ARIC Manuscript Proposal #3937

PC Reviewed: 9/14/21 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

C4R Common Proposal Form (004)

Concise proposals are greatly appreciated! Proposals must be 4 pages or less excluding references

Project title: SARS-Cov-2 Infection and Cognitive Function

Lead investigator(s):
Writing Group Chair: Ryan Demmer
Senior C4 author: Joe Coresh & Sudha Sheshadri

Potential overlap

- Among approved C4R proposals (see website), which ones are the most similar to this proposal?
    - Neurocognitive Data Harmonization Across C4R Cohorts led by Priya Palta
    - Loneliness among older adults during the COVID-19 pandemic. Findings from the Atherosclerosis Risk in Communities (ARIC) Study led by Anna Kucharska-Newton
- Is there any potential overlap? Please explain and describe.
    - If there is potential overlap, please summarize how this proposal is different
      We do not anticipate meaningful overlap. The harmonization methods paper will likely be important for the methods relating this manuscript to future papers. The loneliness manuscript might generate an important covariable for inclusion as an adjustment in this proposal. The lead author of this manuscript has been in communication with the lead authors of the aforementioned manuscripts to coordinate as necessary. **Note, this analysis will aim to only analyze ARIC cognition data using questionnaire and DBS data for covid ascertainment. From preliminary discussions with Priya Palta, it is understood that future papers analyzing multiple C4R cohorts for cognitive outcomes are on the horizon. However, it was also noted that it will likely be a minimum of 6-12 months before data are collected and harmonized across enough cohorts for a critical mass to support a larger meta-analysis. In the short-term, this question is of high relevance and ARIC has cognitive data collected during 2020 nearly ready for analysis and ARIC will also have a large set of cognitive data from summer 2021 in the early fall of 2021. Therefore, we aim to make rapid use of the C4R infrastructure to address the influence of SARS-CoV-2 infection on cognition among the elderly. If we learn that other cohorts have data that are available for analysis by September, 2021 the manuscript could be expanded to include multiple cohorts.

C4R cohort inclusion table:

Cohorts	Include: Yes / No	Co-author*	Comments**
ARIC	Yes (ARIC data have a	Priya Palta,	

	unique timing meriting a dedicated paper in addition to later meta-analytic papers)	Thomas Mosley, Melinda Powers, James Pike, Joe Coresh (Others welcome)	
CARDIA	No		No post-pandemic data.
COPDGene	No		No post-pandemic data.
Familial Interstitial Pneumonia	No		No post-pandemic data.
Framingham	Possibly, pending data availability.	Sudha Sheshadri	Relevant expertise and overview of the topics across C4R-Neuro Cog
Jackson Heart Study	No		No post-pandemic data.
HCHS/SOL	No		No post-pandemic data.
MASALA	No		No post-pandemic data.
MESA	No		No post-pandemic data.
NOMAS	No	Mitch Elkind	Relevant expertise and overview of the topics across C4R-Neuro Cog
REGARDS	Possibly, pending data availability	Mary Cushman	
SARP	No		No post-pandemic data.
SPIROMICS	No		No post-pandemic data.
Strong Heart Study	No		No post-pandemic data.
Other***	N/A		

*If you do not have a co-author identified to represent a cohort, we will be happy to assist you in identifying one.
**Please justify exclusion of any C4R cohort from your proposal.
***If you anticipate including data from another cohort, please indicate which one(s).

Co-authors not already listed above:
Russel Tracy, Mary Cushman (Vermont C4R laboratory), Lizzy Oelsner and Graham Barr (C4R DCC). Final author list and authorship pending interest and contributing cohorts. Additional C4R investigators are **welcome to join**.

Specific aims and hypotheses:

Specific Aim	Hypothesis
To examine whether SARS-CoV-2 infection status and symptom	1. Cognitive function will decline among participants with previous SARS-CoV-2 infection vs. noninfected

severity predict cognitive function after accounting for pre-pandemic risk factors and cognitive function. Thus, change in cognitive function over a relatively short time period pre (<2 years) and post (<1 years) SARS-CoV-2 is the focus.	participants. 2. Cognitive function will decline more among participants with previous hospitalized SARS-CoV-2 infection vs. nonhospitalized infected participants and noninfected participants. 3. Cognitive function decline will not be different among participants with previous mild or asymptomatic SARS-CoV-2 infection vs. noninfected participants.

