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ARIC Manuscript Proposal Number: **#4465**

1.a. Full Title: Impact of inflammation and social determinants of health on delirium

b. Abbreviated Title (Length 26 characters): **Inflammation-SDOH-Delirium in ARIC**

2. Writing Group (alphabetical): Mfon Umoh (First author), Esther Oh, Nicholas S. Reed (Senior author), Charles H Brown, James Russell Pike, Emmanuel Garcia Morales, Josef Coresh, and Shoshana Ballew. Others welcome.

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

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3. Timeline:
Analysis and Manuscript will be completed in 9 months.

4.Rationale:

Delirium and dementia are the most common causes of cognitive impairment in older adults. Delirium is an acute state of confusion characterized by impairments in attention and cognition and has been linked to chronic and progressive loss of cognitive ability. Individuals with dementia are at higher risk for delirium and delirium is a risk factor for dementia and worsens dementia.[1] There is overwhelming evidence that delirium may accelerate cognitive decline.[2-4] In the United States over 2.6 million adults aged 65 years and above develop delirium each year.[5] Delirium is triggered by numerous insults, including acute illness or hospitalization,[6] making it a syndrome that can occur within different clinical settings with significant impact on patient outcomes. Delirium is associated with longer hospital stays, worse cognitive and functional outcomes, and increased mortality.[7-10] As the etiology of delirium is multifactorial, its management can be challenging.

There is evidence supporting several potential mechanisms involved in delirium pathophysiology, including neuronal damage and inflammation.[1,10] Inflammation is thought to play a key role in delirium, though variable associations have been reported between inflammatory markers and delirium incidence.[11-16] Many studies to date on delirium have focused on medical comorbidities and clinical factors present at

the time of a delirium episode and although these are important there is little research on the contributions of inflammation to delirium in prospective cohorts and really no studies evaluating how social determinants of health(SDOH) may influence this relationshop.[17,18] There are individual and neighborhood level factors that may impact the risk of cognitive decline and influence the relationship between inflammation and delirium. A few groups have tried to understand the role of SDOH on cognitive outcomes, [17,19,20] but very little analysis within the ARIC cohort exists.[21,22]

Delirium may be an intervenable risk factor for cognitive decline, but more evidence is needed to understand its relationship to cognitive decline and dementia.[23] The mechanism between how SDOH modify the relationship between inflammation and cognitive decline is complex and likely involves several pathways. Powell et al showed that living in the most disadvantaged neighborhoods was associated with greater than 2 times odds of AD neuropathology, so likely there are biological changes driving differences in cognitive function. Further, there are likely downstream mechanisms that SDOH impact that also influence brain health, like sleep, environmental impacts, and stress which may explain some of this interaction. It is unlikely to be just one pathway involved but rather a concerted effect against pathways that contribute to cognitive resilience. Understanding the connection between delirium and inflammation and the impact of SDOH on this relationship is important. Rolandi and colleagues found that 35% of dementia cases could be attributable to modifiable risk factors, specifically they performed competing risk regression models to obtain sub-hazard ratio (SHR) for each exposure, with death as competing risk and the exposures associated with dementia were included in a multivariable model to estimate their independent influence on dementia; they found that delirium (SHR = 8.70, 95% CI 3.26–23.24, $p < 0.001$) was independently associated with increased dementia risk.[24] The more we understand about delirium , a potentially modifiable risk factor for dementia, the more we can improve our understanding of this condition and work towards improving preventative strategies.

The goal of this project is to evaluate the relationship between biomarkers of inflammation, delirium, and social determinants of health to improve our understanding of how these factors impact cognitive outcomes. Previous studies attempting to examine the influence of SDOH on cognitive decline have mostly focused on individual level markers of social disadvantage and have been limited by size.[17] Most studies examining the relationship between inflammation and delirium have been in preclinical models.[25,26] Prior ARIC studies examining the association between inflammation and cognitive decline have evaluated the effect of exposure at different times in the life course but have not assessed the influence of SDOH on these relationships and have not considered acute cognitive decline that occurs during delirium.[27] We plan to leverage the availability of biomarker data from the ARIC cohort, a well-defined group of participants, with longitudinal data, cognitive assessments at several timepoints to map cognitive changes, and available Medicare claims data to identify delirium incidence.

5. Main Hypothesis/Study Questions:

Aim 1: Examine whether levels or changes in levels of inflammatory marker CRP (between visit 5,6, and 7) are associated with delirium incidence.

Hypothesis: High (cross sectional) and/or increasing(longitudinal) levels of CRP are associated with increased delirium risk.

