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Neurocognitive Effects of Repetitive Low-Level Blast (rLLB) Overpressure Exposure in Humans – a rapid assessment of the evidence

Associate Professor David Heslop
School of Population Health, UNSW

Dr Lauren Fortington
Sydney School of Health Sciences, University of Sydney

Professor Andrew Gardner
Sydney School of Health Sciences, University of Sydney

30th January 2026

Acknowledgement and disclaimer

This report was commissioned by the Australian Government Department of Veterans' Affairs (DVA). However, the views expressed in this report do not necessarily represent the views of the Minister for Veterans' Affairs or the Department of Veterans' Affairs. The Commonwealth does not give any warranty nor accept any liability in relation to the contents of this work.

Suggested citation:

Heslop DJ, Fortington LV, and Gardner AJ. 2026. *Neurocognitive Effects of Repetitive Low-Level Blast (rLLB) Overpressure Exposure in Humans – a rapid assessment of the evidence.* Department of Veterans' Affairs, Australian Government. Canberra: Commonwealth of Australia.

Executive Summary

Repetitive low-level blast (rLLB) exposure has emerged as an occupational exposure of concern in contemporary military contexts, particularly for personnel engaged in breaching, artillery, mortars, heavy weapons, and certain special operations roles. These exposures are typically below thresholds associated with acute blast injury or clinically diagnosed traumatic brain injury. Recent human, animal, and grey literature indicate that cumulative exposure may be associated with measurable acute physiological effects. In some cohorts, persistent behavioural, mental health, neurological and cognitive symptoms and signs are also identified.

Across human studies, rLLB exposure has been associated with transient alterations in cognition, balance, oculomotor function, and blood-based biomarkers following training or operational exposures. In populations with high cumulative exposure to low-level blasts there is evidence of greater symptom burden and higher rates of diagnosed mild traumatic brain injury (mTBI) and neuropsychiatric conditions compared with other military occupational groups. These findings are supported by animal models that demonstrate biological plausibility through consistent evidence of axonal injury, neuroinflammation, vascular disruption, altered neuronal excitability, and metabolic dysfunction following repeated low-level blast exposure.

At the same time, the certainty of the human evidence base remains limited. Exposure metrics are inconsistently defined and often rely on occupational role or self-report rather than objective measurement. Confounding factors, including impact-related mTBI, exposure to higher blast intensities during a career, post-traumatic stress disorder, depression, chronic pain, sleep disturbance, and substance use, are common and frequently exert stronger influence on long-term outcomes than rLLB exposure alone. Longitudinal human data linking rLLB exposure to definitive long-term neurological or neurodegenerative outcomes remain sparse, and no validated exposure thresholds or diagnostic markers currently exist.

As a result, the available evidence outlined in this report supports biological plausibility and association but does not establish causality or permit threshold-based policy decisions.

Within this evidentiary context, several implications arise:

Firstly, rLLB exposure is best understood as a cumulative occupational exposure rather than a discrete injury event. This framing aligns with international defence and veterans' health literature, which increasingly emphasises lifetime brain health and cumulative exposure histories. The evidence suggests that individuals in high blast-risk roles represent identifiable subpopulations with greater cumulative exposure and symptom burden, implying value in improved recognition and documentation of exposure history within existing health and compensation systems, without presupposing deterministic outcomes.

Clinical presentations associated with rLLB exposure are typically multidimensional. Cognitive complaints frequently co-occur with mental health conditions, pain syndromes, and sleep disorders, and current diagnostic tools cannot reliably distinguish rLLB-related effects from these overlapping conditions. This reinforces the importance of holistic, trauma-informed assessment and management pathways that consider rLLB exposure as one contributing factor among many, rather than as a standalone diagnosis. The literature does not support the routine clinical use of advanced imaging or blood biomarkers outside research settings, but it does support careful longitudinal assessment and symptom-focused care.

The evidence base highlights substantial gaps in exposure measurement, longitudinal follow-up, and translational research. While animal studies provide strong mechanistic insight, their applicability to long-term human outcomes remains indirect. Human studies demonstrate consistent patterns of association but lack the methodological precision required for definitive conclusions. These limitations suggest that future

policy and program development must remain flexible, options-based, and transparent about uncertainty, while supporting efforts that improve data quality over time.

Prevention and mitigation efforts are evolving internationally but remain constrained by the absence of validated exposure limits and by practical challenges in operational environments. The literature indicates that precautionary approaches, aimed at reducing unnecessary cumulative exposure and improving exposure awareness, may offer pragmatic intermediate pathways while evidence continues to mature. Engagement with allied defence and veterans' health organisations provides opportunities for shared learning, harmonisation of terminology, and alignment with emerging international standards.

Finally, the review highlights the importance of balanced, evidence-based communication. Public and veteran concern regarding blast exposure and potential links to neurodegeneration is increasing, yet the scientific literature cautions against over-attribution or deterministic narratives, particularly regarding conditions such as Chronic Traumatic Encephalopathy - Neuropathological Change (CTE-NC). Clear communication that distinguishes what is known, what remains uncertain, and why holistic care remains appropriate regardless of causation is central to maintaining trust and supporting veteran wellbeing.

Responses to research questions posed in this review

Research question	Response
How is LLB overpressure exposure defined?	Low-level blast (LLB) overpressure exposure refers to exposure to blast pressure waves that are below thresholds typically associated with acute blast injury or clinically diagnosed traumatic brain injury. These exposures commonly arise from military weapons systems (e.g. breaching charges, artillery, mortars, heavy firearms) and generally involve peak overpressures in the approximate range of 1–6 psi, although higher values are occasionally reported in training or operational contexts. LLB exposure does not usually produce immediate, overt neurological injury but may exert subclinical physiological stress on the brain.
What criteria are used to define repetitive LLB (rLLB) exposure (e.g., duration/frequency/intensity)?	There is no universally accepted definition of rLLB. In the literature, rLLB is operationalised variably using proxies such as occupational role (e.g. breacher, instructor), self-reported blast counts, duration in high-risk roles, or inferred cumulative exposure during training cycles or careers. Frequency, cumulative dose (blast count or impulse), and career duration are more commonly used than precise intensity thresholds. This lack of standardisation is a major limitation of the evidence base.
What assessment process is recommended for individuals presenting with acute or chronic cognitive signs and symptoms associated with rLLB exposure?	The report supports a holistic, multimodal clinical assessment rather than a blast-specific diagnostic test. Recommended assessment integrates clinical history (including blast exposure history), symptom inventories, neuropsychological screening, vestibular and balance assessment, mental health screening (PTSD, depression, anxiety), sleep assessment, and pain evaluation. rLLB exposure should be considered within existing mTBI and mental health pathways rather than as a standalone diagnosis.

What is the reliability and validity of the cognitive assessments designed to assess acute or chronic signs/symptoms associated with rLLB overpressure exposure with respect to (i) clinical history; (ii) alternative diagnoses; and (iii) comorbid diagnoses?	The evidence indicates limited reliability and validity of existing cognitive assessments for isolating rLLB effects. Neuropsychological tests, symptom questionnaires, eye-tracking, balance testing, imaging, and biomarkers demonstrate sensitivity to change but poor specificity. Results are strongly influenced by clinical history, comorbid PTSD, depression, sleep disturbance, chronic pain, and prior impact-related mTBI. No assessment tool has been validated to reliably distinguish rLLB effects from alternative or comorbid diagnoses.
Which military roles are associated with higher levels of rLLB overpressure exposure during (i) training; and (ii) deployment?	High-risk roles consistently include breachers and explosive entry personnel, artillery and mortar crews, heavy-weapons operators, special operations forces, and instructors in blast-intensive training environments. Exposure occurs both during training and deployment, with instructors and career specialists demonstrating the highest cumulative exposure profiles.
What individual, occupational, or environmental factors may protect against the development of cognitive impairment following rLLB overpressure exposure?	Protective factors are incompletely defined but include reduced cumulative exposure, adequate recovery intervals between exposures, effective hearing and head protection, modification of training practices, and management of modifiable health factors such as sleep, mental health, and substance use. Animal studies suggest that mechanical mitigation and modulation of inflammatory pathways may be protective, but human evidence remains preliminary.
Does rLLB overpressure exposure increase susceptibility to clinically diagnosed neurological, psychiatric, or medical conditions?	Human evidence suggests associations between rLLB exposure and increased symptom burden, mTBI diagnoses, and neuropsychiatric conditions, particularly when exposure is cumulative and co-occurs with other stressors. However, causality is not established. Vulnerability appears to be strongly influenced by comorbid PTSD, depression, sleep disturbance, chronic pain, and prior head injuries rather than rLLB exposure alone.
What are the mechanisms by which rLLB overpressure exposure is proposed to affect cognitive functioning in humans?	Animal and translational evidence supports mechanisms including axonal injury, neuroinflammation, vascular and blood-brain barrier disruption, altered neuronal excitability, mitochondrial dysfunction, and neuroimmune activation. These mechanisms provide biological plausibility for observed human symptoms but do not yet establish direct causal pathways in humans.
What brain structures and cognitive processes are affected by rLLB overpressure exposure in humans (neuropathology, neuroimaging, biomarkers)?	Human studies implicate frontal and subcortical networks, white matter tracts, vestibular and oculomotor systems, and salience/default mode networks. Neuroimaging and biomarker studies suggest involvement of axonal and glial pathways, though findings are inconsistent and confounded.

What is the underlying neuropathology associated with rLLB overpressure exposure in humans?	Direct neuropathological evidence in humans is extremely limited. Imaging and biomarker findings suggest possible microstructural white matter changes, neuroinflammatory activity, and metabolic alterations. Animal studies demonstrate more definitive axonal, vascular, and glial pathology, but translation to human disease remains uncertain.
How are cognitive changes assessed following rLLB overpressure exposure?	Assessment relies on symptom reporting, neuropsychological testing, vestibular and balance measures, eye-tracking, and research-grade biomarkers or imaging. No validated rLLB-specific diagnostic framework exists; assessments are best interpreted longitudinally and in clinical context.
What acute cognitive signs and symptoms are associated with rLLB overpressure exposure in humans?	Acute effects include transient cognitive slowing, attention deficits, headache, dizziness, balance disturbance, visual or oculomotor changes, and short-term biomarker elevations. These effects often resolve over hours to days.
What chronic cognitive signs and symptoms are associated with rLLB overpressure exposure in humans?	Chronic findings in high-exposure cohorts include persistent headaches, concentration difficulties, irritability, sleep disturbance, mood dysregulation, and subtle executive or attentional deficits. These are often intertwined with psychiatric and pain comorbidities.
How can rLLB-related symptoms be distinguished from other cognitive or psychiatric conditions (differential diagnosis)?	They generally cannot be reliably distinguished using current tools. Differential diagnosis requires comprehensive assessment addressing PTSD, depression, anxiety, sleep disorders, chronic pain, substance use, neurodegenerative disease, and impact-related mTBI. Attribution to rLLB alone is not supported by current evidence.
Is there any evidence that rLLB overpressure exposure is associated with mTBI (or signs and symptoms of same) in humans?	Epidemiological data suggest that individuals in high blast-risk roles have higher rates of diagnosed mTBI and post-concussive symptoms. However, rLLB may act as a risk modifier rather than an independent cause.
Is there any evidence that rLLB overpressure exposure is associated with neurodegenerative conditions (or signs and symptoms of same) in humans?	Evidence is insufficient to establish an association. Animal studies show biological plausibility for neurodegenerative processes, but human evidence is limited, inconsistent, and low certainty.
What treatment or management strategies are recommended for individuals presenting with acute or chronic cognitive signs and symptoms associated with rLLB exposure?	No rLLB-specific treatments are recommended. Management should follow established guidelines for mTBI, PTSD, depression, sleep disorders, and chronic pain, using multidisciplinary, symptom-focused care.

What is the safety and efficacy of the treatment or management strategies for individuals presenting with acute or chronic cognitive signs and symptoms associated with rLLB overpressure exposure?	Standard rehabilitation and mental health treatments are considered safe and effective for symptom management. Interventions such as hyperbaric oxygen therapy or supplements lack sufficient evidence for routine use.
What prevention strategies are proposed or in use to reduce rLLB exposure or its effects?	Strategies include minimising unnecessary repetitive exposures, modifying training practices, improving documentation and surveillance, piloting blast sensors in training, and monitoring emerging international guidance. No safe exposure thresholds have been established.
What rehabilitation approaches are used for rLLB-related cognitive impairment?	Rehabilitation mirrors mTBI care: cognitive rehabilitation, vestibular therapy, psychological interventions, sleep management, and pain management. Evidence specific to rLLB is limited.
What is known about long-term wellbeing and quality of life impacts for individuals with rLLB-related cognitive symptoms?	Long-term outcomes are driven largely by comorbid mental health conditions, pain, and sleep disorders. rLLB exposure may contribute to cumulative burden, supporting a lifetime brain-health framing, but direct long-term effects remain uncertain.
What is the quality and certainty of the evidence used to address the research questions?	Overall certainty is very low to low. Human studies are limited by observational designs, exposure misclassification, confounding, and small samples. Animal studies provide strong mechanistic insight but are indirect. Evidence supports biological plausibility and association, not causation or threshold-based policy.

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List of abbreviations

Abbreviation	Explanation
ADF	Australian Defence Force
DVA	Department of Veterans' Affairs
UNSW	University of New South Wales
rLLB	Repetitive Low-Level Blast

Glossary

Term / Acronym / Biomarker	Definition
ALS – Amyotrophic Lateral Sclerosis	Progressive neurodegenerative disorder mentioned in long-term risk contexts.
Amyloid PET	Neuroimaging modality assessing amyloid deposition in vivo.
APOE ε4	Genetic polymorphism influencing vulnerability to blast-related injury in animal models.
Autoantibodies (Brain-Reactive)	Immune markers suggesting maladaptive neuroimmune activation following rLLB.
Aβ / Amyloid-Beta Peptide	Peptide involved in neurodegeneration; increased serum levels reported after repetitive low-level rifle overpressure.
BBB – Blood–Brain Barrier	A selective barrier protecting the brain; blast exposure can transiently increase permeability.
Biomarker	A measurable biological indicator of injury, inflammation, or metabolic dysregulation.
Blast Impulse	Time-integrated measure of blast overpressure; may correlate with symptom and metabolomic changes.
Blast Overpressure	The rapid increase in atmospheric pressure generated by an explosive event.
Breacher	A high-risk occupational role involving use of explosive entry charges.
CANSOF	Canadian Special Operations Forces
Central effects	Central effects refer to impacts on the central nervous system (brain and spinal cord), influencing cognition, emotion, sensation, or motor control.
Chronic Traumatic Encephalopathy (CTE)	Neurodegenerative syndrome linked to repetitive head trauma. Cannot currently be diagnosed in living individuals.
Cognitive / Cognition / Cognitive Function	Refers to processes related to acquiring, processing, storing, and using information, including perception, memory, attention, reasoning, and decision-making.
Comorbidity	The presence of multiple interacting health conditions (e.g., PTSD, depression, chronic pain).
Cyclooxygenase / EP3 Pathway	An inflammatory cascade where cyclooxygenase enzymes produce prostaglandins that activate the prostaglandin E receptor 3 on target cells. In some blast injury models, this signalling contributes to secondary injury by amplifying inflammation and disrupting small blood vessel and blood–brain barrier function.

CTE-NC – Chronic Traumatic Encephalopathy—Neuropathological Change	CTE–Neuropathologic Change (CTE-NC) is a pathological diagnosis confirmed only after death by identifying a specific pattern of tau deposition in brain tissue. By contrast Traumatic Encephalopathy Syndrome (TES) is a clinical research construct used in living individuals, based on symptoms and exposure history, and does not establish that CTE pathology is present.
Cumulative Blast Dose	Aggregate measure of blast exposure over time (e.g., frequency × amplitude × impulse).
Cytokines	Inflammatory cytokines are signalling proteins released by immune cells that regulate inflammation and immune responses, and when chronically elevated can contribute to neural dysfunction and disease.
Default Mode	The default mode (or default mode network) is a set of interconnected brain regions that is most active during rest and internally-focused thought, such as self-reflection, memory retrieval, and mind-wandering.
Dosimetry	The measurement and quantification of blast exposure, including pressure wave characteristics, duration, and frequency across repeated events. It is used to estimate cumulative dose and relate exposure levels to injury risk and biological effects.
DTI – Diffusion Tensor Imaging	MRI method assessing white-matter microstructure of the brain.
Executive function	Executive function refers to a set of higher-order cognitive processes that enable planning, inhibition, working memory, flexible thinking, and goal-directed behaviour.
FDG – Fluorodeoxyglucose	PET (Positron Emission Tomography) tracer used to assess neural metabolic activity.
Fronto-parietal networks	Fronto-parietal networks are large-scale brain networks linking frontal and parietal regions that support executive functions such as attention control, working memory, decision-making, and flexible goal-directed behaviour.
GFAP – Glial Fibrillary Acidic Protein	A structural protein found in astrocytes that is released into blood or cerebrospinal fluid when these support cells are injured. It is often elevated after blast exposure and is used as a biomarker of astrocyte damage and central nervous system injury.
Glutamate (Urinary)	A chemical involved in nerve signalling that can be measured in urine as a marker of altered brain and whole-body metabolism. It may be reduced after repeated low-level blast exposure, suggesting changes in excitatory signalling or stress-related metabolic pathways.
Grey Literature (GL)	Technical reports, government documents, and military publications outside peer-reviewed journals.
HVA – Homovanillic Acid	A breakdown product of dopamine that can be measured in urine as an indicator of dopamine turnover. It may be reduced after repetitive blast exposure, suggesting altered dopamine signalling or metabolism.
Impulse (Blast)	See Blast Impulse.
KCNQ / m-Channel	A voltage-gated potassium channel that helps stabilise nerve cell electrical activity and limits excessive firing. In some blast models it is disrupted, and treatments that restore its function can reduce abnormal excitability and protect brain tissue in experimental slice preparations.
Linoleic Acid (Urinary)	An essential dietary fatty acid that can be detected in urine as part of metabolic profiling. It may be elevated after repeated low-level blast

	exposure, reflecting changes in lipid metabolism and inflammatory signalling.
LTP / LTD – Long-Term Potentiation / Long-Term Depression	Long-lasting strengthening or weakening of connections between nerve cells that underpins learning and memory. Blast exposure can disrupt these processes, indicating impaired synaptic function and altered neural network adaptation.
Metabolomic Signatures	Patterns of multiple small molecules in the body - such as lipids, amino acids, and neurotransmitter breakdown products - that shift in response to injury or stress. After blast exposure, these composite profiles can change in characteristic ways and may help indicate exposure effects or biological response pathways.
Mitochondrial Dysfunction	Impaired function of the cell's energy-producing structures, leading to reduced energy generation and inefficient oxygen use. After blast injury, this can drive oxidative stress and contribute to ongoing cellular damage and impaired recovery.
MOS – Military Occupational Specialty	Job classification system used to identify high-risk blast roles used in US Military. Roughly equivalent to ECN/Corps in Australian Army but potentially less well defined in RAN and RAAF.
MRI – Magnetic Resonance Imaging	A medical imaging technique that uses strong magnetic fields and radio waves to generate detailed images of internal tissues, including the brain. In blast research it is used to detect structural injury and functional changes that may not be visible on routine assessment.
mTBI – Mild Traumatic Brain Injury	A form of brain injury that causes transient neurological dysfunction, often with subtle or non-specific symptoms such as headache, dizziness, or cognitive changes. It commonly co-occurs with repeated low-level blast exposure and may contribute to cumulative effects over time.
Neurodegeneration Markers	Measurable molecules that indicate progressive damage or loss of nerve cells and their connections. They include abnormal tau proteins, amyloid-related proteins, synaptic proteins, and inflammatory mediators that can change after injury and signal ongoing pathological processes.
Neurofilament light	Neurofilament light is a structural protein of neuronal axons that is released into cerebrospinal fluid and blood following axonal injury, making it a biomarker of neurodegeneration and neural damage.
Neuroinflammation	An inflammatory response within the brain and spinal cord triggered by injury or other insults. It involves activation of microglia and astrocytes, which can be protective initially but may also drive secondary damage if prolonged or excessive.
Neuropsychological test battery	A neuropsychological test battery is a structured set of standardized tests used to assess multiple cognitive domains (such as memory, attention, language, executive function, and visuospatial skills) to evaluate brain function and identify patterns of impairment.
NFL – Neurofilament Light Chain	A structural protein in nerve cell axons that is released into blood or cerebrospinal fluid when axons are damaged. It can rise shortly after repeated low-level blast exposure and is used as a biomarker of acute axonal injury.
NMDA-Related Metabolites	Small molecules that influence signalling through the N-methyl-D-aspartate receptor, a key pathway for excitatory neurotransmission and synaptic plasticity. After blast exposure, changes in these metabolites may reflect altered excitatory signalling, and some may

	have protective effects by reducing excessive activation and downstream injury.
Occupational Exposure	Exposure to physical, chemical, or environmental hazards that occurs as part of routine work activities. In blast contexts, this includes repeated low-level blast exposure accumulated over time through training or operational duties.
Overpressure	A rapid rise in pressure above normal atmospheric levels produced by an explosive shock wave. It is a key physical driver of blast effects on the body, particularly the lungs, ears, and brain.
PET – Positron Emission Tomography	Positron Emission Tomography (PET) is a neuroimaging technique that uses radiolabelled tracers to measure metabolic activity, blood flow, or molecular processes in the brain.
PPE – Personal Protective Equipment	Protective gear worn to reduce exposure to hazardous forces or environments. In blast settings, it aims to lessen the impact of pressure waves and debris on the body and head.
Proteomic Markers	Patterns of protein changes in blood, cerebrospinal fluid, or tissue that reflect biological responses to injury. After blast exposure, they can indicate oxidative stress, disruption of synaptic function, or damage to cellular structural proteins.
PTSD – Post-Traumatic Stress Disorder	A trauma-related mental health condition characterised by intrusive memories, hyperarousal, avoidance, and negative mood or cognition changes. It commonly co-occurs with blast exposure and can contribute substantially to overall symptom burden and functional impairment.
rLLB – Repetitive Low-Level Blast	Repeated exposure to relatively low-intensity blast pressure waves occurring over time, often during training or occupational activities. Although each exposure may be sub-injurious alone, cumulative effects may contribute to neurological and systemic changes.
ROB 2.0	ROB 2.0 (Risk of Bias 2.0) is a standardized tool used to assess the risk of bias in randomised controlled trials across domains such as randomisation, deviations from intended interventions, missing data, outcome measurement, and reporting.
ROBINS-I	ROBINS-I (Risk Of Bias In Non-randomized Studies of Interventions) is a structured tool used to assess bias in observational and other non-randomised studies by comparing them to an ideal randomised trial across multiple bias domains.
Salience	Salience refers to the brain's process of identifying and prioritising stimuli that are biologically or behaviourally significant
Sensorimotor Function	The integrated processes that link sensation (such as vision, balance, and touch) with movement control and coordination. Animal blast studies show it can be altered after exposure, reflecting disrupted neural pathways involved in balance, gait, and motor performance.
Shock Tube	Laboratory device generating controlled blast waves for experimental studies.
Synaptic Markers	Proteins that support communication between nerve cells and maintain synapse structure and function. After blast exposure, changes in these proteins (such as postsynaptic density protein 95) can indicate synaptic disruption and impaired neural connectivity.
SYRCLE	SYRCLE is a risk-of-bias assessment tool adapted from the Cochrane framework for evaluating bias in animal intervention studies.

Tau (Total / Phosphorylated)	Tau is a neuronal structural protein that stabilises the internal scaffolding of nerve cells. When tau becomes abnormally phosphorylated it can detach and aggregate into neurofibrillary tangles linked to neurodegenerative disease.
TBI – Traumatic Brain Injury	Injury to the brain caused by external forces, including blast.
TBICoE – Traumatic Brain Injury Center of Excellence (United States)	A United States organisation that leads research translation and produces clinical guidance for traumatic brain injury, including blast-related injury and exposure. It provides evidence-informed resources to support assessment, management, and operational policy in military and related settings.
TES – Traumatic Encephalopathy Syndrome	Traumatic Encephalopathy Syndrome (TES) is a clinical syndrome used in research to describe persistent, progressive cognitive, mood, or neurological symptoms seen in some people with a history of repetitive head impacts, when no better explanation is found. It is not a definitive disease diagnosis and does not confirm chronic traumatic encephalopathy (CTE), which can currently only be diagnosed after death. The causative factors are not fully established - repetitive head impacts are considered a necessary exposure, but whether and how they cause TES is uncertain, and symptoms overlap substantially with other conditions such as PTSD, depression, and neurodegenerative disease.
TRICARE	TRICARE is the United States (US) Department of Defense health care program providing medical coverage for active-duty service members, retirees, and their families.
Urinary Biomarkers	Metabolic markers excreted in urine (e.g., HVA, glutamate, linoleic acid).
US SOCOM	United States Special Operations Command
Vestibular	Vestibular refers to the sensory system that detects head movement and spatial orientation, contributing to balance, posture, and stable visual perception.
Warfighter Brain Health	US Department of Defense strategic framework emphasising cumulative lifetime brain health monitoring.
White matter tracts	White matter tracts are bundles of neurons that connect different brain regions, enabling efficient communication and information transfer across neural networks
White-Matter Integrity	The structural health of the brain’s long-range axonal pathways that connect different regions. It is commonly assessed using diffusion tensor imaging, which can detect microstructural disruption after blast exposure.

Introduction

Background

Exposure to repetitive low-level blasts has become a pressing concern in both military and certain occupational settings, where individuals routinely encounter the subtle shockwaves generated by weapons systems or explosive devices (1–5). Unlike severe blast exposure, these lower-intensity events do not typically produce overt injuries or immediate clinical signs of trauma. However, growing evidence suggests that cumulative effects from repeated low-level blasts may have a measurable impact on brain function (3,6–12). Such repeated exposure may lead to subtle but significant disruptions in physiology, cognition and behaviour potentially increasing the risk of long-term neurological outcomes.

Despite the growing recognition of this issue among military personnel and leaders, the existing scientific literature on repetitive low-level blast exposure and potential cognitive outcomes remains limited and variable in quality. Researchers have employed multiple assessment tools, populations, and study designs, making it challenging to draw definitive conclusions. This rapid review seeks to compile and critically appraise recent scientific literature to understand advancements in knowledge that can inform prevention, diagnosis, and management of military personnel exposed to repetitive low-level blasts.

Project context

Both repetitive low-level blast (rLLB) exposures and sport-related concussion have been associated with potential cognitive changes, yet the evidence bases for these two types of mild traumatic brain injury (mTBI) exposures differ in size, maturity, and methodological consistency. Research on sport-related concussion is more extensive and has benefited from decades of growing public and scientific interest, particularly in relation to contact sports such as American and Australian football, ice hockey, and rugby union/league. Large-scale cohort and longitudinal studies focused on athletes have started to investigate a range of short term issues including cognitive performance, symptoms experienced by players (e.g., headache, dizziness, memory problems), and aim to report on long-term outcomes such as chronic mental and physical disease, or brain specific outcomes such as Traumatic Encephalopathy Syndrome (TES) or chronic traumatic encephalopathy neuropathological change (CTE-NC)(8,13–30). As a result, relatively robust clinical guidelines exist for the prevention, identification, immediate management, and return-to-play protocols for concussion in athletes. In contrast, the literature on repetitive low-level blast exposure is comparatively smaller and less cohesive. Studies often involve specific military roles or law enforcement populations with unique stressors and complex exposure histories, including concussion from sport, making it extremely challenging to isolate blast-specific effects. While some investigators have reported subtle but persistent cognitive deficits, such as impaired attention, executive dysfunction, or slowed processing speed, the data remain more varied, and standardised surveillance, diagnostic and management protocols are not yet firmly established (1,2,31–33).

Despite differences in scale, both bodies of literature (sports related concussion and low-level blast) suggest that repeated, subclinical head impact is associated with potential long-term dysfunction. In both contexts, repeated exposures may cause latent or subtle changes that do not always present as overt concussions or injuries but could manifest as subtle deficits on cognitive tests or imaging markers. However, the physical mechanisms and clinical presentation differ. Sport-related concussion typically involves direct impacts (e.g., head collisions with other players, falls onto the ground) and rotational forces on the brain, while low-level blast exposures involve rapid pressure changes that stress the brain through unique pathways (e.g., shockwaves). Moreover, while sport-related concussion research increasingly incorporates advanced imaging and fluid biomarkers, the application of these tools in the study of rLLB exposure remains limited.

Overall, the evidence bases share key insights about the importance of recording exposure and cumulative risk but differ in their scope, standardisation of methods, and clarity regarding definitive outcomes, highlighting a need for more systematic and methodologically robust investigations.

Review aims and scope

The purpose of this Rapid Evidence Assessment (REA) was to review the key evidence concerning rLLB and its physiological, neurological, cognitive and behavioural effects on humans.

The aims of this project were to:

1. Systematically review the contemporary evidence base (peer-reviewed and grey literature).
2. Assess the quality of the evidence base.
3. Identify gaps in the evidence base, that are particularly relevant to DVA, its clients, and stakeholders.
4. Highlight areas for future research that address the identified gaps.

Approach and Methods

Collaborative scoping

There are potentially broad impacts of exposure to rLLB on humans, encompassing physiological, neurological, cognitive, and behavioural effects. UNSW have refined the scope of the REA and organised the questions posed by DVA into 14 key areas of focus (Figure A6.1, Appendix 6).

Emerging evidence concerning collision-sport-related mTBI (some of which is diagnosed as concussion) emphasises the importance of a holistic approach to patient care across the lifespan of an exposed individual (Figure A6.1, Appendix 6). Reflecting this, the REA has been modelled on a holistic approach to patient care, intended not only to offer the best outcomes for DVA, but also to establish a strong foundation on which to develop future policy. Our understanding of collision-sports-related head impacts provides insights into potential similar areas of impact following repetitive blast:

1) Selected cohorts of athletes appear to have pre-existing vulnerabilities to the consequences of repeated head-impact events. Subgroups within athlete populations do appear to have higher rates of cognitive impairment. However, inclusion in higher-risk groups generally only becomes clear after the consequences of long-term exposure develop later in life.
2) Certain types of head-impact mechanisms and exposures in collision sports appear to be associated with higher rates of certain cognitive impairments and neuropathological changes over time.
3) Dose-response data could support the importance of cumulative doses of head-impact events, and potentially magnitude of exposure. However, the evidence on dose-response is still immature and sometimes contradictory.
4) Identification and diagnosis of clinically relevant head impacts in individuals is challenging. Many sport systems have adopted a precautionary approach to syndrome identification (e.g., Sports Concussion Assessment Tool, SCAT).
5) The evidence on associations between repeated head-impact events and longer-term sequelae (e.g., Chronic Traumatic Encephalopathy Neuropathological Change, CTE-NC) remains inconclusive.
6) Numerous overlapping and confounding factors exist between typical head-impact syndromes (e.g., cognitive effects such as conditions associated with CTE-NC) and other cognitive disorders related to age or circumstance (including depression, dementia, and substance use). These complexities make it challenging to establish a definitive link between head-impact events and chronic cognitive conditions, which also tend to emerge with advancing age in comparable populations.

Research Questions

Overall research focus:

- The emerging literature on low-level blast (LLB) overpressure exposure.
- The established literature on the assessment and treatment of blast-caused cognitive impairment.

Building on this focus and following the conceptual framework presented in Figure A6.1 (Appendix 6), UNSW have refined the REA scope to address a series of detailed questions derived from these overarching themes (Table 1).

Table 1 Research questions addressed in the review, aligned to their thematic area

Research Questions	
Definitions	• How is LLB overpressure exposure defined? • What criteria are used to define repetitive LLB (rLLB) overpressure exposure (e.g., duration/frequency/intensity of exposure)?
Metrics and Assessment	• What assessment process is recommended for individuals presenting with acute or chronic cognitive signs and symptoms associated with rLLB exposure? • What is the reliability and validity of the cognitive assessments designed to assess the acute or chronic signs and symptoms associated with rLLB overpressure exposure with respect to: (i) clinical history; (ii) alternative diagnoses; and (iii) comorbid diagnoses?
Occupational Exposures	• Which military roles are associated with higher levels of rLLB overpressure exposure during: (i) training; and (ii) deployment?
Protective Factors	• What individual, occupational, or environmental factors may protect against the development of cognitive impairment following rLLB overpressure exposure?
Vulnerabilities	• Does rLLB overpressure exposure increase susceptibility to clinically diagnosed neurological, psychiatric, or medical conditions?
Mechanisms of Injury	• What are the mechanisms by which rLLB overpressure exposure is proposed to affect cognitive functioning in humans? • What brain structures and cognitive processes are affected by rLLB overpressure exposure in humans (i.e., associated neuropathology, neuroimaging, and biomarkers)?
Underlying Neuropathology	• What is the underlying neuropathology associated with rLLB overpressure exposure in humans?
Assessment	• How are cognitive changes assessed following rLLB overpressure exposure?
Cognitive Change	• What acute cognitive signs and symptoms are associated with rLLB overpressure exposure in humans? • What chronic cognitive signs and symptoms are associated with rLLB overpressure exposure in humans?
Differential Diagnosis	• How can rLLB-related symptoms be distinguished from other cognitive or psychiatric conditions (i.e., differential diagnosis)?
Associations and Confounders	• Is there any evidence that rLLB overpressure exposure is associated with mTBI (or signs and symptoms of same) in humans?

Research Questions	
	• Is there any evidence that rLLB overpressure exposure is associated with neurodegenerative conditions (or signs and symptoms of same) in humans?
Treatment	• What treatment or management strategies are recommended for individuals presenting with acute or chronic cognitive signs and symptoms associated with rLLB exposure? • What is the safety and efficacy of the treatment or management strategies for individuals presenting with the acute or chronic signs and symptoms associated with rLLB overpressure exposure?
Prevention	• What prevention strategies are proposed or used to reduce rLLB exposure or its effects?
Rehabilitation	• What rehabilitation approaches are used for rLLB-related cognitive impairment?
Whole of Life care and wellbeing	• What is known about long-term wellbeing and quality of life impacts for individuals with rLLB-related cognitive symptoms?
Quality Appraisal	• What is the quality and certainty of the evidence used to address the research questions?

Inclusion of both animal and human studies

Inclusion of animal studies can significantly enhance understanding of the underlying pathophysiological mechanisms associated with rLLB exposure, particularly where direct human evidence is limited or ethically unfeasible to obtain. Animal studies provide a controlled environment to isolate variables such as blast intensity, frequency, and interval; factors that are difficult to measure or replicate precisely in human studies. This approach allows more detailed investigation of how repetitive low-level blast (rLLB) exposure affects brain structure and function, including axonal injury, blood-brain barrier disruption, neuroinflammation, and accumulation of biomarkers such as tau protein. Although these changes can usually only be confirmed after death in humans by robust pathology methods, animal studies allow the underlying mechanisms to be tracked over time and experimentally modified, providing insight into causal pathways and disease progression that cannot be directly studied in people.

Animal studies also provide vital translational value when aligned with human clinical findings. For example, confidence in the biological plausibility of human symptoms is strengthened when behavioural outcomes or brain imaging (e.g., EEG, fMRI) for rLLB-exposed animals mirror the findings for rLLB-exposed humans (e.g., military breachers or law enforcement personnel). Including animal studies also supports the development of a plausible mechanistic bridge between subclinical exposure and long-term neurodegenerative risk, which may not yet be fully observable in longitudinal human cohorts. Therefore, incorporating animal studies, particularly those using well-validated models and exposure paradigms reflective of operational conditions, meaningfully complements human data and helps generate a more comprehensive and scientifically robust understanding of the risks associated with rLLB.

Animal studies were thus included in this REA.

Rapid Evidence Assessment Methods

Our approach (described in Appendix 1) utilised the well-known rapid evidence assessment (REA) methodology (34–36) and incorporated strategies aimed at enabling the efficient synthesis of information.

Results

Search Results

The various searches of the academic peer-reviewed literature (see Appendix 6) identified 3426 unique studies. Title and abstract screening was independently conducted by two reviewers, and conflicts were resolved by a third reviewer; 1806 studies were excluded. The remaining 1620 studies underwent independent full-text review by two reviewers, and conflicts were resolved via consensus. A total of 149 studies met all the REA inclusion criteria (Figure A1.1, Appendix 1).

Peer Reviewed Publications

A total of 149 peer-reviewed publications underwent data extraction, quality appraisal, content review, analysis and interpretation. The findings are presented below.

Basic Features of Included Peer-Reviewed Publications

Of the 149 included studies, eighty-one (81) involved humans, and sixty-eight (68) involved animals. Two studies involved both animals and humans within the same study.

Country, population, sample size, study setting, and year of publication are outlined in Appendix 3.

Characteristics of blast overpressures used in the studies

There was substantial variability regarding the blast overpressure characteristics employed during experimentation between animal and human studies, and between studies within these groups.

Blasts produced from explosions or military equipment exhibit a characteristic waveform. When referring to blast overpressure, the *peak overpressure* measurement is the standard number used to indicate the magnitude of the blast event. This is outlined in Figure 1[1]. Finally, blast overpressure can be reported in SI units (kilopascals or kPa) or pounds per square inch (psi). The conversion between psi to kPa is 1 psi = 6.89476 kPa.

