APOE and cortical superficial siderosis in CAA

Meta-analysis and potential mechanisms

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Abstract

Objective

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* genotype and MRI assessment of cSS in 3 distinct settings: (1) stroke clinic patients with symptomatic CAA (i.e., lobar intracerebral hemorrhage, transient focal neurologic episodes) according to the Boston criteria; (2) memory clinic patients; and (3) population-based studies. We compared cSS presence and severity (focal or disseminated vs no cSS) in participants with $\epsilon 2+$ or $\epsilon 4+$ genotype vs the $\epsilon 3/\epsilon 3$ genotype, by calculating study-specific and random effects pooled, unadjusted odds ratios (ORs).

Results

Thirteen studies fulfilled inclusion criteria: 7 memory clinic cohorts ($n = 2,587$), 5 symptomatic CAA cohorts ($n = 402$), and 1 population-based study ($n = 1,379$). There was no significant overall association between *APOE* $\epsilon 4+$ and cSS presence or severity. When stratified by clinical setting, *APOE* $\epsilon 4+$ was associated with cSS in memory clinic (OR 2.10; 95% confidence interval [CI] 1.11–3.99) but not symptomatic CAA patients. The pooled OR showed significantly increased odds of having cSS for *APOE* $\epsilon 2+$ genotypes (OR 2.42, 95% CI 1.48–3.95) in both patient populations. This association was stronger for disseminated cSS in symptomatic CAA cohorts. In detailed subgroup analyses, *APOE* $\epsilon 2/\epsilon 2$ and *APOE* $\epsilon 2/\epsilon 4$ genotypes were most consistently and strongly associated with cSS presence and severity.

Conclusion

CAA-related vasculopathic changes and fragility associated with *APOE* $\epsilon 2+$ allele might have a biologically meaningful role in the pathophysiology and severity of cSS.

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Glossary

A β = β -amyloid; AD = Alzheimer disease; CAA = cerebral amyloid angiopathy; CI = confidence interval; cSS = cortical superficial siderosis; ICH = intracerebral hemorrhage; OR = odds ratio; SWI = susceptibility-weighted imaging; T2*-GRE = T2*-weighted gradient-recalled echo.

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 imaging (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 β -amyloid (A β) deposition in cortical and leptomeningeal arterioles. In patients with CAA, cSS seems to be consistently associated with increased risk of incident⁵ and recurrent⁶ 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 neuropathologic studies remain extremely limited. Understanding the underlying mechanisms and vascular pathology contributing to cSS could be facilitated by identifying associations with *APOE* alleles. Associations between *APOE* ϵ 2 or ϵ 4 alleles with both lobar ICH risk and CAA presence and severity on neuropathology have been previously described. In fact, *APOE* genotype seems 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* ϵ 4 enhances vascular A β deposition in a dose-dependent fashion,¹² while *APOE* ϵ 2 promotes so-called CAA-related vasculopathic changes (vessel cracking, detachment and delamination of the outermost layer of the tunica media, and fibrinoid necrosis) that can lead to vessel rupture.¹³ It is hypothesized that cSS results from bleeding-prone leptomeningeal or superficial cortical arterioles that harbor 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* ϵ 2, 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 analyzing data) designed in-house and finalized in January 2016. This report was prepared with reference to Preferred Reporting Items for Systematic Reviews and Meta-Analyses,¹⁴ Meta-analysis of Observational Studies in Epidemiology¹⁵ 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 2 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 3 distinct settings: (1) patients presenting to stroke clinics with symptomatic sporadic CAA (i.e., lobar ICH, transient focal neurological episodes) according to the validated classic Boston criteria (i.e., cSS was not part of CAA diagnosis); (2) memory clinic patients; and (3) 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 (1 and 2) and are of potential clinical significance. Second, they capture the spectrum of cardinal CAA phenotypes: relatively “pure” stroke presentations (including lobar ICH), 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 2 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 (1) symptomatic CAA; (2) memory clinics; or (3) population-based. For each included study, we extracted information using standard pro formas 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., $\epsilon 3\epsilon 3$, $\epsilon 2\epsilon 3$, $\epsilon 3\epsilon 4$, $\epsilon 4\epsilon 4$, $\epsilon 2\epsilon 2$, $\epsilon 2\epsilon 4$) 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 publications 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 Strengthening the Reporting of Genetic Association Studies (STREGA),¹⁶ Meta-analysis of Observational Studies in Epidemiology (MOOSE)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, College Station, TX) 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 odds ratios (ORs) for cSS presence vs absence among $\epsilon 4$ allele carriers ($\epsilon 4+$) vs the reference genotype $\epsilon 3\epsilon 3$ and among $\epsilon 2$ carriers ($\epsilon 2+$) vs the wild type $\epsilon 3\epsilon 3$. This comparison was selected to avoid potential confounding by mixed effects of $\epsilon 2$ and $\epsilon 4$ in the comparison group. In secondary analyses, we compared cSS severity (focal vs no cSS and disseminated vs no cSS) in participants with an $\epsilon 2+$ or $\epsilon 4+$ genotype vs the $\epsilon 3/\epsilon 3$ 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 ORs and their corresponding 95% confidence intervals (CIs), with the inverse variance method for weighting. We assessed statistical heterogeneity using I^2 statistics and visually through inspection of the forest plot. Values of $\leq 25\%$, 25%–50%, and $\geq 50\%$ 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., $\epsilon 2\epsilon 3$, $\epsilon 3\epsilon 4$, $\epsilon 4\epsilon 4$, $\epsilon 2\epsilon 2$, $\epsilon 2\epsilon 4$ vs $\epsilon 3\epsilon 3$) 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 article. No data are 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 7 memory clinic cohorts (*n* = 2,587), 5 symptomatic nonoverlapping CAA cohorts (*n* = 402), and 1 population-based study including healthy people (*n* = 1,379) (table 1). The memory clinic studies had different inclusion

