APOE genotype and MRI markers of cerebrovascular disease

Systematic review and meta-analysis

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ABSTRACT

Objective: We aimed to examine the association of *APOE* ϵ genotype with MRI markers of cerebrovascular disease (CVD): white matter hyperintensities, brain infarcts, and cerebral microbleeds.

Methods: We performed a systematic review and meta-analysis of 42 cross-sectional or longitudinal studies identified in PubMed from 1966 to June 2012 ($n = 29,965$). This included unpublished data from 3 population-based studies: 3C-Dijon, Framingham Heart Study, and Sydney Memory and Ageing Study. When necessary, authors were contacted to provide effect estimates for the meta-analysis.

Results: *APOE* $\epsilon 4$ carrier status and *APOE* $\epsilon 4\epsilon 4$ genotype were associated with increasing white matter hyperintensity burden (sample size-weighted z score meta-analysis [meta]- $p = 0.0034$ and 0.0030) and presence of cerebral microbleeds (meta odds ratio [OR] = 1.24 , 95% confidence interval [CI] [1.07 , 1.43], $p = 0.004$, and 1.87 [1.26 , 2.78], $p = 0.002$), especially lobar. *APOE* $\epsilon 2$ carrier status was associated with increasing white matter hyperintensity load (z score meta- $p = 0.00053$) and risk of brain infarct (meta OR = 1.41 [1.09 , 1.81], $p = 0.008$).

Conclusions: *APOE* $\epsilon 4$ and *APOE* $\epsilon 2$ were associated with increasing burden in MRI markers for both hemorrhagic and ischemic CVD. While the association of *APOE* $\epsilon 4$ with an increased burden of CVD could be partly contributing to the relationship between *APOE* $\epsilon 4$ and AD, *APOE* $\epsilon 2$ was associated with MRI markers of CVD in the opposite direction compared to AD. *Neurology*® 2013;81:292–300

GLOSSARY

AB = amyloid β ; **AD** = Alzheimer disease; **BI** = brain infarcts; **CAA** = cerebral amyloid angiopathy; **CMB** = cerebral microbleeds; **CVD** = cerebrovascular disease; **DWMH** = deep white matter hyperintensities; **FHS** = Framingham Heart Study; **ICH** = intracerebral hemorrhage; **OR** = odds ratio; **PVH** = periventricular white matter hyperintensities; **Sydney-MAS** = Sydney Memory and Ageing Study; **WMH** = white matter hyperintensities.

The $\epsilon 4$ allele of the *APOE* gene is a major risk factor for dementia and Alzheimer disease (AD).^{1–6} The association of *APOE* with cerebrovascular disease (CVD) is more controversial.⁷ *APOE* $\epsilon 4$ is a risk factor for cerebral amyloid angiopathy (CAA), a major determinant of intracerebral hemorrhage (ICH) in older individuals.¹ Recent data from the International Stroke Genetics Consortium suggest an association of *APOE* $\epsilon 4$ with an increased risk of ICH, mostly lobar,⁸ and an association of the *APOE* $\epsilon 2$ allele with an increased risk and size of lobar ICH.^{8,9} Whether the epsilon polymorphism is also associated with an increased risk of ischemic stroke and MRI markers of CVD is unclear.⁷ MRI markers of CVD—white matter hyperintensities (WMH), brain infarcts (BI), and cerebral microbleeds (CMB)—are powerful predictors of stroke and dementia.^{10–13} They are highly prevalent in older community-dwelling persons,^{14–16} and can be assessed noninvasively and quantitatively in large population-based samples. Dissecting the relationship between *APOE* and MRI

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markers of CVD could provide important clues to the mechanisms underlying the association between *APOE* and risk of dementia. Indeed, although *APOE* is involved in modulating the metabolism and accumulation of amyloid β ($A\beta$), the precise mechanisms underlying its relationship with the risk of dementia are not fully understood.¹ Whether the latter is also partly mediated by CVD, a powerful determinant of dementia risk, could be important for optimizing prevention strategies.

Our aim is to provide a systematic review and meta-analysis of studies evaluating the relationship of *APOE* ϵ genotype with MRI markers of CVD.

METHODS **Search strategy and selection criteria.** A research fellow and a neurologist identified references through searches of PubMed from 1966 to June 14, 2012, using predefined search terms. We also identified articles by reviewing reference lists of relevant articles and through searches of the authors' files. In addition, some studies (3C-Dijon,¹⁷ Framingham Heart Study [FHS],^{18,19} Sydney Memory and Ageing Study [Sydney-MAS]²⁰) provided unpublished data for this review (methods e-1 on the *Neurology*[®] Web site at www.neurology.org).