[1] https://blastinjuryresearch.health.mil/index.cfm/blast_injury_101/science_of_blast

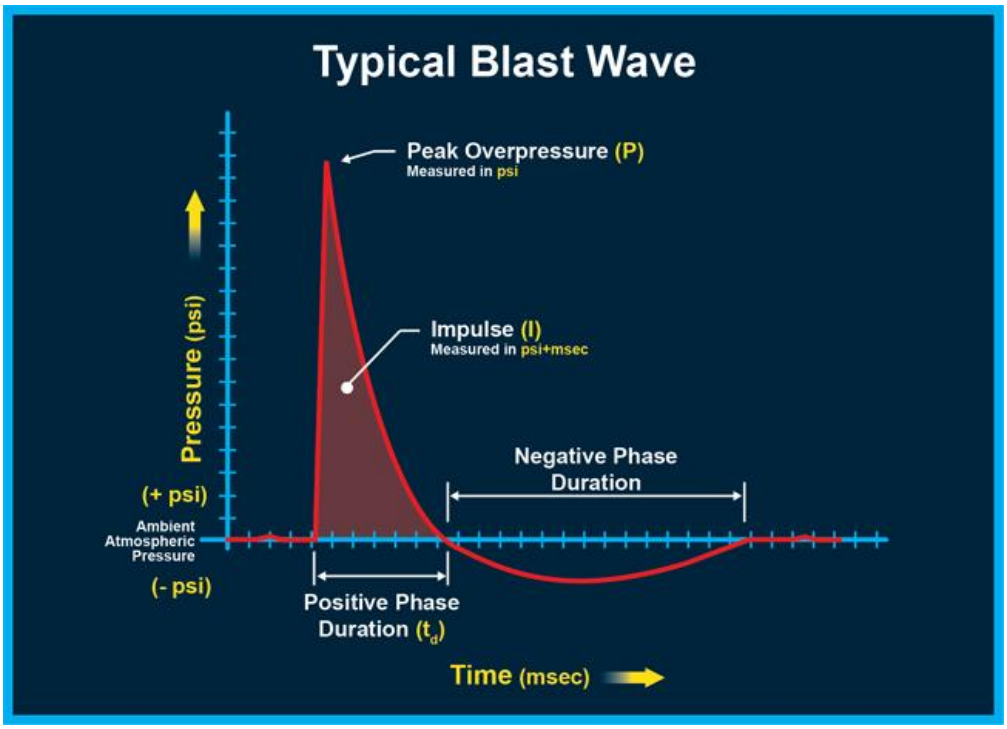

Figure 1 – Archetypal pressure profile produced from a single blast. Peak overpressure (measured in kPa or psi) is used as a marker of overall magnitude when comparing blast intensity.

Seventy-six (76) studies in human populations did not explicitly document levels of rLLB overpressure exposure. Blast overpressure was characterised using several approaches. These included inference from service records and training documentation, broad qualitative descriptions of exposure over defined periods (for example, breachers or training instructors), and self-report by study participants, which in some cases occurred long after the exposure event. The actual exposure levels in the study populations can only be inferred approximately from qualitative intensity and frequency descriptors, underscoring the imprecision that commonly arises in the absence of objective exposure recordings. By contrast, animal studies purporting to study low-level blast generally utilised a far wider range of blast overpressures. This is shown in Figure 2.

For studies where blast overpressure was explicitly recorded, there was substantial variability in exposure. Where specified, human studies utilised overpressures significantly lower than animal studies, approximately in the 4-6 psi range. Blast overpressure is a numerical representation of a complex pressure wave travelling through air and impacting on physical objects in the environment (such as humans, equipment etc). Distance from the source of the blast wave determines the intensity of blast imparted on the object or human, complicated by environmental factors such as reflection and summation of blast waves from surfaces and objects.

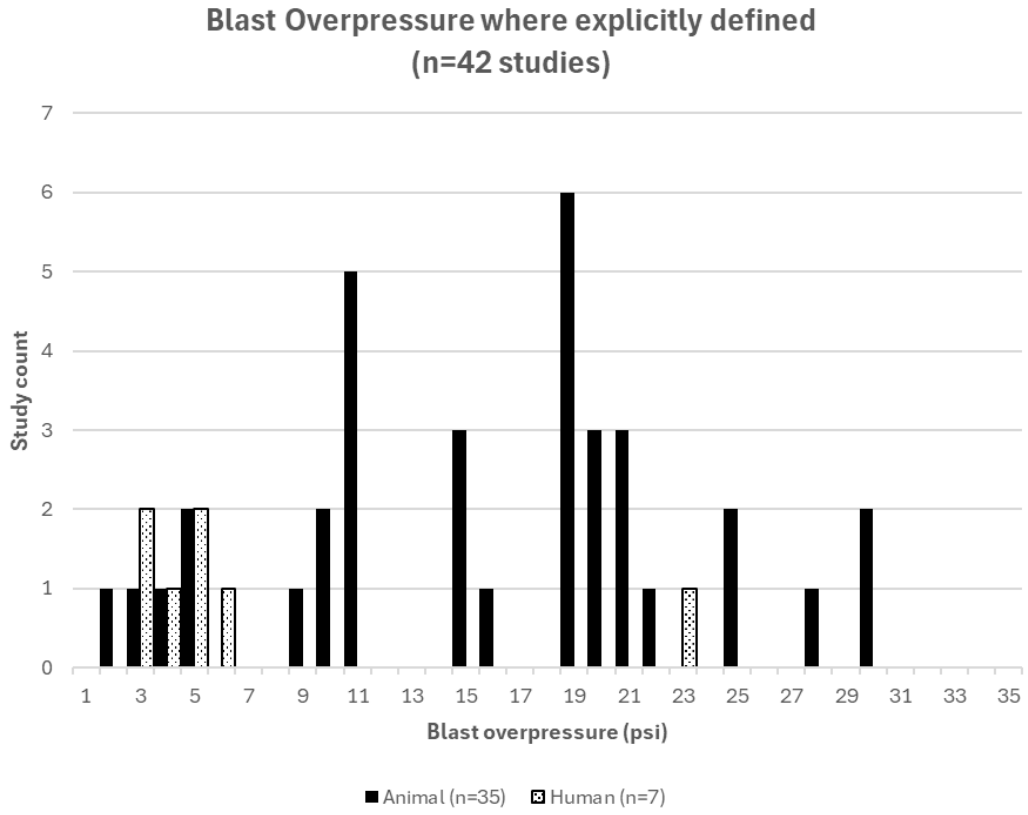

Figure 2 – Study count vs blast overpressure used in studies where blast intensity is explicitly defined (n=42 studies).

Quality of Included Peer-Reviewed Publications

Limitations in Design and Execution (Risk of Bias)

- High risk of bias: 113
- Unclear/Some risk of bias: 16
- Low risk of bias: 20

Most peer-reviewed studies were judged to have a high risk-of-bias due to significant methodological limitations that reduced confidence in the study findings. The source of bias differed fundamentally between study types: animal studies had the capacity for rigorous experimental control but often fail to document it adequately, while human studies face observational design limitations regardless of reporting quality. Animal studies could theoretically improve through better methodology reporting, whereas human studies' observational nature meant some bias was inherent and unavoidable. Both study types shared the limitation of small samples. The combination of animal studies with reporting gaps and human studies with fundamental design constraints meant that very few studies in either category could achieve low risk of bias ratings, contributing substantially to the overall low certainty of evidence across the rLLB literature.

Animal Studies

Animal studies were largely judged to have high risk of bias, though the underlying reasons differed from human studies. The most common issues were inadequate reporting rather than fundamental design flaws: randomisation methods were frequently performed but not described in sufficient detail, allocation concealment was rarely mentioned, and blinding of caregivers and outcome assessors was often unclear or

absent. Small sample sizes (typically 4 to 8 participants per group) were standard for animal research but this introduces potential bias as the contribution of single data points to overall effect size estimates is much greater than experiments with larger sample sizes. Housing randomisation and environmental controls were inconsistently reported, creating concerns about confounding. The minority of animal studies rated as low risk explicitly described randomisation procedures, implemented blinding protocols, and provided complete outcome reporting following SYRCLE tool criteria. Overall, animal studies had the methodological infrastructure for rigorous design but often failed to transparently report key safeguards.

Human Studies

Human studies faced fundamental design limitations that inherently resulted in high risk of bias ratings. The overwhelming majority of studies were observational (many retrospective cohort designs) with no randomisation or blinding possible. The most critical and pervasive issue was reliance on self-reported blast exposure, introducing substantial recall bias and preventing objective dose-response assessment. Self-reported outcomes (symptoms, medical history) were common, compounding measurement error. Small sample sizes (often 20 to 50 participants) were typical in occupational cohorts. Many studies lacked appropriate control groups, enrolled convenience samples or volunteers (selection bias), and exhibited baseline differences between exposure groups on key confounders like age, years of service, and prior mild TBI history. High attrition in longitudinal studies and incomplete outcome data further compromised validity. The few human studies achieving stronger ratings were large administrative database studies with comprehensive medical records, objective outcomes like audiometry or neuroimaging, and robust statistical adjustment for confounders.

Inconsistency (Heterogeneity of Results)

- High inconsistency: 38
- Unclear: 49
- Low inconsistency: 62

Ratings leant toward being *low risk of inconsistency*, indicating generally strong consistency across studies, though a substantial proportion of unclear ratings still suggested some variability. The inconsistency profiles diverged sharply between animal and human research. Animal studies demonstrated mechanistic consistency, repeated blast reliably produced neuroinflammation, blood-brain barrier disruption, and behavioural changes, but with quantitative variability across protocols. Human studies showed a pattern of inconsistency, particularly the troubling dissociation between subjective complaints and objective performance, suggesting that self-report bias and psychological confounding substantially complicated interpretation. When animal and human findings were compared, the mechanistic pathways identified in animals (e.g., tau accumulation, microglial activation) did not always translate to detectable effects in humans, or human effects were only apparent in specific subgroups or measurement modalities. This cross-species inconsistency raised fundamental questions about translatability and whether controlled animal exposures adequately model real-world human rLLB. The convergence of findings across species on some outcomes (e.g., auditory damage, acute biomarker changes) provided stronger evidence than either study type alone, but the frequent divergence in chronic effects and functional outcomes indicates there are still substantial gaps in understanding how animal laboratory findings translate to human clinical populations.

Animal studies

Animal studies showed relatively low inconsistency, However, this was largely because most were single studies without opportunity for heterogeneity assessment (i.e., comparison to similar research). When multiple outcomes were measured within a single animal study, effects generally aligned in direction, for example, behavioural deficits co-occurred with histological changes and molecular markers. Comparisons

to prior animal literature also typically showed consistency in effect direction (e.g., blast exposure consistently increased anxiety-like behaviour, impaired cognition, and caused neuroinflammation), though the magnitude varied based on blast parameters, species, and timing of assessment. Regional and tissue-specific variability was noted (e.g. different brain regions showed different degrees of response) but this can be reflective of biological complexity rather than study inconsistency. Time-dependent effects were observed with some markers (e.g., acute inflammatory upregulation followed by chronic downregulation), potentially representing biphasic responses as opposed to inconsistency. The rare instances of high inconsistency in animal studies involved conflicting biomarker findings, such as some studies reporting cytokine increases while others found decreases, likely attributable to methodological differences in blast intensity, exposure protocols, or assay techniques.

Human studies

Human studies exhibited important inconsistency, with frequent contradictions between subjective and objective measures creating interpretive challenges. While individual studies often showed internal consistency (multiple outcomes pointing in the same direction), findings were inconsistent across studies. For example, self-reported symptoms that were consistently reported in blast-exposed groups were not matched with the same degree of consistency in cognitive testing, or effects disappeared when adjustment was made for factors such as concurrent PTSD and depression. The definition of blast exposure critically influences findings, with different thresholds, recall periods, and severity classifications yielding different effect magnitudes. Interaction effects were common, with blast effects appearing only in combination with psychological comorbidities, raising questions about independent effects. Biomarker studies showed particularly high inconsistency, with some reporting elevated inflammatory markers and others showing reductions, and peripheral blood markers often failing to correlate with neuroimaging findings. Effect sizes were generally small to moderate and varied substantially across studies using different exposure classifications. The most consistent finding was that psychological factors (PTSD, depression, sleep disturbance) were stronger predictors of outcomes than blast exposure alone, with blast often becoming a weak or non-significant predictor in adjusted models.

Indirectness (Population, Intervention, Comparator, Outcome - PICO)

- High level of indirectness: 124
- Unclear: 14
- Low level of indirectness: 11

Most studies displayed high levels of indirectness, indicating that differences in population, intervention, or outcomes was a major concern that limited the applicability of findings. Both animal and human studies suffered serious indirectness that prevented addressing causal questions about blast effects. Animal studies provided direct experimental control over exposure and clear temporal relationships, but modelling of blast exposure was imperfect. Human studies did not measure exposure objectively or were unable to isolate blast effects from confounding psychological, physical, and environmental factors. Triangulation across study types theoretically strengthens inference: mechanisms identified in controlled animal experiments that also appear in observational human studies gain credibility. However, the substantial indirectness in both domains means that even converging evidence must be interpreted cautiously. The proxy exposure measures in human studies are particularly problematic because they introduce misclassification that could either inflate spurious associations or mask true effects, fundamentally limiting the certainty of observational findings regardless of sample size or statistical sophistication.

Animal studies

Animal studies faced unavoidable and serious indirectness that universally warranted downgrading. An obvious fundamental issue is species difference: rodents, ferrets, and chinchillas are imperfect proxies for human neuroanatomy, physiology, and behavioural responses. Behavioural outcomes are indirect: “open field exploration time” is used to represent "anxiety," “elevated plus maze performance” is used for fear-related behaviours, and “novel object recognition” substitutes for memory, but these rodent behaviours only loosely correspond to human impairment. Molecular and histological endpoints (protein expression levels, cell counts, pathway activation) were mechanistic markers several steps removed from clinical symptoms or functional disability. While controlled blast exposures in shock tubes are standardised and reproducible, they differ substantially from chaotic real-world combat or occupational blasts in terms of pressure profiles, duration, body positioning, protective equipment, and concurrent stressors. Follow-up periods of weeks to months captured acute and subacute effects but could not model decades-long neurodegenerative processes. Ex vivo and in vitro models (organotypic brain slices, cultured cells) added another layer of indirectness by removing systemic physiological responses, immune interactions, and whole-organism homeostatic mechanisms.

Human studies

Despite studying the target population, human studies also have substantial indirectness due to proxy exposure measures that introduced uncertainty. The most common and problematic approach was using military occupational specialty (MOS; i.e. job role) as a surrogate for blast exposure, assuming breachers or mortarmen experience more rLLB than controls without measuring actual overpressure, impulse, or cumulative dose. Self-reported blast counts and severity ratings are subjective, prone to recall bias, and lack the precision needed for dose-response assessment. Study populations are highly specialised: nearly all studies focused on male, combat arms, military personnel (particularly breachers, special operations forces, or mortar crews), which well reflects our research question (though notably limits generalisability to women, civilians, athletes, or other blast-exposed populations). Outcomes frequently involved surrogate measures rather than clinical endpoints: biomarker concentrations indicated change but this is not necessarily clinically important; neuroimaging metrics showed structural differences but not functional impairment; symptom questionnaires captured complaints but not objective performance deficits. Cross-sectional designs could not establish temporal relationships between exposure and outcome. Long latency between exposure and assessment in veteran studies (often years or decades) introduced uncertainty about attribution, with intervening experiences potentially confounding observed associations. Military-specific outcomes like administrative separation or deployment-related diagnoses had limited applicability beyond military contexts.

Imprecision (Sample Size and Confidence Intervals)

- High level of imprecision: 117
- Unclear: 13
- Low level of imprecision: 19

In this section, most studies were rated as having a high level of imprecision (e.g., small sample sizes, wide confidence intervals). Imprecision was a universal problem across both animal and human studies, but its implications differed. In animal studies, imprecision was problematic but partially mitigated by experimental control: large effect sizes and consistent patterns across related outcomes provided some confidence despite small samples and absent confidence intervals. In human studies, imprecision was more damaging because it was combined with high heterogeneity, confounding, and measurement error, creating profound uncertainty about true effect sizes. The small effects typical of observational blast exposure studies require

large samples for precise estimation, yet most studies were severely underpowered. The absence of confidence intervals in both animal and human studies was a critical reporting failure that prevented proper evidence synthesis and GRADE assessment: reviewers repeatedly noted they could not determine if estimates crossed thresholds because no confidence intervals were provided. When animal studies with large effect sizes but small samples showed similar directional findings to human studies with small effect sizes but larger samples, the convergence in findings somewhat increased confidence. However, the overall imprecision across the literature meant that precise estimates of effect magnitude were unavailable, and dose-response relationships poorly characterised. This pervasive imprecision necessitated downgrading certainty for virtually all outcomes and limited the ability to make quantitative risk assessments or set exposure thresholds.

Animal studies

Animal studies consistently showed imprecision despite some studies having adequate sample sizes by animal research standards. The typical study included 4 to 8 animals per group, which is conventional for mechanistic research but provides limited statistical power for detecting small effects or interactions. The most critical and near-universal problem was the absence of confidence intervals: nearly all animal studies reported only p-values and means with standard errors or standard deviations, preventing assessment of effect magnitude precision and whether confidence intervals crossed clinically meaningful thresholds. Effect sizes were often not quantified, with results described qualitatively ("increased," "decreased") without standardised metrics. High within-group variability (large SEMs relative to means) was common, reflecting individual animal differences and/or measurement error. Multiple comparisons across brain regions, timepoints, and outcome measures were frequently performed without statistical correction, inflating Type I error risk. Subgroup analyses (e.g., sex-stratified results with 3 to 4 animals per group) were severely underpowered. Sample size justifications and power calculations were virtually never provided. The minority of well-conducted animal studies with low imprecision featured larger samples (15 to 20 per group), narrow standard errors, large effect sizes (e.g., 25% to 40% neuronal loss), and consistent effects across multiple related outcomes that reinforced confidence in findings.

Human studies

Human studies demonstrated severe imprecision that limited interpretability. Sample sizes overwhelmingly fell below the threshold for precision in observational research (i.e., 300 participants), with studies including 30 to 100 participants (and some pilot studies having fewer than 20 participants). Confidence intervals were rarely reported with investigators typically presenting only p-values, preventing readers from judging whether effects were precisely estimated or if confidence intervals crossed null effects or minimum clinically important differences. When confidence intervals were reported, they were frequently wide and often included the null value, indicating substantial uncertainty. Effect sizes tended to be small with considerable overlap between groups, such that wide confidence intervals often included both benefit and harm. Subgroup and interaction analyses were pervasive but critically underpowered; studies attempted to examine effect modification by APOE genotype, sex, PTSD status, or blast severity with sample sizes inadequate for detecting interactions. High variability in key variables compounded problems: self-reported blast exposure counts had standard deviations exceeding means (e.g., mean 337 ± 984 blasts), and symptom severity showed enormous individual differences. Low event rates for specific outcomes (e.g., diagnosed TBI, seizures) provided insufficient events for precise risk estimates. The few human studies with low imprecision were large administrative cohorts (>1000 participants) reporting narrow confidence intervals for common outcomes.

Publication Bias

- High risk of publication bias: 32
- Unclear: 19
- Low risk of publication bias: 98

Most studies had a low risk of publication bias, indicating relatively strong confidence that publication bias is not a major concern in this topic, though some high and unclear ratings warrant caution. Publication bias concerns pervaded both animal and human blast TBI research, primarily reflecting structural problems in the research ecosystem rather than detected fraud or intentional suppression. The universal absence of prospective study registration eliminated the most effective safeguard against selective reporting, making it impossible to determine if unpublished studies with null results existed. The small sample sizes used throughout the field increased the likelihood that published studies over-represent chance positive findings. Military and government sponsorship raised theoretical concerns about research priorities and framing of findings, though reviewers rarely identified specific evidence of sponsor-influenced distortion. The combination of multiple methodological limitations (small samples, no randomisation, proxy measures) with publication bias concerns meant that the published literature likely presents a distorted view of rLLB effects. However, publication bias was difficult to assess using traditional methods like funnel plots because outcomes were heterogeneous, studies not meta-analysable, and sample sizes uniformly small rather than showing asymmetry. The impact of publication bias on overall certainty was generally to add one additional downgrade to already very low or low certainty evidence, reinforcing caution in interpretation but rarely changing conclusions about the serious methodological problems already present. Importantly, despite these concerns, the published literature included many null findings and negative results, suggesting suppression was not occurring, though selective emphasis on positive findings within papers and preference for publishing studies with at least some significant results were likely.

Animal Studies

Animal studies tended to be high risk or unclear risk of publication bias, driven primarily by absence of study registration rather than detected reporting bias. Protocol registration for animal experiments was essentially non-existent, no studies were prospectively registered in repositories, eliminating the transparency that allows for detection of selective outcome reporting or suppressed negative results. Small sample sizes (typically 20 to 40 animals total across groups) increased susceptibility to small-study effects and selective publication of positive findings. Many studies were funded by national governments or military agencies. While such funding may create incentives to prioritise military-relevant outcomes or interpretations, no overt sponsor involvement in study design, analysis, or reporting was evident. Multiple outcomes were typically measured (e.g. behavioural, molecular, and histological), creating opportunities for selective emphasis on statistically significant findings. However, most studies appeared to report all measured outcomes, although it was not possible to independently verify whether these reflected all *a priori* planned measures in the absence of prospectively registered study protocols. The absence of data sharing plans and supplementary materials prevented independent verification. Industry conflicts of interest were rare but notable when present (e.g., authors with commercial interests). Despite these structural concerns, most animal studies showed no clear evidence of selective reporting within the published manuscript: planned outcomes in methods sections appeared to be reported in results, and some studies transparently reported negative findings. The general scientific literature problem of publication bias favouring positive over negative results applied, with failed experiments unlikely to be published, but this was impossible to quantify without trial registries.

Human Studies

Human observational studies similarly lacked protocol registration, though some prospective cohort studies provided methodological papers describing planned analyses. Small sample sizes and pilot study designs created high susceptibility to selective reporting and publication of positive findings. Government, military, and US Department of Veterans Affairs funding was common, with potential influence on reporting priorities; reviewers noted potential for bias in military-sponsored research, though this was speculation rather than detected suppression. Self-report bias in exposure and outcome assessment could inflate associations, potentially favouring publication of spurious positive findings. Studies with significant results in preliminary analyses were more likely to be expanded and published, while those with null findings might remain unpublished, though this publication bias cannot be quantified. Selective outcome emphasis was more detectable in human studies: significant symptom findings were highlighted while null cognitive test results were relegated to supplementary materials or mentioned briefly. Proxy exposure measures (occupational specialty) introduced systematic uncertainty that could drive both false positives and false negatives. Large administrative database studies with more complete reporting and pre-specified analyses showed lower risk. Overall assessment was typically "some concerns" or "high risk" due to lack of registration and small samples, but rarely was actual suppression of data or selective reporting definitively identified.

Overall GRADE Rating

- Very Low: 129
- Low: 18
- Moderate: 2

The overall evidence base for rLLB demonstrated *very low* to *low* certainty across both animal and human study types, with critical limitations that prevented strong conclusions. Only two studies were rated *moderate* certainty of evidence. Animal studies universally faced indirectness barriers that made very low certainty the ceiling regardless of methodological quality, while human studies faced the insurmountable problem that experimental manipulation was unethical, forcing reliance on observational designs with attendant confounding and self-report bias. The parallel evidence streams theoretically strengthened inference through triangulation: findings in controlled animal experiments that also had high similarity and correlates in human observational studies gained credibility and supported the emergence of consensus and scientific agreement on a particular area of enquiry (e.g. mechanism of injury or outcome). However, this convergence could not overcome the fundamental uncertainties within each study type, and the frequent divergence in findings (especially for chronic effects and functional outcomes) added to uncertainty rather than resolving it. The consistency with which studies were downgraded across multiple GRADE domains meant that even large bodies of research on specific topics accumulated into very low certainty evidence. For example, multiple animal studies on neuroinflammation and multiple human studies on post-concussive symptoms still yielded very low certainty conclusions because no amount of replication could overcome the proxy measures and observational designs. The practical implication was that the rLLB literature, despite substantial research investment, remains in an early phase characterised by hypothesis generation, biological plausibility assessment, and association detection rather than definitive causal inference or quantitative risk assessment. Future research achieving higher certainty requires prospective human cohorts with objective blast dosimetry, comprehensive adjustment for confounding, validated clinical endpoints, and adequate sample sizes.

Animal Studies

Animal studies uniformly achieved very low certainty ratings (approximately 95%), with a small minority (5%) rated as low certainty. Animal studies started at low certainty, then were typically downgraded for risk of bias

(unclear randomisation, lack of blinding, small samples), downgraded for indirectness (species difference, proxy behavioural outcomes, controlled exposures unlike real-world blast), and downgraded for imprecision (small samples, no confidence intervals). Publication bias sometimes added additional concern. Even the best-designed animal studies with explicit randomisation, blinded assessment, adequate samples, and complete reporting still faced unavoidable indirectness that precluded higher certainty in outcomes. The very low certainty rating reflects the fundamental limitation that animal models provide mechanistic insight and biological plausibility but cannot definitively establish effects in humans. Reviewers consistently framed animal findings as "hypothesis-generating", providing "mechanistic insight but limited clinical applicability", showing "uncertain translation to humans", and requiring "validation in human studies". The value of animal studies is that they allow controlled manipulation of exposure variables, ability to examine tissues and pathways inaccessible in living humans and establishing biological plausibility but these strengths could not overcome the inherent limitations. The few animal studies reaching low certainty featured large samples, comprehensive outcome batteries, transparent methods, and findings consistent with prior research.

Human Studies

Human studies were also most often rated *very low* (approximately 85%). Observational studies started at low certainty, then accumulated downgrades: for risk of bias (no randomisation, self-report exposure and outcomes, confounding, selection bias), for indirectness (proxy exposure measures, specialised populations, surrogate outcomes), and for imprecision (small samples, no confidence intervals, small effect sizes with wide uncertainty). The cumulative result was that typical human observational studies with 30 to 100 participants, self-reported blast exposure, symptom outcomes, and cross-sectional design received very low certainty ratings. The human studies that were stronger (low certainty) were large administrative cohorts (>1000 participants) with comprehensive medical records, multiple exposures and outcomes, robust statistical adjustment, and consistent findings that withstood sensitivity analyses; the residual uncertainty came from observational design limitations, proxy exposure measures, and inability to establish causality. The two studies achieving moderate certainty were: Belding 2020b (37), which examined self-reported concussion symptomology during deployment-level blast exposure; and Stromberg 2023 (38), which examined mild traumatic brain injury and PTSD symptom severity. These studies featured large samples with adequate power, used validated instruments, controlled for key confounding variables, showed clinically meaningful and consistent effects, and had relatively narrow confidence intervals, though the observational design and reliance on self-report precluded high certainty.

Findings in Human Studies

Overview of Study Designs and Populations

A total of eighty-one (81) studies involved humans. Two (2) of these studies also involved animals in the same study. Seventy (70) were observational designs (51 prospective, 19 retrospective), with additional cross-sectional and case-control studies and a smaller group of randomised or quasi-experimental studies embedded in training settings (e.g., different protective equipment or load conditions) (1,37,39–47).

Participants were primarily:

- Active-duty military personnel in combat arms roles or high blast-risk Military Occupational Speciality (MOS; e.g., infantry, breaching, artillery, mortarmen, special operations) (4,5,42,48–51).
- Veterans with deployment-related concussion or blast histories (3,38,52–57).
- Specific training school cohorts such as students and instructors on breacher or heavy weapons courses (58–65).
- Special operations personnel, notably CANSOF, with high-intensity, and varied blast histories (48,49).

Sample sizes ranged from small pilot mechanistic cohorts (tens of participants) up to large administrative cohorts of hundreds of thousands of service members (37,39,41,42,44).

Blast Intensity, Frequency, and Dose-Response

Explicit Overpressure Magnitudes

Among studies that reported explicit overpressure values, peak incident pressures typically ranged from 1 to 6 psi for most training-level exposures, with some scenarios reaching 10 to 12 psi, and occasional higher exposures around 20 psi in more intense or less mitigated settings (1,6,46,47,59,66,67).

- Very low peaks (< 3 psi) were seen in some training and equipment-comparison studies, often with repetitive exposures within a session (1,66,68).
- Moderate low-level exposures (4 to 6 psi) were typical of many structured breaching evolutions, heavy weapon firing, or controlled low-level blast simulations (6,46,59,67).
- Higher "low-level" exposures (10 to 12 psi) and a small number around 20 psi occurred in less mitigated or close-proximity breaching contexts (47).

Single vs Repetitive Exposures

Several field and training studies contrasted single with repetitive blast exposures within individuals or across groups:

- Single-blast exposures at low intensities (intensity was inferred from participant self-report, role and context such as training-related blasts or heavy weapons use, and was most likely to be in the 1 to 4 psi range).These produced small, transient changes in symptoms (such as hearing changes, headache, balance, dizziness and nausea), cognitive performance, and biomarkers, often returning towards baseline within hours to days (6,61,69).
- Repetitive blasts, even when each event was individually low-level, were associated with larger cumulative deviations in biomarkers, eye-tracking and balance measures, and symptom burden (such as hearing changes, balance disturbance, headache, memory disturbance, fatigue, changes in mood) over the course of training cycles or careers (1,5,46,47,58–60,67,70). In these studies, overpressure ranges were inferred from self-report, role and context such as training related blasts or heavy weapons use but were likely to be in the 1 to 4 psi range.

Across several cohorts there was evidence of a dose-response pattern, where higher cumulative blast counts, cumulative impulse (total amount of overpressure imparted on the person, not just magnitude of peak overpressure), or longer time in high-risk roles were associated with:

- Higher likelihood of persistent neurobehavioral symptoms and psychiatric diagnoses (4,39,41,42,44).
- Greater biomarker elevations and more pronounced or widespread neuroimaging changes (5,11,45,47–49,59,60,71).

Results by Cohort Type

Breachers and Explosive Entry Personnel

A substantial body of evidence came from breacher and explosive entry cohorts, including trainees, instructors, and frequent breaching roles (defined as the use of explosives to gain entry to confined spaces such as buildings; e.g., special forces, engineers) (11,32,45,47,59,60,62–66,72).

Acute effects:

- Immediately post-training, breachers showed increases in blood biomarkers associated with axonal injury and astroglial activation, particularly tau and neurofilament light (47,59,60,72).
- Eye-tracking and balance measures, where assessed, demonstrated subtle decrements immediately following heavy training days (5,73).
- Symptomatically, headache, transient dizziness, and cognitive "fog" were commonly reported after intensive courses (62,63,74).

Chronic/career effects:

High-career breachers and instructors consistently had higher cumulative blast counts and impulses and showed:

- More frequent and severe chronic headaches, irritability, sleep disturbance, and concentration problems than comparison groups (1,63,74).
- Persistent elevation of axonal and inflammatory biomarkers and altered immune or autoantibody profiles, suggesting chronic neuroimmune activation (11,45,46).
- Neuroimaging evidence of microstructural white matter disruption and altered connectivity, particularly in frontal and subcortical networks (5,32,57).

Mortarmen, Heavy Weapons, and Long-Gun Overpressure

Studies focusing on mortarmen, heavy weapons operators, and rifle overpressure showed that rLLB from large-calibre weapons was associated with:

- Increased serum amyloid-beta peptide following repeated .50-calibre rifle overpressure, suggesting serum amyloid-beta peptides may have potential as acute biomarkers of low intensity overpressure sequelae (67).
- Subtle but measurable changes in cognitive performance and balance, especially with repeated exposures over time or when operators also had deployment-related concussions (5).

These cohorts frequently overlapped with breacher roles, but the exposure profile tended to involve more frequent but slightly lower peak pressures (approximately 4 psi) compared with close-range breaching (generally above 4 psi) (5,67).

Special Operations and High-Risk Combat Arms

Special operations forces (e.g., CANSOF, US SOCOM) and other high-risk combat arms cohorts exhibited particularly complex exposure histories, with both training and operational blasts plus additional impact or concussive injuries (4,42,48–51).

In these groups:

- Resting-state and task-based MRI demonstrated altered functional connectivity in salience, default mode, and frontoparietal networks, with patterns that scaled with cumulative blast and concussion history (48,49,51,57).
- Longitudinal analyses showed progressive structural change in white matter tracts in some operators, consistent with cumulative microtrauma (5,49,75).
- Symptomatically, these cohorts had higher burdens of post impact symptoms (such as dizziness, headache, fatigue, visual changes, balance changes, hearing changes), PTSD, and affective dysregulation than lower-exposure comparators (4,38,42,53).

Veterans with Deployment Blast-Related mTBI

Several studies evaluated veterans with deployment-related mild TBI encompassing both repetitive and single blast exposures of low but varying intensity (including rLLB) (3,38,52–57).

Key findings included:

- Higher rates of chronic neurobehavioral symptoms (e.g., dysregulation, irritability, impulsivity) in veterans with blast-related mTBI compared with non-TBI or non-blast TBI controls; deployment-related mild TBI increased dysregulation scores and PTSD severity (38).
- PET imaging showing increased FDG uptake in specific basal ganglia regions (left pallidum) among veterans with blast-related mTBI, consistent with altered metabolic activity (56).
- Early PET and MRI studies suggesting regional amyloid accumulation or microstructural abnormalities in some veterans with chronic blast exposure and cognitive complaints (57,76).

Students vs Instructors in Training Settings

One longitudinal field study followed students and instructors undergoing controlled repetitive blast exposure (58).

- Students (low cumulative career exposure to repetitive and other intensity of blast) showed acute biomarker elevations across multiple time points (6, 24, and 72 hours post-exposure), which tended to return towards baseline over days.
- Instructors (high cumulative career exposure to repetitive and other intensity of blast) displayed higher baseline levels of several brain-injury related biomarkers and inflammatory markers, with smaller relative changes per training event but higher overall biomarker burden (58,64).
- Exposure frequency and blast counts are generally higher in instructors compared with trainees, consistent with a cumulative dose effect (58,64).

Outcome Domains

Symptoms and Clinical Diagnoses

Across large administrative cohorts and focused clinical studies, rLLB exposure and blast-related mTBI were consistently associated with a higher burden of neurobehavioural symptoms and diagnoses.

- Large-scale Marine and Army cohort analyses showed that personnel in high blast-risk Military Occupational Specialisations (MOS) had increased risk of subsequent mTBI diagnoses, post-concussive symptoms, and related medical encounters, compared with low-risk occupations (37,39–42,44).
- Veterans and active-duty personnel with histories of multiple mild TBIs, many of which were blast-related, had more severe PTSD and depressive symptoms, and cognitive complaints (3,4,52–55,74).
- In breacher and heavy-weapon cohorts, chronic headache, sleep disturbance, tinnitus, and irritability were more common in high-exposure personnel than in comparison groups or non-blast controls (45,47,63,74,77).

Cognitive, Neuropsychological, and Behavioural Performance

Exposure to rLLB can cause subtle brain changes that affect thinking, balance, and behaviour even without a diagnosed concussion. Researchers study cognitive, neuropsychological, vestibular, and behavioural functions to detect early impairments in memory, decision-making, coordination, and mood. These assessments help identify cumulative effects and guide prevention and intervention strategies.

Multiple studies examined neuropsychological function, executive function, vestibular function, and behaviour:

- In field and training settings, cognitive testing immediately following blast exposure frequently showed small but detectable decrements in processing speed, attention, dual-task performance, and balance, particularly after multiple exposures within a short window (5,43,61).
- Neuropsychological test batteries in chronically exposed veterans and operators identified subtle deficits in frontal-executive and attention domains, often co-occurring with psychiatric symptoms (50,51,78,79).
- Novel measures such as eye-tracking features and gait/sensorimotor metrics demonstrated changes across exposure periods, supporting the sensitivity of these tools to low-level blast effects (46,47,73).

In a large cohort, deployment-related mTBI was associated with higher dysregulation scores, and the interaction between mTBI and PTSD severity showed complex effects on neurobehavioural outcomes (38).

Neuroimaging (MRI, DTI, PET)

Neuroimaging can detect subtle structural and functional brain changes that may occur after rLLB exposure, even in the absence of clinical symptoms or diagnosed concussion. Imaging provides objective evidence of microstructural damage, altered connectivity, and metabolic changes that behavioural or cognitive tests alone may not reveal. This helps identify early markers of cumulative injury, supports understanding of underlying mechanisms, and informs prevention and rehabilitation strategies. A substantial subset of studies used structural and functional neuroimaging to characterise blast effects.

- DTI and advanced tractography studies reported reduced white matter integrity and altered fibre organisation in veterans with repetitive blast exposure, often in frontal and interhemispheric tracts (5,57,75,80).
- Resting-state fMRI in special operations cohorts revealed altered connectivity in networks subserving attention, salience, and default mode, with associations to both cumulative blast exposure and symptom severity (visual changes, dizziness, headache, balance changes, fatigue, mood changes) (3,48,49,51,55).
- PET imaging showed:
    - Increased FDG uptake in basal ganglia structures among blast-related mTBI veterans (56).
    - Early amyloid PET signals in some chronically exposed veterans with cognitive complaints, though with very low certainty due to small samples and risk of bias (76).

Overall, imaging results indicate structural and functional alterations associated with repetitive blast exposure, but causality and clinical significance remain uncertain due to confounding by concomitant impact injuries and psychological comorbidities (e.g. PTSD).

Biomarkers (Blood, Urine, and Molecular Profiles)

Biomarkers are examined to identify physiological and molecular changes that may signal brain injury or neuroinflammation following rLLB exposure, even when clinical symptoms are absent. Blood, urine, and other molecular profiles can reveal indicators such as neurofilament light, tau protein, or inflammatory cytokines, providing objective evidence of subtle neural damage and cumulative stress. These measures help track early biological responses, support risk assessment, and inform strategies for monitoring and intervention.

At least 20 human studies primarily targeted biomarkers of neural injury, inflammation, and neurodegeneration (6,11,12,43,45–47,56,58–60,66,67,72,76,81–84).

Axonal and astroglial markers:

- Acute increases in tau, neurofilament light (NFL), and GFAP were frequently reported after training blasts and repetitive exposure days, particularly in breachers and high-risk cohorts (47,58–60,84).
- In some cases, baseline levels of axonal and astroglial markers in highly exposed instructors or operators were already higher than in controls, suggesting cumulative or persistent effects (11,45,46,58).

Amyloid and neurodegeneration-related markers:

- Repeated low-level rifle overpressure was associated with increased serum amyloid-beta peptides, proposed as candidate biomarkers of impacts of low-level blast (67).
- Modelling work and PET/amyloid studies explored kinetics of amyloid-beta and related markers in chronically exposed veterans, though the evidence remains sparse and low certainty (76,83).

Immune, autoantibody, and metabolomic profiles:

- Brain-reactive autoantibody profiles and broader immune signatures were altered in repetitively exposed breachers, indicating possible chronic neuroimmune perturbation (11,71).
- A distinct metabolite signature in military personnel with blast exposure was reported (including shifts in lipid and neurotransmitter-related metabolites), but requires validation (66).
- Urinary biomarkers (including homovanillic acid, HVA, glutamate, and specific fatty acids) changed in the context of repeated low-level blast; some decreased (HVA, glutamate) while others increased (linoleic acid), suggesting potential peripheral markers of effects on the central nervous system (12).

