Title
APOE effect on Alzheimer's disease biomarkers in older adults with significant memory concern

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Authors
Risacher, SL
Kim, S
Nho, K
et al.

Publication Date
2015

DOI
10.1016/j.jalz.2015.03.003

Peer reviewed
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APOE effect on Alzheimer’s disease biomarkers in older adults with significant memory concern


Abstract

Introduction: This study assessed apolipoprotein E (APOE) ε4 carrier status effects on Alzheimer’s disease imaging and cerebrospinal fluid (CSF) biomarkers in cognitively normal older adults with significant memory concerns (SMC).

Methods: Cognitively normal, SMC, and early mild cognitive impairment participants from Alzheimer’s Disease Neuroimaging Initiative were divided by APOE ε4 carrier status. Diagnostic and APOE effects were evaluated with emphasis on SMC. Additional analyses in SMC evaluated the effect of the interaction between APOE and [18F]Florbetapir amyloid positivity on CSF biomarkers.

Results: SMC ε4+ showed greater amyloid deposition than SMC ε4−, but no hypometabolism or medial temporal lobe (MTL) atrophy. SMC ε4+ showed lower amyloid beta 1−42 and higher tau/p-tau than ε4−, which was most abnormal in APOE ε4+ and cerebral amyloid positive SMC.

Discussion: SMC APOE ε4+ show abnormal changes in amyloid and tau biomarkers, but no hypometabolism or MTL neurodegeneration, reflecting the at-risk nature of the SMC group and the importance of APOE in mediating this risk.

Keywords: Significant memory concern; SMC; Subjective cognitive decline; SCD; Apolipoprotein E; APOE; Neuroimaging; [18F]Florbetapir PET; [18F]Fluorodeoxyglucose; FDG; PET; Structural magnetic resonance imaging (MRI); Cerebrospinal fluid; CSF; Alzheimer’s Disease Neuroimaging Initiative; ADNI

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http://dx.doi.org/10.1016/j.jalz.2015.03.003
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1. Introduction

Alzheimer’s disease (AD) is the most common age-related neurodegenerative disease, affecting nearly 5.2 million older adults in the United States [1]. Many AD researchers believe that effective treatments for AD will require intervention early in the disease course, even before clinical symptoms [2]. Thus, a significant goal is to identify participants likely to progress to AD (i.e., “at-risk”) before significant cognitive decline.

One group thought to be at risk is cognitively normal older adults with subjective reports of cognitive changes [2–4]. Recently, an international consortium defined this group as subjective cognitive decline (SCD) [3]. In the Alzheimer’s Disease Neuroimaging Initiative (ADNI), a comparable group of older adults were recruited with significant memory concerns (SMC) in the form of self-only complaints exceeding a predefined cut-off score on memory ratings. Previous studies have shown that older adults with SCD/SMC have an increased risk for future progression to AD [5–16] and AD-like changes in neuroimaging and cerebrospinal fluid (CSF) biomarkers [4,13,17–27]. In addition, SCD/SMC participants who are carriers of the most commonly reported genetic variant associated with late onset AD, the apolipoprotein E (APOE) ε4 allele, show greater medial temporal lobe (MTL) hypometabolism and atrophy, increased cerebral amyloid, and altered CSF measures of amyloid and tau [22,23,28,29]. However, to date, no studies have looked at the role of APOE ε4 status in SCD/SMC across a comprehensive multimodal panel of major imaging and CSF AD biomarkers. Evaluating multiple biomarkers in the same cohort will help to define the staging of the SCD/SMC participants in relation to the Jack et al. (2013) model [30] and help determine the implication of APOE genotype for key AD pathophysiological processes, including amyloid deposition, tau hyperphosphorylation, and brain atrophy, in this important at-risk group.

We recently reported on the role of APOE ε4 carrier status on several multimodal biomarkers in early mild cognitive impairment (EMCI) participants and demonstrated a significant association between carrying an APOE ε4 allele and amyloid pathology in both cognitively normal (CN) older adults without complaints and EMCI participants [31]. However, the effect of APOE ε4 carrier status was minimal on CSF tau levels and brain atrophy. Thus, we sought to evaluate a similar question in SCD/SMC participants, as they are cognitively normal and thus less clinically affected than EMCI participants, but are at risk for AD due to subjective memory changes. We now also include [18F]Fluorodeoxyglucose (FDG) positron emission tomography (PET) for these groups and an expanded sample.

