ARIC Manuscript Proposal #2215

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

1.a. Full Title: Development of longitudinal measures of general and domain-specific latent factors for cognitive performance

b. Abbreviated Title (Length 26 characters): Latent cognitive performance

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

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3. Timeline:
Manuscript will be completed by October, 2013.
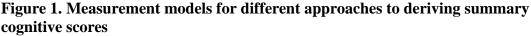
4. Rationale:

Longitudinal studies suggest a large proportion of older adults experience cognitive decline (Hayden et al., 2011; Yaffe et al., 2009). The importance of cognitive performance in everyday functioning is well established; it is a stronger predictor of everyday functioning than most other health characteristics (Burdick et al., 2005; Cahn-Weiner et al., 2002; Christensen et al., 1999; Galanos et al., 1994). A primary objective of ARIC NCS is to evaluate midlife factors (primarily cardiovascular risk factors and markers) which contribute to long-term cognitive decline and cognitive impairments in older adults. Because the ARIC study used a multi-cohort longitudinal design (Thompson
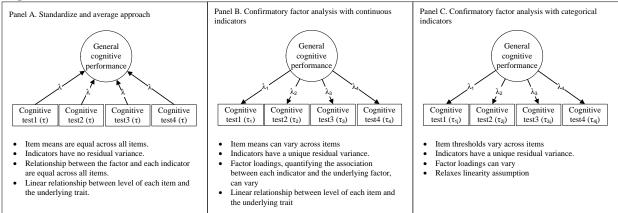
et al., 2011) to assess cognitive performance as early as age 45, the ARIC study is uniquely positioned to identify correlates in midlife of early cognitive decline during later life.

Alcohol use is one such midlife exposure that presents an interesting and meaningful opportunity to determine effects on particular cognitive domains. Although evidence of an association between alcohol and cognitive performance is mixed, a recent study found a specific association between alcohol use, measured during midlife, and phonemic fluency measured 12 years later even after adjusting for attention, memory, and global cognitive performance (Gross et al., 2011). This study did not examine effects of alcohol on changes in cognitive performance, however. Complicating the question, many studies suggest a j-shaped relationship between alcohol and cognition such that non-drinkers and heavy drinkers have poor cognitive performance compared to moderate drinkers (Anttila et al., 2004; Bond et al., 2005; Britton et al.; Cervilla et al., 2000; Elias et al., 1999; Flicker et al., 2005; Galanis et al., 2000; Kalmijn et al., 2002; Leroi, Sheppard, & Lyketsos, 2002; McGuire, Ajani, & Ford, 2007).

Diabetes also has been identified as a risk factor for accelerated cognitive decline (Comijs et al., 2009; Gregg et al., 2000; Knopman et al., 2009; Logroscino et al., 2004). In addition to cognitive decline, diabetes has been associated with incident Alzheimer's disease and vascular dementia (Ahtiluoto et al., 2010; Borenstein et al., 2005), hospitalization with dementia (Alonso et al., 2009), and lower semantic fluency (Arvanitakis et al., 2010).

A complication of studying longitudinal cognitive decline in the ARIC study is that the neuropsychological test battery differed over study waves. There are several ways to combine cognitive data across waves. The most obvious approach would be to use tests that are in common across study waves, discarding information provided by non-common tests. A second common approach involves standardizing each test score in a battery by centering on a sample-specific mean and dividing by a sample-specific standard deviation, and then summing or averaging tests together into a composite z-score (e.g., Willis, 2006; Wilson, 2002) (**Figure 1, panel A**). All tests in the composite are equally weighted. This averaging and standardization approach succeeds in placing cognitive performance on a common scale in a single study wave, but does not address skewed response distributions, does not allow differential weighting of tests, and ultimately does not provide a common metric to facilitate comparisons across waves. Use of averaged, standardized scores is defensible only in single samples or when common measures are available across waves.

