Supplementary Material

Appendix 1: Background to APOE

Apolipoprotein E

The most extensively studied gene in the field of traumatic brain injury (TBI) is undoubtedly *APOE*. Its 34kDa protein has a central role in central nervous system lipid transport, including movement of cholesterol into cells to aid repair processes in damaged neurones. Three common alleles have been characterized (*ε2, 3,* and *4*), which code for protein isoforms E2, E3 and E4. Of these it is the *ε4* allele that confers a confirmed dose-dependent increase in the risk of late onset Alzheimer's disease as well as intracerebral hemorrhage. The neurochemical mechanisms for APOE4's toxic effects have been reviewed extensively by Mahley and Huang. In brief, it is thought that the E4 isoform (which uniquely contains an arginine at residue 112) exhibits a property known as domain interaction, whereby an exposed arginine at residue 61 interacts with the C-terminal domain. This change in the tertiary structure of the peptide results in aberrant cleavage within the endoplasmic reticulum, and subsequent release of neurotoxic fragments into the cytosol, where they impair mitochondrial and cytoskeletal function. There is evidence that APOE4 inhibits neurite outgrowth (unlike E2/ E3 which encourage it) and that release of pro-inflammatory mediators (interleukin 6, nitric oxide) from stimulated microglia is greater in the presence of E4. In addition to direct neurotoxicity, APOE4 carriage may affect TBI outcomes through modulation of oxidant process or inflammation, alteration in cerebrovascular function or blood-brain barrier integrity, as well as other mechanisms. The interested reader is referred to the publications listed below,[1–6] and the growing literature in this area.

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Appendix 2: Search Strategies.

MEDLINE 1946 to present, via National Institute for Health and Care Excellence (NICE) Healthcare Database:

(exp BRAIN INJURIES/ OR exp CRANIOCEREBRAL TRAUMA/ OR ((head* OR brain*) ADJ2 (injur* OR trauma*)).ti,ab) AND (exp GENETIC VARIATION/ OR exp GENOTYPE/ OR genetic*.ti,ab OR mitochond*.ti,ab OR exp INTRACELLULAR SIGNALING PEPTIDES AND PROTEINS/ OR genomic* OR genome OR allele) AND (EXP NEUROPSYCHOLOGICAL TESTS/ OR ''Glasgow outcome'' OR GOS OR functional OR outcome OR discharge OR rehab* OR recover* OR GCS OR ''Glasgow coma'' OR Glasgow OR disability OR mortality OR ICU OR ''intensive care'' OR ''critical care'' OR rankin)

EMBASE 1980 to present, via NICE Healthcare Database:

(exp BRAIN INJURIES/ OR exp CRANIOCEREBRAL TRAUMA/ OR ((head* OR brain*) ADJ2 (injur* OR trauma*)).ti,ab) AND (EXP GENOTYPE/ OR exp GENOTYPE ENVIRONMENT INTERACTION/ OR exp GENETIC POLYMORPHISM/ OR exp DNA POLYMORPHISM/ OR exp SINGLE NUCLEOTIDE POLYMORPHISM/ OR exp INTRACELLULAR SIGNALING/ OR mitochond*.ti,ab OR genetic*.ti,ab OR genomic* OR GENOME OR allele) AND (EXP NEUROPSYCHOLOGICAL BATTERY,LURIA NEBRASKA/ OR exp NEUROPSYCHOLOGICAL TEST/ OR exp NEUROPSYCHOLOGICAL TESTS/ OR exp NEUROPSYCHOLOGY/ OR rankin OR ''Glasgow outcome'' OR GOS OR functional OR outcome OR discharge OR rehab* OR recover* OR GCS OR ''Glasgow coma'' OR Glasgow OR disability OR mortality OR ICU OR ''intensive care'' OR ''critical care'')

CINAHL 1981 to Present, via NICE Healthcare Database:

(exp HEAD INJURIES/ OR exp BRAIN INJURIES/ OR ''traumatic brain injury''.ti,ab OR ((head* OR brain*) ADJ2 (injur* OR trauma*)).ti,ab) AND (exp GENETICS/ OR exp POLYMORPHISM,GENETIC/ OR genetic*.ti,ab OR mitochond*.ti,ab OR genomic* OR genome OR allele)

Google Scholar

(''brain injury'' OR ''head injury'') AND (genetics OR allele OR polymorphism) AND (outcome OR ''glasgow outcome'')

SUPPLEMENTARY TABLE S1. STUDIES EXCLUDED FOLLOWING FULL TEXT REVIEW

Reason for exclusion	*Study identifier*
Conference abstract/letter with insufficient data or data subsequently published in full	Carter 2011,[1] Carter 2012,[2] **Garnett 2003,**[3] Jacobs 2009,[4] **Ponsford 2010,**[5] **Rubio Lopez 2010,**[6] Cousar 2009,[7] Adams 2014,[8] McDevitt 2014,[9] **Nogueras 2014,**[10] Sinha 2014,[11] Yue 2015,[12] **Sorbi 1995**[13]
Outcome data not reported for each genotype/age group individually	**Abrahams 2017,**[14] Ashman 2008[15]
No genotyping performed	Lankford 199416[16]
No genetic variation identified within cohort	Romeiro 2007[17]
Comment letter in response to included study	**Collie 2004,**[18] **Harden 2004**[19]
Ineligible outcome measure	**Hayes 2017,**[20] **Hiekkanen 2007,**[21] **Horsburgh 2000,**[22] **Isoniemi 2006,**[23] **Jiang 2011,**[24] **Kerr 2003,**[25] **Koponen 2004,**[26] **Leclercq 2005,**[27] **Smith 2006,**[28] **Terrell 2008,**[29] **Tanriverdi 2008,**[30] **Tierney 2010,**[31] Neselius 2013,[32] **Xiao-Chuan 2011,**[33] **Nicoll 1995**[34]
Foreign language paper with original manuscript or English translation unavailable	**Krupa 2003,**[35] Martinez 2009[36]
Non-TBI study	**Kutner 2000,**[37] **Lyons 2013**[38]
Full text not available	**Jordan 1997,**[39] **Poovindran 2013,**[40] Willmott 2013[41]

Bold = APOE studies.