The goal of the present study was to evaluate the following hypotheses: (1) older adults with SMC who are APOE ε4 carriers show AD-like pathology on neuroimaging and CSF biomarkers, including increased amyloid deposition, decreased CSF amyloid beta (Aβ)1–42, increased CSF total tau (t-tau) and tau phosphorylated at threonine 181 (p-tau), glucose hypometabolism, and MTL neurodegeneration relative to APOE ε4 noncarriers; and (2) SMC APOE ε4 carriers with cerebral amyloid positivity would show the most abnormalities on CSF biomarkers of amyloid and tau, as these SMC participants carry additional genetic risk and are most likely to show AD-related pathological changes. The analyses associated with the latter hypothesis will allow us to determine whether pathological CSF Aβ1–42 changes are occurring in SMC who are APOE ε4 positive but below the threshold for amyloid PET positivity, as has been suggested by studies in autosomal dominant AD [32]. Furthermore, these analyses will evaluate whether APOE ε4 positive SMC show the most abnormal changes in tau which would suggest that these individuals are at a highest risk for future cognitive decline. In these analyses, CN and EMCI participants were included as boundary groups to better characterize the SMC group.

2. Methods

2.1. Alzheimer’s Disease Neuroimaging Initiative

Data used in the preparation of this article were obtained from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). For more information see Supplementary Material, http://www.adni-info.org, http://adni.loni.usc.edu, and in previous reports [33–38]. Informed consent was obtained according to the Declaration of Helsinki.

2.2. Participants

Participants were included if they were diagnosed as CN, SMC, or EMCI. Diagnosis was made using the standard criteria described in the ADNI-2 procedures manual (http://www.adni-info.org). Briefly, CN participants had no subjective or informant-based complaint of memory decline and normal cognitive performance (adjusted for education level) on the Wechsler Logical Memory Delayed Recall (LM-delayed) and the Mini-Mental State Examination (MMSE); EMCI participants had a memory concern reported by the subject, informant, and/or clinician, abnormal memory function approximately 1 standard deviation below normative performance adjusted for education level on the LM-delayed, a MMSE total score greater than 24, and preserved daily functioning such that a diagnosis of AD could not be made; SMC participants had subjective memory concerns as assessed using the Cognitive Change Index (CCI; total score from first 12 items > 16), which is based on selected items from a larger compilation of measures analyzed in an independent sample [4], no informant-based complaint of memory impairment or decline, and normal cognitive performance on the LM-delayed recall and MMSE.

All diagnostic groups were further divided based on APOE ε4 carrier status (one or more ε4 alleles = APOE
e4 positive [e4+]; no e4 alleles = APOE e4 negative [e4−]). APOE ε2 carriers were included in their respective groups (e4− or e4+), as the distribution of APOE ε2 carriers did not differ across CN, SMC, and EMCI groups. The initial analysis included 594 participants (132 CN e4−, 53 CN e4+, 71 SMC e4−, 33 SMC e4+, 174 EMCI e4−, and 131 EMCI e4+). The targeted analysis in SMC of the potential interaction between APOE ε4 carrier status and amyloid positivity (on [18F]Florbetapir PET) on CSF biomarkers included 90 SMC participants, including 50 APOE ε4− who were amyloid negative (APOE ε4−/Aβ−), 12 APOE ε4− who were amyloid positive (APOE ε4−/Aβ+), 12 APOE ε4+ who were amyloid negative (APOE ε4+/Aβ−), and 16 APOE ε4+ who were amyloid positive (APOE ε4+/Aβ+).

2.3. Clinical and cognitive assessments

Baseline clinical and cognitive performance data was downloaded from the ADNI data repository (http://adni.loni.usc.edu). Participants received a comprehensive battery of clinical and cognitive tests as described in the ADNI-2 manual (www.adni-info.org). In addition to the CCI, subjective or participant-based cognitive complaints were assessed using the Measure of Everyday Cognition (ECog). Cognitive complaints by the study partner regarding the participant’s functioning were also assessed using the ECog (Informant version). We compared the ECog estimate of both participant and informant cognitive complaints between groups to confirm the complaint status of the SMC group, assess the level of complaints within the SMC group relative to CN and EMCI participants, and to evaluate differences in informant-based complaints across these preclinical and prodromal stages of disease.

