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Mild traumatic brain injury does not significantly affect mid-life cognitive functioning within the general population: Findings from a prospective longitudinal birth cohort study

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Abstract

Objective: To determine if differences exist in mid-adulthood cognitive functioning in people with and without a history of mild traumatic brain injury (mTBI).

Setting: Community-based study.

Participants: People born between 01/04/1972 and 31/03/1973 recruited into the Dunedin Multidisciplinary Health and Development Study, who completed neuropsychological assessments in mid-adulthood. Participants who had experienced a moderate or severe TBI were excluded.

Design: Longitudinal, prospective, observational study.

Main Measures: Data were collected on sociodemographic characteristics, medical history, childhood cognition (between 7-11 years) and alcohol and substance dependence (from age 21). mTBI history was determined from accident and medical records (from birth to age 45). Participants were classified as having ≥1 mTBI in their lifetime or no mTBI. The Wechsler Adult Intelligence Scale (WAIS-IV) and Trail Making Tests A and B (between 38 and 45 years) were used to assess cognitive functioning. T-tests, and effect sizes were used to identify any differences on cognitive functioning domains between the mTBI and no mTBI groups. Regression models explored the relative contribution of number of mTBIs and age of first mTBI and sociodemographic/lifestyle variables on cognitive functioning.

Results: Of the 906 participants, 539 (59.5%) had experienced at least one mTBI over their lifetime, with a mean number of 1.98 mTBI (95%CI 1.91-2.05). The mTBI group had significantly

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slower processing speed ($p<0.01$, $d=0.24$) in mid-adulthood compared to no TBI controls, however the effect size was small. The relationship was no longer significant after controlling for childhood cognition, sociodemographic and lifestyle factors. No significant differences were observed for overall intelligence, verbal comprehension, perceptual reasoning, working memory, attention or cognitive flexibility. Childhood cognition was not linked to likelihood of sustaining mTBI later in life.

Conclusion: mTBI histories in the general population were not associated with lower cognitive functioning in mid-adulthood once sociodemographic and lifestyle factors were taken into account.

Keywords

traumatic brain injury; concussion; cognitive function; neuropsychology; mTBI

Introduction

Mild traumatic brain injury (mTBI) affects 27 million people each year across the globe[1] and is an increasing public concern.[2] Many patients recover naturally in the days to weeks following mTBI, however, large prospective observational studies have shown that between 40 and 53% of people can experience persistent symptoms, functional difficulties and reduced satisfaction with life one year post-mTBI.[3–6]

Without access to effective rehabilitation, evidence suggests that self-reported cognitive symptoms, such as taking longer to think, are the most likely to become chronic in the longer-term[3] and can impact on people's ability to function in everyday life and perform well at work.[7,8] Evidence from neuropsychological tests show that mTBI does not appear to impact overall cognition or intelligence but may have a specific impact on certain cognitive domains. For example, a systematic review of neuropsychological outcomes revealed that there were significant differences between mTBI groups and controls on the cognitive domains of working memory, attention, executive functioning and processing speed, but no differences on perceptual organisation, verbal comprehension or motor skills.[9] However, the review integrated data from days to weeks post-injury to several years post-injury making it difficult to differentiate between acute and more persistent effects. Subsequent reviews have shown that effect sizes on different cognitive domains vary considerably across studies.[10] Reasons for this heterogeneity may include small sample sizes, quality of mTBI data available, representativeness of the mTBI samples and differences in tests administered.

In the longer-term post-injury, a meta-analysis of 21 studies revealed that those who experience a mTBI have nearly twice the risk of developing dementia, including Alzheimer's Disease in later life compared non-injured controls.[11] Most studies exploring the potential impacts of mTBI in older adulthood have been focused on athletes who are at high risk of mTBI.[12] For example, in a study of retired elite and community level rugby players and non-contact sport controls, it was revealed that players who had experienced mTBI over their playing career had poorer complex attention, cognitive flexibility and executive functioning. There were no differences in overall cognition, memory, physical response time, or psychomotor speed.[13] The cognitive domains identified in retired athletes

are similar to those revealed in studies of general population samples conducted within a few years of injury, suggesting that mTBI may have an impact in attentional, processing speed, and executive function domains. However, there is currently a lack of research exploring the impact of mTBI in mid-adulthood (i.e., those aged 35-45 years) and in the general population who are less at risk of repetitive mTBI often experienced within the sports context.

