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Long term neuropsychological outcome after head injury: relation to APOE genotype

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Background: Existing evidence suggests that some patients who sustain a head injury suffer cognitive decline many years later, and that head injury and possession of the APOE ε4 allele are each risk factors for Alzheimer's disease.

Objective: To determine whether late cognitive decline after head injury is more prevalent among carriers of APOE ε4.

Methods: A database of head injured patients was used. Initial assessment was at the time of their injury, between 1968 and 1985, and outcome data at six months were available. Their ages at the time of injury ranged between 2 and 70 years. A cohort of 396 subjects was reassessed at a mean of 18 years later, with determination of APOE genotype and detailed neuropyschological testing.

Results: Judging by the Glasgow outcome scale, twice as many patients had deteriorated as improved between six months after injury and the late assessment; 22.2% of APOE ε4 carriers had a good late outcome compared with 30.5% of non-carriers (95% confidence interval for the difference, −0.7% to 17.2%; p = 0.084). There were no clear differences between ε4 carriers and non-carriers in detailed neuropsychological assessments.

Conclusions: Although this study provides additional evidence that a late decline may occur after head injury, there was no clear relation to APOE genotype. Despite the follow up interval of 15 to 25 years, the cohort is still too young (mean age 42.1 years) to assess the risk of Alzheimer's disease.

Evidence is accumulating that early outcome after a head injury is influenced by polymorphism of apolipoprotein E (APOE gene; apolipoprotein E protein). The gene has three common alleles which are designated ε2, ε3, and ε4, and encode corresponding protein isoforms (E2, E3, and E4). In a prospective clinical study using the Glasgow outcome scale, we found a significant association between the possession of APOE ε4 and an unfavourable outcome at six months after head injury.[1] In that study of 93 patients, ε4 carriers were more than twice as likely as non-carriers to have a poor outcome, defined as dead, in a vegetative state, or severely disabled. Similar associations have been reported between the possession of APOE ε4 and the reduced likelihood of recovery of consciousness from post-traumatic coma[2 3] and poor outcome in survivors within the first year after injury.[3 4] In addition to an influence on relatively short term outcome, a relation was proposed between possession of APOE ε4 and the long term consequences for survivors of head injury.[5]

The few prospective studies of outcome decades after head injury have included limited information concerning the initial features of the injury, and the assessments of cognitive function that were done were relatively unsophisticated.[6 7] Nevertheless, such studies suggest that there may be a long term decline. For example, compared with personnel who had peripheral nerve injuries during World War II, those who sustained a head injury had worse cognitive function 30 years later.[7] In a large recent study 50 years after they had sustained a closed head injury, World War II veterans showed a higher prevalence of Alzheimer's disease than controls.[8] In contrast, a long term review of servicemen with focal wartime brain wounds suggested preservation of cognitive abilities.[9]

Information on the association between head injury and long term neurodegeneration has also come from retrospective epidemiological studies of Alzheimer's disease which have identified an association with a previous head injury.[10–15] The largest of these studies found that patients with Alzheimer's disease were substantially more likely to have suffered a head injury with loss of consciousness than non-demented

controls.[15] However, the conclusions of these retrospective studies have been criticised on the basis that they may have been subject to recall bias, and a recent large community based prospective study found no association between a head injury and Alzheimer's disease.[16]

Possession of APOE ε4 is the major genetic risk factor for sporadic Alzheimer's disease.[17] An early study investigating both head injury and APOE ε4 as risk factors for Alzheimer's disease suggested that the interaction may be synergistic,[18] but subsequent larger studies concluded that the effects of these two risk factors are additive or less than additive.[13–15]

Further information on the relation between traumatic brain injury, Alzheimer's disease, and the APOE genotype has come from studies of boxers. Boxers with APOE ε4 have more evidence of chronic brain injury than non-carriers of ε4,[19] and boxers may suffer from cognitive decline as they age (*dementia pugilistica*).[20]

The present study took advantage of a database of patients with severe head injuries who had been studied in Glasgow from the late 1960s to the mid 1980s. The database contains information about the patients, their injury, the initial features including severity and clinical progression, and outcome as assessed by the Glasgow outcome scale[21] six months after the injury. This unique dataset, taking account of early clinical indices, has allowed the investigation of a possible association between APOE genotype and very long term outcome, using detailed neuropsychological assessments. Specifically, we aimed to address the hypothesis that long term survivors of head injury show impairment of cognitive function many years after their injury, controlling for outcome

