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Longitudinal association between phosphatidylcholines, neuroimaging measures of Alzheimer's disease pathophysiology, and cognition in the Mayo Clinic Study of Aging

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ABSTRACT

Plasma phosphatidylcholines (PCs) have been examined in the context of Alzheimer's disease dementia. However, their association with longitudinal changes in amyloid deposition remains unknown. This study investigated the associations of 8 plasma PC levels (PC aa [14:0_14:0], PC aa [16:0_16:0], PC aa [16:0_18:2], PC aa [16:0_22:6], PC aa [18:0_18:0], PC aa [18:0_18:1], PC aa [18:0_20:4], PC aa [18:1_18:1]) with cross-sectional and longitudinal measures of amyloid deposition, Alzheimer's disease–associated neurodegeneration (glucose metabolism and cortical thickness), and cognition (global- and domain-specific) of 1440 cognitively unimpaired participants (47% female, aged 50.7–95.3 years) in the Mayo Clinic Study of Aging. Longitudinally, higher baseline levels of PC aa [16:0_18:2], PC aa [18:0_18:1], and PC aa [18:1_18:1] were associated with slower decline in performance on tests of global cognition and specific cognitive domains. Furthermore, higher baseline levels of plasma PC aa (14:0_14:0) were associated with slower amyloid deposition and cortical thinning after multiple covariable adjustment (age, sex, education, medical comorbidity, dyslipidemia, statin use, and *APOE4* allele presence). Our study findings support an independent association between plasma PC aa (14:0_14:0) with slower amyloid deposition and cortical thinning among cognitively unimpaired older adults.

1. Introduction

Brain amyloid beta (Aβ) deposition and neurodegeneration are hallmark characteristics of Alzheimer's disease (AD) that can be measured in vivo using neuroimaging (Jack et al., 2017). The molecular pathways that contribute to the AD continuum, from brain amyloid deposition to neurodegeneration, cognitive impairment, and dementia are not well understood. More than 60% of the human brain is comprised of lipids (Chang et al., 2009). Compared with cognitively unimpaired (CU) older adults, those with AD dementia have altered lipid levels in brain tissues (Han et al., 2001, 2002; Snowden et al., 2017; Varma et al., 2018) and in cerebrospinal fluid (CSF) (Fonteh et al., 2013, 2014, 2015; Trushina et al., 2013). Notably, altered lipid metabolism is present at the stage of brain amyloid deposition, well before cognitive impairment and dementia manifests. For example, acid sphingomyelinase activity, which metabolizes the phospholipid sphingomyelin to ceramide, was associated with CSF Aβ42 concentration in CU persons (Fonteh et al., 2015). In addition, brain lipid composition (e.g., the ratio of cholesterol to phosphatidylcholines [PCs] of plasma membranes) can influence the integrity and activity of key enzymes, such as gamma secretase, that contribute to amyloid deposition (Holmes et al., 2012), synaptic dysfunction, and neuronal death and contributes to neurodegeneration and cognitive decline (Ledesma et al., 2012). To date, few studies have examined plasma lipids in the context of longitudinal changes of amyloid deposition and

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neurodegeneration. This is important because plasma lipids are known to influence lipids in the brain over time (Chang et al., 2009) and are more easily accessible to measure.

