ARIC Manuscript Proposal #4261 (Revised)

PC Reviewed: 8/8/23	**Status: _____**	**Priority: 2**
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1.a. Full Title: Prevalence of amyloid positivity and other dementia-related biomarkers in the United States

b. Abbreviated Title (Length 26 characters): Brain amyloid prevalence

2. Writing Group:
Writing group members:

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

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3. Timeline:
Begin analyses upon approval.
Submit manuscript for publication no later than April 2024.

4. Rationale:

The aging of the global population is projected to lead to a tripling of dementia cases in the coming decades (GBD 2019). Without adequate medical interventions, healthcare planning, and appropriate policy this has potential to overwhelm the US healthcare system.

Alzheimer's disease (AD) is the most common cause of dementia. The preclinical period of AD begins years before onset of clinical disease diagnosed based on symptoms, which includes not only full AD dementia but also AD-related mild cognitive impairment. AD is characterized by pathophysiologic changes to the brain including accumulation of amyloid plaques and tau neurofibrillary tangles, as well as neurodegeneration or neuronal injury observable through brain imaging and other biomarkers (Jack, Bennett, et al. 2016; Sperling et al., 2011).

Of those observable changes, amyloid beta deposition in the brain is posited to signal the beginning of the pathophysiological cascade of AD, and there is a major effort to intervene on it (Hampel et al., 2021; Sperling et al., 2011). Amyloid beta levels increase monotonically across cognitive status from cognitively normal through clinical AD. High levels of amyloid beta—namely, those meeting threshold criteria for 'amyloid positivity' based on positron emission tomography (PET)—provide differential diagnosis between AD and other dementia subtypes (Dubois et al. 2014; Janssen et al. 2021; Ossenkoppele et al. 2015). Indeed, given the role amyloid is postulated to play in AD pathogenesis, its long prodrome, and non-dementia health conditions that also present with memory problems, there has been a movement to redefine AD as the presence of such brain pathology (Dubois et al., 2014; Sperling et al., 2011).

That said, emerging research suggests tau pathology, even in the absence of amyloid positivity, is associated with worse cognitive performance—an observation not found in persons with amyloid positivity but no tau positivity (Weigand et al., 2020; Weigand, Edwards et al., 2022). However, tau is present in multiple brain diseases and additional work is be needed to accurately use such imaging data to stage individuals along the AD continuum (Weigand, Maass et al., 2022; Vogel et al., 2021). Similarly, presence of transactive response DNA binding protein of 43 kDa (TDP-43) pathology in combination with other brain pathologies significantly increases risk of and rate of progression to dementia (Meneses et al., 2021). The relationship between tau and TDP-43 remains unclear, but some studies have shown that it down-regulates tau expression; it also co-localizes with brain amyloid and tau in AD decedents (Meneses et al., 2021). Additionally, compared to controls, neurons from patients with amyotrophic lateral sclerosis and frontotemporal lobar degeneration (of which frontotemporal dementia is a subgroup) expressed a significantly higher amount of mitochondrial TDP-43. It is also prominent in a more recently termed disease entity, limbic predominant age-related TDP-43 encephalopathy (LATE), in which the brain pathologies include not only TDP-43 proteinopathy but also amyloid and tau pathology (Besser et al., 2020; Nelson et al., 2019). Thus, TDP-43 pathology may play a role in dementia progression or be secondary

reaction (Meneses et al., 2021). Collectively this suggests the high value in studying other AD biomarkers in combination with amyloid.

Specifically, there is a need to understand the population prevalence of preclinical AD biomarker positivity (i.e. biomarker evidence of AD in persons without dementia) in the US to inform efforts to prevent AD, understand its preclinical progression, target prevention efforts to vulnerable groups, and inform policy and healthcare planning, especially given the recent FDA approval of two anti-amyloid immunotherapies and the promise of drugs in development (Alzheimer's Disease Facts and Figures, 2023; Cummings et al. 2021; Gustavsson et al. 2023; Salloway et al., 2022; van Dyk et al., 2023). However, existing estimates of amyloid positivity in persons without dementia are limited because of concerns about the generalizability of the samples that form the basis of those estimates (Brookmeyer et al., 2018; Gustavsson et al., 2023; Jansen et al. 2015, 2022; Parnetti et al., 2019). Reinforcing the concern for lack of generalizability of any one sample to another, a recent systematic review and meta-analysis summarizing amyloid positivity rates across the NIA-AA criteria found evidence of substantial heterogeneity of estimates across samples (Parnetti et al., 2019). Importantly, the Alzheimer's Association has specifically stated that they will not include national-level prevalence estimates of preclinical AD in their annual *Facts and Figures* report until there is a validated calculation of the number of individuals in this stage (Alzheimer's Disease Facts and Figures, 2023).

