Apolipoprotein E4 polymorphism and outcomes from traumatic brain injury : a living systematic review and meta-analysis

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TITLE

The Apolipoprotein E4 polymorphism and outcomes from traumatic brain injury: a living systematic review and meta-analysis

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The APOE4 polymorphism & TBI: a systematic review

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ABSTRACT

The mortality of traumatic brain injury (TBI) has been largely static despite advances in monitoring and imaging techniques. Substantial variance exists in outcome, not fully accounted for by baseline characteristics or injury severity, and genetic factors likely play a role in this variance. The aims of this systematic review were to examine the evidence for a link between the Apolipoprotein E4 (APOE4) polymorphism and TBI outcomes and, where possible, to quantify the effect size via meta-analysis.

We searched EMBASE, MEDLINE, CINAHL and grey literature in December 2017. We included studies of APOE genotype in relation to functional adult TBI outcomes. Methodological quality was assessed using the Quality in Prognostic Studies Risk of Bias Assessment Instrument and the prognostic studies adaptation of the GRADE tool. In addition we contacted investigators and included an additional 160 patients whose data had not been made available for previous analyses, giving a total sample size of 2593 patients.

Meta-analysis demonstrated higher odds of a favourable outcome following TBI in those not possessing an ApoE ε4 allele as compared to ε4 carriers and homozygotes (OR 1.39, 95% CI 1.05 to 1.84, p = 0.02). The influence of APOE4 on neuropsychological functioning following TBI remained uncertain, with multiple conflicting studies. We conclude that the ApoE ε4 allele confers a small risk of poor outcome following TBI, with analysis by TBI severity not possible based on the currently available published data. Further research into the long term neuropsychological impact and risk of dementia is warranted.

KEYWORDS

Traumatic brain injury; genetics; outcome; prognosis; living systematic reviews

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MANUSCRIPT

Introduction

Traumatic Brain Injury (TBI) is a substantial health problem, which shows substantial variance in outcome, only about a third of which can be accounted for by known covariates.[1] There is an increasing interest in exploring whether some of the unexplained variance may arise from genetic differences in processes involved in cognitive reserve, injury mechanisms, repair mechanisms, or neurodegenerative processes. Several genes have been explored in this context, and the polymorphisms studied include those coding for Brain Derived Neurotrophic Factor (*BDNF*), cytokine, neurotransmitter and mitochondrial gene families, and other individual candidate genes. However, the commonest focus of study in this context has been variations in the *APOE* gene, which codes for Apolipoprotein E. Since the original report[2] of worse outcomes in TBI patients possessing the ε4 allele of Apolipoprotein E (*APOE*), a large number of studies have tested the influence of sequence variants in specific genes on mortality, functional and neuropsychological outcomes. The mechanisms by which APOE polymorphisms might modulate these outcomes are detailed in the Supplementary Appendix. This manuscript is one of a pair of systematic reviews addressing the effect of genetic variation in TBI, and will concentrate on the effect of the *ε*4 allele of *APOE*. A companion systematic review, which addresses non-*APOE* genes, has recently been published.[3]

APOE is undoubtedly the most extensively studied gene in the field of TBI. It codes for a 34kDa protein, which has a central role in CNS lipid transport, including movement of cholesterol into cells to aid repair processes in damaged neurones. Three common alleles have been characterised (*ε2, 3,* and *4*), which code for protein isoforms E2, E3 and E4. The literature to date supports an association between possession of the *ε4* allele and a variety of negative neuropsychiatric outcomes, including a dose-dependent increase in the risk of late onset Alzheimer's disease as well as intracerebral haemorrhage.[4] There is some evidence that APOE2 may exert a neuroprotective effect opposite to that of E4, but its relatively low population incidence is a limiting factor in research. The neurochemical mechanisms for toxic effects of APOE4 have been reviewed extensively.[5] In brief, it is thought that the E4 isoform (which uniquely contains an arginine replacing a cysteine at

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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, releasing neurotoxic fragments into the cytosol, where they impair mitochondrial and cytoskeletal function, potentially leading to cellular apoptosis. There is evidence that APOE4 inhibits neurite outgrowth (unlike E2/E3, which encourage it) and that release of pro-inflammatory mediators (IL-6, nitric oxide) from stimulated microglia is greater in the presence of E4. Traumatic brain injury involves a mechanical insult triggering a complex pathogenic process, with inflammation and neurotoxicity featuring prominently in the development of secondary brain injury.[6] As the E4 isoform has been shown to exhibit a number of pathological functions with respect to these processes, it has been hypothesised that TBI patients who are homo- or heterozygous for the *ε4* allele may experience a more severe TBI for a given cause of injury, with greater secondary injury and impaired capacity for recovery.

With regard to the previously published data on this topic, there have been many reviews that have tried to collate the available data at different times. For brevity, we have concentrated on the most recent of these, which examine the effect of APOE genotype on global functional outcome from TBI, both of which reported an increased incidence of poor outcome in carriers of the risk of the *ε4* allele.[7,8] . A separate meta-analysis, examining purely cognitive outcome measures, found that no firm association between APOE alleles and post-TBI function could be demonstrated.[9] A narrative systematic review of APOE and TBI outcomes reported a deleterious effect of APOE4 on functional outcomes in severe TBI but no consistent association in milder injury.[10]

The aim of this meta-analysis and systematic review is to provide a comprehensive report of the association between APOE variants (focusing on the effect of possession of an *ε4* allele) and outcome in adults suffering TBI. We have divided outcomes of interest into "global" measures such as the Glasgow Outcome Score, which represent overall levels of disability after injury, and more detailed neuropsychiatric and cognitive assessments such as measures of verbal reasoning and executive functioning. We report a meta-analysis of

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global outcomes, and narratively summarise the evidence regarding neuropsychiatric & cognitive recovery. It is important to point out that our meta-analysis includes substantial unpublished data not available to those authors of the recent meta-analyses discussed above; concordances and discordances with these reviews are covered in detail in the Discussion section.

Materials & Methods

This review was conducted and reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.[11] A protocol was registered on 06/10/2014 with the University of York's International Prospective Register of Systematic Reviews (PROSPERO) database (registration number CRD42014013623, available at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014013623).

This review is being prepared as a 'living systematic review' as part of the CENTER-TBI project (www.center-tbi.eu).[12] A living systematic review is a high quality, up-to-date online summary of health research that is updated as new research becomes available.[13] In practice, this means that the searches will be re-run and any new studies incorporated into the review. We will seek to publish regular updates.

Search methods for identification of studies

In May 2014, EMBASE, MEDLINE and CINAHL (all via NICE Healthcare Databases) and Google Scholar were searched for published studies, and conference abstracts published in peer reviewed journals indexed in the above databases. Developed with search experts at Monash University's National Trauma Research Institute (NTRI), the search strategies used a combination of keywords and MeSH terms (see Online Appendix). Study reference lists were manually reviewed to identify relevant publications not identified by the search strategy. Conference abstracts prompted further PubMed searches to discover whether the data had subsequently been published in full. Searches were re-run in August 2015, November 2016 and December 2017 using the identical protocol.

Selection Criteria

Citations were downloaded into Endnote (Thomson Reuters), duplicates removed, and were then screened by one author (CAM) on title/abstract using the following selection criteria:

1. Adult (16+) TBI patients
2. A functional outcome measure of any type, reported by patient genotype – this included the Glasgow Outcome Scale (GOS), Glasgow Outcome Scale – Extended (GOS-E), modified Rankin Scale (mRS), Disability Rating Scale (DRS), Neurobehavioral Rating Scale (NRS); as well as neuropsychological measures.
3. English language

Studies were excluded if they dealt with in-vitro/animal work, or included non-TBI/paediatric patients and did not report separate outcome data for the adult TBI cohort. Studies reporting non-functional outcome measures, such as histological findings at post-mortem, were also excluded.

After screening the remaining citations were reviewed in full text independently by 2 authors (CAM & VFJN/FAZ) to assess them for eligibility. Disagreements regarding eligibility were resolved by consensus, and referral to a third reviewer (DKM) was not required.

Quality Assessment

Risk of bias was assessed using the Quality In Prognostic Studies (QuIPS) criteria, a validated domain-based tool for quality assessment of prognostic studies.[14] Two authors (CAM and VFJN/FAZ) independently completed the QuIPS for each study, and then reached a final judgement on each of the six domains by consensus. In line with the guidance given by the team who developed QuIPS, no overall rating of quality is assigned to each study.

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Data Extraction

Citations and full text files were uploaded to Covidence (www.covidence.org). Two authors (CAM, and either VFJN or FAZ) worked independently, resolving disagreements through consensus. The following characteristics were extracted:

1. Inclusion/exclusion criteria
2. Baseline characteristics, where possible for each genotype within the cohort:
    a. Cohort gender composition
    b. Age (mean ± SD if available)
    c. TBI severity according to the Glasgow Coma Score (GCS) which was quantified, wherever possible, as mean GCS ± SD, or GCS grouped according to existing guidelines for classification.[15]
3. Outcome data (see below).
4. Funding source(s).