References for Supplementary Table S1

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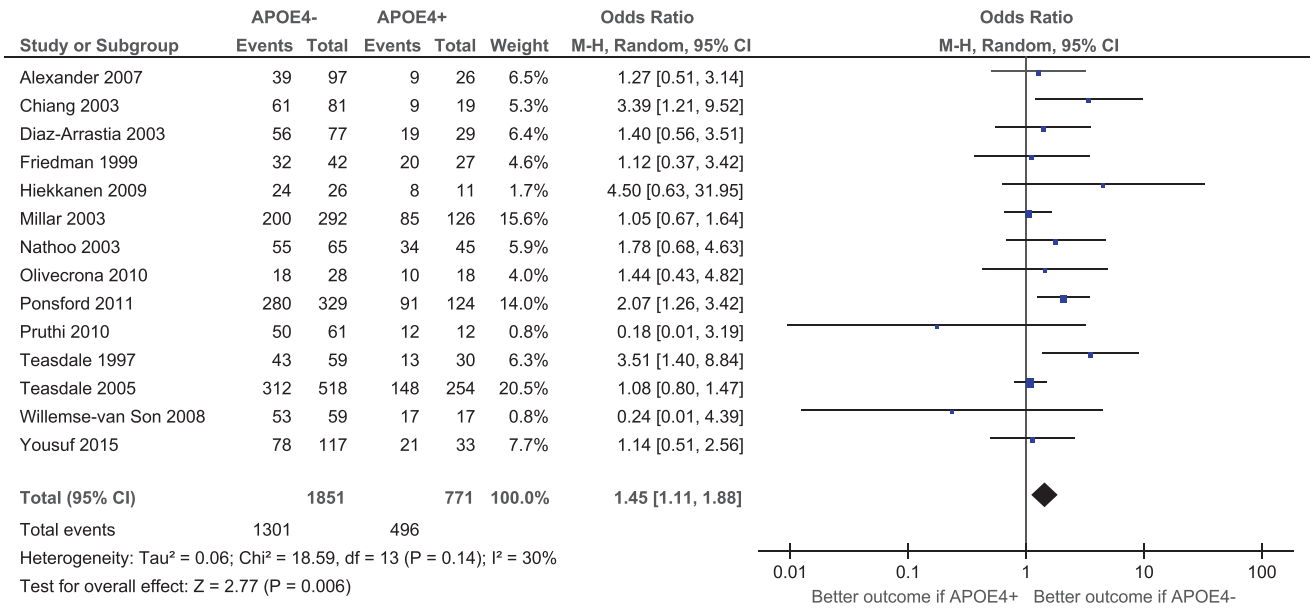
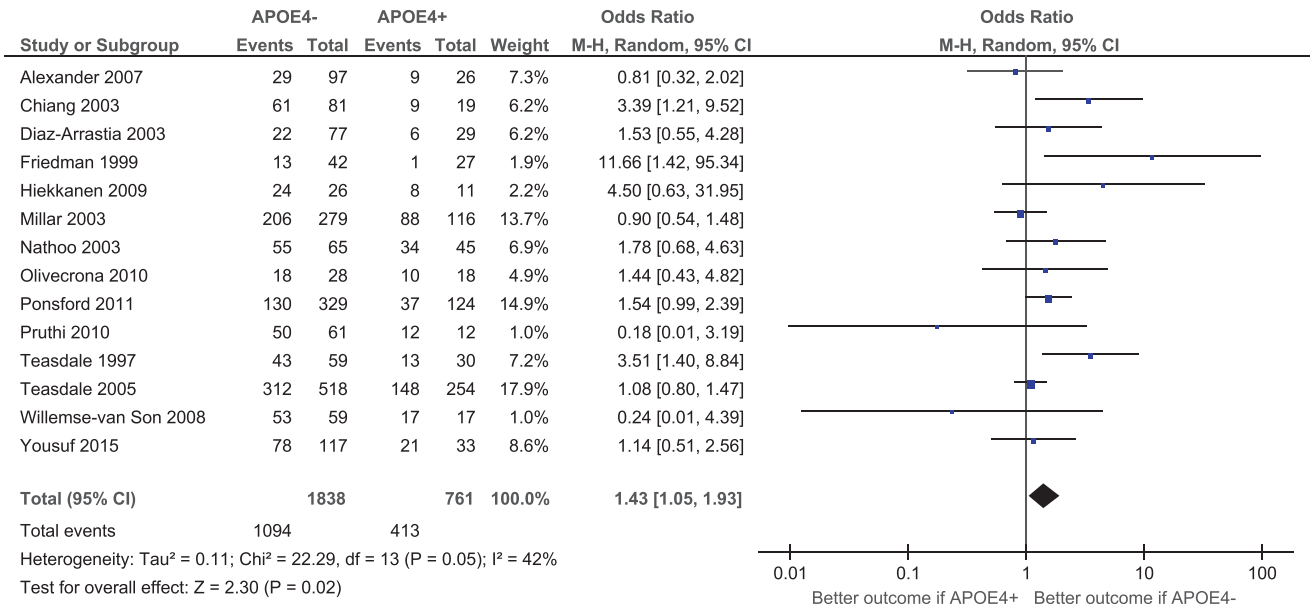
SUPPLEMENTARY TABLE S2. RISK OF BIAS OF REVIEWED STUDIES

