1H-MRS metabolites and rate of β-amyloid accumulation on serial PET in clinically normal adults

OPEN

ABSTRACT

Objective: To assess whether noninvasive proton magnetic resonance spectroscopy (1H-MRS) tissue metabolite measurements at baseline can predict an increase in the rate of β-amyloid (Aβ) accumulation on serial PET in clinically normal (CN) older adults.

Methods: Consecutive participants aged 60 years and older (n = 594) from the Mayo Clinic Study of Aging who were CN at baseline and who underwent 1H-MRS from the posterior cingulate voxel and longitudinal 11C-Pittsburgh compound B (PiB)-PET were included. The rate of Aβ accumulation by serial cortical PiB standardized uptake value ratios was estimated as a function of baseline 1H-MRS metabolite ratios and time using mixed-effect models adjusted for age, sex, and APOE ε4. Effect of APOE ε4 on the relationship between baseline MRS and an increased rate of Aβ accumulation was also assessed.

Results: Among all participants, a higher myo-inositol (mI)/creatine (p = 0.011) and a lower N-acetylaspartate/ml (p = 0.006) at baseline were associated with an increased Aβ accumulation over time after adjusting for age, sex, and APOE ε4. APOE ε4 did not modify the association of baseline 1H-MRS metabolite ratios and rate of Aβ accumulation. However, APOE ε4 carriers accumulated Aβ faster than noncarriers regardless of the baseline Aβ load (p = 0.001).

Conclusion: Among CN older adults, early metabolic alterations on 1H-MRS and APOE ε4 status are independently associated with an increased rate of Aβ accumulation. Our findings could have important implications for early diagnosis and identification of individuals for secondary prevention trials, because an increased rate of Aβ accumulation in CN older adults may confer a higher risk for cognitive decline and mild cognitive impairment. Neurology® 2017;89:1391-1399

GLOSSARY

Aβ = β-amyloid; AD = Alzheimer disease; Cho = choline; CN = clinically normal; Cr = creatine; MCI = mild cognitive impairment; mI = myo-inositol; MPRAGE = magnetization-prepared rapid acquisition gradient echo; MRS = magnetic resonance spectroscopy; NAA = N-acetylaspartate; PC = posterior cingulate; PiB = Pittsburgh compound B; SUVR = standardized uptake value ratio; WM = white matter.

Twenty to forty percent of clinically normal (CN) older adults have significant β-amyloid (Aβ) load on cross-sectional PET.1-3 An increased rate of Aβ accumulation may put them at a higher risk for cognitive decline4 and mild cognitive impairment (MCI).5 Cost-effective and noninvasive biomarkers that can predict a further increase in Aβ accumulation over time are necessary for better identification of at-risk individuals who may benefit from preventive and disease-modifying strategies.

In CN older adults, elevated myo-inositol (mI), a marker of glial activation, has been associated with a higher Aβ load on PET.6,7 a lower CSF Aβ1-42,7 and a higher Aβ density in an autopsy-confirmed cohort.8 Moreover, an elevated mI has been found in APOE ε4 carriers with no evidence of Aβ deposition on PET.7 Although the mechanistic relationship between APOE ε4 and elevated mI is unclear, it has been suggested that APOE ε4 enhances glial activation and

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modulates the relationship between Aβ and glial activation.9−11 However, the APOE ε4 effect on magnetic resonance spectroscopy (MRS) metabolite levels among CN elderly has been equivocal.9,10,11 Further, all of the studies examining MRS, Aβ-related pathology, and APOE ε4 were cross-sectional.

Our objective was to investigate the association of MRS metabolite ratios from a posterior cingulate (PC) gyrus voxel at baseline with the change in Aβ accumulation over time on serial amyloid PET in CN older adults drawn from a population-based sample. A secondary objective was to assess whether APOE ε4 modifies the relationship between MRS metabolites and the rate of Aβ accumulation.

