APOE and cortical superficial siderosis in CAA: Meta-analysis and potential mechanisms

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Abstract

Objectives: To assess potential mechanisms of cortical superficial siderosis (cSS), a central MRI biomarker in cerebral amyloid angiopathy (CAA), we performed a collaborative meta-analysis of APOE associations with cSS presence and severity.

Methods: We pooled data from published studies reporting APOE genotypes and MRI assessment of cSS, in three distinct settings: (a) stroke clinic patients with symptomatic CAA (i.e. lobar intracerebral hemorrhage, transient focal neurological episodes) according to Boston criteria; (b) memory clinic patients; and (c) population-based studies. We compared cSS presence and severity (focal or disseminated vs. no cSS) in participants with e2+ or e 4+ genotype vs. the e3/e3 genotype, by calculating study-specific and random effects pooled, unadjusted ORs.

Results: Thirteen studies fulfilled inclusion criteria: seven memory clinic cohorts (n=2587), five symptomatic CAA cohorts (n=402) and one population based study (n=1379). There was no significant overall association between APOE e4+ and cSS presence or severity. When stratified by clinical setting, APOE e4+ was associated with cSS in memory clinic (OR: 2.10; 95%CI: 1.11-3.99), but not symptomatic CAA patients. The pooled OR showed significantly increased odds of having cSS for APOE e2+ genotypes (OR: 2.67, 95% CI 2.31-3.08), in both patient populations. This association was stronger for disseminated cSS in symptomatic CAA cohorts. In detailed subgroup analyses, APOE e2/e2 and APOE e2/e4 genotypes were most consistently and strongly associated with cSS presence and severity.

Conclusion: CAA-related vasculopathic changes and fragility associated with APOE e2+ allele might have a biologically meaningful role in the pathophysiology and severity of cSS.

Introduction

Cortical superficial siderosis (cSS) is detected as curvilinear hypointensities following the cortical surface on blood-sensitive T2*-weighted gradient-recalled echo (T2*-GRE) and susceptibility-weighted (SWI) MRI sequences.[1] It is generally thought that cSS reflects deposits of blood-breakdown products in the outermost cortical layers from, often occult, convexal subarachnoid hemorrhage.[1, 2] cSS is particularly common in advanced cerebral amyloid angiopathy (CAA) (prevalence 40-60%),[1, 3, 4] a small vessel disease that results from amyloid-β deposition in cortical and leptomeningeal arterioles. In CAA patients, cSS seems to be consistently associated with increased risk of incident[5] and recurrent[6] lobar intracerebral hemorrhage (ICH), including early recurrence,[7] as well as future dementia.[8] cSS is hence now considered a third cardinal hemorrhagic signature of CAA,[1, 9] alongside multiple strictly lobar cerebral microbleeds and lobar ICH. It is also included in the modified Boston criteria, as a specific MRI biomarker of the disease.[2]

The emerging clinical relevance of cSS, either as direct contributor to CAA-related impairment or a biomarker of the disease's presence, severity and course, raises questions about the mechanisms of this imaging lesion. However, data from neuropathological studies remain extremely limited. Understanding the underlying mechanisms and vascular pathology contributing to cSS could be facilitated by identifying associations with Apolipoprotein E (APOE) alleles. Associations between APOE e2 or e4 alleles with both lobar ICH risk and CAA presence and severity on neuropathology have been previously described. In fact, APOE genotype seem to be the single most important genetic determinant of CAA pathophysiology, identified to date.[10, 11] The current hypothesis, albeit supported by limited data, is that APOE e4 enhances vascular amyloid-β deposition in a dose-dependent fashion,[12] while APOE e2 promotes, so-called, CAA-related vasculopathic changes (vessel cracking, detachment and delamination of the outermost layer of the tunica media and fibrinoid necrosis) which can lead to vessel rupture.[13] It is hypothesized that cSS results from bleeding-prone leptomeningeal or superficial cortical arterioles that harbour advanced CAA and associated vasculopathic changes.[1]

To gain further insights into potential mechanisms of cSS in CAA and small vessel disease, we performed a collaborative meta-analysis of all available published studies that provided APOE data according to cSS presence and severity. Since cSS appears to convey high risk of recurrent ICH, it might segregate with APOE genotypes that are associated with CAA-

related vasculopathic changes. Hence, we specifically tested the hypothesis that cSS presence and severity is associated with APOE e2, a marker of CAA-related small vessel fragility.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

The study was performed according to a predefined protocol (i.e. before collecting and analysing data) designed in house and finalised in January 2016. This report was prepared with reference to the PRISMA,[14] the MOOSE[15] guidelines and the Cochrane Handbook for Systematic Reviews of Interventions.

Study identification and selection criteria

We sought all studies of adult humans published in any language that reported APOE genotype data and had cSS assessment on MRI, regardless of whether any association between the two was reported. We searched PubMed and Embase (from inception to January 2016 and updated in November 2017) using a combination of keyword search and MeSH terms, i.e. ("cortical superficial siderosis" OR "convexity siderosis" OR "convexal siderosis" OR "cortical hemosiderosis" OR siderosis OR hemosiderosis) AND (APOE OR "apolipoprotein E"). We also screened the references lists of all relevant studies and reviews identified, and searched Google Scholar for other studies citing potentially eligible relevant studies. We included relevant studies with >20 participants, including studies that recruited individuals from three distinct settings: (a) patients presenting to stroke clinics with symptomatic sporadic CAA (i.e. lobar intracerebral haemorrhage, transient focal neurological episodes) according to the validated classic Boston criteria (i.e. cSS was not part of CAA diagnosis); (b) memory clinic patients; and (c) participants from population-based studies. The rationale for including individuals from these different clinical settings was twofold. First, they represent the most likely clinical scenarios in which cSS in small vessel disease is detected on MRI (a and b) and are of potential clinical significance. Second, they capture the spectrum of cardinal CAA phenotypes: relatively "pure" stroke presentations (including lobar intracerebral haemorrhage), cognitive impairment/dementia, or incidental findings in elderly healthy populations.

We excluded case reports, small case series, and studies including hereditary/familial forms of CAA. Two authors independently selected eligible studies, resolving disagreements

by discussion. When two or more studies with overlapping cohorts existed, we included only the study providing the most data about the association and the largest number of participants.

Data extraction

Eligible studies were classified according to the primary clinical setting as (a) symptomatic CAA; (b) memory clinics; or (c) population-based. For each included study, we extracted information using standard proformas on publication year, country in which the study was conducted, study design, participant source and baseline demographic/clinical characteristics.