PCs (i.e., diacyl PC [PC aa]) are a group of plasma lipids that have been examined in relation to mild cognitive impairment (MCI) and AD dementia (Casanova et al., 2016; Klavins et al., 2015; Li et al., 2016a,b; Mapstone et al., 2014; Toledo et al., 2017; Varma et al., 2018). However, the association between baseline plasma PCs and longitudinal changes in amyloid deposition or AD-associated neurodegeneration among CU older adults has not been examined. Furthermore, PCs have 2 fatty acyl chains that have distinctive biological implications (Liebisch et al., 2013) but are typically not measured in studies of PCs in AD because of difficulty in obtaining proper standards or more intensive assays (Casanova et al., 2016; Klavins et al., 2015; Li et al., 2016a,b; Mapstone et al., 2014; Toledo et al., 2017; Varma et al., 2018). The objective of this study was to examine the cross-sectional and longitudinal associations of 8 plasma PCs with neuroimaging measures of amyloid deposition and neurodegeneration and with cognitive decline among 1440 CU older adults in the Mayo Clinic Study of Aging (MCSA). These 8 PCs (PC aa [14:0_14:0], PC aa [16:0_16:0], PC aa [16:0_18:2], PC aa [16:0_22:6], PC aa [18:0_18:0], PC aa [18:0_18:1], PC aa [18:0_20:4], and PC aa [18:1_18:1]) were measured using analyte specific standards to provide chain length information on fatty acyl groups, which are annotated using a separator "_" (Liebisch et al., 2013). For example, PC aa (16:0_18:2) indicates fatty acyl 16:0 and 18:2 at either sn-1 or sn-2 position. We also determined whether these associations were modified by sex or elevated brain amyloid (for measures of cognition and neuroimaging measures of neurodegeneration).

2. Methods

2.1. Study population

The MCSA is a population-based epidemiological cognitive aging study of residents of Olmsted County, MN (Petersen et al., 2010; Roberts et al., 2008), who were initially sampled using the Rochester Epidemiology Project medical records linkage system. Beginning in 2004, the MCSA enrolled residents aged 70–89 years and in 2012 residents aged 50 years and older. For the present study, we included 1440 CU participants at baseline with 8 plasma PC concentrations measured and cross-sectional and longitudinal cognitive function assessed. A subset of these individuals also had at least one visit with Aβ Pittsburgh Compound B positron emission tomography (PiB-PET) (n = 1162), fludeoxyglucose (FDG)-PET (n = 1155), and magnetic resonance imaging of cortical thickness (n = 1275) in AD signature regions. This study was approved by the Mayo Clinic and the Olmsted Medical Center institutional review boards in Rochester, Minnesota. All participants provided written informed consent at the time of enrollment.

2.2. Participant assessment

MCSA visits occur every 15 months and include a physician examination, an interview by a study coordinator, and neuropsychological testing administered by a psychometrist. The physician examinations included a review of the participant's medical history, a complete neurological examination, and administration of the short test of mental status. Study coordinator interviews reviewed participant demographic information, medical history, and completion of the participant and informant Clinical Dementia Rating scale.

Neuropsychometric testing included 9 tests covering 4 domains: memory [Auditory Verbal Learning Test Delayed Recall Trial (Rey, 1964), Wechsler Memory Scale–Revised Logical Memory-II and Visual Reproduction-II (Wechsler, 1987)], language [Boston Naming Test (Kaplan et al., 1983), category fluency (Strauss et al., 2006)], visuospatial skills [WAIS-R Picture Completion and Block Design subtests (Wechsler, 1981)], and attention [Trail Making Test B (Reitan, 1958; Strauss et al., 2006), WAIS-R Digit Symbol subtest (Wechsler, 1981)]. Using the mean and standard deviation (SD), test scores were converted to z-scores. Global cognition was calculated using the z-transformed averages of the 4 cognitive domains.

2.3. Assessment of covariates

Demographic variables (e.g., age, sex, and education) were collected by self-report during the in-clinic examination. Medical conditions (e.g., dyslipidemia) and the Charlson comorbidity index (Charlson et al., 1987) were determined for each participant by medical record abstraction using the medical records linkage system of the Rochester Epidemiology Project (St Sauver et al., 2012). Participants were asked to bring all their medications with them for each clinic visit, and the type and dose were recorded. Participants' blood samples were used to determine *APOE* genotypes.

