ARIC Manuscript Proposal #2557

PC Reviewed: 5/12/15	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Plasma phospholipids and mild cognitive impairment / dementia in ARIC

b. Abbreviated Title (Length 26 characters):
Plasma phospholipids and cognition

2. Writing Group:
Writing group members:

Danni Li, Alvaro Alonso, Jeff Misialek, John Eckfeldt; Eric Boerwinkle; Rebecca Gottesman; Richey Sharrett; Tom Mosley; Joe Coresh; Lisa Wruck; David Knopman;

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

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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:
Analysis to be done over the next 2 months. A final draft will be completed in 2 months afterwards.

4. Rationale:

There is growing interest in the discovery of biomarkers for the occurrence of mild cognitive impairment (MCI) and dementia. These biomarkers could help identify individuals more likely to develop these conditions at a time when preventive intervention might be effective. Some of the existing biomarkers of early disease have limitations because they are invasive (e.g. biomarkers in cerebrospinal fluid) or expensive (e.g. brain amyloid imaging). Blood based biomarkers might be a useful alternative. In a recent paper, Mapstone et al identified a panel of 10 phospholipids that predicted phenoconversion to amnestic MCI or Alzheimer's type dementia in a 2-3 year timeframe. However, this study was based on a small sample size and concerns about the quality of MCI/dementia characterization exist. As an initial step to validate the biomarkers identified in the Mapstone paper, and taking advantage of the rich neurocognitive data collected as part of the ARIC-NCS exam, we will examine cross-sectionally whether concentrations of these phospholipids are associated with the prevalence of MCI or dementia in a subset of ARIC participants. Results from this analysis will be useful to validate the results previously reported by Mapstone and colleagues, and as initial data for a potential larger study of lipidomic markers of cognitive decline and dementia in the ARIC cohort.

5. Main Hypothesis/Study Questions:

A panel of 10 phospholiphids (PC aa C36:6, PC aa C38:0, PC aa C38:6, PC aa 40:1, PC aa 40:2, PC aa 40:6, PC ae C40:6, Lyso PC a C18:2, Propionyl-L-carnitine, and Hexadecenoyl-L-carnitine (C16:1)) is associated with prevalence of AD-type MCI or dementia in the ARIC population.

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).

<u>Study populations</u>

A cross-sectional study design includes 440 participants from ARIC Visit 5 with 1:2 ratio of normal to MCI/ Dementia (approximately 145 normals and 295 with MCI/dementia).

These participants are sampled from all black and white Stage 2 participants with available never-thawed samples, excluding participants with unknown etiology. Pure AD will be defined as primary etiologic dx of AD with no secondary dx, AD+2ary is primary dx of AD plus at least one secondary dx, No AD will be all others (excluding unknowns). We include "No AD" because we will test how specific these phospholipids biomarkers are for AD-type MCI or dementia, although we understand the limitation that there are not many of those "No AD" (~ dozen of them) included in either category.

Cases (MCI and Dementia) are sampled with a goal to generate a sample so it is representative of the Stage 2 population cases with adequate representation of syndromic diagnosis, race and etiologic diagnosis. Therefore, these cases are sampled

proportionately within 12 strata defined by MCI/dementia * Race * etiologic dx, and no stratum is over-sampled.

Controls are sampled with a goal to generate a sample that is frequency matched to the cases (MCI/dementia) on race and age (in aggregate across syndrome and etiology). Age group is defined by the median age in the sampled cases.

Exposure of interests

Please see the list of 185 metabolites (at the end of this manuscript proposal). For the primary analysis, we will focus our analysis on the following 10 phospholipids: PC aa C36:6, PC aa C38:0, PC aa C38:6, PC aa 40:1, PC aa 40:2, PC aa 40:6, PC ae C40:6, Lyso PC a C18:2, Propionyl-L-carnitine, and Hexadecenoyl-L-carnitine (C16:1).

Outcome

ARIC Visit 5 Syndromic diagnosis (MCI or Dementia) and Etiological diagnosis (Pure AD, AD+2ary, and No AD)

Other Variables

Covariates to be considered in our analysis include: age, sex, race/center, education level, occupation, APO ε4 status (number of APOE ε4 alleles), cigarette smoking. We will explore other cardiovascular risk factors as potential confounders (e.g., alcohol consumption, physical activity, body mass index, systolic blood pressure, use of antihypertensive medication, diabetes, total cholesterol, HDL-cholesterol, triglycerides, prevalent CHD, prevalent HF, and prevalent stroke). In our analysis, we will use covariates assessed at visit 5, when plasma phospholipids are measured.