In the case of studies covering global functional outcomes (e.g. GOS/GOS-E, mRS, NRS, DRS, mortality), scores were extracted at all available time points for each genotype. The total numbers of patients assigned a given score at each time point were extracted and used to calculate the number of patients with a "favourable" outcome. Categorical scales were dichotomised in line with previously recognised methods for defining "favourable" outcomes, i.e. GOS 4 to 5, GOS-E 5 to 8.[16] When authors reported self-defined favourable or unfavourable outcomes without a breakdown of the underlying raw categorical data, this was extracted instead. If ordinal data were not available, the mean scores and standard deviations (or standard errors/95% confidence intervals) were extracted. In studies dealing with neuropsychological scales or other outcomes (e.g. measures of fatigue), reports of statistically significantly differences between genotype results (at the alpha level selected by the study's authors) were extracted, with a narrative note made of non-significant results. In the case of no significant results being reported, a narrative note of negative findings was made.

Data synthesis

Studies were subdivided for analysis by outcome measures. Where studies were sufficiently homogenous (in terms of gene studied, patient characteristics and outcome

measured) they were pooled statistically using RevMan 5.3 (Nordic Cochrane Centre 2014).[17] Only studies reporting global functional outcome scores in relation to APOE genotype were entered into meta-analysis.

The quality of evidence contributing to each pooled outcome was assessed according to the GRADE framework, modified for prognostic studies.[18] This examines eight factors; six that can downgrade the evidence (phase of investigation, study limitations, inconsistency, indirectness, imprecision, publication bias) and two that can increase it (moderate or large effect size, exposure-response gradient).

For the meta-analysis, outcome was extracted for dichotomised genotypes (APOE4 carriers vs non-carriers), with outcome scores dichotomised as GOS 4-5/GOS-E 5-8 representing a "favourable outcome". The primary meta-analysis was of outcome data at six months; one study (by Ponsford[19]) did not report six-month data, and so the next available time point (12 months) was used instead. Throughout the review, where not otherwise specified, "unfavourable outcome" or "poor outcome" is in reference to a GOS score of 1-3, or a GOS-E of 1-4, with "good" or "favourable" outcome referring to GOS 4-5 or GOS-E 5-8.

We employed the random effects model implemented in RevMan (Nordic Cochrane Centre 2014).[17] Between-study heterogeneity was explored with the Chi-squared test, and quantified using the I^2 statistic. Significant heterogeneity was defined as I^2>50%. A pooled effect estimate for the total study population was calculated as Mantel-Haenzel odds ratios and 95% confidence intervals (see http://handbook.cochrane.org/chapter_9/9_4_4_3_random_effects_method.htm for details). We defined the clinical importance of the observed associations as small (OR <2.5), moderate (2.5-4.25), or large (>4.25), in line with the definition proposed in a recent Cochrane prognostic review.[18]

Sensitivity analysis

During the data extraction process it became clear that there was variation in the manner in which outcome data were reported and interpreted by authors. Willmott et al[20] for

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example use a GOS-E score of 7 to 8 (living independently/return to work) as a marker of "good recovery" for their analyses. We recognize that identical odds ratios might be assumed if the GOS-E is considered as an ordinal scale, as is done with proportional odds regression analysis[21]. In addition, some studies reported outcome data over significantly longer time scales, ranging from 36 months to 25 years. The time point chosen for meta-analysis and outcome dichotomisation employed was not based on a priori scientific evidence, but reflected the most common practice of authors in the field. Post-hoc sensitivity analyses were therefore constructed:

1. 6 month outcome data (or next available time point) with GOS-E dichotomised in line with Willmott et al.
2. Last available time point, with GOS 4/5 or GOS-E 5-8 representing "favourable outcome".
3. Last available time point, with the Wilmott dichotomisation of GOS-E.
4. 6 month outcome data (or next available time point) but omitting studies rated as high risk of bias in 1 or more QuIPS domains.

Assessment of publication bias

For studies included in the meta-analysis, we examined funnel plot asymmetry (which may indicate the presence of publication bias), using RevMan 5.3 software (The Nordic Cochrane Centre). Where data was unable to be pooled we assessed the likelihood of publication bias qualitatively, based on included study characteristics, and the advice of experts within and beyond the author team about the possibility of relevant unpublished studies.

Results

Search Results

A total of 6925 citations were identified through database searches (see Figure 1). After removing duplicates, 6272 were screened on citation and abstract, with 6030 excluded. We obtained 242 citations in full text (including 91 review articles), of which 50 studies were excluded. The reasons for exclusion included non-TBI study populations and ineligible outcome measures (see Supplementary Table 1 for full details).

[FIGURE 1]

Included studies

Forty-nine studies examining APOE[2,19,22-68] were identified. Of these, twenty-one reported a global outcome such as GOS or GOSE,[2, 16, 19-33, 55, 59-61] and of these studies, fourteen[2, 16, 19, 22-28, 31-32, 55] provided sufficient detail for meta-analysis (see Table 1; which includes all 21 studies, and specifies the studies that were included in the meta-analysis). Study designs consisted of 38 prospective cohort studies, 10 retrospective cohort studies and 1 case-control study. Population sizes were heterogeneous; 21 studies included 100 or more patients and the remaining 28 less than 100.

[TABLE 1]

Our meta-analysis included data on 2593 subjects, of which 160 were additional individual patient data from two previous publications,[22,28] which were kindly provided by the study authors as the published manuscript did not contain enough data to be included in previous meta-analyses. We also contacted the corresponding authors of three other papers[23,24,33] to source raw data, but did not receive responses, preventing us from including these studies in our meta-analysis. We nonetheless include more patients than two recent meta-analyses.[8,7]

Risk of bias

The studies all constitute observational research, and in most there were areas of methodological weakness, even in otherwise well conducted studies. In 25 studies, one or more domains were judged to be at high risk of bias. For 13 studies this was due to concern regarding significant attrition of the study cohort, especially if demographic homogeneity between patients who did and did not drop out was not demonstrated by the authors. The included studies' risk of bias ratings for each of the 6 QuIPs domains can be seen in Supplementary Table 2.

Apolipoprotein E genotype and meta-analysis of functional outcomes

Twenty one studies investigated the relationship between APOE genotype and functional outcome in adult patients. Fourteen of these studies reported data in sufficient detail (or provided it on request) to allow entry into meta-analysis.

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The absence of the APOE4 genotype was associated with a significant increase in the odds of a favourable outcome in patients with TBI (OR 1.39, 95% CI 1.05 to 1.84, p = 0.02, see Figure 2). The low quality of the evidence meant that the confidence in this effect size was low. Due to the prevalence of mixed severity patient populations, subgroup analysis by TBI severity was deemed inappropriate – only two papers (Alexander[19] & Olivecrona[28]) studied purely severe TBI cohorts. The results of the four sensitivity analyses provided effect sizes which were consistent with the primary meta-analysis (Supplementary Figures 1-4, Appendix 8-11). Moderate heterogeneity was noted within the studies, with an I^2 statistic of 37%. The sensitivity analysis including only high quality studies (Supplementary Figure 4, Appendix 11) demonstrated a slightly stronger effect estimate (OR 1.58, 95% CI 1.11 – 2.24, p=0.01) but with slightly higher overall heterogeneity (I^2 45%).

[FIGURE 2]

The quality of the evidence for the association between APOE and functional outcome was rated as low, due to serious study limitations - most studies rated as moderate risk of bias. According to the GRADE framework for prognostic studies, this means our confidence in the effect estimate is limited and that the true effect may be substantially different from the estimate of the effect.[18] Details of the GRADE framework assessment can be found in the Supplementary Materials (Supplementary Table 3; Appendix 5). A funnel plot showed no evidence of publication bias in the reviewed literature (Figure 3).

[FIGURE 3]

Studies not included in meta-analysis

Studies which provided global outcome measures, but insufficient detail for meta-analysis, and those that reported on endpoints other than global outcomes, are summarised in Table 2. For studies that were not included in the meta-analysis, this table provides readers with a summary of the reported direction of effect (or absence of effect) of ApoE genotype on the endpoints of interest.

[TABLE 2]

Amongst studies which collected but did not fully publish global outcome measures, conflicting results were found. In studies of severe TBI patients, Lichtman et al[47] reported worse outcomes for APOE4+ patients on the Functional Independence Measure (driven by

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poor motor recovery), and Mejia[67] describe an association between APOE3+ genotypes and improved DRS scores at 6 months (including APOE 3/4 heterozygote patients). Chamelian[24] found no difference in mean GOS at 6 months amongst mild-mod TBI patients while Ost and colleagues[33] found an increase in mortality amongst APOE4+ men. Nielson and colleagues could not demonstrate an association between poor outcome and APOE genotype in their topological data analysis of the TRACK-TBI cohort.[63] Miller[48] found no effect of APOE genotype on early or delayed post-traumatic seizure occurrence in a severe TBI cohort. Jiang et al[43] suggest that APOE4 carriage increases the odds of early clinical deterioration within the first 7 days after injury, with Olivecrona[64] observing higher maximum intracranial pressures and an increased risk of requiring decompressive craniectomy within 36 hours of injury. Jiang et al extend their findings to the A-419T polymorphism in the APOE gene promoter region in a separate paper[42] and Lendon,[45] studying the G-219T promoter SNP, found the TT genotype experienced significantly worse outcomes at 6 months on the GOS scale.

