ARIC Manuscript Proposal #2264

PC Reviewed: 11/12/13  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1.a. Full Title: General health and cognitive decline in older adults

b. Abbreviated Title (Length 26 characters): gen health and cognition

2. Writing Group:
   Writing group members: Dmitry Kats, Priya Palta, Mehul Patel, Michelle Snyder, Ada Al Qunaibet, Anna Kucharska-Newton, Thomas Mosley, Lisa Wruck, David Knopman, Alvaro Alonso and Gerardo Heiss

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

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3. Timeline: Perform analyses beginning with ARIC visit 1 data. Complete paper within five months after ARIC-NCS Stage 3 data distribution.

4. Rationale:
   Many chronic diseases are associated with lower levels of cognitive performance at older age,\(^1\textsuperscript{-8}\) which suggests that common health problems in aging adults, such as
ischemic heart disease, may simultaneously lead to cognitive decline and result in neurocognitive disease. The association between general health status and cognition has been investigated using self-assessed general health as a potentially valid proxy for health status, given its predictive ability of mortality and various serious health outcomes.\textsuperscript{9-16} However, the data from these past studies have been primarily cross-sectional\textsuperscript{17-21} with conflicting findings. Alternatively, ARIC-NCS data are well-suited to scrutinize the longitudinal relationship between health status and cognitive decline through the availability of annually collected measures of general health (both self-reported and objective variables) and a rich set of cognitive domain assessments. We will thus use the ARIC cohort to examine whether self-rated general health predicts cognitive decline in adults as they approach older age. Concurrently, to further understand how self-appraised general health affects cognitive decline, the independent effects of objectively-assessed measures of physical and mental health burden on cognitive decline will be tested. We will also explore potential modifications by physical and mental health burden on the association of self-rated health and cognitive decline.

5. **Main Hypothesis/Study Questions:**

Aim 1: To quantify trajectories of self-rated general health and objectively-measured physical and mental health burden from visits 1 to 5

   Hypothesis 1: The trajectory of self-rated general health declines from visits 1 to 5, whereas the scores of physical and mental health burden gradually increase between visit 1 and 5.

Aim 2: To quantify the association of self-rated general health, annually assessed from visits 1 to 5, and cognitive decline from visits 2 to 5

   Hypothesis 2: Worsening self-rated general health from visits 1 to 5 is associated with greater cognitive decline from visits 2 to 5.

Aim 3: To determine the temporality of the association between self-rated general health, annually assessed from visits 1 to 5, and cognitive decline from visits 2 to 5

   Hypothesis 2: Worsening self-rated general health from visits 1 to 5 predicts greater cognitive decline from visits 2 to 5.

Aim 4: To quantify the associations of objectively-assessed measures of physical and mental health burden, collected annually from visits 1 to 5, and cognitive decline from visits 2 to 5

   Hypothesis 4: Worsening objectively-assessed measures of both physical and mental health burden from visits 1 to 5 are associated with greater cognitive decline from visits 2 to 5.
Aim 5: To determine the temporality of the associations between objectively-assessed measures of physical and mental health burden, collected annually from visits 1 to 5, and cognitive decline from visits 2 to 5

Hypothesis 5: Worsening objectively-assessed measures of both physical and mental health burden from visits 1 to 5 predict greater cognitive decline from visits 2 to 5.

Aim 6: To determine whether physical health burden modifies the association of self-rated health and cognitive decline from visits 2 to 5

Hypothesis 6: The association of self-rated general health from visits 1 to 5 and cognitive decline from visits 2 to 5 is stronger among participants with increasing physical health burden from visits 1 to 5.

Aim 7: To determine whether mental health burden modifies the association of self-rated health and cognitive decline from visits 2 to 5

Hypothesis 7: The association of self-rated general health from visits 1 to 5 and cognitive decline from visits 2 to 5 is stronger among participants with increasing physical health burden.