Figure 1. Measurement models for different approaches to deriving summary cognitive scores

Panel A. Standardize and average approach

General cognitive performance

Cognitive test1 (τ) | Cognitive test2 (τ) | Cognitive test3 (τ) | Cognitive test4 (τ)

- Item means are equal across all items.
- Indicators have no residual variance.
- Relationship between the factor and each indicator are equal across all items.
- Linear relationship between level of each item and the underlying trait.

Panel B. Confirmatory factor analysis with continuous indicators

General cognitive performance

λ_1 λ_2 λ_3 λ_4

Cognitive test1 (τ_1) | Cognitive test2 (τ_2) | Cognitive test3 (τ_3) | Cognitive test4 (τ_4)

- Item means can vary across items
- Indicators have a unique residual variance.
- Factor loadings, quantifying the association between each indicator and the underlying factor, can vary
- Linear relationship between level of each item and the underlying trait

Panel C. Confirmatory factor analysis with categorical indicators

General cognitive performance

λ_1 λ_2 λ_3 λ_4

Cognitive test1 (τ_{1j}) | Cognitive test2 (τ_{2j}) | Cognitive test3 (τ_{3j}) | Cognitive test4 (τ_{4j})

- Item thresholds vary across items
- Indicators have a unique residual variance.
- Factor loadings can vary
- Relaxes linearity assumption

An alternative is to use confirmatory factor analysis (CFA) to derive composite scores based on continuously distributed individual tests (**Figure 1, panel B**). Tests may be weighted differently depending on empirical correlations, and be composed of sub-tests or items with different difficulties. This approach can be used to calibrate cognitive tests into common factors across study waves even when different, but overlapping, sets of cognitive tests were administered. Tests can be weighted differently, and item means and standard deviations are not fixed to be equal. This approach is more flexible than the average z-score approach, but may still obscure non-linearity in the relationship between cognitive tests and the underlying latent cognitive trait. In other words, there is no reason to assume the distance between each score increment on the underlying trait is the same across the range of a test. For example, decline in the Mini-Mental State Examination (MMSE) from 30 to 28 suggests more severe decline than decline from 10 to 8 (Folstein et al., 1975; Proust-Lima et al., 2007).

A fourth approach to calibrating cognitive performance across study waves is to estimate a confirmatory factor analysis for cognitive performance in which cognitive test items are categorical (**Figure 1, panel C**). This is a useful approach for test items that are heavily skewed. In this approach, cognitive tests are discretized to relax the assumption of linearity of the relationship between underlying cognitive performance and performance level on a test. The underlying factor has interval instead of ordinal scaling properties (Stevens, 1946). Discretization may be viewed as a limitation, because it represents a loss of information. However, as most cognitive tests are timed tests or counts, and thus have skewed distributions, it might be inappropriate to treat them as continuous indicators in CFA.

The main objective of this study is to derive latent factors representing general cognitive performance, memory, language, and executive functioning/speed of information processing from neuropsychological performance data available from waves 2 (1990-92), 4 (1996-98), and 5 (2011-13) of the ARIC study. We will identify and adjust for differential item functioning for cognitive test items attributable to race (white and black). We will then calibrate factors for cognitive performance at waves 2 and 4 to be on the same scale as the wave 5 factor, thus facilitating longitudinal analyses. Finally, we

will determine the extent to which diabetes and alcohol consumption measured during midlife are associated with changes in general cognitive function, memory, and executive function across the adult life course.

This proposal will develop methods which will be shared with additional proposals on cognitive decline. The intent is also to test assumptions to inform the utility, strengths and limitations of the structural equation modeling approach.