2.4. MCI and dementia diagnostic determination

For each participant, performance in a cognitive domain was compared with the age-adjusted scores of CU individuals previously obtained using Mayo's Older American Normative Studies (Ivnik et al., 1992). This approach relies on prior normative work and extensive experience with the measurement of cognitive abilities in an independent sample of participants from the same population. Participants with scores around 1 SD below the age-specific mean in the general population were considered for possible cognitive impairment. A final decision about impairment in a cognitive domain was made after considering education, occupation, visual or hearing deficits, and reviewing all other participant information. The diagnosis of MCI was made by a consensus agreement between the study coordinator, examining physician, and neuropsychologist using published criteria (Petersen, 2004). The diagnosis of dementia (Frances, 1994) was based on published criteria. Participants who performed in the normal range and did not meet criteria for MCI or dementia were deemed CU. Only individuals who were deemed CU at baseline were included in the current analyses. Participants were not excluded from the analyses if they developed MCI or dementia over the follow-up.

2.5. Neuroimaging measures

Aβ PiB-PET images were acquired with a PET/computed tomography operating in 3-dimensional mode and the details of the acquisition can be found in the study by Lowe et al., 2009. A fully automated image processing pipeline was used as described previously (Jack et al., 2008; Senjem et al., 2008). Aβ (i.e., global cortical PiB-PET retention ratio) was computed by calculating the median uptake over voxels in the prefrontal, orbitofrontal, parietal, temporal, anterior cingulate, and posterior cingulate/precuneus regions of interest (ROIs) for each subject and dividing this by the median uptake over voxels in the cerebellar gray matter ROI of the atlas (Lopresti et al., 2005). We examined Aβ as a continuous variable in the regression analyses. We dichotomized participants as amyloid positive or negative (Aβ+/Aβ−) based on a cutoff of 1.4 (Jack et al., 2015) for the descriptive tables and when examining Aβ as an effect modifier.

FDG-PET was obtained on the same day as the Aβ PIB scan and consisted of four 2-minute dynamic frames acquired from 30–38 minutes after injection of ^{18}FDG. FDG values were

nonsharpened and were not partial volume–corrected. FDG-PET regional standardized uptake value ratio (SUVR) values were derived in a similar manner to the PIB-PET scans. The FDG AD signature meta-ROI was defined as the average of uptake in defined voxels in angular gyrus, posterior cingulate gyrus, and middle/inferior temporal gyrus normalized to the pons and vermis (Landau et al., 2011).

T1-weighted magnetic resonance imaging scans were acquired on 3T GE scanners using a sagittal 3D magnetization prepared rapid acquisition gradient recalled echo sequence with acquisition parameters of repetition time/echo time/inversion time—2300/3/900 ms with voxel dimensions of 1.20 × 1.015 × 1.015 mm (Jack et al., 2008). We used FreeSurfer version 5.3 for computation of cortical thicknesses and used the composite of entorhinal, inferior temporal, fusiform, and middle temporal regions (Jack et al., 2017). We used cortical thickness as a continuous measure in the regression analyses. We dichotomized participants as AD neurodegeneration negative or positive (N–/N+) based on a cutoff of 2.74 mm (Jack et al., 2015) for the descriptive tables.

2.6. Blood collection

Blood was collected in ethylenediaminetetraacetic acid tubes in-clinic after an overnight fast. The blood was centrifuged for 10 minutes at 2000 × g at 4 °C, aliquoted in 500 μL aliquots, and stored at −80 °C for future analyses, thus avoiding freeze-thaw cycles before the current analyses.

2.7. Phospholipids measurement

The quantitation of plasma PCs was accomplished using liquid chromatography electrospray ionization tandem mass spectrometry, using an AB SCIEX 6500 mass spectrometer with an electrospray ionization probe and interfaced with a ultra-high performance liquid chromatography (UHPLC) system in the positive multiple-reaction monitoring mode. The UHPLC system consisted of an Agilent 1290 binary pump, thermostatted column compartment, and sampler. The injection volume was 2 μL for lipid extracts. Lipid extracts were chromatographically resolved using a Halo Penta HILIC UHPLC column, 2.1 × 150 mm, 2.7 mm (Mac-Mod, Chadds Ford, PA, PN: 92812-705). Mobile phase A was acetonitrile/methanol/0.5% formic acid/5 mm ammonium formate (95/5, by volume ratio, v/v). Mobile phase B was water/0.5% formic acid/5 mm ammonium formate. The solvent flow rate was 0.7 mL/min. The valve, sample loop, and needle were washed with 50% acetonitrile: 50% methanol for 25 seconds. The column temperature was kept at 50 °C. Lipid extracts were prepared using Biomek FX (Beckman Coulter, Brea, CA). Twenty microliter of plasma sample was added to a 2-mL 96-well plate. Internal standard mixture was added to the samples. PCs were extracted using a modified Bligh-Dyer 2-phase extraction method. After being dried under warm nitrogen gas, the samples were reconstituted in 600 μL of acetonitrile/methanol/5 mm ammonium formate (70/30 by volume ratio, v/v). The lipid extract was then diluted 10-fold before analysis.

