McMaster University | HEALTH FORUM

Rapid Evidence Profile

Examining the long-term risks of sub-concussive exposures among occupationally exposed members of the military

22 March 2024

[MHF product code: REP 69]

Box 1: Evidence and other types of information

+ Global evidence drawn upon

Evidence syntheses selected based on relevance, quality, and recency of search

+ Forms of domestic evidence used (🍁 = Canadian)

Evaluation

Data analytics

*** Additional notable features**

Prepared in the equivalent of three-business days using an 'all hand- on deck' approach

Context

- Mild traumatic brain injuries (mTBIs) include both concussions, which occur when symptoms are experienced immediately after the incident, and sub-concussions, which occur when no immediate symptoms are present.
- mTBIs are the most common traumatic brain injury affecting military personnel, but are also among the most difficult to diagnose, particularly for sub-concussions.
- Following significant literature documenting the association between concussions and neurodegenerative conditions, there is increasing concern about the possible link between sub-concussions and neurodegeneration, particularly chronic traumatic encephalopathy (CTE), which causes damage or death to parts of the brain over time.
- This rapid evidence profile aims to examine the long-term risks of repetitive sub-concussive exposures among occupationally exposed members of the military.

Questions

1) What is known about the association between repetitive sub-concussive exposures and the long-term risks of neurodegenerative conditions (e.g., chronic traumatic encephalopathy, Alzheimer's disease, other forms of dementia) for occupationally exposed members of the military, and do these risks vary by sex?

High-level summary of key findings

- We included 52 evidence documents, of which we deemed 32 to be highly relevant, including seven evidence syntheses and 25 single studies.
- Despite a significant volume of literature and increase in recent research in this area, we were unable to conclude whether there is an association between repetitive sub-concussive exposures and neurodegenerative conditions, largely because of challenges defining and measuring sub-concussions.
- One recent medium-quality evidence synthesis and one single study specifically examined the association of repetitive sub-concussions and neurodegeneration and found a weak association among former football and soccer athletes for diseases including dementia, amyotrophic lateral sclerosis, and Parkinson's disease.

- Many of the included evidence syntheses and single studies define mTBIs broadly including both sub-concussive and concussive exposures and point to an association between repetitive mTBIs and neurodegenerative conditions.
- In addition to findings based on association, findings from neuroimaging studies of Veterans and athletes as well as animal models (rat and mice) point to a number of changes in the brain as a result of sub-concussive exposures, many of which are also biomarkers for neurodegenerative conditions.
- Finally, we identify novel ways of measuring sub-concussive exposures, including a recent U.S. study that uses 'e-type silhouettes' equipped with pressure gauges to determine the pressure from blast exposures that special operations forces are exposed to during training.

Framework to organize what we looked for

- Type of repetitive sub-concussive exposure
  - Blast
    - Primary (i.e., resulting from high pressure or overpressure created by explosions)
    - Secondary (i.e., resulting from strong winds following the blast wave that propel fragments and debris towards the body)
    - Tertiary (i.e., resulting from strong blast winds and pressure gradients that can accelerate and cause blunt force injury)
    - Quaternary (i.e., resulting from other explosive products and from exposure to toxic substances that can cause burns, blindness, and inhalation injuries)
    - Quinary (i.e., resulting from post-detonation environmental contaminants including chemical, biological, and radiological substances)
  - Non blast
  - Mixed
  - mTBI (broadly defined, inclusive of both sub-concussive and concussive exposures)
- Neurodegenerative conditions
  - Chronic traumatic encephalopathy (CTE)
  - Alzheimer's disease
  - Dementia (all cause)

Box 2: Approach and supporting materials

At the beginning of each rapid evidence profile, we engage a subject matter expert who helps us to scope the question and ensure relevant context is taken into account in the summary of the evidence.

We identified evidence addressing the question by searching Health Systems Evidence, PubMed, and hand-searching the Forces in Mind Trust research repository. All searches were conducted on 4 March 2024. The search strategies used are included in Appendix 1. In contrast to synthesis methods that provide an in-depth understanding of the evidence, this profile focuses on providing an overview and key insights from relevant documents.

We searched for full evidence syntheses (or synthesis-derived products such as overviews of evidence syntheses) and protocols for evidence syntheses.

