ARIC Manuscript Proposal #3763

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SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: The inflammatory plasma proteome and incident dementia: The ARIC Study

b. Abbreviated Title (Length 26 characters): Inflammation and dementia

2. Writing Group:

Writing group members: Keenan A. Walker (first author); Jingsha Chen; Pascal Schlosser; Myriam Fornage; Chinenye Ugoji; Adrienne Tin; Ron C. Hoogeveen, Kevin Sullivan; Peter Ganz; Rebecca F. Gottesman; Thomas H. Mosley; Eric Boerwinkle; Christie M. Ballantyne; Josef Coresh; others welcome

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

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3. Timeline: completion of all analyses is expected to take 6-18 months; manuscript submission will likely occur in the summer or fall of 2021.

4. Rationale:

Systemic inflammation is a biological process that occurs with increasing age and as a result of clinical and subclinical disease, tissue injury, and social and environmental factors.[1–3] Systemic inflammation has been causally implicated in age-related conditions, such as cardiovascular disease, and drugs targeting inflammatory protein expression have proven successful in reducing disease risk.[4] Over the past three decades, observational and pharmaco-epidemiological has provided support for the relevance of systemic inflammation in the development of dementia, particularly dementia resulting from Alzheimer's disease.[5–8] Our group and others have demonstrated that individuals with high levels of inflammatory proteins in middle adulthood are at greater risk for cognitive decline,[9] incident mild cognitive impairment,[10] late-life atrophy in regions vulnerable to AD pathology,[11,12] white matter dysfunction,[13,14] and cerebrovascular disease.[15,16] Consistent with these reports are studies which show that individuals who take anti-inflammatory drugs (e.g., NSAIDS and TNF-alpha blockers) for extended periods during midlife are at reduced risk for developing dementia.[8,17,18] In spite of these findings, clinical trials conducted on prodromal and early AD patients to reduce dementia risk using anti-inflammatory (NSAIDS, aspirin, and steroids) have been negative.[19–21] The above findings highlight a potential role for inflammation in AD, but underscore the need for additional insights regarding the role of timing, disease stage, and the diversity of relevant molecular pathways.

Few studies have used a data-driven approach to identify biologically-relevant networks of inflammatory proteins, and even fewer have examined how these protein networks relate to dementia risk.[1,22–24] We hypothesize that multiple networks of highly connected inflammatory proteins exist, each network with one or more unique hub protein(s), upstream regulator(s), and cell-type(s) of origin (monocytes, Th1/Th17 lymphocytes). We propose to conduct an in-depth characterization of the role of systemic inflammation in dementia risk. As part of this analysis, we will use protein measurements from ARIC visit 3 and visit 5 SomaScan v.4 platforms to identify networks of inflammatory proteins, henceforth referred to as inflammatory protein networks (IPNs). We will relate quantitative measures of IPN expression to dementia risk and cognitive decline, and determine the replicability of these IPNs in external cohorts with similar SomaScan proteomic measurements. To determine whether dementia-associated IPNs are causally implicated in AD risk or the emergence of AD endophenotypes (e.g, CSF/PET amyloid and tau levels) we will use a two-sample Mendelian randomization or polygenic risk score approach to determine the genetic overlap between protein quantitative trait loci for IPN expression and traits of interest (e.g., AD and AD biomarkers). In addition, we will use publicly available gene expression databases (e.g., GTEx) to determine the tissue(s) and immune cells most strongly enriched for IPN pQTLs.

The current analyses build on the results of our recent manuscript "Large-scale plasma proteomic analysis identifies proteins and pathways associated with dementia risk," which identified the plasma proteomic signature associated with subsequent dementia risk in older adults within the ARIC cohort (currently under review). Pathway analysis conducted as part of this study strongly implicated inflammatory and innate immune pathways and Mendelian randomization analyses causally implicated two dementia-associated proteins known to regulate aspects of immune function and inflammatory signaling. For the purpose of this analysis, we have preliminary data that identifies multiple IPNs at visit 5, one of which has been associated with dementia risk. The analyses outlined in this proposal represent a primary aim of Keenan Walker's funded K23 award associated with Ancillary Study 2018.21.