METHODS Participants. Consecutive participants aged ≥60 years were drawn from the ongoing population-based, longitudinal Mayo Clinic Study of Aging,13,14 between January 2006 and May 2016. To be included in this imaging study, participants were required to be CN at baseline when MRS and amyloid PET were performed and have at least one follow-up amyloid PET. The diagnostic process and criteria for being clinically normal are described in appendix e-1 at Neurology.org. A total of 594 participants meeting inclusion criteria and passing image quality control were included in the analyses. The final cohort flowchart is provided as figure e-1. Blood was collected to determine the APOE ε4 carrier status.

Change in Aβ accumulation over time was assessed using all available follow-up amyloid PET examinations on an individual. Consecutive participants had 1 (n = 416; 70%), 2 (n = 144; 24.6%), 3 (n = 29; 4.8%), or 4 (n = 5; 0.6%) follow-up PET scans performed approximately every 15 months.

Standard protocol approvals, registrations, and participant consents. The Mayo Clinic and Olmsted Medical Center institutional review boards approved the study. Every participant provided written informed consent.

1H-MRS and MRI studies. Baseline MRS and MRI were performed at 3T using an 8-channel phase array coil (GE Healthcare, Waukesha, WI). A 3D high-resolution T1-weighted magnetization-prepared rapid acquisition gradient echo (MPRAGE) scan was acquired for anatomic segmentation and region labeling of PET and localization of 1H-MRS voxel.

A point-resolved spectroscopic sequence was acquired with repetition time/echo time 2,000/50 ms with a single voxel of 2 × 2 × 2 cm³ placed in the midsagittal MPRAGE image including right and left PC gyri and inferior precunes. Although the transverse relaxation time of N-acetylaspartate (NAA) and choline (Cho) is longer than ml, a single short echo time of 30 ms allowed measurements of all 3 metabolites in participants within the Alzheimer disease (AD) continuum.15 Metabolites were quantified using the automated proton brain examination/single-voxel package, and their intensities were scaled by creatine (Cr), a standard reference. Individual voxel placement and magnetic resonance spectra were visually evaluated by a trained image analyst for quality control. A trained image analyst reviewed the location of the MRS voxel and evaluated water suppression, baseline distortions, or lipid contamination. Voxels that did not include the PC location according to the predetermined anatomic landmarks and spectra with poor water suppression, lipid contamination, or baseline distortions failed quality control and were excluded. Although the spectral fit was not measured quantitatively, the quantification of metabolite ratios failed if the spectral fit was poor.

PET studies. 11C-Pittsburgh compound B (PiB)-PET/CT images were acquired using a GE scanner (GE Healthcare). Participants were injected with the PiB tracer (average activity 625 MBq; range 385−723) and a low-dose CT scan was acquired for attenuation correction. Forty to sixty minutes postinjection, a 20-minute dynamic PET scan consisting of four 5-minute frames was acquired. These 4 frames were averaged to create a single statistical image.

Cortical Aβ retention for each PiB image was calculated as a global cortical standardized uptake value ratio (SUVR).16 For measuring change over time in PiB uptake, we used a previously published SUVR measurement technique, which was demonstrated to improve reliability and plausibility for serial measurements compared to traditional cross-sectional approaches.17 This technique uses a reference region of eroded supratentorial white matter (WM) segmented using MRI, combined with the whole cerebellum andpons. In brief, each PiB scan is rigidly registered to its corresponding T1-weighted MRI. Each MRI is segmented using SPM1219 with an in-house population-specific template and several population-specific measure alterations previously described.19 These segmentations are used for locating supratentorial WM for the reference region. The target region and the cerebellar/pons regions included as part of the reference region were each localized using a corresponding in-house atlas19 that was nonlinearly registered to each corresponding MRI using the advanced normalization tools symmetric normalization algorithm,20 resampled using nearest-neighbor interpolation, and refined using the tissue segmentations described above. Automated registration and segmentation steps were each visually confirmed for acceptable quality. SUVRs were then calculated from PiB scans as the mean of all voxels in the target region normalized by the mean of all voxels in the reference region.

