ARIC Manuscript Proposal #2700

PC Reviewed: 1/12/16	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Plasma phospholipids and physical function in ARIC

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

2. Writing Group:
Writing group members:

Danni Li, Alvaro Alonso, Jeff Misialek, Fang Yu, B. Gwen Windham

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]**

First author: **Danni Li**
Address: 420 Delaware St SE, MMC609, Minneapolis, MN 55455

Phone: 612-626-0299 Fax: 612-625-1121
E-mail: dannili@umn.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: **Alvaro Alonso**
Address: 1300 S 2nd St, Suite 300
Epidemiology and Community Health
University of Minnesota

Phone: 612 626 8597 Fax:
E-mail: alonso@umn.edu

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

4. Rationale:

Physical function, such as activities of daily living (ADL), is significantly impacted in dementia, in particular dementia due to Alzheimer's disease (AD), the leading cause of dementia [1]. As dementia progresses, patients experience a gradual loss in activities of daily living [2]. The physical function impairment in AD and other non-AD dementia (e.g., Lewy Body Dementia) places a significant burden on caregivers and is leading cause of nursing home placement [3, 4]. Physical function decline is also one of the key factors to distinguish mild cognitive impairment (MCI) and dementia [5], and is significantly related to the severity of AD[6]. In addition to ADL, poor performance in specific areas of physical function are associated with an increased risk of dementia and AD [7]. Previous work has documented altered concentrations of plasma phospholipids in brains of aging, cognitive function decline, MCI and dementia [8-10]. Furthermore, plasma phospholipids were associated with cognitive functioning during middle adulthood [11], the risk of decline in verbal fluency [12], and a significant reduction in risk of developing all-cause dementia [13]. Phospholipids are essential components of all biological membranes, and are required for normal cellular structure and function. In individuals with AD, oxidative stress and lipid peroxidation of membrane phospholipids alters phospholipids [14], which may alter their abilities to maintain normal cellular function, and therefore contribute to decline in physical function. However, it is unknown whether plasma phospholipids are associated with ADL and/or physical performance in specific areas of physical function (i.e., lower extremity function by Short Physical Performance Battery [SPPB] and gait speed) in older adults. Furthermore, cognitive impairment is associated with functional decline in persons with AD [15]. Therefore, cognition may mediate the association of phospholipids and physical function. Identification of plasma biomarkers that are related to physical function may provide clues into those pathophysiological features of such decline, which in turn, could lead to novel approach for predicting progression in physical function decline as well as therapeutic approaches directly aimed at improving physical function. This study aims to determine the association between plasma phospholipids and physical function. Previously, we conducted a cross-sectional study of the association of phospholipids and prevalence of MCI /dementia, which included 441 participants from ARIC Visit 5 with 1:1:1 ratio of normal, MCI, and Dementia. Physical function of these 441 participants were also assessed in ARIC Visit 5, which included ADL, and physical performance in specific areas of physical function (i.e., lower extremity function by Short Physical Performance Battery [SPPB] and gait speed).

5. Main Hypothesis/Study Questions:

Our primary hypothesis of the association of plasma phospholipids and physical function is based on our previous findings of the association of plasma phospholipids and prevalence of MCI and dementia. We hypothesize those phospholipids that were associated with MCI / dementia or cognitive function will be also associated with worse physical function. Specifically:

Hypothesis 1: higher concentrations of PC aa C40:2, PC aa 36:6, SM(OH) C22:1, PC aa C36: 5, PC aa C38:1, SM C26:0, SM (OH) C22: 2, and SM (OH) C24: 1, will be associated with higher levels of physical function

Hypothesis 2: higher concentrations of asymmetric dimethylarginine (ADMA), hydroxybutyryl-L-carnitine [C4-OH (C3-DC)], octadecanoyl-L-carnitine (C18), and lysoPC a C16: 1 will be associated with lower levels of physical function.

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 populations

A cross-sectional study design includes 441 participants from ARIC Visit 5 with 1:1:1 ratio of normal, MCI, and 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).

Cases (MCI and Dementia) were 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 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). Our primary analysis will focus on the 12 phospholipids in Hypotheses 1 and 2. Additional, hypothesis-generating exploratory analysis will assess the association of the remaining 173 metabolites with physical function. We will consider adjustment for multiple comparison. This exploratory analysis will be our alternative strategy.

Outcome

Physical function outcomes: ADL/Instrument ADLs from the AFU/sAFU forms obtained at or near Visit 5 [16] and physical performance in specific areas of physical function (i.e., lower extremity function by Short Physical Performance Battery [SPPB] and gait speed) obtained at Visit 5 [17]. SPPB is a performance assessment comprised of 3 tasks: 1). Repeated chair stands, 2). Standing balance, and 3) a 4-meter usual-paced walk in those with and without a walk aid (meters/second). The SPPB score ranges from 0-12,

with lower scores indicating poorer function. Gait speed (meters/second) ranges from ~0.4 to 1.8.