5.   Main Hypothesis/Study Questions:

1. To derive composite factors of general cognitive performance, memory, language, and executive function/processing speed.
    a. Approach: We will use confirmatory factor analysis to develop factors and describe their psychometric properties.
    b. Hypothesis 1: Cognitive indicators measure cognitive performance similarly across visits. This will improve the ability to look at changes even from visits (e.g. 2 and 4) that have fewer indicator tests.
2. To identify and adjust for differential item functioning for cognitive test items attributable to race.
    a. Hypothesis 2: Cognitive indicators measure cognitive performance in a similar fashion across racial groups.
3. To determine the extent to which alcohol consumption measured during midlife is associated with baseline levels and changes in general cognitive performance, memory, language, and executive function across the adult life course.
    a. Hypothesis 3: We hypothesize that a j-shaped relationship exists between alcohol and cognitive decline exists, and further that effects are strongest for executive functioning and speeded tasks.
4. To determine the extent to which diabetes measured during midlife is associated with changes in general cognitive performance, memory, language, and executive function across the adult life course.
    a. Hypothesis 4: We hypothesize that diabetes is associated with steeper general cognitive decline. We have no hypotheses regarding domain-specific effects, but will examine associations.

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 observational study of N=14,623 community-living older adults who participated in ARIC for up to 23 years in waves 2 (1990-92), 4 (1996-98), and 5 (2011-13).

Table 1. Study sample sizes at each wave

ARIC study wave (visit)	Sample size
Wave 2	14,348
Wave 4	11,656
Wave 5	5,742 (ongoing)

Outcome: Level and annual pace of change in general and domain-specific cognitive performance. A unique challenge of ARIC is that the neuropsychological battery changed over time. Specifically, three tests (phonemic fluency, delayed word recall, and digit symbol substitution) were administered at waves 2 and 4. A more thorough battery of 11 tests was administered at visit 5 (Table 2).

Table 2. Descriptive statistics for cognitive variables across ARIC visits (N=14,348)

Cognitive test	Wave2 1990-92 mean (SD)	Wave4 1996-98 mean (SD)	Wave5 2011-13 mean (SD)
Delayed word recall	6.6 (1.5)	6.6 (1.6)	5.2 (1.9)
Logical Memory I and II (sum of recall)			19.0 (8.1)
Incremental Learning			1.3 (0.6)
Trail Making Test, Part A (log transformed)			1.7 (0.5)
Trail Making Test, Part B (log transformed)			0.7 (0.5)
Digit symbol substitution	44.6 (14.2)	43.5 (13.5)	37.9 (12.2)
Digit span backwards			5.5 (2.0)
Semantic fluency			16.1 (5.1)
Boston Naming, 30-item			24.6 (5.5)
Phonemic fluency	33.1 (12.5)	33.4 (12.6)	32.8 (12.3)
Clock time			10.6 (1.0)

Exposure: Self-reported frequency and quantity of alcohol consumption (Aim 3) was collected during wave 2 for specific types of alcohol (beer, liquor, wine). Diabetes (Aim 4) will be classified into three levels based on self-report and objectively collected data from ARIC wave 2: no diabetes, undiagnosed diabetes based on elevated glycated hemoglobin, and diagnosed diabetes.
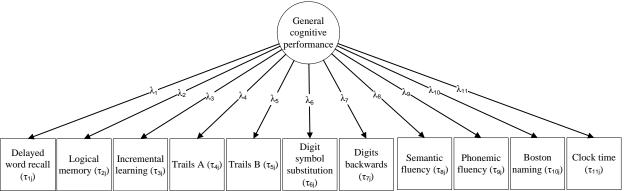
Statistical analysis:

Aim 1. To derive composite factors of general cognitive performance, memory, language, and executive function/processing speed.