Statistical analysis. We used mixed-effects models to model repeated PiB SUVR values as a function of baseline MRS metabolite ratios for all participants. We incorporated random slopes and intercepts for each participant (estimating the correlation between the slopes and intercepts). The primary predictor of interest involved an interaction of baseline MRS ratio with time, because we were interested in longitudinal change in Aβ accumulation. Models included the nested time and MRS ratio at baseline as is proper for an evaluation of interaction with time. A significant interaction of MRS ratio at baseline with time would indicate that the increase in the rate of Aβ accumulation on serial PET depends upon the value of the MRS ratio at baseline. A significant association between baseline MRS ratio and Aβ accumulation in the model would indicate that the MRS ratio was associated with consistently higher Aβ accumulation across all serial PET measurements in a given participant but not with an increased rate of accumulation. The models also accounted for effects of baseline age, sex, and APOE ε4 status. We computed the 3-way interactions of baseline MRS ratios and APOE ε4 status with time to assess whether APOE ε4 modifies the relationship between baseline metabolite MRS ratios and change over time in Aβ accumulation on serial PET.

Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and R statistical software version 3.1.1 (R-
was associated with consistently higher Aβ load across all serial PET examinations in a given participant (p = 0.02; table e-1). However, NAA/Cr was not associated with an increased rate of Aβ accumulation (p = 0.18; figure e-2). Cho/Cr was associated neither with Aβ load across serial PET (p = 0.28) nor with rate of Aβ accumulation (p = 0.47; table e-1).

APOE ε4 was associated with consistently higher Aβ load across all serial PiB SUVR measurements (p < 0.001). Furthermore, the interaction of APOE ε4 with time (p < 0.001) was associated with an increased rate of Aβ accumulation, taking into account baseline age, sex, and time with baseline age interaction (table 3, model 1; figure 1). However, an accelerated rate of Aβ accumulation in APOE ε4 carriers compared to noncarriers may be because APOE ε4 carriers have higher baseline Aβ load.16 Nevertheless, when we compared rates of Aβ accumulation between a subset of our APOE ε4 carriers (n = 149) and noncarriers matched on age, sex, and baseline Aβ load to a subset of our noncarriers (n = 149), the interaction between APOE ε4 and time remained significant (p = 0.001; table 3, model 2) using mixed-effect model with a random block design to account for matching. Therefore, APOE ε4 carriers accumulated Aβ at an accelerated rate compared to APOE ε4 noncarriers even when they had a similar baseline Aβ load (figure 1).

Finally, we assessed whether APOE ε4 status modified the relationship between the baseline metabolites and increased rate of Aβ accumulation using a 3-way interaction of baseline metabolites, APOE ε4, and time among all. None of these interactions was significant, including for mI/Cr × APOE ε4 × time (p = 0.35) and for NAA/ml × APOE ε4 × time (p = 0.90). Therefore, longitudinally, APOE ε4 status did not modify the relationship between MRS metabolites and rate of Aβ accumulation on serial PET.

RESULTS Participants’ characteristics at baseline are listed in table 1. Although a higher mI/Cr at baseline was only borderline associated with a higher Aβ load across all serial PET of a given participant (p = 0.06), it is more important that it was significantly associated with a greater increase in rate of Aβ accumulation (p = 0.011), adjusting for baseline age, sex, APOE ε4, and the interaction between APOE ε4 and age (table 2). Similarly, a lower baseline NAA/ml was associated with consistently higher Aβ load across all serial PETs of a given participant (p = 0.007), but moreover, it was associated with an increased rate of Aβ accumulation (p = 0.006), adjusting for the same covariates (table 2). Figure 1 illustrates the estimated increase in rate of Aβ accumulation by baseline MRS ratios and by APOE ε4 with specific estimated values shift according to age, sex, and APOE ε4. Figure 2 shows the 3 individuals from the current cohort, their magnetic resonance spectra at baseline, and associated Aβ load at baseline and at follow-up.

Mixed-effect models for the remaining metabolite ratios showed that a lower baseline NAA/Cr was associated with consistently higher Aβ load across all serial PET examinations in a given participant (p = 0.02; table e-1). However, NAA/Cr was not associated with an increased rate of Aβ accumulation (p = 0.18; figure e-2). Cho/Cr was associated neither with Aβ load across serial PET (p = 0.28) nor with rate of Aβ accumulation (p = 0.47; table e-1).