We included studies testing the association of *APOE* genotype with at least one of the 3 MRI markers of CVD (WMH, BI, CMB), limited to those in adults.

The following were exclusion criteria: 1) evaluation of markers of CVD by CT scan only; 2) sample size <50 individuals; 3) studies evaluating separately the effect of each single nucleotide polymorphism comprising the *APOE* $\epsilon 4$ allele (methods e-1).

Data extraction. We extracted the following data from the studies: sample size, study population (general population vs high-risk individuals), mean age, MRI characteristics and sequences, definition of the markers of CVD, measure of the association between *APOE* genotype and MRI markers, *APOE* genotypes used as reference, and adjustment variables when applicable. For measures of association between *APOE* genotype and MRI markers, we recorded odds ratios (ORs) for dichotomous MRI markers and standardized mean differences (measuring the difference in units of SD) or regression coefficients for continuous MRI markers; when none was available, raw numbers or mean values and SD by genotype group were used to compute OR or standardized mean differences, respectively. When none could be extracted, authors were contacted to provide those. If measures of association remained unavailable thereafter, qualitative results were reported. Two authors (S.D., S. Schilling) extracted the above information from each study, resolving any disagreement by discussion.

Variable definition. The study population was defined as "general population" when the analysis was performed in a community-based setting or on participants described as "healthy individuals," and as "high-risk population" when the study was conducted on persons selected for the presence of prevalent diseases such as cognitive impairment, stroke, depression, dementia, hypertension, or leukoaraiosis (or in populations enriched by design in persons with such prevalent disease). We excluded studies on white matter lesions occurring in inflammatory or neurodegenerative conditions and studies on WMH in monogenic cerebrovascular diseases (methods e-2).

In cross-sectional studies, WMH burden was studied as a dichotomized variable (presence vs absence or extensive vs low WMH burden), or as a continuous variable (grade from a semiquantitative visual scale or quantitatively measured volume). When computing ORs from raw numbers for WMH grades, we used the most severe grade vs all others. Some studies distinguished periventricular WMH (PVH) and deep WMH (DWMH). Whenever possible, we used results for global WMH, but when only PVH and DWMH were available, we used PVH in our primary meta-analysis and ran a secondary analysis using DWMH instead of PVH (methods e-2). In longitudinal studies, change in WMH grade or volume was retrieved. BI (or CMB) were defined by the presence of one or more BI (or CMB) vs none. Some studies distinguished CMB according to their location (lobar vs deep or infratentorial). In longitudinal studies, presence of incident CMB was evaluated.

Table e-1 details study quality criteria, including sample size, whether reference group and adjustment variables were specified, whether allele frequencies were reported for *APOE* $\epsilon 4$ and *APOE* $\epsilon 2$, type of WMH quantification, WMH measure used for analysis, and whether methods for differentiating BI from dilated perivascular spaces were specified.

Statistical analyses. Meta-analysis was performed when at least 3 studies were available for the same outcome. Associations of WMH, BI, and CMB with the following genotype groups were summarized: *APOE* $\epsilon 4$ carriers ($\epsilon 4+$), homozygous *APOE* $\epsilon 4$ carriers ($\epsilon 44$), and *APOE* $\epsilon 2$ carriers ($\epsilon 2+$) (methods e-3). The reference group was *APOE* $\epsilon 4$ noncarriers (*APOE* $\epsilon 4-$) and *APOE* $\epsilon 2$ noncarriers (*APOE* $\epsilon 2-$) in most studies (some excluded *APOE* $\epsilon 24$ carriers), and *APOE* $\epsilon 33$ in the others. When several adjustment models were used, we included the least adjusted one. For quantitative measures of WMH burden, we used models accounting for total intracranial volume whenever available. We also ran secondary analyses using the most adjusted data. When both continuous and dichotomous measurements of WMH burden were available, we used the continuous data.