One of the challenges in studying the impacts of mTBI on cognitive functioning is controlling for the complexity of factors that could influence the relationship. Sociodemographic and health factors, such as education level, socioeconomic status and substance use have all been strongly associated with cognitive functioning on neuropsychological tests in non-injured populations.[14] There are also likely to be a number of injury related factors that could impact the relationship, such as the number of TBIs experienced over the lifetime and age at first TBI. Yet the influence of these factors has not been well controlled for in studies to date. Further, current studies have been hindered by a reliance on retrospective data, selection bias or a focus on specific groups, such as the military or athletes. One of the strongest predictors of later-life cognitive functioning is early life cognitive functioning.[15] Consequently, in order to detect the specific impact of injury on cognition, pre-injury assessments of cognition are needed, yet are rarely prospectively available. The Dunedin Multidisciplinary Health and Development Study which has systematically assessed injuries and cognition over participants' lifetimes offers a unique opportunity to determine if there are any impacts of mTBI on cognitive functioning in mid-life whilst controlling for premorbid cognitive ability and alcohol and substance use. This study aims to determine if differences exist in cognitive functioning in mid-adulthood between adults with and without a history of mild traumatic brain injury (mTBI) and to explore the impact of age of first injury and number of lifetime TBI.

Methods

Participants are members of the Dunedin Multidisciplinary Health and Development Study, a longitudinal investigation of health and behaviour in a population-representative birth cohort of 1,037 individuals (91% of eligible births; 52% male) born between 1 April 1972 and 31 March 1973 in Dunedin, New Zealand (NZ). The longitudinal study was established at age 3 years based on residence in the province.[16] Assessments were conducted at birth and at ages 3, 5, 7, 9, 11, 13, 15, 18, 21, 26, 32, 38, and most recently at age 45 years, when 94% of the 997 participants still alive took part. Each study member was brought to the research unit for a day of interviews and examinations at each assessment timepoint. The cohort represents the full range of socioeconomic status on NZ's South Island, and as adults they match the NZ National Health and Nutrition Survey on adult health indicators (e.g., BMI, smoking, physical activity, GP visits).[17] Study participants were primarily of NZ European ethnicity (93% self-identified as White). Written informed consent was obtained from participants at each phase of assessment. The study was approved by the NZ Southern Health and Disability Ethics Committee (Ref: 17/STH/25).

Assessments

Sociodemographic characteristics for the sample were extracted from the main participant database. The person's average childhood socioeconomic status was assessed using the Elley and Irving (1976) scale. This scale categorises the occupation of both parents/guardians into one of six groups based upon the educational levels and income associated with that occupation using data from the NZ census. The scale ranges from 1="unskilled labourer" to 6="professional." The average of the highest SES level from either parent until participants reached age 15 was used to reflect the socioeconomic conditions experienced by participants as they grew up.

Alcohol and substance dependence were assessed using the Diagnostic Interview Schedule (DIS) at ages 21, 26, 32 38 and 45 years. Responses on this interview were used to classify whether the participant had experienced a period of dependence (Using Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) at age 21 and (DSM-IV criteria) at ages 26, 32, 38, and 45. Due to very low rates of use of substances such as cocaine or heroin, only data on alcohol and cannabis use were used in the analysis. Participants were categorised as having a least one period of dependence on alcohol or cannabis, or having no lifetime use or occasional use without dependence.

Cognitive functioning: The Wechsler Adult Intelligence Scale for Children (WISC) was completed at 7, 9, and 11 years of age. The average Full Scale Intelligence Quotient (FSIQ) score of assessments was used to account for early life cognitive functioning.

The Wechsler Adult Intelligence Scale (WAIS-IV) was completed at the age 38 and 45 assessments to measure cognitive functioning across different domains in mid-adulthood. The WAIS-IV consists of 10 different sub tests such as describing how two words or concepts are similar, arranging blocks in a pattern stated in a visual image, recalling number sequences in forwards or backwards order or linking symbols and numbers using a key. Tests are scored for both accuracy and time. Subtest scores as well as full scale intellectual quotient (FSIQ) scores as well as index scores for processing speed, working memory, perceptual reasoning and verbal comprehension were calculated using age-related normative data based on combinations of subtest scores.[18] The average score for each cognitive domain taken from the two assessments were used in the analysis. For the 5.0% of study members who did not complete the WAIS at both time periods, the single available score was used. These data are referred to as "age 45" data from this point forward.

In addition to the WAIS-IV, the Trail Making Test A was used to assess attention and processing speed and Test B[19] was used to assess cognitive flexibility (requiring an additional set shifting executive functioning requirement to switch between tasks).[20] The time to complete each trial was recorded. If more than 5 minutes was taken on either trial the test was stopped.[20] Test scores on each trial (A and B) were averaged between age 38 and age 45 assessments to enhance reliability of measurement by accounting for any factors affecting performance on a given day (e.g., feeling tired after a poor night's sleep). Raw scores on each portion of the test were converted to z-scores using age-related normative data.[20]

