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Article:

Eramudugolla, R, Bielak, AA, Bunce, D et al. (3 more authors) (2014) Long-term cognitive correlates of traumatic brain injury across adulthood and interactions with APOE genotype, sex, and age cohorts. *Journal of the International Neuropsychological Society*, 20 (4). 444 - 454. ISSN 1355-6177

<https://doi.org/10.1017/S1355617714000174>

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Appears in: *Journal of the International Neuropsychological Society* (Accepted version)

Long-term cognitive correlates of Traumatic Brain Injury across adulthood and interactions
with *APOE* genotype, sex and age-cohort.

Ranmalee Eramudugolla¹, Allison A. M. Bielak³, David Bunce⁴, Simon Easteal², Nicolas
Cherbuin¹, Kaarin J. Anstey¹

¹ Centre for Research on Aging, Health and Wellbeing, ²John Curtin School of Medical
Research, Australian National University,
Australia

³Department of Human Development & Family Studies, Colorado State University, Fort
Collins, Colorado.

⁴Institute of Psychological Sciences, Faculty of Medicine and Health, University of Leeds,
Leeds, United Kingdom.

Word count: 4247

Tables 2, Figures 3

Abstract 199

Corresponding Author: Ranmalee Eramudugolla

Ranmalee Eramudugolla DPsych
Centre for Research on Aging, Health and Wellbeing
Australian National University
Canberra ACT 0200, Australia
Ph + 61 2 61251456. Fax + 61 2 61250733
email: ranmalee.eramudugolla@anu.edu.au

Abstract

Objective: There is continuing debate about long-term effects of brain injury. We examined a range of TBI variables (TBI history, severity, frequency, and age of injury) as predictors of cognitive outcome over 8 years in an adult population, and interactions with *APOE* genotype, sex and age-cohort.

Methods: Three randomly sampled age cohorts (20-24, 40-44, 60-64 years at baseline; N= 6333) were each evaluated three times over eight years. TBI variables, based on self-report, were separately modelled as predictors of cognitive performance using linear mixed effects models.

Results: TBI predicted longitudinal cognitive decline in all three age groups. *APOE* $\epsilon 4^+$ genotypes in the young and middle-aged groups predicted lower baseline cognitive performance in the context of TBI. Baseline cognitive performance was better for young females than males but this pattern reversed in middle age and old age.

Conclusions: The findings suggest TBI history is associated with long-term cognitive impairment and decline across the adult lifespan. A role for *APOE* genotype was apparent in the younger cohorts but there was no evidence that it is associated with impairment in early old age. The effect of sex and TBI on cognition varied with age-cohort, consistent with a proposed neuroprotective role for oestrogen.

Keywords: cognitive decline, epidemiology, head injury, dementia, prospective study

The role of traumatic brain injury (TBI) in long-term cognitive impairment and decline remains controversial. Although studies have reported that a history of TBI is a risk factor for late-life cognitive impairment and neurodegenerative disease, including Alzheimer's dementia (Lye & Shores, 2000; Plassman et al., 2000; Wang et al., 2012), it is clear that other factors modify this relationship, including injury severity (Rohling et al., 2011) frequency (D. H. Smith, Johnson, & Stewart, 2013), age (Teasdale, Nicoll, Murray, & Fiddes, 1997), as well as genetics (Friedman, Froom, & Sazbon, 1999) and sex (Stein, 2001).

Because these factors influence mechanisms of recovery from TBI and susceptibility to later neuropathology (see Dardiotis, Grigoriadis, & Hadjigeorgiou, 2012; Lye & Shores, 2000), it is important to understand their role in long-term cognitive outcomes post-TBI. A major difficulty in comparing findings across studies is the variety of head-injury variables examined, study duration, sensitivity of outcome measures and other key factors reported. Furthermore, very few studies have focused on multiple factors of interest such as genotype and sex within the one sample to understand their relative contribution to TBI outcome (Ost et al., 2008; Ponsford et al., 2011), or TBI in relation to neurodevelopment and change across the lifespan (Teasdale, Murray, & Nicoll, 2005). Findings from these studies suggest the relationship between TBI outcome and factors such as genotype, may vary with sex and age. The present study uses a large, prospective dataset to examine three factors of current interest: *APOE* genotype, sex and age, in relation to neuropsychological outcome after TBI. In addition, a range of TBI variables were examined in the one sample, including severity, frequency and age of first injury, with the objective of understanding how these TBI variables interact with the above factors to explain cognitive outcome across the lifespan.