Rationale (300 words maximum):

Significance	A variety of infections have been repeatedly linked to risk for incident dementia.[1-3] Recent small-scale studies have noted clear cognitive deficits among patients recovering from SARS-CoV-2 infection/COVID-19 disease.[4] Given the high cumulative incidence of SARS-CoV-2 infection and the heightened susceptibility of elderly individuals at increased risk for cognitive decline, further investigation of the relationship between SARS-CoV-2 infection and short-term cognitive decline is warranted. Importantly, most prior studies have not used a well-defined baseline assessment of cognition pre-infection which is necessary for evaluating intra-individual change, an outcome which is far more robust to confounding by non time varying confounders (e.g., sex, race, genetics). Likewise, having uninfected controls with the same longitudinal change is critical for rigorous inferences.
Relevant prior literature	See Bibliography.
Summary of proposed study	We propose to assess the relationship between SARS-CoV-2 infection (based on questionnaire and serology data) and trends in cognitive function among ARIC participants in collaboration with the C4R consortium. We expect that this analysis will largely rely on data collected in ARIC given the timing of extensive cognitive batteries that were administered shortly before, during and following 2020. However, C4R investigators are welcome to join this manuscript and we'd love to consider relevant data with a similar design. We anticipate that this paper will focus on the specific advantages of the ARIC design, while other cohorts may have different advantages leading to other papers and meta-analyses that will have the benefits of generalizability while having to focus on some common features of all included studies.
Justification for use of C4R	We want to coordinate our efforts using ARIC data with C4R collaborators. Furthermore, C4R funded DBS serology testing will be useful for inferring mildly symptomatic and asymptomatic infection status.

Data:

	Variables needed	Questions and

		comments*
Exposure(s)	SARS-CoV-2 infection status based on wave 1 questionnaire data and DBS serology data. The primary exposure envisioned is categorized as: i) infection vs. none. The secondary exposure variable envisioned is categorized as: i) hospitalized-infection, ii) moderate symptomatic infection; iii) mildly symptomatic/asymptomatic infection, iv) infection-free controls.	Categories will be collapsed if numbers require it.
Outcome(s)	Global cognitive function factor scores based on: Memory: Delayed Word Recall Test (replaced with CERAD for V8 phone-based assessment) Executive function/speed of processing: Digit Span Backward, Trail Making Test A; Trail Making Test B. Language: Animal Naming Score; Word Fluency Test. Timing: Visit 7 pre-pandemic (2018-2019); Visit 8 post-pandemic (2020-2021).	*For ARIC we will use phone-based assessments of cognition among n=3,224 (we will also evaluate all eligible at v7 to assess LTF patterns)
Covariates	Age, sex, race/ethnicity, education, neighborhood, SES, height, smoking, alcohol consumption, BMI, blood pressure, prior stroke, CAD, diabetes, APOE genotype. Visit 7 global cognitive function z-scores including: Memory: Delayed Word Recall; Logical Memory Test; Incidental Learning. Executive function/speed of processing: Digit Symbol Substitution; Digit Span Backward, Trail Making Test A; Trail Making Test B. Language: Animal Naming Score; Boston Naming Test; Word Fluency Test.	*The v7 cognition adjustments can be operationalized a s full-score or a subscore consisting of only visit 8 cognitive tests.

*For meritorious proposals, we will work with you to assess the status of data harmonization of variables of interest.

