1a. Full Title: Are plasma lipid variables associated with Alzheimer disease predictive of earlier cognitive decline?

1b. Abbreviated Title (26 characters): cholesterol and cognition

2. Writing Group:
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3. Timeline: This analysis and manuscript should be completed between October, 2001, and April, 2002.

4. Rationale: Loss of cognitive ability with aging sometimes but not always leads to Alzheimer dementia, a degenerative disease believed to begin in midlife, decades before its symptoms become prominent in old age. If the Alzheimer disease process does begin early, then some midlife decline in cognitive function may be expected in people at risk for developing Alzheimer disease. Recently the list of risk factors for Alzheimer disease has been expanded to include plasma cholesterol variables that also affect risk of atherosclerosis.
Recent studies indicate that higher levels of LDL cholesterol and total serum cholesterol are associated with Alzheimer disease\textsuperscript{1,2,3,5,6}. Conversely, higher levels of HDL cholesterol carry lower risk\textsuperscript{4}. The cholesterol-lowering statin drugs also decrease the risk of Alzheimer disease\textsuperscript{7}.

Whereas the published studies were cross-sectional correlations of lipid variables with diagnosed Alzheimer disease, this proposal is for a longitudinal study of correlations between lipid variables and cognitive decline measured in middle-aged or elderly persons who do not have distinct Alzheimer disease. Further, this study of data on the large ARIC cohort will be an important contribution, because the few published studies linking LDL and HDL cholesterol to Alzheimer dementia have involved fewer than 500 subjects, except Kivipelto et al.\textsuperscript{2} which reports on 1449 subjects. Only the study by on statin drugs\textsuperscript{7} was based on a large population (greater than 60,000).

One previous ARIC study (#672) tested two of the same lipid variables in a longitudinal study of cognitive decline from visit 2 to visit 4 (Knopman et al., 2001). Results were negative; however, the two variables high LDL cholesterol and use of statin drugs were run as part of a composite defined as "hyperlipidemia." Since the most recent literature indicates that high LDL cholesterol and statin drug use affect risk for Alzheimer disease in opposite directions, it seems worthwhile to test these again as separate variables for correlation with cognitive decline. We will use the previous study as a template for this study, and an author of the previous study, T. Mosley, is a member of the present writing group.

5. **Main Hypothesis:** Lipid variables that are risk factors for Alzheimer disease also predict measurable cognitive decline in middle-aged and elderly subjects who do not have distinct Alzheimer disease.

6. **Data (variables, time window, source, inclusions/exclusions):**
   **Variables**
   - cognitive group (word recall, digit symbol transfer, and word fluency)
   - total serum cholesterol
   - HDL cholesterol
   - LDL cholesterol (total serum cholesterol - HDL cholesterol)
   - ratio HDL/LDL cholesterol (to be calculated)
   - statin drug use (there were 1067 users of statin drugs at Visit 4)

**Sample Size** for these variables is approximately 11,300
**Statistical Analysis**

The relationship between lipids and changes in cognitive functioning will be investigated using general linear models. The main outcome of interest for this study is change in cognitive functioning, so simple differences in these measures between Visit 2 and Visit 4 will be used as the dependent variables. The three scales will be considered separately, so no adjustment for multiple testing will be applied. Of major interest are descriptions of the bivariate relationships between changes in cognitive functioning and the various lipid levels at Visit 2; however, multivariate general linear models that include those variables associated with both cognitive functioning and lipids will also be investigated using Akaike’s Information Criteria (AIC) to aid in model selection.

**Time Window**

- visit 2
- visit 4 (longitudinal)

**Source**

ARIC cohort

**Inclusions/Exclusions**

- **Demographic covariates:** age, education, race, gender, center
- **Lifestyle covariates:** physical activity, smoking, ETOH intake
- **Medical status exclusions:** prevalent diabetes, hypertension and use of anti-hypertensive agents, prevalent heart disease, and carotid IMT. Incident stroke, incident MI, and revascularization procedure occurring between Visit 2 and Visit 4 will also cause exclusion.

### 7.a. Will the data be used for non-CVD analysis in this manuscript?

_X___ Yes   ____ No

### 7.b. If Yes, is the author aware that the file ICTDER02 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 ICTDER02 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 ICTDER02 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://bios.unc.edu/units/cscc/ARIC/stdy/studymem.html](http://bios.unc.edu/units/cscc/ARIC/stdy/studymem.html)  ___X___ Yes  _______ No

References Cited