2.4. [18F]Florbetapir PET scans

Preprocessed [18F]Florbetapir PET scans (coregistered, averaged, standardized image and voxel size, uniform resolution) were downloaded from Laboratory of Neuro Imaging (http://adni.loni.usc.edu). Images were pre-processed by the ADNI PET core and locally as previously described [31,34]. Scans were intensity-normalized using a pons ROI to create [18F]FDG SUVR images. Mean SUVR values were extracted from two ROIs, including a global cortical ROI generated from an independent comparison of baseline ADNI-1 [18F]Pittsburgh Compound B SUVR scans (regions where AD > CN) and an anatomically-defined bilateral precuneus ROI [39]. A total of 17 participants (5 CN e4−, 2 CN e4+, 5 SMC e4+, 4 EMCI e4−, 1 EMCI e4+) were excluded from [18F]Florbetapir analyses for missing data.

2.5. [18F]FDG PET scans

Preprocessed [18F]FDG PET scans (Coregistered, Averaged, Standardized Image and Voxel Size, Uniform Resolution) were downloaded from LONI (http://adni.loni.usc.edu) and processed as has been previously described [31,34]. Scans were then intensity-normalized using a pons ROI to create [18F]FDG SUVR images. Mean SUVR values were extracted from two ROIs, including a global cortical ROI generated from an independent comparison of baseline ADNI-1 [18F]FDG SUVR scans (regions where CN > AD) and an anatomically-defined bilateral parietal lobe ROI [39]. A total of 15 participants (4 CN e4−, 1 CN e4+, 2 SMC e4−, 5 SMC e4+, 3 EMCI e4−) were excluded from [18F]FDG PET analyses for missing data.

2.6. Structural MRI

All available baseline structural MRI scans were downloaded from LONI for included participants. Scans were corrected before download as previously described (www.adni.loni.usc.edu; [33,40]). Scans were processed using Freesurfer version 5.1, as described in previous reports [31,41,42], to extract hippocampal volumes, entorhinal cortex thickness measures, and total intracranial volume (ICV). If two MRI scans were available, values were averaged for each participant from both processed scans. A total of 4 participants (1 CN e4−, 3 SMC e4−) were excluded from this analysis for missing data.

2.7. CSF biomarkers

Lumbar punctures and CSF sample preparation were completed as described in the ADNI manual (http://adni.loni.usc.edu/research/protocols/biospecimens-protocols/). CSF Aβ1–42, t-tau, and p-tau were measured using the multiplex xMAP Luminox platform with the Innogenetics/Fujirebio AlzBio3 research use only immunoassay kit based reagents (Fujirebio, Ghent, Belgium) as described previously [43]. Analysis and quality control procedures appear online (http://adni.loni.usc.edu). CSF aliquots in this analysis were collected at the baseline ADNI-Grand Opportunity (GO)2 visit and were scaled to the ADNI-1 baseline data set using linear regression to use the abnormal cut-off values that were previously established [44]. 86 participants (20 CN e4−, 11 CN e4+, 9 SMC e4−,
2 SMC e4+, 21 EMCI e4–, 23 EMCI e4+) were excluded from CSF analyses for missing data.

2.8. Statistical analyses

For the initial analyses, we evaluated the effect of diagnosis and APOE e4 status on target measures using two-way ANCOVA for continuous variables and a chi-square test for categorical variables implemented in SPSS 21.0 (SPSS Statistics 21, IBM Corporation, Somers, NY). Post-hoc analyses used a Bonferroni correction for multiple comparisons. Specifically, the effects of diagnosis, APOE e4 carrier status, and their interaction on demographics, clinical and psychometric test performance, patient and informant cognitive complaints, regional amyloid deposition ([18F]Florbetapir SUVR), regional glucose metabolism ([18F]FDG SUVR), brain atrophy (hippocampal volume and entorhinal cortex thickness), and CSF levels of Aβ1–42, t-tau, and p-tau were assessed. We tested for the normality of the evaluated measures and found that the measures of CSF amyloid and tau, [18F]Florbetapir SUVR, and entorhinal cortex thickness were not normally distributed. We log-transformed these variables and repeated the previous analyses. However, this log-transformation did not alter the findings observed with the raw variables. Therefore, we present the findings obtained by the analysis of the raw values in the present report. A further targeted analysis in SMC participants of an interaction between APOE e4 carrier status and amyloid positivity established using [18F]Florbetapir PET scans (cut-off of 1.52 in the global cortical ROI) was selected due to maximal classification of AD vs. CN patients in the full ADNI-GO/2 sample and amyloid positive vs. negative defined using a previously reported cut-off ([45]) was completed. Specifically, a two-way ANCOVA was used to evaluate the effect of APOE e4 status, amyloid positivity, and their interaction on CSF levels of Aβ1–42, t-tau, and p-tau. All PET and CSF biomarker analyses were covaried for age and gender. Analyses of cognition were covaried for age, gender, and years of education. Finally, analyses of brain atrophy were covaried for age, gender, and total ICV. Given the known association of depressive symptoms with subjective cognitive decline, we repeated the analyses including the total score of the Geriatric Depression Scale (GDS) as a covariate. Inclusion of the GDS total score as a covariate did not change any of the observed results and thus, is not included in the final results presented in the present report.

