ARIC Manuscript Proposal #3752

PC Reviewed: 12/8/20	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association of Carotid Intima-Media Thickness with Beta-Amyloid Deposition: The ARIC-PET Study

b. Abbreviated Title (Length 26 characters): **cIMT and beta-amyloid**

2. Writing Group:
Writing group members: Wendy Wang, Rebecca F. Gottesman, Michelle L. Meyer, Timothy M. Hughes, Kevin J. Sullivan, Kamakshi Lakshminarayan, Pamela L. Lutsey

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

First author: Wendy Wang
Address: Division of Epidemiology and Community Health
1300 South 2nd St, Suite 300
Minneapolis, MN 55455

Phone: (612) 626-7755
E-mail: wang5694@umn.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: Pamela L. Lutsey
Address: Division of Epidemiology and Community Health
1300 South 2nd St, Suite 300
Minneapolis, MN 55455

Phone: (612) 624-5812 Fax: (612) 624-0315
E-mail: lutsey@umn.edu

3. Timeline:
Data analysis to begin immediately; pen draft expected in 6 months

4. Rationale:

Elevated carotid intima-media thickness (cIMT), a marker of carotid atherosclerosis, has been prospectively association with an increased risk for dementia,[1,2] including in the Atherosclerosis Risk in Communities (ARIC) Study.[3] Prior to the development of dementia, changes in the brain, such as increased levels of β-amyloid, may occur.[4] It has been hypothesized that amyloid accumulation in the brain, which may begin years before clinical symptoms, leads to the development of Alzheimer's disease.[5] In addition, carotid atherosclerosis may reduce cerebral blood flow,[6,7] which in turn may increase the risk of cerebral hypoperfusion[8] and ultimately lead to dementia.[9] Animal models have found that cerebral hypoperfusion results in amyloid plaque development and accumulation;[10–12] however, this relationship in humans is not well characterized. Cerebral hypoperfusion due to induced bilateral common carotid artery stenosis has shown to increase β-amyloid deposition in mice.[10] A small study in humans (n=11) reported that hypoperfusion did not induce increased β-amyloid accumulation.[13] Alternatively, cIMT may represent the cumulative effect of vascular risk factors,[14] which have previously been shown to be associated with elevated β-amyloid deposition,[15] over the course of one's life.

Few studies have assessed the relationship between markers of atherosclerosis and β-amyloid accumulation. A small cross-sectional study (n=34) reported no association between cIMT and cerebral amyloid.[16] Another cross-sectional study found no association between carotid stenosis and β-amyloid burden in a Korean community-based cohort.[17] The Swedish BioFINDER subcohort, which originates from the Malmö Diet and Cancer Study, reported the highest quartile of IMT (>0.81mm) was prospectively associated with greater odds of abnormal β-amyloid when compared to the lowest IMT quartile (OR [95% CI]: 2.26 [1.03, 4.95]) after adjusting for age; however, this association attenuated after further adjustment for sex, vascular risk factors, and APOE ε4.[18] In ARIC, there was no evidence of an association between intracranial atherosclerotic disease and β-amyloid among participants free of dementia.[19]

As the relationship between cIMT and β-amyloid remains unclear, additional research is warranted, particularly in nondemented populations. Given the availability of brain amyloid measures, the ARIC-PET study is well-suited to investigate this relationship. We propose to analyze the prospective association between cIMT in midlife with β-amyloid deposition in late life.

5. Main Hypothesis/Study Questions:

Aim: To determine the prospective association of cIMT with β-amyloid deposition.

Hypothesis: Participants with greater cIMT at midlife are associated with greater β-amyloid deposition in late-life.

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 2 to PET scan (~visit 5).

Inclusion/Exclusion

Participants who completed the ARIC-PET study will be included in this analysis. Exclusion criteria includes missing cIMT data, races other than Black or white, Blacks from the MN and MD centers, and those with missing covariates.

Exclusion criteria for involvement in ARIC-PET study: We excluded individuals with a history of: 1) radiation therapy, chemotherapy, or surgery in the 6 weeks prior to the ARIC-PET visit; 2) clinically significant liver or renal dysfunction; 3) prolonged QT interval; 4) drug or alcohol abuse. We allowed use of anticholinergic medications or memantine if the dose was stable for $\geq$3 months preceding the PET scan. ARIC-PET also excluded participants with dementia; however, visit 5 was not yet fully adjudicated at the time of PET scan and one ARIC-PET participant was given a diagnosis of dementia. Therefore, we will exclude this participant in our analysis.

Variables

Exposure: cIMT will be measured using the 6-site imputed IMT variable and will be represented as a continuous variable and in tertiles.

Primary outcome: Standardized uptake value ratio (SUVR) of β-amyloid deposition from visit 5 PET will be our primary outcome. Global mean cortical SUVR, which is a weighted average based on region of interest volumes, is known to be typically impacted by Alzheimer's disease. Due to the highly skewed distribution, the SUVR will be dichotomized at the sample median of 1.2, with values >1.2 considered positive.

Other confounders/covariates (collected from visit 2): age, sex, race, APOE ε4, education (from visit 1), body mass index (BMI), systolic blood pressure, antihypertensive medication use, smoking status, diabetes

Statistical analysis

- Baseline characteristics will be described using mean ± SD for continuous variables and proportions for categorical variables, stratified by cIMT tertiles.
- Logistic regression will be used to estimate the association of cIMT with elevated β-amyloid deposition.
- The following models will be used:
  - Model 1 will adjust for age, sex, race, and APOE ε4.
  - Model 2 will adjust for model 1 plus BMI, smoking status, and education.
  - Model 3 will adjust for model 2 plus systolic blood pressure, antihypertensive medications, and diabetes.
- Interactions by age, sex, race, and APOE ε4 will be analyzed by including a cross-product term in the model. Stratified models will be reported when appropriate.