TBI History: All accident reports and medical records were obtained for the study participants from across all assessment timepoints. Before the age of 15 the parent/guardian was asked to report all accidents and medical events. From the 16-year assessment upwards, the participant was asked about any accidents or medical events that had occurred since the previous assessment. Additionally, data was extracted from the NZ Accident Compensation Corporation and Ministry of Health databases on any accidents or medical events experienced by the study participants. In NZ, every person is allocated a unique National Health Index number which enables identification of government records linked to a particular person over their lifetime. Relevant incidents were identified where there was a risk of TBI identified by two researchers independently (99.8% agreement). If there was any doubt or disagreement between the researchers, the incident was retained for further review. Details of these incidents were entered into a database including a description of the accident, where the information was collected from (e.g., medical record or self-report), if the person sought medical attention after the injury, discharge information, diagnostic codes, details of all injuries sustained, age of injury, and if there was any note of severity of TBI or duration of loss of consciousness. Each potential injury was then reviewed independently by two clinicians against the criteria established to determine if a TBI had occurred (Supplementary Information 1). MTBI was confirmed when the description of the incident indicated a mTBI was likely, where there was evidence of an external force to the head or body and indications of altered consciousness such as feeling dazed or confused or loss of consciousness.[21]. Moderate and severe TBI were classified as injuries where there was a loss of consciousness of >30 minutes or where there was evidence of abnormal imaging and/or medical diagnosis of a moderate or severe TBI. Data on TBI history were then extracted and merged with the Dunedin longitudinal assessment dataset.

Statistical Analysis

Means and standard deviations (SD) or medians and interquartile ranges (dependent on the distribution of each variable) were used to describe the characteristics of the sample and TBI history. Differences in the characteristics and cognitive functioning of those affected by mTBI and those with no mTBI history were determined using Chi-square and T-test (dependent on whether the data met parametric assumptions). Multiple linear regression models were used to determine relative impact of mTBI variables (e.g., number and age of first injury) alongside other variables known to influence cognitive functioning (including childhood cognitive functioning, sex, childhood socioeconomic status, alcohol and cannabis dependence and education). ANOVA was used to determine if childhood cognitive functioning predisposed participants to an increased risk of mTBI in later life.

Results

Of the 1037 participants from the initial cohort 40 (3.9%) had died prior to the age 45 assessment. There were an additional 59 (5.7%) who declined or who could not be located, 15 (1.4%) had experienced a moderate to severe TBI, and 17 (1.6%) who did not complete the neuropsychological assessment at either age 38 or 45. There were 906 participants who were included in the analysis (Figure 1). Attrition analysis was conducted using childhood IQ and SES to determine whether participants in the age 45 data collection were

representative of the original cohort. No significant differences in childhood IQ were found between the full cohort, those still alive or those seen at age 45. However, those who were deceased by the age 45 data collection had significantly lower IQ's in childhood than those who were still alive (t=2.09, p=0.04).

Characteristics of participants included in the analysis are shown in Table 1. Of these, 539 participants (59.5%) had experienced a least one mTBI over their lifetime. Of those who experienced at least one mTBI, the mean number of injuries sustained was 1.98 (95% confidence intervals 1.91-2.05). There were 451 (49.8%) participants who experienced at least one TBI before age 25. As shown in Table 1, participants who had experienced at least one mTBI in their lifetime were more likely to be male, have lower levels of education, at least one period of alcohol or cannabis dependence, and poorer self-reported physical health.

To test if participants who had experienced at least one mTBI in their lifetime had significantly lower cognitive functioning than those with no TBI history, we compared scores at age 45 for each cognitive domain (Table 2). There was a significant difference between the groups on the WAIS-IV domain of processing speed, but the effect size was small. There were no differences between the groups on overall cognitive functioning, verbal comprehension, perceptual reasoning, working memory, attention or cognitive flexibility.

To determine if the number of TBI over the lifetime and age of first mTBI was linked to midlife cognitive functioning, multiple regression was used to test the unadjusted association and adjusted for childhood cognition, sociodemographic factors and alcohol and substance use as shown in Table 3. A higher number of mTBI was only significantly associated with lower processing speed. However, the number of mTBI no longer remained significant in the full regression model which accounted for childhood cognition, sociodemographic factor and alcohol/substance use (Table 3).

As would be expected, childhood IQ significantly contributed to all midlife cognitive functioning across all domains.

Regression models showed that age of first injury only had an association with lower perceptual reasoning in midlife but there was no association to the other cognitive domains (Table 4.)

To determine if lower childhood cognition predisposed individuals to TBI, we conducted an ANOVA between Childhood cognitive functioning (IQ) scores and number of TBI by age 45. There was no association between early life cognition and number of TBI experienced F=1.37, p=0.25.

Discussion

This prospective study revealed that there were no significant differences in cognitive functioning between adults with a history of mTBI or controls. Age of first mTBI and number of mTBI also did not have a significant association with cognitive functioning in mid-adulthood once sociodemographic and lifestyle factors were taken into account. Early cognitive functioning levels were not found to predispose individuals to an increased risk of

mTBI. The findings suggest that in the general population, where few people are exposed to the repetitive mTBI observed in sport, there is no evidence of impact of mTBI on cognitive functioning in mid-adulthood.

