ARIC Manuscript Proposal #4490

PC Reviewed:07/09/24 **Status: _____** **Priority: 2**

1.a. Full Title: Do plasma biomarkers have additive value beyond age and cognitive domain profiles for predicting incident dementia?

b. Abbreviated Title (Length 26 characters): Plasma biomarkers & dementia

2. Writing Group:
Writing group members: David S Knopman, James R Pike, Yifei Lu, Sheila Burgard, Michael Griswold, B. Gwen Windham, Rebecca F Gottesman, Marilyn S Albert, Keenan A Walker, Kevin J Sullivan, Sevil Yasar, Alden L Gross, Joe Coresh, Priya Palta

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

First author: David Knopman
Department of Neurology
Mayo Clinic
Rochester, MN 55905
Phone: 507 538 1038
Fax: 507 538 6012
E-mail: knopman@mayo.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: Thomas H Mosley
MIND Center
University of Mississippi Medical Center
2500 North State Street
Jackson, MS 39216
Phone: 601-984-2763
Fax: 601-815-3422
Email: tmosley@umsmed.edu

3. Timeline: We will conduct the analysis and draft the manuscript within 6 months of approval.

4. Rationale:

Disease specific biomarkers, such as plasma phosphorylated tau 181 (p-Tau181) and the ratio of amyloid β (Aβ) 42 to Aβ40, provide unique pathological information potentially relevant to etiology. Those biomarkers also provide information about prognosis, but questions remain whether these provide unique information above and beyond other more easily measured

characteristics. Age and cognitive status have a large impact on predicting subsequent decline to dementia in persons who are initially not demented. Biomarkers relevant to later life dementia are also strongly related to age and to the degree of cognitive impairment. Indeed, one of the key characteristics of dementia-related biomarkers is that biomarker levels differ between impaired and unimpaired persons. The question to be addressed with this proposal is: "To what extent do plasma biomarkers – Aβ42/Aβ40, p-Tau181, glial fibrillary acidic protein (GFAP), and neurofilament light (NfL) – provide independent prognostic information about risk for future dementia when cognitive status and age are accounted for?"

In ARIC analyses recently accepted for publication, we found that there is a hierarchy of cognitive domain profiles (all domain impaired > amnestic multidomain > amnestic single domain > non-amnestic single domain cognitive impairment) that distinguished in an ordered way between different levels of risk for incident dementia. The differences in outcomes across the spectrum of domain-specific cognitive impairment was large. Similarly so was the risk for progression to dementia according to age. If the empirically-derived high risk cognitive profiles and age are also related cross-sectionally to plasma biomarkers, it is reasonable to ask whether or not there is added value from plasma biomarkers for predicting incident dementia when cognitive profiles and age are accounted for.

The hypothesis to be tested in the proposed analysis is that plasma biomarkers – specifically Aβ42/Aβ40, p-Tau181, GFAP, and NfL – provide additive value about incident dementia beyond age and cognitive status in non-demented persons. Previously, Lu and colleagues (In Press) conducted a similar analysis among ARIC participants classified as cognitively normal (CN) or as having mild cognitive impairment (MCI). Associations were seen for all plasma biomarkers, but the point estimates were larger in CN than in MCI.

The alternative hypothesis is that the plasma biomarkers provide no or insubstantial additional prognostic information if age and domain-specific cognitive status are available. While plasma biomarkers might be additive with categorical MCI or CN diagnoses, it may be because those with abnormal plasma biomarkers are more likely to be older and to have more aggressive cognitive domain-specific subtypes.

A secondary aim is to examine differences in plasma biomarker types. In addition to having practical value, clarification of the added value of plasma biomarkers also sheds light on whether Alzheimer's disease (AD)-specific processes (as proxied by AD-specific biomarkers p-Tau181and Aβ42/Aβ40) accelerate decline compared to non-AD processes, and whether the extent of non-specific neurodegeneration (as proxied by NfL or GFAP, non-specific plasma biomarkers) predicts more rapid decline. Cognitive impairment implies underlying neurodegeneration, whether from a degenerative disease or cerebrovascular disease. Biomarkers that are not specific to a single disease might have a stronger relationship to cognitively-impactful neurodegeneration compared to a disease-specific biomarkers because many etiologies separate from AD may contribute to the neurodegeneration (Kawas, et al., 2015; Power, et al., 2018; Schneider, Arvanitakis, Bang, & Bennett, 2007; White, et al., 2016). An AD specific biomarker may have lower positive predictive value than a nonspecific biomarker because the latter better accounts for the totality of neurodegenerative causes. On the other hand, if one particular disease, such as AD, has a uniquely accelerated likelihood of rapid decline, the disease specific biomarker might have strong positive predictive value.

