A Multimodal Assessment of the Long-Term Effects of Concussions in Adults over age Fifty

by

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We acknowledge and respect the Lək̓ʷəŋən (Songhees and Xʷsepsəm/Esquimalt) Peoples on whose territory the university stands, and the Lək̓ʷəŋən and W̱SÁNEĆ Peoples whose historical relationships with the land continue to this day.

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Abstract

Concussion, a form of mild traumatic brain injury (mTBI), is often viewed as a transient event with limited long-term impact. However, growing evidence suggests that concussions may carry lasting neurobiological consequences, particularly in older adults. This dissertation explores the long-term effects of concussion in adults over the age of fifty using a multimodal research framework that includes a systematic review and meta-analysis, a cross-sectional observational study, and a cognitive training intervention. Chapter two presents a comprehensive meta-analysis examining whether a history of mTBI is associated with an increased risk of developing dementia. The analysis included over 18,000 mTBI cases and revealed that individuals with prior mTBI are nearly twice as likely to develop dementia compared to those without, supporting the classification of concussion as a significant environmental risk factor for neurodegeneration. Chapter three investigated cognitive performance, brain structure, and serum biomarkers in older adults with and without a history of concussion. While traditional cognitive testing did not show significant group-level differences, participants with concussion histories exhibited relationships between levels of neurofilament light chain and decreased white matter integrity, suggesting ongoing or residual neural vulnerability that may not yet be behaviorally apparent. Chapter four evaluated whether a 12-week cognitive training intervention could support brain health and plasticity in aging adults. The program led to a significant increase in brain-derived neurotrophic factor, although cognitive and structural outcomes remained unchanged. These findings highlight the potential for targeted neuroplasticity interventions in at-risk individuals. Together, these studies provide converging evidence that having a history of concussion is associated with both increased dementia risk and subtle, persistent changes in brain health. The results underscore the

importance of early identification, ongoing monitoring, and the development of preventative strategies to support cognitive aging in individuals with a history of concussion.

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Abbreviations

3D-MOT	Three-Dimensional Multiple Object Tracking
AAN	American Academy Of Neurology
AD	Alzheimer's Disease
ADHD	Attention Deficit Hyperactivity Disorder
ADNI	Alzheimer's Disease Neuroimaging Initiative
APOE	Apolipoprotein E
AUC	Area Under The Curve
BDNF	Brain Derived Neurotrophic Factor
CHII	Cumulative Head Impact Index
CI	Confidence Interval
CIC	Catastrophic Illness Certificate
CSHA	Canadian Study Of Health And Aging
CSF	Cerebral Spinal Fluid
CTE	Chronic Traumatic Encephalopathy
CV	Coefficient Of Variation
CVLT-2	California Verbal Learning Test - Second Edition
DS	Digit Span
DTI	Diffusion Tensor Imaging
ET	Time To Echo
FA	Fractional Anisotropy

FDR	False Discovery Rate
FSL	Fmrib Software Library
GCS	Glasgow Coma Scale
GFAP	Glial Fibrillary Acidic Protein
HR	Hazard Ratio
IL-10	Interleukin 10
LEGEND	Longitudinal Examination to Gather Evidence of Neurodegenerative Disease
LOAD	Late Onset Alzheimer's Disease
LOC	Loss Of Consciousness
MCI	Mild Cognitive Impairment
MD	Mean Diffusivity
MMSE	Mini Mental State Examination
MOCA	Montreal Cognitive Assessment
mTBI	Mild Traumatic Brain Injury
NDI	National Death Index
NfL	Neurofilament Light Chain
NHI	National Health Index
NHIRD	National Health Insurance Research Database
NPI	Non-Pharmacological Intervention
NPR	National Patient Register
OHIP	Ontario Health Insurance Program
OR	Odds Ratio

PCS	Post Concussion Syndrome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PSaC	Persisting Symptoms after Concussion
PTA	Post Traumatic Amnesia
pTAU-217	Phosphorylated Tau - Site 217
ROC	Receiver Operating Characteristic
RT	Repetition Time
SD	Standard Deviation
SDMT	Symbol Digit Modalities Task
SIMOA	Single Molecular Array
STMS	Short Test of Mental Status
TBI	Traumatic Brain Injury
TBSS	Tract Based Spatial Statistics
TMT A/B	Trail Making Test (A And B)
TNF-α	Tumor Necrosis Factor Alpha
USCDC	United States Centre For Disease Control

Dedication

My graduate school journey has been anything but solitary. Though it's often described as a long, winding, and bumpy road, I've been incredibly fortunate. With the support of the remarkable people who walked beside me, I've made it over the bumps, through the valleys, and am so excited to be nearing the end of this journey!

Eric, thank you for your unconditional love and support (even when I am hangry). Solo and Skye, thank you for all the puppy cuddles and making me feel like the best doggy-mum in the world!

Mom (also known as Moopy), thank you for all the homemade spaghetti sauce, 8:00am drive-to-work phone calls and for being my biggest cheerleader. Grandma (also known as Goopy) thank you for always being excited to hear about my research and for always reminding me that I do, in fact, deserve to treat myself. Michael and Catherine, thank you for being the best in-laws in the world. I am excited to join the group of "Dr. Hedin's"!

To my chosen sisters, there are not enough thank yous in the world. Kaity, when you're around I know I will always sparkle. Ally and Kara, you are the best friends I could ask for. Your kindness and compassion is endless, and I am forever grateful. Hannah, words cannot describe what you mean to me, thank you for always being here for me, even when you're 4475km away.

To my supervisor Brian, thank you for allowing me to shine and for creating opportunities for me to challenge myself, learn and grow. To my Christie lab mates, you have been so supportive, and made graduate school a genuinely enjoyable experience. Jamie and Emma, it has been an absolute pleasure to see you two become the brightest, most dedicated and thoughtful graduate students I have ever had the pleasure working with.

I would also like to thank my participants. It has been a pleasure getting to know all of the amazing people who donated their time to this study. Without you I would not be here today. Lastly, to Taylor Swift, if you were to “ask me what I learned from all those years”, and “ask me what I learned from all those tears”, I’d say this, the most important lesson I’ve taken from graduate school is to always surround yourself with people you love, follow your passions, and be proud of your curiosity. I listened to your entire discography more times than I can count over these past six years, and you never failed to motivate me to persevere. For that, I am endlessly grateful.

“To me fearless isn't not having fears, it's not that you're not afraid of anything. I think that being fearless is having a lot of fears, but you jump anyway.”

-Taylor Swift

Chapter 1

Introduction

1.1 Preface

This dissertation examines the relationship between mild traumatic brain injuries (mTBI) and chronic pathophysiological responses related to neurodegeneration through three distinct but interconnected studies. First, I investigated whether having a concussion, a type of mTBI, increases the risk of dementia by conducting a systematic review and meta-analysis. This work, titled *Does Mild Traumatic Brain Injury Increase the Risk for Dementia? A Systematic Review and Meta-Analysis*, was published in *Journal of Alzheimer's Disease* in 2020 and serves as the foundation for building research to investigate the link between concussions and dementia. Second, I present my research on multi-modal detection methods designed to differentiate between adults with and without a history of concussion. It highlights how traditional, one-dimensional approaches to long-term concussion assessment may not be sensitive enough to detect subtle changes commonly associated with neurodegeneration. This study integrated cognitive testing, magnetic resonance imaging and blood-based biomarker assessment and has been prepared for submission to *Journal of Neurotrauma*.

Third, I shift the focus to prevention, examining three-dimensional multiple object tracking as cognitive training to support adults with and without histories of concussion. This section includes findings from a twelve-week intervention aimed at preserving cognitive function in those at greater risk of neurodegeneration due to a history of concussion. This paper has also been prepared for submission to *Journal of Neurotrauma*.

Together, these three papers contribute to a broader understanding of how concussions influence long-term brain health, from risk assessment, to early detection, and ultimately prevention.

1.2 Traumatic brain injuries

A Traumatic Brain Injury (TBI) refers to an alternation in brain function or pathology, caused by an external force,[1] and these injuries are classified into three discrete categories: mild, moderate and severe.[2] In Canada, hospitalizations from TBIs occur at a rate greater than 21,000 per year, equating to a new hospitalization every twenty-five minutes. Concussions are a type of mild traumatic brain injury, and in a 2019 random sampling of nearly 20,000 Canadians over age twelve, 1.6% reported sustaining at least one concussion that year, 0.2% of which were not diagnosed. Extrapolated to the broader Canadian population, that equates to 75, 240 people who suspect an injury, but did not seek treatment.[3] Moderate and severe TBIs are significant risk factors for many health-related conditions including Parkinson's disease, reduced quality of life, and higher levels of anxiety and depression;[4–6] however, the relationship between these ailments and mTBI is more widely debated, likely due to the long-standing ideology suggesting these injuries are harmless. Further, concussions are commonly portrayed in the media as an injury that only happens in professional sports, like football and hockey. In reality, mTBIs account for up to 90% of the yearly 64 to 74 million new TBIs globally, and many of these are sustained outside of sport.[7,8] Researchers and professionals have been trying to develop a universal definition of concussion, and for the purpose of this dissertation, the definition provided by the International Collaboration on mTBI Prognosis was used. This definition of concussion is as follows: "an acute brain injury resulting from mechanical energy to the head from external physical forces, including loss of consciousness for 30 minutes or less, posttraumatic amnesia for less than 24 hours, and a Glasgow Coma Score of 13-15 after 30 minutes post injury or upon the first

presentation for healthcare".[9] In 2023, a new definition of concussion was published that includes six key criteria: mechanism of injury, clinical signs, acute symptoms, clinical examination and laboratory findings, neuroimaging and that symptoms cannot be accounted for by confounding factors.[10]After an impact, the majority of concussion symptoms normally reside after two to four weeks of recovery;[11,12] however a subset of patients experience concussion symptoms for prolonged periods (i.e. three months and longer); a condition known as post-concussion syndrome (PCS),[13,14] or more recently coined Persisting Symptoms after Concussion (PSaC).[15] This dissertation explores long-term effects of these injuries. To avoid potential comorbidities of PCS/PSaC, "long-term" is defined as a minimum of 1 year since the last concussive event, with no ongoing presentation of the original injury symptoms. Further, this dissertation includes both clinically diagnosed and suspected mild TBIs as explanatory variables to better elucidate relationships between diagnosed versus total injuries.

1.3 Dementias and neurodegeneration

With improvements in health care and living conditions, the average age of our population has been increasing slowly and steadily, and given that age is the largest risk factor for dementia it is predicted that over 132 million adults will be living with dementia worldwide by 2050.[16] In Canada, there are over 6.8 million adults over age 65, having grown by almost 1 million in the past four years.[17] This aging trend is mirrored globally, where the proportion of the population aged 65 and older is expected to double from 8.5% in 2015 to 17% by 2050.[18] It is essential to highlight that dementia is not a normal part of aging, nor is it an acceleration of the normal aging process.[19] Normal aging includes a natural decline in cognitive abilities ranging from memory, executive functions, reasoning, spatial abilities, attention and language, while dementia involves pathological processes including neurodegeneration, amyloid-beta accumulation, and tau protein

abnormalities.[19] Dementia, also known as “major neurocognitive disorder” in the Diagnostic and Statistical Manual of Mental Disorders, is a clinical syndrome defined by a set of predetermined symptoms, including the impairment of independent living.[20] Due to the progressive nature of dementia, different stages of cognitive impairment have been explored. One stage is known as Mild cognitive impairment (MCI), a clinical condition characterized by noticeable cognitive deficits that exceed typical age-related changes, yet do not significantly interfere with daily functioning. Although MCI is considered a transitional phase between healthy aging and dementia, not all cases of MCI progress to dementia.[19,21] Understanding the clinical and pre-stages of neurodegeneration is critical to identify populations most at risk.

1.4 Alzheimer’s Disease

Dementia is an umbrella term for the symptoms of several types of neurodegeneration. Alzheimer’s disease (AD) is the most common form, accounting for between 60-80% of cases.[22] Biologically, AD is characterized by two main pathological hallmarks, extracellular amyloid beta plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein. These changes lead to synaptic dysfunction, neuronal loss, and widespread brain atrophy, particularly in regions critical for memory and cognition such as the hippocampus and cortex.[19,21] AD is a multifactorial condition influenced by both modifiable and non-modifiable factors. Non-modifiable factors include advancing age, which is the strongest predictor of Alzheimer's disease, family history, which accounts for around 2% of cases, and genetic predisposition, especially the presence of the APOE E4 allele, which is linked to increased amyloid beta accumulation and reduced clearance.[19,23] Modifiable risk factors reflect hazards associated with everyday life, such as low physical activity, smoking and poor diet, all of which can contribute to neuroinflammation and oxidative stress, exacerbating any existing neuronal damage and

neurodegeneration.[24] Social isolation and low cognitive engagement have been linked to decreased cognitive reserve, which refers to the brain's ability to compensate for damage and maintain function. Lower cognitive reserve may accelerate neurodegeneration.[25] Although these are classified as “modifiable” risk factors, the term can be misleading. Many of these risks are influenced by external circumstances, socioeconomic status and chance events, making them only partially within an individual’s control. Therefore, it may be more appropriate to view “modifiable” risk factors as potential intervention targets for reducing disease incidence, rather than as solely the individual’s responsibly to modify their behaviour.

1.5 The relationship between brain injury and dementia

A lesser thought of modifiable risk is traumatic brain injury.[26] Moderate-to-severe TBIs are a well-known and significant risk factor for dementia later in life;[27–29] however, recent evidence indicates that even sustaining a single mTBI may increase the risk of dementias.[30,31] Chapter two presents a comprehensive review and meta-analysis that critically examines the relationship between mTBI and dementia, providing insight into mTBI and an increased likelihood of later neurodegenerative conditions, further underscoring the importance of addressing this risk factor. Although the precise neuropathological mechanisms underlying this association remain unclear, several pathways have been suggested. One hypothesis is that mTBIs may exacerbate neuroinflammation, and contribute to chronic disruptions in tau or amyloid-beta protein dynamics, such as increased tau phosphorylation and accumulation, and impaired clearance or overproduction of amyloid-beta.[32] Another hypothesis is that an mTBI may interact with the natural aging process and other risk factors, potentially accelerating the onset of neurodegenerative changes. It is possible that individuals with histories of mTBI are more vulnerable to these changes, leading to a higher incidence of dementia compared to those without

such histories. Further research into the biological pathways linking mTBI and dementia could inform targeted interventions, and support proactive management of TBI at all levels of severity.

1.6 Cognitive assessments and neuroimaging for early identification of AD

Performance on cognitive tasks, such as neuropsychological evaluations of memory and executive function, alongside structural brain measures like hippocampal volume, cortical thickness, and diffusion tensor imaging (DTI) metrics (*e.g.* fractional anisotropy (FA) and mean diffusivity (MD)) can highlight indicators of dementia progression.[19] Some pathological aging characteristics include worsened episodic memory, executive functions and attention, specifically divided attention.[19] When assessing cognitive function as a marker of pre-clinical AD, decreased performance of episodic memory, executive functions and attention before the age of 65 may be indicative of neuropathological aging.[19] Neuropsychological assessments are extremely beneficial, as the tests are standardized and can be scored relatively quickly. However, cognitive tests also present challenges: changes in function can be very subtle; individual tests often engage multiple overlapping cognitive domains; and studies show discrepancies between cross-sectional and longitudinal cognitive data.[33,34] Regardless, these assessments are extremely useful for determining cognitive functions.

Age-related neurodegeneration includes the gradual loss of neurons and synaptic connections in areas like the pre-frontal cortex, hippocampus and temporal lobes.[19] This process is considered a normal aspect of aging, and these changes can often be seen using neuroimaging. However, in AD, neurodegeneration follows a more specific and accelerated pattern, particularly involving grey matter loss in the dorsolateral and medial prefrontal cortex, as well as the parietal and lateral temporal regions. These changes can begin as early as midlife in individuals carrying the APOE E4 allele, who are at a higher genetic risk.[35] Interestingly, midlife AD-indicative

degeneration is often paired with increased grey matter in other regions of the brain, suggesting there may be some compensatory mechanisms occurring.[35]

Pathological progression is also associated with white matter loss, commonly in the corpus callosum, the superior longitudinal fasciculus, and the cingulum, a structure connecting the hippocampus to the cingulate cortex.[36] In particular, loss of integrity in the posterior corpus callosum (*i.e.* splenium) has been linked to cognitive decline in aging populations.[37] Even cognitively healthy APOE ε4 carriers exhibit subtle white matter changes by midlife, for example, lower FA and higher diffusivity in posterior callosal fibers compared to non-carriers.[37,38] Identifying such microstructural changes is important, as they may serve as early neuroimaging markers of AD before clinical symptoms manifest.

Similarly, adults with a history of concussion can demonstrate long-term structural and microstructural brain changes that mirror an accelerated aging or neurodegenerative process. Advanced DTI analyses have revealed that previously concussed retired athletes show widespread reductions in FA accompanied by increases in MD across multiple white matter tracts, despite otherwise normal-appearing MRI scans.[39] These differences were mainly observed in fronto-parietal pathways and the anterior corpus callosum, and these differences were significantly associated with declines in episodic memory performance.[39] This suggests that concussion-related diffuse axonal injury and demyelination can exacerbate age-related neurodegenerative changes potentially heightening vulnerability to conditions like AD. Consistent with this, a small study found middle-aged adults who sustained a concussion decades earlier perform worse on relational memory tasks and have smaller hippocampal volumes than their non-injured peers.[40] Together, it is clear that abnormal neuroimaging findings, particularly

in white matter integrity, can be detected following concussion and prior to dementia onset, offering a promising avenue for identifying people with higher risk.

1.7 Blood based biomarkers for chronic mTBI and early detection of neurodegeneration

Fluid-based biomarkers are increasingly investigated as markers of neurodegeneration, and show promise for detection of disease and effectiveness of interventions. Classically, investigations of have involved the collection of cerebral spinal fluid (CSF). While the use of spinal CSF has benefits, mainly its continuity with brain CSF, the collection process is invasive and painful. Peripheral blood markers are of increasing interest due to their accessibility and promising results. For example, phosphorylated-tau217 (pTau-217) has been shown to differentiate between stages of AD, and outperform plasma and spinal CSF amyloid beta (Aβ) 42/Aβ40 in predicting brain amyloid levels measured by positron emission tomography.[41,42] While the Aβ42/Aβ40 ratio has long been considered a key biomarker of amyloid pathology, this suggests that pTau-217 may offer greater accuracy and sensitivity. Neurofilament light (NfL), a general marker of axonal degeneration, is another promising blood-based biomarker for early identification of AD. In a longitudinal study of 1583 participants, researchers found increased NfL levels at baseline could differentiate between those who developed MCI or AD and those who didn't.[43] Increased plasma NfL was also associated with baseline CSF markers, decreased hippocampal volume, cortical thickness, increased ventricle size, and decreased cognitive performance.[43]

Biomarkers of glial activation and neuroinflammation, such as glial fibrillary acidic protein (GFAP), interleukin-10 (IL-10) and Tumor Necrosis Factor Alpha (TNF-α), have further been associated with the development of AD.[44,45] GFAP is an intermediate filament protein exclusively expressed by astrocytes in the central nervous system (CNS), and plasma levels of GFAP have been found to predict amyloid-beta accumulation, and have discriminatory levels in

individuals with AD compared to cognitively healthy controls, such that those with AD have increased levels.[46,47] IL-10, an anti-inflammatory cytokine that shows non-AD specific fluctuations, but can be a useful tool to investigate intervention efficacy concerning CNS inflammation.[48] Further, higher IL-10 levels have also been observed in cognitively healthy older adults with amyloid-positive PET scans, indicating a compensatory immune response that may be detectable well before clinical symptoms emerge.[49] TNF-α is a pro-inflammatory cytokine found to increase during the progression of AD.[50] Elevated TNF-α is associated with both MCI and early AD, supporting its role in chronic neuroinflammation and disease progression.[45,50] Notably, many of these biomarkers also show abnormal patterns in the months and years following a concussion, even after clinical symptoms have resolved. For example, NfL can remain elevated for over a year post-injury, particularly in individuals with more severe or repeated concussions, and is linked to progressive white matter degeneration.[51] GFAP, though often elevated acutely, may persist at higher levels in the chronic phase after more severe injuries.[52] Chronic inflammation, marked by sustained TNF-α and other cytokine elevation, has similarly been observed up to a year after mild traumatic brain injury.[53] While the trajectories differ, with AD biomarkers rising slowly over years and concussion-related changes spiking and then resolving or plateauing (Figure 1.1) the overlapping molecular profiles suggest that prior concussions may lower the threshold for future neurodegenerative processes. Together these molecules may serve as a panel to indirectly measure brain health in people at a heightened risk of neurodegeneration following concussion.

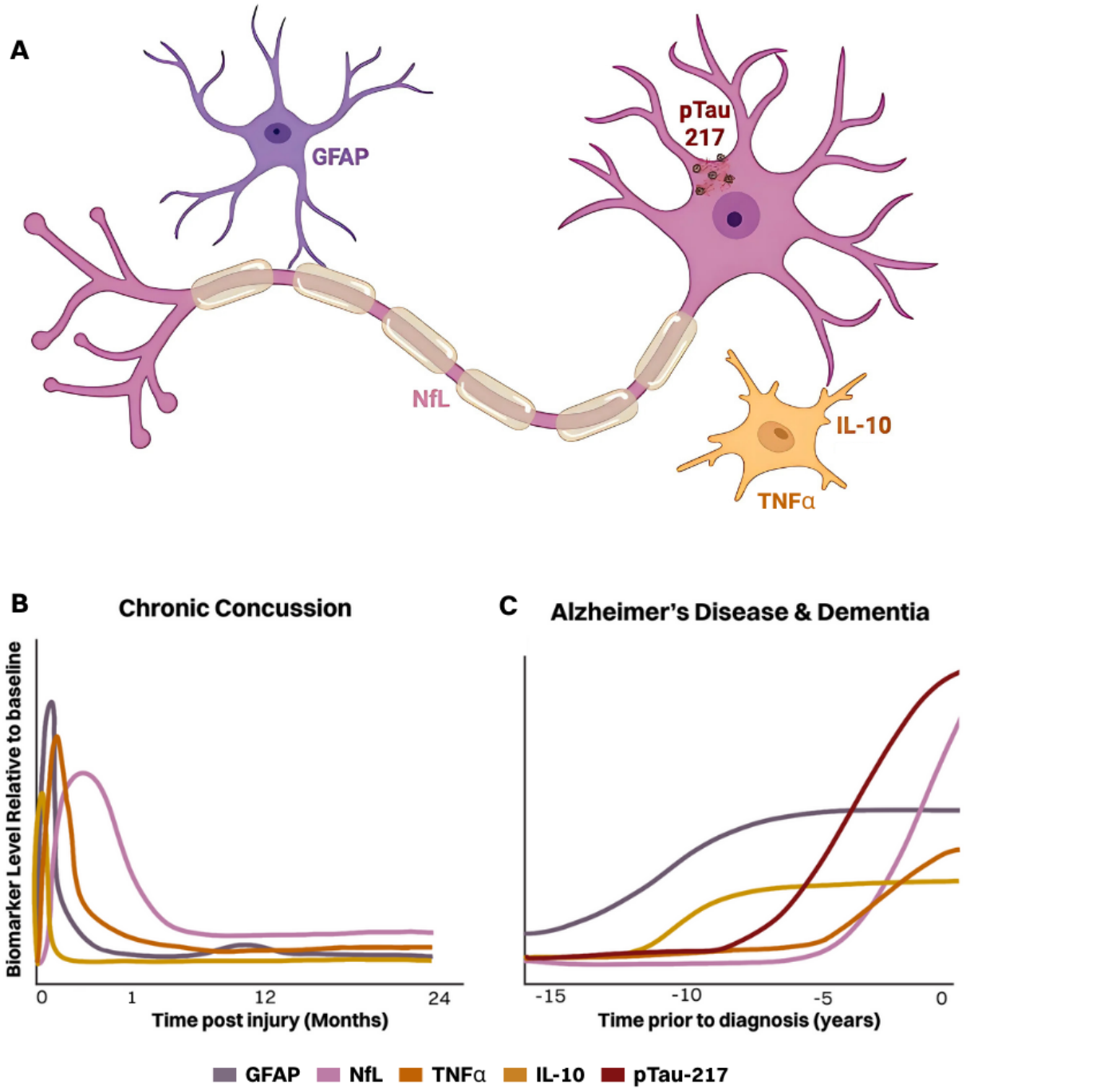


Figure 1.1. *Cellular origins and timeline of neurobiological biomarkers relevant to chronic concussion and neurodegeneration.*

(A) Neurofilament light chain (NfL, pink) is released from damaged axons of neurons, serving as a marker of axonal injury. Glial fibrillary acidic protein (GFAP, purple) is expressed by

astrocytes, reflecting astroglial activation and injury response. Phosphorylated tau 217 (pTau-217, red) accumulates in neurons during Alzheimer's disease-related neurofibrillary tangle formation. Interleukin-10 (IL-10, yellow) and tumor necrosis factor-alpha (TNFα, yellow) are cytokines predominantly produced by microglia, indicating anti- and pro-inflammatory activity, respectively. Figure created using BioRender. (B) Relative biomarker trajectories following a concussion over a 24-month period. GFAP peaks acutely within hours post-injury and decline rapidly, with some people experiencing a transient increase months after injury. TNFα peaks rapidly, and declines, but can have slight elevations years after injury. IL-10 rises quickly and normalizes within weeks. NfL shows a delayed peak around 7–10 days post-injury and gradually declines, remaining elevated for several months. All trajectories are illustrative and not to exact scale. (C) Longitudinal changes in the years leading up to Alzheimer's disease. GFAP and IL-10 begin to 10 to 15 years prior to diagnosis, followed by gradual increases in TNF-α and NfL, which sharply increase in the years prior to diagnosis. pTau-217 begins a sharp rise up to 10 years before AD. All trajectories are hand drawn for illustrative purposes and not to exact scale.

1.8 Early interventions for individuals at risk of dementia

There is no cure for dementia and there is a lack of interventions that have proven efficacy in significantly slowing the progression of disease. Both pharmacological and non-pharmacological interventions (NPIs) exist. NPIs are not disease specific, and typically target a wide array of clinical characteristics of disease. One benefit of NPIs is that there are typically few adverse side effects, and therefore can be employed at any disease stage. A large area of NPI research includes identifying preventative, neuroprotective measures for dementia and MCI. Cognitive training for individuals with dementia is an attractive NPI; however, study results have been mixed, and meta-analysis have yielded mostly negative results.[54,55] It seems that targeting

cognitive training to adults prior to AD diagnosis is a better route, with generally positive results.[54,56–58] Three-dimensional multiple object tracking (3D-MOT) may represent a promising avenue for cognitive intervention in adults at risk for dementia, particularly those with a history of concussion. This dynamic training paradigm engages a wide array of cognitive processes, including sustained and divided attention, working memory, visual processing speed, and spatial awareness, all of which are often vulnerable in individuals with TBI and in the early stages of neurodegenerative decline. 3D-MOT has already shown efficacy in enhancing neuroplasticity and cognitive performance in aging populations using a commercially available software called NeuroTracker (Figure 1.2).[56,59] Moving forward, determining strategies to reduce dementia risk, including identifying risk factors and finding early intervention methods for individuals at risk is necessary. Given that all TBI severities are known to drive neuropathological change associated with dementia, establishing early detection and preventative measures for this population is extremely important.

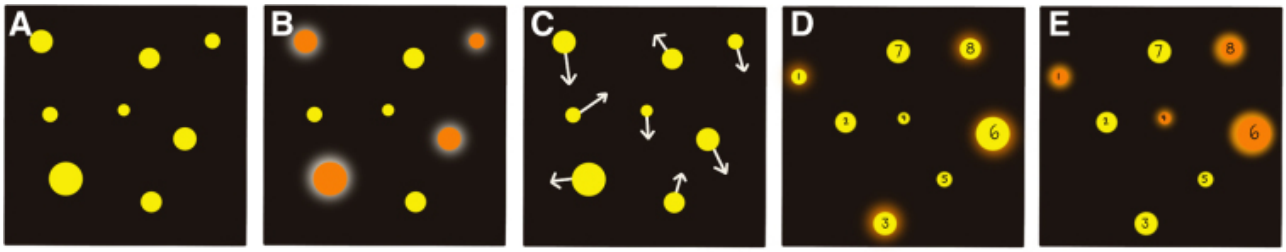


Figure 1.2. *Depiction of the five stages of a NeuroTracker CORE mode trial.*

(A) Eight yellow balls are presented in 3D space. (B) Four targets are presented in orange with a white halo. (C) All balls go back to yellow and move in random directions for 8 sec. The goal of the task is to track the original targets throughout the moving period. (D) Balls stop moving and are numerically labeled. The participant identifies the original four targets using the mouse or corresponding keys. Selected balls have an orange halo. (E) Feedback is provided. The correct targets are identified in orange with an orange halo. The cycle then restarts and

continues for the remaining trials. The speed of the balls is adjusted based on the success of the previous trial. Completion of 20 trials completes one session. Figure and caption created by Taylor Snowden-Richardson, published in Neurotrauma Reports, Snowden (2023).[60]

Chapter 2

Published: Does Mild Traumatic Brain Injury Increase the Risk for Dementia? A Systematic Review and Meta-Analysis.