- Inverse probability weighting will be used to account for attrition due to death, visit non-attendance, and selection into brain MRI study (given that PET participants were recruited from the brain MRI cohort).

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? ____ 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)?

#2511: vascular risk factors and brain amyloid deposition (Gottesman)
#2544: arterial stiffness and beta-amyloid deposition (Hughes)
#3024: ICAD and brain amyloid (Gottesman)

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* _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.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.

References:

1. Oijen M van, Jong FJ de, Witteman JCM, Hofman A, Koudstaal PJ, Breteler MMB. Atherosclerosis and risk for dementia. *Annals of Neurology*. 2007;61:403–410.

2. Wendell CR, Waldstein SR, Ferrucci L, O'Brien RJ, Strait JB, Zonderman AB. Carotid atherosclerosis and prospective risk of dementia. *Stroke*. 2012;43:3319–24.

3. Wang W, Norby FL, George KM, Alonso A, Mosley T, Gottesman RF, Meyer ML, Lutsey PL. Abstract 34: Association of Carotid Intima-Media Thickness and Other Carotid Ultrasound Features With Incident Dementia in The Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS). *Circulation*. 2020;141:A34–A34.

4. Alzheimer's Association. 2020 Alzheimer's disease facts and figures. *Alzheimer's & Dementia*. 2020;16:391–460.

5. Hardy JA, Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. *Science*. 1992;256:184–185.

6. Moroni F, Ammirati E, Magnoni M, D'Ascenzo F, Anselmino M, Anzalone N, Rocca MA, Falini A, Filippi M, Camici PG. Carotid atherosclerosis, silent ischemic brain damage and brain atrophy: A systematic review and meta-analysis. *International Journal of Cardiology*. 2016;223:681–687.

7. Sojkova J, Najjar SS, Beason-Held LL, Metter EJ, Davatzikos C, Kraut MA, Zonderman AB, Resnick SM. Intima-Media Thickness and Regional Cerebral Blood Flow in Older Adults. *Stroke*. 2010;41:273–279.

8. Bokkers RPH, van der Worp HB, Mali WPTM, Hendrikse J. Noninvasive MR imaging of cerebral perfusion in patients with a carotid artery stenosis. *Neurology*. 2009;73:869–875.

9. de la Torre JC. Critically attained threshold of cerebral hypoperfusion: the CATCH hypothesis of Alzheimer's pathogenesis. *Neurobiology of Aging*. 2000;21:331–342.

10. Okamoto Y, Yamamoto T, Kalaria RN, Senzaki H, Maki T, Hase Y, Kitamura A, Washida K, Yamada M, Ito H, Tomimoto H, Takahashi R, Ihara M. Cerebral hypoperfusion accelerates cerebral amyloid angiopathy and promotes cortical microinfarcts. *Acta Neuropathol*. 2012;123:381–394.

11. Zhiyou C, Yong Y, Shanquan S, Jun Z, Liangguo H, Ling Y, Jieying L. Upregulation of BACE1 and β-Amyloid Protein Mediated by Chronic Cerebral Hypoperfusion Contributes to Cognitive Impairment and Pathogenesis of Alzheimer's Disease. *Neurochem Res*. 2009;34:1226–1235.

12. Koike MA, Green KN, Blurton-Jones M, LaFerla FM. Oligemic Hypoperfusion Differentially Affects Tau and Amyloid-β. *The American Journal of Pathology*. 2010;177:300–310.

13. Hansson O, Palmqvist S, Ljung H, Cronberg T, van Westen D, Smith R. Cerebral hypoperfusion is not associated with an increase in amyloid β pathology in middle-aged or elderly people. *Alzheimer's & Dementia*. 2018;14:54–61.

14. Romero JR, Preis SR, Beiser A, DeCarli C, D'Agostino RB, Wolf PA, Vasan RS, Polak JF, Seshadri S. Carotid Atherosclerosis and Cerebral Microbleeds: The Framingham Heart Study. *J Am Heart Assoc*. 2016;5:e002377.

15. Gottesman RF, Schneider ALC, Zhou Y, Coresh J, Green E, Gupta N, Knopman DS, Mintz A, Rahmim A, Sharrett AR, Wagenknecht LE, Wong DF, Mosley TH. Association Between Midlife Vascular Risk Factors and Estimated Brain Amyloid Deposition. *JAMA*. 2017;317:1443–1450.

16. Reed BR, Marchant NL, Jagust WJ, DeCarli CC, Mack W, Chui HC. Coronary risk correlates with cerebral amyloid deposition. *Neurobiol Aging*. 2012;33:1979–1987.

17. Kang KM, Lee JH, Yi D, Choi HJ, Lee E, Lee Y, Lee J-Y, Kim YK, Sohn BK, Sohn C-H, Lee DY, for the KBASE Research Group. Association of carotid and intracranial stenosis with Alzheimer's disease biomarkers. *Alz Res Therapy*. 2020;12:106.

18. Gustavsson A, van Westen D, Stomrud E, Engström G, Nägga K, Hansson O. Midlife Atherosclerosis and Development of Alzheimer or Vascular Dementia. *Ann Neurol*. 2020;87:52–62.

19. Gottesman RF, Mosley TH, Knopman DS, Hao Q, Wong D, Wagenknecht LE, Hughes TM, Qiao Y, Dearborn J, Wasserman BA. Association of Intracranial Atherosclerotic Disease With Brain β-Amyloid Deposition: Secondary Analysis of the ARIC Study. *JAMA Neurol*. 2020;77:350.