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

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Abstract

Background—This study assessed *APOE* ε4 carrier status effects on Alzheimer's disease (AD) 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 ADNI 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 [^{18}F]Florbetapir amyloid positivity on CSF biomarkers.

Results—SMC ε4+ showed greater amyloid deposition than SMC ε4−, but no hypometabolism or MTL atrophy. SMC ε4+ showed lower Aβ1–42 and higher tau/p-tau than ε4−, which were most abnormal in *APOE* ε4+ and cerebral amyloid positive SMC.

Conclusion—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; [^{18}F]Florbetapir PET; [^{18}F]Fluorodeoxyglucose (FDGb) PET; structural magnetic resonance imaging (MRI); cerebrospinal fluid (CSF); Alzheimer's Disease Neuroimaging Initiative (ADNI)

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 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], as well as 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, as well as 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 the 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], as well as 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 [^{18}F]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 Aβ1–42, increased CSF total tau (t-tau) and phosphorylated tau (p-tau), glucose hypometabolism, and MTL neurodegeneration relative to *APOE* ε4 non-carriers; 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]. Further, these analyses will evaluate whether *APOE* ε4 positive SMC show the most abnormal changes in tau which would suggest these individuals are at 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

2a. Alzheimer's Disease Neuroimaging Initiative (ADNI)

Data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). For more information see the 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.

2b. 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 Exam (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, 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* ε4 positive (ε4+); no ε4 alleles = *APOE* ε4 negative (ε4−)). *APOE* ε2 carriers were included in their respective groups (ε4− or ε4+), as the distribution of *APOE* ε2 carriers did not differ across CN, SMC, and EMCI groups. The initial analysis included 594 participants (132 CN ε4−, 53 CN ε4+, 71 SMC ε4−, 33 SMC ε4+, 174 EMCI ε4−, and 131 EMCI ε4+). The targeted analysis in SMC of the potential interaction between *APOE* ε4 carrier status and amyloid positivity (on [^{18}F]Florbetapir positron emission tomography (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+).

2c. 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.

2d. [^{18}F]Florbetapir PET scans

Pre-processed [^{18}F]Florbetapir PET scans (Coregistered, Averaged, Standardized Image and Voxel Size, Uniform Resolution) were downloaded from LONI (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 whole cerebellum reference region to create standardized uptake value ratio (SUVR) images. The effect of diagnosis and *APOE* ε4 carrier status on [^{18}F]Florbetapir SUVR was assessed on a voxel-wise basis using a two-way analysis of covariance (ANCOVA), masked for the whole brain, and covaried for age and gender. Significant results were displayed at a voxel-wise threshold of $p<0.001$ (uncorrected

for multiple comparisons (unc.)) and minimum cluster size (k) of 300 voxels. A more stringent voxel-wise statistical threshold of $p<0.05$ (FWE), k = 10 voxels was also evaluated in SMC (Supplemental Figure 1). Statistical Parametric Mapping 8 (SPM8; Wellcome Department of Cognitive Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) was used for all processing and voxel-wise analysis. Mean SUVR values were extracted using MarsBaR [39] from two regions of interest (ROIs), including a global cortical region generated from an independent comparison of ADNI-1 [^{11}C]Pittsburgh Compound B SUVR scans (regions where AD > CN) and an anatomically-defined bilateral precuneus ROI [39]. 14 participants (5 CN ε4−,2 CN ε4+, 2 SMC ε4+, 4 EMCI ε4−, 1 EMCI ε4+) were excluded from [^{18}F]Florbetapir analyses for missing data.

2e. [^{18}F]FDG PET scans

Pre-processed [^{18}F]FDG PET scans (Coregistered, Averaged, Standardized Image and Voxel Size, Uniform Resolution) were downloaded from LONI (http://adni.loni.usc.edu) and preprocessed as has been previously described [31, 34]. Scans were then intensity-normalized using a pons ROI to create [^{18}F]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 [^{18}F]FDG SUVR scans (regions where CN > AD) and an anatomically-defined bilateral parietal lobe ROI [39]. 15 participants (4 CN ε4−, 1 CN ε4+, 2 SMC ε4−, 5 SMC ε4+, 3 EMCI ε4−) were excluded from [^{18}F]FDG PET analyses for missing data.

2f. Structural MRI

All available baseline structural MRI scans were downloaded from LONI for included participants. Scans were corrected prior to 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. If two MRI scans were available, values were averaged for each participant from both processed scans. 6 participants (1 CN ε4−, 4 SMC ε4−, 1 EMCI ε4−) were excluded from this analysis for missing data.

2g. 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 tau phosphorylated at threonine 181 (p-tau) were measured using the multiplex xMAP Luminex 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-GO/2 visit and were scaled to the ADNI-1 baseline dataset using linear regression in order to use the abnormal cutoff values that were previously established [44].