The prevalence of mTBI found in this sample, (with 49.8% of participants experiencing at least one mTBI by age 25), is higher than found in previous studies of 30%.[22] This is likely to reflect differences in injury identification. The current study utilised parent-reported accident records and medical records until age 16. In contrast the previous study only accessed medical appointments before age 16 with self-reported injuries only recorded after age 16. The use of self-reported accident records routinely gathered over participant's lifetimes, in addition to medical records is a strength of this study, given evidence that up 28% of cases of mTBI do not present to their GP, accident or medical clinic or hospital post-injury.[23] To be classified as an mTBI case in this analysis, there needed to be sufficient data of a likely mechanism of injury, sufficient force (e.g., high speed or height of fall), indication of the head being indicated specifically (e.g., lacerations, facial fractures or bruising) or alterations in level of consciousness (e.g. feeling dazed and confused). Despite the higher prevalence it is anticipated that some injuries were not identified due to insufficient information being provided within the medical or accident record to meet the inclusion criteria. Under-reporting of mTBI may also reflect that NZ Accident Compensation Corporation (national compensation provider) medical records only became available from the year 2000 and Ministry of Health data only captures hospital visits following mTBI (and does not include primary care consultations). Additionally, some people may have experienced a mTBI whilst overseas which would not have been captured in NZ medical records.

There were no differences observed in cognitive functioning in mid-adulthood between mTBI cases and controls. This finding contrasts with the findings from a previous systematic review which concluded that there was evidence of effects of mTBI on processing speed, attention, memory and executive functioning cognitive domains.[9] The difference in findings is likely to reflect that the majority of the current sample (64.6%) experienced their mTBI more than 10 years prior to the age 45 assessment. The findings of the previous review included data obtained from assessments conducted several months post-injury and may therefore be more reflective of the short-term effects of mTBI on cognitive functioning. The findings of this study indicate that impacts of mTBI on cognitive functioning are unlikely to persist in the longer term.

The findings of this study also contrast with studies conducted in the context of sport, where mTBI and particularly repetitive mTBI has been linked to poorer cognitive functioning.[24] The difference in findings between this study of the general population and studies in the context of sport, may be due to the current sample being less exposed to the repetitive mTBI impacts, sustained in quick succession that can occur during engagement in high-risk sports such as rugby or football. The average number of injuries in our sample was 1.98. Studies in sport have shown that cognitive impacts and structural changes in the brain are more likely observed following multiple (3 or more) mTBI.[25] However, a linear dose response has not been consistently observed and there was no evidence of this in the current study.[12] It is likely that there may be other injury-related factors influencing the relationship

between mTBI history and later life outcomes, such as whether the person had recovered from a previous injury before another was sustained, symptom burden and type of injury sustained, as well as the medical advice and treatment that they received following injury. Further, many studies of the impact of mTBI in sport have been based on retrospective designs.[12] The longitudinal prospective design of this cohort and comprehensive life-course data enabled the relative contribution of mTBI on cognitive functioning to be explored. The findings from this study highlight the importance of studies in sport to consider the relative impact of mTBI alongside education, pre-injury cognitive functioning and cannabis dependence.

The small difference observed in processing speed before taking into account sociodemographic and lifestyle factors may reflect the risk of diffuse axonal injury (DAI) following mTBI. While heterogeneous and not easily observed using conventional neuroimaging tools,[26] deficits in information processing speed are among the earliest and most prominent cognitive manifestations in mTBI and are associated with extent of DAI.[27] For example, use of Diffuse Tensor Imaging (DTI) revealed that increased abnormal white matter clusters were significantly associated with reduced information processing speed ($p < .05$) in addition to mood and post-concussion symptoms.[28]

There is evidence from previous studies that the impacts of sustaining a mTBI in childhood may impact on behaviours such as increased hyperactivity and risk of conduct disorders[29] However, limited evidence suggests that there is a lasting impact on cognitive functioning in the longer term.[29,30] The findings from this study that age of first injury was not associated with cognitive functioning in mid adulthood in this study supports these findings. Consequently, the current findings may provide reassurance for parents/guardians that a single childhood injury is unlikely to result in longer term difficulties with cognitive functioning in later life. There was no evidence that those with lower cognitive functioning had an increased predisposition of sustaining a mTBI in later life.

