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## PAPER

# Effects of apolipoprotein E genotype on outcome after ischaemic stroke, intracerebral haemorrhage and subarachnoid haemorrhage

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Additional data are available online at <http://www.jnnp.bmjournals.com/supplemental>

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**Background:** Rodent models of acute ischaemic stroke and head injury suggest that apolipoprotein E (APOE) genotype influences neuronal repair, regeneration and survival after brain injury. Possession of an APOE  $\epsilon 4$  allele is associated with poor outcome after head injury in clinical studies. APOE might therefore influence outcome after acute stroke in humans.

**Objective and methods:** To comprehensively search, identify, assess and carry out meta-analyses of studies reporting on the association between APOE and the combined outcome of death or dependency, or death alone, several months after ischaemic stroke, intracerebral haemorrhage (ICH) or subarachnoid haemorrhage (SAH).

**Results:** Main analyses included data from nine studies on 2262 patients (1453 with ischaemic stroke, 199 with ICH and 610 with SAH). Overall,  $\epsilon 4+$  genotypes were not significantly associated with risk of death or dependency several months after stroke. However, there was significant heterogeneity between studies, and between the three pathological types of stroke.  $\epsilon 4+$  genotypes were associated with increased death or dependency after SAH (relative risk (RR) 1.40, 95% confidence interval (CI) 1.06 to 1.84), with a trend towards a similar association with ICH (RR 1.38, 95% CI 0.99 to 1.92), but not with ischaemic stroke (RR 0.98, 95% CI 0.85 to 1.12). Results were similar for death alone.

**Conclusions:** APOE may differentially affect outcome after the three main pathological types of stroke. Further, large studies are needed to confirm or refute these findings, and to assess the possibility of an interaction between the effects of APOE and age.

In contrast with the many studies assessing the role of various candidate genes in the causation of stroke and its subtypes,<sup>1–3</sup> the role of genetic factors influencing outcome after acute stroke has been relatively little studied in humans.<sup>4–5</sup> However, studies on animal models of stroke comparing outcomes among genetically manipulated animals with those among wild-type animals suggest that this should be a promising subject, which may ultimately improve our understanding of the pathways of neuronal protection and recovery, and even lead to new therapeutic insights.<sup>4–6</sup>

The apolipoprotein E gene (APOE) is one of the most widely studied genes in vascular and neurodegenerative diseases. Its protein product is a 34-kDa glycoprotein with three common isoforms, E2, E3 and E4, encoded by the alleles  $\epsilon 2$ ,  $\epsilon 3$  and  $\epsilon 4$ , respectively, giving rise to six genotypes, the  $\epsilon 3/\epsilon 3$  genotype occurring in about 50–66% of people in most populations.<sup>7</sup> APOE has a major role in lipid redistribution, which is important for membrane maintenance and repair in the brain, and in the regulation of synaptic remodelling during or after brain injury.<sup>8–11</sup> Rodent models of head injury and ischaemic stroke suggest that APOE influences neuronal repair, regeneration and survival after brain injury.<sup>6–11</sup> In clinical studies, possession of an APOE  $\epsilon 4$  allele is associated with poor outcome after head injury.<sup>5</sup> These observations suggest that APOE might influence outcome after acute stroke in humans, but clinical studies have produced conflicting results.<sup>5</sup>

Here, we use systematic review and meta-analysis methods to assess the effect of APOE on outcome after the three main pathological types of acute stroke: ischaemic stroke, intracerebral haemorrhage (ICH) and subarachnoid haemorrhage (SAH).

## METHODS

### Study identification and selection

We sought all available published studies on the influence of APOE on outcome (death or the combination of death or dependency) after acute stroke in adult humans. We identified studies by searching Medline and Embase from 1966 to May 2005 (search strategy in box 1), the reference lists of relevant papers thus identified and recent textbooks on stroke or stroke genetics. We included only studies that analysed the main pathological stroke types separately. For studies with more than one publication describing results on overlapping groups of patients, we included only the largest of the available published datasets to avoid double counting. We requested summary data from the authors of two studies for which relevant data had been obtained but were not reported in the publications. We independently selected relevant studies, resolving disagreements by discussion.