Statistical analysis

Metabolite levels will be log transformed. A multinomial logistic regression will be used to assess the association of individual phospholipids with prevalence of MCI or dementia. Separate analysis will be performed based on etiological groups of MCI and Dementia.

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__ (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"?
__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 1010: Omega-3 fatty acids, hypertension and risk of cognitive decline among older adults (Beydoun). This published manuscript studied the n-3 fatty acids which are components of phospholipids and cognition.

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* 2014.14)

___ 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.

References:

Mapstone M, Cheema AK, Fiandaca MS, et al Plasma phospholids identify antecedent memory impairment in older adults, Nature Medicine, 2014

List of 185 analytes:

Acylcarnitines	
Abbreviation	***Biochemical Name***
C0	DL-Carnitine
C2	Acetyl-L-carnitine
C3	Propionyl-L-carnitine
C3:1	Propenoyl-L-carnitine
C3-OH	Hydroxypropionyl-L-carnitine
C4	Butyryl-L-carnitine
C4:1	Butenyl-L-carnitine
C4-OH (C3-DC)	Hydroxybutyryl-L-carnitine (Malonyl-L-carnitine)
C5	Valeryl-L-carnitine
C5:1	Tiglyl-L-carnitine
C5:1-DC	Glutaconyl-L-carnitine
C5-DC (C6-OH)	Glutaryl-L-carnitine (Hydroxyhexanoyl-L-carnitine)
C5-M-DC	Methylglutaryl-L-carnitine
C5-OH (C3-DC-M)	Hydroxyvaleryl-L-carnitine (Methylmalonyl-L-carnitine)
C6 (C4:1-DC)	Hexanoyl-L-carnitine (Fumaryl-L-carnitine)
C6:1	Hexenoyl-L-carnitine
C7-DC	Pimelyl-L-carnitine
C8	Octanoyl-L-carnitine
C8:1	Octenoyl-L-carnitine
C9	Nonayl-L-carnitine
C10	Decanoyl-L-carnitine
C10:1	Decenoyl-L-carnitine
C10:2	Dacadienyl-L-carnitine
C12	Dodecanoyl-L-carnitine
C12:1	Dodecenoyl-L-carnitine
C12-DC	Dodecanedioyl-L-carnitine
C14	Tetradecanoyl-L-carnitine
C14:1	Tetradecenoyl-L-carnitine
C14:1-OH	Hydroxytetradecenoyl-L-carnitine
C14:2	Tetradecadienyl-L-carnitine
C14:2-OH	Hydroxytetradecadienyl-L-carnitine
C16	Hexadecanoyl-L-carnitine
C16:1	Hexadecenoyl-L-carnitine
C16:1-OH	Hydroxyhexadecenoyl-L-carnitine
C16:2	Hexadecadienyl-L-carnitine
C16:2-OH	Hydroxyhexadecadienyl-L-carnitine
C16-OH	Hydroxyhexadecanoyl-L-carnitine
C18	Octadecanoyl-L-carnitine
C18:1	Octadecenoyl-L-carnitine
C18:1-OH	Hydroxyoctodecenoyl-L-carnitine
C18:2	Octadecadienyl-L-carnitine

Amino Acids	
Abbreviation	***Biochemical Name***
Ala	Alanine
Arg	Arginine
Asn	Asparagine
Asp	Aspartic Acid
Cit	Citrulline
Gln	Glutamine
Glu	Glutamic Acid
Gly	Glycine
His	Histidine
Ile	Isoleucine
Leu	Leucine
Lys	Lysine
Met	Methionine
Orn	Ornithine
Phe	Phenylalanine
Pro	Proline
Ser	Serine
Thr	Threonine
Trp	Tryptophan
Tyr	Tyrosine
Val	Valine