5. Main Hypothesis/Study Questions:

Objective 1. Using approximately 600 inflammatory plasma proteins measured using the SomaScan platform, identify midlife and late-life **inflammatory protein networks (IPN)** using weighted correlation network analysis (WGCNA) and Netboost dimension reduction.

H1a. Three to five modules of inflammatory proteins (IPNs) will be identifiable during midlife (visit 3) and late-life (visit 5).

H1b. Identified IPNs will be enriched for immunologically-relevant biological pathways.

Objective 2. Determine whether expression of specific plasma IPNs during midlife and late-life is associated with dementia risk and cognitive decline.

H2a. At midlife and late-life, one or more IPNs representing pro-inflammatory signaling are associated with dementia risk and cognitive decline.

H2b. Hub proteins (i.e., proteins with high IPN module membership) identified in dementia-associated IPNs are themselves associations with dementia risk and cognitive decline.

H2c. Midlife and late-life dementia-associated IPNs and individual hub proteins are associated with MRI-defined markers of neurodegeneration and PET-defined cortical amyloid.

Objective 3. Determine whether mid- to late-life change in midlife IPN expression is associated with subsequent dementia risk and cognitive decline.

H3. Individuals who experience the greatest change in midlife IPN expression between midlife (visit 3) and late-life (visit 5) are at increased risk for dementia and cognitive decline.

Objective 4. Determine the replicability of (1) midlife IPNs in the Whitehall II cohort and (2) late-life IPNs in the AGES-Reykjavik cohort.

H4. Midlife IPNs are approximately replicable in Whitehall II (age: 33-55). Late-life IPNs are approximately replicable in AGES-Reykjavik (age: 76.2 [5.4]). IPNs associated with dementia risk in ARIC are related to adverse neurocognitive outcomes in Whitehall II and AGES-Reykjavik.

Objective 5. Determine (a) whether dementia-associated IPN proteins overlap with the protein products of Alzheimer's disease GWAS risk variants identified in the International Genomics of Alzheimer's Project (IGAP), and (b) whether expression of dementia-associated IPN varies based on common AD risk variants.

H5a. Dementia-associated IPNs identified during midlife are enriched for proteins regulated by Alzheimer's disease genetic risk variants.

H5b. Common AD risk variants on or near immunologically-relevant genes (e.g., *CD33*, *CR1,* and *MS4A*), relate to expression of dementia-associated IPNs during midlife.

Objective 6. Determine whether the genetic predisposition for greater dementia-associated IPN expression also influences AD risk and expression of AD endophenotypes (CSF and PET biomarkers) using a two-sample Mendelian randomization or polygenic risk score approach.

H6. pQTLs for dementia-associated IPNs overlap with AD risk variants. This analysis will support a causal relationship between dementia-associated IPNs identified during midlife and Alzheimer's disease.