Integrated Dose-Response Findings

Examining dose-response relationships can help to understand whether cumulative exposure to rLLB, measured through blast count, impulse, or composite dose scores, correlates with cognitive, neuroimaging, or biomarker outcomes. These analyses help determine thresholds for risk, identify patterns of cumulative burden, and inform exposure guidelines for operational settings.

Several analyses explicitly related cumulative exposure indices (blast count, impulse, or composite dose scores) to outcomes:

- Cumulative blast impulse predicted changes in neurobehavioural and symptom measures across training periods, supporting a quantitative dose-response association even within the low-level range (1).
- Administrative cohorts linked blast-risk MOS and deployment history to increased odds of subsequent mTBI, post-concussive diagnoses, and psychiatric conditions (37,39–42,44).
- Imaging and biomarker studies showed greater abnormalities with higher cumulative exposure; however, separating the effects of blast from impact TBI and psychological trauma remained challenging (5,45,49,57).

Interventional Studies

Two human studies investigated a field intervention that used jugular vein compression to reduce low-level blast impacts. Low-level blast models incorporating jugular vein compression neck collars demonstrated partial moderation of brain functional changes and white matter alterations, suggesting that mechanical modification of venous outflow and head biomechanics could reduce injury severity (85,86).

Cross-Cutting Patterns Across Studies

A synthesis of the REA findings from human studies (across blast intensity, study type, and cohorts) indicates that:

- Single low-level blast exposures (approximately 1 to 5 psi) in healthy trainees usually produced mild, transient changes in symptoms and objective measures.
- rLLB exposures (particularly in career breachers, special operations, and heavy-weapon operators) were associated with cumulative abnormalities in:
    - Symptom burden (headache, sleep, cognitive and mood symptoms).
    - Cognitive, vestibular, and behavioural performance.

    - Structural and functional neuroimaging.
    - Blood, urine, and immune biomarkers of neural injury and inflammation.
- Large cohort data suggest increased risk of clinically recognised mTBI and neuropsychiatric diagnoses in high blast-risk MOS compared with lower blast-risk military occupations (37,39–42,44).
- The strength of these associations is modulated by cumulative dose, with instructors and high-career exposure groups demonstrating the largest and most persistent deviations across outcomes (5,45,58,60,64).

This overall pattern is consistent across the human studies included in the REA, despite differences in study designs, measures, and certainty ratings.

Findings in Animal Studies

Sixty-eight included studies involved animals, with two also involving humans. These studies examined the effects of low-level blast exposure in rodents, ferrets, swine, and *in vitro* / slice models (experiments on neural tissue and cell cultures outside of the living body in controlled laboratory environments). Most were controlled experimental blast models of mild TBI, often using repetitive exposure paradigms to mirror occupational patterns seen in breachers and combat arms personnel.

Study Designs, Species, and Experimental Paradigms

The majority of animal studies were animal intervention experiments or in vitro slice/culture models, frequently with randomisation to different blast intensities, frequencies, or treatment groups (87–95). Rodent studies (rats and mice) were most common (1,9,68,70,77,89,90,92–94,96–135,135–140), with additional ferret and large-animal work referenced for white-matter-rich brains with biomechanical similarity to human brain (80,141–145), and brain slice cultures used for mechanistic intervention work not otherwise able to be studied outside of these models (135,136).

Two studies included both human and animal participants to link mechanisms across species (1,80), using experimental blast in animals to support observational data from veterans or high-risk occupational cohorts.

In animal studies blast was predominantly delivered via shock-tube systems with single and repeated blast protocols. Some of these animal studies manipulated blast magnitude and number of exposures to derive dose-response relationships (111,112).

Blast Intensity and Exposure Dose-Response

Blast Magnitude

Examining different pressure levels can help to identify thresholds for injury, characterise mechanisms underlying subtle versus severe damage, and model cumulative exposure scenarios that are difficult to replicate in humans. This approach provides critical insights into the biological plausibility of rLLB-related outcomes in humans and informs operational safety guidelines.

Animal studies spanned a wide range of incident overpressures, from very low-level blast (LLB) analogues to moderate and higher blast magnitudes:

- Low-level blast paradigms approximated human training exposures and were used in multiple rodent studies of mTBI (9,89,90,92,99,108).
- Repetitive mild blast paradigms were common, exposing animals to multiple low- or moderate-level blasts over days or weeks, to model cumulative occupational exposure (9,89,90,93,108,117,134,135).

- Some animal studies compared different intensities and frequencies within the same experiment, demonstrating that both higher peak overpressure and greater number of blasts produced more severe neuropathological and behavioural changes (111,112).

Single vs Repetitive Blast

Researchers examined single versus repetitive blast exposure to understand how cumulative blast events influence injury severity and persistence. Across animal studies, repetitive blast produced markedly more persistent and widespread injury than single-blast exposure:

- In a rat study, rLLB (but not single low-level blast) led to long-term neurobehavioral impairments and selective cortical neuronal loss (90).
- In a mouse study of repetitive blast showed post-trauma seizures and increased neuronal excitability over months of follow-up, indicating chronic epileptogenic potential (89).
- Repeated low-level blast exposures produced chronic vascular, astrocytic, and inflammatory changes that were absent or minimal after single blasts (9,92,108).

Neuropathology and Structural Brain Changes

Axonal and White Matter Injury

Axonal and white matter integrity is critical for efficient brain communication. Repetitive LLB exposure can cause subtle disruptions in these structures, even without overt symptoms. Damage to axons or white matter can impair signal transmission, leading to cognitive and functional deficits over time. Monitoring these areas helps detect early microstructural changes, assess cumulative injury risk, and guide protective or rehabilitative strategies.

Diffuse axonal injury and white matter disruption were among the most consistent findings in animal studies:

- Using fluorescent cellular markers in mice, repetitive blast produced white matter axonal pathology detectable in vivo, confirming structural connectivity damage after low-level blast (100).
- Experimental studies in rodents and ferrets reported axonal damage and associated behavioural deficits, with histological evidence of axonal swellings, transport interruption, and myelin abnormalities (122,123,144).
- Brain slice studies showed long-term alterations in axonal conduction and synaptic transmission following repeated blast-equivalent stimuli (135).

Astrocytic and Vascular Pathology

Astrocytes and cerebral blood vessels play key roles in maintaining brain homeostasis and supporting neuronal health. Exposure to rLLB can disrupt astrocytic function and vascular integrity, leading to impaired blood-brain barrier regulation, altered neurovascular coupling, and increased neuroinflammation. Examining these changes helps identify early signs of metabolic stress and vascular compromise, which are critical for understanding cumulative brain injury risk and guiding protective interventions.

Multiple rat studies demonstrated chronic vascular and glial pathology after repetitive low-level blast:

- Low-level blast exposure induced chronic vascular damage, astrocytic degeneration, and vascular-associated neuroinflammation in rats, suggesting long-term microvascular injury and glial cell injury (92).
- Longer term observational studies reported local inflammation, synaptic alterations, and neuronal degeneration months after repetitive blast, highlighting persistent focal pathology (9).
- Additional experiments identified intramural hematomas and astrocytic infiltration around injured vessels, indicating long-standing vascular-glial interactions in repetitive low-level blast injury (108).

- In mice, progressive long-term spatial memory loss after blast was accompanied by myelin-related abnormalities and oligodendrocytic changes (116,123).

Blood-Brain Barrier (BBB) and Cerebrovascular Function

The blood-brain barrier (BBB) and cerebrovascular system are essential for protecting neural tissue and regulating nutrient and waste exchange. Repetitive LLB exposure can compromise BBB integrity and disrupt vascular function, allowing harmful substances to enter the brain and triggering neuroinflammation. Assessing these changes helps identify early vascular stress, monitor potential pathways for chronic brain injury, and guide strategies to preserve cerebral health.

Several studies specifically examined BBB integrity and cerebrovascular regulation:

- Experimental studies documented sex-dependent BBB alterations following blast exposure, suggesting biological sex modifies BBB vulnerability (138).
- Datasets integrating molecular and vascular measures described chronic vascular disruption, astrocytic end-foot changes, and microhemorrhages after rLLB exposure (92,108).
- Nitric oxide synthase signalling was implicated in cerebellar dysfunction following blast, linking vascular and neuronal injury (121).

Molecular, Cellular, and Systems-Level Mechanisms

Neuroinflammation and Glial Activation

Neuroinflammation and glial activation are key indicators of the brain's immune response to injury. Repetitive LLB can trigger activation of microglia and astrocytes, leading to chronic inflammatory signalling and potential neuronal damage. Monitoring these processes helps detect early pathological changes, understand mechanisms of cumulative stress, and guide strategies to mitigate long-term neurodegenerative risk. Inflammatory signalling was a central theme:

- Repeated blast exposures produced pronounced microglial and astrocytic activation, with elevated cytokine expression across brain regions (90,92,113,115,117).
- Cytokine profiling in rodent brains showed regional differences in inflammatory signatures following low-level blast (both repetitive and non-repetitive), including modulators of synaptic plasticity and neuronal survival (113).
- Long-term inflammatory changes persisted well beyond the acute phase, aligning with late-stage histopathology and behavioural deficits (9,108,117).

Ion Channels, Excitability, and Epileptogenesis

Ion channels regulate neuronal excitability and maintain electrical stability in the brain. Repetitive LLB exposure can alter ion channel function, disrupt homeostasis, and increase neuronal hyperexcitability, which may contribute to seizure susceptibility and epileptogenesis. Studying these mechanisms helps identify early electrophysiological changes, assess long-term neurological risk, and guide preventive strategies for abnormal brain activity. Several studies focused on neuronal excitability and channel dysfunction:

- A mouse study of repetitive blast TBI revealed post-trauma seizures and increased neuronal excitability, suggesting a mechanistic link to epilepsy risk (89).
- Brain slice (organotypic hippocampal) studies of repeated blast showed electrophysiological deficits and impaired long-term potentiation, effects that were amenable to recovery using exposure of tissue to certain pharmaceuticals being investigated as potential therapies (94,135,136).

- Interventions targeting the m-channel (Kv7/KCNQ) and related excitability pathways reduced abnormal firing and conferred neuroprotection in blast-exposed tissue (94).

Monoaminergic and Spinal Motor Pathways

Monoaminergic systems and spinal motor pathways are essential for regulating mood, arousal, and motor control. Repetitive LLB can disrupt neurotransmitter balance and impair descending motor circuits, potentially leading to changes in behaviour, coordination, and neuromuscular function. Examining these pathways helps identify subtle neurochemical and motor alterations, supporting early detection of functional deficits and informing targeted interventions. Rodent studies examined monoamine systems and motor function:

- Repetitive blast-induced TBI in rats led to altered monoaminergic levels, spasticity, and balance deficits, highlighting downstream effects on spinal and brainstem circuits (93).
- Follow-up work showed reduced epinephrine concentrations in the lumbar spinal cord after repetitive blast, linking neurochemical shifts to impaired motor function (134).

Mitochondrial and Metabolic Dysfunction

Mitochondria are essential for energy production and cellular resilience. Exposure to rLLB can impair mitochondrial function and disrupt metabolic pathways, reducing energy availability and increasing oxidative stress. These changes can compromise neuronal survival and contribute to long-term neurodegeneration. Monitoring mitochondrial and metabolic health helps identify early bioenergetic deficits and guide interventions to maintain brain function. Metabolic and mitochondrial disturbances were widely observed:

- Repetitive low-level blast exposure in rodents produced mitochondrial dysfunction, including impaired oxidative phosphorylation and altered energy metabolism (117).
- Metabolic profiling revealed hippocampal metabolic alterations shortly after blast, including shifts in key metabolites linked to neuronal viability (120).
- Proteomic analyses of the hippocampus after repeated blast identified widespread proteomic changes associated with synaptic function, cytoskeletal stability, and stress responses (118).

Amyloid, Tau, and Neurodegenerative Signatures

Amyloid and tau proteins are hallmark indicators of neurodegenerative processes. Repetitive LLB exposure may accelerate abnormal protein aggregation and signalling pathways linked to chronic traumatic encephalopathy (CTE) and other dementias. Tracking these signatures provides insight into long-term risks, helps identify early pathological changes, and supports strategies to prevent progressive neurodegeneration. Several animal experiments characterised neurodegeneration-related pathways:

- Studies reported laterality and region-specific tau phosphorylation following repeated blast, with progressive cognitive and PTSD-like behavioural changes (124,126).
- Repetitive LLB was also associated with improvements in some behavioural or cognitive measures under specific conditions, suggesting complex, possibly compensatory neuroplastic responses (125).
- Expression of GFAP and tau after blast was systematically characterised in animal studies, providing histological correlates to the serum GFAP and tau changes seen in humans (144).

Behavioural, Cognitive, and Affective Outcomes

Anxiety, Fear, and Stress-Related Behaviour

Repetitive LLB exposure can influence circuits regulating cognition, mood, and stress responses, leading to anxiety, fear, and altered affective behaviour even without overt injury. Assessing these outcomes helps

identify functional consequences of cumulative exposure, supports early intervention, and informs strategies to maintain psychological resilience. Many rodent studies demonstrated affective and anxiety-like changes after blast exposure:

- Low-level blast exposure in rats altered anxiety-like behaviour and changed gene activity in the amygdala, a brain region critical for fear and emotional regulation. These findings suggest that even blasts too weak to cause visible brain injury can still disrupt limbic circuits involved in mood and stress, potentially explaining anxiety symptoms seen after repeated low-level exposure (99).
- Affective profiling studies showed changes in anxiety-like behaviour and emotional responsiveness after blast exposure, including heightened fear reactions and altered coping behaviours. These animal responses resemble key features of human anxiety disorders and post-traumatic stress, supporting their relevance as models for understanding blast-related mental health outcomes (126,132).
- Studies combining blast-induced brain injury with stress-based trauma paradigms found stronger behavioural and brain effects than either exposure alone. This indicates that blast exposure can interact with psychological stress to worsen anxiety- and fear-related outcomes, highlighting the importance of addressing both physical and psychological factors in blast-exposed populations (126).

Cognitive and Memory Impairments

Cognitive and memory functions rely on intact neural networks and efficient communication between brain regions. Exposure to rLLB could disrupt these networks, leading to deficits in attention, processing speed, and memory consolidation. Monitoring these impairments helps detect early functional changes, assess cumulative impact, and guide strategies to preserve cognitive health. Spatial and recognition memory deficits were common:

- Repetitive LLB caused long-term spatial memory loss, with progressive decline over time, accompanied by myelin and white matter abnormalities (90,116,123).
- Blast-related studies showed impairments in hippocampal-dependent tasks, including maze-based spatial learning and recognition memory, consistent with hippocampal and cortical pathology described above (89,90,118,120).

Motor, Balance, and Sensory Outcomes

Motor coordination, balance, and sensory processing depend on integrated neural and vestibular systems. Repetitive LLB can disrupt these pathways, leading to subtle impairments in gait, posture, and sensory perception. Assessing these outcomes helps detect functional deficits early, evaluate cumulative effects, and guide rehabilitation strategies to maintain physical performance and safety. Motor and sensory sequelae featured prominently:

- Repetitive blast exposure, predominantly at low-level overpressures, resulted in persistent balance deficits, spasticity, and altered locomotor performance in rodent models. These functional impairments were associated with reduced spinal monoaminergic signalling - particularly adrenaline operating as a neurotransmitter - and delayed cerebellar neurovascular and Purkinje cell pathology, indicating combined spinal and cerebellar contributions to post-blast motor dysfunction, pathology consistent with the motor impairments seen in animals (93,121,134).
- Visual and thermal sensitivity were affected in some studies, although sex did not consistently modify visual outcomes -IL-1 pathway mutations conferred partial recovery of visual deficits, pointing to inflammatory contributions (91,119).
- Long-term exposure to LLB altered sensorimotor function and oculomotor/visual metrics in translational models aligned with SWAT / breaching exposures (33,85,86).

Hearing, Vestibular, and Peripheral Outcomes

Auditory and vestibular systems are highly sensitive to blast-related pressure changes. Repetitive LLB can damage cochlear structures, impair balance mechanisms, and affect peripheral sensory pathways, leading to hearing loss, dizziness, and spatial disorientation. Monitoring these outcomes helps detect early sensory deficits, assess cumulative impact, and guide interventions to maintain functional performance and safety. Several rodent and large-animal studies focused on auditory and vestibular injury:

- Blast-induced hearing impairment in rats was linked to cochlear and central auditory pathway damage, with measurable shifts in auditory thresholds and hair cell pathology (70).
- Studies of repeated blast-related acoustic trauma evaluated ear protection and pharmacological strategies (e.g., liraglutide, a GLP-1 analogue) and showed partial mitigation of hearing damage (141–143).
- Blast exposure dysregulated night-time melatonin levels and associated circadian signals, potentially linking vestibular and central autonomic disturbance to sleep-wake disruptions (110).

Genetic and Individual Susceptibility Factors

Genetic makeup and individual variability could influence how the brain responds to rLLB exposure. It is thought that certain genetic profiles, pre-existing conditions, and lifestyle factors could increase vulnerability to neuroinflammation, metabolic stress, and neurodegeneration. Understanding these susceptibility factors helps personalise risk assessment, predict long-term outcomes, and guide targeted prevention and intervention strategies. Some animal studies examined genetic moderators of blast-induced injury:

- Experiments using IL-1 pathway mutant mice showed partial recovery of visual outcomes, highlighting a causal role of pro-inflammatory cytokine signalling in blast-related visual dysfunction (91).
- Animal work conducted prior to this rapid review window examining APOE ε4 mutations indicated that APOE genotype reduces susceptibility to (and influences recovery from) blast injury, paralleling more recent studies examining similar human genetic risk patterns for mTBI and neurodegeneration (146).

Therapeutic and Protective Interventions.

Pharmacological Interventions

Pharmacological interventions target pathways such as neuroinflammation, oxidative stress, and excitotoxicity to preserve neural integrity and reduce long-term risk. Evaluating these interventions could help guide evidence-based treatments, optimise recovery, and enhance resilience against cumulative brain injury. A substantial subset of animal studies tested acute or chronic pharmacological interventions:

- Pharmacological interventions to reduce electrophysiological deficits following blast TBI (94) showed that channel modulators and anti-inflammatory agents could partially restore normal synaptic function.
- In brain slice studies, COX inhibition and EP3 receptor blockade reduced excitotoxic and inflammatory damage after repeated blast, improving electrophysiological outcomes (136).
- Partial microglial depletion attenuated long-term electrophysiological deficits and structural damage in brain slice (organotypic hippocampal) experimental models, indicating a key role for microglia in chronic blast pathology (135).
- Additional work with (2R,6R)-hydroxy-nor-ketamine (an NMDA-related metabolite) in blast-exposed rats suggested potential functional improvements and altered neural network activity (109).

Protective Equipment and Mechanical Mitigation

Protective equipment and mechanical mitigation strategies aim to reduce the physical forces transmitted to the body and brain during rLLB exposure. Innovations in helmet design, body armour, and environmental

shielding can help attenuate pressure waves and minimize biomechanical stress. Evaluating these measures supports the development of effective solutions to lower injury risk and enhance operational safety. Animal studies also evaluated physical mitigation strategies:

- Comparisons across different shock-tube configurations and intensity patterns highlighted that experimental setup and method of exposing the brain under experimental conditions significantly influences injury pattern, emphasising the importance of standardised and replicable mechanical modelling to support translational of research findings (111,112).

Alcohol and Other Post-Injury Modifiers

Post-injury factors such as alcohol use and other lifestyle modifiers can significantly influence recovery and long-term outcomes after rLLB. Alcohol may exacerbate neuroinflammation, oxidative stress, and metabolic dysfunction, increasing vulnerability to cognitive and behavioural impairments. Understanding these modifiers helps refine risk assessment, guide rehabilitation strategies, and promote protective behaviours to optimise recovery. Factors relevant to human post-injury lifestyle factors were explored in the mouse:

- In a mouse study of mild blast-induced traumatic brain injury, short-term post-injury alcohol consumption was associated with reduced anxiety-like behaviour and improved short-term memory at one-week post-injury. In contrast, continued alcohol consumption for three weeks after exposure resulted in significant long-term memory impairment. These delayed cognitive deficits were accompanied by increased oxidative stress, demonstrated by elevated acrolein adducts in the hippocampus, retrosplenial cortex, and medial amygdala, indicating a synergistic pathological interaction between blast exposure and prolonged alcohol intake (140).

Cross-Study and Cross-Species Patterns

Taken together, the animal studies show a coherent pattern of blast-related injury:

- Repetitive low-level blast produces cumulative pathology, including chronic vascular injury, astrocyte and microglia activation, axonal damage, and persistent neuroinflammation (9,89,90,92,93,108,117,134).
- Behavioural outcomes span anxiety-like behaviour, spatial and recognition memory deficits, motor and balance disturbances, and seizure susceptibility, closely mirroring human symptom clusters (3,89,93,99,116,123,126,132,134).
- Molecular and cellular mechanisms implicate excitability (ion channels), neuroinflammation, BBB breakdown, mitochondrial dysfunction, and early tau/amyloid changes, providing mechanistic substrates for the human biomarker signals observed in breachers and veterans (118,120,121,135,136,144).
- Intervention studies demonstrate that multiple elements of the blast injury cascade are modifiable - including microglial activation, COX-EP3 signalling, excitability, and venous biomechanics - supporting plausible therapeutic and protective strategies for human translation (94,109,135,136,141–143).

Overall, the animal studies in this dataset provide mechanistic and causal evidence that rLLB can induce persistent structural, molecular, and functional brain injury. These studies delineate several candidate pathways and interventions that align with, and help explain, the human observational findings.

Findings in the Grey Literature

A total of 57 grey literature sources were identified and underwent analysis and quality assessment (where appropriate). The Summary of Findings (SoF) table for the grey literature sources are provided in Appendix 5. A broad thematic analysis and commentary on the content and relevance of these sources is provided below.

Features of Grey Literature Sources

Mass Media

Across the United States, United Kingdom, Canada, Australia, and New Zealand, defence organisations are now openly recognising that blast overpressure from common military weapons poses a genuine risk of brain injury (particularly shoulder-fired systems, heavy weapons, breaching charges, and repeated low-level training blasts). The US Department of Defense has released new mandatory exposure-control standards and is rolling out predictive modelling tools and blast-dose tracking systems. Concurrently, major US research programs such as the "INVestigating traIning assoCiated blasT pAthology" (INVICTA study) and Army-wide baseline cognitive testing are aiming to clarify the neurological effects of repeated low-level blast exposure. Parallel work by the United States Army Medical Research and Development Command (USAMRDC) is focused on developing algorithms and sensors to predict, measure, and mitigate injury risk before and during training events.

Internationally, similar concerns are emerging. The UK Ministry of Defence has formally admitted that some of its weapon systems can cause brain injuries and has accepted liability in some compensation cases. New Zealand has issued warnings to troops and adjusted training protocols. Australian Defence Force personnel, particularly in elite units, have expressed growing concern that chronic blast exposure from their own weapons is impairing cognition. Together, these developments point to a rapid and coordinated shift in policy underpinned by emerging scientific and clinical data: militaries are moving away from viewing blast solely as an acute battlefield hazard and toward recognising the cumulative, long-term neurological risks associated with routine training exposures.

Research and Technical Reports

Traumatic brain injury (TBI) and blast-related harm in military populations are now framed not as isolated clinical events but as chronic, occupational, and systems-level problems. The grey literature corpus from US Department of Defense (DoD) entities, Traumatic Brain Injury Center of Excellence (TBICoE), NATO, RAND Corporation, and USAMRDC (GL_30–GL_57) collectively trace a trajectory from the recognition of the scale of the problem, through to mechanistic and clinical investigation, and increasingly coordinated, but not completely harmonised, policy and practice responses.

Expanding Surveillance and Recognition of Occupational Risk

Across the TBICoE Annual Reports there is a clear shift from episodic TBI management toward a lifetime brain health paradigm based on occupational risk. TBICoE describes sustained and expanding surveillance of TBI within the Military Health System, documenting more than 468,000 first-time TBIs since 2000, and highlighting the predominance of mild injuries (GL_32). Advanced registries, longitudinal datasets, and congressionally mandated studies on blast overpressure and long-term outcomes are central to this evolving surveillance enterprise (GL_31, GL_35, GL_36).

At the same time, independent evaluation reveals that surveillance is both incomplete and biased. The DoD Inspector General's report concludes that mandated screening, follow-up, and return-to-duty processes are inconsistently implemented, that providers frequently fail to use the required Military Acute Concussion Evaluation (MACE 2) tool, and that 41% of diagnosed TBIs receive no documented follow-up (GL_33). Inconsistent coding practices further compromise case identification, rendering burden estimates and longitudinal analyses unreliable (GL_33). RAND testimony to the US Senate reinforces that underreporting and underdiagnosis are driven not only by system issues but also by stigma, fear of career consequences, limited awareness, and structural barriers to care (GL_57).

Taken together, these documents depict a system that has invested heavily in surveillance infrastructure and analytic capability, yet continues to underestimate true TBI and blast burden due to point-of-care gaps, sociocultural disincentives to reporting, and technical challenges in tracking low-level, cumulative exposures (GL_30–32, GL_33, GL_35, GL_36, GL_39, GL_42, GL_57).

Mechanisms and Pathophysiology: From Blast Physics to Neurodegeneration

A second major theme is the deepening (though still incomplete) understanding of the mechanisms by which blast and head trauma affect the brain and other organ systems. Multi-national and multi-agency technical reports provide a conceptual and methodological backbone for blast research. NATO Science and Technology Office (STO) documents call for standardised terminology, exposure metrics, animal models, and computational approaches to improve reproducibility and comparability across studies (GL_43, GL_44). The IFBIC proceedings echo this need and highlight innovations in sensor technology, physiologic response modelling, and long-term monitoring of blast-exposed cohorts (GL_41).

Biomedical research reports provide additional tissue- and organ-level detail. Work on tympanic membrane biomechanics demonstrates that sub-rupture blast overpressures (35-55 kPa) can cause microstructural fibre damage, reduced elastic modulus, and altered frequency-dependent mobility; changes that are consistent with hearing deficits after non-rupturing blast events (GL_45). Pre-clinical concussion models show that repeated injuries lead to broader and more persistent metabolic dysfunction, particularly thalamic glucose hypometabolism, than single events, even when chronic neurodegenerative pathology is not evident histologically (GL_47).

With respect to neurodegeneration, the evidence is mixed and often contradictory. A transgenic rat model of Alzheimer's disease (TgF344-AD) indicates that repeated moderate TBI in older animals accelerates amyloid plaque maturation, induces focal tauopathy, and amplifies neuroinflammatory changes, consistent with TBI exacerbating pre-existing pathology (GL_46). However, TBICoE's information paper on neurodegenerative disease concludes that while many observational human studies suggest associations between TBI (especially moderate–severe or repeated) and later Alzheimer's disease, Parkinson's disease, or ALS; other high-quality studies do not, and causal pathways remain unproven (GL_55). A TBICoE research review on CTE is especially explicit in warning against deterministic narratives linking repetitive head impacts to specific clinical syndromes; it stresses that CTE can only be diagnosed neuropathologically, that incidence is unknown, and that most popular claims about CTE and behaviour are not supported by robust data (GL_49).

Evidence regarding rLLB exposures is similarly cautious. RAND's reviews and DoD state-of-the-science syntheses confirm that repeated subconcussive blast exposures occur in many military occupational specialties and that animal models demonstrate plausible mechanisms for cognitive impairment and neurodegeneration at relatively low pressures (3–10 psi) (GL_39, GL_42). However, human data are limited by reliance on self-report, inadequate exposure quantification, and confounding by concomitant injuries and psychosocial stressors (GL_39, GL_42, GL_57). Across this corpus, an emerging consensus is that rLLB is a potential risk to neurological health, supported more strongly by animal than human data, and that no safe threshold has been identified (GL_39, GL_42, GL_43).

Clinical Manifestations, Comorbidities, and Outcomes

The clinical picture that emerges is one of complex, overlapping symptom clusters rather than neatly separable diagnoses. TBICoE's review on mTBI and PTSD emphasizes the high co-occurrence of these conditions in military and veteran populations, substantial symptom overlap, and the difficulty of differentiating them using current neuropsychological, imaging, or biomarker approaches (GL_50). Rather

than seeking a single discriminating test, the review advocates comprehensive, trauma-informed clinical assessment and integrated treatment strategies.

Pain is highlighted as both a primary and secondary driver of long-term disability after TBI. The TBICoE 2024 review describes post-TBI pain as highly prevalent—particularly after mTBI—and often co-occurring with PTSD, depression, and sleep disturbances (GL_53). It outlines multiple pain mechanisms (nociceptive, neuropathic, inflammatory, central, psychogenic), notes that female sex, multiple TBIs, and severe acute pain are key risk factors, and stresses that pain can significantly delay recovery and return to duty (GL_53).

Suicide risk in TBI-exposed populations is also addressed explicitly. TBICoE's 2024 review concludes that TBI (especially moderate to severe injuries and multiple TBIs) is associated with increased suicidal ideation, attempts, and mortality, but largely through its interactions with comorbid mental health conditions, chronic pain, and sleep disorders (GL_51). Most military TBIs are mild, and while mTBI may contribute to vulnerability, suicide remains statistically rare. The review underscores the importance of guideline-concordant screening (e.g., PHQ-9, C-SSRS), addressing co-occurring psychiatric conditions, and reinforcing protective factors such as social connection and meaningful activity (GL_51).

The literature on multiple concussions and repetitive subconcussive impacts shows that cumulative injuries are associated with more severe and prolonged symptoms, headaches, mood disturbance, and cognitive deficits; particularly among athletes and military personnel (GL_52). Neuroimaging findings suggest microstructural white matter changes and altered cerebral metabolism; however, results vary across studies (GL_52). These clinical and neurobiological patterns collectively reinforce the view that TBI in military settings is best understood as a chronic, exposure-related condition embedded in a broader matrix of psychological, physical, and social stressors.

Evaluation of Interventions: From Clinical Care to Adjunctive Therapies

The corpus is notably cautious regarding therapeutic interventions that have gained public attention. TBICoE's information paper on hyperbaric oxygen therapy (HBOT) concludes that, despite promising animal data, large, methodologically robust human trials, many conducted within DoD, show no meaningful or durable benefit of HBOT for TBI or post-concussive symptoms (GL_56). Improvements seen in smaller, lower-quality studies tend to disappear with longer follow-up, while better-controlled trials consistently find that HBOT performs no better than sham (GL_56). The report highlights that HBOT is neither FDA-approved nor reimbursed by TRICARE/VA for TBI indications and warns that offering it may be costly and potentially damaging to patient trust when promised benefits fail to materialise (GL_56).

Similarly, a TBICoE information paper reviewing omega-3 supplementation (US Defense Health Agency, DHA/US Environmental Protection Authority, EPA) concludes that while preclinical data for DHA/EPA are robust, supporting anti-inflammatory, neuroprotective, and cognitive benefits, clinical evidence remains sparse and inconsistent (GL_54). Some studies in athletes and warfighters suggest reduced biomarkers of axonal injury or faster symptom resolution, but optimal dosing, timing, and clinical relevance remain unclear (GL_54). Up to 5 g/day DHA/EPA appears safe for healthy adults, but there is insufficient evidence to change clinical guidelines for TBI prevention or treatment at this time (GL_54).

In contrast, there is more positive evidence for the refinement of clinical processes and guidelines within standard non-pharmacologic and multimodal care. TBICoE's annual reports highlight iterative updates to clinical tools (e.g., MACE 2, Progressive Return to Activity) and expanded training and education of providers across the Military Health System (GL_30–32). However, evaluation data from DoDIG reveal that implementation is inconsistent, with significant gaps in the use of mandated tools, timely follow-up, and standardised referral pathways (GL_33). TBICoE's pain review underscores the importance of interdisciplinary, largely non-pharmacologic treatment approaches, and caution with long-term

pharmacotherapy, but also notes that evidence for many complementary and alternative interventions is still limited (GL_53).

The burn and blast-related trauma literature reveals a similar pattern: substantial conceptual clarity regarding what needs to be improved (early resuscitation, infection control, wound coverage, effective analgesia, and prolonged field care protocols), but limited empirical evidence from well-controlled studies, especially in austere or contested environments (GL_40, GL_48).

Prevention, Protection, and Exposure Mitigation

Prevention and exposure mitigation are prominent, especially in documents focused on blast. Longitudinal blast studies demonstrate that body-worn sensors can reliably capture exposure data in training environments with "Tier 1" weapon systems and that such data can be quality-controlled and integrated into health and exposure record systems (GL_36). Yet, these reports also acknowledge that current technology is not yet suited to operational combat settings and that there are major gaps in safety guidance, including inconsistent or absent exposure limits for different systems and occupational roles (GL_35, GL_36).

RAND reviews and NATO reports converge on the need for validated exposure metrics and criteria, emphasizing that many existing standards are derived from high-level blast or acute injury models and may not be appropriate for chronic, low-level occupational exposures (GL_39, GL_42, GL_43, GL_44). Multiple documents recommend establishing lifetime blast exposure logs, enhancing MOS-specific preventive strategies, and enforcing existing standards more rigorously (GL_39, GL_42, GL_57). Prevention also encompasses improved PPE, helmet design, and training modifications, though evidence for the effectiveness of many innovations is preliminary (GL_52).

The literature on blast-related burns broadens the prevention agenda to include environmental and operational factors that influence both injury occurrence and the feasibility of timely evacuation and definitive care (GL_40, GL_48). These reports call for better prevention technologies, updated field-care protocols suited to prolonged evacuation times, and systematic investment in burn-care capacity along the full continuum from point of injury to rehabilitation (GL_40, GL_48).

Policy, Strategy, and System-Level Coordination

At the system level, the DoD Warfighter Brain Health Research Strategy offers a comprehensive framework that integrates many of these strands into seven research areas spanning hazard identification, surveillance, detection, performance enhancement, protection, advanced diagnostics, and treatment/rehabilitation (GL_34). It explicitly links research priorities to operational requirements, emphasising emerging threats (including directed energy and environmental stressors), exposure-response modelling, sensor and biomarker development, clinical decision support, and veteran-focused long-term care (GL_34).

TBICoE annual reports portray the Centre as a central node in this ecosystem, leading or contributing to numerous research projects, clinical guideline developments, education and training initiatives, and dissemination activities across the Military Health System, VA, academia, and other federal agencies (GL_30–32). These activities include apps, fact sheets, podcasts, regional education coordination, and large-scale awareness campaigns, all aligned to the broader DoD Warfighter Brain Health Strategy (GL_30–32, GL_34).

However, the Inspector General's evaluation and RAND testimony provide a counterpoint, showing that strategic direction and resource investment do not automatically translate into consistent practice on the ground (GL_33, GL_57). They highlight the importance of clear policy requirements, standardised programs of record, robust oversight mechanisms, and aligned funding streams, as well as the need to address cultural and stigma-related barriers that inhibit reporting and care (GL_33, GL_57).

Internationally, NATO STO and International Forum on Blast Injury Countermeasures (IFBIC) documents demonstrate growing multinational collaboration in data standards, sensor validation, modelling approaches, and terminology, recognising that many blast-related challenges are shared across allied militaries and that pooling expertise is essential for progress (GL_41, GL_43, GL_44).

Synthesis and Key Gaps

Overall, the grey literature depicts a system in the midst of transition – from a primarily event-driven, concussion-focused model of care to a broader, lifetime warfighter brain health paradigm that recognises cumulative exposures, comorbidities, and complex long-term trajectories (GL_30–32, GL_34, GL_39, GL_42, GL_51–GL_55). There is substantial progress in surveillance infrastructure, mechanistic understanding, guideline development, and strategic alignment. Yet, several cross-cutting gaps remain prominent:

- Under-identification and incomplete surveillance due to inconsistent clinical implementation, coding variability, stigma, and structural barriers (GL_33, GL_57).
- Limited longitudinal human data on cumulative low-level blast, multiple concussions, and their long-term neurological, psychiatric, and functional outcomes (GL_35, GL_36, GL_39, GL_42, GL_52).
- Unresolved questions about neurodegeneration, with mixed evidence linking TBI to Alzheimer's disease, Parkinson's disease, ALS, and CTE, and substantial risk of over-interpretation in public discourse (GL_46, GL_49, GL_55).
- Insufficient validation of biomarkers and imaging tools for differential diagnosis (e.g., mTBI vs PTSD) and prognostication (GL_47, GL_50).
- Incomplete evaluation of preventive technologies and protective equipment, particularly in real-world operational settings (GL_36, GL_41, GL_43, GL_52).
- Gaps between policy and practice, where high-level strategies and guidelines are not consistently reflected in frontline clinical care and unit-level practices (GL_30–34, GL_57).

The corpus therefore supports a clear agenda for future work: large, rigorously designed longitudinal studies; standardised, interoperable exposure metrics; integrated biopsychosocial models of outcomes; stronger evaluation of preventive and therapeutic interventions; and organisational reforms that close the gap between strategic intent and care delivery. In this evolving picture, TBI and blast-related brain health are best understood as chronic, exposure-mediated, system-level challenges requiring coordinated scientific, clinical, and policy responses across the life course of the warfighter (GL_30–GL_57).

Information and Guidance for Personnel and Providers

US Department of Defense (DHA), Traumatic Brain Injury Center of Excellence (TBICoE), and Veterans Affairs (VA) guidance consistently emphasise improved recognition, assessment, and early management of mild traumatic brain injury (mTBI), concussion, and blast-related exposures in military settings. Multiple clinical guidance documents (GL_1–GL_6) provide structured evaluation frameworks for acute concussion, recurrent or multiple concussions, post-traumatic headaches, and the complex interface between mTBI, PTSD, and behavioural or mood disturbances. They highlight overlapping symptom profiles, risks of cumulative injury, blast-overpressure mechanisms, and the need for vigilant screening – particularly in operational environments where subtle cognitive or behavioural changes may impact performance and readiness. Quick-reference care pathways further support frontline decision-making, outlining staged return-to-activity protocols, red-flag symptoms, referral triggers, and monitoring expectations for both acute and recurrent injuries.

