

Appendices

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Rapid Evidence Profile

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

22 March 2024

[MHF product code: REP 69]

Appendix 1: Methodological details

We use a standard protocol for preparing rapid evidence profiles (REP) to ensure that our approach to identifying research evidence is as systematic and transparent as possible in the time we were given to prepare the profile.

Engaging subject matter experts

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

Identifying research evidence

For this REP, we searched Health Systems Evidence and PubMed for:

- 1) evidence syntheses
- 2) protocols for evidence syntheses that are underway
- 3) single studies.

We searched <u>Health Systems Evidence</u> using an open search for (mTBI OR concussion OR brain injury). We searched <u>PubMed</u> using an open search for (sub*concussion OR sub*concussive OR mTBI OR "mild traumatic brain injury") AND (neurodegenerative OR "chronic traumatic encephalopathy" OR CTE OR Alzheimer* OR dementia OR Parkinson* OR "motor neuron disease") and included a filter for the past 10 years. Links provide access to the full search strategy.

In addition, we hand searched the Forces in Mind Trust repository.

Each source for these documents is assigned to one team member who conducts hand searches (when a source contains a smaller number of documents) or keyword searches to identify potentially relevant documents. A final inclusion assessment is performed both by the person who did the initial screening and the lead author of the rapid evidence profile, with disagreements resolved by consensus or with the input of a third reviewer on the team. The team uses a dedicated virtual channel to discuss and iteratively refine inclusion/exclusion criteria throughout the process, which provides a running list of considerations that all members can consult during the first stages of assessment.

During this process we include published, pre-print, and grey literature. We do not exclude documents based on the language of a document. However, we are not able to extract key findings from documents that are written in languages other than Chinese, English, French, or Spanish. We provide any documents that do not have content available in these languages in an appendix containing documents excluded at the final stages of reviewing. We excluded documents that did not directly address the research questions and the relevant organizing framework.

Assessing relevance and quality of evidence

We assess the relevance of each included evidence document as being of high, moderate, or low relevance to the question.

Two reviewers independently appraised the quality of the guidelines we identified as being highly relevant using AGREE II. We used three domains in the tool (stakeholder involvement, rigour of development and editorial independence) and classified guidelines as high quality if they were scored as 60% or higher across each of these domains.

Two reviewers independently appraise the methodological quality of evidence syntheses that are deemed to be highly relevant. Disagreements are resolved by consensus with a third reviewer if needed. AMSTAR rates overall methodological quality on a scale of 0 to 11, where 11/11 represents an evidence synthesis of the highest quality. High-quality evidence syntheses are those with scores of eight or higher out of a possible 11, medium-quality evidence syntheses are those with scores between four and seven, and low-quality evidence syntheses are those with scores less than four. It is important to note that the AMSTAR tool was developed to assess evidence syntheses focused on clinical interventions, so not all criteria apply to those pertaining to health-system arrangements or to economic and social responses. Where the denominator is not 11, an aspect of the tool was considered not relevant by the raters. In comparing ratings, it is therefore important to keep both parts of the score (i.e., the numerator and denominator) in mind. For example, an evidence synthesis that scores 8/8 is generally of comparable quality to another scoring 11/11; both ratings are considered 'high scores.' A high score signals that readers of the evidence synthesis can have a high level of confidence in its findings. A low score, on the other hand, does not mean that the evidence synthesis should be discarded, merely that less confidence can be placed in its findings and that the evidence synthesis needs to be examined closely to identify its limitations. (Lewin S, Oxman AD, Lavis JN, Fretheim A. SUPPORT Tools for evidence-informed health Policymaking (STP): 8. Deciding how much confidence to place in a systematic review. Health Research Policy and Systems 2009; 7 (Suppl1): S8.)

Preparing the profile

Each included document is cited in the reference list at the end of the REP. For all included guidelines, evidence syntheses, and single studies (when included), we prepare a small number of bullet points that provide a summary of the key findings, which are used to summarize key messages in the text. Protocols and titles/questions have their titles hyperlinked, given that findings are not yet available.

We then draft a summary that highlights the key findings from all highly relevant documents (alongside their date of last search and methodological quality).

Upon completion, the REP is sent to the subject matter expert for their review.

Appendix 2: Summary of key findings from included evidence syntheses and single studies

Types of findings	Summary of key findings from included evidence syntheses and single studies
Findings about the association between mTBIs and neurodegenerative conditions	• A recent medium-quality evidence synthesis of case-control and cohort studies found a weak association between repetitive sub-concussive exposures among former football and soccer athletes and depression and neurodegenerative diseases, including dementia (all causes), amyotrophic lateral sclerosis, and Parkinson's disease (1)
	• A recent low-quality evidence synthesis of longitudinal studies exploring combat-related brain injuries found an association between repetitive brain injuries and neurodegenerative diseases, including dementia and Parkinson's disease; however, the evidence synthesis included brain injury of any severity but not specific to sub-concussive events (2)
	• Two recent medium-quality and one recent low-quality evidence synthesis found an increased risk of Alzheimer's disease and Parkinsonism (especially Parkinson's disease) among those who had experienced mild traumatic brain injuries (mTBIs), but mTBIs were defined broadly and included concussions (3-5)
	 A recent single study found a greater incidence of mTBI was associated with decreased resiliency and greater vulnerability to neurodegenerative symptoms in Special Operation Force members exposed to blasts (6) The study notes that increased number of mTBIs may reduce the physiological recovery and increase symptoms from blast exposure,
	 Three recent single studies using Veterans Health Administration databases found a history of blast-related or mixed mTBI (broadly defined) was associated with an increased risk of developing neurodegenerative conditions, including Parkinson's disease, dementia, and Alzheimer's disease; however, no information on the number or type of blasts or contact-related mTBIs was provided (7-9) Individuals with exposure were more likely to be male and have a comorbid mental health condition (7)
	• A recent single study found Veterans with high-risk roles including exposure to blasts, motor accidents, and physical assaults experienced cognitive decline similar to those with early-onstage Parkinson's disease and at a higher rate than healthy controls or Veterans without the same exposures (10)
	• An older single study of amateur football players found self-reported executive function impairments later in life, regardless of self-reported concussions, suggesting that successive sub-concussive injuries may be as damaging as self-reported concussions (11)
Findings from neuroimaging about the effects of repeated sub- concussive exposures	• A recent low-quality evidence synthesis found that while the presence of the APOE-e4 allele does not increase the susceptibility of mTBI, APOE-e4 allele carriers appear to be more likely to sustain white matter injury following repetitive mTBIs, which may result in worsened courses of chronic traumatic encephalopathy (CTE) (12)
	• Two single studies showed that Veterans exposed to repeated primary blasts had excess retention of tau-protein at grey-white junctions in the brain in regions where CTE tauopathy is commonly observed, elevated levels of neurofilament light chain proteins, and greater perivascular space, all of which may be indications for neurodegenerative disorders (13; 14)
	• Similarly, a second recent single study of Veterans with a history of mTBIs and post-traumatic stress disorder (PTSD) found increased levels of extracellular vesicle and neurofilament light chain, which may be used as biomarkers for PTSD and neurodegeneration (15)
	• A single study of college football players found the frequency and number of sub-concussive impacts was associated with changes in neurofilament light chain, which is a biomarker for select neurodegenerative conditions including dementia, Parkinson's disease, and amyotrophic lateral sclerosis (16)
	• A recent single study found levels of tau proteins were higher in military members with a history of mTBI (defined broadly) and PTSD than among those without a history of mTBI (17)
	• A recent single study found a positive history of mTBIs was associated with reduced N200 amplitude to targets and novel distractors, but these were mediated by depression and anxiety symptoms and hearing (18)