Study ID	*Study participation*	*Study attrition*	*Prognostic factor Mx*	*Outcome Mx*	*Confounding*	*Statistical Ax and reporting*
Alexander 2007	Moderate	Moderate	Moderate	Low	Low	Low
Chiang 2003	Low	Low	Moderate	Low	Moderate	Low
Diaz-Arrastia 2003	Low	High	High	Low	Moderate	Low
Friedman 1999	Moderate	Moderate	Moderate	Low	High	Moderate
Hiekkanen 2009	Low	Low	Low	Moderate	Moderate	High
Millar 2003	Moderate	High	Moderate	Low	Moderate	Low
Nathoo 2003	Moderate	Moderate	Low	Low	Moderate	Moderate
Olivecrona 2010	Low	Moderate	Low	Low	Moderate	Moderate
Ponsford 2011	Moderate	Moderate	Low	Moderate	Moderate	Moderate
Pruthi 2010	Moderate	High	High	Low	High	Moderate
Teasdale 2005	Moderate	Low	Moderate	Low	Moderate	Low
Teasdale 1997	Moderate	Moderate	Moderate	Low	Low	Moderate
Willemse-van Son 2008	Moderate	Low	Moderate	Low	Moderate	Low
Yousuf 2015	Moderate	Low	Moderate	Moderate	Moderate	Moderate
Anderson 2009	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Ariza 2006	Moderate	High	Moderate	Low	Low	Low
Banks 2015	High	Low	Moderate	Moderate	High	High
Chamelian 2004	Moderate	Low	Low	Moderate	Moderate	Low
Crawford 2002	Moderate	Low	Moderate	Moderate	Moderate	Low
Eramudugolla 2014	Low	Moderate	Low	Moderate	High	Low
Han 2007	Moderate	Moderate	Moderate	Low	Moderate	Low
Han 2009	Moderate	Low	Moderate	Moderate	High	Low
Isoniemi 2006	Moderate	High	Moderate	Low	High	Low
Jiang 2006	Moderate	Low	Moderate	Moderate	Moderate	Low
Kristman 2008	Moderate	High	Moderate	Low	Low	Low
Lee 2017	Low	High	Low	Low	High	Moderate
Liberman 2002	Low	High	Moderate	Low	Low	Low
Lichtman 2000	Moderate	High	Moderate	Moderate	Moderate	Low
Mejia 2016	High	Moderate	Moderate	Low	Moderate	Moderate
Merritt	Low	Moderate	Low	Low	High	Low
Miller 2010	Low	Moderate	Moderate	Low	Moderate	Moderate
Müller 2009	Moderate	High	Moderate	Low	Moderate	Moderate
Nielson 2017	Low	Low	Low	Low	Moderate	Low
Noé 2010	Low	High	High	Low	Moderate	Moderate
Olivecrona 2012	High	Moderate	Moderate	Moderate	Moderate	Moderate
Olivecrona 2017	Moderate	Low	Moderate	Low	Moderate	Moderate
Ost 2008	Low	Low	Moderate	Low	High	High
Padgett 2016	Low	Moderate	Low	Low	Moderate	Low
Rapoport 2008	Low	Moderate	Moderate	Moderate	Moderate	Moderate
Røe 2016	High	High	Moderate	Low	Moderate	High
Shadli 2011	Moderate	Low	Moderate	Low	Moderate	Low
Sundström 2004	Low	Low	Moderate	Moderate	Moderate	Low
Sundström 2007 (1)	Low	Low	Moderate	High	High	Low
Sundström 2007 (2)	High	Low	Moderate	Moderate	Moderate	Moderate
Teasdale TW 2000	High	Low	Moderate	High	Moderate	Moderate
Yue 2017	Low	Low	Low	Moderate	Moderate	Low
Jiang 2007	Moderate	Low	Moderate	Moderate	Moderate	Low
Lendon 2003	High	High	Low	Moderate	Moderate	Low

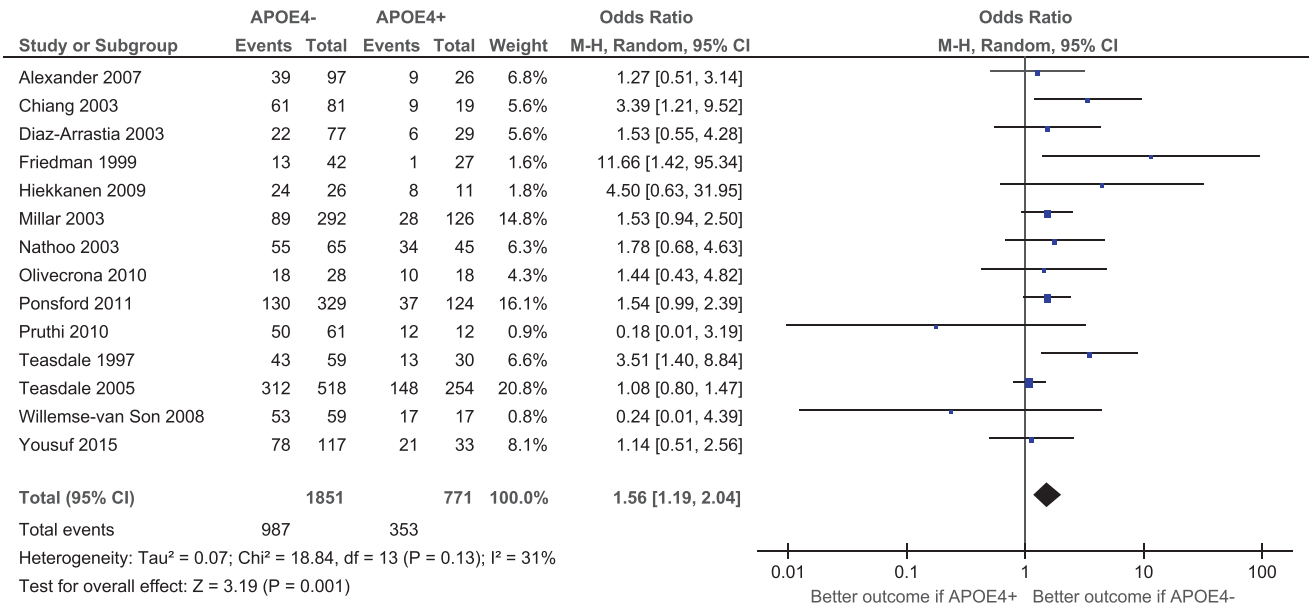
Ax, analysis; Mx, measurement.