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*:**

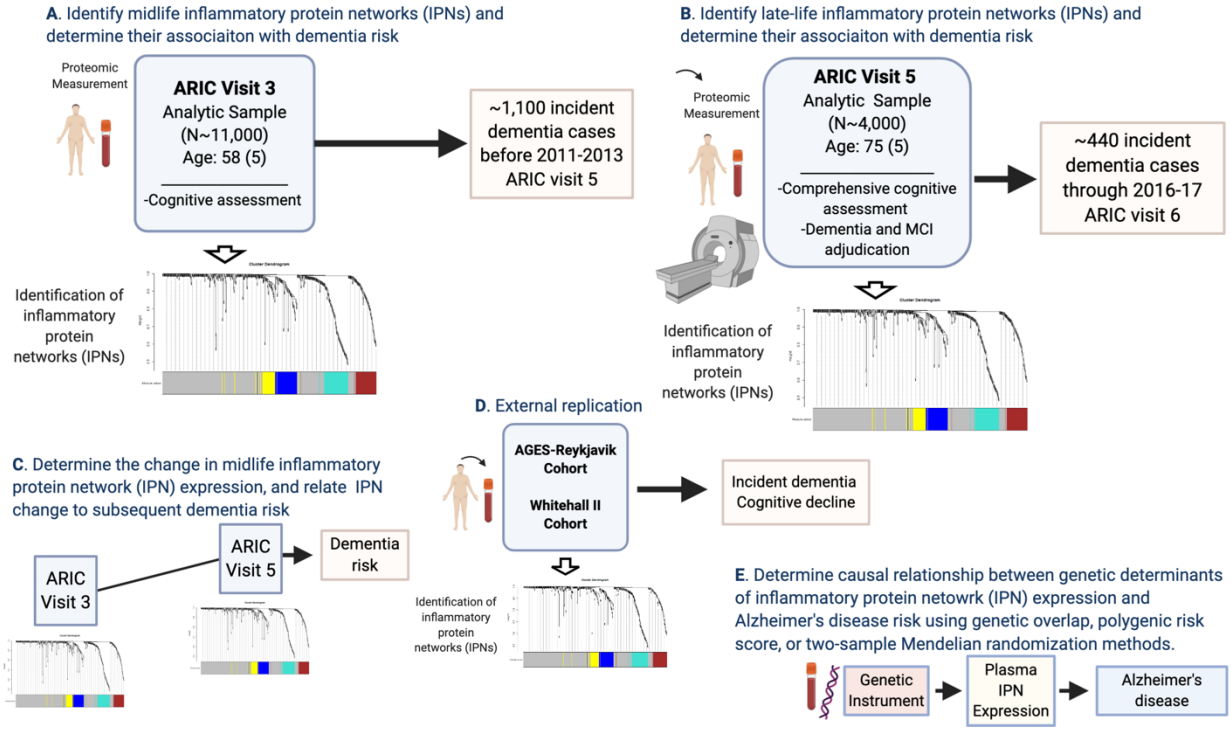

Figure 1. *Study design. (A, B) Plasma Inflammatory Protein Networks (IPNs) will be defined using Weighted Correlation Network Analysis (WGCNA) or Netboost algorithms from ~600 inflammatory proteins measured ARIC visit 3 and visit 5. IPNs will be functionally profiled and hub proteins for each network will be identified. Quantitative indicators of IPN expression will be related to dementia risk, cognitive decline, and neuroimaging characteristics. (C) Change in IPN expression between ARIC visits 3 and 5 will be related to dementia risk after visit 5. (D) The reproducibility of plasma IPNs will be determined using external cohorts. (E) Protein quantitative trait loci (pQTLs) for IPN expression will be identified using GWAS. Genetic overlap between pQTLs and Alzheimer's disease risk variants and variants coding for Alzheimer's disease endophenotypes (CSF/PET Aß and tau) will be examined using a two-sample Mendelian randomization or polygenic risk score approach.*

Inclusion criteria: We will include all participants who (1) have SOMAscan protein measurements available from blood collected at visits 3 or 5.

Exclusion Criteria: We will exclude non-white and non-black participants and non-white participants in Washington Co. and Minnesota, participants missing the education level variable, and participants missing information needed to classify cognitive status (i.e., normal/MCI/dementia classification) after Visit 3.

Exposure/independent variables:
Proteomic measurement (exposure variables): Using plasma collected at ARIC visits 3 (1992-95) and visit 5 (2011-13), proteins were measured using a Slow Off-rate Modified Aptamer (SOMAmer)-based capture array (SomaLogic, Inc, Boulder, Colorado). Using chemically modified nucleotides, this process transforms protein signals to a nucleotide signal quantifiable using relative florescence on microarrays. Previous work indicates a median intra- and inter-run coefficient of variation of approximately 5% and intra-class correlation coefficients of ~0.9.[25–28] Using the methods described below, inflammatory proteins will be grouped into modules or **inflammatory protein networks** (**IPNs**) based on protein-protein correlations.