Types of findings	Summary of key findings from included evidence syntheses and single studies
	• A recent single study of Veterans with a history of repetitive sub-concussive exposures found decreases in retinal axon, which is correlated with a loss of visual function and central nervous system function that is also seen in persons with Alzheimer's (19)
	• A recent single study of Veterans found that three or more sub-concussive exposures were associated with decreased cerebral blood flow in the parietal lobe, a pathology that is also seen in persons with Alzheimer's disease (20)
	• A recent single study found a dose-response relationship between blast exposure and white matter integrity, with worsening degeneration appearing over time and with greater numbers of exposure (21)
	• A recent single study of former national football league players found a greater number of repetitive head injuries was associated with an increase in microglial activation and high cerebrospinal fluid t-tau concentrations, which in turn could indicate downstream CTE-related neurodegeneration (22)
	• A recent single study found differences in white matter following sub-concussive exposure during hockey, with females displaying a greater change in white matter in the right hemisphere as compared to males (23)
	• A recent single study of post-9/11 veterans who were combat deployed and suffered possible concussive events found sustaining a high number of mTBIs over a variety of time periods was associated with elevated p-tau in exosomes and plasma total tau, which may in turn have implications for cognitive and functional outcomes later in life as p-tau levels have been linked to increased risk of mild cognitive impairment and Alzheimer's disease (24)
Findings from animal models on the effects of repeated sub-	• A recent single study found primary blast exposure in rats resulted in significant changes in the hippocampus and a decline in synaptic connections in the CA1 region of the hippocampus, which could be considered an early biomarker of dementia (25)
concussive exposures	• Four recent single studies found repeated primary blast exposure among rats resulted in abnormal p-tau accumulation as well as endogenous tau deformities and reduced expression of synaptic proteins (13; 26-28)
	• A recent single study of male mice found repetitive mTBIs showed similarities in the phospholipid profiles to those of mice with Alzheimer's disease, which may be used to identify a link between the two conditions (29)
	• A recent single study of rats experiencing mTBIs from blast exposure demonstrated reduction in volume of the hippocampus and cerebellum (30)
	• A recent single study found blast-related mTBIs in mice demonstrated phosphorylated tauopathy chronic inflammation and neurodegeneration that may increase the risk of developing CTE (31)
Findings about new methods of measuring or monitoring sub-	• A recent low-quality evidence synthesis identified imaging modalities that can be used for in-vivo indicators of CTE and Alzheimer's disease, with the most promising being positron emission tomography (PET) imaging with tau-binding radioligands (32)
concussive exposures	• A recent single study found that cervical joint position error tests may be valuable in tracking changes and/or identifying deficits in sensorimotor function across time as a result of sub-concussive incidents, such as headings in soccer (33)
	 A recent single study found the use of e-type silhouettes can support the measurement of cumulative blast exposure during trainings, which can add to a military history of blast exposure and support triage prevention and treatment approaches The study provided estimates of blast exposure for occupational training of special forces; total estimates were exposure to 36.8 psi, 184 psi weekly, and 2760 psi cumulative pressure exposure throughout training (34)

Dimension of	Declarative title and key findings	Relevance	Living	Quality	Last year	Availability	Equity
organizing framework		rating	status	(AMSTAR)	literature	of GRADE	considerations
 Type of repetitive sub- concussive exposure Mixed Neurodegenerative conditions Dementia Parkinson's disease Other movement disorders Biological sex Male Other factors that may affect long-term risks Co-morbid PTSD or mental health conditions 	 Weak associations exist between repetitive sub-concussive exposure, depression, and neurodegenerative diseases in professional athletes (1) This study explored the risk of adverse events associated with sports-related concussions. No studies reported on females, preventing an understanding of adverse events in female athletes with sports related concussions. The type or number of repetitive sub-concussive exposure was not reported. Weak associations were seen for neurodegenerative conditions (e.g., dementia, amyotrophic lateral sclerosis, Parkinson's disease) and playing professional soccer and football. In most studies, important confounders were not considered (e.g., genetic, mental health, multiple exposure). Depression was associated with mild traumatic brain injury (mTBI) exposure. 	High	No	7/9	2022	Not available	• Gender/sex
 Type of repetitive sub- concussive exposure Blast Primary Neurodegenerative conditions Dementia Parkinson's disease High-risk military occupations and roles Other factors that may affect long-term risks Mis- or delayed diagnosis Co-morbid PTSD or mental health conditions 	 Mild traumatic brain injury in Veterans is linked to 1) biomarker differences with biofluid and neuroimaging trends, 2) clinical symptoms with sensation, sleep, pain, cognition, and mental health, and 3) neurodegenerative diseases like dementia and Parkinson's (2) This review summarized longitudinal studies exploring the long- term effects of combat-related brain injury. This review identified biomarkers of brain injury. There is an increase in biofluids in the exosomal microRNA and plasma and exosomal proteins in the acute stage, but it is unclear if this persists in the post-acute period. Unique neuroimaging trends involve decreased functional connectivity in the default mode network and relationships with the ventricle brain ratio. This review identified clinical symptoms of brain injury: differences including sensory dysfunction involving impaired vision, hearing, and balance changes in neuroendocrine function disturbed sleep patterns and a link to obstructive sleep apnea, which may interact with mental health conditions like posttraumatic stress disorder 	High	No	0/9	Not stated	Not available	• None identified

Appendix 3: Key findings from evidence syntheses

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Living status	Quality (AMSTAR)	Last year literature searched	Availability of GRADE profile	Equity considerations
Type of repetitive sub-	 increased risk for chronic pain and inappropriate opioid use increased risks for depression, anxiety, and post-traumatic stress disorder (PTSD) cognitive dysfunction involving comprehension, working memory, and speed processing. The broad and sometimes overlapping symptoms of brain injury create challenges with diagnosis and management. Repetitive sub-concussive exposure has been linked to neurodegenerative diseases. The likelihood of receiving a Dementia diagnosis ranged from 1.4 to 2.6 times higher in Veterans with an mTBI, compared to those without. The likelihood of receiving a Parkinson's disease diagnosis ranged from 1.5 to 1.8 times higher in Veterans with an mTBI, compared to those without. 	Medium	No	4/9	2016	No	• None
 concussive exposure Mixed Neurodegenerative conditions CTE Alzheimer's Biological sex Male Other factors that may affect long-term risks Co-morbid PTSD or mental health conditions 	 impairments and mental health problems in some individuals (35) The review examines the possible long-term effects of sport-related concussions. Sub-concussive is defined as repetitive transfer of mechanical energy to the brain at enough force to injure axonal or neuronal integrity, but not to be expressed in clinical symptoms. The review identified 47 studies relating to possible long-term problems with brain health associated with sport-related concussion. No concussions were possible with respect to the effects of subconcussive impacts because: there are no established definition of sub-concussive impact or injury; an impact may or may not cause an injury and it is difficult to determine if an injury has in fact occurred; and the biomechanical features and thresholds for quantifying an impact and identifying an injury have not been agreed upon. Imaging studies of athletes reveal some structural changes to the brain including cortical thinning, cavum septi pellucidi (CSP), functional changes in brain metabolism, microstructural differences in white matter and accumulations of tau protein, but there are some methodological weaknesses with these studies. Cross-sectional clinical studies show cognitive deficits or decrements and psychological health problems (mainly 						reported

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Living status	Quality (AMSTAR)	Last year literature searched	Availability of GRADE profile	Equity considerations
	depression) among former professional athletes with a history of concussions.						
 Type of sub- concussive exposure mTBI (broadly defined) Neurodegenerative conditions Alzheimer's disease 	 A history of mTBIs increased the risk of Alzheimer's disease (3) The review defines an mTBI as an acute brain injury following an external force to the head, often resulting in confusion, loss of consciousness, post-traumatic amnesia, and other transient symptoms. The meta-analysis quantitatively assesses the nature of the relationship between mTBI and the subsequent risk of developing Alzheimer's disease. The meta-analysis only included studies where the time between the mTBI and the presence of Alzheimer's disease was greater than five years. Mild traumatic brain injury is a risk factor for future Alzheimer's disease, with a pooled analysis of five studies demonstrating an overall 18% increase in risk compared to people who had experienced no mTBIs. 	High	No	6/11	2020	No	• None reported
 Type of sub- concussive exposure Mixed Neurodegenerative conditions CTE 	In general, the presence of the APOE allele was not found to increase the susceptibility for mTBI, nor was it found to be predictive of chronic traumatic encephalopathy (CTE), but carriers may exhibit elevated cognitive difficulties during the progression of the disease course (12)	High	No	3/9	2018	No	• None reported
 Types of sub- concussive exposure mTBI (broadly defined) Neurodegenerative conditions Alzheimer's disease Dementia (all cause) 	 The systematic review and meta-analysis supports an association between remote mTBI (here defined as a concussive episode) and later diagnosis of dementia including Alzheimer's disease; however, included studies had significant heterogeneity (4) The review defined an mTBI as "an acute brain injury resulting from mechanical energy to the head from external physical forces, including loss of consciousness for 30 minutes or less, post-traumatic amnesia, and a Glasgow Coma score of 13-15 after 30 minutes post-injury or upon first presentation for healthcare." The review included 21 person-based studies (i.e., not animal studies) of which six were included in a meta-analysis. Twelve studies aimed to identify the risk of dementia, of which eight found an increased risk in at least one subset of the examined population. 	High	No	2020	3/9	No	• None reported