5. Main Hypothesis / Study Questions:

Principal Question: What is the additive prognostic value of plasma biomarkers of AD and neurodegeneration among participants who were diagnosed as dementia-free during a clinic-based assessment at ARIC Visit 5 (2011-13)?

Primary Hypotheses:

1. Dementia-free participants at ARIC Visit 5 with lower levels of Aβ42/Aβ40 and higher levels of p-Tau181, NfL, and GFAP will exhibit a higher rate of incident dementia, even after adjusting for age and domain-specific cognitive status.
2. Predictive models that incorporate plasma biomarkers will have greater accuracy than models that only use age and domain-specific cognitive status.

Secondary Hypothesis:

1. Biomarkers that are more specific for AD (Aβ42/Aβ40, p-Tau181) will have a smaller association with incident dementia than biomarkers of neurodegeneration (NfL, GFAP).

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 observational study of 1,614 community-living older adults with dementia surveillance between ARIC Visit 5 (2011-13) and Visit 8 (2020). Data from Visit 9 (2021-2022) will be integrated into the analysis if available before the manuscript is completed.

Exclusion Criteria: The design and selection for this study is based on participants who previously enrolled in a neuroimaging substudy. A subsample of participants from Visit 5 were screened for eligibility for the substudy (Knopman, et al., 2015). Participants were eligible if they had no contraindications and previously participated in an ARIC brain magnetic resonance imaging (MRI) study (Mosley, et al., 2005), had evidence of cognitive impairment, or were part of a random sample of participants without cognitive impairment. Among participants who completed a valid MRI scan at Visit 5 (N=1977), a subset (N=1826) had analyzable plasma samples. Participants for whom cognitive domain Z scores could not be generated due to missing information (N=42) will be excluded from this subset. Participants who are not White or Black and participants in Maryland or Minnesota who are not White will be removed due to small sample sizes within each subgroup (N=7). Participants whose cognitive status could not be determined (N=2) or who were diagnosed with dementia at or before Visit 5 (N=161) will also be excluded.

Outcome:

Incident Dementia (Level 3). The primary outcome will be time until incident dementia. Dementia was ascertained utilizing an established protocol (Knopman, et al., 2016) based on the National Institute on Aging-Alzheimer's Association criteria (Albert, et al., 2011; McKhann, et al., 2011) and the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013). A diagnosis of CN, MCI, or dementia was rendered based on a

comprehensive, in-person neurocognitive examination administered at Visit 5, prior cognitive assessments performed at Visit 2 and Visit 4, and an informant interview conducted at Visit 5. A computer algorithm generated a preliminary determination which was validated by an expert panel of clinicians and neuropsychologists.

The neurocognitive examination at Visit 5 included the Mini Mental State Exam (MMSE) (Folstein, Folstein, & McHugh, 1975), Blessed scale (Blessed, Tomlinson, & Roth, 1968; Blessed, Tomlinson, & Roth, 1988), Digit Span Backwards (DSB) (Wechsler, 1987), Boston Naming Test (BNT) (Williams, Mack, & Henderson, 1989), Word Fluency Test (WFT) (Benton & Hamsher, 1976), Animal Naming Score (ANS) (Benton & Hamsher, 1976), Digit Symbol Substitution (DSS) (Wechsler, 1987), Trail Making Tests A (TMTA) and B (TMTB) (Reitan, 1958), Incidental Learning (ILR) (Ryan & Lopez, 2001), Logical Memory Test (LMT) (Wechsler, 1987), and the Delayed Word Recall (DWR) (Knopman & Ryberg, 1989). The examinations at Visit 2 and Visit 4 were limited to the WFT, DSS, and DWR. The informant interview at Visit 5 comprised the Clinical Dementia Rating (CDR) (Hughes, Berg, Danziger, Coben, & Martin, 1982), Functional Activities Questionnaire (FAQ) (Pfeffer, Kurosaki, Harrah, Chance, & Filos, 1982), and the Neuropsychiatric Inventory (NPI-Q) (Cummings, et al., 1994; Kaufer, et al., 2000). When an informant could not be identified and interviewed, the CDR and FAQ was administered directly to the participant.

The in-person neurocognitive examination protocol and informant interview was repeated at Visit 6 and Visit 7. The same protocol was initiated in January 2020 for Visit 8 but stopped in March 2020 due to the coronavirus pandemic. A modified phone-based protocol was implemented between July and December 2020. The phone-based battery administered to the participant included the 10-item orientation subscale from the MMSE, the Blessed scale, the DSB, the ANS, an adaptation of the WFT limited to the letters F and A, and two newly adopted tests—the oral version of the TMTA and TMTB (Ricker & Axelrod, 1994) and the Consortium to Establish a Registry for Alzheimer's Disease Word List (CERAD) (Morris, Mohs, Rogers, Fillenbaum, & Heyman, 1988). The informant interview procedures were unchanged.

