ARIC Manuscript Proposal #2211

PC Reviewed: 9/10/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Midlife psychosocial factors and cognitive decline
b. Abbreviated Title (Length 26 characters): psych and cognition

2. Writing Group:
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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 2 data. Complete paper within three months after ARIC-NCS Stage 3 data distribution.

4. Rationale:
Both the nature and timing of the relationship between depression and cognitive outcomes remain uncertain. Multiple studies have uncovered strong associations between depression

or depressive symptomatology and cognitive function[1-4], cognitive decline[5], mild cognitive impairment (MCI)[6,7] as well as dementia[8-18] among adults past the age of 60. Cross-sectional studies of middle-aged adults, for the most part, have also reported significant associations between depressive disorders and executive dysfunction but inconsistent findings for verbal memory and learning function outcomes[19]. Having depression at mid-life was significantly associated with an increased risk of Alzheimer's disease in a case-control study[20] as well.

Prospective examinations beginning with younger adults, on the other hand, have demonstrated conflicting findings. For instance, using data from the Baltimore Longitudinal Study of Aging, beginning at a mean age of 55 years, the number of depressive episodes exhibited a significant association with the risk of dementia but not MCI over 25 years.[21] However, a cohort study with adults at a mean age of 40 years at baseline did not reveal a statistically significant difference in cognitive change between those with and without depression.[22] Stemming from a more recent investigation, an increased risk of dementia was reported for those with depressive symptoms at mid-life (40-55 years of age) and a further increased risk of dementia for those who also had a diagnosis of depression later in life.[23] The discrepancies in the results of these prospective studies can be partially attributed to several limitations, including how depressive symptoms are measured and the lack of confirmation of dementia through operational criteria or neuroimaging.

Based on the limitations and inconsistencies across the relevant literature, the precise role of depressive psychopathology in cognitive decline and the developing stages of MCI and dementia requires additional research.[5,23-26] Debate persists whether depressive symptomatology is merely a prodromal expression, a co-occurring condition or in fact a risk factor for cognitive decline and subsequent dementia.[9,23-27] Further insight is also needed regarding the extent of the mechanism between interpersonal support and cognitive decline up to dementia, given that examination of social support has been primarily limited to older adults (i.e., 65 years and up) with conflicting findings for the cognitive outcomes that were investigated.[28]

This study attempts to establish a clearer knowledge of the temporal associations involving these psychosocial states, presenting at mid-life, and a series of cognitive outcomes subsequently developing later in life by taking advantage of prospective ARIC cohort data, equipped with more than 14,000 participants aged 48-67 years at visit 2 as well as a collection of extensive, multidimensional cognitive assessments and diagnoses. We will first examine how the severity of depressive symptoms and level of interpersonal support at visit 2 are each associated with cognitive decline approximately 21 years later up to visit 5. From there, we will determine if there is dysfunctional cognitive decline up to visit 5 by depressive symptomatology and level of interpersonal support using quantitatively established criteria based on the magnitude and reliability of the change in cognitive function. We also aim to determine whether the severity of depressive symptoms and level of interpersonal support at middle age are each associated with an increased risk for the development of MCI and dementia later in life. Simultaneously, we will explore modification of all of these associations by age, race, gender and vascular conditions to identify heterogeneity by subgroups.

5. Main Hypothesis/Study Questions:

Aim 1: To determine whether the severity of depressive symptoms at visit 2 is associated with accelerated cognitive decline from visits 2 to 5

> Hypothesis 1: Greater severity of depressive symptoms at visit 2 is significantly associated with accelerated cognitive decline from visits 2 to 5.

Aim 2: To determine whether the level of interpersonal support at visit 2 is associated with accelerated cognitive decline from visits 2 to 5

> Hypothesis 2: Worse level of interpersonal support is significantly associated with accelerated cognitive decline from visits 2 to 5.

Aim 3: To determine whether the severity of depressive symptoms at visit 2 is associated with dysfunctional cognitive decline from visits 2 to 5

> Hypothesis 3: Greater severity of depressive symptoms at visit 2 is significantly associated with a higher proportion of participants who experience dysfunctional cognitive decline from visits 2 to 5.