Figure 1 Flow chart of study identification and selection

cSS = cortical superficial siderosis.

Table 1 Basic characteristics and methodologic aspects of included studies

Study	Country (period)	Setting/participants source	Study size ^a	Mean age	Male, %	Dementia, %	MRI sequence	Field strength	ET, ms	ST, mm	cSS rating
CAA cohorts											
Boulouis et al., 2017^{18,b}	USA	Probable CAA without ICH/stroke clinic	62	75	57	10	T2*-GRE	1.5T	50	5	2 Trained raters by consensus
Charidimou et al., 2016^{19,b}	USA	Clinical CAA/ICH	197	74	49	?	T2*-GRE	1.5T	50	5	1 Trained rater (k =)
Charidimou et al., 2015^{20,b}	USA	Pathologically proven CAA	53	73	45	?	T2*-GRE/SWI	1.5T	—	—	1 Trained rater
Shomanesh et al., 2014^{4,b}	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., 2015²¹	Spain	Convenience biomarkers cohort of CAA patients with and without cSAH	25	79	52	28	T2*-GRE	1.5T	—	—	Not reported
Memory clinic/nonsymptomatic CAA cohorts											
Shams et al., 2016²²	Sweden	Consecutive memory clinic series	520	63	47	35	T2*-GRE/SWI	3T	—	—	2 Trained raters by consensus
Charidimou et al., 2016^{23,b}	USA	Consecutive memory clinic series	68	73	44	43	T2*-GRE	3T	20–25.7	5	1 Trained rater
Na et al., 2015²⁴	Korea	Memory clinic patients with PET/MRI/CSF analysis	232	72	42	?	T2*-GRE	3T	—	—	2 Trained raters (k = 0.92)
Zonneveld et al., 2014²⁵	Netherlands (2010–2012)	Memory clinic–based Amsterdam Dementia Cohort	610	66	56	41	SWI	3T	—	—	1–2 Trained raters (k = 0.81)
Yates et al., 2014²⁶	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 et al., 2013²⁷	Alzheimer's Disease Neuroimaging Initiative (2010–2012)	Alzheimer's Disease Neuroimaging Initiative	451	73	55	8	T2*-GRE	3T	—	—	Trained raters
Singapore cohort	Singapore	Memory clinics in 2 centers	458	~70	51	34	SWI	3T	20	1	Trained raters

