ARIC Manuscript Proposal #4015 (Amended)

PC Reviewed: 6/11/24 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Exploring Common Biological Pathways Underlying Insulin Resistance and dementia using Genetic and Omic Tools

b. Abbreviated Title (Length 26 characters): Omic study of Insulin Resistance in dementia

2. Writing Group:
Authorship for publication: first author C. Sarnowski, last author A. Morrison

ARIC investigators members:
Chloé Sarnowski, Jeewoen Shin, Bing Yu, Han Chen, Thomas Mosley, Jan Bressler, Myriam Fornage, Jim Pankow, Alanna Morrison

All members of the relevant ARIC working groups will be given the opportunity to be a coauthor. Authorship order will be determined by author contribution to the work.

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

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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3. Timeline:
The paper proposal will be circulated to the relevant ARIC working groups for approval before starting analyses. Analyses will be conducted in the next 1-2 years. The paper(s) will be written in the next 1-2 years.

4. Rationale:

Insulin resistance (IR) is defined as the failure of target tissues to respond optimally to insulin and has been reported associated with cognitive impairment, dementia and neurodegeneration.

Insulin levels in cerebrospinal fluid, despite being much lower than in plasma, are correlated with peripheral insulin levels, indicating that most of the insulin in the brain derives from circulating pancreatic insulin. Peripheral IR, measured by the homeostasis model assessment of IR (HOMA-IR), has been shown to positively correlate with brain Aβ deposition in Alzheimer's Disease (AD) patients, to be associated with increased accumulation of Aβ (over the course of 2 yrs) in cognitively healthy adults, to negatively correlate with grey matter volume in AD patients, and to be associated with higher risk of AD (within 3yrs of baseline) in patients free of dementia and diabetes. Increased peripheral IR was also shown to correlate with worse cognitive scores and with higher concentrations of both CSF phosphorylated and total tau in cognitively healthy adults [1].

It is not clear yet how peripheral and brain IR, cognition and dementia relate to one another. A better understanding of the mechanisms by which peripheral IR contributes to dementia and how these mechanisms differ from known risk factors involved in neurological diseases is important. Genetic and omic studies have the potential to fill this gap in knowledge by revealing omic markers of IR associated with dementia and related traits.

5. Main Hypothesis/Study Questions:

To better characterize the role of IR in dementia and to evaluate how the mechanisms by which IR predisposes to dementia differ from known mechanisms involved in pathogenesis of neurological disorders.

Based on preliminary data, the working hypothesis is that feature selection can help to reveal regulatory mechanisms influenced by IR in genes with a relevant function to the brain.

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).

We aim to determine what are the molecular signatures of IR associated with dementia, and to apply newly developed statistical method to assess the joint genetic effect at these signatures.

Studies

We propose to leverage genetic and omic (epigenomic and proteomic) data from the Atherosclerosis Risk in Communities Study (ARIC) to study the regulatory mechanisms that underlie IR and contribute to dementia.

Phenotype Definition

We propose to use:

- Three measures of insulin resistance and sensitivity: 1) HOMA-IR, based on fasting glucose (FG) and fasting insulin (FI) measurements; 2) the triglyceride-glucose index (TyG), based on FG and fasting triglycerides measurements [2,3]; and 3) the triglyceride-glucose-body mass index (TyG-BMI), based on FG, fasting triglycerides and BMI measurements. [4] Prevalent

all-cause dementia using ARIC NCS criteria at visit 5: an adjudicated syndromic diagnosis of mild cognitive impairment or dementia [4]. Controls will be defined as participants who are cognitively normal and age 65 or older.

In addition to prevalent all-cause dementia, we propose to study additional quantitative related traits:

- Brain imaging phenotypes (total cerebral brain, hippocampal, intracranial, and lateral ventricular volumes, and white matter hyperintensities) derived from brain imaging (MRI).
- General cognitive function, derived by calculating the first unrotated principal component using scores for at least three cognitive tests that assess different cognitive domains. The CHARGE consortium has previously performed two genome-wide association studies (GWAS) of general cognitive function and the ARIC study contributed cohort-specific results for use in both of these meta-analyses [5,6]. The advantage of using this summary measure of cognitive performance rather than the global and domain specific factor score previously developed by ARIC-NCS [7] is that it will facilitate and optimize replication as per our prior genetic work in CHARGE, since many cohorts such as the Framingham Heart Study (FHS), the Cardiovascular Health Study (CHS), Genetic Epidemiology Network of Arteriopathy (GENOA), and the Rotterdam Study (RS), have already constructed this outcome variable in order to participate in the GWAS.