Participants in deeply-phenotyped samples typically differ across many important characteristics from the population to whom such research is meant to be applied, leading to prevalence or effect estimates that are not readily generalizable from a given sample to the population of interest. For example, our prior work (Gianattasio et al., 2021) has shown that associations between risk factors, cognitive test outcomes, and imaging outcomes differ significantly and meaningfully between one such deeply-phenotyped sample, Alzheimer's Disease Neuroimaging Initiative ([ADNI]; Alzheimer's Disease Neuroimaging Initiative, 2017; Veitch et al., 2019), and a community-based sample, the Atherosclerosis Risk in Communities Study (ARIC). The full potential of deeply-phenotyped samples will not be realized until inferences can validly be extended to broader samples more representative of the true at-risk population. Use of 'transport' estimators—statistical approaches from causal inference that seek to address this challenge of extending inferences from a potentially highly selected sample to broader populations—may allow for improved generalizability of findings from a single sample to other populations, even when the sample is not directly drawn from that larger population. Broader use of these approaches could greatly facilitate research in AD due to the availability of highly-selected, deeply phenotyped samples and challenges of collecting biomarker and imaging data from large, population-based samples. However, while theoretically sound, it remains unclear whether this approach can be validly applied in this context, given the strong and untestable assumptions that are required for validity.

Here, our primary objective is to explore the feasibility and validity of using transport estimators in the context of preclinical AD, and if appropriate to use these transport approaches to estimate the national prevalence of preclinical amyloid and tau positivity among persons without dementia in the United States.

To accomplish this, we aim to first validate whether transportability estimators perform their stated purpose of quantitatively improving external validity by applying them to transport the prevalence of preclinical amyloid positivity in persons who are cognitively normal or who have MCI in a highly selected sample, ADNI, to persons who are cognitively normal or who have MCI in a target community-based sample, ARIC. Comparison of the estimated (transported from ADNI) to actual (measured in ARIC) levels of amyloid positivity, overall and across age, sex, race/ethnicity, and APOE status, will serve as a "validation" or benchmark of our approach. If estimates for preclinical amyloid positivity in ARIC derived from transporting ADNI data mimic those obtained in ARIC, we will take this as evidence that the necessary assumptions underlying these approaches are not substantially violated and will proceed with using transport estimators to estimate national prevalence of multiple dementia-related biomarkers among persons without dementia, including amyloid, tau, and TDP-43. This will be accomplished by handling ADNI and/or ARIC as the sample(s) to which we apply appropriate transport estimators to estimate bounds on the real population prevalence of dementia-related biomarker positivity across age, sex, race/ethnicity, and APOE in a *nationally representative* sample of persons without dementia. These aims are dependent; however, should the validation of the transport estimators fail in the first aim, that would be an important finding unto itself.

5. Main Hypothesis/Study Questions:

Our primary objective is to estimate the national prevalence of preclinical amyloid positivity in the United States.

1) We will estimate preclinical amyloid positivity in ARIC by applying transport estimators in ADNI, to validate whether transportability estimators perform their stated purpose.
2) We will estimate the US prevalence of preclinical amyloid positivity by transporting data from ADNI and/or ARIC to a nationally representative sample, informed by the performance of the transport estimators in our validation aim.
3) We will estimate the US prevalence of preclinical tau and TDP-43 pathology, by transporting data from ADNI to the US population, to complement understanding of AD pathophysiology and biomarkers.

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:
Cross-sectional analysis using ARIC Visit 5 data and ADNI baseline and screening data from ADNI.

<u>Inclusion/Exclusion:</u>

The ARIC sample will be limited to White and Black participants at Visit 5 who participated in the ARIC-PET Amyloid Imaging Study, with non-missing data on age, sex, education, race, and APOE, with normal cognition or mild cognitive impairment.

Similar exclusion/inclusion criteria will be applied to the ADNI screening/baseline visit data, with the ADNI sample restricted to persons with normal cognition and mild cognitive impairment.

Characteristics of Interest:

Amyloid: We previously defined amyloid positivity following convention (Gianattasio et al., 2021), which considers global florbetapir standardized uptake value ratios (SUVRs) based on cortical regions of interest, dichotomized and defined as 'positive' *according to study-specific cutoffs* (1.11 in ADNI, 1.20 in ARIC) (Gottesman et al., 2016; Landau & Jagust, 2015). Although the PET protocols in ADNI and ARIC are very similar, they are not identical; additionally, study-specific cutoffs are used to define PET positivity in the literature. It is not necessarily clear that two different cutpoints in two different studies mean the same thing. For this reason, in addition to using study-specific cutpoints, we will consider also defining positivity using the *same* cutpoint for both studies.