2.1 Abstract

2.1.1 Background:

Mild traumatic brain injury (mTBI) is a putative risk factor for dementia; however, despite having apparent face validity, the evidence supporting this hypothesis remains inconclusive. Understanding the role of mTBI as a risk factor is becoming increasingly important given the high prevalence of mTBI, and the increasing societal burden of dementia.

Our objective was to use the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) format to determine if an association exists between mTBI and dementia and related factors, and to quantify the degree of risk.

2.1.2 Methods:

In this format, two authors conducted independent database searches of PubMed, PsycInfo, and CINAHL using three search blocks to find relevant papers published between 2000 and 2020. Relevant studies were selected using pre-defined inclusion/exclusion criteria, and bias scoring was performed independently by the two authors before a subset of studies was selected for meta-analysis. Twenty-one studies met the inclusion criteria for this systematic review.

2.1.3 Results:

The meta-analysis yielded a pooled odds ratio of 1.96 (95% CI 1.698–2.263), meaning individuals were 1.96 times more likely to be diagnosed with dementia if they had a prior mTBI.

Most studies examining neuropsychiatric and neuroimaging correlates of dementia found subtle, persistent changes after mTBI.

2.1.4 Conclusion:

These results indicate that mTBI is a risk factor for the development of dementia and causes subtle changes in performance on neuropsychiatric testing and brain structure in some patients.

2.2 Introduction

Despite the benign nature of the term, mild traumatic brain injury is a significant risk factor for many serious conditions. An mTBI is defined as "an acute brain injury resulting from mechanical energy to the head from external physical forces, including loss of consciousness for 30 minutes or less, post-traumatic amnesia for less than 24 hours, and a Glasgow Coma Score of 13–15 after 30 minutes post-injury or upon first presentation for healthcare" (1). Aside from the immediate and short-term effects of an mTBI, there is an increasing body of evidence linking mTBI to the development of long-term psychiatric and neurological conditions that include depression, bipolar disorder, and neurodegenerative diseases (2). The constellation of neurodegenerative diseases linked to mTBI includes chronic traumatic encephalopathy (CTE), a tauopathy that has gained attention due to its prevalence in professional athletes from the National Football League (3). The incidence of mTBI is also high in the general population, with as many as 42 million people suffering an mTBI worldwide each year (4). Thus, there is growing pressure to better understand the pathophysiology and long-term risks associated with mTBI to help direct treatment and prevention strategies to alleviate a growing health care burden. Understanding mTBI in an aging population presents additional challenges. Cognitive abilities, including memory, processing speed, and reasoning, are thought to naturally decline with age (5). The diagnosis of mild cognitive impairment (MCI) was introduced to identify individuals

who demonstrate greater cognitive decline than seen in typical aging but have not yet reached dementia-level impairment (6). Unlike MCI, a diagnosis of dementia requires impairments in daily-life functions in addition to cognitive difficulties (7). Five main cognitive domains may be impaired during cognitive decline: learning and memory, language, visuospatial, executive, and psychomotor (7). An MCI diagnosis typically requires one of these areas to be impaired, but several must be impaired for a diagnosis of dementia (7). MCI is a risk factor for further neurodegeneration; for example, a 2009 meta-analysis found a 9.6% annual conversion rate of MCI to dementia in an adjusted clinical setting, and 4.9% in community studies (8). Dementia is a term that encompasses several age-related neurodegenerative disorders that affect a large portion of the population: up to 7.2% of Canadians over the age of 65 and nearly 20% of Canadians over the age of 80 (9, 10). Of all the dementias, Alzheimer's disease (AD) is the most common, accounting for up to 80% of diagnoses (11). While our understanding of dementia etiology remains limited, several dementia risk factors have been identified. The Alzheimer's Society of Canada describes many risk factors for AD and other dementias including modifiable factors like high blood pressure and cholesterol, as well as non-modifiable factors such as sex and genetics (12). Although risk factors are not causes of disease on their own, understanding and managing risk factors is an important strategy to minimize susceptibility to disease. This is especially important in the context of dementia, due to the lack of disease-modifying treatments. Improving early diagnosis of dementia is important, as early detection has been found to have health, social, and societal benefits (13). Currently, collecting a medical history and conducting a mental status examination is standard practice for the diagnosis of both MCI and dementia. Medical history is used to assess if the patient has impairment in daily functioning, while the mental status examination is used to assess the level of cognitive impairment (7). Several

cognitive assessments exist for diagnosing cognitive impairments, such as the Montreal Cognitive Assessment (MOCA), the Short Test of Mental Status (STMS), and the Mini-Mental State Examination (MMSE). These assessments also serve as objective measures of global cognitive functioning. There is a large interest in the early detection of MCI and dementia; protein biomarkers and advanced imaging techniques have shown promising results, but more research is needed (14, 15). Since current treatments for AD and other dementias mainly focus on symptom control, strategies to reduce dementia risk involve controlling the known risk factors (16) and early detection (17). Identification of these risk factors and early detection methods will allow future researchers to target interventions toward people at high risk of developing dementia.

Regarding traumatic brain injuries, it seems that a clear relationship exists between moderate and severe brain injury and the development of dementia (18–21). However, it is notable that the methodological rigor of studies that assess the association between TBI, dementia, and AD has recently been questioned (22), and further the association between TBI, AD, and other apolipoprotein E (APOE) specific neurodegeneration has been debated (21). A 2013 review of neuroimaging studies suggests that moderate to severe TBIs cause reductions in total brain volume, dynamic degeneration of white matter, and loss of connectivity, all of which could predispose the brain to dementia later in life (23). However, the relationship between mTBI and dementia is less understood and has become an extensive area of research largely in part to the finding of CTE in NFL players (24). In 2004, the World Health Organization Collaborating Centre Task Force on mTBI found inconclusive evidence around mTBI and dementia after examining three studies carried out in the 1990s (25). More recently, a 2014 meta-analysis did not demonstrate a relationship between mTBI and subsequent MCI/dementia (26), although, only

one study was included in the analysis. While a 2016 meta-analysis suggested a positive correlation, only a small number of studies specifically examined mTBI and dementia, few of these used recent criteria for defining mTBI, and most were published before 2005 (2). Due to the widespread prevalence of mTBI and the high clinical burden of MCI and dementia, identifying whether mTBI interacts with the development of these degenerative diseases is of high importance.

Given the inconsistencies in the body of evidence around mTBI and dementia (2, 26), we aimed to provide an update of the literature in this area with this systematic review. Our objectives were to identify recent publications that examine remote mTBI (an injury sustained years in the past) and dementia, to quantify any associated risk, and to identify gaps and methodological issues in the literature to help direct future research. We also included MCI, and associated factors, in our search strategy because of the strong association between MCI and the subsequent development of dementia. Should strong evidence link mTBI to dementia, appropriate measures can be taken to identify at-risk populations and implement prevention measures. Conversely, strong evidence against mTBI as a risk factor for dementia may reduce the need for dementia risk management in favor of treatments that target other mTBI complications.

2.3 Methods

The methodology for this review was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis framework and is reported following the PRISMA 2009 checklist (Supplementary Table 2.1); the review protocol was not registered (27). To identify primary, peer-reviewed articles published between 2000 and 2020 that characterized the risk of developing MCI and dementia after a remote history of mTBI, three blocks of search terms were developed. The first block of search terms identified mTBI studies and included the following

terms: “concuss*”, “mild traumatic brain injur*”, “mTBI”, “mild head impact”, “mild head inj*. The second concerned the development of MCI/dementia and included the following terms: “Mild cognitive impairment”, “neurocognitive impairment”, “cognitive decline”, “cognitive impairment”, “mild neurocognitive disorder”, “major neurocognitive disorder”, “delirium”, “preclinical Alzheimer’s”, “neurodegenerative diseases”, “Alzheimer*”, “dementia*”. The third search block was meant to exclude review articles, and contained the terms “review”, meta-analysis”, “meta-review”, and “literature review”. The first block and second blocks were separated by an “AND” modifier, while the third block was separated by a “NOT” modifier. Using these search blocks, the co-first authors independently searched the databases PubMed, CINAHL, and PsycInfo and exported results found between the years 2000 and 2020 to the Mendeley© citation manager. Following the PRISMA flow diagram protocol, duplicates were removed and all papers were screened using the inclusion/exclusion criteria (Table 2.1). The authors also conducted forward and reverse searches of previous review articles to ensure all relevant papers were included in this review. Papers selected in the screening process were read in full and assessed for eligibility as defined by the search criteria. The remaining papers were compared between authors and any discrepancies were discussed and resolved. A total of 21 papers were included in this review (Fig. 2.1). Studies were included if they were primary research papers available in full text and published in English after 2000, included human subjects, included a measure of assessing cognitive impairment, and included a clinical diagnosis of mTBI. Conversely, studies were excluded if they violated any of the inclusion criteria, only examined treatments, or examined only the acute effects of mTBI (rather than the long-term effects of a remote injury). A list of relevant full-text articles was generated and read in full to create a final list of papers for inclusion in this review. After the generation of the final list,

relevant information from the selected studies was extracted by the co-first authors. Relevant information included outcome measures, findings related to dementia risk, and population characteristics.

Table 2.1. Inclusion/Exclusion criteria

Inclusion Criteria	**Exclusion Criteria**
1. Primary, peer-reviewed studies	1. Studies that only examined treatments
2. English	2. Non-primary research papers (reviews, posters, abstracts)
3. Human	3. Published in a language other than English
4. 2000-present	4. Non-human studies
5. Full text available	5. No full-text available
6. Used a screening tool used to diagnose MCI or Dementia, such as the MMSE or MOCA or a clinical diagnosis	6. Examines the acute effects of the injury exclusively and not long-term neurodegenerative changes
7. Used a clinical diagnosis of mTBI according to the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury and the Centers for Disease Control and Prevention or a similar definition	7. No use of a screening tool such as the MMSE, MoCA or a clinical diagnosis of MCI/Dementia
8. No clinical diagnosis of mTBI	

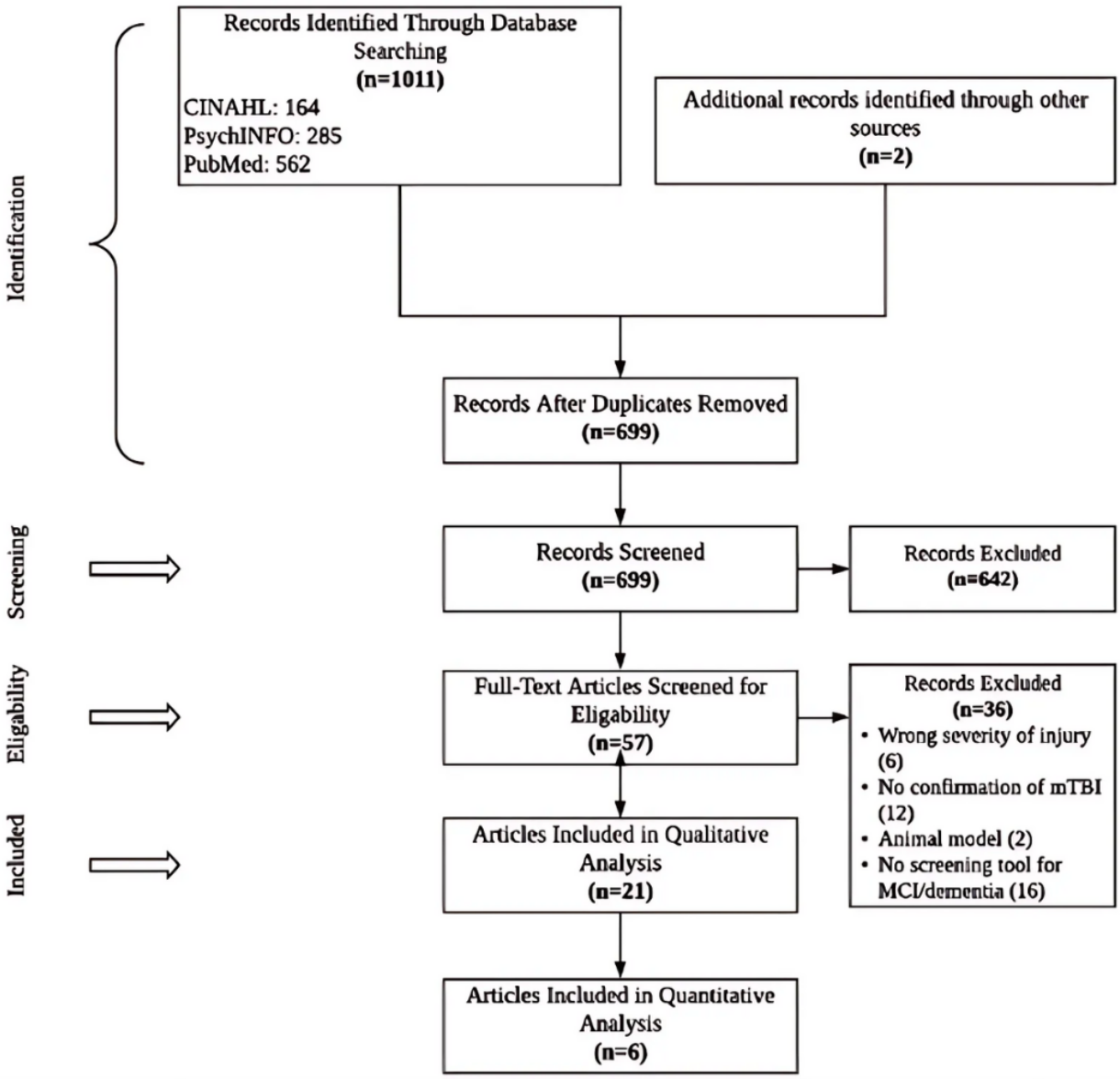


Figure 2.1. *Graphical depiction of the search process.*

After duplicate removal, articles identified through database searching were screened using their title and abstract for inclusion, generating a final list of 57 full text articles to screen for inclusion in the systematic review.

Bias scoring was performed independently by two authors using the Scottish Intercollegiate Guidelines (28). The authors individually answered a checklist of questions regarding the methodology of each study, and from that studies were classified as high quality, acceptable, or unacceptable (Supplementary Table 2.2). Discrepancies between authors were resolved by consensus.

A subset of studies was selected for inclusion in a meta-analysis. To be included in the meta-analysis, studies had to include the risk of dementia after sustaining an mTBI as an outcome measure and quantify this risk using an odds ratio. Also, the authors had to provide the raw data needed to perform the meta-analysis (see Table 2.2 for narrow inclusion/exclusion criteria). Data were pulled directly from the publications where possible; for four studies, the authors were contacted directly to obtain data. Pooled odds ratios (ORs), 95% confidence intervals (CIs), and tests for heterogeneity were performed using MedCalc Statistical Software (29). A random effects model was chosen to account for any potential variations in effect size caused by potential covariates in the selected participant populations. OR weights for each study were assigned based on the inverse of their respective variances. The meta-analysis forest plot was made using the ggplot2 package for Rstudio (30).

Table 2.2. Narrow inclusion/exclusion criteria for inclusion in the meta-analysis

Inclusion Criteria	**Exclusion Criteria**
Provided an objective measure of dementia risk using an odds ratio or equivalent measure	Data was not available and authors did not provide data after being contacted

2.3 Results

2.3.1 Study selection

The co-first authors individually performed a literature search of the PubMed, CINAHL, and PsycInfo databases to find a total of 1,011 studies for initial screening. After removing duplicates, 699 studies remained and the abstracts were screened for relevance. Following the screening, 57 full-text articles were assessed for eligibility, while 642 did not meet the inclusion/exclusion criteria. From the full-text articles, 36 were excluded: six had the wrong severity of injury, twelve had no confirmation of mTBI, two used animal models, while 16 did not use a screening tool for MCI/dementia. A total of 21 studies were included in this review, six of which were included in the quantitative analysis (see Fig. 2.1 for a stepwise breakdown of the search process).

2.3.2 Objective risk of dementia after mTBI

The outcome measures of twelve studies concerned identifying the risk of cognitive impairment (i.e. MCI, dementia, AD) following mTBI (31–42). Specifics about each study, including population characteristics, definitions of mTBI and dementia used, outcome measures, time between injury and diagnosis, main findings and bias scores can be found within Table 2.3.

Table 2.3. Objective risk of dementia following mTBI

Paper	Population Characteristics	mTBI Definition	Outcome Measures	Time between injury and dementia diagnosis	Findings	Bias Score	Main effect of remote mTBI
Barnes et al., 2018 (31)	Veterans who had received a TBI diagnosis (*n*=178,779), and a propensity matched sample (*n*=178,779) recruited from the Veterans Health Administration	TBI evaluations performed by trained professional, recorded using ICD-9 codes	A diagnosis of dementia as defined by ICD-9 codes	3.6y (all TBI severities)	After adjustment for age, medical comorbidities, and psychiatric disorders, the adjusted HR for dementia diagnosis was 2.36 (95% CI, 2.10, 2.66) for mild TBI without LOC; 2.51 (95% CI, 2.29–2.76) for mild TBI with LOC; 3.19 (95% CI, 3.05–3.33) for mTBI with LOC unknown	HQ	Increased risk of dementia

Paper	Population Characteristics	mTBI Definition	Outcome Measures	Time between injury and dementia diagnosis	Findings	Bias Score	Main effect of remote mTBI
Helmes et al., 2011 (32)	A subset of Canadian adults recruited from the CHSA-I and CHSA-II (*n*=2,431) who scored below cut-off on a global cognitive screening tool. Reassessment occurred 5y after initial intake.	Self-report confirmed by informant, TBI with LOC 0–30min	A diagnosis of dementia (DSM-III-R)	27.8y (SD=22.6) (all TBI severities)	Having a history of mTBI did not improve the predictive ability of dementia diagnosis. Age remained the most related factor.	A	No change in risk of dementia
Lee et al., 2013 (32)	A general population of Taiwanese adults who had sustained an mTBI (*n*=28,551), and controls who had not sustained an mTBI (692,382). Data was obtained from the NHI database	ICD-9 codes were used to identify mTBI	Presence of dementia or AD	1.0y (95% CI 0.77–1.23)	In adults aged 65+, the adjusted HR was 3.27 (95% CI, 2.67–4.00).	HQ	Increased risk of dementia
Li et al., 2016 (36)	Adults aged 55–90 who had sustained a TBI (*N*=79; mTBI=71), and a non-TBI control group (*n*=1197). Data was obtained from ADNI database	Self-reported concussion history corroborated by informants at ADNI clinical site	Age of Onset of MCI or AD	Age at injury=35.4 (SD=24.8)	Adults with mTBI history have earlier ages of onset of MCI than controls by about 4y (*p*=0.016)	A	Earlier age of onset of MCI
Liao et al., 2020 (37)	A general population of Taiwanese adults aged 65+with a history of LOAD (*n*=4,600) and a matched control group (*n*=4,600). Data was obtained from both the NHIRD or CIC databases.	ICD-9 codes were used to identify mTBI	Identification of factors associated with LOAD	Not reported	Incidence of concussion up to 4y prior to LOAD diagnosis has significant positive effects on incidence (total effects; 0.050)	A	Increased risk of LOAD
McMillan et al., 2014 (38)	A general population of patients from a Glasgow hospital identified as having mTBI (*n*=2,428), a matched non-head related injury control group (*n*=2,428), and a matched control group (*n*=2,428).	GCS score between 13–15	Identification of death rates and comorbidities 15y post injury	Not reported	In adults aged under 65 at baseline, 15y later dementia rates in the mTBI group were 0.37/1000/y, while the control group had a rate of 0.14/1,000/y	U	Increased risk of dementia* *No statistical tests conducted
Nordström &Nordström, 2018 (39)	A general population of Swedish adults with data available in the Swedish National Patient Register. The first cohort was	ICD-10 codes were used to identify mTBI	Diagnosis of dementia using ICD 8–10 codes	15.3y for total cohort	Risk of dementia after mTBI has a dose dependent relationship, with mild TBIs having less associated risk than severe or multiple TBIs.	HQ	Increased risk of dementia

Paper	Population Characteristics	mTBI Definition	Outcome Measures	Time between injury and dementia diagnosis	Findings	Bias Score	Main effect of remote mTBI
	prospectively followed after mTBI (*n*=491,252), the second cohort consisted of siblings with discordant TBI status (*n*=93,940) and the third cohort was a retrospective case-control cohort (*n*=404,877).				The adjusted OR for mTBI and dementia was 1.63 (95% CI 1.57–1.70), 1.49 (95% CI 1.23–1.80) and 1.59 (95% CI 1.54–1.65) in cohorts 1, 2 and 3, respectively		
Plassman et al., 2000 (40)	World War II Veterans who has sustained a TBI (*n*=1,422), pneumonia (*n*=1,740), or a non-head related injury (*n*=2,282). Participants were recruited from the pension database for Veteran Affairs.	mTBI categorized using a scale described by Frankowski et al., 1985 (78)	Cognitive assessments, neuropsychological tests, *APOE* genotype, diagnosis of AD	Not reported	The mTBI group showed no significant risk of dementia or AD	A	No change in risk of AD
Redelmeier et al., 2019 (41)	General population of adults aged 66+with a diagnosis of concussion, and who were prescribed a statin (*n*=7,058), and who were not prescribed a statin (*n*=21,757), and a non-head related injury control group prescribed a statin (*n*=77,898), and not prescribed a statin (*n*=229,992). Data was obtained from the OHIP database.	ICD-9 codes were used to identify mTBI	Presence of dementia according to ICD-9 codes from OHIP database, with diagnosis on 2 separate dates to avoid false positives	3.9 y for all patients	Patients not receiving a statin had a dementia incidence of 43 cases per 1,000 patients annually, which is greater than 2x the population norm	HQ	Increased risk of development of dementia
Sercy et al., 2020 (42)	General population of adults who sought treatment for mTBI (*n*=964) or another injury (*n*=5,567), recruited from six level 1 trauma centers across the US. Medical information was obtained from the USCDC NDI database.	ICD-9 codes were used to identify mTBI	Mortality, causes of death and comorbidities after mTBI	5 y	OR of patients with a history of mTBI developing a neurodegenerative disease was found to be 1.62 (95% CI 0.88–2.98)	A	Increased risk of developing a neurogenerative disease
Sundström et al., 2007 (33)	Dementia patients (*n*=181) and controls (*n*=362) data obtained from Betula prospective longitudinal study of	Self-reports corroborated by medical record in	Risk of dementia and *APOEε*4 genotyping	More than 5 y before diagnosis	*APOE* positive status increased the risk of developing dementia with head injury	U	Increases risk only in *APOE4*+ patients

Paper	Population Characteristics	mTBI Definition	Outcome Measures	Time between injury and dementia diagnosis	Findings	Bias Score	Main effect of remote mTBI
	memory, health and aging.	some patients; ability of patient to perform cognitive tests taken as indicative of mild injury					
Yang et al., 2019 (34)	General Taiwanese population with craniofacial trauma and mTBI (*n*=399,057), facial bone fracture (*n*=23,890), or moderate to severe TBI (*n*=149,475). Data was obtained from the NHIRD database.	ICD-9 codes were used to identify mTBI	Incidence of dementia in patients with various types of head injuries	Not reported	A standardized incidence ratio for mTBI and dementia was found to be 1.78 (95% CI; 1.73–184)	HQ	Increased risk of development of dementia following mTBI

Acronyms are separated by column. *Population Characteristics:* CHSA, Canadian Study of Health and Aging; mTBI, mild traumatic brain injury; NHI, National Health Index; TBI, traumatic brain injury; ADNI, Alzheimer's Disease Neuroimaging Initiative; NHIRD, National Health Insurance Research Database; CIC, Catastrophic Illness Certificate; OHIP, Ontario Health Insurance Program; USCDC, United States Centre for Disease Control; NDI, National Death Index. *mTBI Definition:* ICD-9, International Classification of Disease - 9th edition; LOC, loss of consciousness; GCS, Glasgow Coma Scale. *Outcome Measures:* DSM, Diagnostic and Statistical Manual for Mental Disorders –Third Edition; MCI, mild cognitive impairment; AD, Alzheimer's disease, LOAD, late onset Alzheimer's disease; APOE, Apolipoprotein E. *Time Between Injury and Dementia Diagnosis:* y, year; SD, standard deviation; CI, confidence interval. *Findings:* HR, hazard ratio; OR, odds ratio. *Bias Score:* HQ, high quality, A, acceptable, U, unacceptable.

Three retrospective studies considered the effects of mTBI on the development and/or onset of later-life dementias (including AD) (31, 34). Two studies found an increased proportion of people diagnosed with dementia had a history of at least one mTBI (31, 34), while the third found no

change in the number of people diagnosed with dementia (32). Barnes et al. (2018) (31) examined the relationship between TBI severity, loss of consciousness (LOC), and dementia diagnosis in 357,558 Veterans. The researchers found an adjusted hazard ratio for dementia diagnosis of 2.36 (95% CI, 2.10, 2.66) for mTBI without LOC; 2.51 (95% CI, 2.29–2.76) for mTBI with LOC; and 3.19 (95% CI, 3.05–3.33) for mTBI with LOC unknown (31). Yang et al. (2019) (34) assessed dementia risk following craniofacial trauma in 501,889 patients. Researchers found that patients with past mTBI were more likely to be diagnosed as having dementia later in life than matched controls (2.75% versus 1.28%; $p<0.01$), further, the same team found a standardized incidence ratio of 1.78 (1.73–1.84) for mTBI and dementia. Helmes et al. (2001) (32) investigated the development of dementia in adults with a history of mTBI using samples from two separate waves of the community-based Canadian Study of Health and Aging. Participants who identified as having a TBI before the first wave were followed up within the second wave to assess cognitive status five years later. The researchers found that having a history of mTBI was not associated with a dementia diagnosis.

Six prospective studies considered the effects of mTBI on the development of later-life dementias (including AD) (33, 40–42). Five of the six papers found increased rates of dementia diagnosis in at least one subset of individuals (33, 42); however, one of these papers did not use statistical assessments to verify this conclusion (38). The objective of Lee et al. (2013) (35) was to identify the incidence of dementia in Taiwanese patients aged 18+ with and without histories of concussion. A total of 720,933 adults were followed for 8 years post-injury. In all participants, researchers found the adjusted hazard ratio to be 3.26 (95% CI, 2.69–3.94), and in adults 65+ the hazard ratio was 3.27 (95% CI, 2.67–4.00) for the diagnosis of dementia following remote mTBI. McMillan et al. (2014) (38) explored mortality rates and associated comorbidities 15 years after mTBI in a

sample of 7,284 adults in Glasgow. At admission, after mTBI the mean age was 39 (range 14–98), and 15 years later the dementia rate in those with mTBI was 0.37/1000/year versus case controls (0.14/1000/year). However, no statistical assessments were done due to low power. Redelmeier et al. (2019) (41) tested whether statin use is associated with a change in risk of dementia in older adults after a concussion; for this review, we are only reporting on the group that did not receive a statin. It was found that mTBI control patients accounted for 3,677 dementia cases over 85,339 patient-years (mean, 3.9 years), equal to an incidence of 43/1,000 patients annually, greater than twice the normal population. Sercy et al. (2020) (42) explored the mortality rate and causes of death in mTBI patients five-years post-injury, and found an odds ratio of 1.62 (95% CI, 0.88–2.98) for the development of a neurodegenerative disease, although this was not specific to dementia. Sundström et al. (2007) (33) examined 181 subjects with dementia and 362 controls and assessed the prevalence of mTBI using a case definition provided by the authors. They found that mTBI conferred an increased risk of dementia in only carriers of *APOE* ε4 genotype. In contrast, Plassman et al. (2000) (40) investigated the association between mTBI and dementia in a military population. The researchers found no effect of mTBI on the development of later-life dementia (hazard ratio: 2.56, 95% CI: 0.68 to 9.67), no difference in age of onset of dementia, and no interaction effect between mTBI and *APOE* ε4 genotype on the risk of dementia.

Two studies retrospectively examined if a history of mTBI influences the age of onset in adults with a clinical diagnosis of MCI and/or dementias (36, 37). Liao et al. (2020) (37) examined how prior conditions, including mTBI, are associated with the development of late-onset AD in a general Taiwanese population. In this sample of 9,200 adults aged 65+, mTBI within 9 years was positively associated with late onset AD diagnosis. Li et al. (2016) (36) assessed if a history of TBI and severity are associated with the age of onset of MCI and dementia. Researchers found

that mTBI is related to an earlier age of onset than adults with no history of mTBI (68.5±1.1 years; 95% CI 66.3–70.7 versus 70.9±0.2 years; 95% CI 70.5–71.4).