We initially developed this method to measure 21 PCs because, based on pilot data, they were some of the most abundant PCs in plasma and they had different chain lengths with different degree of saturations (i.e., 1, 2, 3, or 4 double bonds). However, not all these 21 PCs were measured with analyte-specific standards because they were either commercially unavailable (i.e., from Avanti Lipids) or they were very expensive to make. Therefore, for this analysis, we only focused on the 8 PCs measured by analyte-specific standards for which we knew the fatty acyl chain lengths on the PCs. These 8 PC levels were each quantified by the ratio of analyte and internal standard, and an 8-point calibration curve, obtained by serial dilution of an analyte-specific standard from 0.5 to 500 ng/mL. The odd chain of PC aa (21:0_21:0) purchased from Avanti Lipids (SKU: 850370P) was used as an internal standard. These 8 PC levels were reported in ng/mL.

2.8. Statistical analysis

Linear mixed effect models were used to examine the cross-sectional and longitudinal associations between these 8 plasma PCs (modeled in Z-scores) and each neuroimaging and cognitive outcome. The models included terms for baseline PC level (indicating the cross-sectional association between each PC and outcome), time (indicating change in the outcome over the follow-up), and the interaction between each PC and time (indicating the longitudinal association between each baseline PC level and change

Table 1
Demographics of the study population

Characteristics	Total (N = 1440)
Age	
N	1440
Mean (SD)	71.1 (9.9)
Range	(50.7–95.3)
Gender	
Female	680 (47.2%)
Male	760 (52.8%)
Education (y)	
N	1440
Mean (SD)	14.8 (2.6)
Range	(8.0–20.0)
Baseline cognitive status	
CU	1440 (100.0%)
Any E4 allele	
No	1052 (73.1%)
Yes	388 (26.9%)
Charlson comorbidity index	
N	1430
Mean (SD)	2.8 (2.9)
Range	(0.0–21.0)
Dyslipidemia	
Unknown	10
No	277 (19.4%)
Yes	1153 (80.6%)
Statin use	
No	735 (51.0%)
Yes	705 (49.0%)
Abnormal PIB at baseline	
PIB-PET imaging not available	265
Normal	834 (71.0%)
Abnormal	341 (29.0%)
Abnormal FDG at baseline	
FDG-PET imaging not available	272
Normal	623 (53.3%)
Abnormal	545 (46.7%)
Abnormal cortical thickness at baseline	
MRI imaging not available	152
Normal	756 (58.7)
Abnormal	532 (41.3%)
Follow-up time (y)	
Cognitive measures (N = 1440)	
Mean (SD)	4.1 (1.6)
Range	(1.0–8.0)
MRI (N = 739)	
Mean (SD)	2.5 (0.8)
Range	(2.0–6.0)
PET (N = 1166)	
Mean (SD)	1.8 (0.9)
Range	(1.0–5.0)
Plasma sample storage time (y)	
N	1440
Mean (SD)	5.2 (1.8)
Range	(1.9–8.5)

Key: CU, cognitively unimpaired; FDG, fludeoxyglucose; PET, positron emission tomography; PIB, Pittsburgh Compound B; SD, standard deviation.