Despite increasing knowledge of the molecular processes in brain injury, clinical and epidemiological evidence has been far from unanimous in supporting patterns of associations predicted by molecular studies. The biological response to TBI is highly variable across individuals and injury mechanisms. In general, neurotrauma initiates a complex cascade of molecular processes within the brain some of which exacerbate neuronal death and others which are neuroprotective. These processes include neuroinflammation, oxidative stress, excitotoxicity, apoptotic cell death, neurodegeneration, and plasticity. Of the several genes identified as influencing this molecular response to injury, the gene for apolipoprotein E is the most studied and pertinent to the question of late-life neurodegeneration after TBI (Dardiotis et al., 2012; Kokjohn, Maarouf, & Roher, 2011; Liu, Kanekiyo, Xu, & Bu, 2013).

Compared to TBI patients who carry only the $\epsilon 2$ and $\epsilon 3$ isoforms of the APOE gene, carriers of the $\epsilon 4$ isoform are more likely to die post-injury (Teasdale et al., 1997), have a longer length of coma (Sorbi et al., 1995), greater neurological deficits (Friedman et al., 1999), as well as poorer functional outcome several years following rehabilitation (Ponsford et al., 2011). The mechanisms underpinning the effect of APOE genotype are not well understood, but may influence the degree of A β plaque deposition within the brain (Johnson, Stewart, & Smith, 2010). Acute effects of TBI such as widespread axonal injury, leads to the rapid accumulation of amyloid precursor proteins (APP) within the damaged axons (Gentleman, Nash, Sweeting, Graham, & Roberts, 1993) along with a co-accumulation of compounds that promote A β formation. This process can persist chronically (Chen, Johnson, Uryu, Trojanowski, & Smith, 2009). While some studies suggest that APP plays a protective role post-TBI (Thornton, Vink, Blumbergs, & VanDen Heuvel, 2006), individuals with APOE $\epsilon 4^+$ genotype experience increased post-injury A β deposition and reduced A β clearance (Hartman et al., 2002), which may in turn lead to an increased risk of A β plaque formation characteristic of dementia pathology. Compared to APOE $\epsilon 3$, the APOE $\epsilon 4$ isoform of the apolipoprotein E is also less able to repair synapses and protect neurons in the event of injury (Zhong, Scarce-Levie, Ramaswamy, & Weisgraber, 2008), thus hindering recovery in TBI patients with APOE $\epsilon 4^+$ genotype.

Some epidemiological studies support this link between APOE genotype and TBI outcome and suggest the combination of TBI history and APOE $\epsilon 4^+$ genotypes significantly elevates the risk of long-term cognitive decline or Alzheimer's disease, beyond the effect of either TBI or APOE $\epsilon 4^+$ genotype alone (Katzman et al., 1996; Rohling et al., 2011; Sundstrom et al., 2007; Tang et al., 1996). The majority of these studies have included participants carrying the $\epsilon 2$ allele within the reference group despite evidence that $\epsilon 2$ may protect against degenerative neuropathology (Liu et al., 2013). Evidence for the influence of APOE genotype on TBI outcome is not unanimous, however, as others report cognitive decline decades after severe TBI but with no relationship to APOE $\epsilon 4^+$ genotype (Millar, Nicoll, Thornhill, Murray, & Teasdale, 2003), and similarly no relationship with cognitive decline within the first two years following mild-moderate TBI (Chamelian, Reis, & Feinstein, 2004; Rapoport et al., 2008). While there are numerous methodological differences across all studies, it is notable that the latter works used only mild/moderate TBI cases (Chamelian et al., 2004; Rapoport et al., 2008) or a mixed-age sample with no information on the distribution of ages (Millar et al., 2003). TBI severity is a known factor influencing cognitive outcome and decline (Plassman

et al., 2000; Polusny et al., 2011), and recently age has also been found to influence TBI outcome.

Age may influence the brain's response to injury (e.g., Adelson et al., 2001) and also the role of *APOE* $\epsilon 4^+$ in the recovery process (Blackman, Worley, & Strittmatter, 2007). Some have suggested that the effect of the $\epsilon 4$ allele on brain biology and function may be beneficial in the young but deleterious at older ages (Han & Bondi, 2008). Although evidence for this type of association in healthy individuals' cognitive performance is mixed (Bunce, Anstey, Burns, Christensen, & Easteal, 2011; Ihle, Bunce, & Matthias, 2012), a number of studies that have used young adult samples (aged in their 20s and 30s) report *improved* global outcome (Willemsse-van Son, Ribbers, Hop, van Duijn, & Stam, 2007) or faster recovery from TBI on neuropsychological measures of attention, executive function and episodic memory (Han et al., 2007). These studies however, had no older cohort against which the differential influence of APOE could be compared, and both used samples that were all or mostly male. Other works have reported the reverse pattern of findings (Teasdale et al., 2005) where the *APOE* $\epsilon 4^+$ genotype was associated with poorer global outcome 6 months post injury in young patients. This difference decreased with increasing age, such that genotype was unrelated to outcome in the older patients.