### Data extraction

From each study selected, we extracted information on year of publication; setting and country; subjects' ethnicity; number of subjects; definition of acute stroke; whether or not recruitment was consecutive; subjects' mean age and sex distribution; method, definition and timing of outcome assessment; blinding of genotyping to outcome assessment, and of outcome assessors to genotype; and genotyping samples and methods. We extracted data on the numbers of subjects who had died or were dead or dependent at the

**Abbreviations:** APOE, apolipoprotein E gene; ICH, intracerebral haemorrhage; SAH, subarachnoid haemorrhage

**Box 1: Search strategy for Medline**

1. apolipoproteins/ or apolipoproteins e/
2. ((apolipoprotein\$ adj e) or (apoprotein\$ adj e) or apo-e or apo e or apoe).tw.
3. ((apolipoprotein\$ adj e2) or (apoprotein\$ adj e2) or apo-e2 or apo e2 or apoe2).tw.
4. ((apolipoprotein\$ adj e3) or (apoprotein\$ adj e3) or apo-e3 or apo e3 or apoe3).tw.
5. ((apolipoprotein\$ adj e4) or (apoprotein\$ adj e4) or apo-e4 or apo e4 or apoe4).tw.
6. ((apolipoprotein\$ adj e5) or (apoprotein\$ adj e5) or apo-e5 or apo e5 or apoe5).tw.
7. ((apolipoprotein\$ adj e7) or (apoprotein\$ adj e7) or apo-e7 or apo e7 or apoe7).tw.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp cerebrovascular disorders/ or exp basal ganglia cerebrovascular disease/ or exp brain ischemia/ or exp carotid artery diseases/ or exp cerebrovascular accident/ or exp hypoxia-ischemia, brain/ or exp intracranial arterial diseases/ or exp "intracranial embolism and thrombosis"/ or exp intracranial hemorrhages/ or vasospasm, intracranial/
10. (stroke\$ or apoplexy or cerebral vasc\$ or cerebrovasc\$ or cva\$).tw.
11. 9 or 10
12. 8 and 11
13. limit 12 to human

A similar strategy was designed for Embase.

end of follow-up with genotypes containing or not containing the  $\epsilon 4$  allele ( $\epsilon 4+$  genotypes), and with or without the  $\epsilon 2+$  genotype. We independently extracted the information from each study, resolving disagreements by discussion.

**Statistical analyses**

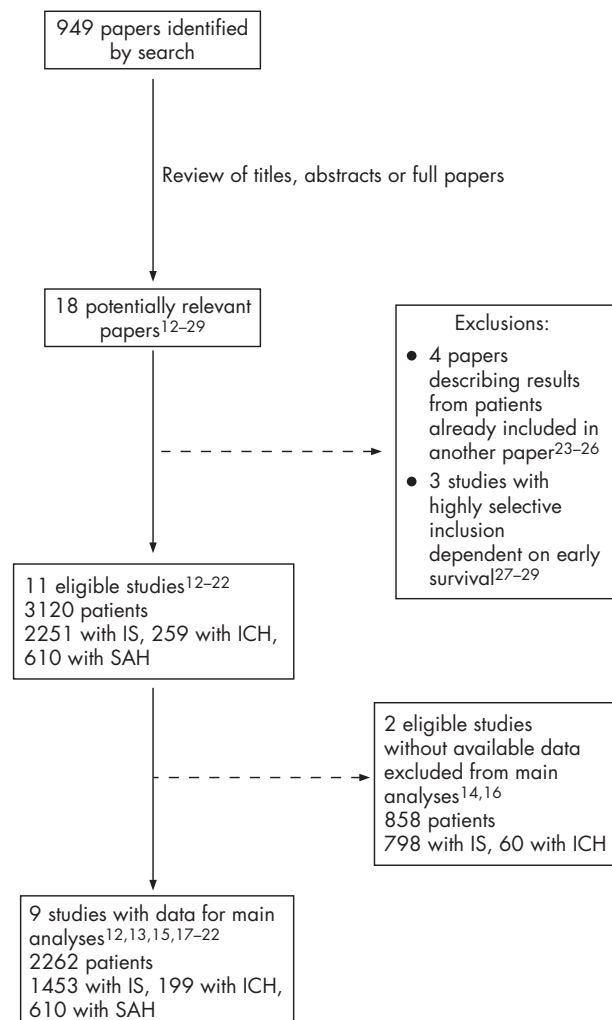
We assessed the effects of  $\epsilon 4+$  versus  $\epsilon 4-$  genotypes (primary analysis) and those of  $\epsilon 2+$  versus  $\epsilon 2-$  genotypes (secondary analysis) on death and death or dependency by calculating study-specific and fixed effects pooled relative risks (RRs) using Cochrane RevMan software (V.4.2; <http://www.cc-ims.net/RevMan>). We used the  $\chi^2$  test to assess heterogeneity between studies and different pathological types of stroke.