Among participants who did not complete the in-person or phone-based neurocognitive examination after Visit 5, a classification of dementia or dementia-free was assigned based on the Telephone Interview for Cognitive Status-Modified (TICSm) (Brandt, Spencer, & Folstein, 1988; Knopman, et al., 2010; Welsh, Breitner, & Magruder-Habib, 1993) administered to the participant and adjusted for education, an informant interview comprising the CDR and FAQ, an Ascertain Dementia Eight-Item Informant Questionnaire (AD8) (Galvin, et al., 2005), or a phone-based Six-Item Cognitive Screener (SIS) (Callahan, Unverzagt, Hui, Perkins, & Hendrie, 2002) administered to the participant. If the participant was lost to follow-up or deceased, prior hospitalization discharge codes as well as diagnostic codes from death certificates were used to identify incident dementia (Alonso, et al., 2009; Schneider, et al., 2013). When dementia was identified through an informant interview, hospitalization record, or death certificate, the date of onset was estimated to occur 180 days before the documented incident or interview. Participants without a dementia diagnosis from any source were censored at the latest available assessment, interview, or hospitalization record. Deceased participants without dementia were censored 180 days prior to the date of death. In the absence of information from these sources, censoring occurred on December 31st, 2020.

Primary Predictors:

Plasma Biomarkers. At Visit 5, ethylenediaminetetraacetic acid whole-blood samples were collected and placed in an ice bath until plasma was separated by centrifugation. Plasma was divided into aliquots in 1.5-mL tubes, frozen, and stored in -80°C freezers. Plasma samples were analyzed by the Advanced Research and Diagnostic Laboratory at the University of Minnesota. Plasma was thawed immediately before being aliquoted, plated, and analyzed by HD-X instruments that measured multiple biomarkers simultaneously using the single molecule array technology (Simoa) Neurology 4-Plex E (N4PE) from Quanterix (Billerica, MA). Simoa is an ultrasensitive, digital immunoassay platform that can detect proteins in plasma at sub-femtomolar concentrations. (Rissin, et al., 2010; Wilson, et al., 2016) The N4PE assay included measures of Aβ40 and Aβ42 which quantified the accumulation of extracellular amyloid plaques, NfL which quantified axonal injury, and GFAP which quantified inflammation and astrocytic activation. A singleplex assay for p-Tau181 measured intracellular neurofibrillary tangles. Precision, detection limits, and test-retest reliability of the Quanterix Simoa platform in the ARIC cohort have been previously reported (Lu, et al., In Press).

Before examining the prognostic value of plasma biomarkers, the ratio of Aβ42 to Aβ40 will be calculated and measures of p-Tau181, NfL, and GFAP will be base 2 log transformed. Thresholds for high versus low levels of each plasma biomarker will be identified based on the Youden index (Pierce, 1884; Youden, 1950) from an analysis of participants at Visit 5 who were classified as unimpaired (CN) or impaired (MCI or dementia). Predictors of incident dementia that will be tested include the following.

1. Continuous measures of Aβ42/Aβ40, log2 p-Tau181, log2 NfL, and log2 GFAP.
2. Binary classifications (high versus low) of each plasma biomarker created by dichotomizing continuous measures at biomarker-specific thresholds defined based on the Youden index.

Cognitive Domain Z Scores. A confirmatory factor analysis (CFA) (Gross, et al., 2015) identified three cognitive domains at Visit 5—(1) a language domain measured by the BNT, WFT, and ANS, (2) an executive function domain comprising the DSS, TMTA, and TMTB, and (3) a memory domain derived from the ILR, LMT, and DWR. Factor scores for each domain were generated for each participant who completed one or more cognitive tests included in the domain. A subsample (N=2609) of participants were selected for developing regression models to define a normative range who did not have any of the following exclusion criteria.