Table 2
Spearman correlations between levels of the 8 plasma PCs Spearman correlation coefficient (Rho) and *p* value

Phospholipid	PC aa (16:0_16:0)	PC aa (16:0_18:2)	PC aa (16:0_22:6)	PC aa (18:0_18:0)	PC aa (18:0_18:1)	PC aa (18:0_20:4)	PC aa (18:1_18:1)
PC aa (14:0_14:0)	0.5645 <0.0001	0.41909 <0.0001	0.06882 0.009	0.39119 <0.0001	0.52577 <0.0001	0.09239 0.0004	0.39622 <0.0001
PC aa (16:0_16:0)		0.61207 <0.0001	0.26389 <0.0001	0.57382 <0.0001	0.62354 <0.0001	<0.0001	<0.0001
PC aa (16:0_18:2)			0.18979 <0.0001	0.37043 <0.0001	0.68877 <0.0001	0.08913 0.0007	0.86127 <0.0001
PC aa (16:0_22:6)				−0.12371 <0.0001	0.22353 <0.0001	0.31945 <0.0001	0.16122 <0.0001
PC aa (18:0_18:0)					0.71375 <0.0001	0.14444 <0.0001	0.51165 <0.0001
PC aa (18:0_18:1)						0.3175 <0.0001	0.84931 <0.0001
PC aa (18:0_20:4)							0.21088 <0.0001

Key: PC, phosphatidylcholines.

in outcome). We specified a random intercept and random slope and used an unstructured covariance matrix. Because the mixed models account for varying amounts of follow-up in patients, missing data were not quantified. Multivariable models adjusted for age, sex, education, medical comorbidity, dyslipidemia, statin use, and *APOE4* allele presence. Elevated brain amyloid deposition (i.e., PIB-PET SUVR>1.4) and sex were also examined as effect modifiers. Plasma PC levels between participants with neuroimaging and those without was compared using the Kruskal–Wallis tests. A Bonferroni correction for multiple testing was applied to each outcome, and *p* values <0.00625 were considered statistically significant, whereas *p* values <0.05 were considered trends in association. Spearman correlations were used to assess correlations between the 8 plasma PCs. All analyses were performed using SAS (SAS Institute, Cary, NC).

3. Results

This study included 1440 CU participants (47% female) with mean (SD) age of 71.1 (9.9) years, mean (SD) education of 14.8 (2.6) years, mean (SD) follow-up of cognitive data of 4.1 (2.1) years and follow-up for those with amyloid PET of 1.8 (0.9) years, and mean (SD) plasma sample storage time of 5.2 (1.8) years (Table 1). Among participants who had neuroimaging scans available, 29.0% had elevated brain Aβ; 46.7% and 41.3% had abnormal neurodegeneration by glucose metabolism and cortical thickness, respectively. Levels of plasma PCs in the CU participants with available neuroimaging scans did not differ from those without neuroimaging, with the exception that PC aa (16:0_22:6) was higher in participants with neuroimaging measures (median [IQR] 85,547 ng/mL [67,839– 107,012] vs. 76,815 ng/mL [64,146–98,357], *p* value 0.005). Overall, these 8 PCs were positively correlated (coefficients ranging from 0.06882 to 0.86127, *p* values <0.01), with the exception of PC aa (16:0_22:6) and PC aa (18:0_18:0) (Table 2). PC aa (16:0_18:2), PC aa (18:1_18:1), and PC aa (18:0_18:1) had the strongest correlations with Spearman rho's of 0.85 (between PC aa [16:0_18:2] and PC aa [18:1_18:1]) and 0.86 (between PC aa [18:1_18:1] and PC aa [18:0_18:1]).

In cross-sectional univariable analysis, higher levels of PC aa (14:0_14:0), (16:0_18:2), (18:0_18:1), and (18:1_18:1) were significantly associated with better performance on tests of global cognition, memory, language, and attention. Higher PC aa (16:0_16:0) and (18:0_20:4) were also associated with better performance on tests of memory and attention, respectively (Fig. 1; Supplementary Table 1). Similarly, higher levels of PC aa (16:0_18:2), (18:0_18:1), and (18:1_18:1) were cross-sectionally associated with lower Aβ PET SUVR, higher cortical thickness and higher glucose metabolism (i.e., less AD pathophysiology). Higher PC aa (14:0_14:0) was associated with higher glucose metabolism only (Fig. 1; Supplementary Table 2). In cross-sectional multivariable analysis that adjusted for age, sex, education, medical comorbidity, dyslipidemia, statin use, and *APOE4* allele, these associations were attenuated except for PC aa (18:1_18:1) whose association with FDG-PET was maintained.