A key strength of the study was its prospective longitudinal design, premorbid assessment of cognitive functioning and multiple assessments over the participants lifetimes encompassing injury, lifestyle and cognitive measures. However, the structured and focused nature of cognitive testing within a research setting may mask more subtle cognitive issues experienced in the real-world context where there are many demands on a person's attention, distractors in the environment and the need to multi-task. An additional limitation is that the Trail Making Test B is often used as a measure of executive functioning[20] yet, executive functioning is a complex cognitive domain involving cognitive flexibility, planning and organisation, decision making and behaviour regulation. Consequently, only the cognitive flexibility aspect of executive functioning was assessed in this study and other aspects of executive functioning need further investigation. Further, the study was not able to explore any links to increased risk of neurodegenerative disorders due to the age of participants. A high proportion of the sample identified as being of European ethnicity/white 93% slightly higher than 87% based on population census data for the Dunedin region affecting generalisability of the results to NZ's indigenous populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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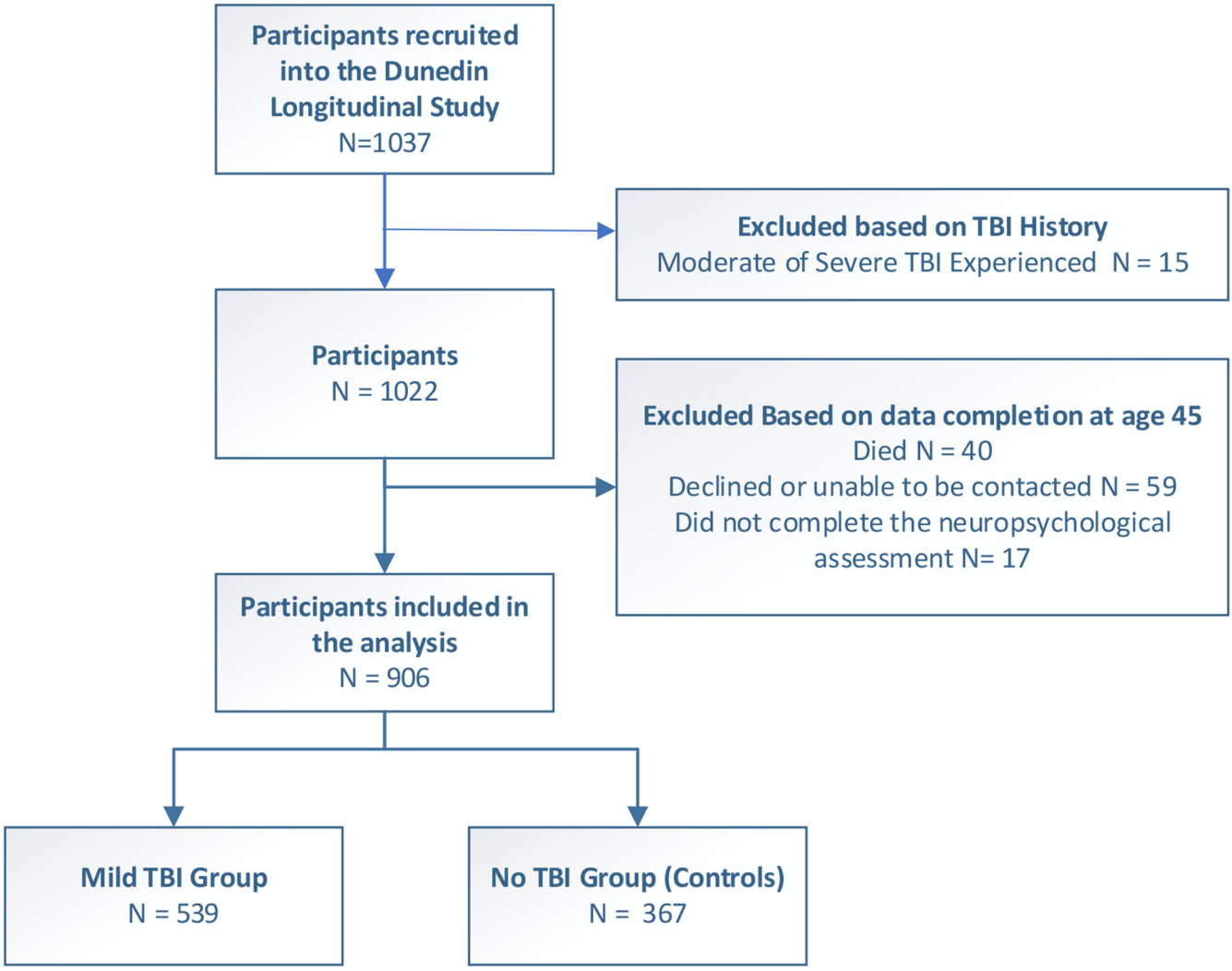

Figure 1.
Participant flowchart

Table 1.