Other Variables

Covariates to be considered in our analysis include: age, sex, race/center, education level, , 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 addition, we will add cognitive status (NC, MCI, and Dementia), and MMSE as potential mediators (i.e., the association between phospholipids and physical function would be mediated through cognition) In our analysis, we will use covariates assessed at visit 5, when plasma phospholipids are measured.

Statistical analysis

Metabolite levels will be log transformed. Depending on the outcome variables, multinomial logistic regressions and/or multi-linear regression will be used to assess the association of individual phospholipids with physical function tests.

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__ 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"

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:

[1] Pereira F, Yassuda M, Oliveira A, Forlenza O. Executive dysfunction correlates with impaired functional status in older adults with varying degrees of cognitive impairment. International Psychogeriatrics 2008; 20:1104.

[2] Beck CK, Frank LB. Assessing functioning and self-care abilities in Alzheimer disease research. Alzheimer disease and associated disorders 1996; 11:73-80.

[3] Gallagher D, Mhaolain AN, Crosby L, et al. Dependence and caregiver burden in Alzheimer's disease and mild cognitive impairment. American journal of Alzheimer's disease and other dementias 2011; 26:110-114.

[4] Wattmo C, Wallin ÅK, Londos E, Minthon L. Risk factors for nursing home placement in Alzheimer's disease: a longitudinal study of cognition, ADL, service utilization, and cholinesterase inhibitor treatment. The Gerontologist 2011; 51:17-27.

[5] Knopman DS, Boeve BF, Petersen RC, Essentials of the proper diagnoses of mild cognitive impairment, dementia, and major subtypes of dementia. Mayo Clinic Proceedings: Elsevier, 2003: 1290-1308.

[6] Ashford JW, Kumar V, Barringer M, et al. Assessing Alzheimer severity with a global clinical scale. International Psychogeriatrics 1992; 4:55-74.

[7] Wang L, Larson EB, Bowen JD, van Belle G. Performance-based physical function and future dementia in older people. Archives of Internal Medicine 2006; 166:1115-1120.

[8] Grimm MO, Grösgen S, Riemenschneider M, Tanila H, Grimm HS, Hartmann T. From brain to food: Analysis of phosphatidylcholins, lyso-phosphatidylcholins and phosphatidylcholin–plasmalogens derivates in Alzheimer's disease human post mortem brains and mice model via mass spectrometry. Journal of Chromatography A 2011; 1218:7713-7722.

[9] Klein J. Membrane breakdown in acute and chronic neurodegeneration: focus on choline-containing phospholipids. Journal of Neural Transmission 2000; 107:1027-1063.

[10] Pettegrew JW, Panchalingam K, Hamilton RL, McClure RJ. Brain membrane phospholipid alterations in Alzheimer's disease. Neurochemical Research 2001; 26:771-782.

[11] Muldoon MF, Ryan CM, Sheu L, Yao JK, Conklin SM, Manuck SB. Serum phospholipid docosahexaenonic acid is associated with cognitive functioning during middle adulthood. Journal of Nutrition 2010; 140:848-853.

[12] Beydoun MA, Kaufman JS, Satia JA, Rosamond W, Folsom AR. Plasma n−3 fatty acids and the risk of cognitive decline in older adults: the Atherosclerosis Risk in Communities Study. American Journal of Clinical Nutrition 2007; 85:1103-1111.

[13] Schaefer EJ, Bongard V, Beiser AS, et al. Plasma phosphatidylcholine docosahexaenoic acid content and risk of dementia and Alzheimer disease: the Framingham Heart Study. Archives of Neurology 2006; 63:1545-1550.

[14] Markesbery WR. Oxidative stress hypothesis in Alzheimer's disease. Free Radical Biology and Medicine 1997; 23:134-147.

[15] Tekin S, Fairbanks LA, O'Connor S, Rosenberg S, Cummings JL. Activities of daily living in Alzheimer's disease: neuropsychiatric, cognitive, and medical illness influences. The American Journal of Geriatric Psychiatry 2002; 9:81-86.

[16] Windham BG, Griswold ME, Lirette S, et al. Effects of Age and Functional Status on the Relationship of Systolic Blood Pressure With Mortality in Mid and Late Life: The ARIC Study. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences 2015:glv162.

[17] Burke BT, Köttgen A, Law A, et al. Physical Function, Hyperuricemia, and Gout in Older Adults. Arthritis care & research 2015; 67:1730-1738.

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