Tau: There are different *approaches* to defining tau positivity as well as different potential *thresholds* for identifying positivity across studies including ADNI (Mishra et al., 2017; Weigand, Maass et al., 2022). A recent review (Weigand, Maass et al., 2022) examines these in detail, with ADNI as a case study where the authors systematically varied methodological decision points. We will discuss these options with experts and co-authors.

TDP-43: Confirmation of limbic predominant age-related TDP-43 encephalopathy (LATE) is only possible in the postmortem brain. However, TDP-43 is accessible in blood and cerebrospinal fluid (Feneberg et al., 2018). Collaborative studies on biomarker development/validation/testing in CSF or plasma, including for TDP-43, are underway in ADNI currently (https://adni.loni.usc.edu/wp-content/themes/freshnews-dev-v2/documents/bio/biomarker%20methods%20and%20tools.pdf) and by others using Simoa assays (e.g., Alvarez-Sanchez et al., 2023; Katisko et al., 2022).

We may consider transport of additional dementia-related biomarkers.

Because of the methodologic approach we are taking, our goal will be to include any covariates that predict the outcome (i.e. amyloid, tau, TDP-43) and/or that we believe may predict sample membership. We will assess this quantitatively as well as substantively based on field knowledge. Variables we expect to *consider* (beyond age, sex, race, and APOE) as either inclusion criteria or covariates to be included in the transport models include:

- Sociodemographic characteristics, e.g.,
    - education,

    - marital status;
- Cognitive status, e.g.,
    - cognitively normal versus MCI,
    - cognitive performance; and
- Clinical characteristics, e.g.,
    - blood pressure,
    - history of hypertension,
    - blood cholesterol and triglycerides.

If there is substantial missingness on important covariates, we will use multiple imputation by chained equations to impute missing data.

Statistical Analyses:

We are proposing a multi-aim project. The methodologic approach undergirding each aim is the same. As described above, these aims begin with a validation / proof of concept exercise consisting of 'transporting' estimated amyloid positivity to ARIC from ADNI (overall and by age, sex, race/ethnicity, and APOE4), followed by scaling those estimates to a nationally representative sample, and possibly extending the approach to another high-value dementia-related biomarkers of interest (tau and/or TDP-43).

The core components required to estimate a population parameter in a target population (e.g., ARIC, the US population) from a nonprobability sample (e.g., ADNI) without bias, stated simply, are 1) you [think you] know what the confounders are and have measured them (exchangeability), all the subgroups characterized by those confounders are in your sample (positivity), and the sample distribution can be adjusted to match the target population with respect to those confounders, assuming they don't already (composition; *vs* consistency or treatment variation irrelevance described when transporting treatment effects from trials) (Mercer et al., 2017).

Aim 1: Transport validation study

We propose to apply the transport estimators in ADNI to produce expected prevalence of preclinical amyloid positivity in ARIC by key exposures/risk correlates, and then compare the expected to actual observed prevalence in ARIC (i.e., a 'known' benchmark).

We will pool the ARIC and ADNI datasets, with an indicator for dataset. We will run unadjusted and adjusted linear regressions to examine associations between each of the independent variables with the outcome and will examine heterogeneity across levels of covariates and independent variables as well as with the dataset indicator. We will assess covariate balance between ADNI and ARIC (see, e.g., Hayes-Larson et al., 2022; Stuart & Rhodes, 2017). Similarity and differences in findings will be summarized in tables and figures.

We will apply several estimator approaches for extending inferences from clinical or otherwise highly selected samples to more generalized or different target populations. These include outcome modeling (e.g., g-computation), inverse odds of sampling weights (IOSW), and doubly-robust weighted least squares (or, alternatively, TMLE) to transport

prevalence estimates from ADNI to the ARIC sample, and compare the transported estimates to those directly estimated in ARIC (Dahabreh et al. 2019; Rudolph et al. 2014; Westreich et al., 2017). For example, to implement IOSW, we develop selection/participation weights to serve as the primary method of handling the differences between ADNI and ARIC. This involves first estimating the propensity that each observation is from ADNI or ARIC, following by calculating weights for ADNI participants (inverse odds of ADNI selection given their covariate profile multiplied by the unconditional odds of participating in ADNI), applying the weights and re-assessing covariate balance and refining the model as needed, and then using weighted ADNI data to estimate prevalence of amyloid positivity in ARIC. The propensity model will also incorporate any nonresponse adjustment and bias correction that has been applied to the reference population (e.g., ARIC, when transporting from ADNI to ARIC).