2h. Statistical analyses

For the initial analyses, we evaluated the effect of diagnosis and *APOE* ε4 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* ε4 carrier status, and their interaction on demographics, clinical and psychometric test performance, patient and informant cognitive complaints, regional amyloid deposition ([^{18}F]Florbetapir SUVR), regional glucose metabolism ([^{18}F]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 normality of the evaluated measures and found that the measures of CSF amyloid and tau, [^{18}F]Florbetapir SUVR, and entorhinal cortex thickness were not normally distributed. We log-transformed these variables and repeated the above analyses. However, this log-transformation did not alter the findings observed with the raw variables. Therefore, we present the findings obtained by analysis of the raw values in the present report. A further targeted analysis in SMC participants of an interaction between *APOE* ε4 carrier status and amyloid positivity established using [^{18}F]Florbetapir PET scans (cutoff 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 cutoff [45]) was completed. Specifically, a two-way ANCOVA was used to evaluate the effect of *APOE* ε4 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 intracranial volume (ICV). Given the known association of depressive symptoms with subjective cognitive decline, we repeated the analyses including the total score of the Geratric 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

3a. Demographics, cognition, and cognitive complaints

Effects of diagnosis and *APOE* ε4 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 ($p<0.05$), while only age was associated with *APOE* ε4 status ($p=0.003$). 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 ($p<0.001$), with EMCI showing impairment relative to CN and/or SMC on all cognitive measures ($p<0.05$). EMCI had greater self- and informant-based complaints than CN and/or SMC on the ECog ($p<0.05$). SMC participants had greater self-based complaints than CN in all domains and greater informant-based complaints in the memory domain only (specifically SMC ε4− > CN; $p<0.05$). *APOE* ε4 carrier status was also significantly associated with selected measures of memory and executive performance

(all p<0.05), with ε4+ participants showing poorer performance than ε4−. See Table 1 for complete results.

3b. Voxel-wise analysis of amyloid PET

A main effect of *APOE* ε4 carrier status was observed with *APOE* ε4 + participants showing greater amyloid deposition than *APOE* ε4− participants across diagnostic groups in nearly the entire cortex (Figure 1A; voxel-wise threshold p<0.001 (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 (Figure 1B; voxel-wise threshold p<0.001 (unc.); k = 300 voxels). A significant effect of *APOE* ε4 carrier status was also observed within each diagnostic group. Similar to our previous report in a smaller sample, CN and EMCI ε4+ participants showed greater amyloid deposition in widespread cortical regions than CN and EMCI ε4− participants, respectively (Figures 1C and 1E). Similar patterns were observed in SMC participants, with ε4+ showing greater amyloid deposition in frontal, parietal, cingulate, temporal, and occipital lobar regions than ε4− (Figure 1D). When a more stringent statistical threshold was applied, SMC ε4+ showed greater amyloid deposition in the bilateral cingulate and frontal, parietal, and temporal lobes than SMC ε4− (Supplemental Figure 1). No regions showed higher amyloid deposition in ε4− than ε4+ in either the main effect analysis or within each diagnostic group.

3c. Regional analysis of amyloid PET

Regional estimates of amyloid showed a similar pattern to that observed in the voxel-wise analyses (Figure 2). Global cortical (Figure 2A) and bilateral precuneus (Figure 2B) amyloid deposition were significantly associated with both diagnosis (global cortical: p=0.004; precuneus: p=0.006) and *APOE* ε4 carrier status (Figure 2A; both p<0.001). In both regions, ε4+ showed greater amyloid deposition than ε4− within each diagnostic group (for global cortex: CN ε4+ > CN ε4−, p=0.052; all other comparisons p<0.05). Further, SMC ε4+ and EMCI ε4+ participants showed greater amyloid deposition in both ROIs than CN ε4−, SMC ε4−, and EMCI ε4− participants (all p<0.05). Finally, EMCI ε4+ had greater amyloid deposition in the global cortical ROI than CN ε4+ (p<0.05).

3d. Glucose metabolism

Diagnosis was significantly associated with glucose metabolism in both the global cortical (p=0.001) and the mean parietal lobe (p=0.048) measures. Further, a significant interaction effect between diagnosis and *APOE* ε4 carrier status was observed in both regions (global cortical ROI: p=0.014; mean parietal ROI: p=0.016). On post-hoc comparison, EMCI ε4+ had reduced glucose metabolism in the global cortical ROI (Figure 3A) relative to CN ε4−, SMC ε4−, SMC ε4+, and EMCI ε4− (all p<0.05). The mean parietal lobe glucose metabolism was only significantly reduced in EMCI ε4+ relative to EMCI ε4− upon post-hoc comparison (p<0.05).

3e. Medial temporal lobe neurodegeneration

Hippocampal volume (Figure 3C) and entorhinal cortex thickness (Figure 3D) were associated with diagnosis (hippocampal volume: p<0.001; entorhinal cortex thickness:

p=0.003). Post-hoc comparisons showed that hippocampal volume was reduced in EMCI ε4+ and ε4− relative to CN ε4− and SMCI e4+ (all p<0.05). Hippocampal volume was also significantly reduced in EMCI ε4− relative to CN ε4+ (p<0.05). Entorhinal cortex thickness was reduced in EMCI ε4− relative to CN ε4− participants (p<0.05).

