ARIC Manuscript Proposal #3888

PC Reviewed: 7/13/21	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Hospitalization with Infection and Incidence of Dementia in the Atherosclerosis Risk in Communities (ARIC) Cohort.

b. Abbreviated Title (Length 26 characters): Hospitalization with Infection and Incident Dementia

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

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3. Timeline:
Analysis to begin immediately; draft expected in approximately late summer 2021.

4. Rationale:

Dementia describes a variety of symptoms affecting memory, cognitive ability, and behavior. Although reversible forms of the dementia exist, often dementia is a non-reversible condition – making prevention and management of its causing agents of crucial importance. Most often, dementia and its causes affect elderly populations, resulting from progressive pathologies and accumulation of lifetime risk-augmenting events. Various conditions and diseases have been recognized as causes of dementia, with Alzheimer's disease (AD) being the most common culprit [1]. AD was estimated to affect 5 million elderly adults in the US in 2014, with prevalence projected to reach 14 million by 2060 [2]. In the vast majority of cases, AD is a late-onset disease, occurring in those older than 65 years old, with no identifiable or single causes. [1].

Various mechanisms have been proposed as underlying causes of dementia, and specifically AD. Among these, the brain's innate immune system and neuroinflammation are hypothesized to be integral to AD onset and progression [1]. Inflammatory stress and chronical activation of glial cells is a defining characteristic of AD pathology [1]. The primary immune cells in the brain, microglia, have been hypothesized to promote neuron damage and death and have a major role in the initiation of amyloid-ß plaque formation and in tau pathology build-up. These cells function similarly to macrophages [3], and have a complex activation system, utilizing a variety of signaling receptors with extreme sensitiveness to environmental clues, including the presence of pathogens or pro-inflammatory molecules [1]. It has recently been demonstrated that microglia have great variety in activation phenotypes, in addition to the pro-inflammatory (M1) and reparative (M2) characteristic of macrophages [1]. Among these, a 'neurodegenerative' phenotype has been proposed, characterized by induction of pro-inflammatory and phagocytotic genes [4].

Neuroinflammation and the activation of the brain's immune system are hypothesized to be promoted by a variety of acute illnesses including infections, suggesting that the latter is a causing factor in AD, dementia, and neurodegeneration [1]. Various mechanisms may link systemic infection to neuroinflammation and neurodegeneration, including the release of pro-inflammatory signaling molecules and of damaging substances, such as pathogen antigens, endotoxins, or reactive oxygen species [1].

The association between infection and dementia or neurodegenerative disease has been reported in previous studies, both experimental and observational – including in ARIC. Of note, Brown et al (2015) showed that hospitalization due to various factors, including severe infection, is associated to cognitive decline over a 11-year period [5]. Walker et al (2018), utilized ARIC data over a 24-year period (Visits 1-5) to show that participants who were hospitalized are more likely to have greater white matter hyperintensity volume and lower white matter microstructural integrity [6]. Further, they showed that compared to those hospitalized with no infections, participants who had major infections had significantly smaller Alzheimer's Disease Signature Region volumes and larger ventricular volumes.

A study by *Sipila et al*. published in 2020 on the preprint server medRxiv, found that any hospitalized infection was associated to an increase in risk of dementia (HR = 1.6 [95% CI: 1.47-1.72]), over a median follow up of 19 years in 3 Finnish cohorts [7]. Further, they found that various infections types, notably of gram-negative bacteria and herpesvirus, are associated to even higher risk of dementia [7]. The authors findings were replicated in a sensitivity analysis utilizing data from the UK Biobank, over a median follow-up of 9 years [7].

Utilizing ARIC-NCS to investigate the association between hospitalization with infections and dementia may address some of the key limitations in *Sipila et al*. First, the ARIC-NCS cohort has a more diverse group, which would greatly increase generalizability. Second, the ARIC-NCS has a more stringent ascertainment of dementia, which included several cognitive exams, more standard diagnosis, and data sources with increased reliability and accuracy. Third, the ARIC-NCS cohort has equal or longer follow-up period, with visit 7 being as long as 29-32 years. This maximum follow up would be similar to that in the Finnish cohorts utilized in *Sipila et al*. (30.8 years, median of 19 years), and much greater than that of the UK Biobank cohort (11.1 years, median of 9 years). Fourth, *Sipila et al* did not account for APOE-ε4 genotype, which is a major risk factor for AD, and available in ARIC-NCS. Lastly, the authors classified infections based solely on pathogens subtypes. In addition to this classification, we plan to utilize a bodily system and infection type classification, which could add great insight to the analysis.

5. Main Hypothesis/Study Questions:

Participants who experienced hospitalization with infection during the follow-up will have higher incidence of dementia compared to those who did not have any hospitalization with infections.

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).

Design:
Prospective cohort study, utilizing data from baseline through the most recent follow-up.

Exclusion Criteria:
- Due to small sample sizes, we will exclude Asian and Native American participants in any study center and Black participants in Minneapolis or Washington Country.

Exposure Variables:
The primary exposure variable will be any hospitalization with infection, based on ICD codes from surveillance of hospitalization discharge lists or abstracted from participant/proxy annual report. In an effort to capture major infection events, we will account only for infections in the first five positions of the ICD code listing. Both ICD-9 and ICD-10 codes will be included; we cross-walked ICD-10 to ICD-9 codes and reviewed for face validity.