Sex may also moderate the relationship between TBI and long-term cognitive outcome in adulthood. There is evidence that circulating estrogen and progesterone have neuroprotective roles in mouse models of brain damage (Ardelt et al., 2012; Stein, 2001). For example, female rats show less brain damage than male rats and ovariectomised female rats and senescent rats show the same degree of brain damage as male rats (see Roof and Hall, 2000). Estrogen and progesterone are thought to minimize secondary injury post-TBI by reducing oxidative stress and neuronal death, as well as reducing cerebral oedema and enhancing synaptogenesis (Stein, 2001). Consistent with such findings, two meta-analyses of case-control studies have found a stronger association between past TBI and Alzheimer's disease diagnosis in males than in females (Fleminger, Oliver, Lovestone, Rabe-Hesketh, & Giora, 2003; Mortimer et al., 1991). However, a meta-analysis of functional outcomes post-injury found poorer return-to-work and somatic-symptoms outcomes in females (Farace & Alves, 2000), and other studies have failed to find any effect of sex on TBI outcome (Renner et al., 2012). Some findings suggest that sex may also interact with genotype in predicting outcome of TBI. For example Ponsford et al. (2011) reported that negative outcomes in *APOE* $\epsilon 4^+$

patients were more apparent in females than males, and particularly in patients aged over 55 years. The authors surmised that older females may experience less neuroprotection from estrogen and be more vulnerable to the effects of *APOE* $\epsilon 4^+$. Others have reported that the negative effect of *APOE* $\epsilon 4^+$ on outcome following severe TBI is more apparent in males than females (albeit in a sample with mixed ages from 8 to 81 years) (Ost et al., 2008).

The complex interactions that appear to influence TBI outcome are difficult to examine in small samples with limited age cohorts and duration of follow-up. Here, we use a large prospectively studied sample to investigate several self-reported TBI variables (severity, age of injury, and frequency) and their interaction with sex and *APOE* genotype as predictors of cognitive performance. Additionally, we implement a lifespan approach by separately studying these interactions in young, middle-aged and older adults.

Method

Study population

The study population was from the Personality and Total Health (PATH) Project. The sample for the PATH project has previously been described in detail (Anstey et al., 2011) and has been shown to be representative of the 2001 Australian Census data for the area (Anstey et al., 2011). In brief, we surveyed three cohorts aged 20-24, 40-44 and 60-64 years at baseline with four yearly follow-up. The sampling frames were derived from the electoral roll in Canberra and Queanbeyan, Australia. Electoral registration and voting are compulsory for Australian citizens. Figure 1 displays the full PATH sample (N=7485) and the samples excluded from analysis (N=220) (see exclusion criteria below). At Wave 1, 2077 of the selected participants in the 20s cohort had data for both TBI and *APO* $\epsilon 4^+$ genotype, 2124 participants in the 40s cohort had both TBI and *APOE* genotype data, and 2132 participants in the 60s cohort had both TBI and *APOE* genotype data.

[Figure 1 here]

Exclusion/inclusion criteria

To examine the association between head injury and cognitive change, participants with any history of cerebrovascular events (including ‘mini-strokes’ and TIAs) or epilepsy at baseline were excluded from the analysis. The 60s cohort included a small number of participants with dementia and mild cognitive disorders as classified by a previously described clinical assessment (Anstey et al., 2011) including comprehensive cognitive and neuropsychiatric evaluation. Thus, data from a total of 6333 participants were available for analysis at Wave 1. Sample attrition at each wave was due to death, loss to follow up, and refusal to respond to study-related questions, and represented on average 6.5% and 16% at wave 1 and 2 respectively.

