ARIC Manuscript Proposal #2898

PC Reviewed: 12/13/16 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Plasma phospholipids and brain MRI measures of grey and white matter disease in ARIC-NCS

b. Abbreviated Title (Length 26 characters):
Phospholipids and brain MRI

2. Writing Group:
Writing group members:

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

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3. Timeline:

Analysis to be done over the next 6 months. A final draft will be completed in 6 months afterwards.

4. Rationale:

Phospholipids such as phosphatidylcholines (PC) and sphingomyelins (SM) are abundant lipid species both in white and grey matter of the brain.[1] In particular, sphingomyelins are present in white matter in higher levels than phosphatidylcholines. Previously, in a cross-sectional study, we found an association between phospholipids and cognitive status (i.e, normal, MCI, and dementia).[2] In addition to cognitive decline, brain volume loss is common in older adults, is used as a biomarker of the neurodegeneration that occurs in Alzheimer's disease (AD) and vascular dementia, as well as in aging and the preclinical phase of dementia (i.e., mild cognitive impairment [MCI]).[3-5] Although brain volume loss in gray matter (e.g., cortical, hippocampal) is generally believed to contribute to declines in cognition, it is increasingly recognized that white matter damage (e.g., small vessel and microvascular disease, typically detected in current clinical settings as white matter hyperintensities on MRI) are also highly prevalent in older adults and linked to decline in cognitive function.[6] Furthermore, the most common etiology of dementia in older adults includes mixed vascular pathology and AD pathology, both of which commonly occur with aging and in the setting of MCI. [7,8] Given the differential abundance of lipid species in white and grey matter, it is possible that changes in homeostasis of different peripheral phospholipid species (i.e., phosphatidylcholines and sphingomyelins) could be related to distinctive patterns of brain volume loss.

Gonzalez et al. demonstrated the association of peripheral sphingolipids with variation in white matter microstructure measured 10 years later in older adults.[9] Despite this evidence that peripheral sphingomyelins may be associated with certain brain MRI measures of brain MRI, it remains unknown whether different peripheral phospholipid species (i.e., phosphatidylcholines and sphingomyelins) correlate with patterns of brain volume loss simultaneously in white and gray matter in older adults (e.g., cognitive normal, MCI, and dementia). Furthermore, no studies have examined plasma phospholipids including sphingomyelins and thickness-based gray matter measures, which are better biomarkers than volume-based measures in cross-sectional studies,[10] because thickness-based measures are not affected by head size.

The objective of this study is to determine the relationship between peripheral phospholipids and brain MRI measures of white matter hyperintensities and cortical thickness (equivalent of gray matter volume) in a cross-sectional study in the 2011-13 ARIC-NCS. Previously, we demonstrated a significant association between plasma phospholipids with cognitive status (MCI/dementia) in 441 individuals (153 normal, 145 MCI, and 143 dementia) in the 2011-2013 ARIC-NCS.[2] We will use the already-collected plasma phospholipids data and brain MRI measures in the 2011-13 ARIC-NCS.

5. Main Hypothesis/Study Questions:

We have selected the following specific PCs and SMs to be associated with more favorable measures of brain morphology, because of their demonstrated association with cognitive status in our previous study.[2]

1. Higher levels of plasma PCs (i.e., PC aa C36: 5, PC aa 36:6) and SMs (i.e., SM C26:0, SM(OH) C22:1, SM (OH) C22: 2, SM (OH) C24:1) are associated with thicker cortical thickness.

2. Higher levels of plasma PCs (i.e., PC aa C36: 5, PC aa 36:6) and SMs (i.e., SM C26:0, SM(OH) C22:1, SM (OH) C22: 2, SM (OH) C24:1) are associated with lower volume of white matter hyperintensities (WMH).

3. Higher levels of plasma PCs (i.e., PC aa C36: 5, PC aa 36:6) and SMs (i.e., SM C26:0, SM(OH) C22:1, SM (OH) C22: 2, SM (OH) C24:1) are associated with lower numbers of lacunar infarcts.

4. Total cholesterol, HDL-cholesterol, and triglycerides will also be used as predictors in the above hypotheses as well. Including these lipids will help to determine changes in PCs and SMs are due to more global lipid changes (which we know occurs with increasing cognitive impairment) compared to specific changes in specific lipids.