3f. CSF measures of Aβ1–42, t-tau, and p-tau

Significant independent effects of both diagnostic group (p=0.023) and *APOE* ε4 carrier status (p<0.001) on CSF Aβ1–42 were observed (Figure 4A). On post-hoc analysis, ε4+ participants showed lower CSF Aβ1–42 than ε4− participants regardless of diagnostic group (all p<0.05). Significant effects of diagnosis and *APOE* ε4 carrier status, as well as their interaction, on CSF t-tau were observed (Figure 4B; diagnosis: p<0.001, *APOE*: p<0.001, interaction: p=0.002), with EMCI ε4+ showing higher t-tau levels than CN ε4−, CN ε4+, SMC ε4−, and EMCI ε4− (all p<0.05) on post-hoc analysis. Only *APOE* ε4 carrier status was associated with CSF p-tau level (Figure 4C; p<0.001). On post-hoc analysis, EMCI and SMC ε4+ participants showed higher p-tau levels than CN, SMC, and EMCI ε4− participants (all p<0.05).

3g. Interaction of *APOE* ε4 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* ε4 carrier status on CSF amyloid and tau measures in SMC (Figure 5). A significant relationship between cerebral amyloid deposition and CSF Aβ1–42 was observed (Figure 5A; p<0.001). *APOE* ε4 carrier status was also independently associated with CSF Aβ1–42 (p<0.001. Upon post-hoc analysis, decreasing CSF Aβ1–42 level by the interaction of amyloid and/or *APOE* ε4 positivity was seen (Figure 5A), as SMC *APOE* ε4−/Aβ− showed higher CSF Aβ1–42 levels than SMC *APOE* ε4+/Aβ+, as well as those carrying either an *APOE* ε4 allele (*APOE* ε4+/Aβ−) or are amyloid positive (*APOE* ε4−/Aβ+) (all p<0.05). In addition, SMC *APOE* ε4+/Aβ− had higher CSF Aβ1–42 levels than *APOE* ε4+/Aβ+ (p<0.05). *APOE* ε4 carrier status was significantly associated with CSF t-tau level in SMC participants (Figure 5B; p=0.009). Only the difference between *APOE* ε4+/Aβ+ and *APOE* ε4−/Aβ− was significant on post-hoc analysis (*APOE* ε4+/Aβ+ > *APOE* ε4−/Aβ−; p=0.008). *APOE* ε4 carrier status and amyloid positivity were both independently associated with CSF p-tau level (Figure 5C; *APOE*, p = 0.014; amyloid positivity, p = 0.010). *APOE* ε4+/Aβ+ showed increased p-tau levels relative to *APOE* ε4−/Aβ− SMC participants on post-hoc analysis (p<0.001).

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 *APOE* ε4 non-carriers. Similar patterns of increased amyloid deposition related to the presence of an *APOE* ε4 allele were also observed in CN and EMCI groups, as previously reported [31]. However, glucose metabolism and MTL neurodegeneration were not associated with *APOE* carrier status in SMC participants.

Instead, glucose hypometabolism and MTL atrophy were associated with the presence of mild memory impairment (i.e., EMCI). CSF levels of Aβ1–42 were significantly lower in SMC *APOE* ε4+ relative to SMC *APOE* ε4−, 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 [^{18}F]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 progression to dementia to self-based complaints [5]. Further, 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 towards 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 non-significant trend, the SMC participants showed this strikingly different pattern of *APOE* effects on metabolism and atrophy than CN or EMCI participants, suggesting 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 prior to onset of the clinical changes [52]. Further, a previous study in older adults with SCD/SMC demonstrated a quadratic 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 amyloid accumulation is one of the earliest measurable pathophysiological changes associated with AD prior to 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 prior to 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 [^{18}F]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 [^{18}F]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. Further, the observed reduction in CSF Aβ1–42 in SMC *APOE* ε4 carriers who were amyloid negative on [^{18}F]Florbetapir PET may suggest that changes in amyloid are detectable in CSF before amyloid PET scans or that CSF Aβ changes are not only 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 the present 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 non-carriers. 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 disease vulnerability of older adults with SCD/SMC, as well as the impact of genetic background.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

Aβ	amyloid-beta
AD	Alzheimer's Disease
ADNI	Alzheimer's Disease Neuroimaging Initiative

ANCOVA	analysis of covariance
APOE	apolipoprotein E gene
CCI	Cognitive Complaint Index
CDR-SB	Clinical Dementia Rating scale – Sum of Boxes
CN	cognitively normal older adults
CSF	cerebrospinal fluid
DX	diagnosis
E-Cog	Assessment of Everyday Cognition
EMCI	early mild cognitive impairment
F	female
FDG	fluorodeoxyglucose
FWE	family-wise error rate
GDS	Geriatric Depression Scale
Inf	Informant-based
LM	Weschler's Logical Memory test
LONI	Laboratory of Neuro Imaging
M	male
MCI	mild cognitive impairment
MMSE	Mini-Mental State Exam
MNI	Montreal Neurologic Institute
MoCA	Montreal Cognitive Assessment
MRI	magnetic resonance imaging
MTL	medial temporal lobe
NS	not significant
PET	positron emission tomography
PSEN1	presenilin 1 gene
p-val	p value
PT	patient-based
p-tau	tau phosphorylated at threonine 181
RAVLT	Rey Auditory Verbal Learning Test
ROI	region of interest
SCD	subjective cognitive decline

SMC	significant memory concern
SPM8	Statistical Parametric Mapping 8
SUVR	standardized uptake value ratio
t-tau	total tau
WM	white matter

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Research in context

Systematic Review

In order to investigate our primary research question on *APOE* effects in 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*.

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 these may be linked to cognitive decline.