*Measures**Head-injury variables*

Participant responses to TBI questions were combined across the three waves of data collection to form the following variables: (1) history of head injury, (2) number of head injuries sustained, (3) severity of head injury, and (4) age of first head injury (see Table 1). Data on the cause of TBI was also collected, but not analysed in the present study due to small samples, but is nevertheless presented in a descriptive format in Table 2. The variable ‘Severity of TBI’ consisted of two levels – mild TBI and moderate/severe TBI. Mild TBI represented those who reported having a serious head injury but who reported a loss of consciousness (LOC) of less than 60 minutes or a period of memory loss (post-traumatic amnesia (PTA)) up to 1 day. Moderate to severe TBI was defined as cases who reported a loss of consciousness of 60 minutes or more and PTA of more than 1 day (Table 1). LOC has been used as an index of TBI severity in other epidemiological studies, and although the more commonly accepted cut-off for LOC in mild TBI is <30 minutes, this time interval was unavailable in the PATH dataset to enable this categorization. Thus the more stringent cut-off was used here. As indicated in Table 1, the TBI frequency data was collected only for those injuries with a LOC>15 minutes, and therefore does not include milder TBIs.

[Table 1 here]

Cognitive measures

Cognitive testing relevant to the present paper included the following tests of episodic memory (delayed recall after the first trial of the California Verbal Learning Test (CVLT)

(Baddeley, Emslie, & Nimmo-Smith, 1993)), verbal ability/vocabulary (Spot-the-Word test (STW) (Delis, Kramer, Kaplan, & Ober, 1987)), processing speed (Symbol-Digit Modalities test (A. Smith, 1982)), working memory (Digit-Span backwards (Wechsler, 1955)), and simple reaction time.

APOE genotyping

DNA was extracted from buccal swabs using QIAGEN DNA Blood kits (#51162; QIAGEN, Hilden, Germany). Two single-nucleotide polymorphisms (SNPs; *rs429358* and *rs7412*) were genotyped to identify *APOE* genotypes comprised of the *APOE*- $\epsilon 2$, - $\epsilon 3$ and - $\epsilon 4$ alleles using TaqMan assays (Life Technologies, Carlsbad, CA) as previously described (Jorm et al., 2007). All genotypes containing the $\epsilon 4$ allele were combined as the composite *APOE* $\epsilon 4^+$ ($\epsilon 4/\epsilon 4$; $\epsilon 4/\epsilon 3$; $\epsilon 4/\epsilon 2$) genotype. Because of the potential protective effects of *APOE* $\epsilon 2$ allele, we excluded individuals with $\epsilon 3/\epsilon 2$ and $\epsilon 2/\epsilon 2$ from the reference group. Thus *APOE* $\epsilon 4^+$ was compared against *APOE* $\epsilon 3/\epsilon 3$.

Procedure

Participants were assessed individually either at their home or at The Australian National University. A trained interviewer administered all neuropsychological tests. Participants used a palmtop computer to answer the survey questions, with assistance from the interviewer if required. The study was approved by the Australian National University Research Ethics Committee, the protocol was completed in accordance with the Helsinki Declaration, and all participants provided written consent.

Statistical Analyses

Four head injury variables were investigated as predictors of cognitive performance. Separate linear mixed-effects models were created for each head injury variable, in which sex, *APOE* genotype, age cohort, time in study, and their interactions were modelled as predictors (fixed effects) of cognitive performance. Raw scores on the cognitive tests were standardized relative to each age cohort and converted to *T*-scores (Mean=50, *SD*=10). For all cognitive tests, including reaction time measures, higher *T*-scores represent better performance. Each model was adjusted for participants' level of education and baseline BMI. Intercept and time in study were modelled as random effects. Specifically, we were interested in significant interactions between head injury and time, indicating that groups defined according to their head injury status showed different rates of cognitive change. The results of these analyses

are reported under longitudinal analyses (Table 3). We also examined interactions between head injury and *APOE* $\epsilon 4$ genotype, and head injury and sex which are reported under Baseline Effects in Table 3.

Results

Cohort sample characteristics

The three age cohorts varied significantly in baseline demographic characteristics including sex, body mass index and years of education (see Table 2). *APOE* genotype frequencies did not vary with age group ($p=0.10$) and were consistent with Hardy-Weinberg equilibrium predictions within each sample ($p>0.05$ for all) and with other previously published estimates. TBI characteristics differed across the three age cohorts. The youngest age cohort had a higher frequency of self-reported serious head-injuries, more childhood injuries, and more reports of multiple head-injuries than did the older age cohorts. The middle aged cohort reported a higher frequency of moderate/severe head-injury relative to the other cohorts. The cohorts also differed in the cause of TBI, with more traffic related TBIs in middle aged and more sports related TBI in the young cohort.