One study included both prospective and retrospective analyses (39). Nordstrom & Nordstrom (2018) assessed all inhabitants of Sweden aged 50 years and over. In the first cohort, 164,334 individuals with TBI were age and sex-matched to two individuals between 1964 and 2012, and the National Patient Register (NPR) was prospectively searched for diagnosis of dementia. In patients with mTBI, the adjusted odds ratio of developing dementia in the 48 years follow up was 1.63 (95% CI, 1.57–1.70). The second cohort involved siblings in the NPR who had different diagnoses of TBI (i.e., no TBI versus TBI), to control for familial factors. Researchers found a slight increase in dementia rates in the second cohort with an adjusted odds ratio of 1.49 (95% CI, 1.23–1.80). The third cohort was a prospective analysis of individuals diagnosed with dementia in the NPR. Researchers found a small increase in having a history of mTBI in adults diagnosed with dementia (aOR, 1.59; 95% CI, 1.54–1.65). In all cohorts, mTBI had the weakest association with dementia when compared with severe TBI and repeated TBIs.

2.3.3 Meta-analysis of quantitative studies

Six studies met the narrow criteria (Table 2.2) and were included in the meta-analysis (31, 39–41). Using a random-effects OR model, prior mTBI was found to be associated with the later development of dementia (OR 1.96, 95% CI 1.698–2.263, $p<0.001$) (Fig. 2.2, Table 2.4). The studies exhibited a high degree of heterogeneity ($I^2=97.30\%$).

Table 2.4. Pooled Odds Ratio for developing dementia after remote mTBI

Study	Intervention	Controls	Odds Ratio	95% CI	Weight (%) Random
Barnes et al., 2018 (31)	3,972/91,888	4,698/174,081	1.629	1.560 to 1.701	21.01
Lee et al., 2013 (35)	127/28,424	944/691,438	3.283	2.727 to 3.952	15.87
Nordström &Nordström, 2018 (39)	5,846/108,463	7,314/216,077	1.626	1.570 to 1.684	21.14
Redelmeier et al., 2019 (41)	3,677/21,757	19,717/229,992	2.169	2.087 to 2.254	21.09
Yang et al., 2019 (34)	4,451/394,607	2,497/394,607	1.791	1.705 to 1.882	20.89
Total (random effects)	18,073/645,139	35,170/170,6195	**1.972**	1.705 to 2.281	100

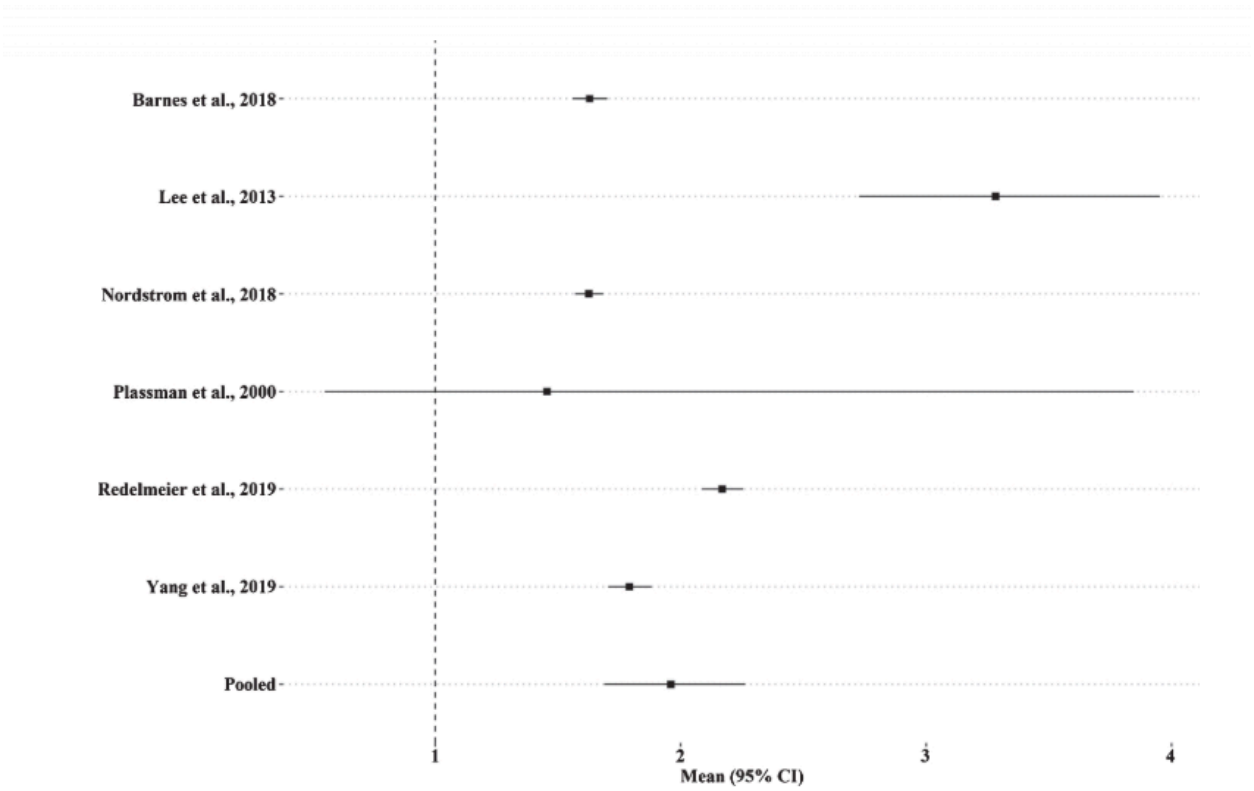


Figure 2.2*. Forest plot of individual and pooled ORs for studies included in the meta-analysis.*

2.3.4 Structural and neuropsychiatric changes after mTBI

We identified nine studies that examined structural and/or neuropsychiatric outcomes associated with MCI/dementia after remote mTBI (Table 2.5). For inclusion of this section, studies had to use a global cognitive screening tool, such as the MMSE or MOCA, to delineate cognitive function. Specifics about each study, including population characteristics, the definition of mTBI and measures of global cognitive functions used, outcome measures, time between injury and diagnosis, main findings and bias scores can be found within (Table 2.5).

Table 2.5 Structural and neuropsychiatric changes after mTBI

Paper	Population Characteristics	mTBI Definition	Outcome Measures	Findings	Bias Score	Main effect of remote mTBI
Esopenko et al., 2017 (48)	Former pro hockey players recruited through NHL Alumni Association (*n*=33) with age matched controls from the community (*n*=18)	A blow to the head followed by clinical symptoms	Performance on neuropsych tests, cognitive tests, and *APOE4* status	Alumni tested significantly worse on executive function tests but not cognitive tests. No association between *APOE4* status and cognitive test performance. Two alumni were excluded due to low MOCA score.	A	Decreased neuropsych performance
Hart et al., 2013 (44)	Retired NFL players with mTBI history (*n*=32), and without (*n*=2) recruited from NFL Players Association meeting and healthy, matched controls (*n*=85)	AAN Practice Parameter Guidelines for grading concussion (1997).	Performance on neuropsych tests, neurological assessment, neuroimaging, dementia or MCI diagnosis	No correlation between neuropsychiatric measured and concussions. Total white matter lesion volumes significantly different in mTBI with cognitive impairment group. Lower incidence of dementia in retired players, higher incidence of MCI.	A	Increased risk of MCI, white matter reduction
Montenigro et al., 2017 (49)	n=93 former football players, High school *n*=17, College *n*=76, Participants were subset of ongoing longitudinal study (LEGEND)	CDC definition of concussion	Performance on cognitive neuropsych tests	Cumulative Head Impact Index predicts risk of cognitive impairment later in life	A	Increased risk of later life cognitive impairment
Ozen et al., 2015 (51)	Elderly patients with remote TBI history; mTBI *n*=5, Control *n*=15, recruited from Waterloo Research in Aging Pool	American Congress of Rehabilitation Medicine definition (1993)	Performance on neuropsych tests, self-report scales, open-ended interviews	No difference between mTBi, mod/severe TBI on any measure, but no statistics were performed to assess effects of TBI severity on performance	U	No effect was detected
Strain et al., 2015 (43)	Former NFL athletes with no memory impairment (*n*=20), NFL athletes with MCI (*n*=8), Cognitively	AAN Practice Parameter Guidelines for grading concussion (1997)	Performance on neuropsych tests, hippocampal volume assessment	Former NFL athletes without cognitive impairment performed worse than healthy controls. Athletes with concussion had lower	A	Decreased neuropsych. performance and hippocampal volume

Paper	Population Characteristics	mTBI Definition	Outcome Measures	Findings	Bias Score	Main effect of remote mTBI
	healthy controls (*n*=21), controls with MCI (*n*=6) recruited from NFL Players Association.			hippocampal volumes at all age ranges.		
Tremblay et al., 2013 (46)	mTBI group (*n*=15), control group (*n*=15), all participants were university athletes between age of 51 and 75 recruited with the help of university athletics organization	2009 Consensus Statement on Concussion in Sports	Performance on neuropsych tests, *APOEε*4 genotyping, neuroimaging	Reduced performance on most neuropsych tests and diminished cortical thickness and enlarged ventricle size in mTBI group, which are considered a marker for MCI development	HQ	Decreased neuropsych performance, and imaging changes analogous to MCI
Tremblay et al. 2019 (45)	Remote mTBI (*n*=15) patients recruited from university athletics associations with matched controls (*n*=15) recruited from community, recent mTBI (*n*=19) recruited from ER with matched controls (*n*=25).	2009 Consensus Statement on Concussion in Sports	MMSE and neuroimaging	Total brain volume did not differ between mTBI to control, but diffusivity was increased in remote mTBI group only in the corpus callosum and frontal white matter; no difference on MMSE	A	White matter reduction
Wammes et al., 2017 (50)	Young healthy (*n*=22) and young mTBI (*n*=17) recruited from university, older healthy (*n*=22) and older mTBI (*n*=21) recruited from Waterloo Research in Aging Pool	Any closed head injury that resulted from the head being hit, the head striking an object, or any acceleration/deceleration force that resulted in LOC (1 min to 6 h) or PTA (1 min to 7 days)	Performance on neuropsych tests and Autobiographical interview	Remote mTBI had little effect on neuropsych testing, semantic priming, or autobiographical interview content	A	Little to no effect of remote mTBI
Yang et al., 2015 (47)	mTBI+MCI/D (*n*=6), mTBI without MCI/D	CDC definition of concussion	Performance on cognitive tests, *APOEε*4	No statistics performed on cognitive tests, but loss of consciousness was	A	Increased dementia risk with LOC, no

Paper	Population Characteristics	mTBI Definition	Outcome Measures	Findings	Bias Score	Main effect of remote mTBI
	(*n*=21), healthy controls (*n*=10) all recruited from the Taiwan National Health Insurance database		genotyping, Neuroimaging	identified as a risk factor for dementia. Allele frequency of *APOE4* was significantly higher in mTBI+D group than controls; Amyloid accumulation was higher in mTBI+D but no difference between mTBI - D and HC group		changes in amyloid levels

NHL, National Hockey League, NFL, National Football League; AAN, American Academy of Neurology; MCI, mild cognitive impairment; LEGEND, Longitudinal Examination to Gather Evidence of Neurodegenerative Disease; CDC, Center for Disease Control and Prevention; TBI, traumatic brain injury; MMSE, Mini-Mental Status Examination; LOC, loss of consciousness; PTA, post-traumatic amnesia; ADHD, attention deficit hyperactivity disorder.

The following four studies all used MRI imaging to assess brain volume changes in addition to neuropsychiatric testing. Strain et al. (2015) assessed 28 retired NFL athletes in Texas with an mTBI history by using tests of verbal episodic memory and neuroimaging (43). They found that verbal episodic memory was reduced in athletes compared to controls. Furthermore, hippocampal volume was significantly diminished compared to healthy controls at all age groups in athletes with at least 1 mTBI, but not in athletes without an mTBI history; this difference appeared more pronounced at increasing ages. In another study examining professional athletes, Hart et al. (2013) (44) assessed retired NFL athletes who had an mTBI history using neurocognitive assessments and neuroimaging. They found significant group differences in tests of naming, word-finding and visual and verbal episodic memory in cognitively impaired NFL players compared to controls, but no correlations between the number of mTBIs and years played in the NFL (44). Neuroimaging studies using diffusion tensor imaging revealed increased

diffusivity in regions of white matter in impaired NFL players, particularly in the frontal, parietal, and temporal regions and corpus callosum, and changes in blood flow between impaired players and healthy controls. These findings were similar to those of Tremblay et al. (2019) (45), who examined mTBI patients with different ages at mTBI onset using diffusion-weighted imaging. Remote mTBI patients had increased white matter abnormalities in the frontal region and anterior corpus callosum compared to controls, whereas recent mTBI patients had no significant differences in these parameters compared to controls (45). Finally, Tremblay et al. (2013) (46) recruited former university-level athletes with and without an mTBI history and evaluated them using neuropsychiatric testing and MRI of anomalies in neurometabolites and structure. The mTBI group had reduced episodic and semantic memory, abnormal neurometabolites in the medial temporal region and prefrontal cortex, increased ventricle size, and reduced cortical thickness relative to controls (46).

One study primarily examined amyloid accumulation using positron emission tomography. Yang et al. (2015) (47) identified remote mTBI patients and controls and found that cognitive performance and mean amyloid accumulation scores were not significantly different between normal mTBI and control groups, but were different in mTBI patients with dementia. Four studies used neuropsychiatric testing as an outcome measure, but not neuroimaging or risk of dementia (47). Esopenko et al. (2017) (48) assessed National Hockey League (NHL) alumni with a concussion history compared to healthy controls, and found that the NHL group performed significantly lower on tests of executive and intellectual function. They also found that executive and intellectual function was associated with the number of concussions within the NHL group. However, the NHL group performed similarly to controls on objective tests of cognition, and APOE ε4 status was not associated with neuropsychological impairment in this study (48).

Montenigro et al. (2017) (49) assessed repetitive head impacts using a cumulative head impact index (CHII) in 93 former amateur football players and found that the risk of mood, behavioral and cognitive impairment increased with CHII score in a dose-dependent manner. Those with the highest CHII exposure were 9-times more likely to develop objective cognitive impairment, as assessed by the Brief Test of Adult Cognition by Telephone, later in life (49). Wammes et al. (2017) (50) assessed young and old participants with and without remote mTBI to assess the effect of remote mTBI on lingering memory issues. They found significant effects of mTBI on word recall in elderly remote mTBI patients, but most neuropsychological testing revealed no significant differences compared to age-matched controls (50). Finally, Ozen et al. (2015) (51) assessed older adults with and without a TBI history, but only five adults in the TBI group had a mild injury. Though neuropsychological test performance appeared reduced in the mTBI group compared to non-TBI controls, the study included only a small number of participants with mTBI, and no statistical analysis was performed on the mTBI data (51).

2.3 Discussion

This review and meta-analyses of studies published between January 2000 and March 2020 revealed an increase in the risk of dementia following a history of diagnosed mTBI, with a pooled odds ratio of 1.96 (95% CI 1.698–2.263, $p<0.001$) and subtle evidence of persistent changes in neuropsychiatric test performance and imaging. Previous reviews on this topic have yielded mixed conclusions; Godbolt et al. (2014) (26) reported that mTBI does not increase the risk dementia development, while Perry et al. (2016) (2) reported that mTBI does increase risk of dementia. While we believe that this review provides a compelling argument that a history of diagnosed mTBI increases the risk of dementia, we also acknowledge that a risk factor is simply an increased chance of developing a disease, rather than a definitive cause. This review has been

split into two main components: identifying the risk of dementia after mTBI and identifying dementia-related factors after mTBI, such as structural and cognitive abnormalities. This differentiation was made to create a comprehensive review that provides both quantitative and qualitative evidence about the risk of dementia after mTBI. It is important to identify risk factors for dementia, as they serve as a starting place for clinicians and researchers to identify interventions for at-risk individuals.

2.3.1 Objective risk of dementia after mTBI

We included twelve studies that aimed to identify the risk of dementia years after mTBI (31–42). Of the twelve studies included, eight found an increased risk of dementia after mTBI in at least one subset of the examined population (31–35, 38–42), and two studies found that a history of mTBI affects the onset of dementia (36, 37). Overall it appears that prior mTBI increases the risk of developing later dementia. This is in contrast to the review conducted by Godbolt et al. (2014) (26); however, the current review was able to capture information from eleven studies deemed "High Quality" or "Acceptable", while Godbolt et al. (2014) only captured one (26). These discrepancies may stem from differences between inclusion criteria for the respective review; for example, in the current review, included studies must have used physician-diagnosed concussions, have had the head injury confirmed by an informant, and/or read a strictly defined definition of concussion to participants to assist in their assessment of injuries. We made this a criterion to exclude studies where participants who are potentially at risk of dementia and may have a history of mTBI are asked to remember mTBI events throughout their life. Due to the memory problems associated with mTBI and dementia, this raises the potential of study bias; this was not an inclusion criterion in the other reviews. In their review, Godbolt et al. (2014) (26) recommended that future researches ensure they produce studies with appropriate methodology

and enough power to draw conclusions from. Eight studies included in this review, all of which were deemed to have appropriate power and low risk of bias, have been published since the Godbolt et al. (2014) (26) review, and so we applaud the researchers for acknowledging the paucity of research in the area and designing studies to address these gaps.

It is worth noting that a majority of the studies in this section searched health databases to investigate any associations between mTBI and dementia. While this is an excellent method to ensure accurate diagnoses, it opens a discussion regarding universal health coverage. Data collected in this manner may be most generalizable when coming from countries that provide universal health coverage, and comparisons between countries with different types of healthcare systems should be taken with caution (52). Notably, studies based in Taiwan used data from the National Health Insurance program which provides universal health insurance and enrolls up to 99% of the population (34, 37). In countries where universal health care is unavailable, people may be less likely to see a physician for a multitude of reasons, including financial barriers and limited resources, which may affect the results of database searches. Another challenge exists in retrospectively searching databases, regardless of universal healthcare, in that historically, fewer people may have seen a physician for diagnosis of mTBI due to the previous misconception of concussions and mTBI as an insignificant event. A Canadian study found that concussion rates were stable between 1994/1995–2005/2006 (53). However, by 2014 an increase in reporting by up to 250% was observed without any indication of a plateau. This trend was observed in both sexes, young and older populations, and sport and non-sport related injuries, and likely represents increased awareness of concussion and mTBI (53).

2.3.2 Meta-analysis of quantitative studies

This meta-analysis supports an association be-tween remote mTBI and a later diagnosis of dementia, including AD. For this meta-analysis, only studies that explicitly reported mTBI and dementia rates were included. If this information was not provided in the paper, we contacted the authors to gain this information. In one case, we were not able to contact the authors, and so the data was not included in the present analysis. We also only included studies that were rated as high quality or acceptable to reduce bias in our results. Because we only included studies that assessed the occurrence of mTBI prior to one-year before dementia diagnosis, we feel confident in the directionality of this association.

TBI is the strongest environmental risk factor for the later development of dementia (54). It seems that the severity of impact plays a role in the risk of dementia such that more severe impacts have more associated risk (2, 39), but the role of repetitive injuries is still under investigation (2). To compare the current finding to non-brain injury-related risk factors, vascular risk factors (e.g., diabetes, hypertension, and obesity) have ORs ranging from 2.0–2.3 (55). Further, an OR between 1.80–9.05 has been observed between the APOE ε4 allele and the development of AD (56). While these risk factors may not be directly comparable, it is noteworthy that we have identified an odds ratio similar to these classically associated risk factors.

The current meta-analysis only includes data from six studies. While it provides evidence that there is an association between remote mTBI and later development of dementia, more research is needed in this area to better determine the strength of association.

2.3.3 Neuropsychiatric changes after mTBI

We included four studies that used neuropsychiatric test performance as the primary outcome measure. Overall, mTBI seems to result in mildly reduced performance on several

neuropsychiatric tests, though some studies did not detect an effect. Most studies that examined subjective measures of cognitive function after mTBI found persistent deficits in domains such as executive function and visual, verbal and episodic memory, and one study found a dose-dependent increase in risk for a variety of cognitive impairments after mTBI. However, three papers found little changes in neuropsychiatric testing between control and mTBI groups. Taken together, these results are consistent with other systematic reviews conducted in the field that report subtle changes in cognition in some patients following mTBI, especially after repeated injuries (57, 58). This is well illustrated by a systematic review of eleven meta-analyses, which reported that despite an overall good prognosis for the vast majority of mTBI patients, a subset of patients suffered from persistent cognitive deficits (58). Furthermore, patients with repeated head injury were at a larger risk for reduced cognitive performance (59). Despite these findings, it is important to emphasize that some reviews report essentially complete recovery after mTBI and that the majority of patients with an mTBI recover (60). Overall though, the large body of evidence suggests that a small subset of mTBI patients, especially those with repeated injuries, have persistent, subtle cognitive impairment. This impairment could be associated with dementia through persistent damage and a reduction in cognitive reserve (61), through association with a long-term neurodegenerative process such as tau deposition or amyloid aggregation or could be an independent deficit unrelated to dementia.

2.3.4 Neuroimaging changes after mTBI

We included five studies that used neuroimaging changes as the primary outcome measure. Neuro-imaging mainly revealed changes in white matter volume, particularly in the medial temporal and frontal regions. The vulnerability of these regions to white matter abnormalities

after TBI has been reported elsewhere, and they are considered susceptible to impact due to their mobility and proximity to bony structures (62).

All the neuroimaging studies included in this review found at least some significant differences in patients with a history of mTBI, most of whom were professional athletes. These included alterations in white matter tracts and brain volume in areas associated with memory, such as the hippocampus. One study found similar changes in white matter tracts in patients with post-concussive syndrome (63), and similar trends were identified in a recent systematic review (64). While residual, long-term structural changes similar to those found in post-concussive syndrome are concerning enough, some evidence exists that white matter abnormalities seen in mTBI have similarities with those seen in AD (65). These abnormalities include changes in the corpus callosum and temporal regions (such as the parahippocampal gyrus), both of which were affected by mTBI (66, 67).

In summary, the neuroimaging and neuropsychiatric studies presented provide potential explanations for the increased risk of dementia seen in mTBI patients. Firstly, it is possible that following mTBI, persistent injury to the hippocampus, white matter tracts and other regions causes affected individuals to be more vulnerable to the age-related brain changes associated with dementia that affect similar regions. Alternatively, mTBI could trigger a long-term neurodegenerative process that becomes clinically apparent only with age, analogous to the tau-related changes seen in patients with CTE (68). These changes may be associated with altered levels of neurometabolites, which has already been demonstrated in symptomatic CTE patients retired from the NFL (69).

2.3.5 Risk of bias and limitations

The intent of rating the bias within studies is to better identify the validity of results concerning the current review, and is not done to discredit any research conducted in this area. Out of 21 studies, six were rated as high quality, twelve as acceptable, and three as unacceptable using the Scottish Intercollegiate Guidelines (20). High quality studies had to meet most items on the bias scoring checklist, have a high enough sample size, and have no major methodological issues. Acceptable studies also met most of the guidelines but had some methodological issues. The most common issues involved a combination of the following: low statistical power, nonstandard definitions of mTBI, poor controls, selective reporting of data, and conducting neuropsychiatric tests without a trained professional. A 2007 study by Sundström et al. (33) was rated as unacceptable because of their definition of mTBI. Although the authors used structured interviews and medical records to examine head impact history, their justification of mild severity was inappropriate. The authors stated that participants had only sustained mild injuries, and this statement was based on an assumption that any participant who had sustained a TBI and was able to carry out a test battery had a mild injury. Given that most patients who survive moderate to severe TBI can function without assistance (70), we felt that this definition of mTBI was unable to accurately distinguish TBI severity. Due to the high probability of participants in the mTBI group having sustained a more severe injury, we were unable to draw strong conclusions from this paper. Although the studies by Ozen et al. (2015) (51) and McMillan et al. (2014) (38) were well done in terms of methodology, for our purposes, they were considered unacceptable, as no statistical analyses were performed on the specific results of interest (i.e., the association between remote mTBI and later development of dementia or related indicators). Because no statistical analyses were performed, results due to chance cannot be ruled out, and firm conclusions cannot be drawn.

One limitation of our review is that we did not analyze the effect of the number of mTBIs; some of the differences between studies are likely mediated by different exposure levels. Most of the studies included in this review did not include information on the number of injuries, so we were not able to examine this important variable. While evidence suggests that a single TBI may cause amyloid and tau pathology, the effect of a single mTBI is unclear (71). Conversely, repetitive injuries have been studied as a risk factor for neurodegenerative disorders such as CTE (72), and pathological changes such as alterations in cerebral blood flow (73). Presumably, patients with more mTBI exposure are more susceptible to developing dementia, and those with fewer injuries may have a much lower risk. Another potential limitation is that we only included studies that used a clinical diagnostic tool such as the MMSE/MoCA as a screening measure or outcome, and that a clinical definition of mTBI had to be met. Although these criteria were intended to help capture only relevant, high quality studies, it is possible that they led us to exclude relevant papers. Furthermore, we were unable to include one study in the present meta-analysis because we were unable to acquire the relevant numbers after contacting the authors. The exclusion of this study may have resulted in a slight overestimate of the risk of dementia using our pooled OR. Finally, we did not measure the risk of bias across studies, so our conclusions may have been affected by factors such as publication bias.

2.3.6 Future directions

This review highlights a putative association between dementia and mTBI, and discusses long-term neuroimaging and neuropsychiatric changes after mTBI. Future epidemiological studies should compare the effect of multiple versus single mTBIs to determine what level of mTBI exposure causes a significant increase in dementia risk. To better understand the mechanism of this risk, further longitudinal studies investigating tau and amyloid accumulation in mTBI

patients should be conducted. In addition, this review provides a starting point for clinicians and researchers to develop prevention strategies for individuals at risk of developing dementia due to a history of mTBI. From this review, it is apparent that people with a history of mTBI show alterations in tracts, reduced brain volume in areas associated with memory, and slight decreases in cognitive performance, all of which may be risk factors for later development of dementia. While there is currently no cure for dementia, much research has focused on preventative mechanisms including exercise-based, cognitive training, and mindfulness techniques. Erickson et al. (2011) demonstrated that aerobic exercise training leads to increased hippocampal volume and associated improvements in spatial memory in healthy older adults (74). Furthermore, Musteata et al. (2019) demonstrated improvements in cognitive performance in healthy older adults, while Spaner et al. (2019) demonstrated cognitive improvements in adults with subjective memory complaints following cognitive training programs (75, 76). Another intervention under investigation is mindfulness training, a type of meditation. Hölzel et al. (2011) found that 8-weeks of mindfulness training increased grey matter volume in region specific areas, including the left hippocampus (77). Pharmacological treatments, such as cholesterol management via statins, are a further area of interest in reducing dementia risk post-concussion. One study included in this review also included a patient group prescribed statins post-injury and found that patients who took statins following mTBI had a 13% decreased risk of dementia development (41). Future researchers should investigate if these types of intervention programs have benefits to individuals at risk of dementia due to remote mTBI.

2.4 Conclusions

Remote mild traumatic brain injury confers an increased risk of dementia, with a pooled odds ratio of 1.96 (95% CI 1.698–2.263). In addition, neuropsychiatric and neuroimaging tests reveal

long-term deficits and changes in brain structure after mTBI, that are associated with MCI and dementia. Future research should continue to examine mechanistic links between mTBI and dementia, and aim to identify risk management strategies in mTBI patients susceptible to dementia.

2.5 Disclosure statement

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/20-0662r2).

2.6 Chapter 2 References

1. Kristman VL, Borg J, Godbolt AK, Salmi LR, Cancelliere C, Carroll LJ, Holm LW, Nygren-De Boussard C, Hartvigsen J, Abara U, Donovan J, Cassidy JD (2014) Methodological issues and research recommendations for prognosis after mild traumatic brain injury: Results of the international collaboration on mild traumatic brain injury prognosis. Arch Phys Med Rehabil 95 (3 Suppl), S265–277. Crossref. PubMed.
2. Perry DC, Sturm VE, Peterson MJ, Pieper CF, Bullock T, Boeve BF, Miller BL, Guskiewicz KM, Berger MS, Kramer JH, Welsh-Bohmer KA (2016) Association of traumatic brain injury with subsequent neurological and psychiatric disease: A meta-analysis. J Neurosurg 124, 511–526. Crossref. PubMed. Web of Science.
3. Mckee AC, Cantu RC, Nowinski CJ, Hedley-Whyte T, Gavett BE, Budson AE, Santini VE, Lee H-S, Kubilus CA, Stern RA (2009) Chronic traumatic encephalography in athletes: Progressive tauopathy after repetitive head injury. J Neuropathol Exp Neurol 68, 709–735. Crossref. PubMed.
4. Gardner RC, Yaffe K (2015) Epidemiology of mild traumatic brain injury and neurodegenerative disease. Mol Cell Neurosci 66, 75–80. Crossref. PubMed.

