1. 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:

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

Name: Alden L. Gross
Address: 2024 E. Monument St, Suite 2-700
         Baltimore, MD 21205
         Phone: 443 287-7196
         Fax: 410 614-9625
         E-mail: aldgross@jhsph.edu

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).
   Name: A. Richey Sharrett
   Address: 615 N Wolfe St, Room W6009B
            Baltimore, MD 21205

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; Leroy, 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; Knapman 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.
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
**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)

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

**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.**

![Diagram of unidimensional confirmatory factor analysis model](image)

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.**

![Diagram of second-order confirmatory factor analysis model](image)
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.
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:**


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.


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?
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.csc.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.csc.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.