Table 1 Early clinical data

	Known to be dead	Contacted and assessed	Remainder
Sample size	242	396	495
Year of injury			
Median	1979	1980	1976
Interquartile range	1976 to 1983	1977 to 1985	1974 to 1983
Age at injury (years)			
Mean	46.7	23.9	27.0
SD	17.4	15.3	17.6
Male	194 (80.2)	291 (73.5)	397 (80.2)
Cause of injury			
Road traffic accident	92 (39.0)	261 (66.6)	300 (61.3)
Fall under influence of alcohol	82 (34.7)	28 (7.1)	56 (11.5)
Other	62 (26.3)	103 (26.3)	133 (27.2)
Major extracranial complication	51 (21.2)	155 (39.2)	173 (35.0)
Lucid interval	82 (36.0)	69 (18.1)	111 (23.2)
GCS at A&E			
3–8	151 (74.4)	272 (85.0)	297 (79.8)
9–12	17 (8.4)	21 (6.6)	39 (10.5)
13–15	35 (17.2)	27 (8.4)	36 (9.7)
Non-reacting pupils at A&E	44 (22.4)	39 (11.8)	43 (11.4)
Injury type*			
Diffuse	59 (24.4)	233 (58.8)	265 (53.5)
Evacuated mass	154 (63.6)	140 (35.4)	187 (37.8)
Non-evacuated mass	29 (12.0)	23 (5.8)	43 (8.7)
GOS at six months			
Vegetative/severe disability	129 (55.4)	101 (25.6)	116 (23.6)
Moderate disability	57 (24.5)	126 (31.9)	151 (30.7)
Good recovery	47 (20.2)	168 (42.5)	225 (45.7)

Information on demographic features, type of injury, clinical severity, treatment, and outcome at six months of 1133 survivors of a head injury studied prospectively at the Institute of Neurological Sciences, Glasgow, UK between 1968 and 1985. Values are n or n (%). *Pattern of injury from imaging and operative findings. A&E, accident and emergency department; GCS, Glasgow coma score; GOS, Glasgow outcome scale.

at six months, and that this impairment could be more prevalent among APOE ε4 carriers.

METHODS
Ethical approval
The Southern General Hospital ethics committee approved the study. Additional approval came from all 14 regional health boards in Scotland which were contacted to confirm registration of patients with general practitioners. Approval was also obtained from the local general practitioner subcommittees, as we required the consent of the patient's GP before contacting the patient.

Sample
The population comprised the database of 1133 patients who had sustained a severe head injury and had been studied in the acute stage in the Department of Neurosurgery, Institute of Neurological Sciences at the Southern General Hospital, Glasgow, between 1968 and 1985. For the entire group of 1133 patients the age range at injury was < 1 to 82 years. For the 396 patients who were assessed, the age range was 2 to 70 years. Patients had to have survived for at least six months following their original injury to be included in the study. The tracing of patients began with the general practitioner recorded at the time of discharge from hospital and progressed if necessary to searches of the community health index, SMR1 forms, and registrar general data to identify those lost to follow up through death.

Patient contact
The general practitioner of the patients who were traced was contacted, informed of the details of the study, and asked for permission to contact the patient. Following GP consent, a letter was written to each patient informing them of the study and asking them to participate by completing a consent form. A contact telephone number was offered to allow the patient an opportunity to discuss the study further with the team

before consenting. When the patient was unable to give consent, the next of kin or legal guardian was consulted. The initial contact letter was followed up by a telephone call, where possible, to discuss potential participation in the study.