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: Prospective cohort study beginning with ARIC visit 1

Exclusion Criteria: Prospective cohort study beginning with ARIC visit 1

- Aim 1
  - Missing self-rated health at visit 1

- Aim 2
  - Missing cognitive assessments at visit 2
  - Missing self-rated health prior to visit 2

- Aim 3
  - Missing cognitive assessments at visit 2
  - Missing self-rated health prior to visit 2
  - Missing data on the presence of physical and mental health conditions before visit 2

Participants who develop dementia will be included in the analyses. Excluding these individuals, who likely have the greatest cognitive decline and worse physical and mental health, may result in too conservative of a bias. However, participants who developed dementia may not have remained in the cohort by the time of the cognitive interview at visit 5, and so their changes in cognitive function will not be observed. We will follow recommendations developed in the ARIC NCS for individuals who are
missing cognitive measures at visit 5.

**Metrics/Measures:**

**Self-assessment of general health**

- Annual Follow-up Questionnaire administered annually through visit 5
- Participants were asked to self-rate their general health (physical and mental) in relation to their peers of the same age.
  - “Over the past year, compared to other people your age, would you say that your health has been excellent, good, fair or poor?”, and participants selected one of the four choices.
- An ordinal variable will be created for analyses of the exposure of self-rated general health, representing these four choices (1 = poor, 2 = fair, 3 = good, 4 = excellent).

**Burden of physical health conditions**

- Burden of physical health conditions will be assessed using ICD-9 codes from hospitalization records as well as cardiovascular conditions, general health status, invasive procedures and other health-related events, beginning at visit 1. Annual follow-up information for these data is also available through visit 5.
- The Charlson Comorbidity Index\textsuperscript{22-25}, a scale commonly employed by health (including ARIC) researchers to measure burden of disease, will be utilized to derive a count variable from these multiple objective sources of information.
  - Through the Charlson Comorbidity Index scale, a scoring system is first applied based on the presence of 16 physical health conditions:
    - One point will be allotted for each of the following conditions: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, COPD, connective tissue disease, peptic ulcer disease, diabetes mellitus (if uncomplicated) and liver disease (if mild)
    - Two points will be allotted for each of the following conditions: diabetes mellitus (if end-organ damage), moderate to severe chronic kidney disease, Hemiplegia, leukemia, malignant lymphoma and solid tumor (if non-metastatic)
    - Three points will be allotted for liver disease (if moderate to severe)
    - Six points will be allotted for solid tumor (if metastatic) and AIDS.
    - A separate score for age is also included as part of the Charlson score: 0 points for age ≤40 years, 1 point for age 41-50 years, 2 points for age 51-60 years, 3 points for age 61-70 years and 4 points for age 71-80 years. However, since age is adjusted for as a covariate in analyses, the age element of the Charlson score will be omitted to avoid any potential over-adjustment that may bias our results.
  - The Charlson index variable will be updated annually (retaining any previous and not incorporating any newly appearing diagnoses of these 16 conditions into the count, as they are all chronic) to track the development of physical health burden, beginning at visit 1.
- As a sensitivity analysis, we will explore classification of the Charlson index using three categories: ≤1, 2-3 and >3. These cut-points are in line with a previous study utilizing ARIC data.26
- Another option for quantifying the burden of physical health conditions will be taken into account, which uses specified disability weights, generated utilizing data from more than 30,000 respondents contacted through population-based, random-sample surveys, as applied in The State of US Health, 1999-2010 study.27
- Alternate instruments within the literature, such as the Cumulative Illness Rating Scale28, Index of Coexisting Disease29 and Kaplan Index30, will be considered for derivation of the physical health burden variable in this study as well.

**Burden of mental disorders**
- To incorporate an objective assessment of mental health burden, an annually-updated score will be formed based on disability weights designed in Dutch studies31-33 that are refined to allow adjustment for co-morbid disorders. In ARIC, mental health diagnoses are captured using ICD-9 codes of 291-319 from annual hospitalization records.
- As with the objectively-assessed physical health burden variable, this variable will be annually updated (given availability of data) to track objectively-assessed mental health burden, beginning at visit 1.

**Cognitive performance**
All participants in ARIC were assessed on cognitive function at visits 2, 4 and 5 using three standardized tests: the Digit Symbol Substitution Test (DSST) of the Wechsler Adult Intelligence Scale-Revised (WAIS-R), the Delayed Word Recall Test (DWRT) and the Word Fluency Test (WFT), also referred to as the Controlled Oral Word Association Test (COWA) of the Multilingual Aphasia Examination. The DSST tests executive function and processing speed, the DWRT measures verbal learning and immediate memory, and the WFT assesses executive function and expressive language.

