DUNEDIN STUDY CONCEPT PAPER FORM

Provisional Paper Title: Does mild TBI affect neuropsychological functioning in mid-adulthood?

Proposing Author: Alice Theadom

Author's Email: alice.theadom@aut.ac.nz

P.I. Sponsor: Richie Poulton
(if the proposing author is a student or colleague of an original PI)

Today's Date: 26/07/2021

Please describe your proposal in 2-3 pages with sufficient detail for helpful review.

Objective of the study:

There is currently concern as to whether mild traumatic brain injuries (TBIs, including concussion) have longer-term impacts, particularly in relation to cognitive functioning.

Previously it was believed the majority of people who experienced a mild TBI recovered quickly from these injuries within a few weeks or days. It has only recently emerged that nearly half of those affected by a mild TBI go on to experience persistent symptoms impacting on functioning in daily life.[1,2] There is evidence that cognitive impairments are the most persistent. In the longer term, evidence from retired rugby and non-contact sports athletes has shown that a history of concussion can affect neuropsychological functioning in the domains of complex attention, cognitive flexibility and executive functioning.[3] The impact on cognition may be exacerbated by the cumulative effects of multiple injuries sustained over time.[4,5]

Ones of the challenges in studying the influence of mild TBI on cognitive functioning is controlling for the complexity of factors that could influence the link, such as number of early lifetime TBIs, age of first exposure to TBI, time since last injury, education level, pre-injury cognitive functioning, socioeconomic status, substance use and psychological history.[6] Many studies have also been hindered by retrospective data, selection bias or a focus on specific groups, such as athletes rather than the general population. The objective of this analysis is to utilize the comprehensive longitudinal data from the Dunedin Study which has systemically monitored all accidents over participants' lifetimes, collected neuropsychological data at

several timepoints alongside sociodemographic information to try and disentangle effects of mild TBI on cognitive functioning in mid adulthood.

Research questions:

1. Are there significant differences in cognitive functioning between adults who have experienced at least one mild TBI and than those without a TBI history?
2. Does mild TBI affect specific cognitive domains in comparison to those without a TBI history?
3. Does the number of injuries or age of first injury influence links between mild TBI and cognition after controlling for years of education, highest childhood socio-economic status, mental health, alcohol and substance use and early childhood injury?

Data analysis methods:

Descriptive statistics will be used to describe the proportion of people affected by TBI over their lifetime, the distribution of age of first TBI and total number of TBIs and mechanism.
For analysis of the longitudinal data, a nested case-control design will be used.
Sociodemographic data will be used to describe characteristics of those affected by TBI and those who were not and comparison between the two groups made using Chi-square and t-tests dependent on the distribution of the variable data.
The study population will be selected based on individuals that have lived to 45 years or older. The population will be split into two groups based on TBI history. The cases will be participants who have experienced at least one mTBI between ages 7 and 45. The controls will be those that have not experienced a brain injury between 7 and 45 years of age. Exclusion criteria will include those who died or, were lost to follow-up prior to phase 45 assessment and those who have experienced a moderate or severe TBI. Nonparametric signed ranked test will be used to test for the median of paired differences. Linear regression models will be used to determine the association between TBI history and cognitive outcomes. Adjustment for mean IQ (based on WISC scores assessed at ages 7, 9 and 11) will be made. Covariates will include age group, gender, ethnicity, and highest socio-demographic status, TBI prior to age 7, years of education, mental health, alcohol/substance misuse (potential mediators) and age of first TBI.

Variables needed at which ages:

TBI history by participant (Number of lifetime TBI)
Age at time of first TBI
Study number
Cognitive functioning as assessed by the WAIS neuropsychological assessment,
(including full scale IQ, Verbal Comprehension Index (VCI), Perceptual Reasoning Index (PRI), Working Memory Index (WMI), Processing Speed Index (PSI) as well as subtest scores age 45)
Trail making tests A and B age 45
WISC total IQ at ages, 7, 9 and 11
Sex
Highest childhood SES (See Wertz paper)
Years of education
High substance use categorized as ‘never used or no regular use’ and ‘regular use identified in

at least one phase' from phases 18, 21,26,32 and 38.
High alcohol use categorized as evidence of problematic used in at least one phase between phases 18, 21, 26, 32 and 28, Yes or No
General Health Questionnaire age 45

Significance of the Study (for theory, research methods or clinical practice):
This study will help determine if there are any longer-term effects of mild TBI on cognitive functioning in mid adulthood and if the age at injury or number of injuries influences this link. This will be important to support provision of treatments to improve cognitive functioning after mild TBI and if domain specific, which areas of cognitive functioning interventions need to be targeted. The findings will also be important to inform those at high risk of injury about the potential consequences so that they can make informed decisions about engaging in, preventing and returning to activities after injury.