As data from two eligible studies were unavailable and so excluded from our main analyses (see below), we carried out sensitivity analyses for the  $\epsilon 4+$  versus  $\epsilon 4-$  comparison to assess what effect a range of plausible results for these studies might have had on our conclusions (additional data are available online at <http://www.jnnp.bmjournals.com/supplemental>).

**RESULTS****Characteristics of included studies**

The 949 articles identified by our search yielded 18 potentially relevant papers,<sup>12–29</sup> from which we selected 11 eligible studies on 3120 subjects.<sup>12–22</sup> We had to exclude two of these from our main analyses, as outcome data that had been collected were unavailable in the publications, and the authors could not provide us with unpublished summary data.<sup>14,16</sup> Thus, we included nine studies on 2262 subjects in our main analyses (fig 1). Table 1 summarises the details.

The studies were mainly conducted in European countries on white people, but one in the USA was conducted on



**Figure 1** Selection of studies for inclusion.

Caucasians and African Americans,<sup>17</sup> and two were on Chinese patients.<sup>18–21</sup> All were hospital based. Six studies recruited consecutively admitted patients,<sup>13–14,18–20,22</sup> one recruited patients from a randomised trial of thrombolysis for acute ischaemic stroke (ie, highly selected patients),<sup>15</sup> two stated that the patients were “unselected”,<sup>12,16</sup> and two did not state whether recruitment was consecutive or in some way selective.<sup>17,21</sup>

Genotype and outcome data were available for 1898 of the 2262 (84%) subjects from the nine studies in our main analyses. All had data on  $\epsilon 4+$  genotypes, whereas only five had data on  $\epsilon 2+$  genotypes.<sup>13,15,17,21,22</sup> One study included both IS and ICH patients.<sup>12</sup> Mean age was 69 years in the IS patients, 68 years in the ICH patients, and 51 years in the SAH patients. Around half of the patients were male.

Eight of the nine studies in the main analyses provided data on the combined outcome of death or dependency, defined on the basis of the Glasgow Outcome Scale in the five studies on SAH,<sup>18–22</sup> discharge to an institution in one study,<sup>12</sup> the modified Rankin Scale and the Barthel index in one study,<sup>13</sup> and the modified Rankin Scale, Barthel index, Glasgow Outcome Scale and National Institutes of Health Stroke Scale in another.<sup>15</sup> We used the modified Rankin Scale data for our analyses for these last two studies. Only four of the nine studies in the main analyses presented data separately on death.<sup>13,14,17,19</sup> Outcomes were assessed at 3 months in five studies,<sup>12,13,15,21,22</sup> at 6 months in three