Longitudinally, higher levels of PC aa (16:0_18:2), (18:0_18:1), and (18:1_18:1) were significantly associated with slower decline in performance on tests of global cognition. In addition, higher levels of these 3 PCs were associated with slower decline in performance on tests of specific cognitive domains: PC aa (16:0_18:2) on tests of attention and visuospatial function; PC aa (18:0_18:1) on test of visuospatial function; and PC aa (18:1_18:1) on tests of memory, language, attention, and visuospatial function. Higher levels of PC aa (14:0_14:0) were significantly associated with slower Aβ PET SUVR accumulation and cortical thinning (Fig. 1; Supplementary Table 2). These significant associations were maintained in the multivariable analysis. In additional analyses, there was a significant amyloid interaction with PC (14:0_14:0), such that a higher level of this PC when amyloid deposition was elevated was associated with better visuospatial function. (Supplementary Tables 3 and 4). We did not find any interactions between the PCs and sex for any outcome.

4. Discussion

In the present study, we comprehensively investigated both cross-sectional and longitudinal associations between 8 plasma PCs and AD-associated neuroimaging (amyloid, glucose metabolism, cortical thickness in AD signature regions) and cognitive measures (global and 4 specific domains) among 1440 CU participants in the MCSA. The study's most meaningful and novel findings were as follows: (1) higher baseline levels of plasma PC aa (16:0_18:2), (18:0_18:1), and PC aa (18:1_18:1) were significantly associated with slower decline in performance on tests of global- and domain-specific cognition after multivariable adjustment; (2) higher baseline levels of plasma PC aa (14:0_14:0) were significantly associated with slower Aβ PET SUVR accumulation and less cortical thinning over time after multivariable adjustment.

Previous studies have examined cross-sectional associations of plasma PCs with various outcomes in the context of AD. For example, higher levels of PC aa C36:6 was found to be associated with a lower frequency of MCI and dementia (Klavins et al., 2015; Li et al., 2016a) and higher levels of PC ae C36:2 with higher levels of CSF $A\beta_{1-42}$ (Toledo et al., 2017). Longitudinal associations between