Continued

Table 1 Basic characteristics and methodologic aspects of included studies (continued)

Study	Country (period)	Setting/participants source	Study size ^a	Mean age	Male, %	Dementia, %	MRI sequence	Field strength	ET, ms	ST, mm	cSS rating
Population-based cohorts											
Pichler et al., 2017 ²⁸	USA (2011–2016)	Mayo Clinic Study of Aging	1,412	62–78	53	<9	T2*-GRE	3T	20	3.3	Trained raters

Abbreviations: CAA = cerebral amyloid angiopathy; cSAH = convexal subarachnoid hemorrhage; cSS = cortical superficial siderosis; ET = echo time; ICH = intracerebral hemorrhage; MGH = Massachusetts General Hospital; ST = slice thickness; SWI = susceptibility-weighted imaging; T2*-GRE = T2*-weighted gradient-recalled echo.

In detail: Reference 4: MGH ICH/CAA cohort since 1995—this is a research, advanced MRI CAA-ICH cohort. None of the patients are included in cohorts corresponding to references 20, 18, or 35. Around 10% of the patients might be overlapping with reference 18. Reference 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 reference 19. Reference 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 references 4, 19, or 20. Reference 19: MGH ICH cases—this is a consecutive clinical ICH cohort, from which CAA-related ICH were included in our analysis. The cohort might be overlapping by 10% with reference 4 and reference 20 cohorts. Reference 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 article.

^a Number of eligible participants genotyped and assessed for cSS.

^b Cohorts originating from a single center (MGH). We note minimal sample overlap among these included studies and cohorts originating from MGH. Most of these different cohorts are completely independent (i.e., different clinical setting/recruitment, clinical presentation, inclusion criteria, inception). However, there is a possibility of ~5%–10% (or lower) overlap among 3 of the MGH cohorts (references 4, 19, and 20). Please note that it is not possible to definitely identify potentially overlapping patients among the 2 cohorts and exclude them, due to different coding and anonymization of the patient data and samples.

criteria and dementia prevalence (table 1). The symptomatic CAA studies included 2 cohorts presenting with stroke syndromes other than ICH, 1 with pure CAA-ICH, and 2 with both CAA-ICH and CAA non-ICH presentations. Four out of these 5 CAA cohorts were derived from different studies completed at the same center,^{4,18–20} but included largely nonoverlapping patient cohorts (i.e., different clinical settings/recruitment, clinical presentation, inclusion criteria, inception). In detail (see footnote in table 1), 1 of these 4 single-center cohorts,⁴ an advanced research MRI study of CAA-related ICH, 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 cohort¹⁹ might have slightly overlapped (~10%) with a pathology-based cohort of CAA patients.²⁰ Mean age was between 63 and 75 years and about half of all participants were male. Most studies were conducted in predominantly white populations in centers from Europe, the United States, or Australia, while 2 studies were conducted in 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 1.5T 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%, I² 59%, *p* = 0.02) in memory clinic patients, 47% (95% CI 38%–56%, I² 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%, I² 48%, *p* = 0.07) and 17% (95% CI 13%–22%, I² 24%, *p* = 0.26), respectively. The overall pooled prevalence of disseminated cSS was 1% (95% CI 0%–1%, I² 9%, *p* = 0.36) vs 28% (95% CI 20%–36%, I² 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%, I² 17%, *p* = 0.30) in memory clinic patients and 37% (95% CI 26%–49%, I² 60%, *p* = 0.04) in symptomatic CAA cases (*p* < 0.001 between the 2 groups).