Future directions

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

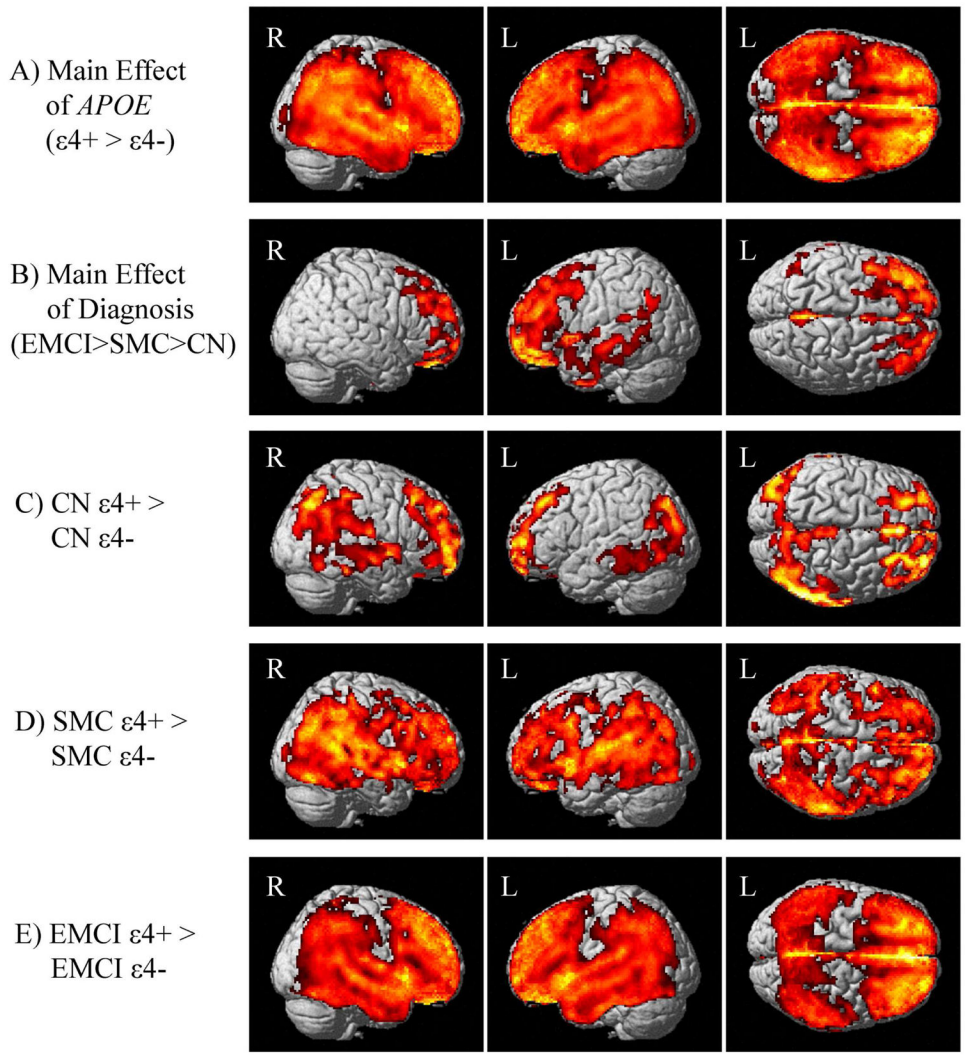

Figure 1. Impact of diagnosis and *APOE* ε4 carrier status on cerebral amyloid deposition

(A) Voxel-wise analysis of [^{18}F]Florbetapir 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 voxel-wise threshold of $p<0.001$ (uncorrected for multiple comparisons); minimum voxel size (k) = 300 voxels, which corresponds to a cluster-wise threshold of $p<0.05$ (family-wise error (FWE) correction for multiple comparison).

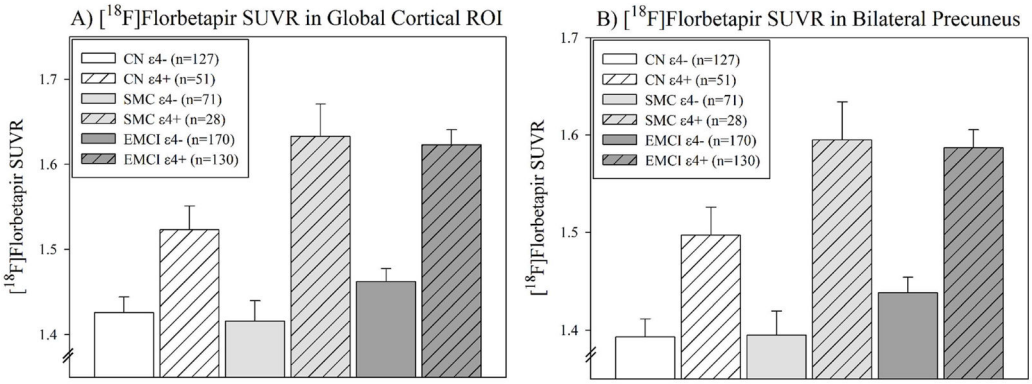

Figure 2. Impact of diagnosis and *APOE* ε4 carrier status on regional amyloid deposition