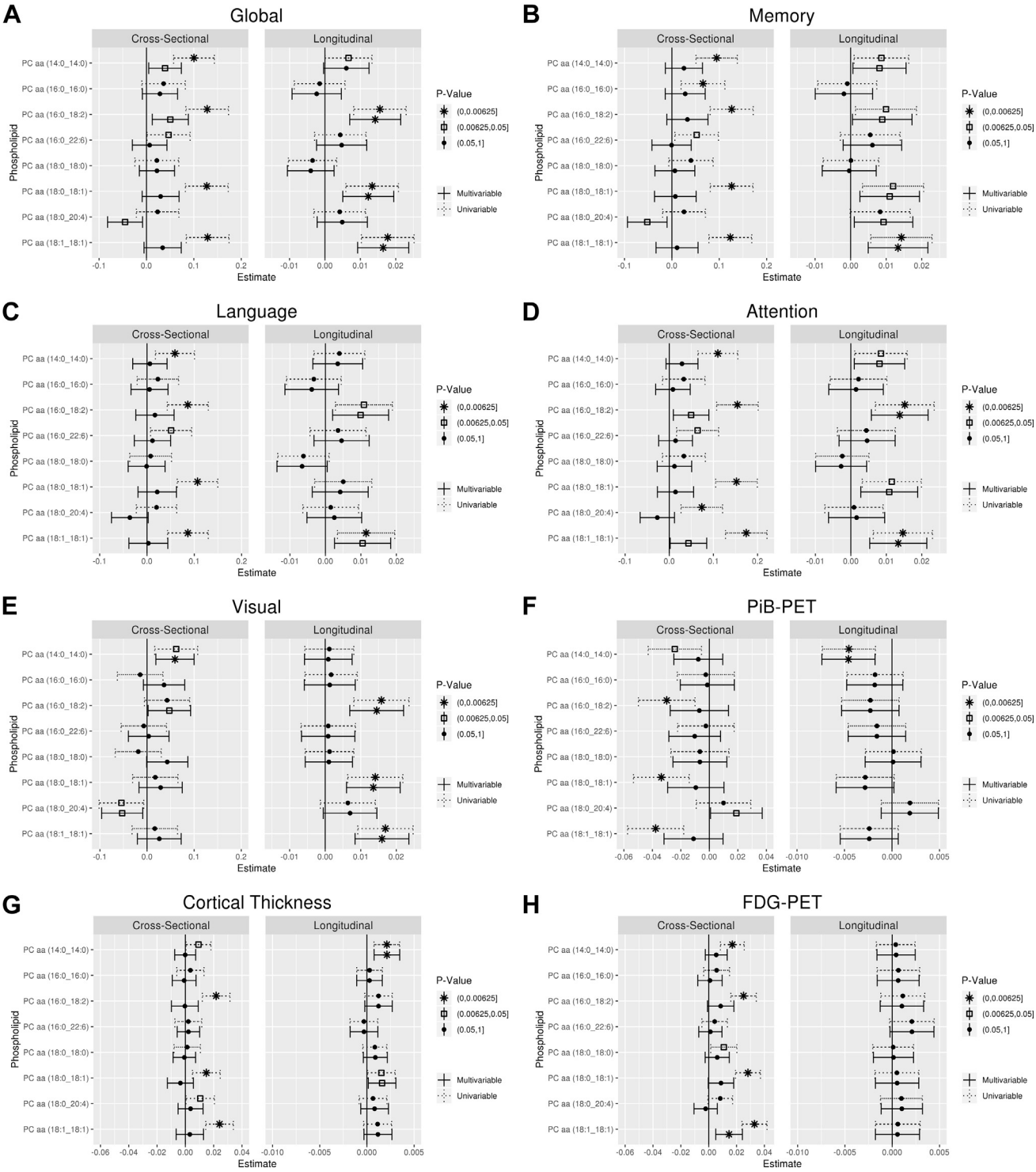

Fig. 1. Forest plots of estimate (SE, 95% confidence interval) of univariable and multivariable cross-sectional and longitudinal analyses between 8 plasma PCs (per 1-SD difference) and cognitive and neuroimaging measures in the MCSA study. (A) Global Cognition; (B) Memory; (C) Language; (D) Attention; (E) Visuospatial Function; (F) PiB-PET; (G) Cortical Thickness; (H) FDG-PET. Multivariable model: age, sex, education, medical comorbidity, dyslipidemia, statin use, and *APOE4* allele presence. Abbreviations: MCSA, Mayo Clinic Study of Aging; SD, standard deviation.

various PCs and cognitive decline among older adults with CU (Li et al., 2016b), MCI and dementia (Toledo et al., 2017), brain ventricular volume changes in MCI (Toledo et al., 2017), and AD progression (e.g., from normal to MCI or AD or from MCI to AD) (Casanova et al., 2016; Li et al., 2016b; Mapstone et al., 2014; Varma et al., 2018) have also been noted. For example, elevated levels of PCs (i.e., PC ae C40:3, PC ae C42:4, and PC ae C44:4) have been associated with slower Alzheimer's disease Assessment Scale-Cognition decline and less brain ventricular changes (Toledo et al., 2017). Because this study measured plasma PCs using an in-house method with analyte-specific standards, we were able to distinguish fatty acids in PCs, unlike the Biocrates P180 kits used by previous studies (Casanova et al., 2016; Klavins et al., 2015; Li et al., 2016a,b; Mapstone et al., 2014; Toledo et al., 2017; Varma et al.,