[Table 2 here]

Results of Linear Mixed-Effects Models

*Baseline effects involving *APOE* $\epsilon 4$*

Interactions between *APOE* genotype and TBI in predicting baseline cognitive performance was evident only in the 20s and 40s cohort. There were no effects relating to *APOE* genotype in the 60s cohort (Table 3). In the 20s cohort, history of head injury predicted lower baseline episodic memory performance in *APOE* $\epsilon 4$ carriers compared to non-carriers (i.e. *APOE* $\epsilon 3$ homozygotes) with *APOE* $\epsilon 4$ carriers scoring on average 5.40 ($SEM=1.79$) *T*-score points lower than non-carriers ($p<0.05$; Figure 2A). In the 20s cohort, moderate/severe head injury in *APOE* $\epsilon 4$ carriers was also associated with poorer memory (see Figure 2B, Table 3), and similarly *APOE* $\epsilon 4$ carriers reporting childhood TBI also had poorer memory (Figure 2C). However, *APOE* $\epsilon 4$ carriers reporting first TBI as an adult showed better verbal ability than did non-carriers (Figure 2D). *APOE* $\epsilon 4$ genotype in the context of multiple TBI predicted poor episodic memory in the 20s cohort (Figure 2E). In the 40s cohort, *APOE* $\epsilon 4$ carriers who

sustained their first TBI as a child had slower response times than did non-carriers reporting childhood TBI ($B=5.92$, ($SEM=2.15$), $p<0.01$) (Figure 2E).

[Figure 2 here]

Baseline effects involving sex

Interactions between gender and TBI in predicting baseline cognitive performance was apparent in all three age groups, although the pattern of association differed across cohorts. In the 20s cohort, males with TBI in adulthood demonstrated poorer verbal ability relative to females (Figure 3A). Males with a single TBI also had poorer verbal ability relative to females (Figure 3B). In the 40s cohort, childhood TBI was associated with poorer memory in females relative to males, and females reporting a single TBI had reduced processing speed compared to males (Figure 3D) ($B=4.86$, ($SEM=1.92$), $p<0.05$). A similar pattern was apparent in the 60s cohort. Here, female participants reporting moderate/severe TBI had reduced memory performance relative to their male counterparts ($B=8.75$, ($SEM=4.58$), $p<0.05$). Females reporting mild TBI also had slower reaction times compared to males ($B=4.88$, ($SEM=2.50$), $p<0.05$).

[Figure 3 here]

Longitudinal effects

TBI history predicted longitudinal decline in episodic memory (by -0.39 ($SEM=0.13$) T -score points per year ($p<0.01$; see Table 3) in the 20s cohort, and also in the 40s cohort (by -0.27 ($SEM=0.13$), $p<0.01$). Individuals aged in their 60s who reported a history of TBI showed longitudinal decline in speed of processing, where performance slowed by 0.26 ($SEM=0.10$) T -scores per year ($p<0.05$) (Table 3). In this cohort, a similar rate of decline in processing speed was associated with reporting a single TBI relative to no TBI. Multiple TBI was associated with decline in memory for the 20s cohort, while single TBI predicted decline in memory in the 40s cohort. In the 20s cohort, both the childhood TBI and adulthood TBI were associated with decline in memory scores over time (Table 3). Adulthood TBI was also associated with longitudinal reduction in memory scores for the 40s cohort, whereas this variable was associated with decline in processing speed for the 60s cohort.

[Table 3 here]

Discussion

Four head injury variables were investigated as predictors of longitudinal cognitive change and baseline cognitive performance within three age cohorts. In addition to finding TBI-related cognitive decline in young as well as older adults, the results indicated that sex and *APOE* genotype interacted with TBI to predict baseline differences in cognitive performance in a number of cognitive domains. However, these interactions varied across age-groups.

Role of APOE genotype

The cognitive performance of adults in their 20s and 40s was significantly predicted by the interaction between TBI and *APOE* genotype. We found that *APOE* $\epsilon 4$ carriers in their 20s with a history of TBI had poorer baseline episodic memory performance compared to non-carriers. TBI severity also interacted with genotype in this age group, such that participants with moderate to severe injury and the *APOE* $\epsilon 4^+$ genotypes had poorer episodic memory relative to non-carriers with moderate/severe injuries. One possibility is that the detrimental influence of genotype on memory in the 20s cohort may have been driven by severity of injury, and would not be apparent in the absence of those with moderate/severe TBI. In the middle-aged cohort, *APOE* genotype predicted slower reaction time in the context of childhood TBI. These findings contrast with reports that young *APOE* $\epsilon 4$ carriers have *better* global or cognitive outcomes after TBI than non-carriers (Han et al., 2007; Willemse-van Son et al., 2007), and also broader studies indicating that *APOE* $\epsilon 4^+$ genotypes confer cognitive benefits in cognitively normal young adults (Mondadori et al., 2007). The only finding that may support the pattern of results in these previous works is that *APOE* $\epsilon 4$ carriers reporting adulthood TBI in the 20s cohort demonstrated better verbal ability than did non-carriers.