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Living status	Quality (AMSTAR)	Last year literature searched	Availability of GRADE profile	Equity considerations
	 The meta-analysis found prior mTBI was associated with the later development of dementia, but studies exhibited a high degree of heterogeneity. Other included studies found subtle but persistent changes in neuropsychiatric test performance and imaging. 					Ŷ	
 Type of sub- concussive exposure mTBI (broadly defined) Neurodegenerative conditions Parkinson's disease Other movement disorders 	 <u>Concussions are a significant risk factor for Parkinsonism and</u> <u>particularly for the development of Parkinson's disease</u> (5) The review defines mTBI as a concussion (i.e., symptomatic). The meta-analysis of 18 studies found a significant association between those with a history of mTBI developing parkinsonism and Parkinson's disease, but found insufficient data for tics and akathisia. 	Medium	No	2023	6/11	No	• None reported
 Type of sub- concussive exposure mTBI (broadly defined) Neurodegenerative conditions CTE Alzheimer's disease 	 The review identified imaging modalities that can be used for invivo indications of CTE and Alzheimer's, with the most promising being PET imaging with a tau-binding radioligand (32) The review evaluates the utility of neuroimaging in the diagnosis of CTE by reviewing recent evidence for changes in neuroimaging biomarkers. 	High	No	2016	2/9	No	• None reported

	Dimension of organizing	Study features	Summary of study sample and intervention	Declarative title and key findings	Relevance rating	Equity consider-
	framework				U	ations
	 Type of repetitive sub-concussive exposure Blast Primary Neurodegenerative conditions Alzheimer's disease Dementia Other factors that may affect long- term risks Mis- or delayed diagnosis 	Date of publication: May 2021 Place published: United States Methods: Cross-sectional	 This study looked at hippocampal explants in rats with induced rapid shockwaves, replicating military primary blast exposure. 	 After primary blast exposure in rats, there are significant changes in the neurocircuitries of the hippocampus, which can be used to explore early biomarkers and risk factors for dementia in human military members (25) This study hypothesized that after a blast exposure, areas in the brain involved in emotional memories and social behaviours showed similar neuronal changes to cognitive disorders, like dementia. This study found that blast exposure caused changes in the neurocircuitries of the hippocampus in rats. Synaptophysin in the dense hippocampal neuropil was the most evident change. Within 24 hours of blast exposures, levels of glutamate receptor subunits, synaptophysin, GluAI, synapsing IB, neural cell adhesion molecule 180, and AT8-positive tau decreased. The greater the size of the blast, the greater the decline in synaptic connections. The synaptic pathology after blast exposure was more subtle than mild traumatic brain injuries, which may explain issues with diagnosis and enhanced risk of dementia. 	High	None identified
•	 Type of repetitive sub-concussive exposure Blast Primary Neuro- degenerative conditions Chronic traumatic encephalopath y 	Date of publication: October 2021 Place published: United States Methods: Longitudinal	 A total of 10 adult male rats were included in this study; five were controls and five were exposed to blasts. The rats were exposed to three blast exposures (one per day for three consecutive days). A total of 17 males participated in this study: 	 In rats and Veterans exposed to multiple blasts, biomarkers for traumatic encephalopathy related to tauopathy, neurofilament light proteins, and somatodendritic redistribution was seen; future investigation is needed to confirm findings (13) This study investigated biomarkers related to chronic traumatic encephalopathy in rats and humans exposed to blasts. Biological changes were seen in rats after repeated blast exposure including: o decreases in p-tau like immunoreactivity and somatodendritic redistribution, within six to 12 weeks o abnormal p-tau accumulation in astroglia 	High	• None identified

Appendix 4: Key findings from single studies

Dimension of organizing	Study features	Summary of study sample and intervention	Declarative title and key findings	Relevance rating	Equity consider-
framework				_	ations
 Biological sex Male 		10 veterans with blast exposure and cognitive and behaviour complaints, compared to seven healthy controls.	 despite delivering the blast at the centre of the brain, the right hemisphere appeared to be most affected; no explanation on this occurrence was identified. Biological changes were seen in Veterans after repeated blast exposure were seen including: excess cortical retention of f [18F]AV1451 in white/grey matter junctions across brain regions, suggesting evidence of tauopathy elevated levels of neurofilament light chain proteins. These results can support future efforts in determining biomarkers for chronic traumatic encephalopathy in human Veterans. 		
 Type of repetitive sub-concussive exposure Mixed Neuro- degenerative conditions Parkinson's disease 	Date of publication: 15 May 2018 Place published: United States Methods: Retrospective cohort study	 Data of 325, 870 patients (50% wuth history of mTBI) were included in this study). Data was sought from Veteran Health Administration databases during 2002 to 2014. 	 <u>A history of traumatic brain injury is associated with a 56%</u> increased risk of developing Parkinson's disease in Veterans from the Veteran Health Administration 2002–2014 database, highlighting the long-term effects of brain injury (7) This study assessed the risk of developing Parkinson's disease after a mild traumatic brain injury (mTBI) in Veterans. Individuals with mTBI exposure were more likely to be male and have a comorbid mental health condition. A history of mTBI was associated with 56% increased risk developing a two-years-earlier age Parkinson's disease diagnosis, regardless of other demographic factors. No information on the type of blast, number of blasts, or military role was reported. The findings of this study illustrate the need for long term follow-up of mTBI. 	High	• None identified
 Type of repetitive sub-concussive exposure Blast Primary Neuro- degenerative conditions Other factors that may affect long- term risks 	Date of publication: 28 June 2019 Place published: United States Methods: Longitudinal	 Frozen mice brain tissue was obtained for this study. The mice experienced either one or multiple mTBI using a 20-psi blast wave. Tau oligomers were assessed at four time points: (1) 24 hours after blast, (2) three weeks after single blast, (3) three 	 There are differences in polymorphism strain, synaptic protein expression, enzyme digestion, and seeding in single versus repetitive mTBI in mice, which provides insight on mechanisms of neurodegeneration in multiple injury (26) This study compared tau oligomers in frozen mice brain tissue exposed to single and repetitive mTBI. Differences in the tau polymorphisms strains were seen in single versus repetitive mTBI. After TBI, endogenous tau deforms led to toxicity and neurodegeneration; this was more prevalent after repetitive exposure. Repetitive exposure can decrease the level of expression of synaptic proteins more than single exposure. 	High	• None identified