For BI and CMB, we calculated pooled ORs using an inverse variance-weighted meta-analysis. A fixed-effects meta-analysis was used in the absence of heterogeneity and a random-effects model if heterogeneity between studies was significant (heterogeneity p value <0.05 or I^2 >50%). For WMH burden, we combined results from all studies using a sample size-weighted z score-based meta-analysis. This approach accounts for the fact that WMH burden was measured on different scales and analyzed either quantitatively or qualitatively across studies (methods e-3). We also calculated pooled ORs or standardized mean differences separately for studies using dichotomous or continuous measures of WMH burden, using an inverse variance-weighted meta-analysis. In secondary analyses, we ran a sample size-weighted z score-based meta-analysis for associations with continuous measures of WMH burden, as studies used different quantitative or semiquantitative measurements, and performed separate meta-analyses in the general population and in high-risk populations.

We applied a Bonferroni correction for multiple testing, accounting for the 3 tested phenotypes (WMH, BI, and CMB), yielding a significance threshold of $p < 0.0166$, although this may be conservative given the strong correlation between WMH, BI, and CMB.^{12,21,22}

Meta-analysis was performed using the Cochrane RevMan (version 5.1) software (<http://www.cc-ims.net/RevMan/current.htm>) for inverse variance-weighted meta-analyses and R (<http://cran.r-project.org>) for sample size-weighted z score-based meta-analyses. Graphs were obtained using the *rmeta* package in R (<http://cran.r-project.org/web/packages/rmeta/index.html>).

RESULTS The initial literature search identified 237 articles, of which 44 met the inclusion criteria. We

excluded 5 articles because they overlapped with another larger study and added unpublished data from 3 studies (3C-Dijon, FHS, and Sydney-MAS). Hence, the total number of articles included in this systematic review was 42, comprising 29,965 subjects.

APOE ε4 and MRI markers of CVD. APOE ε4 and WMH. APOE ε4+ and WMH. When combining the 27 available studies (n = 18,309, 14,491 in the general population and 3,818 in high-risk populations, tables e-2 and e-3)^{2,3,5,11,13,21,23–41} (FHS, Sydney-MAS, unpublished data) in a sample size–weighted *z* score–based meta-analysis, APOE ε4+ was significantly associated with increasing WMH burden: $p_{z \text{ score}} = 0.0034$.

A meta-analysis restricted to studies using continuous WMH burden and providing standardized mean differences (n = 8,917, 8,405 in the general population and 512 in high-risk populations)^{2,3,11,24,26,30,33,35,36,38,39} (Sydney-MAS, unpublished data) yielded a borderline nominal association of APOE ε4+ with increasing WMH burden: pooled standardized mean difference = 0.047 (95% confidence interval 0.0006, 0.094) ($p = 0.05$) ($p_{z \text{ score}} = 0.0631$) (figure 1A). When adding studies using continuous WMH but providing regression coefficients (n = 4,004)^{5,40,41} (FHS, unpublished data), in a sample size–weighted *z* score–based meta-analysis, the association was $p_{z \text{ score}} = 0.0028$.

Analyzing studies using dichotomized WMH burden assessment (n = 5,282, 3,627 in the general population and 1,655 in high-risk populations)^{21,23,25,27–29,31,32,34,37} revealed no significant association of APOE ε4+ with large WMH burden: pooled OR = 1.07 (0.93, 1.22) ($p = 0.34$) ($p_{z \text{ score}} = 0.39$) (figure 1A). Results were similar after adding one study using a 3-class variable for WMH with ordinal logistic regression (n = 106, $p_{z \text{ score}} = 0.44$).¹³

Four small studies (n = 420 in high-risk populations) could not be included in this meta-analysis^{e21,e22,e25,e28}; one found a significant association between APOE ε4+ and WMH.^{e22}

APOE ε4+ and WMH progression. Two studies (n = 2,304 in the general population) did not report any significant association between APOE ε4+ and WMH progression (table e-4).^{e32,e33}

APOE ε44 and WMH. When meta-analyzing 12 studies (n = 7,494, 6,254 in the general population, 1,240 in high-risk populations, tables e-2 and e-3)^{3,11,13,21,28,30,31,37–39} (Sydney-MAS, FHS, unpublished data) in a sample size–weighted meta-analysis, APOE ε44 was significantly associated with increasing WMH burden: $p_{z \text{ score}} = 0.0030$.

Combining studies using continuous WMH and providing standardized mean differences (n = 2,447, 2,119 in the general population, 328 in high-risk populations)^{3,11,30,38,39} (Sydney-MAS, unpublished data) yielded a significant association between APOE ε44

and increasing WMH burden: pooled standardized mean difference = 0.41 (0.17, 0.65) ($p = 0.0009$) ($p_{z \text{ score}} = 0.0016$) (figure 1B). When adding one study providing regression coefficients (n = 1,574) (FHS, unpublished data), the association was still nominally significant: $p_{z \text{ score}} = 0.032$.

