ARIC Manuscript Proposal Form

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1.a. Full Title: The Association Between Late Life Depression and Brain Amyloid Accumulation: The ARIC-PET Study

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

2. Writing Group [please provide a middle initial if available; EX: Adam L Williams]:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _SK_ **[please confirm with your initials electronically or in writing]**

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (The ARIC author should be involved enough in ARIC to be able to point the lead author to appropriate ancillary study PIs and to be able to search ARIC manuscript proposals if the lead author doesn't have the access needed to do such a search).
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3. Timeline: Analysis completed and abstract submitted by Spring 2023; Manuscript prepared and submitted in ~6-8 months.

4. Rationale: Late life depression (LLD) has been associated with a twofold increase in incident dementia risk, particularly dementia associated with Alzheimer's disease (AD) [1, 2, 3]. While not formally distinguished from Major Depressive Disorder, LLD is characterized by persistent depressive symptoms occurring in individuals 65 or older. Among the constellation of neuropsychiatric symptoms affecting older adults, LLD stands as the most prominent, projected to impact an estimated 31.8% of older adults globally [4]. When compared to early-onset depression, LLD is associated with reduced quality of life, executive dysfunction, cardiovascular comorbidities, and greater mortality [5, 6].

The relationship between LLD and dementia is intricate and multifaceted, with its underlying mechanisms remaining inadequately understood. Existing studies suggest that depression might serve as an early manifestation during the preclinical stages of Alzheimer's dementia [7]. Neuropathological changes have been established to precede clinical AD diagnoses by as much as 25 years, positioning depressive symptomatology as a potential non-cognitive precursor of future dementia [8,9]. Conversely, a wealth of evidence supports the notion that depression functions as a risk factor for dementia development. A meta-analysis encompassing a participant pool of over 100,000 individuals concluded that a history of depression heightened the likelihood of subsequent AD diagnosis later in life (OR:1.53) [2]. Additionally, a 14-year longitudinal investigation on elderly men with depression showed a graded correlation between depressive symptom severity and dementia risk, with individuals exhibiting more severe symptoms facing an elevated risk [10]. Further studies suggest an increase in dementia risk with each additional depressive episode and every incremental point on the 10-item CES-D scale [11, 12]. These findings emphasize the potential predictive value of LLD in the context of dementia and more specifically, Alzheimer's disease. Evaluating biomarkers for dementia etiology, such as for AD specifically, could contribute to understanding of the underlying mechanisms linking depression with dementia more broadly.

The amyloid cascade hypothesis is a widely recognized model that seeks to explain Alzheimer's Disease pathogenesis, positing that the accumulation of Amyloid-β 42 protein plaques in the brain triggers cognitive decline and neurodegenerative changes [13]. Amyloid-β (Aβ) peptides are continuously produced within neurons and cleared through the cerebrospinal fluid and blood-brain barrier into the plasma [14]. Numerous investigations have demonstrated that reduced Aβ42 levels and Aβ42/Aβ40 ratio in the plasma correlate with cognitive decline and eventual AD [15, 16]. Interestingly, a three-year study revealed that cognitively intact individuals with LLD exhibited significantly lower plasma Aβ42/Aβ40 ratios compared to controls, suggesting a potential influence of depressive symptoms on Aβ dynamics [17]. Increased platelet activation, hippocampal integrity loss, and elevations in corticotropin releasing hormone are all proposed mechanisms explaining how depression can influence Aβ dynamics [18, 19, 20].

Beyond soluble Aβ, the utilization of Florbetapir-PET, known for its strong affinity for Aβ and extended half-life, offers the opportunity to detect brain Aβ deposition individuals with

preclinical AD, years before observable clinical symptoms [21]. Research utilizing Florbetapir-PET imaging has found increased brain amyloid deposition in specific areas among individuals with lifetime and subsyndromal depressive symptoms [22, 23]. Conversely, results from the ADNI depression project indicate that individuals with LLD may have less brain Aβ deposition than non-depressed controls [24]. This array of findings could be attributed to methodological disparities across studies, including selection bias, and may be further influenced by differences across studies in participant age, race, educational background, APOE ε4 allele status, and vascular comorbidities.

Only a few studies with limited sample sizes have examined the association between LLD and Aβ brain deposition via Florbetapir-PET imaging. Moreover, the examination of this association within a biracial sample is nonexistent. Existing research highlights Aβ divergence across racial groups and sex; The ARIC-PET study found that Black race and female sex was associated with higher Aβ brain deposition, regardless of differences in vascular risk factors, cognitive status, and APOE genotype [25]. This suggests that the contribution of LLD to amyloid pathology may differ between demographic groups. More cross-sectional and longitudinal studies with large, racially diverse sample sizes are necessary to uncover potential mechanisms underlying the link between LLD and dementia.