Aim 2: Examine whether levels of inflammatory proteins (previously ran on ARIC participant samples from samples collected at visit 5 available from SOMALogic platform) are associated with delirium incidence. Inflammatory biomarkers of interest include IL-6, and TNF-alpha receptor, given these have been shown previously to be associated with delirium.[28-31]

Hypothesis: High (cross sectional) levels of inflammatory markers are associated with increased delirium risk.

Aim 3: Examine if the association between inflammatory biomarkers and delirium is modified by SDOH, including income, education, and Area Deprivation Index (ADI).

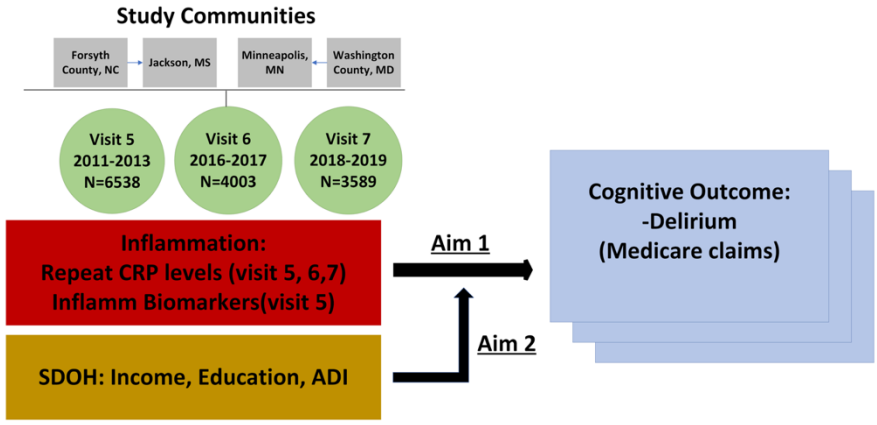
Hypothesis: SDOH modify the relationship between inflammation and delirium. More disadvantageous SDOH (lower income, less education, higher ADI) will strengthen the relationship between inflammatory biomarkers and delirium.

Aim 4: (Exploratory) Evaluate whether delirium is associated with long term cognitive decline beyond hospitalization only. Building from prior work in ARIC.[32]

Hypothesis: Delirium hastens cognitive decline; we expect slope of cognitive scores to be steeper decline after hospitalization with delirium episode.

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 and longitudinal analysis within a prospective cohort.



Adapted from: Wright J, Folsom A, Coresh J, et al. The ARIC (Atherosclerosis Risk In Communities) Study. *J Am Coll Cardiol.* 2021 Jun, 77 (23) 2939–2959.**https://doi.org/10.1016/j.jacc.2021.04.035**

Study population:

ARIC participants age 65+ with available Medicare claims data and inflammatory biomarkers (inflammatory proteins measured in SOMALogic) available at visit 5, CRP available at visit 5,6,7.

Exposure:

The primary exposure is inflammation as measured by extensive array of ~350 inflammatory proteins from blood (measured at visits 5). Specifically, we are interested in CRP, TNF-alpha and IL-6. We are interested in both the level of the individual proteins and the changes in inflammatory proteins between the visits, similar to what has been done previously.[33]

For exploratory aim 4 delirium will be treated as an exposure variable.

Moderator:

Another variable we will investigate is SDOH, at individual level (income, education) and neighborhood level (Area deprivation index (ADI)). We will assess this variable as a possible moderator of the relationship between inflammation and delirium. ADI characterizes neighborhoods by combining several sociodemographic indicators into a census block group-level index of disadvantage. ADI data will be downloaded from the 2018 v3.0 publicly available dataset and linked to ARIC data using Census block group of the patient's address in 2018. ADI data will be downloaded from the 2018 v3.0 publicly available dataset and linked to ARIC data using Census block group from patient's address in 2018.

Outcome:

Our outcomes of interest are cognitive decline and delirium. Neurocognitive factor scores generated from repeat cognitive assessments available in ARIC dataset at each visit timepoint.[34,35] Delirium will be assessed using Medicare claims data from ARIC participants during hospitalizations.

Covariates:

We will include socio-demographic factors; age, sex, race-location, years of education, and income. We will consider health related covariates, including medical diagnosis of DM, HTN(midlife and late life blood pressure patterns), History of MI/TIA/Stroke, information about chronic inflammatory disease diagnoses (i.e., lupus, gout, and arthritis), APOE-4 status (0/1/2 ε4 alleles), report of baseline anti-inflammatory medication use (yes/no), long-term use of anti-inflammatory medication (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], arthritis medication), and frailty status (FRAILTY51 or FRAILTY52). Baseline cognition will also be considered.

Inclusion/Exclusion criteria:

We will only include participants with complete fee-for-service claims data for years of interest given outcome of interest, delirium, will be obtained from Medicare records.