Complementing these clinical guides, a suite of information sheets (GL_7–GL_17) provides accessible summaries for clinicians, leaders, and service members. Topics include biomarker research progress,

epidemiological trends in global TBI incidence, low-level blast science, and the interactions between mTBI and comorbidities such as PTSD or alcohol misuse. These documents reinforce the importance of integrated care models, early reporting, and leadership engagement in maintaining force health protection. They also underscore ongoing capability gaps, particularly in diagnostic devices, biomarker validation, and understanding long-term neurobehavioral effects of rLLB, highlighting TBICoE's and DHA's continued research efforts to improve assessment tools, protective strategies, and evidence-based care for warfighters across deployment and garrison settings.

Grey Literature Summary

Across all Grey Literature sources, the central theme is a rapidly expanding but still fragmented effort to understand, track, prevent, and treat traumatic brain injury and blast-related health effects in military populations. Evidence shows progress in surveillance systems, clinical tools, and research, especially in biomechanics, biomarkers, and blast exposure monitoring, but persistent challenges in clinical implementation, inconsistent TBI identification, and inadequate longitudinal data that impede force readiness and policy decision-making. Repeated LLB exposure is increasingly recognised as a significant occupational hazard with no established safe threshold. Prevention and protective strategies are advancing but remain incomplete. Major knowledge gaps persist in long-term outcomes, neurodegeneration, burn/blast polytrauma, and comorbidity management. The overarching strategic direction emphasises integrated, multidisciplinary, longitudinal, and prevention-focused approaches, supported by enterprise-wide coordination, cultural change, and international collaboration.

Quality of Grey Literature Sources

Three reports were formal research artefacts. These underwent QUADS analysis. The results of the analysis are presented in Table 2.

Table 2. QUADS analysis of research related grey literature

ID	GL_45	GL_46	GL_47
Title	Biomechanical Modelling and Measurement of Blast Injury and Hearing Protection Mechanisms	Neuropathology and Immune Biomarker Discovery in a Rat Model of Alzheimer's Disease, TgF344-AD, with Single or Repetitive Traumatic Brain Injury	Evaluation of Clinically Relevant Prognostic Indicators in a Model of Mild TBI/Concussion
Year	2020	2021	2022
Country	USA	USA	USA
Organisation	USAMRDC	USAMRDC	USAMRDC
1. Theoretical or conceptual underpinning to the research	Strong	Strong	Strong
2. Statement of research aim/s	Inconsistent	Strong	Strong
3. Clear description of research setting and target population	Strong	Strong	Strong
4. The study design is appropriate to address the stated research aim/s	Strong	Strong	Strong

5. Appropriate sampling to address the research aim/s	Moderate	Moderate	Moderate
6. Rationale for choice of data collection tool/s	Strong	Weak	Strong
7. The format and content of data collection tool is appropriate to address the stated research aim/s	Strong	Moderate	Strong
8. Description of data collection procedure	Strong	Strong	Very Strong
9. Recruitment data provided	Weak	Strong	Strong
10. Justification for analytic method selected	Strong	Moderate	Moderate
11. The method of analysis was appropriate to answer the research aim/s	Strong	Moderate	Strong
12. Evidence that the research stakeholders have been considered in research design or conduct.	Weak	Moderate	Weak
13. Strengths and limitations critically discussed	Strong	Strong	Moderate

Other grey literature sources did not undergo QUADS analysis as they were not research-oriented; thus, they were not able to be evaluated in accordance with the research criteria.

Discussion

The findings of this REA reinforce growing concerns about the potential cognitive impacts of rLLB exposure in military and related occupational settings. Consistent with recent literature, repeated exposure to low-intensity overpressure events, while not typically associated with overt injury, has been linked to subtle changes in cognitive performance, balance, symptom expression (visual changes, hearing changes, headache, irritability, fatigue), and selected neurophysiological measures (6,8–10,12). Evidence from high-exposure cohorts (such as breachers and heavy-weapons personnel) suggests a pattern of acute, and in some cases persistent, alterations in cognitive functioning and biomarkers. These observations are broadly consistent with the hypothesis that cumulative exposure to subclinical blast events may contribute to measurable neural stress over time (1–3).

Mechanistic studies in animals provide further support for this interpretation, demonstrating axonal disruption, neuroinflammatory responses, mitochondrial dysfunction, and microvascular changes following rLLB exposures (7,9,11). These biological findings align with human imaging and biomarker studies that report changes in markers such as GFAP, NFL, tau, and selected metabolic signatures in repetitively exposed populations. Nevertheless, the clinical significance of these alterations remains uncertain. The available human studies vary widely in exposure definitions, study designs, and outcome measures, and relatively few include long-term follow-up capable of assessing enduring or progressive effects.

Comparison with the more mature sport-related concussion literature highlights clear differences in methodological coherence, sample sizes, and the availability of validated clinical guidelines (13,21,27,29). Whereas sport concussion research has benefited from decades of sustained scientific inquiry and standardised protocols, the rLLB evidence base remains fragmented and heterogeneous, limiting the development of definitive diagnostic criteria or exposure thresholds. Nonetheless, both areas of research

suggest that repeated subclinical neurotrauma may carry cumulative effects and that improved documentation of exposure histories is critical for both clinical assessment and research. Continued investment in systematic exposure measurement, harmonised methodologies, and longitudinal cohort studies will be essential to advance understanding of rLLB and to clarify its relationship to cognitive outcomes in military personnel.

Table 3 outlines the responses to the research questions posed in this Rapid Evidence Assessment (REA).

Table 3 – Responses to research questions posed in this review

Research question	Response
How is LLB overpressure exposure defined?	Low-level blast (LLB) overpressure exposure refers to exposure to blast pressure waves that are below thresholds typically associated with acute blast injury or clinically diagnosed traumatic brain injury. These exposures commonly arise from military weapons systems (e.g. breaching charges, artillery, mortars, heavy firearms) and generally involve peak overpressures in the approximate range of 1–6 psi, although higher values are occasionally reported in training or operational contexts. LLB exposure does not usually produce immediate, overt neurological injury but may exert subclinical physiological stress on the brain.
What criteria are used to define repetitive LLB (rLLB) exposure (e.g., duration/frequency/intensity)?	There is no universally accepted definition of rLLB. In the literature, rLLB is operationalised variably using proxies such as occupational role (e.g. breacher, instructor), self-reported blast counts, duration in high-risk roles, or inferred cumulative exposure during training cycles or careers. Frequency, cumulative dose (blast count or impulse), and career duration are more commonly used than precise intensity thresholds. This lack of standardisation is a major limitation of the evidence base.
What assessment process is recommended for individuals presenting with acute or chronic cognitive signs and symptoms associated with rLLB exposure?	The report supports a holistic, multimodal clinical assessment rather than a blast-specific diagnostic test. Recommended assessment integrates clinical history (including blast exposure history), symptom inventories, neuropsychological screening, vestibular and balance assessment, mental health screening (PTSD, depression, anxiety), sleep assessment, and pain evaluation. rLLB exposure should be considered within existing mTBI and mental health pathways rather than as a standalone diagnosis.
What is the reliability and validity of the cognitive assessments designed to assess acute or chronic signs/symptoms associated with rLLB overpressure exposure with respect to (i) clinical history; (ii) alternative	The evidence indicates limited reliability and validity of existing cognitive assessments for isolating rLLB effects. Neuropsychological tests, symptom questionnaires, eye-tracking, balance testing, imaging, and biomarkers demonstrate sensitivity to change but poor specificity. Results are strongly influenced by clinical history, comorbid PTSD, depression, sleep disturbance, chronic pain, and prior impact-related mTBI. No assessment tool has been validated to

diagnoses; and (iii) comorbid diagnoses?	reliably distinguish rLLB effects from alternative or comorbid diagnoses.
Which military roles are associated with higher levels of rLLB overpressure exposure during (i) training; and (ii) deployment?	High-risk roles consistently include breachers and explosive entry personnel, artillery and mortar crews, heavy-weapons operators, special operations forces, and instructors in blast-intensive training environments. Exposure occurs both during training and deployment, with instructors and career specialists demonstrating the highest cumulative exposure profiles.
What individual, occupational, or environmental factors may protect against the development of cognitive impairment following rLLB overpressure exposure?	Protective factors are incompletely defined but include reduced cumulative exposure, adequate recovery intervals between exposures, effective hearing and head protection, modification of training practices, and management of modifiable health factors such as sleep, mental health, and substance use. Animal studies suggest that mechanical mitigation and modulation of inflammatory pathways may be protective, but human evidence remains preliminary.
Does rLLB overpressure exposure increase susceptibility to clinically diagnosed neurological, psychiatric, or medical conditions?	Human evidence suggests associations between rLLB exposure and increased symptom burden, mTBI diagnoses, and neuropsychiatric conditions, particularly when exposure is cumulative and co-occurs with other stressors. However, causality is not established. Vulnerability appears to be strongly influenced by comorbid PTSD, depression, sleep disturbance, chronic pain, and prior head injuries rather than rLLB exposure alone.
What are the mechanisms by which rLLB overpressure exposure is proposed to affect cognitive functioning in humans?	Animal and translational evidence supports mechanisms including axonal injury, neuroinflammation, vascular and blood-brain barrier disruption, altered neuronal excitability, mitochondrial dysfunction, and neuroimmune activation. These mechanisms provide biological plausibility for observed human symptoms but do not yet establish direct causal pathways in humans.
What brain structures and cognitive processes are affected by rLLB overpressure exposure in humans (neuropathology, neuroimaging, biomarkers)?	Human studies implicate frontal and subcortical networks, white matter tracts, vestibular and oculomotor systems, and salience/default mode networks. Neuroimaging and biomarker studies suggest involvement of axonal and glial pathways, though findings are inconsistent and confounded.
What is the underlying neuropathology associated with rLLB overpressure exposure in humans?	Direct neuropathological evidence in humans is extremely limited. Imaging and biomarker findings suggest possible microstructural white matter changes, neuroinflammatory activity, and metabolic alterations. Animal studies demonstrate more definitive axonal, vascular, and glial pathology, but translation to human disease remains uncertain.

How are cognitive changes assessed following rLLB overpressure exposure?	Assessment relies on symptom reporting, neuropsychological testing, vestibular and balance measures, eye-tracking, and research-grade biomarkers or imaging. No validated rLLB-specific diagnostic framework exists; assessments are best interpreted longitudinally and in clinical context.
What acute cognitive signs and symptoms are associated with rLLB overpressure exposure in humans?	Acute effects include transient cognitive slowing, attention deficits, headache, dizziness, balance disturbance, visual or oculomotor changes, and short-term biomarker elevations. These effects often resolve over hours to days.
What chronic cognitive signs and symptoms are associated with rLLB overpressure exposure in humans?	Chronic findings in high-exposure cohorts include persistent headaches, concentration difficulties, irritability, sleep disturbance, mood dysregulation, and subtle executive or attentional deficits. These are often intertwined with psychiatric and pain comorbidities.
How can rLLB-related symptoms be distinguished from other cognitive or psychiatric conditions (differential diagnosis)?	They generally cannot be reliably distinguished using current tools. Differential diagnosis requires comprehensive assessment addressing PTSD, depression, anxiety, sleep disorders, chronic pain, substance use, neurodegenerative disease, and impact-related mTBI. Attribution to rLLB alone is not supported by current evidence.
Is there any evidence that rLLB overpressure exposure is associated with mTBI (or signs and symptoms of same) in humans?	Epidemiological data suggest that individuals in high blast-risk roles have higher rates of diagnosed mTBI and post-concussive symptoms. However, rLLB may act as a risk modifier rather than an independent cause.
Is there any evidence that rLLB overpressure exposure is associated with neurodegenerative conditions (or signs and symptoms of same) in humans?	Evidence is insufficient to establish an association. Animal studies show biological plausibility for neurodegenerative processes, but human evidence is limited, inconsistent, and low certainty.
What treatment or management strategies are recommended for individuals presenting with acute or chronic cognitive signs and symptoms associated with rLLB exposure?	No rLLB-specific treatments are recommended. Management should follow established guidelines for mTBI, PTSD, depression, sleep disorders, and chronic pain, using multidisciplinary, symptom-focused care.
What is the safety and efficacy of the treatment or management strategies for individuals presenting with acute or chronic cognitive signs and symptoms associated with rLLB overpressure exposure?	Standard rehabilitation and mental health treatments are considered safe and effective for symptom management. Interventions such as hyperbaric oxygen therapy or supplements lack sufficient evidence for routine use.

What prevention strategies are proposed or in use to reduce rLLB exposure or its effects?	Strategies include minimising unnecessary repetitive exposures, modifying training practices, improving documentation and surveillance, piloting blast sensors in training, and monitoring emerging international guidance. No safe exposure thresholds have been established.
What rehabilitation approaches are used for rLLB-related cognitive impairment?	Rehabilitation mirrors mTBI care: cognitive rehabilitation, vestibular therapy, psychological interventions, sleep management, and pain management. Evidence specific to rLLB is limited.
What is known about long-term wellbeing and quality of life impacts for individuals with rLLB-related cognitive symptoms?	Long-term outcomes are driven largely by comorbid mental health conditions, pain, and sleep disorders. rLLB exposure may contribute to cumulative burden, supporting a lifetime brain-health framing, but direct long-term effects remain uncertain.
What is the quality and certainty of the evidence used to address the research questions?	Overall certainty is very low to low. Human studies are limited by observational designs, exposure misclassification, confounding, and small samples. Animal studies provide strong mechanistic insight but are indirect. Evidence supports biological plausibility and association, not causation or threshold-based policy.

Limitations

Interpretation of the findings in this review is constrained by several limitations within the underlying literature. A key challenge is the substantial heterogeneity across studies in exposure characterisation, including differences in blast metrics, sensor technologies, occupational contexts, and the frequency and intensity of exposures. Many studies are cross-sectional or involve small, specialised cohorts, reducing generalisability and limiting causal inference. Confounding by co-occurring factors such as impact-related mild traumatic brain injury, psychological stress, PTSD, chronic pain, and sleep disturbance remains pervasive and is not consistently controlled for in study designs.

The translation of mechanistic evidence from animal and experimental studies to human populations presents additional limitations. Experimental paradigms often employ controlled blast exposures that differ in amplitude, waveform, and context from real-world military conditions, reducing the applicability of certain mechanistic findings to operational settings. Biomarker and neuroimaging studies, while promising, face limitations in sensitivity, specificity, and reproducibility, precluding their routine use for clinical decision-making in rLLB-exposed populations.

This review also reflects constraints inherent to rapid evidence assessment (REA), including potential omission of very recent studies and reduced depth of methodological critique compared with a full systematic review. The grey literature, although informative for policy and operational context, varies widely in methodological rigour and may exclude relevant non-public defence documents. Collectively, these limitations highlight the need for more methodologically robust, longitudinal, and standardised research to clarify the cognitive implications of repetitive low-level blast exposure.

Overall Implications

The sources reviewed in this rapid assessment of the evidence (REA) highlight a consistent pattern across human observational studies, animal studies, and grey literature: repetitive low-level blast (rLLB) exposure is associated with measurable acute and, in some cohorts, persistent cognitive, physiological and symptom changes (such as balance, hearing, visual, fatigue, irritability, headache). However, the certainty of this evidence is variable, long-term causal pathways remain incompletely defined, and multiple confounding factors, including impact-related mTBI, psychological trauma, chronic pain, and sleep disturbance, limit the strength of conclusions that can be drawn. Against this backdrop, approaches to policy, clinical practice, surveillance, and research must remain proportionate, transparent about uncertainty, and aligned with achievable near-term improvements.

Based on the reviewed literature, several evidence-informed approaches can be interpreted in response to repetitive low-level blast exposure.

First, the human evidence base indicates that personnel in high blast-risk roles, such as breachers, artillery operators, mortarmen, and some special operations personnel, experience greater symptom burden and higher rates of mTBI diagnoses than those in lower-risk occupations. Grey literature from international defence organisations similarly emphasises the growing recognition of rLLB as an occupational exposure requiring improved documentation. In light of this, a tiered approach to exposure surveillance could include, for example, enhancing the capture of blast-exposure history within existing clinical documentation. A more structured option would be the development of a targeted exposure registry focused on high-risk roles, while a longer-term research-oriented option could involve supporting a longitudinal cohort to better understand cumulative exposure and subsequent health trajectories. These approaches acknowledge both the observed association between cumulative exposure and symptomatology, and the current absence of validated thresholds or exposure limits.

Similarly, the clinical literature supports a model of care that recognises the multidimensional nature of post-rLLB symptoms. Across studies, rLLB-related cognitive changes frequently co-occur with psychological conditions, particularly PTSD and depression, chronic pain and sleep disturbance. These comorbidities, rather than isolated cognitive deficits, appear to contribute most strongly to long-term impairment and reduced quality of life. Explicit rLLB exposure prompts could be integrated into existing assessment pathways along with guidance for clinicians that summarises typical symptom clusters, known overlaps with other conditions, and the current limitations of diagnostic tools. For more complex presentations, piloting a specialist or virtual consultation pathway may support consistent assessment and management while acknowledging the present limitations in definitive diagnostic testing.

The reviewed evidence identifies substantial gaps in longitudinal human studies, biomarker validation, and the relationship between rLLB and long-term neurodegeneration. While advanced imaging and blood biomarkers such as tau, NFL, GFAP, and amyloid species show promise in research contexts, the literature does not yet support their routine clinical application. Consequently, it may be necessary to maintain a cautious stance regarding advanced diagnostic technologies, reserving their use for research settings or specific clinical indications. In parallel, investment in Australian collaborative research, particularly studies linking human exposure profiles to mechanistic findings from animal models, may play an important role in strengthening future decision-making.

Prevention and mitigation strategies in training and operational environments are evolving internationally but remain constrained by the absence of agreed safe thresholds and the practical limitations of sensor technologies in real-world settings. The review suggests that precautionary approaches aimed at reducing

unnecessary repetitive exposures, alongside pilot programs evaluating body- or weapon-mounted sensors, may offer pragmatic intermediate steps. Engagement with allied partners in NATO, the United States, and the United Kingdom may also help ensure that Australia benefits from emerging harmonised terminology, exposure metrics, and early policy learning.

Finally, given the degree of public attention on blast-related brain injury and concern regarding possibly related conditions such as chronic traumatic encephalopathy neuropathological change (CTE-NC), there is a need for evidence-based communication with veterans and clinicians. The grey literature repeatedly highlights the risks of under-recognition, stigma-related under-reporting, and conversely, the risk of over-attribution of symptoms to blast or CTE without adequate evidence. Therefore, clear informational materials could be co-designed for both clinicians and veterans that outline what is known, what remains uncertain, and the importance of early support for symptoms regardless of causative mechanism.

In summary, the evidence base supports a cautious but proactive approach. The available data justify enhanced documentation of blast exposure, holistic and trauma-informed assessment, continued investment in research, and careful monitoring of international developments. At the same time, the absence of definitive exposure thresholds or validated diagnostic tools underscores the need for flexibility and options-based policy development. The approaches outlined above therefore aim to provide a suite of feasible, evidence-aligned measures that acknowledge current limitations while supporting improved care and long-term outcomes for veterans exposed to repetitive low-level blast.

Conclusion

This REA demonstrates that rLLB exposure is increasingly recognised as a relevant occupational hazard in military contexts. Converging indications from human observational studies, animal studies, and international grey literature suggesting that cumulative exposure may contribute to subtle cognitive, physiological, mental health and increased presence of troubling symptoms (visual changes, hearing changes, irritability, fatigue, headache). While the mechanistic evidence from animal studies is strong and coherent, the human evidence, although suggestive of dose-response patterns in high-risk roles, remains limited by methodological variability, confounding factors, and inconsistent exposure measurement. Across all domains, there is currently insufficient certainty to establish causal pathways or definitive long-term outcomes, particularly in relation to neurodegeneration, although the biological plausibility is supported by the preclinical literature.

Despite these uncertainties, the reviewed evidence provides a valuable foundation for understanding potential risks, improving assessment processes, and guiding prudent future policy and research directions. The findings support a holistic, multi-domain view of brain and behavioural health in rLLB-exposed personnel, emphasising the influential roles of comorbid conditions such as PTSD, depression, chronic pain, and sleep disturbance. At the same time, international developments highlight the importance of improving exposure documentation, strengthening surveillance, and investing in translational research that is capable of linking human exposures to validated biological markers and long-term functional outcomes. These aligned insights suggest that meaningful progress is achievable through incremental, evidence-informed steps rather than prescriptive or threshold-based approaches that current data cannot justify.

Overall, the reviewed evidence calls for a balanced, precautionary posture that acknowledges both the observed associations and the substantial gaps that remain. This means supporting actions that improve exposure recognition, enhance clinician and veteran understanding, building an Australian contextualised evidence-base capable of informing future policy with confidence. Continued investment in research, surveillance, and cross-sector collaboration will be essential to refine understanding of rLLB and to ensure

that veterans receive the most appropriate, scientifically grounded care as knowledge in this field continues to evolve.

Appendix 1 – Results Detail

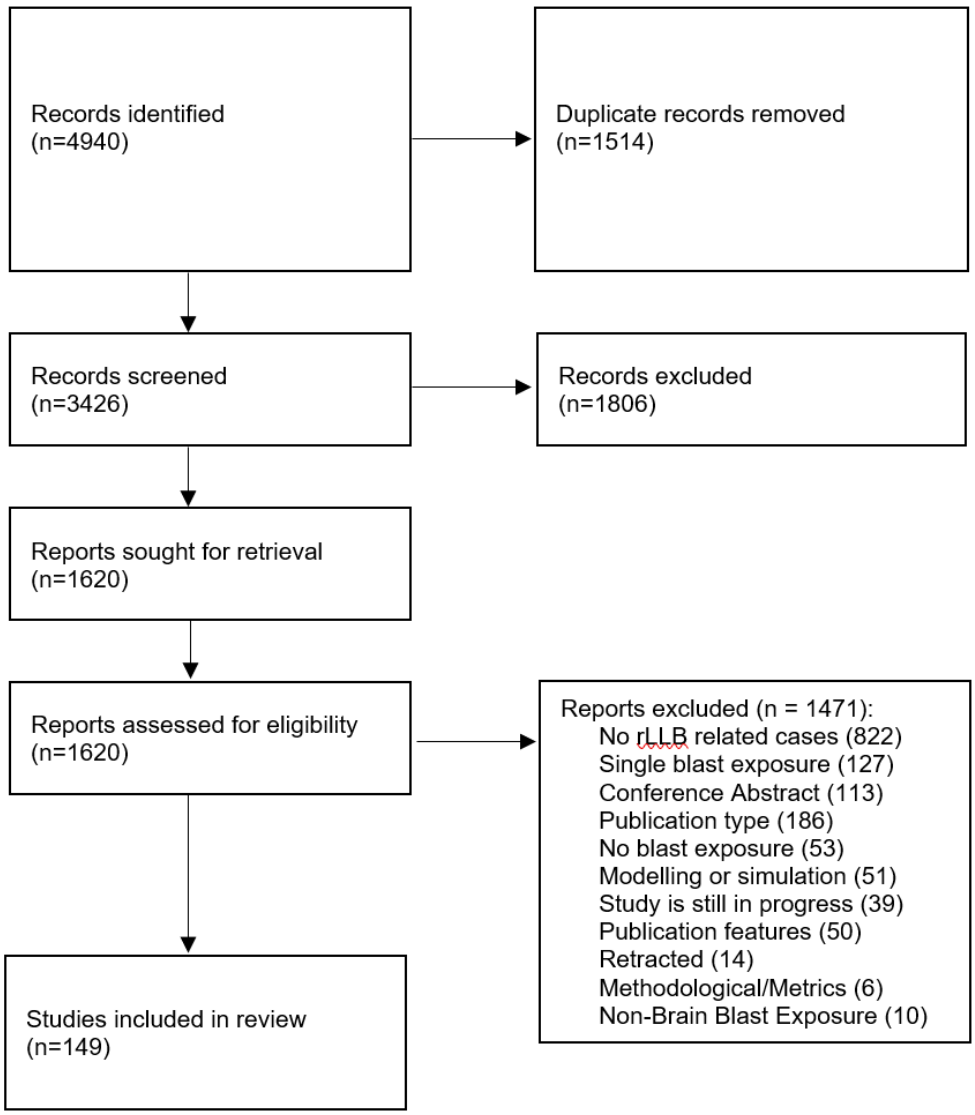

Figure A1.1 - PRISMA compliant flowchart outlining the results of the review process.

Year of Publication

Numbers of publications by year of publication is summarised below in Table A1.1.

Year	Number
2019	6
2020	25
2021	32
2022	17
2023	25
2024	23
2025	21

Table A1.1 – Publication counts by Year of Publication

Appendix 2 - Excluded Peer-Reviewed Publications

A total of 1,471 studies that underwent full-text review were excluded. The reasons for exclusion are presented in Table A2.1 below. Although a single primary reason was assigned to each study, multiple exclusion criteria may have applied. The most clearly identifiable reason for exclusion was documented for each study, with no predetermined hierarchy or prioritisation of exclusion criteria applied.

Table A2.1 - Reasons for exclusion.

Reason for exclusion (full text)	Number of studies
No rLLB related cases (e.g., mixed causes and numbers of blast/mTBI)	822
Single blast exposure (e.g., civilian explosions, some animal studies)	127
Conference abstract	113
Publication type out-of-scope (e.g., narrative review, commentary)	186
No blast exposure (i.e., mTBI from impact or falls)	53
Modelling or simulation studies (e.g., Finite element, computer models)	51
Study is still in progress (e.g., clinical trial registrations where data collection or analysis is still ongoing)	39
Publication features (e.g., language, no access to full text, pre-2019)	50
Retracted	14
Methodological/metrics-based outcomes (e.g. evaluation frameworks)	6
Non-brain blast exposure (e.g., lung)	10
Total	**1471**

During the full-text review process, reviewers noted that a considerable number of excluded studies retained potential relevance for understanding the impacts of rLLB, despite not meeting the REA inclusion criteria. In particular, many studies were excluded because they involved populations with mixed causes of injury or reported results for combined populations rather than specifically for individuals exposed to rLLB. To capture insights from this body of work, a simplified thematic analysis was undertaken to identify the primary thematic focus of these studies and qualitatively assess their scientific proximity to rLLB research. The findings of this analysis are summarised in Table A2.3 and discussed below.

Table A2.3 - Summary of excluded studies - Not-rLLB (n=461) and Unclear if rLLB (n=361)

Themes covered	Not-rLLB	Proportion	Unclear if rLLB	Proportion
TBI but not mTBI	341	73%	250	69%
mTBI or Concussion	221	47%	221	61%
Cognitive Impacts	203	43%	139	39%
Focus on PTSD	196	42%	175	48%
Involved Blast Exposure	77	17%	108	30%
Physiological Implications	40	9%	49	14%
Neurological Imaging	34	7%	62	17%
Animal Study	19	2%	8	1%
Total	461		361	

Thematic patterns in the “Unclear if rLLB” and “Not rLLB” groups

A substantial number of excluded studies retained potential relevance to understanding the impacts of repetitive low-level blast (rLLB), despite not meeting the inclusion criteria. Many of these studies addressed blast-related injuries or cognitive outcomes but lacked sufficient detail to to confirm the characteristics of the exposure (i.e., repetitive or low-level blast). Common reasons for exclusion included mixed injury populations, varying numbers of impacts (none, single and/or multiple), or reporting results for combined cohorts rather than specifically for individuals exposed to rLLB.

Thematic analysis of this group revealed recurring patterns. A large proportion focused on mild traumatic brain injury (mTBI), post-traumatic stress disorder (PTSD), and cognitive outcomes. Approximately half referenced mTBI or concussion, one-third examined PTSD-related symptoms, and a notable subset employed animal studies. Neuroimaging and biomarker studies were prevalent, indicating an emphasis on detecting subtle neural or physiological changes. Many studies relied on indirect exposure indicators—such as occupational specialty, deployment history, or self-reported blast experience—without clear quantification of overpressure magnitude or repetition frequency.

Although methodologically insufficient for inclusion in analyses targeting repetitive, sub-concussive exposures, these studies represent a transitional evidence base. They reflect growing recognition of cumulative effects and chronic symptomatology associated with sub-threshold exposures, particularly in recent publications (2023-2025), where some studies began quantifying exposure frequency even if overpressure levels remained undefined. This evolution underscores the conceptual proximity of these studies to rLLB research and their potential value in informing future investigations.

Methodological Limitations

A consistent limitation across the 'unclear exposure' studies was definitional ambiguity. Terminology such as 'repetitive blast', 'low-level exposure', or 'blast history' was often used without specifying precise operational or exposure criteria. Similarly, several studies referred to included cohorts, such as Operation Iraqi Freedom (OIF), and inferred exposure levels based on this service history, without direct measurement or detailed documentation. Consequently, comparability across studies remains limited. However, this literature provides methodological momentum toward establishing standardised frameworks. Many of the included works employed multi-modal designs – integrating neuroimaging, physiological, and cognitive metrics, which are directly applicable to rLLB study designs.

Moreover, animal studies within this group, while often using higher overpressure magnitudes, reinforce the biological plausibility of cumulative sub-concussive effects. Human studies with longitudinal or occupational samples offer complementary observational evidence. Collectively, these studies demonstrate the growing sophistication of blast exposure research, even where exposure characterisation remains incomplete.

Policy Implications

The diversity and size of the studies where it was unclear if rLLB was included is reflective of a research field in transition – one that acknowledges the significance of repeated low-intensity blast exposure but remains impacted and constrained by inadequate standards and definitions. Compared with the 'not rLLB' group, the “unclear if rLLB” studies show closer thematic alignment with rLLB mechanisms and outcomes, emphasising mild TBI, chronic cognitive changes, and a degree of PTSD comorbidity similar to the studies included in this review. However, such ambiguity negatively impacts on the generalisability of published studies to areas such as rLLB. Equally it impacts negatively on the methodological rigor and designing and reporting of

research data that could allow for future re-analysis if emerging efforts to harmonise blast exposure metrics for military personnel are realised in the future.

These observations have important implications:

1) The formalisation and broad scale adoption of frameworks defining the fundamental supports for blast exposure research.
2) Understanding the inherent limitations and biases associated with historical approaches to identifying clinically recognisable brain effects due to lower intensity head impacts (i.e. concussion and “sub-concussion”, mTBI, rLLB, etc.).
3) Standardising the approach to quantifying exposure to all types of blast – defining pattern, dosing (cumulative and instantaneous), and type in a standard manner.
4) Systematically measuring (or estimating) blast exposure burdens, from both acute exposures and cumulative (longitudinal) doses, in both serving and ex-serving populations.

Appendix 3 – Peer Reviewed Literature

Study ID	Title (citation)	Population	Setting	Country
Agoston 2022	Blood-Based Biomarkers of Repetitive, Subconcussive Blast Overpressure Exposure in the Training Environment: A Pilot Study (58)	Human	Heavy weapons training (HWT) in San Diego, California, USA	USA
Anderson 2021	The Neurobehavioral Effects of Buprenorphine and Meloxicam on a Blast-Induced Traumatic Brain Injury Model in the Rat (96)	Rat	Preclinical laboratory	USA
Arora 2025	Lipidomic Analysis Reveals Systemic Alterations in Servicemen Exposed to Repeated Occupational Low-Level Blast Waves (147)	Human	Defence Research & Development Organisation laboratory, Proof & Experimental Establishment, Chandipur, India	India
Arun 2021	Phosphorylated neurofilament heavy chain in the cerebrospinal fluid is a suitable biomarker of acute and chronic blast-induced traumatic brain injury (87)	Rat	Association for Assessment and Accreditation of Laboratory Animal Care–accredited facility using an advanced blast simulator.	USA
Arun 2020	Blast Exposure Leads to Accelerated Cellular Senescence in the Rat Brain (88)	Rat	Blast-Induced Neurotrauma Branch, Walter Reed Army Institute of Research, United States	USA
Baskin 2021	Repetitive Blast Exposure Increases Appetitive Motivation and Behavioral Inflexibility in Male Mice (97)	Mouse	Laboratory shock tube (VA Puget Sound/University of Washington)	USA
Baskin 2023	Timing matters: Sex differences in inflammatory and behavioral outcomes following repetitive blast mild traumatic brain injury (148)	Mouse	VA Puget Sound Health Care System, Seattle, WA, USA (shock-tube laboratory)	USA
Belding 2024	Traumatic brain injury and occupational risk of low-level blast exposure on adverse career outcomes: an examination of administrative and medical separations from Service (2005–2015) (149)	Human	Population-level military administrative and medical database	USA
Belding 2021a	Occupational Risk of Low-Level Blast Exposure and TBI-Related Medical Diagnoses: A Population-Based Epidemiological Investigation (2005–2015) (39)	Human	U.S. military personnel across branches; data from NHRC CHAMPS database (2005–2015)	USA
Belding 2021b	Potential Health and Performance Effects of High-Level and Low-Level Blast: A Scoping Review of Two Decades of Research (150)	Not Applicable	Publication Review	USA
Belding 2020a	Blast Exposure and Risk of Recurrent Occupational Overpressure Exposure Predict Deployment TBIs (40)	Human	U.S. Marine Corps	USA
Belding 2020b	Self-reported concussion symptomology during deployment: differences as a function of injury mechanism and low-level blast exposure (37)	Human	Self-report survey administered within 30 days of return from deployment (PDHA) across U.S. Marines.	USA
Belding 2023	Single and repeated high-level blast, low-level blast, and new-onset self-reported health conditions in the U.S. Millennium Cohort Study: An exploratory investigation (151)	Human	U.S. service members and veterans participating in the prospective Millennium Cohort Study	USA
Belding 2021c	The Persistence of Blast- versus Impact-Induced Concussion Symptomology Following Deployment (41)	Human	US Marine Corps	USA
Bera 2025	Identification of serum biomarkers for blast-induced traumatic brain injuries: low vs high-intensity exposure in a rat model (98)	Rat	Uniformed Services University of the Health Sciences laboratory, Bethesda, MD, USA.	USA

Study ID	Title (citation)	Population	Setting	Country
Blaze 2020	Blast-Related Mild TBI Alters Anxiety-Like Behavior and Transcriptional Signatures in the Rat Amygdala (99)	Rat	Naval Medical Research Center and James J. Peters VA Medical Center animal facilities	USA
Boutte 2021	Neurotrauma biomarker levels and adverse symptoms among military and law enforcement personnel exposed to occupational overpressure without diagnosed traumatic brain injury (6)	Human	Four US Department of Defense and civilian law enforcement training sites	USA
Bradshaw 2021	Repetitive Blast Exposure Produces White Matter Axon Damage without Subsequent Myelin Remodeling: In Vivo Analysis of Brain Injury Using Fluorescent Reporter Mice (100)	Mouse	Uniformed Services University of the Health Sciences, Bethesda, Maryland, USA	USA
Braun 2024	Macroscopic changes in aquaporin-4 underlie blast traumatic brain injury–related impairment in glymphatic function (80)	Human	Human post-mortem tissue from the Department of Defense Uniformed Services University Brain Tissue Repository; animal experiments at VA Puget Sound	USA
Bugay 2020	A Mouse Model of Repetitive Blast Traumatic Brain Injury Reveals Post-Trauma Seizures and Increased Neuronal Excitability (89)	Mouse	University of Texas Health Science Center, San Antonio, Texas, USA	USA
Callahan 2019	Sensory sensitivity and posttraumatic stress disorder in blast-exposed veterans with mild traumatic brain injury (52)	Human	VA Portland Health Care System (USA)	USA
Campos-Pires 2023	Repetitive, but Not Single, Mild Blast TBI Causes Persistent Neurological Impairments and Selective Cortical Neuronal Loss in Rats (90)	Rat	Preclinical laboratory	UK
Carr 2020	Association of MOS-Based Blast Exposure With Medical Outcomes (42)	Human	US Department of Defense healthcare system; administrative data from 2005–2015	USA
Champagne 2021	Characterizing changes in network connectivity following chronic head trauma in special forces military personnel: a combined resting-fMRI and DTI study (48)	Human	Queen's University, Kingston, Ontario, Canada	Canada
Champagne 2025	Longitudinal analysis highlights structural changes in grey- and white-matter within military personnel exposed to blast (49)	Human	Military personnel in Canada	Canada
Chiariello 2023	Chronicity of repeated blast traumatic brain injury associated increase in oxycodone seeking in rats (101)	Rat	Laboratory using shock tube	USA
Chung 2025	Effects of Blast- and Impact-Related Concussion on Persistent Sleep Problems (152)	Human	Naval Health Research Center	USA
Clausen 2021	Assessment of Neuropsychological Function in Veterans With Blast-Related Mild Traumatic Brain Injury and Subconcussive Blast Exposure (78)	Human	VA Mid-Atlantic MIRECC post-deployment mental health repository, Durham VA Health Care System, Duke University (United States)	USA
Crabtree 2024	Modeling Highly Repetitive Low-level Blast Exposure in Mice (153)	Mouse	VA Puget Sound shock-tube laboratory	USA
Dahal 2024	microRNA profile changes in brain, cerebrospinal fluid, and blood following low-level repeated blast exposure in a rat model (103)	Rat	Walter Reed Army Institute of Research, Silver Spring, Maryland, USA	USA