Studies examining WMH as a dichotomous variable (n = 3,399, 2,487 in the general population, 912 in high-risk populations)^{21,28,31,37} showed a nominally significant association of APOE ε44 with increasing WMH burden: pooled OR = 1.63 (1.004, 2.64) ($p = 0.048$) ($p_{z \text{ score}} = 0.046$) (figure 1B). Adding one study using a 3-class WMH variable with ordinal logistic regression (n = 74) did not modify this association ($p_{z \text{ score}} = 0.039$).¹³

One study (n = 56 in high-risk populations) could not be included in this meta-analysis and reported a significant association between APOE ε44 and increasing WMH.^{e22}

APOE ε44 and WMH progression. One longitudinal study from the general population reported a significant association of APOE ε44 with worsening WMH burden (table e-4).³

APOE ε4 and BI. APOE ε4+ and BI. In a meta-analysis including 7 studies (n = 8,223, 8,005 in the general population, 218 in high-risk populations)^{4,11,24,34,37} (3C-Dijon, FHS, unpublished data), APOE ε4+ was not associated with BI: pooled OR = 1.03 (0.90, 1.18) ($p = 0.67$) (figure e-1, table e-5). One study (n = 82 in high-risk populations) could not be included in this meta-analysis and did not report any association between APOE ε4+ and BI.³²

APOE ε44 and BI. APOE ε44 was not associated with BI in a meta-analysis including 4 studies (n = 6,029, 5,956 in the general population, 73 in high-risk populations)^{11,37} (3C-Dijon, FHS, unpublished data): pooled OR = 0.86 (0.29, 2.52) ($p = 0.79$) (figure e-2, table e-5).

We did not identify longitudinal studies assessing the relationship between APOE genotype and incident BI.

APOE ε4 and CMB. APOE ε4+ and CMB. Meta-analyzing 9 studies (n = 6,698, 5,387 in the general population and 1,311 in high-risk populations, tables e-6 and e-7)^{11,12,21,22,34,42–44} (FHS, unpublished data) yielded a significant association of APOE ε4+ with an increased risk of CMB: pooled OR = 1.24 (1.07, 1.43) ($p = 0.004$) (figure 2A), which was significant for lobar (n = 3,689, pooled OR = 1.34 [1.09, 1.64], $p = 0.006$) but not deep CMB (n = 3,777, pooled OR = 1.15 [0.89, 1.49], $p = 0.29$).^{12,21,43,44} Of note, results were significant in the general population but not in the smaller subset of studies performed in high-risk populations, comprising participants with diverse preexisting conditions (ICH, cerebral ischemia, hypertension, AD, other neurologic disorders).

Figure 1 Meta-analysis of studies testing the association between APOE ϵ 4+ and white matter hyperintensities burden and between APOE ϵ 44 and white matter hyperintensities burden

(A) Meta-analysis of studies testing the association between APOE ϵ 4+ and white matter hyperintensities (WMH) burden: fixed-effects inverse variance-weighted meta-analysis for studies on APOE ϵ 4+ and continuous WMH (providing standardized mean differences) (heterogeneity test: $I^2 = 24\%$, $p = 0.20$) (i); secondary meta-analyses in the general population (heterogeneity test: $I^2 = 39\%$, $p = 0.11$) and in high-risk populations (heterogeneity test: $I^2 = 0\%$, $p = 0.63$) also using a fixed-effects inverse variance-weighted meta-analysis. Fixed-effects inverse variance-weighted meta-analysis for APOE ϵ 4+ and dichotomized WMH (heterogeneity test: $I^2 = 0\%$, $p = 0.65$) (ii); secondary meta-analyses in the general population (heterogeneity test: $I^2 = 0\%$, $p = 0.46$) and in high-risk populations (heterogeneity test: $I^2 = 0\%$, $p = 0.74$) also using a fixed-effects inverse variance-weighted meta-analysis. Secondary analyses using random-effects meta-analyses yielded similar results (figure e-4). Additive model: additive genetic model relating the number of copies of the ϵ 4 allele to WMH volume. (B) Meta-analysis of studies testing the association between APOE ϵ 44 and WMH burden. Fixed-effects inverse variance-weighted meta-analysis on WMH burden studied as a continuous (heterogeneity test: $I^2 = 8\%$, $p = 0.36$) (i) and as a dichotomous variable (heterogeneity test: $I^2 = 0\%$, $p = 0.93$) (ii). For secondary analyses using a random-effects model, see figure e-5. APOE ϵ 4+ = APOE ϵ 4 carrier status; FHS = Framingham Heart Study; HTN = hypertension; OR = odds ratio; p = p value from inverse variance-weighted meta-analysis; p_z score = p value from sample size-weighted z score-based meta-analysis; SMD = standardized mean deviation; Sydney MAS = Sydney Memory and Ageing Study.