Analysis plan:

- Primary analyst(s): James Pike
- Brief statistical plan, organized by specific aim
    - We approach this analysis plan assuming only ARIC data will be included. If other cohorts have relevant data ready for analysis by September 2021, the analysis plan will be expanded as appropriate, including methods for harmonization of cognitive instruments. The primary outcome for this manuscript will be cognitive function at ARIC visit 8 operationalized as a global factor score (GFS) for general cognitive performance. The GFS has been described in detail previously[5] and used in prior ARIC publications.[6,7] Briefly, the GFS is a score comprising the battery of cognitive tests conducted during V8 (see variable table above). The GFS can be interpreted in a similar fashion to a z-score because it is scaled to have mean=0 and variance=1. Multivariable regression models will regress V8 GFS on SARS-CoV-2 infection/severity status. Adjustments will be made as follows: model 1: age, sex, race/ethnicity, study center, education, APOE genotype and visit 7 GFS; model 2: smoking, alcohol consumption, BMI, blood pressure; model 3: prior stroke, prevalent CAD, prevalent diabetes model 4: a model without V7 (prepandemic) cognitive function adjustments to assess the influence of confounding by prepandemic cognition.

- Secondary analyses will be conducted for specific cognitive domains using tests common to both v7 and v8 (DSB, ANS, WFT)
- Subgroup analyses will be performed by race/ethnicity, sex, APOE status and study site.

Additional considerations of primary importance to C4R approval -- please comment:

- Inclusion of women and minorities: Sex and race differences will be explored in subgroup analyses.
  - Treatment of sex as a biological variable
  - Appropriate analysis and interpretation of differences by race and ethnicity
- Consideration of social determinants of health: Information on SES such as education and neighborhood will be incorporated.
- Use (or non-use) of genetic data: APOE genotype requested.
- Respect for data sharing restrictions on Strong Heart Study data: Yes, if SHS data are included.

References:

1. Demmer RT, Norby FL, Lakshminarayan K, Walker KA, Pankow JS, Folsom AR, Mosley T, Beck J and Lutsey PL. Periodontal disease and incident dementia: The Atherosclerosis Risk in Communities Study (ARIC). *Neurology*. 2020;95:e1660-e1671. PMC7713724. PMID:32727837.
2. Brown CHt, Sharrett AR, Coresh J, Schneider AL, Alonso A, Knopman DS, Mosley TH and Gottesman RF. Association of hospitalization with long-term cognitive and brain MRI changes in the ARIC cohort. *Neurology*. 2015;84:1443-53. PMC4395884. PMID:25762715.
3. Warren-Gash C, Forbes HJ, Williamson E, Breuer J, Hayward AC, Mavrodaris A, Ridha BH, Rossor MN, Thomas SL and Smeeth L. Human herpesvirus infections and dementia or mild cognitive impairment: a systematic review and meta-analysis. *Sci Rep*. 2019;9:4743. PMC6426940. PMID:30894595.
4. Jaywant A, Vanderlind WM, Alexopoulos GS, Fridman CB, Perlis RH and Gunning FM. Frequency and profile of objective cognitive deficits in hospitalized patients recovering from COVID-19. *Neuropsychopharmacology*. 2021. PMC7884062. PMID:33589778.
5. Gross AL, Power MC, Albert MS, Deal JA, Gottesman RF, Griswold M, Wruck LM, Mosley TH, Jr., Coresh J, Sharrett AR and Bandeen-Roche K. Application of Latent Variable Methods to the Study of Cognitive Decline When Tests Change over Time. *Epidemiology*. 2015;26:878-87. PMC4819068. PMID:26414855.
6. Palta P, Chen H, Deal JA, Sharrett AR, Gross A, Knopman D, Griswold M, Heiss G and Mosley TH. Olfactory function and neurocognitive outcomes in old age: The Atherosclerosis Risk in Communities Neurocognitive Study. *Alzheimers Dement*. 2018;14:1015-1021. PMC6097922. PMID:29605223.
7. Palta P, Sharrett AR, Deal JA, Evenson KR, Gabriel KP, Folsom AR, Gross AL, Windham BG, Knopman D, Mosley TH and Heiss G. Leisure-time physical activity sustained since midlife and preservation of cognitive function: The Atherosclerosis Risk in Communities Study. *Alzheimers Dement*. 2019;15:273-281. PMC6368879. PMID:30321503.