Participant Characteristics

	No history of mTBI N=367		At least one mTBI N=539		Test of Difference	P
	N	%	N	%		
Sex						
Female	243	66.2	208	38.6	X^2=66.6	<0.01
Male	124	3.8	331	61.4		
Highest educational attainment						
School certificate or lower	90	24.5	167	30.9	X^2=8.8	0.01
High School or equivalent	142	38.7	222	41.2		
University degree or higher	134	36.5	150	27.8		
Missing	1	<1	0	0.0		
Cannabis use						
No use or occasional use	324	88.3	417	77.4	X^2=19.5	<0.01
≥1 period of dependence	39	10.6	118	21.9		
Missing	4	1.1	4	<1		
Alcohol use						
Never used or regular drinker but no dependence	264	71.9	327	60.7	X^2=14.0	<0.01
≥1 period of dependence	99	27.0	209	38.8		
Missing	4	1.1	3	<1		
Major comorbidity						
No	273	74.4	398	73.8	X^2=0.03	0.85
Yes	94	25.6	141	26.2		
Current Health Status						
Fair/poor	21	5.7	60	11.1	X^2= 8.6	0.01
Good	126	34.3	161	29.9		
Excellent/Very good	220	60.0	318	59.0		
Number of lifetime mTBIs						
no TBI events	367	100	0	0.0	-	-
1 TBI event	-	-	201	37.3	-	-
2 TBI events	-	-	148	27.5	-	-
3 or more TBI events	-	-	190	35.3	-	-
Age at time of 1st mTBI						
0-4			160	29.7		
5-9			100	18.6		
10-14			98	18.2		
15-19			70	13.0		

	No history of mTBI N=367		At least one mTBI N=539		Test of Difference	P
	N	%	N	%		
20-24			23	4.3		
25-29			12	2.2		
30-34			16	3.0		
35-39			24	4.5		
40-45			36	6.7		
Time since last reported injury in years						
Past 12 months			21	3.9		
Past 5 years			109	20.2		
Between 6 and 10 years ago			61	11.3		
Within 20 years			64	11.9		
Within 30 years			96	17.8		
Within 40 years			134	24.9		
>40 years ago			54	10.0		
	Mean	SD	Mean	SD		
Highest childhood socioeconomic status (birth to 15 years) Mean (SD)	3.9	1.1	3.7	1.2	t=1.8	0.07
Average Childhood IQ (WISC IQ 7,9 and 11 years) Mean (SD)	101.3	13.3	100.6	14.2	t=0.8	0.42

Table. 2.

Comparison of average cognitive domain test scores between those with mTBI history and those with no history

Cognitive Domains	No mTBI N=367	At least one mTBI N=539		
	Mean (SD)	Mean (SD)	T-test P value	Effect Size
Full Scale IQ (WAIS-IV)	100.0 (15.1)	98.4 (14.7)	0.12	0.11
Verbal Comprehension Index (WAIS-IV)	99.8 (14.6)	98.9 (14.3)	0.38	0.06
Perceptual Reasoning Index (WAIS-IV)	100.9 (16.0)	100.2 (15.4)	0.51	0.04
Processing Speed Index (WAIS-IV)	100.3 (14.3)	97 (14.6)	<0.01	0.23
Working Memory Index (WAIS-IV)	99.3 (15.2)	99.4 (14.8)	0.93	0.01
Attention and Processing Speed (Trail Making Test A z-score)	0.1 (1.1)	0.0 (1.1)	0.16	0.09
Cognitive Flexibility (Trail Making Test B z-score)	−0.1 (1.2)	−0.3 (1.3)	0.07	0.16

Table 3.

Unadjusted association between number of TBI and cognition in mid-adulthood and adjusted for sociodemographic and lifestyle variables.

Cognitive Outcome	Model 1 No. of TBI on cognition			Model 2 No. of TBI on cognition adjusting for childhood IQ			Model 3 No. of TBI on cognition controlling for sociodemographic factors (SES, education, gender)			Model 4 No. of TBI on cognition adjusting for alcohol and substance use			Model 5 No. of TBI adjusting for all factors		
	Estimate	SE	p	Estimate	SE	p	β	SE	p	β	SE	p	β	SE	p
Full Scale IQ (WAIS-IV)															
1 mTBI*	−2.05	1.30	0.11	−0.57	0.84	0.50	−0.68	1.12	0.54	−1.44	1.28	0.26	−0.10	0.82	0.90
2 mTBI*	0.76	1.44	0.6	−0.48	0.93	0.61	0.39	1.23	0.75	1.18	1.42	0.41	−0.19	0.90	0.83
3 or more mTBI*	−3.17	1.32	0.02	−1.93	0.85	0.02	−1.67	1.17	0.15	−1.87	1.34	0.16	−0.89	0.87	0.31
Childhood IQ	-	-	-	0.82	0.02	<0.01	-	-					0.73	0.03	<0.01
Childhood SES							2.79	0.39	<0.01				0.23	0.30	0.45
HS Grad/BA or higher∞							16.25	1.28	<0.01				6.57	1.03	<0.01
School Certificate∞							5.86	1.58	<0.01				2.40	1.17	0.04
Female≠							-1.95	0.88	0.03				−0.48	0.66	0.46
Alcohol Dependence Θ										−2.50	1.09	0.02	−2.41	0.69	<0.01
Cannabis Dependence ϕ										−4.53	1.37	<0.01	−1.38	0.90	0.12
Verbal Comprehension Index (WAIS-IV)															
1 mTBI*	−1.61	1.28	0.21	−0.22	0.95	0.82	−0.85	1.10	0.44	−1.14	1.28	0.37	−0.25	0.93	0.79
2 mTBI*	0.28	1.42	0.85	−0.87	1.05	0.41	−0.66	1.21	0.59	0.60	1.42	0.67	−1.08	1.03	0.29
3 or more mTBI*	−1.23	1.30	0.34	0.05	0.96	0.96	−0.28	1.15	0.81	−0.44	1.33	0.74	0.11	0.99	0.91
Childhood IQ				0.71	0.03	<0.01							0.57	0.03	<0.01
Childhood SES							3.38	0.39	<0.01				1.29	0.34	<0.01
HS Grad/BA or higher∞							13.84	1.27	<0.01				7.18	1.18	<0.01
School Certificate∞							3.76	1.57	0.02				1.73	1.35	0.19