Determination of APOE genotype
APOE genotypes were determined from buccal swabs which were obtained by rubbing a cytology brush on the inner surface of the patient's cheek for approximately 15 seconds. The brush was then inserted into an Eppendorf tube containing 400 µl of ethanol and agitated. Following storage at 4°C, samples were centrifuged at 11 600 × g for 30 seconds to pellet the cells and the ethanol was decanted. The pelleted samples were dried on a heat block at 55°C for 30 minutes, digested with proteinase K (100 µl/ml) at 56°C for one hour, and then heated to 95°C for 10 minutes to inactivate the proteinase K. Using 0.8 µl of the proteinase digest as the template, hot start polymerase chain reaction (PCR) amplification was undertaken with standard primers[22] in a reaction volume of 15 µl (40 cycles of consisting 94°C for one minute, 65°C for one minute, and 72°C for two minutes). The PCR products were digested with *Hha*1 for a minimum of three hours. The products of digestion were separated according to size by polyacrylamide gel electrophoresis, stained with ethidium bromide, and viewed by ultraviolet transillumination.

Assessment
Early clinical data
Data were available for all patients concerning the nature and severity of the head injury judged by clinical features, including the Glasgow coma score,[23] and pupil reactivity, treatment, and outcome at six months on the Glasgow outcome scale.[21]

Long term outcome
The comprehensive assessment was conducted in the research laboratory, or, where this proved impracticable, in the patient's home.

Table 2 Early clinical data according to APOE genotype assessment

	APOE genotype	
	ε4 negative	ε4 positive
Sample size	279	117
Year of injury		
Median	1980	1981
Interquartile range	1977 to 1984	1978 to 1985
Age at injury (years)		
Mean	24.9	21.5
SD	15.6	14.2
Male	210 (75.3)	81 (69.2)
Cause of injury		
Road traffic accident	181 (65.8)	80 (68.4)
Fall under influence of alcohol	20 (7.3)	8 (6.8)
Other	74 (26.9)	29 (24.8)
Major extracranial complication	101 (36.3)	54 (46.2)
Lucid interval	48 (17.8)	21 (18.6)
GCS at A&E		
3–8	184 (82.9)	88 (89.8)
9–12	17 (7.7)	4 (4.1)
13–15	21 (9.5)	6 (6.1)
Non-reacting pupils at A&E	24 (10.4)	15 (15.3)
Injury type*		
Diffuse	166 (59.5)	67 (57.3)
Evacuated mass	97 (34.8)	43 (36.8)
Non-evacuated mass	16 (5.7)	7 (6.0)
GOS at six months		
Vegetative/severe disability	73 (26.2)	28 (24.1)
Moderate disability	86 (30.8)	40 (34.5)
Good recovery	120 (43.0)	48 (41.4)
NART error score		
1–18	62 (22.2)	24 (20.5)
19–28	69 (24.7)	27 (23.1)
29–48	65 (23.3)	26 (22.2)
Not completed	83 (29.7)	40 (34.2)

Early clinical data for the 396 of 1133 patients who were successfully followed up for late assessment 15 to 25 years after injury, divided into APOE ε4 carriers and non-carriers.
Values are n or n (%).
*Pattern of injury from imaging and operative findings.
A&E, accident and emergency department; GCS, Glasgow coma score; GOS, Glasgow outcome scale; NART, national adult reading test.

Table 3 General assessment of late outcome according to APOE genotype

	APOE genotype	
	ε4 negative	ε4 positive
MMSE, raw scores		
0–23	64 (22.9)	27 (23.1)
24–27	74 (26.5)	30 (25.6)
28–29	75 (26.9)	29 (24.8)
30	66 (23.7)	31 (26.5)
MMSE , centile scores		
≤1%	77 (27.6)	35 (29.9)
2–30%	52 (18.6)	23 (19.7)
31–69%	79 (28.3)	28 (23.9)
70–100%	71 (25.4)	31 (26.5)
Composite performance, centile scores		
Test incomplete	100 (35.5)	35 (29.9)
1–17%	51 (18.3)	35 (29.9)
18–30%	66 (23.7)	21 (17.9)
31–100%	62 (22.2)	26 (22.2)
GOSE at follow up*		
Vegetative/lower severe disability	52 (17.8)	24 (19.0)
Upper severe disability	40 (13.7)	17 (13.5)
Lower moderate disability	83 (28.4)	38 (30.2)
Upper moderate disability	28 (9.6)	19 (15.1)
Lower good recovery	41 (14.0)	15 (11.9)
Upper good recovery	48 (16.4)	13 (10.3)

General assessment of functional outcome 15 to 25 years after a head injury for carriers and non-carriers of APOE ε4.
Values are n (%).
*These results are based on 418 patients: the 396 who underwent neuropsychological assessment together with a further 22 where GOSE and APOE genotype were available.
GOSE, extended Glasgow outcome scale; MMSE, mini-mental state examination.