Primary outcome variables:
Incident Dementia after visit 5: We will relate measures of visit 5 IPN expression to incident dementia occurring between visits 5 and 6 (2015-2017). We will use dementia cases measured through visit 7, if the data are available. Dementia will be defined using both the information from the full visit 6 examination with expert committee diagnosis and information captured in annual follow-up (AFU) interviews using the Six Item Screener (SIS) and the Ascertain Dementia 8-item Informant Questionnaire (AD8). Date of dementia onset will be captured using the SIS and AD8, and dementia diagnosis will be confirmed at visit 6 for those who attend visit 6. For participants who attended visit 5, but not visit 6, the SIS, AD8, hospital discharge codes, and death certificates will be used to define dementia diagnosis and date of onset.

Incident Dementia after visit 3: We will relate measures of visit 3 IPN expression to incident dementia occurring through visit 5. Dementia occurring through visit 5 was ascertained at three levels. Consistent with the dementia classification after visit 5 (above), the proposed analysis will use dementia classified in person (level 1), using telephone interview (level 2), and using ICD-9 hospital discharge codes and death certificates (level 3). As a sensitivity analysis, visit 3 IPNs found to be associated with dementia occurring through visit 5 may also be related to dementia occurring through visit 6 or 7.

Secondary outcomes:
Cognitive Decline: We will also relate measures of visit 5 IPN expression to 10-year cognitive decline between visits 5 and 7 using the global factor score. We will relate measures of visit 3 IPN expression to 20-year cognitive decline between visits 3 and 5 using the global factor score. As a sensitivity analysis, visit 3 IPNs found to be associated with 20-year cognitive decline may also be related to 30-year cognitive decline between visits 3 and 7.

Total and Regional Brain Volume. 3T MRIs were conducted in approximately 2,000 participants at visit 5 as part of the ARIC Neurocognitive Study (NCS). At each ARIC site, a common set of sequences were performed for all participants: MP-RAGE, Axial T2*GRE, Axial T2 FLAIR, and Axial DTI. Acquisition sequences for the ARIC visit 5 MRI have been described in detail previously.[29] We will relate measures of visit 3 and visit 5 IPN expression to total and regional

brain volumes. We are particularly interested in total brain volume, lobar volume (frontal, temporal, parietal, occipital), and AD signature region volume (i.e., the combined volume of the parahippocampal, entorhinal, inferior parietal lobules, hippocampus, and pre- cuneus) for the current study.

White Matter Hyperintensity (WMH) Volume. We will also relate measures of visit 3 and visit 5 IPN expression to WMH volume. WMH volume (mm^3) was be assessed quantitatively from FLAIR images using a computer-aided segmentation program (FLAIR-histoseg) to assess the total volumetric burden.[30] All analyses of WMH volume and total and regional brain volume will be adjusted for total intracranial volume.

Amyloid Status: Using data from participants enrolled in the ARIC-PET study, we will examine the association of midlife and late-life IPN levels with cortical amyloid, as defined using florbetapir PET. Cortical amyloid status will be examined as a dichotomous variable (standardized uptake value ratio >1.2) and a continuous variable.

Analytic Plan

Objective 1. Identify biologically meaningful midlife and late-life inflammatory protein networks (IPN) using weighted correlation network analysis (WGCNA) and Netboost.

Weighted correlation network analysis (WGCNA) and Netboost. WGCNA and Netboost will be used to identify networks of correlated proteins within the set of approximately 600 inflammatory proteins using the full set of participants with available SomaScan proteins at visits 3 and 5. WGCNA and Netboost convert the protein-protein correlation matrix into an adjacency matrix that filters weak correlations based on a power threshold chosen to meet scale-free topology criteria. These algorithms use hierarchical cluster analyses and dynamic tree cutting implemented to group proteins based on patterns of coexpression. After modules are identified, module expression values (module eigenproteins [MEs]) are calculated from the first principal component of each module for each participant. These values represent measures of IPN expression that can be related to participant traits and outcomes. Module membership (kME), defined as the correlation between individual proteins within a module and the module eigenprotein value, will be used to identify IPN hub proteins. For all analyses, we will check for consistency between WGCNA and Netboost methods.

Functional profiling. To determine the biological relevance of each IPN, we will determine whether IPNs are enriched with proteins from specific biological pathways using the g:Profiler toolkit.[31] Using g:Profiler, we will query Gene Ontology (GO),[32,33] Kyoto Encyclopedia of Genes and Genomes (KEGG),[34] and WikiPathways[35] functional enrichment databases. Additionally, Ingenuity Pathway Analysis (IPA) will be used to identify upstream regulators associated with each IPN.