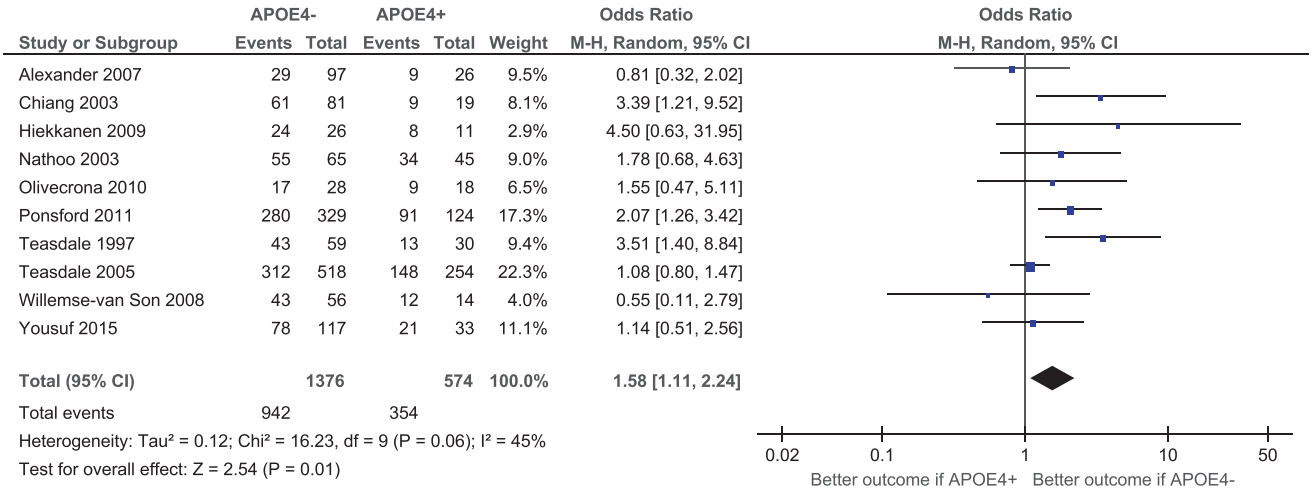
SUPPLEMENTARY FIG. S1. Sensitivity analysis 1 - Global Outcome (last recorded score, all studies).



SUPPLEMENTARY FIG. S2. Sensitivity analysis 2—Global Outcome (6 months or closest, GOS 4-5/GOS-E 7-8, all studies). GOS, Glasgow Outcome Score.



SUPPLEMENTARY FIG. S3. Sensitivity analysis 3—Global Outcome (last recorded score, GOS 4-5/GOS-E 7-8, all studies). GOS, Glasgow Outcome Score.



SUPPLEMENTARY FIG. S4. Sensitivity analysis 4—Global outcome (6-month data or closest, omitting high risk of bias studies).

Supplementary Table S3. Grading of Recommendations Assessment, Development and Evaluation (GRADE) Evaluation of APOE Studies with regard to Global Outcomes

Prog factor	n	*Studies (*n*)*	*Cohorts (*n*)*	*Effect size (CI)*	*Phase*	*SL*	*Inc*	*Ind*	*Imp*	*Pub bias*	*Effect size*	*Dose effect*	*Overall quality*
APOE	2593	14	14	OR 1.39 (1.05–1.84)	2	X	✓	✓	✓	✓	–	–	Low

Publication bias assessed by Funnel Plot.
✓ = no serious limitations.
X = serious limitations.
– = not present.
Prog, prognostic: CI, confidence interval; SL, study limitations; Inc, inconsistency; Ind, indirectness; Imp, imprecision; OR, odds ratio.

SUPPLEMENTARY TABLE S4. RESULTS OF STUDIES' EFFECT OF APOE ON OTHER OUTCOMES

Anderson 2009	Treatment/Comparator	OC	6 mo	12 mo	Comment
			M	M	No SD's given in tables; scores reported
	APOE4- (n = 36)	SRT, Sum of Recall	81	83	are M SRCL scores following adjustment
	APOE4+ (n = 15)	SRT, Sum of Recall	71	71	for seizure occurrence, TBI severity, education and genotype. APOE4- perform better at both testing points: p = 0.027 at 6 months p = 0.012 at 12 months No comparisons significant prior to above adjustments.