Cognitive state

Premorbid intellectual function was estimated with the national adult reading test (NART). Current orientation and function were assessed by the mini-mental state examination (MMSE) and neuropsychological tests sensitive to cognitive decline associated with head injury and the prodromal stage of dementia. Memory function was assessed with subtests of the Wechsler memory scale (WMS: logical memory, verbal and visual paired associates, and visual reproduction) and the graded naming test. Executive and attentional processes were assessed with the Stroop neuropsychological screening test, verbal fluency (letter and category generation), and the digit span test from the WMS.

Emotional state

Self reported depression, distress, and psychiatric symptoms were assessed respectively with the Beck depression inventory, general health questionnaire (GHQ-28), and symptom check list-90 (SCL-90).

Physical health, social, family and employment status

A comprehensive questionnaire obtained data on a wide range of social and health variables including alcohol and drug use, subsequent head injuries, or stroke, and was completed by the patient, relative, or carer as appropriate.

Outcome

The extended Glasgow outcome scale (GOSE)[24][25] was used to determine the level of disability and "overall" outcome.

Statistical methods

The scores for the individual neuropsychological tests were converted to centiles from available normative data. The tests were grouped into five domains (verbal memory, visual memory, attention, language, and executive function) and the centile scores averaged within each domain to give an overall score per domain. These five summary scores were in turn averaged to produce a single "composite performance score" after the method of Fox and colleagues.[26] The method has the advantage of minimising type 1 error by reducing the number of statistical tests that would otherwise be conducted on the individual cognitive tests.

Analysis of the neuropsychological scores was hampered by the fact that some of the patients were unable to complete all the tests. To overcome this problem, the composite performance score and MMSE scores (both raw scores and centile norms) were grouped into approximate quartiles, assigning individuals who were unable to complete a test to the lowest quartile for that test. The formal analyses are based on these quartile scores.

The association between the possession of an APOE ε4 allele and cognitive function was assessed formally using ordinal logistic regression to adjust for the early clinical data. The response variables for these analyses were the quartile scores for MMSE (both raw scores and centile scores) and for the composite performance score. A similar analysis was used for the full GOSE score, with the one patient who was assessed as vegetative being grouped into the lower severe disability category. The results both with and without adjustment for key baseline variables are summarised in terms of the common odds ratio together with the corresponding 95% confidence intervals. An odds ratio of 1 would correspond to no effect, and values greater than 1 would indicate that possession of an APOE ε4 allele is associated with poor function.

Table 4   Ordinal logistic regression analyses assessing the relation between possession of one or more APOE ϵ4 alleles and function as assessed at late follow up

	Unadjusted analysis			Adjusted analysis*		
Outcome measure	Common odds ratio†	95% CI	p Value	Common odds ratio†	95% CI	p Value
MMSE, raw score	0.94	0.64 to 1.39	0.772	1.18	0.72 to 1.95	0.507
MMSE, centile score	1.07	0.73 to 1.58	0.733	1.31	0.80 to 2.16	0.288
Composite performance score	0.97	0.66 to 1.44	0.896	1.07	0.62 to 1.83	0.807
GOSE‡	1.19	0.82 to 1.72	0.356	1.36	0.84 to 2.19	0.212

Statistical analysis of the data presented in table 3 of the general assessment of functional outcome 15 to 25 years after a head injury for carriers and non-carriers of of APOE ϵ4.
*Adjusted for year of injury, age at injury, Glasgow coma score and pupil reaction at the accident and emergency department, type of injury, Glasgow outcome scale at six months, and national adult reading test.
†A common odds ratio of greater than 1 would indicate that possession of an *APOE* ϵ4 allele is associated with poor function.
‡These results are based on 418 patients: the 396 who underwent neuropsychological assessment together with a further 22 where GOSE and *APOE* genotype were available.
CI, confidence interval; GOSE, extended Glasgow outcome scale; MMSE, mini-mental state examination.