Apolipoprotein E and neuropsychological outcomes

Studies investigating the effects of APOE4 carriage on neuropsychological outcomes also reported conflicting results. A broad overview of how the published evidence has been reported can be found in Supplementary Table 4 & 5 (Appendix 6 & 7). Regarding measures of working memory and verbal recall, Han[39] found that APOE4 carriers actually outperform APOE4– patients at 5 weeks post injury, whereas Anderson[37] and Crawford[38] demonstrated the opposite effect at 6 months. Shadli,[52] Padgett[61] and Millar[29] all found no difference in performance on multiple tests of executive functioning, working memory and verbal recall, despite in the case of Millar having demonstrated a significant difference in GOS between genotypes. Han et al[40] also found that change in job status (to a less demanding workload) following TBI was predicted by number of post-concussive symptoms and premorbid IQ amongst APOE4– patients, but by degree of memory impairment alone in APOE4+ patients, perhaps suggestive that a higher premorbid IQ does not protect against post-TBI cognitive impairment to the same degree amongst APOE4+ patients. Hodgkinson analysed 100 patients with severe TBI undergoing rehabilitation, and could find no cognitive differences between APOE genotypes at 6 months.[68] Liberman[46]

showed that APOE4+ predicts worse performance on tests of mental arithmetic (PASAT2.8 serial addition) 3 weeks after injury, but that patients have recovered to similar levels regardless of genotype by 6 weeks. A large Australian cohort of prior TBI patients analysed by Eramudugolla demonstrated significantly worse episodic memory performance in young APOE carriers (aged 20-24 at recruitment), and slower reaction times in middle aged APOE4+ TBI patients. The effect size in the younger cohort was driven chiefly by those with moderate or severe injuries, and no APOE4 x TBI interaction could be detected in the oldest (60-64 year old) cohort.[57] Merritt,[60] studying college athletes who had suffered a mild TBI in the last 3 months, showed an increase in post-concussive symptom burden amongst APOE4 carriers, and Banks[59] found worse verbal memory performance amongst APOE4+ combat sports participants. This latter finding was nonetheless not associated with a decrease in hippocampal or thalamic volume, leaving the physiological underpinnings of APOE4 mediated cognitive impairment unclear.

In the longer term, although the quality of evidence is variable, several publications suggest that APOE4 carriage predisposes to some degree of accelerated cognitive decline in the context of TBI, but no complete agreement between studies. Rapoport[51] et al found no increased incidence of dementia in the 2 years following TBI, regardless of genotype, whereas Isoniemi[41] followed patients up at an average of 30 years from injury, and found that APOE4+ subjects display greater deterioration on a composite neuropsychological battery, performing on average 7.4 SD below the norm for age. This difference however was driven entirely by the development of dementia in 6 of the 19 APOE4+ subjects, with no cognitive decline in the other 13. No APOE4– patients had developed dementia at follow-up, consistent with the well documented dementia risk associated with the ε4 allele. Sundström and colleagues have reported on head injury patients from the Betula longitudinal study being conducted in Sweden, which has recruited 4000 subjects from the general population since 1988 and carries out 5 yearly tests relating to ageing, cognition, and health. They report a significant deterioration in task performance amongst APOE4+ patients in 3 of 9 cognitive domains tested,[53] with increased measures of fatigue,[54] and an increased risk of developing dementia during the study period.[55] They found an odds ratio for developing dementia in the years following TBI in APOE4+ subjects (compared to

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APOE4- non-TBI controls) of 5.2 (95% CI 2-14), compared to 3 (95% CI 1.9-4.7) for APOE+ non-TBI controls, and 0.9 (95% CI 0.4-1.8) for APOE4– TBI patients. This suggests that the dementia risk in APOE4 carriers may be amplified following TBI.

Synthesis of the main results

We found 14 studies eligible for meta-analysis. Our main finding in this regard is that the overall effect of the APOE4 allele on early functional outcomes from TBI is a negative impact, which is quantified as small, based on criteria in a recent Cochrane prognostic review.[15] Over longer time scales such as those addressed by Isoniemi[41] and Sundström,[53-55] the evidence suggests that TBI may provide an additive factor in the already elevated background risk of dementia amongst APOE4+ patients. This increased incidence of dementia may account for worse performance on neurocognitive testing during long term follow-up.

It is worth noting that the drivers of poor outcome in some of the studies relating APOE4 allele carriage to cognitive outcome were not uniform across the study populations, and may have been heavily influenced by performance on a subset of cognitive tests, or the development of late dementia. While the implications for clinical practice remain to be defined, taken together, it seems reasonable to conclude that the APOE4 allele may have an adverse effect on neurocognitive recovery from TBI and dementia incidence over the long term, with a small impact on the acute clinical course and early outcome.

Discussion

An extensive research effort has been expended on uncovering associations between candidate genetic variants and TBI outcomes. It is likely that genetic variation constitutes a contributing influence rather than being a dominant driver of outcome in TBI, and the integration of this emerging information into clinical practice is still a work in progress. Genetic profiling might provide an additional prognostic factor which could be used to refine current prognostic schemes, with the more accurate prognostication allowing better risk adjustment in research and audit. It might also aid therapy stratification, either by targeting treatment based on risk of poor outcome, or based on mechanistic differences in

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patient subgroups. The first of these options would be realised by any improvement in overall prognostication. The second, while possible in principle,[69] will only be possible in practice if we identify mechanistic correlates that drive the differences in outcome impact from genetic variation. Because the clinical course of TBI is indeed a complex trait, successfully identifying genetic variants with an effect on outcome will require large sample sizes of homogenously characterized individuals. With regard to prognosis, there are currently no genetic variants which have been incorporated into existing models, although *APOE* represents an obvious candidate in this context.

On the basis of our meta-analysis we conclude that *APOE* ε4 has a small impact on shorter term outcomes (over a time scale of months to 2 years), as measured by functional assessments such as GOS or GOS-E. The conclusion of earlier publications, that the effect of APOE4 is more pronounced amongst severe TBI patients, could not be tested with sufficient statistical rigour based on the available evidence.

Assessment of data and analysis quality

We are confident that we identified all relevant published studies in the field of TBI genetics using a comprehensive search strategy, in line with PRISMA guidance. Unpublished data which have been provided to us were unavailable to previous systematic meta-analyses,[7,8] which added an additional 160 patients, resulting in a total of 2593 patients.

There are nonetheless limitations to this review. The summarized studies are underpowered, and the likelihood is high that negative results exist, but have not ever been published. Only one reviewer carried out the initial screening of studies (although full text review was carried out by two separate authors). It is likely we have missed studies published in the non-English literature. With the exception of four papers entered into meta-analysis, the remaining studies cover largely Caucasian populations, and in almost all studies the majority of patients were male. This former observation reflects the ethnic composition of the countries that are involved in leading TBI research and the latter the demographics of real-world TBI populations. We are confident that our main finding, that

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APOE4 has a small effect on initial recovery, is an accurate assessment of the true effect size, and is generalisable to adult non-penetrating TBI populations.

As can be seen from the Risk of Bias judgements (Supplementary Table 2), methodological quality was variable, and most publications were rated as having medium or high Risk of Bias in one or more domains. There are three major methodological limitations which were common across the studies analysed. The majority of studies contained mixed severity cohorts, with generally small cohort sizes; the few larger cohorts contained both paediatric and adult patients across all severities and attempt to control for this later through regression analysis. Current large multi-centre international research collaborations that form part of the International Traumatic Brain Injury Research Initiative (InTBIR; https://intbir.nih.gov/) aim to address these issues by recruiting large, well-characterised TBI cohorts.

The effect size that we demonstrate are similar to those demonstrated in genetic association studies in other acute neurological diseases such as stroke,[70] and if confirmed, could be important to contribute to a multivariable prognostic profile. Further, given the substantial interest in developing amyloid modifying therapies in Alzheimer's disease, these potentially present a target for therapy and therapy stratification. However, while our analysis is in keeping with an effect of *APOE* e4 carriage on outcome, our confidence in the magnitude of this effect size is limited by the quality and heterogeneity of the contributing studies. We note that publication bias for positive candidate gene association studies has been demonstrated in other clinical contexts.[71,72] Our funnel plot (Figure 3) suggested no such bias in our analysis. The other major issues relate to the research and statistical approaches used by many groups. The traditional alpha for statistical significance (0.05) is frequently thought to be inadequately rigorous when considering multiple gene assays, necessitating large and well-designed trial populations. Hirschhorn[73] and Nakaoka[74] highlight further potential methodological pitfalls in their reviews of commonly reported genetic associations, such as linkage disequilibrium and ethnic admixture as potential causes of false positive results. Both Hirschhorn and Lohmueller[75] emphasise the need for very large cohorts in order to suitably power studies, and suggest

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that data should always be published in sufficient detail to enable meta-analysis. This latter criterion is notably not met in the current TBI genetic literature.