Aim 4: To determine whether the level of interpersonal support at visit 2 is associated with dysfunctional cognitive decline from visits 2 to 5

> Hypothesis 4: Worse level of interpersonal support at visit 2 is significantly associated with a higher proportion of participants who experience dysfunctional cognitive decline from visits 2 to 5.

Aim 5: To determine whether the severity of depressive symptoms at visit 2 is associated with an increased risk of the onset of MCI up to visit 5

> Hypothesis 5: Greater severity of depressive symptoms is associated with an increased risk of the onset of MCI up to visit 5.

Aim 6: To determine whether the level of interpersonal support at visit 2 is associated with an increased risk of the onset of MCI up to visit 5

> Hypothesis 6: Worse level of interpersonal support at visit 2 is associated with an increased risk of the onset of MCI up to visit 5

Aim 7: To determine whether the severity of depressive symptoms at visit 2 is associated with an increased risk of the onset of dementia up to visit 5

> Hypothesis 7: Greater severity of depressive symptoms is associated with an increased risk of the onset of dementia up to visit 5.

Aim 8: To determine whether the level of interpersonal support at visit 2 is associated with an increased risk of the onset of dementia up to visit 5

Hypothesis 8: Worse level of interpersonal support at visit 2 is associated with an increased risk of the onset of dementia up to visit 5.

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 with ARIC visit 2 as baseline.

Exclusion Criteria:
If <10% of the data are missing, participants that meet any of the following criteria will be excluded from this study:

- Absent from or missing more than three questions related to the assessment of depressive symptoms at visit 2 (aims 1, 2, 4 and 6)
- Absent from or missing more than three questions related to the assessment of interpersonal support at visit 2 (aims 1, 3, 5 and 7)
- Missing cognitive tests at visit 2 (aims 1-3)

Participants who develop MCI or dementia will be included in the analyses of aims 1-4, as exclusion of these individuals, who most likely demonstrate the greatest cognitive decline and have more severe depressive symptoms[29], may pose too large of a conservative bias on the measures of association. Participants who developed MCI or dementia earlier in life 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. Therefore, for all individuals who did not complete a cognitive interview at visit 5, we will look into application of special methods explored by ARIC-NCS for missing cognitive outcomes.

Exposures:
Severity of depressive symptoms

- The Vital Exhaustion Questionnaire (tabbed as Part B of the Health and Life Profile) was used to self-assess depressive symptoms at visit 2.
- Possible scores for this 21-item questionnaire range from 0 to 42, with a higher score indicating more depressive symptoms.
- This questionnaire has been utilized to measure depression as an exposure in two known studies.[30,31] The most recent of these[30] examined the association between anger proneness, depression and low social support with peripheral arterial disease also using ARIC data and so will serve as the model to guide construction of the psychosocial exposures in this study.
- Hence, overall depressive symptom scores will be classified into tertiles, with the lowest level of depressive symptoms as the reference point.
    - *Note:* Alternate options for quantification will also be explored.

Level of interpersonal support

- Interpersonal support questions were self-assessed at visit 2 in Part A of the Health

and Life Profile, originating from the Interpersonal Support Evaluation List, a 40-item questionnaire designed to assess the perception of available social support.

- Twenty-four (six questions from four subscales) of the 29 questions that appear in ARIC represent the Perceived Social Support Scale used for this study. Total point values ranged from 6 to 24, with lower scores indicating higher levels of perceived social support.
- Similar to the depressive symptoms variable, overall scores for interpersonal support will be grouped into tertiles, with the highest level of perceived social support as the reference point, as was also performed in the previously mentioned study.[30]
    - *Note:* Alternate options for quantification will also be explored.

Effect Modification:
Analyses will be performed stratified by age group at visit 2 (e.g., 48-54, 55-60 and 61-67 years at visit 2). Additionally, modification of the measure of effect of the psychosocial exposures on cognition by race/center, sex, diabetes and hypertension will be explored.

Covariates: age, sex, race/center, hypertension, diabetes, smoking, coronary heart disease, heart failure, stroke, alcohol use, total cholesterol, HDL cholesterol, ApoE genotype, education, income and exposure to medications known to adversely affect cognition. For analyses, covariates will either be fixed (i.e., sex) or time-varying if available in the data.

Outcomes:
Cognitive Function and Cognitive Decline
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 memory, executive function and processing speed, the DWRT measures verbal learning and recent memory, and the WFT assesses executive function and expressive language.