Dimension of organizing framework	Study features	Summary of study sample and intervention	Declarative title and key findings	Relevance rating	Equity consider- ations
 Number of sub-concussive exposures 		weeks after repetitive blast, and (4) three weeks after sham treatment.	 Differences in proteinase K enzyme digestion and FRET seeding was seen between conditions, suggesting that TBI frequencies cause differences in tau oligomeric strains. This study provides insights on the mechanisms of neurodegeneration following multiple blast exposure. 		
 Type of repetitive sub-concussive exposure Mixed Neuro- degenerative conditions Dementia High-risk military occupations and roles 	Date of publication: September 2018 Place published: United States Methods: Cohort study	 Data from 151,354 Veterans who had an mTBI and a propensity- matched sample of 178,779 was obtained using the Veteran Health Administration database between 2001 to 2014. Most participants were likely to have had high- risk occupations and blast exposure, though occupation was not specified. The type of exposure was not specified. 	 Mild traumatic brain injury, regardless of severity, type, or number of exposure, and other health conditions, was associated with a two times risk in a dementia diagnosis in United States Veterans between 2001 to 2014 (8) This study examined associations between traumatic brain injury severity and dementia diagnosis in United States Veterans. mTBI was associated with a two-times risk in dementia diagnosis, regardless of other psychiatric or physical health conditions. It could also be concluded that individuals have long lasting cognitive disorders after mTBI exposure, which is categorized as dementia. 	High	• None identified
 Type of repetitive sub-concussive exposure Mixed Neuro- degenerative conditions Dementia High-risk military occupations and roles Other factors that may affect long- term risks Number of sub-concussive exposures Co-morbid PTSD or 	Date of publication: 8 October 2021 Place published: United States Methods: Cross-sectional	 A total of 152 military members with combat exposure participated in this study. The type of exposure or participant occupation was not specified. 	 Differences in event-related auditory potential are seen in people with repetitive mTBI, in comparison to single exposure; these changes can be used as biomarkers for dementia risk (18) This study explored the relationship between mTBI history, event-related potentials (ERP), and conditions comorbid with dementia. This study found that auditory event-related potentials are affected by chronic mTBI. Repetitive mTBI showed more auditory attentive and preattentive ERPs compared to single mTBI. The meso-frontal control networks showed decreased responsiveness in persons with a history of mTBI. This was also correlated with internalized psychopathology and hearing loss. The findings of this study suggest that auditory event-related potential risk. 	High	• None identified

	Dimension of organizing framework	Study features	Summary of study sample and intervention	Declarative title and key findings	Relevance rating	Equity consider- ations
	mental health conditions					
•	Type of repetitive sub-concussive exposure o Mixed Neuro- degenerative conditions o Alzheimer's disease High-risk military occupations and roles Other factors that may affect long- term risks o Number of sub-concussive exposures o Co-morbid PTSD or mental health conditions	Date of publication: 1 March 2017 Place published: United States Methods: Cross-sectional	 A total of 160 Veterans who had combat exposure were included in this study. Approximately 47% of participants had more than one mTBI. A total of 112 participants had a lifetime PTSD diagnosis. About 24% of participants had an mTBI related to blast injury, while the remaining participants had a non- military related injury. 	 Single exposure to mild traumatic brain injury can interact with genetic factors to increase cortical thinning, affecting memory performance and causing neurodegenerating associated with Alzheimer's disease (9) This study explored the association between mTBI, post-traumatic stress disorder (PTSD), and genetic risk factors with cortical thickness in persons with Alzheimer's disease. mTBI exposure and high polygenic risk was associated with reduced cortical thickness in persons with Alzheimer's disease. This suggests that mTBI interacts with genetics to affect neurodegeneration. Cortical thinning accelerated continuously post-injury in persons with a genetic risk of Alzheimer's disease. These factors were associated with delayed episodic memory recall, suggesting that cortical thickness plays a role in memory performance. Neither repetitive mTBI nor PTSD had an effect on the relationship between genetic risk and cortical thickness in persons with Alzheimer's disease. These findings highlight the need to monitor long-term consequences of mTBI. 	High	• None identified
• • • •	Type of repetitive sub-concussive exposure • Blast • Primary Neuro- degenerative conditions • Alzheimer's disease Biological sex • Male Other factors that may affect long- term risks	Date of publication: 19 February 2019 Place published: United States Methods: Longitudinal	• A total of eight male mice were included in this study (four mTBi and four sham injury condition).	 Male mice models for mTBI and Alzheimer's disease show similarities in phospholipid profiles that can be used to identify the mechanistic links between the two conditions (29) This study explored the relationship between repetitive mTBI and Alzheimer's disease in male mice. An increased in phosphatidylcholine, phosphatidylethanolamine, and phosphatidylinositol was seen in the hippocampus 24 hours after and six to 12 months after repetitive mTBI. An increased in phosphatidylcholine and phosphatidylinositol was seen in the cortex three months after repetitive mTBI. Similarities were seen between mTBI and Alzheimer's rat models. Both models showed increased in in lysoPC and sphingomyelin levels and AA to DHA ratio, which signifies neuroinflammation. 	High	• None identified

	Dimension of organizing framework	Study features	Summary of study sample and intervention	Declarative title and key findings	Relevance rating	Equity consider- ations
	 Number of sub-concussive exposures 			 This suggests that neuroinflammation from mTBI could be a mechanism behind Alzheimer's disease. The relationship between mTBI and phospholipid profiles related to Alzheimer's requires future investigation, as there were inconsistent findings across different levels. 		
•	Type of repetitive sub-concussive exposure o Mixed Neuro- degenerative conditions Other factors that may affect long- term risks o Number of sub-concussive exposures o Co-morbid PTSD or mental health conditions	Date of publication: 6 October 2021 Place published: United States Methods: Cross-sectional	 A total of 144 participants were included in this study: 25 control, 60 mTBI and PTSD, and 40 no mTBI and PTSD. The type of brain injury was not reported. The occupation of participants was not reported. 	 Increased extracellular vesicle, neurofilament light chain plasma, and miRNA levels are found in Veterans with mTBI and PTSD; these molecular changes may be used as biomarkers for PTSD and neurodegeneration (15) This study compared molecular biomarkers of PTSD in Veterans with an mTBI. Participants with an mTBI and PTSD showed higher PTSD symptoms, extracellular vesicle (EV) levels, and neurofilament light chain plasma levels. EV levels continued to be associated with PTSD symptom severity when accounting for number of TBIs and time since last injury. miRNAs in the glucocorticoid receptor signalling pathway were differentially regulated in participants with increased PTSD symptoms. miRNA have been linked to neurodegenerative diseases. This change could also be due to medication use, but this information was not captured. 	High	• None identified
•	Type of repetitive sub-concussive exposure o Mixed Neurodegenerative conditions o Alzheimer's disease	Date of publication: 22 December 2020 Place published: United States Methods: Longitudinal	 A total of 139 Veterans participated in this study (69 with mTBI and 70 control). No information on type of injury or occupation was reported. 	 Decreases in retinal axon was correlated with loss of visual function and central nervous system function in Veterans with a history of repetitive sub-concussive exposure and may be used as a biomarker for neurodegeneration (19) This study explored changes in retinal layer thickness in Veterans with history of mTBI. Retinal axons reduced over time in Veterans with repetitive sub-concussive exposure. This marker is also seen in persons with Alzheimer's disease. Visual function and central nervous system function also showed progressive declines in Veterans with mTBI. 	High	• None identified
•	Type of repetitive sub-concussive exposure o Mixed	Date of publication: August 2019 Place published: United States	• A total of 107 military members participated in this study (mTBI=84 and controls=18).	 Tau plasma was higher in participants with an mTBI and chronic PTSD symptoms (17) This study explored the relationship between biomarkers of neurological symptoms following an mTBI and PTSD. 	High	None identified

Dimension of organizing framework	Study features	Summary of study sample and intervention	Declarative title and key findings	Relevance rating	Equity consider- ations
 Neuro- degenerative conditions Other factors that may affect long- term risks Co-morbid PTSD or mental health conditions 	Methods: Cross-sectional	 No information on type of injury or occupation was reported. 	• Given that tau plasma is associated with neurodegenerative disorders, this study contributes to the understanding of the relationship with mTBI, mental health, and neurodegeneration.		
 Type of repetitive sub-concussive exposure Blast Primary Neuro-degenerative conditions High-risk military occupations and roles 	Date of publication: 22 August 2023 Place published: United States Methods: Cross-sectional	 A total of 223 Special Operation Forces members participated in this study (123 mTBI and 100 controls). All participants had recovered from injuries. 	 Greater perivascular space burden is found in Special Operation Force members who had experienced primary blasts and may be a biomarker for neurodegeneration after an mTBI (14) This study explored associations between perivascular spaces, military career role, and mTBI in Special Operation Forces military members. Perivascular space and mTBI history were positively correlated. Participants who were earlier in their career, and thus lower in rank and had greater exposure to blasts, had a greater burden of perivascular space. Perivascular space has been documented to be important in removing metabolic waste; excess waste can lead to neurodegeneration. Greater burden on perivascular space might be due to neuroinflammation preventing waste removing. Given that all participants had recovered from injuries, this may indicate that, perivascular space burden may be a biomarker of long-term mTBI impacts. 	High	• Occupation
 Type of repetitive sub-concussive exposure Mixed Neuro- degenerative conditions Parkinson's disease 	Date of publication: 17 November 2021 Place published: United States Methods: Cross-sectional	 A total of 114 participants were included in this study. Participants were organized into four groups: 1) healthy controls, 2) Veterans, 3) Veterans with an mTBI, and 4) persons with Parkinson's disease. 	 Young Veterans with high-risk roles may experience subtle cognitive decline like persons with early-onstage Parkinson's disease (10) This study explored the cognitive domains related to mTBI and Parkinson's disease. Neurodegeneration and mTBI may impact specific and subtle cognitive functions. Veterans with an mTBI performed similarly to participants with early-stage Parkinson's Disease on verbal fluency tests, indicating cognitive decline. 	High	None identified