Agreements and disagreements with other reviews

Two other meta-analyses of the effects of the APOE4 allele on functional TBI outcomes have been published. Zhou et al[7] used 7 studies, all contained in our analysis, but excluded one[29] when sensitivity analysis showed that its inclusion was responsible for the significant between-study heterogeneity. On the basis of the remaining 6 studies they concluded that APOE4 carriage was associated with a higher risk of poor outcomes 6 months post-injury (Risk ratio 1.49, 95% CI, 1.11–2.00). A second meta-analysis by Zeng et al[8] contained data from 13 studies. Of these, 9 are included in our meta-analysis. The remaining 4 comprise a study of paediatric TBI,[76] a study in which the outcome measured was worsening of CT scan findings,[77] a study in a journal not listed on the databases we searched,[78] and results taken from a letter of reply[79] to a paper we deemed ineligible.[80] Zeng et al did not report on six papers (comprising 915 patients) which are included in our review, including Ponsford[19] which is the second largest cohort that we included. The authors did not include a list of their excluded studies, so it is not possible to ascertain why studies we chose to include did not form part of their analysis. Zeng et al concluded that the APOE4 allele was associated with lower odds of a good prognosis (OR=0.68, 95% CI: 0.48–0.96, p=0.027), and performed subgroup analyses which revealed a slightly larger effect size if only severe TBI is included.

Our overall result is similar to these two preceding meta-analyses – we find that there is an odds ratio indicative of favourable outcomes among APOE4 non-carriers of 1.39 (95% CI 1.05 to 1.84, p = 0.02). As our study selection process identified only two papers with purely severe TBI patients, we did not deem it appropriate to perform a subgroup analysis of severe TBI. Sensitivity analysis revealed similar effect sizes regardless of time point post-injury or definition of “favourable” vs “unfavourable” outcomes.

A narrative systematic review of the APOE TBI literature by Lawrence[10] containing 69 studies reported an overall negative influence of APOE4 on outcome and incidence of

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dementia following TBI, with a more marked effect in severe TBI. The same authors conclude that APOE4 may impair neuropsychological functioning following severe TBI. The review contains multiple studies excluded from our review, as they included Paediatric TBI research, and papers with non-functional outcomes such as measures of cerebral blood flow and coagulation. The authors also stratify papers (including many discussed in this review) by TBI severity, even if the studies contain heterogeneous cohorts with a simple or absolute majority of one degree of TBI severity and do not report separate data for each injury strata. We considered employing a subgroup analysis of this nature for our meta-analysis (severe vs mild/moderate injury) but following advice from our statisticians and methodologists decided it was not appropriate.

Padgett et al performed a meta-analysis of studies analysing APOE genotype in relation to cognitive function in the first 12 months post-TBI.[9] They report that no significant differences could be demonstrated for either general cognitive function or test subdomains analysing verbal, visual and working memory. Meta-analysis of cognitive subdomains involved pooling results of different tests (e.g. CVLT and RAVLT) and sections of tests analysing differing aspects of the same subdomain (e.g. RAVLT immediate and delayed recall). We decided not to perform a pooled meta-analysis of such studies, as the cohorts and cognitive batteries involved in the published literature are heterogeneous. The studies covered by Padgett are all discussed individually in our review. Necessarily due to the design of meta-analyses, many studies discussed in our manuscript are omitted from the Padgett publication (for example Eradmudugolla's study of a >6000 patient cohort) although the authors note these in their Discussion section. Padgett et al raise the need for future TBI genomic research to use large cohorts and investigate gene x gene and allele dose interactions, a recommendation with which we wholeheartedly agree.

Mechanisms by which APOE4 might contribute to worse outcome

The mechanisms by which APOE4 carriage might drive worse outcomes in TBI has been the subject of much investigation and speculation, and has included direct neurotoxicity, modulation of tau biology, abnormal cerebrovascular function, effects on the blood brain barrier, inflammation, and oxidant injury. In addition, pre-injury level of education is one

of the strongest predictors of outcome from mild traumatic brain injury (alongside age and pre-existing psychiatric disorder).[2] It is therefore plausible that any pre-morbid genetic disposition to reduced cognitive function may indirectly impair recover. An analysis of the relevant literature is beyond the scope of this review, but is briefly summarised in Appendix 2 of the Supplementary material.

Conclusion

The APOE4 allele has a small impact on the acute clinical course following TBI, but the evidence for its effect on neuropsychological recovery remains incomplete. Genetic association studies of complex traits have repeatedly demonstrated that with sufficient sample sizes, genetic influences can be identified. There is no reason to suspect that outcome from TBI should be any different. What have been missing are large cohorts of TBI patients, who have been both richly and homogeneously characterized. Now that such cohorts are being ascertained, there is every reason to be optimistic that the genetic influences on TBI outcome will emerge. These discoveries will be the first step toward making genetics useful in TBI care.

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Table 1. Characteristics of studies of Apolipoprotein E gene (measuring Glasgow Outcome Scale/Glasgow Outcome Scale – Extended)

Italicised studies could not be entered into meta-analysis due to paucity of data.

			Participants						
						Injury 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, %)**	**Outcome reported**
Alexander 2007[20]	ITU (USA)	Pros. cohort	APOE4+: 97	33.7 ± 14.6	72 (74.2)	5.7 ± 1.4	NR	NR	NR	APOE4+ had higher (better) GOS at 3, 6, 12 months & slightly lower at 24 months; none statistically significant once GCS & age controlled for.
			APOE4-: 26	31 ± 14.5	21 (80.8)	5.4 ± 1.4	NR	NR	NR	
Ariza 2006[21]	*Hosp. (Spain)*	*Pros. coho*	*APOE4+: 67*	*28.7 ± 11.47*	*53 (79.7)*	*7.8 2 ±*	*NR*	*NR*	*NR*	*No statistically*

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		rt				*2.2 4*				*significant association between genotype and GOS-E at mean 215 (SD 23) days post injury.*
			APOE4-: 10	*37.7 ± 18.31*	*7 (70)*	*7.1 ± 2.8 1*	*NR*	*NR*	*NR*	
Chameli an 2004[22]	*Clinic (Canad a)*	*Pros. coho rt*	*APOE4-: 71*	*34.1 ± 12.3*	*44 (62)*	*NR*	*NR*	*(91)*	*(9)*	*No statistically significant association between genotype and GOS at 6 months.*
			APOE4+: 19	*31.2 ± 13.3*	*10 (52.6)*	*NR*	*NR*	*(88.2)*	*(11.8)*	
Chiang 2003[23]	Hosp. (Taiwa n)	Pros. coho rt	APOE4+: 81	42.6 (15 - 86)	61 (76.3)	NR	30 (37)	20 (24.7)	31 (38.3)	Significantly more APOE4+ had unfavourab le 6 months GOS
			APOE4-: 19	46.4 (22 - 79)	16 (84.2)	NR	10 (52.6)	4 (21.1)	5 (26.3)	
Diaz-Arrastia 2003[24]	Hosp. (USA)	Pros. coho rt	APOE4-: 77	38.8 ± 19.7	52 (67.5)	11 ± 4.5	25 (32.5)	9 (14.8)	43 (56.3)	No statistically significant association between
			APOE4+:	40 ± 19	18	10. 8 ±	10 (33.3	4	15	

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			29		(62.1)	4.7	)	(14.8)	(51.8)	genotype and GOS-E at 6 months.
Friedman 1999[25]	Clinic (Israel)	Pros. cohort	APOE4-: 42	38.2 ± 14.6	NR	NR	(55.6)	NR	NR	Statistically significant worse outcome on proprietary outcome scale at 6 months for APOE4+.
			APOE4+: 27	31.8 ± 14.1	NR	NR	(80)	NR	NR	
Hiekkanen 2009[26]	Hosp. (Finland)	Pros. cohort	APOE4-: 26	41.4±17.4	19 (73.1 %)	NR	9 (34.6)	12 (46.2 %)	5 (19.2 %)	No statistically significant association between genotype and GOS-E at 12 months.
			APOE4+: 11	46.3±14.6	8 (72.3 %)	NR	2 (18.2)	6 (54.5 %)	3 (27.3 %)	
Millar 2003[27]	Clinic (UK)	Retr. cohort	APOE4-: 279	24.9 ± 15.6	210 (75.3)	NR	184 (82.9)	17 (7.7)	21 (9.5)	No statistically significant association between genotype and GOS at
			APOE4+: 116	21.5 ± 14.2	81 (69.2)	NR	88 (89.8)	4 (4.1)	6 (6.1)	