A global measure of cognition was derived in the ARIC-NCS data by first averaging 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 ARIC visit 2. The resulting score has a mean of 0 and standard deviation of 1 at ARIC 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 TICS[32-34] will be utilized.

Analyses will be performed on each of the three tests separately and the global measure of cognition.

MCI and Dementia

A thorough, three-stage process is currently being utilized to assess diagnoses of MCI and dementia. This process commenced with a comprehensive neurocognitive test battery at Stage I, which involved a structured interview and a series of neuropsychological tests. Those then examined at Stage I who (1) had low neurocognitive test scores indicating possible dementia or MCI, (2) were surviving participants from the ARIC Brain MRI Study or (3) made up a random sample of all other individuals, were requested to participate in Stages II and Stage III. Please refer to Appendix I for specific information regarding this three-stage process and assessment of MCI and dementia.

For analyses related to dementia, we will examine diagnoses of Alzheimer's disease (AD) and vascular dementia (VaD) as distinct outcomes as well as a separate outcome representing a diagnosis of AD, VaD or both.

Statistical Analyses:

Aims 1 and 2

Previous research has noted the existence of informative dropout for vascular exposures and cognitive outcomes that may conservatively bias the results of this study. To account for the potential of a similar bias for the exposures used in this study, multivariate random effects linear models and shared parameter models will be utilized to examine associations between the severity of depressive symptoms and level of interpersonal support on cognitive decline. Additionally, methods such as models with inverse-probability-of-attrition weights will also be considered to account for the effects of selective attrition. Finally, we will examine issues created by competing risks, given that individuals die before they experience cognitive impairment or dementia.

Aims 3 and 4

From there, we will examine whether the degree of cognitive change from visit 2 to 5 differs in terms of functionality by severity of depressive symptoms and level of interpersonal support using the two-step Jacobson-Truax (JT) method[35,36], which provides sufficient estimates of what can be characterized as dysfunctional change.[37-39] The first step of the JT method involves establishing a cutoff point that separates the "functional" population from the "dysfunctional" population. When adequate norms for such a cutoff point are lacking, as in the case for cognitive decline, a quantitatively-established cutoff point, called *Cutoff A*, is utilized.[40] *Cutoff A* designates the functional population as participants with cognitive scores (global and specific domains) that are 2 *SD*s or more from the mean cognitive scores at visit 2. The second step determines whether a participant's changes in cognitive scores from visit 2 to 5 are reliable rather than a product of measurement error by comparing each participant's change in cognitive scores from visit 2 to 5 to the standard errors, referred to as the Reliable Change Index (RCI).

These two steps are used to classify participants into one of five categories: recovered (participant has passed *Cutoff A* and the RCI in the positive direction), improved (participant has passed the RCI in the positive direction but not *Cutoff A*), unchanged (participant has not passed either criterion), deteriorated (participant has passed the RCI in the negative direction) and non-meaningful deterioration.

We will compare the proportion of participants who fall within these five categories of cognitive change by the severity of depressive symptoms as well as level of interpersonal support, using logistic regression, ordinal logistic regression or t-tests. We will begin the analyses by utilizing ordinal logistical regression but also look into application of these other methods, based on which option provides the most preferred way to report the findings.

Aims 5-8
Cox proportional hazards models with fixed and time-dependent covariates[41-43] will be used to examine the individual effects of the level of depressive symptomatology and interpersonal support on the incidence of MCI and dementia up to visit 5, with adjustment for fixed parameters and time-varying covariates.

Duration Metric:
Time elapsed since ARIC visit 2 will serve as the time metric in the longitudinal models used in this study.

Potential Limitations:
The main exposures of interest in this study, depressive symptoms and interpersonal support, were measured only once through the ARIC cohort at visit 2, which does not allow for intra-individual variability in these exposures to be considered. Despite this drawback, if significant results are demonstrated (e.g., if dysfunctional cognitive decline is considerably more common in participants who report a greater severity of depressive symptoms or lower level of interpersonal support at mid-life, and such participants experience the highest risk of MCI and dementia), these findings would point to midlife psychosocial characteristics as playing key roles within the development mechanism of cognitive decline up through neurocognitive disease. Detecting such associations would simultaneously pave the way for future, large-scale prospective studies on cognitive outcomes that incorporate repeated and richer longitudinal measurements of these psychosocial factors to further elucidate the timing and specifics of their effects.