We will perform confirmatory factor analyses (CFA) of the ARIC neuropsychological battery at wave 5. Factor analysis is a statistical approach for
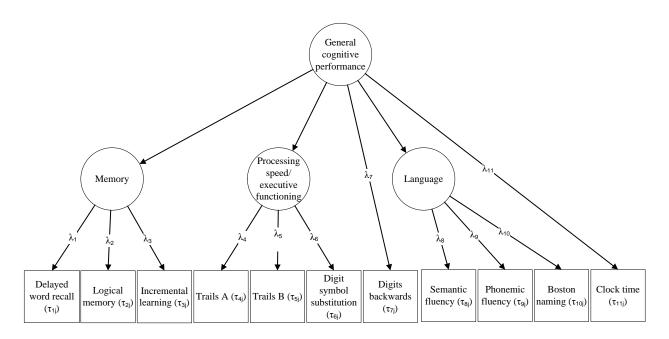
studying common covariation or interrelationships among a set of variables (e.g., cognitive test scores) by deriving a set of common underlying factors (**Figure 2**). We will compare different ways of scaling tests by treating them as continuously distributed, by specifying a Tobit link function for skewed tests, or by categorizing some or all tests that are not normally distributed. We will examine normalized residuals of correlations to identify violations of local independence (**Figure 3** shows one way to parameterize such a model). All models will be estimated using a full information maximum likelihood function with robust standard errors.

Figure 2. Unidimensional confirmatory factor analysis model of general cognitive performance at ARIC visit 5.

Note. Two types of parameters are estimated for each cognitive indicator, a slope (λ) and an intercept or series of thresholds (τ). Slopes characterize the strength of the relationship between the latent variable and an indicator. Items with larger slopes are more highly weighted in factor estimation. For continuously distributed variables, a single intercept is estimated (analogous to the constant term in linear regression). For categorical variables with k categories, k-1 thresholds are estimated and correspond to boundaries where the sample's probability of responding correctly is 50% for one group relative to the next. This diagram corresponds to a general cognitive factor; we will develop similar models for language, speed of processing/executive functioning, and memory. Visuospatial ability is measured by one item, Clock time, and needs no factor.
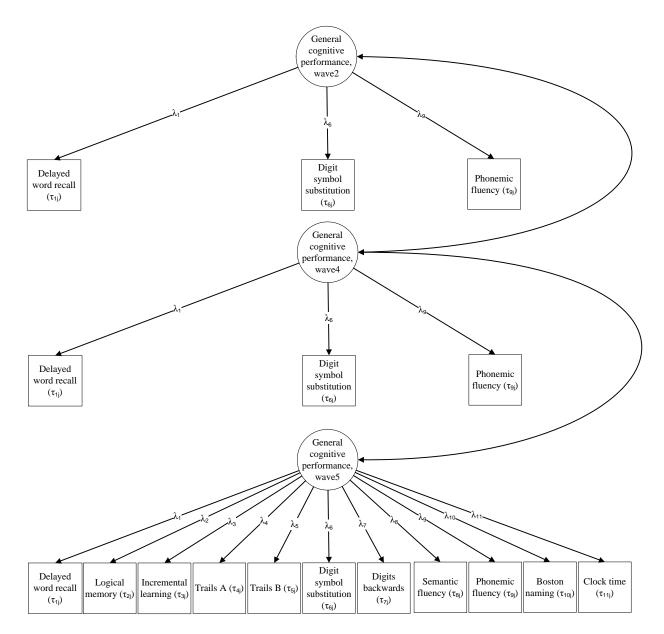
Figure 3. Second-order confirmatory factor analysis model of general cognitive performance at ARIC visit 5.

General cognitive performance

Memory — λ_1, λ_2, λ_3

Processing speed/ executive functioning — λ_4, λ_5, λ_6

λ_7

Language — λ_8, λ_9, λ_{10}

λ_{11}

Delayed word recall (τ_{1j}) | Logical memory (τ_{2j}) | Incremental learning (τ_{3j}) | Trails A (τ_{4j}) | Trails B (τ_{5j}) | Digit symbol substitution (τ_{6j}) | Digits backwards (τ_{7j}) | Semantic fluency (τ_{8j}) | Phonemic fluency (τ_{9j}) | Boston naming (τ_{10j}) | Clock time (τ_{11j})

Note. Based on prior experience and research using ARIC data (Rawlings et al., in preparation) and other datasets (Park et al., 2011), we anticipate that a model which takes into account extra correlations between like cognitive tests will fit better to the data.