5. Harada CN, Natelson Love MC, Triebel KL (2013) Normal cognitive aging. Clin Geriatr Med 29, 737–752. Crossref. PubMed.

6. Petersen RC (2009) Early diagnosis of Alzheimer's disease: Is MCI too late? Curr Alzheimer Res 6, 324–330. Crossref. PubMed.

7. Knopman DS, Petersen RC (2014) Mild cognitive impairment and mild dementia: A clinical perspective. Mayo Clin Proc 89, 1452–1459. Crossref. PubMed.

8. Mitchell AJ, Shiri-Feshki M (2009) Rate of progression of mild cognitive impairment to dementia - Meta-analysis of 41 robust inception cohort studies. Acta Psychiatr Scand 119, 252–265. Crossref. PubMed.

9. Drummond N, Birtwhistle R, Williamson T, Khan S, Garies S, Molnar F (2016) Prevalence and management of dementia in primary care practices with electronic medical records: A report from the Canadian Primary Care Sentinel Surveillance Network. CMAJ Open 4, E177–E184. Crossref. PubMed.

10. Manuel DG, Garner R, Finès P, Bancej C, Flanagan W, Tu K, Reimer K, Chambers LW, Bernier J (2016) Alzheimer's and other dementias in Canada, 2011 to 2031: A microsimulation Population Health Modeling (POHEM) study of projected prevalence, health burden, health services, and caregiving use. Popul Health Metr 14, 37. Crossref. PubMed.

11. Crous-Bou M, Minguillón C, Gramunt N, Molinuevo JL (2017) Alzheimer's disease prevention: From risk factors to early intervention. Alzheimers Res Ther 9, 1–9. Crossref. PubMed.

12. Alzheimer Society of Canada, https://alzheimer.ca/en/Home.

13. Prince M, Bryce R, Ferri C (2011) World Alzheimer Report 2011. The benefits of early diagnosis and intervention. Alzheimer's Disease International, London. 90

14. Gyebnár G, Szabó Á, Sirály E, Fodor Z, Sákovics A, Salacz P, Hidasi Z, Csibri É, Rudas G, Kozák LR, Csukly G (2018) What can DTI tell about early cognitive impairment? - Differentiation between MCI subtypes and healthy controls by diffusion tensor imaging. Psychiatry Res Neuroimaging 272, 46–57. Crossref. PubMed.

15. Sheinerman KS, Tsivinsky VG, Crawford F, Mullan MJ, Abdullah L, Umansky SR (2012) Plasma microRNA biomarkers for detection of mild cognitive impairment. Aging (Albany. NY) 4, 590–605. Crossref. PubMed. Web of Science.

16. Weller J, Budson A (2018) Current understanding of Alzheimer's disease diagnosis and treatment. F1000Res 7, F1000 Faculty Rev-1161. Crossref. PubMed.

17. Weimer DL, Sager MA (2009) Early identification and treatment of Alzheimer's disease: Social and fiscal outcomes. Alzheimers Dement 5, 215–226. Crossref. PubMed.

18. Barnes DE, Kaup A, Kirby KA, Byers AL, Diaz-Arrastia R, Yaffe K (2014) Traumatic brain injury and risk of dementia in older veterans. Neurology 83, 312–319. Crossref. PubMed. Web of Science.

19. Gardner RC, Rubenstein R, Wang KKW, Korley FK, Yue JK, Yuh EL, Mukherje P, Valadka AB, Okonkwo DO, Diaz-Arrastia R, Manley GT (2018) Age-related differences in diagnostic accuracy of plasma glial fibrillary acidic protein and tau for identifying acute intracranial trauma on computed tomography: A TRACK-TBI study. J Neurotrauma 35, 2341–2350. Crossref. PubMed.

20. Wang HK, Lin SH, Sung PS, Wu MH, Hung KW, Wang LC, Huang CY, Lu K, Chen HJ, Tsai KJ (2012) Population based study on patients with traumatic brain injury suggests

increased risk of dementia. J Neurol Neurosurg Psychiatry 83, 1080–1085. Crossref. PubMed.

21. Huang CH, Lin CW, Lee YC, Huang CY, Huang RY, Tai YC, Wang KW, Yang SN, Sun YT, Wang HK (2018) Is traumatic brain injury a risk factor for neurodegeneration? A meta-analysis of population-based studies. BMC Neurol 18, 1–8. Crossref. PubMed.

22. Hicks AJ, James AC, Spitz G, Ponsford JL (2019) Traumatic brain injury as a risk factor for dementia and Alzheimer disease: Critical review of study methodologies. J Neurotrauma 36, 3191–3219. Crossref. PubMed.

23. Bigler ED (2013) Traumatic brain injury, neuroimaging, and neurodegeneration. Front Hum Neurosci 7, 395. Crossref. PubMed.

24. Omalu BI, DeKosky ST, Minster RL, Kamboh MI, Hamilton RL, Wecht CH (2005) Chronic traumatic encephalopathy in a National Football League player. Neurosurgery 57, 128–133. Crossref. PubMed.

25. Carroll LJ, Cassidy JD, Peloso PM, Borg J, von Holst H, Holm L, Paniak C, Pépin M; WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury (2004) Prognosis for mild traumatic brain injury: Results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. J Rehabil Med (43 Suppl), 84-105. Crossref.

26. Godbolt AK, Cancelliere C, Hincapié CA, Marras C, Boyle E, Kristman VL, Coronado VG, Cassidy JD (2014) Systematic review of the risk of dementia and chronic cognitive impairment after mild traumatic brain injury: Results of the international collaboration on mild traumatic brain injury prognosis. Arch Phys Med Rehabil 95, S245–S256. Crossref. PubMed.

27. Moher D, Liberati A, Tetzlaff J, Altman DG, Altman D, Antes G, Atkins D, Barbour V, Barrowman N, Berlin JA, Clark J, Clarke M, Cook D, D'Amico R, Deeks JJ, Devereaux PJ, Dickersin K, Egger M, Ernst E, Gøtzsche PC, Grimshaw J, Guyatt G, Higgins J, Ioannidis JPA, Kleijnen J, Lang T, Magrini N, McNamee D, Moja L, Mulrow C, Napoli M, Oxman A, Pham B, Rennie D, Sampson M, Schulz KF, Shekelle PG, Tovey D, Tugwell P (2009) Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. Ann Intern Med 151, 264–269. Crossref. PubMed.

28. Harbour R, Miller J (2001) A new system for grading recommendations in evidence based guidelines. Br Med J 323, 334–336. Crossref. PubMed.

29. MedCalc Statistical Software version 16.4.3. MedCalc Software bv, Ostend, Belgium. https://www.medcalc.org.

30. Wickham H (2016) ggplot2: Elegant Graphics for Data Analysis. Springer-Verlag, New York. Crossref.

31. Barnes DE, Byers AL, Gardner RC, Seal KH, Boscardin WJ, Yaffe K (2018) Association of mild traumatic brain injury with and without loss of consciousness with dementia in US Military Veterans. JAMA Neurol 75, 1055–1061. Crossref. PubMed.

32. Helmes E, Østbye T, Steenhuis RE (2011) Incremental contribution of reported previous head injury to the prediction of diagnosis and cognitive functioning in older adults. Brain Inj 25, 338–347. Crossref. PubMed.

33. Sundström A, Nilsson L-G, Cruts M, Adolfsson R, Van Broeckhoven C, Nyberg L (2007) Increased risk of dementia following mild head injury for carriers but not for non-carriers of the APOE epsilon4 allele. Int Psychogeriatr 19, 159–165. Crossref. PubMed.

34. Yang J-R, Kuo C-F, Chung T-T, Liao H-T (2019) Increased risk of dementia in patients with craniofacial trauma: A nationwide population-based cohort study. World Neurosurg 125, e563–e574. Crossref. PubMed.

35. Lee Y-K, Hou S-W, Lee C-C, Hsu C-Y, Huang Y-S, Su Y-C (2013) Increased risk of dementia in patients with mild traumatic brain injury: A nationwide cohort study. PLoS One 8, e62422. Crossref. PubMed.

36. Li W, Risacher SL, McAllister TW, Saykin AJ (2016) Traumatic brain injury and age at onset of cognitive impairment in older adults. J Neurol 263, 1280–1285. Crossref. PubMed.

37. Liao J-Y, Lee CT-C, Lin T-Y, Liu C-M (2020) Exploring prior diseases associated with incident late-onset Alzheimer's disease dementia. PLoS One 15, e0228172. Crossref. PubMed.

38. McMillan TM, Weir CJ, Wainman-Lefley J (2014) Mortality and morbidity 15 years after hospital admission with mild head injury: A prospective case-controlled population study. J Neurol Neurosurg Psychiatry 85, 1214–1220. Crossref. PubMed.

39. Nordström A, Nordström P (2018) Traumatic brain injury and the risk of dementia diagnosis: A nationwide cohort study. PLoS Med 15, e1002496. Crossref. PubMed.

40. Plassman BL, Havlik RJ, Steffens DC, Helms MJ, Newman TN, Drosdick D, Phillips C, Gau BA, Welsh-Bohmer KA, Burke JR, Guralnik JM, Breitner JC (2000) Documented head injury in early adulthood and risk of Alzheimer's disease and other dementias. Neurology 55, 1158–1166. Crossref. PubMed.

41. Redelmeier DA, Manzoor F, Thiruchelvam D (2019) Association between statin use and risk of dementia after a concussion. JAMA Neurol 76, 887–896. Crossref. PubMed.

42. Sercy E, Orlando A, Carrick M, Lieser M, Madayag R, Vasquez D, Tanner A 2nd, Rubin B, Bar-Or D (2020) Long-term mortality and causes of death among patients with mild traumatic brain injury: A 5-year multicenter study. Brain Inj 34, 556–566. Crossref. PubMed.

43. Strain JF, Womack KB, Didehbani N, Spence JS, Conover H, Hart JJ, Kraut MA, Cullum CM (2015) Imaging correlates of memory and concussion history in retired National Football League athletes. JAMA Neurol 72, 773–780. Crossref. PubMed.

44. Hart JJ, Kraut MA, Womack KB, Strain J, Didehbani N, Bartz E, Conover H, Mansinghani S, Lu H, Cullum CM, Cullum M (2013) Neuroimaging of cognitive dysfunction and depression in aging retired national football league players: A cross-sectional study. JAMA Neurol 70, 326–335. Crossref. PubMed.

45. Tremblay S, Desjardins M, Bermudez P, Iturria-Medina Y, Evans AC, Jolicoeur P, De Beaumont L (2019) Mild traumatic brain injury: The effect of age at trauma onset on brain structure integrity. Neuroimage Clin 23, 101907. Crossref. PubMed.

46. Tremblay S, De Beaumont L, Henry LC, Boulanger Y, Evans AC, Bourgouin P, Poirier J, Théoret H, Lassonde M (2013) Sports concussions and aging: A neuroimaging investigation. Cereb Cortex 23, 1159–1166. Crossref. PubMed.

47. Yang S-T, Hsiao I-T, Hsieh C-J, Chiang Y-H, Yen T-C, Chiu W-T, Lin K-J, Hu C-J (2015) Accumulation of amyloid in cognitive impairment after mild traumatic brain injury. J Neurol Sci 349, 99–104. Crossref. PubMed.

48. Esopenko C, Chow TW, Tartaglia MC, Bacopulos A, Kumar P, Binns MA, Kennedy JL, Müller DJ, Levine B (2017) Cognitive and psychosocial function in retired professional hockey players. J Neurol Neurosurg Psychiatry 88, 512–519. Crossref. PubMed.

49. Montenigro PH, Alosco ML, Martin BM, Daneshvar DH, Mez J, Chaisson CE, Nowinski CJ, Au R, McKee AC, Cantu RC, McClean MD, Stern RA, Tripodis Y (2017) Cumulative head impact exposure predicts later-life depression, apathy, executive dysfunction, and cognitive impairment in former high school and college football players. J Neurotrauma 34, 328–340. Crossref. PubMed.

50. Wammes JD, Good TJ, Fernandes MA (2017) Autobiographical and episodic memory deficits in mild traumatic brain injury. Brain Cogn 111, 112–126. Crossref. PubMed.

51. Ozen LJ, Fernandes MA, Clark AJ, Roy EA (2015) Evidence of cognitive decline in older adults after remote traumatic brain injury: An exploratory study. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn 22, 517–533. Crossref. PubMed.

52. Ridic G, Gleason S, Ridic O (2012) Comparisons of health care systems in the United States, Germany and Canada. Mater Sociomed 24, 112–120. Crossref. PubMed.

53. Gordon KE, Kuhle S (2018) 'Reported concussion' time trends within two national health surveys over two decades. Brain Inj 32, 843–849. Crossref. PubMed.

54. Smith DH, Johnson VE, Stewart W (2013) Chronic neuropathologies of single and repetitive TBI: Substrates of dementia? Nat Rev Neurol 9, 211–221. Crossref. PubMed.

55. Kloppenborg RP, van den Berg E, Kappelle LJ, Biessels GJ (2008) Diabetes and other vascular risk factors for dementia: Which factor matters most? A systematic review. Eur J Pharmacol 585, 97–108. Crossref. PubMed.

56. Jun G, Naj AC, Beecham GW, Wang LS, Buros J, Gallins PJ, Buxbaum JD, Ertekin-Taner N, Fallin MD, Friedland R, Inzelberg R, Kramer P, Rogaeva E, St George-Hyslop P, Cantwell LB, Dombroski BA, Saykin AJ, Reiman EM, Bennett DA, Morris JC, Lunetta KL, Martin ER, Montine TJ, Goate AM, Blacker D, Tsuang DW, Beekly D,

Cupples LA, Hakonarson H, Kukull W, Foroud TM, Haines J, Mayeux R, Farrer LA, Pericak-Vance MA, Schellenberg GD (2010) Meta-analysis confirms CR1, CLU, and PICALM as Alzheimer disease risk loci and reveals interactions with APOE genotypes. Arch Neurol 67, 1473–1484. Crossref. PubMed. Web of Science.

57. Frencham KAR, Fox AM, Maybery MT (2005) Neuropsychological studies of mild traumatic brain injury: A meta-analytic review of research since 1995. J Clin Exp Neuropsychol 3, 334–51. Crossref.

58. Karr JE, Areshenkoff CN, Garcia-Barrera MA (2014) The neuropsychological outcomes of concussion: A systematic review of meta-analyses on the cognitive sequelae of mild traumatic brain injury. Neuropsychology 28, 321–336. Crossref. PubMed.

59. Belanger HG, Vanderploeg RD (2005) The neuropsychological impact of sports-related concussion: A meta-analysis. J Int Neuropsychol Soc 11, 345–357. Crossref. PubMed.

60. Schretlen DJ, Shapiro AM (2003) A quantitative review of the effects of traumatic brain injury on cognitive functioning. Int Rev Psychiatry 15, 341–349. Crossref. PubMed.

61. Bigler ED, Stern Y (2015) Traumatic brain injury and reserve. In Handbook of Clinical Neurology Elsevier B.V., pp. 691-710. Crossref.

62. McAllister TW (2011) Neurobiological consequences of traumatic brain injury. Dialogues Clin Neurosci 13, 287–300. Crossref. PubMed.

63. Messé A, Caplain S, Paradot G, Garrigue D, Mineo JF, Soto Ares G, Ducreux D, Vignaud F, Rozec G, Desal H, Pélégrini-Issac M, Montreuil M, Benali H, Lehéricy S (2011) Diffusion tensor imaging and white matter lesions at the subacute stage in mild traumatic brain injury with persistent neurobehavioral impairment. Hum Brain Mapp 32, 999–1011. Crossref. PubMed.

64. Biagianti B, Stocchetti N, Brambilla P, Van Vleet T (2020) Brain dysfunction underlying prolonged post-concussive syndrome: A systematic review. J Affect Disord 262, 71–76. Crossref. PubMed.

65. Fakhran S, Yaeger K, Alhilali L (2013) Symptomatic white matter changes in mild traumatic brain injury resemble pathologic features of early Alzheimer dementia. Radiology 269, 249–257. Crossref. PubMed.

66. Yoshiura T, Mihara F, Koga H, Ohyagi Y, Noguchi T, Togao O, Ogomori K, Miyoshi K, Yamasaki T, Kaneko K, Ichimiya A, Kanba S, Honda H (2006) Mapping of subcortical white matter abnormality in Alzheimer's disease using diffusion-weighted magnetic resonance imaging. Acad Radiol 13, 1460–1464. Crossref. PubMed.

67. Van Hoesen GW, Augustinack JC, Dierking J, Redman SJ, Thangavel R (2006) The parahippocampal gyrus in Alzheimer's disease: Clinical and preclinical neuroanatomical correlates. Ann N Y Acad Sci 911, 254–274. Crossref.

68. Katsumoto A, Takeuchi H, Tanaka F (2019) Tau pathology in chronic traumatic encephalopathy and Alzheimer's disease: Similarities and differences. Front Neurol 10, 980. Crossref. PubMed.

69. Lin AP, Ramadan S, Stern RA, Box HC, Nowinski CJ, Ross BD, Mountford CE (2015) Changes in the neurochemistry of athletes with repetitive brain trauma: Preliminary results using localized correlated spectroscopy. Alzheimers Res Ther 7, 13. Crossref. PubMed. Web of Science.

70. Jochems D, van Wessem KJP, Houwert RM, Brouwers HB, Dankbaar JW, van Es MA, Geurts M, Slooter AJC, Leenen LPH (2018) Outcome in patients with isolated moderate to severe traumatic brain injury. Crit Care Res Pract 2018, 3769418. PubMed.

71. Washington PM, Villapol S, Burns MP (2016) Polypathology and dementia after brain trauma: Does brain injury trigger distinct neurodegenerative diseases, or should they be classified together as traumatic encephalopathy? Exp Neurol 275 Pt 3, 381–388. Crossref. PubMed.

72. Maroon JC, Winkelman R, Bost J, Amos A, Mathyssek C, Miele V (2015) Chronic traumatic encephalopathy in contact sports: A systematic review of all reported pathological cases. PLoS One 10, e0117338. Crossref. PubMed.

73. Clark AL, Weigand AJ, Bangen KJ, Merritt VC, Bondi MW, Delano-Wood L (2020) Repetitive mTBI is associated with age-related reductions in cerebral blood flow but not cortical thickness. J Cereb Blood Flow Metab. Crossref

74. Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, Kim JS, Heo S, Alves H, White SM, Wojcicki TR, Mailey E, Vieira VJ, Martin SA, Pence BD, Woods JA, McAuley E, Kramer AF (2011) Exercise training increases size of hippocampus and improves memory. Proc Natl Acad Sci U S A 108, 3017–3022. Crossref. PubMed.

75. Musteata S, Yoshida K, Baranzini D, Spaner C, Taneja C, Abutalebi J, Christie BR, Author C (2019) Perceptual-cognitive training can improve cognition in older adults with subjective cognitive decline. Ageing Sci Ment Health Stud 3(6), 1–15.

76. Spaner CR, Musteata S, Kenny RA, Gawryluk JR, Hofer S, Christie BR (2019) 3-Dimensional multiple object tracking training can enhance selective attention, psychomotor speed, and cognitive flexibility in healthy older adults. Ageing Sci Ment Health Stud 3(4), 1–12.

77. Hölzel BK, Carmody J, Vangel M, Congleton C, Yerramsetti SM, Gard T, Lazar SW (2011) Mindfulness practice leads to increases in regional brain gray matter density. Psychiatry Res 191, 36–43. Crossref. PubMed.

78. Frankowski RF, Annegers JF, Whitman S (1985) Epidemiological and descriptive studies. Part I: The descriptive epidemiology of head trauma in the United States. In Central Nervous System Trauma Status Report, Becker DP, Povlishock JT, eds. National Institute of Neurological and Communicative Disorders and Stroke, Bethesda, pp. 33-43.

Chapter 3

Detection: Using multi-modal assessments to distinguish between adults with and without histories of concussion

3.1 Abstract

3.1.1 Background:

Concussions are a form of mild traumatic brain injury that are being increasingly recognized as a risk factor for dementia, particularly in aging adults. However, the subtle nature of these injuries and the limitations of single-modality assessments may obscure important concussion-related outcomes. This study aimed to investigate the long-term consequences of concussions in aging adults using a multimodal approach, including neuropsychological assessment, diffusion tensor imaging and blood-based biomarker analysis.

3.1.2 Methods:

Seventy-one community-dwelling adults aged 50–81 were enrolled, and asked to complete neuropsychological testing, diffusion tensor imaging, and blood collection. Participants were grouped based on history of diagnosed or self-reported concussion, contact sport exposure, and number of past injuries. Cognitive assessments included measures of attention, memory and processing speed. Serum biomarkers included neurofilament light chain (NfL), glial fibrillary acidic protein, phosphorylated tau (pTau-217), brain derived neurotrophic factor, interleukin-10 (IL-10) and tumor necrosis factor alpha. White matter integrity was assessed using tract-based spatial statistics to evaluate fractional anisotropy (FA) and mean diffusivity (MD).

3.1.3 Results:

Participants with a history of concussion exhibited lower serum NfL levels compared to controls (FDR-adjusted $p < 0.05$). However, higher NfL levels within the concussion group were associated with poorer verbal fluency and widespread decreases in FA and increases in MD. Participants with multiple concussions showed elevated IL-10, while those with contact sport experience showed higher pTau-217 levels. ROC analysis revealed that a combined biomarker model most effectively classified concussion exposure (AUC = 0.82 for multiple concussions).

3.1.4 Conclusions:

This study highlights potential long-term effects following concussion that may not be detectable with traditional assessments alone. Multimodal assessment offers a more nuanced understanding of concussion sequelae in aging and may help identify those at greatest risk for cognitive decline.

3.2 Introduction

Mild traumatic brain injuries (mTBIs), often referred to as concussions, are an extremely prevalent neurological condition, with an estimated global burden of 42 million cases yearly.[1,2] Aging adults are unique, as they are particularly vulnerable to concussions, with adults over age 65 accounting for over 80,000 TBI-related emergency room visits each year, and adults over 75 having the highest rate of TBI-associated complications and mortality.[3] Although these numbers are alarming, they are likely a vast underrepresentation of the true burden of injury, especially when considering long-term effects. Epidemiological studies suggest that the number of yearly concussions is rising, however, this may be due to better diagnostic criteria, and better understanding of the injury.[4] Falls are the leading cause of TBI in older adults, and the combination of age-related fragility and under-recognition of injury highlights the need for further attention to concussion-effects in this population.

The acute symptoms of concussion are typically transient, with 80% of people recovering within a few weeks.[5–7] However, there is growing evidence of long-term consequences of injury, especially in aging populations.[8–10] A recent meta-analysis found that even a single diagnosed mild-TBI is associated with a nearly two-fold increase in the odds of developing dementia, compared to adults who had never experienced an mTBI.[10] Beyond diagnoses of dementia, subtle but persistent changes have been observed in neuroimaging studies of adults with histories of concussion. For example, findings from the Baltimore Longitudinal Study of Aging show increased white-matter atrophy and microstructural degradation in frontal and temporal lobes in adults with histories of concussions compared to non-injured adults.[8] Importantly, these changes were observed in the absence of cognitive deficits, highlighting the need for sensitive measures in this population.[8]

Characterizing the long-term effects of concussions likely requires an approach that spans multiple domains including function and structure. A majority of post-concussion outcomes examine one modality (for example, only cognitive performance, or neuroimaging metrics), and often in small sample sizes.[11] Having a one-dimensional focus may lead to false negatives, as it could fail to detect the full spectrum of concussion-related changes, especially subtle differences in the presence of compensatory mechanisms. Alternatively, multimodal evaluation can provide a more sensitive and holistic understanding of concussion sequalae in aging adults. Advanced neuroimaging techniques like diffusion tensor imaging (DTI) are capable of detecting microstructural white matter abnormalities that may result from past mTBIs, even when conventional neuroimaging approaches appear normal.[12] Neuropsychological testing offers quantitative assessment of cognitive domains including memory, executive functions and processing speed, that could be affected by prior mTBIs.[13] Blood-based biomarkers can provide insight into molecular and physiological signatures of neural injury and neurodegeneration that may persist long after the initial injury.[14] By capturing structural, cognitive, and biological factors, multimodal assessment may detect concussion-related abnormalities that might be missed by any single measure alone.

The present study uses a multidisciplinary approach to investigate long-term differences between adults with and without histories of concussion, and concussion-based metrics. We studied 71 community-dwelling adults over the age of 50 with and without histories of concussion and experience in contact sport. To focus on potential enduring-effects, we excluded participants who had a concussion within the past year. Given our population, we defined concussion history group broadly to include individuals with any lifetime history of concussion, whether formally diagnosed or strongly suspected based on self-report of characteristic injury events and

symptoms. This definition was chosen to account for the high rate of undiagnosed injuries and to ensure we captured the full spectrum of concussion exposure. Analyses were completed based on diagnosed concussions, total reported concussions, and years in contact sport to account for the effects of potential repeated subconcussive exposures. All participants underwent MRI scans to assess white matter integrity, a partial battery of neuropsychological testing, and a panel of blood biomarkers. We hypothesized that traditional single-modality comparisons might reveal minimal between group differences, but that by combining these measures we would uncover clearer group differences that may provide insight into the long-term effects of concussions.

3.3 Methods

3.3.1 Ethical considerations

This study was approved by the University of Victoria Human Research Ethics Board (protocol 21-0591). All participants provided informed written consent prior to starting the study, and verbal consent at each appointment.

3.3.2 Study population

Participants were recruited to the present study between May 2022 and March 2025 using community posters, word-of-mouth and REACH BC. Participants that expressed interest were sent the study eligibility information, and those who met the criteria were able to book an intake appointment. Participants were eligible if they were between 50 and 90 years old, had normal or corrected vision, and had no diagnosis of a neurodegenerative disease (e.g., dementia, subjective cognitive decline), and were able to come to the University of Victoria for blood collection and West Coast Medical Imaging for their MRI. For those with a history of concussion, the injury must have occurred more than one year prior, and they must not be experiencing any persistent concussion symptoms. Exclusion criteria for the MRI component included certain medical

implants (*e.g.*, pacemakers, cochlear implants, metal implants from surgery), metallic foreign bodies (*e.g.*, shrapnel, bullet fragments), specific dental work (*e.g.*, magnet-held prosthetics, extensive metal dental work), and some tattoos or non-removable metal jewelry. Individuals meeting these exclusion criteria were allowed to participate in the study, but did not receive an MRI.

3.3.3 Intake interview

After participants expressed interest an intake interview was scheduled. These could be performed using an online platform like ZOOM, by phone, or in person, depending on the participants' preferences. After consent was obtained, the research assistant collected general demographics and information related to history of concussion, sporting history and education.

3.3.4 Neuropsychological assessment

Standardized neuropsychological assessments were administered by students in the Neuropsychology stream of clinical psychology at the University of Victoria. Neuropsychological assessments were conducted via ZOOM for all participants. If participants did not have access to a computer and webcam at home, they were able to come to the laboratory to use our equipment, however, the assessments were still conducted virtually. The assessments included measures of verbal fluency (FAS test), verbal learning and memory (California Verbal Learning Test, CVLT-2), working memory and processing speed (Symbol Digit Modalities Test, SDMT; Digit Span, DS), executive function (Trail Making Test, TMT A/B) and global cognitive function (Mini Mental State Exam, MMSE). Participants were provided with verbal instructions prior to each test, and allowed to take breaks as needed. Appointments took approximately one hour to complete. Data were collected on paper and stored in password-protected digital files for analysis.

3.3.5 Serum collection

Venous blood samples were collected by team members with certificates in phlebotomy. Blood draws were performed using a serum separator tube vacutainer system with a 21- or 23-gauge butterfly needle, prioritizing the median cubital vein, followed by the cephalic or basilic veins if necessary. After cleaning the puncture site with a 70% alcohol wipe, up to 60mL of blood was collected into vacutainer tubes, which were inverted 10 times to ensure proper mixing. Samples were allowed to clot for 30 minutes before centrifugation at 1500g for 10 minutes. The resulting serum aliquots were processed in a biosafety level 2 laboratory and stored at -80°C for future analysis.

3.3.6 Serum analysis

Serum analyses were conducted using the Single Molecular Array (SIMOA) HD-X platform. The Neurology 2-Plex assay measured neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP), with a coefficient of variation (CV) of 2.4% and between-plate variability of 16.7% for GFAP, and a CV of 4.1% with between-plate variability of 8.6% for NfL. Single-plex plates were used to assess phosphorylated tau217 (pTau-217), brain derived neurotrophic factor (BDNF), interleukin-10 (IL-10), and tumor necrosis factor-alpha (TNF-α). All samples were measured in duplicate, yielding an average CV of 6.8% and between-plate variability of 29.1% for IL-10. For pTau-217, the within-sample CV was 11.0%, with a between-plate CV of 31.07%. BDNF had a within-sample CV of 3.6% and between-plate variability of 10.7%. TNF-α showed a within-sample CV of 8.7% and a between-plate CV of 17.4%.