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? **__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 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.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.

Appendix I:

Diagnoses of MCI and dementia are currently being made utilizing an in-depth three-stage process summarized as so: All 7,229 participants who were recruited for visit 5 were invited to receive a comprehensive neurocognitive test battery at Stage I. Those then examined at Stage I who (1) had low neurocognitive test scores indicating possible dementia or MCI, (2) were surviving participants from the ARIC Brain MRI Study in 2004-2006 or (3) made up a random sample of all other individuals, were requested to participate in Stage II (retinal photography, informant interviews and neurological examination for dementia) as well as Stage III (neuroimaging). Stage I assessment involves a structured interview to update medical history and medications, anthropometry, blood pressure, ankle-brachial index, specimen collection along with a 1-hour series of neuropsychological tests to identify potential dementia and MCI cases. Stage II includes retinal photography, additional laboratory assays on specimens collected at Stage I, a neurological examination and assessment of functional status and psychiatric symptoms. Stage III consists of neuroimaging in which examinations at home or long term care facilities will be available for participants unable to come to the clinic. For individuals from our study's original cohort that end up being recruited for Visit 5, those with suspected dementia or MCI after two stages of evaluation, including a clinic and home visit, have their data reviewed by an adjudication committee composed of experts in dementia diagnosis.

MCI is assessed based on published criteria.[44] For diagnosis, three criteria must be met: (1) an objective cognitive deficit must be present (i.e., any cognitive domain score ≥1.5 SD below normal) that represents a decline from past level of functioning (using past ARIC testing or the Clinical Dementia Rating Scale [CDR][45,46]), (2) normal or only minimally impaired functional status (CDR of 0 or 0.5) and (3) either the participant or informant reports a cognitive complaint. MCI is split up into four groups by type (from the scheme in use by the National Institute on Aging Alzheimer's Disease Centers Program for the Uniform Data Set) as amnestic or non-amnestic, single or multiple domain.[44] Additionally, a fifth category ('Impaired Not MCI') is established for subjects whose functional and cognitive status falls in the MCI range, but whose clinical picture does not match MCI criteria. An etiological classification of the MCI from among the categories of presumed degenerative, vascular, psychiatric, medical-systemic illness or other is also noted by adjudicators using their best clinical judgment.

The diagnosis of dementia will follow the Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition (DSM-IV) criteria and will require deficits in performance (cognitive domain score ≥2 SD below normal in ≥2 domains), that are sufficient to affect daily living activities (CDR ≥1.0), that represent a decline from prior level of functioning.[47] Quantification of the decline in functional status will be based on the CDR from participant assessment as well as informant interviews. Decline in cognitive functioning will be established through comparison with prior ARIC test scores and the CDR. The dementia criteria are designed to pinpoint subjects with syndromes that may include relatively preserved memory functions (e.g., frontotemporal dementia). Hence, a memory deficit is not necessary for dementia diagnosis.

A diagnosis of AD that appears in the data is made according to the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.[48] This diagnosis requires that the individual meet criteria for dementia (based on DSM-IV criteria).

When MRI data are available, VaD will be diagnosed utilizing the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria.[49] Such will require DSM-IV criteria for dementia, evidence of cerebrovascular disease (defined in the Stage II neurological exam and by neuroimaging) and a relationship between the cognitive impairment and cerebrovascular disease. Subtypes include probable VaD, VaD with AD, and VaD with other cause of dementia.

When MRI data are not attainable, VaD diagnosis will require a diagnosis of dementia (as above), evidence of cerebrovascular disease from the neurological exam and modified Hachinski Ischemic Index items, which mimic the non-imaging portions of the NINDS-ARIEN criteria.[50,51] Key Hachinski items include abrupt or stepwise deterioration of cognition in association with clinical stroke, focal neurological signs consistent with cerebrovascular lesions and focal neurological symptoms consistent with vascular lesions. Other elements of the original Ischemic Index are deemed to be inadequate and thus omitted. Subtypes will include possible VaD, VaD with AD, and VaD with other cause of dementia.

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