RESULTS

From the initial cohort of 1133 patients who were alive at six months following their head injury, 242 (21.4%) were confirmed as being dead by the time of the long term follow up (mean follow up interval 18 years). In all, 396 (35%) were traced and assessed using the battery of neuropsychological tests. The remaining 495 patients (43.7%) were not fully assessed for the following reasons: no trace (n = 182); traced but no response (n = 138); patient refused (n = 76); patient not in Scotland, or remote (n = 83); general practitioner advised us not to contact the patient (n = 16).

Table 1 gives a summary of the early clinical data for these three groups of patients. Overall the patients who had detailed neuropsychological assessments were very similar to the "remainder" group. However, the patients who had died between six months after their injury and the time of the study differed substantially from the other two groups in the following ways: they were older at the time of injury; they were more likely to have sustained their injury as a result of a fall while under the influence of alcohol; they were less likely to have had a road traffic accident; they were more likely to have had an intracranial mass lesion; they were less likely to have had diffuse brain injury; and at six months after their injury they were more likely to have been in the vegetative/severe disability group and less likely to have had a good recovery. These features, shown in table 1 to be associated with mortality, are in accord with expectations.

Table 2 gives the same early clinical information, together with NART scores, for the patients who were fully assessed, divided into APOE ϵ4 carriers and non-carriers. Of the 396 patients, 117 (29.5%) were APOE ϵ4 carriers. The APOE ϵ4 negative and positive groups were broadly similar, although the APOE ϵ4 positive patients were younger at the time of injury (mean (SD) age: 21.5 (14.2) *v* 24.9 (15.6) years; 95% confidence interval (CI), 0.2 to 6.5 years; p = 0.039), more were pedestrians in a road traffic accident, and more suffered major extracranial complications. More APOE ϵ4 carriers had a low Glasgow coma score (3–8) than non-carriers (89.8% *v* 82.9%; 95% CI, −0.8% to 14.7%; p = 0.11). There was little difference in their status six months after their injury as assessed by the Glasgow outcome scale, with 41.4% of APOE ϵ4 carriers having a good recovery compared with 43.0% of non-carriers.

The late functional outcome measures for the APOE ϵ4 carriers and non-carriers are summarised in table 3: 22.2% of APOE ϵ4 carriers had a good recovery according to their GOSE, compared with 30.5% non-carriers (95% CI, −0.7% to 17.2%; p = 0.084). There was no trend for the difference between carriers and non-carriers of APOE ϵ4 to be more marked at older ages; in fact for the under 50s the observed difference in the proportion with good recovery is 10%, which is greater than the difference observed overall. There were no clear and consistent differences between the two groups for MMSE or the global impairment score. The results of the formal statistical comparisons using ordinal logistic regression with and without adjustment for the key clinical variables including GOSE at six months are shown in table 4. There was no evidence of any association between possession of APOE ϵ4 and late functional outcome using these measures.

The results of the neuropsychological assessments of late outcome for APOE ϵ4 carriers and non-carriers are shown in table 5. Although there was a slight tendency for carriers to be less likely to have performed well in tests of visual memory, attention, and language, there were no significant differences between the two groups (table 6). Among patients who were severely disabled at six months, APOE ϵ4 carriers performed consistently worse than non-carriers in their late assessments, but this tendency was not present among patients who were moderately disabled or had good recovery at six months (data not shown).

Table 5   Detailed neuropsychological assessments of late outcome according to APOE genotype

	APOE genotype	
	ϵ4 negative	ϵ4 positive
Verbal memory, centile scores		
Test incomplete	70 (25.1)	28 (23.9)
1–4%	70 (25.1)	33 (28.2)
4–18%	77 (27.6)	21 (17.9)
18–100%	62 (22.2)	35 (29.9)
Visual memory, centile scores		
Test incomplete	90 (32.3)	29 (24.8)
1–10%	50 (17.9)	29 (24.8)
10–25%	64 (22.9)	31 (26.5)
25–100%	75 (26.9)	28 (23.9)
Attention, centile scores		
Test incomplete	49 (17.6)	22 (18.8)
1–30%	93 (33.3)	41 (35.0)
30–50%	56 (20.1)	30 (25.6)
50–100%	81 (29.0)	24 (20.5)
Language, centile scores		
Test incomplete	54 (19.4)	21 (17.9)
1–2%	84 (30.1)	41 (35.0)
2–21%	63 (22.6)	32 (27.4)
21–100%	78 (28.0)	23 (19.7)
Executive function, centile scores		
Test incomplete	87 (31.2)	33 (28.2)
1–8%	57 (20.4)	29 (24.8)
8–25%	73 (26.2)	30 (25.6)
25–100%	62 (22.2)	25 (21.4)

