

ARIC Manuscript Proposal # 3302

PC Reviewed: 12/11/18

Status: _____

Priority: 2

SC Reviewed: _____

Status: _____

Priority: _____

1.a. Full Title: The association of blood lipid levels and late-life brain amyloid accumulation

b. Abbreviated Title (Length 26 characters): Lipids and Amyloid

2. Writing Group:

Writing group members: Melinda C. Power (last), Erin Bennett (first), Rebecca F. Gottesman, Dean Wong, Thomas Mosley, Timothy Hughes, others welcome

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

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3. Timeline:

Completion 4-6 months following approval.

4. Rationale:

Efforts to identify risk factors for Alzheimer's disease have had varying levels of success. In part, this may be attributable to use of symptom-based diagnostic criteria when identifying Alzheimer's disease dementia in epidemiological studies and the high prevalence of mixed dementia. Using florbetapir PET scans to quantify amyloid plaque build-up in the brain, which is hypothesized to contribute directly to the development of dementia, is a more objective measure of an individual's Alzheimer's-related pathologic burden. In addition, it is possible to measure amyloid build-up before an individual presents with clinical symptoms, reducing the chances of associations being due to reverse causality. Numerous risk factors for amyloid plaque accumulation in the brain have been suggested as a result of epidemiological studies. In particular, vascular risk factors are thought to contribute to amyloid accumulation, either by causing more amyloid deposition or by reducing clearance of amyloid plaques.(1) Because amyloid accumulation appears to begin 10 to 20 years before the onset of clinical symptoms(2), measuring midlife risk factors are likely relevant to subsequent amyloid burden. In support of this, midlife vascular risk factors have consistently been associated with higher amyloid burden(3, 4), while studies of late-life vascular risk factors have yielded mixed results.(5-8)

One vascular risk factor of particular interest is blood lipid levels. Overall, null associations between cross-sectional late-life lipid levels and amyloid accumulation have been seen in most studies, including the Ginkgo Evaluation of Memory (GEM) study(9) and the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort(10). Alternately, studies looking at midlife lipid levels and incident dementia have suggested a possible positive association, but results have varied.(11) While some cohort studies suggest that inflated total cholesterol in midlife predicts incident dementia or cognitive decline(11), others have found null associations(12), or have only found associations between longitudinal decrease in blood lipid levels and incident dementia(11, 13, 14). Specifically in the ARIC cohort, researchers have found a null association between midlife lipids and 25-year incident dementia(15) and a positive association between midlife lipids and 20-year cognitive change(16). Reasons for conflicting findings may include using different measures of midlife blood lipid levels (i.e. measuring total

cholesterol vs. total triglycerides), using study populations with different baseline characteristics, and the advent of statins, which lowered lipid levels for much of the population beginning in the late 1980s. Animal and cell culture studies have pointed to a potential mechanism whereby cholesterol contributes to amyloid deposition in the brain(13), suggesting the need to determine whether this associations exists on a population level.

To date, one group of researchers using data from the Swedish BioFINDER Study cohort has examined the association between midlife lipid levels (total cholesterol, triglycerides, HDL, and LDL) and late-life brain amyloid accumulation. Investigators found that while higher midlife triglycerides and LDL were significantly associated with abnormal amyloid 20 years later, total cholesterol and HDL fell short of significance.(4) There were limitations to this study that merit verification of their reported findings with different cohorts. Participants in the Swedish BioFINDER Study were all white, limiting the generalizability of their results to diverse populations. In addition, only 134 participants had amyloid-beta PET scan data, reducing the investigators' ability to detect smaller significant associations.

Finally, no other study has considered whether change in lipid levels from midlife to late-life is associated with late-life amyloid burden to our knowledge. The association between lipid level decline and incident dementia has been consistently proposed, even before the advent of statins. In 2007, Stewart et al. found that, after adjusting for statin use, cholesterol decline over 26 years remained significantly associated with incident dementia diagnosis in the Honolulu-Asia Aging Study.(14) A study using data from the Prospective Population Study of Women in Sweden also found that greater decline in cholesterol levels from mid- to late-life predicted increased risk of dementia diagnosis later in life. Because most measures of blood lipids were taken before the advent of statins, controlling for statin use did not alter these results.(13) While the association between lipid level decline and incident dementia has been consistently proposed, it is unclear whether this association is mediated by amyloid.

As such, we propose to describe the relationship between midlife lipid levels and brain amyloid accumulation in the ARIC-PET Study. Specifically, we will assess whether higher midlife total cholesterol and triglycerides predict amyloid burden in nondemented individuals in the racially-diverse ARIC cohort. We will also determine whether a greater decline in lipids from midlife to late life is associated with late-life amyloid accumulation, and how this association varies according to statin use. This research will contribute to our understanding of how lipids may contribute to amyloid accumulation and to eventual dementia and cognitive decline.

5. Main Hypothesis/Study Questions:

We hypothesize that higher midlife total cholesterol and triglycerides as measured at visit 1 will be significantly associated with abnormal amyloid burden. We also hypothesize that greater decline in lipid levels from midlife to late-life will predict higher amyloid burden, and that this relationship will be (1) stronger in black participants than in white participants, (2) attenuated by statin use.

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).

Exclusions:

No lipid data at visit 1, no PET-imaging data at visit 5. Those who were included in the ARIC-PET imaging study had specific exclusion criteria; in summary, participants were excluded if they had contraindication to MRI, were heavy alcohol users or had renal failure, or met the clinical diagnosis of dementia. Only participants from the Jackson, MS, Forsyth County, NC, and Washington County, MD field centers were enrolled.

Independent variables:

Midlife total cholesterol, HDL, LDL, and total triglyceride levels. In participants who have lipid data for both visit 1 and visit 5, the average change in lipid levels from visit 1 to visit 5 also be calculated and treated as an independent variable in secondary analyses.