This study aims to comprehensively investigate the association between LLD and brain amyloid burden in the ARIC-PET cohort. We hypothesize that individuals with LLD will exhibit higher Florbetapir uptake, a proxy for Aβ plaque burden. Building upon this primary hypothesis, we also hypothesize that the persistence of depressive symptoms between midlife and late life will be associated with elevated global cortical brain amyloid as assessed by PET imaging during late life. We expect to see variations in amyloid deposition across distinct brain regions, with prior research indicating heightened amyloid burden in the bilateral precuneus associated with depression [22]. Furthermore, this study seeks to discern potential racial and sex disparities by exploring whether certain race/gender combinations with LLD exhibit higher global amyloid burden compared to their counterparts. These hypotheses collectively aim to elucidate the intricate interplay between LLD and amyloid burden, enhancing our understanding of potential pathways linking mood disorders and neurodegenerative processes. The identification of significant associations has clinical implications for the early prevention of Alzheimer's disease through targeted interventions addressing modifiable risk factors.

5. Main Hypothesis/Study Aims:

1. LLD is associated with elevated global cortical brain amyloid by PET in late life, in adults without dementia.
2. Persistent depressive symptoms from midlife through late life are associated with elevated global cortical brain amyloid by PET.
3. The association between LLD and global cortical brain amyloid will differ based on race and sex in the ARIC-PET cohort. We hypothesize that the association between LLD and brain amyloid is stronger in those with Black race and female sex.
4. (Exploratory) LLD is associated with greater amyloid burden in the bilateral precuneus, with other regions showing weaker or absent associations

6. Design and analysis - please address the following aspects:

a) **inclusion/exclusion**
b) **study design**
c) **outcome and other variables of interest with specific reference to the time of their collection**
d) **summary of data analysis**
e) **Any anticipated methodologic limitations or challenges if present**

Study Design: This study is cross-sectional.

Participant inclusion/exclusion: All ARIC-PET participants without dementia will be eligible for inclusion (n = 345; one ARIC-PET participant who was ultimately given a research diagnosis of dementia at the time of the PET visit will be excluded from the analysis). In addition, participants with missing CES-D at visit 5 or with history of stroke will be excluded.

Independent Variables: LLD will be evaluated by a score ≥ 9 on the 11-item Center of Epidemiological Depression Scale (CES-D) at visit 5. The CES-D includes 11 items used to assess frequency of depressive symptoms in the past week. Scores range from 0-22, with higher scores indicative of more depressive symptomatology. A score ≥ 9 is clinically suggestive of depression [26]. CES-D will primarily be analyzed dichotomously at scores ≥ 9 vs scores < 8, but CES-D will be evaluated continuously as well.

Depressive symptoms at midlife will be characterized by scores on the Maastricht questionnaire of vital exhaustion at visit 2. Vital exhaustion is a measure of feelings of excessive fatigue, demoralization, and irritability. As depressive symptoms and vital exhaustion are shown to be correlated (r = 0.62) [27], vital exhaustion scores will act as a proxy for midlife depressive symptoms. The Maastricht questionnaire is a 21-item questionnaire in which responses are totaled to obtain an overall vital exhaustion score. Scores range from 0-42, with higher scores indicative of more vital exhaustion. A score ≥ 14 is clinically suggestive of vital exhaustion [28]. Scores will be dichotomized at a cutoff score of 14, which is standard in prior analyses of vital exhaustion.

Outcomes: Florbetapir-PET global cortical standardized uptake volume ratio (SUVR) is the primary outcome. Measurements of global cortical SUVR are based on the weighted average of precuneus, orbitofrontal cortex, prefrontal cortex, superior frontal cortex, lateral temporal lobe, parietal lobe, occipital lobe, anterior cingulate, and posterior cingulate. In relation to exploratory Hypothesis #4, we will also examine the SUVR of each cortical region. Due to skewedness, SUVR will be analyzed dichotomously at the study median of 1.2, which is standard in prior ARIC-PET analyses.

Additional Covariates: Time-constant covariates include demographic variables such as age, race, sex, level of education, and APOE status. In addition, vascular risk factors from visit 5 (i.e., smoking status, drinking status, BMI, prevalent coronary heart disease, diabetes, and hypertension) will be used as covariates.