Study ID	Title (citation)	Population	Setting	Country
DeGasperi 2024	Metabotropic Glutamate Receptor 2 Expression Is Chronically Elevated in Male Rats With Post-Traumatic Stress Disorder Related Behavioral Traits Following Repetitive Low-Level Blast Exposure (154)	Rat	Research facility at James J. Peters VA Medical Center	USA
DeGasperi 2023	Progressive transcriptional changes in the amygdala implicate neuroinflammation in the effects of repetitive low-level blast exposure in male rats (104)	Rat	Research laboratory at James J. Peters VA Medical Center	USA
DeGasperi 2025	Serotonin 5-HT2A receptor expression is chronically decreased in the anterior cerebral cortex of male rats following repetitive low-level blast exposure (106)	Rat	Naval Medical Research Command (Silver Spring, MD) and James J. Peters VA Medical Center (Bronx, NY), USA	USA
Dickerson 2020	Glial Activation in the Thalamus Contributes to Vestibulomotor Deficits Following Blast-Induced Neurotrauma (107)	Rat	Center for Injury Biomechanics, Virginia Tech University and Salem VA Medical Center (United States)	USA
Dickstein 2021	Brain and blood biomarkers of tauopathy and neuronal injury in humans and rats with neurobehavioral syndromes following blast exposure (155)	Human	Icahn School of Medicine at Mount Sinai and Uniformed Services University of Health Sciences recruitment sites	USA
Diociasi 2025	Distinct Functional MRI Connectivity Patterns and Cortical Volume Variations Associated with Repetitive Blast Exposure in Special Operations Forces Members (156)	Human	Comprehensive Brain Health and Trauma Program (ComBHaT) at Home Base	USA
Edwards 2021	Neuronally-derived tau is increased in experienced breachers and is associated with neurobehavioral symptoms (60)	Human	National Institutes of Health Clinical Center (USA)	USA
Edwards 2022	Elevations in Tumor Necrosis Factor Alpha and Interleukin 6 From Neuronal-Derived Extracellular Vesicles in Repeated Low-Level Blast Exposed Personnel (157)	Human	National Institutes of Health (NIH) campus, Walter Reed Army Institute of Research (United States)	USA
Edwards 2020	Blast exposure results in tau and neurofilament light chain changes in peripheral blood (59)	Human	Field training sites during a 10-day advanced explosive breacher course in the United States.	USA
Evans 2020	Sex Does Not Influence Visual Outcomes After Blast-Mediated Traumatic Brain Injury but IL-1 Pathway Mutations Confer Partial Rescue (91)	Mouse	University of Iowa and Iowa City VA Health Care System	USA
GamaSosa 2025	Intramural hematomas and astrocytic infiltration precede perivascular inflammation in a rat model of repetitive low-level blast injury (108)	Rat	Animal research facility at James J. Peters VA Medical Center and Walter Reed Army Institute of Research	USA
GamaSosa 2023	Late chronic local inflammation, synaptic alterations, vascular remodeling and arteriovenous malformations in the brains of male rats exposed to repetitive low-level blast overpressures (9)	Rat	Laboratory shock tube exposure	USA

Study ID	Title (citation)	Population	Setting	Country
GamaSosa 2021	Low-level blast exposure induces chronic vascular remodeling, perivascular astrocytic degeneration and vascular-associated neuroinflammation (92)	Rat	Laboratory shock tube exposure	USA
Gilmore 2025	Investigating the neural network correlates of apathy, disinhibition, and executive dysfunction in active-duty United States Special Operations Forces (158)	Human	Massachusetts General Hospital (Boston) ReBlast study	USA
Gilmore 2024	Impact of repeated blast exposure on active-duty United States Special Operations Forces (159)	Human	Massachusetts General Hospital Athinoula A. Martinos Center for Biomedical Imaging	USA
Glikstein 2025	Five-Year Serial Brain MRI Analysis of Military Members Exposed to Chronic Sub-Concussive Overpressures (32)	Human	Canadian Special Operations Forces Command, Ottawa Hospital	Canada
Govindarajulu 2022	Blast Exposure Dysregulates Nighttime Melatonin Synthesis and Signaling in the Pineal Gland: A Potential Mechanism of Blast-Induced Sleep Disruptions (110)	Rat	Walter Reed Army Institute of Research animal facility	USA
Haran 2021a	Acute neurocognitive deficits in active duty service members following subconcussive blast exposure (61)	Human	Marine Corps units deployed in Afghanistan	USA
Haran 2021b	Chronic Effects of Breaching Blast Exposure on Sensory Organization and Postural Limits of Stability (62)	Human	National Institutes of Health Clinical Center and Naval Medical Research Center, USA	USA
Harper 2024	Increasing the number and intensity of shock tube generated blast waves leads to earlier retinal ganglion cell dysfunction and regional cell death (111)	Mouse	University of Iowa laboratory and VA Center for the Prevention and Treatment of Visual Loss.	USA
Hayes 2022	The association between blast exposure and transdiagnostic health symptoms on systemic inflammation (81)	Human	Translational Research Center for TBI and Stress Disorders (VA Boston)	USA
Hetzer 2024	Model matters: Differential outcomes in traumatic optic neuropathy pathophysiology between blunt and blast-wave mediated head injuries (112)	Mouse	Laboratory	USA
Heyburn 2021	Repeated Low-Level Blast Acutely Alters Brain Cytokines, Neurovascular Proteins, Mechanotransduction, and Neurodegenerative Markers in a Rat Model (115)	Rat	Walter Reed Army Institute of Research Advanced Blast Simulator facility	USA
Heyburn 2023a	Differential effects on TDP-43, piezo-2, tight-junction proteins in various brain regions following repetitive low-intensity blast overpressure (114)	Rat	Walter Reed Army Institute of Research advanced blast simulator facility	USA
Heyburn 2023b	Neuroinflammation Profiling of Brain Cytokines Following Repeated Blast Exposure (113)	Rat	Walter Reed Army Institute of Research Advanced Blast Simulator facility	USA
Honig 2021	Progressive long-term spatial memory loss following repeat concussive and subconcussive brain injury in mice, associated with	Mouse	University of Tennessee Health Science Center, Memphis, USA	USA

Study ID	Title (citation)	Population	Setting	Country
	dorsal hippocampal neuron loss, microglial phenotype shift, and vascular abnormalities (116)			
Howard 2024	An Objective Assessment of Neuromotor Control Using a Smartphone App After Repeated Subconcussive Blast Exposure (160)	Human	Multi-site heavy weapons training environments	USA
Hubbard 2023	Mitochondrial Dysfunction After Repeated Mild Blast Traumatic Brain Injury Is Attenuated by a Mild Mitochondrial Uncoupling Prodrug (117)	Rat	University of Kentucky and Lexington Veterans' Affairs Healthcare System	USA
Hunfalvay 2022	Long-Term Effects of Low-Level Blast Exposure and High-Caliber Weapons Use in Military Special Operators (33)	Human	Controlled laboratory using RightEye eye-tracking system	USA
Iacono 2024	Proteomic Changes in the Hippocampus after Repeated Explosive-Driven Blasts (118)	Rat	Uniformed Services University, Bethesda, MD	USA
Jiang 2023a	Hearing protection and damage mitigation in Chinchillas exposed to repeated low-intensity blasts (143)	Chinchilla	University of Oklahoma laboratory	USA
Jiang 2023b	Mitigation of Hearing Damage With Liraglutide Treatment in Chinchillas After Repeated Blast Exposures at Mild-TBI (142)	Chinchilla	Laboratory animal facility	USA
Jiang 2022	Mitigation of hearing damage after repeated blast exposures in animal model of chinchilla (141)	Chinchilla	University of Oklahoma laboratory.	USA
Kallakuri 2024	Anxiety-like Characteristics, Forepaw Thermal Sensitivity Changes and Glial Alterations 1 Month After Repetitive Blast Traumatic Brain Injury in Male Rats (119)	Rat	Laboratory animal facility at Wayne State University, Detroit (USA)	USA
Kontos 2024	Comparison of Vestibular/Ocular Motor Screening (VOMS) and Computerized Eye-tracking to Identify Exposure to Repetitive Head Impacts (69)	Human	Canadian special operations forces units	Canada
Kulinski 2023	Acute Hearing Deficits associated with Weapons Exposure in Section 734 Blast Overpressure Study (BOS) (161)	Human	Nine U.S. military training environments across various weapons systems	USA
Kulinski 2025	Estimated dose–response relationship between impulse noise exposure and temporary threshold shift in tactical training environments (162)	Human	Military training ranges and ranges where breaching and weapons training occurred	USA
Kumari 2023	Acute metabolic alterations in the hippocampus are associated with decreased acetylation after blast induced TBI (120)	Rat	Institute of Nuclear Medicine and Allied Sciences, Delhi, India	India
Lange 2022	Clinical utility of PTSD, resilience, sleep, and blast as risk factors to predict poor neurobehavioral functioning following traumatic brain injury: A longitudinal study in U.S. military service members (163)	Human	Defense and Veterans Brain Injury Center (multiple U.S. military medical facilities)	USA

Study ID	Title (citation)	Population	Setting	Country
Lange 2020	Longitudinal trajectories and risk factors for persistent postconcussion symptom reporting following uncomplicated mild traumatic brain injury in U.S. Military service members (164)	Human	Defense and Veterans Brain Injury Center longitudinal TBI study	USA
Lee 2022	The dynorphin/kappa opioid receptor mediates adverse immunological and behavioral outcomes induced by repetitive blast trauma (68)	Mouse	Laboratory	USA
Leiva-Salinas 2023	Early Brain Amyloid Accumulation at PET in Military Instructors Exposed to Subconcussive Blast Injuries (76)	Human	Fort Leonard Wood military base (Missouri) and University of Missouri imaging facility	USA
Liu 2024	Association of Blast Exposure in Military Breaching with Intestinal Permeability Blood Biomarkers Associated with Leaky Gut (82)	Human	Military breaching training environment	USA
Logsdon 2020	Nitric oxide synthase mediates cerebellar dysfunction in mice exposed to repetitive blast-induced mild traumatic brain injury (121)	Mouse	Veterans Affairs Puget Sound Health Care System laboratory	USA
Martindale 2025	Blast exposure and long-term diagnoses among veterans: a millennium cohort study investigation of high-level blast and low-level blast (44)	Human	Veterans Health Administration medical records in the United States	USA
Martindale 2020	Influence of Blast Exposure on Cognitive Functioning in Combat Veterans (43)	Human	VA medical centres and research facilities in the United States	USA
Martindale 2021	Research letter: Blast exposure and brain volume (165)	Human	W. G. Hefner VA Healthcare System (USA)	USA
McEvoy 2024	Cumulative Blast Impulse Is Predictive for Changes in Chronic Neurobehavioral Symptoms Following Low Level Blast Exposure during Military Training (1)	Mouse and Human	Preclinical laboratory (helium-driven shock tube) and U.S. Special Operations 6-week explosive breaching training course	USA
Merritt 2020	Associations Between Multiple Remote Mild TBIs and Objective Neuropsychological Functioning and Subjective Symptoms in Combat-Exposed Veterans (53)	Human	VA San Diego Healthcare System outpatient clinics, USA	USA
Miller 2022	A Distinct Metabolite Signature in Military Personnel Exposed to Repetitive Low-Level Blasts (66)	Human	Canadian Forces Base Gagetown and Defence Research and Development Canada Toronto Research Centre	Canada
Miyai 2021	Axonal damage and behavioral deficits in rats with repetitive exposure of the brain to laser-induced shock waves: Effects of inter-exposure time (122)	Rat	Laboratory (Japan Ground Self Defense Force and National Defense Medical College)	Japan
Modica 2020	Hearing Loss and Irritability Reporting Without Vestibular Differences in Explosive Breaching Professionals (63)	Human	Audiology Unit, National Institute on Deafness and Other Communication Disorders, Bethesda, MD (USA)	USA
Nakashima 2022	Repeated Occupational Exposure to Low-level Blast in the Canadian Armed Forces: Effects on Hearing, Balance, and Ataxia (64)	Human	Canadian Armed Forces training and range facilities	Canada
Nonaka 2021	Behavioral and Myelin-Related Abnormalities after Blast-Induced Mild Traumatic Brain Injury in Mice (123)	Mouse	Laboratory (Uniformed Services University and National Institute on Alcohol Abuse and Alcoholism)	USA

Study ID	Title (citation)	Population	Setting	Country
Norris 2025	Modeling biomarker kinetics of Aβ levels in serum following blast (83)	Human	Military weapons training environment	USA
Parsey 2023	Chronic frontal neurobehavioural symptoms in combat-deployed military personnel with and without a history of blast-related mild traumatic brain injury (79)	Human	Military deployment in Afghanistan or Landstuhl Regional Medical Center (Germany)	USA
Pattinson 2019	Concurrent Mild Traumatic Brain Injury and Posttraumatic Stress Disorder Is Associated With Elevated Tau Concentrations in Peripheral Blood Plasma (166)	Human	Defense and Veterans Brain Injury Center longitudinal TBI study sites	USA
PerezGarcia 2021a	Laterality and region-specific tau phosphorylation correlate with PTSD-related behavioral traits in rats exposed to repetitive low-level blast (124)	Rat	Laboratory	USA
PerezGarcia 2021c	Repetitive Low-Level Blast Exposure Improves Behavioral Deficits and Chronically Lowers Aβ42 in an Alzheimer Disease Transgenic Mouse Model (125)	Mouse	Research facility at the James J. Peters VA Medical Center and collaborating institutions	USA
Garcia 2023	(2R,6R)-Hydroxynorketamine Treatment of Rats Exposed to Repetitive Low-Level Blast Injury (109)	Rat	Naval Medical Research Center and James J. Peters VA Medical Center animal facilities	USA
PerezGarcia 2021b	Progressive Cognitive and Post-Traumatic Stress Disorder-Related Behavioral Traits in Rats Exposed to Repetitive Low-Level Blast (126)	Rat	Laboratory	USA
PerezGarcia 2021d	Transcranial Laser Therapy Does Not Improve Cognitive and PTSD-Related Behavioral Traits in Rats Exposed to Repetitive Low-Level Blast Injury (127)	Rat	Preclinical laboratory	USA
Phipps 2020	Characteristics and Impact of U.S. Military Blast-Related Mild Traumatic Brain Injury: A Systematic Review (167)	Human	Military medical facilities and veteran populations	USA, Italy, Lebanon
Powell 2024	Mild Traumatic Brain Injury and Career Stage Associate with Visible Perivascular Spaces in Special Operations Forces Soldiers (168)	Human	University of North Carolina and Fort Liberty research sites	USA
Powell 2023	The Neurophysiological Effects of Blast Exposure and Mild Traumatic Brain Injury in Special Operations Forces Soldiers (169)	Human	Human Movement Science Curriculum, University of North Carolina at Chapel Hill	USA
Rao 2023	Changes in Eye Tracking Features Across Periods of Overpressure Exposure (73)	Human	U.S. Army Special Operations Command and FBI training environments in the USA	USA
Ravula 2022a	Animal model of repeated low-level blast traumatic brain injury displays acute and chronic neurobehavioral and neuropathological changes (129)	Rat	New Jersey Institute of Technology and Walter Reed Army Institute of Research laboratories.	USA
Ravula 2024	MCC950 Attenuates Microglial NLRP3-Mediated Chronic Neuroinflammation and Memory Impairment in a Rat Model of Repeated Low-Level Blast Exposure (130)	Rat	Preclinical laboratory	USA

Study ID	Title (citation)	Population	Setting	Country
Ravula 2022b	Repeated low-level blast induces chronic neuroinflammation and neurobehavioral changes in rat models (128)	Rat	Shock tube facility at New Jersey Institute of Technology, USA	USA
Rhind 2024	Circulating Brain-Reactive Autoantibody Profiles in Military Breachers Exposed to Repetitive Occupational Blast (11)	Human	Defence Research and Development Canada laboratories	Canada
Rhind 2025	Repetitive low-level blast exposure alters circulating myeloperoxidase, matrix metalloproteinases, and neurovascular endothelial molecules in experienced military breachers (71)	Human	Canadian Forces School of Military Engineering and Defence Research facilities	Canada
Robey 2025	Chronic neurobehavioral and neuropathological consequences of repeated blast exposure in P301S transgenic tau rats (131)	Rat	Uniformed Services University of the Health Sciences (USUHS) animal facility	USA
Rowland 2021	Alterations in the Topology of Functional Connectomes Are Associated with Post-Traumatic Stress Disorder and Blast-Related Mild Traumatic Brain Injury in Combat Veterans (170)	Human	W.G. (Bill) Hefner VA Healthcare System and Mid-Atlantic MIRECC	USA
Rowland 2024	Considerations for the assessment of blast exposure in service members and veterans (171)	Human	Salisbury VA Healthcare System and Mid-Atlantic MIRECC, USA	USA
Rowland 2020	Sequelae of blast events in Iraq and Afghanistan war veterans using the Salisbury Blast Interview: A CENC study (54)	Human	Mid-Atlantic MIRECC and Salisbury VA Medical Center (USA)	USA
Schmitt 2021	Blast-induced injury responsive relative gene expression of traumatic brain injury biomarkers in human brain microvascular endothelial cells (172)	Human	University at Buffalo, Institute for Lasers, Photonics and Biophotonics and School of Medicine and Biomedical Sciences.	USA
Schwerin 2021	Expression of GFAP and Tau Following Blast Exposure in the Cerebral Cortex of Ferrets (144)	Ferret	Laboratory (Uniformed Services University of the Health Sciences)	USA
Shea 2025	Impact of Low-Level Blast Exposure From Military Training and Career Cumulation on Hearing Outcomes (173)	Human	Canadian Armed Forces training courses using controlled explosives	Canada
Sigler 2023	Repeated Low-Level Blast Exposure Alters Urinary and Serum Metabolites (12)	Human	Urban Mobility Breacher Course, Fort Leonard Wood, MO, USA	USA
Smith 2020	Hearing Damage Induced by Blast Overpressure at Mild TBI Level in a Chinchilla Model (145)	Chinchilla	University of Oklahoma laboratory experiment	USA
Solar 2024	Repetitive subconcussion results in disrupted neural activity independent of concussion history (174)	Human	Canadian Armed Forces / Defence Research; magnetoencephalography and fMRI conducted at research facilities in Canada.	Canada
Song 2019	Proteomic Analysis and Biochemical Correlates of Mitochondrial Dysfunction after Low-Intensity Primary Blast Exposure (175)	Mouse	University of Missouri open-field blast facility.	USA
Statz 2019	Affective profiling for anxiety-like behavior in a rodent model of mTBI (132)	Rat	Laboratory at Naval Medical Research Center; animals exposed in shock tube to 74.5 kPa (~11 psi) overpressure under isoflurane anesthesia.	USA

Study ID	Title (citation)	Population	Setting	Country
Stone 2020	Functional and Structural Neuroimaging Correlates of Repetitive Low-Level Blast Exposure in Career Breachers (176)	Human	University of Virginia; evaluations performed in one-day session	USA
Stone 2024	Neurological Effects of Repeated Blast Exposure in Special Operations Personnel (3)	Human	Military operational personnel in the United States; Special Operations Command collaboration	USA
Strickler 2025	Exposure to Acute Psychological Trauma Prior to Blast Neurotrauma Results in Alternative Behavioral Outcomes (133)	Rat	Laboratory setting at Virginia Tech; animal facilities.	USA
Stromberg 2023	Mild traumatic brain injury, PTSD symptom severity, and behavioral dyscontrol: a LIMBIC-CENC study (38)	Human	LIMBIC-CENC prospective longitudinal study across 11 U.S. recruitment sites	USA
Terry 2024	Increased [18F]Fluorodeoxyglucose Uptake in the Left Pallidum in Military Veterans with Blast-Related Mild Traumatic Brain Injury (56)	Human	VA Puget Sound Health Care System, Seattle, Washington, USA.	USA
Thangavelu 2020	Overpressure Exposure From .50-Caliber Rifle Training Is Associated With Increased Amyloid Beta Peptides in Serum (67)	Human	Single training site for .50-caliber sniper rifle course	USA
Tschiffely 2020	Assessing a Blast-Related Biomarker in an Operational Community: Glial Fibrillary Acidic Protein in Experienced Breachers (177)	Human	Military breacher training environment	USA
Tsuda 2024	Reduction of epinephrine in the lumbar spinal cord following repetitive blast-induced traumatic brain injury in rats (134)	Rat	Animal facility at North Florida/South Georgia Veterans Health System and University of Florida	USA
Tsuda 2020	Altered monoaminergic levels, spasticity, and balance disability following repetitive blast-induced traumatic brain injury in rats (93)	Rat	Malcom Randall VA Medical Center and University of Florida laboratories.	USA
Turk 2021	Head Injury Exposure in Veterans Presenting to Memory Disorders Clinic: An Observational Study of Clinical Characteristics and Relationship of Event-Related Potentials and Imaging Markers (178)	Human	VA Boston Healthcare System memory disorders clinic	USA
Uzunalli 2021	Structural disruption of the blood–brain barrier in repetitive primary blast injury (179)	Rat	Laboratory; shock tube exposure	USA
Varghese 2023a	Inhibition of cyclooxygenase and EP3 receptor improved long term potentiation in a rat organotypic hippocampal model of repeated blast traumatic brain injury (136)	Rat	Laboratory; cultures sealed and exposed to blast waves in shock tube to mimic mild blast injury.	USA
Varghese 2023b	Partial Depletion of Microglia Attenuates Long-Term Potentiation Deficits following Repeated Blast Traumatic Brain Injury in Organotypic Hippocampal Slice Cultures (135)	Rat	Laboratory at Columbia University or participating institution	USA
Varghese 2022	Pharmacological Interventions to Reduce Electrophysiological Deficits Following Blast Traumatic Brain Injury (94)	Rat	Laboratory (in vitro)	USA
Vartanian 2021	Neuropsychological, Neurocognitive, Vestibular, and Neuroimaging Correlates of Exposure to Repetitive Low-Level Blast Waves: Evidence From Four Nonoverlapping Samples of Canadian Breachers (51)	Human	Canadian Armed Forces breacher training courses	Canada

Study ID	Title (citation)	Population	Setting	Country
Vartanian 2022	Blast effects on post-concussive and mental health outcomes: data from Canadian Armed Forces breachers and snipers (4)	Human	Recruitment at Canadian Forces Base Petawawa and Denison Armoury in Ontario; measurements taken before and after a training exercise.	Canada
Vartanian 2020	Blast in Context: The Neuropsychological and Neurocognitive Effects of Long-Term Occupational Exposure to Repeated Low-Level Explosives on Canadian Armed Forces' Breaching Instructors and Range Staff (50)	Human	Canadian Forces School of Military Engineering (CFSME), Canada; participants recruited via electronic poster among CFSME staff and Denison Armory controls.	Canada
Vaughn 2025	Effect of blast exposure on sensorimotor gating and fear memory (137)	Rat	Laboratory using compressed gas shockwave tube to deliver blast overpressures	USA
Velmurugan 2025	Sex-dependent blood-brain barrier alterations following repeated mild blast traumatic brain injury at varying inter-injury intervals (138)	Rat	Laboratory using McMillan blast device to deliver 11 psi overpressure blasts	USA
Vigil 2023	Acute Treatment with the M-Channel (Kv7, KCNQ) Opener Retigabine Reduces the Long-Term Effects of Repetitive Blast Traumatic Brain Injuries (139)	Mouse	University of Texas Health San Antonio; US Army Institute of Surgical Research	USA
Vorn 2022a	A Pilot Study of Whole-Blood Transcriptomic Analysis to Identify Genes Associated with Repetitive Low-Level Blast Exposure in Career Breachers (84)	Human	Participants were recruited through military and law enforcement networks and studied at the NIH Clinical Center in the United States.	USA
Vorn 2022b	Elevated Axonal Protein Markers Following Repetitive Blast Exposure in Military Personnel (72)	Human	Breaching training program at Fort Leonard Wood, USA, with blast exposure training sessions.	USA
Wachtler 2025	Exploring Calcium Channels as Potential Therapeutic Targets in Blast Traumatic Brain Injury (180)	Not Applicable	Laboratory	Germany; United States of America; Switzerland
Walker 2023	Headache among combat-exposed veterans and service members and its relation to mild traumatic brain injury history and other factors: a LIMBIC-CENC study (74)	Human	Secondary analysis of the LongTerm Impact of Military Relevant Brain Injury Consortium – Chronic Effects of Neurotrauma Consortium (LIMBICCENC) cohort in the United States.	USA
Wang 2020b	Blast-induced hearing impairment in rats is associated with structural and molecular changes of the inner ear (70)	Rat	Blast-Induced Neurotrauma Branch, Walter Reed Army Institute of Research (USA)	USA
Wang 2025	Impact of prior exposures on biomarkers of blast during military tactical training (46)	Human	Military training site (breaching course) in USA	USA
Wang 2020c	DNA Methylation Patterns of Chronic Explosive Breaching in U.S. Military Warfighters (45)	Human	Two training sites at Fort Leonard Wood, Missouri (USA)	USA
Wang 2020a	Acute and Chronic Molecular Signatures and Associated Symptoms of Blast Exposure in Military Breachers (47)	Human	U.S. Army explosive entry training sites (special operations and combat engineer courses)	USA

Study ID	Title (citation)	Population	Setting	Country
Ware 2019	A Preliminary High-Definition Fiber Tracking Study of the Executive Control Network in Blast-Induced Traumatic Brain Injury (57)	Human	Michael E. DeBakey VA Medical Center, Baylor College of Medicine, and University of Houston	USA
Williamson 2022	Using Body-worn Accelerometers to Detect Physiological Changes During Periods of Blast Overpressure Exposure (65)	Human	U.S. Army Special Operations Command and FBI explosive training sites	USA
Woodall 2023	Repetitive Low-level Blast Exposure and Neurocognitive Effects in Army Ranger Mortarmen (5)	Human	U.S. Army Rangers at Fort Benning, GA, USA; military training environment	USA
Wooten 2021	Apolipoprotein E (APOE) e4 Status Moderates the Relationship Between Close-Range Blast Exposure and Cognitive Functioning (146)	Human	VA Boston Healthcare System and affiliated research centers	USA
Wright 2025	Glial activation and nociceptive neuropeptide elevation associated with the development of chronic post-traumatic headache following repetitive blast exposure (77)	Rat	Virginia Tech Advanced Blast Simulator facility	USA
Yuan 2019	Impact of Low-Level Blast Exposure on Brain Function after a One-Day Tactile Training and the Ameliorating Effect of a Jugular Vein Compression Neck Collar Device (85)	Human	SWAT breacher training site in Cincinnati, Ohio, with pre- and post-training assessments at Cincinnati Children's Hospital Medical Center	USA
Yuan 2021	White Matter Alteration Following SWAT Explosive Breaching Training and the Moderating Effect of a Neck Collar Device: A DTI and NODDI Study (86)	Human	SWAT explosive breacher training course	USA
Zhang 2024	Temporal differential effects of post-injury alcohol consumption in a mouse model of blast-induced traumatic brain injury (140)	Mouse	Purdue University laboratories (shock tube apparatus)	USA

Appendix 4 – GRADE Table

Study ID	Risk of Bias (RoB) Limitations in Design and Execution	Inconsistency for All outcomes	Indirectness for All outcomes	Imprecision for All outcomes	Publication Bias	Upgrades and Downgrades	Overall GRADE
Agoston 2022	high	high	high	high	low	RoB (significant), indirectness, imprecision	Very Low
Anderson 2021	low	unclear	high	unclear	low	RoB (some concerns), inconsistency, indirectness, imprecision	Very Low
Arora 2025	high	low	high	high	low	RoB (significant), imprecision Upgraded	Very Low
Arun 2020	high	low	high	high	low	RoB (significant)	Very Low
Arun 2021	high	low	high	high	high	RoB (significant), indirectness, imprecision	Very Low
Baskin 2021	high	low	high	high	high	RoB (significant)	Very Low
Baskin 2023	unclear	low	high	high	low	None	Very Low
Belding 2020a	high	low	high	high	low	RoB (significant), indirectness	Very Low
Belding 2020b	high	low	high	low	low	RoB (significant), Upgraded (large sample size)	Moderate
Belding 2021a	high	low	high	low	high	RoB (significant), indirectness Upgraded	Low
Belding 2021b	high	high	high	high	low	RoB (significant)	Low
Belding 2021c	high	high	high	high	high	RoB (significant), indirectness	Very Low
Belding 2023	high	high	high	low	low	RoB (significant), indirectness. Upgraded (dose–response)	Low

Study ID	Risk of Bias (RoB) Limitations in Design and Execution	Inconsistency for All outcomes	Indirectness for All outcomes	Imprecision for All outcomes	Publication Bias	Upgrades and Downgrades	Overall GRADE
Belding 2024	low	high	low	low	low	RoB (some concerns), indirectness	Low
Bera 2025	high	high	high	high	high	RoB (significant)	Very Low
Blaze 2020	unclear	high	high	high	low	RoB (some concerns), indirectness, imprecision	Very Low
Boutte 2021	high	low	low	high	low	RoB (significant)	Low
Bradshaw 2021	low	low	high	high	unclear	RoB (some concerns)	Very Low
Braun 2024	high	low	unclear	high	low	RoB (significant)	Very Low
Bugay 2020	high	high	high	high	low	RoB (significant), indirectness, imprecision	Very Low
Callahan 2019	high	high	high	high	high	RoB (significant), imprecision	Very Low
Campos-Pires 2023	low	low	high	high	low	RoB (some concerns), indirectness, imprecision, publication bias	Very Low
Carr 2020	high	low	high	low	low	RoB (significant), indirectness Upgraded	Low
Champagne 2021	high	low	high	high	high	RoB (significant), imprecision	Very Low
Champagne 2025	high	unclear	high	high	high	RoB (significant), indirectness, imprecision	Very Low

Study ID	Risk of Bias (RoB) Limitations in Design and Execution	Inconsistency for All outcomes	Indirectness for All outcomes	Imprecision for All outcomes	Publication Bias	Upgrades and Downgrades	Overall GRADE
Chiariello 2023	low	low	high	high	low	RoB (some concerns), indirectness, imprecision	Very Low
Chung 2025	low	low	high	low	low	RoB (some concerns) Upgraded (large effect)	Low
Clausen 2021	high	high	low	high	high	RoB (significant), imprecision	Very Low
Crabtree 2024	high	low	high	low	low	RoB (significant)	Very Low
Dahal 2024	high	low	high	low	low	RoB (significant), indirectness, imprecision	Very Low
DeGasperi 2023	low	low	high	high	low	RoB (some concerns), indirectness, imprecision	Very Low
DeGasperi 2024	low	high	high	low	low	RoB (some concerns), indirectness, imprecision	Very Low
DeGasperi 2025	high	low	high	high	low	RoB (significant), inconsistency, indirectness, imprecision	Very Low
Dickerson 2020	low	high	high	high	low	RoB (some concerns), indirectness, imprecision	Very Low
Dickstein 2021	high	unclear	high	high	unclear	RoB (significant)	Very Low
Diociasi 2025	high	low	high	high	low	RoB (significant)	Low

Study ID	Risk of Bias (RoB) Limitations in Design and Execution	Inconsistency for All outcomes	Indirectness for All outcomes	Imprecision for All outcomes	Publication Bias	Upgrades and Downgrades	Overall GRADE
Edwards 2020	low	low	low	high	low	RoB (some concerns)	Low
Edwards 2021	low	low	high	high	low	RoB (some concerns), imprecision	Very Low
Edwards 2022	high	unclear	high	high	high	RoB (significant), indirectness, imprecision	Very Low
Evans 2020	low	high	high	low	low	RoB (some concerns), indirectness	Very Low
GamaSosa 2021	unclear	low	high	high	unclear	RoB (some concerns)	Very Low
GamaSosa 2023	low	low	high	high	high	RoB (some concerns)	Very Low
GamaSosa 2025	high	high	high	high	high	RoB (significant), indirectness, imprecision	Very Low
Garcia 2023	unclear	unclear	high	high	low	RoB (some concerns), publication bias	Very Low
Gilmore 2024	high	high	high	high	low	RoB (significant), indirectness, imprecision	Low
Gilmore 2025	high	high	high	high	high	RoB (significant), inconsistency, indirectness, imprecision	Very Low
Glikstein 2025	high	low	high	high	unclear	RoB (significant)	Very Low
Govindarajulu 2022	high	low	high	high	high	RoB (significant), indirectness, imprecision	Very Low

Study ID	Risk of Bias (RoB) Limitations in Design and Execution	Inconsistency for All outcomes	Indirectness for All outcomes	Imprecision for All outcomes	Publication Bias	Upgrades and Downgrades	Overall GRADE
Haran 2021a	high	high	high	high	low	RoB (significant), indirectness, imprecision	Very Low
Haran 2021b	low	unclear	high	high	low	RoB (significant), imprecision	Very Low
Harper 2024	high	high	high	high	low	RoB (significant)	Very Low
Hayes 2022	high	unclear	high	high	low	RoB (significant)	Very Low
Hetzer 2024	high	high	high	high	low	RoB (significant), indirectness, imprecision	Very Low
Heyburn 2021	high	high	high	high	high	RoB (significant), indirectness, imprecision	Very Low
Heyburn 2023a	low	high	high	high	low	RoB (some concerns), indirectness, imprecision	Very Low
Heyburn 2023b	high	high	high	unclear	high	RoB (significant), indirectness, imprecision	Very Low
Honig 2021	high	high	high	high	low	RoB (significant), indirectness, imprecision	Very Low
Howard 2024	high	high	high	high	high	RoB (significant)	Very Low
Hubbard 2023	low	low	high	low	low	RoB (some concerns), indirectness, imprecision	Very Low
Hunfalvay 2022	high	low	high	high	low	RoB (significant), indirectness,	Very Low

Study ID	Risk of Bias (RoB) Limitations in Design and Execution	Inconsistency for All outcomes	Indirectness for All outcomes	Imprecision for All outcomes	Publication Bias	Upgrades and Downgrades	Overall GRADE
						imprecision, publication bias	
Iacono 2024	high	low	high	high	high	RoB (significant)	Very Low
Jiang 2022	high	low	high	high	high	RoB (significant)	Very Low
Jiang 2023a	high	high	high	high	low	RoB (significant), indirectness, imprecision	Very Low
Jiang 2023b	low	high	high	high	low	RoB (some concerns)	Very Low
Kallakuri 2024	low	high	high	high	high	RoB (some concerns)	Very Low
Kontos 2024	high	low	high	high	unclear	RoB (significant), imprecision	Very Low
Kulinski 2023	high	low	low	low	low	RoB (some concerns)	Low
Kulinski 2025	high	low	low	high	unclear	RoB Upgraded (dose–response)	Very Low
Kumari 2023	high	high	high	high	high	RoB (significant), inconsistency, imprecision	Very Low
Lange 2020	high	high	high	high	high	RoB (significant), indirectness, imprecision	Very Low
Lange 2022	high	low	high	high	high	RoB (significant), inconsistency, indirectness	Low
Lee 2022	high	low	high	high	high	RoB (some concerns)	Very Low
Leiva-Salinas 2023	high	low	unclear	high	high	RoB (significant)	Very Low

Study ID	Risk of Bias (RoB) Limitations in Design and Execution	Inconsistency for All outcomes	Indirectness for All outcomes	Imprecision for All outcomes	Publication Bias	Upgrades and Downgrades	Overall GRADE
Liu 2024	high	low	high	high	high	RoB (significant), indirectness, imprecision	Very Low
Logsdon 2020	high	low	high	low	high	RoB (some concerns), indirectness, imprecision	Very Low
Martindale 2020	high	low	high	high	low	RoB (significant)	Very Low
Martindale 2021	high	low	high	high	low	RoB (significant), imprecision	Low
Martindale 2025	low	low	high	low	low	RoB (some concerns) .Upgraded (large effect)	Low
McEvoy 2024	high	low	high	high	low	RoB (significant), imprecision Upgraded	Very Low
Merritt 2020	high	low	high	high	low	RoB (significant), indirectness, imprecision	Very Low
Miller 2022	high	low	high	high	low	RoB (significant)	Very Low
Miyai 2021	high	unclear	high	high	low	RoB (significant)	Very Low
Modica 2020	high	unclear	high	high	low	RoB (significant)	Very Low
Nakashima 2022	high	unclear	high	high	low	RoB (significant), indirectness, imprecision	Very Low
Nonaka 2021	high	unclear	high	high	low	RoB (significant), indirectness, imprecision	Very Low
Norris 2025	high	unclear	high	high	low	RoB (significant), publication bias	Very Low

Study ID	Risk of Bias (RoB) Limitations in Design and Execution	Inconsistency for All outcomes	Indirectness for All outcomes	Imprecision for All outcomes	Publication Bias	Upgrades and Downgrades	Overall GRADE
Parsey 2023	high	low	low	low	low	RoB (significant)	Low
Pattinson 2019	high	unclear	high	high	low	RoB (significant)	Very Low
PerezGarcia 2021a	unclear	unclear	high	high	unclear	RoB (some concerns), indirectness, imprecision	Very Low
PerezGarcia 2021b	high	unclear	high	high	low	RoB (significant)	Very Low
PerezGarcia 2021c	high	high	high	high	low	RoB (significant), indirectness, imprecision, publication bias	Very Low
PerezGarcia 2021d	unclear	low	high	high	low	RoB (some concerns), inconsistency, indirectness, imprecision	Very Low
Phipps 2020	high	high	high	high	unclear	RoB (significant), inconsistency, indirectness, imprecision	Very Low
Powell 2023	high	unclear	high	high	low	RoB (significant)	Very Low
Powell 2024	high	unclear	high	unclear	low	RoB (significant), indirectness	Very Low
Rao 2023	high	unclear	unclear	high	unclear	RoB (significant), imprecision Upgraded	Very Low
Ravula 2022a	unclear	unclear	high	high	low	RoB (some concerns)	Very Low

Study ID	Risk of Bias (RoB) Limitations in Design and Execution	Inconsistency for All outcomes	Indirectness for All outcomes	Imprecision for All outcomes	Publication Bias	Upgrades and Downgrades	Overall GRADE
Ravula 2022b	high	unclear	high	high	low	RoB (significant), indirectness, imprecision	Very Low
Ravula 2024	unclear	unclear	high	high	unclear	RoB (some concerns), indirectness, imprecision, publication bias	Very Low
Rhind 2024	high	unclear	high	high	low	RoB (significant)	Very Low
Rhind 2025	high	unclear	unclear	high	low	RoB (significant), imprecision	Very Low
Robey 2025	unclear	high	high	high	low	RoB (some concerns), indirectness, imprecision	Very Low
Rowland 2020	high	unclear	low	unclear	low	RoB (significant), imprecision	Very Low
Rowland 2021	high	high	high	unclear	high	RoB (significant), inconsistency, indirectness	Very Low
Rowland 2024	high	high	high	unclear	low	RoB (significant), inconsistency, indirectness	Very Low
Schmitt 2021	high	unclear	high	high	low	RoB (significant)	Very Low
Schwerin 2021	unclear	unclear	high	high	low	RoB (some concerns)	Very Low
Shea 2025	high	unclear	unclear	high	low	RoB (significant), imprecision	Very Low
Sigler 2023	high	low	unclear	high	low	RoB (significant), indirectness, imprecision	Very Low

Study ID	Risk of Bias (RoB) Limitations in Design and Execution	Inconsistency for All outcomes	Indirectness for All outcomes	Imprecision for All outcomes	Publication Bias	Upgrades and Downgrades	Overall GRADE
Smith 2020	high	unclear	high	high	low	RoB (significant), indirectness, imprecision	Very Low
Solar 2024	high	unclear	high	high	unclear	RoB (significant)	Very Low
Song 2019	unclear	low	high	high	low	RoB (some concerns)	Very Low
Statz 2019	high	unclear	high	high	low	RoB (significant), indirectness, imprecision	Very Low
Stone 2020	high	unclear	high	high	low	None	Very Low
Stone 2024	high	unclear	high	unclear	low	RoB (significant)	Very Low
Strickler 2025	unclear	unclear	high	high	low	RoB (some concerns)	Very Low
Stromberg 2023	unclear	low	unclear	low	low	RoB (some concerns), Upgraded (sample size)	Moderate
Terry 2024	high	unclear	high	unclear	low	RoB (significant)	Very Low
Thangavelu 2020	high	unclear	high	high	unclear	RoB (significant), indirectness, imprecision	Very Low
Tschiffely 2020	high	unclear	high	high	low	RoB (significant), indirectness, imprecision	Very Low
Tsuda 2020	low	low	unclear	high	low	RoB (some concerns)	Very Low
Tsuda 2024	high	unclear	high	high	low	RoB (significant), indirectness, imprecision	Very Low

Study ID	Risk of Bias (RoB) Limitations in Design and Execution	Inconsistency for All outcomes	Indirectness for All outcomes	Imprecision for All outcomes	Publication Bias	Upgrades and Downgrades	Overall GRADE
Turk 2021	high	unclear	high	high	unclear	RoB (significant), indirectness, imprecision	Very Low
Uzunalli 2021	high	unclear	high	high	high	RoB (significant)	Very Low
Varghese 2022	high	unclear	high	high	unclear	RoB (significant), inconsistency, indirectness, imprecision	Very Low
Varghese 2023a	high	unclear	high	high	low	RoB (significant), indirectness, imprecision	Very Low
Varghese 2023b	high	unclear	high	high	low	RoB (significant), indirectness, imprecision	Very Low
Vartanian 2020	high	high	unclear	high	low	RoB (significant), imprecision	Very Low
Vartanian 2021	high	low	high	high	low	RoB (significant), indirectness, imprecision	Very Low
Vartanian 2022	high	unclear	high	unclear	unclear	RoB (significant)	Very Low
Vaughn 2025	high	low	unclear	low	low	RoB (significant), indirectness, imprecision	Very Low
Velmurugan 2025	high	unclear	high	high	low	RoB (significant), indirectness, imprecision	Very Low
Vigil 2023	high	low	unclear	unclear	unclear	RoB (significant)	Very Low
Vorn 2022a	high	unclear	high	high	low	RoB (significant), indirectness, imprecision	Very Low

Study ID	Risk of Bias (RoB) Limitations in Design and Execution	Inconsistency for All outcomes	Indirectness for All outcomes	Imprecision for All outcomes	Publication Bias	Upgrades and Downgrades	Overall GRADE
Vorn 2022b	high	low	high	unclear	unclear	RoB (significant), indirectness, imprecision	Very Low
Wachtler 2025	high	high	high	low	unclear	RoB	Very Low
Walker 2023	unclear	low	unclear	low	low	RoB (some concerns)	Low
Wang 2020a	high	unclear	high	unclear	low	RoB (significant), indirectness, imprecision	Very Low
Wang 2020b	unclear	low	high	high	low	RoB (some concerns), indirectness, imprecision	Very Low
Wang 2020c	high	unclear	unclear	high	low	RoB (significant), indirectness, imprecision	Very Low
Wang 2025	high	unclear	high	high	low	RoB (significant), indirectness, imprecision	Very Low
Ware 2019	high	low	unclear	high	low	RoB (significant)	Very Low
Williamson 2022	high	unclear	high	high	high	RoB (significant), indirectness, imprecision	Very Low
Woodall 2023	high	low	low	high	unclear	RoB (significant), imprecision	Very Low
Wooten 2021	unclear	low	low	high	high	RoB (some concerns)	Very Low
Wright 2025	high	low	high	high	low	RoB (significant)	Very Low
Yuan 2019	high	high	high	high	low	RoB (significant), indirectness, imprecision	Low

Study ID	Risk of Bias (RoB) Limitations in Design and Execution	Inconsistency for All outcomes	Indirectness for All outcomes	Imprecision for All outcomes	Publication Bias	Upgrades and Downgrades	Overall GRADE
Yuan 2021	high	high	low	unclear	high	RoB (significant), indirectness, imprecision, publication bias	Low
Zhang 2024	high	low	high	high	low	RoB (significant)	Very Low

Note: Downgrading decisions were applied in accordance with GRADE guidance and reflect considerations of risk of bias, indirectness, inconsistency, and imprecision across the contributing evidence. Detailed justifications for individual downgrading decisions are provided in the accompanying evidence assessment and methods sections.