Dimens organi frame	sion of izing work	Study features	Summary of study sample and intervention	Declarative title and key findings	Relevance rating	Equity consider- ations
 High-risl occupati roles Type of 	k military ions and repetitive	Date of publication:	 mTBIs were a result of blast injuries, motor accidents, and physical assault. On average individuals had approximately three mTBIs. The mean age of Veteran participants and healthy controls ranged from 30–33. The mean age of participants with Parkinson's disease was 68.5. A total of 74 Veterans 	 Phonemic verbal fluency, working memory, and visuospatial memory was consistent across healthy controls and Veteran groups. 	High	• None
 Type of sub-cond exposure o Mixe Neuro- degenera condition Alzh disea Dem Other fa may affe term risk Num sub-o expo 	e e ative ns teimer's teimer's teimer's teimer's tectors that tect long- tes to f concussive osures	February 2021 Place published: United States Methods: Cohort study	participated in this study (27 no mTBI, 26 one to two mTBI, and 21 three or more mTBI).	 with decreased cerebral blood flow, a pathology seen in persons with Alzheimer's disease (20) This study examined risk factors for dementia in Veterans with and without a history of mTBI. Higher age was associated with decreased cerebral blood flow in the parietal lobe in participants with three or more mTBIs. This is associated with functional changes with Alzheimer's disease. Number of mTBI was not associated with age-related cortical thickness a priori, suggesting that changes associated with repetitive mTBI occur before age-related changes. 		identified
 Type of sub-cond exposure o Blast p Neuro- degenera condition 	repetitive cussive e t Primary ative ns	Date of publication: August 2015 Place published: United States Methods: Cross-sectional	• A total of 249 participants were included in this study (blast exposed=190 and blast unexposed=59).	 <u>Time since blast exposure and severity of exposure can lead to</u> <u>neurodegenerative changes, reducing white matter integrity</u> (21) This study examined the association between blast exposure and cortical integrity. Participants with blast exposure showed greater reduction in white matter integrity. A dose response was seen as the greater the blast injury, the greater reduction in white matter integrity. 	High	• None identified

	Dimension of organizing framework	Study features	Summary of study sample and intervention	Declarative title and key findings	Relevance rating	Equity consider- ations
				 Degeneration appeared to worsen with time, regardless of age or other comorbidities. 		
•	Type of repetitive sub-concussive exposure o Blast • Primary Neuro- degenerative conditions	Date of publication: 11 January 2018 Place published: United States Methods: Longitudinal	 Rat models who had experienced induced mTBIs were included in this study. Diffusion tensor imaging was used seven days (acute) and 90 days (chronic) post-injury. 	 <u>Repetitive mTBI and time is associated with changes in brain</u> volume and diffusion, suggesting that the long-term impacts of brain injury lead to neurodegeneration (30) This study explored microstructural changes in the brain following mTBI in rats. In both the acute and chronic stages of injury, decreases in brain volume and diffusion were identified. Localized volume increases ipsilateral to blast waves seven days post-injury. Volume reductions were seen in the hippocampus and cerebellum in the chronic stage. This suggests that injury and time interact causing neurodegeneration. 	High	• None identified
•	Type of repetitive sub-concussive exposure o Blast • Primary Neuro- degenerative conditions o Chronic traumatic encephalopath y Other factors that may affect long- term risks o Number of sub-concussive exposures	Date of publication: 23 December 2014 Place published: United States Methods: Longitudinal	 Mice models underwent induced mild traumatic brain injury. Mice were organized into three groups: controls, single mTBI, and repetitive mTBI. Mice in the repetitive mTBI group underwent six concussive impacts daily, for seven days. 	 Repetitive sub-concussive exposures are associated with longer persistence of neuroinflammation and pau proteins, compared to single exposure in mice models (27) This study explored the mechanisms of chronic traumatic encephalopathy in mice models. In single mTBI rats, increased phos tau proteins were seen seven days and one month post-injury; it did not persist at the six-month time point. In repetitive mTBI rats, increased phos tau proteins were seven days, one month, and six months post-injury. This group also showed increased astrogliosis and microglia activation. The repetitive mTBI condition demonstrated similar neuropathology as persons with chronic traumatic encephalopathy. 	High	• None identified
•	Type of repetitive sub-concussive exposure o Blast • Primary	Date of publication: August 2013 Place published: United States Methods: Cross-sectional	• A blast neurotrauma mouse model that recapitulated CTE-linked neuropathology in wild- type C57BL/6 mice two weeks after exposure to a single blast.	 <u>There are common pathogenic determinants and mechanistic</u> <u>evidence leading to chronic traumatic encephalopathy (CTE) in</u> <u>blast-exposed military veterans (</u>31) Blast-related TBI represents a neuropsychiatric spectrum disorder that clinically overlaps with CTE. 	High	None identified

Dimension of organizing framework	Study features	Summary of study sample and intervention	Declarative title and key findings	Relevance rating	Equity consider- ations
 Neurodegenerative conditions CTE Other factors that may affect long-term risks Co-morbid PTSD or mental health conditions 			 Blast-exposed mice demonstrated phosphorylated tauopathy, myelinated axonopathy, micro vasculopathy, chronic neuroinflammation, and neurodegeneration. The findings revealed that blast exposure may increase risk for later development of CTE and associated neurobehavioral sequelae. 		
 Type of sub- concussive exposure Blast Mixed mTBI (broadly defined) Neuro- degenerative conditions Alzheimer's disease Dementia (all cause) High-risk military occupations and roles Other factors that may affect long- term risk Number of sub-concussive exposures 	Date of publication: 2018 Place published: United States Methods: Cross-sectional	 98 post-9/11 era serving military members and Veterans who were combat-deployed and suffered possible concussive events (PCE) but have since been diagnosed with a spectrum of mTBI exposures. 	 Sustaining a high number of mTBI over a variety of time periods is associated with elevations of p-tau in exosomes and plasma total tau, which may in turn have implications for cognitive and functional outcomes later in life (24) Concentrations of tau proteins with exosomes differ in a sample of Veterans with repetitive mTBIs and specifically that exosomal p-tau is high in those reporting three or more mTBIs. This is relevant as elevated p-tau levels have been linked to a greater risk of older patients with mild cognitive impairment to develop Alzheimer's. The definition of mTBI in this study was established through an interview process and as a result may include both concussive and sub-concussive events. 	High	• None
 Type of sub- concussive exposure Non-blast 	Date of publication: 2020 Place published: United States	• 40 current female collegiate club soccer athletes between 18 and 25 with a minimum of four years of heading experience.	The cervical joint position error test tool may be valuable in tracking changes and or identifying deficits in cervical sensorimotor function across time as a result of sub-concussive incidents such as headings in soccer (33)	High	None reported