Sphingolipids	
Abbreviation	***Biochemical Name***
SM (OH) C14:1	Hydroxysphingomyelin C14:1
SM (OH) C16:1	Hydroxysphingomyelin C16:1
SM (OH) C22:1	Hydroxysphingomyelin C22:1
SM (OH) C22:2	Hydroxysphingomyelin C22:2
SM (OH) C24:1	Hydroxysphingomyelin C24:1
SM C16:0	Sphingomyelin C16:0
SM C16:1	Sphingomyelin C16:1
SM C18:0	Sphingomyelin C18:0
SM C18:1	Sphingomyelin C18:1
SM C20:2	Sphingomyelin C20:0
SM C22:3	Sphingomyelin C22:3
SM C24:0	Sphingomyelin C24:0
SM C24:1	Sphingomyelin C24:1
SM C26:0	Sphingomyelin C26:0
SM C26:1	Sphingomyelin C26:1

Glycerophospholipids			
Abbreviation	***Biochemical Name***	***Abbreviation***	***Biochemical Name***
lysoPC a C14:0	Lysophosphatidylcholine acyl C14:0	PC aa C40:6	Phosphatidylcholine diacyl C40:6
lysoPC a C16:0	Lysophosphatidylcholine acyl C16:0	PC aa C42:0	Phosphatidylcholine diacyl C42:0
lysoPC a C16:1	Lysophosphatidylcholine acyl C16:1	PC aa C42:1	Phosphatidylcholine diacyl C42:1
lysoPC a C17:0	Lysophosphatidylcholine acyl C17:0	PC aa C42:2	Phosphatidylcholine diacyl C42:2
lysoPC a C18:0	Lysophosphatidylcholine acyl C18:0	PC aa C42:4	Phosphatidylcholine diacyl C42:4
lysoPC a C18:1	Lysophosphatidylcholine acyl C18:1	PC aa C42:5	Phosphatidylcholine diacyl C42:5
lysoPC a C18:2	Lysophosphatidylcholine acyl C18:2	PC aa C42:6	Phosphatidylcholine diacyl C42:6
lysoPC a C20:3	Lysophosphatidylcholine acyl C20:3	PC ae C30:0	Phosphatidylcholine acyl-alkyl C30:0
lysoPC a C20:4	Lysophosphatidylcholine acyl C20:4	PC ae C30:1	Phosphatidylcholine acyl-alkyl C30:1
lysoPC a C24:0	Lysophosphatidylcholine acyl C24:0	PC ae C30:2	Phosphatidylcholine acyl-alkyl C30:2
lysoPC a C26:0	Lysophosphatidylcholine acyl C26:0	PC ae C32:1	Phosphatidylcholine acyl-alkyl C32:1
lysoPC a C26:1	Lysophosphatidylcholine acyl C26:1	PC ae C32:2	Phosphatidylcholine acyl-alkyl C32:2
lysoPC a C28:0	Lysophosphatidylcholine acyl C28:0	PC ae C34:0	Phosphatidylcholine acyl-alkyl C34:0
lysoPC a C28:1	Lysophosphatidylcholine acyl C28:1	PC ae C34:1	Phosphatidylcholine acyl-alkyl C34:1
PC aa C24:0	Phosphatidylcholine diacyl C24:0	PC ae C34:2	Phosphatidylcholine acyl-alkyl C34:2
PC aa C26:0	Phosphatidylcholine diacyl C26:0	PC ae C34:3	Phosphatidylcholine acyl-alkyl C34:3
PC aa C28:1	Phosphatidylcholine diacyl C28:1	PC ae C36:0	Phosphatidylcholine acyl-alkyl C36:0
PC aa C30:0	Phosphatidylcholine diacyl C30:0	PC ae C36:1	Phosphatidylcholine acyl-alkyl C36:1
PC aa C30:2	Phosphatidylcholine diacyl C30:2	PC ae C36:2	Phosphatidylcholine acyl-alkyl C36:2
PC aa C32:0	Phosphatidylcholine diacyl C32:0	PC ae C36:3	Phosphatidylcholine acyl-alkyl C36:3
PC aa C32:1	Phosphatidylcholine diacyl C32:1	PC ae C36:4	Phosphatidylcholine acyl-alkyl C36:4
PC aa C32:2	Phosphatidylcholine diacyl C32:2	PC ae C36:5	Phosphatidylcholine acyl-alkyl C36:5