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										6 months or GOS-E at 15-25 years post injury.
Nathoo 2003[28]	Hosp. (S Africa)	Pros. cohort	APOE4-: 65	24.8 ± 9.1	NR	12.3 ± 2.8	NR	NR	NR	No statistically significant association between genotype and GOS at 6 months.
			APOE4+: 45	28.4 ± 13.7	NR	12.8 ± 2.1	NR	NR	NR	
Nielson 2017[61]	*Hosp. (USA)*	*Pros. cohort*	*Total: 586*	*43.3 ± 18.5*	*419 (71.5 %)*		*42 (7.6)*	*28 (5.1)*	*480 (87.3)*	*No statistically significant association between genotype and GOS-E at 3 or 6 months.*
Olivecrona 2010[29]	ITU (Sweden)	Pros. cohort	APOE4-: 28	33 ± 13.2	NR	5.3 ± 1.59	NR	NR	NR	Statistically significant worse dichotomised GOS in APOE4+ at 3 months but not at
			APOE4+: 18	38.7 ± 17	NR	5.2 ± 1.7	NR	NR	NR	

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									12 or 24 months
Olivecrona 2012[30]	*Hosp. (Sweden)*	*Pros. cohort*	*APOE4-: NR*	*33.0 ± 2.5 (SEM)*	*NR*	*5 (3 - 8)*	*NR*	*NR*	*NR*	*No statistically significant association between genotype and GOS-E at 3 months.*
			APOE4+: NR	*38.7 ± 4.0 (SEM)*	*NR*	*6 (3 - 8)*	*NR*	*NR*	*NR*	
Olivecrona 2017[62]	*ITU (Sweden)*	*Retr. cohort*	*APOE4-DC: 8*	*35.2 ± 4.4*	*5 (62.5)*	*4 (3-7)*	*46 (100)*			*Statistically significant higher incidence of decompressive craniectomy in APOE4+ group but no reported association between genotype and GOS-E at 6 months.*
			APOE4+ DC: 11	*40.1 ± 5.1*	*6 (54.5)*	*5 (3-8)*				
			Non-DC: 27	*33.2 ± 2.8*	*20 (74.1)*	*6 (3-8)*				

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Ost 2008[31]	*ITU (USA)*	*Pros. cohort*	*APOE4-: 70*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*Statistically significantly higher mortality in APOE4+ at 12 months; no significant association between genotype and overall GOS-E at 12 months reported.*
			APOE4+: 26	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	
Ponsford 2011[16]	Rehab. (Aust.)	Pros. cohort	APOE4-: 329	NR	NR	NR	253 (56.4)	67 (14.9)	129 (28.7)	Statistically significant higher levels of severe disability in APOE4+ and overall significant association between APOE4+ and worse GOS-E at 1-2 years.
			APOE4+: 124	NR	NR	NR	86 (55.8)	27 (17.5)	41 (26.6)	

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			APOE4-: 61	42.5 ± 14.4	48 (78.7)	NR	NR	NR	NR	No statistically significant association between genotype and GOS at 6 months.
Pruthi 2010[32]	Hosp. (India)	Pros. cohort	APOE4+: 12	35.7 ± 11.1	10 (83.3)	NR	NR	NR	NR	
Røe 2016[60]	*Hosp. (Norway)*	*Pros. Cohort*	*APOE4-: 107* *APOE4+: 22*	*40 ± 18*	*105 (81)*		*129 (100)*			*No statistically significant association between genotype and GOS-E at 12 months.*
			APOE4-: 630	35 ± 21.6	536 (81)	NR	191 (30)	121 (19)	332 (52)	No statistically significant association between APOE4+ and dichotomised GOS at 6 months; significant interaction between
Teasdale 2005[33]	Hosp. (UK)	Pros. cohort	APOE4+: 303	35 ± 21.8	261 (81)	NR	76 (24)	57 (18)	181 (58)	

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										APOE4+ genotype and worse outcome once initial motor score, CT findings and pupil reaction controlled for
Teasdale 1997[1]	Hosp. (UK)	Pros. cohort	APOE4-: 63	41.9	NR	NR	11 (18.3)	11 (18.3)	38 (63.3)	Statistically significant association between APOE4+ and worse outcome (dichotomised GOS) at 6 months.
			APOE4+: 29	34.3	NR	NR	11 (37.9)	8 (27.6)	10 (34.5)	
Willemse-van Son 2008[34]	Hosp. (Neth.)	Pros. cohort	APOE4-: 59	33.6 ± 12.9	45 (73)	6.9 ± 3.0	NR	NR	NR	Statistically significant association between APOE4+ genotype and improved
			APOE4+: 17	33.2 ± 11.4	12 (71)	6.8 ± 2.7	NR	NR	NR	

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										outcome (GOS) at 18 and 36 but not 3/6/12/24 months.
Yousuf 2015[56]	Hosp. (India)	Pros. cohort	APOE4-: 117	41±15.7	96 (82.1 %)		24 (20.5 %)	42 (35.9 %)	51 (43.8 9 %)	No statistically significant association between genotype and GOS at 6 months.
			APOE4+: 33	38±14.5	27 (81.8 %)		9 (18.1 8 %)	12 (36.3 6 %)	12 (36.3 6 %)	

Table 2 Abbreviations: Aust. = Australia, DC = decompressive craniectomy, GCS = Glasgow Coma Scale, GOS = Glasgow Outcome Scale, GOS-E = Glasgow Outcome Scale – Extended, Hosp. = hospital, ICP = intracranial pressure, ITU = Intensive therapy unit, , m = mean, M = male, mths = months, mod. = moderate, Neth. = Netherlands, NRS – R = Neurobehavioural Rating Scale – Revised, n = number, NR = not reported, Pros. = prospective, rehab = rehabilitation, retr. = retrospective, S = South, SD = standard deviation, SEM = Standard error of the mean, sev. = severe, y = years.

Table 2. Summary of non-meta analysis papers' results

Type of outcome	Effect of APOE e4 allele on outcome (total study cohort size in brackets)		
	Positive impact	**No impact/uncertain**	**Negative impact**
Global scales (GOS, GOS-E, DRS, FIM) & Clinical (seizure incidence, need for DC, mortality)		Ariza 2006 (77)* Chamelian 2004 (90)* Mejia 2016 (170) Miller 2010 (322) Nielson 2017 (586)* Olivecrona 2012 (48)* Røe 2016 (129)* Total n=1,422	Lichtman 2000 (31) Olivecrona 2017 (46)* Öst 2008 (96)* Jiang 2006 (110) Total n=283
Neuropsychological	Han 2007 (78)	Eramudugolla 2014 (6333) Han 2009 (46) Kristman 2008 (318) Lee 2017 (189) Liberman 2002 (78) Padgett 2016 (142) Shadli 2011(19) Hodgkinson (100) Total n=7,225	Anderson 2009 (51) Ariza 2006 (77) Banks 2016 (120) Crawford 2002 (110) Merritt 2016 (42) Müller 2009 (59) Noé 2010 (67) Sundström 2004 (34) Teasdale 2000 (39) Yue 2017 (114) Total n=713
Dementia incidence		Rapoport 2008 (49)	Isoniemi 2006 (61) Sundström 2007a

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			(31) Sundström 2007b (71) Total n=163
Total number of subjects studied	78	8,696	1,159

APOE studies classified by type of outcome and authors' interpretation of results. Studies included in meta-analysis not included. TBI cohort sizes for each paper given in brackets. Papers reporting multiple outcomes listed in "Negative impact" if any outcome measure statistically significant for negative outcome and remainder of outcomes showed no effect. Studies with an asterisk (*) are also featured in Table 1.

GOS = Glasgow outcome scale, GOS-E = Glasgow outcome scale – extended, DRS = disability rating scale, FIM = functional independence measure, DC = decompressive craniectomy.

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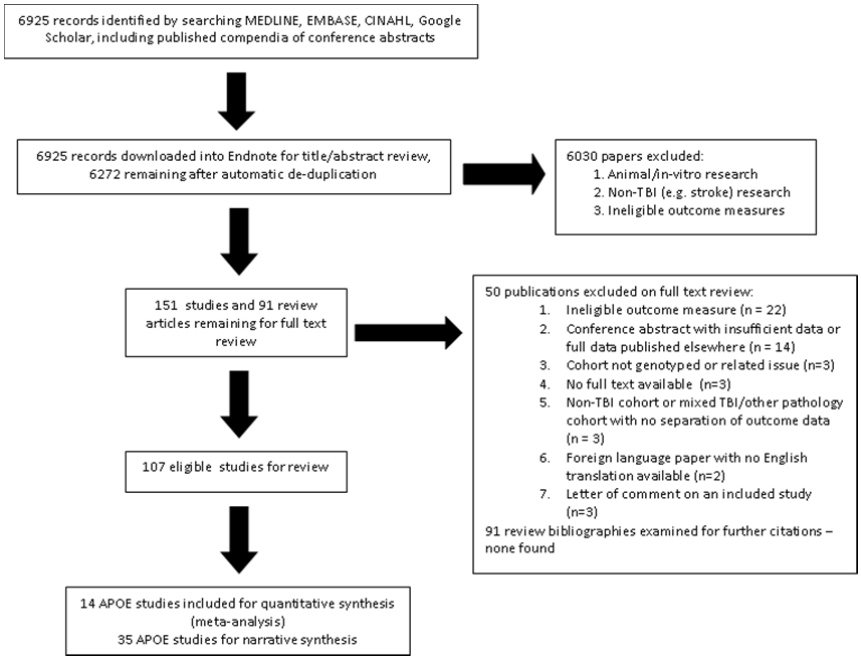

