TO: ARIC Publication Committee

Colleagues: please find enclosed a manuscript proposal submitted on behalf of Priya Palta (who is away from the office). Please note that the list of proposed co-authors is relatively large, and that several are known to be away from their offices at this time. The majority of the co-authors has not yet reviewed/approved the enclosed proposal.

The descriptive analyses listed in the attached are potentially important to inform the preparation of the ARIC-NCS renewal proposal however, and thus time-sensitive. We therefore request conditional approval of this proposal, to be able to access the data and prepare descriptive statistics of: V2 3-test score (categorized); V6-V5 change in the global cognitive factor score; V6-V5 change in the global cognitive factor score

An updated manuscript proposal will be submitted once reviewed and approved by all co-authors.

Gerardo
ARIC Manuscript Proposal # 3207

1.a. Full Title: Minimal Cognitive Decline

b. Abbreviated Title (Length 26 characters): Minimal cognitive decline

2. Writing Group:

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

First author:
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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 descriptive analyses proposed below are intended for expedited attention as possibly relevant to the ARIC-NCS proposal being developed. Completion of the manuscript expected within 10 months of approval of this proposal.

4. Rationale:
   Background
   A substantial proportion of individuals remain cognitively normal throughout their lifetime, some with AD and other brain pathology and others with brain pathology at lower than expected levels. (1-5) Recent research has focused on optimal or successful aging without cognitive decline in the oldest old. [6, 7, 8] It has also been reported that certain individuals remain free of
brain pathology at advanced ages, a characteristic found to be associated with several lifestyle factors (9), and distinguishing, as some would describe it “normal aging” versus loss of cognitive function associated with “pathological aging”. (10)

Accumulating evidence also suggests that certain lifestyle, behavioral, psychosocial and genetic factors are inversely associated with the progression of brain disease (11-19). With a focus on opportunities for preventing or delaying the onset of late life dementias, several reviews summarized the evidence regarding potentially modifiable risk factors for dementia, i.e. diabetes, midlife hypertension, midlife obesity, smoking, depression, cognitive inactivity, low educational attainment, and physical inactivity. (20) Dietary patterns, such as the Mediterranean diet, also are associated with lower dementia risk (21, 22). Although relying on stringent assumptions, the projected effects of risk factor reduction on prevalence of clinically diagnosed AD have been estimated by calculating population attributable risks, addressing various scenarios of AD dementia cases that might be prevented by individual risk factor reductions worldwide and in the USA. (20) Accounting for non-independence among AD dementia risk factors, Norton et al. (23) highlighted the potential for primary prevention of AD dementia by suggesting that 1/3rd of probable AD dementia cases worldwide is attributable to modifiable risk factors.

More recently, lifetime and current intellectual and physical activities have been reported to be protective against neurocognitive decline and also dementia. Education (1, 2), occupation (3) cognitive and intellectual enrichment activities (25-29) as well as physical activity (13-16) have been identified as possible targets for preventive strategies for ADRD. In contrast, Vemuri and colleagues (25) reported that intellectual and physical activity were not associated with ADP, whereas intellectual lifestyle factors accounted for a significant degree of variability in cognitive performance among non-demented individuals. Vemuri and colleagues subsequently reported (26) that both vascular cerebral vascular pathology as well as amyloid pathologies are predictors of cognitive decline in non-demented older adults, and that their effects on cognitive decline was independent of each other (and additive when they co-occurred). Also in this report, an index derived from a combination of education and occupational job-level score influenced cognitive trajectories. Primary occupation throughout life, and weekly cognitive activity in midlife offset the deleterious effect of each type of pathology on the cognitive trajectories. (26)

While there is considerable evidence that greater intellectual enrichment can aid in delaying the onset of cognitive impairment overall (18, 25-27), the putative protective role of cognitive reserve has also been addressed in settings of high risk of ADRD. Defining cognitive “resilience” as above-average cognitive trajectories in the Health ABC cohort, Kaup and colleagues observed that enhancement of cognitive activities and improvement of various psychosocial and health factors are promoters of cognitive resilience among black and white carriers of APOE ε4. (28)

The literature also suggests that protection against cognitive decline and brain pathology is multidimensional, and should be viewed as a net profile of effects from all factors shown to be associated with less cognitive impairment in the elderly, of their additive or interactive effects,
and the timing of the occurrence over the life course (early life, mid-life and late life). Multi-domain dementia risk scores have shown that linear combinations of several risk factors achieve satisfactory discrimination in predicting dementia risk. (24, 29-30)

Terms and Systematization
Based on the observed discrepancies between degree of pathology and cognition (1-3), the reserve hypothesis has been most widely used to assess the phenomenon of relatively good cognition in the face of brain disease. This has been variously described as neuroprotection or resilience, whether in an active (31, 32) or passive (33, 34) form. Widely used, but frequently not well defined, concepts include cognitive reserve (efficiency and compensation), brain reserve (quantitative developmental aspects of brain structure), brain maintenance (lower susceptibility to age-related brain pathology), or general concepts such as brain compensation and neuroprotection. A systematization recently developed by Arenaza-Urquijo and Vemuri (35) identifies the two distinct mechanisms of (a) avoiding pathology and (b) coping with pathology; the former is referred to as resistance (preservation) and the latter as resilience. The latter aligns well with the clinical and public health perspectives on preventing cognitive decline, and coping with a high burden of risk factors or brain pathology.