3. Results

3.1. Demographics, cognition, and cognitive complaints

Effects of diagnosis and APOE e4 carrier status on demographics, clinical and neuropsychological test performance, and patient- and informant-based complaints are shown in Table 1. Age and education level were different among diagnostic groups (P < .05), whereas only age was associated with APOE e4 status (P = .003). Gender was significantly associated with the interaction of diagnosis and APOE e4 carrier status only. Unsurprisingly, clinical and neuropsychological test performance was significantly different among diagnostic groups (P < .001), with EMCI showing impairment relative to CN and/or SMC on all cognitive measures (P < .05). EMCI had greater self- and informant-based complaints than CN and/or SMC on the ECog (P < .05). SMC participants had greater self-based complaints than CN in all domains and greater informant-based complaints in the memory domain only (specifically SMC e4− > CN; P < .05). APOE e4 carrier status was also significantly associated with selected measures of memory and executive performance (all P < .05), with e4+ participants showing poorer performance than e4−. See Table 1 for complete results.

3.2. Voxel-wise analysis of amyloid PET

A main effect of APOE e4 carrier status was observed with APOE e4+ participants showing greater amyloid deposition than APOE e4− participants across diagnostic groups in nearly the entire cortex (Fig. 1A; voxel-wise threshold P < .001 [unc.]; k = 300 voxels). A main effect of diagnosis was also observed (EMCI > SMC > CN), with significant clusters seen in primarily the frontal, temporal, and medial parietal cortices (Fig. 1B; voxel-wise threshold P < .001 [unc.]; k = 300 voxels). A significant effect of APOE e4 carrier status was also observed within each diagnostic group. Similar to our previous report in a smaller sample, CN and EMCI e4+ participants showed greater amyloid deposition in widespread cortical regions than CN and EMCI e4− participants, respectively (Fig. 1C and E). Similar patterns were observed in SMC participants, with e4+ showing greater amyloid deposition in frontal, parietal, cingulate, temporal, and occipital lobar regions than e4− (Fig. 1D). When a more stringent statistical threshold was applied, SMC e4+ showed greater amyloid deposition in the bilateral cingulate and frontal, parietal, and temporal lobes than SMC e4− (Supplementary Fig. 1). No regions showed higher amyloid deposition in e4− than e4+ in either the main effect analysis or within each diagnostic group.

3.3. Regional analysis of amyloid PET

Regional estimates of amyloid showed a similar pattern to that observed in the voxel-wise analyses (Fig. 2). Global cortical (Fig. 2A) and bilateral precuneus (Fig. 2B) amyloid deposition were significantly associated with both diagnosis (global cortical: P = .004; precuneus: P = .006) and APOE e4 carrier status (Fig. 2A; both P < .001). In both regions, e4+ showed greater amyloid deposition than e4− within each diagnostic group (for global cortex: CN e4+ > CN e4−, P = .052; all other comparisons P < .05). Furthermore,
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Abbreviations: CN, cognitively normal older adults; SMC, significant memory concern; EMCI, early mild cognitive impairment; DX, diagnosis; APOE, APOE ε4 carrier status; P-value: M, male; F, female; CDR-SB, Clinical Dementia Rating scale Sum of Boxes; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; LM, Weschler’s Logical Memory test; RAVLT, Rey Auditory Verbal Learning Test; E-Cog, Measurement of Everyday Cognition; PT, patient-based; Inf, Informant-based; NS, not significant.

*Adjusted means and analysis of variance (ANOVA) P-values include age, gender, and years of education as covariates.

