cognitive performance (global factor score) as a secondary outcome

H2: Change in plasma Aβ from midlife to late-life (Visit 3 to Visit 5) will be associated with adjusted risk of MCI/dementia at Visits 5 and 6.

i. Greater increase in Aβ40 will be associated with higher risk of MCI/dementia

ii. Greater decline in Aβ42 will be associated with higher risk of MCI/dementia

iii. Greater decline in Aβ42:40 ratio and/or other non-linear combinations will be associated with higher risk of MCI/dementia

iv. We will also investigate V5 and V6 cognitive performance (global factor score) as a secondary outcome

H3: Late-life plasma Aβ (Visit 5, average age 77.2 years) will be associated with incidence of MCI (Level 1) and dementia (Level 3) through V6 and V7*

i. Higher Aβ40 will be associated with higher incidence of MCI/dementia

ii. Higher Aβ42 will be associated with lower incidence of MCI/dementia

iii. Higher Aβ42:40 ratio and/or other non-linear combinations will be associated with lower incidence of MCI/dementia

iv. We will also investigate change in cognitive performance (global z-score) from V5 to V6 and V7* as a secondary outcome

*V7 adjudicated outcomes when available

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

Inclusion Criteria: Subset of ARIC Visit 3 and ARIC-NCS participants with quantified plasma Aβ (N = 2,588) for associations with Visit 5 and Visit 6 cognitive status.

Exclusion Criteria: For analyses examining incident events after V5 we will exclude participants with dementia at V5

Outcomes:
Primary
- V5: adjudicated Level-1 cognitive status (normal, MCI, dementia)
- V6: worst adjudicated Level-3 cognitive status from V5 through V6 (Example: participant with dementia at V5 who died before V6 is counted as dementia; see table below)
- V5-V6 incident Level-3 dementia
    - Participants adjudicated as normal at V5 who transition to MCI or Dementia

Secondary
- Surveillance-based Level-3 dementia from V3 throughout the study follow-up
- V5 and V6 cognitive function (global factor score)

Table. V5-V6-Surveillance Cognitive Status

		Visit 6 Only			**Visit 6 + Surveillance**			
					Dementia		No Dementia	
Visit 6 Status		Normal	MCI	Dementia	Death	Missing	Death	Missing
Visit 5	Normal	**Normal (n = 760)**	**MCI (n = 146)**	**Dementia (n = 97)**	**Dementia (n = 0)**	**Dementia (n = 0)**	**Death (n = 65)**	. (n = 240)
	MCI	**MCI† (n = 298)**	**MCI (n = 169)**	**Dementia (n = 241)**	**Dementia (n = 0)**	**Dementia (n = 0)**	**MCI (n = 85)**	**MCI (n = 218)**
	Dementia	**Dementia (n = 0)**	**Dementia (n = 0)**	**Dementia (n = 259)**	**Dementia (n = 0)**	**Dementia (n = 0)**	**Dementia (n = 0)**	**Dementia (n = 0)**
	Unknown	. (n = 1)	. (n = 1)	. (n = 4)	. (n = 0)	. (n = 0)	. (n = 2)	. (n = 2)

†Planned sensitivity analysis

Predictor(s)
Continuous measures of plasma Aβ will be implemented in several cross-temporal modeling frameworks:

1. Midlife plasma Aβ level associations with cognitive status at V5, V6, and Level-3 surveillance dementia time-to-event
    a. V3 plasma Aβ40

b. V3 plasma Aβ42
c. V3 plasma Aβ42:Aβ40 and non-linear Aβ42 and Aβ40 combinations

2. Change in plasma Aβ level from midlife to late-life associations with cognitive status at V5, V6, and Level-3 surveillance dementia time-to-event among non-demented participants (V5 cognitive status)
a. Change in plasma Aβ40 V3 to V5
b. Change in plasma Aβ42 V3 to V5
c. Change in plasma Aβ42:Aβ40 and non-linear Aβ42 and Aβ40 combinations V3 to V5

3. Late-life plasma Aβ level associations with incident MCI/Dementia (Level-3) at V6 and V7 among non-demented participants (V5 cognitive status)
a. V5 plasma Aβ40
b. V5 plasma Aβ42
c. V5 plasma Aβ42:Aβ40 and non-linear Aβ42 and Aβ40 combinations

Covariates
Time-invariant demographic variables, including race-site, sex, and education will be extracted from Visit 1. Presence or absence of an apolipoprotein (APOE) ε4 allele will be extracted from genotyping. Primary covariates will include age, sex, race-center, education, and plasma amyloid quantification batch. Potential modifiers of interest are sex and race-center, given interest in sex and race differences in rates of dementia and risk factors. Covariates will be extracted from Visit 3, incorporating time-varying covariates and conditions, as feasible.

***Statistical Analysis*:**
Exploration:
Initial stages of analyses will involve data cleaning, variable development, and exploratory data analyses (EDA). Graphical EDA will examine the nature and extent of potential nonlinear relationships using smoothing splines and surfaces.

Primary analyses:
We will use multinomial regression and generalized linear models to examine cross-sectional associations of plasma Aβ with cognitive status (normal, MCI, dementia) and cognitive function adjusted for covariates listed above. Analyses involving adjudicated cognitive status from Visit 5 through Visit 6 will incorporate inverse probability for attrition and selection weighting (IPW) to examine potential selection bias due to cohort attrition (missingness) and sub-study inclusion across visits.

Additional analyses: Time to dementia or death
We will use competing-risks survival regression using dates (via surveillance, Level-3) for death and dementia to characterize the association of plasma Aβ with time to progression from normal cognition to dementia or death. Non-proportional hazards and flexible baseline hazard functions will be examined due to the differential rates of dementia diagnoses occurring through surveillance versus visit ascertainment.

Additional analyses: Functional forms of aβ42 and aβ40
In addition to the Aβ42:Aβ40 ratio, we will use fractional polynomial models and multivariate clustering to explore flexible parameterization of Aβ42 and Aβ40 joint effects. Supported functional forms will be fit using the multinomial regression models from our primary analyses. Potential utility will be described using model fit diagnostics. C-statistics will be calculated for Aβ42 and Aβ40 at midlife and late-life to compare strength as predictors of MCI/dementia.

Limitations

1. Plasma Aβ measurement based on an older assay method.
2. The sample for the proposed study is highly selected, and conditioned on Visit 5 participation. The sample of 2588 participants included all individuals exhibiting atypical cognitive status during Visit 5 exam, and an age-stratified random sample of cognitively normal participants. Visit 3 plasma Aβ assessment was dependent on Visit 5 plasma Aβ assessment; therefore, there is no attrition/death in this sample between Visit 3 and Visit 5.

7.a. Will the data be used for non-CVD analysis in this manuscript? __X__ Yes ____ 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? __X__ 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? __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 file ICTDER03 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/aric/mantrack/maintain/search/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)?

MP#3354: Plasma beta-amyloid and late-onset epilepsy: The ARIC Neurocognitive Study
MP#2511: Vascular risk factors and brain amyloid deposition: The ARIC-PET Study
MP#2466: The ARIC-PET Amyloid Imaging Study: Differences in Brain Amyloid deposition by Age, Race, Sex, and ApoE genotype

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)

___ 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 https://www2.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.

Acknowledged

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.

Acknowledged

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