For our planned meta-analyses, we extracted, or required from authors summary-level data on numbers of participants with each APOE genotype (i.e. e3e3, e2 e3, e3e4, e4e4, e2e2, e2e4) according to cSS presence and severity (focal or disseminated) where available. A structured data extraction form was created and completed as far as possible by entering data from the relevant publication(s) and/or circulated to authors and a collaborative group was established. We also extracted information on the MRI sequence characteristics used for cSS detection and the rating methods used for cSS classification.

Quality and risk of bias assessment

We assessed each study against a list of quality criteria we devised based on study size, cohort recruitment method (prospective vs. other), blinding of cSS ratings and APOE genotype data, quality of genotyping, blood-sensitive MRI sequence type used, criteria of cSS assessment and inter-rater agreement. These criteria were created using elements with reference to the STREGA (Strengthening the Reporting of Genetic Association Studies)[16], MOOSE (Meta-analysis of Observational Studies in Epidemiology)[15] recommendations and consensus standards for cSS assessment and rating.[1]

Statistical analysis and synthesis

We performed meta-analyses using Stata 13.0 (StataCorp LP, Texas) and considered a p value of <0.05 to imply statistical significance. In our primary analyses, we calculated study-specific and random effects pooled, unadjusted ORs for cSS presence vs. absence among e4 allele carriers (e4+) versus the reference genotype e3e3 and among e2 carriers (e2+) versus the wild type e3e3. This comparison was selected, to avoid potential confounding by mixed effects of e2 and e4 in the comparison group. In secondary analyses, we compared cSS severity (focal vs. no cSS and disseminated vs. no cSS) in participants with an e2+ or e4+ genotype vs. the e3/e3 genotype. In analyses looking at cSS severity (i.e. focal or disseminated cSS) the

comparison groups included only patients without cSS. Meta-analyses were performed both separately by study setting/population, and overall. In all analyses we used a random effects model with DerSimonian-Laird weights,[17] using odds ratios (OR) and their corresponding 95% CIs, with the inverse variance method for weighting. We assessed statistical heterogeneity using I-squared statistics and visually through inspection of the forest plot. Values of ≤25%, 25% to 50%, and ≥50% were defined as low, moderate, and high degrees of heterogeneity, respectively. We explored publication bias with funnel plots. As a subanalysis, and to reveal potential dose-effect relationships, we have also explored the association between all different APOE genotypes (i.e. e2 e3, e3e4, e4e4, e2e2, e2e4 vs. e3e3) and cSS presence and severity in the whole population and across different clinical settings. To assess robustness of the methods, we repeated all the above analyses using the fixed effects method.

Data availability statement

All relevant data and methods are reported in the manuscript. No data available in public repositories.

Results

Characteristics and quality of included studies

From 33 publications identified in our literature search, we identified 13 relevant studies fulfilling our inclusion criteria and pooled in meta-analyses (Figure 1). Study populations comprised seven memory clinic cohorts (n=2587), five symptomatic non-overlapping CAA cohorts (n=402) and one population based study including healthy people (n=1379) (Table 1). The memory clinic studies had different inclusion criteria and dementia prevalence (Table 1). The symptomatic CAA studies included two cohorts presenting with stroke syndromes other than ICH, one with pure CAA-ICH, and two with both CAA-ICH and CAA non-ICH presentations. Four out of these five CAA cohorts were derived from different studies completed at the same centre,[4, 18-20] but included largely non-overlapping patient cohorts (i.e. different clinical settings/recruitment, clinical presentation, inclusion criteria, inception etc.). In detail (see footnote in Table 1), one of these four single centre cohorts,[4] an advanced research MRI study of CAA-related ICH patients have included around 10% of overlapping patients with a separate consecutive clinical ICH cohort,[19] from which CAA-related lobar ICH were included in our analysis, based on our best estimates. This latter clinical CAA cohort[19] might have slightly overlapped (~10%) with a pathology-based cohort of CAA patients.[20] Mean

age was between 63-75 years and about half of all participants were male. Most studies were conducted in predominantly white populations in centres from Europe, USA or Australia, while two studies were conducted on Asia. The distribution of the ethnicity of participants in each study was not available.

There was variation in overall study quality (Table 2), including sample size and retrospective vs. prospective designs. The genotyping quality was generally good when assessed against current reporting standards. Studies varied in the type of blood-sensitive sequences used for cSS detection (e.g. T2*-GRE vs. SWI), as well as MRI field strength, with all cohorts on symptomatic CAA patient populations using 1.5 T MRI, while memory clinic studies were performed at 3T MRI. The methods of cSS assessment were reliable and largely in line with current consensus recommendations in the field.[1] For details on quality assessment and individual scores of included studies in the meta-analysis, see Table 2.

Pooled prevalence and severity of cSS in included studies

The pooled prevalence of cSS presence was 2% (95%CI: 2%-3%, I^2: 59%, p=0.02) in memory clinic patients, 47% (95%CI: 38%-56%, I^2: 66%, p=0.02) in symptomatic CAA patients and 1% (95%CI: 1%-2%) in the single population-based study included in our analysis. The overall pooled prevalence of focal cSS in memory clinic vs. symptomatic CAA patients was 1% (95%CI: 1%-2%, I^2: 48%, p=0.07) and 17% (95%CI: 13%-22%, I^2: 24%, p=0.26) respectively. The overall pooled prevalence of disseminated cSS was 1% (95%CI: 0%-1%, I^2: 9%, p=0.36) vs. 28% (95%CI: 20%-36%, I^2: 60%, p=0.04) in memory clinic vs. symptomatic CAA cohorts respectively. In all comparisons, the prevalence of cSS (presence and severity) was higher in symptomatic CAA vs. memory clinic patients (p<0.0001). Among patients with any cSS, the prevalence of focal cSS was 67% (95%CI: 55%-79%, I^2: 17%, p=0.30) in memory clinic patients and 37% (95%CI: 26%-49%, I^2: 60%, p=0.04) in symptomatic CAA cases (p<0.001 between the two groups).

Meta-analyses: APOE e4 and e2 and cSS presence and severity

The results of the main analyses of the association between APOE e4 and e2 with cSS presence are summarised in Figure 2. Compared to participants with an APOE e3/e3 genotype, pooled overall results showed no increased odds of cSS presence in participants with APOE e4+ genotype (Figure 2A). When stratified by clinical subgroups, APOE e4+ genotype was associated with cSS presence in memory clinic patients, but not symptomatic CAA patients (Figure 2A). The pooled OR showed increased odds of having cSS for APOE e2+ genotypes (OR 2.67, 95%CI: 2.31-3.08) with no statistical heterogeneity between study

results (Figure 2B). This association was strong in both memory clinic and symptomatic CAA cohorts (Figure 2B).