Once models with acceptable fit to the wave 5 data are identified, we will calibrate factors for general and domain-specific cognitive performance at waves 2 and 4 to be on the same scale as the wave 5 factor by constraining item discrimination parameters for like items to be equivalent over time (**Figure 4**).

Figure 4. Confirmatory factor analysis with multiple ARIC study waves and model parameter constraints imposed to force measurement equivalence across wave.

General
cognitive
performance,
wave2

λ_1

λ_6

λ_9

Delayed
word recall
(τ_{1j})

Digit
symbol
substitution
(τ_{6j})

Phonemic
fluency (τ_{9j})

General
cognitive
performance,
wave4

λ_1

λ_6

λ_9

Delayed
word recall
(τ_{1j})

Digit
symbol
substitution
(τ_{6j})

Phonemic
fluency (τ_{9j})

General
cognitive
performance,
wave5

λ_1 λ_2 λ_3 λ_4 λ_5 λ_6 λ_7 λ_8 λ_9 λ_{10} λ_{11}

Delayed
word recall
(τ_{1j})

Logical
memory (τ_{2j})

Incremental
learning (τ_{3j})

Trails A (τ_{4j})

Trails B (τ_{5j})

Digit
symbol
substitution
(τ_{6j})

Digits
backwards
(τ_{7j})

Semantic
fluency (τ_{8j})

Phonemic
fluency (τ_{9j})

Boston
naming (τ_{10j})

Clock time
(τ_{11j})

Note. Item slope and threshold parameters for delayed word recall, digit symbol substitution, and phonemic fluency are constrained to be equal over time. This measurement equivalence ensures that the latent factor measured at different points in time is measuring the same underlying construct in the same way, despite missing data.

Missing data handling. There are with aspects of missing data: missing data in specific indicators and missing data due to a missed visit. With respect to the first aspect, missing data on specific cognitive tests are assumed to be missing at random conditional on variables in the measurement model, and handled using maximum likelihood methods during estimation of the model (McArdle et al., 2009). Technically, visits 2 and 4 have missing data on the eight new tests administered during visit 5. This approach is reasonable because an implicit assumption

underlying latent variable models is that indicators are exchangeable with each other. The systematic missingness in cognitive tests in ARIC by wave was completely determined by study investigators, and is thus independent of a participant's underlying level on the latent variable representing cognitive functioning. With respect to the second aspect of missing data, during inferential modeling in Aims 3 and 4 we will consider inverse probability weights, expanded measurement models, and examine other models that account for non-ignorable missingness using a latent shared parameter model (SPM), pattern mixture model (PMM), sensitivity analysis, or another approach.

Aim 2. To identify and adjust for differential item functioning for cognitive test items attributable to race.

Performance on a test should be contingent only on the underlying cognitive ability being estimated, and not attributable to extraneous factors such as race. Just as the metric on a ruler must be invariant across different objects, so should item parameters estimated by a CFA model for general or domain-specific cognitive function. This aim is crucial for providing unbiased, high-quality estimates of cognitive performance.

To the extent that performance on cognitive tests differ as a function of race, multiple indicators/multiple causes (MIMIC) model analysis will help identify and correct measurement bias (Jöreskog & Goldberger, 1975). A MIMIC model is a confirmatory factor analysis in which indicators (a cognitive test item) and the latent factor (general or domain-specific cognitive function) are simultaneously regressed on a predictor (e.g., race). Differences in underlying ability by race are modeled simultaneously with each item response function. This allows us to determine whether there is a relationship between an indicator and a predictor, controlling for overall cognitive function. Any differential item functioning can be corrected by retaining effects of the covariate on the indicator, thus removing bias attributable to that predictor.