The lack of clear operational definitions of these concepts has led to ambiguity and inconsistent approaches in the literature on preclinical ADRD and cognitive decline. Until consensus on terminology is reached in the ARIC-NCS community this proposal will use the terms ‘minimal cognitive decline’ and ‘high burden of risk for cognitive decline’ in order to assess and characterize the factors that promote minimal cognitive decline, in the presence/absence of a high burden of risk. The latter is based on the documented effects of risk factors for cognitive impairment (and pathology) such as ApoEε4, advanced age, diabetes, elevated blood pressure, cerebrovascular small vessel disease or neurodegenerative changes on MRI. Operational definitions are proposed below.

5. Aims/Study Questions:
Our long term goal is to contribute information that enables effective preventive strategies by which individuals and groups can follow pathways of healthy or “exceptional” brain aging, and mitigate the neurocognitive effects of brain pathology.

The aims of these analyses are:

i. Identify and characterize factors that promote minimal cognitive decline from both mid-life to older adulthood and over the well characterized interval between ARIC visits 5 and 6 (less-than-expected cognitive decline with age)

ii. Identify and characterize factors that promote minimal cognitive decline in the setting of a high burden of risk factors for cognitive decline

iii. Assess the presence of (pre-specified) effect modification between exposures (e.g., ApoEε4, high risk factor burden) and protective factors on cognitive decline in late life

iv. Identify the timing over the life course of detectable effects of factors that promote minimal cognitive decline.
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).

Analytic Approach
Examine the patterns of cognitive decline from distributions of V5 score, V6 score and V5-6 change, by age, race-center, sex

Consider operational definitions of age-related minimal cognitive decline, based on the constructs proposed in the literature and on the distributional patterns observed in the ARIC-NCS examinees, by race-center, sex

Examine the distribution of putative protective factors according to minimal cognitive decline in late life, by RF burden and carrier status for ApoE ε4

Assess the presence of effect modification between risk factors and protective factors on cognitive decline in late life

Perform multi-level analysis of individual and contextual protective factors, and identify the timing over the life course of detectable effects of factors that protect against cognitive decline.

A complementary approach can be considered to quantify the discordance between predicted and observed characteristics. Such an approach was originally proposed within the framework of cognitive reserve (32) and has been used by several investigators, and has been shown to predict cognitive decline (36). Although an analytic treatment of resilience on a continuous scale is appealing it is however a reductionist approach, and largely model-dependent in that it is defined by error that is unexplained. We do not propose to use it here.

Measurements
Minimal cognitive decline
Cognitive decline in the lowest (least decline) 25%tile, stratified by age (5 years), sex and race-center. Stratify by ApoE ε4 alleles, diabetes, smoking, uncontrolled hypertension

Potential effect modifiers
ApoE ε4 (0, 1, >1 allele), diabetes, smoking, elevated blood pressure, sedentary behavior

Putative protective factors (promoting minimal cognitive decline)
Protective factors potentially contributing to minimal cognitive impairment are behavioral, lifestyle, socio-economic, and brain structure and integrity. Among the genetic variants associated with cognition, only ApoE ε4 will be considered.
- Education: 3 classes (<high school, high school or equivalent, > high school)
- Occupational complexity
- Socioeconomic position – lifetime, mid-life, late life (refs. 37, 38)
- Social support, social isolation (ref. 39, 40)
“Optimal” levels of blood pressure, HbA1c, BMI, smoking
Hypertension at or below treatment target
Healthy eating index (HEI)
“Life’s simple 7”

Individual and neighborhood life course socioeconomic factors and scoring adapted from Carson AP (ref. 37) and Roberts C (ref 38).

<table>
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<th>Life Epoch</th>
<th>Individual Variable</th>
<th>Individual Variable Value</th>
<th>Neighborhood Variable</th>
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<td>Dwellings Occupied by Owner</td>
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**Outcomes**

**Cognitive trajectories**
V2 3-test score (categorized)
V6-V5 change in the global cognitive factor score.
V6-V5 change in the global cognitive factor score
Minimal MRI small vessel disease (lacunes and WMH volume) and atrophy

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes   __X__ 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? ____ 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? ____ 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 file ICTDER03 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)?

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 (_ARIC-NCS_)  
____ 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 https://www2.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

References