Regional analysis of amyloid deposition on [^{18}F]Florbetapir PET showed that *APOE* ε4+ participants had greater amyloid deposition than *APOE* ε4− participants in (A) a global cortical region of interest, as well as within the (B) bilateral precuneus, across all diagnostic groups (*APOE* ε4 carrier status: both $p<0.001$). Diagnostic group was also significantly associated with amyloid deposition in both target regions (diagnosis: both $p<0.01$). In Bonferroni-corrected post-hoc pair comparisons, SMC and EMCI ε4+ participants showed higher amyloid than CN ε4−, SMC ε4−, and EMCI ε4− participants in both ROIs (all $p<0.05$), CN ε4+ participants had higher amyloid than CN ε4− in the global cortex (A; $p=0.052$) and bilateral precuneus (B; $p<0.05$), and EMCI ε4+ participants had greater amyloid deposition in the global cortical ROI than CN ε4+ participants (A; $p<0.05$). No significant interaction effect of diagnostic group and *APOE* ε4 carrier status was observed, although a trend for an interaction effect on global cortical amyloid deposition was observed (A; $p=0.084$).

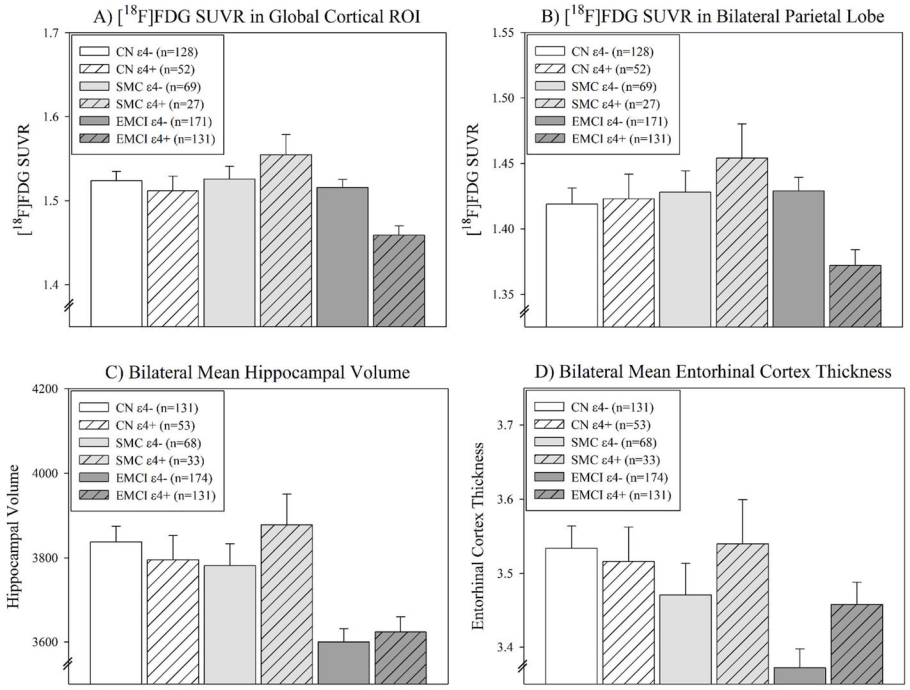

Figure 3. Relationship of diagnosis and *APOE* ε4 carrier status with regional glucose metabolism and medial temporal atrophy

The effect of diagnostic group and *APOE* ε4 carrier status on (A) global cortical or (B) parietal lobe glucose metabolism, (C) hippocampal volume, and (D) entorhinal cortex thickness was evaluated. No significant independent effect of *APOE* ε4 carrier status on across CN, SMC, or EMCI participants in any measure interest was observed, although diagnosis was significant for global hypometabolism region (A; p=0.001), mean parietal hypometabolism (B; p=0.048), and hippocampal (C; p<0.001) and entorhinal cortex (D; p=0.003) atrophy. A significant interaction effect on hypometabolism, but not atrophy, between diagnosis and *APOE* ε4 carrier status was observed (global cortex: p=0.014; mean parietal lobe: p=0.016). Post-hoc analyses showed that EMCI ε4+ participants had reduced glucose metabolism relative CN ε4−, SMC ε4−, SMC ε4+, and EMCI ε4− in the global cortical region (A; all p<0.05) and relative to EMCI ε4− participants only in the mean parietal lobe (B; p<0.05). Further, 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 SMCI ε4+ participants, as well as in EMCI ε4− participants relative to CN ε4+ participants (all p<0.05). (D) Entorhinal cortex thickness was reduced in EMCI ε4− relative to CN ε4− participants (p<0.001).