If we are unable to produce comparable estimates using transport estimators, we will explore whether an imbalanced distribution of unknown and/or unmeasurable confounders or positivity violations drives this finding. If so, we will consider whether comparable estimates can be achieved using transport estimators within a more restricted subpopulation. As a potential additional sensitivity analysis, we will consider examining alternate SUVR cutpoints for defining amyloid positivity, as this has been shown to affect variation by APOE4 and age in ARIC (Gottesman et al., 2016).

If we are able to achieve comparable estimates of amyloid positivity prevalence from transporting ADNI data and direct observation in ARIC, we will proceed to the next two aims and position the paper as focused on these goals. If not, we will write this as a methods paper to share our experience and discuss in detail what might be needed to meet the underlying assumptions of the method.

Aim 2: Estimation of population prevalence of preclinical amyloid positivity in the US
We propose to estimate the US national prevalence of preclinical amyloid positivity by handling ADNI and/or ARIC as the sample(s) to which we apply transport estimators (e.g., IOSW, as above). This will allow us to estimate bounds on the real population prevalence of amyloid positivity across age, sex, race/ethnicity, and APOE in a nationally representative sample. For the nationally representative US sample, we are considering use of NHATS (https://nhats.org), BRFSS (https://www.cdc.gov/brfss/index.html), HRS (https://hrs.isr.umich.edu), and US Census data. The final choice of dataset will be made based on availability of needed variables from the transport estimator that best recovers the ADNI-ARIC transport (aim 1) balanced against information needed to identify characteristics of the subset of older U.S. adults without dementia.

Aim 3: Estimation of population prevalence of preclinical tau and TDP-43 pathology in the US
We propose to further estimate the US prevalence of preclinical tau and TDP-43, by transporting data from ADNI to the US population. ADNI, as in aim 1, would serve as the selected population, and the nationally representative sample would be selected as in aim 2 for our target population. The same transport estimators will be applied here, as before, informed by prior performance and any possible analytic challenges encountered.

Strengths and Limitations

The chief challenge with the use of these transport estimators is meeting their assumptions. In the trial transport literature, consistency, exchangeability over exposure in the 'randomized' sample, and positivity of exposure should hold for well-defined exposures when 'randomized' (i.e., our approach to handling age, sex, race/ethnicity, and APOE4 as 'randomized' in ADNI) (Dahabreh et al., 2020). For estimating a population parameter using a nonprobability, highly selected sample, our main foci are achieving positivity of participation, exchangeability over selection/participation, and correctly specifying a model to replicate the target composition on the confounding variables—some of which may be more difficult in practice. We will engage with our expert collaborators to interrogate these assumptions.

We acknowledge that ARIC itself is not a population-representative sample at the time of Visit 5, given selective attrition, and ARIC-PET was designed to be a study of individuals without dementia. However, it began as a population-representative sample and is one of the few community-based samples with amyloid PET imaging and so remains a reasonable validation target.

Similarly, we focus on preclinical dementia biomarker prevalence (i.e. prevalence among those without dementia). While prevalence of amyloid positivity among persons with dementia is well characterized, prevalence of other dementia-related biomarkers is less well characterized; however, generation of such statistics is beyond the scope of the current proposed paper.

Transport data rely on identification of characteristics that influenced inclusion into the sample. While we cannot know what these are, we can rely on the broad experience of the ARIC investigators and broader epidemiologic field to understand what factors influence participation and continued participation, including reference to the factors identified as important in work on multiply imputing cognition in ARIC (Rawlings et al., 2017).

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/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)?

- 2466_The ARIC-PET Amyloid Imaging Study- Differences in Brain Amyloid deposition by Age, Race, Sex, and ApoE genotype | Rebecca Gottesman
- 3439 & 3493_When are representative samples necessary for generalizability? A comparison between ADNI and ARIC | Gianattasio, Kan Zhang
- 3897_Individual and neighborhood socioeconomic status and elevated brain amyloid: The ARIC-PET study | Sydney Ragland
- 4080_Association Between Mid-Life Social Factors and Estimated Late-Life Amyloid Burden: the Atherosclerosis Risk in Communities (ARI | Renee Groechel
- 3302_The association of blood lipid levels and late-life brain amyloid accumulation | Melinda Power
- 3746_The association between criteria air pollutant exposure and late-life amyloid burden | Erin Bennett

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* 1999.01, 2009.29 and 2017.01**)**

___ 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 http://www.cscc.unc.edu/aric/forms/

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.

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