As the primary exposure, hospitalization with infection, will be treated as a binary time-varying exposure (0 = *no hospitalization with infection*; 1 = *hospitalization with infection*). In further analyses, we will account for hospitalization with infection as a nominal time-varying exposure (0 = *no hospitalization with infection*; 1 = 1st *hospitalization with infection; 2 = 2*nd *hospitalization with infection;* …) as to capture the cumulative burden of the exposure on disease.
Non-infection related hospitalizations will be considered as a comparison group for a sensitivity analysis (0 = *hospitalization with no infection;* 1 = *hospitalization with infection*).

In subanalyses, exposures will be further defined as infections due to each of the following infection types: I) Pneumonia; II) Urinary Tract Infection; III) Bloodstream Infection; IV) Cellulitis/Osteomyelitis. Additional infection subtypes will be considered based on clinical interest and having a sufficient number of infection events observed prior to dementia onset. Based on a power calculation utilizing all ARIC data available (15792 observations, 2939 cases of dementia), a minimum of 261 cases of a given infection subtype would be necessary to detect a 50% increase in dementia risk with 80% power and a level of significance of 95%. This minimum will be re-calculated once the exclusion criteria are applied.

Outcome Variables:

The primary outcome will be incidence of dementia, using all available information (i.e. 'Level 3' dementia). Time to outcome will be defined as the time from baseline until first diagnosis of dementia, censoring at death, the last available follow-up, or study withdrawal. The nature of person-time contributed (ie. exposed vs unexposed person-time) will be determined accounting infections as a time-varying exposure, as described above.

Other Variables:
Other variables to be included are participant sex, age at baseline and at hospitalization, race/center, drinking and smoking habits, health insurance status, education and other measures of socioeconomical status, comorbidities (diabetes, hypertension, chronic kidney disease, cardiovascular disease, etc), inflammatory markers, and APOE-ε4 genotype.

The utilization of APOE-ε4 genotype as a two-level (carrier vs non-carrier) or three-level (ε4 homozygotes, ε4 heterozygotes, or non-carriers) will depend on sample size of the analysis being conducted to assure adequate precision.

Data Analysis:
The primary analysis method will be time-to-event analysis, utilizing Cox Proportional Hazards models. All participants will be considered unexposed at baseline and thus contribute unexposed person-time time. At the first incidence of infection, a participant will start to contribute exposed person-time until the end of follow-up. In the event of multiple infections, the first incidence will be used as exposure date in primary analysis of any type of infection – regardless of other infections thereafter.

In further analyses investigating specific infection types, only the date of an infection type that matches that specific analysis will be utilized, regardless of other infection events before or after. A false discovery rate-controlling procedure will be used to account for multiple comparisons in these analyses.

Further analysis accounting for effect measure modification by APOE-ε4 carrier status (as described previously) will be considered due to evidence of APOE-ε4 genotype being influential in the risk of dementia, including through interaction with systemic inflammation [8].

Three sensitivity analysis will be conducted.

- First, we will repeat the primary analysis utilizing infection events in the first position of the ICD code listing. This is intended as an even more stringent exposure ascertainment, accounting for major infection events only.
- Second, we will repeat the primary analysis removing participants with a diagnosis of dementia within 10 years of follow-up initiation, to decrease the likelihood of reverse causation.
- Third, we will repeat the primary analysis with the comparator group for exposure (*hospitalization with infection*) operationalized as *hospitalization with no-infection*, in an effort to account for the risk of outcome that may be attributable to other hospitalizations, such as cardiovascular disease events. This will be operationalized using the ARIC hospitalization file and matching on, at the time of hospitalization, age (± 3 years), sex, race-center, and date of hospitalization (± 3 months) [9].

Anticipated Limitations:
Given the nature of the outcome, the potential for reverse causation is an important limitation. However, we plan to conduct a secondary analysis with more stringent outcome timing guidelines in an effort to account for this issue.

Another potential limitation is that of competing risks, as hospitalized participants may be more likely to die than controls, thus having less time for outcome ascertainment. A sensitivity analysis accounting for non-infection hospitalized events as the comparator (controls) group will be utilized to evaluate the impact of competing risks.

As an additional limitation, the infection ICD codes have not been validated in most instances. We intend to do a variety of subanalyses, exploring how different types of infections or pathogens may be associated to dementia. Some of these analyses might be underpowered due to a smaller number of recorded infection events within a given type. Lastly, conducting these various subtype analyses could increase the false discovery rate due to multiple comparisons. This will be accounted for through false discovery rate-controlling procedures.

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 (APOE genotype only) 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"? ____ 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)?

The following published paper is closely related:
Hospitalization with major infection and incidence of end-stage renal disease: the Atherosclerosis Risk in Communities Study. (2020). Junichi Ishigami, Logan T Cowan, Ryan T Demmer, Pamela L Lutsey, Josef Coresh, Kunihiro Matsushita. Mayo Clin Proc. 95(9):1928-1938.

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* ___2008.06____)
___ 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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