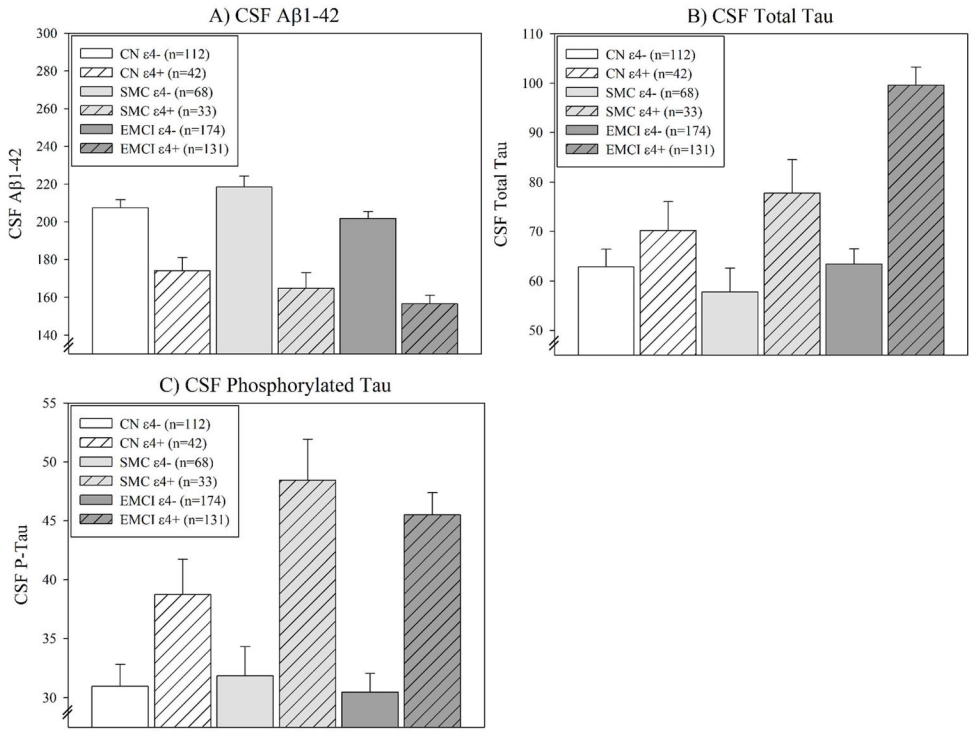

Figure 4. Relationship of diagnosis and *APOE* ε4 carrier status with CSF protein levels

Diagnostic group and *APOE* ε4 carrier status were significantly associated with CSF levels of (A) Aβ1–42, (B) t-tau, and (C) phosphorylated tau (p-tau). (A) CSF Aβ1–42 levels showed a significant independent effect of both diagnostic group (p=0.023) and *APOE* ε4 carrier status (p<0.001) but no interaction effect. On post-hoc analysis, ε4+ participants showed lower CSF Aβ1–42 than ε4− participants regardless of diagnostic group (i.e., CN ε4−, SMC ε4−, EMCI ε4− > CN ε4+, SMC ε4+, EMCI ε4+; all p<0.05). (B) Significant independent effects of diagnosis and *APOE* ε4 carrier status (p<0.001), as well as an interaction effect between diagnostic group and *APOE* ε4 carrier status (p=0.002), on CSF t-tau were also observed. EMCI ε4+ participants showed higher t-tau levels than CN ε4−, CN ε4+, SMC ε4−, and EMCI ε4− participants (all p<0.05) on post-hoc analysis. (C) CSF p-tau level was significantly associated with *APOE* ε4 carrier status only (p<0.001). On post-hoc analysis, EMCI and SMC ε4+ participants showed higher p-tau levels than CN, SMC, and EMCI ε4− participants (all p<0.05).