1. Self-reported race other than white or black
2. Unknown level of education
3. Apolipoprotein ε4 alleles detected from blood samples analyzed (Hsu, et al., 2005) using the TaqMan assay (Applied Biosystems, Foster City, CA)
4. Adjudicated diagnosis of MCI or dementia at Visit 5
5. Neurological disease detected by the NPI-Q at Visit 5
6. Use of cholinomimetics at Visit 5
7. A score below 22 on the MMSE at Visit 5
8. Possible clinical depression as determined by the Center for Epidemiological Studies Depression scale (Radloff, 1977) at Visit 5

9. Wide Range Achievement Test 3 (WRAT3) (Wilkinson, 1993) less than 10 or missing at Visit 5
10. Prior hospitalization for stroke at or before Visit 5
11. Significant decline in the WFT, DSS, and DWR measured at Visits 2, 4, and 5
12. Impairment detected by the TICSm, CDR, FAQ, SIS, or AD8 at or before Visit 6
13. Self-reported memory problems at or before Visit 6
14. Hospitalization discharge code for dementia at or before Visit 6

Using this subsample, race-stratified linear regression models were fit to the data and used to calculate estimated factor scores for each participant for the cognitive domains of language, executive function, and memory based on each individuals education, age, and WRAT3 score. Cognitive domain Z scores were calculated for each participant as the difference between the CFA generated factor score and the regression-based estimated factor score divided by the root-mean-squared error from the race-specific linear regression model. The resulting Z score will be used to test the following predictors of incident dementia.

1. Continuous Z scores for the cognitive domains of language, executive function, or memory.
2. Binary classifications (normal versus abnormal) of each cognitive domain created by dichotomizing the Z score at -1.5.
3. A nominal predictor denoting (a) no abnormal domains, (b) abnormal memory domain only, (c) abnormal language domain only, (d) abnormal executive function domain only, (e) abnormal language and executive function domains (multidomain non-amnestic impairment), (f) abnormal memory domain plus abnormal language or executive function domains (multidomain amnestic impairment), or (g) abnormal memory, language, and executive function domains.

Covariates:

Multiple time-invariant confounders will be incorporated into the analysis. Date of birth, race, sex, and education (less than high school, high school or equivalent, or greater than high school) were obtained via self-report. Date of birth will be used to calculate age at Visit 5. Race will be adapted into a categorical classification of field center and race (Minnesota-White, Maryland-White, North Carolina-White, North Carolina-Black, and Mississippi-Black).

During clinic-based examinations, body weight was measured to the nearest 0.1 kilogram and height was recorded to the nearest centimeter. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Creatinine was measured using a modified kinetic Jaffé method (Coresh, et al., 2002; Levey, et al., 2006). Cystatin C was measured using a particle-enhanced immunonephelometric assay (Siemens Healthcare Diagnostics, Tarrytown, NY) (Parrinello, et al., 2015). A creatinine-cystatin C estimated glomerular filtration rate (eGFR) was generated using 2021 Chronic Kidney Disease Epidemiology Collaboration equations (Inker, et al., 2021). The presence of APOE ε4 alleles was ascertained by the TaqMan assay (Applied Biosystems, Foster City, CA) (Blair, et al., 2005).

Statistical Analysis:

All analyses will be conducted in SAS (version 9.4). To mitigate bias introduced by selecting ARIC participants who previously enrolled in a neuroimaging substudy, sampling weights were computed as the product of inverse sampling fractions and the inverse probability of enrollment (Knopman, et al., 2015). These weights will be applied in most analyses.

Unweighted descriptive statistics of participant characteristics stratified by subsequent dementia or high versus low levels of each plasma biomarker will be examined utilizing $\chi 2$ tests, t tests, and Cochran-Armitage trend tests. A weighted matrix will depict Pearson correlation coefficients between (1) age, (2) cognitive domain z-scores, and (3) plasma biomarkers. A second weighted matrix will depict Spearman correlation coefficients between (1) median age, (2) baseline cognitive diagnosis of CN or MCI, (3) single domain cognitive impairment, (4) multidomain cognitive impairment, and (5) high levels of a single plasma biomarker. Weighted cumulative incidence curves that account for the competing risk of death will be generated for each plasma biomarker in the full sample and subsamples defined by (1) median age, (2) race, (3) sex, (4) education, (5) the presence of APOE ε4 alleles, (6) cognitive diagnosis, (7) single domain cognitive impairment, and (8) multidomain cognitive impairment.

Weighted Poisson regression models with robust error variance will be used to estimate crude, unadjusted incidence rates of dementia with 95% confidence intervals (CI) per 1000 person-years for (1) median age, (2) cognitive diagnosis, (3) single domain cognitive impairment, (4) multidomain cognitive impairment, and (5) high levels of a single plasma biomarker. Incidence rates will also be estimated from a model that integrates sex, education, race-center, the presence of APOE ε4 alleles, BMI, and eGFR as time-invariant covariates. A final model will estimate incidence rates associated with high levels of each plasma biomarker after additionally adjusting for age and domain-specific cognitive status. Weighted unadjusted and covariate-adjusted hazard ratios will be generated from Fine-Gray models (1999) that account for the competing risk of death. Supremum tests will be performed and Schoenfeld residuals will be inspected to verify the proportional hazards assumption prior to model fitting. The assumption of linearity will be evaluated by examining Martingale residuals.