We appraised the methodological quality of evidence syntheses that were deemed to be highly relevant using AMSTAR. AMSTAR rates overall quality on a scale of 0 to 11, where 11/11 represents a review of the highest quality. The AMSTAR tool was developed to assess reviews focused on clinical interventions, so not all criteria apply to evidence syntheses pertaining to delivery, financial, or governance arrangements within health systems or to broader social systems.

A separate appendix document includes:
1) methodological details (Appendix 1)
2) key findings from included evidence syntheses and primary studies (Appendix 2)
3) details about each identified synthesis (Appendix 3)
4) details about each identified single study (Appendix 4)
5) documents that were excluded in the final stages of review (Appendix 5).

This rapid evidence profile was prepared in the equivalent of three days of a 'full-court press' by all involved staff.

    - Parkinson's disease
    - Other movement disorders (e.g., ataxia, motor neuron disease)
- High-risk military occupations and roles
- Biological sex
    - Male
    - Female
- Other factors that may affect long-term risks
    - Number of sub-concussive exposures
    - Early or immediate return to high-risk activities
    - Nature of protective equipment available (including the consistency with which it is worn and whether it fits correctly)
    - Mis- or delayed diagnosis
    - Co-morbid post-traumatic stress disorder (PTSD) or mental health conditions

What we found

We included 52 evidence documents, of which we deemed 32 to be highly relevant. The 32 documents include seven evidence synthesis and 25 single studies, of which 16 (one evidence synthesis and 15 single studies) focus on military and Veteran populations.

Documents were included and determined to be highly relevant if they focused on sub-concussive exposures (or included definitions of mTBIs that were inclusive of sub-concussive exposures) and included a focus on neurodegenerative conditions.

Coverage by and gaps in included evidence documents

Despite a significant volume of literature and an increase in recent research in this area, we were unable to conclude whether there is an association between repetitive sub-concussive exposures and neurodegenerative conditions. This is largely a result of there being no conclusive definition for sub-concussive exposures (in part due to no conclusive determination of biomarkers for sub-concussive exposures) and limited methods that document when sub-concussive exposures take place. We did find evidence of associations between mTBIs more broadly (including concussive exposures) and neurodegenerative conditions, as well as evidence of biomarkers from repetitive sub-concussive exposures that share biomarkers for neurodegenerative conditions.

With respect to coverage of the framework above:

- all the literature (with the exception of select animal models) that analyzed blast-related and mixed exposure is focused on military personnel and Veterans
- findings about non-blast exposure were predominantly derived from athletes, such as football, hockey, and soccer players
- all neurodegenerative conditions in the framework were covered, with most having a larger focus on CTE and Alzheimer's disease
- evidence documents about high-risk military occupations and roles largely focused on those with combat exposure, notably special operations forces and 'breachers' (i.e., individuals trained to enter buildings using force, often explosives)
- most of the literature pertained to biological males, except for one study examining differences in male and female hockey players (1)
- evidence documents addressed other factors that may affect long-term risk, which cover both repeated sub-concussive exposures and their relative risk as compared to single exposures, as well as the mediating and potentially compounding effect of PTSD on mTBIs.

What existing evidence syntheses and highly relevant single studies tell us about the association between repeated sub-concussive exposures and neurodegenerative conditions

While the evidence regarding the association between repeated sub-concussive exposures and neurodegenerative conditions remains inconclusive, findings from the identified literature point to this being a rapidly evolving evidence base. We organized this literature into four categories of findings:
1) about the association between mTBIs and neurodegenerative conditions
2) from neuroimaging on the effects of repeated sub-concussive exposures
3) from animal models on the effects of repeated sub-concussive exposures
4) about new methods of measuring or monitoring sub-concussive exposures.

Findings about the association between mTBIs and neurodegenerative conditions

Two documents, one recent medium-quality evidence synthesis and one recent single study, specifically examined the association of repetitive sub-concussive exposures and neurodegeneration. The evidence synthesis found a weak association between repetitive sub-concussive exposures among former football and soccer athletes and neurodegenerative diseases, including dementia, amyotrophic lateral sclerosis, and Parkinson's disease.(2) A recent single study examined amateur football players with no medical history of concussion found self-reported executive function impairments later in life, regardless of self-reported concussions, suggesting that sub-concussive injuries may be as damaging as self-reported concussions.(3) The study did not report associations with specific neurodegenerative conditions.