Table 2 Key quality indicators of pooled studies

Study reference	Study size			Design (R-0, P-1)	Blinding (MRI to genotype)	cSS criteria clearly defined	cSS interobserver agreement	T2*-GRE (0) vs SWI (1)	Genotyping reporting	Total score (0–8)
	≤100	101–200	>200							
Boulouis et al., 2017 ¹⁸	✓			0	✓	✓	✓	0	1	4
Charidimou et al., 2016 ¹⁹		✓		0	✓	✓	X	0	1	4
Charidimou et al., 2015 ²⁰	✓			0	✓	✓	X	0	1	3
Shomanesh et al., 2014 ⁴	✓			1	✓	✓	X	0	1	4
Martínez-Lizana et al., 2015 ²¹	✓			0	✓	✓	X	0	1	3
Shams et al., 2016 ²²			✓	0	✓	✓	✓	0	1	6
Charidimou et al., 2016 ²³	✓			0	✓	✓	X	0	1	3
Na et al., 2015 ²⁴			✓	1	✓	✓	✓	0	1	7
Zonneveld et al., 2014 ²⁵			✓	1	✓	✓	✓	1	1	8
Yates et al., 2014 ²⁶		✓		1	✓	✓	✓	1	1	7
Kantarci et al., 2013 ²⁷			✓	0	✓	✓	X	0	0	4
Singapore cohort			✓	1	✓	✓	X	1	1	7
Pichler et al., 2017 ²⁸			✓	1	✓	✓	X	0	1	6

Abbreviations: cSS = cortical superficial siderosis; SWI = susceptibility-weighted imaging; T2*-GRE = T2*-weighted gradient-recalled echo.

Scoring system: For each key quality indicator listed, each study got 1 point if fulfilled. For the 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 SWI (SWI-1) and 0 points if they used T2*-GRE (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).

Meta-analyses: *APOE* $\epsilon 4$ and $\epsilon 2$ and cSS presence and severity

The results of the main analyses of the association between *APOE* $\epsilon 4$ and $\epsilon 2$ with cSS presence are summarized in figure 2. Compared to participants with an *APOE* $\epsilon 3/\epsilon 3$ genotype, pooled overall results showed no increased odds of cSS presence in participants with *APOE* $\epsilon 4+$ genotype (figure 2A). When stratified by clinical subgroups, *APOE* $\epsilon 4+$ 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* $\epsilon 2+$ genotypes (OR 2.42, 95% CI 1.48–3.95) 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).

Figure 2 Forest plots: cSS presence and *APOE* $\epsilon 4+$ or *APOE* $\epsilon 2+$ vs *APOE* $\epsilon 3/\epsilon 3$

These data were not available to pool in the single population-based study that reported on *APOE* and cSS. Overall, pooled results showed that, compared to patients with an $\epsilon 3/\epsilon 3$ genotype, those with an $\epsilon 4+$ genotype did not have increased

odds of having either focal or disseminated cSS (figure 3A). Memory clinic patients showed only a nonsignificant trend for an association with *APOE* $\epsilon 4+$ genotype and cSS burden (figure 3A). Overall, patients with *APOE* $\epsilon 2+$ genotype had

Figure 3 Subanalysis summary results

(A) Subanalysis summary results of the effect of *APOE* $\epsilon 4+$ vs *APOE* $\epsilon 3/\epsilon 3$ genotype on the presence of focal and disseminated cortical superficial siderosis (cSS), according to clinical setting and overall. (B) Subanalysis summary results of the effect of *APOE* $\epsilon 2+$ vs *APOE* $\epsilon 3/\epsilon 3$ 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 odds ratios (ORs) and their 95% confidence interval (CI) for each comparison. Study-specific ORs are not shown. CAA = cerebral amyloid angiopathy.

increased odds for an association with disseminated, but not focal, cSS (figure 3B). When stratified by clinical setting, focal cSS was associated with *APOE* $\epsilon 2+$ 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* $\epsilon 2+$ 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 $\epsilon 3/\epsilon 3$) and cSS presence and burden are summarized in table 3. In the overall analysis of all the cohorts together, the most consistent associations with higher effect sizes were seen with *APOE* $\epsilon 2/\epsilon 2$ and *APOE* $\epsilon 2/\epsilon 4$ 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* $\epsilon 4/\epsilon 4$, while the stronger link was with the *APOE* $\epsilon 2/\epsilon 4$ genotype (table 3). Among symptomatic CAA cohorts, only *APOE* $\epsilon 2/\epsilon 3$ and *APOE* $\epsilon 2/\epsilon 4$ were associated with disseminated cSS (table 3). Of note, the *APOE* $\epsilon 4/\epsilon 4$ 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,²⁹ and their association with *APOE* genotype. Drawing data from >4,000 participants of relevant studies and different clinical setting, our main results indicated that cSS, especially disseminated cSS, is most strongly associated with *APOE* $\epsilon 2+$ genotype. This overall association was consistent and did not vary significantly according to clinical setting. We found that *APOE* $\epsilon 4+$ genotype was overall not associated with cSS presence or burden. However, *APOE* $\epsilon 4+$ 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* $\epsilon 2+$ genotype based on the unadjusted pooled ORs (2.10 vs 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 $\epsilon 2/\epsilon 2$ and $\epsilon 2/\epsilon 4$ genotypes.