Crawford 2002	Treatment/Comparator	OC	6 months		Comment
			M	SD	
	APOE4- (n = 80)	Learning slope	0.91	0.63	Table shows memory test domains of California
		Trial 5	8.91	3.64	Verbal Learning Test - all four results significant
		Short-Delay Free Recall	6.63	4.2	for APOE4+ performing worse than APOE4-
		Long-Delay Free Recall	6.8	4.29	Learning slope p = 0.036
	APOE4+ (n = 30)	Learning slope	0.62	0.63	Trial 5 p = 0.033
		Trial 5	7.23	3.42	Short-Delay Free Recall p = 0.019
		Short-Delay Free Recall	4.5	4.07	Long-Delay Free Recall p = 0.022
		Long-Delay Free Recall	4.63	4.54	

Han 2007	Treatment/Comparator	OC	4–5 weeks post TBI		Comments
			M	SD	APOE4+ perform better, p = 0.008. As a secondary
	APOE4- (n = 62)	CVLT List A	38.75	9.46	outcome, groups reanalysed with adjustment for differing
	APOE4+ (n = 16)	CVLT List A	46.19	10.85	proportions of mild/moderate TBI - following this 2 measures of D-KEFS and one on WAIS become ''near significant'' for better performance in APOE4+ (p = 0.2–0.8) and CVLT measure becomes less significant (p = 0.04). Severity balanced subgroups created by random selection of participants and re-analysis of new balanced groups.

Han 2009	Comments
	Authors present a hierarchical tree model from ODA for predicting job status change following TBI: APOE4+: greater immediate vs delayed memory differences (CVLT-II change in long delay as a % of short delay free recall) predicts no job change p = 0.005594; 6/7 correctly classified as no job change, 8/9 correctly classified as job change. APOE4-: job change is predicted by recognition memory (CVLT-II) if >18.5 on Kennedy-Johnson Postconcussive Symptom Scales, but by (WASI) IQ score if fewer postconcussive symptoms.

Isoniemi 2006	Treatment/Comparator	OC	Baseline		Follow-up		Comment
			M	SD	M	SD	MDB = mild deterioration battery. Eight tests from other scales
	APOE2+ (n = 10)	MDB score	3.9	3.7	3.7	5.38	(e.g. WASI), with 'deterioration points' awarded depending
	APOE3/3 (n = 32)	MDB score	2.5	3.96	3.5	5.09	on how far below norm of age/education controlled group
	APOE4+ (n = 19)	MDB score	4.4	3.92	7.4	5.23	a subject is. 1 point = 1.5 SD below norm, 2 points = 2 SD below norm, 3 points = 3 SD below norm. Maximum score = 24 points, the higher a subject's score, the further below the norm that individual is performing. p = 0.034 for worse performance in APOE4+ vs others by ANOVA at follow-up (i.e. higher scores at follow-up; stands up to Bonferroni correction). No statistically significant difference in baseline scores between groups.

Jiang 2006	Treatment/Comparator	APOE4+ %	APOE4- %	Comments
	Clinical deterioration (n = 19)	36.8	63.2	Following adjustment for age, sex, smoking, alcohol, mechanism,
	Clinical stabilisation (n = 91)	11	89	GCS, CT findings, APOE4 carriers found to be statistically significantly over-represented in clinical deterioration group: OR for deterioration (APOE4+ vs APOE4-) 4.725 (1.511–14.780) p = 0.008

Kristman 2008	Treatment/Comparator	OC	4 years		Comments
			M	SD	Relative risk for concussion rate
	APOE4- (n = 239)	Concussion rate per 10,000 exposures	6.7	23.3	(APOE4+ vs 4-): RR 1.2 (0.5–2.6)
	APOE4+ (n = 79)	Concussion rate per 10,000 exposures	7.9	24.7	

(*continued*)

SUPPLEMENTARY TABLE S4. (CONTINUED)

Liberman 2002	Treatment/Comparator	OC	3 weeks post-TBI Difference in M score (APOE4+ vs APOE4-)	SE	Comment
	APOE4- (n = 62) vs APOE4+ (n = 18)	Grooved pegboard	−16.3	5.5	PASAT = paced auditory serial addition test; subject presented with 3 numbers and must state sums of a+b then b+c, e.g ''3, 5 and 9'' - correct response ''8 and 14''. '2.8s' in name refers to speed at which digits are presented. Values presented are adjusted difference in Ms and SE for APOE4+ vs APOE4-. At 3 weeks, p = 0.005 for pegboard and p = 0.004 for PASAT. Whilst initial performance impaired to a greater extent in APOE4+ patients 3 weeks following TBI, this difference had disappeared by 6 weeks (all p values >0.1)
		PASAT 2.8s trial	−3.3	1.1	

Lichtman 2000	Treatment/Comparator	OC	6 months M	SD	Comment
	APOE4- (n = 24)	FIM corrected for coma	121.3	6.37	Functional Independence Measure (FIM) (after adjustment for coma) lower in APOE4+ subjects p = 0.050, i.e. e4 allele predisposes to poorer rehabilitation outcome. This is driven by worse motor outcome - p = 0.026 for worse motor FIM in APOE4+, p = 0.247 for sensory FIM.
	APOE4+ (n = 7)	FIM corrected for coma	117.9	6.61	

Miller 2010	Comments
	No statistically significant association between APOE genotype and either early or delayed post-traumatic seizures (PTS). Only four E4 homozygous patients in cohort, of whom two developed late PTS - authors conclude that 4/4 may be a risk genotype for delayed onset PTS.