All clinical studies provided relevant data for meta-analyses of APOE genotypes and cSS severity (focal or disseminated). These data were not available to pool in the single population-based study which reported on APOE and cSS. Overall, pooled results showed that, compared to patients with an e3/e3 genotype, those with an e4 + genotype did not have increased odds of having either focal or disseminated cSS (Figure 3A). Memory clinic patients showed only a non-significant trend for an association with APOE e4 + genotype and cSS burden (Figure 3A). Overall, patients with APOE e2+ genotype had increased odds for an association with disseminated, but not focal, cSS (Figure 3B). When stratified by clinical setting, focal cSS was associated with APOE e2+ genotype in memory clinic patients, and showed a strong trend with disseminated cSS in this population (Figure 3B). In symptomatic CAA cohorts, only disseminated cSS was associated with APOE e2+ genotype. There was no evidence of publication bias and statistical heterogeneity was low to moderate across analyses (data provided in each forest plot)

Subgroup meta-analyses: different APOE genotypes and cSS presence and severity

The detailed results of subanalyses exploring the association between all different APOE genotypes (vs. e3/e3) and cSS presence and burden are summarised in Table 3. In the overall analysis of all the cohorts together, the most consistent associations with higher effect sizes were seen with APOE e2/e2 and APOE e2/e4 genotypes (Table 3). The associations were different when stratified by the clinical setting. In memory clinic cohorts, cSS presence and severity was also associated with APOE e4/e4, while the stronger link was with the APOE e2/e4 genotype (Table 3). Among symptomatic CAA cohorts, only APOE e2/e3 and APOE e2/e4 were associated with disseminated cSS (Table 3). Of note, the APOE e4/e4 genotype was associated with marginally lower odds of having disseminated cSS in symptomatic CAA patients (OR: 0.24; 95%CI: 0.06-0.92, p=0.038, see Table 3). The statistical heterogeneity for these subanalyses ranged from low, to moderate and high (Table 3).

Discussion

The current meta-analysis provides a comprehensive assessment on cSS,[1] CAA,[21] and their association with APOE genotype. Drawing data from >4000 participants of relevant studies

and different clinical setting, our main results indicated that cSS, especially disseminated cSS, is most strongly associated with APOE e2+ genotype. This overall association was consistent and did not vary significantly according to clinical setting. We found that APOE e4+ genotype was overall not associated with cSS presence or burden. However, APOE e4+ genotype results varied depending on the clinical setting, with memory clinic patients (but not symptomatic ICH patients) showing an association with cSS, albeit weaker compared to APOE e2+ genotype based on the unadjusted pooled ORs (2.10 versus 3.28 respectively). In the detailed subanalyses looking at individual APOE genotypes and cSS burden, the most consistent associations with higher effect sizes were seen with the e2/e2 and e2/e4 genotypes.

Although it can be challenging to infer specific pathophysiological mechanisms from genetic associations, the most straightforward and parsimonious explanation for our results is that cSS is indeed a strong and specific MRI biomarker for more advanced or active CAA. These results confirm our prespecified hypothesis, are consistent with prior observations in the field, with what is presumed to be the effect of APOE e2 vs. e4 on underlying CAA-related vasculopathic changes, and with the emerging clinical relevance of cSS as an independent risk factor for future symptomatic ICH. APOE genotype is the single most important genetic determinant in CAA pathophysiology.[10, 11] APOE e4 appears to enhance vascular amyloid-β deposition in a dose-dependent fashion,[12] while APOE e2 promotes vasculopathic changes (vessel cracking, vessel-within-vessel appearance and fibrinoid necrosis) which can lead to vessel rupture.[13] A previous meta-analysis investigating APOE associations with cerebral microbleeds found that strictly lobar microbleeds (a putative marker of CAA presence) was related to APOE e4 + allele (OR: 1.35, 95%CI: 1.10–1.66, p=0.005), but not APOE e2.[22] This result was consistent for any cerebral microbleeds presence in a more recent comprehensive meta-analysis.[23] The dissociation of the relationship between APOE genotype and cerebral microbleeds vs. cSS has implications for discerning potential mechanisms. APOE e4 might predispose to the particular kind of CAA-related vessel thickening postulated to lead to microscopic intraparenchymal hemorrhage (e.g. strictly lobar cerebral microbleeds).[24] In contrast, APOE e2 might promote the most severe stages or aggressive phenotype of CAA pathology that precede rupture, especially in leptomeningeal vessels, hence contributing to MRI-visible superficial CAA-related bleeds (aka cSS) in multiple spatially separated foci.[4, 20] A recent neuropathological study used a detailed grading system for assessing CAA in parenchymal and leptomeningeal vessels separately.[25] In a sample of Alzheimer's disease and non-demented elderly control brains, APOE e2 was a much stronger risk factor for CAA

development, especially in leptomeningeal vessels, compared to APOE e4 (OR: 10.93; 95%CI: 4.33-27.57 vs. 1.69; 0.92-3.10, respectively).[25] Fittingly, an inverse relationship has been observed between greater lobar cerebral microbleed counts and cSS in advanced CAA, suggesting the possibility of differing CAA phenotypes that are driven in part by APOE genotype, and marked by the predominance of either cSS or CMBs MRI patterns.[4,22]

These inferences would also be in line with several clinical observations in the field. APOE e2 is already known to be associated with CAA-related ICH, perhaps causally,[26] also predisposing to larger volumes of CAA-related bleeding.[27] cSS is independently associated with future ICH risk in CAA, both recurrent[6, 28] and first lobar ICH.[5] In fact, clinical cohorts which incorporated and investigated both cSS and strictly lobar microbleeds in relation to future ICH, demonstrated that cSS, but not microbleeds, is the strongest independent risk factor for CAA-ICH.[5, 6, 28] Also, there is preliminary evidence that APOE e4 may be associated with CAA type 1 (where CAA is found in cortical capillaries) and APOE e2 with CAA type 2 (where cerebrovascular amyloid is primarily deposited in leptomeningeal and cortical vessels sparing cortical capillaries).[29] A recent neuropathological study which validated a detailed CAA grading system showed that all individuals with the APOE e2/e2 genotype had CAA-type 2, while the APOE e4/e4 genotype was associated with CAA type 1 (OR 8.0; 95% CI 2.8-23.3).[25] Finally, though the exact pathophysiological mechanisms underlying cSS remain debatable,[1] MRI-detected cSS seems to reflect repeated episodes of superficial bleeding from CAA-laden bleeding-prone leptomeningeal vessels.[1] Thus cSS may be a strong marker of not only more severe CAA, but CAA with more fragile, rupture-prone vessels, thereby, heralding a risk of subsequent ICH.[6, 30] APOE e2 driven vascular injury in CAA, in combination with other risk factors, could influence pathways providing initiation sites for cSS and hence future lobar ICH risk.