Figure 2 Meta-analysis of studies testing the association between *APOE* $\epsilon 4+$ and cerebral microbleeds and between *APOE* $\epsilon 44$ and cerebral microbleeds

(A) Meta-analysis of studies testing the association between *APOE* $\epsilon 4+$ and cerebral microbleeds (CMB). Fixed-effects inverse variance-weighted meta-analysis (heterogeneity test: $I^2 = 0\%$, $p = 0.88$); secondary meta-analysis in the general population (heterogeneity test: $I^2 = 0\%$, $p = 0.45$) and in high-risk population (heterogeneity test: $I^2 = 0\%$, $p = 0.96$) also using a fixed-effects inverse variance-weighted meta-analysis. For secondary analysis using a random-effects model, see figure e-7. (B) Meta-analysis of studies testing the association between *APOE* $\epsilon 44$ and CMB. Fixed-effects inverse variance-weighted meta-analysis (heterogeneity test: $I^2 = 11\%$, $p = 0.34$). For secondary analysis using a random-effects model, see figure e-7. *APOE* $\epsilon 4+$ = *APOE* $\epsilon 4$ carrier status; FHS = Framingham Heart Study; OR = odds ratio.

***APOE* $\epsilon 44$ and CMB.** *APOE* $\epsilon 44$ was significantly associated with an increased risk of CMB in a meta-analysis combining 6 studies ($n = 5,158$, 4,798 in the general population, 360 in high-risk populations, tables e-6 and e-7)^{11,12,21,22,42} (FHS, unpublished data): pooled OR = 1.87 (1.26, 2.78) ($p = 0.002$) (figure 2B).

***APOE* $\epsilon 4$ and incident CMB.** One study ($n = 654$ in the general population)^{e41} reported a significant association of *APOE* $\epsilon 44$ but not *APOE* $\epsilon 4+$ with incident lobar CMB (table e-8). Another study ($n = 197$ in high-risk populations) did not report any association between *APOE* $\epsilon 4+$ and incident CMB (table e-8).^{e42}

***APOE* $\epsilon 2$ and MRI markers of CVD.** ***APOE* $\epsilon 2$ and WMH.** *APOE* $\epsilon 2+$ and WMH. In a sample size-weighted meta-analysis including 9 studies ($n = 6,669$, 5,282 in the general population, 1,387 in high-risk populations,

table e-9)^{21,23,31,34,35,39} (3C-Dijon, FHS, Sydney-MAS, unpublished data), *APOE* $\epsilon 2+$ was significantly associated with increasing WMH burden: $p_{z\text{ score}} = 0.00053$.

Combining studies using WMH as a continuous variable ($n = 2,708$, all general population)^{35,39} (3C-Dijon, Sydney-MAS, unpublished data) showed a non-significant trend of association between *APOE* $\epsilon 2+$ and WMH burden: pooled standardized mean difference = 0.03 (−0.01, 0.07) ($p = 0.20$) ($p_{z\text{ score}} = 0.07$) (figure 3A). This was similar when adding one study using continuous WMH but providing regression coefficients ($n = 2,353$) (FHS, unpublished data), $p_{z\text{ score}} = 0.09$. In a meta-analysis of 4 studies examining WMH as a dichotomous variable ($n = 1,608$, 221 in the general population, 1,387 in high-risk populations),^{21,23,31,34} *APOE* $\epsilon 2+$ was significantly associated with increasing WMH burden: pooled OR = 1.80 (1.35, 2.42) ($p = 0.00008$) ($p_{z\text{ score}} = 0.00011$) (figure 3A).

***APOE* $\epsilon 2$ and BI.** *APOE* $\epsilon 2+$ and BI. In a meta-analysis including 4 studies ($n = 4,446$, 4,345 in the general population, 101 in high-risk populations, table e-10)^{23,34} (3C-Dijon, FHS, unpublished data), *APOE* $\epsilon 2+$ was significantly associated with BI: pooled OR = 1.41 (1.09, 1.81) ($p = 0.008$) (figure 3B).