Appendix 5 – Grey Literature

ID	Title	Year	Country	Organisation	Source Type	URL	Summary
GL_1	Clinical Pearls - Mild Traumatic Brain injury and PTSD	2023	USA	DHA	Clinical Guidance	https://health.mil/Reference-Center/Publications/2023/09/29/Mild-TBI-and-PTSD-Clinical-Pearls	Focuses on co-occurrence of mTBI and PTSD, overlapping symptoms, importance of screening, blast-related mechanisms, and integrated rehab with behavioural strategies.
GL_2	Assessment and Management of Headache Following Concussion/ Mild Traumatic Brain Injury: Guidance for the Primary Care Manager	2024	USA	TBICoE	Clinical Guidance	https://health.mil/Reference-Center/Publications/2024/03/05/Management-of-Headache-Following-ConcussionmTBI-Clinical-Recommendation	Guidance for assessing and managing post-traumatic headache, medication overuse, comorbidities, and treatment pathways.
GL_3	Clinical Pearls - Mild Traumatic Brain Injury and Multiple Concussions	2024	USA	TBICoE	Clinical Guidance	https://health.mil/Reference-Center/Publications/2024/03/28/Multiple-Concussion-Clinical-Pearls	Addresses evaluation/management of multiple concussions, cumulative risk, monitoring, and return-to-duty considerations.
GL_4	Recurrent Concussion Evaluation	2025	USA	TBICoE	Clinical Guidance	https://health.mil/Reference-Center/Publications/2025/04/23/Recurrent-Concussion-Evaluation	Covers evaluation framework for recurrent concussions, cumulative injury risk, and special assessment pathways.

ID	Title	Year	Country	Organisation	Source Type	URL	Summary
GL_5	Acute Concussion Care Pathway - Information for Providers	2024	USA	TBICoE	Clinical Guidance	https://health.mil/Reference-Center/Fact-Sheets/2024/05/07/Acute-Concussion-Care-Pathway-Fact-Sheet	Quick reference for acute concussion identification, activity progression, monitoring, and referral triggers.
GL_6	DOD Blast Overpressure Provider Support Tool	2024	USA	TBICoE	Clinical Guidance	https://health.mil/Reference-Center/Fact-Sheets/2025/09/16/Blast-Overpressure-Provider-Support-Tool	Guidance for clinicians managing blast-overpressure exposure, low-level blast effects, assessment, and monitoring.
GL_7	DVBIC-TBICoE 15-Year Studies Research Findings: Blood-Based Biomarkers of TBI	2024	USA	DHA	Information Sheet	https://health.mil/Reference-Center/Publications/2024/10/16/DVBIC-TBICoE-15Year-Studies-Research-Findings-Blood-Based-Biomarkers-of-TBI	Summarizes 15 years of biomarker research, progress, limitations, and future directions.

ID	Title	Year	Country	Organisation	Source Type	URL	Summary
GL_8	Changes in Behavior, Personality or Mood Following Concussion/ Mild Traumatic Brain Injury	2023	USA	DHA	Information Sheet	https://health.mil/Reference-Center/Fact-Sheets/2023/05/22/Changes-in-Behavior-Personality-or-Mood-Following-Concussion-mTBIFact-Sheet	Highlights behavioral and mood sequelae post-mTBI, encourages screening and early referral.
GL_9	Leader policy guidance for management of Mild Traumatic Brain Injury/Concussion in the Deployed Setting	2023	USA	DHA	Information Sheet	https://health.mil/Reference-Center/Fact-Sheets/2023/06/14/Leader-Policy-Guidance-for-Mild-TBI-Concussion-in-the-Deployed-Setting-Fact-Sheet	Guidance for leaders on mTBI recognition, operational impacts, duty decisions, and readiness.
GL_10	What is Low Level Blast	2023	USA	VA	Information Sheet	https://health.mil/LLB	What is Low Level Blast
GL_11	PTSD and other Stress-Related Disorders Following Concussion/ Mild TBI	2023	USA	TBICoE	Information Sheet	https://www.health.mil/Reference-Center/Fact-Sheets/2023/12/14/Concussion-mTBI-and-PTSD-Fact-Sheet	Explains overlap of mTBI and PTSD for service members, symptom similarities, and care pathways.

ID	Title	Year	Country	Organisation	Source Type	URL	Summary
GL_12	Management of Headache Following Concussion/ mTBI Fact Sheet	2024	USA	TBICoE	Information Sheet	https://health.mil/Reference-Center/Fact-Sheets/2024/03/06/Managing-Headaches-Following-Concussion-Fact-Sheet	Simplified overview of post-traumatic headache types, assessment, and management.
GL_13	Traumatic Brain Injury and Alcohol Misuse	2024	USA	TBICoE	Information Sheet	https://www.health.mil/Reference-Center/Fact-Sheets/2024/05/07/TBI-and-Alcohol-Misuse	Describes interaction between TBI and alcohol misuse, increased risks, and integrated care.
GL_14	Medical Devices for the Assessment of Traumatic Brain Injury Fact Sheet	2024	USA	TBICoE	Information Sheet	https://health.mil/Reference-Center/Fact-Sheets/2025/02/20/Medical-Devices-for-Assessment-of-TBI	Reviews diagnostic devices and monitoring tools relevant to TBI, capabilities, and gaps.
GL_15	DOD Numbers for Traumatic Brain Injury Worldwide	2024	USA	TBICoE	Information Sheet	https://www.health.mil/Reference-Center/Reports/2025/08/21/2024-DOD-Worldwide-Numbers-for-TBI	Presents global incidence, severity breakdowns, deployment vs non-deployment trends.

ID	Title	Year	Country	Organisation	Source Type	URL	Summary
GL_16	What is TBICoE doing to help warfighters exposed to low-level blast?	2023	USA	TBICoE	Information Sheet	https://www.health.mil/Military-Health-Topics/Warfighter-Brain-Health/Brain-Health-Topics/Low-Level-Blast-Exposure	Overview of low-level blast impacts, research gaps, and brain health considerations.
GL_17	Blast Overpressure Service Member Fact Sheet	2024	USA	TBICoE	Information Sheet	https://www.health.mil/Reference-Center/Fact-Sheets/2025/09/16/Blast-Overpressure-Service-Member-Fact-Sheet	Explains blast overpressure effects, symptoms, reporting, and readiness strategies.
GL_18	118th Congress (2023-2024): Blast Overpressure Safety Act	2024	USA	US Congress	Legislation	https://www.congress.gov/bill/118th-congress/senate-bill/4109/text	The Blast Overpressure Safety Act (H.R. 8025) is a comprehensive legislative proposal aimed at reducing, tracking, and treating concussive and subconcussive brain injuries among U.S. military personnel, particularly those caused by blast overpressure during training and operations. The bill mandates standardized neurocognitive assessments, creation of detailed blast exposure and TBI logs, integration of exposure data into lifelong health records, and rigorous oversight through Inspector General audits and recurring congressional reports. It establishes the Warfighter Brain Health Initiative, sets exposure thresholds, creates training and monitoring requirements, and directs the development of safer weapons systems. The Act also expands specialized care through programs for Special Operations Forces and formalizes the National Intrepid Center of Excellence as a program of record, ensuring interdisciplinary treatment and research for TBI and related conditions. Collectively, the legislation strengthens prevention, monitoring, research, clinical care, and transparency across the Department of Defense to address blast-related brain injuries and their long-term impacts.

ID	Title	Year	Country	Organisation	Source Type	URL	Summary
GL_19	Establishing care and treatment at VA for blast overpressure exposure	2024	USA	US Congress	Letter	https://democrats-veterans.house.gov/imo/media/doc/establishing_care_and_treatment_at_va_for_blast_overpressure_exposure_-_final_w_signatures.pdf	The letter urges the U.S. Department of Veterans Affairs to take immediate action to recognize, track, and compensate health conditions caused by repeated occupational exposure to low-level blast overpressure in servicemembers who fire heavy weapons. Citing DoD research, clinical guidance, and emerging scientific evidence, the Members of Congress argue that chronic sub-concussive blast exposure—often sustained during routine training—causes measurable and lasting brain injury, including cognitive deficits, memory problems, mood changes, and other neurological effects. They request that VA use its existing authority to establish a new Environmental Health Registry for Occupational Blast Overpressure Exposure and create presumptive service connections for related conditions, supported by a dedicated working group and National Academies review. The letter emphasizes that these exposures are inherent to military readiness across multiple generations of veterans and that timely action is necessary to ensure affected servicemembers and veterans receive appropriate care and benefits.
GL_20	USAMRDC Supports Development of Capability to Predict BlastInjury Exposure During Training	2024	USA	DVIDS	Media	https://www.army.mil/article/273486/usamrdc_supports_development_of_capability_to_predict_blast_injury_exposure_during_training	The U.S. Army Medical Research and Development Command's Blast Injury Research Coordinating Office is developing a Blast Overpressure Tool to model and predict blast shock-wave exposure during live-fire training, helping range managers and instructors position personnel to reduce harmful overpressure exposure. This tool uses data from live fire exercises to generate visualizations and guidance on safe distances and exposure zones for heavy weapons, with the aim of improving training safety and mitigating cognitive and physical effects of repeated blast exposure.
GL_21	DOD Spells Out New Requirements to Counter Blast Overpressure Risks	2024	USA	DoW	Media	https://www.war.gov/News/News-Stories/Article/Article/3873928/dod-spells-out-new-requirements-to-counter-blast-overpressure-risks/	The U.S. Department of Defense issued a policy memorandum signed by Deputy Secretary of Defense Kathleen Hicks that establishes new requirements to manage and mitigate the risks to brain health from blast overpressure (BOP) generated by weapons systems, including standoff distances, exposure tracking, and training standards. The policy directs enhanced risk management actions - such as tracking personnel exposed to BOP, integrating blast risk into weapons acquisition decisions, and expanding cognitive health assessments - while emphasizing that these measures aim to preserve readiness without unduly restricting essential training.

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GL_22	Army begins cognitive testing at Initial Entry Training	2024	USA	US Army	Media	https://www.army.mil/article/279293/army_begins_cognitive_testing_at_initial_entry_training#:~:text=Fort%20Sill%2C%20Oklahoma%2C%20home%20of,by%20the%20end%20of%202024.	The U.S. Army has started baseline cognitive assessments for new recruits during Initial Entry Training as part of a broader effort to monitor and reduce brain health risks, with all services scheduled to implement similar testing by the end of 2024. This permanent cognitive monitoring program, building on a long-standing assessment tool, aims to track brain function over soldiers' careers, support early detection of cognitive changes, and incorporate blast overpressure considerations into brain health strategies.
GL_23	INVICTA Study: Uncovering Blast Exposure's Impact on Special Operations Forces	2025	USA	USUHS	Media	https://news.usuhs.edu/2025/04/invicta-study-uncovering-blast.html	The Uniformed Services University's five-year INVICTA study investigates how low-level blast overpressure exposures during heavy weapon training affect neurological functions such as memory, gait, sensory processing, and brain health in Special Operations Forces and Range Safety Officers. Results are already influencing training practices and aim to improve protective measures and risk stratification to safeguard service members' brain health and readiness.
GL_24	MoD accepts British Army weapons systems can cause brain damage in soldiers	2025	UK	ITV Corporation	Media	https://www.itv.com/news/2025-07-22/mod-admits-british-army-weapons-systems-are-causing-brain-damage-in-soldiers	The UK Ministry of Defence has acknowledged for the first time that blast overpressure from some British Army weapons systems can cause brain injury in service personnel, with repeated exposures likely affecting *thousands* of current soldiers and veterans. This admission follows recognition that "low-level blasts" from heavy weapons such as mortars and machine guns can lead to microscopic brain damage and long-term neurological effects, prompting calls for further research and policy action to better understand and mitigate these risks.

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GL_25	MoD Admits Their Weapons Blasts Cause Brain Injury	2025	UK	Veterans Welfare Group	Media	https://veteranswelfaregroup.co.uk/news/mod-admits-liability-for-brain-injuries-casused-by-their-weapons/	The UK Ministry of Defence has accepted liability that repeated blast exposure from British Army weapons systems can cause brain injury in soldiers, marking a significant shift in official recognition of blast-related harm. The admission strengthens the position of affected veterans seeking medical recognition and compensation, and underscores growing evidence that low-level, repetitive blast overpressure can lead to lasting neurological damage.
GL_26	New Zealand Defence Force's new brain injury warning to troops over weapons and explosives	2024	NZ	NZ Herald	Media	https://www.nzherald.co.nz/nz/new-zealand-defence-forces-new-brain-injury-warning-to-troops-over-weapons-and-explosives/4TVF2MOHHRD7DCHZOOEHKXRSDI/	The New Zealand Defence Force has warned its personnel that exposure to certain weapons and explosives, including repeated low-level blasts from heavy calibre weapons, can cause brain damage and cognitive symptoms, and has issued a health directive with safety guidance to mitigate this risk. The directive highlights the need for monitoring and managing exposures and also notes that Veterans' Affairs currently lacks a formal compensation pathway for blast-related brain injury despite acknowledging the potential harm.
GL_27	The enemy within: Blasts from Australian soldiers' own weapons may be causing brain injury	2024	Australia	ABC News	Media	https://www.abc.net.au/news/2024-08-20/elite-adf-soldiers-concern-blasts-from-own-weapons-brain-injury/104154038	The ABC reports that Australian Defence Force personnel, including special forces and trainers, are experiencing symptoms such as chronic headaches, memory loss, irritability, and cognitive decline that veterans and some clinicians link to repeated blast overpressure from firing their own weapons during training, even without combat exposure. The coverage highlights concerns that these blast-related brain injuries are often unrecognised or misdiagnosed as PTSD, with calls for better monitoring, research, and recognition of the neurological impacts of routine heavy weapons use.

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GL_28	Statement by Deputy Secretary of Defense Kathleen Hicks on Blast Overpressure Risk-Management Policy Memorandum	2024	USA	DoW	Memorandum	https://www.war.gov/News/Releases/Release/Article/3868333/statement-by-deputy-secretary-of-defense-kathleen-hicks-on-blast-overpressure-r/#:~:text=To%20maintain%20that%20advantage%2C%20I,Brain%20Health%20(WBH)%20Initiative.	Deputy Secretary of Defense Kathleen Hicks announced a new Department of Defense policy memorandum that formally recognises blast overpressure as a brain health risk and mandates risk-management measures across training, operations, and weapons system lifecycles. The policy aligns blast exposure management with the Warfighter Brain Health Initiative, requiring exposure tracking, mitigation strategies, and leadership accountability while balancing force readiness with long-term cognitive health protection.
GL_29	Required Clinical Tools and Procedures for the Assessment and Clinical Management of Mild Traumatic Brain Injury (mTBI)/Concussion in Non-Deployed Setting	2021	USA	DHA	Procedural Instruction	https://health.mil/Reference-Center/Publications/2025/06/26/DHA-PI-6490-04-Required-Clinical-Tools-and-Procedures-for-Assessment-and-Management-of-Mild-TBI-in-Non-Deployed-Setting	This Defense Health Agency Procedural Instruction outlines the mandatory clinical tools and procedures for assessing and managing mild traumatic brain injury (mTBI)/concussion in non-deployed settings, requiring use of the Military Acute Concussion Evaluation, Version 2 (MACE 2), progressive return-to-activity (PRA) protocols, and structured documentation in the Electronic Health Record. It defines responsibilities across DHA leadership, Military Departments, and Medical Treatment Facilities to ensure standardized evaluation, timely follow-up, training, and compliance monitoring. The instruction mandates early assessment after potentially concussive events, tracking symptoms with validated tools such as the Neurobehavioral Symptom Inventory, and comprehensive documentation using the Tri-Service Workflow forms. It also emphasizes training for clinicians, availability of resources, and alignment with broader DoD policies to improve outcomes and reduce morbidity from mTBI/concussion.

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GL_30	TBICoE Annual Report 2024	2024	USA	TBICoE	Report	https://health.mil/Reference-Center/Reports/2025/03/13/2024-TBICoE-Annual-Report	The 2024 TBICoE Annual Report outlines a year of major progress in advancing warfighter brain health through research, clinical support, surveillance, and dissemination initiatives. Key achievements include launching the Warfighter Brain Health Provider Toolkit app, contributing extensively to national conferences and the Military Health System Research Symposium, and advancing longitudinal studies on the long-term effects of TBI. The report highlights strengthened interagency collaboration, updated clinical recommendations, including guidance on post-traumatic headache and low-level blast exposure, and expanded training and education efforts across the Military Health System. With over 34 active research studies, numerous publications, and broad engagement through podcasts, videos, and awareness campaigns, TBICoE continues to drive evidence-based improvements in TBI care, readiness, and outcomes for service members, veterans, and their families.
GL_31	TBICoE Annual Report 2023	2023	USA	TBICoE	Report	https://health.mil/Reference-Center/Reports/2024/03/29/2023-TBICoE-Annual-Report	The 2023 Traumatic Brain Injury Center of Excellence Annual Report highlights TBICoE's major contributions to warfighter brain health, including expanded surveillance of TBI across the Military Health System, development of new clinical tools and fact sheets—especially on low-level blast exposure—and delivery of extensive provider training and public education initiatives. The report describes broad collaborations across the Department of Defense, VA, academic partners, and federal agencies; substantial research output including congressionally mandated studies on blast overpressure and long-term outcomes of TBI; and strong dissemination efforts through podcasts, newsletters, social media, and regional education coordinators. It emphasizes TBICoE's leadership in advancing the DOD Warfighter Brain Health Strategy, ongoing evaluation of TBI clinical care, and translation of emerging research into practical guidance, all while preparing for leadership transition and continued mission growth.

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GL_32	TBICoE Annual Report 2022	2022	USA	TBICoE	Report	https://health.mil/Reference-Center/Reports/2023/03/21/2022-TBICoE-Annual-Report	The TBICoE 2022 Annual Report outlines the Defense Health Agency's central efforts to protect and improve warfighter brain health through coordinated surveillance, clinical guidance, research, and education. Key achievements include leadership of the Warfighter Brain Health Initiative, major updates to clinical tools such as MACE 2 and Progressive Return to Activity, ongoing surveillance documenting over 468,000 first-time TBIs since 2000, and large-scale research programs on blast exposure and long-term TBI outcomes. The Center expanded outreach through Brain Injury Awareness Month, podcasts, digital communications, and more than 2,100 regional training sessions, while generating significant scientific output, over 40 peer-reviewed publications and active collaboration with more than 50 partners. Overall, the report highlights a year of strengthened clinical support, robust research productivity, and broad educational impact across the Military Health System.
GL_33	Evaluation of the DoD's Management of Traumatic Brain Injury	2023	USA	DoDIG	Report	https://www.dodig.mil/reports.html/article/3346218/evaluation-of-the-dods-management-of-traumatic-brain-injury-dodig-2023-059/	This report evaluates how effectively the U.S. Department of Defense identifies, manages, and tracks traumatic brain injuries (TBIs) among Service members, finding that the DoD does not consistently implement required screening, follow-up, or return-to-duty processes, leading to under-identification, inconsistent care, and unreliable surveillance data. Providers frequently do not use the mandated MACE 2 tool, follow-up care is often delayed or absent (with 41% receiving no follow-up), referral pathways vary widely, and inconsistent ICD coding prevents accurate TBI reporting. Resource gaps, such as non-standard equipment, lack of dedicated funding, and variations in Intrepid Spirit Center capabilities, further undermine quality of care. The report concludes that these deficiencies impair readiness, hinder long-term health management, and reduce visibility into the true burden of TBI, recommending clearer policy requirements, strengthened oversight, standardized programs of record, and integrated profiling processes.

ID	Title	Year	Country	Organisation	Source Type	URL	Summary
GL_34	Department of Defense Warfighter Brain Health Research Strategy	2024	USA	DoD	Report	https://www.health.mil/Reference-Center/Publications/2024/01/01/DOD-Warfighter-Brain-Health-Research-Strategy	The DoD Warfighter Brain Health Research Strategy (January 2024) outlines a comprehensive framework to optimize, protect, and restore the cognitive, physical, and psychological health of U.S. warfighters across their careers. It defines seven major research areas—identifying brain health hazards, improving surveillance, detecting changes in brain status, enhancing cognitive and physical performance, protecting warfighters from exposures, advancing assessment and diagnostic capabilities, and improving treatment and rehabilitation. The document emphasizes understanding emerging threats (including blast, blunt, chemical/biological, directed energy, and environmental stressors), developing accurate exposure-response models, creating advanced sensors and biomarkers, strengthening clinical decision tools, and ensuring long-term care that extends into veterans' services. The strategy aims to align research with operational requirements, accelerate translation of findings into materiel and policy, and ultimately improve readiness, reduce preventable long-term impacts of brain injury, and enhance quality of life for service members and veterans.
GL_35	Longitudinal Medical Study on Blast Pressure Exposure of Members of the Armed Forces - Initial Report	2018	USA	DoD	Report	https://health.mil/Reference-Center/Reports/2023/12/19/Longitudinal-Medical-Study-on-Blast-Pressure-Exposure	An interim U.S. Department of Defense report outlining the methods and action plan for a congressionally mandated longitudinal medical study on blast pressure exposure among Armed Forces personnel. It explains the background concerns about brain health effects from blast overpressure, details the multi-study approach across five lines of inquiry (surveillance, weapon systems, exposure environment, blast characterization, and health/performance), and describes a large cross-agency workgroup coordinating research, data collection, risk mitigation, and translation of findings into military safety policy. The report emphasizes tracking blast exposure, evaluating health and cognitive impacts, standardizing measurement methods, focusing on high-risk occupations and weapon systems, and overcoming challenges such as operational constraints and confounders. A phased timeline is provided, underscoring the overarching goal of improving training and operational protocols to better protect warfighters.

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GL_36	Longitudinal Medical Study on Blast Pressure Exposure of Members of the Armed Forces	2023	USA	DoD	Report	https://health.mil/Reference-Center/Reports/2023/12/19/Longitudinal-Medical-Study-on-Blast-Pressure-Exposure	This report outlines the U.S. Department of Defense's multi-year Blast Overpressure Studies (BOS) initiative, conducted in response to congressional direction to evaluate the health impacts of blast pressure exposure on Service members. It describes a series of pilot studies using body-worn sensors to monitor and analyze blast exposure during training with key "Tier 1" weapon systems, demonstrating that exposure data can be collected, quality-controlled, and integrated into existing DoD health and exposure record systems, though not yet feasible in combat settings. The report highlights known cognitive, neurological, and medical effects associated with blast exposure, identifies gaps and inconsistencies in safety guidance, and details new tools, policies, and interim risk-mitigation measures, including exposure reporting prototypes, updated safety planning resources, and a new ICD-10 diagnostic code. While the technology and scientific understanding of blast-related injury remain limited, particularly for real-time health risk prediction—the DoD concludes that exposure monitoring is feasible in controlled environments and intends to continue refining standards, conducting cost-benefit analyses, and developing training and clinical materials to better protect Service members' brain health.
GL_37	FY21 Science & Technology Efforts & Programs Prevention, Mitigation, and Treatment of Blast Injuries	2021	USA	BIRCO	Report	https://blastinjuryresearch.health.mil/assets/docs/ea_report/FY21_Report_to_the_Executive_Agent.pdf	The FY21 report outlines the organisation's mission to serve as the authoritative source for defense-related medical knowledge, highlighting major achievements across evidence-based practice, health policy development, digital knowledge platforms, and clinician education. It describes substantial progress in creating and disseminating clinical practice guidelines, strengthening partnerships with military and federal agencies, expanding digital delivery of medical expertise, and supporting readiness through training, analytics, and research. The report emphasises operational impacts, cost-effective knowledge delivery, and the organisation's evolving role in shaping high-quality, standardised military healthcare, while also recognising ongoing challenges and priorities for future capability development
GL_38	FY20 Science & Technology Efforts & Programs Prevention, Mitigation, and Treatment of Blast Injuries	2021	USA	BIRCO	Report	https://blastinjuryresearch.health.mil/assets/docs/ea_report/FY20_Report_to_the_Executive_Agent.pdf	This report provides a comprehensive account of activities undertaken by the Project Management Office (PMO) for FY2020 in support of the Executive Agent for the Defense Civilian Training Corps (DCTC). It outlines program objectives, governance structures, training pipelines, and strategic initiatives aimed at strengthening civilian workforce readiness across defense-related domains. The document details progress on curriculum development, partnerships with academic institutions, budget and staffing metrics, performance indicators, and risk management processes. It highlights accomplishments achieved during the fiscal year, identifies ongoing challenges, and presents recommendations to enhance program effectiveness and alignment with long-term workforce planning goals.

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GL_39	The Neurological Effects of repeated Exposure to Military Occupational Blast - A Review of the Scientific Literature	2018	USA	RAND Corporation	Report	https://www.rand.org/content/dam/rand/pubs/conf_proceedings/CF300/CF380z1/RAND_CF380z1.pdf	This report summarizes the 2018 Department of Defense State-of-the-Science Meeting on low-level blast exposure and concludes that although repeated subconcussive blasts clearly occur across many military occupations, the scientific evidence linking such exposures to neurological harm remains limited and incomplete. The proceedings describe emerging research showing potential functional deficits, neuroendocrine changes, and possible neurodegeneration associated with repeated blast exposure, alongside challenges in measurement, inconsistent definitions, and major gaps in understanding long-term outcomes. The expert panel recommends enforcing existing DoD exposure standards, developing high-quality longitudinal studies, advancing large-animal and translational research, improving assessment tools and protective practices, and expanding access to weapon- and occupation-specific exposure data to better safeguard service members and guide future policy.
GL_40	Mitigating the Effects of Blast-Related Burn Injuries from Prolonged Field Care to Rehabilitation and Resilience	2020	USA	RAND Corporation	Report	https://www.rand.org/content/dam/rand/pubs/conf_proceedings/CFA800/CFA807-2/RAND_CFA807-2.pdf	This report examines how the U.S. military can better understand and manage blast-related burn injuries during prolonged field care, especially in future conflicts where evacuation delays are likely. Drawing on scientific literature, Department of Defense grey literature, and expert workshops, the authors identify major gaps in research and capability, particularly in burn resuscitation, infection prevention, wound coverage, pain management, and the physiological effects of combined blast and burn trauma. The report highlights that current knowledge is limited mostly to case studies from recent conflicts, underscoring the need for improved data collection, targeted research investments, enhanced training for medics, and development of technologies and protocols that support extended prehospital burn care in austere and contested environments.
GL_41	Proceedings from the 6th International Forum on Blast Injury Countermeasures (IFBIC)	2022	USA	MITRE	Report	https://blastinjuryresearch.health.mil/index.cfm/news_and_highlights/facilitating_collaboration/news/IFBIC-2022	The 6th International Forum on Blast Injury Countermeasures (May 9–11, 2022) brought together more than 120 international experts to share emerging research, develop collaborations, and identify knowledge gaps in the prevention, diagnosis, and treatment of blast-related injuries. The report highlights advances in physiologic blast response research, including studies on low-level and repeated blast exposure, biomarkers, neurological effects, and long-term monitoring; progress in blast sensor development and validation; and innovations in modeling and simulation to better understand injury mechanisms. It also summarizes consensus discussions on improving blast exposure documentation, refining sensor technologies, enhancing predictive injury criteria, and strengthening international data-sharing. Key recommendations call for improved longitudinal monitoring, standardized reevaluation of blast devices, expanded clinical and epidemiological studies, and deeper exploration of blast biomechanics and protective interventions.

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GL_42	Neurological Effects of Repeated Exposure to Military Occupational Levels of Blast	2020	USA	RAND Corporation	Report	https://www.rand.org/pubs/research_reports/RR2350.html	This report is a comprehensive review of 74 human, animal, and bioengineering studies examining how repeated low-level blast exposure in military settings may affect the central nervous system. The authors find that while consistent evidence in humans is limited, largely due to methodological variation, reliance on self-reported exposure, and confounding from combat-related injuries, animal models demonstrate plausible biological mechanisms for neurological impacts, particularly in cognitive domains, where multiple studies show learning and memory deficits after blast exposures as low as 3-10 psi. The review highlights that no clear safe exposure threshold has been established, and that many gaps remain, including insufficient longitudinal human research, lack of standardized exposure measurement, and minimal evidence regarding motor or neurosensory outcomes. Overall, the report concludes that repeated low-level blast exposure is a potential risk to neurological health, supported more strongly by animal data than human data, and underscores the need for better exposure tracking, improved study design, and targeted research to inform policy and protective strategies.
GL_43	STO Technical Report TR-HFM-270 Framework for Modeling and Simulation of Human Lethality, Injury, and Impairment from Blast-Related Threats	2023	NATO	NATO Science and Technology Organisation	Report	https://publications.sto.nato.int/publications/STO%20Technical%20Reports/STO-TR-HFM-270/$$TR-HFM-270-ALL.pdf	This report is an evaluation of blast exposure and blast injury within military training scenarios, outlining standardized methods for collecting, recording, and reporting blast overpressure data. It reviews current knowledge on blast physiologic effects, sensor performance, and exposure limits, and proposes harmonized frameworks to improve data quality and comparability across NATO nations. The report also identifies gaps in existing research, particularly regarding the cumulative and long-term health consequences of low-level blast exposure, and recommends coordinated multinational studies, improved wearable sensor standards, and consistent risk-management practices to better protect personnel routinely exposed to blast during training and operations.

ID	Title	Year	Country	Organisation	Source Type	URL	Summary
GL_44	STO Technical Report TR-HFM-234 Environmental Toxicology of Blast Exposures: Injury Metrics, Modelling, Methods and Standards	2018	NATO	NATO Science and Technology Organisation	Report	https://www.sto.nato.int/document/environmental-toxicology-of-blast-exposures-injury-metrics-modelling-methods-and-standards-2/	This report presents a comprehensive framework to improve the understanding, measurement, and mitigation of blast injuries across NATO nations. It establishes standardized guidelines for epidemiological data collection, laboratory reproduction of blast exposures, and the use of animal models, supported by a unified Dictionary of Blast Injury Terms. The document also highlights challenges in blast injury research, such as variability in experimental methods, limited comparability between studies, and the complex multisystem nature of blast trauma, while promoting computational modeling, standardized reporting, and multinational collaboration to enhance prevention, diagnosis, and treatment of blast-related injuries.
GL_45	Biomechanical Modeling and Measurement of Blast Injury and Hearing Protection Mechanisms	2020	USA	USAMRDC	Research Report	https://apps.dtic.mil/sti/pdfs/AD1074289.pdf	This report compiles several experimental and modelling studies examining how blast overpressure affects the human and chinchilla tympanic membrane (TM), focusing on both mechanical property changes and blast-wave transmission dynamics. Using intact human temporal bones and animal models, the studies apply controlled sub-rupture blast exposures and measure TM responses with techniques such as micro-fringe projection, laser Doppler vibrometry, finite element modelling, and split Hopkinson tension bar testing. Across experiments, blast exposure, typically delivered at 35-55 kPa, consistently causes microstructural fiber damage, reduced elastic modulus (approx 20% in humans, approx 53% in chinchillas), lower failure pressure, and frequency- and location-dependent increases in TM mobility, particularly around 3-4 kHz. Modelling validates these findings and shows how altered collagen fiber properties change TM surface motion and stress distribution, helping to explain hearing deficits after non-rupturing blast events. Collectively, the work strengthens biomechanical understanding of blast-induced auditory injury and aims to improve predictive models of TM damage and middle-ear sound transmission.

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GL_46	Neuropathology and Immune Biomarker Discovery in a Rat Model of Alzheimer's Disease, TgF344-AD, with Single or Repetitive Traumatic Brain Injury	2021	USA	USAMRDC	Research Report	https://apps.dtic.mil/sti/tr/pdf/AD1063953.pdf	The report describes a multi-year project investigating how traumatic brain injury (TBI) may contribute to the development or acceleration of Alzheimer's disease (AD) using a transgenic rat model (TgF344-AD) subjected to single or repeated controlled cortical impact injuries. While mild or single injuries in younger animals did not induce detectable AD-related pathology, repeated moderate TBI in 12-month-old AD-model rats accelerated the maturation of diffuse amyloid-beta plaques into dense-cored plaques, induced early tauopathy at the impact site, and triggered widespread astrogliosis, supporting the hypothesis that TBI exacerbates existing AD pathology rather than initiating it. Biomarker analyses (MRI, plasma cytokines, extracellular vesicles) showed high variability and limited reliability, though tissue-based pathology was robust. The project was significantly delayed by the COVID-19 pandemic and animal-breeding constraints, but it yielded important research infrastructure, including construction of a dedicated blast-TBI facility, and provided a validated model for future studies on the mechanistic links between TBI and AD.
GL_47	Evaluation of Clinically Relevant Prognostic Indicators in a Model of Mild TBI/Concussion	2022	USA	USAMRDC	Research Report	https://apps.dtic.mil/sti/trecms/pdf/AD1132060.pdf	This report summarizes a multi-year preclinical research program evaluating whether acute biomarkers, specifically FDG-PET measures of brain glucose metabolism and serum microRNA profiles, can predict long-term neurological and cognitive outcomes after single or repeated mild traumatic brain injury (mTBI) in a military-relevant rodent concussion model. Using the WRAIR Projectile Concussive Impact system, researchers found that concussion induces acute metabolic disruptions, with repeated injuries producing broader and more persistent abnormalities, particularly in thalamic glucose uptake. While early sensorimotor deficits and gait disruptions were evident, most behavioural impairments resolved by six months, and no chronic neurodegenerative pathology (amyloid or phosphorylated tau) was detected. Serum microRNA changes were modest after isolated mTBI but were more pronounced when concussion was combined with polytrauma (hypoxemia and haemorrhagic shock), which also amplified traditional blood biomarkers (GFAP, NF-L, UCH-L1). Overall, the findings support FDG-PET as a sensitive acute indicator of concussion-related metabolic dysfunction, highlight the importance of repeated and combined injuries in worsening metabolic responses, and provide groundwork for improving prognostic assessment in mTBI.