Our study benefited from thorough ascertainment of the totality of evidence to date on the topic, within the two clinical settings in which CAA is most commonly considered. The first setting consists of patients diagnosed in stroke clinics with relatively advanced symptomatic CAA, while memory clinic patients and healthy elderly are heterogeneous participants who mostly do not have advanced CAA (instead, mild to moderate CAA commonly accompanies Alzheimer's neurodegenerative pathology in memory clinic patients). This fact explains the much higher proportion of cSS in the symptomatic CAA group and might partly account for the different relationship with APOE e4. We note the higher

frequency of APOE e4 in patients from memory clinics, at least in part, due to the relationship between this genotype and its well-known predisposition to Alzheimer's disease (instead, APOE e2 variant confers reduced risk for Alzheimer's disease and thus has lower frequency in memory clinics).[31] Similar to Alzheimer's disease, as noted above, histopathological studies in CAA indicate that APOE e4 has an equivalent role in CAA by promoting vascular amyloid-β deposition; APOE e2 however, has a different effect - it increases vessel wall damage caused by cerebrovascular amyloid deposition. In other words, the hypothesis is that APOE e4 increases the likelihood of having CAA among memory clinic patients (identified clinically by the presence of cSS). Among symptomatic CAA patients with already advanced (or enriched in) underlying cerebrovascular amyloid deposition, it doesn't increase the likelihood of cSS – in this group, APOE e2 comes into play (especially in a dose-depended and synergistic fashion with APOE e4 gene).

Our findings in the subanalyses of detailed APOE genotypes and associations with cSS presence and burden, probably account for the prevalence and differential effects of e4 and e2 in Alzheimer's disease and CAA. However, these subanalyses need to be interpreted with caution, under the prism of the following additional considerations. The relatively small sample size contributing to each subanalysis (e.g. according to clinical setting, focal or disseminated cSS etc.) and rarity of certain alleles and genotypes, resulted in wide 95% confidence intervals. Due to the increased number of subanalyses, we run the risk of multiple comparisons. Hence, they should be considered hypothesis-generating, highlighting possible trends, effect sizes and potential mechanistic pathways to be explored in further studies on cSS. It is important to again point out that the associations between cSS presence/burden and specific APOE genotypes, require, to some extent, different interpretation in memory clinic vs. symptomatic CAA cohorts. In memory clinic patients, APOE genotype-cSS associations are driven by the presence of substantial underlying CAA pathology that is denoted by cSS. In other words, cSS in memory clinic cohorts, identifies patients with advanced CAA (i.e. beyond the mild CAA, often a common "innocent bystander" in this setting) - the known risk factor of originally developing cerebrovascular amyloid-β accumulation is APOE e4 and e2. Symptomatic CAA cohorts, are by definition enriched with cerebrovascular amyloid-β pathology and hence APOE-cSS associations are driven/indicating more specific (or predominant) pathophysiological mechanisms at play, especially within the most severe cases of cSS (i.e. disseminated cSS). It is possible that the APOE e2/e4 genotype may represent double hit for the superficial vessels, promoting not only amyloid deposition but also vessel wall cracking in

the most vulnerable arterioles in CAA. In the setting of advanced cerebrovascular amyloid-β pathology, it is not surprising that only this 'double hit' genotype of APOEe2/APOEe4 shows a strong link with disseminated cSS. These hypotheses require external validation and direct support from experimental studies. Future studies should also investigate the effect of APOE genotypes on cSS progression and interactions with future CAA-related ICH risk.

Some limitations of our study need to be acknowledged. The design of included studies, case selection, and MRI parameters for cSS detection were variable. Patients from symptomatic CAA cohorts underwent brain MRI at 1.5T, while other cohorts at 3T. While the consisted MRI field strength within clinical setting sub-groups is reassuring, in the overall analyses, the difference could influence the sensitivity for cSS detection and rating. In the same vein, blood-sensitive sequences used for cSS detection were also variable across studies, including both T2*-GRE and SWI. Though the variable MRI parameters is a potentially important limitation for this sort of meta-analysis, no data exist on how sensitivity for cSS classification is affected by different MRI sequences. Considering that cSS represents a much higher volume of blood-breakdown products (i.e. hemosiderin) compared for example to cerebral microbleeds, the differences in MRI sensitivity might not be very pronounced. None of the included studies fulfilled all our methodologic quality indicators. There is likely a number of studies that could not be included in the current meta-analysis simply because they did not report on either APOE or cSS, reflecting the fact that cSS is a relatively new addition in the spectrum of CAA MRI markers. This raises the issue of potential confounding and selection bias, which is hard to address. It should be emphasised that, despite including all available data from relevant publications, the overall sample size for certain subgroup meta-analyses was relatively small. This limits the precision of the pooled results, especially in combination with the low prevalence of cSS in the memory clinic studies. In a memory clinic setting, one should recognise the known relative rarity of APOE e2 genotypes and the confounding effect of the presence of dementia and Alzheimer's type pathology. While CAA and Alzheimer's disease are linked in the context of cognitive impairment populations, their precise relationship remains poorly understood.[32] This and other considerations could partly explain the weak association observed between cSS presence and APOE e4 in the memory clinic cohorts. For example, both CAA and neurodegenerative pathology contribute to cognitive impairment in the elderly[33] and APOE e4 is a well-known risk factor for both cerebrovascular and parenchymal amyloid accumulation. Nevertheless, quite reassuringly, the association with APOE e2 and cSS was consistently detected in memory clinic patients and with stronger effect

size than the APOE e4 association. Lastly, our meta-analysis was performed at a group level, which means that generated pooled estimates are not adjusted for any confounders that might influence the association between APOE status and cSS, including age, sex and other MRI markers of small vessel disease. It is thus possible that reported associations are overstated. It could be argued that our unadjusted group-level meta-analysis is exploratory, providing a rough indication of likely effect sizes across populations for the APOE-cSS link, setting the scene for a more detailed individual-patient level meta-analysis. We are hoping to pursue this in the future in a large collaborative study.