APOE ε4 was associated with consistently higher Aβ load across all serial PiB SUVR measurements (p < 0.001). Furthermore, the interaction of APOE ε4 with time (p < 0.001) was associated with an increased rate of Aβ accumulation, taking into account baseline age, sex, and time with baseline age interaction (table 3, model 1; figure 1). However, an accelerated rate of Aβ accumulation in APOE ε4 carriers compared to noncarriers may be because APOE ε4 carriers have higher baseline Aβ load.16 Nevertheless, when we compared rates of Aβ accumulation between a subset of our APOE ε4 carriers (n = 149) and noncarriers matched on age, sex, and baseline Aβ load to a subset of our noncarriers (n = 149), the interaction between APOE ε4 and time remained significant (p = 0.001; table 3, model 2) using mixed-effect model with a random block design to account for matching. Therefore, APOE ε4 carriers accumulated Aβ at an accelerated rate compared to APOE ε4 noncarriers even when they had a similar baseline Aβ load (figure 1).

Finally, we assessed whether APOE ε4 status modified the relationship between the baseline metabolites and increased rate of Aβ accumulation using a 3-way interaction of baseline metabolites, APOE ε4, and time among all. None of these interactions was significant, including for mI/Cr × APOE ε4 × time (p = 0.35) and for NAA/ml × APOE ε4 × time (p = 0.90). Therefore, longitudinally, APOE ε4 status did not modify the relationship between MRS metabolites and rate of Aβ accumulation on serial PET.

DISCUSSION In this large cohort of CN older adults, mean age of 74, drawn from a population-based sample, we demonstrated that noninvasive and inexpensive baseline MRS metabolite levels are associated with an increased rate of Aβ accumulation on serial PET. Lower NAA/ml and higher mI/Cr at baseline were associated with an increased rate of Aβ accumulation taking into account age at baseline, sex, and APOE ε4 status. APOE ε4 carriers accumulated Aβ faster than noncarriers. APOE ε4 status did not alter the relationship between baseline metabolite levels and rate of Aβ accumulation and both MRS metabolites and APOE ε4 likely are independently associated with an increased Aβ accumulation over time.

An elevated mI/Cr has been consistently associated with biomarkers of elevated Aβ in CN adults cross-sectionally.7,8,23,6 Moreover, in the transgenic

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Table 1  Participants’ (n = 594) characteristics at baseline

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>74.4 (7.3)</td>
</tr>
<tr>
<td>Male</td>
<td>343 (58)</td>
</tr>
<tr>
<td>APOE ε4 carrier</td>
<td>169 (29)</td>
</tr>
<tr>
<td>Education, y</td>
<td>14.73 (2.70)</td>
</tr>
<tr>
<td>Short test of mental status</td>
<td>35.06 (2.24)*</td>
</tr>
<tr>
<td>NAA/Cr</td>
<td>1.68 (0.11)</td>
</tr>
<tr>
<td>Cho/Cr</td>
<td>0.63 (0.08)</td>
</tr>
<tr>
<td>mI/Cr</td>
<td>0.51 (0.06)</td>
</tr>
<tr>
<td>NAA/ml</td>
<td>3.35 (0.57)</td>
</tr>
<tr>
<td>PiB SUVR, mean (SD)</td>
<td>1.50 (0.33)</td>
</tr>
<tr>
<td>PiB SUVR, median (range)</td>
<td>1.37 (1.18-1.93)</td>
</tr>
<tr>
<td>Follow-up time, y, mean (SD)</td>
<td>3.26 (1.50)</td>
</tr>
<tr>
<td>Follow-up time, y, median (range)</td>
<td>2.67 (1-9.17)</td>
</tr>
</tbody>
</table>

Abbreviations: Cho = choline; Cr = creatine; ml = myo-inositol; NAA = N-acetylaspartate; PiB = 11C-Pittsburgh compound B; SUVR = cortical standardized uptake value ratio. APOE ε4 status was missing in 1 and short test of mental status in 8 participants. Mean (SD) is listed for continuous variables unless otherwise noted and counts and proportions (%) are listed for categorical variables.