Another possible explanation for the discrepancy between ours and previous findings is that our results reflect longer-term cognitive outcomes associated with retrospective TBI history, whereas prior studies focused on relatively shorter-term outcomes (1 month to 3 years post TBI). Young participants in our study who reported adulthood TBI would have been only a few years post-TBI. Our findings are instead consistent with that of Teasdale et al (2005) who reported a negative impact of *APOE* $\epsilon 4$ genotype on TBI outcome in young patients – an effect which became negligible with advancing age. We recently examined *APOE* genotype as a predictor of cognitive performance in healthy participants of the PATH dataset and failed to find evidence of a beneficial effect of *APOE* $\epsilon 4^+$ genotype in the young cohort (Bunce et

al., In Press). The present work extends this to show that such a relationship is not evident in this dataset even in the context of TBI.

The fact that we found no association between baseline cognition, TBI and *APOE* genotype for adults in their 60s contrasts with several studies (Plassman et al., 2000; Rohling et al., 2011; Sundstrom et al., 2007). However it is consistent with others that have failed to find a relationship between genotype and long-term cognitive outcome in older adults (Rapoport et al., 2008; Teasdale et al., 2005). It is also possible that any associations between *APOE* genotype and cognitive outcome in older adults may have been masked by an interaction with sex as was reported by Ponsford et al (2011) in their study. We did not examine interactions between genotype and sex in our study.

Role of sex

Our findings suggest that the interaction between sex and TBI in predicting cognitive outcome varies across the lifespan. Specifically, we found that compared to females, males in their 20s with a single head injury or TBI as an adult had poorer verbal. In contrast, the effect of sex was largely reversed in both the older cohorts, with females showing lower baseline cognitive performance following TBI. Middle-aged females with multiple TBIs had poorer episodic memory than did males, and females a single TBIs had slower processing speed relative to males. Similarly, in the 60s females reporting either a mild or moderate TBIs had slower reaction times and memory respectively than did males in these categories. Although we did not directly examine participant levels of oestrogen and progesterone in this study or control for hormone replacement therapy, the pattern of associations between sex, age and cognitive correlates of TBI is consistent with age-related changes in the level of female hormones. A similar pattern was observed by Ponsford et al (2011) where global outcome two years post-TBI was poorer in females than in males over the age of 55 years. Oestrogen is thought to act as a potent antioxidant in the context of injury, while progesterone may act to reduce neuronal hyperexcitability post-injury (Roof & Hall, 2000). Furthermore, oestrogen therapy has been found to improve outcomes following cerebral ischemia and TBI in experimental models (Roof & Hall, 2000; Stein, 2001). Previous reports also indicate greater history of TBI amongst males with Alzheimer's disease, but not in females (Fleminger et al., 2003; Mortimer et al., 1991). While our study suggests that cognitive outcomes are poorer for older females with TBI history, it is not clear whether this will trigger or exacerbate

pathological decline and dementia. Further follow-up of this sample will provide insight into the relationship between sex, TBI and dementia.

TBI and cognitive decline

Our data show that 8-year cognitive decline was significantly predicted by self-reported TBI. In the 20s and 40s cohorts, TBI predicted significant decline in episodic memory but this was not apparent in the older cohort. It is possible that effects on episodic memory reduce over time, but this result may also reflect a greater difficulty in recalling events in the older cohort. Further, the oldest cohort had the lowest baseline scores in episodic memory, and this may have made detection of subsequent decline more difficult. In older adults, however, we found that TBI predicted long-term cognitive decline primarily in speed of processing (Millar et al., 2003; Sundstrom et al., 2007). We did not find TBI variables to predict progressive decline in episodic memory in this age group, which contrasts with some previous studies (Rohling et al., 2011). Together with the findings for *APOE* genotype, our data for the older adults suggest that a history of TBI is associated with late-life cognitive decline and impairment in this relatively young older cohort, but there was no evidence for a role for *APOE* genotype in TBI related impairment in this age group (Millar et al., 2003). Decline in other cognitive domains, and in particular memory, may emerge as the cohort ages. The rate of decline observed in this study is relatively small, amounting to a fraction of a standard score per year. While this is of little clinical significance the pattern of interaction with genotype and sex is of interest for understanding outcomes in specific patient groups.