Cognitive Outcome	Model 1 No. of TBI on cognition			Model 2 No. of TBI on cognition adjusting for childhood IQ			Model 3 No. of TBI on cognition controlling for sociodemographic factors (SES, education, gender)			Model 4 No. of TBI on cognition adjusting for alcohol and substance use			Model 5 No. of TBI adjusting for all factors		
	Estimate	SE	p	Estimate	SE	p	β	SE	p	β	SE	p	β	SE	p
Female ǂ							−3.58	0.86	<0.01				−2.47	0.74	<0.01
Alcohol Dependence Θ										−2.07	1.08	0.06	−1.78	0.78	0.02
Cannabis Dependence ϕ										−2.28	1.37	0.09	0.70	1.02	0.49
Perceptual Reasoning Index (WAIS-IV)															
1 mTBI *	−1.43	1.38	0.30	−0.26	1.08	0.81	−0.54	1.27	0.67	−0.90	1.38	0.51	−0.14	1.09	0.90
2 mTBI *	0.99	1.53	0.52	0.05	1.19	0.97	0.53	1.40	0.71	1.35	1.53	0.38	0.16	1.19	0.90
3 or more mTBI *	−1.16	1.41	0.41	−0.06	1.09	0.96	−0.03	1.33	0.98	0.06	1.43	0.97	0.75	1.15	0.51
Childhood IQ				0.72	0.03	<0.01							0.64	0.03	<0.01
Childhood SES							2.37	0.44	<0.01				0.09	0.40	0.82
HS Grad/BA or higher ∞							13.37	1.45	<0.01				5.25	1.36	<0.01
School Certificate ∞							3.38	1.79	0.06				0.90	1.55	0.56
Female ǂ							−2.70	0.99	0.01				−1.45	0.86	0.09
Alcohol Dependence Θ										−1.95	1.17	0.10	−2.00	0.91	0.03
Cannabis Dependence ϕ										−4.39	1.47	<0.01	−1.95	1.18	0.09
Processing Speed Index (WAIS-IV)															
1 mTBI *	−3.01	1.27	0.02	−2.31	1.13	0.04	−0.59	1.20	0.63	−2.41	1.25	0.05	−0.31	1.10	0.77
2 mTBI *	−0.85	1.41	0.55	−1.83	1.24	0.14	−0.03	1.32	0.98	−0.34	1.38	0.80	−0.44	1.20	0.71
3 or more mTBI *	−6.0 4	1.30	<0.01	−5.34	1.14	<0.01	−2.73	1.26	0.03	−4.47	1.30	<0.01	−2.03	1.16	0.08
Childhood IQ				0.50	0.03	<.001							0.48	0.04	<0.01
Childhood SES							0.89	0.42	<0.01				−0.77	0.40	0.06