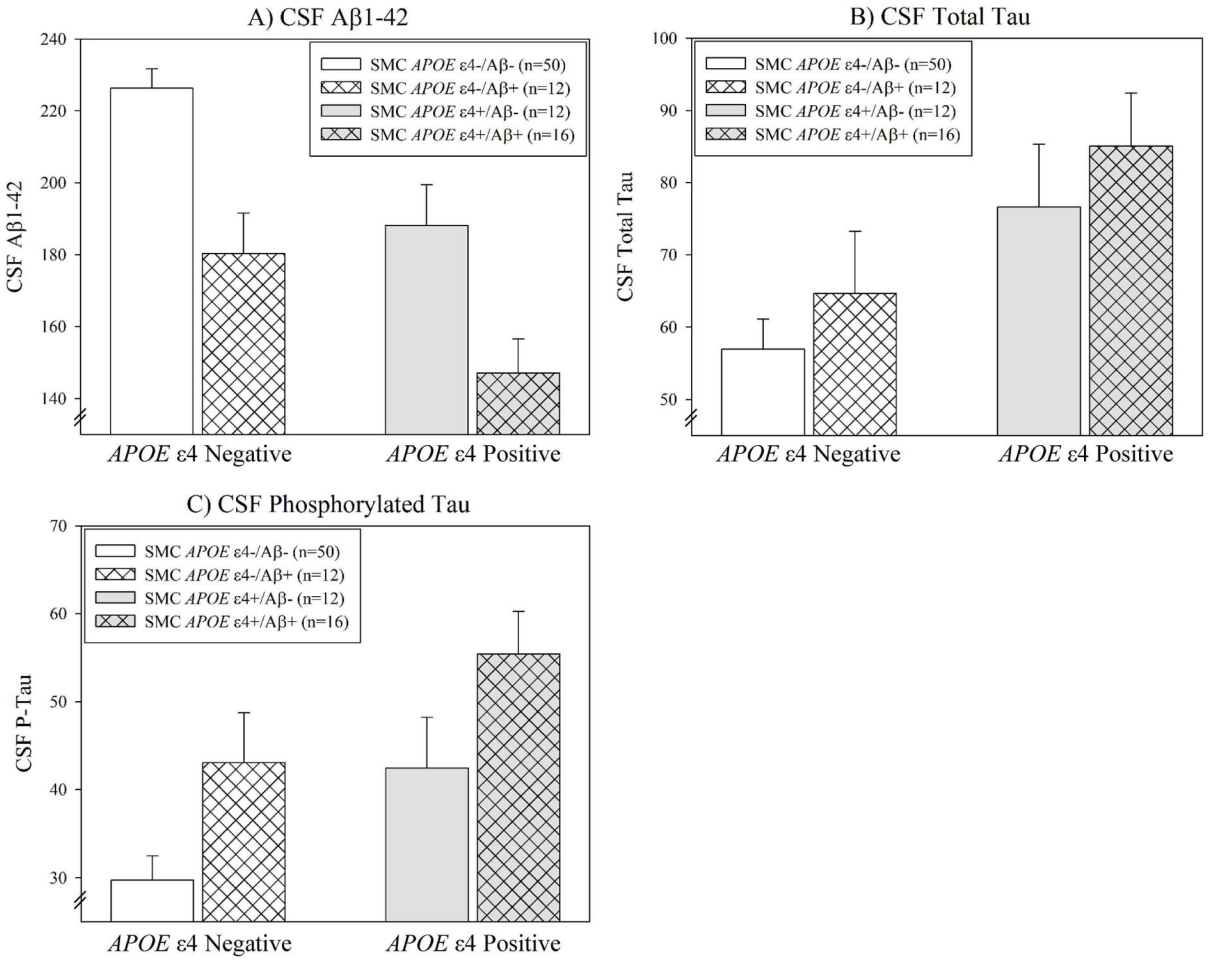

Figure 5. Effect of *APOE* ε4 carrier status and amyloid positivity on CSF biomarkers in SMC participants

(A) Significant independent effects of *APOE* ε4 carrier status and cerebral amyloid status (positive or negative), but no interaction effect, on CSF Aβ1–42 were observed (both $p<0.001$). Post-hoc analysis indicated a pattern of decreasing CSF level Aβ1–42 by the interaction of amyloid positivity and *APOE* ε4+ was seen with SMC *APOE* ε4−/Aβ− showing higher levels than SMC *APOE* ε4+/Aβ+, SMC *APOE* ε4+/Aβ−, and SMC *APOE* ε4−/Aβ+, and SMC *APOE* ε4+/Aβ− showing higher CSF Aβ1–42 levels than SMC *APOE* e4+/Aβ+ (all $p<0.05$). (B) *APOE* ε4 carrier status, but not amyloid positivity or the interaction, was significantly associated with CSF t-tau level in the SMC participants ($p=0.009$). SMC *APOE* ε4+/Aβ+ showed higher t-tau levels than SMC *APOE* ε4−/Aβ− on Bonferroni-corrected post-hoc analysis ($p=0.008$). (C) Both *APOE* ε4 carrier status and amyloid positivity were independently associated with CSF p-tau level (*APOE* ε4 carrier status, $p = 0.014$; amyloid positivity, $p = 0.010$), but again no interaction was observed. Similar to the t-tau analyses, SMC *APOE* ε4+/Aβ+ had greater CSF p-tau levels than SMC *APOE* ε4−/Aβ− on post-hoc analysis ($p<0.001$).