Dependent variables:

Global cortical measure of amyloid, using florbetapir PET scans, calculated as a weighted average of standardized uptake value ratios (SUVRs) in various regions of the brain, as described elsewhere, with cerebellar gray matter as the reference.(17) Abnormal amyloid uptake will be defined as $SUVR > 1.2$ and treated as a dichotomous variable.

Covariates:

For analyses of V1 lipids: Age, sex, race-center, APOE e4 status, V1 BMI, V1 hypertension, and V1 diabetes.

For analyses of V1 and V5 lipids: Age, sex, race-center, APOE e4 status, V1&V5 BMI, V1&V5 hypertension, and V1&V5 diabetes.

Effect modifiers:

Visit 5 statin use

Statistical Analyses:

For analyses using measures of midlife lipid levels, we propose to use logistic regression to assess the association between midlife TC, HDL, LDL, and triglycerides and risk of having abnormal amyloid burden (SUVR>1.2). All analyses will be adjusted for age, race/center, gender, APOE e4 status, and lipid lowering medication use. We will also consider models that additionally adjust for potential intermediates, including body mass index, diabetes, and hypertension. We will use multiplicative interaction terms to assess effect modification.

For secondary analyses using change in lipid levels from midlife to late-life, we propose to use logistic regression to assess the relationship between change in lipid levels and abnormal amyloid burden (SUVR>1.2). We will quantify the change in lipids from midlife to late-life (our exposures) in two ways. First, we will subtract Visit 1 from Visit 5 to create a change score and will use this as our dependent variable, adjusting for both Visit 1 and Visit 5 values of time-varying covariates. Second, we will use linear mixed effects models to estimate person-specific trajectories of lipids. If a linear trajectory is appropriate, we will use the person-specific slope of the linear trajectory as our dependent variable. If a linear trajectory is not appropriate, we will create categories for different trajectories for use as our dependent variable. In this scenario, we will adjust for time-dependent variables in our linear mixed effects model, rather than in our final model.

Sensitivity analyses will consider weighting to address selection into the PET sub-sample. We will also consider continuous SUVR.

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? ___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.csc.unc.edu/atic/mantrack/maintain/search/dtSearch.html>

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)?

#2201r; Lipids, statins, and 20-year cognitive change: The ARIC-Neurocognitive Study (Power et al)

#2200r; Lipids, statins, and dementia: The ARIC-Neurocognitive Study (Power et al)

#2544; Arterial Stiffness and B-Amyloid Deposition in the ARIC-PET Study (Hughes et al)

#2466; The ARIC-PET Amyloid Imaging Study: Differences in Brain Amyloid deposition by Age, Race, Sex, and ApoE genotype (Gottesman et al)

#3119; Vascular risk factors, brain amyloid deposition, and cognitive decline: The ARIC-PET Study (Gottesman et al)

#2822; Subclinical cerebrovascular disease and brain amyloid deposition: The ARIC-PET Study (Gottesman et al)

#3024; Intracranial atherosclerotic disease and brain amyloid deposition: The ARIC Study (Gottesman et al)

#3011; Systemic inflammation and brain amyloid deposition: The ARIC-PET Study (Walker et al)

#2955; Cardiac dysfunction and brain amyloid deposition: The ARIC-PET Study (Gottesman et al)

#2511; Vascular risk factors and brain amyloid deposition: The ARIC-PET Study (Gottesman et al)

#3042; Association of midlife cognition, cognitive decline, and education with late-life cerebral B-amyloid deposition (Rawlings et al)

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

11.b. If yes, is the proposal

- A. primarily the result of an ancillary study (list number* __2009.29__)**
- 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.csc.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.csc.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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2. Jack CR, Jr., Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol* 2010;9(1):119-28.
3. Gottesman RF, Schneider AL, Zhou Y, Coresh J, Green E, Gupta N, et al. Association Between Midlife Vascular Risk Factors and Estimated Brain Amyloid Deposition. *JAMA* 2017;317(14):1443-1450.
4. Nagga K, Gustavsson AM, Stomrud E, Lindqvist D, van Westen D, Blennow K, et al. Increased midlife triglycerides predict brain beta-amyloid and tau pathology 20 years later. *Neurology* 2018;90(1):e73-e81.
5. Choi HJ, Byun MS, Yi D, Choe YM, Sohn BK, Baek HW, et al. Association Between Serum Triglycerides and Cerebral Amyloidosis in Cognitively Normal Elderly. *Am J Geriatr Psychiatry* 2016;24(8):604-612.
6. Marchant NL, Reed BR, DeCarli CS, Madison CM, Weiner MW, Chui HC, et al. Cerebrovascular disease, beta-amyloid, and cognition in aging. *Neurobiol Aging* 2012;33(5):1006 e25-36.
7. Rabin JS, Schultz AP, Hedden T, Viswanathan A, Marshall GA, Kilpatrick E, et al. Interactive Associations of Vascular Risk and beta-Amyloid Burden With Cognitive Decline in Clinically Normal Elderly Individuals: Findings From the Harvard Aging Brain Study. *JAMA Neurol* 2018;75(9):1124-1131.

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12. Alonso A, Mosley TH, Jr., Gottesman RF, Catellier D, Sharrett AR, Coresh J. Risk of dementia hospitalisation associated with cardiovascular risk factors in midlife and older age: the Atherosclerosis Risk in Communities (ARIC) study. *J Neurol Neurosurg Psychiatry* 2009;80(11):1194-201.
13. Mielke MM, Zandi PP, Shao H, Waern M, Ostling S, Guo X, et al. The 32-year relationship between cholesterol and dementia from midlife to late life. *Neurology* 2010;75(21):1888-95.
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