Beyond repetitive sub-concussive exposures, four evidence syntheses (two recent medium-quality and two recent low-quality) and four single studies reported associations between mTBIs (broadly defined) and an increased risk for developing neurodegenerative conditions, including Alzheimer's disease, dementia, and Parkinson's disease.(4-11) The four studies focused primarily on U.S. Veterans with a history of blast and combat exposure.(8-11)

Two studies reported dose-response relationships, whereby an increased number of mTBIs reduced physiological recovery and increased symptoms following exposure.(3; 12)

Findings from neuroimaging on the effects of repetitive sub-concussive exposures

Though neuroimaging studies do not demonstrate associations between sub-concussive exposures and neurodegenerative disorders, they are critical for understanding the mechanisms of brain injuries and can point towards the development of neurodegenerative disorders over the long-term.

For repeated blast and mixed exposures, neuroimaging studies reported the following changes to Veterans' brains:
- increased cortical retention, elevated levels of neurofilament light chain proteins and increased perivascular space, all of which may be indicators of neurodegeneration (13; 14)
- reduction in auditory event-related potential, which may be a biomarker for future dementia risk (15)
- decreases in retinal axon and central nervous system function, which is also seen in individuals with Alzheimer's disease (16)
- reduction in cerebral blood flow following three or more sub-concussive exposures, which is also seen in persons with Alzheimer's disease (17)
- reduction in white matter integrity (18)
- elevated p-tau in exosomes and plasma total tau, which has been linked to increased risk for mild cognitive impairment and Alzheimer's disease.(19)

With respect to non-blast and non-military related sub-concussive exposures, neuroimaging studies revealed the following changes to athletes' brains:
- increased neurofilament light chain proteins, which is a biomarker for neurodegeneration (20)

- increased microglial activation and high cerebrospinal fluid t-tau concentrations, which could indicate downstream CTE-related neurodegeneration (21)
- reductions in white matter integrity, with greater reduction in the right hemisphere among females.(1)

Two studies also examined the combined effect of mTBIs (defined broadly) and PTSD among Veterans and identified increased levels of extracellular vesical, neurofilament light chain, and tau proteins.(22; 23)

Finally, one recent low-quality evidence synthesis examined the role of the APOE-e4 allele and found that while it does not increase susceptibility for an mTBI, it does appear to increase likelihood of sustaining white matter injury following repetitive mTBIs, which may result in worsened courses of CTE and other neurodegenerative conditions.(24)

Findings from animal models on the effects of repeated sub-concussive exposures

Though animal models can be challenging to extrapolate implications for humans, they allow for experimentation to better understand the relationship between sub-concussive exposures and neurodegeneration. Seven studies exposing rats and mice to repeated primary blasts identified the following resulting changes to their brains:

- reduction in the hippocampus and a decline in synaptic connections, which may be an early biomarker for dementia
- abnormal p-tau accumulation, endogenous tau deformities, and reduced expression of synaptic proteins
- phosphorylated tau proteins, which may increase the risk of developing CTE.(13; 25-30)

Findings about new methods for measuring or monitoring sub-concussive exposures

Finally, we identified one recent low-quality evidence synthesis and two single studies that provided insights into methods for measuring impacts from sub-concussive exposures.

One recent low-quality evidence synthesis identified modalities that can be used for in-vivo indicators of CTE and Alzheimer's disease, with the most promising being positron emission tomography imaging with tau-binding radioligands.(31)

A recent single study found that the cervical joint position error test may be valuable in tracking changes and/or identifying deficits in sensorimotor function across time because of sub-concussive incidents.(32)

Finally, a recent study used 'e-type silhouettes' equipped with blast pressure gauges to measure the pressure from cumulative blasts that special operative forces are exposed to while in training. The study suggested this can be added to an individual's military history to understand lifetime exposure and to support future prevention and triage approaches.(33)

Waddell K, Dass R, Grewal E, Wilson MG. Rapid evidence profile #69: Examining the long-term risks of sub-concussive exposures among occupationally exposed members of the military. Hamilton: McMaster Health Forum, 22 March 2024.