We have conducted preliminary analyses which have identified four IPNs using a set of 580 inflammatory proteins measured at visit 5 (see **Appendix 1** at the end of this proposal). Each module consists of approximately 40 to 70 unique proteins. Functional profiling of these IPNs

confirms their role in inflammation/immune function, but also highlights biological differences among modules.

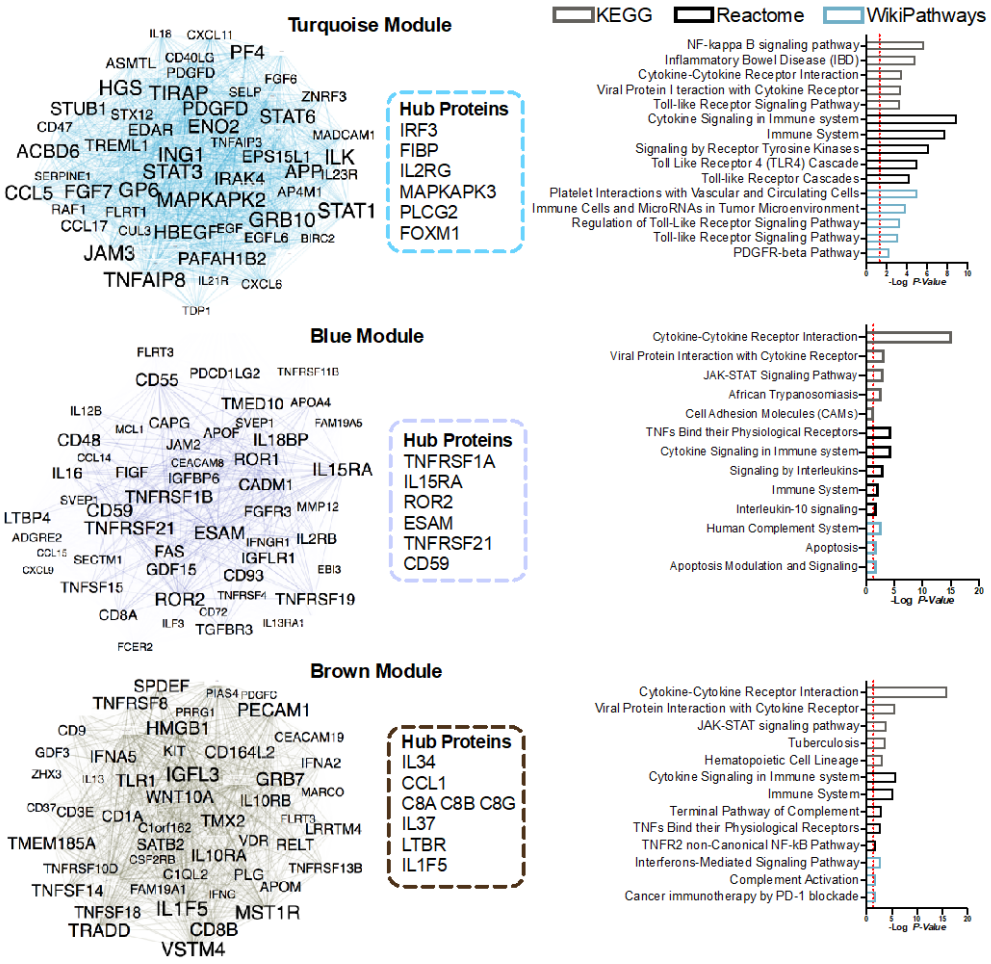

Figure 2. *Three inflammatory protein networks (IPNs) identified among 580 visit 5 inflammatory proteins using weighted correlation network analysis (WGCNA). Functional enrichment of IPNs was assessed using KEGG, Reactome, and WikiPathway databases. The size of nodes (protein names) represents module membership. The shading of the edges represents degree of protein-protein connectedness (adjacency).*