**Table 1** Characteristics of studies included

First author, year of publication	Setting, country	Ethnicity	Consecutive recruitment	Stroke definition	Follow-up method	Number of subjects (number with APOE and outcome data)	Men (%)	Mean age (years)	Time of outcome assessment	Outcomes with data available
<b>Studies on ischaemic stroke</b>										
McCarron, <sup>12</sup> 1998	University Hospital Stroke Unit, Scotland	Caucasian	Patients unselected	Acute IS proved on CT or MR brain scan	Scottish death register and database of hospital discharge records	640 (616)	47	71	3 months	Poor outcome (dead or living in an institution)
McCarron, <sup>13</sup> 2000	University Hospital Stroke Unit, Scotland	Caucasian	Y	Acute IS proved on CT or MR brain scan	Patients observed prospectively (further details not given)	189 (157)	47	69	3 months	Poor outcome (mRS 4–6); death
Catto, <sup>14</sup> 2000*	University Hospital, UK	Caucasian	Y	Acute IS proved on CT brain scan	UK national death register	60 (60)	50†	73†	Median 2.4 years	Death
Broderick, <sup>15</sup> 2001	Hospitals in the USA participating in trial of tPA versus placebo, USA	Caucasian	N	Acute IS proved on CT brain scan	Examination	624 (409)	61	67	3 months	Unfavourable outcome (mRS 2–6)
MacLeod, <sup>16</sup> 2001*	University Hospital Stroke Unit, UK	Caucasian	Patients unselected	Acute IS proved on CT brain scan	Patients observed prospectively (further details not given)	266 (266)	56	65.7	?	Unfavourable outcome (mRS 3–6)
<b>Studies on intracerebral haemorrhage</b>										
McCarron, <sup>12</sup> 1998	University Hospital Stroke Unit, Scotland	Caucasian	Patients unselected	ICH proved on CT or MR brain scan	Scottish death register and database of hospital discharge records	74 (67)	45	74	3 months	Poor outcome (dead or living in an institution)
McCarron, <sup>17</sup> 1999	University Hospital, USA	Mixed: 73% Caucasian, 27% African American	?	CT-proved diagnosis of ICH considered secondary to hypertension, cerebral amyloid angiopathy or thrombolysis	?	125 (102)	52	64	Hospital discharge	Death
Catto, <sup>14</sup> 2000*	University Hospital, UK	Caucasian	Y	ICH proved on CT brain scan	UK national death register	532 (532)	?	?	Median 2.4 years	Death
<b>Studies on subarachnoid haemorrhage</b>										
Leung, <sup>18</sup> 2002	University Hospital, China	Chinese	Y	Spontaneous aneurysmal SAH confirmed by CT or lumbar puncture and CT angiography +/- digital subtraction angiography	Face-to-face or telephone interviews with patient or carers	72 (72)	35	58	6 months	Unfavourable outcome (GOS 1–3)
Niskakangas, <sup>19</sup> 2001	University Hospital Neurosurgery Department, Finland	Caucasian	Y	Spontaneous aneurysmal SAH confirmed by CT and catheter angiography	Examination, telephone interview or postal questionnaire	126 (108)	40	52	6 months	Unfavourable outcome (GOS 1–3); death
Dunn, <sup>20</sup> 2001	University Hospital Neurosurgery Department, Scotland	Caucasian	Y	Spontaneous SAH confirmed by CT scan or lumbar puncture	Telephone interview	125 (96)	40	49	6 months	Unfavourable outcome (GOS 1–3)

Table 1 Continued

First author, year of publication	Setting, country	Ethnicity	Consecutive recruitment	Stroke definition	Follow-up method	Number of subjects (number with APOE and outcome data)	Men (%)	Mean age (years)	Time of outcome assessment	Outcomes with data available
Tang, <sup>21</sup> 2003	Hospital Neurosurgery Department, China	Chinese	?	Aneurysmal SAH confirmed by CT brain scan and digital subtraction angiography with or without surgery	Examination or telephone interview	120 (104)	48	45	3 months	Unfavourable outcome (GOS 1–3)
Ruigrok, <sup>22</sup> 2005	University Hospital, The Netherlands	Caucasian	Y	Aneurysmal SAH confirmed by CT brain scan and CT or conventional angiography	?	167 (167)	48	53	3 months	Death or dependency (GOS 1–3)

?, not stated or unclear; APOE, apolipoprotein E gene; CT, computed tomography; GOS, Glasgow Outcome Scale; ICH, intracerebral haemorrhage; IS, ischaemic stroke; ivPA, intravenous tissue plasminogen activator; MR, magnetic resonance; mRS, modified Rankin Score; N, no; SAH, subarachnoid haemorrhage; Y, yes.

\*Not included in the main analyses.