In exploratory analyses, the covariate-adjusted Fine-Gray model will be expanded to test for multiplicative and additive interactions (Knol & VanderWeele, 2012; VanderWeele & Knol, 2014) between each biomarker and (1) median age, (2) race, (3) sex, (4) education, (5) the presence of APOE ε4 alleles, (6) cognitive diagnosis, (7) single domain cognitive impairment, and (8) multidomain cognitive impairment. Statistical significance for interaction will be defined as $P < .05$. Subsequent stratified analyses will examine effect modification by (1) median age, (2) race, (3) sex, (4) education, (5) the presence of APOE ε4 alleles, (6) cognitive diagnosis, (7) single domain cognitive impairment, and (8) multidomain cognitive impairment.

Weighted time-dependent receiver operator characteristic (ROC) curves and the corresponding area under the curve (AUC) will be generated from a Fine-Gray competing risk model. Curves will be visualized at 2, 4, 6, and 8 years after the baseline for the following models.

- Model 1: Age
- Model 2: Cognitive domain z-scores
- Model 3: Aβ42/Aβ40
- Model 4: p-Tau181
- Model 5: NfL

- Model 6: GFAP
- Model 7: All four biomarkers
- Model 8: Age and cognitive domain z-scores
- Model 9: Age and Aβ42/Aβ40
- Model 10: Age and p-Tau181
- Model 11: Age and NfL
- Model 12: Age and GFAP
- Model 13: Age and all four biomarkers
- Model 14: Cognitive domain z-scores and Aβ42/Aβ40
- Model 15: Cognitive domain z-scores and p-Tau181
- Model 16: Cognitive domain z-scores and NfL
- Model 17: Cognitive domain z-scores and GFAP
- Model 18: Cognitive domain z-scores and all four biomarkers
- Model 19: Age, cognitive domain z-scores, and Aβ42/Aβ40
- Model 20: Age, cognitive domain z-scores, and p-Tau181
- Model 21: Age, cognitive domain z-scores, and NfL
- Model 22: Age, cognitive domain z-scores, and GFAP
- Model 23: Age, cognitive domain z-scores, and all four biomarkers

An accompanying matrix will depict the difference in AUCs between each model along with 95% CIs generated via bootstrapping. A separate matrix will be prepared for 2, 4, 6, and 8 years after the baseline. In supplemental analyses, time-dependent AUC and ROC curves will be generated for each biomarker separately and collectively in subsamples defined by (1) median age, (2) race, (3) sex, (4) education, (5) the presence of APOE ε4 alleles, (6) cognitive diagnosis, (7) single domain cognitive impairment, and (8) multidomain cognitive impairment.

Methodologic Limitations:

This investigation has several limitations. Although plasma biomarkers of AD and neurodegeneration have the potential to be cost-effective, non-invasive measurements with prognostic value to patients and clinicians, they are less precise than cerebrospinal fluid biomarkers due to extra-cerebral production and levels (Hansson, et al., 2022; Jack, et al., 2018; Tsiknia, et al., 2022). Moreover, among the existing platforms for analyzing plasma, Quanterix Simoa is known to be less accurate for certain biomarkers such as p-Tau181 (Ashton, et al., 2023; Bayoumy, et al., 2021). Consequently, improvements in predictive accuracy may be underestimated in the proposed analysis. It is also important to acknowledge that the analytic sample is restricted to a subset of participants from the ARIC study who survived to late-life and were eligible for a MRI substudy. Although selection bias will be mitigated through the use of sampling weights, generalization to a community-dwelling population may be limited.

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 (APOE genotype only)

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"? ____ 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)?

Knopman DS, Pike JR, Gottesman RF, Sharrett AR, Windham BG, Mosley TH, Sullivan KJ, Albert MS, Walker KA, Yasar S, Burgard S, Li D, Gross AL. Patterns of cognitive domain abnormalities enhance discrimination of dementia risk prediction: The ARIC study. Alzheimer's & Dementia. 2024. In Press.

Lu Y, Pike JR, Chen J, Walker K, Sullivan KJ, Thyagarajan B, Mielke MM, Lutsey PL, Knopman DS, Gottesman RF, Sharrett AR, Coresh J, Mosley TH, Palta P. Changes in Alzheimer's disease blood biomarkers and associations with incident all-cause dementia. JAMA. 2024. In Press.

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* _____)

___ 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/

This proposal will use data from the following ancillary studies: 2008.06 (ARIC-NCS)

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.