Objective 2. ***Determine whether expression of plasma IPNs during midlife and late-life is associated with dementia risk and cognitive decline.***

Relating IPNs to incident dementia. The primary analysis will use Cox proportional hazard regression models to examine the association of each IPN ME with incident dementia. Separate models will be constructed for each IPN ME, although we will also consider a model that includes all individual IPN MEs. We will use multiple models to examine the effect of potential confounders. **Model 1** will adjust for potentially confounding demographic variables, including age at sample acquisition, sex, race-study center, education, and *APOE* ε4 status. **Model 2** will additionally adjust models for eGFR, given the known association of plasma protein level with

kidney function. **Model 3** will additionally adjust for cardiovascular risk factors (i.e., BMI, hypertension, diabetes, and current smoking) and anti-inflammatory medication use. If dementia-associated IPNs are identified, we will examine the association of dementia-associated IPN hub proteins with dementia risk. Hub proteins will be defined based on protein-specific module membership (e.g., kME >0.8). For hub protein analyses, FDR or Bonferroni correction will be applied to determine statistical significance.

Relating IPNs to cognitive decline. Secondary analyses will examine the association of IPN MEs with cognitive decline using linear mixed effect models with an unstructured covariance matrix. An ME*time term will be the variable of interest. The three covariate-adjusted models described above will be used for this analysis with addition time*covariate terms. Sensitivity analyses using MICE (Multivariate Imputation by Chained Equations) will be used for analyses of cognitive decline.

Relating IPNs to neuroimaging variables. Secondary analyses will examine the association of IPN MEs with visit 5 MRI characteristics, including total brain, Alzheimer's disease signature region, and white matter hyperintensity (WMH) volume. If sample size permits, additional exploratory analyses will examine the association of IPN MEs with total cortical florbetapir (amyloid) PET uptake (measured as standardized value uptake ratio [SUVR]). Multivariable linear regression will be used for these analyses with the set of covariates described above. Total intracranial volume will also be included as a covariate for MRI analyses.

Objective 3. Determine whether mid- to late-life change in midlife IPN expression is associated with subsequent dementia risk and cognitive decline.

This analysis will focus on the visit 3/midlife IPNs (**IPN_M**). To calculate a mid- to late-life change in IPN_M, we will construct synthetic IPN_M's using visit 5 proteins. Thus, for each participant we will be able to calculate IPN_M MEs at visits 3 and 5 and an IPN_M change score ($IPN_{M\text{-}Change} = IPN_{M5} - IPN_{M3}$). Thus, all participants who attended visits 3 and 5 will receive an $IPN_{M\text{-}Change}$ score for each IPN_M. Using use Cox proportional hazard regression models, we will relate IPN_M change scores to dementia risk after visit 5. $IPN_{M\text{-}Change}$ score scores may also be related to cognitive decline. The three covariate-adjusted models described above will be used for this analysis.

Objective 4. Determine the replicability of midlife and late-life IPNs.

Examination of network preservation across cohorts. We will use WGCNA and Netboost network module preservation statistics to assess the conservation of IPNs across different cohorts. We will use one or more of several techniques for evaluating module conservation, which have been described previously.[36] Visit 5 IPNs defined in ARIC will be compared to IPNs defined in AGES-Reykjavik. The AGES-Reykjavik cohort has implemented a custom-designed Novartis SomaScan 5K platform which measures 5,034 SOMAmers representing 4,137 distinct human proteins. At the time of protein measurement, average participant age was 76 (SD 5), comparable to that of visit 5 ARIC participants (age: 75 [SD 5]). Visit 3 IPNs defined in ARIC will be compared to IPNs defined in Whitehall II. The Whitehall II study measured proteins in

plasma using SomaScan v.4. At the time of protein measurement, participants ranged in age from 33 to 55, an age range that is similar to that of ARIC participants at visit 3 (age: 58 [SD 5]).

Relating validated networks to dementia risk and cognitive decline. If there is evidence for a preservation of IPNs in external cohorts, we will (1) relate AGES-Reykjavik IPNs to dementia risk in the AGES-Reykjavik cohort and (2) relate Whitehall II IPNs to cognitive decline in the Whitehall II cohort. Cognition, rather than dementia, will likely be used as the primary outcome for Whitehall II because of the relatively low number of incident dementia cases.