*Maximum score is 38 points.40
Table 2  Estimated rate of β-amyloid (Aβ) accumulation by baseline myo-inositol (mI)/creatine (Cr) and N-acetylaspartate (NAA)/ml ratios

<table>
<thead>
<tr>
<th></th>
<th>Estimate (SE)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-0.628 (0.087)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time, y</td>
<td>-0.024 (0.09)</td>
<td>0.03</td>
</tr>
<tr>
<td>Baseline age</td>
<td>0.008 (0.001)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>0.034 (0.014)</td>
<td>0.013</td>
</tr>
<tr>
<td>APOE e4</td>
<td>0.118 (0.018)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline ml/Cr ratio</td>
<td>0.223 (0.018)</td>
<td>0.06</td>
</tr>
<tr>
<td>APOE e4 with time interaction</td>
<td>0.011 (0.002)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline age with time interaction</td>
<td>0.001 (0.000)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline ml/Cr ratio with time interaction</td>
<td>0.029 (0.011)</td>
<td>0.011</td>
</tr>
<tr>
<td>NAA/ml with time interaction as primary predictor</td>
<td>-0.003 (0.001)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Coefficient estimates with their SE and p values are reported for the rate of Aβ accumulation as the response. The predictor of primary interest is an interaction of baseline ml/Cr ratio with time and then baseline NAA/ml ratio with time, which are 2 metabolite ratios significantly associated with the change [increase and decrease] in rate of Aβ accumulation. The interaction with time is illustrated in figure 1. The individual effects of other variables that contribute to the model fit are also shown.

mI/Cre with time interaction as primary predictor

Coefficient estimates with their SE and p values are reported for the rate of Aβ accumulation as the response. The predictor of primary interest is an interaction of baseline mI/Cr ratio with time and then baseline NAA/ml ratio with time, which are 2 metabolite ratios significantly associated with the change [increase and decrease] in rate of Aβ accumulation. The interaction with time is illustrated in figure 1. The individual effects of other variables that contribute to the model fit are also shown.

murine AD model, a passive immunization with anti-Aβ antibodies lessened the ml/Cr in the treatment arm compared to placebo. In the current longitudinal cohort, we demonstrated findings that suggest an elevated mI/Cre as a predictor of an accelerated Aβ accumulation over time on serial PET.

NAA/Cr ratio, a marker of neuronal viability and synaptic integrity, is reduced in participants with MCI25 and AD,15,26,27 but not in CN older adults, suggesting that a decline in NAA/Cr is preceded by an increased ml/Cr during the course of AD. In line with this, an autopsy-confirmed study8 demonstrated an association between a lower NAA/Cr and an increased rate of Aβ accumulation. Lower NAA/ml has predicted progression from CN to MCI in a population-based cohort29 and only a lower NAA/ml among routinely examined MRS ratios correlated with both greater tau and Aβ burden at autopsy.8 The current study supports the composite NAA/ml ratio as a marker of increased longitudinal Aβ accumulation in CN older adults.

Although Cho/Cr has been associated with a higher Aβ load on PET,7,25 and a worse cognitive performance in CN older adults,6,9 we did not observe an association of Cho/Cr and rate of Aβ accumulation. No association was found between Cho/Cr and AD-related pathology in an autopsy-confirmed cohort,8 and the significance of Cho/Cr during the progression of AD remains unclear.

APOE e4 status did not modify the relationship between baseline MRS metabolites and rate of Aβ accumulation on serial PET. Instead, APOE e4 was independently associated with an accelerated Aβ accumulation. Whereas the relationship between a higher Aβ load in APOE e4 carriers has been well-established cross-sectionally,5,30,31 the effect of APOE e4 status on longitudinal Aβ accumulation in CN older adults has not been clarified, likely due to small sample sizes, various PiB uptake measurement approaches, and different interpretation of contributing effects of baseline Aβ load, age, sex, and number of available follow-up PET scans.32-34 Moreover, APOE e4 effect on longitudinal Aβ accumulation may be mediated by baseline Aβ load,16 which is higher in APOE e4 carriers than noncarriers. Higher baseline Aβ load is a risk factor for increased Aβ accumulation over time.16 However, our finding of longitudinally accelerated Aβ accumulation in APOE e4 carriers with similar baseline Aβ load to APOE e4 noncarriers indicates that APOE e4 carriers accumulate Aβ faster than noncarriers, regardless of baseline Aβ levels.