A global measure of cognition was derived in the ARIC-NCS data using the race-specific, baseline Z-scores of the three separate tests of cognitive function. Test-specific Z-scores were standardized at follow-up visits to visit 2. The resulting score has a mean of 0 and standard deviation of 1 at visit 2. Alternatively, we will look into utilization of race-specific stratified analyses instead of race-specific Z-scores, which has recently been recommended.

Some participants were absent from visit 5 but have available Telephone Interview for Cognitive Status (TICS) data. For such participants, the DWRT equivalent from the TICS34-36 will be utilized.

Change in domain-specific cognitive function and global cognition, will be measured from visits 2 to 5 (approximately 21 years later).

**Covariates**
Age, sex, race/center, ApoE genotype, income and education will serve as covariates in
For analyses, covariates will either be fixed (i.e., sex) or time-varying when available.

Stratification:
All analyses will be stratified by age group (e.g. 48-54, 55-60 and 61-67 years at visit 2) to provide age-specific trends.

Statistical Analyses:
Aim 1:
Descriptive analyses will first be performed to evaluate how self-appraised general health and physical and mental health burden are distributed from visits 1 to 5. These preliminary results may demonstrate that the effects of these exposures on cognitive decline are better assessed by developing different longitudinal trajectories of the variables from visits 1 to 5 or by considering them as time-dependent exposures without building any actual trajectories.

Aims 2 and 3:
We will examine the effect of time-varying self-assessed general health on cognitive decline using marginal structural models. Depending on how self-ratings of general health are distributed through time, we will consider alternative options for modeling its association with cognitive decline.

Aims 4-7:
Similar analyses will be performed in aims 4-7 for the exposures of objectively-assessed physical and mental health burden. Interactions for physical and mental health burden will be tested in the final general health regression model.

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Previous ARIC studies have detected informative dropout for vascular risk factors and cognitive measures at baseline that may conservatively bias the results of this study. If selective attrition is demonstrated within the data, methods such as inverse-probability-of-attrition weights will be considered to account for any potential biases.

Duration Metric:
Time elapsed since ARIC visit 1 will serve as the time metric for all analyses

Potential Limitations:
A high proportion (i.e., ≥10%) of data is expected to be missing for the cognitive outcomes used in our analyses. Thus, multiple imputation methods will be investigated to account for attrition bias that may misconstruct the results. It is worth noting that ARIC researchers have shown that attrition did not have an effect on an assortment of associations, although this may not be the case with the cognitive outcomes used in this study.

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 (apoE genotype)  ____ 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/search.php  
   ____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)?  

   MS# 1982: Estimation of cognitive change from repeat measures in observational studies; associations with education: the ARIC NCS  

   MS# 1742: Schneider ALC, Sharrett AR, Patel MD, Alonso A, Coresh J, Mosley T, Selnes O, Selvin E, Gottesman RF. Education and cognitive change over 15 years: the ARIC Study. J. Amer Geriatrics Soc. Accepted 2012  

   MS# 1973: Cardiovascular exposures, cognitive decline, and depression in whites and blacks  

   MS# 1858: Midlife occupation and 1990-2006 cognitive decline  

   MS# 2033: Cognitive domains in elderly ARIC blacks and whites  

   MS# 2135: Abnormal sleep characteristics and cognitive change: The Atherosclerosis Risk in Communities Study (ARIC)  

   MS# 2160: Diabetes and cognitive change over 20 years: the Atherosclerosis Risk in
Communities Study

MS# 672: Changes in cognitive test scores in the ARIC cohort over a 6-year period (Visit 2 to Visit 4) and their correlation with vascular risk factors

MS# 1121: Cognitive change over 12 years and its relationship to cardiovascular risk factors: ARIC MRI Study

MS# 1418: Glycemic control (hemoglobin A1c), cognitive decline and dementia risk: The Atherosclerosis Risk in Communities (ARIC) Study

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  
____ 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 at http://www.cscc.unc.edu/aric/forms/

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.csc.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.
References:


18. Webera, D., & Skirbekka, V. Do subjective health measures predict cognitive and physical health among older adults globally?