3.3.7 Imaging data acquisition

DTI data were collected by a trained MRI technician alongside a study team member at West Coast Medical Imaging. Imaging parameters included a repetition time (TR) of 8000 ms, echo

time (TE) of 101 ms, a 90° flip angle, 52 slices, and a voxel size of 1.4 × 1.4 × 2.0 mm. Each scan acquired 48 images, comprising 45 diffusion-weighted images (b = 1000 s/mm²) and 3 non-diffusion-weighted images (b = 0 s/mm²). The total acquisition time for the DTI images was approximately 6 minutes, and the entire scans were approximately 30 minutes in length.

3.3.8 Data analysis

The cohort included in this study was split into four binary variables of interest related to concussion metrics based on self-reported data collected at the intake interview. The first split was based on adults with a history of diagnosed concussions, the second was based on history of suspected (but not necessarily diagnosed) concussions, third was based on those who had multiple suspected concussions, and fourth based on who reported playing contact sports. All statistical analyses were completed in R Studio V 4.4.3 and FSL (FMRIB Software Library) for neuroimaging data. Between-group comparisons of continuous demographic and outcome variables (*e.g.*, serum biomarker levels, cognitive scores) were performed using independent samples t-tests. Categorical variables (*e.g.*, sex) were compared using chi-squared tests. For multiple comparisons within each modality (*e.g.*, across serum biomarkers or neuropsychological tests), p-values were corrected using False Discovery Rate (FDR).

Serum biomarker values were natural log-transformed to correct for non-normal distributions prior to analysis. Linear regression models were used to examine associations between biomarker levels and variables such as age, sex, years of contact sport, number of diagnosed concussions, and time since injury. Interaction terms were included in some models to test moderation effects to examine whether relationships between blood-based biomarkers and cognitive performance differed by concussion history.

Neuroimaging data were analyzed using tract-based spatial statistics (TBSS). Preprocessing included eddy current and motion correction, brain extraction, and tensor fitting to generate fractional anisotropy (FA) and mean diffusivity (MD) maps. FA images were nonlinearly registered to standard space, skeletonized, and subjected to voxel-wise statistical comparisons. Group differences in DTI metrics and associations between biomarkers and white matter integrity were tested using general linear models in FSL's randomise tool with threshold-free cluster enhancement, controlling for multiple comparisons at $p < 0.05$ (family-wise error corrected).

Receiver operating characteristic (ROC) curves were generated to assess the discriminative ability of individual and combined serum biomarkers in classifying concussion history (e.g., diagnosed concussion, contact sport participation, multiple concussions). Area under the curve (AUC) values were calculated to evaluate model performance.

3.4 Results

3.4.1 Participant demographics

A total of 71 participants completed at least one component (neuropsychological, biological, structural) of the study. Participants had an average age of 65.23 (± 8.85), and had 16 years of education on average (±2.4). Table 3.1 summarizes the participant demographic information, split by variable of interest. With the exception of years of education between those with and without a suspected concussion, there were no statistical differences between groups. A subset of 51 participants completed the MRI component of this study.

Table 3.1. Participant demographic information.

Information in brackets refers to those without the variable of interest. *; $p < 0.05$

	Reported Concussions	Diagnosed Concussions	Multiple Concussions	Contact Sports
N + (n -)	51 (20)	41 (30)	36 (35)	30 (41)
Age - years	64.8 ± 8.60 (68.85 ± 8.37)	63.6 ± 8.56 (67.4 ± 8.74)	63.9 ± 7.75 (67.6 ± 9.24)	63.7 ± 9.33 (66.1 ± 8.5)
Sex	M = 20, F = 21 (M = 6, F = 14)	M = 17, F = 24 (M = 9, F = 21)	M = 16, F = 20 (M = 10, F = 25)	M = 15, F = 13 (M = 11, F = 32)
Education - years	15.52 ± 2.46 (17.2 ± 1.79)*	15.8 ± 2.43 (16.3, 2.37)	15.72 ± 2.28 (16.28 ± 2.51)	15.67 ± 2.82 (16.2 ± 2.08)
Time Since Injury - years	16.36 ± 18.25	13.30 ± 16.44	12.81 ± 15.72	18.39 ± 19.70 (13.89 ± 16.41)

3.4.2 Group differences in individual biomarkers

3.4.2.1 Biological markers

3.4.2.1.1 Neurofilament light chain is elevated in people without any history of concussion

We split our participant pool based on differing concussion metrics, including a diagnosed history of concussion and a self-reported (but not necessarily diagnosed) concussion. Regardless of classification, those with history of concussion had lower levels of NfL compared to the uninjured control groups (Figures 2.1 and 2.2, diagnosed: $t(69)= 3.13$, $p = 0.0028$, FDR adjusted $p = 0.0166$); reported: $t(69) = 2.194$, $p = 0.032$, FDR adjusted $p = 0.0366$).

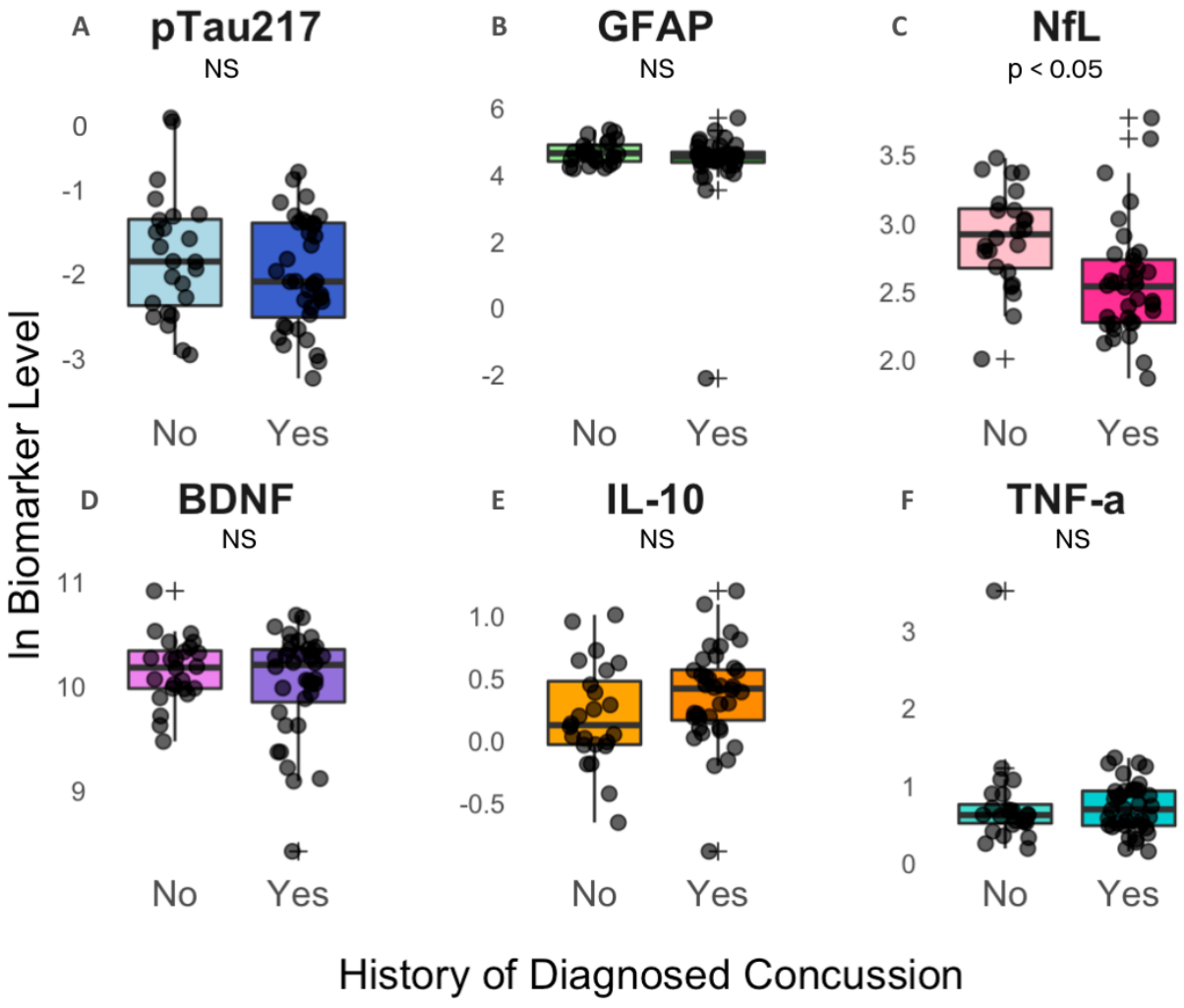


Figure 3.1. *Boxplots showing serum biomarker levels in adults with and without a history of diagnosed concussion.*

Biomarkers include pTau-217 (A), GFAP (B), NfL (C), BDNF (D), IL-10 (E), and TNF-α (F). Each boxplot represents the median, interquartile range, and individual data points, with outliers indicated by "+" symbols. The x-axis represents individuals with (Yes) and without (No) a history of diagnosed concussion. Statistical significance was determined using independent t-

tests, with non-significant results labeled as "NS". NfL showed a significant difference ($p < 0.05$), while all other biomarkers did not reach statistical significance.

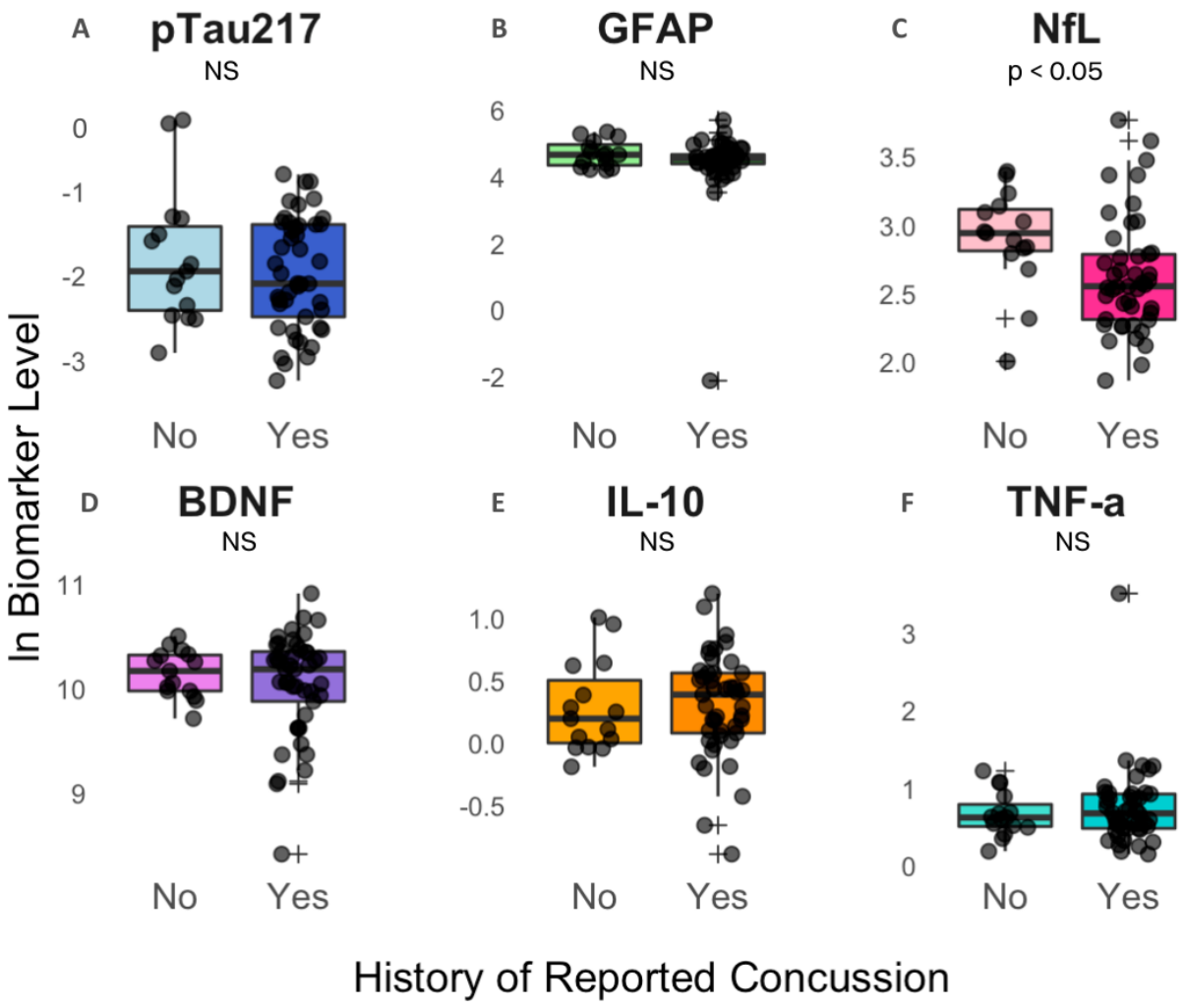


Figure 3.2. *Boxplots showing serum biomarker levels in adults with and without a history of reported concussion.*

Biomarkers include pTau-217 (A), GFAP (B), NfL (C), BDNF (D), IL-10 (E), and TNF-α (F). Each boxplot represents the median, interquartile range, and individual data points, with

outliers indicated by "+" symbols. The x-axis represents individuals with (Yes) and without (No) a history of reported concussion. Statistical significance was determined using independent t-tests, with non-significant results labeled as "NS". NfL showed a significant difference ($p < 0.05$), while all other biomarkers did not reach statistical significance.

3.4.2.1.2 IL-10 levels are elevated in people with repeated concussion exposures

We also saw lower NfL in those with multiple reported concussion exposures, compared to people without any or only one concussion (Figure 3.3, $t(69) = 2.424$, $p = 0.0184$), however, this was not statistically significant when controlling for multiple comparisons (FDR adjusted $p = 0.111$). Adults with histories of multiple concussions had elevated levels of IL-10 ($t(69) = -2.66$, $p = 0.0099$, FDR adjusted p-value = 0.0497), and TNF-α, but values were not statistically significant after correction for TNF-α ($t(69) = -2.08$, $p = 0.041$, FDR adjusted $p = 0.165$).

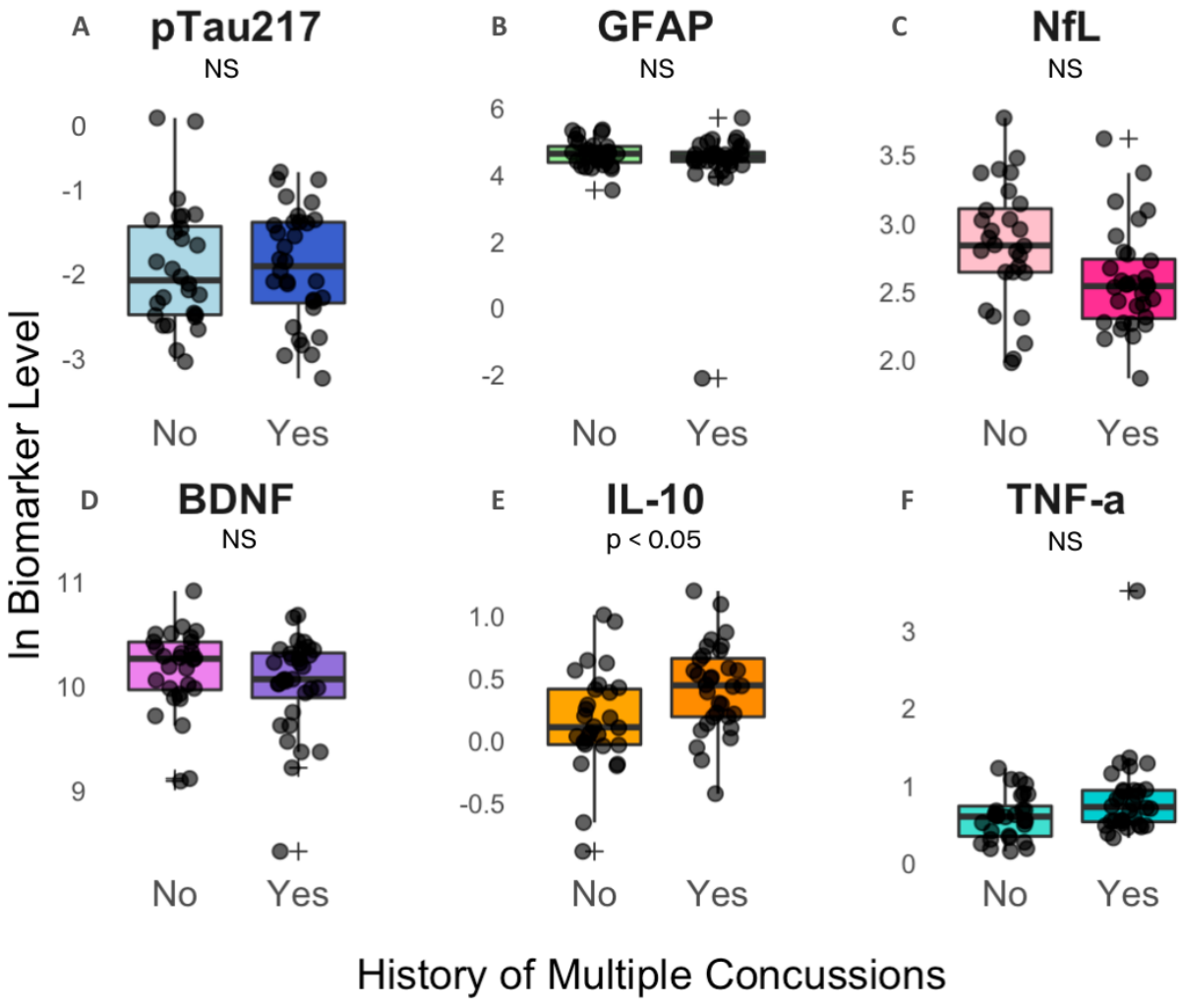


Figure 3.3. *Boxplots showing serum biomarker levels in adults with and without a history of multiple reported concussions.*

Biomarkers include pTau-217 (A), GFAP (B), NfL (C), BDNF (D), IL-10 (E), and TNF-α (F). Each boxplot represents the median, interquartile range, and individual data points, with outliers indicated by "+" symbols. The x-axis represents individuals with (Yes) and without (No) a history of multiple concussion. Statistical significance was determined using independent t-

tests, with non-significant results labeled as "NS". NfL was decreased in adults with histories of multiple concussions compared to those without ($p < 0.05$). IL-10 and TNF-α levels were elevated in adults with histories of multiple concussions, compared to those without.

3.4.2.1.3 pTau-217 is elevated in people who have experience in contact sports

When separating the group by history of contact sport exposure, adults who had played contact sports had elevated levels of pTau-217 compared to their non-contact sporting counterparts (Figure 3.4, $t(69) = -3.53$, $p = 0.00081$, FDR adjusted $p = 0.016$). There were no other biomarker differences between groups.

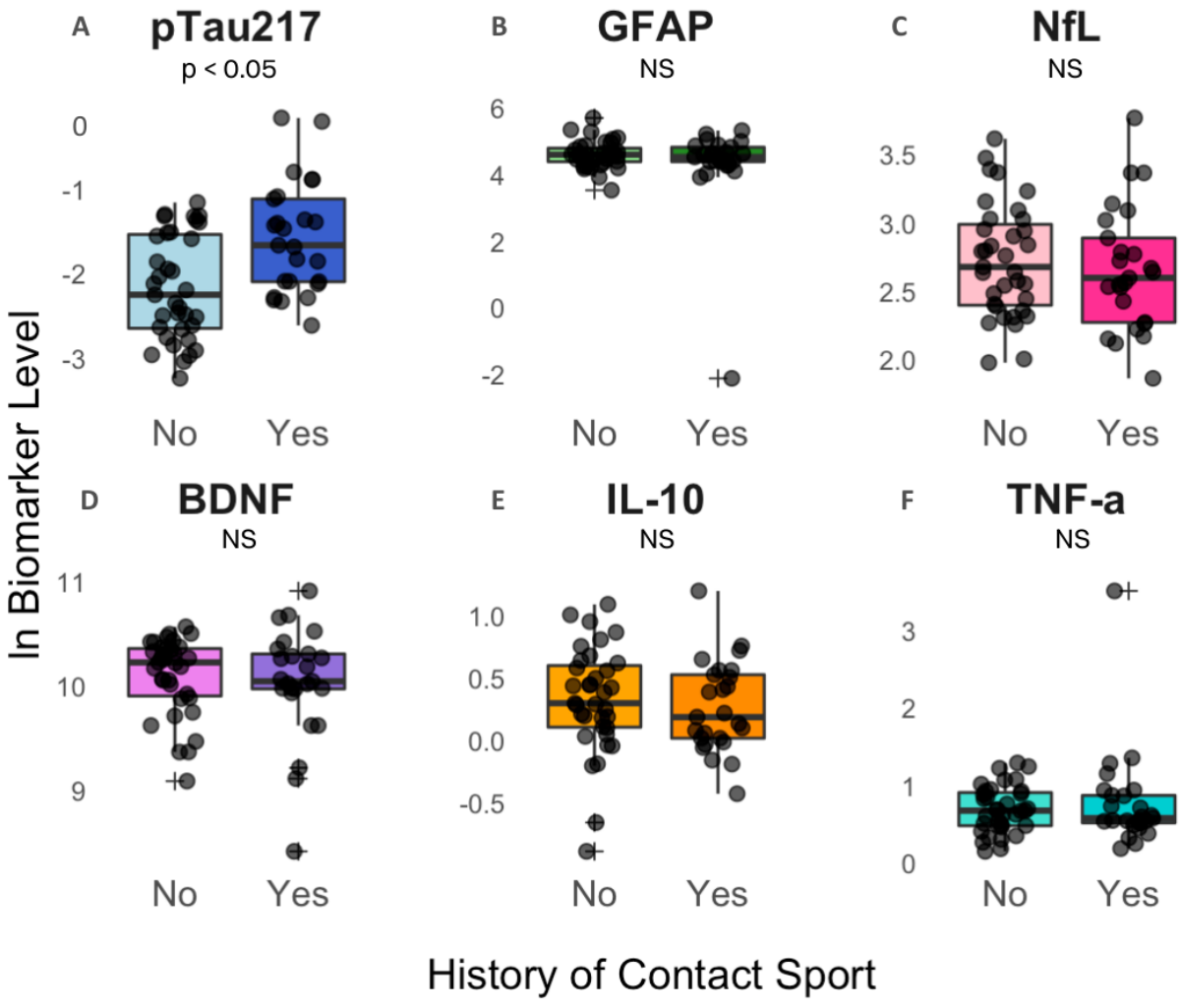


Figure 3.4. *Boxplots showing serum biomarker levels in adults with and without a history of contact sport exposure.*

Biomarkers include pTau-217 (A), GFAP (B), NfL (C), BDNF (D), IL-10 (E), and TNF-α (F). Each boxplot represents the median, interquartile range, and individual data points, with outliers indicated by "+" symbols. The x-axis represents individuals with (Yes) and without (No) a history of contact sport exposure. Statistical significance was determined using independent t-

tests, with non-significant results labeled as "NS". pTau-217 levels were elevated in those with a history of contact sport exposure, compared to adults without.

3.4.2.1.4 Association between serum biomarkers, years of contact sport, time since injury and number of total concussions

We used a series of linear regressions to examine the relationships between years of contact sport participation, time since most recent injury, number of diagnosed concussions, age, and sex with natural log-transformed biomarker concentrations. Age was the strongest predictor associated with NfL ($\beta = 0.0258$, $p < 0.001$), but not with other biomarkers ($p > 0.05$). Years of sport participation was significantly associated with pTau-217 ($\beta = 0.0273$, $p = 0.00965$), but not with other biomarkers. The number of diagnosed concussions was significantly associated with IL-10 ($\beta = 0.0566$, $p = 0.00071$) and GFAP ($\beta = -0.0903$, $p = 0.025$), suggesting potential inflammatory responses. Sex was a significant predictor only for IL-10 ($\beta = -0.2337$, $p = 0.0456$), with males showing lower levels. The models explained 9.0% to 31.3% of the variance in biomarker levels, with the strongest model being for NfL ($R^2 = 0.3132$, $p = 0.0010$). Full models are shown in Table 3.2.

Table 3.2. Linear regression results to predict biomarker levels based on history of concussion metrics. (β, p value).

Biomarker	Years of Contact Sport	Time Since Recent Injury	Number of Total Reported Concussions	Age	Sex	R^2	Model p-value
NfL	(-0.0049, 0.41)	(-0.0009, 0.765)	(0.0038, 0.812)	(0.0258, 4.6e-05)	(-0.16, 0.178)	0.3132	0.001

pTau-217	(0.0273, 0.00965)	(-0.0055, 0.303)	(0.0101, 0.718)	(0.0144, 0.159)	(0.0408, 0.841)	0.213	0.02296
IL-10	(-0.0056, 0.335)	(-4e-05, 0.989)	(0.0566, 0.00071)	(0.0055, 0.336)	(-0.2337, 0.0456)	0.2453	0.0091
TNF-α	(-0.0027, 0.717)	(-0.0052, 0.185)	(0.0385, 0.0642)	(0.0014, 0.853)	(0.0387, 0.794)	0.0901	0.3989
GFAP	(0.0048, 0.737)	(0.0036, 0.632)	(-0.0903, 0.025)	(0.019, 0.186)	(0.1491, 0.602)	0.1708	0.0697
BDNF	(-0.0062, 0.377)	(-0.0044, 0.223)	(0.0054, 0.777)	(0.0005, 0.947)	(0.0737, 0.595)	0.0396	0.8209

3.4.2.2 Diffusion Tensor Imaging

3.4.2.2.1 Adults with diagnosed concussions show regionally specific increased fractional anisotropy compared to adults without

Comparison of factional anisotropy and mean diffusivity values between groups revealed a small region of increased FA in the diagnosed group ($p < 0.05$, controlled for multiple comparisons), however, no differences in MD values. These differences were noted in the left cerebral white matter (MNI152 Coordinates: -16.32, 1.52, 49.79), and along the right fronto-occipital fasciculus (MNI152 Coordinates: 40.72, -33.4, -6.8) (Figure 3.5).

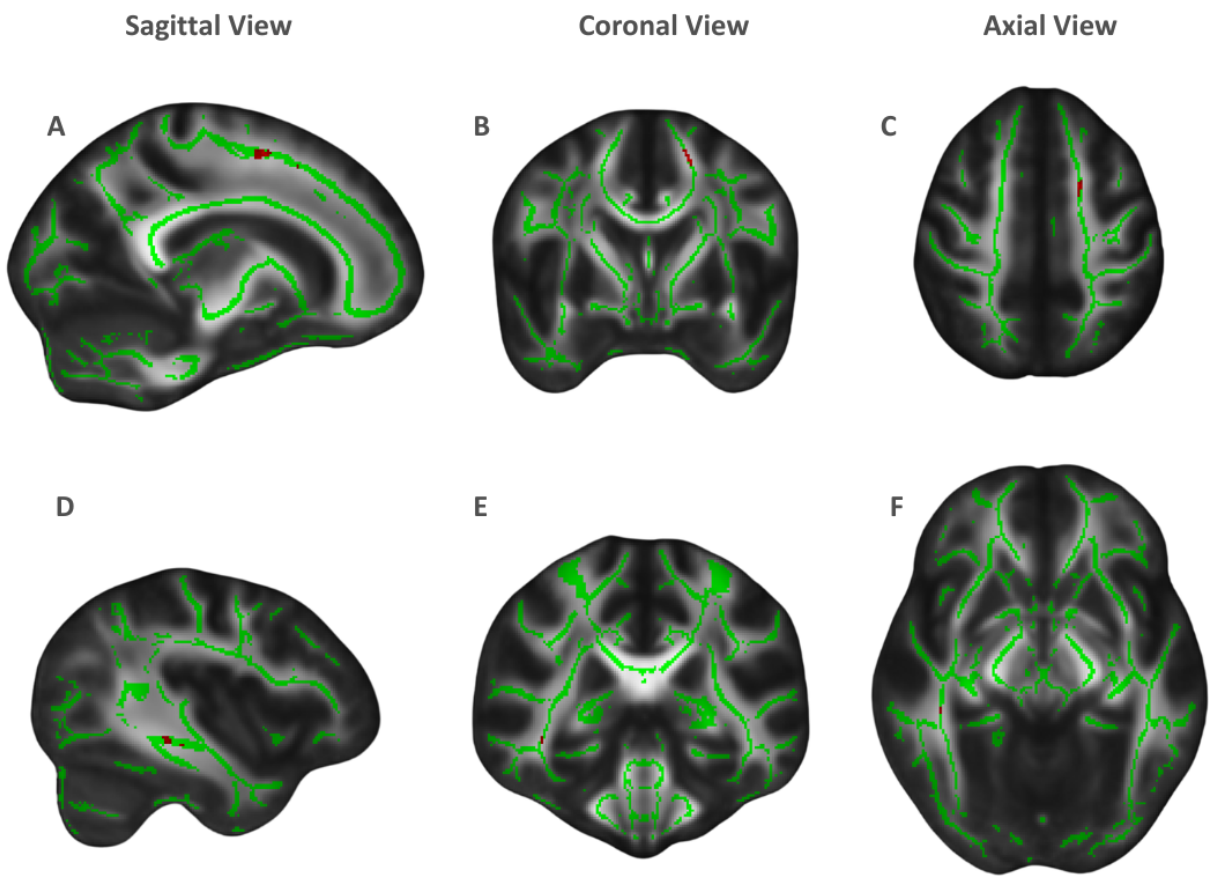


Figure 3.5. *Comparison of fractional anisotropy between adults with and without diagnosed concussions.*

Standardized FRIB58 skeletonized white matter tracts (green) are overlaid on the standardized FMIB58 FA image. Small regions of increased FA in the diagnosed group (red) were identified in the left cerebral white matter (top, MNI152 Coordinates: -16.32, 1.52, 49.79) and along the right fronto-occipital fasciculus (bottom, MNI152 Coordinates: 40.72, -33.4, -6.8). No significant group differences were observed in MD values. Panel labels correspond to different views: (A, D) Sagittal, (B, E) Coronal, and (C, F) Axial.