Although it can be challenging to infer specific pathophysiologic 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, and are consistent with prior observations in the field, with what is presumed to be the effect of *APOE* $\epsilon 2$ vs $\epsilon 4$ 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* $\epsilon 4$ appears to enhance vascular A β deposition in a dose-dependent fashion,¹² while *APOE* $\epsilon 2$ 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* $\epsilon 4+$ allele (OR 1.35, 95% CI 1.10–1.66, $p = 0.005$), but not *APOE* $\epsilon 2$.³⁰ This result was consistent for any cerebral microbleeds presence in a more recent comprehensive meta-analysis.³¹ The dissociation of the relationship between *APOE* genotype and cerebral microbleeds vs cSS has implications for discerning potential mechanisms. *APOE* $\epsilon 4$ might predispose to the particular kind of CAA-related vessel thickening postulated to lead to microscopic intraparenchymal hemorrhage (e.g., strictly lobar cerebral microbleeds).³² In contrast, *APOE* $\epsilon 2$ 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 neuropathologic study used a detailed grading system for assessing CAA in parenchymal and leptomeningeal vessels separately.³³ In a sample of Alzheimer disease (AD) and elderly control brains without dementia, *APOE* $\epsilon 2$ was a much stronger risk factor for CAA development, especially in leptomeningeal vessels, compared to *APOE* $\epsilon 4$ (OR 10.93, 95% CI 4.33–27.57 vs 1.69, 0.92–3.10, respectively).³³ 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 cerebral microbleed MRI patterns.^{4,30}

These inferences would also be in line with several clinical observations in the field. *APOE* $\epsilon 2$ is already known to be associated with CAA-related ICH, perhaps causally,³⁴ also predisposing to larger volumes of CAA-related bleeding.³⁵ cSS is independently associated with future ICH risk in CAA, both recurrent^{6,36} and first lobar ICH.⁵ In fact, clinical cohorts that 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.^{5,6,36} Also, there is preliminary evidence that *APOE* $\epsilon 4$ may be associated with CAA type 1 (where CAA is found in cortical capillaries) and *APOE* $\epsilon 2$ with CAA type 2 (where cerebrovascular amyloid is primarily deposited in leptomeningeal and cortical vessels sparing cortical capillaries).³⁷ A recent neuropathologic study that validated a detailed CAA grading system showed that all individuals with the *APOE* $\epsilon 2/\epsilon 2$ genotype had CAA type 2, while the *APOE* $\epsilon 4/\epsilon 4$ genotype was associated with CAA type 1 (OR 8.0, 95% CI 2.8–23.3).³³ Finally, though the exact pathophysiologic

Table 3 Detailed meta-analysis results for the association between different *APOE* genotypes (vs $\epsilon 3/\epsilon 3$) and cSS presence and burden

	<i>APOE</i> genotype				
	$\epsilon 4/\epsilon 3$	$\epsilon 4/\epsilon 4$	$\epsilon 2/\epsilon 3$	$\epsilon 2/\epsilon 2$	$\epsilon 2/\epsilon 4$
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					
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					

Continued

Table 3 Detailed meta-analysis results for the association between different APOE genotypes (vs ε3/ε3) and cSS presence and burden (continued)

	APOE genotype			
	ε4/ε3	ε4/ε4	ε2/ε3	ε2/ε4
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	2.13 (0.30–15.24); p = 0.451
Heterogeneity	46.5%; p = 0.113	0%; p = 0.759	32.6%; p = 0.204	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	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 = 0.460

Abbreviations: CAA = cerebral amyloid angiopathy; CI = confidence interval; cSS = cortical superficial siderosis; OR = odds ratio. For the analyses including focal cSS and disseminated cSS, the comparison groups included only patients without cSS. Heterogeneity (I², p value).