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Table 1

Demographic, Cognitive Performance, and Patient and Informant Complaints

	CN ε4− (n=132)	CN ε4+ (n=53)	SMC ε4− (n=71)	SMC ε4+ (n=33)	EMCI ε4− (n=174)	EMCI ε4+ (n=131)	DX p-val	*APOE* p-val	DX by *APOE* p-val	Significant Pairs (Bonferroni p<0.05)
Age (years)	73.7 (6.1)	71.8 (6.4)	72.5 (5.7)	70.3 (5.2)	71.6 (7.3)	70.0 (7.5)	0.015	0.003	0.938	CN− > EMCI+
Education (years)	16.7 (2.5)	16.2 (2.6)	16.6 (2.7)	17.2 (2.0)	16.1 (2.6)	15.8 (2.7)	0.009	0.770	0.298	None
Gender (M, F)	68, 64	21, 32	31, 40	12, 21	88, 86	81, 50	0.078	0.491	0.021	n/a
CDR-SB	0.03 (0.12)	0.04 (0.17)	0.09 (0.19)	0.06 (0.17)	1.22 (0.68)	1.39 (0.85)	<0.001	0.359	0.174	EMCI+/− > SMC+/−, CN+/−
GDS Total[6]	0.8 (1.1)	0.4 (1.0)	1.2 (1.1)	1.0 (1.3)	1.8 (1.5)	1.7 (1.5)	<0.001	0.112	0.707	EMCI+/− > CN+/−; EMCI− > SMC+/−; SMC− > CN+
MMSE Total Score[6]	29.1 (1.3)	28.9 (1.2)	28.9 (1.2)	29.0 (1.2)	28.5 (1.4)	28.1 (1.7)	<0.001	0.171	0.304	CN+/−, SMC+/− > EMCI+; CN− > EMCI−
MoCA Total Score[1,6]	25.8 (2.3)	25.6 (2.4)	25.5 (2.8)	25.3 (2.5)	24.1 (2.9)	23.5 (3.2)	<0.001	0.188	0.609	CN+/−, SMC− > EMCI+/−; SMC+ > EMCI+
LM-Immediate Recall[6]	14.5 (2.8)	13.5 (3.0)	14.5 (2.7)	13.4 (4.2)	11.0 (2.8)	11.1 (2.5)	<0.001	0.012	0.072	CN+/−, SMC+/− > EMCI+/−
LM-Delayed Recall[6]	13.6 (2.9)	13.0 (3.2)	13.1 (3.0)	12.7 (3.8)	8.9 (1.9)	9.1 (1.6)	<0.001	0.208	0.183	CN+/−, SMC+/− > EMCI+/−
RAVLT Total[6]	46.6 (10.8)	44.4 (10.0)	46.1 (9.5)	43.3 (10.4)	40.8 (10.9)	38.2 (10.5)	<0.001	0.005	0.954	CN−, SMC− > EMCI+/−; CN+ > EMCI+
RAVLT Delayed[6]	7.8 (4.2)	7.2 (3.7)	7.8 (4.0)	6.5 (3.9)	6.2 (4.2)	5.4 (3.9)	<0.001	0.017	0.784	CN−, SMC− > EMCI+/−; CN+ > EMCI+
Animal Fluency[6]	21.3 (5.4)	22.2 (5.1)	19.9 (5.2)	19.7 (5.6)	19.1 (5.2)	18.1 (5.0)	<0.001	0.843	0.135	CN+/− > EMCI+/−
Trailmaking B[2,6]	76.7 (38.3)	83.9 (50.0)	88.8 (49.7)	89.8 (35.6)	91.6 (40.7)	111.0 (59.4)	<0.001	0.030	0.134	EMCI+ > SMC−, CN+/−
Memory Composite[6]	0.94 (0.52)	0.87 (0.56)	0.91 (0.46)	0.81 (0.48)	0.59 (0.50)	0.45 (0.47)	<0.001	0.013	0.731	CN+/−, SMC− > EMCI+/−; SMC+ > EMCI+
Executive Function Composite[6]	0.88 (0.74)	0.82 (0.75)	0.71 (0.75)	0.60 (0.82)	0.56 (0.72)	0.29 (0.79)	<0.001	0.022	0.258	EMCI−, SMC−, CN+/− > EMCI+; CN− > EMCI−
ECog PT: Memory[3,5]	1.54 (0.44)	1.51 (0.42)	1.94 (0.56)	2.01 (0.58)	2.23 (0.69)	2.29 (0.66)	<0.001	0.564	0.688	EMCI+/−, SMC+/− > CN+/−; EMCI+/− > SMC−
ECog PT: Executive[3,5]	1.26 (0.32)	1.24 (0.34)	1.42 (0.36)	1.55 (0.40)	1.62 (0.58)	1.69 (0.56)	<0.001	0.236	0.440	EMCI+/− > CN+/−; EMCI+ > SMC−; SMC+ > CN−
ECog PT: Global[3,5]	1.31 (0.29)	1.30 (0.32)	1.54 (0.33)	1.65 (0.38)	1.76 (0.54)	1.82 (0.50)	<0.001	0.257	0.566	EMCI+/−, SMC+/− > CN+/−; EMCI+/− > SMC−
ECog Inf: Memory[4,5]	1.24 (0.38)	1.29 (0.31)	1.62 (0.55)	1.50 (0.44)	1.96 (0.70)	2.10 (0.77)	<0.001	0.764	0.202	EMCI+/− > SMC+/−, CN+/−; SMC− > CN+/−
ECog Inf: Executive[4,5]	1.16 (0.36)	1.17 (0.27)	1.31 (0.45)	1.24 (0.32)	1.54 (0.55)	1.66 (0.70)	<0.001	0.656	0.243	EMCI+/− > SMC+/−, CN+/−
ECog Inf: Global[4,5]	1.14 (0.25)	1.18 (0.26)	1.33 (0.37)	1.25 (0.26)	1.57 (0.48)	1.71 (0.62)	<0.001	0.475	0.108	EMCI+/− > SMC+/−, CN+/−

APOE = *APOE* ε4 carrier status; CDR-SB = Clinical Dementia Rating scale – Sum of Boxes; CN = cognitively normal older adults; DX = diagnosis; E-Cog = Assessment of Everyday Cognition; EMCI = early mild cognitive impairment; F = female; GDS = Geriatric Depression Scale; Inf = Informant-based; LM = Weschler's Logical Memory test; M = male; MMSE = Mini-Mental State Exam; MoCA = Montreal Cognitive Assessment; NS = not significant; p-val = p value; PT = patient-based; RAVLT = Rey Auditory Verbal Learning Test; SMC = significant memory concern

[1] 7 participants missing data (2 CN ε4−, 1 SMC ε4−, 1 SMC ε4+, 1 EMCI ε4−, 1 EMCI ε4+)

[2] 5 participants missing data (1 CN ε4+, 3 EMCI ε4−, 1 EMCI ε4+)

[3] 12 participants missing data (1 CN ε4−, 2 CN ε4+, 1 SMC ε4−, 1 SMC ε4+, 3 EMCI ε4−, 4 28 participants missing data (5 CN ε4−, 1 CN ε4+, 2 SMC ε4−, 3 SMC ε4+, 9 EMCI ε4−, 8 EMCI ε4+)

[5] Adjusted means and ANOVA p-values include age and gender as covariates

[6] Adjusted means and ANOVA p-values include age, gender, and years of education as covariates 1 EMCI ε4+)