Müller 2009	Comments
	Authors calculated an ''impairment index'': (number of parameters with score >1.5 SD variation from norm) / (total number of parameters) i.e. impairment index of 0 implies subject has not scored worse than norm on any measure, index of 1 implies worse than norm on every measure. Once adjusted for GCS, CT/MRI findings, S-100B, age - APOE4+ had higher 6 month impairment index than APOE4- (difference 0.08, 95%CI 0.03–0.14, p = 0.006), and a smaller reduction in impairment index from baseline to followup (i.e. lesser recovery) p = 0.046

Noé 2010	Treatment/Comparator	OC	APOE4+ % of cohort	Comment
	PTA cohort (n = 67)	Emergence from PTA	25.4% (n = 14)	APOE4 incidence in those who were in PTA but emerged during the study period, and those who did not emerge, did not differ significantly. Amongst those already out of PTA at admission, there was a genotype effect on scores (both at admission and at followup); for the WMI WAIS-III there was a ''Time x Genotype'' interaction for the degree of improvement in TAVEC (spanish language CVLT) scores - APOE4 performed worse and had improved less at follow-up.
		Persistent PTA	25% (n = 3)	

Rapoport 2008	Treatment/Comparator	OC	1 year	2 years	Comment
	TBI	Dementia	4/49 (8.2%)	1/30 (3.3%)	Chi-squared for effect of TBI on MCI/development of dementia p = 0.882
		Mild cog impairment	2/49 (4.1%)	2/30 (6.7%)	
	Controls	Dementia	0/68	0/46	Chi-squared for TBIxAPOE on MCI/development of dementia p = 0.127 i.e. no observed effect of either TBI or APOE4 on development of cognitive difficulties in this cohort
		Mild cog impairment	5/68 (7.4%)	2/46 (4.3%)	

Shadli 2011	Comments
	No differences between APOE4+ and APOE4- groups on any of AVLT, COWA, WCST, trail making test B. Both groups perform poorly initially but improved significantly and to a statistically similar level between week 6 and month 6 post-injury.

(*continued*)

Sundström 2004	Treatment/Comparator	OC	Pre-injury M	Pre-injury SD	Post-injury M	Post-injury SD	Comment
	TBI APOE4- (n = 23)	Recall (divided)	3.96	0.88	3.78	1.09	Verbal recall of word lists immediately following presentation tested under conditions of focussed attention during encoding, and divided attention during encoding (distractor task consisting of sorting cards according to colour). APOE4+ subjects had a significant drop in performance on the divided attention task following head injury, whereas APOE4- subjects, and matched APOE4+ non-TBI controls did not suffer a decline in performance between the 2 testing points ($p < 0.05$). 10 participants had a pre-post injury drop of >1 SD on 2 or more tests - 6 were APOE4+ (6/11, 54% of that genotype) and 4 APOE- (4/23, 17%) - $P < 0.05$ for association between genotype and significant decline in performance on multiple tests.
	TBI APOE4+ (n = 11)	Recall (divided)	4.45	1.21	3.64	0.81	

Sundström 2007 (1)	Treatment/Comparator	Outcome	APOE4+ (n = 12) %	APOE4+ (n = 12) n	APOE4- (n = 19) %	APOE4- (n = 19) n	Comment
	mild TBI (n = 31)	Fatigue post-injury	58	7	32	6	Total numbers of APOE4+/- subjects not given in paper; calculated from % of whole mTBI group with fatigue post-injury and % with fatigue for each genotype. APOE4+ mTBI subjects more fatigued than APOE4- mTBI subjects post-injury ($p < 0.05$), and more fatigued than APOE4+ controls post-injury ($p = 0.02$). APOE4- mTBI subjects were not more fatigued post-injury than APOE4- controls (32% vs 21%, $p = 0.52$).

Sundström 2007 (2)	Treatment/Comparator	OC	APOE4+ number affected (%)	N	APOE4- number affected (%)	N	Comment
	Dementia (n = 181)	Head injury	13 (14.9%)	87	12 (12.8%)	94	OR for dementia following head injury, via comparison to non-head injured APOE4- subjects (reference):
		No head injury	74 (85.1%)	87	82 (87.2%)	94	
	Controls (n = 362)	Head injury	10 (10.5%)	95	36 (13.5%)	267	TBI APOE4 + 5.2 (2.0–14.0) $p < 0.001$
		No head injury	85 (89.5%)	95	231 (86.5%)	267	TBI APOE4- 0.9 (0.4–1.8) (NS) control APOE4 + 3.0 (1.9–4.7) $p < 0.001$ i.e. increased risk of dementia following mTBI only manifests in APOE4+ subjects, by exacerbating their already higher background risk.

Teasdale 2000	Comments	
	Cohort includes CVA and TBI patients admitted to rehab, with no separate raw data for TBI subjects. Authors do report that overall at 1 year follow-up APOE4+ subjects were more disabled (and APOE4- less disabled) relative to pre-admission on measures of cognition, depression, impulsivity, somatization, motivation, isolation and communication, remains significant when analysing purely TBI cases ($p < 0.025$). Overall the groups differed on global scale by 0.87 SD.	

Jiang 2007	Treatment/Comparator	APOE promoter-491 AA %	APOE promoter-491 AT/TT %	Comments
	Clinical deterioration (n = 19)	84.20%	15.80%	Higher proportion of -491AA deteriorate than AT/TT.
	Clinical stabilisation (n = 91)	67%	33%	OR for clinical deterioration if -491AA genotype (vs AT/TT) - OR 11.681 (1.824–74.49) $p = 0.009$ (after adjustment for injury severity, age, GCS, CT findings, smoking, gender, alcohol, age).

Eramudugolla 2014	APOE4 status x History of TBI x Age	Outcome	Comments
		CVLT, reaction time, Wechser working memory test	In the youngest cohort, APOE4 carriers who reported a TBI erformed worse than APOE3 homozygotes on measures of episodic memory - on subgroup analysis this was driven by moderate/severe TBI subjects. On average APOE4 carriers whose first TBI was as a child performed better on verbal ability than APOE3 homozygotes. In 40s cohort only those with childhood TBI had different performance based on genotype (APOE4 carriers slower reaction times). No genotype effect in oldest cohort.