A cross-sectional study by Voevodskaya et al.7 demonstrated that already cognitively normal APOE e4 carriers with still normal Aβ biomarker levels had elevated ml/Cr. It was suggested that ml/Cr may be an early biomarker of Aβ accumulation.35 Our findings support this hypothesis by showing that an elevated ml/Cr ratio in older adults is associated with an increased rate of Aβ accumulation. In addition, we showed that the relationship between MRS metabolite alterations and rates of Aβ accumulation is independent of APOE e4 status. Taken together, these findings suggest that cross-sectional MRS metabolite alterations may occur in APOE e4 carriers because of their risk of increased Aβ accumulation over time.

Higher baseline Aβ load increases the risk of cognitive decline over time in CN older adults.54,56 However, a recent cut point for Aβ positivity on PET in CN older adults57 was based on repeated
measurements of Aβ accumulation. Using repeated measurements, the reliable worsening in Aβ accumulation was identified and served as cut point. Moreover, a few studies demonstrated that an increased rate of Aβ accumulation on PET is associated with cognitive decline over time in CN and progression to MCI. Therefore identifying those who accumulate Aβ faster over time provides additional and valuable information on at-risk individuals beyond cross-sectional measurements, which do not provide any information on disease progression. However, so far, the biomarkers that would identify such individuals have been scarce. Identifying those who accumulate Aβ faster can have important implications for early diagnosis and selecting at-risk individuals for secondary preventive interventions targeted to reduce Aβ accumulation rate. It is possible that interventions might be more effective in those who are still clinically normal but on the way to higher rates of Aβ accumulation. Our current findings suggest that both MRS metabolite alterations and APOE ε4 status independently are associated with accelerated rates of Aβ accumulation.

We did not dichotomize the participants as amyloid-positive or -negative by a cut point, although this popular approach may have practical advantages. Instead, we treated serial PiB SUVR as continuous measures that allowed us to include the CN participants with the full range of PiB SUVR values. Cut point may create a gray zone where sub-threshold but important relationships might be obscured. For example, the biological difference
between those participants who are close to the cut point, but arbitrarily fall into opposite groups, or a minor longitudinal change that moves a participant from one group to another by a given cut point might be negligible. On the contrary, a large difference in PiB SUVR among 2 participants who are in the same PiB group and a large change in PiB SUVR in a participant over time without a change in PiB group designation by cut point may be very meaningful. Finally, the cut point for amyloid positivity for longitudinal amyloid measurements remains to be established.

Strengths of this study are the large sample of individuals drawn from a single population with serial amyloid PET including a large subset of APOE ε4 carriers matched to noncarriers on demographics and baseline Aβ load. In this cohort, Aβ accumulation over time was measured using a modified reference region that has demonstrated an improved reliability and plausibility for serial measurements compared to traditional cross-sectional approaches.17

The limitations of our study are similar to those of other studies using participants drawn from a population-based sample, such as the presence of various subthreshold pathologies in CN older adults, which may increase the variability of MRS metabolite measurements and weaken some of the studied relationships. However, the levels of MRS ratios in the current cohort of CN older adults were consistent with previous studies by others and by our group,9,29,38 including an autopsy-confirmed study on MRS correlates of Aβ accumulation.8 Our proportion of CN APOE ε4 carriers (29%) was similar to previous reports,5,25,38 including an autopsy-confirmed study on MRS correlates of Aβ accumulation.8 However, we cannot exclude the potential for participation or survival bias because more educated and generally healthier participants may be more willing to participate longitudinally in imaging studies,29 and our findings may not be...
However, it is an interaction of increased rate of Aβ accumulation on serial PET as response in the whole cohort (n = 594). The effects of individual variables contributing to the model fit are shown. Model 1 shows that APOE ε4 status is associated with a consistently higher Aβ load across all serial PET in a given participant. However, it is an interaction of APOE ε4 status with time, which is associated with an increased rate of Aβ accumulation (visualized in figure 1). Model 2 compares estimated rate of Aβ accumulation between a subset of our APOE ε4 carriers (n = 149) matched on baseline age, sex, and baseline Aβ load to noncarriers (n = 149), showing that APOE ε4 carriers accumulate Aβ faster than noncarriers.