13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript.
____ Yes __X__ No

14. Relevant References:

Albert, M., DeKosky, S., Dickson, D., Dubois, B., Feldman, H., Fox, N., . . . Phelps, C. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia, 7*(3), 270-279. doi:10.1016/j.jalz.2011.03.008

Alonso, A., Mosley, T. J., Gottesman, R., Catellier, D., Sharrett, A., & Coresh, J. (2009). Risk of dementia hospitalisation associated with cardiovascular risk factors in midlife and older age: the Atherosclerosis Risk in Communities (ARIC) Study. *Journal of Neurology, Neurosurgery, and Psychiatry, 80*(11), 1194-1201. doi:10.1136/jnnp.2009.176818

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders, DSM-5.* Washington, DC.

Ashton, N., Puig-Pijoan, A., Milà-Alomà, M., Fernández-Lebrero, A., García-Escobar, G., González-Ortiz, F., . . . Suárez-Calvet, M. (2023). Plasma and CSF biomarkers in a memory clinic: Head-to-head comparison of phosphorylated tau immunoassays. *Alzheimer's & Dementia*, *19*(5), 1913-1924. doi:10.1002/alz.12841

Bayoumy, S., Verberk, I., den Dulk, B., Hussainali, Z., Zwan, M., van der Flier, W., . . . Teunissen, C. (2021). Clinical and analytical comparison of six Simoa assays for plasma P-tau isoforms P-tau181, P-tau217, and P-tau231. *Alzheimer's Research & Therapy, 131*(1), 198. doi:10.1186/s13195-021-00939-9

Benton, A., & Hamsher, K. (1976). *Multilingual Aphasia Examination.* Iowa City, IA: University of Iowa.

Blessed, G., Tomlinson, B., & Roth, M. (1968). The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. *The British Journal of Psychiatry, 114*(512), 797-811. doi:10.1192/bjp.114.512.797

Blessed, G., Tomlinson, B., & Roth, M. (1988). Blessed-Roth Dementia Scale. *Psychopharmacology Bulletin, 24*(4), 705-708.

Brandt, J., Spencer, M., & Folstein, M. (1988). The Telephone Interview for Cognitive Status. *Neuropsychiatry, Neuropsychology, & Behavioral Neurology, 1*(2), 111-117.

Callahan, C., Unverzagt, F., Hui, S., Perkins, A., & Hendrie, H. (2002). Six-item screener to identify cognitive impairment among potential subjects for clinical research. *Medical Care, 40*(9), 771-781. doi:10.1097/00005650-200209000-00007

Coresh, J., Astor, B., McQuillan, G., Kusek, J., Greene, T., Van Lente, F., & Levey, A. (2002). Calibration and random variation of the serum creatinine assay as critical elements of using equations to estimate glomerular filtration rate. *American Journal of Kidney Diseases, 39*(5), 920-929. doi:10.1053/ajkd.2002.32765

Cummings, J., Mega, M., Gray, K., Rosenberg-Thompson, S., Carusi, D., & Gornbein, J. (1994). The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology, 44*(12), 2308-2314. doi:10.1212/wnl.44.12.2308

Fine, J., & Gray, R. (1999). A proportional hazards model for the subdistribution of a competing risk. *Journal of the American Statistical Association, 94*(446), 496-509. doi:10.1080/01621459.1999.10474144

Folstein, M., Folstein, S., & McHugh, P. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12*(3), 189-198. doi:10.1016/0022-3956(75)90026-6

Galvin, J., Roe, C., Powlishta, K., Coats, M., Muich, S., Grant, E., . . . Morris, J. (2005). The AD8: a brief informant interview to detect dementia. *Neurology, 65*(4), 559-564. doi:10.1212/01.wnl.0000172958.95282.2a

Gross, A., Power, M., Albert, M., Deal, J., Gottesman, R., Griswold, M., . . . Bandeen-Roche, K. (2015). Application of latent variable methods to the study of cognitive decline when tests change over time. *Epidemiology, 26*(6), 878-887. doi:10.1097/EDE.0000000000000379

Hansson, O., Edelmayer, R., Boxer, A., Carrillo, M., Mielke, M., Rabinovici, G., . . . Teunissen, C. (2022). The Alzheimer's Association appropriate use recommendations for blood biomarkers in Alzheimer's disease. *Alzheimer's & Dementia, 18*(12), 2669-2686. doi:10.1002/alz.12756

Hsu, C., Kao, W., Coresh, J., Pankow, J., Marsh-Manzi, J., Boerwinkle, E., & Bray, M. (2005). Apolipoprotein E and progression of chronic kidney disease. *JAMA, 293*(23), 2892-2899. doi:10.1001/jama.293.23.2892