This rapid evidence profile was funded by the Chronic Pain Centre of Excellence for Canadian Veterans and the Atlas Institute for Veterans and Families, which in turn are funded by Veterans Affairs Canada. The McMaster Health Forum received both financial and in-kind support from McMaster University. The views expressed in the rapid evidence profile are the views of the authors and should not be taken to represent the views of the Chronic Pain Centre for Excellence for Canadian Veterans, the Atlas Institute for Veterans and Families or McMaster University.

References

1. Sollmann N, Echlin PS, Schultz V, et al. Sex differences in white matter alterations following repetitive subconcussive head impacts in collegiate ice hockey players. *Neuroimage Clinical* 2018; 17: 642-649.
2. Iverson GL, Castellani RJ, Cassidy JD, et al. Examining later-in-life health risks associated with sport-related concussion and repetitive head impacts: A systematic review of case-control and cohort studies. Brtit*ish Journal of Sports Medicine* 2023; 57(12): 810-821.
3. Montenigro PH, Alosco ML, Martin BM, et al. Cumulative head impact exposure predicts later-life depression, apathy, executive dysfunction, and cognitive impairment in former high school and college football players *Journal of Neurotrauma* 2017; 34(2): 328-340.
4. Cifu D. Clinical research findings from the long-term impact of military-relevant brain injury consortium-Chronic Effects of Neurotrauma Consortium (LIMBIC-CENC) 2013-2021. *Brain Injuries* 2022; 36(5): 587-597.
5. Graham A, Livingston G, Purnell L, Huntley J. Mild traumatic brain injuries and future risk of developing alzheimer's disease: Systematic review and meta-analysis. *Journal of Alzheimers Disease* 2022; 87(3): 969-979.
6. Snowden TM, Hinde AK, Reid HMO, Christie BR. Does mild traumatic brain injury increase the risk for dementia? A systematic review and meta-analysis. *Journal of Alzheimer's Disease* 2020; 78(2): 757-775.
7. Khan N, Romila L, Ciobica A, Burlui V, Kamal FZ, Mavroudis I. Mild traumatic brain injury as a risk factor for parkinsonism, tics, and akathisia: A systematic review and meta-analysis. *Life* 2023; 14(1): 32.
8. Gardner RC, Byers AL, Barnes DE, Li Y, Boscardin J, Yaffe K. Mild TBI and risk of Parkinson disease: A chronic effects of neurotrauma consortium study. *Neurology* 2018; 90(20): e1771-e1779.
9. Barnes DE, Byers AL, Gardner RC, Seal KH, Boscardin WJ, Yaffe K. Association of mild traumatic brain injury with and without loss of consciousness with dementia in US military veterans. *Journal of the American Medical Association Neurology* 2018; 75(9): 1055-1061.
10. Hayes JP, Logue MW, Sadeh N, et al. Mild traumatic brain injury is associated with reduced cortical thickness in those at risk for Alzheimer's disease. *Brain* 2017; 140(3): 813-825.
11. Nejtek VA, James RN, Salvatore MF, Alphonso HM, Boehm GW. Premature cognitive decline in specific domains found in young veterans with mTBI coincide with elder normative scores and advanced-age subjects with early-stage Parkinson's disease. *PLoS One* 2021;16(11): e0258851.
12. Powell JR, Hopfinger JB, Giovanello KS, et al. Mild traumatic brain injury history is associated with lower brain network resilience in soldiers. Brain Communications 2023; 5(4): fcad201.
13. Dickstein DL, De Gasperi R, Gama Sosa MA, et al. Brain and blood biomarkers of tauopathy and neuronal injury in humans and rats with neurobehavioral syndromes following blast exposure. Molecular Psychiatry 2021; 26(10): 5940-5954.
14. Powell JR, Zong X, Weinstein JM, DeLellis SM, Kane SF, Means GE, Mihalik JP. Mild traumatic brain injury and career stage associate with visible perivascular spaces in special operations forces soldiers Annals in *Biomedical Engineering* 2024: Feb 23.
15. Manning Franke L, Perera RA, Aygemang AA, et al. Auditory evoked brain potentials as markers of chronic effects of mild traumatic brain injury in mid-life. *Clinical Neurophysiology* 2021; 132(12): 2979-2988.
16. Gilmore CS, Lim KO, Garvin MK, et al. Association of optical coherence tomography With longitudinal neurodegeneration in Veterans With chronic mild traumatic brain injury. *Journal of the American Medical Association Network Open* 2020; 3(12): e2030824.