In conclusion, our study supports previous findings that TBI predicts long-term cognitive decline in older adults. In addition we found TBI predicted cognitive decline in younger adults. Furthermore, *APOE* genotype and sex interacted with TBI history in predicting baseline cognitive impairment, and these interactions varied across the three age cohorts. Strengths of the present study include its prospective design, follow-up of over 6000 community based individuals over a period of 8 years, and use of standard neuropsychological measures. Our study also included three age cohorts and multiple TBI variables to provide a thorough examination of TBI relationships with long-term cognitive performance. Significant limitations of the present study include the retrospective self-report of injuries, the non-standard categorization of mild and moderate/severe TBI, and the significantly lower number of reported TBIs in the older cohorts. Further, there was also limited information regarding the timing of TBI events relative to the cognitive assessments.

Acknowledgements

The authors are grateful to the PATH Chief Investigators, Chantal Meslin, Patricia Jacomb, Karen Maxwell, and the PATH interviewers. Susan Tan and Karen Nunweek provided technical assistance with the *APOE* genotyping. The study was supported by National Health and Medical Research Council (NHMRC) of Australia Unit Grant No. 973302, Program Grant No. 179805, NHMRC project grant No. 157125, grants from the Australian Rotary Health Research Fund, and the Australian Brewers Foundation. Prof Anstey was funded by NHMRC Fellowships No. 1002560, and Dr Cherbuin by ARC Fellowship 120100227. Dr Bunce was funded by the Leverhulme Trust, UK. The authors declare there are no financial or other relationships that could be interpreted as a conflict of interest affecting this manuscript.

Conflicts of interest.

The authors have no conflicts of interest to declare.

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Table 1 TBI Variables

TBI Variable	Items and categorisation	Wave*
History of TBI	“Have you ever had a serious head injury that interfered with your memory, made you lose consciousness or caused a blood clot in your brain?” (Yes/No†)	2,3
Frequency	“How many head injuries have you had where you became unconscious for more than 15 minutes?” (continuous)	1,2,3
Severity	Mild: serious head injury with LOC <60 minutes or a period of memory loss up to 1 day†† Moderate/Severe: LOC ≥ 60 minutes and period of memory loss of more than 1 day††	2,3
Age of first TBI	“How old were you when you had the (first) head injury” (Categorised: Child(<18 years) /Adult(≥18 years))	1,2,3

* Questions for wave 3 pertained to the period since the last interview at wave 2.

† Those responding “uncertain” were excluded from analyses when using this variable.

†† assumed to represent post-traumatic amnesia (PTA)

Table 2 Baseline characteristics of the study population according to age cohort

	Age Cohort			<i>p</i>
	20	40	60	
N	2077	2124	2132	
Age at baseline (years)	22.61(1.51)	42.62(1.49)	62.51(1.51)	
Female (%)	1108(53.3)	1145(53.9)	1056(49.5)	<0.01
BMI(kgm ²)	23.57(4.1)	26.35(5.2)	26.86(5.30)	<0.001
Years of education	14.21(1.50)	14.43(2.28)	13.90(2.74)	<0.001
<i>APOE</i> genotype (%)				0.10
$\epsilon 3/\epsilon 3$	1285(61.9)	1244(58.6)	1287(60.4)	
$\epsilon 2/\epsilon 2$ or $\epsilon 2/\epsilon 3$	233(11.2)	294(13.8)	261(12.2)	
$\epsilon 4^+$	559(26.9)	586(27.6)	584(27.4)	
History of TBI (%)				<0.001
Yes	207(10.0)	183(8.6)	99(4.6)	
No	1870(90.0)	1941(91.4)	2033(95.4)	
TBI severity (%)				<0.001
Mild	176(8.5)	128(6.0)	66(3.1)	
Moderate/Severe	31 (1.5)	55(2.6)	33(1.5)	
Frequency of TBI (%)				
Single	107(5.2)	112(5.3)	69(3.2)	<0.001
Multiple	100(4.8)	71(3.3)	30(1.4)	
Age of first TBI (%)				<0.001
Child (<18 years)	138(6.7)	89(4.2)	42(2.0)	
Adult (≥ 18 years)	57 (2.8)	88(4.2)	55(2.6)	
Cause of TBI (%)				<0.001
Traffic accident	30(1.4)	68(3.2)	45(2.1)	
Sport	89(4.3)	59(2.8)	25(1.2)	
Assault	16(0.8)	8(0.4)	0(0.0)	
Fall	59(2.8)	30(1.4)	19(0.9)	
Other	13(0.6)	18(0.9)	10(0.5)	