Dimension of organizing framework	Study features	Summary of study sample and intervention	Declarative title and key findings	Relevance rating	Equity consider- ations
	<i>Methods:</i> Pre- and post-test				
 Type of sub- concussive exposure o Blast High-risk military occupations and roles 	Date of publication: 2023 Place published: United States Methods: Modelling study	 Use of e-type silhouettes mounted to wooden target stands and equipped with blast gauges for each of the interior breaching training, using flashbang, single strand roll-up interior charge, 300 grain explosive cutting tape, and jelly charge explosives. 	 Using e-type silhouettes can support the measurement of cumulative blast exposure during training of special operation forces members, which can be added to a military history of blast exposure and supported to triage prevention and treatment approaches (34) The study aims to measure occupation blast exposure in a close quarter battle training environment and to use those outcomes to develop a cumulative blast exposure estimate model, Establishing blast exposure estimates during routine occupation training could be an important advance in documenting cumulative occupational exposure across a broad range of service members. Mean blast exposures were calculated for each silhouette that would undergo training, for flashbangs (n=93), single strand roll-up interior charge (n=80), 300 grain explosive cutting tape (n=28), and jelly charge (n=71). Mean peak blast exposure was 1.97 pounds per square inch (psi) for flashbangs, 3.88 psi for single strand roll-up interior charge. Total estimates find that during training special forces members are exposed to 36.8 psi daily, 184 psi weekly, and 2,760 psi through a full training cycle of cumulative pressure exposure. 	High	• None reported
 Type of sub- concussive exposure o Non-blast 	Date of publication: 2018 Place published: Canada Methods: Cross-sectional	• 35 Canadian university ice hockey players that played in the 2011–2012 season.	 Sex differences in structural alterations in white matter were identified following exposure to repeated sub-concussive injury (23) Sex-specific differences were found in the diffusion measures over the course of one ice hockey season, with significant voxel clusters observed in several regions in the brain. Changes in white matter diffusivity over time can be observed during aging but have also been associated with a variety of psychiatric or neurological diseases. Sex differences in the change of white matter were predominantly located in the right hemisphere. 	High	• Sex/gender

Dimension of organizing	Study features	Summary of study sample and intervention	Declarative title and key findings	Relevance rating	Equity consider-
Type of sub- concussive exposure o Non-blast	Date of publication: 2019 Place published: Boston Methods: Cross-sectional	• 18 college football players that have no previous history of concussions wore a mouthguard that measure the frequency and magnitude of head accelerators.	 Frequency and magnitude of sub-concussive impacts were found to be associated to changes in the neurofilament light chain and may be a clinically useful peripheral marker in tracking acute brain damage in contact sports (16) Neurofilament light chain is a viable biomarker for neuronal damage associated with TBI as well as for select neurodegenerative diseases including frontotemporal dementia, Huntington's disease, multiple sclerosis, Parkinson's disease, and amyotrophic lateral sclerosis. Players sustained a median of 23 hits. The greater the number of hits and greater the magnitude of the hit were associated with an increase in the neurofilament light chain layers 	High	None reported
 Type of sub- concussive exposure o Non-blast Neurodegenerative conditions o Dementia (all cause) 	Date of publication: 2017 Place published: United States Methods: Cross-sectional	93 amateur football players with no history of concussion and no participation in other sports.	 A dose-response relationship between cumulative head impact and risk for later-life cognitive impairment, self-reported executive dysfunction, depression, apathy, and behavioural dysregulation (11) The study developed and validated a metric to estimate an athletes' total cumulative exposure to repeated head impact from football and to use this to evaluate the association between the cumulative head impact index and later-life cognitive, behavioural, and mood impairment. The cumulative head impact index was developed based on individual self-report measures of athletic exposure at each level played and a measure of estimated head impact received per season, based on data from published helmet accelerometer studies. College players as compared to high school players had higher cumulative head impact index from more years of education and more seasons played. 	High	None reported
 Type of sub- concussive exposure Non-blast Neurodegenerative conditions CTE 	Date of publication: 2018 Place published: United States Methods: Cross-sectional	• 68 former national football league players and 21 controls underwent lumbar puncture.	 In a small sample of former NFL players, a greater number of repetitive head injuries and increase microglial activation were associated with high cerebrospinal fluid t-tau concentrations, which could indicate downstream CTE-related neurodegeneration (22) The study examined cerebrospinal fluid protein analysis from repetitive head impacts including concentration of total tau, phosphorylated tau, and AB1-42 and their association with repetitive head injury in former NFL players. 	High	• None reported

	Dimension of organizing framework	Study features	Summary of study sample and intervention	Declarative title and key findings	Relevance rating	Equity consider- ations
•	Type of repetitive sub-concussive exposure o Blast • Primary Neurodegenerative conditions o Chronic traumatic encephalo- pathy Biological sex o Male Other factors that may affect long- term risks o Number of sub-concussive exposures	Date of publication: January 2018 Place published: United States Methods: Longitudinal	 A total of 32 male mice were grouped into four conditions: 1) single sham, 2) repetitive sham, 3) repetitive mild traumatic brain injury (mTBI), and 4) single mTBI. 	 Single and repeated mTBI in male mice can cause irreversible differences in neurobehaviour, with repeated mTBI creating more challenges, highlighting the chronicity and long-term impacts of mTBI on neurodegeneration (36) The study explored changes in motor coordination, learning deficits, cognitive function, and anxiety-like behaviours in male mice who had an induced mTBI, in comparison to mice without. Single and repeated mTBI in mice can cause irreversible differences in the neurobehaviour, with repeated mTBi creating more challenges. Challenges included issues with learning, working memory, spatial memory, and vestibular motor coordination. Neuronal changes included axonal degeneration and neuroinflammation in subcortical white matter. With treatment, mice showed progress, but never returned to their initial function and the symptoms of mTBI could progressively worsen over time. Based on these findings, the authors recommend that mTBI be considered a chronic health condition and be treated over the course of one's lifespan. 	Medium	• None identified
•	Type of repetitive sub-concussive exposure • Blast • Primary High-risk military occupations and roles Biological sex • Male	Date of publication: 9 September 2021 Place published: United States Methods: Longitudinal	 A total of 115 male military members participated in this study (52 community controls, 18 deployed no mTBI, and 45 deployed and mTBI). 	 <u>Blast mTBI and deployment are associated with changes with</u> <u>miRNA expression in cerebrospinal fluid as differences in miRNA</u> <u>expression and receptor signalling of senescence and ephrin was</u> <u>found</u> (37) This study explored the effects of blast mild traumatic brain injury and deployment on miRNA expression in the cerebrospinal fluid in male military members. 	Medium	• Gender
•	Type of repetitive sub-concussive exposure o Mixed Neuro- degenerative conditions	Date of publication: 15 August 2022 Place published: United States Methods: Cross-sectional	 A total of 88 participants (28 with PTSD and 60 with PTSD + mTBI). The type of mTBI was not specified. All participants had been deployed and therefore may have had more exposure to blasts. 	 mTBI and PTSD can interact to increase neurodegeneration and decreases in cortical thickness (38) This study explored the combined impacts of PTSD and mTBI on cortical integrity. Participants with greater PTSD symptoms had reduced cortical thickness, volume, and surface area. A greater association between age and cortical change was seen in the mTBI + PTSD group. 	Medium	• None identified

	Dimension of organizing framework	Study features	Summary of study sample and intervention	Declarative title and key findings	Relevance rating	Equity consider- ations
•	 High-risk military occupations and roles Other factors that may affect long-term risks Co-morbid PTSD or mental health conditions. 			 This suggests that the interaction between mTBI and PTSD may increase neurodegeneration. Longitudinal studies are needed to better understand this relationship. 		
•	Type of repetitive sub-concussive exposure o Blast • Primary Biological sex o Male Neuro- degenerative conditions o Parkinson's disease Other factors that may affect long- term risks Number of sub- concussive exposures	Date of publication: 26 November 2022 Place published: United States Methods: Longitudinal	 Male rats were used for this study. The animals experienced an eight induced mTBIs, with 14-day intervals. 	 <u>Repetitive mTBIs in male rats were associated with increased</u> <u>pTau expression, similar to the pathology of Parkinson's disease</u> (28) This study explores the relationship between repetitive mTBI and Parkinson's disease in male rat models. 	Medium	• None identified
•	Type of repetitive sub-concussive exposure o Mixed Neuro- degenerative conditions High-risk military occupations and roles	Date of publication: 20 September 2019 Place published: United States Methods: Cohort study	 A total of 608,516 participants were included in this study (434,378 no mTBI and 93,003 mTBI). Participants with an mTBI were more likely to be of lower ranks and more likely to be exposed to sub-concussive events 	 Veterans with a mild traumatic brain injury exhibit phenotypes of moderately healthy + decline, 2) polytrauma, and 3) polytrauma improvement; future research is needed to understand factors underlying phenotypes (39) This study explored phenotypes in Veterans with an mTBI and Veterans without an mTBI. A total of five phenotypes were derived: moderately healthy, mental health, moderately healthy + decline, polytrauma, and polytrauma + improvement. The most common phenotypes were the moderately healthy phenotype and mental health comorbidity phenotype. 	Medium	• Occupation