***APOE* $\epsilon 2$ and CMB.** *APOE* $\epsilon 2+$ and CMB. In a meta-analysis including 7 studies ($n = 5,389$, 4,508 in the general population, 881 in high-risk populations, figure e-3, table e-11)^{12,21,34,42–44} (FHS, unpublished data), *APOE* $\epsilon 2+$ was not associated with CMB (pooled OR = 1.09 [0.89, 1.32], $p = 0.41$), lobar CMB ($n = 3,003$, pooled OR = 1.19 [0.91, 1.55], $p = 0.20$), or deep CMB ($n = 3,228$, pooled OR = 1.03 [0.70, 1.52], $p = 0.87$).^{12,21,43,44}

***APOE* $\epsilon 2+$ and incident CMB.** One study^{e42} ($n = 197$ in high-risk populations) found a significant association between *APOE* $\epsilon 2+$ and incident CMB (table e-12), while another study did not ($n = 563$ in the general population)^{e41} (table e-12).

DISCUSSION In this systematic review and meta-analysis comprising 42 studies on 29,965 participants, *APOE* $\epsilon 4+$ (mostly *APOE* $\epsilon 44$) and *APOE* $\epsilon 2+$ genotypes were associated with increasing WMH load, *APOE* $\epsilon 4+$ genotype was associated with an increased prevalence of CMB, especially lobar, and *APOE* $\epsilon 2+$ genotype was associated with a higher frequency of BI.

One previous systematic review had examined the association between *APOE* $\epsilon 4$ carrier status and WMH burden, including 24 studies on 8,546 individuals, reporting no significant association.⁴⁵ An earlier qualitative review had reached a similar conclusion.⁴⁶ However, previous reviews did not examine the association of *APOE* $\epsilon 44$ or *APOE* $\epsilon 2$ with WMH.⁴⁵ Besides, since then, data from 12 additional studies on the association between *APOE* $\epsilon 4$ carrier status

Figure 3 Meta-analysis of studies testing the association between *APOE* $\epsilon 2+$ and white matter hyperintensities burden and between *APOE* $\epsilon 2+$ and brain infarcts

A(i) Association between *APOE* $\epsilon 2+$ and continuous WMH

(ii) Association between *APOE* $\epsilon 2+$ and dichotomized WMH

B Association between *APOE* $\epsilon 2+$ and BI

(A) Meta-analysis of studies testing the association between *APOE* $\epsilon 2+$ and white matter hyperintensities (WMH) burden. Fixed-effects inverse variance-weighted meta-analysis for studies on *APOE* $\epsilon 2+$ and continuous WMH (providing standardized mean differences) (heterogeneity test: $I^2 = 41\%$, $p = 0.17$) (i); all studies are from the general population. Fixed-effects inverse variance-weighted meta-analysis for *APOE* $\epsilon 2+$ and dichotomized WMH (heterogeneity test: $I^2 = 45\%$, $p = 0.14$) (ii). For secondary analysis using a random-effects model, see figure e-8. (B) Meta-analysis of studies testing the association between *APOE* $\epsilon 2+$ and brain infarcts (BI). Fixed-effects inverse variance-weighted meta-analysis (heterogeneity test: $I^2 = 25\%$, $p = 0.26$). For secondary analysis using random-effects model, see figure e-9. *APOE* $\epsilon 2+$ = *APOE* $\epsilon 2$ carrier status; FHS = Framingham Heart Study; OR = odds ratio; p = p value from inverse variance-weighted meta-analysis; p z score = p value from sample size-weighted z score-based meta-analysis; SMD = standardized mean difference; Sydney MAS = Sydney Memory and Ageing Study.

and WMH burden have become available, thus increasing power to detect associations.