Most of the symptomatic CAA cohorts suitable for meta-analysis came from a single centre. We acknowledge the potential for some overlap among these cohorts – while we do not have all the detailed data on overlapping patients, based on the different clinical setting/recruitment, clinical presentation, inclusion criteria, inception points etc., this overlap is minimal and ranges between 5-10%, as summarised in Table 1 footnote. Any potential overlap between these cohorts is random and unlikely to have affected our main results. However, due to this limitation, our findings will benefit from further validation and updated meta-analyses. The plausible suggestion of different APOE influences on the severity and type of amyloid deposition in the vessel wall and advanced vasculopathic changes suggested in the interpretation of our current findings, are based on limited data.[34] In particular, further studies on the proposed differential effects of e4 and e2 alleles will be valuable. However, it is reasonable to provide an informed discussion based on these biological hypotheses and assumptions, in an effort to start building a pathophysiology model of cSS that could explain both clinical and research findings and help develop hypothesis-driven studies in the field. Finally, the vascular damage pathways leading to cSS must be only partly influenced by APOE e2 as evidenced by the fact that a number of cSS cases are also found within the APOE e3/e3 genotype.

Notwithstanding these caveats, our results provide useful data to partly settle the question in favor of a link between APOE e2+ genotype and cSS in CAA. The pathophysiologic implication is that APOE e2 influences the risk of cSS through promoting the most severe stages of CAA pathology that are associated with rupture. These results are also in line with cSS being a strong hemorrhagic MRI signature in CAA and the likely "smoking gun" of bleeding risk. Future research efforts on the topic require methodologically robust, large studies adhering to current reporting standards,[1, 35] and collaborative data pooling efforts. Based on

the totality of current evidence, our study suggests a biologically meaningful association between the APOE e2 + genotype and severe cSS in patients with CAA, probably as a result of the role of e2 in the severity of vasculopathy in CAA-affected leptomeningeal and very superficial cortical vessels. The exact pathophysiological mechanisms that underlie these associations should be investigated, as they might define targets for therapeutic interventions in CAA.

Authors and their individual contributions to the manuscript

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Tables

Table 1. Basic characteristics and methodological aspects of included studies.

Study	Country (period)	Setting-Participants source	Study size*	Mean age	Male (%)	Dementia (%)	MRI sequence	Field strength	ET (ms)	ST (mm)	cSS rating
CAA cohorts											
†Charidimou et al. 2017[18]	USA	Probable CAA without ICH – stroke clinic	62	75	57%	10%	T2*-GRE	1.5T	50	5	2 trained raters by consensus
†Charidimou 2016[19]	USA	Clinical CAA-ICH	197	74	49%	?	T2*-GRE	1.5T	50	5	1 trained rater (k=)
†Charidimou 2015[20]	USA	Pathologically-proven CAA	53	73	45%	?	T2*-GRE/SWI	1.5T	-	-	1 trained rater
†Shomanesh 2014[4]	USA	CAA research cohort	79	71	70%	10%	T2*-GRE/SWI	1.5T	25	5	1 trained rater (k=0.79)
Martínez-Lizana et al. 2015[36]	Spain	Convenience biomarkers cohort of CAA patients with and without cSAH	25	79	52%	28%	T2*-GRE	1.5T	-	-	Not reported
Memory clinic/non-symptomatic CAA cohorts											
Shams 2016[37]	Sweden	Consecutive memory clinic series	520	63	47%	35%	T2*-GRE/SWI	3T	-	-	2 trained raters by consensus
†Charidimou 2016[38]	USA	Consecutive memory clinic series	68	73	44%	43%	T2*-GRE	3T	20-25.7	5	1 trained rater
Na 2015[39]	Korea	Memory clinic patients with PET/MRI/CSF analysis	232	72	42%	?	T2*-GRE	3T			2 trained raters (k=0.92)
Zonneveld 2014[40]	Netherlands (2010-2012)	Memory clinic–based Amsterdam Dementia Cohort	610	66	56%	41%	SWI	3T	-	-	1-2 trained raters (k=0.81)
Yates 2014[41]	Australia	Melbourne Neuroimaging Cohort of the Australian Imaging, Biomarkers and Lifestyle Study of Ageing	174	74	40%	23%	SWI	3T	-	-	2 trained raters (k~0.8)

Kantarci 2013[42]	ADNI (2010-2012)	Alzheimer's Disease Neuroimaging Initiative (ADNI)	451	73	55%	8%	T2*-GRE	3T	-	-	Trained raters
Singapore cohort	Singapore	Memory clinics in two centres	458	~70	51%	34%	SWI	3T	20	1	Trained raters
Population-based cohorts											
Pichler at al. 2017[43]	USA (2011-2016)	Mayo Clinic Study of Aging	1412	62-78	53%	<9%	T2*-GRE	3T	20	3.3	Trained raters

* number of eligible participants genotyped and assessed for cSS; R: retrospective study; P: prospective study; ?:unknown

† Cohorts originating from a single centre (Massachusetts General Hospital-MGH). We note minimal sample overlap among these included studies and cohorts originating from MGH. Most of these different cohort are completely independent (i.e. different clinical setting/recruitment, clinical presentation, inclusion criteria, inception etc.). However, there is a possibility of ~5-10% (or lower) overlap between 3 of the MGH cohorts (Ref. 4, 19 and 20). Please note that it is not possible to definitely identify potentially overlapping patients among the two cohorts and exclude them, due to different coding and anonymization of the patient data and samples.

In detail:

-Ref. 4: MGH ICH/CAA cohort since 1995 – this is a research, advanced MR imaging CAA-ICH cohort. None of the patients are included in cohorts corresponding to Ref. 20, 18 or 35. Around 10% of the patients might be overlapping with Ref. 18.

-Ref. 20: MGH 1997-2012 – this is a neuropathology-based cohort of CAA patients, irrespective of clinical presentation, with available tissue. Around 5% or less of the patients might be overlapping with Ref. 19.

-Ref. 18: MGH stroke and memory 1994-2015 – this is a "probable CAA" cohort according to the modified Boston criteria of patients presenting without ICH, in stroke clinics or specialty CAA clinics at our group. There is no overlap with Ref. 4, 19, or 20.

-Ref. 19: MGH ICH cases – this is an consecutive clinical ICH cohort, from which CAA-related lobar ICH were included in our analysis. The cohort might be overlapping by 10% with Ref. 4 and Ref. 20 cohorts.