Aim 3. To determine the extent to which alcohol consumption measured during midlife is associated with baseline levels and changes in general cognitive performance, memory, language, and executive function across the adult life course.

Aim 4. To determine the extent to which diabetes measured during midlife is associated with changes in general cognitive performance, memory, language, and executive function across the adult life course.

We will examine the question with random effects growth models of changes in cognitive performance. A growth process is comprised of random effects for the baseline intercept or initial level, a linear rate of change or trajectory, and other parameters as needed (e.g., quadratic change). Alcohol use will be the primary exposure of interest in **Aim 3**. Diabetes will be the primary exposure of interest in

Aim 4. We will allow for nonlinear associations in the association between alcohol and cognition by categorizing alcohol consumption. Models will allow us to examine the degree to which the exposures, measured during ARIC study wave 2, are associated with levels and changes in general cognitive performance, memory, language, and executive functioning/processing speed. We plan to use age as the timescale of interest. Models will control for sex, education, depression, stroke, visual impairment, heart disease, hypertension, physical activity, and smoking. Effects of attrition on these associations will be utilized by methods (e.g. inverse probability weights or shared parameter models) consistent with recommendations of the NCS Analysis Workgroup.

We will examine the fit of inferential models using residual diagnostics, pseudo-r^2 statistics, and assorted graphical tools (Singer & Willet, 2003).

References:

Ahtiluoto S, Polvikoski T, Peltonen M, et al. Diabetes, Alzheimer disease, and vascular dementia: a population based neuropathologic study. *Neurology*. Sep 28 2010;75(13):1195-1202.

Alonso A, Mosley TH, Jr., Gottesman RF, Catellier D, Sharrett AR, Coresh J. Risk of dementia hospitalisation associated with cardiovascular risk factors in midlife and older age: the Atherosclerosis Risk in Communities (ARIC) study. *J Neurol Neurosurg Psychiatry*. Nov 2009;80(11):1194-1201.

Anttila, T., Helkala, E. L., Viitanen, M., Kåreholt, I., Fratiglioni, L., Winblad, B., Soininen, H., Tuomilehto, J., Nissinen, A., & Kivipelto, M. (2004). Alcohol drinking in middle age and subsequent risk of mild cognitive impairment and dementia in old age: A prospective population based study. *British Medical Journal*, 329, 539.

Arvanitakis Z, Bennett DA, Wilson RS, Barnes LL. Diabetes and cognitive systems in older black and white persons. *Alzheimer Dis Assoc Disord*. Jan-Mar 2010;24(1):37-42.

Bond, G. E., Burr, R. L., McCurry, S. M., Rice, M. M., Borenstein, A. R., & Larson, E. B. (2005). Alcohol and cognitive performance: A longitudinal study of older Japanese Americans. The Kame project. *International Psychogeriatrics*, 17, 1–16.

Borenstein AR, Wu Y, Mortimer JA, et al. Developmental and vascular risk factors for Alzheimer's disease. *Neurobiol Aging*. Mar 2005;26(3):325-334.

Britton, A., Singh-Manoux, A., & Marmot, M. (2004). Alcohol consumption and cognitive function in the Whitehall II Study. *American Journal of Epidemiology*, 160, 240–247.

Burdick, D. J., Rosenblatt, A., Samus, Q. M., Steele, C., Baker, A., Harper, M., ... Rosenblatt, A. (2005). Predictors of functional impairment in residents of assisted-living facilities: The Maryland Assisted Living Study. *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences*, 60, 258–264.

Cahn-Weiner, D. A., Boyle, P. A., & Malloy, P. F. (2002). Tests of executive function predict instrumental activities of daily living in community-dwelling older individuals. *Applied Neuropsychology*, 9, 187–191.