1Missing data of seven participants (two CN ε4−, one SMC ε4−, one SMC ε4+, one EMCI ε4−, one EMCI ε4+).
2Missing data of five participants (one CN ε4+, three EMCI ε4−, one EMCI ε4+).
3Missing data of 12 participants (1 CN ε4−, 2 CN ε4+, 1 SMC ε4−, 1 SMC ε4+, 3 EMCI ε4−, 1 EMCI ε4+).
4Missing data of 28 participants (5 CN ε4−, 1 CN ε4+, 2 SMC ε4−, 3 SMC ε4+, 9 EMCI ε4−, 8 EMCI ε4+).
5Adjusted means and ANOVA P-values include age and gender as covariates.
Fig. 1. Impact of diagnosis and apolipoprotein E (APOE) ε4 carrier status on cerebral amyloid deposition (A) voxel-wise analysis of [18F]Florbetapir positron emission tomography (PET) scans showed a main effect of APOE ε4+ carrier status such that APOE ε4+ participants had greater amyloid deposition than APOE ε4− participants in nearly the entire cortex. (B) A main effect of diagnostic group (EMCI > SMC > CN) was also observed in more restricted regions of the frontal, temporal, and medial parietal cortices. Significant effects of APOE ε4 carrier status within diagnostic groups were also observed, including in (C) CN participants (127 CN ε4+, 51 CN ε4−), (D) SMC participants (71 SMC ε4−, 28 SMC ε4+), and (E) EMCI participants (170 EMCI ε4−, 130 EMCI ε4+) in widespread cortical regions, including in the frontal, parietal, temporal, and occipital lobes. No regions showed higher amyloid deposition in APOE ε4 non-carriers than APOE ε4 carriers. Figure is displayed at a voxel-wise threshold of $P < .001$ (uncorrected for multiple comparisons); minimum voxel size ($k$) = 300 voxels, which corresponds to a cluster-wise threshold of $P < .05$ (family-wise error [FWE] correction for multiple comparison). Abbreviations: EMCI, early mild cognitive impairment; SMC, significant memory concern; CN, cognitively normal.
SMC e4+ and EMCI e4+ participants showed greater amyloid deposition in both ROIs than CN e4−, SMC e4−, and EMCI e4− participants (all \( P < .05 \)). Finally, EMCI e4+ had greater amyloid deposition in the global cortical ROI than CN e4+ (\( P < .05 \)).

3.4. Glucose metabolism

Diagnosis was significantly associated with glucose metabolism in both the global cortical (\( P = .001 \)) and the mean parietal lobe (\( P = .048 \)) measures. Furthermore, a significant interaction effect between diagnosis and APOE e4 carrier status was observed in both regions (global cortical ROI: \( P = .014 \); mean parietal ROI: \( P = .016 \)). On post-hoc comparison, EMCI e4+ had reduced glucose metabolism in the global cortical ROI (Fig. 3A) relative to CN e4−, SMC e4−, SMC e4+, and EMCI e4− (all \( P < .05 \)). The mean parietal lobe glucose metabolism was only significantly reduced in EMCI e4+ relative to EMCI e4− on post-hoc comparison (\( P < .05 \)).

3.5. Medial temporal lobe neurodegeneration

Hippocampal volume (Fig. 3C) and entorhinal cortex thickness (Fig. 3D) were associated with diagnosis (hippocampal volume: \( P < .001 \); entorhinal cortex thickness: \( P = .003 \)). Post-hoc comparisons showed that hippocampal volume was reduced in EMCI e4+ and e4− relative to CN e4− and SMC e4+ (all \( P < .05 \)). Hippocampal volume was also significantly reduced in EMCI e4− relative to CN e4+ (\( P < .05 \)). Entorhinal cortex thickness was reduced in EMCI e4− relative to CN e4− participants (\( P < .05 \)).

3.6. CSF measures of Aβ1–42, t-tau, and p-tau

Significant independent effects of both diagnostic group (\( P = .023 \)) and APOE e4 carrier status (\( P < .001 \)) on CSF Aβ1–42 were observed (Fig. 4A). On post-hoc analysis, e4+ participants showed lower CSF Aβ1–42 than e4− participants regardless of diagnostic group (all \( P < .05 \)). Significant effects of diagnosis and APOE e4 carrier status, and their interaction, on CSF t-tau were observed (Fig. 4B; diagnosis: \( P < .001 \), APOE: \( P < .001 \), interaction: \( P = .002 \)), with EMCI e4+ showing higher t-tau levels than CN e4−, CN e4+, SMC e4−, and EMCI e4− (all \( P < .05 \)) on post-hoc analysis. Only APOE e4 carrier status was associated with CSF p-tau level (Fig. 4C; \( P < .001 \)). On post-hoc analysis, EMCI and SMC e4+ participants showed higher p-tau levels than CN, SMC, and EMCI e4− participants (all \( P < .05 \)).