Dimension of organizing framework	Study features	Summary of study sample and intervention	Declarative title and key findings	Relevance rating	Equity consider- ations
 Other factors that may affect long- term risks Number of sub- concussive exposures 			 Only participants without mTBI showed the moderately healthy phenotype. Only participants with an mTBI showed the moderately healthy + decline, polytrauma, and polytrauma+ improvement phenotype. This suggests a need to look at the impacts of mTBI over time to understand the factors leading to decline and improvement. Impacts of mTBI that may lead to different phenotypes but were not explored could be the presence of mental health, number of exposure, and available resources. Individuals with the polytrauma + improvement phenotype showed the least number of adverse events, indicating resiliency or access to treatment. Understanding phenotypes of mTBI and corresponding factors can help predict risk factors of neurodegeneration. 		
 Type of repetitive sub-concussive exposure Blast Neuro-degenerative conditions High-risk military occupations and roles Other factors that may affect long-term risks Number of sub-concussive exposures 	Date of publication: 27 July 2023 Place published: United States Methods: Cross-sectional	 A total of 152 with (82) and without (70) multiple mTBI history participated in this study. Participants were required to have no other health conditions. Participants were on average 32 years old. Approximately 24% of participants had one to two exposures and 28% had three or more exposures. Special operation forces military members have high involvement in global conflict and are more likely to be exposed to blasts; however, the nature of blasts experienced by this population was not specified. 	 Greater incidence of mTBI is associated with decreased resiliency and greater vulnerability to neurodegenerative symptoms in Special Operation Force members exposed to blasts (6) This study compared global and local efficiency assortative coefficient in Special Operations Forces (SOF) military members with and without mTBI history. Participants with a higher incidence of mTBI showed lower assortative coefficient. Greater assortative corresponds to more interconnected and resilient brain networks. This could mean that more exposure to mTBIs lead to weaker brain network resilience, meaning a lack of physiological recovery. This could also mean that lower assortative leads to greater vulnerability to developing mTBI symptoms following a blast exposure. There was no significant difference in global or local efficiency between groups. Longitudinal research is needed to understand the direction of this relationship, as well as risk and protective factors for neurodegeneration. 	Medium	• None identified

Dimension of organizing	Study features	Summary of study sample and intervention	Declarative title and key findings	Relevance rating	Equity consider-
 Type of repetitive sub-concussive exposure Non-blast Neuro- degenerative conditions Alzheimer's disease 	Date of publication: June 2022 Place published: United States Methods: Cross/sectional	 Compared an Alzheimer's disease dementia group with an mTBI history (n=10) to a matched Alzheimer's disease control group (n=20). Measures of cognitive function, cerebral glucose metabolism, and markers of amyloid and tau deposition were taken. 	 mTBI may serve as a risk factor for Alzheimer's disease by leading to an increase in tau formation and neuronal injury (40) Higher levels of phosphorylated tau reflects greater formation of neurofibrillary tangles, whereas higher total tau reflects increased neuronal damage. Alzheimer's disease is the only condition well-known to show increases in both phosphorylated tau and total tau. 	Low	None identified
 Type of repetitive sub-concussive exposure Non-blast Neuro- degenerative conditions CTE 	Date of publication: July 2016 Place published: United States Methods: Case report	 A former 56-year-old rugby player with CTE presented. Retrospectively examined brain MRI and PET scans obtained during life. 	 This report presented the first description of blood-brain barrier dysfunction in a pathologically proven CTE case (41) The underlying molecular pathobiology of CTE remains unclear to link the development of CTE to concussive injuries in athletes and military personnel. The blood-brain barrier was found disrupted in regions of dense perivascular p-tau accumulation. This suggests a vascular component in the post-concussion cascade of events may lead to the development of a progressive degenerative disorder. 	Medium	None identified
 Type of repetitive sub-concussive exposure Mixed Neuro- degenerative conditions Other movement disorders (e.g., ataxia, motor neuron disease) High-risk military occupations and roles 	Date of publication: June 2018 Place published: United States Methods: Cross/sectional	• Compared military personnel with mild TBIs (mTBIs) (n=42) to those without TBIs (n=22) in concentrations of tau, amyloid-beta, and cytokines.	 Greater tau elevations may contribute to chronic post-concussive symptoms that develop following mTBIs (42) Participants were classified as having an mTBI if they reported an event in which they sustained a blow to the head (from fragments, vehicular, blast, blow to the head, or fall) and had a loss of consciousness of 20 minutes or less. The study reported elevated concentrations of exosomal tau, amyloid beta, and cytokine IL-10 in the military personnel with mTBI group compared to the controls; post-concussive symptoms were most related to exosomal tau elevations. 	Medium	• None identified

	Dimension of organizing framework	Study features	Summary of study sample and intervention	Declarative title and key findings	Relevance rating	Equity consider- ations
•	Type of repetitive sub-concussive exposure o Non-blast Neurodegenerative conditions o Other movement disorders (e.g., ataxia, motor neuron disease) Other factors that may affect long- term risks o Number of	Date of publication: February 2017 Place published: China Methods: Cross/sectional	Used the Sprague Dawley rats to develop the animal models of repetitive mTBI and single mTBI in order to detect the neurobehavioral changes.	 The activation of chronic microglia and astrocyte could lead to the dysregulation of inflammatory cytokines, which may play a role in neurodegeneration after repetitive mTBI (43) Repetitive mTBI led to more severe behavioural injuries including more activated microglia cells, astrocytes, higher levels of TNF-α and IL-6, and the expression of IL-10 was lower compared with the single TBI group. The levels of total tau and p-tau remained the same between both studied groups. The repetitive mTBI group showed significant impairment in spatial learning and memory. 	Medium	• None identified
•	sub-concussive exposures Type of repetitive sub-concussive exposure o Non-blast Neuro- degenerative conditions o Alzheimer's disease Other factors that may affect long- term risks o Number of sub-concussive exposures	Date of publication: December 2018 Place published: United States Methods: Longitudinal	Generated time- dependent molecular profiles of response to r- mTBI and Alzheimer's disease pathogenesis in mouse models using unbiased proteomic analyses.	 <u>There is molecular overlap in the potential biomarkers between repetitive mTBI and Alzheimer's disease to suggest interrelationship (44)</u> The study identified key related molecules and pathways common to age-related changes in Alzheimer's disease models and chronic post-injury changes in their mTBI model. This involved production of nitric oxide and reactive oxygen species, liver X receptor/retinoid X receptor activation, and upregulation of inflammatory responses. 	Medium	• None identified
•	Type of repetitive sub-concussive exposure o Non-blast	Date of publication: January 2018 Place published: Canada Methods: Cross/sectional	• Included 53 retired Canadian Football League players, 25 age- and education-matched healthy controls, and controls from the	 Multiple concussions may contribute to pathology associated with greater age-related atrophy and result in earlier focal atrophy (45) This study tested that repeated concussions may be associated with smaller regional brain volumes, poorer cognitive performance, and behavioural symptoms among former professional football players compared to healthy controls. 	Medium	• None identified