Christensen, H., Mackinnon, A. J., Korten, A. E., Jorm, A. F., Henderson, A. S., Jacomb, P., & Rodgers, B. (1999). An analysis of diversity in the cognitive performance of elderly community dwellers: Individual differences in change scores as a function of age. *Psychology and Aging*, 14, 365–379.

Cervilla, J. A., Prince, M., Joels, S., Lovestone, S., & Mann, A. (2000). Long-term predictors of cognitive outcome in a cohort of older people with hypertension. *British Journal of Psychiatry*, 177, 66–71.

Comijs HC, Kriegsman DM, Dik MG, Deeg DJ, Jonker C, Stalman WA. Somatic chronic diseases and 6-year change in cognitive functioning among older persons. *Archives of Gerontology and Geriatrics*. Mar-Apr 2009;48(2):191-196.

Elias, P. K., Elias, M. F., D'Agnostino, R. B., Silbershatz, H., & Wolf, P. A. (1999). Alcohol consumption and cognitive performance in the Framingham Heart Study. *American Journal of Epidemiology*, 150, 580–589.

Flicker, L., Almeida, O. P., Acres, J., Le, M. T., Tuohy, R. J., Jamrozik, K., Hankey, G., & Norman, P. (2005). Predictors of impaired cognitive function in men over the age of 80 years: Results from the Health in Men Study. *Age and Ageing*, 34, 77–80.

Folstein MF, Folstein SE, McHugh PR. 1975. "Mini–mental state": A practical guide for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research* 12, 189–198.

Galanis, D. J., Joseph, C., Masaki, K. H., Petrovitch, H., Ross, G. W., & White, L. (2000). A longitudinal study of drinking and cognitive performance in elderly Japanese American men: The Honolulu-Asia Aging Study. *American Journal of Public Health*, 90, 1254–1259.

Galanos, A. N., Fillenbaum, G. G., Cohen, H. J., & Burchett, B. M. (1994). The comprehensive assessment of community dwelling elderly: Why functional status is not enough. *Aging*, 6, 343–352.

Gregg EW, Yaffe K, Cauley JA, Rolka DB, Blackwell TL, Narayan KM, Cummings SR. (2000). Is diabetes associated with cognitive impairment and cognitive decline among older women? Study of Osteoporotic Fractures Research Group. *Arch Intern Med.,* 160(2):174-80.

Gross, A.L., Rebok, G.W., Ford, D.E., Chu, A.Y., Gallo, J.J., Liang, K., Meoni, L.A., Shihab, H.M., Wang, N., & Klag, M.J. (2011). Alcohol consumption and domain-specific cognitive function in older adults: Longitudinal data from the Johns Hopkins Precursors Study. *Journal of Gerontology: Psychological Sciences*, 66, 39-47.

Hayden KM, Reed BR, Manly JJ, Tommet D, Pietrzak RH, …, Jones RN. (2011a). Cognitive decline in the elderly: an analysis of population heterogeneity. *Age Ageing*, 40(6):684-9.

Jöreskog K, Goldberger AS (1975). Estimation of a Model with a Multiple Indicators and Multiple Causes of a Single Latent Variable", *Journal of American Statistical Association*, 70, 631-639.

Kalmijn, S., van Boxtel, M. P. J., Verschuren, M. W. M., Jolles, J., & Launer, L. J. (2002). Cigarette smoking and alcohol consumption in relation to cognitive performance in middle age. *American Journal of Epidemiology*, 156, 936–944.

Knopman DS, Mosley TH, Catellier DJ, Coker LH. Fourteen-year longitudinal study of vascular risk factors, APOE genotype, and cognition: the ARIC MRI Study. *Alzheimers Dement*. May 2009;5(3)207-214.

Leroi, I., Sheppard, J. M., & Lyketsos, C. G. (2002). Cognitive function after 11.5 years of alcohol use: Relation to alcohol use. *American Journal of Epidemiology*, 156, 747–752.