3.7. Interaction of APOE e4 carrier status and amyloid PET positivity in SMC participants

Finally, we sought to investigate the potential interaction effect of cerebral amyloid deposition (measured using \([^{18}F]\) Florbetapir PET) and APOE e4 carrier status on CSF amyloid and tau measures in SMC (Fig. 5). A significant relationship between cerebral amyloid deposition and CSF Aβ1–42 was observed (Fig. 5A; \( P < .001 \)). APOE e4 carrier status was also independently associated with CSF Aβ1–42 (\( P < .001 \)). On post-hoc analysis, decreasing CSF Aβ1–42 level by the interaction of amyloid and/or APOE e4 positivity was seen (Fig. 5A), as SMC APOE e4−/Aβ− showed higher CSF Aβ1–42 levels than SMC e4−/Aβ− and SMC e4+/Aβ− participants.
APOE ε4/αβ+, and those carrying either an APOE ε4 allele (APOE ε4+/αβ−) or are amyloid positive (APOE ε4−/αβ+) (all P < .05). In addition, SMC APOE ε4+/αβ− had higher CSF αβ1–42 levels than APOE ε4+/αβ+ (P < .05). APOE ε4 carrier status was significantly associated with CSF p-tau level in SMC participants (Fig. 5B; P = .009). Only the difference between APOE ε4+/αβ+ and APOE ε4−/αβ− was significant on post-hoc analysis (APOE ε4+/αβ+ > APOE ε4−/αβ−; P = .008). APOE ε4 carrier status and amyloid positivity were both independently associated with CSF p-tau level (Fig. 5C; APOE, P = .014; amyloid positivity, P = .010). APOE ε4+/αβ+ showed increased p-tau levels relative to APOE ε4−/αβ− SMC participants on post-hoc analysis (P < .001).

4. Discussion

Our goal was to investigate the impact of APOE ε4 carrier status on measures of cognition and cognitive complaints, cerebral amyloid deposition, glucose metabolism, MTL neurodegeneration, and CSF biomarkers of Aβ1–42, t-tau, and p-tau in older adults with SMC. APOE ε4 positive SMC participants showed increased amyloid deposition throughout the cortex relative to SMC ε4− participants in any measure interest was observed, although diagnosis was significant for global cortical hypometabolism (A; P = .001), mean parietal hypometabolism (B; P = .048), and hippocampal (C; P < .001) and entorhinal cortex (D; P = .003) atrophy. A significant interaction effect on hypometabolism, but not atrophy, between diagnosis and APOE ε4 carrier status was observed (global cortex: P = .014; mean parietal lobe: P = .016). Post-hoc analyses showed that EMCI ε4+ participants had reduced glucose metabolism relative to CN ε4−, SMC ε4−, SMC ε4+, and EMCI ε4− in the global cortical region (A; all P < .05) and relative to EMCI ε4− participants only in the mean parietal lobe (B; P < .05). Furthermore, post-hoc comparisons showed that (C) hippocampal volume was significantly reduced in EMCI participants regardless of APOE ε4 carrier status relative to CN ε4− and SMC ε4+ participants, and in EMCI ε4− participants relative to CN ε4+ participants (all P < .05). (D) Entorhinal cortex thickness was reduced in EMCI ε4− relative to CN ε4− participants (P < .001). Abbreviations: EMCI, early mild cognitive impairment; SMC, significant memory concern; CN, cognitively normal.
with the presence of mild memory impairment (i.e., EMCI). CSF levels of Aβ1–42 were significantly lower in SMC APOE ε4 carriers relative to SMC APOE ε4+1, similar to CN and EMCI (as previously reported [31]). CSF t-tau levels were higher in APOE ε4 carriers across all diagnostic groups, although the effect within SMC participants (APOE ε4+ > APOE ε4−) on post-hoc analysis was not significant. On the other hand, CSF p-tau levels were significantly greater in SMC APOE ε4+ relative to SMC APOE ε4−, an effect also observed in EMCI. Finally, we observed the greatest CSF amyloid and tau abnormalities in SMC participants who were both APOE ε4 carriers and positive for cerebral amyloid on [18F]Florbetapir PET.