Dimension of organizing framework	Study features	Summary of study sample and intervention	Declarative title and key findings	Relevance rating	Equity consider- ations
 Neuro- degenerative conditions Other movement disorders (e.g., ataxia, motor neuron disease) 	Date of tublication: August	Cambridge Centre for Aging and Neuroscience database for validation.	 This study reported exaggerated hippocampal volume loss and memory impairment in former professional athletes who report only concussions. This study did not measure sub-concussive blows amongst the participants and four players reported no concussions. It is possible that professional players of contact sports will experience hits to the head but may not report having a concussion, especially if they do not experience persistent post-concussive symptoms. This in vivo model of repetitive mTBL observed key short- and 	Medium	None
 Type of repetitive sub-concussive exposure Non-blast Neuro- degenerative conditions CTE Other factors that may affect long- term risks Number of sub-concussive exposures 	Date of publication: August 2018 Place published: United States Methods: Cross/sectional	• 40 male Sprague-Dawley rats were randomly assigned to receive 0, 1, or 3x mTBI spaced five days apart.	 Inits in vivo model of repetitive in FBI observed key short- and long-term pathological and functional changes in clinical concussive injury, and the typical hallmarks of progressive CTE (46) The goal of the study was to develop and characterize a novel model of repetitive mTBI that accurately reproduces the key short and long-term functional and histopathological features seen clinically. Repetitive mTBI resulted in mild spatial and recognition memory deficits, upward trend of anxiety-like behaviour, and increases in beta-amyloid precursor protein immunoreactivity were observed in repetitive mTBI animals at 12 weeks, indicating long-term changes in axonal integrity. 	Medium	• None identified
 Neurodegenerative conditions Dementia (all cause) 	Date of publication: July 2020 Place published: United States Methods: Retrospective, cross/sectional	 Administrative data of a random sample of 176 cases of post-9/11 deployed veterans under 65 years of age. 	 <u>A previously used algorithm for detecting dementia in older</u> <u>Veterans is not supported for use in younger adult samples and</u> <u>results in a significantly high number of false positives (47)</u> The study examined the accuracy of an algorithm used to determine early-onset dementia in older Veterans. 73% of early-onset dementia diagnoses identified using existing algorithms were identified as false positives in the overall sample. This increased to approximately 85% among those with mTBI. 	Low	• None identified
 Type of repetitive sub-concussive exposure Mixed 	<i>Date of publication:</i> November 2021 <i>Place published:</i> United States	• Participants (n=144) included 81 Veterans with a history of mTBI and 63 Veteran controls (VCs) without a history of mTBI.	 Depression, PTSD, combat exposure, history of remote mTBI, and neurobehavioral symptoms are strong predictors of health-related quality of life particularly in the categories of physical health and social functioning (48) This study investigated the health-related quality of life in Veterans with and without a history of mTBI. 	Low	None identified

Dimension of organizing framework	Study features	Summary of study sample and intervention	Declarative title and key findings	Relevance rating	Equity consider- ations
 High-risk military occupations and roles Other factors that may affect long-term risks Co-morbid PTSD or mental health conditions 	Methods: Cross/sectional	• Participants completed questionnaires measuring combat exposure, depressive and PTSD symptoms, and neurobehavioral symptoms.	• The mTBI group demonstrated poorer health-related quality of life on the Physical Role Functioning, General Health, and Social Functioning subscales of the questionnaire.		
 Types of sub- concussive exposure mTBI (broadly defined) High-risk military occupations and roles 	Date of publication: 2016 Place published: United States Methods: Cross-sectional	• Non-deployed active-duty service members with a new mTBI diagnosis in the calendar year of 2012.	 Service members with a history of mTBIs tended to be between the ages 18 and 34 (49) The study identified that service members with new mTBIs tended to be between the ages of 18 and 34 and relatively junior, two-thirds had a history of deployment, and about 10 percent reported having received treatment for a previous mTBI. Treatment for health conditions that often co-occur with mTBI was more frequent in the six months after mTBI diagnosis compared with the six months before. The treatment of mTBIs typically includes limiting physical and mental activity and to remain in a low stimulus environment immediately after a concussion. 	Low	None identified
 Type of sub- concussive exposure Blast Primary Secon-dary Tertiary mTBI (broadly defined) 	Date of publication: 2018 Place published: United States Methods: Case-control	124 Veterans of Operations Enduring and Iraqi Freedom with self- reported traumatic combat experiences or blast exposure to explosive blasts during their most recent deployment.	 <u>Comparable P3b amplitude reduction was recorded in all three</u> affected groups and may be an index of brain pathology after combat trauma, yet the diminished brain response fails to differentiate independent effects of blast-related mTBI or severity of PTSD symptomatology (50) P3b is a sub-component of the P300 brain response index of attentional allocation capacity and working member updating. Reduced P3b amplitude has been shown to reflect cognitive dysfunction in subjects with mTBI. mTBI was defined as having symptoms including altered consciousness, loss of consciousness for less than 30 minutes, post-traumatic amnesia up to 24 hours, and neurological symptoms. 	Low	• None reported
• Types of sub- concussive exposure	Date of publication: 2023	• 1,685 participants with variable lifetime mTBI	A greater number of lifetime mTBIs was associated with more impactful headaches, and a higher prevalence of headaches were found for mTBIs stemming from blast-related mechanisms (51)	Medium	• Sex/gender

Dimension of organizing framework	Study features	Summary of study sample and intervention	Declarative title and key findings	Relevance rating	Equity consider- ations
 Blast Mixed Neuro-degenerative conditions High-risk military occupations and roles Biological sex Male Female Other factors that may affect long-term risks Number of sub-concussive exposures 	Place published: United States Methods: Cross-sectional	 histories, ranging from none to over 10. Clinical diagnosis of mTBI was assessed using a multi-step process through a face-to-face interview, whereby all potential concussive events were noted and then placed into an algorithm before a final clinical diagnosis was provided by Veterans Affairs/Department of Defence. 	 Of 1,685 combat-exposed current and former military members, 19% had a negative history of mTBIs, 47% were thought to have sustained between one and two mTBIs, while 34% were thought to have three or more. Of those with a history of mTBIs, 64% were combat, 65% non-combat, and 38% blast-related. At the time of enrolment 65% of individuals reported have recently experienced a headache; this prevalence was significantly higher with those with more lifetime mTBIs. Females had the highest odds ratio of experiencing headaches and the strongest association with higher headache impact. 		
 Type of sub- concussive exposure Blast Non-blast mTBI (broadly defined) High-risk military occupations and roles 	Date of publication: 2023 Place published: United States Methods: Cross-sectional	 40 Veterans with a history of mTBI and a control group of 29 Veterans with no history of mTBI. mTBI was defined as a loss of consciousness for under 30 minutes, alternation of consciousness up to 24 hours, and/or post- traumatic amnesia. 	 Subjective memory complaints were associated with reduced cortical thickness in frontal and temporal brain regions independent of PTSD symptoms and objective memory performance (52) These associations were only found in Veterans with a history of mTBI and not in those with no history of head injury. For younger Veterans with a history of mTBI, subjective experience of memory difficulties after mild neurotrauma may reflect underlying differences in brain morphometry independent of traditional neurocognitive testing. 	Medium	• None reported

Appendix 5: Documents excluded at the final stages of reviewing

Document type	Hyperlinked title		
Evidence syntheses	Association of traumatic brain injury with subsequent neurological and psychiatric disease: A meta-analysis		
	Emergency physician training on mild traumatic brain injury: A systematic review		
	The anatomy of concussion and chronic traumatic encephalopathy: A comprehensive review		
	Helmet efficacy against concussion and traumatic brain injury: A review		
	Mild traumatic brain injury: A review		
Evidence syntheses that do not	Epidemiology of mild traumatic brain injury and neurodegenerative disease		
meet standards for inclusion	The role of TDP-43 in military relevant TBI and chronic neurodegeneration		
	Long-term cognitive and neuropsychiatric consequences of repetitive concussion and head-impact exposure		
	Relationship of traumatic brain injury to chronic mental health problems and dementia in military veterans		
	Sex and gender considerations in concussion research		
	Blood brain barrier dysfunction and delayed neurological deficits in mild traumatic brain injury induced by blast shock waves		
	Post-traumatic neurodegeneration and chronic traumatic encephalopathy		
	Chronic effects of mild neurotrauma: Putting the cart before the horse?		
	Alzheimer's Dementia due to suspected CTE from sub-concussive head impact		
Single studies	Is sex an indicator of prognosis after mild traumatic brain injury: A systematic analysis of the findings of the World Health Organization		
	Collaborating Centre Task Force on Mild Traumatic Brain Injury and the International Collaboration on Mild Traumatic		
	Acute cognitive impairment after traumatic brain injury predicts the occurrence of brain atrophy patterns similar to those observed in Alzheimer's		
	disease		
	Acute cognitive deficits after traumatic brain injury predict Alzheimer's disease-like degradation of the human default mode network		
	A case of Alzheimer's disease following mild traumatic brain injury		

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.



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