Detailed neuropsychological assessments of outcome in 396 subjects 15 to 25 years after a head injury for carriers and non-carriers of APOE ϵ4.
Values are n (%).

Table 6 Ordinal logistic regression analyses of the relation between possession of one or more APOE ε4 alleles and detailed neuropsychological assessments at late follow up

Outcome measure	Unadjusted analysis			Adjusted analysis*		
	Common odds ratio†	95% CI	p Value	Common odds ratio†	95% CI	p Value
Verbal memory	0.90	0.61 to 1.32	0.574	0.83	0.50 to 1.38	0.468
Visual memory	0.92	0.63 to 1.36	0.690	0.94	0.56 to 1.56	0.806
Attention	1.22	0.83 to 1.81	0.307	1.54	0.94 to 2.53	0.089
Language	1.18	0.80 to 1.74	0.396	1.34	0.80 to 2.24	0.265
Executive function	0.98	0.67 to 1.45	0.938	1.23	0.74 to 2.06	0.421

Statistical analysis of the data presented in table 5 of the detailed neuropsychological assessments of outcome in 396 subjects 15 to 25 years after a head injury for carriers and non-carriers of APOE ε4.
*Adjusted for year of injury, age at injury, Glasgow coma score, and pupil reaction at the accident and emergency department, injury type, Glasgow outcome scale at six months, and national adult reading test score.
†A common odds ratio of greater than 1 would indicate that possession of an APOE ε4 allele is associated with poor function.
CI, confidence interval.

Table 7 Change in Glasgow outcome scale from six months after injury to late follow up in APOE ε4 carriers and non-carriers

	ε4 negative	ε4 positive
Improved	15.8%	12.7%
Unchanged	54.5%	56.3%
Deteriorated	29.8%	31%

Relative to their status at six months, approximately twice as many patients had deteriorated (126 patients, 30.2%, 95% CI, 28.0% to 32.5%) as had improved (60 patients, 14.4%, 95% CI, 12.7% to 16.2%) at late follow up (table 7). APOE ε4 carriers did not differ significantly in this respect from non-carriers.

DISCUSSION

In this study we show that a high proportion of surviving patients who were assessed 15 to 25 years after a head injury were severely impaired. Furthermore, comparison of the Glasgow outcome scale scores indicated that a deterioration occurred between the six month assessment and the late assessment in almost one third of cases, whereas improvement over this period was relatively uncommon. Late deterioration in this study was only measured by a functional outcome (the Glasgow outcome scale), and such an outcome may reflect various factors—for example, lack of rehabilitation. This finding supports previous studies suggesting that late deterioration may occur after head injury.[6–8] An important advantage of the present study is that detailed comparisons could be made relating to the nature and severity of the injury, the early outcome, and the outcome many years later.

About 22% of APOE ε4 carriers had a good late outcome, compared with 31% of non-carriers (95% CI for the difference, −0.7% to 17.2%; p = 0.084), despite the fact that APOE ε4 carriers and non-carriers were very similar at their six month assessments after the injury. In view of the evidence that head injury is a risk factor for Alzheimer's disease, neuropsychological tests were chosen to target functions that are likely to be affected in the prodromal stages of Alzheimer's disease. These detailed tests were not done 15 to 25 years ago at the time of the initial six month follow up assessment, and so no direct comparison of these functions at the two time points is possible. Nonetheless, the use of centile scores derived in comparison with normative values for the tests to describe the degree of cognitive impairment does give an absolute measure of current functioning and confirms the profound impairment suffered by a large proportion of such patients. APOE ε4 carriers who in their early assessments were severely disabled

according to the Glasgow outcome scale did show a tendency to perform consistently worse than non-carriers in the late neuropsychological tests, but this finding was not replicated among patients with moderate disability or good recovery at six months.