Note. BMI = body mass index at baseline, TBI = traumatic brain injury

Table 3 TBI as a predictor of baseline and longitudinal cognitive function (*B* coefficients (standard errors))

TBI Variable in Mixed Model	Interacting Variables [§]	Cognitive skill (outcome variable)	Age Cohort			
			20s	40s	60s	
Baseline Effects involving <i>APOE</i> $\epsilon 4^+$						
History of TBI	Yes	<i>APOE</i> $\epsilon 4^+$	Episodic Memory	-5.40(1.79)**		
Severity of TBI	Moderate/Severe	<i>APOE</i> $\epsilon 4^+$	Episodic Memory	-5.89(1.84)**		
Age of first TBI	First TBI as a child	<i>APOE</i> $\epsilon 4^+$	Episodic Memory	-5.90(2.14)**		
	First TBI as a child	<i>APOE</i> $\epsilon 4^+$	Reaction time	-5.92(2.15)**		
	First TBI as an adult	<i>APOE</i> $\epsilon 4^+$	Verbal Ability	2.82(1.29)*		
Frequency of TBI	Multiple	<i>APOE</i> $\epsilon 4^+$	Episodic Memory	-7.32(2.51)**		
Baseline Effects involving sex						
Severity of TBI	Moderate/Severe	Male	Episodic Memory	8.75(4.58)*		
	Mild	Male	Reaction Time	4.88(2.50)*		
Age of first TBI	First TBI as a child	Male	Episodic Memory	6.72(3.21)*		
	First TBI as an adult	Male	Verbal Ability	-2.09(0.88)*		
Frequency of TBI	Single	Male	Verbal Ability	-1.45(0.72)*		
	Single	Male	Processing Speed	4.86(1.92)*		
Longitudinal Effects						
History of TBI	Yes	Time	Episodic Memory	-0.39(0.13)**	-0.27(0.13)*	
	Yes	Time	Processing speed			-0.26(0.10)*

Frequency of TBI	Single	Time	Episodic Memory		-0.35(0.17)*	
	Multiple	Time	Episodic Memory	-0.53(0.20)*		
	Single	Time	Processing speed			-0.25(0.12)*
Age of first TBI	First TBI as a child	Time	Episodic Memory	-0.37(0.16)*		
	First TBI as an adult	Time	Episodic Memory	-0.43(0.20)*	-0.40(0.17)*	
	First TBI as an adult	Time	Processing speed			-0.24(0.12)*

[§] Comparison group for all TBI terms is the No TBI group; comparison group for genotype is *APOE ε3/ε3*, and for sex comparison is to Female.

* $p < 0.05$, ** $p < 0.01$

Figure Captions

Figure 1. Flow chart of sample selection and follow-up.*Study sample excludes participants reporting baseline stroke or epilepsy.

Figure 2. TBI as a predictor of baseline cognitive: interactions with *APOE* genotype.

(A) TBI history and genotype as predictor of episodic memory in 20s cohort (B) TBI severity and *APOE* genotype as predictors of episodic memory in 20s cohort (C) Age of first TBI and *APOE* genotype as predictors of episodic memory in 20s (D) Age of first TBI and genotype as predictors of verbal ability in 20s cohort (E) TBI frequency and genotype as predictors of memory in 20s cohort (F) Age of first TBI and genotype as predictors of reaction time in 40s cohort. (Error bars represent +/-1 SEM)

Figure 3. TBI as a predictor of baseline cognitive performance: interactions with sex.

(A) Age of first TBI cause and sex as predictors of verbal ability in 20s cohort (B) TBI frequency and sex as predictors of verbal ability in 20s cohort (C) Age of first TBI and *APOE* genotype as predictors of memory in 40s cohort. (D) TBI frequency and sex as predictors of processing speed in 40s cohort. (E) TBI severity and sex as predictors of memory in 60s cohort. (F) TBI severity and sex as predictors of reaction time in 60s cohort (Error bars represent +/-1 SEM).