Hughes, C., Berg, L., Danziger, W., Coben, L., & Martin, R. (1982). A new clinical scale for the staging of dementia. *The British Journal of Psychiatry, 140*, 566-572. doi:10.1192/bjp.140.6.566

Inker, L., Eneanya, N., Coresh, J., Tighiouart, H., Wang, D., Sang, Y., . . . Collaboration, C. K. (2021). New creatinine- and cystatin c-based equations to estimate GFR without race. *New England Journal of Medicine, 385*(19), 1737-1749. doi:10.1056/NEJMoa2102953

Jack, C. J., Bennett, D., Blennow, K., Carrillo, M., Dunn, B., Haeberlein, S., . . . Sperling, R. (2018). NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimer's & Dementia, 14*(4), 535-562. doi:10.1016/j.jalz.2018.02.018

Kaufer, D., Cummings, J., Ketchel, P., Smith, V., MacMillan, A., Shelley, T., . . . DeKosky, S. (2000). Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. *The Journal of Neuropsychiatry and Clinical Neurosciences, 12*(2), 233-239. doi:10.1176/jnp.12.2.233

Kawas, C., Kim, R., Sonnen, J., Bullain, S., Trieu, T., & Corrada, M. (2015). Multiple pathologies are common and related to dementia in the oldest-old: The 90+ Study. *Neurology, 85*(6), 535-542. doi:10.1212/WNL.0000000000001831

Knol, M., & VanderWeele, T. (2012). Recommendations for presenting analyses of effect modification and interaction. *International Journal of Epidemiology, 41*(2), 514-520. doi:10.1093/ije/dyr218

Knopman, D., & Ryberg, S. (1989). A verbal memory test with high predictive accuracy for dementia of the Alzheimer type. *Archives of Neurology, 46*(2), 141-145. doi:10.1001/archneur.1989.00520380041011

Knopman, D., Gottesman, R., Sharrett, A., Wruck, L., Windham, B., Coker, L., . . . Mosley, T. J. (2016). Mild cognitive impairment and dementia prevalence: The Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS). *Alzheimer's & Dementia (Amsterdam, Netherlands), 2*, 1-11. doi:10.1016/j.dadm.2015.12.002

Knopman, D., Griswold, M., Lirette, S., Gottesman, R., Kantarci, K., Sharrett, A., . . . Investigators, A. N. (2015). Vascular imaging abnormalities and cognition: mediation by cortical volume in nondemented individuals: Atherosclerosis Risk in Communities-Neurocognitive Study. *Stroke, 46*(2), 433-440. doi:10.1161/STROKEAHA.114.007847

Knopman, D., Roberts, R., Geda, Y., Pankratz, V., Christianson, T., Petersen, R., & Rocca, W. (2010). Validation of the telephone interview for cognitive status-modified in subjects with normal cognition, mild cognitive impairment, or dementia. *Neuroepidemiology, 34*(1), 34-42. doi:10.1159/000255464

Levey, A., Coresh, J., Greene, T., Stevens, L., Zhang, Y., Hendriksen, S., . . . Collaboration, C. K. (2006). Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Annals of Internal Medicine, 145*(4), 247-254. doi:10.7326/0003-4819-145-4-200608150-00004

Lu, Y., Pike, J., Chen, J., Walker, K., Sullivan, K., Thyagarajan, B., . . . Palta, P. (In Press). Changes in Alzheimer's disease blood biomarkers and associations with incident all-cause dementia. *JAMA*.

McKhann, G., Knopman, D., Chertkow, H., Hyman, B., Jack, C. J., Kawas, C., . . . Phelps, C. (2011). The diagnosis of dementia due to Alzheimer’s disease: recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease. *Alzheimer's & Dementia, 7*(3), 263-269. doi:10.1016/j.jalz.2011.03.005

Morris, J., Mohs, R., Rogers, H., Fillenbaum, G., & Heyman, A. (1988). Consortium to establish a registry for Alzheimer's disease (CERAD) clinical and neuropsychological assessment of Alzheimer's disease. *Psychopharmacology Bulletin, 24*(4), 641-652.