†Of total patients in study (n = 592, including 60 with ICH).

studies<sup>18–20</sup> and at hospital discharge in one study.<sup>17</sup> Follow-up was generally by examination or telephone interview. Outcomes were assessed blind to genotype and vice versa in all but one study that did not comment on blinding.<sup>17</sup>

All studies used blood samples for DNA extraction, and one also used buccal smears.<sup>19</sup> Genotype analysis was by restriction enzyme digestion of the polymerase chain reaction product in all but one study, which assessed APOE genotypes indirectly by measuring the apolipoprotein E protein phenotypes.<sup>15</sup>

### Effects on death or dependency—main analyses

Overall, there was no significant effect of  $\epsilon 4+$  versus  $\epsilon 4-$  genotypes (summary RR 1.08, 95% confidence interval (CI) 0.96 to 1.21; fig 2). However, there was significant heterogeneity between the studies ( $\chi^2_{8} = 25.4$ ,  $p = 0.001$ ), some of which seemed to be accounted for by the pathological type of stroke. We found no significant effect on ischaemic stroke (RR 0.98, 95% CI 0.85 to 1.12), but found a trend towards an association with poor outcome after ICH (RR 1.38, 95% CI 0.99 to 1.92) and a significant association with poor outcome after SAH (RR 1.40, 95% CI 1.06 to 1.84). There was significant heterogeneity between the pooled results for the three pathological types of stroke ( $\chi^2_{2} = 10.4$ ,  $p = 0.005$ ), and residual heterogeneity between the results of the five studies on SAH (fig 2).

There was no significant effect of  $\epsilon 2+$  versus  $\epsilon 2-$  genotypes, either overall or for the pathological types of stroke considered separately. However, the reliability of these analyses is limited, as they were based on less than half of the available data.

### Effects on death—main analyses

The pattern of the results for  $\epsilon 4+$  versus  $\epsilon 4-$  genotypes was similar to that for death or dependency, although less than half of the total subjects contributed to these analyses. Overall, there was a just significant increase in the risk of death with an  $\epsilon 4+$  genotype (RR 1.24, 95% CI 0.92 to 1.67). There was no significant effect for ischaemic stroke (RR 1.08, 95% CI 0.75 to 1.55), but  $\epsilon 4+$  genotypes conferred a non-significant trend towards an increased risk of death for patients with ICH (RR 1.63, 95% CI 0.89 to 2.98) and SAH (RR 1.98, 95% CI 0.72 to 5.49). However, as there was no statistically significant heterogeneity between results of the individual studies or the three pathological types of stroke, these subgroup analyses should be interpreted with caution (fig 3).

Data on the effects of  $\epsilon 2+$  versus  $\epsilon 2-$  genotypes were available for only about one third of the available data, making the reliability of the results limited. There was no significant effect on death overall or for the separate pathological types of stroke.

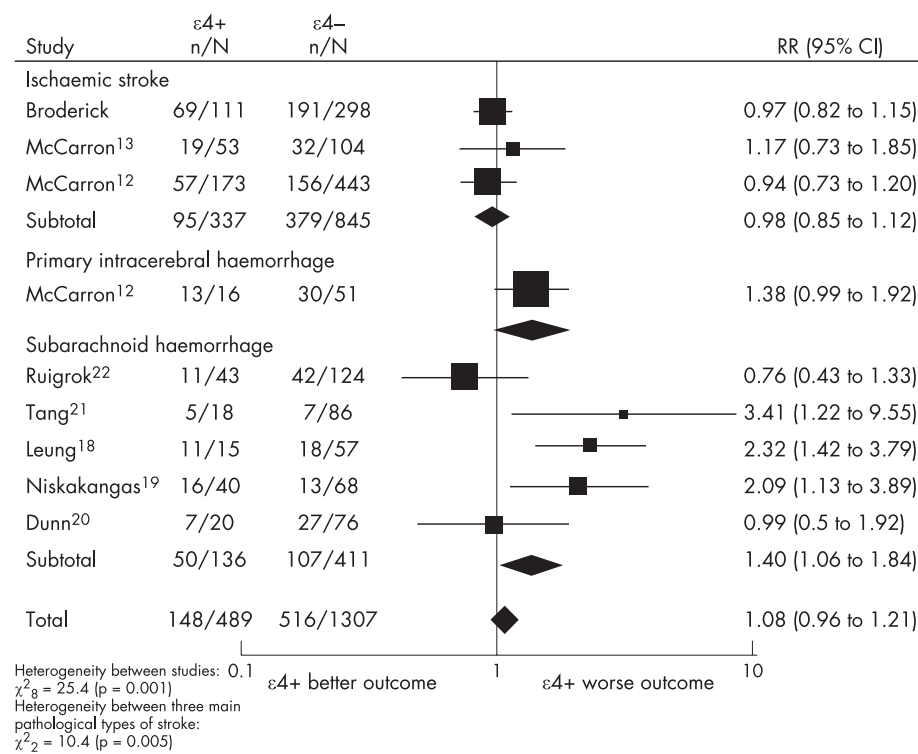
Most studies provided both unadjusted results and results adjusted for potential confounders of the association between APOE and outcome. Unadjusted and adjusted results were generally very similar, although in two of the studies on SAH, the association of  $\epsilon 4+$  genotypes with poor outcome became more extreme after adjustment.<sup>18 19</sup>