(*continued*)

SUPPLEMENTARY TABLE S4. (CONTINUED)

Banks 2015	APOE4 status	Thalamic & hippocampal volume, verbal memory scores	Conference abstract. Combat sports participants. Worse performance on verbal memory scores amongst APOE4+ participants but no differences in thalamic or hippocampal volume on imaging between genotypes.
Merritt 016	APOE4 status	Post Concussion Symptom Scale	APOE4+ college athletes with had increased post-concussive symptom burden by PCSS (on average tested 7.8 days post injury).
Padgett 2016	Three APOE genotype groups	COWAT, TMT, WAIS-III	No difference in measures of working memory between any of the three genotypes studied (3/4 & 4/4 vs 3/3 vs 2/3 & 2/2)
Mejia 2016	APOE genotype	Multilinear regression for factors associated with lower DRS	Age and APOE3 containing genotypes (2/3, 3/3, 3/4) associated with better outcome (lower DRS) at $p < 0.05$

SUPPLEMENTARY TABLE S5. CHARACTERISTICS OF STUDIES OF APOE GENE (MEASURING ALL OTHER OUTCOMES)

			Participants							
						Severity				
Study ID	*Setting (country)*	*Design*	*Number (n=)*	*Age (m, SD or range)*	*Gender (M, %)*	*GCS (m± SD)*	*GCS 3–8 (n, %)*	*GCS 9–12 (n, %)*	*GCS 13–15 (n, %)*	*OC*
Anderson 2009	Hosp. (USA)	Retr. cohort	APOE4-: 36	33.9±11.8	32 (89)	NR	53% uncons. >24h, 28% 1–24h, 19% <24h			SRT
			APOE4+: 15	38.2±10.1	13 (87)	NR	40% uncons. >24h, 53% 1–24h, 7% <24h			
Banks 2015	Com. (USA)	Retr. Cohort	Total: 120	28	NR	NR	NR	NR	NR	Hippocampal & thalamic volume on MRI, verbal memory testing
Crawford 2002	Hosp. (USA)	Pros. cohort	APOE4-: 80	33.6±14.2	(100)	8±4.38	NR	NR	NR	CVLT
			APOE4+: 30	32.3±11.6	(100)	8.17±4.24	NR	NR	NR	
Eramudugolla 2014	Com. (Australia)	Retr. cohort	20s: 2077	22.61±1.51	969 (46.7)	Mild: 176 (8.5%)	Mod/sev: 31 (1.5%)			CVLT, reaction time, Wechsler WM
			40s: 2124	42.62±1.49	979 (46.1)	Mild: 128 (6%)	Mod/sev: 55 (2.6%)			
			60s: 2132	62.51±1.51	1076(50.5)	Mild: 66 (3.1%)	Mod/sev: 33 (1.5%)			
Han 2007	Hosp. (USA)	Pros. cohort	APOE4-: 62	25.3±5.8	59 (95.2)	NR	0	19 (30.6)	43 (69.4)	CVLT
			APOE4+: 16	22.6±3.8	13 (81.3)	NR	0	8 (50)	8 (50)	
Han 2009	Hosp., (USA)	Pros. cohort	APOE4-: 30	25.2±6.1	29 (96.7)	NR	0	13 (43.3)	17 (56.7)	Change in job
			APOE4+: 16	22.6±3.8	13 (81.3)	NR	0	8 (50)	8 (50)	
Isoniemi 2006	Hosp. (Finland)	Retr. cohort	APOE2+: 10	60.6±12.2	5 (50)	NR	7 (70)	1 (10)	2 (20)	MDB
			APOE3/3: 32	59.4±8.9	23 (72)	NR	16 (50)	9 (28)	7 (22)	
			APOE4+: 19	61.4±10.6	14 (74)	NR	9 (47)	4 (21)	6 (32)	
Jiang 2006	Hosp. (China)	Pros. cohort	Clin. det: 19	NR	15 (78.9)	NR	10 (52.6)	GCS >8: 28 (30.8)		APOE4 incidence between groups
			Clin. Stab: 91	NR	65 (71.4)	NR	9 (47.4)	GCS >8:63 (69.2)		
Kristman 2008	Com. (Canada)	Pros. cohort	APOE4-: 239	20.4±2.3	127 (53.1)	≥1 prev. conc'n: 130 (56)				Conc'n rate*
			APOE4+: 79	20.9±2.8	37 (46.8)	≥1 prev. conc'n: 45 (62.5)				
Lee 2017	Hosp. (Taiwan)	Pros. cohort	APOE4-: 154	40.1±15.15	60 (39)	14.9±0.38	0	0	154	Sleep quality (PSQI)
			APOE4+: 35	42.2±14.76	16 (45.7)	15±0	0	0	35	
Liberman 2002	Hosp. (USA)	Pros. cohort	APOE4-: 79	33.9% <30, 32.3% 30–49, 33.9% 50+	(56.6)	NR	(0)	(8.1)	(91.9)	PASAT, GPT
			APOE4+: 18	22.2% <30, 50% 30–49, 27.8% 50+	(72.2)	NR	(0)	(16.7)	(83.3)	
Lichtman 2000	Hosp. (USA)	Pros. cohort	APOE4-: 24	34.3±18.1	17 (70.8)	Coma length (days±SD)=36.4±58.3				FIM (6)
			APOE4+: 7	39.8±15.3	5 (71.4)	Coma length (days±SD)=7.5±8.5				
Mejia 2016	Hosp. (USA)	Pros. cohort	Total: 170	NR	134 (78.8)	NR	170 (100)	0	0	DRS at 3 & 6 months
Merritt 2016	Com. (USA)	Retr. Cohort	APOE4-: 27	20±1.59	23 (85.2)	NR	All mTBI, 3 (11.1%) loss of consciousness			Post-Concussion Symptom Scale (average 7.8 days post injury)
			APOE4+: 15	19.93±1.39	12 (80)	NR				
Miller 2010	ITU (USA)	Pros. cohort	APOE4-: 243	NR	(77)	100% GCS 3–8, median GCS 6				Seizures
			APOE4+: 79	NR	NR					
Müller 2009	Hosp. (Norway)	Pros. cohort	Whole cohort: 59	35.1 (18 – 74)	47 (79.7)	14.7±0.57	NR	NR	NR	Impairment index
Noé 2010	Rehab. (Spain)	Pros. cohort	Pers. PTA; 12	39.9±18.2	48 (71.6)	4.6±2.3		NR		APOE4 incidence betw. gps; WAIS, TAVEC**
			Emer. PTA: 55	29.2±14.5		7.1±10.6		NR		
			Not in PTL: 59	29.5±10.5	42 (71.2)	NR		NR		