-Ref. 35: MGH memory clinic 2007-2010 – a generic, unselected memory clinic patient cohort (without ICH or stroke-like syndromes), not overlapping with any of the other MGH cohorts cited in our paper.

Table 2. Summary of key quality indicators of pooled studies.

Study Reference	Study size			Design (R-0, P-1)	Blinding (MRI to genotype)	cSS criteria clearly defined	cSS inter-observer agreement	T2*-GRE (0) vs. SWI (1)	Genotyping reporting	Total score (0-8)
	≤100	101-200	>200							
Charidimou et al. 2017[18]	✓			0	✓	✓	✓	0	1	4
Charidimou 2016[19]		✓		0	✓	✓	X	0	1	4
Charidimou 2015[20]	✓			0	✓	✓	X	0	1	3
Shomanesh 2014[4]	✓			1	✓	✓	X	0	1	4
Martínez-Lizana et al. 2015[36]	✓			0	✓	✓	X	0	1	3
Shams 2016[37]			✓	0	✓	✓	✓	0	1	6
Charidimou 2016[38]	✓			0	✓	✓	X	0	1	3
Na 2015[39]			✓	1	✓	✓	✓	0	1	7
Zonneveld 2014[40]			✓	1	✓	✓	✓	1	1	8
Yates 2014[41]		✓		1	✓	✓	✓	1	1	7
Kantarci 2013[42]			✓	0	✓	✓	X	0	0	4
Singapore cohort			✓	1	✓	✓	X	1	1	7

Pichler at al. 2017[43]			✓	1	✓	✓	x	0	1	6

Scoring system: For each key quality indicator listed, each study got 1 point if fulfilled. For the design "Design" criterion, studies got 1 point if they were prospective (P-1) and 0 points if retrospective (R-0). For blood-sensitive MRI sequences, accounting for the different sensitivities in detecting and assessing cSS, studies got 1 point if they used susceptibility-weighted imaging (SWI-1) and 0 points if they used T2*-weighted gradient-recalled echo (T2*-GRE-0). For study sizes, studies got 0-2 points depending on the number of included patients, i.e. ≤100, 101-200 or >200 patients, respectively. The total score was calculated by adding all the points for each individual key quality indicator, thus ranging from 0 (lowest quality) to 8 (highest quality).

Table 3. Detailed meta-analyses results for the association between different APOE genotypes (vs. e3/e3) and cSS presence and burden. For the analyses including focal cSS and disseminated cSS, the comparison groups included only patients without cSS.

	APOE genotype	e4/e3	e4/e4	e2/e3	e2/e2	e2/e4
OVERALL	***cSS presence***					
	OR (95%CI)	0.87 (0.41-1.83) p=0.712	1.27 (0.49-3.28) p=0.617	***2 (1.20-3.32) p=0.008***	***3.41 (1.13-10.3) p=0.029***	***3.96 (1.85-8.51) p<0.0001***
	Heterogeneity	52.5%, p=0.017	63.2%, p=0.002	0%, p=0.804	0%, p=0.530	8.5%; p=0.362
	Focal cSS					
	OR (95%CI)	0.85 (0.40-1.82) p=0.683	1.53 (0.67-3.50) p=0.312	1.56 (0.78-3.12) p=0.213	***6.01 (1.53-23.59) p=0.010***	***3.85 (1.52-9.78) p=0.005***
	Heterogeneity	31.4%; p=0.140	36%; p=0.102	0%; p=0.563	4.4%; p=0.388	9.7%; p=0.351
	Disseminated cSS	11	10	9	7	9
	OR (95%CI)	0.93 (0.46-1.87) p=0.839	0.96 (0.28-3.28) p=0.951	***2.64 (1.38-5.06) p=0.003***	***5.29 (1.60-17.55) p=0.006***	***5.61 (2.45-12.84) p<0.0001***
	Heterogeneity	13.4%; p=0.316	53.5%; p=0.022	0%; p=0.696	0%; p=0.639	0.8%; p=0.427
MEMORY CLINIC COHORTS	***cSS presence***					
	OR (95%CI)	1.60 (0.60-4.23) p=0.347	***4.63 (2.14-10.02) p<0.0001***	***3.41 (1.45-8.01) P=0.005***	***11.72 (2.33-58.8) P=0.003***	***7.12 (2.25-22.56) P=0.001***
	Heterogeneity	35.1%; p=0.161	0%; p=0.848	0%; p=0.906	0%; p=0.834	0%; p=0.617
	Focal cSS					
	OR (95%CI)	1.49 (0.61-3.66) p=0.383	***4.79 (1.99-11.52) P<0.0001***	2.92 (1.05-8.12) P=0.40	***17.37 (3.34-172.1) P=0.001***	***7.35 (2.25-24.0) P=0.001***
	Heterogeneity	0%; p=0.466	0%; p=0.981	0%; p=0.986	0%; p=0.934	0%; p=0.939
	Disseminated cSS					
	OR (95%CI)	2.17 (0.70-6.74) p=0.179	***5.32 (1.53-18.53) P=0.009***	***5.04 (1.24-20.42) P=0.023***	***18.09 (2.67-122.5) P=0.003***	***10.21 (1.65-63.26) P=0.013***
	Heterogeneity	0%; p=0.679	05; p=0.716	0%; (p=0.570)	0%; p=0.706	21.1%; p=0.283
SYMPTOMATIC CAA COHORTS	***cSS presence***					
	OR (95%CI)	0.47 (0.17-1.32) p=0.151	0.32 (0.13-0.77) P=0.11	1.49 (0.79-2.81) P=0.213	1.15 (0.25-5.23) P=0.857	2.94 (0.93-9.34) P=0.067
	Heterogeneity	56.5%; p=0.056	20.5%; p=0.284	0%; p=0.646	0%; p=0.802	26.1%; p=0.247
	Focal cSS					
	OR (95%CI)	0.51 (0.15-1.68) p=0.268	0.41 (0.16-1.04) P=0.060	0.83 (0.24-2.87) P=0.767	0.77 (0.08-7.60) P=0.825	2.13 (0.30-15.24) P=0.451
	Heterogeneity	46.5%; p=0.113	0%; p=0.759	32.6%; p=0.204	0%; p=0.738	52.6%; p=0.096
	Disseminated cSS					
	OR (95%CI)	0.57 (0.23-1.42) p=0.224	***0.24 (0.06-0.92) P=0.038***	***2.22 (1.38-5.06) P=0.033***	2.39 (0.51-11.12) P=0.268	***4.56 (1.76-11.84) P=0.002***
	Heterogeneity	24.1%; p=0.261	33.4%; p=0.199	0%; p=0.643	0%; p=0.639	0%; p=0.460