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.^{6,38} APOE ε2-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 2 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 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 ε4. We note the higher frequency of APOE ε4 in patients from memory clinics, at least in part, due to the relationship between this genotype and its well-known predisposition to AD (instead, APOE ε2 variant confers reduced risk for AD and thus has lower frequency in memory clinics).³⁹ Similar to AD, as noted above, histopathologic studies in CAA indicate that APOE ε4 has an equivalent role in CAA by promoting vascular Aβ deposition; APOE ε2, however, has a different effect—it increases vessel wall damage caused by cerebrovascular amyloid deposition. In other words, the hypothesis is that APOE ε4 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 does not increase the likelihood of cSS—in this group, APOE ε2 comes into play (especially in a dose-dependent and synergistic fashion with APOE ε4 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 ε4 and ε2 in AD 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) and rarity of certain alleles and genotypes resulted in wide 95% CIs. 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 mild CAA, often a common “innocent bystander” in this setting)—the known risk factor of originally developing cerebrovascular A β accumulation is *APOE* ϵ 4 and ϵ 2. Symptomatic CAA cohorts are by definition enriched with cerebrovascular A β pathology and hence *APOE*–cSS associations are driven/indicating more specific (or predominant) pathophysiologic mechanisms at play, especially within the most severe cases of cSS (i.e., disseminated cSS). It is possible that the *APOE* ϵ 2/ ϵ 4 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 A β pathology, it is not surprising that only this double hit genotype of *APOE* ϵ 2/*APOE* ϵ 4 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 measures for cSS detection were variable. Patients from symptomatic CAA cohorts underwent brain MRI at 1.5T, other cohorts at 3T. While the consisted MRI field strength within clinical setting subgroups 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 measures 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 are 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 difficult to address. It should be emphasized 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 recognize the known relative rarity of *APOE* ϵ 2 genotypes and the confounding effect of the presence of dementia and Alzheimer type pathology. While CAA and AD are linked in the context of cognitive impairment populations, their precise relationship remains poorly understood.⁴⁰ This and other considerations could partly explain the weak association observed

between cSS presence and *APOE* ϵ 4 in the memory clinic cohorts. For example, both CAA and neurodegenerative pathology contribute to cognitive impairment in the elderly⁴¹ and *APOE* ϵ 4 is a well-known risk factor for both cerebrovascular and parenchymal amyloid accumulation. Nevertheless, reassuringly, the association with *APOE* ϵ 2 and cSS was consistently detected in memory clinic patients and with stronger effect size than the *APOE* ϵ 4 association. Finally, 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 center. 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, and inception points, this overlap is minimal and ranges between 5% and 10%, as summarized in the 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.⁴² In particular, further studies on the proposed differential effects of ϵ 4 and ϵ 2 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* ϵ 2 as evidenced by the fact that a number of cSS cases are also found within the *APOE* ϵ 3/ ϵ 3 genotype.

Notwithstanding these caveats, our results provide useful data to partly settle the question in favor of a link between *APOE* ϵ 2+ genotype and cSS in CAA. The pathophysiologic implication is that *APOE* ϵ 2 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,^{1,9} and collaborative data pooling efforts. Based on the totality of current evidence,

our study suggests a biologically meaningful association between the *APOE* $\epsilon 2+$ genotype and severe cSS in patients with CAA, probably as a result of the role of $\epsilon 2$ in the severity of vasculopathy in CAA-affected leptomeningeal and very superficial cortical vessels. The exact pathophysiologic mechanisms that underlie these associations should be investigated, as they might define targets for therapeutic interventions in CAA.

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Kejal Kantarci, MD	Mayo Clinic, Rochester, MN	Author	Major role in the acquisition of data, revised the manuscript for intellectual content
Ashkan Shoamanesh, MD	McMaster University, Hamilton, Canada	Author	Major role in the acquisition of data, revised the manuscript for intellectual content
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Appendix (continued)

Name	Location	Role	Contribution
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Appendix (continued)

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