Objective 5. Determine (a) whether dementia-associated IPN proteins overlap with the protein products of Alzheimer's disease GWAS risk variants identified in the International Genomics of Alzheimer's Project (IGAP), and (b) whether expression of dementia-associated IPNs varies based on common AD risk variants.

Examining whether proteins making up dementia-associated IPNs are enriched for proteins coded by AD risk genes. We will use AD risk single nucleotide polymorphism summary statistics from the International Genomics of Alzheimer's Project (IGAP). Variant-gene mapping has been conducted previously using MAGMA (Multi-marker Analysis of GenoMic Annotation).[37] Statistical analysis of protein overlap between dementia-associated IPN proteins and protein products of AD risk variants will be conducted using a program such as GENOVA (GENe Overlap Analysis).

Determining whether AD risk variants are associated with expression of dementia-associated IPNs. Twenty-one of the 29 identified Alzheimer's disease risk variants are known to be immunologically relevant (**Figure 2**) and thus may represent regulators of peripheral inflammatory protein level.[38] We suspect that AD risk variants will influence IPN expression during middle adulthood, well before the typical age of dementia onset. To test this hypothesis, we will determine whether possession of the risk genotype for immunologically-relevant AD risk genes is associated with IPN expression. We will use linear regression, adjusted for age, sex, study site, and genome-wide association studies (GWAS) principal components.

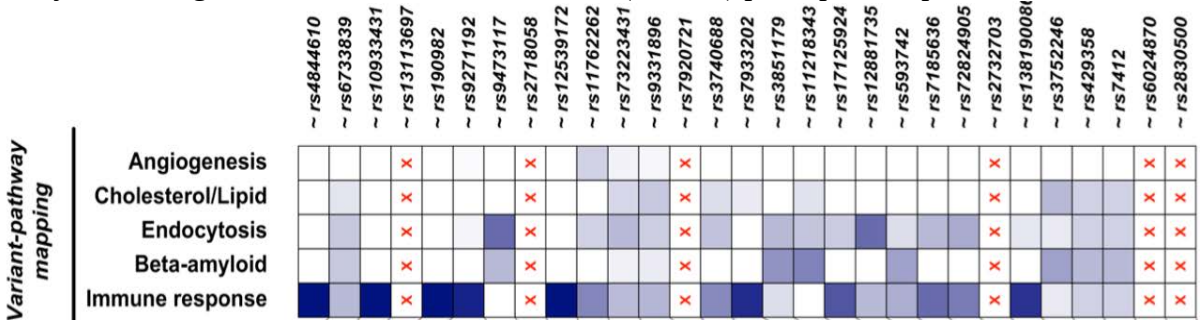

Figure 3. *Twenty-nine Alzheimer's disease risk variants and their functionally annotated biological pathways. These results were derived from a multi-method variant-gene and gene-pathway mapping conducted by Tesi and colleagues. Figure adapted from Tesi et al., 2019.*

Objective 6. Determine whether the genetic predisposition for greater dementia-associated IPN expression also influences AD risk and expression of AD endophenotypes (CSF and PET biomarkers) using a two-sample Mendelian randomization or polygenic risk score approach.

We will conduct genome-wide association studies (GWAS) to identify *cis*- and *trans* genetic variants associated with level of IPN expression (i.e., IPN protein quantitative trait loci [pQTLs]). Using identified IPN pQTLs, we will use a two-sample Mendelian randomization approach to estimate the potential causal relationships between IPN expression and Alzheimer's disease. Alternatively, we will consider a polygenic risk score approach.