### Sensitivity analyses

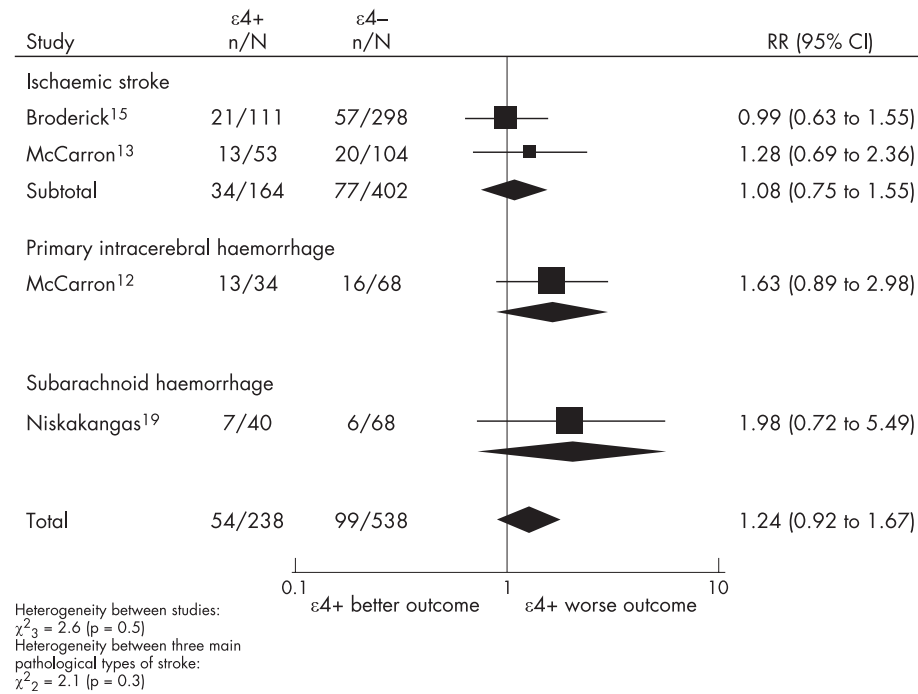
Tables A and B provided online at <http://www.jnnp.bmjournals.com/supplemental> show detailed results. Including plausible values for the eligible studies with unavailable data did not affect the results of our meta-analyses of the effect of  $\epsilon 4+$  genotypes on outcome after ischaemic stroke.<sup>14 16</sup> However, including plausible data for ICH from Catto *et al*<sup>14</sup> produced a range of results, which included the possibilities of either no effect or an adverse effect on death after intracerebral haemorrhage.

### DISCUSSION

These results suggest that  $\epsilon 4$  carriers may be at increased risk of poor outcome (death or dependency, or death alone) several months after ICH or SAH, but not that after ischaemic stroke.