Figure 1. Study Selection Flowchart

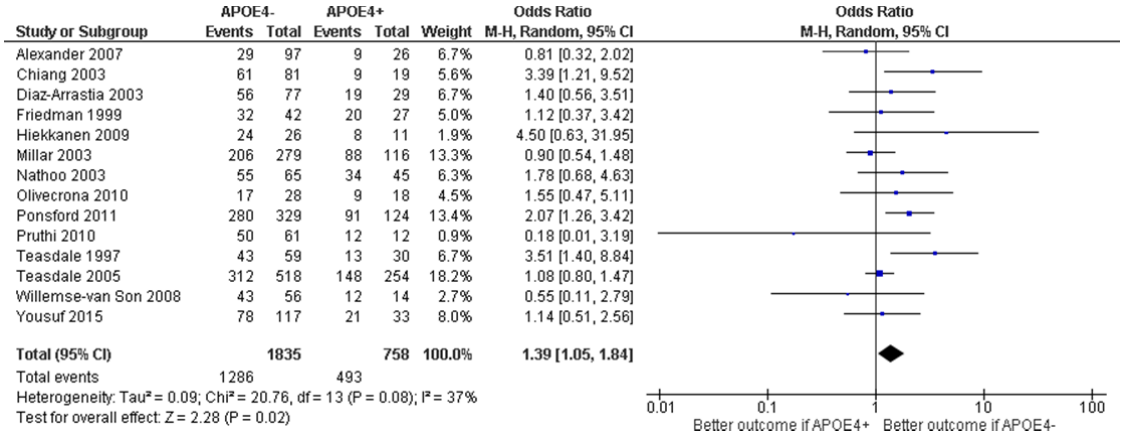

Figure 2. Meta-analysis of the effect of APOE4 on TBI outcome

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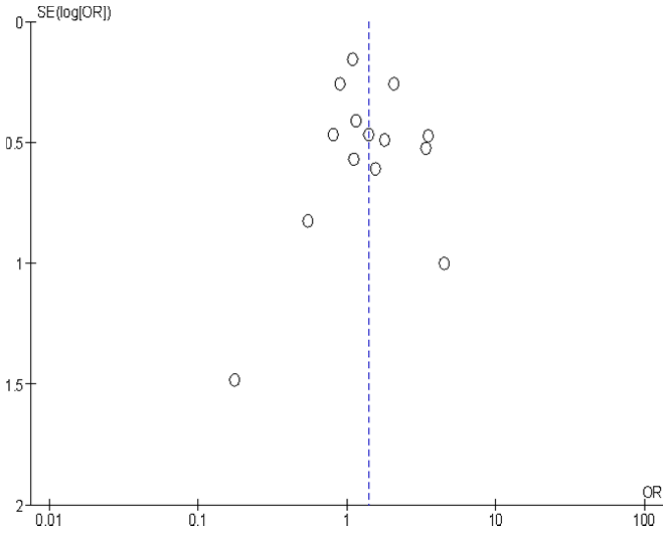

Figure 3. Funnel Plot for Primary Meta-analysis: Global outcome (6 month data or closest, all studies)

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SUPPLEMENTARY MATERIAL (ONLINE APPENDIX)

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Appendix 1: Search Strategies

MEDLINE 1946 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 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")

Appendix 2: Background to APOE

Apolipoprotein E

The most extensively studied gene in the field of TBI is undoubtedly *APOE*. Its 34kDa protein has a central role in CNS lipid transport, including movement of cholesterol into cells to aid repair processes in damaged neurones. Three common alleles have been characterised (*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 haemorrhage. The neurochemical mechanisms for APOE4's toxic effects have been reviewed extensively by Mahley & 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 (IL-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, and the growing literature in this area.

1: Main, B.S., Villapol, S., Sloley, S.S., Barton, D.J., Parsadanian, M., Agbaegbu, C., Stefos, K., McCann, M.S., Washington, P.M., Rodriguez, O.C., and Burns, M.P. (2018). Apolipoprotein E4 impairs spontaneous blood brain barrier repair following traumatic brain injury. Mol.
Neurodegener 13, 17. doi: 10.1186/s13024-018-0249-5.

2: Cao, J., Gaamouch, F.E., Meabon, J.S., Meeker, K.D., Zhu, L., Zhong, M.B., Bendik, J., Elder, G., Jing, P., Xia, J., Luo, W., Cook, D.G., and Cai, D. (2017). ApoE4-associated phospholipid dysregulationcontributes to development of Tau hyper-phosphorylation after traumatic brain

injury. Sci Rep 7, 11372. doi: 10.1038/s41598-017-11654-7.

3: Teng, Z., Guo, Z., Zhong, J., Cheng, C., Huang, Z., Wu, Y., Tang, S., Luo, C., Peng, X., Wu, H.,

Sun, X., and Jiang, L. (2017). ApoE Influences the Blood-Brain Barrier Through the NF-κB/MMP-9 Pathway After Traumatic Brain Injury. Sci Rep 7, 6649. doi: 10.1038/s41598-017-06932-3.

4: Zlokovic, B.V. (2013). Cerebrovascular effects of apolipoprotein E: implications for Alzheimer disease. JAMA Neurol 70, 440-444. doi: 10.1001/jamaneurol.2013.2152.

5: Mahley, R.W., and Huang, Y. (2012). Apolipoprotein e sets the stage: response to injury triggers neuropathology. Neuron 76, 871-885. doi: 10.1016/j.neuron.2012.11.020.

6: Ferguson, S., Mouzon, B., Kayihan, G., Wood, M., Poon, F., Doore, S., Mathura, V., Humphrey, J., O'Steen, B., Hayes, R., Roses, A., Mullan, M., and Crawford, F. (2010). Apolipoprotein E genotype and oxidative stress response to traumatic brain injury. Neuroscience 168, 811-819. doi: 10.1016/j.neuroscience.2010.01.031.

Appendix 3: Studies excluded following full text review (Supplementary Table 1)

Bold = APOE studies

Reason for exclusion	Study Identifier
Conference abstract/letter with insufficient data or data subsequently published in full	Carter 2011,[81] Carter 2012,[82] Garnett 2003,[83] Jacobs 2009,[84] Ponsford 2010,[85] Rubio Lopez 2010,[86] Cousar 2009,[87] Adams 2014,[88] McDevitt 2014,[89] Nogueras 2014,[90] Sinha 2014,[91] Yue 2015,[92] Sorbi 1995[79]
Outcome data not reported for each genotype/age group individually	Abrahams 2017,[93] Ashman 2008[94]
No genotyping performed	Lankford 1994[95]
No genetic variation identified within cohort	Romeiro 2007[96]
Comment letter in response to included study	Collie 2004,[97] Harden 2004[98]
Ineligible outcome measure	Hayes 2017,[99] Hiekkanen 2007,[100] Horsburgh 2000,[101] Isoniemi 2006,[102] Jiang 2011,[103] Kerr 2003,[104] Koponen 2004,[105] Leclercq 2005,[106] Smith 2006,[107] Terrell 2008,[108] Tanriverdi 2008,[109] Tierney 2010,[110] Neselius 2013,[111] Xiao-Chuan 2011,[112] Nicoll 1995[80]
Foreign language paper with original manuscript or English translation unavailable	Krupa 2003,[113] Martinez 2009[114]
Non-TBI study	Kutner 2000,[115] Lyons 2013[116]
Full text not available	Jordan 1997,[117] Poovindran 2013,[118] Willmott 2013[119]

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Appendix 4: Risk of bias of reviewed studies (Supplementary Table 2)

Abbreviations: Ax = analysis, Mx = measurement

Study ID	Study Participation	Study Attrition	Prognostic Factor Mx	Outcome Mx	Confounding	Statistical Ax & 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

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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

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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	Moderat	High	High	Low

			e			
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

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Appendix 5. Grading of Recommendations Assessment, Development and Evaluation (GRADE) Evaluation of APOE studies with regard to global outcomes (Supplementary

Progn 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

Table 3)

SL = study limitations, Inc = inconsistency, Ind = indirectness, Imp = imprecision.

Publication bias assessed by Funnel Plot.