Mendelian randomization analysis. As displayed in **Figure 3**, we will use identified pQTLs for dementia-associated IPNs as instrumental variables to estimate the causal relation of dementia-associated IPNs with Alzheimer's disease risk and the expression of Alzheimer's disease biomarkers.[39] For Mendelian randomization analyses of Alzheimer's disease and Alzheimer's disease biomarkers (e.g., amyloid, total and p-tau) we will use publicly available GWA data from recent Alzheimer's disease GWAS studies.[40,41] By working with collaborators (e.g., EMIF-Oxford investigators) who have previously conducted GWAS on other biomarkers, including CSF YKL-40 and NfL, we will also be able to determine whether IPN expression overlaps genetically with CSF-defined neuroinflammation and neurodegeneration. Mendelian randomization analyses will estimate causal effects using the inverse variance weighted method.[42] We will also use Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) to exclude potential outliers with pleiotropic effects. Median weighted and Egger regression methods will also be applied in sensitivity analyses. [43,44]

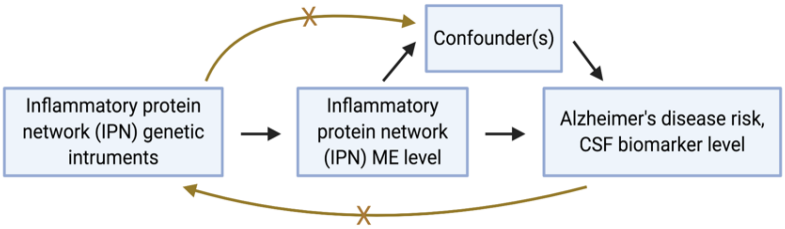

***Figure 4**. Conceptualization of Mendelian randomization model*

Polygenic risk score (PRS) analysis. Using summary statistics from the dementia-associated IPN GWAS, we will use the PRSice pipeline to create a PRS for plasma IPN expression. PRSice will clump SNPs to eliminate bias related to linkage disequilibrium, after which weighting will be applied IPN-related variants. We will examine multiple p-value thresholds (ranging from $P<5.0x10^{-8}$ to $P<5.0x10^{-5}$. Using external GWAS summary statistics for AD and AD endophenotypes, we will calculate the estimated effects for groups of IPN-associated variants.

Genotyping and imputation. Imputation has been previously conducted in ARIC using Human Reference Panel [HRC] for white participants and 1000G phase 3v5 for black participants. The Illumina Infinium HumanExome BeadChip v1.0 array exome chip was used to identify variants across the genome, with a focus on protein-coding variants and splice sites.[45]

Genetic association analysis overview. We will identify common (minor allele frequency [MAF] ≥ 5%) variants associated with IPN expression (ME) using race-stratified linear regression adjusting for age, sex, study site, and GWAS principal components. For Mendelian randomization, pQTLs will be identified at genome-wide significance (two-sided *P*-value <5 x 10^{-8}) and LD pruned (R^2>0.8).[46]

Tissue and Cell Enrichment Analysis. Using publicly available gene expression datasets (e.g., GTEx), we will also determine whether there is tissue- or cell-specific enrichment for dementia-associated IPN pQTLs. This will be conducted using gene overlap analysis with a program such as SNPsea, GENOVA, or Bayesian test for colocalization.[47–49] This analysis will allow us to determine whether dementia-associated plasma IPNs are likely to originate from specific tissues (e.g., adipose tissue, heart, spleen) or cell types (e.g., monocytes, Th1, or Th17 cells).

Limitations. As in all omic analyses, the validity of measurement of different proteins varies across the large number of proteins. The discovery effort is focused on identifying and validating new proteomic networks and network-trait associations. Lack of sufficiently strong signal is not evidence of no association with a given protein since lack of signal may be due to limited power for a host of reasons including the need to be conservative when adjusting for multiple comparisons.

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/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)?

MP# 3051. The association of middle and late-life blood pressure with conversion to MCI and dementia: The ARIC Study

MP# 3058. The association of late-life glycemia status with 3-year late-life cognitive decline and incident MCI/dementia: The ARIC Study

MP# 3903. Multi-omic data integration using systems approaches for mechanistic understanding of disease in the Atherosclerosis Risk in Communities (ARIC) Study

MP#3113. Identification of novel genetic variants associated with Alzheimer's disease in the Alzheimer's Disease Sequencing Project (ADSP)

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* 2017.27_)
"Proteomic longitudinal ARIC study: SOMAscan of multiple visits"

___ 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.
Understood

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.
Understood

Reference

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