Heterogeneity (I^2, p-value)

Figures

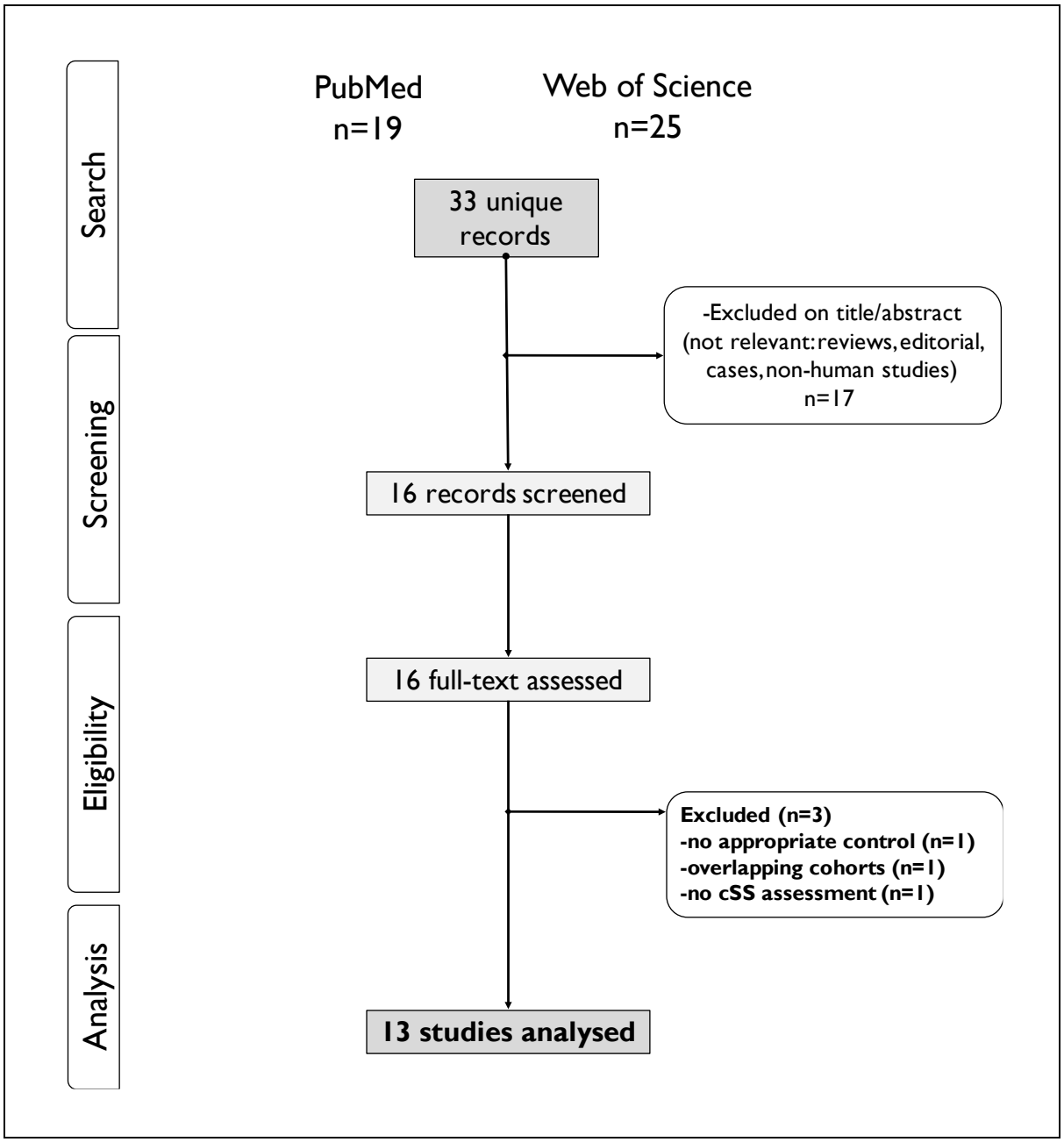

Figure 1. Flow chart of study identification and selection.