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 population

A cross-sectional study design includes 441 participants from ARIC Visit 5/NCS with 1:1:1 ratio of cognitively normal, MCI, and dementia, for whom both plasma phospholipids biochemical data and brain MRI measures were available. We had sampled these 441 participants by selecting approximately 73 cases from each MCI/race group and dementia/group. Cognitively normal controls were frequency matched to the combined MCI/dementia group by APOE genotype, age, sex, race, education and study center. We measured 188 plasma metabolites (105 of phospholipids) of these 441 participants. For this study, we will include the participants on the basis of their available brain MRI measures in the 2011-13 ARIC-NCS.

Exposure of interests

Our primary analysis will focus on the 6 phospholipids in hypotheses 1, 2, 3 and 4. Additional, hypothesis-generating exploratory analysis will assess the association of the remaining 182 metabolites (we will also consider excluding those metabolites that had very high CVs [e.g., > 30%] in the QC analysis done by the ARIC coordinating center). We will consider adjustment for multiple comparisons. This exploratory analysis will be our alternative strategy. Please see the list of 188 metabolites (at the end of this manuscript proposal).

Outcome variables

Lacunar infracts and White matter hyperintensities (WMH) volume: Brain MRI using 3D-1.5T equipment quantified the presence of lacunar infarcts and volumes of WMH following a standardized protocol.[11]

Cortical thickness (equivalent of gray matter volume): The ARIC MRI Reading Center used Freesurfer (version 5.1) to perform thickness measurement. AD signature is a composite of thickness measurement in the entorhinal, fusiform, parahippocampal, mid-temporal, inferior-temporal, and angular-gyrus ROIs that will be extracted from the ARIC-NCS MRI scans obtained at visit 5/NCS. [10]

Other Variables

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

Statistical analysis

Metabolite levels will be log transformed. Imaging outcome variables will be transformed as well when necessary (e.g., WMH). For all outcome variables except lacunar infarcts, multivariable linear regression will be used; for lacunar infarcts, binary logistic or Poisson regression will be used. We will address multiple comparisons (e.g., Bonferroni correction). We will at the association of these metabolites with brain MRI measures in each cognitive group (i.e., normal, MCI, and dementia) separately first, and then if similar, combine them.

Sample weights will be calculated as the inverse of the probability of being selected to this analysis given selection variables (race, diagnosis) and weights will be incorporated in the analysis, using appropriate statistical approaches to adjust standard error estimation. In addition, sampling weights of getting brain MRI will be incorporated in the analysis as well.

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? _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 #2557, "Plasma phospholipids and mild cognitive impairment / dementia in ARIC"
MS #2558, "Plasma fatty acids and cognitive decline: the ARIC Neurocognitive Study"
MS #2700, "Plasma phospholipids and physical function in ARIC"
MS #2865, "Inflammatory biomarkers at midlife and late-life and brain atrophy in older adults: the 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* __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:

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3. Sepulcre J, Schultz AP, Sabuncu M, Gomez-Isla T, Chhatwal J, Becker A, et al. In Vivo Tau, Amyloid, and Gray Matter Profiles in the Aging Brain. *The Journal of Neuroscience.* 2016;36(28):7364-7374.
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6. Snyder HM, Corriveau RA, Craft S, Faber JE, Greenberg SM, Knopman D, et al. Vascular contributions to cognitive impairment and dementia including Alzheimer's disease. *Alzheimers Dement.* 2015;11(6):710-717.

7. Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Neurology.* 2007;69(24):2197-2204.
8. James BD, Bennett DA, Boyle PA, Leurgans S, Schneider JA. Dementia from Alzheimer disease and mixed pathologies in the oldest old. *JAMA.* 2012;307(17):1798-1800.
9. Gonzalez CE, Venkatraman VK, An Y, Landman BA, Davatzikos C, Bandaru VVR, et al. Peripheral sphingolipids are associated with variation in white matter microstructure in older adults. *Neurobiol. Aging.* 2016;43:156-163.
10. Schwarz CG, Gunter JL, Wiste HJ, Przybelski SA, Weigand SD, Ward CP, et al. A large-scale comparison of cortical thickness and volume methods for measuring Alzheimer's disease severity. *Neuroimage-Clinical.* 2016;11:802-812.
11. Palta P, Wei J, Meyer M, Power MC, Deal JA, Jack CR, et al. Abstract MP100: Arterial Stiffness and Pressure Amplification Associated with Markers of Cerebral Microvascular Disease: The Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS). *Circulation.* 2016;133(Suppl 1):AMP100-AMP100.

List of 188 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