Cognitive Outcome	Model 1 No. of TBI on cognition			Model 2 No. of TBI on cognition adjusting for childhood IQ			Model 3 No. of TBI on cognition controlling for sociodemographic factors (SES, education, gender)			Model 4 No. of TBI on cognition adjusting for alcohol and substance use			Model 5 No. of TBI adjusting for all factors		
	Estimate	SE	p	Estimate	SE	p	β	SE	p	β	SE	p	β	SE	p
HS Grad/BA or higher[∞]							12.24	1.37	<0.01				4.92	1.37	<0.01
School Certificate[∞]							6.79	1.70	<0.01				4.05	1.57	0.01
Female[ǂ]							5.33	0.94	<0.01				6.09	0.87	<0.01
Alcohol Dependence[Θ]										−2.12	1.06	0.05	−1.17	0.92	0.20
Cannabis Dependence[ϕ]										−6.04	1.33	<0.01	−3.13	1.19	0.01
Working Memory Index (WAIS-IV)															
1 mTBI[*]	−0.38	1.32	0.78	0.79	1.06	0.46	−0.08	1.24	0.95	0.10	1.32	0.94	0.41	1.08	0.71
2 mTBI[*]	2.47	1.46	0.09	1.54	1.18	0.19	1.74	1.37	0.20	2.74	1.46	0.06	1.31	1.19	0.27
3 or more mTBI[*]	−1.73	1.35	0.20	−0.86	1.08	0.43	−1.68	1.31	0.20	−1.07	1.38	0.44	−1.32	1.15	0.25
Childhood IQ				0.64	0.03	<0.01							0.59	0.03	<0.01
Childhood SES							2.06	0.44	<0.01				−0.05	0.40	0.91
HS Grad/BA or higher[∞]							10.89	1.42	<0.01				3.15	1.35	0.02
School Certificate[∞]							3.06	1.76	0.08				0.53	1.55	0.73
Female[ǂ]							−4.02	0.97	<0.01				−3.06	0.86	<0.01
Alcohol Dependence[Θ]										−2.02	1.12	0.07	−2.03	0.91	0.02
Cannabis Dependence[ϕ]										−2.05	1.41	0.15	−0.80	1.18	0.50
Processing Speed (Trail Making Test A z-score)															
1 mTBI[*]	−0.15	0.10	0.14	−0.10	0.09	0.29	−0.04	0.10	0.66	−0.12	0.10	0.23	−0.03	0.09	0.75
2 mTBI[*]	0.00	0.11	0.97	−0.05	0.10	0.60	0.03	0.11	0.79	0.01	0.11	0.90	−0.01	0.10	0.92
3 or more mTBI[*]	−0.20	0.10	0.05	−0.16	0.10	0.09	−0.06	0.10	0.55	−0.12	0.10	0.23	−0.03	0.10	0.75

Cognitive Outcome	Model 1 No. of TBI on cognition			Model 2 No. of TBI on cognition adjusting for childhood IQ			Model 3 No. of TBI on cognition controlling for sociodemographic factors (SES, education, gender)			Model 4 No. of TBI on cognition adjusting for alcohol and substance use			Model 5 No. of TBI adjusting for all factors		
	Estimate	SE	p	Estimate	SE	p	β	SE	p	β	SE	p	β	SE	p
Childhood IQ				0.03	0.00	<0.01							0.03	0.00	<0.01
Childhood SES							0.06	0.04	0.08				−0.05	0.03	0.16
HS Grad/BA or higher[∞]							0.64	0.11	<0.01				0.14	0.12	0.21
School Certificate[∞]							0.44	0.14	0.00				0.24	0.13	0.07
Female[≠]							0.17	0.08	0.03				0.20	0.07	0.01
Alcohol Dependence [Θ]										−0.10	0.08	0.23	−0.07	0.08	0.342
Cannabis Dependence [ϕ]										−0.36	0.10	0.00	−0.27	0.10	0.01
Cognitive Flexibility (Trail Making Test B z-score)															
1 mTBI[*]	−0.22	0.11	0.04	−0.14	0.09	0.13	−0.09	0.11	0.40	−0.17	0.11	0.11	−0.05	0.10	0.61
2 mTBI[*]	0.08	0.12	0.53	0.00	0.10	0.96	0.10	0.12	0.39	0.11	0.12	0.34	0.07	0.11	0.48
3 or more mTBI[*]	−0.31	0.11	0.01	−0.24	0.10	0.01	−0.14	0.11	0.21	−0.22	0.11	0.06	−0.10	0.10	0.34
Childhood IQ				0.04	0.00	<0.01							0.04	0.00	<0.01
Childhood SES							0.10	0.04	0.01				−0.06	0.04	0.11
HS Grad/BA or higher[∞]							0.92	0.12	<0.01				0.31	0.12	0.01
School Certificate[∞]							0.45	0.15	<0.01				0.24	0.14	0.08
Female[≠]							0.15	0.08	0.06				0.24	0.08	<0.01
Alcohol Dependence [Θ]										−0.10	0.09	0.26	−0.05	0.08	0.52
Cannabis Dependence [ϕ]										−0.36	0.12	<0.01	−0.17	0.10	0.10

[*] reference = no TBI events,

[∞] reference = no school certificate

$\neq_{\text{reference = male}}$

$\Theta_{\text{reference = no alcohol use or dependence}}$

$\phi_{\text{reference = no cannabis use or dependence}}$

Table 4.

Determining if age of first injury influences mid-life cognitive functioning

Outcome	Estimate	SE	P	LCI	UCI
Full Scale IQ (WAIS-IV)	−0.09	0.05	0.08	−0.20	0.01
Verbal Comprehension Index (WAIS-IV)	−0.10	0.05	0.06	−0.20	0.01
Perceptual Reasoning Index (WAIS-IV)	−0.14	0.05	0.01	−0.25	−0.03
Processing Speed Index (WAIS-IV)	−0.03	0.05	0.59	−0.13	0.07
Working Memory Index (WAIS-IV)	−0.04	0.05	0.48	−0.14	0.07
Processing Speed (Trail Making Test A z-score)	−0.00	0.00	0.86	−0.01	0.01
Cognitive Flexibility (Trail Making Test B z-score)	−0.00	0.00	0.39	−0.01	0.01