The findings in this study support prior findings regarding the importance of APOE genotype in preclinical stages of late-onset AD. We found an increase in amyloid deposition and abnormal levels of CSF amyloid and tau in older adults with SMC, which was strongly associated with APOE ε4 carrier status. However, we did not observe differences in glucose metabolism and MTL atrophy in this population, even in SMC APOE ε4+, as has been previously reported [4,13,17,19,21,23,28,46,47]. Given the previous research in participants with SCD/SMC, the lack of hypometabolism or atrophy is somewhat surprising. However, the absence of these findings is potentially due to different participant recruitment, as SMC participants in the present study were recruited on the basis of subjective memory concerns, whereas many previous reports included participants who also had informant-based complaints. In fact, informant-based complaints have been shown to provide additional predictive ability for the progression to dementia to self-based complaints [5]. Furthermore, the lack of an APOE effect on MTL atrophy in all groups and metabolism in CN and SMC participants...
is also surprising given previous findings [48,49]. However, the previously observed differences were mild and differences in methodology likely resulted in the lack of significance in the present study, despite a slight trend for decreased glucose metabolism and hippocampal volume in ε4/CN.

Interestingly, we observed a trend toward higher cortical glucose metabolism and larger hippocampal volume in SMC APOE ε4, although this did not reach significance after Bonferroni-correction possibly due to the relatively small group size and attenuated power or an unknown confounding variable. Although only a nonsignificant trend, the SMC participants showed this strikingly different pattern of APOE effects on metabolism and atrophy than CN or EMCI participants, suggesting that individuals with SMC may have different processes taking place than the latter groups. Further cross-sectional and longitudinal studies of changes in SCD/SMC samples are warranted to determine if these seemingly anomalous findings are of pathophysiological significance. It is noteworthy that previous studies have observed increased cortical thickness in at-risk populations, including in middle-aged APOE ε4 carriers [50], CN who are transitioning to become CSF Aβ positive [51], and asymptomatic PSEN1 mutation carriers before the onset of the clinical changes [52]. Furthermore, a previous study in older adults with SCD/SMC demonstrated a quadratic

![Fig. 5. Effect of apolipoprotein E (APOE) ε4 carrier status and amyloid positivity on cerebrospinal fluid (CSF) biomarkers in SMC participants.](image-url)
pattern of longitudinal MTL atrophy, with initial volume increases followed by decreases [22]. Future studies with longitudinal follow-up and larger samples will be important in determining the significance of this finding. If confirmed, mechanistic studies would also be indicated to determine the processes underlying these increases. In any case, this finding highlights the potential difference of SMC from CN participants and suggests that individuals with significant self-complaints may have a different pattern of pathology and risk than those without.

Most of the observed results provide further support of the Jack et al. model of AD biomarkers [30], suggesting that amyloid accumulation is one of the earliest measurable pathophysiological changes associated with AD before cognitive decline and that hypometabolic and atrophic changes primarily occur with early clinical symptoms. This study also supports the hypothesis that APOE ε4 genotype alters the hypothesized model by pushing the system in favor of early amyloid accumulation, even in cognitively normal older adults. Extension of the Jack et al. model to include an SMC stage before MCI appears warranted, as these participants represent an at-risk group. However, in contrast to the Jack et al. model, we observed an increased level of p-tau and a trend toward increased glucose metabolism and hippocampal volume in APOE ε4 + SMC participants. These findings deviate from both the Jack et al. model and previous work in autosomal dominant AD [32] and may suggest a more complicated interaction between CSF and imaging biomarkers of neurodegeneration in the earliest stages of disease. However, given the limited detection power and significance of this finding, additional studies would be needed to fully explore this possibility. The present results also provide support for the importance of genetic variation in determining likelihood and extent of amyloid accumulation, even in preclinical stages such as SMC, which may be an important consideration for enrichment strategies for therapeutic trial enrollment based on very mildly symptomatic and/or asymptomatic patients. The availability of tau imaging using one of the newly developed tau PET ligands [53,54] could lead to further revisions in this hypothetical sequence of biomarker changes [30].