*Note this is a matched analysis.

<table>
<thead>
<tr>
<th>Table 3: Estimated rate of β-amyloid (Aβ) accumulation by APOE ε4 status</th>
<th>Estimate (SE)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1: APOE ε4 as primary predictor in the whole cohort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>-0.747 (0.078)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time, y</td>
<td>-0.037 (0.008)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline age</td>
<td>0.008 (0.001)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>0.034 (0.014)</td>
<td>0.014</td>
</tr>
<tr>
<td>APOE ε4</td>
<td>0.117 (0.016)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline age with time interaction</td>
<td>0.001 (0.000)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>APOE ε4 with time interaction</td>
<td>0.011 (0.002)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 2: APOE ε4 as primary predictor in subset of APOE ε4 carriers matched to noncarriers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>-0.036 (0.018)</td>
<td>0.043</td>
</tr>
<tr>
<td>Time, y</td>
<td>0.017 (0.002)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>APOE ε4</td>
<td>0.004 (0.004)</td>
<td>0.34*</td>
</tr>
<tr>
<td>APOE ε4 with time interaction</td>
<td>0.006 (0.002)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Coefficient estimates with their SE and p values are reported for the rate of Aβ accumulation on serial PET as response in the whole cohort (n = 594). The effects of individual variables contributing to the model fit are shown. Model 1 shows that APOE ε4 status is associated with a consistently higher Aβ load across all serial PET in a given participant. However, it is an interaction of APOE ε4 status with time, which is associated with an increased rate of Aβ accumulation (visualized in figure 1). Model 2 compares estimated rate of Aβ accumulation between a subset of our APOE ε4 carriers (n = 149) matched on baseline age, sex, and baseline Aβ load to noncarriers (n = 149), showing that APOE ε4 carriers accumulate Aβ faster than noncarriers.

*Note this is a matched analysis.

entirely generalizable to other populations of CN adults. Finally, an inclusion of those ≥60 years old does not allow studying the relationship between rate of Aβ accumulation and MRS metabolites at an even earlier stage of AD pathophysiology. However, younger adults do not show sufficient increase in rate of Aβ accumulation to model longitudinal process. Increase in the rate of Aβ accumulation on serial PET in those younger than 60 is minimal35-39 and limited in capturing potential associations with baseline MRS metabolites.

MRS is a noninvasive and inexpensive technique that can be part of a standard clinical magnetic resonance examination, including in clinical trials. However, for these purposes, the standardization and optimization of multicenter MRS studies are necessary. Moreover, a longitudinal investigation of serial MRS metabolites to estimate progression of Aβ in participants within the AD continuum would provide additional information on the temporal ordering between the alterations in MRS metabolites and Aβ pathophysiology.

AUTHOR CONTRIBUTIONS

Dr. Nedelka: study concept and design, analysis and interpretation of the data, drafting the manuscript. S.A. Pryzbylski: design and analysis or interpretation of the data, critical revision of the manuscript for important intellectual content. T. Lesnick: design and analysis or interpretation of the data, drafting the manuscript, critical revision of the manuscript for important intellectual content. Dr. Lowe: acquisition of data, critical revision of the manuscript for important intellectual content. Dr. Schwaab: data analysis, critical revision of the manuscript for important intellectual content. Dr. Machulda: acquisition of data, critical revision of the manuscript for important intellectual content. Dr. Mielke: acquisition of data, critical revision of the manuscript for important intellectual content. Dr. Roberts: acquisition of data, critical revision of the manuscript for important intellectual content. Dr. Kremers: analysis or interpretation of the data, critical revision of the manuscript for important intellectual content. Dr. Boeve: acquisition of data, critical revision of the manuscript for important intellectual content. Dr. Kupersman: acquisition of data, critical revision of the manuscript for important intellectual content. Dr. Petersen: acquisition of data, critical revision of the manuscript for important intellectual content. Dr. Jack: acquisition of data, critical revision of the manuscript for important intellectual content. Dr. Knopman: study concept and design, acquisition of data, interpretation of the data, drafting the manuscript, critical revision of the manuscript for important intellectual content.

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REFERENCES


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