ID	Title	Year	Country	Organisation	Source Type	URL	Summary
GL_48	The Effect of Blast-Related Burn Injuries from Prolonged Field Care to Rehabilitation and Resilience. A Review of the Scientific Literature		USA	RAND Corporation	Review	https://www.rand.org/pubs/research_reports/RRA807-1.html	This report provides a comprehensive scientific review of blast-related burn injuries across the full continuum of military care, from initial injury and prolonged field care through acute management, long-term treatment, rehabilitation, and resilience. It outlines the purpose and methodology of the Ninth DoD State-of-the-Science Meeting, reviews epidemiology, mechanisms, prevention strategies, diagnostic tools, treatment approaches, and chronic-care innovations, and identifies major knowledge gaps affecting service members with blast-related burns. The authors emphasize the particular challenges presented by facial, airway, and multi-system injuries; the prolonged transport times often faced in deployed environments; complications such as infection; and the need for improved prevention technologies, field-care protocols, and rehabilitation research. The report concludes with preliminary recommendations for future military medical research and policy development in order to strengthen burn prevention, acute and prolonged field care, surgical and critical care capacity, and long-term recovery support for injured service members.
GL_49	Research Review on Chronic Traumatic Encephelopathy	2023	USA	TBICoE	Review	https://health.mil/Reference-Center/Publications/2023/03/17/TBICoE-Research-Review-Chronic-Traumatic-Encephalopathy	This is a comprehensive research review on Chronic Traumatic Encephalopathy (CTE), outlining current scientific understanding, uncertainties, and misconceptions surrounding the condition. It explains that CTE is a progressive neurodegenerative disease defined only by a specific post-mortem pattern of perivascular, irregular tau deposition at the depths of cortical sulci. The review stresses that while repetitive head impacts are associated with CTE pathology, the causal pathways, incidence, dose–response relationships, and individual risk factors remain unclear, and there is no validated clinical diagnostic test for living patients. It highlights that many widely publicized claims about CTE, such as deterministic links to behavioural changes, suicide, or cognitive decline, are not supported by robust evidence, with existing studies often affected by selection bias and methodological limitations. The report calls for cautious interpretation of current findings, emphasizes the need for large, prospective, multidisciplinary studies, and warns against overstating conclusions that extend beyond the available data.

ID	Title	Year	Country	Organisation	Source Type	URL	Summary
GL_50	Research Review on Mild Traumatic Brain Injury and Posttraumatic Stress Disorder	2023	USA	TBICoE	Review	https://health.mil/Reference-Center/Publications/2023/09/29/TBICoE-Research-Review-Mild-TBI-and-PTSD	This review synthesises contemporary evidence on the complex relationship between mild traumatic brain injury (mTBI) and post-traumatic stress disorder (PTSD), particularly in military and veteran populations but with relevance to civilians as well. It examines epidemiology, shared and distinct risk factors, overlapping symptom profiles, diagnostic challenges, neurocognitive and neuroimaging findings, and the effects of blast versus non-blast injuries. The review highlights that mTBI and PTSD frequently co-occur, mutually exacerbate symptom severity, and complicate clinical assessment due to overlapping cognitive, emotional, and somatic features. It summarizes biomarkers, neurophysiological signatures, and imaging modalities explored to differentiate the conditions, while noting that no single test reliably distinguishes them. The document concludes with recommendations emphasizing comprehensive clinical evaluation, trauma-informed care, longitudinal monitoring, and integrated treatment approaches tailored to the unique neuropsychological and psychosocial burdens faced by affected individuals.
GL_51	Research Review on Suicide and Traumatic Brain Injury January	2024	USA	TBICoE	Review	https://health.mil/Reference-Center/Publications/2024/03/12/Suicide-and-TBI-Research-Review	This report provides an up-to-date synthesis of evidence on the relationship between traumatic brain injury (TBI) and suicide risk in U.S. military personnel and veterans, noting that while suicide rates remain a major public health concern, TBI - particularly moderate to severe injuries and multiple TBIs - appears to increase the likelihood of suicidal ideation, attempts, and death, largely through its interaction with comorbid conditions such as depression, PTSD, chronic pain, and sleep disorders. It highlights that most military TBIs are mild, yet even mild TBI may contribute to elevated suicide risk when combined with psychological health conditions or deployment-related trauma. The review outlines demographic and occupational risk patterns, emphasizes that screening should follow VA/DoD clinical practice guidelines (e.g., PHQ-9, C-SSRS), and identifies protective factors such as social connection, resilience, meaningful activity, and access to mental health care. It concludes that although TBI contributes to suicide vulnerability, suicide remains statistically rare, and effective prevention requires addressing co-occurring psychiatric conditions, improving treatment engagement, and strengthening evidence-based approaches for individuals with both TBI and suicidality.

ID	Title	Year	Country	Organisation	Source Type	URL	Summary
GL_52	Research Review on Multiple Concussions and Repetitive Subconcussive Head Impacts	2024	USA	TBICoE	Review	https://health.mil/Reference-Center/Publications/2024/03/28/TBICoE-Research-Review-Multiple-TBI-Multiple-Concussion	This review summarizes recent evidence showing that multiple concussions and repetitive subconcussive head impacts can cause cumulative neurological harm, including white-matter microstructural changes, metabolic disruption, impaired cerebral blood flow, and persistent cognitive, psychological, and physical symptoms. Military personnel and athletes are the two groups most affected, with risks influenced by exposure patterns, injury mechanisms, and prior concussion history. Across both populations, multiple concussions are associated with more severe and longer-lasting symptoms—such as headaches, sleep disturbance, mood disorders, and cognitive deficits—although some findings vary due to study design differences. Evaluation and management protocols have become more structured, including standardized acute assessment tools (e.g., MACE 2, SCAT6) and progressive return-to-activity guidelines, with stricter oversight for individuals with repeated injuries. Prevention efforts focus on helmet design improvements and potential neuroprotective supplements, though evidence for effective treatments remains preliminary. Overall, growing recognition of long-term risks has driven stronger policies, but key gaps remain in understanding mechanisms, long-term outcomes, and effective interventions.
GL_53	Research Review on Pain and Traumatic Brain Injury	2024	USA	TBICoE	Review	https://health.mil/Reference-Center/Publications/2024/08/29/TBICoE-Research-Review-Pain-and-TBI	This review summarizes current evidence on pain associated with traumatic brain injury (TBI) in military populations, describing how pain is common after TBI, especially mild TBI, and contributes substantially to long-term disability, reduced quality of life, and delayed recovery. It outlines the major types of post-TBI pain (nociceptive, neuropathic, inflammatory, centralized, psychogenic), key risk factors (including female sex, multiple TBIs, loss of consciousness, and severe acute pain), and the frequent co-occurrence of neuropsychiatric symptoms such as PTSD, depression, and sleep-wake disturbances, all of which complicate management. The review also describes emerging insights into pathophysiology, including altered pain modulation and neuroinflammatory mechanisms, and highlights the challenges of pain evaluation in TBI due to limitations of self-report measures, noting a need for more objective biomarkers. Treatment recommendations emphasize an interdisciplinary, primarily non-pharmacologic approach, cautious use of pharmaceuticals, and a focus on functional recovery and return to duty, while acknowledging that evidence for some alternative therapies remains limited.

ID	Title	Year	Country	Organisation	Source Type	URL	Summary
GL_54	Omega-3 Supplements for Mild Traumatic Brain Injury	2025	USA	TBICoE	Review	https://health.mil/Reference-Center/Publications/2025/05/15/Information-Paper-on-Omega-3-Supplements-for-Mild-Traumatic-Brain-Injury	This information paper reviews current evidence on omega-3 fatty acids for the prevention and treatment of mild traumatic brain injury (mTBI), concluding that while preclinical studies consistently show neuroprotective, anti-inflammatory, and cognitive benefits, particularly involving DHA and EPA, clinical research in humans remains limited and inconsistent. Athletes and warfighters often have low omega-3 status, and supplementation may reduce biomarkers of axonal injury and shorten symptom recovery in some studies, but no clear clinical protocols, optimal dosing, or durable benefits have been established. Up to 5 g/day of DHA/EPA is generally considered safe for healthy adults, yet applicability to TBI-risk populations is uncertain, and bleeding risk remains theoretical rather than evidence-based. Overall, omega-3s show promise as a prophylactic and therapeutic adjunct, but current evidence does not justify changes to VA/DoD clinical guidelines, and well-designed randomized trials are needed to determine true clinical impact.
GL_55	Information Paper on Neurodegenerative Diseases and Traumatic Brain Injury	2025	USA	TBICoE	Review	https://health.mil/Reference-Center/Publications/2025/07/24/Neurodegenerative-Diseases-and-Traumatic-Brain-Injury-Information-Paper	This information paper reviews current evidence on whether traumatic brain injury (TBI) increases the risk of developing neurodegenerative diseases—specifically Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS). While many observational studies suggest that moderate to severe TBI, and in some cases mild TBI, are associated with later cognitive decline, earlier onset of symptoms, and elevated biomarkers linked to Alzheimer's and Parkinson's disease, other well-designed studies show no such relationship, highlighting major methodological limitations, confounding factors, and heterogeneous injury mechanisms. Evidence for a link between TBI and ALS is even more inconsistent and limited. Overall, the report concludes that TBI may contribute to pathological processes that influence neurodegeneration, but clear causal pathways remain unproven; long-term, biomarker-informed, rigorously controlled studies are needed. These findings have implications for military personnel, whose occupational exposures may elevate risk and who may benefit from emerging early diagnostic biomarkers and treatment strategies.

ID	Title	Year	Country	Organisation	Source Type	URL	Summary
GL_56	Information Paper on Hyperbaric Oxygen Therapy and Traumatic Brain Injury	2025	USA	TBICoE	Review	https://health.mil/Reference-Center/Publications/2025/07/25/Hyperbaric-Oxygen-Therapy-and-TBI	This information paper concludes that although animal studies suggest hyperbaric oxygen therapy (HBOT) may have neuroprotective effects, the totality of human clinical evidence, especially from large, methodologically rigorous Department of Defense trials, shows no meaningful or lasting benefit of HBOT for traumatic brain injury (TBI) or post-concussion symptoms. Across multiple randomized controlled trials and follow-up studies, HBOT performs no better than well-designed sham controls, and any short-term improvements reported in smaller or lower-quality studies typically disappear by 3-12 months. The paper highlights substantial methodological flaws in studies claiming positive effects, ongoing inconsistencies in HBOT dosing and control-condition design, and a lack of FDA approval or TRICARE/VA coverage for TBI indications. Overall, the evidence indicates that recommending HBOT for TBI is unsupported, potentially costly, and risks undermining patient trust when expected outcomes fail to materialize.
GL_57	Repeated Exposure to Low-Level Military Occupational Blasts An Overview of the Research, Critical Gaps, and Recommendations (Addendum)	2024	USA	RAND Corporation	Testimony	https://www.rand.org/content/dam/rand/pubs/testimonies/CTA3200/CTA3250-2/RAND_CTA3250-2.pdf	This document is an addendum to testimony provided to the U.S. Senate concerning the health risks of repeated low-level blast exposure among military personnel. It outlines expert responses to senators' questions on the relationship between traumatic brain injury (TBI) and mental health conditions, the benefits of MOS-specific prevention strategies, and the value of maintaining blast-exposure logs. Although the author avoids clinical assertions, the testimony highlights substantial evidence of underreporting of TBIs due to stigma, fears of career repercussions, limited awareness, and structural barriers within the military health system. It recommends improving education, reducing stigma, enhancing access to care, providing validated safety equipment, and implementing targeted prevention and monitoring strategies to safeguard service members' long-term health and readiness.

Appendix 6 – Methodological Reference

Collaborative Scoping

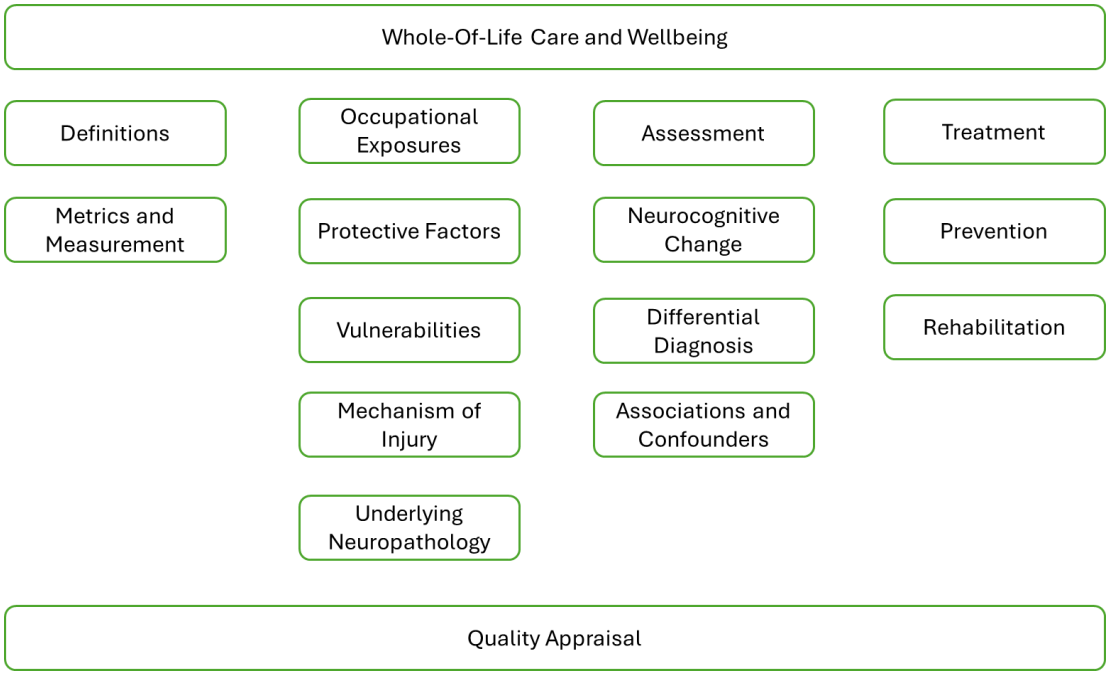

Figure A6.1. Conceptualisation of categories of evidence that will be examined in this project addressing specific questions posed by DVA in bridging or intersecting areas of evidence.

Information Sources

The review drew on multiple information sources (Table A6.1). UNSW collaborated with an academic librarian to ensure the literature search was comprehensive.

Table A6.1 Information sources accessed through the search process

Peer reviewed literature:	Medline (via PubMed), Embase, Cochrane Library (including CENTRAL), Web of Science, Scopus, CINAHL, PsycINFO, SafetyLit
Grey Literature sources:	Web searching services (Google Scholar, Bing, Yahoo etc.) **Australia:** Department of Veterans' Affairs (DVA), Australian Institute of Health and Welfare (AIHW), Trove (National Library of Australia), Australian Institute of Sport (for relevant concussion/TBI related research), Safe Work Australia **UK:** Ministry of Defence, Royal British Legion, King's Centre for Military Health Research (KCMHR), Parliamentary Office of Science and Technology (POST), Public Health England, National Institute for Health and Care Excellence (NICE), Health and Safety Executive (HSE), EthOS (Electronic Theses Online Service) - British Library, ISRCTN Registry **Canada:** DND/CAF Publications, DRDC Publications, Veterans Affairs Canada (VAC), Canadian Institute for Military and Veteran Health Research (CIMVHR), Public Health Agency of Canada (PHAC) **Europe:** NATO Medical Publications and Science and Technology Organisation, Community Research and Development Information Service (CORDIS), National Ministries of Health (various), Ministries of Defence (various), System for Information on Grey Literature in Europe (SIGLE, now OpenGrey) **USA:** National Institutes of Health (NIH), Defense Technical Information Center (DTIC), Army Medical Research and Development Command (USAMRDC), Department of Veterans Affairs, Centers for Disease Control

	and Prevention (CDC), National Academies, ClinicalTrials.gov, Mine Safety and Health Administration, NIOSH, OSHA **Global:** International Society of Explosives Engineers (ISEE), International Council on Mining and Metals (ICMM), International Labour Organisation (ILO) and national chapters **Societies:** Relevant collision sporting professional bodies and international federations (e.g. IOC, NFL, NHL, CFL, NRL, AFL, RFU (UK), World Rugby etc) where research relevant to repeated blast exposure may be present. Professional Publications (non-indexed) such as Journal of Special Operations Medicine (JSOM) **Dissertations:** ProQuest Dissertations and Theses

Eligibility criteria

Peer Reviewed Sources

Studies included in this systematic review comprised peer-reviewed and grey literature (Table 1), focusing on the effects of rLLB exposure in human and animal studies. To qualify, studies had to explicitly define rLLB as blast exposures below the threshold typically associated with acute traumatic injury and involve multiple exposures over time. Eligible studies reported physiological, neurological, behavioural, or cognitive outcomes and provided clear methodologies for both blast exposure and outcome assessment. Both observational and experimental designs were considered. Only studies published in English and offering sufficient methodological detail to enable assessment of study quality and risk of bias were included. Case reports, narrative reviews, editorials, and conference abstracts without full text were excluded (Table A6.2).

Table A6.2. Inclusion and exclusion criteria for peer reviewed literature

Inclusion Criteria	Exclusion Criteria
• **Population:** Human or animal participants. • **Exposure:** Repetitive low-level blast (rLLB), defined as multiple exposures to blast events below the threshold of acute traumatic injury. • **Outcomes:** Studies reporting on physiological, neurological, behavioural, or cognitive outcomes. • **Study Design:** Experimental (e.g., randomized controlled trials, laboratory studies) or observational (e.g., cohort, case-control, cross-sectional) studies, case series, systematic reviews. • **Language:** Published in English. • **Publication Type:** Peer-reviewed, full-text articles, or relevant grey literature (**organisationally or professionally endorsed**). • **Methodological Clarity:** Sufficient detail provided to assess study quality and risk of bias (e.g., blast exposure parameters, outcome assessment methods). • **Date of publication:** Last 5 years (for initial review).	• **Exposure:** Studies focusing on single blast exposures or exposures above the threshold for acute traumatic injury. • **Outcomes:** Studies not assessing relevant physiological, neurological, behavioural, or cognitive outcomes. • **Study Design:** Individual case reports, narrative reviews, commentaries, editorials, and conference abstracts without accessible full text. • **Language:** Non-English publications. • **Publication Type:** Non-peer-reviewed sources, grey literature that is not organisationally or professionally endorsed, ephemera. • **Methodological Limitation:** Insufficient detail to evaluate study quality or blast exposure methodology. • **Date of publication:** Greater than last 5 years (for initial review).

Grey Literature

Grey literature sources were searched manually. Initial identification of grey literature was conducted by:

1) Using open-source search databases such as Google Scholar, Bing and Yahoo, among other platforms. This was supplemented by open-source AI-driven aggregator search and cross-referencing tools such as ChatGPT and Microsoft Copilot.

2) Direct website visits to relevant government websites that are not typically indexed, or are protected from AI searching via copyright/access agreements, were also conducted.

Grey literature artefacts were consolidated into a standalone database of references, aggregating appropriate source specific metadata and keywords.

Rapid Evidence Assessment Methodology

Our approach utilised the well-known rapid evidence assessment (REA) methodology (34–36) and incorporated strategies aimed at enabling the efficient synthesis of information. To support this, data sources were deliberately chosen to reduce unproductive search efforts and enhance the retrieval of relevant published literature. The review process and findings were reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (181). To manage the review process, UNSW used Covidence™ - a web-based collaboration software that streamlines the production of reviews.

A comprehensive, PRISMA-compliant search strategy was employed to identify peer-reviewed literature examining the cognitive effects of repetitive low-level blast (rLLB) exposure. Electronic databases including MEDLINE (via PubMed), Embase, PsycINFO, Web of Science, and Cochrane CENTRAL were systematically searched from inception to 23 August 2025. UNSW combined MeSH terms and free-text keywords related to blast exposure (e.g., “low level blast”, “blast overpressure”), repetition (e.g., “repetitive”, “chronic”), and cognitive outcomes (e.g., “memory”, “attention”, “executive function”). The initial search terms are presented in Appendix 4.

Searches were limited to English-language, peer-reviewed studies involving human or animal participants, and articles published since 2019. Additional efforts to ensure comprehensiveness of searching included handsearching reference lists of relevant studies and reviews and contacting authors and field experts to identify unpublished or ongoing work. All search strategies and results were documented in accordance with PRISMA 2020 guidelines to ensure transparency and reproducibility.

Quality Assessment

Peer-Reviewed Literature

In this rapid review, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method (182) was employed to systematically assess and synthesise the quality of the included studies. GRADE is a best practice and accepted framework (183,184) for downgrading or upgrading the certainty of evidence based on five assessment domains – i) risk of bias, ii) inconsistency, iii) indirectness, iv) imprecision, and v) publication bias. By applying these criteria, the review team categorised the overall confidence in each body of evidence (high, moderate, low, or very low), thus providing clear guidance on the strength of the findings.

Grade assessment criteria

Limitations in Design and Execution (Risk of Bias)

Risk of Bias refers to aspects of how a study was designed or conducted that may systematically influence the results, potentially affecting their validity or accuracy.

Individual studies were assessed for risk of bias using appropriate tools (e.g., ROB 2.0 for randomised trials, ROBINS-I for non-randomised studies, SYRCLE for animal studies), considering issues such as allocation concealment, blinding, incomplete outcome data, selective reporting, and deviations from intended interventions. Studies judged to have serious or critical risk of bias contributed to downgrading the overall certainty of the evidence.

Inconsistency (Heterogeneity of Results)

Heterogeneity of Results refers to variation in findings across different studies or analyses, indicating that results are not uniform and may differ in magnitude or direction.

Inconsistency was evaluated by examining variability in effect estimates across studies. Statistical heterogeneity was assessed using the I^2 statistic and visual inspection of forest plots. Substantial unexplained heterogeneity ($I^2 > 50\%$) or widely varying point estimates indicate the need for downgrading.

Indirectness (Population, Intervention, Comparator, Outcome - PICO)

Indirectness refers to differences between the study conditions and the specific population, intervention, comparison, or outcomes of interest, which may limit how directly the results apply to the question being asked.

The applicability of evidence was assessed by comparing study populations, exposures (e.g., rLLB intensity/duration), comparators (e.g., no blast or single blast), and cognitive outcomes to those defined in the review's PICO criteria. Studies with indirect measures (e.g., proxy outcomes or populations not representative of the target group) were considered for downgrading.

Imprecision (Sample Size and Confidence Intervals)

Imprecision refers to uncertainty in study results due to limited data, where small sample sizes or wide confidence intervals reduce confidence in the estimated effect.

Imprecision was evaluated based on the width of confidence intervals and the total number of participants/events. Downgrading for imprecision occurred if confidence intervals included both meaningful harm and benefit or if sample sizes were insufficient to provide robust estimates (e.g., fewer than 300 participants in total or low event counts).

Publication Bias

Publication bias refers to the tendency for studies with positive or significant results to be published more often than studies with negative or inconclusive findings, which can distort the overall evidence base.

Potential publication bias was evaluated using funnel plots when ≥10 studies were available and by considering small-study effects. Selective outcome reporting was assessed by comparing protocols to reported outcomes where possible. Asymmetry in funnel plots or evidence of missing studies led to downgrading for publication bias. The potential influence of funding sources and sponsorship on study outcomes was also considered.

Overall GRADE Rating

Overall GRADE rating summarises the level of confidence that the available evidence reflects the true effect, considering study quality, consistency, relevance, precision, and potential bias.

Following assessment across the five GRADE domains (risk of bias, inconsistency, indirectness, imprecision, and publication bias), the overall certainty of evidence for each cognitive outcome was rated as high, moderate, low, or very low. The final GRADE ratings and individual domain scores were summarised in a Summary of Findings (SoF) table. This structured approach ensured transparency and consistency in evaluating and presenting the strength of evidence that informed conclusions on the cognitive impacts of rLLB.

Grey Literature

To assess the quality of grey literature included in the review, the Quality Assessment with Diverse Studies (QuADS) tool (185) was used. This tool was specifically designed to evaluate the methodological quality of studies employing mixed, multiple, or diverse research methods. QuADS comprised 13 criteria assessing aspects such as clarity of theoretical framework, justification of study design, relevance of data sources, transparency of analytical methods, and reflexivity. Its structured and adaptable format made it well suited for appraising grey literature, such as technical reports and government publications, that did not conform to conventional academic standards but still contained valuable empirical data. Use of QuADS ensured a consistent and rigorous approach to evaluating the quality and credibility of non-peer-reviewed evidence included in the review.

Search Strategy (initial)

Topic Area: Blast Exposure (particularly low-level and repetitive)

MeSH Terms:

- “Blast Injuries”[mesh]
- “Brain Injuries, Traumatic”[mesh]

Free text:

- "low-level blast".tw
- "repetitive blast exposure".tw
- "repeated blast exposure".tw
- "subconcussive blast".tw
- "sub-threshold blast".tw
- "mild blast exposure".tw
- "occupational blast exposure".tw
- "breacher".tw
- "blast overpressure".tw
- “multiple blast exposures”.tw

Topic Area: Repetition/Chronicity

Free text:

- "repetitive".tw
- "chronic exposure".tw
- "cumulative exposure".tw
- "multiple exposures".tw
- "repeated".tw

Topic Area: Neurological and/or Cognitive Effects

MeSH Terms:

- “Neuropsychological Tests”[mesh]

- “Cognition Disorders”[mesh]
- “Cognition”[mesh]
- “Neurobehavioral Manifestations”[mesh]
- “Neurodegenerative Diseases”[mesh]

Free text:

- “neurocognitive”.tw
- “executive function”.tw
- “processing speed”.tw
- “neurobehavioural”.tw
- “cognitive performance”.tw
- “neuropsychological”.tw
- “mood disturbance”.tw
- “cognitive decline”.tw
- “psychiatric”.tw
- “all-cause dementia”.tw
- “traumatic brain injury”.tw
- “chronic traumatic encephalopathy”.tw
- “CTE-NC”.tw
- “TBI”.tw
- “mTBI”.tw
- “concussion”.tw
- "neurocognitive impairment".tw
- "cognitive decline".tw
- "cognitive dysfunction".tw
- "executive function".tw
- "memory impairment".tw
- "attention deficits".tw
- "processing speed".tw
- "neurobehavioral effects".tw
- "mood disturbances".tw
- "psychiatric sequelae".tw

Topic Area: Population

Free text:

- "military personnel".tw
- "veterans".tw
- "special forces".tw
- "law enforcement".tw
- "breachers".tw
- "occupational exposure".tw

References

1. McEvoy C, Crabtree A, Case J, Means GE, Muench P, Thomas RG, et al. Cumulative Blast Impulse Is Predictive for Changes in Chronic Neurobehavioral Symptoms Following Low Level Blast Exposure during Military Training. Mil Med. 2024 Aug 30;189(9–10):e2069–77.

2. McBirney S. Repeated Exposure to Low-Level Military Occupational Blasts: An Overview of the Research, Critical Gaps, and Recommendations [Internet]. RAND Corporation; 2024 [cited 2025 Mar 28]. Report No.: CT-A3250-1. Available from: https://www.rand.org/pubs/testimonies/CTA3250-1.html

3. Stone JR, Avants BB, Tustison NJ, Gill J, Wilde EA, Neumann KD, et al. Neurological Effects of Repeated Blast Exposure in Special Operations Personnel. Journal of Neurotrauma. 2024 Apr 1;41(7–8):942–56.

4. Vartanian O, Rhind SG, Nakashima A, Tenn C, Lam TK, Shiu M, et al. Blast effects on post-concussive and mental health outcomes: Data from Canadian Armed Forces breachers and snipers. Journal of Military, Veteran and Family Health. 2022 Sep 1;8(s2):82–96.

5. Woodall JLA, Sak JA, Cowdrick KR, Bove Muñoz BM, McElrath JH, Trimpe GR, et al. Repetitive Low-level Blast Exposure and Neurocognitive Effects in Army Ranger Mortarmen. Military Medicine. 2023 Mar 20;188(3–4):e771–9.

6. Boutté AM, Thangavelu B, Nemes J, LaValle CR, Egnoto M, Carr W, et al. Neurotrauma Biomarker Levels and Adverse Symptoms Among Military and Law Enforcement Personnel Exposed to Occupational Overpressure Without Diagnosed Traumatic Brain Injury. JAMA Netw Open. 2021 Apr 16;4(4):e216445.

7. Brackstone K, Head MG, Perelli-Harris B. Effects of blast exposure on anxiety and symptoms of post-traumatic stress disorder (PTSD) among displaced Ukrainian populations. Acharya B, editor. PLOS Glob Public Health. 2024 Apr 11;4(4):e0002623.

8. Dretsch MN, Silverberg N, Gardner AJ, Panenka WJ, Emmerich T, Crynen G, et al. Genetics and Other Risk Factors for Past Concussions in Active-Duty Soldiers. Journal of Neurotrauma. 2017 Feb 15;34(4):869–75.

9. Gama Sosa MA, De Gasperi R, Pryor D, Perez Garcia GS, Perez GM, Abutarboush R, et al. Late chronic local inflammation, synaptic alterations, vascular remodeling and arteriovenous malformations in the brains of male rats exposed to repetitive low-level blast overpressures. acta neuropathol commun. 2023 May 12;11(1):81.

10. Hines SE, Gaitens JM, Brown CH, Glick DR, Chin KH, Reback MA, et al. Self-reported respiratory outcomes associated with blast exposure in post 9/11 veterans. Respiratory Medicine. 2022 Oct;202:106963.

11. Rhind SG, Shiu MY, Vartanian O, Tenn C, Nakashima A, Jetly R, et al. Circulating Brain-Reactive Autoantibody Profiles in Military Breachers Exposed to Repetitive Occupational Blast. IJMS. 2024 Dec 21;25(24):13683.

12. Sigler A, Wu J, Pfaff A, Adetunji O, Nam P, James D, et al. Repeated Low-Level Blast Exposure Alters Urinary and Serum Metabolites. Metabolites. 2023 May 8;13(5):638.

13. Conley AC, Cooper PS, Karayanidis F, Gardner AJ, Levi CR, Stanwell P, et al. Resting State Electroencephalography and Sports-Related Concussion: A Systematic Review. Journal of Neurotrauma. 2019 Jan;36(1):1–13.

14. Edwards S, Lee R, Fuller G, Buchanan M, Tahu T, Tucker R, et al. 3D Biomechanics of Rugby Tackle Techniques to Inform Future Rugby Research Practice: a Systematic Review. Sports Med - Open. 2021 Dec;7(1):39.

15. Gardner A, Kay-Lambkin F, Stanwell P, Donnelly J, Williams WH, Hiles A, et al. A Systematic Review of Diffusion Tensor Imaging Findings in Sports-Related Concussion. Journal of Neurotrauma. 2012 Nov;29(16):2521–38.

16. Gardner A, Iverson GL, Levi CR, Schofield PW, Kay-Lambkin F, Kohler RMN, et al. A systematic review of concussion in rugby league. Br J Sports Med. 2015 Apr;49(8):495–8.

17. Gardner A, Iverson GL, McCrory P. Chronic traumatic encephalopathy in sport: a systematic review. Br J Sports Med. 2014 Jan;48(2):84–90.

18. Gardner A, Iverson GL, Stanwell P. A Systematic Review of Proton Magnetic Resonance Spectroscopy Findings in Sport-Related Concussion. Journal of Neurotrauma. 2014 Jan;31(1):1–18.

19. Gardner AJ, Iverson GL, Williams WH, Baker S, Stanwell P. A Systematic Review and Meta-Analysis of Concussion in Rugby Union. Sports Med. 2014 Dec;44(12):1717–31.

20. Gardner AJ, Tan CO, Ainslie PN, Van Donkelaar P, Stanwell P, Levi CR, et al. Cerebrovascular reactivity assessed by transcranial Doppler ultrasound in sport-related concussion: a systematic review. Br J Sports Med. 2015 Aug;49(16):1050–5.

21. Iverson GL, Gardner AJ, Terry DP, Ponsford JL, Sills AK, Broshek DK, et al. Predictors of clinical recovery from concussion: a systematic review. Br J Sports Med. 2017 Jun;51(12):941–8.

22. Iverson GL, Williams MW, Gardner AJ, Terry DP. Systematic Review of Preinjury Mental Health Problems as a Vulnerability Factor for Worse Outcome After Sport-Related Concussion. Orthopaedic Journal of Sports Medicine. 2020 Oct 1;8(10):2325967120950682.

23. Iverson GL, Williams MW, Gardner AJ, Terry DP. Systematic Review of Preinjury Mental Health Problems as a Vulnerability Factor for Worse Outcome After Sport-Related Concussion. Orthopaedic Journal of Sports Medicine. 2020 Oct 1;8(10):2325967120950682.

24. Luoto TM, Raj R, Posti JP, Gardner AJ, Panenka WJ, Iverson GL. A Systematic Review of the Usefulness of Glial Fibrillary Acidic Protein for Predicting Acute Intracranial Lesions following Head Trauma. Front Neurol. 2017 Dec 4;8:652.

25. Manley G, Gardner AJ, Schneider KJ, Guskiewicz KM, Bailes J, Cantu RC, et al. A systematic review of potential long-term effects of sport-related concussion. Br J Sports Med. 2017 Jun;51(12):969–77.

26. McCormack S, Till K, Wenlock J, Whitehead S, Stokes KA, Bitcon M, et al. Contributors to negative biopsychosocial health or performance outcomes in rugby players (CoNBO): a systematic review and Delphi study protocol. BMJ Open Sport Exerc Med. 2022 Oct;8(4):e001440.

27. McCrory P, Meeuwisse WH, Kutcher JS, Jordan BD, Gardner A. What is the evidence for chronic concussion-related changes in retired athletes: behavioural, pathological and clinical outcomes? Br J Sports Med. 2013 Apr;47(5):327–30.

28. Panenka WJ, Gardner AJ, Dretsch MN, Crynen GC, Crawford FC, Iverson GL. Systematic Review of Genetic Risk Factors for Sustaining a Mild Traumatic Brain Injury. Journal of Neurotrauma. 2017 Jul;34(13):2093–9.

29. Silverberg ND, Gardner AJ, Brubacher JR, Panenka WJ, Li JJ, Iverson GL. Systematic Review of Multivariable Prognostic Models for Mild Traumatic Brain Injury. Journal of Neurotrauma. 2015 Apr 15;32(8):517–26.

30. Terry DP, Büttner F, Huebschmann NA, Gardner AJ, Cook NE, Iverson GL. Systematic Review of Pre-injury Migraines as a Vulnerability Factor for Worse Outcome Following Sport-Related Concussion. Front Neurol. 2022 Jun 20;13:915357.

31. Edlow BL, Bodien YG, Baxter T, Belanger HG, Cali RJ, Deary KB, et al. Long-Term Effects of Repeated Blast Exposure in United States Special Operations Forces Personnel: A Pilot Study Protocol. Journal of Neurotrauma. 2022 Oct 1;39(19–20):1391–407.

32. Glikstein R, Melkus G, Portela De Oliveira E, Brun-Vergara ML, Schwarz BA, Ramsay T, et al. Five-Year Serial Brain MRI Analysis of Military Members Exposed to Chronic Sub-Concussive Overpressures. Magnetic Resonance Imaging. 2025 Jan;61(1):415–23.

33. Hunfalvay M, Murray NP, Creel WT, Carrick FR. Long-Term Effects of Low-Level Blast Exposure and High-Caliber Weapons Use in Military Special Operators. Brain Sciences. 2022 May 23;12(5):679.

34. Popay J, Roberts H, Sowden A, Petticrew M, Arai L, Rodgers M, et al. Guidance on the conduct of narrative synthesis in systematic reviews: A product from the ESRC Methods Programme [Internet]. Lancaster University; 2006 [cited 2025 Mar 19]. Available from: http://rgdoi.net/10.13140/2.1.1018.4643

35. Sirriyeh R, Lawton R, Gardner P, Armitage G. Reviewing studies with diverse designs: the development and evaluation of a new tool. Evaluation Clinical Practice. 2012 Aug;18(4):746–52.

36. Varker T, Forbes D, Dell L, Weston A, Merlin T, Hodson S, et al. Rapid evidence assessment: increasing the transparency of an emerging methodology. Evaluation Clinical Practice. 2015 Dec;21(6):1199–204.

37. Belding JN, Fitzmaurice S, Englert RM, Koenig HG, Thomsen CJ, Olaghere da Silva U. Self-Reported Concussion Symptomology during Deployment: Differences as a Function of Injury Mechanism and Low-Level Blast Exposure. J Neurotrauma. 2020;37(20):2219–26.

38. Stromberg KM, Martindale SL, Walker WC, Ou Z, Pogoda TK, Miles SR, et al. Mild traumatic brain injury, PTSD symptom severity, and behavioral dyscontrol: a LIMBIC-CENC study. Frontiers in Neurology. 2023;14.

39. Belding JN, Englert R, Bonkowski J, Thomsen CJ. Occupational Risk of Low-Level Blast Exposure and TBI-Related Medical Diagnoses: A Population-Based Epidemiological Investigation (2005-2015). Int J Environ Res Public Health. 2021;18(24).

40. Belding JN, Fitzmaurice S, Englert RM, Lee I, Kowitz B, Highfill-McRoy RM, et al. Blast Exposure and Risk of Recurrent Occupational Overpressure Exposure Predict Deployment TBIs. Military Medicine. 2020;185(5–6):E538–44.