We also completed a targeted analysis within SMC participants to examine the potential for an interaction between APOE ε4 carrier status and cerebral amyloid positivity determined using [18F]Florbetapir PET. SMC participants who were both APOE ε4 carriers and amyloid positive had the most abnormal CSF amyloid and tau levels. If SMC participants were either an APOE ε4 carrier or amyloid positive on [18F]Florbetapir PET, they appeared to have intermediate levels of CSF Aβ1–42, t-tau, and p-tau between those carrying both risk factors and those carrying neither risk factor. These findings suggest that although APOE ε4 genotype and amyloid deposition are highly linked, these factors may have independent and/or additive effects on amyloid and tau in SMC. Furthermore, the observed reduction in CSF Aβ1–42 in SMC APOE ε4 carriers who were amyloid negative on [18F]Florbetapir PET may suggest that changes in amyloid are detectable in CSF before amyloid PET scans or that CSF Aβ changes are not fully reflective of amyloid aggregation.

This study has a few notable limitations. First, as previously discussed, SMC participants in the present report were recruited based on self-reported complaints of cognitive decline in the absence of informant-perceived decline. Previous studies have shown the importance of informant-based complaints in both cognitively normal and impaired populations [5]. Therefore, the evaluated SMC participants may not be fully representative of the greater population of older adults with SCD/SMC. Future studies of participants with self-based and/or informant-based complaints with longitudinal assessment of AD biomarkers will help to elucidate the impact of self vs. informant complaints on AD pathology and risk. Second, only a single genetic factor (APOE ε4 carrier status) was evaluated in this study. Future studies targeting other genetic variants in SMC are warranted. Third, the present study only evaluated cross-sectional data. Studies of longitudinal outcome and rate of AD biomarker change may provide additional information about dynamic changes in SCD/SMC. Finally, a number of additional AD biomarkers were not evaluated in the present report. Future studies investigating additional imaging and CSF biomarkers may elucidate other changes occurring in SMC.

In sum, APOE ε4 positive older adults with SMC show increased cerebral amyloid, reduced CSF Aβ1–42, increased CSF p-tau, and a trend for increased CSF t-tau relative to APOE ε4 noncarriers. Other AD biomarkers showed minimal association to APOE in SMC. Targeted analyses suggest that SMC participants who were both APOE ε4+ and positive for cerebral amyloid showed the most abnormal CSF Aβ1–42, t-tau, and p-tau levels. Future longitudinal studies of dynamic processes occurring in this at-risk population will elucidate the disease vulnerability of older adults with SCD/SMC, and the impact of genetic background.

Acknowledgments and Funding

Data collection and sharing for this project was funded by the Alzheimer’s Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: Alzheimer’s Association; Alzheimer’s Drug Discovery Foundation; Arclon Biotech; BioClinica, Inc.; Biogen Idec Inc.; Bristol-Myers Squibb Company; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; Euroimmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Medpace, Inc.; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis...
Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Synarc Inc.; and Takeda Pharmaceutical Company. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer’s Disease Cooperative Study at the University of California, San Diego. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California. ADNI was also supported by NIH grants P30 AG010129, K01 AG030514, and the Dana Foundation. Additional support for analyses included in the present report was provided by the following sources: NIA R01 AG19771 (to AJS), P30 AG010133-18S1 (to Dr. Bernardino Ghetti and AJS), National Library of Medicine (NLM) R01 LM011360 (to LS and AJS), NLM R00 LM011384 (to KN), the Alzheimer’s Association (New Investigator Research Grant to SLR), the Indiana University Health-Indiana University School of Medicine Strategic Research Initiative CTSI (to SLR), and P30 AG010129 (to LAB).

**Supplementary data**

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jalz.2015.03.003.

**RESEARCH IN CONTEXT**

1. Systematic review: To investigate our primary research question on APOE effects in significant memory concern (SMC), we searched PubMed for: “cognitive complaints (CC),” “subjective cognitive decline (SCD),” “neuroimaging,” and “apolipoprotein E (APOE).” We then combined the returned articles to generate a summary on biomarkers in SMC/SCD/CC and the role of APOE.

2. Interpretation: Our results provide new evidence that APOE is a major mediator of amyloid and tau abnormalities in SMC, suggesting that these abnormalities occur before cognitive symptoms in this population. However, metabolism and atrophy were not affected, suggesting that these may be linked to cognitive decline.

3. Future directions: To confirm the current findings, additional analyses with larger and more diverse samples and longitudinal studies would be beneficial. Additional Alzheimer’s disease biomarkers not evaluated in the present report may also elucidate the pathophysiological processes occurring in SMC participants. Finally, the assessment of the impact of other genetic variants beyond APOE would expand this work.

**References**