References:

1. McMahon P, Hricik A, Yue JK, et al. Symptomatology and Functional Outcome in Mild Traumatic Brain Injury: Results from the Prospective TRACK-TBI Study. *Journal of Neurotrauma.* 2013;31 Epub ahead of print.
2. Theadom A, Parag V, Dowell T, et al. Persistent problems 1 year after mild traumatic brain injury: a longitudinal population study in New Zealand. *British Journal of General Practice.* 2016;66(642):e16-23.
3. Hume P, Theadom A, Lewis GN, et al. A Comparison of Cognitive Function in Former Rugby Union Players Compared with Former Non-Contact-Sport Players and the Impact of Concussion History. *Sports Med.* 2016;Aug 24(Epub ahead of print).
4. MacFarlane MP, Glenn TC. Neurochemical cascade of concussion. *Brain Injury.* 2015;29:139-153.
5. Signoretti S, Lazzarino G, Tavazzi B, Vagnozzi R. The pathophysiology of concussion. *PM R 3.* 2011;Suppl 2:359-368.
6. LoBue C, Munro C, Schaffert J, et al. Traumatic Brain Injury and Risk of Long-Term Brain Changes, Accumulation of Pathological Markers, and Developing Dementia: A Review. *J Alzheimers Dis.* 2019;Epub ahead of print.

Data Security Agreement

Provisional Paper Title	Does mild TBI affect neuropsychological functioning in mid-adulthood?
Proposing Author	Alice Theadom
Today's Date	09/11/2021

Please keep one copy for your records and return one to the PI Sponsor

Please initial your agreement: (customize as necessary)

AT	I am current on Human Subjects Training [CITI www.citigrogram.org] or equivalent.
AT	My project is covered by the Dunedin Study's ethics approval
AT	I will treat all data as "restricted" and store in a secure fashion. My computer or laptop is: • encrypted (recommended programs are FileVault2 for Macs, and Bitlocker for Windows machines) • password-protected • configured to lock-out after 15 minutes of inactivity AND • has an antivirus client installed as well as being patched regularly.
AT	I will not "sync" the data to a mobile device.
AT	In the event that my laptop with data on it is lost, stolen or hacked, I will immediately contact my PI Sponsor or Study Director, Richie Poulton (richie.poulton@otago.ac.nz).
AT	I will not share the data with anyone, including my students or other collaborators not specifically listed on this concept paper.
AT	I will not post data online or submit the data file to a journal for them to post. *Some journals are now requesting the data file as part of the manuscript submission process. The Dunedin Study Members have not given informed consent for unrestricted open access, so we have a managed-access process. Speak to your PI Sponsor or Richie Poulton for strategies for achieving compliance with data-sharing policies of journals.*
AT	I will delete all data files from my computer after the project is complete. Collaborators and trainees may not take a data file away from the office. The data remains the property of the Study and cannot be used for further analyses without an approved concept paper for new analyses.

Signature: _____ _____

CONCEPT PAPER RESPONSE FORM

A To be completed by the proposing author:

Provisional Paper Title	Does mild TBI affect neuropsychological functioning in mid-adulthood?
Proposing Author	Alice Theadom
Other Contributors	Suzanne Barker-Collo, Varsha Parag, Avshalom Caspi, Terrie Moffitt, Richie Poulton, Sandhya Ramrakha, Sean Hogan **Temi – anyone else from your team?**
Potential Journals	
Today's Date	11/11/21
Intended Submission Date	

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B. To be completed by potential co-authors:

☐ Approved ☐ Not Approved ☐ Let's discuss, I have concerns

Comments: _____

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Please check your contribution(s) for authorship:

	Conceptualizing and designing the longitudinal study
	Conceptualizing data collection protocols and creating variables
	Data collection
	Conceptualizing and designing this specific paper project
	Statistical analyses and interpretation (or reproducibility check)
	Writing
	Reviewing manuscript drafts
	Final approval before submission for publication
	Agreement to be accountable for the work

	Acknowledgment only, I will not be a co-author

Signature: _____