Logroscino G, Kang JH, Grodstein F. Prospective study of type 2 diabetes and cognitive decline in women aged 70-81 years. *BMJ*. 2004 Mar 6;328(7439):548.

McArdle JJ, Grimm KJ, Hamagami F, Bowles RP, Meredith W. (2009). Modeling life-span growth curves of cognition using longitudinal data with multiple samples and changing scales of measurement. *Psychol Methods*, 14(2):126-49. doi: 10.1037/a0015857.

McGuire, L. C., Ajani, U. A., & Ford, E. S. (2007). Cognitive functioning in late life: The impact of moderate alcohol consumption. *Annals of Epidemiology*, 17, 93–99.

Park, L.Q., Gross, A.L., Pa, J., McLaren, D., Johnson, J.K., Mitchell, M., Manly, J.J., for the Alzheimer's Disease Neuroimaging Initiative (2012). Confirmatory factor analysis of the ADNI neuropsychological battery. *Brain Imaging and Behavior*, 6(4), 528-539.

Proust-Lima C, Amieva H, Dartigues JF, Jacqmin-Gadda H. (2007). Sensitivity of four psychometric tests to measure cognitive changes in brain aging-population-based studies. *Am J Epidemiol*., 1;165(3), 344-50.

Rawlings AM, Bandeen-Roche K, Carlson MC, Coker LH, Gottesman RF, Mosley TH, Penman AD, Selnes OA, Sharret AR.(manuscript in preparation; MP2033). Cognitive domains in elderly blacks and whites in the Atherosclerosis Risk in Communities Neurocognitive Study.

Singer, JB, & Willet, JD. Applied *Longitudinal Data Analysis: Modelling Change and Event Occurrence*. New York: Oxford University Press, 2003.

Stevens, S.S. (1946). On the theory of scales of measurement. *Science*, 103(2684), 677–680.

Thompson WK, Hallmayer J, O'Hara R, Alzheimer's Disease Neuroimaging Initiative. (2011). Design considerations for characterizing psychiatric trajectories across the lifespan: Application to effects of APOE e4 on cerebral cortical thickness in Alzheimer's disease. *American Journal of Psychiatry*, 168:894-903.

Willis SL, Tennstedt SL, Marsiske M, Ball K, Elias J, ..., ACTIVE Study Group. (2006). Long-term effects of cognitive training on everyday functional outcomes in older adults. *JAMA*, 296, 2805–2814.

Wilson RS, Beckett LA, Barnes LL, Schneider JA, Bach J, Evans DA, Bennett DA. (2002). Individual differences in rates of change in cognitive abilities of older persons. *Psychol Aging*, 17: 179–93.

Yaffe K, Fiocco AJ, Lindquist K, Vittinghoff E, Simonsick EM, Newman AB, Satterfield S, Rosano C, Rubin SM, Ayonayon HN, Harris TB; Health ABC Study. (2009). Predictors of maintaining cognitive function in older adults: the Health ABC study. *Neurology*, 9;72(23):2029-35.

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?   N/A
  ____ 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 (APOE) Yes _____ 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"?   N/A
       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)?**

MP2033. Cognitive domains in elderly ARIC blacks and whites. Rawlings et al.
1121. Cognitive change over 12 years and its relationship to cardiovascular risk factors
ARIC MRI Study (Knopman et al.)
1066. Metabolic Syndrome, Diabetes and Decline in Cognitive Function (McNeill et al)
MS1871. Type 2 diabetes and cognitive decline over 14 years, accounting for mortality
(Mayeda, E. R.)
Diabetes and cognitive change over 20 years: the Atherosclerosis Risk in Communities
Study (Rawlings AR)
Association between alcohol consumption and cognitive impairment: The ARIC
Neurocognitive Study (Jones SB)

**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   N/A
       **X   A. primarily the result of an ancillary study (list number* ARIC-NCS,
1999.01)**
       ___   **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/

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