3.4.2.2.2 History of concussion metrics are not linearly related to FA and MD

A general linear model was applied to assess voxel wise associations across the white matter skeleton. After correcting for multiple comparisons, there were no statistically significant correlations between FA or MD and the history of concussion-based variables.

3.4.2.3 Neuropsychological Testing

3.4.2.3.1 Few differences in cognitive performance across history of concussion metrics

Adults with and without histories of diagnosed concussions performed remarkably similar across the panel of cognitive assessments (Table 3.3). The only group difference observed was on the Verbal Fluency (Animals) Z-score, in which adults with a history of concussion performed worse than the no-injury group ($t(69) = 3.37$, $p = 0.001$, FDR adjusted $p = 0.029$, cohen's $d = 0.81$), there were no statistically significant differences between groups when correcting for multiple comparisons using a false discovery rate correction (Table 3).

Table 3.3. Statistical analysis results for cognitive measures, split between HoC metric.

* indicates statistically significant values after correcting for multiple comparisons.

Variable	**HoC Metric**	t statistic	p value	Cohen's D	p value (FDR)
SDM Oral	Diagnosed Concussions	0.61	0.54	0.15	0.76
SDM Oral Z		0.65	0.52	0.16	0.76
Trails A		-2.42	0.02	-0.58	0.11
Trails A Z		2.62	0.01	0.63	0.11
Trails B		-0.06	0.96	-0.01	0.99
Trails B Z		0.24	0.81	0.06	0.97
MMSE		0.34	0.74	0.08	0.93
Verbal Fluency (F)		0.45	0.65	0.11	0.87
Verbal Fluency (A)		2.18	0.03	0.52	0.16
Verbal Fluency (S)		0.11	0.92	0.03	0.99

Verbal Fluency (FAS)		1.01	0.32	0.24	0.60
Verbal Fluency Repeats		-0.68	0.50	-0.16	0.76
Verbal Fluency FAS Z		1.28	0.21	0.31	0.51
VF Animals		2.45	0.02	0.59	0.11
Verbal Fluency (Animal Repeats)		-1.79	0.08	-0.43	0.27
Verbal Fluency Animal Z		3.37	0.00	0.81	0.02*
Longest Digit Span Forward		1.26	0.21	0.30	0.51
Digit Span Forward Raw		1.72	0.09	0.41	0.27
Longest Digit Span Backward		0.01	0.99	0.00	0.99
Digit Span Backward Raw		-0.11	0.92	-0.03	0.99
Longest Digit Span Sequencing		0.80	0.42	0.19	0.73
Digit Span Sequencing Raw		0.99	0.33	0.24	0.60
Digit Span Total Raw		1.03	0.30	0.25	0.60
Digit Span Scaled Score		1.73	0.09	0.41	0.27
SDM Oral	Reported Concussions	-0.01	0.99	0.00	0.99
SDM Oral Z		0.25	0.80	0.07	0.99
Trails A		-1.13	0.26	-0.30	0.87
Trails A Z		1.36	0.18	0.36	0.87
Trails B		0.69	0.49	0.18	0.87
Trails B Z		-0.06	0.95	-0.02	0.99
MMSE		0.57	0.57	0.15	0.98
Verbal Fluency (F)		-0.05	0.96	-0.01	0.99

Verbal Fluency (A)		1.40	0.17	0.37	0.87
Verbal Fluency (S)		-1.31	0.19	-0.35	0.87
Verbal Fluency (FAS)		-0.03	0.97	-0.01	0.99
Verbal Fluency Repeats		-0.43	0.67	-0.11	0.87
Verbal Fluency FAS Z		0.27	0.78	0.07	0.99
Verbal Fluency (Animals)		0.78	0.44	0.21	0.99
Verbal Fluency (Animal Repeats)		-1.50	0.14	-0.40	0.87
Verbal Fluency Animal Z		1.49	0.14	0.39	0.87
Longest Digit Span Forward		0.85	0.40	0.22	0.87
Digit Span Forward Raw		1.09	0.28	0.29	0.87
Longest Digit Span Backward		0.75	0.46	0.20	0.87
Digit Span Backward Raw		0.67	0.50	0.18	0.87
Longest Digit Span Sequencing		0.52	0.61	0.14	0.87
Digit Span Sequencing Raw		0.93	0.36	0.25	0.99
Digit Span Total Raw		1.11	0.27	0.29	0.87
Digit Span Scaled Score		2.14	0.04	0.57	0.99
SDM Oral	Repeated Concussions	-0.08	0.94	-0.02	0.99
SDM Oral Z		0.01	0.99	0.00	0.99
Trails A		-0.96	0.34	-0.23	0.87
Trails A Z		1.22	0.23	0.29	0.87
Trails B		0.90	0.37	0.21	0.87
Trails B Z		-0.40	0.69	-0.09	0.99

MMSE		0.51	0.61	0.12	0.98
Verbal Fluency (F)		-0.04	0.97	-0.01	0.99
Verbal Fluency (A)		0.92	0.36	0.22	0.87
Verbal Fluency (S)		-1.75	0.08	-0.42	0.87
Verbal Fluency (FAS)		-0.37	0.71	-0.09	0.99
Verbal Fluency Repeats		-0.72	0.47	-0.17	0.87
Verbal Fluency FAS Z		-0.21	0.83	-0.05	0.99
Verbal Fluency (Animals)		-0.01	0.99	0.00	0.99
Verbal Fluency (Animal Repeats)		-1.55	0.12	-0.37	0.87
Verbal Fluency Animal Z		0.90	0.37	0.21	0.87
Longest Digit Span Forward		-1.04	0.30	-0.25	0.87
Digit Span Forward Raw		-0.81	0.42	-0.19	0.87
Longest Digit Span Backward		-1.15	0.25	-0.27	0.87
Digit Span Backward Raw		-1.09	0.28	-0.26	0.87
Longest Digit Span Sequencing		0.67	0.50	0.16	0.87
Digit Span Sequencing Raw		0.33	0.74	0.08	0.99
Digit Span Total Raw		-0.66	0.51	-0.16	0.87
Digit Span Scaled Score		0.12	0.91	0.03	0.99
SDM Oral	Contact Sports	-0.50	0.62	-0.12	0.92
SDM Oral Z		-0.58	0.57	-0.14	0.92
Trails A		0.90	0.37	0.22	0.92
Trails A Z		-0.66	0.51	-0.16	0.92

Trails B	0.06	0.96	0.01	0.96
Trails B Z	0.36	0.72	0.09	0.92
MMSE	-1.42	0.16	-0.34	0.92
Verbal Fluency (F)	0.26	0.79	0.06	0.92
Verbal Fluency (A)	0.83	0.41	0.20	0.92
Verbal Fluency (S)	0.21	0.83	0.05	0.92
Verbal Fluency (FAS)	0.49	0.62	0.12	0.92
Verbal Fluency Repeats	-0.80	0.43	-0.19	0.92
Verbal Fluency FAS Z	0.73	0.47	0.17	0.92
Verbal Fluency (Animals)	0.88	0.38	0.21	0.92
Verbal Fluency (Animal Repeats)	0.14	0.89	0.03	0.93
Verbal Fluency Animal Z	1.00	0.32	0.24	0.92
Longest Digit Span Forward	-1.08	0.28	-0.26	0.92
Digit Span Forward Raw	-0.36	0.72	-0.09	0.92
Longest Digit Span Backward	0.32	0.75	0.08	0.92
Digit Span Backward Raw	0.20	0.84	0.05	0.92
Longest Digit Span Sequencing	1.11	0.27	0.27	0.92
Digit Span Sequencing Raw	1.03	0.31	0.25	0.92
Digit Span Total Raw	0.38	0.71	0.09	0.92
Digit Span Scaled Score	0.97	0.34	0.23	0.92

3.4.3 Multi-modal approach to examine history of concussion metrics

3.4.3.1 Relationship between blood-based biomarkers, neuroimaging and history of concussion

To examine the relationship between DTI and serum biomarkers, we applied a series of general linear models while controlling for the number of total concussions. Results revealed significant negative relationships in FA between pTau-217 throughout the brain, including along the right fronto-occipital fasciculus (MNI58 Coordinates: 36.7, -17.5, -6.63, Figure 3.6), bi-lateral inferior longitudinal fasciculi (MNI58 Coordinates: -20.5/22.1, -58.2, 30.58, Figure 3.6), and the right cingulum (MNI58 Coordinates: 23.01, -43.8, 0.56, Figure 3.6). After controlling for multiple comparisons there was no relationship between pTau-217 and MD.

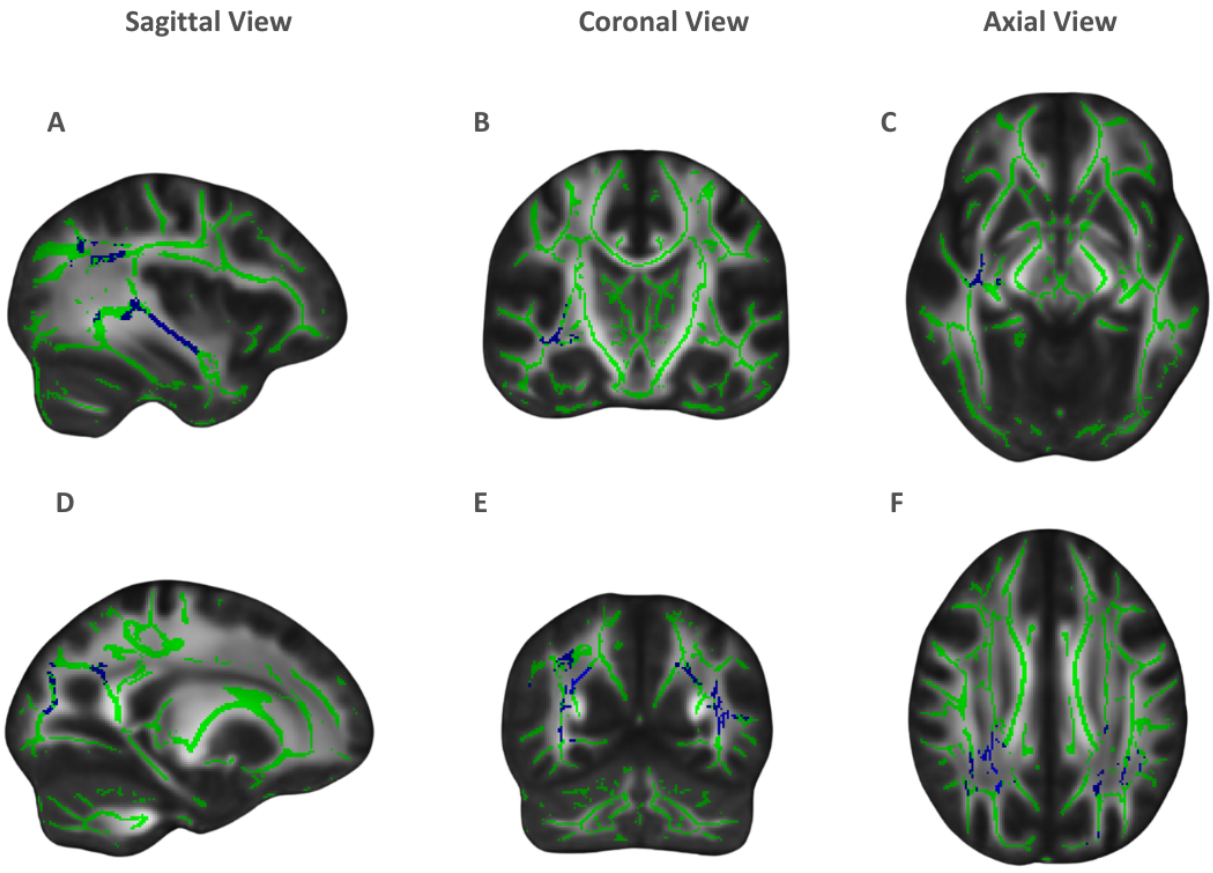


Figure 3.6. *Relationship between pTau-217 and FA in white matter.*

The standardized white matter skeleton (green) is overlaid on the mean FA image, with regions of significant negative associations between pTau-217 and FA, controlled for number of concussions highlighted in blue ($p < 0.05$). Significant clusters were observed along the right fronto-occipital fasciculus (MNI58 Coordinates: 36.7, -17.5, -6.63), bilateral inferior longitudinal fasciculi (MNI58 Coordinates: -20.5/22.1, -58.2, 30.58), and the right cingulum (MNI58 Coordinates: 23.01, -43.8, 0.56). No significant associations were found between pTau-217 and mean diffusivity (MD) after correction for multiple comparisons. Panel labels correspond to different views: (A, D) Sagittal, (B, E) Coronal, and (C, F) Axial.

Significant negative correlations between NfL and FA were observed throughout the brain when controlling for the number of total concussions someone has sustained. Regions of significant association include the anterior thalamic radiation bilaterally (MNI58 Coordinates: -19.63/20.2, 48.6, 8.47, Figure 3.7), the right cingulum (MNI58 Coordinates: 21.1, -35.8, -8.12, Figure 3.7), and the left longitudinal fasciculus (MNI58 Coordinates: -38.9, -3.19, 23.5, Figure 3.7). A statistically significant positive correlation was observed between MD and NfL along the right posterior corona radiata (MNI58 Coordinates: 29.0, -36.4, 19.65, Figure 3.7).

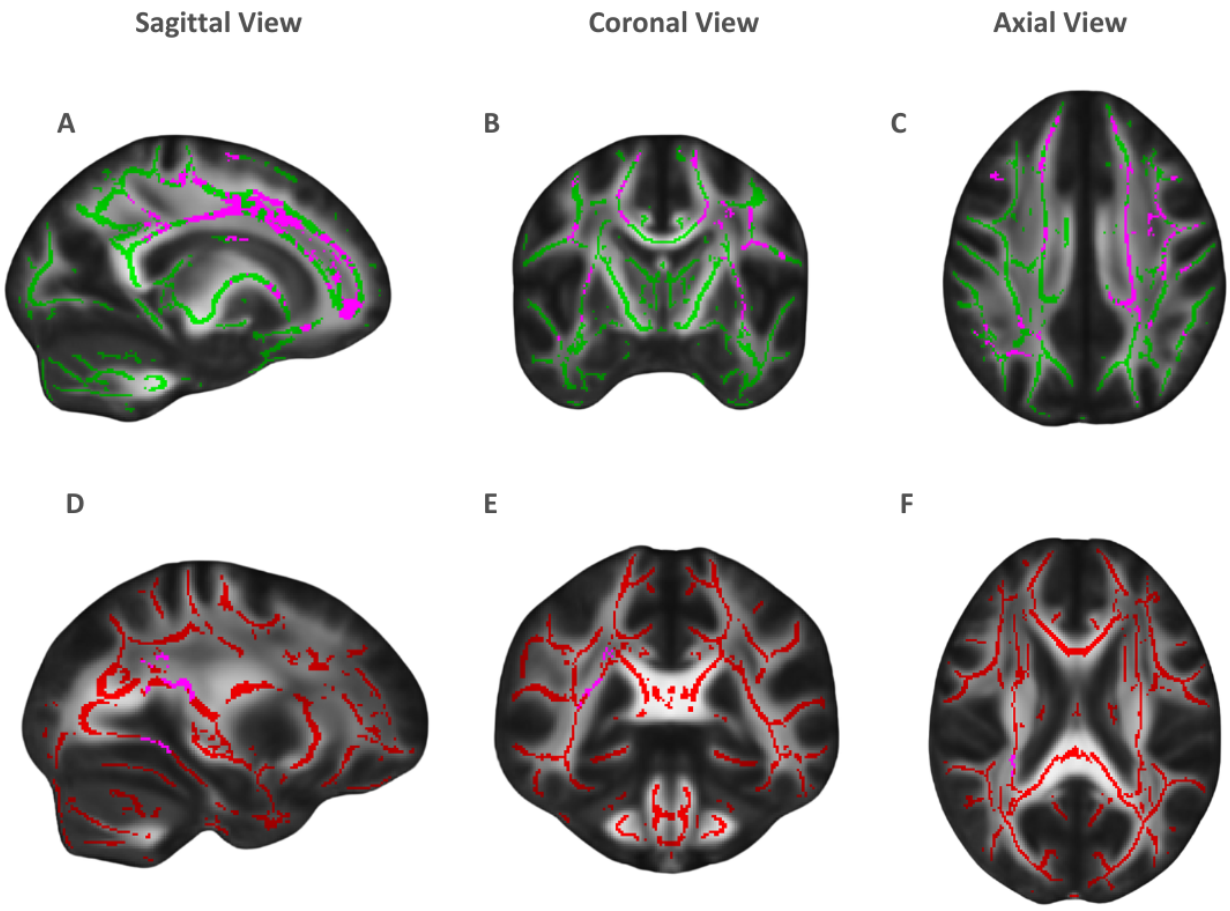


Figure 3.7. *Relationship between NfL and DTI metrics controlled for number of concussions. The top row (A–C) displays the standardized white matter skeleton (green) overlaid on the mean FA image, with regions showing significant associations between NfL and FA highlighted in pink. The bottom row (D–F) shows the same results for mean diffusivity (MD), with the white matter skeleton in red and significant associations also highlighted in pink. Significant negative correlations between NfL and FA were observed throughout the brain, including the anterior thalamic radiation bilaterally (MNI58 Coordinates: -19.63/20.2, 48.6, 8.47), the right cingulum (MNI58 Coordinates: 21.1, -35.8, -8.12), and the left longitudinal fasciculus (MNI58 Coordinates: -38.9, -3.19, 23.5). A statistically significant positive correlation between MD and*

NfL was identified along the right posterior corona radiata (MNI58 Coordinates: 29.0, -36.4, 19.65).

A positive relationship between serum IL-10 and FA was observed when controlling for total number of concussions. Regions of association include the right anterior thalamic radiation, and the forceps minor (MNI58 Coordinates: 19.6, 30.6, 19.3, Figure 3.8). While a negative relationship was observed along the right posterior corona radiata between IL-10 and MD (MNI58 Coordinates: 28.53, -36.9, 20.44, Figure 3.8).

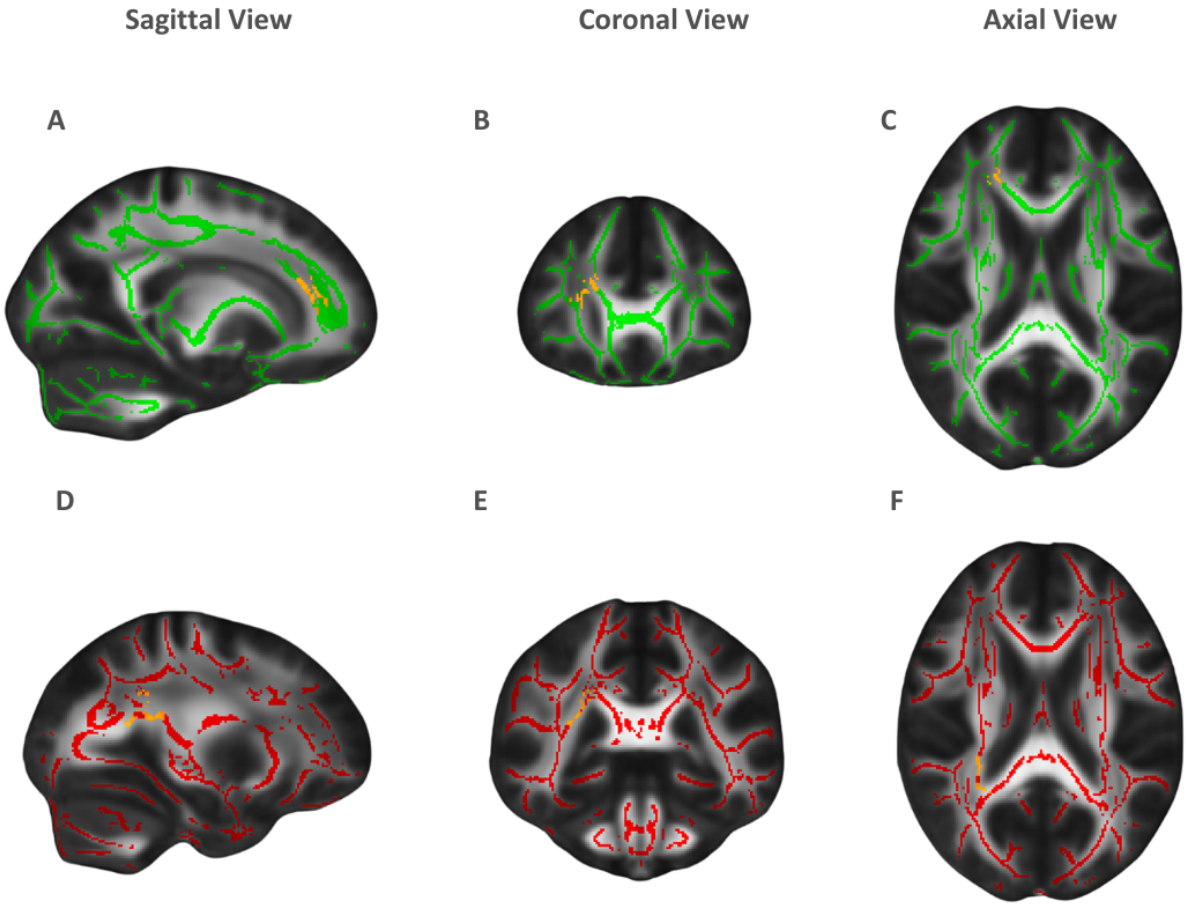


Figure 3.8. *Relationship between serum IL-10 and DTI metrics controlled for number of concussions.*

The top row (A–C) displays the standardized white matter skeleton (green) overlaid on the mean FA image, with significant positive associations between IL-10 and FA highlighted in gold. Significant clusters were observed in the right anterior thalamic radiation and the forceps minor (MNI58 Coordinates: 19.6, 30.6, 19.3). The bottom row (D–F) displays the mean diffusivity (MD) results, with the white matter skeleton in red and regions showing a significant negative relationship between IL-10 and MD highlighted in gold, specifically along the right posterior corona radiata (MNI58 Coordinates: 28.53, -36.9, 20.44).

3.4.3.2 Serum-based biomarkers can predict history of concussion metrics

ROC curves were used to assess the ability of individual and combined biomarkers to predict history of concussion metrics. In all comparisons, the combined model outperformed individual biomarkers, suggesting that a multi-marker approach provides the most robust classification of concussion-related histories. The AUC values were observed in the model to predict a history of multiple concussions (AUC = 0.817), followed by diagnosed concussion (AUC = 0.740), contact sport history (AUC = 0.707), and total reported concussion (AUC = 0.694) (Figure 3.9).

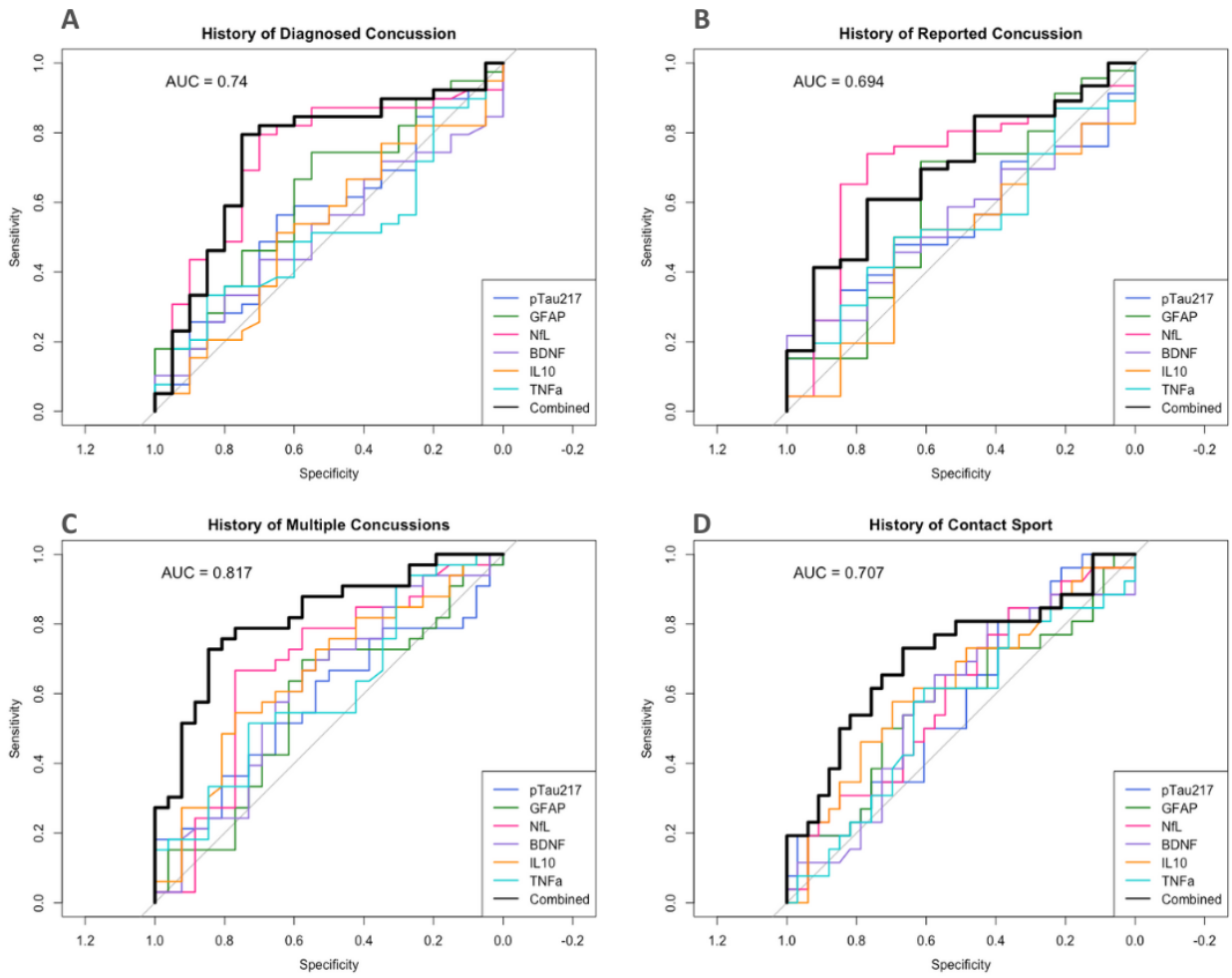


Figure 3.9. *ROC curves for predicting history of concussion metrics using individual serum biomarkers and a combined model.*

(A) History of diagnosed concussion (AUC = 0.74), (B) History of reported concussion (AUC = 0.694), (C) History of multiple concussions (AUC = 0.817), and (D) History of contact sport participation (AUC = 0.707). The combined model (black line) consistently outperforms individual biomarkers, including pTau-217 (blue), GFAP (green), NfL (pink), BDNF (purple), IL-10 (orange), and TNFα (turquoise).

3.4.3.3 NfL levels are associated with cognitive performance and history of concussion metrics

We used linear regression to examine the relationship between plasma biomarkers and cognitive performance while controlling for age. We found NfL levels were associated with verbal fluency performance, and that these relationships differed according to history of concussion (Figure 3.10). When examining how diagnosed concussion history may moderate this relationship a linear regression model controlling for age revealed a significant interaction between log-transformed NfL and concussion history ($\beta = -20.80$, $p = 0.008$). Among participants without a history of diagnosed concussion, higher NfL was associated with better verbal fluency performance ($\beta = 15.15$, $p = 0.028$), while the opposite was observed in those with a diagnosed concussion (Figure 10, panel A). This relationship was also observed for total reported concussions ($p = 0.012$, panel B), and repeated injuries ($p = 0.007$, panel C), but not for history of contact sport ($p = 0.514$, panel D).