Data analysis

Aim 1: To examine the association of inflammatory marker CRP and delirium we will use CRP levels at visit 5,6, and 7, and delirium as measured by Medicare claims from 2011-2019. For cross sectional analysis, we will use linear mixed effect models and cox proportional hazards survival analysis. We will include the Fine-Gray competing risk model for death. We will evaluate delirium incidence from 2011-2019. Model assumptions of linearity and constant residual variance will be assessed graphically using LOWESS (locally weighted scatterplot smoothing) and residual diagnostic plots. The primary exposure - systemic inflammation will be evaluated based on level of CRP measured at visit 5. For longitudinal analyses, this will be modeled in two ways using change in CRP levels (slope) at as exposure. Additionally, to examine the association of change in inflammatory marker CRP over time and delirium we will use the change in CRP levels (slope) at visit 5,6, and 7. We will use the Poisson robust family variance model, which produces prevalence risk ratio. Also, we will use the negative binomial regression model for incidence of delirium, which provides an infinite rate ratio which considers time. Alternatively, we may use general additive models or general estimating equations (GEE) with robust standard variance to evaluate the association of change in CRP from 3 visits (visit 5,6,7) to examine year over year change in risk. These will provide baseline risk across 2011-2019. From this, we can assess delirium risk as CRP changes. Additionally, we may model relationship between cognitive scores and inflammation as a spline, pre and post delirium as another variable in model for those with this outcome over the period of interest. Further, sensitivity analyses will be conducted to evaluate the impact of any delirium diagnoses within study timeframe.

Aim 2: We plan to run similar analyses as described in cross sectional analysis of aim 1. The primary exposure - systemic inflammation will be evaluated based on level of inflammatory proteins measured at

visit 5. We plan to assess individual inflammatory biomarkers as listed. We will also consider generating an inflammation composite score, similar to what has been done previously. [27]

Aim 3: To examine if the association between inflammatory biomarkers and delirium is modified by SDOH- income, education, and ADI will be examined as effect modifiers using linear effect models. We will use three level models, including repeated assessments (level 1) nested within participants (level 2) nested within neighborhoods (level 3); planning for 3-level mixed effects models and 2-level time-to-event models to examine whether interactions occur at the neighborhood level or the individual level when considering whether SDOH moderate the relationship between inflammation and delirium. Alternatively, we may estimate the cumulative incidence of delirium using Kaplan-Meier curves, stratified by inflammation (from threshold specified within existing literature) and SDOH variables, and then test SDOH X inflammatory score interactions in Cox models.

Aim 4: We will plot cognitive factor scores over time for individuals with hospitalization with delirium episode(s) and those for individuals with hospitalization without delirium incidence, including both before and after timepoints. There will likely be a lot of variability in this measurement, but this exploratory aim will serve as preliminary analysis to understand cognitive trends after delirium for future work. We may consider generating matched controls (individuals with propensity match score with hospitalization without delirium episode) to have a group for comparison and evaluate cognitive score slopes.

Given our analysis includes assessment of change in cognition over time we may run into attrition or selection biases given the longitudinal nature of the data, as it is likely that more physically active and cognitively intact individuals remain in the study for longer, to bypass this limitation sensitivity analyses will be conducted and missing data for cognitive measures will be imputed. Specifically, multiple imputation will be used for missing covariates. Multiple imputation with auxiliary variables will also be used to address informative attrition in analyses of cognitive decline. For time-to-event models we may use inverse probability weighting to address informative censoring.

Analyses will be conducted using STATA version 18.

Limitations/challenges:
Because the ARIC study includes 4 distinct sites, the findings may not broadly apply. The associations identified with neighborhood level disadvantage may be explained by center-level variation in the evaluation process of delirium rather than neighborhood-associated factors. To bypass this limitation, we will conduct sensitivity analyses within group and across group comparisons comparing sites. Another challenge will be identifying the outcome delirium based on Medicare claims data; others have found fewer patients with delirium diagnoses in claims data than clinically expected, which may reflect underdiagnosis, variable-diagnosis, and under-coding. [36] As our outcome, delirium, is assessed from Medicare claims records, we have a small sample size to work within. However, although limited by size and limitation of lack of sensitivity when using claims records, we benefit from the high specificity in using this type of data and hope to be able to better understand the relationship between inflammation and delirium and cognitive changes after delirium from this work. An additional limitation is the context of an episode of delirium is limited to within a hospitalization, a majority of delirium identified occurs during hospitalization,[37]so this is reflective of real-world data. This study's findings will provide important information that may encourage additional studies related to inflammation, SDOH, and delirium.

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? ____ Yes __X__ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the current derived consent file ICTDER05 must be used to exclude those with value RES_DNA = “No use/storage DNA”? ____ Yes ____ No

9. The lead author 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)?

None (no work related to delirium , inflammation, and SDOH)

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

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