**Figure 2** Meta-analysis of effect of apolipoprotein E ε4+ genotypes on death or dependency several months after acute stroke. n, number dead or dependent at time of outcome assessment; N, number with specified genotype. Squares represent point estimates of relative risks, with size proportional to the statistical weight of each study. Horizontal lines correspond to 95% CI. Pooled relative risks are shown as diamonds, whose width is their 95% CI.



**Figure 3** Meta-analysis of effect of the apolipoprotein E ε4+ genotypes on death several months after acute stroke. n, number who had died by the time of outcome assessment; N, number with specified genotype. Squares represent point estimates of relative risks, with size proportional to the statistical weight of each study. Horizontal lines correspond to 95% CI. Pooled relative risks are shown as diamonds, whose width is their 95% CI.



However, it is important to consider whether the apparently deleterious effect of  $\epsilon 4+$  genotypes on outcome after ICH or SAH could be a false-positive finding. Residual confounding seems unlikely to explain our findings, as unadjusted and adjusted results were generally similar. However, various potential sources of bias could lead to false-positive results. Firstly, publication bias (where the results of small positive studies are more likely to be published than those of small negative studies) could explain why the pooled results of the smaller studies on ICH and SAH (mean number of subjects 116) were positive, whereas those of the larger studies on ischaemic stroke (mean number of subjects 484) were not. Publication bias has often been identified in systematic reviews of observational epidemiological studies,<sup>30</sup> including candidate gene studies—for example, our own study on the role of APOE in incidence of different pathological types of stroke.<sup>3</sup> Secondly, reporting bias could have affected our findings, as data on both outcomes of interest were not available from all studies. Thirdly, selection and “loss-to-follow-up” biases may have affected our results because, although several studies recruited consecutive patients, patients had to survive long enough to give consent and provide a sample for DNA; the most severely affected patients with stroke who died early were inevitably excluded. In addition, outcome data were not available for all recruited patients, and one study on ICH reported outcome at discharge from hospital, which may have introduced bias if time to discharge varied between APOE genotype groups.<sup>17</sup>

Could the result of no apparent effect on outcome after ischaemic stroke be a false-negative finding? This seems less likely, particularly as two additional eligible studies for which we were unable to obtain data found no association between APOE and outcome after ischaemic stroke, and including plausible values for these in sensitivity analyses did not alter our findings.<sup>14–16</sup> Our meta-analysis of effects on death or dependency after ischaemic stroke included studies with varying outcome definitions, but this seems unlikely to have affected the overall results, as the RRs for the different studies were similar. Another possibility is that we may have missed an effect on outcome after ischaemic stroke because of an interaction with age. The patients in the studies on ischaemic stroke were slightly older than those with haemorrhagic stroke, particularly SAH. A recent study found that the effect of  $\epsilon 4+$  genotypes on death or severe disability 6 months after acute head injury was age dependent. The association was most pronounced in participants aged <15 years and diminished with increasing age.<sup>31</sup> This raises the possibility that an association between the APOE genotype and outcome after ischaemic stroke might be detectable only in patients with a mean age at least several years below that of the ischaemic stroke patients in the studies in our review, and that the association between APOE genotype and outcome after ICH or SAH may be stronger with decreasing age. However, given the small difference in mean age between the patients with ischaemic stroke, ICH and SAH, this seems unlikely to be the only reason for the difference in results between haemorrhagic and ischaemic types of stroke.

The explanation for the apparent differences between the effects on different pathological types of stroke, if real, is uncertain. Some studies have suggested that the effects on SAH might be due to an association of  $\epsilon 4+$  genotypes with delayed ischaemic neurological deficit.<sup>20–32</sup> A study exploring the reasons for the association between  $\epsilon 4+$  genotypes and poor outcome after ICH found no detectable effect of APOE on haematoma or oedema volumes.<sup>17</sup> Another study that examined whether the effects of APOE on coagulation profiles might explain the different effects on outcome after ischaemic stroke and ICH found inconclusive results.<sup>25</sup>

In summary, our results suggest that APOE may affect outcome after ICH and SAH, but not after ischaemic stroke. Larger studies are needed to confirm or refute these findings, and to assess the possibility of an interaction between the effects of the APOE genotype and age. If the apparent differences between the pathological types of stroke are confirmed, research into the reasons for this should improve our understanding of the role of apolipoprotein E in recovery after stroke, and may ultimately lead to new therapeutic insights.