Omic data

We will use DNA methylation profiles (normalized methylation beta) measured in peripheral blood and plasma levels of proteins (SomaScan).

Visit for phenotypic and omic data

Having both phenotypic and omic data measured at the same visit would be ideal. We propose to analyze methylation, proteomic, and phenotypic data measured at visit 5, if available at the time of analysis. Alternatively, we will use methylation and proteomic data measured at visit 2/3, insulin measured at visit 1, cognition measured at visit 2, brain MRI volumes measured at visit 3/5, and prevalent all-cause dementia at visit 5.

Analyses

1) We will first conduct omic association studies of IR to identify omic markers associated with IR using linear mixed-effects model. Significance thresholds will be defined after Bonferroni correction to account for multiple testing. We will exclude participants with type 2 diabetes (defined based on self-reported physician diagnosis or use of hypoglycemic medications, or participants exceeding FG or HbA1c cut points). We will adjust analyses for age, sex, estimated white blood cell fractions (Houseman), body mass index (BMI), and control probes PCs (to adjust for technical variation). We will then evaluate the association of the IR-associated omic markers with prevalent dementia and related traits (general cognitive function, brain volumes, and white matter hyperintensities) using similar models. We will define significance based on a Bonferroni correction for the number of tests performed. Sensitivity analyses will be performed by adjusting or stratifying on known cardiovascular risk factors (smoking status, alcohol consumption, physical activity, diabetes, hypertension, total cholesterol level, and BMI). Machine-learning techniques will also be used to identify omic markers contributing to dementia or related traits mentioned above.

2) We plan on conducting epigenetic association analyses of proteins levels to evaluate the local epigenetic regulation of the proteins identified associated with IR and/or dementia and related traits.

3) We will apply JEM [8], a new statistical method that we have developed, to genetic and omic loci involved in both IR and dementia to evaluate individual and joint effect of genetic variants on DNA methylation and proteins while leveraging tissue specific annotations of the genetic variants. We will first perform analyses at the omic markers identified in the first analysis (described above). We will then extend the analysis to loci reported associated with both IR and dementia in the literature.

For both analyses, we will look for replication in CHARGE cohorts with available phenotypic and omic data, such as FHS, CHS, MESA, or Rotterdam.

References

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7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes __X__ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The file ICTDER 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 current derived consent file ICTDER05 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/aricproposals/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)?

We have identified three ARIC paper proposals, listed below, that aimed to perform epigenetic analyses of glycemic traits. The outcomes of interest in our proposal are neurological traits (prevalent dementia, general cognitive function, brain volumes, and white matter hyperintensities). In our plan, the EWAS will only be a pre-screening step to identify CpGs that will be tested for association with neurological outcomes. The three next ARIC paper proposals propose omic association analyses for neurological outcomes but do not focus on insulin resistance.

- **DNA methylation associated with glycemic traits and type 2 diabetes in multi-ethnic analyses: CHARGE consortium**
  Proposal Lead Author: Pankow, J

- **DNAm markers associated with type 2 diabetes and glycemic biomarkers in African Americans: The Atherosclerosis Risk in Communities (ARIC) Study**
  Proposal Lead Author: Venkataraghavan, S.

- **Novel DNA methylation sites of glucose and insulin homeostasis and their integrative cross-omics analysis**

Proposal Lead Author: Liu, JL
PubMed ID: 31197173

- **Cerebral white matter hyperintensities on MRI and acceleration of epigenetic aging: the atherosclerosis risk in communities study**
  Proposal Lead Author: Fornage, M
  PubMed ID: 31630168
  EWAS of WMH in CHARGE including ARIC accepted in Brain

- **Proteomic Analysis Identifies Circulating Proteins Associated With Plasma Amyloid-β and Incident Dementia.**
  Proposal Lead Author: Tin, A
  PubMed ID: 37519456

- **Investigating relationships between an MRI measure of brain aging with proteomics and cognition**
  Proposal Lead Author: Casanova, R

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes _X___ No

11.b. If yes, is the proposal

___ 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 https://sites.cscc.unc.edu/aric/approved-ancillary-studies

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PubMed Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.