Important differences between the present study and that of Teasdale et al in 1997[1] prevent a direct comparison of the findings. In the 1997 report we included admissions of all severities, and our indicator for an adverse association with the possession of APOE ε4 included death as an outcome. In contrast, the present study included only subjects who had survived for six months after their injury and who in addition were alive and available for follow up 15 to 25 years later. Only 396 patients from the original database of 1133 patients (35%) could be traced and fully assessed, leaving considerable scope for selective loss of either APOE ε4 carriers or non-carriers. Furthermore, we have recently shown in a prospective study of cardiac surgery patients that those who drop out from follow up of cognitive function are the ones with the greatest cognitive impairment,[27] resulting in an underestimation of the prevalence and degree of impairment. Although a prospective study would be required to test this hypothesis fully, there is, however, evidence that this selective loss did not occur. Of the subjects assessed in this study, 117 of the 396 (29.5%) were carriers of APOE ε4 and this is close to the values for our previous prospective studies of consecutively admitted patients with head injuries: 32.2% (30 of 93[1]) and 32.5% (349 of 1075; unpublished observations), respectively.

The role of the APOE genotype has been explored in relation to relatively short term outcome in the response to forms of acute brain injury other than trauma. For example, APOE ε4 has been found to be associated with poor outcome following spontaneous intracerebral haemorrhage, cardiopulmonary resuscitation, cardiac bypass surgery, and possibly subarachnoid haemorrhage, but not apparently after ischaemic stroke.[28 29] The mechanisms underlying these associations are unclear at present but both human and animal neuropathological studies have highlighted the importance of apolipoprotein E in the acute response to brain injury.[28 29] After brain injury there are marked alterations in the cellular localisation of apolipoprotein E, most notably with an increase in neuronal immunoreactivity. Studies of genetically modified mice have provided further evidence that apolipoprotein E modulates the response to injury.[28 29] For example, apolipoprotein E deficient mice have more severe lesions than wild type mice, and mice bearing the human ε4 allele have more severe lesions than those with ε3. Apolipoprotein E seems to have a direct neuroprotective role, as neuronal damage after entorhinal cortex lesioning and global ischaemia in APOE deficient mice is ameliorated by intraventricular infusion of apolipoprotein E. Mechanisms involving apolipoprotein E which are of potential relevance to the response to acute injury[28 29] concern deposition of amyloid β protein, the maintenance of cytoskeletal

integrity, protection from oxidative stress, and modulation of the response to excitotoxicity. APOE ε4 predisposes to atherosclerosis, ischaemic heart disease, cerebral amyloid angiopathy, and altered blood coagulation, which could compromise cardiovascular integrity in patients with injuries resulting from trauma. Of potential relevance to longer term outcome, apoliprotein E is involved in the delivery of cholesterol to neurones required for neurite outgrowth and synaptogenesis,[30] clearance of degeneration products, and microglial activation, and in the maintenance of the cholinergic system.[28 29]

Despite the 15 to 25 year period of follow up in this study, the subjects assessed were still relatively young (mean (SD) age, 42.1 (15.0) years) in the context of age related cognitive decline and the onset of sporadic Alzheimer's disease. Thus the study of World War II veterans which showed an association of head injury with Alzheimer's disease involved an interval between injury and assessment of approximately 50 years in subjects now aged mostly in their 70s.[8] Likewise, patients in epidemiological studies of Alzheimer's disease which identified head injury as a risk factor were also older—with, for example, the onset of dementia at age 69.9 (9.0) years in the report by Guo et al.[15] Even in a study which identified onset of dementia at an earlier age in Alzheimer's disease patients with a history of traumatic brain injury,[14] the median age of onset was 76 years for men and 80 years for women. In the study reported here only 60 of the 396 patients assessed were over the age of 60. The relatively small number of old subjects available for inclusion in this study may be in part because the early selection was biased towards younger patients, and in part because of the high rate of mortality in older subjects, both in the acute and the follow up phase. It is possible that if this cohort of head injured patients was to be assessed again at a later time point, a clearer relation of APOE genotype to cognitive decline might be found.

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