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## NEUROLOGICAL PICTURE .....

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### Susac's syndrome: effective combination of immunosuppression and antiplatelet treatment

Susac's syndrome is a rare disease predominantly affecting young women. The syndrome is characterised by the triad of encephalopathy, branch retinal artery occlusions (BRAO) and hearing loss.<sup>1–3</sup> An inflammatory or vascular background, or both, for this small vessel disease is controversially discussed. Therapeutic options are rare.

A 17-year-old girl without a remarkable medical history presented with several episodes of acute psychosis, nausea, dysarthria, ataxia, visual field defects, asymmetrical hearing loss and prodromal migrainous headache. Fluorescence angiography showed branch retinal artery occlusions (fig 1). Audiometry showed sensorineural pancochlear bilateral hypacusis. Magnetic resonance imaging showed hyperintense snowball-like lesions of the corpus callosum (fig 2).<sup>4</sup> These clinical investigations confirmed the diagnosis of Susac's syndrome. Risk factors such as smoking, reduced protein S activity, oral contraception and prodromal viral infection of the respiratory tract were found. Treatment with high-dose glucocorticoids during the acute episodes, and a secondary prophylactic treatment with nimodipine and aspirin, was effective in both reducing the severity of acute symptoms and preventing further episodes.<sup>5</sup>

From the presented case, we conclude that (1) the triad of encephalopathy, branch retinal artery occlusions and sudden hearing loss in young women strongly suggests Susac's syndrome; (2) snowball-shaped lesions in the corpus callosum appear highly specific for the clinical diagnosis of Susac's syndrome; and (3) the use of high-dose glucocorticoids in the acute phase of the disease and prophylactic treatment with aspirin and nimodipine seem to be beneficial for these patients, but has to be evaluated prospectively in larger studies.

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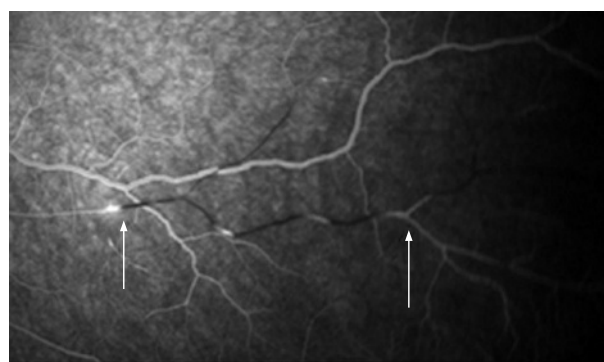
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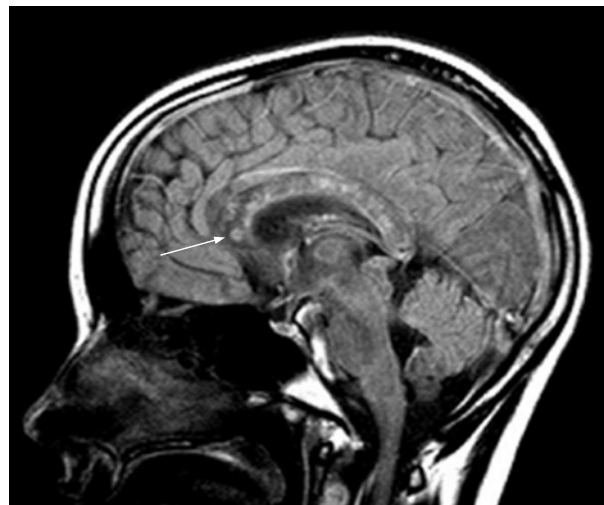
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**Figure 1** Hyperfluorescent retinal arterial wall plaques, branch retinal artery occlusion and retrograde vessel filling. Arrows indicate leakage of retinal arteries.



**Figure 2** Sagittal T2-weighted image (fluid-attenuated inversion recovery) showing multiple microinfarctions in the corpus callosum. Note the ring-shaped lesion in the rostral genu, possibly representing a residual snowball lesion (indicated by an arrow).