Mosley, T. J., Knopman, D., Catellier, D., Bryan, N., Hutchinson, R., Grothues, C., . . . Szklo, M. (2005). Cerebral MRI findings and cognitive functioning: the Atherosclerosis Risk in Communities study. *Neurology, 64*(12), 2056-2062. doi:10.1212/01.WNL.0000165985.97397.88

Parrinello, C., Grams, M., Couper, D., Ballantyne, C., Hoogeveen, R., Eckfeldt, J., . . . Coresh, J. (2015). Recalibration of blood analytes over 25 years in the Atherosclerosis Risk in

Communities Study: impact of recalibration on chronic kidney disease prevalence and incidence. *Clinical Chemistry, 61*(7), 938-947. doi:10.1373/clinchem.2015.238873
Pfeffer, R., Kurosaki, T., Harrah, C. J., Chance, J., & Filos, S. (1982). Measurement of functional activities in older adults in the community. *Journal of Gerontology, 37*(3), 323-329. doi:10.1093/geronj/37.3.323
Pierce, C. (1884). The numerical measure of the success of predictions. *Science, 4*(93), 453-454. doi:10.1126/science.ns-4.93.453.b
Power, M., Mormino, E., Soldan, A., James, B., Yu, L., Armstrong, N., . . . Schneider, J. (2018). Combined neuropathological pathways account for age-related risk of dementia. *Annals of Neurology, 84*(1), 10-22. doi:10.1002/ana.25246
Radloff, L. (1977). The CES-D Scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement, 1*(3), 385-401. doi:10.1177/014662167700100306
Reitan, R. (1958). Validity of the trail making test as an indicator of organic brain damage. *Perceptual and Motor Skills, 8*, 271-276. doi:10.2466/PMS.8.7.271-276
Ricker, J., & Axelrod, B. (1994). Analysis of an oral paradigm for the trail making test. *Assessment, 1*(1), 47-52. doi:10.1177/1073191194001001007
Rissin, D., Kan, C., Campbell, T., Howes, S., Fournier, D., Song, L., . . . Duffy, D. (2010). Single-molecule enzyme-linked immunosorbent assay detects serum proteins at subfemtomolar concentrations. *Nature Biotechnology, 28*(6), 595-599. doi:10.1038/nbt.1641
Ryan, J., & Lopez, S. (2001). Wechsler adult intelligence scale-III. In W. Dorfman, & M. Hersen, *Understanding psychological assessment. Perspectives on individual differences.* New York, NY: Kluwer Academic/Plenum Publishers.
Schneider, A., Gottesman, R., Mosley, T., Alonso, A., Knopman, D., Coresh, J., . . . Selvin, E. (2013). Cognition and incident dementia hospitalization: results from the Atherosclerosis Risk in Communities Study. *Neuroepidemiology, 40*(2), 117-124. doi:10.1159/000342308
Schneider, J., Arvanitakis, Z., Bang, W., & Bennett, D. (2007). Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Neurology, 69*(24), 2197-2204. doi:10.1212/01.wnl.0000271090.28148.24
Tsiknia, A., Edland, S., Sundermann, E., Reas, E., Brewer, J., Galasko, D., . . . ADNI. (2022). Sex differences in plasma p-tau181 associations with Alzheimer's disease biomarkers, cognitive decline, and clinical progression. *Molecular Psychiatry, 27*(10), 4314-4322. doi:10.1038/s41380-022-01675-8
VanderWeele, T., & Knol, M. (2014). A tutorial on interaction. *Epidemiologic Methods, 3*(1), 33-72. doi:10.1515/em-2013-0005
Wechsler, D. (1987). *Wechsler Memory Scale-Revised.* San Antonio, Texas: Psychological Corporation.
Welsh, K., Breitner, J., & Magruder-Habib, K. (1993). Detection of dementia in the elderly using telephone screening of cognitive status. *Neuropsychiatry, Neuropsychology, Behavioral Neurology, 6*(2), 103-110.
White, L., Edland, S., Hemmy, L., Montine, K., Zarow, C., Sonnen, J., . . . Montine, T. (2016). Neuropathologic comorbidity and cognitive impairment in the Nun and Honolulu-Asia Aging Studies. *Neurology, 86*(11), 1000-1008. doi:10.1212/WNL.0000000000002480

Wilkinson, G. (1993). *Wide Range Achievement Test: WRAT3*. Wilmington, DE : Wide Range, Inc.

Williams, B., Mack, W., & Henderson, V. (1989). Boston naming test in Alzheimer's disease. *Neuropsychologia, 27*(8), 1073-1079. doi:10.1016/0028-3932(89)90186-3

Wilson, D., Rissin, D., Kan, C., Fournier, D., Piech, T., Campbell, T., . . . Duffy, D. (2016). The Simoa HD-1 Analyzer: a novel fully automated digital immunoassay analyzer with single-molecule sensitivity and multiplexing. *Journal of Laboratory Automation, 21*(4), 533-547. doi:10.1177/2211068215589580

Youden, W. (1950). Index for rating diagnostic tests. *Cancer, 3*(1), 32-35. doi:10.1002/1097-0142(1950)3:1<32::AID-CNCR2820030106>3.0.CO;2-3