✓ = no serious limitations

X = serious limitations

-- = not present

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Appendix 6. Results of studies effect of APOE on other outcomes (Supplementary Table 4)

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Anderson 2009	Treatment / Comparator	OC	6 mo	12 mo	Comment
			M	M	No SD's given in tables; scores reported are M SRCL scores following adjustment 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.
	APOE4- (n=36)	SRT, Sum of Recall	81	83	
	APOE4+ (n=15)	SRT, Sum of Recall	71	71	

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 Verbal Learning Test - all four results significant for APOE4+ performing worse than APOE4- Learning slope p=0.036 Trial 5 p=0.033 Short-Delay Free Recall p=0.019 Long-Delay Free Recall p=0.022
		Trial 5	8.91	3.64	
		Short-Delay Free Recall	6.63	4.2	
		Long-Delay Free Recall	6.8	4.29	
	APOE4+ (n=30)	Learning slope	0.62	0.63	
		Trial 5	7.23	3.42	

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		Short-Delay Free Recall	4.5	4.07	
		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 outcome, groups reanalysed with adjustment for differing 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.
	APOE4- (n=62)	CVLT List A	38.75	9.46	
	APOE4+ (n=16)	CVLT List A	46.19	10.85	
Han 2009	Comments				
	Authors present a hierarchical tree model from ODA for predicting job status change				

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	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.

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	APOE2+ (n=10)	MDB score	3.9	3.7	3.7	5.38	Eight tests from other scales (e.g. WASI), with 'deterioration points' awarded depending on how far below norm of age/education controlled group 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.
	APOE3/3 (n=32)	MDB score	2.5	3.96	3.5	5.09	
	APOE4+ (n=19)	MDB score	4.4	3.92	7.4	5.23	

Jiang 2006	Treatment / Comparator	APOE4+	APOE4-	Comments
		%	**%**	Following adjustment for age, sex, smoking, alcohol, mechanism, 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
	Clinical deterioration (n=19)	36.8	63.2	
	Clinical stabilisation (n=91)	11	89	

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

Liberman 2002	Treatment / Comparator	OC	3 weeks post-TBI		Comment
			Difference in M score (APOE4+ vs APOE4-)	SE	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".
	APOE4-	Grooved	-16.3	5.5	

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	(n=62) vs APOE4+ (n=18)	pegboard			'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		Comment
			M	SD	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=24)	FIM corrected for coma	121.3	6.37	
	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

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	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

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		Mild cog impairment	2/49 (4.1%)	2/30 (6.7%)	p=0.882 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
	Controls	Dementia	0/68	0/46	
		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.

			Pre-injury		Post-injury		
	Treatment / Comparator	OC	M	SD	M	SD	Comment
Sundström 2004	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+
	TBI APOE4+ (n=11)	Recall (divided)	4.45	1.21	3.64	0.81	

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							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.
	Treatment / Comparator	Outcome	APOE4+ (n=12)		APOE4- (n=19)		Comment
			%	n	%	n	
Sundström 2007 (1)	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	Treatment /	OC	APOE4+		APOE4-		Comment

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2007 (2)	Comparator		number affected (%)	N	number affected (%)	N	OR for dementia following head injury, via comparison to non-head injured APOE4- subjects (reference): TBI APOE4+ 5.2 (2.0-14.0) p<0.001 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.
	Dementia (n=181)	Head injury	13 (14.9%)	87	12 (12.8%)	94	
		No head injury	74 (85.1%)	87	82 (87.2%)	94	
	Controls (n=362)	Head injury	10 (10.5%)	95	36 (13.5%)	267	
		No head injury	85 (89.5%)	95	231 (86.5%)	267	

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
		%	**%**	Higher proportion of -491AA

	Clinical deterioration (n=19)	84.20%	15.80%	deteriorate than AT/TT. 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).
	Clinical stabilisation (n=91)	67%	33%	
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 performed 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.	
Banks 2015	APOE4 status	Thalamic & hippocampal volume,	Conference abstract. Combat sports participants. Worse performance on verbal memory scores amongst APOE4+ participants but no differences in thalamic or hippocampal	

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		verbal memory scores	volume on imaging between genotypes.
Merritt 2016	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 $p<0.05$

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Appendix 7: Supplementary Table 5 –Characteristics of studies of APOE gene (measuring all other outcomes)

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			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 ± 4.2	NR	NR	NR	

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Eramudugolla 2014	Com. (Australia)	Retr. cohort	20s: 2077 40s: 2124 60s: 2132	22.61±1.51 42.62±1.49 62.51±1.51	969 (46.7) 979 (46.1) 1076(50.5)	Mild: 176 (8.5%) Mild: 128 (6%) Mild: 66 (3.1%)		Mod/sev: 31 (1.5%) Mod/sev: 55 (2.6%) Mod/sev: 33 (1.5%)	CVLT, reaction time, Wechsler WM
Han 2007	Hosp. (USA)	Pros. cohort	APOE4-: 62 APOE4+: 16	25.3 ± 5.8 22.6 ± 3.8	59 (95.2) 13 (81.3)	NR NR	0 0	19 (30.6) 8 (50)	43 (69.4) 8 (50)	CVLT
Han 2009	Hosp., (USA)	Pros. cohort	APOE4-: 30 APOE4+: 16	25.2 ± 6.1 22.6 ± 3.8	29 (96.7) 13 (81.3)	NR NR	0 0	13 (43.3) 8 (50)	17 (56.7) 8 (50)	Change in job
Isoniemi 2006	Hosp. (Finland)	Retr. cohort	APOE2+: 10 APOE3/3: 32 APOE4+: 19	60.6 ± 12.2 59.4 ± 8.9 61.4 ± 10.6	5 (50) 23 (72) 14 (74)	NR NR NR	7 (70) 16 (50) 9 (47)	1 (10) 9 (28) 4 (21)	2 (20) 7 (22) 6 (32)	MDB
Jiang 2006	Hosp. (China)	Pros. cohort	Clin. det: 19 Clin. Stab: 91	NR NR	15 (78.9) 65 (71.4)	NR NR	10 (52.6) 9 (47.4)	GCS >8: 28 (30.8) GCS >8:63 (69.2)		APOE4 incidence between groups
		Pros.	APOE4-:	20.4 ±	127	≥1 prev. conc'n: 130				Conc'n

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Kristman 2008	Com. (Canada)	cohort	239 APOE4+: 79	2.3 20.9 ± 2.8	(53.1) 37 (46.8)	(56) ≥1 prev. conc'n: 45 (62.5)				rate*
Lee 2017	Hosp. (Taiwan)	Pros. cohort	APOE4-: 154 APOE4+: 35	40.1 ± 15.15 42.2 ± 14.76	60 (39) 16 (45.7)	14.9 ± 0.38 15 ± 0	0 0	0 0	154 35	Sleep quality (PSQI)
Liberman 2002	Hosp. (USA)	Pros. cohort	APOE4-: 79 APOE4+: 18	33.9%<30, 32.3% 30-49, 33.9% 50+ 22.2%<30, 50% 30-49, 27.8% 50+	(56.6) (72.2)	NR NR	(0) (0)	(8.1) (16.7)	(91.9) (83.3)	PASAT, GPT
Lichtman 2000	Hosp. (USA)	Pros. cohort	APOE4-: 24 APOE4+: 7	34.3 ± 18.1 39.8 ± 15.3	17 (70.8) 5 (71.4)	Coma length (days±SD) = 36.4±58.3 Coma length (days±SD) = 7.5±8.5				FIM (6)
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 APOE4+:	20±1.59 19.93±1.	23 (85.2) 12 (80)	NR NR	All mTBI, 3 (11.1%) loss of consciousness			Post-Concussion

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			15	39					78 Symptom Scale (average 7.8 days post injury)
Miller 2010	ITU (USA)	Pros. cohort	APOE4-: 243 APOE4+: 79	NR NR	(77) NR	100% GCS 3-8, median GCS 6			Seizures
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 Emer. PTA: 55 Not in PTL: 59	39.9 ± 18.2 29.2 ± 14.5 29.5 ± 10.5	48 (71.6) 42 (71.2)	4.6 ± 2.3 7.1 ± 10.6 NR	NR NR NR			APOE4 incidence betw. gps; WAIS, TAVEC**
Padgett 2016	Com. (Australia)	Pros. Cohort	APOE4+: 37 APOE3/E3: 92 APOE2+:	40.62±17.47 39.89±16.89 41.37±17	19 (51) 49 (53) 9 (69)	NR NR NR	1 (4.8) 4 (5.7) 0	1 (4.8) 3 (2.8) 0	34 (70.27) 82 (86.8) 12	COWAT, TMT, WAIS-III (testing on remission from

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			13	.69				(92.3)	PTA). All genotypes missing some severity data.
Rapoport 2008	Hosp. (Canada)	Pros. case-control	TBI n=69 Controls n=78	67 ± 7.9 68.0 ± 8.5	(47.8) (48.1)	NR	0	32 (46.4)	37 (53.6)	Dementia or MCI (1, 2 y)
Shadli 2011	Hosp. (Malaysia)	Pros. cohort	APOE4-:13 APOE4+: 6	26.1 ± 6.8 25.0 ± 8.63	NR NR	13.3 ± 2.06 13.0 ± 2.00	NR NR			WCST, TMT, RAVLT, COWAT
Sundström 2004	Com. (Sweden)	Retr. cohort	APOE4-: 23 APOE4+: 11	55.9 ± 12.6 58.2 ± 16.3	11 (47.8) 6 (54.5)	NR NR	Single mTBI: 19 (82.6) Single mTBI: 9 (81.8)	>1 mTBI: 4 (17.4) >1 mTBI: 2 (18.2)		Word recall
Sundström 2007 (1)	Com. (Sweden)	Retr. cohort	TBI: 31	55.2 ± 13.6	18 (58.1)	NR	NA	NA	(100) mTBI	Fatigue