(*continued*)

SUPPLEMENTARY TABLE S5. (CONTINUED)

			Participants							
						Severity				
Study ID	*Setting (country)*	*Design*	*Number (n=)*	*Age (m, SD or range)*	*Gender (M, %)*	*GCS (m± SD)*	*GCS 3–8 (n, %)*	*GCS 9–12 (n, %)*	*GCS 13–15 (n, %)*	*OC*
Padgett 2016	Com. (Australia)	Pros. Cohort	APOE4+: 37	40.62±17.47	19 (51)	NR	1 (4.8)	1 (4.8)	34 (70.27)	COWAT, TMT, WAIS-III (testing on remission from PTA). All genotypes missing some severity data.
			APOE3/E3: 92	39.89±16.89	49 (53)	NR	4 (5.7)	3 (2.8)	82 (86.8)	
			APOE2+: 13	41.37±17.69	9 (69)	NR	0	0	12 (92.3)	
Rapoport 2008	Hosp. (Canada)	Pros. case-control	TBI n=69	67±7.9	(47.8)	NR	0	32 (46.4)	37 (53.6)	Dementia or MCI (1, 2 y)
			Controls n=78	68.0±8.5	(48.1)					
Shadli 2011	Hosp. (Malaysia)	Pros. cohort	APOE4-:13	26.1±6.8	NR	13.3±2.06	NR			WCST, TMT, RAVLT, COWAT
			APOE4+:6	25.0±8.63	NR	13.0±2.00	NR			
Sundström 2004	Com. (Sweden)	Retr. cohort	APOE4-: 23	55.9±12.6	11 (47.8)	NR	Single mTBI: 19 (82.6)		>1 mTBI: 4 (17.4)	Word recall
			APOE4+: 11	58.2±16.3	6 (54.5)	NR	Single mTBI: 9 (81.8)		>1 mTBI: 2 (18.2)	
Sundström 2007 (1)	Com. (Sweden)	Retr. cohort	TBI: 31	55.2±13.6	18 (58.1)	NR	NA	NA	(100) mTBI	Fatigue
Sundström 2007 (2)	Com. (Sweden)	Retr. cohort	Dementia: 181	73.2±7.8	59 (32.6)	NR	Single mTBI: 25 (13.8)		>1 mTBI: 4 (2.21%)	Incidence of dementia following mild TBI
			Controls:362	72.6±7.5	118 (32.6)	NR	Single mTBI: 46 (12.7)		>1 mTBI: 11 (3.04)	
Teasdale TW 2000	Rehab. (Denm.)	Pros. cohort	APOE4-: 29	31.4±10	19 (65)	TBI: 14 (48)	NR	NR	NR	EBIQ (1 y)
			APOE4+: 10	38.6±12.5	6 (60)	TBI: 4 (40)	NR	NR	NR	
Yue 2017	Hosp. (USA)	Pros. cohort	APOE4-: 79	39.7±16.5	49 (62)	NR	16 (20%) GCS 13–14, 63 (80%) GCS 15			CVLT-II
			APOE4+: 35	49.6±13.6	30 (38)	NR	7 (20%) GCS 13–14, 28 (80%) GCS 15			
					APOE Promoter Gene					
Jiang 2007	Hosp. (China)	Retr. cohort	Deteriorated 19	NR	15 (78.9)	NR		GCS <8: 10 (52.6) GCS >8: 28 (30.8)		Incidence of early clinical deterioration
			Stabilised 91	NR	65 (71.4)	NR		GCS <8: 9 (47.4) GCS >8: 63 (69.2)		
Lendon 2003	Hosp. (UK)	Retr. cohort	TBI: 90	38 (<1–82)	(82)	NR	NR	NR	NR	GOS (6)

COWAT, Controlled Oral Word Association Test, CVLT, California Verbal Learning Test, betw., between, clin., clinical, com., community, conc'n, concussion, Denm.=Denmark, det., deterioration, EBIQ, European Brain Injury Questionnaire, Emer=emerging from. FIM=Functional Independence Measure, GCS, Glasgow Coma Scale, GCS=Glasgow Outcome Scale, gps., groups, GPT, Grooved Pegboard Test, hosp.=hospital, ITU=Intensive Therapy Unit, m=mean, M, male, MDB, Mild Deterioration Battery, mTBI, mild traumatic brain injury, OC, outcome, NA, not applicable, NR, not reported, PASAT, Paced Auditory Serial Addition Test, Pers., persistent, PSQI=Pittsburgh Sleep Quality Index, PTA, post-traumatic amnesia, prev.=previous, Pros., prospective, Rehab., rehabilitation, RAVLT=Rey Auditory Verbal Learning Test, retr., retrospective, SD, standard deviation, SRT, Selective Reminding Test, stab., stabilization, TAVEC, Test de Aprendizaje Verbal Complutense (Spanish CVLT), TBI, Traumatic brain injury, TMT, Trail making test, WAIS, Wechsler Adult Intelligence Scale, WCST, Wisconsin Card Sorting Test, WM, Wechsler Working Memory testing. *Measured as concussion rate per 10,000 sports exposures over 4 years, **measured after emergence from post-traumatic amnesia