PC aa C32:3	Phosphatidylcholine diacyl C32:3	PC ae C38:0	Phosphatidylcholine acyl-alkyl C38:0
PC aa C34:1	Phosphatidylcholine diacyl C34:1	PC ae C38:1	Phosphatidylcholine acyl-alkyl C38:1
PC aa C34:2	Phosphatidylcholine diacyl C34:2	PC ae C38:2	Phosphatidylcholine acyl-alkyl C38:2
PC aa C34:3	Phosphatidylcholine diacyl C34:3	PC ae C38:3	Phosphatidylcholine acyl-alkyl C38:3
PC aa C34:4	Phosphatidylcholine diacyl C34:4	PC ae C38:4	Phosphatidylcholine acyl-alkyl C38:4
PC aa C36:0	Phosphatidylcholine diacyl C36:0	PC ae C38:5	Phosphatidylcholine acyl-alkyl C38:5
PC aa C36:1	Phosphatidylcholine diacyl C36:1	PC ae C38:6	Phosphatidylcholine acyl-alkyl C38:6
PC aa C36:2	Phosphatidylcholine diacyl C36:2	PC ae C40:1	Phosphatidylcholine acyl-alkyl C40:1
PC aa C36:3	Phosphatidylcholine diacyl C36:3	PC ae C40:2	Phosphatidylcholine acyl-alkyl C40:2
PC aa C36:4	Phosphatidylcholine diacyl C36:4	PC ae C40:3	Phosphatidylcholine acyl-alkyl C40:3
PC aa C36:5	Phosphatidylcholine diacyl C36:5	PC ae C40:4	Phosphatidylcholine acyl-alkyl C40:4
PC aa C36:6	Phosphatidylcholine diacyl C36:6	PC ae C40:5	Phosphatidylcholine acyl-alkyl C40:5
PC aa C38:0	Phosphatidylcholine diacyl C38:0	PC ae C40:6	Phosphatidylcholine acyl-alkyl C40:6
PC aa C38:1	Phosphatidylcholine diacyl C38:1	PC ae C42:0	Phosphatidylcholine acyl-alkyl C42:0
PC aa C38:3	Phosphatidylcholine diacyl C38:3	PC ae C42:1	Phosphatidylcholine acyl-alkyl C42:1
PC aa C38:4	Phosphatidylcholine diacyl C38:4	PC ae C42:2	Phosphatidylcholine acyl-alkyl C42:2
PC aa C38:5	Phosphatidylcholine diacyl C38:5	PC ae C42:3	Phosphatidylcholine acyl-alkyl C42:3
PC aa C38:6	Phosphatidylcholine diacyl C38:6	PC ae C42:4	Phosphatidylcholine acyl-alkyl C42:4
PC aa C40:1	Phosphatidylcholine diacyl C40:1	PC ae C42:5	Phosphatidylcholine acyl-alkyl C42:5
PC aa C40:2	Phosphatidylcholine diacyl C40:2	PC ae C44:3	Phosphatidylcholine acyl-alkyl C44:3
PC aa C40:3	Phosphatidylcholine diacyl C40:3	PC ae C44:4	Phosphatidylcholine acyl-alkyl C44:4
PC aa C40:4	Phosphatidylcholine diacyl C40:4	PC ae C44:5	Phosphatidylcholine acyl-alkyl C44:5
PC aa C40:5	Phosphatidylcholine diacyl C40:5	PC ae C44:6	Phosphatidylcholine acyl-alkyl C44:6

Biogenic Amines	
Abbreviation	***Biochemical Name***
Ac-Orn	Acetylornithine
ADMA	Asymmetric dimethylarginine
alpha-AAA	alpha-Aminoadipic acid
c4-OH-Pro	c4-Hydroxyproline
Carnosine	Carnosine
Creatinine	Creatinine
DOPA	Dihydroxyphenylalanine
Dopamine	Dopamine
Histamine	Histamine
Kynurenine	Kynurenine
Met-SO	Methioninesulfoxide
Nitro-Tyr	Nitrotyrosine
PEA	Phenylethylamine
Putrescine	Putrescine
SDMA	Symmetric dimethylarginine
Serotonin	Serotonin
Spermidine	Spermidine
Spermine	Spermine
t4-OH-Pro	t4-Hydroxyproline
Taurine	Taurine
total DMA	Total dimethylarginine

Hexoses	
Abbreviation	***Biochemical Name***
H1	Hexose