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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)

Table 3 Abbreviations: 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, n = number, 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. = stabilisation, 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

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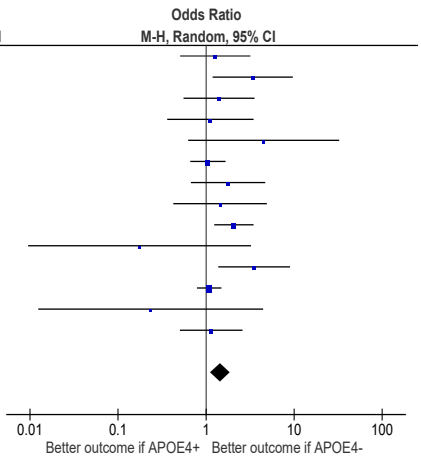
Appendix 8: Sensitivity analysis 1 - Global Outcome (last recorded score, all studies)

Study or Subgroup	APOE4- Events	Total	APOE4+ Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Alexander 2007	39	97	9	26	6.5%	1.27 [0.51, 3.14]
Chiang 2003	61	81	9	19	5.3%	3.39 [1.21, 9.52]
Diaz-Arrastia 2003	56	77	19	29	6.4%	1.40 [0.56, 3.51]
Friedman 1999	32	42	20	27	4.6%	1.12 [0.37, 3.42]
Hiekkanen 2009	24	26	8	11	1.7%	4.50 [0.63, 31.95]
Millar 2003	200	292	85	126	15.6%	1.05 [0.67, 1.64]
Nathoo 2003	55	65	34	45	5.9%	1.78 [0.68, 4.63]
Olivecrona 2010	18	28	10	18	4.0%	1.44 [0.43, 4.82]
Ponsford 2011	280	329	91	124	14.0%	2.07 [1.26, 3.42]
Pruthi 2010	50	61	12	12	0.8%	0.18 [0.01, 3.19]
Teasdale 1997	43	59	13	30	6.3%	3.51 [1.40, 8.84]
Teasdale 2005	312	518	148	254	20.5%	1.08 [0.80, 1.47]
Willemse-van Son 2008	53	59	17	17	0.8%	0.24 [0.01, 4.39]
Yousuf 2015	78	117	21	33	7.7%	1.14 [0.51, 2.56]
Total (95% CI)		**1851**		**771**	**100.0%**	**1.45 [1.11, 1.88]**
Total events	1301		496			

Heterogeneity: Tau² = 0.06; Chi² = 18.59, df = 13 (P = 0.14); I² = 30%
Test for overall effect: Z = 2.77 (P = 0.006)



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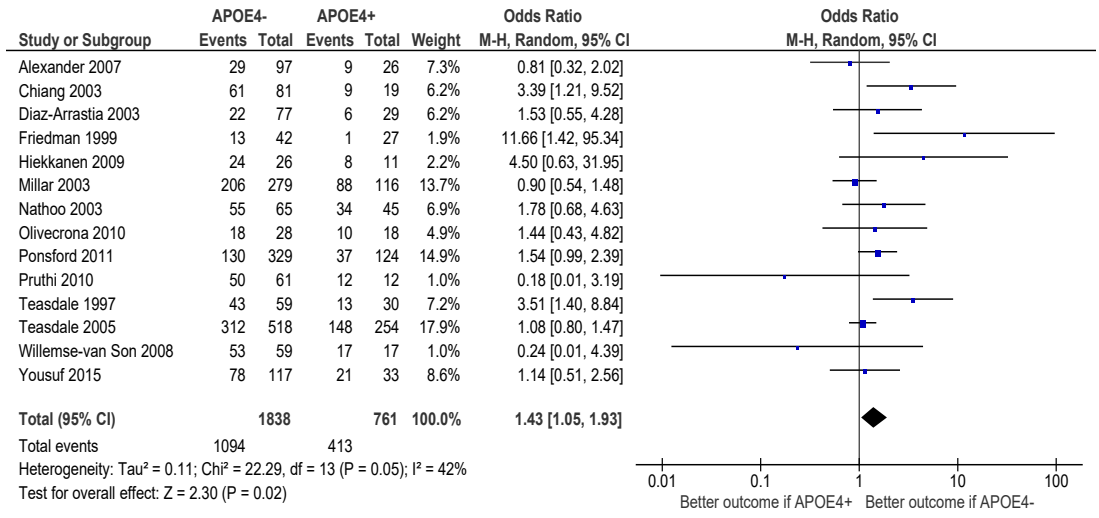
Appendix 9: Sensitivity Analysis 2 - Global Outcome (6 months or closest, GOS 4-5/GOS-E 7-8, all studies)



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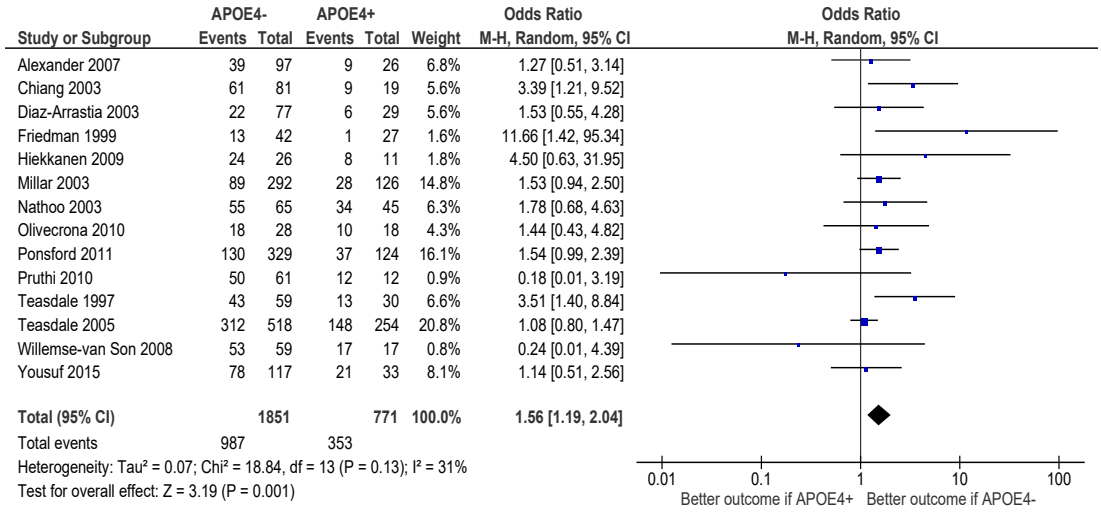
Appendix 10: Sensitivity analysis 3 - Global Outcome (last recorded score, GOS 4-5/GOS-E 7-8, all studies)



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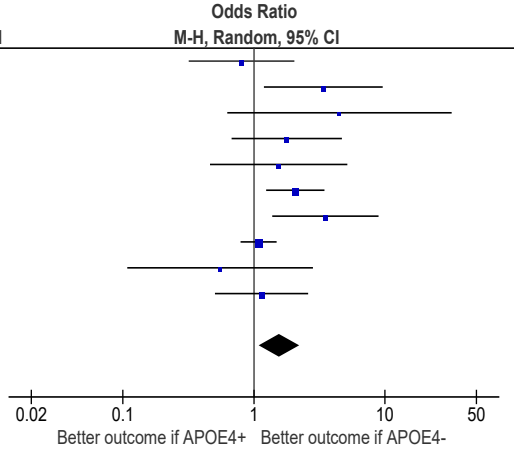
Appendix 11: Sensitivity analysis 4 - Global outcome (6 month data or closest, omitting high risk of bias studies)

Study or Subgroup	APOE4- Events	Total	APOE4+ Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Alexander 2007	29	97	9	26	9.5%	0.81 [0.32, 2.02]
Chiang 2003	61	81	9	19	8.1%	3.39 [1.21, 9.52]
Hiekkanen 2009	24	26	8	11	2.9%	4.50 [0.63, 31.95]
Nathoo 2003	55	65	34	45	9.0%	1.78 [0.68, 4.63]
Olivecrona 2010	17	28	9	18	6.5%	1.55 [0.47, 5.11]
Ponsford 2011	280	329	91	124	17.3%	2.07 [1.26, 3.42]
Teasdale 1997	43	59	13	30	9.4%	3.51 [1.40, 8.84]
Teasdale 2005	312	518	148	254	22.3%	1.08 [0.80, 1.47]
Willemse-van Son 2008	43	56	12	14	4.0%	0.55 [0.11, 2.79]
Yousuf 2015	78	117	21	33	11.1%	1.14 [0.51, 2.56]
Total (95% CI)		**1376**		**574**	**100.0%**	**1.58 [1.11, 2.24]**
Total events	942		354			

Heterogeneity: Tau² = 0.12; Chi² = 16.23, df = 9 (P = 0.06); I² = 45%
Test for overall effect: Z = 2.54 (P = 0.01)



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