2018). Thus, the direct comparison between this and previous studies, which only specify the total carbon atoms and not the specific chain lengths, is not feasible. In addition, the Biocrates p180 kits do not measure PC aa 28:0, a PC aa (14:0_14:0) equivalent. Thus, this study is novel in that it measures 8 PCs with chain length information on fatty acyl groups and demonstrates longitudinal associations between elevated baseline PC aa (14:0_14:0), (16:0_18:2), (18:0_18:1), or (18:1_18:1) and better brain health over time (i.e., neuroimaging measures of AD pathophysiology or performance on tests of global- or domain-specific cognition).

Cortical thickness and glucose metabolism track distinct aspects of the AD pathophysiological process, namely neuronal loss and reduction in synaptic activity, respectively (Jack et al., 2010), and are known to have limited agreement (Alexopoulos et al., 2014). Therefore, it is not surprising that we found an association between plasma PC aa (14:0_14:0) and cortical thickness but not FDG-PET. Furthermore, although our results suggest that PC aa (14:0_14:0), (16:0_18:2), (18:0_18:1), and (18:1_18:1) may contribute to distinct aspects of the AD pathophysiological process (i.e., amyloid deposition and neurodegeneration vs. cognition), we are hesitant to draw strong conclusions because the mechanisms by which higher levels of these plasma PCs contribute to distinct aspects of the AD pathophysiological process remain unclear. Nevertheless, the association between higher baseline levels of plasma PC aa (14:0_14:0) and slower amyloid accumulation is consistent with the previously reported relationship between higher myristic acid (14:0) (presumably higher PC aa [14:0_14:0]) and increased HDL cholesterol and ApoA-I (Zock et al., 1994). Our finding is also consistent with previous studies reporting that HDL and ApoA-1 have important roles in promoting cerebrovascular integrity (Halliday et al., 2016) and reducing neuroinflammation (Lewis et al., 2010), both of which have been linked to less amyloid deposition (Lee et al., 2008; Pop et al., 2013) and neurodegeneration (Qin et al., 2007). Furthermore, PC (16:0_18:2) and (18:1_18:1) are the 2 most abundant PCs in plasma (Serna et al., 2015). PCs in plasma may affect lipid compositions in the brain over time, which affects activities of key enzymes of amyloid beta processing, synaptic functions, and neuronal survivals (Ayciriex et al., 2016; Holmes et al., 2012; Ledesma et al., 2012) that ultimately contribute to amyloid deposition, neurodegeneration, and cognitive decline over time.

Strengths of this study include the large sample size, longitudinal analyses of both imaging and cognitive measures, and the characterization of fatty acids of the PCs. The latter provides molecular information on the PC species implicated in AD. This information is important because the unequivocal molecular information on PC species is necessary to design experimental studies to delineate the mechanisms by which these plasma PCs contribute to amyloid deposition. However, limitations of the study also warrant consideration. First, we did not measure plasma PCs at multiple time points, so it is unclear how changes in PC aa (14:0_14:0), (16:0_18:2), (18:0_18:1), and (18:1_18:1) are related to changes in amyloid deposition, neurodegeneration, and cognition. Second, we cannot eliminate the influence of diets on plasma PCs because this study did not collect diet information. However, this study cohort represents a primarily Caucasian population from a restricted geographic area and as such can be considered relatively homogenous regarding lifestyle and dietary habits. Finally, whether these study findings apply to other race and ethnic groups beyond Caucasian remains unknown.

5. Conclusions

Plasma PCs have been examined in the context of AD with various cognitive, neuroimaging, and CSF biomarker measures. This study builds on previous studies and demonstrates that higher baseline levels of plasma PC aa (14:0_14:0), PC aa (16:0_18:2), (18:0_18:1), and PC aa (18:1_18:1) were associated with slower Aβ accumulation and less cortical thickness thinning and cognitive decline over time in older persons without cognitive impairment.

Disclosure

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurobiolaging.2019.03.005.

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