Mechanisms underlying associations of *APOE* genotypes with WMH burden are unclear.⁴⁷ CAA, a condition characterized by A β accumulation in the media of cerebral and leptomeningeal arterioles⁴⁸ that is highly prevalent in aging populations,⁴⁹ is one potential mediator. Indeed, although CAA primarily affects cortical arterioles, *APOE* $\epsilon 4$ -enhanced thickening of the affected arterial wall by amyloid deposits causes reduction of the vessel lumen,^{48,50} potentially leading to reduced blood flow in distal perfusion zones of the white matter.⁵¹ Supporting this hypothesis, *APOE* $\epsilon 4$ was recently shown to be associated with occipital distribution of WMH, a location where

CAA predominates.⁵² The vasculopathic abnormalities associated with the *APOE* $\epsilon 2$ allele in CAA patients,⁵⁰ including fibrinoid necrosis and blood-brain barrier damage,⁵³ might also affect small arteries in the white matter.⁵⁴ ApoE also plays a key role in lipid metabolism, but it is unclear whether *APOE* isoforms differentially influence lipid metabolism in the brain,¹ and the relationship between lipid levels and white matter disease is not well established.²⁷ Inflammation may also contribute to the observed relation of *APOE* $\epsilon 2$ and *APOE* $\epsilon 4$ with increasing WMH burden.⁵⁵

To date, no meta-analysis has evaluated the relationship between *APOE* ϵ polymorphism and MRI-defined BI, to our knowledge. The absence of a significant association between *APOE* $\epsilon 4$ and BI is in line with the lack of robust association between *APOE* $\epsilon 4$ and ischemic stroke found in a recent meta-analysis,⁷ although we may have been underpowered for this phenotype. Interestingly, we found a significant association between *APOE* $\epsilon 2$ and BI, consistent with the association between *APOE* $\epsilon 2$ and WMH burden, especially dichotomized extensive WMH; additional studies are needed to explore this relationship further, including analyses focused on lacunar brain infarcts, a more homogeneous entity reflecting primarily small-artery disease.

A systematic review recently addressed the relationship between the *APOE* ϵ polymorphism and CMB, including a meta-analysis on 7 studies.⁵⁶ In line with our results, they found that *APOE* $\epsilon 4$ carriers had a significantly increased risk of having at least one CMB compared to *APOE* $\epsilon 33$ carriers,⁵⁶ with a stronger association for lobar CMB. They did not find a significant relationship between *APOE* $\epsilon 2$ and CMB, regardless of their location. Their review did not consider recessive models, and we included 3 additional studies in our meta-analysis.

We observed a significant association of *APOE* $\epsilon 4$ with CMB, which was even stronger for *APOE* $\epsilon 44$. The association of *APOE* $\epsilon 4$ with an increased risk of CMB, especially lobar, is consistent with recent data showing a significant relationship between *APOE* $\epsilon 4$ and lobar ICH.^{7,8} The association of *APOE* $\epsilon 4$ with intracerebral bleeding is thought to be primarily mediated by CAA,⁸ representing a major cause of ICH in older individuals.⁵⁷ Histopathologic data suggest that *APOE* $\epsilon 4$ enhances A β deposition in the vessel wall.⁵⁰ Although we did not identify any significant association of *APOE* $\epsilon 2$ with CMB, the sample size was smaller and for lobar CMB there was a trend for an association in the same direction as for *APOE* $\epsilon 4$. *APOE* $\epsilon 2$ has been associated with an increased risk of lobar ICH,⁸ and with larger hematoma volumes,⁹ possibly by increasing vessel wall damage caused by A β deposition,⁹ thus leading to increased vulnerability of vessels surrounding the hematoma.⁵⁰ Hence $\epsilon 2$ carriers

might be more predisposed to larger, symptomatic hematomas but not microhemorrhages.

This is the largest systematic review and meta-analysis on the association of the *APOE* ϵ polymorphism with several MRI markers of CVD. A substantial effort was made to obtain additional unpublished information by contacting authors. In contrast with previous reviews, we have studied concomitantly several markers of ischemic and hemorrhagic CVD. Moreover, we combined all studies on *APOE* and WMH, including studies using WMH as a continuous or dichotomous variable, by performing a sample size–weighted *z* score–based meta-analysis, thus increasing sample size and power to detect associations. In addition, we have summarized information on the effect of *APOE* ϵ 2 and *APOE* ϵ 4, whenever available.