41. Belding JN, Khokhar B, Englert RM, Fitzmaurice S, Thomsen CJ. The Persistence of Blast- Versus Impact-Induced Concussion Symptomology Following Deployment. J Head Trauma Rehabil. 2021;36(6):E397–405.

42. Carr W., Kelley A.L., Toolin C.F., Weber N.S. Association of MOS-Based Blast Exposure With Medical Outcomes. Frontiers in Neurology. 2020;11:619.

43. Martindale SL, Ord AS, Rowland JA. Influence of blast exposure on cognitive functioning in combat veterans. Neuropsychology. 2020;34(7):735–43.

44. Martindale SL, Kolaja CA, Belding JN, Liu L, Rull RP, Trone DW, et al. Blast exposure and long-term diagnoses among veterans: a millennium cohort study investigation of high-level blast and low-level blast. Front Neurol. 2025;16:1599351.

45. Wang Z, Wilson CM, Ge Y, Nemes J, LaValle C, Boutté A, et al. DNA Methylation Patterns of Chronic Explosive Breaching in U.S. Military Warfighters. Front Neurol. 2020;11:1010.

46. Wang Z, Sun S, Liu Q, Kranfli AA, Nemes J, Sullan M, et al. Impact of prior exposures on biomarkers of blast during military tactical training. Front Neurol. 2025;16:1589742.

47. Wang Z., Wilson C.M., Mendelev N., Ge Y., Galfalvy H., Elder G., et al. Acute and Chronic Molecular Signatures and Associated Symptoms of Blast Exposure in Military Breachers. Journal of Neurotrauma. 2020;37(10):1221EP – 1232.

48. Champagne AA, Coverdale NS, Ross A, Murray C, Vallee I, Cook DJ. Characterizing changes in network connectivity following chronic head trauma in special forces military personnel: a combined resting-fMRI and DTI study. Brain Inj. 2021;35(7):760–8.

49. Champagne AA, Coverdale NS, Skinner C, Schwarz BA, Glikstein R, Melkus G, et al. Longitudinal analysis highlights structural changes in grey- and white-matter within military personnel exposed to blast. Brain Inj. 2025;39(6):509–17.

50. Vartanian O, Tenn C, Rhind SG, Nakashima A, Di Battista AP, Sergio LE, et al. Blast in Context: The Neuropsychological and Neurocognitive Effects of Long-Term Occupational Exposure to Repeated Low-Level Explosives on Canadian Armed Forces' Breaching Instructors and Range Staff. Front Neurol. 2020;11:588531.

51. Vartanian O, Coady L, Blackler K, Fraser B, Cheung B. Neuropsychological, Neurocognitive, Vestibular, and Neuroimaging Correlates of Exposure to Repetitive Low-Level Blast Waves: Evidence From Four Nonoverlapping Samples of Canadian Breachers. Mil Med. 2021;186(3–4):e393–400.

52. Callahan ML, Storzbach D. Sensory sensitivity and posttraumatic stress disorder in blast exposed veterans with mild traumatic brain injury. Applied Neuropsychology: Adult. 2019;26(4):365–73.

53. Merritt VC, Jurick SM, Crocker LD, Sullan MJ, Sakamoto MS, Davey DK, et al. Associations between multiple remote mild TBIs and objective neuropsychological functioning and subjective symptoms in combat-exposed veterans. Archives of Clinical Neuropsychology. 2020;35(5):491–505.

54. Rowland JA, Martindale SL, Spengler KM, Shura RD, Taber KH. Sequelae of blast events in Iraq and Afghanistan War veterans using the Salisbury Blast Interview: a CENC study. Brain injury. 2020;34(5):642–52.

55. Stone JR, Avants BB, Tustison NJ, Wassermann EM, Gill J, Polejaeva E, et al. Functional and Structural Neuroimaging Correlates of Repetitive Low-Level Blast Exposure in Career Breachers. J Neurotrauma. 2020;37(23):2468–81.

56. Terry G, Pagulayan KF, Muzi M, Mayer C, Murray DR, Schindler AG, et al. Increased [(18)F]Fluorodeoxyglucose Uptake in the Left Pallidum in Military Veterans with Blast-Related Mild

Traumatic Brain Injury: Potential as an Imaging Biomarker and Mediation with Executive Dysfunction and Cognitive Impairment. J Neurotrauma. 2024;41(13–14):1578–96.

57. Ware AL, Biekman B, Hachey R, MacLeod M, Bird W, Pathak S, et al. A preliminary high-definition fiber tracking study of the executive control network in blast-induced traumatic brain injury. Journal of Neurotrauma. 2019;36(5):686–701.

58. Agoston DV, McCullough J, Aniceto R, Lin IH, Kamnaksh A, Eklund M, et al. Blood-Based Biomarkers of Repetitive, Subconcussive Blast Overpressure Exposure in the Training Environment: A Pilot Study. Neurotrauma Rep. 2022;3(1):479–90.

59. Edwards KA, Leete JJ, Tschiffely AE, Moore CY, Dell KC, Statz JK, et al. Blast exposure results in tau and neurofilament light chain changes in peripheral blood. Brain Injury. 2020;34(9):1213–21.

60. Edwards KA, Greer K, Leete J, Lai C, Devoto C, Qu BX, et al. Neuronally-derived tau is increased in experienced breachers and is associated with neurobehavioral symptoms. Sci Rep. 2021;11(1):19527.

61. Haran FJ, Handy JD, Servatius RJ, Rhea CK, Tsao JW. Acute neurocognitive deficits in active duty service members following subconcussive blast exposure. Appl Neuropsychol Adult. 2021;28(3):297–309.

62. Haran FJ, Zampieri C, Wassermann EM, Polejaeva E, Dell KC, LoPresti ML, et al. Chronic Effects of Breaching Blast Exposure on Sensory Organization and Postural Limits of Stability. J Occup Environ Med. 2021;63(11):944–50.

63. Modica CM, Johnson BR, Zalewski C, King K, Brewer C, King JE, et al. Hearing Loss and Irritability Reporting Without Vestibular Differences in Explosive Breaching Professionals. Front Neurol. 2020;11:588377.

64. Nakashima A, Vartanian O, Rhind SG, King K, Tenn C, Jetly CR. Repeated Occupational Exposure to Low-level Blast in the Canadian Armed Forces: Effects on Hearing, Balance, and Ataxia. Military Medicine. 2022 Jan 4;187(1–2):e201–8.

65. Williamson JR, Kim J, Halford E, Smalt CJ, Rao HM. Using Body-worn Accelerometers to Detect Physiological Changes During Periods of Blast Overpressure Exposure. Annu Int Conf IEEE Eng Med Biol Soc. 2022;2022:926–32.

66. Miller MR, DiBattista A, Patel MA, Daley M, Tenn C, Nakashima A, et al. A Distinct Metabolite Signature in Military Personnel Exposed to Repetitive Low-Level Blasts. Front Neurol. 2022;13:831792.

67. Thangavelu B., LaValle C.R., Egnoto M.J., Nemes J., Boutte A.M., Kamimori G.H. Overpressure Exposure From.50-Caliber Rifle Training Is Associated With Increased Amyloid Beta Peptides in Serum. Frontiers in Neurology. 2020;11:620.

68. Lee SJ, Logsdon AF, Yagi M, Baskin BM, Peskind ER, Raskind MM, et al. The dynorphin/kappa opioid receptor mediates adverse immunological and behavioral outcomes induced by repetitive blast trauma. J Neuroinflammation. 2022;19(1):288.

69. Kontos AP, Zynda AJ, Minerbi A. Comparison of Vestibular/Ocular Motor Screening (VOMS) and Computerized Eye-tracking to Identify Exposure to Repetitive Head Impacts. Mil Med. 2024;189(11–12):2291–7.

70. Wang Y., Urioste R.T., Wei Y., Wilder D.M., Arun P., Sajja V., et al. Blast-induced hearing impairment in rats is associated with structural and molecular changes of the inner ear. Scientific reports. 2020;10(1):10652.

71. Rhind SG, Shiu MY, Tenn C, Nakashima A, Jetly R, Sajja VSSS, et al. Repetitive Low-Level Blast Exposure Alters Circulating Myeloperoxidase, Matrix Metalloproteinases, and Neurovascular Endothelial Molecules in Experienced Military Breachers. Int J Mol Sci. 2025;26(5).

72. Vorn R, Naunheim R, Lai C, Wagner C, Gill JM. Elevated Axonal Protein Markers Following Repetitive Blast Exposure in Military Personnel. Front Neurosci. 2022;16:853616.

73. Rao HM, McGuire SM, Halford E, Smalt CJ. Changes in Eye Tracking Features Across Periods of Overpressure Exposure. Mil Med. 2023;188(11–12):e3398–406.

74. Walker WC, Clark SW, Eppich K, Wilde EA, Martin AM, Allen CM, et al. Headache among combat-exposed veterans and service members and its relation to mild traumatic brain injury history and other factors: a LIMBIC-CENC study. Frontiers in Neurology. 2023;14.

75. Martindale SL, Ord AS, Rule LG, Rowland JA. Effects of blast exposure on psychiatric and health symptoms in combat veterans. Journal of Psychiatric Research. 2021 Nov;143:189–95.

76. Leiva-Salinas C, Singh A, Layfield E, Flors L, Patrie JT. Early Brain Amyloid Accumulation at PET in Military Instructors Exposed to Subconcussive Blast Injuries. Radiology. 2023;307(5):e221608.

77. Wright A, Murphy SF, VandeVord PJ. Glial activation and nociceptive neuropeptide elevation associated with the development of chronic post-traumatic headache following repetitive blast exposure. Neurobiol Pain. 2025;17:100178.

78. Clausen AN, Bouchard HC, Welsh-Bohmer KA, Morey RA. Assessment of Neuropsychological Function in Veterans With Blast-Related Mild Traumatic Brain Injury and Subconcussive Blast Exposure. Front Psychol. 2021;12:686330.

79. Parsey CM, Kang HJ, Eaton JC, McGrath ME, Barber J, Temkin NR, et al. Chronic frontal neurobehavioural symptoms in combat-deployed military personnel with and without a history of blast-related mild traumatic brain injury. Brain Injury. 2023 Aug 24;37(10):1127–34.

80. Braun M, Sevao M, Keil SA, Gino E, Wang MX, Lee J, et al. Macroscopic changes in aquaporin-4 underlie blast traumatic brain injury-related impairment in glymphatic function. Brain. 2024;147(6):2214–29.

81. Hayes JP, Pierce ME, Valerio KE, Miller MW, Huber BR, Fortier CB, et al. The association between blast exposure and transdiagnostic health symptoms on systemic inflammation. Neuropsychopharmacology. 2022;47(9):1702–9.

82. Liu Q, Wang Z, Sun S, Nemes J, Brenner LA, Hoisington A, et al. Association of Blast Exposure in Military Breaching with Intestinal Permeability Blood Biomarkers Associated with Leaky Gut. Int J Mol Sci. 2024;25(6).

83. Norris C, Garimella HT, Carr W, Boutté AM, Gupta RK, Przekwas AJ. Modeling biomarker kinetics of Aβ levels in serum following blast. Front Neurol. 2025;16:1548589.

84. Vorn R, Edwards KA, Hentig J, Yun S, Kim HS, Lai C, et al. A Pilot Study of Whole-Blood Transcriptomic Analysis to Identify Genes Associated with Repetitive Low-Level Blast Exposure in Career Breachers. Biomedicines. 2022;10(3).

85. Yuan W, Barber Foss KD, Dudley J, Thomas S, Galloway R, DiCesare C, et al. Impact of low-level blast exposure on brain function after a one-day tactile training and the ameliorating effect of a jugular vein compression neck collar device. Journal of Neurotrauma. 2019;36(5):721–34.

86. Yuan W, Dudley J, Slutsky-Ganesh AB, Leach J, Scheifele P, Altaye M, et al. White Matter Alteration Following SWAT Explosive Breaching Training and the Moderating Effect of a Neck Collar Device: A DTI and NODDI Study. Mil Med. 2021;186(11–12):1183–90.

87. Arun P, Rossetti F, Eken O, Wilder DM, Wang Y, Long JB. Phosphorylated Neurofilament Heavy Chain in the Cerebrospinal Fluid Is a Suitable Biomarker of Acute and Chronic Blast-Induced Traumatic Brain Injury. J Neurotrauma. 2021;38(20):2801–10.

88. Arun P., Rossetti F., Wilder D.M., Sajja S., Van Albert S.A., Wang Y., et al. Blast Exposure Leads to Accelerated Cellular Senescence in the Rat Brain. Frontiers in Neurology. 2020;11:438.

89. Bugay V., Bozdemir E., Vigil F.A., Chun S.H., Holstein D.M., Elliott W.R., et al. A Mouse Model of Repetitive Blast Traumatic Brain Injury Reveals Post-Trauma Seizures and Increased Neuronal Excitability. Journal of Neurotrauma. 2020;37(2):248EP – 261.

90. Campos-Pires R, Ong BE, Koziakova M, Ujvari E, Fuller I, Boyles C, et al. Repetitive, but Not Single, Mild Blast TBI Causes Persistent Neurological Impairments and Selective Cortical Neuronal Loss in Rats. Brain Sci. 2023;13(9).

91. Evans LP, Boehme N, Wu S, Burghardt EL, Akurathi A, Todd BP, et al. Sex Does Not Influence Visual Outcomes After Blast-Mediated Traumatic Brain Injury but IL-1 Pathway Mutations Confer Partial Rescue. Invest Ophthalmol Vis Sci. 2020;61(12):7.

92. Gama Sosa MA, De Gasperi R, Pryor D, Perez Garcia GS, Perez GM, Abutarboush R, et al. Low-level blast exposure induces chronic vascular remodeling, perivascular astrocytic degeneration and vascular-associated neuroinflammation. Acta Neuropathol Commun. 2021;9(1):167.

93. Tsuda S, Golam M, Hou J, Nelson R, Bernavil P, Richardson K, et al. Altered monoaminergic levels, spasticity, and balance disability following repetitive blast-induced traumatic brain injury in rats. Brain Res. 2020;1747:147060.

94. Varghese N. Pharmacological Interventions to Reduce Electrophysiological Deficits following Blast Traumatic Brain Injury [Internet]. [United States -- New York]: Columbia University; 2022. Available from: https://www.proquest.com/dissertations-theses/pharmacological-interventions-reduce/docview/2715447062/se-2?accountid=14757

95. Varghese N, Amelinez-Robles NE, Morrison B 3rd. GABA(A) receptor subunit modulation reversed electrophysiological network alterations after blast exposure in rat organotypic hippocampal slice cultures. Exp Neurol. 2023;364:114388.

96. Anderson LM, Samineni S, Wilder DM, Lara M, Eken O, Urioste R, et al. The Neurobehavioral Effects of Buprenorphine and Meloxicam on a Blast-Induced Traumatic Brain Injury Model in the Rat. Front Neurol. 2021;12:746370.

97. Baskin B, Lee SJ, Skillen E, Wong K, Rau H, Hendrickson RC, et al. Repetitive Blast Exposure Increases Appetitive Motivation and Behavioral Inflexibility in Male Mice. Front Behav Neurosci. 2021;15:792648.

98. Bera A, Subhramanian M, Sharma P. Identification of Serum Biomarkers for Blast-induced Traumatic Brain Injuries: Low vs. High-intensity Exposure in a Rat Model. In Vivo. 2025;39(4):1840–51.

99. Blaze J, Choi I, Wang Z, Umali M, Mendelev N, Tschiffely AE, et al. Blast-Related Mild TBI Alters Anxiety-Like Behavior and Transcriptional Signatures in the Rat Amygdala. Front Behav Neurosci. 2020;14:160.

100. Bradshaw DVJ, Kim Y, Fu A, Marion CM, Radomski KL, McCabe JT, et al. Repetitive Blast Exposure Produces White Matter Axon Damage without Subsequent Myelin Remodeling: In Vivo Analysis of Brain Injury Using Fluorescent Reporter Mice. Neurotrauma Rep. 2021;2(1):180–92.

101. Chiariello R, McCarthy C, Glaeser BL, Shah AS, Budde MD, Stemper BD, et al. Chronicity of repeated blast traumatic brain injury associated increase in oxycodone seeking in rats. Behav Brain Res. 2023;438:114181.

102. Crabtree A, McEvoy C, Muench P, Ivory RA, Rodriguez J, Omer M, et al. Modeling Highly Repetitive Low-level Blast Exposure in Mice. JoVE. 2024 May 24;(207):66592.

103. Dahal S, Kakulavarapu RV, Heyburn L, Wilder D, Kumar R, Dimitrov G, et al. microRNA Profile Changes in Brain, Cerebrospinal Fluid, and Blood Following Low-Level Repeated Blast Exposure in a Rat Model. J Neurotrauma. 2024;

104. De Gasperi R, Gama Sosa MA, Perez Garcia GS, Perez GM, Abutarboush R, Kawoos U, et al. Progressive Transcriptional Changes in the Amygdala Implicate Neuroinflammation in the Effects of Repetitive Low-Level Blast Exposure in Male Rats. J Neurotrauma. 2023;40(5–6):561–77.

105. De Gasperi R, Gama Sosa MA, Perez Garcia G, Perez GM, Pryor D, Morrison CLA, et al. Metabotropic Glutamate Receptor 2 Expression Is Chronically Elevated in Male Rats With Post-Traumatic Stress Disorder Related Behavioral Traits Following Repetitive Low-Level Blast Exposure. J Neurotrauma. 2024;41(5–6):714–33.

106. De Gasperi R, Perez Garcia G, Gama Sosa MA, Perez GM, Abutarboush R, Kawoos U, et al. Serotonin 5-HT2A receptor expression is chronically decreased in the anterior cerebral cortex of male rats following repetitive low-level blast exposure. Front Neurol. 2025;16:1594335.

107. Dickerson M.R., Bailey Z.S., Murphy S.F., Urban M.J., VandeVord P.J. Glial Activation in the Thalamus Contributes to Vestibulomotor Deficits Following Blast-Induced Neurotrauma. Frontiers in Neurology. 2020;11:618.

108. Gama Sosa MA, De Gasperi R, Lind RH, Pryor D, Vargas DC, Perez Garcia GS, et al. Intramural hematomas and astrocytic infiltration precede perivascular inflammation in a rat model of repetitive low-level blast injury. J Neuropathol Exp Neurol. 2025;84(4):337–52.

109. Garcia GP, Perez GM, Gasperi RD, Sosa MAG, Otero-Pagan A, Abutarboush R, et al. (2R,6R)-Hydroxynorketamine Treatment of Rats Exposed to Repetitive Low-Level Blast Injury. Neurotrauma Rep. 2023;4(1):197–217.

110. Govindarajulu M, Patel MY, Wilder DM, Long JB, Arun P. Blast exposure dysregulates nighttime melatonin synthesis and signaling in the pineal gland: a potential mechanism of blast-induced sleep disruptions. Brain sciences. 2022;12(10).

111. Harper MM, Boehme NA, Dutca L, Navarro V. Increasing the number and intensity of shock tube generated blast waves leads to earlier retinal ganglion cell dysfunction and regional cell death. Exp Eye Res. 2024;239:109754.

112. Hetzer SM, O'Connell C, Lallo V, Robson M, Evanson NK. Model matters: Differential outcomes in traumatic optic neuropathy pathophysiology between blunt and blast-wave mediated head injuries. Exp Neurol. 2024;372:114613.

113. Heyburn L, Batuure A, Wilder D, Long J, Sajja VS. Neuroinflammation Profiling of Brain Cytokines Following Repeated Blast Exposure. Int J Mol Sci. 2023;24(16).

114. Heyburn L, Dahal S, Abutarboush R, Reed E, Urioste R, Batuure A, et al. Differential effects on TDP-43, piezo-2, tight-junction proteins in various brain regions following repetitive low-intensity blast overpressure. Front Neurol. 2023;14:1237647.

115. Heyburn L, Abutarboush R, Goodrich S, Urioste R, Batuure A, Wheel J, et al. Repeated Low-Level Blast Acutely Alters Brain Cytokines, Neurovascular Proteins, Mechanotransduction, and Neurodegenerative Markers in a Rat Model. Front Cell Neurosci. 2021;15:636707.

116. Honig MG, Dorian CC, Worthen JD, Micetich AC, Mulder IA, Sanchez KB, et al. Progressive long-term spatial memory loss following repeat concussive and subconcussive brain injury in mice, associated with dorsal hippocampal neuron loss, microglial phenotype shift, and vascular abnormalities. Eur J Neurosci. 2021;54(5):5844–79.

117. Hubbard WB, Vekaria HJ, Velmurugan GV, Kalimon OJ, Prajapati P, Brown E, et al. Mitochondrial Dysfunction After Repeated Mild Blast Traumatic Brain Injury Is Attenuated by a Mild Mitochondrial Uncoupling Prodrug. J Neurotrauma. 2023;40(21–22):2396–409.

118. Iacono D, Hatch K, Murphy EK, Cole RN, Post J, Leonessa F, et al. Proteomic Changes in the Hippocampus after Repeated Explosive-Driven Blasts. J Proteome Res. 2024;23(1):397–408.

119. Kallakuri S, Sadik N, Davidson CJ, Gheidi A, Bosse KE, Bir CA, et al. Anxiety-like Characteristics, Forepaw Thermal Sensitivity Changes and Glial Alterations 1 Month After Repetitive Blast Traumatic Brain Injury in Male Rats. Ann Neurosci. 2024;09727531241248976.

120. Kumari M, Arora P, Sharma P, Hasija Y, Rana P, D'souza MM, et al. Acute metabolic alterations in the hippocampus are associated with decreased acetylation after blast induced TBI. Metabolomics. 2023;19(1):5.

121. Logsdon A.F., Schindler A.G., Meabon J.S., Yagi M., Herbert M.J., Banks W.A., et al. Nitric oxide synthase mediates cerebellar dysfunction in mice exposed to repetitive blast-induced mild traumatic brain injury. Scientific reports. 2020;10(1):9420.

122. Miyai K, Kawauchi S, Kato T, Yamamoto T, Mukai Y, Yamamoto T, et al. Axonal damage and behavioral deficits in rats with repetitive exposure of the brain to laser-induced shock waves: Effects of inter-exposure time. Neurosci Lett. 2021;749:135722.

123. Nonaka M, Taylor WW, Bukalo O, Tucker LB, Fu AH, Kim Y, et al. Behavioral and Myelin-Related Abnormalities after Blast-Induced Mild Traumatic Brain Injury in Mice. J Neurotrauma. 2021;38(11):1551–71.

124. Perez Garcia G, De Gasperi R, Gama Sosa MA, Perez GM, Otero-Pagan A, Pryor D, et al. Laterality and region-specific tau phosphorylation correlate with PTSD-related behavioral traits in rats exposed to repetitive low-level blast. Acta Neuropathol Commun. 2021;9(1):33.

125. Perez Garcia G, De Gasperi R, Tschiffely AE, Gama Sosa MA, Abutarboush R, Kawoos U, et al. Repetitive Low-Level Blast Exposure Improves Behavioral Deficits and Chronically Lowers Aβ42 in an Alzheimer Disease Transgenic Mouse Model. J Neurotrauma. 2021;38(22):3146–73.

126. Perez Garcia G, Perez GM, De Gasperi R, Gama Sosa MA, Otero-Pagan A, Pryor D, et al. Progressive Cognitive and Post-Traumatic Stress Disorder-Related Behavioral Traits in Rats Exposed to Repetitive Low-Level Blast. J Neurotrauma. 2021;38(14):2030–45.

127. Perez Garcia G, Perez GM, Otero-Pagan A, Abutarboush R, Kawoos U, De Gasperi R, et al. Transcranial Laser Therapy Does Not Improve Cognitive and Post-Traumatic Stress Disorder-Related Behavioral Traits in Rats Exposed to Repetitive Low-Level Blast Injury. Neurotrauma Rep. 2021;2(1):548–63.

128. Ravula AR. Repeated Low-Level Blast Induces Chronic Neuroinflammation and Neurobehavioral Changes in Rat Models. [United States -- New Jersey]: New Jersey Institute of Technology; 2022.

129. Ravula AR, Rodriguez J, Younger D, Perumal V, Shao N, Rama Rao KV, et al. Animal model of repeated low-level blast traumatic brain injury displays acute and chronic neurobehavioral and neuropathological changes. Exp Neurol. 2022;349:113938.

130. Ravula AR, Murray KE, Rao KVR, Pfister BJ, Citron BA, Chandra N. MCC950 Attenuates Microglial NLRP3-Mediated Chronic Neuroinflammation and Memory Impairment in a Rat Model of Repeated Low-Level Blast Exposure. J Neurotrauma. 2024;41(11–12):1450–68.

131. Robey C, Grillakis A, Fan A, Liu J, Tucker LB, Fu AH, et al. Chronic Neurobehavioral and Neuropathological Consequences of Repeated Blast Exposure in P301S Transgenic Tau Rats. Neurotrauma Rep. 2025;6(1):374–90.

132. Statz JK, Ciarlone SL, Goodrich JA, McCarron RM, Walker PB, Norris JN, et al. Affective profiling for anxiety-like behavior in a rodent model of mTBI. Behavioural Brain Research. 2019;368.

133. Strickler J, Murphy S, Athanasaw K, Bowyer N, VandeVord PJ. Exposure to Acute Psychological Trauma Prior to Blast Neurotrauma Results in Alternative Behavioral Outcomes. eNeuro. 2025;12(3).

134. Tsuda S, Golam M, Hou J, Wang KKW, Thompson FJ, Bose P. Reduction of epinephrine in the lumbar spinal cord following repetitive blast-induced traumatic brain injury in rats. Neural Regen Res. 2024;19(7):1548–52.

135. Varghese N, Morrison B 3rd. Partial Depletion of Microglia Attenuates Long-Term Potentiation Deficits following Repeated Blast Traumatic Brain Injury in Organotypic Hippocampal Slice Cultures. J Neurotrauma. 2023;40(5–6):547–60.

136. Varghese N, Morrison B 3rd. Inhibition of cyclooxygenase and EP3 receptor improved long term potentiation in a rat organotypic hippocampal model of repeated blast traumatic brain injury. Neurochem Int. 2023;163:105472.

137. Vaughn MN, Geyer MA, Powell SB, Ng L, Risbrough VB, Halberstadt AL. Effect of blast exposure on sensorimotor gating and fear memory. Physiol Behav. 2025;300:115029.

138. Velmurugan GV, Prajapati S, Tran S, Miller C, Burke B, Hubbard WB. Sex-dependent blood-brain barrier alterations following repeated mild blast traumatic brain injury at varying inter-injury intervals. Exp Neurol. 2025;392:115325.

139. Vigil FA, Belchior H, Bugay V, Bazaldua II, Stoja A, Dantas DC, et al. Acute Treatment with the M-Channel (K(v)7, KCNQ) Opener Retigabine Reduces the Long-Term Effects of Repetitive Blast Traumatic Brain Injuries. Neurotherapeutics. 2023;20(3):853–69.

140. Zhang Z, Xiao T, Hall MR, Crodian JS, Alford AK, Kimbrough A, et al. Temporal differential effects of post-injury alcohol consumption in a mouse model of blast-induced traumatic brain injury. Neuroscience. 2024;562:239–51.

141. Jiang S, Welch P, Sanders S, Gan RZ. Mitigation of Hearing Damage After Repeated Blast Exposures in Animal Model of Chinchilla. J Assoc Res Otolaryngol. 2022;23(5):603–16.

142. Jiang S, Sanders S, Gan RZ. Mitigation of Hearing Damage With Liraglutide Treatment in Chinchillas After Repeated Blast Exposures at Mild-TBI. Mil Med. 2023;188(Suppl 6):553–60.

143. Jiang S, Sanders S, Gan RZ. Hearing protection and damage mitigation in Chinchillas exposed to repeated low-intensity blasts. Hear Res. 2023;429:108703.

144. Schwerin SC, Chatterjee M, Hutchinson EB, Djankpa FT, Armstrong RC, McCabe JT, et al. Expression of GFAP and Tau Following Blast Exposure in the Cerebral Cortex of Ferrets. J Neuropathol Exp Neurol. 2021;80(2):112–28.

145. Smith K.D., Chen T., Gan R.Z. Hearing Damage Induced by Blast Overpressure at Mild TBI Level in a Chinchilla Model. Military medicine. 2020;185(Supplement 1):248EP – 255.

146. Wooten T, Sullivan DR, Logue MW, Fonda JR, Fortier CB, DeGutis J, et al. Apolipoprotein E (APOE) ε4 Status Moderates the Relationship Between Close-Range Blast Exposure and Cognitive Functioning. J Int Neuropsychol Soc. 2021;27(4):315–28.

147. Arora P, Sharma A, Trivedi R, Sharma P, Padhy S, Shah S, et al. Lipidomic Analysis Reveals Systemic Alterations in Servicemen Exposed to Repeated Occupational Low-Level Blast Waves. Military Medicine. 2025 Jan 16;190(1–2):107–15.

148. Baskin BM, Logsdon AF, Janet Lee S, Foresi BD, Peskind E, Banks WA, et al. Timing matters: Sex differences in inflammatory and behavioral outcomes following repetitive blast mild traumatic brain injury. Brain, Behavior, and Immunity. 2023 May;110:222–36.

149. Belding JN, Bonkowski J, Englert R. Traumatic brain injury and occupational risk of low-level blast exposure on adverse career outcomes: an examination of administrative and medical separations from Service (2005-2015). Front Neurol. 2024;15:1389757.

150. Belding JN, Englert RM, Fitzmaurice S, Jackson JR, Koenig HG, Hunter MA, et al. Potential Health and Performance Effects of High-Level and Low-Level Blast: A Scoping Review of Two Decades of Research. Front Neurol. 2021;12:628782.

151. Belding JN, Kolaja CA, Rull RP, Trone DW. Single and repeated high-level blast, low-level blast, and new-onset self-reported health conditions in the U.S. Millennium Cohort Study: An exploratory investigation. Front Neurol. 2023;14:1110717.

152. Chung SY, Harrison EM, Englert RM, Belding JN. Effects of Blast- and Impact-Related Concussion on Persistent Sleep Problems. J Head Trauma Rehabil. 2025;40(1):E66–74.

153. Modeling Highly Repetitive Low-level Blast Exposure in Mice. United States; 2024.

154. De Gasperi R, Gama Sosa MA, Perez Garcia G, Perez GM, Pryor D, Morrison CLA, et al. Metabotropic Glutamate Receptor 2 Expression Is Chronically Elevated in Male Rats With Post-Traumatic Stress Disorder Related Behavioral Traits Following Repetitive Low-Level Blast Exposure. J Neurotrauma. 2024;41(5–6):714–33.

155. Dickstein DL, De Gasperi R, Gama Sosa MA, Perez-Garcia G, Short JA, Sosa H, et al. Brain and blood biomarkers of tauopathy and neuronal injury in humans and rats with neurobehavioral syndromes following blast exposure. Mol Psychiatry. 2021;26(10):5940–54.

156. Diociasi A, Iaccarino MA, Sorg S, Lubin EJ, Wisialowski C, Dua A, et al. Distinct Functional MRI Connectivity Patterns and Cortical Volume Variations Associated with Repetitive Blast Exposure in Special Operations Forces Members. Radiology. 2025;315(1):e233264.

157. Edwards KA, Leete JJ, Smith EG, Quick A, Modica CM, Wassermann EM, et al. Elevations in Tumor Necrosis Factor Alpha and Interleukin 6 From Neuronal-Derived Extracellular Vesicles in Repeated Low-Level Blast Exposed Personnel. Front Neurol. 2022;13:723923.

158. Gilmore N, McKinney IR, Tseng CEJ, Greve DN, Maffei C, Healy BC, et al. Investigating the neural network correlates of apathy, disinhibition, and executive dysfunction in active-duty United States Special Operations Forces. Brain Imaging Behav. 2025;19(3):627–36.

159. Gilmore N, Tseng CEJ, Maffei C, Tromly SL, Deary KB, McKinney IR, et al. Impact of repeated blast exposure on active-duty United States Special Operations Forces. Proc Natl Acad Sci U S A. 2024;121(19):e2313568121.

160. Howard CK, Yamada M, Dovel M, Leverett R, Hill A, Manlapaz KA, et al. An Objective Assessment of Neuromotor Control Using a Smartphone App After Repeated Subconcussive Blast Exposure. Sensors (Basel). 2024;24(21).

161. Kulinski D, Carr W, Garfield BA, Salib J, Dirks C, Sheffield B, et al. Acute Hearing Deficits associated with Weapons Exposure in Section 734 Blast Overpressure Study (BOS). Mil Med. 2023;188(Suppl 6):666–73.

162. Kulinski D, Smalt CJ, Carr W, Russell J, Hecht Q, Brzuska A, et al. Estimated dose-response relationship between impulse noise exposure and temporary threshold shift in tactical training environments. J Acoust Soc Am. 2025;157(3):1926–37.

163. Lange RT, French LM, Bailie JM, Merritt VC, Pattinson CL, Hungerford LD, et al. Clinical utility of PTSD, resilience, sleep, and blast as risk factors to predict poor neurobehavioral functioning following traumatic brain injury: a longitudinal study in U.S. military service members. Quality of life research. 2022;31(9):2411–22.

164. Lange RT, Lippa SM, Bailie JM, Wright M, Driscoll A, Sullivan J, et al. Longitudinal trajectories and risk factors for persistent postconcussion symptom reporting following uncomplicated mild traumatic brain injury in U.S. Military service members. The Clinical Neuropsychologist. 2020;34(6):1134–55.

165. Martindale SL, Shura RD, Rostami R, Taber KH, Rowland JA. Research letter: blast exposure and brain volume. Journal of head trauma rehabilitation. 2021;36(6):424–8.

166. 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 Traumatic Stress. 2019;32(4):546–54.

167. Phipps H, Mondello S, Wilson A, Dittmer T, Rohde NN, Schroeder PJ, et al. Characteristics and Impact of U.S. Military Blast-Related Mild Traumatic Brain Injury: A Systematic Review. Frontiers in Neurology. 2020;11.

168. Powell JR, Zong X, Weinstein JM, DeLellis SM, Kane SF, Means GE, et al. Mild Traumatic Brain Injury and Career Stage Associate with Visible Perivascular Spaces in Special Operations Forces Soldiers. Ann Biomed Eng. 2024;52(10):2812–7.

169. Powell JR. The Neurophysiological Effects of Blast Exposure and Mild Traumatic Brain Injury in Special Operations Forces Soldiers [Internet]. [United States -- North Carolina]: The University of North Carolina at Chapel Hill; 2023. Available from: https://www.proquest.com/dissertations-theses/neurophysiological-effects-blast-exposure-mild/docview/2816719742/se-2?accountid=14757

170. Rowland JA, Stapleton-Kotloski JR, Martindale SL, Rogers EE, Ord AS, Godwin DW, et al. Alterations in the Topology of Functional Connectomes Are Associated with Post-Traumatic Stress Disorder and Blast-Related Mild Traumatic Brain Injury in Combat Veterans. J Neurotrauma. 2021;38(22):3086–96.

171. Rowland JA, Martindale SL. Considerations for the assessment of blast exposure in service members and veterans. Frontiers in neurology. 2024;15:e1383710–e1383710.

172. Schmitt RR, Kaliyappan K, Muthaiah VPK, Ignatowski TA, Prasad PN, Mahajan SD. Blast-induced injury responsive relative gene expression of traumatic brain injury biomarkers in human brain microvascular endothelial cells. Brain research. 2021;1770:147642.

173. Shea K, Vartanian O, Rhind SG, Tenn C, Nakashima A. Impact of Low-Level Blast Exposure From Military Training and Career Cumulation on Hearing Outcomes. Military Medicine. 2025 Mar 4;

174. Solar KG, Ventresca M, Zamyadi R, Zhang J, Jetly R, Vartanian O, et al. Repetitive subconcussion results in disrupted neural activity independent of concussion history. Brain Commun. 2024;6(5):fcae348.

175. Song H, Chen M, Chen C, Cui J, Johnson CE, Cheng J, et al. Proteomic analysis and biochemical correlates of mitochondrial dysfunction after low-intensity primary blast exposure. Journal of Neurotrauma. 2019;36(10):1591–605.

176. Stone JR, Avants BB, Tustison NJ, Wassermann EM, Gill J, Polejaeva E, et al. Functional and Structural Neuroimaging Correlates of Repetitive Low-Level Blast Exposure in Career Breachers. J Neurotrauma. 2020;37(23):2468–81.

177. Tschiffely A.E., Statz J.K., Edwards K.A., Goforth C., Ahlers S.T., Carr W.S., et al. Assessing a Blast-Related Biomarker in an Operational Community: Glial Fibrillary Acidic Protein in Experienced Breachers. Journal of Neurotrauma. 2020;37(8):1091EP – 1096.

178. Turk KW, Marin A, Schiloski KA, Vives-Rodriguez AL, Uppal P, Suh C, et al. Head injury exposure in veterans presenting to memory disorders clinic: An observational study of clinical characteristics and relationship of event-related potentials and imaging markers. Frontiers in Neurology. 2021;12.

179. Uzunalli G, Herr S, Dieterly AM, Shi R, Lyle LT. Structural disruption of the blood-brain barrier in repetitive primary blast injury. Fluids Barriers CNS. 2021;18(1):2.

180. Wachtler N, O'Brien R, Ehrlich BE, McGuone D. Exploring Calcium Channels as Potential Therapeutic Targets in Blast Traumatic Brain Injury. Pharmaceuticals (Basel). 2025;18(2).

181. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 Mar 29;n71.

182. Schünemann HJ, Higgins JPT, Vist GE, Glasziou P, Akl EA, Skoetz N, et al. Completing 'summary of findings' tables and grading the certainty of the evidence. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al., editors. Cochrane Handbook for Systematic Reviews of Interventions. Wiley-Blackwell; 2019. p. 375–402.

183. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008 Apr 26;336(7650):924–6.

184. World Health Organization . WHO Handbook for Guideline Development. World Health Organization; 2015.

185. Harrison R, Jones B, Gardner P, Lawton R. Quality assessment with diverse studies (QuADS): an appraisal tool for methodological and reporting quality in systematic reviews of mixed- or multi-method studies. BMC Health Serv Res. 2021 Dec;21(1):144.