17. Clark AL, Weigand AJ, Bangen KJ, Merritt VC, Bondi MW, Delano-Wood L. Repetitive mTBI is associated with age-related reductions in cerebral blood flow but not cortical thickness. *Journal of Cerebral Blood Flow Metabolism* 2021; 41(2): 431-444.

18. Trotter BB, Robinson ME, Milberg WP, McGlinchey RE, Salat DH. Military blast exposure, ageing and white matter integrity. *Brain* 2015; 138(Pt 8): 2278-2292.

19. Kenney K, Qu B-X, Lai C, et al. Higher exosomal phosphorylated tau and total tau among veterans with combat-related repetitive chronic mild traumatic brain injury. *Brain Injury* 2018; 32(10): 1276-1284.

20. Rubin LH, Tierney R, Kawata K, et al. NFL blood levels are moderated by subconcussive impacts in a cohort of college football players. *Brain Injuries* 2019; 33(4): 456-462.

21. Alosco ML, Tripodis Y, Fritts NG, et al. Cerebrospinal fluid tau, Aβ, and sTREM2 in former National Football League Players: Modeling the relationship between repetitive head impacts, microglial activation, and neurodegeneration. *Alzheimers and Dementia* 2018; 14(9): 1159-1170.

22. Pattinson CL, Gill JM, Lippa SM, Brickell TA, French LM, Lange RT. Concurrent mild traumatic brain injury and posttraumatic stress disorder is associated with elevated tau concentrations in peripheral blood plasma. *Journal of Trauma and Stress* 2019;32(4): 546-554.

23. Guedes VA, Lai C, Devoto C, et al. Extracellular vesicle proteins and microRNAs are linked to chronic post-traumatic stress disorder symptoms in service members and Veterans With mild traumatic brain injury. *Front Pharmacology* 2021; 12: 745348.

24. Deng H, Ordaz A, Upadhyayula PS, et al. Apolipoprotein E epsilon 4 genotype, mild traumatic brain injury, and the development of chronic traumatic encephalopathy. *Medical Science* 2018; 6(3): 78.

25. Almeida MF, Piehler T, Carstens KE, et al. Distinct and dementia-related synaptopathy in the hippocampus after military blast exposures. *Brain Pathology* 2021; 31(3): e12936.

26. Bittar A, Bhatt N, Hasan TF, et al. Neurotoxic tau oligomers after single versus repetitive mild traumatic brain injury. *Brain Communications* 2019; 1(1): fcz004.

27. Petraglia AL, Plog BA, Dayawansa S, et al. The pathophysiology underlying repetitive mild traumatic brain injury in a novel mouse model of chronic traumatic encephalopathy. *Surgical Neurology International* 2014; 5: 184.

28. Delic V, Karp JH, Guzman M, et al. Repetitive mild TBI causes pTau aggregation in nigra without altering preexisting fibril induced Parkinson's-like pathology burden. *Acta Neuropathologica Communications* 2022; 10(1): 170.

29. Badea A, Kamnaksh A, Anderson RJ, Calabrese E, Long JB, Agoston DV. Repeated mild blast exposure in young adult rats results in dynamic and persistent microstructural changes in the brain. *Neuroimage Clinical* 2018; 18: 60-73.

30. Goldstein LE, Fisher AM, Tagge CA, et al. Chronic traumatic encephalopathy in blast-exposed military veterans and a blast neurotrauma mouse model. *Science Translational Medicine* 2012; 4(134): 134ra60.

31. Sparks P, Lawrence T, Hinze S. Neuroimaging in the diagnosis of chronic traumatic encephalopathy: A systematic review. *Clinical Journal of Sport Medicine* 2020; 30 Suppl 1: S1-s10.

32. Cheever K, Howard JT, Kawata K. Clinical changes in cervical neuromuscular control following subconcussive impacts. *Journal of Sports Rehabilitation* 2020; 30(3): 467-474.

33. McEvoy CB, Crabtree A, Powell JR, Meabon JS, Mihalik JP. Cumulative blast exposure estimate model for special operations forces combat soldiers. *Journal of Neurotrauma* 2023; 40(3-4): 318-325.