Data Analysis: Descriptive statistical analysis for all covariates will be completed. The association between LLD and global cortical SUVR will be analyzed with logistic regression. For hypothesis 2, four combined variables, reflecting different levels of persistent depressive symptoms, will be created: vital exhaustion/LLD, no vital exhaustion/LLD, vital exhaustion/no LLD, and no vital exhaustion/no LLD. The association between each categorical combined variable and global cortical SUVR will be analyzed via logistic regression with the no vital exhaustion/ no LLD as the reference group. In a secondary analysis we will also explore if history of antidepressant use (defined as positive report of use at Visit 5, although we may also consider any prior use, which would be defined as positive if ever reported in earlier visits) is associated with global cortical SUVR, aiming to include more patients with depression history (this is a secondary analysis as antidepressant use is known to be nonspecific to individuals with history of depression). Additionally, for hypothesis 4, a logistic regression model will investigate the connection between LLD and SUVR in the bilateral precuneus as well as in several other regions of interest.

A three-step model for adjustment will be utilized for each of the above analyses. Model 1 will be adjusted for age, sex, race, level of education and APOE status. Model 2 will adjust for hypertension, diabetes, and coronary heart disease, as well as covariates in Model 1. Model 3 will include adjustment for all forementioned covariates in addition to smoking status, drinking status, and BMI. We will consider a final model (Model 4) adding white matter hyperintensity volumes (and total intracranial volume) and/or other measures of cerebrovascular disease burden (i.e., microbleeds, lacunes).

Sensitivity analyses will be generated, restricting analysis for those with normal cognition and no APOE e4 alleles, in separate analyses. In addition, a separate sensitivity analysis will be used to consider other SUVR cutoffs (i.e., 1.11). To ensure an unbiased and representative sample, we will also consider calculating the inverse probability of not being selected into PET and using these weights to weight the sample back to the visit 5 population.

Limitations:

- Selection bias of those recruited for ARIC-PET may limit generalizability of results. Participants enrolled in the ARIC-PET study reflect a population that are generally healthier, can tolerate PET scans, and are without dementia. Further, individuals with more severe depression are less likely to participate in a research study, potentially leading to selection bias that excludes those with more severe depression.
- The study's cross-sectional design restricts the ability to establish a causal link between LLD and amyloid, and although we have no individuals with dementia in the cohort, reverse causation could still be present, reducing our ability to make conclusions about the direction of any potential causal relationship.
- The use of combined categorical variables (which incorporate vital exhaustion and CES-D) cannot entirely eliminate the potential for reverse causation.
- Vital exhaustion is not a direct measure of depressive symptoms.
- Scores ≥ 9 on the CES-D are not fully translational to a clinical diagnosis of LLD.

f) Will the author need Limited data to complete the proposed manuscript? ☐ Yes, Limited data is needed (Provide a brief (2-3 sentences) justification for requesting PHI data) . ☒ No, De-identified data will be sufficient.

*Please note, Limited dataset access is strict and rarely provided. Limited data includes identifiable information such as dates (birthdays, visit dates, etc.). CMS, Genomic, Geocoded, Proteomics/Somalogic, and other -omic data all fall under the limited data category. De-identified data does not include dates. All dates are date adjusted to "Days since Visit 1".

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? (Non-ARIC analysis means that the authors are not regarded as ARIC investigators and the "ARIC author" is essentially just a facilitator rather than an integral part of the writing group.) ☐ Yes ☒ 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 is distributed to ARIC PIs annually, 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? ☐ 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"? ☐ Yes ☐ No

9. The lead author or the "sponsoring" ARIC 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 website at: https://aric.cscc.unc.edu/aric9/proposalsearch [ARIC Website□Publications□Proposal Search]

☒ 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)?
MP4252 - The association between midlife and late-life risk factor and chronic disease clusters and late-life depression

MP1019 - Comparison of measurement performance of the Vital Exhaustion and Depression (MQ) scale across race and sex groups

MP4156 – Social Factors, Amyloid Burden, and Dementia: the ARIC-PET Study

MP4080 - Association Between Mid-Life Social Factors and Estimated Late-Life Amyloid Burden: the Atherosclerosis Risk in Communities (ARIC) Study

MP4235 - Predictors of change in blood-based biomarkers of Alzheimer's disease pathology and neurodegeneration measured from mid- to late-life and their associations with late-life measures of brain health in the Atherosclerosis Risk in Communities (ARIC) Study

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or does it use current [or ongoing] ancillary study data (this includes ACHIEVE)? ☒ Yes ☐ No → Skip to question 12

11.b. If yes to 11.a., is the proposal

☒ **A. primarily the result of an ancillary study**

☐ **B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables)**

11.c. If yes to 11.a., list number* _2009.29_

*ancillary studies are listed by number
https://aric.cscc.unc.edu/aric9/researchers/ancillary_studies/approved_ancillary_studies [ARIC Website□Ancillary Studies□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 https://aric.cscc.unc.edu/aric9/publications/policies_forms_and_guidelines [ARIC Website□Publications□Publication Policies, Forms, and Guidelines]. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

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