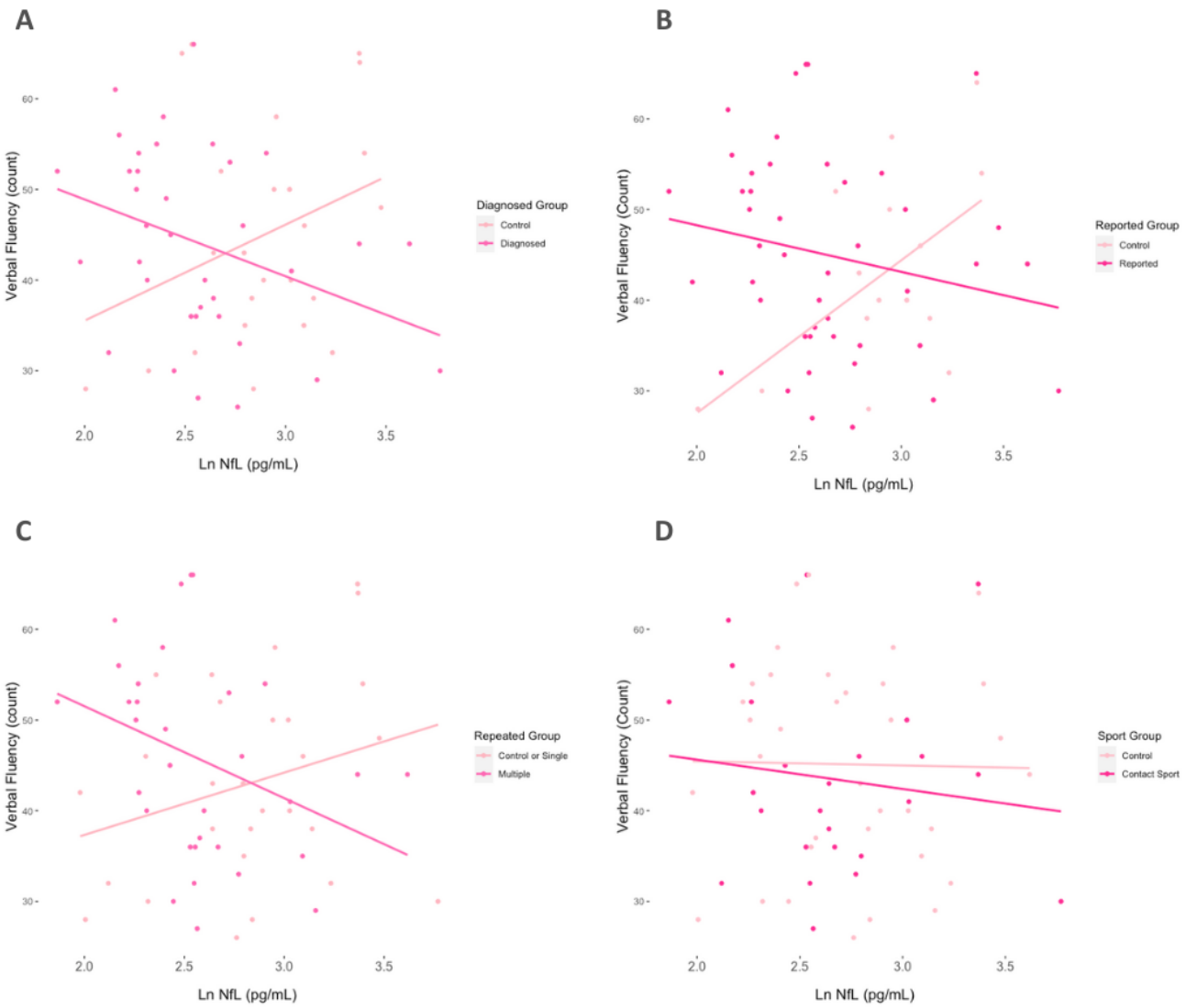


Figure 3.*10.* *Interaction between serum NfL, (natural log-transformed) and history of concussion metrics in predicting verbal fluency (FAS raw scores).*

*Each panel shows a linear regression model controlling for age and examining the interaction between NfL and a history of concussion metric. (A) Diagnosed concussion history (*p = *0.008), (B) Total reported concussions (*p = *0.012), (C) Repeated concussions (*p = *0.007), and (D) History of contact sport (*p = *0.514). The significant interaction in panels A, B and C indicate that NfL is positively associated with verbal fluency in the control groupings (light pink) but*

negatively associated in the concussion metric groupings (dark pink). No interaction was observed for contact sport history.

3.5 Discussion

This study investigated the long-term effects of concussion in aging adults using a multimodal approach, including neuroimaging, cognitive testing, and blood-based biomarkers. While traditional single-modality analyses revealed few significant group differences, several interrelated findings emerged when examining the interactions between modalities, providing novel insight into the subtle, lingering effects of concussion in later life.

3.5.1 Unexpected and emerging serum biomarker patterns for long-term concussion effects

One of the most striking and initially counterintuitive findings was that NfL levels were elevated in participants without any history of concussion, across both diagnosed and self-reported metrics. Given that NfL is a well-established marker of axonal injury,[15] this pattern contradicts the expectation that NfL would be higher in individuals with a history of concussions, and patterns that have been seen in more severe injuries.[16] In contrast to NfL, elevated pTau-217 levels were observed in participants with a history of contact sport, aligning with previous work suggesting a link between repeated head impacts and Alzheimer's-related tau pathology.[17] This finding was also reflected in linear regression models, where years of contact sport predicted pTau-217 levels, independent of age. Interestingly, pTau-217 levels showed a negative correlation with FA in key white matter tracts, including the right fronto-occipital fasciculus and bilateral inferior longitudinal fasciculi, suggesting a potential pathway by which tau-related pathology might translate into subtle microstructural changes. These results suggest that contact sport exposure may prime a cascade involving tau dysregulation and white matter degradation, even in the absence of overt cognitive symptoms.

The finding that IL-10 was elevated in participants with repeated concussions suggests a possible compensatory anti-inflammatory response. Notably, higher serum IL-10 levels were associated with increased FA and decreased MD in specific tracts, including the anterior thalamic radiation and forceps minor. These results mirror associations between inflammatory markers and white matter integrity that have been noted in other neurological conditions including depression and schizophrenia.[18,19] These results may indicate that anti-inflammatory cytokines like IL-10 could play a neuroprotective or modulatory role, possibly mitigating some of the structural consequences of repeated head trauma. However, given IL-10's context-dependent effects, further work is needed to determine whether this reflects resilience or ongoing immune dysregulation.

3.5.2 Linking microstructural alterations to serum biomarkers of injury

While no widespread group differences in DTI metrics were found, adults with a diagnosed concussion history exhibited small, localized increases in FA. Although increased FA is traditionally interpreted as indicating better white matter integrity, in post-injury contexts it may instead reflect glial scarring, remyelination, or restricted extracellular space due to axonal compaction.[20] A recent meta-analysis of four studies exploring long-term white matter changes after concussion identified multiple regions of increased FA in months and years following concussions, however, this meta-analysis focussed on sport related injury, and a majority of studies focussed on young adults.[21] In the present study, the regions showing increased FA, specifically the left cerebral white matter and right fronto-occipital fasciculus, partially overlapped with regions showing negative associations between FA and both pTau-217 and NfL, suggesting a spatial convergence between biochemical and structural signals of injury. This

raises the possibility that increased FA in this context may mark areas of long-term neurobiological reorganization following concussion.

3.5.3 Opposing NfL-cognition associations in individuals with and without concussion history

Cognitive performance showed few between-group differences, apart from verbal fluency standardized scores in the animals subcategory. However, differences were revealed when examining biomarker interactions. Specifically, NfL was positively associated with verbal fluency in controls, but negatively associated with performance in individuals with concussion history. This interaction, consistent across several concussion metrics (diagnosed, total, repeated), suggests that NfL may serve as a marker of neurodegeneration in the context of prior brain injury, further, these findings are consistent with other studies examining the association between NfL and cognition.[22,23]

3.5.4 Neurofilament light may connect multimodal metrics

The unexpected finding that adults with concussions have lower serum NfL compared to controls could reflect long-term neuroprotective adaptations or "preconditioning" effects triggered by the past injury. One hypothesis is that a mild brain injury engages compensatory mechanisms that confer resilience against ongoing age-related axonal degeneration. This idea parallels the phenomenon of ischemic preconditioning, where brief events such as transient ischemic attacks can induce tolerance to subsequent strokes.[24] Over time, the injured brain may undergo remodeling, pruning the most vulnerable axons and reinforcing more resilient neural pathways, potentially accompanied by a chronic downregulation of neuroinflammatory activity. Similar to how a mild inflammatory challenge (*e.g.* low-dose lipopolysaccharide) can dampen later neuroinflammatory responses, a prior concussion might recalibrate the brain's environment,

reducing baseline axonal turnover and NfL release.[24,25] Such altered axonal vulnerability due to long-term remodeling could explain why NfL levels were lower, in people with histories of one concussion (diagnosed or suspected), but not in those with multiple concussions. Conversely, within the concussion subgroupings those with higher NfL appear to be individuals in whom these potentially protective adaptations are incomplete or failing. Higher serum NfL levels in the concussion groupings were linked to worse cognitive performance, specifically poorer verbal fluency, and to white matter abnormalities (decreased FA and increased MD in multiple tracts). This pattern aligns with current literature showing that elevated NfL generally signifies ongoing neuroaxonal damage that correlates with cognitive deficits and loss of white matter integrity in aging and neurodegeneration.[26–28] In other words, concussion survivors who have not achieved the proposed compensatory remodeling exhibit a biomarker profile (*i.e.* higher serum NfL) indicative of continued axonal breakdown, which manifests as poorer cognition and microstructural degeneration on DTI. Taken together, these observations support a model in which a remote concussion can set in motion dual outcomes: in some older individuals it induces a lasting neuroprotective state (evidenced by low NfL and preserved function), while in others it leaves a legacy of heightened vulnerability (evidenced by high NfL, white matter damage, and poorer cognitive performance). This could be viewed as a balance between compensatory neuroplastic changes and chronic neuropathological processes. Future studies could explore whether the "preconditioned" low-NfL state reflects reduced neuroinflammatory signaling or other protective modifications, and why certain concussion survivors escape long-term axonal injury whereas others progress to deficits.

3.5.5 Clinical implications for multimodal research

Together, these findings support the utility of a multimodal approach in uncovering subtle, long-term effects of concussion that may not be evident in any one domain. The convergence between serum biomarkers like pTau-217, NfL and Il-10 and white matter degradation and the interaction between NfL and cognitive outcomes, point toward a network of compensatory and degenerative processes that are partially modulated by injury history. Importantly, these relationships may only be detectable through integrated analyses that span biological, structural, and functional domains. These results have potential clinical relevance for monitoring aging adults with past concussion and contact sport exposure. While overt cognitive decline may not yet be present, subclinical biomarker and white matter changes may foreshadow future vulnerability, warranting early preventive or neuroprotective interventions.

3.6 Limitations and future directions

While this study supports the notion of long-term effects of concussions, it has several limitations. The sample size is small with only 71 adults taking part. Based on these numbers, at present we are only able to detect large effect sizes which increases the risk for Type II errors, meaning that subtle differences may have been missed. The exploratory nature of the study led to a grouping strategy based on four different metrics of concussion history. While this approach allowed exploration of risk factors, it created overlapping groups. This design means someone with a real but undiagnosed concussion could be classified as a 'control' in some analyses (*e.g.,* in the 'diagnosed concussion' group), potentially confounding the between-group effects. Future research with larger cohorts is needed to power comparisons between more discrete groups, such as a 'no injury' group versus 'suspected injury' and 'diagnosed injury' groups. Further, while we included sex and time since injury as predictors in the regression analysis, several confounding variables were unexplored. These include genetic predispositions, such as APOE status, which is

a known risk factor for both dementia and potentially worse outcomes after TBI. Further, detailed lifestyle factors such as diet, exercise, smoking, and alcohol use were not accounted for and could act as significant confounders. Another consideration is that the primary exposure, a history of concussion, was assessed via self-report during an intake interview. This method is subject to recall bias, as participants were asked to remember injuries that may have occurred decades prior. Despite these challenges, this study provides the first steps in the right direction for analysing long term effects of concussions.

3.7 Conclusions

This study demonstrates how a multimodal approach can provide insight into the subtle, long-term effects of concussion in aging adults. While traditional single-modality comparisons revealed few between-group differences, integrated analyses across blood-based biomarkers, neuroimaging, and cognition revealed distinct signatures associated with concussion history. Patterns of altered NfL, pTau-217, and white matter microstructure suggest that concussion may trigger long-lasting changes in neural integrity, and that these may not be uniformly pathological. This paper highlights the need for individualized, longitudinal monitoring in older adults with past concussions. Future work should explore whether these biomarker and imaging profiles can predict cognitive trajectories or serve as early indicators of neurodegenerative risk.

3.7 Chapter 3 References

1. Gardner RC, Yaffe K. Epidemiology of mild traumatic brain injury and neurodegenerative disease. Mol Cell Neurosci 2015;66(Pt B):75–80; doi: 10.1016/j.mcn.2015.03.001.

2. Cassidy JD, Carroll LJ, Peloso PM, et al. Incidence, risk factors and prevention of mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. J Rehabil Med 2004;(43 Suppl):28–60; doi: 10.1080/16501960410023732.

3. Thompson HJ, McCormick WC, Kagan SH. Traumatic Brain Injury in Older Adults: Epidemiology, Outcomes, and Future Implications. J Am Geriatr Soc 2006;54(10):1590–1595; doi: 10.1111/j.1532-5415.2006.00894.x.

4. Langer L, Levy C, Bayley M. Increasing Incidence of Concussion: True Epidemic or Better Recognition? The Journal of Head Trauma Rehabilitation 2020;35(1):E60; doi: 10.1097/HTR.0000000000000503.

5. Broglio SP, Puetz TW. The effect of sport concussion on neurocognitive function, self-report symptoms and postural control : a meta-analysis. Sports Med 2008;38(1):53–67; doi: 10.2165/00007256-200838010-00005.

6. Henry LC, Elbin RJ, Collins MW, et al. Examining Recovery Trajectories After Sport-Related Concussion With a Multimodal Clinical Assessment Approach. Neurosurgery 2016;78(2):232–241; doi: 10.1227/NEU.0000000000001041.

7. Collins MW, Grindel SH, Lovell MR, et al. Relationship between concussion and neuropsychological performance in college football players. JAMA 1999;282(10):964–970; doi: 10.1001/jama.282.10.964.

8. June D, Williams OA, Huang C-W, et al. Lasting consequences of concussion on the aging brain: Findings from the Baltimore Longitudinal Study of Aging. Neuroimage 2020;221:117182; doi: 10.1016/j.neuroimage.2020.117182.

9. Mavroudis I, Kazis D, Petridis FE, et al. The Association Between Traumatic Brain Injury and the Risk of Cognitive Decline: An Umbrella Systematic Review and Meta-Analysis. Brain Sciences 2024;14(12):1188; doi: 10.3390/brainsci14121188.

10. Snowden TM, Hinde AK, Reid HMO, et al. Does Mild Traumatic Brain Injury Increase the Risk for Dementia? A Systematic Review and Meta-Analysis. J Alzheimers Dis 2020;78(2):757–775; doi: 10.3233/JAD-200662.

11. Wilke S, Prehn K, Taud B, et al. Multimodal Assessment of Recurrent MTBI across the Lifespan. J Clin Med 2018;7(5):95; doi: 10.3390/jcm7050095.

12. Asken BM, DeKosky ST, Clugston JR, et al. Diffusion tensor imaging (DTI) findings in adult civilian, military, and sport-related mild traumatic brain injury (mTBI): a systematic critical review. Brain Imaging and Behavior 2018;12(2):585–612; doi: 10.1007/s11682-017-9708-9.

13. Kontos AP, Sufrinko A, Womble M, et al. Neuropsychological Assessment Following Concussion: an Evidence-Based Review of the Role of Neuropsychological Assessment Pre-

and Post-Concussion. Curr Pain Headache Rep 2016;20(6):38; doi: 10.1007/s11916-016-0571-y.

14. Newcombe VFJ, Ashton NJ, Posti JP, et al. Post-acute blood biomarkers and disease progression in traumatic brain injury. Brain 2022;145(6):2064–2076; doi: 10.1093/brain/awac126.

15. Shahim P, Politis A, van der Merwe A, et al. Neurofilament light as a biomarker in traumatic brain injury. Neurology 2020;95(6):e610–e622; doi: 10.1212/WNL.0000000000009983.

16. Spitz G, Hicks AJ, McDonald SJ, et al. Plasma biomarkers in chronic single moderate–severe traumatic brain injury. Brain 2024;147(11):3690–3701; doi: 10.1093/brain/awae255.

17. Vasilevskaya A, Taghdiri F, Multani N, et al. Tau-PET in retired contact sport athletes. Alzheimer's & Dementia 2023;19(S3):e067743; doi: 10.1002/alz.067743.

18. Sammer G, Neumann E, Blecker C, et al. Fractional anisotropy and peripheral cytokine concentrations in outpatients with depressive episode: a diffusion tensor imaging observational study. Sci Rep 2022;12(1):17450; doi: 10.1038/s41598-022-22437-0.

19. Fu G, Zhang W, Dai J, et al. Increased Peripheral Interleukin 10 Relate to White Matter Integrity in Schizophrenia. Front Neurosci 2019;13; doi: 10.3389/fnins.2019.00052.

20. Budde MD, Janes L, Gold E, et al. The contribution of gliosis to diffusion tensor anisotropy and tractography following traumatic brain injury: validation in the rat using Fourier analysis of stained tissue sections. Brain 2011;134(8):2248–2260; doi: 10.1093/brain/awr161.

21. Hellewell SC, Nguyen VPB, Jayasena RN, et al. Characteristic patterns of white matter tract injury in sport-related concussion: An image based meta-analysis. NeuroImage: Clinical 2020;26:102253; doi: 10.1016/j.nicl.2020.102253.

22. Dhana A, DeCarli C, Dhana K, et al. White matter hyperintensity, neurofilament light chain, and cognitive decline. Ann Clin Transl Neurol 2022;10(3):321–327; doi: 10.1002/acn3.51720.

23. Ramani S, Berard JA, Walker LAS. The relationship between neurofilament light chain and cognition in neurological disorders: A scoping review. Journal of the Neurological Sciences 2021;420:117229; doi: 10.1016/j.jns.2020.117229.

24. Stetler RA, Leak RK, Gan Y, et al. Preconditioning Provides Neuroprotection in Models of CNS Disease: Paradigms and Clinical Significance. Prog Neurobiol 2014;0:58–83; doi: 10.1016/j.pneurobio.2013.11.005.

25. Mizobuchi H, Soma G-I. Low-dose lipopolysaccharide as an immune regulator for homeostasis maintenance in the central nervous system through transformation to neuroprotective microglia. Neural Regen Res 2021;16(10):1928–1934; doi: 10.4103/1673-5374.308067.

26. Desai P, Dhana K, DeCarli C, et al. Examination of Neurofilament Light Chain Serum Concentrations, Physical Activity, and Cognitive Decline in Older Adults. JAMA Netw Open 2022;5(3):e223596; doi: 10.1001/jamanetworkopen.2022.3596.

27. Schultz SA, Strain JF, Adedokun A, et al. Serum neurofilament light chain levels are associated with white matter integrity in autosomal dominant Alzheimer's disease. Neurobiology of Disease 2020;142:104960; doi: 10.1016/j.nbd.2020.104960.

28. Saraste M, Bezukladova S, Matilainen M, et al. High serum neurofilament associates with diffuse white matter damage in MS. Neurol Neuroimmunol Neuroinflamm 2020;8(1):e926; doi: 10.1212/NXI.0000000000000926.

Chapter 4

Prevention: Three-Dimensional Multiple Object Tracking to Improve Brain Health in Adults over age 50

4.1 Abstract

4.1.1 Background:

Computerized cognitive training, such as three-dimensional multiple object tracking (3D-MOT), using NeuroTracker, has shown promise in enhancing cognitive performance in aging populations. However, the neurobiological mechanisms supporting these effects, particularly in relation to cognitive and structural outcomes, remain underexplored.

4.1.2 Methods:

Forty-four older adults were randomized to a 12-week 3D-MOT training group or a waitlist control group. Training involved twice-weekly sessions using the NeuroTracker CORE protocol. Pre- and post-intervention assessments included standardized neuropsychological assessments, diffusion tensor imaging and serum analysis of biomarkers. Data were analyzed using repeated-measures ANOVA, voxel-wise paired t-tests, estimation statistics, and exploratory linear modeling.

4.1.3 Results:

Participants in the intervention group exhibited high adherence and improved in-task performance throughout NeuroTracker training. A significant increase in serum BDNF was observed in the intervention group (mean difference = 9540 pg/mL (95% confidence interval: 3,670, 15,400)), while the control group showed no change. No significant improvements in

neuropsychological performance or DTI metrics were detected in the intervention group compared to controls. Exploratory analysis revealed a significant reduction in repetition errors on verbal fluency tasks among participants with a history of concussion following training.

4.1.4 Conclusions:

3D-MOT training may enhance neurotrophic support in older adults, as evidenced by increased BDNF, even in the absence of measurable cognitive or structural brain changes. Exploratory findings suggest potential benefits for individuals with a history of concussion. Future research should explore optimal training doses, include active control conditions, and investigate long-term and subgroup-specific outcomes.

Keywords:

NeuroTracker, 3D-MOT, aging, BDNF, cognitive training, concussion, diffusion tensor imaging, white matter, neuroplasticity

4.2 Introduction

As the global population ages, preserving cognitive function and preventing neurodegenerative decline have become pressing public health goals.[1] Cognitive functions naturally decline as we age, with some functions declining as early as late twenties and early thirties.[2,3] Early interventions that strengthen cognitive reserve are especially important for adults over 50, when subtle age-related cognitive changes can become more noticeable. Various approaches to enhance cognition, from puzzle games and music therapy to healthy lifestyle changes, have been explored, but their real-world benefits tend to be modest and context-dependent.[4,5]

In recent years, computerized cognitive training has gained traction as an accessible strategy for promoting brain health in aging. One promising tool is three-dimensional multiple object tracking (3D-MOT), which engages users in tracking several moving targets in a dynamic 3D space. This task requires the integration of multiple cognitive domains including attention, working memory, and processing speed.[6] The high attentional load and multitasking nature of 3D-MOT create a rich environment that may translate to improved everyday cognitive function. Prior studies suggests that 3D-MOT training can yield cognitive benefits for older adults. For example, after training on a 3D-MOT task, older adults improved their in-task performance to the point that their in-task learning rate matched that of younger adults.[7] Such findings indicate that age-related cognitive slowing can be mitigated through intensive perceptual-cognitive exercise. Beyond improvements on the training task itself, transfer to standard cognitive measures has been reported. For example, one study in healthy older individuals found that an 8-week 3D-MOT training regimen led to significantly better performance in selective attention, cognitive flexibility, and psychomotor speed compared to a no-training control group.[8] Similarly, Musteata et al. (2019) reported that older adults with subjective cognitive decline showed notable

gains in memory and executive function after 14 sessions of NeuroTracker training, relative to controls.[9] In that study, the training group improved on tests of verbal memory and a set-shifting task, suggesting enhancement of both memory and cognitive flexibility. Although further validation is needed, these early findings position 3D-MOT as a compelling tool to support cognitive resilience in aging populations.

A key advantage of 3D-MOT training is its scalability and accessibility, which make it suitable as an early intervention. Recently it has been demonstrated that NeuroTracker training can be effectively delivered in a home setting to older adults.[6] In a feasibility study, participants over 60 years old used an at-home 3D-MOT setup (with simple 3D glasses and a laptop) twice weekly for five weeks. The at-home trainees exhibited high adherence (~90% session completion) and significant improvements in tracking performance across sessions, comparable to those of an in-lab training group.[6] This convergence of at-home and laboratory results suggests that 3D-MOT is not only efficacious but also logistically feasible for widespread use. The ability to engage in NeuroTracker training at home, without specialized equipment means that older adults can access this cognitive exercise early and regularly. By lowering barriers to participation, interventions can reach broader segments of the aging population, including those who have mobility limitations or live in remote areas.[10]

Previous studies on 3D-MOT have mainly used neuropsychological tests, task-specific performance and electroencephalograms as outcome measures.[7–9,11] At this point, no studies have examined structural or biological changes that may be induced following a period of 3D-MOT training. Diffusion tensor imaging (DTI) metrics, specifically fractional anisotropy (FA) and mean diffusivity (MD), can be used as indicators of white matter microstructural integrity.[12] These measures are sensitive to age-related neural changes and plasticity,[12] and there is evidence

that intensive cognitive training can slow white matter degradation in older adults over a one year period.[13] Further, shorter-term interventions have shown transient improvements in white matter metrics. One study observed a decrease in hippocampal MD after a 4-month spatial navigation training,[14] while another found increased FA in the corpus callosum following just a month of intensive reasoning practice.[15] Although these initial changes faded after training stopped,[14] they demonstrate that the aged brain retains a degree of white matter plasticity**.** Blood-based biomarkers can provide a minimally invasive route to investigate biological mechanisms associated with cognitive and structural changes. The process of learning is thought to be underpinned by the processes of neuroplasticity.[16] Brain Derived Neurotrophic Factor (BDNF) is a neuron-growth factor that supports neuroplasticity by promoting synaptic growth, neuronal survival, and modulating cortical thickness.[17] Previous studies have found the BDNF levels modulate the cognitive effects seen in cognitive training,[18] however, this has yet to be tested specifically in 3D-MOT.

Concussions, a type of mild traumatic brain injury (mTBI), are characterized by transient alterations in neurological function following biomechanical force to the head, typically without overt structural damage detectable on conventional imaging.[19] Despite the typically transient symptoms, a substantial body of evidence indicates that concussions can have persistent long-term effects.[20–22] Recent findings using NeuroTracker demonstrate that 3D-MOT performance can be impaired long after a concussion, especially in older adults.[23] Given these findings, an exploratory aim of this study is to examine the role of prior concussions in modulating the efficacy of 3D-MOT in middle and older-aged adults.

4.3 Methods

4.3.1 Ethical considerations

The study received ethical approval from the University of Victoria Human Research Ethics Board (protocol #21-0591). Written informed consent was obtained from all participants prior to enrollment, with verbal consent reaffirmed at each appointment.

4.3.2 Study population

Participants were recruited between May 2022 and March 2025 through community posters, word-of-mouth referrals, and the REACH BC platform. Individuals who expressed interest were provided with study eligibility details, and those meeting inclusion criteria were invited to schedule an intake appointment. Eligibility criteria included being between 50 and 90 years of age, having normal or corrected-to-normal vision, no diagnosis of a neurodegenerative condition (e.g., dementia, subjective cognitive decline), and the ability to attend appointments at the University of Victoria for blood collection and at West Coast Medical Imaging for MRI scanning. For participants with a history of concussion, eligibility required that the injury occurred more than one year prior to enrollment to allow assessment of long-term effects. Exclusion criteria for the MRI component included the presence of certain medical implants (*e.g.*, pacemakers, cochlear implants, surgically implanted metal hardware), metallic foreign bodies (*e.g.*, shrapnel, bullet fragments), specific dental materials (*e.g.*, magnet-retained prostheses, extensive metal dental work), and some tattoos or piercings. Individuals who did not meet the MRI eligibility criteria were still allowed to participate in the broader study but were not scanned.

4.3.3 Study design

This study was conducted as a pilot randomized controlled trial. Following the provision of informed consent, eligible participants were randomly assigned in a 1:1 ratio to either the 12-week 3D-MOT intervention group or the waitlist control group. Randomization was performed

using a simple, computer-generated sequence that was created prior to participant enrollment. To prevent selection bias, allocation concealment was maintained throughout the recruitment process; the research staff responsible for enrolling participants were unaware of the upcoming group assignments in the sequence.

4.3.4 Intake interview

Interested participants were scheduled for an intake interview, which could be conducted via an online platform (e.g., Zoom), by phone, or in person, according to their preference. After consenting to the study, a research assistant collected general demographic information, as well as details regarding concussion history, sports participation, and educational background.

4.3.5 Neuropsychological assessment

Neuropsychological assessments were administered remotely via Zoom for all participants. For individuals without access to a computer and webcam at home, in-lab accommodations were provided using university equipment; however, all assessments remained virtual. Assessments were conducted by graduate students in the Neuropsychology stream of the Clinical Psychology program at the University of Victoria. The standardized battery included tests of verbal fluency (FAS and Animals), verbal learning and memory (California Verbal Learning Test–Second Edition; CVLT-II), working memory and processing speed (Digit Span; Symbol Digit Modalities Test, SDMT), executive function (Trail Making Test Parts A and B), and global cognitive function (Mini-Mental State Examination, MMSE). Verbal instructions were given before each task, and participants were permitted to take breaks as needed. Each session lasted approximately one hour. Data were recorded on paper and digitized into password-protected files for analysis.