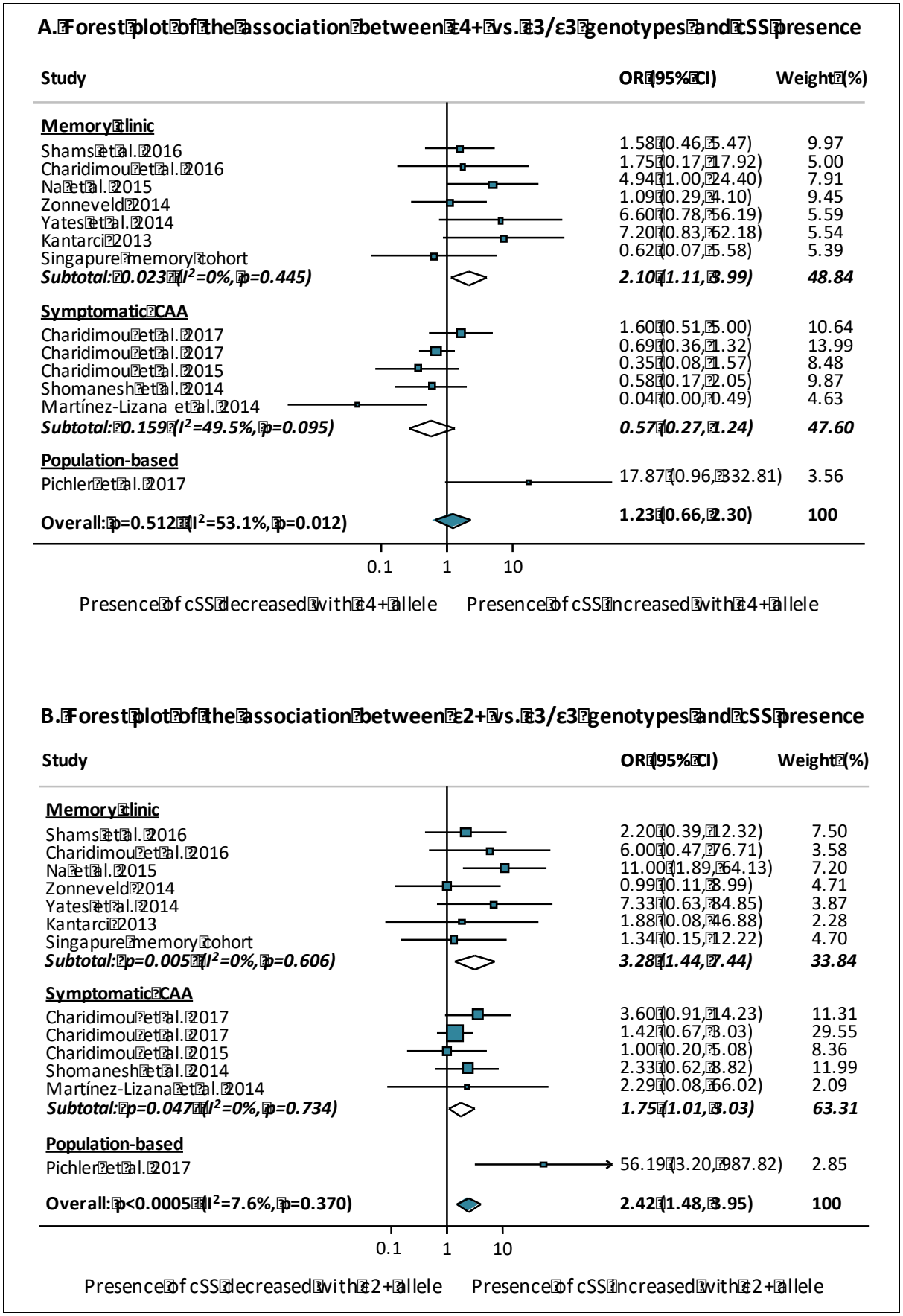

Figure 2. Forest plots of the association between cSS presence and (A) APOE e4+ vs APOE e3/e3 genotype, and (B) APOE e2+ vs APOE e3/e3 genotype. Meta-analyses were performed

using a random effects model. Studies are displayed in order of publication date. The squares represent study-specific odds ratios (ORs), with their size proportional to their statistical weight. Diamonds represent pooled ORs, and their 95% CI, stratified by clinical setting and overall.

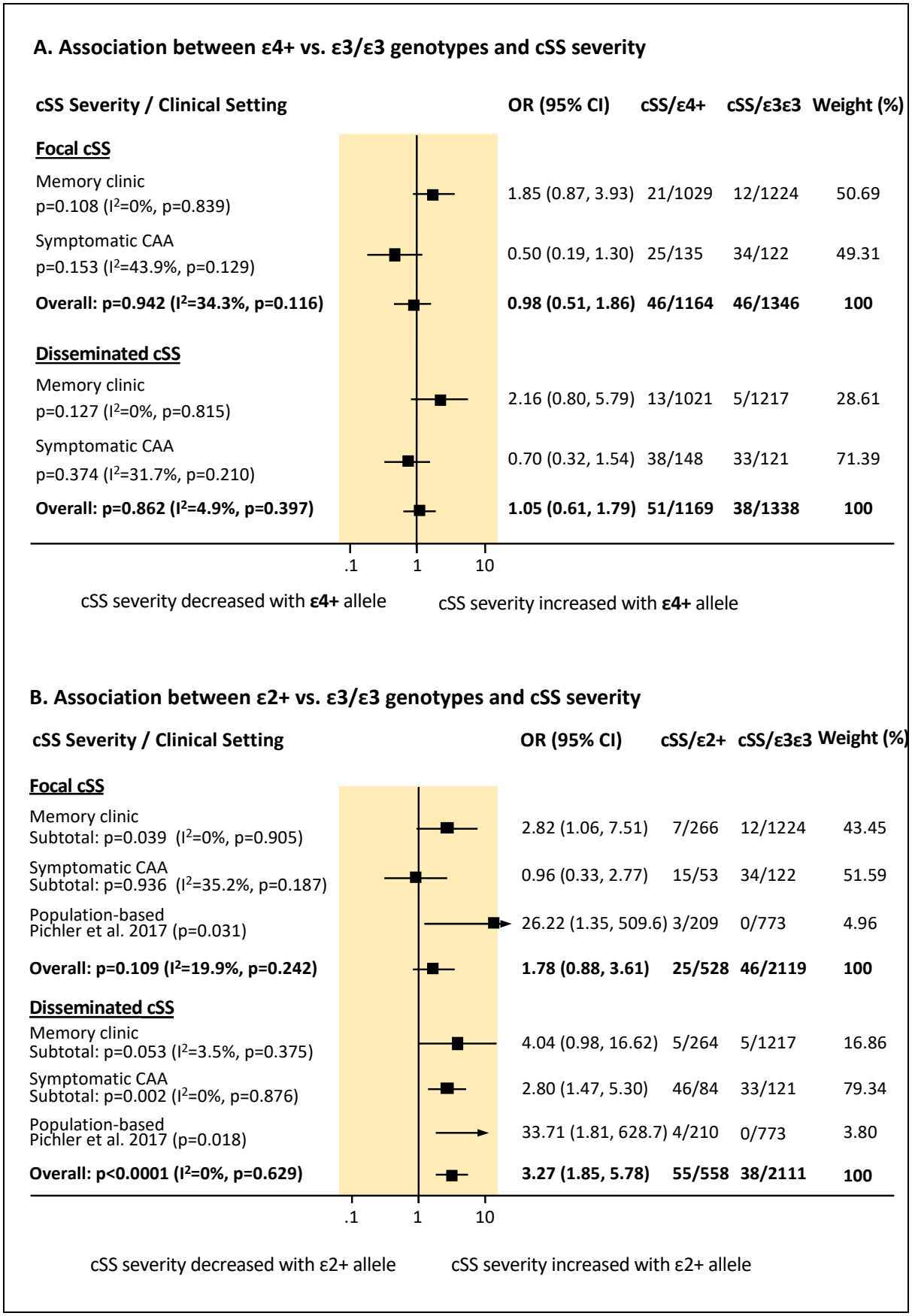

Figure 3. (A) Subanalyses summary results of the effect of APOE e4+ vs APOE e3/e3 genotype on the presence of focal and disseminated cSS, according to clinical setting and

overall. (B) Subanalyses summary results of the effect of APOE e2+ vs APOE e3/e3 genotype on the presence of focal and disseminated cSS, according to clinical setting and overall. The comparison groups included only patients without cSS. The columns on the right of the forest plots denote the number of participants included in each analysis. Diamonds represent the overall pooled ORs, and their 95% CI for each comparison. Study-specific OR are not shown.

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