We were limited by the fact that most studies provided effect estimates for *APOE* ϵ 4 carriers vs non-carriers only, with varying reference groups. Many studies have used *APOE* ϵ 4– and *APOE* ϵ 2– as reference groups, rather than *APOE* ϵ 3, which may have reduced our power to detect associations. Indeed, the fact that the relationship of *APOE* ϵ 4 and *APOE* ϵ 2 with MRI markers of CVD appears to be in the same direction, including *APOE* ϵ 2 carriers in the reference group for *APOE* ϵ 4 carriers, and vice versa, might have attenuated differences. Although we accounted for statistical heterogeneity by using a random-effects model when appropriate, there were differences between studies concerning MRI characteristics, definition of MRI markers, and adjustment variables. The detection of CMB is strongly correlated with magnetic strength⁵⁸ and some studies included in this meta-analysis were performed on MRI scanners <1.5 T; this may have led to an underestimation of CMB prevalence and consequently reduced power to detect associations. Populations differed in terms of age distribution and vascular risk profile, which was partly accounted for in secondary meta-analyses performed separately in the general population or in groups at high risk of cerebrovascular disease (figures 1A, 2A and B, e-3, e-4, e-6, e-7, and e-10). Of note, most individuals included in the meta-analyses were community participants, and, whenever possible, we have shown that significant associations were maintained when restricting analyses to the general population. The vast majority of studies were performed in Caucasians; given the large differences in *APOE* ϵ allele distributions worldwide,⁸ our results may not be generalizable to other ethnic groups. Finally, as in all systematic reviews and meta-analyses of published data, we cannot exclude some degree of publication bias, although we have tried to minimize it by systematically adding unpublished results from 3 large population-based samples. Confirmation of our findings could be

obtained in the future by prospective meta-analyses within large consortia using harmonized phenotypic criteria and analytical models.

APOE ϵ 4 and *APOE* ϵ 2 were associated with increasing burden in MRI markers for both hemorrhagic and ischemic CVD. WMH, CMB, and lacunar BI (the vast majority of BI) are prominent features of cerebral small-vessel disease⁵⁹ and are strongly correlated in both community and hospital-based samples.^{12,21,22} It is therefore expected that they may share some genetic determinants.⁴⁷ However, it is intriguing to note that *APOE* ϵ 2 was associated with an increased burden of MRI-based CVD, while it has a protective effect on the occurrence of AD.⁶⁰ Hence, while the association of *APOE* ϵ 4 with an increased burden of CVD could be partly contributing to the relationship between *APOE* ϵ 4 and AD, *APOE* ϵ 2 was associated with MRI markers of CVD in the opposite direction compared to AD.

Future studies evaluating simultaneously in the same dataset the association of *APOE* with MRI markers of ischemic and hemorrhagic CVD could help elucidate whether these associations are independent or reflect the strong correlation between the phenotypes. Examining neuropathologic correlates of MRI-based CVD and their association with *APOE* genotypes could also help in understanding the pathophysiologic link between *APOE* and CVD. Finally, studies focusing on the influence of age and hypertension on the relationship between *APOE* and CVD could further contribute to deciphering the complex relationship of *APOE* with vascular brain aging.^{2,26}

AUTHOR CONTRIBUTIONS

Mrs. Sabrina Schilling: acquisition of data, analysis and interpretation, statistical analysis, drafting/revising the manuscript. Dr. Anita L. DeStefano: acquisition of data, drafting/revising the manuscript. Dr. Perminder S. Sachdev: acquisition of data, drafting/revising the manuscript. Mr. Seung Hoan Choi: acquisition of data, drafting/revising the manuscript. Dr. Karen A. Mather: acquisition of data, drafting/revising the manuscript. Dr. Charles D. DeCarli: drafting/revising the manuscript. Dr. Wei Wen: acquisition of data, drafting/revising the manuscript. Dr. Peter Høgh: acquisition of data, drafting/revising the manuscript. Dr. Naftali Raz: acquisition of data, drafting/revising the manuscript. Dr. Rhoda Au: drafting/revising the manuscript. Dr. Alexa Beiser: drafting/revising the manuscript. Dr. Philip A. Wolf: drafting/revising the manuscript. Dr. José Rafael Romero: drafting/revising the manuscript. Dr. Yi-Cheng Zhu: drafting/revising the manuscript. Dr. Kathryn L. Lunetta: acquisition of data, drafting/revising the manuscript. Dr. Lindsay Farrer: drafting/revising the manuscript. Dr. Carole Dufouil: drafting/revising the manuscript. Dr. Lewis H. Kuller: acquisition of data, drafting/revising the manuscript. Dr. Bernard Mazoyer: drafting/revising the manuscript. Dr. Sudha Seshadri: acquisition of data, drafting/revising the manuscript. Dr. Christophe Tzourio: acquisition of data, drafting/revising the manuscript. Dr. Stéphanie Debette: study concept and design, analysis and interpretation, statistical analysis, study supervision or coordination, drafting/revising the manuscript.

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DISCLOSURE

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