4.3.6 Serum collection

Venous blood samples were collected by trained team members certified in phlebotomy. Blood was collected using a serum separator tube vacutainer system and a 21- or 23-gauge butterfly needle. Team members prioritized the median cubital vein, with the cephalic or basilic veins used as alternatives when necessary. The puncture site was disinfected with a 70% isopropyl alcohol wipe prior to collection. Up to 60 mL of blood was drawn into vacutainer tubes, which were inverted 10 times and left to clot at room temperature for 30 minutes before centrifugation at 1500 × g for 10 minutes. Serum aliquots were processed in a biosafety level 2 laboratory and stored at –80°C for analysis.

4.3.7 Serum analysis

Serum biomarker analysis was performed using the Single Molecule Array (Simoa) HD-X platform. The Neurology 2-Plex assay was used to quantify neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP), yielding coefficients of variation (CV) of 4.1% (between-plate CV: 8.6%) for NfL and 2.4% (between-plate CV: 16.7%) for GFAP. Additional biomarkers including phosphorylated tau 217 (pTau-217), brain-derived neurotrophic factor (BDNF), interleukin-10 (IL-10), and tumor necrosis factor-alpha (TNF-α) were assessed in duplicate using single-plex assays. For IL-10, the average within-sample CV was 6.8%, with between-plate variability of 29.1%. The pTau-217 assay exhibited a within-sample CV of 11.0% and a between-plate CV of 31.1%. BDNF showed a within-sample CV of 3.6% and between-plate variability of 10.7%, while TNF-α had a within-sample CV of 8.7% and a between-plate CV of 17.4%.

4.3.8 Imaging data acquisition

DTI data were acquired at West Coast Medical Imaging by a certified MRI technician in coordination with a member of the research team. Scanning parameters included a repetition time

(TR) of 8000 ms, echo time (TE) of 101 ms, a 90° flip angle, 52 axial slices, and a voxel resolution of 1.4 × 1.4 × 2.0 mm. Each scan consisted of 48 images: 45 diffusion-weighted volumes (b = 1000 s/mm²) and 3 non-diffusion-weighted (b = 0 s/mm²) baseline images. DTI acquisition lasted approximately 6 minutes, with the full MRI session totaling around 30 minutes.

4.3.9 Intervention and waitlist control

Participants in the intervention group completed at-home cognitive training using the NeuroTracker CORE program over a 12-week period. Training was conducted twice per week, for a total of 24 training days. This protocol was adapted from Snowden et al. (2023), who demonstrated the feasibility of remote 3D-MOT training in older adults.[6] Participants accessed the NeuroTracker software using personal computers or laptops and red-blue anaglyph glasses provided by the research team. Participants were allowed to borrow equipment from the research team if they did not have access to a computer or 20-24" monitor. Each CORE session lasted approximately seven minutes and involved tracking multiple moving spheres in a 3D virtual space while seated in a distraction-free environment. Participants were instructed to complete three CORE sessions per training day, equating to about 21 minutes of training. The program uses a staircase method to adjust task difficulty in real time by increasing or decreasing the speed of object motion based on participant performance. Prior to beginning the training schedule, all participants completed a familiarization session to ensure comfort with the software interface and testing protocol. Progress was monitored remotely through the NeuroTracker platform, and participants received weekly check-ins from the research team to support adherence, address technical issues, and encourage continued engagement.

Participants randomly assigned to the waitlist control group were told to continue activities as normal. Participants were asked to refrain from starting any new physical and cognitive programs during this period. The researchers sent weekly check-ins to waitlist control participants to ensure the same amount of team interaction. At the end of their participation, the waitlist control group was provided the NeuroTracker equipment if requested.

4.3.10 12-week follow up

Follow-up assessments were conducted approximately 12 weeks after baseline to evaluate changes following the intervention. Procedures mirrored those at intake, including neuropsychological testing, blood collection, and MRI scanning, with all measures administered by the same trained personnel where possible. To minimize practice effects, the alternate form of CVLT-II was used at follow-up. All other assessments and protocols remained consistent with baseline procedures to ensure comparability across time points.

4.3.11 Statistical analysis

All statistical analyses were conducted using R Studio V 4.4.3, and FSL (FMRIB Software Library) for neuroimaging data. Descriptive statistics were used to summarize participant demographics, and independent samples *t*-tests and chi-square tests were used to compare baseline characteristics between the intervention and control groups.

For neuropsychological outcomes, repeated-measures ANOVAs were used to evaluate the main effects of time and group, as well as the group-time interaction. Data were inspected for normality using Q-Q plots and Shapiro-Wilk tests. The results of the Shapiro-Wilk tests indicated that the residuals for the primary neuropsychological outcomes did not significantly deviate from a normal distribution (all $p > .05$). This was further supported by visual inspection of the Q-Q plots. Since the assumptions of normality and homogeneity of variances were met,

the use of parametric tests, including repeated-measures ANOVA, was considered appropriate for analyzing the cognitive data. To explore whether intervention effects varied based on concussion history, linear models were fit with three-way interactions (group- time-concussion history) for each outcome.

For neuroimaging data, tract-based spatial statistics were used to perform voxel-wise paired *t*-tests on FA and MD. Group-level comparisons were conducted to assess changes from pre- to post-intervention and waitlist control periods. Threshold-Free Cluster Enhancement (TFCE) was applied to correct for multiple comparisons, and significance was set at $p < 0.05$ (corrected).

Pre-to-post changes in blood-based biomarkers were assessed using estimation statistics with 5,000 bootstrap resamples and bias-corrected and accelerated confidence intervals. Estimation statistics were selected over traditional hypothesis testing to emphasize the magnitude and precision of effects, rather than relying solely on *p*-values. This approach offers a more nuanced interpretation of group differences and was particularly appropriate given the small sample size and exploratory nature of the biomarker analysis. Paired mean differences were calculated separately for each group using the dabestr package in R studio.

Lastly, an exploratory Pearson correlation analysis was conducted on a subset of 10 participants to assess associations between changes in NT performance and blood biomarker levels. Change scores were calculated as post-intervention minus pre-intervention values, and results were visualized using a heatmap of the correlation matrix.

4.4 Results

4.4.1 Participant demographics

A total of 44 participants completed at least one component (neuropsychological, biological, structural) of the study. Participants had an average age of 66.2 years (± 8.93), and had 17.7

years of education on average (±2.9). A total of 24 participants had sustained a self-reported concussion prior to beginning the study, with an average time since injury of 7.41 (±5.21) years. Table 4.1 summarizes the participant demographic information, split by intervention and control groups. There were no statistical differences between groups. A subset of 23 participants completed the MRI, and 16 had blood biomarkers completed before and after intervention.

Table 4.1. Participant demographic information.

* indicates $p < 0.05$

	Intervention	**Control**
N	23	21
Age - years	65.6 ± 8.25	66.9 ± 9.92
Sex	M = 9, F = 14	M = 10, F = 11
Education - years	17.9 ± 2.44	17.3 ± 3.46
History of Concussion	No = 10, Yes = 13	No = 10, Yes = 11

4.4.2 NeuroTracker training improvements over 12 weeks

Of the 23 people who participated in the intervention, 100% participated for 12 weeks. Adherence to the intervention was very good, with 16 completing every session, and only one person completing less than 80% of sessions. Of 72 total sessions, the average number of sessions completed was 67.4 ± 8.48.

All participants improved their NeuroTracker scores over the intervention, indicating they got better at the task ($t(22) = 7.84$, $p < 0.001$). There was no statistical difference in improvement from their first sessions to their final sessions between adults with and without histories of concussion (Table 4.2, Figure 2.1).

Table 4.2. NeuroTracker metrics divided by history of concussion status.

	History of Concussion	**No History of Concussion**
N	13	10
Average First Session Score	0.670 ± 0.257	0.744 ± 0.584
Average Final Session Score	1.28 ± 0.390	1.30 ± 0.623
Average % Improvement	106 ± 64.5	132 ± 103

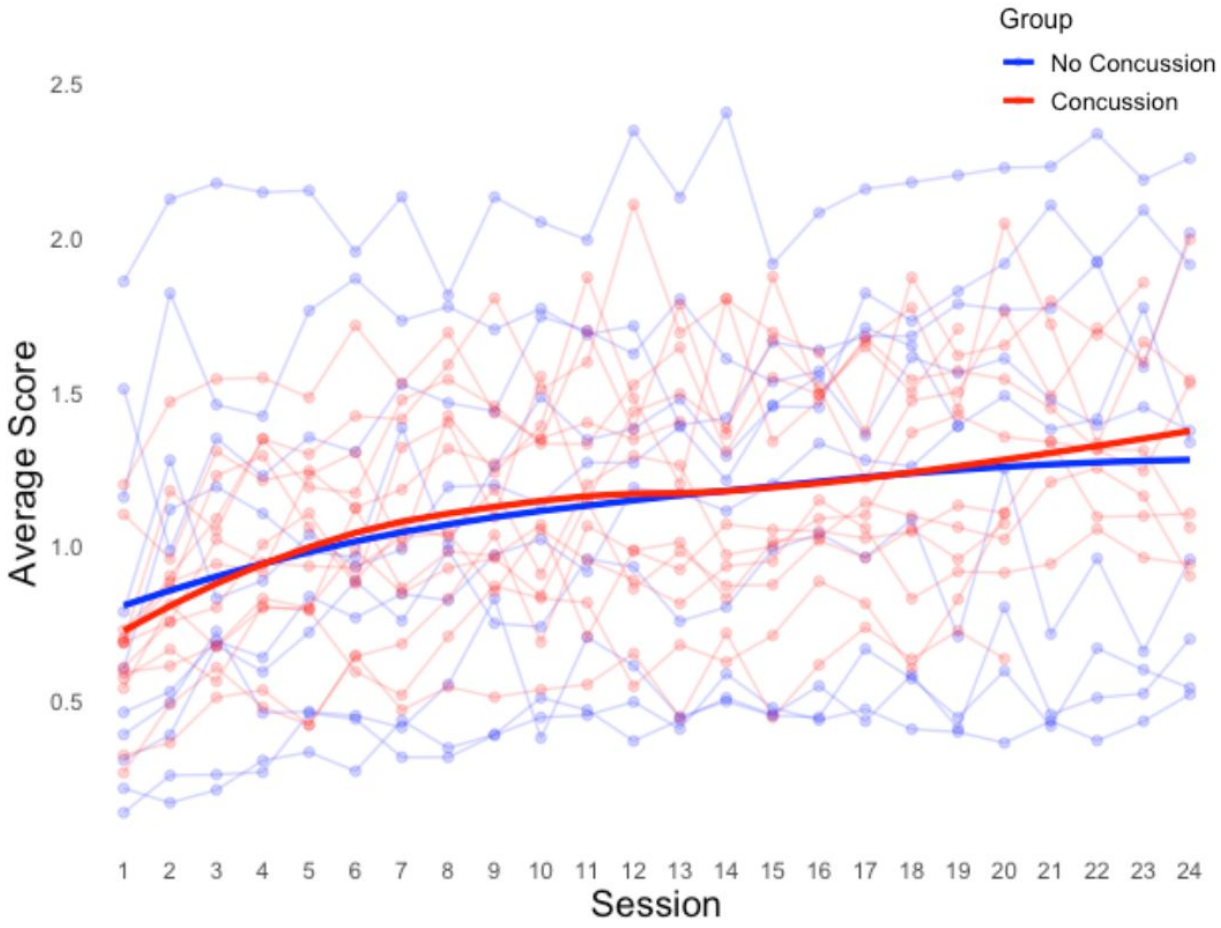


Figure 4.1. *NeuroTracker improvement across the intervention period.*

Each session represents the average of three CORE trials completed on the same training day. Individual trajectories are shown as semi-transparent lines, with bold smoothed trend lines depicting average performance over time for participants with a history of concussion (red) and those without (blue).

4.4.3 No effects of intervention on neuropsychological measures

Repeated-measures ANOVA revealed several main effects of time across the neuropsychological measures (Table 4.3). No significant main effects of group were observed after correction for multiple comparisons, except for the MMSE, which showed a mean difference of one point

between the control and intervention group. Further, no significant group x time interactions were observed for any measures, suggesting that both groups demonstrated similar patterns of change over time.

Table 4.3. Results from repeated measures ANOVA, to examine the effects of group and time, and the group x time interaction on cognitive performance.

There were no significant interactions between group and time. Statistically significant p values are indicated using *.

Variable	Effect	**F statistic**	**P value**	Generalized eta squared
SDM Oral Raw	Group	0.044	0.835	0.001
	Time	3.136	0.084	0.014
	Group:Time	0.732	0.397	0.003
TrailsA Raw	Group	0.062	0.805	0.001
	Time	1.630	0.209	0.005
	Group:Time	0.139	0.711	0.000
TrailsB Raw	Group	0.225	0.637	0.005
	Time	0.058	0.812	0.000
	Group:Time	1.869	0.179	0.006
MMSE	Group	9.535	0.004*	0.129
	Time	0.729	0.398	0.006
	Group:Time	0.461	0.501	0.004
VF F raw	Group	0.263	0.611	0.005
	Time	1.077	0.305	0.007
	Group:Time	0.716	0.402	0.005
VF A Raw	Group	0.001	0.981	0.000
	Time	6.480	0.015*	0.026
	Group:Time	0.266	0.609	0.001

VF S Raw	Group	1.729	0.196	0.033
	Time	1.592	0.214	0.007
	Group:Time	3.544	0.067	0.014
VF FAS Raw	Group	0.770	0.385	0.016
	Time	2.682	0.109	0.009
	Group:Time	2.365	0.132	0.008
FAS R	Group	0.000	0.983	0.000
	Time	1.554	0.219	0.011
	Group:Time	1.034	0.315	0.008
VF Animals	Group	0.217	0.644	0.004
	Time	0.342	0.562	0.001
	Group:Time	0.577	0.452	0.002
Animals R	Group	0.302	0.586	0.004
	Time	0.582	0.450	0.006
	Group:Time	0.165	0.686	0.002
LDSF	Group	1.999	0.165	0.034
	Time	3.896	0.055*	0.024
	Group:Time	0.025	0.875	0.000
DS Fwd Raw	Group	1.307	0.259	0.024
	Time	1.091	0.302	0.005
	Group:Time	0.236	0.630	0.001
LDSB	Group	0.708	0.405	0.012
	Time	1.542	0.221	0.010
	Group:Time	1.106	0.299	0.007
DS Back Raw	Group	1.094	0.302	0.020
	Time	1.621	0.210	0.008
	Group:Time	0.812	0.373	0.004

LDSS	Group	1.066	0.308	0.018
	Time	5.202	0.028*	0.032
	Group:Time	0.016	0.901	0.000
DS Seq	Group	0.802	0.376	0.014
	Time	7.117	0.011*	0.041
	Group:Time	0.682	0.414	0.004
DS Total Raw	Group	1.558	0.219	0.030
	Time	5.466	0.024*	0.022
	Group:Time	0.071	0.792	0.000
TrialsAll	Group	1.322	0.257	0.024
	Time	9.199	0.004*	0.046
	Group:Time	0.977	0.329	0.005
SDFR	Group	0.130	0.721	0.003
	Time	4.503	0.040	0.018
	Group:Time	0.050	0.824	0.000
SDCR	Group	0.989	0.326	0.018
	Time	6.978	0.012*	0.032
	Group:Time	1.065	0.308	0.005
LDFR	Group	0.751	0.391	0.014
	Time	4.558	0.039*	0.020
	Group:Time	0.096	0.759	0.000
LDCR	Group	0.457	0.503	0.009
	Time	7.848	0.008*	0.035
	Group:Time	0.257	0.615	0.001
Total Learning	Group	1.172	0.285	0.018
	Time	5.110	0.029*	0.040
	Group:Time	0.360	0.552	0.003

Proactive	Group	1.157	0.288	0.015
	Time	0.029	0.866	0.000
	Group:Time	0.520	0.475	0.006
Total Rep	Group	0.436	0.513	0.008
	Time	4.580	0.038*	0.021
	Group:Time	0.022	0.883	0.000
Total Int	Group	0.482	0.492	0.009
	Time	0.019	0.891	0.000
	Group:Time	0.019	0.891	0.000

Abbreviations: SDM; Symbol Digit Modality. SDM Oral Raw; Symbol Digit Modalities Test – Oral version, TrailsA/B Raw; Trail Making Test Part A/B, MMSE; Mini-Mental State Examination, VF F/A/S Raw; Verbal Fluency for letters F, A, and S, VF FAS Raw; Verbal Fluency total across F, A, and S, FAS R; FAS repetition errors, VF Animals; Verbal Fluency – Animal naming, Animals R; Animal Fluency repetition errors, LDSF/LDSB/LDSS; Longest Digit Span Forward/Backward/Sequencing, DS Fwd/Back/Seq Raw; Digit Span Forward/Backward/Sequencing total correct, DS Total Raw; Digit Span total score, TrialsAll; Combined Trail Making score, SDFR/SDCR; Short Delay Free/Cued Recall, LDFR/LDCR; Long Delay Free/Cued Recall, Total Learning; Total learning across trials, Proactive; Proactive interference errors, Total Rep; Total repetition errors, Total Int; Total intrusion errors.

4.4.4 NeuroTracker training may uniquely benefit adults with histories of concussion

To examine whether the intervention effect on neuropsychological outcomes differed by concussion history, linear models were fit for each measure including a three-way interaction between group, time, and concussion status. A significant three-way interaction was observed for total repetitions on verbal fluency ($\beta = –2.26$, $SE = 1.06$, $p = .036$), indicating that participants in the intervention group with a concussion history showed greater reductions in repetition errors

from pre- to post-intervention compared to those without concussion. A similar trend was observed for repetitions in the animals subset of verbal fluency (β = –2.04, SE = 0.56, p = .041). Together these results suggest that NeuroTracker training may uniquely benefit adults with a history of concussion.

4.4.5 NeuroTracker intervention does not change neuroimaging markers

Voxel wise paired t-tests were conducted to compare FA and MD values before and after the intervention (n =14) or waitlist control (n = 9) period to assess if 3D-MOT was associated with neurostructural changes. No significant differences were observed between pre- and post-intervention or waitlist timepoints for either metric at any voxel across the white matter skeleton (TFCE-corrected p > 0.05).

4.4.6 NeuroTracker intervention may support production of BDNF

The intervention group showed an increase of serum BDNF levels from pre- to post-intervention, with a paired mean difference of 9,540 pg/mL (95% CI: 3,670, 15,400). In contrast, the control group exhibited a small decrease of -1,650 pg/mL (95% CI: -10,900, 9,130) (Figure 2.2). No other statistically significant biomarker changes were observed (Table 4.4).

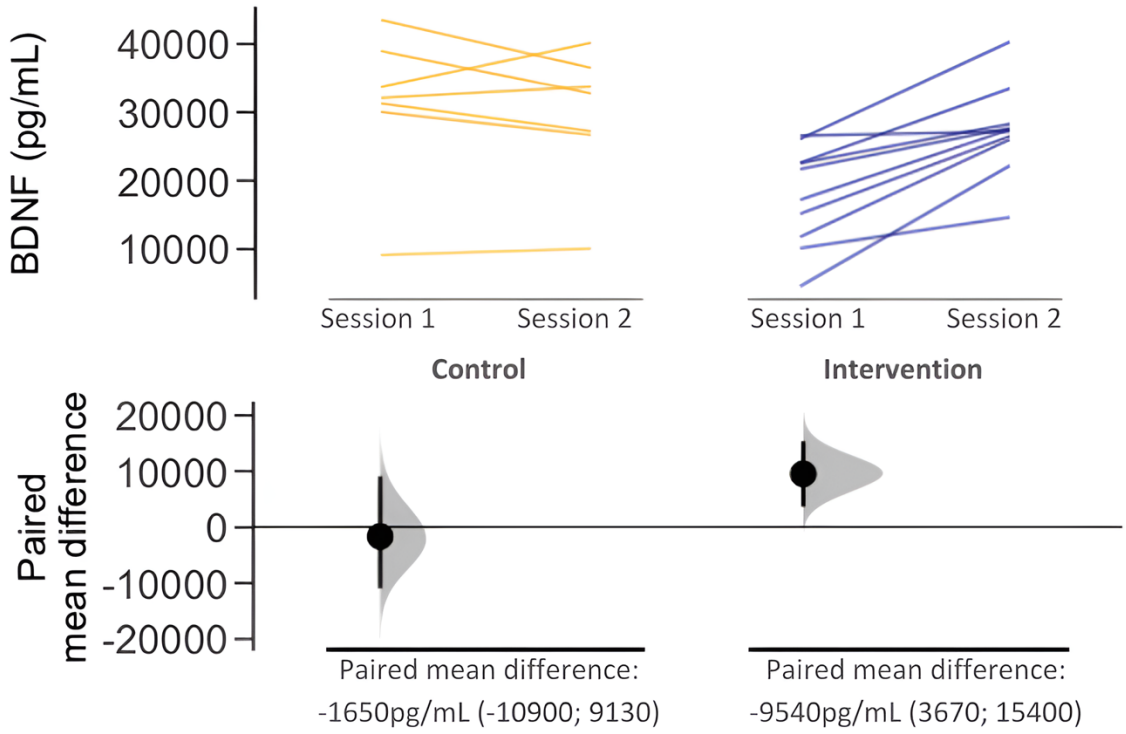


Figure 2.2. *Paired pre-post changes in BDNF levels for the control and intervention groups. The upper panels show individual participant trajectories between Session 1 (pre-) and Session 2 (post-intervention), with yellow lines representing the control group and blue lines representing the intervention group. Lower panels display the bootstrap distributions of paired mean differences with 95% bias-corrected and accelerated confidence intervals. Only the intervention group showed a statistically meaningful increase in BDNF (mean difference = 9,540 pg/mL, 95% CI (3,670, 15,400)).*

Table 4.4. Paired mean differences and 95% confidence intervals for pre- to post-intervention changes in blood-based biomarkers, estimated using 5,000 bootstrap resamples.

Results are reported separately for the control and intervention groups. Confidence intervals are bias-corrected and accelerated. Results in bold indicate comparisons for which the 95% CI did not include zero, suggesting a potentially meaningful intervention-related change.

Biomarker	Group	Paired Mean Difference (pg/mL)	95% Confidence Interval
BDNF	Control	-1650	(-10,900, 9,130)
	Intervention	**9540**	**(3,670, 15,400)**
GFAP	Control	-7.83	(-53.1, 43.7)
	Intervention	-2.29	(-63, 54.5)
pTau-217	Control	-0.0341	(-0.113, 0.0348)
	Intervention	0.0187	(-0.0871, 0.123)
NfL	Control	-1.35	(-13.3, 8.24)
	Intervention	1.24	(-3.26, 6.33)
IL-10	Control	0.178	(-0.416, 1.08)
	Intervention	-0.102	(-0.444, 0.217)

TNF-α	Control	0.255	(-0.236, 0.969)
	Intervention	-0.116	(-0.704, 0.45)

4.4.7 Exploratory associations between biomarker and NeuroTracker changes

To determine if change in NT scores were associated with the increase in BDNF levels, we conducted a correlation analysis to assess the relationships between changes in blood-based biomarkers and changes in NT scores following the intervention in a sample of 10 participants (Figure 2.3). Among the associations with change in NeuroTracker scores (Δ NT), the strongest observed relationship was a moderate negative correlation with Δ IL-10 (r = –0.42). Positive weak correlations between Δ NT and Δ BDNF (r = 0.27), Δ pTau-217 (r = 0.19), and Δ GFAP (r = 0.17) were also observed. Several biomarkers were strongly correlated with each other. For example, Δ NfL and Δ GFAP showed a strong positive correlation (r = 0.85), and Δ pTau-217 was strongly correlated with both Δ GFAP (r = 0.75) and Δ IL-10 (r = 0.72).

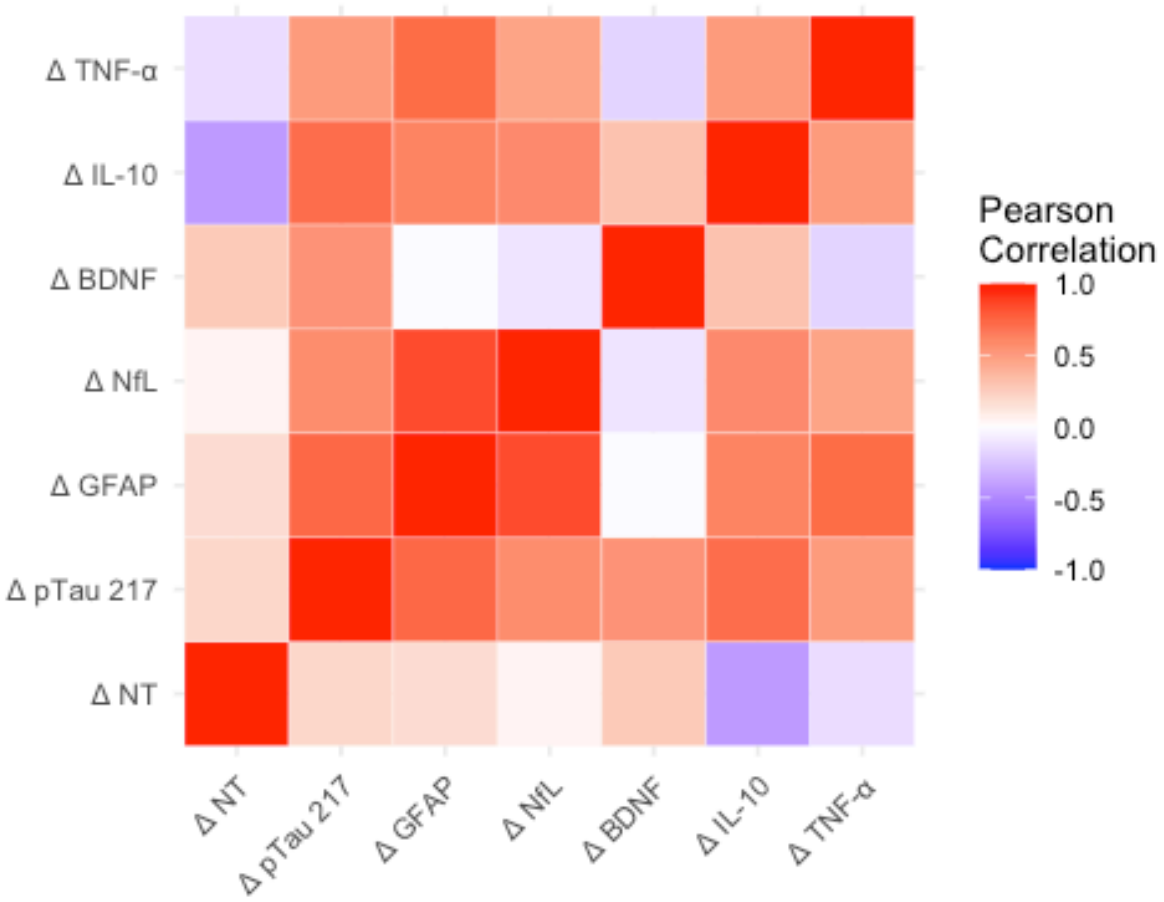


Figure 4.3. A *heatmap showing Pearson correlations between changes in blood-based biomarkers and NT performance (Δ NT) following intervention.*

The strongest correlation between Δ NT was a moderate negative correlation with Δ IL-10 (r = -0.42).

4.5 Discussion

This study investigated the impact of 12 weeks of 3D-MOT with NeuroTracker training on cognitive functions, white matter microstructure and blood-based biomarkers in adults over age 50. While significant increases in brain-derived neurotrophic BDNF were observed after the intervention, it did not result in significant improvements in neuropsychological performance or

DTI metrics. Importantly, exploratory analyses suggested that participants with a history of concussion may derive unique benefits from this training.

4.5.1 Participant adherence and task learning

Adherence to the 12-week 3D-MOT training was excellent, with participants completing an average of over 93% of assigned sessions. All participants improved on the 3D-MOT task itself, demonstrating learning and engagement. This supports prior findings that older adults retain the capacity to improve on perceptually demanding tasks and exhibit substantial neural plasticity when provided with consistent training opportunities.[24] Importantly, there was no difference in the degree of task improvement between individuals with and without a history of concussion, suggesting that despite any prior brain injury, adults can successfully engage in and benefit from perceptual-cognitive training in terms of performance on the trained task.

4.5.2 NeuroTracker training may support BDNF production in the absence of neurostructural and cognitive changes

A key finding in this study was that participants who completed 12 weeks of 3D-MOT training showed a robust increase in serum BDNF, whereas the waitlist control group showed no change. BDNF is a neurotrophin that supports neuroplasticity through synaptic growth.[17] These findings align with emerging evidence that cognitively stimulating activities can favorably influence neurotrophic factors in older adults. Notably, Ledreux et al. (2019) observed that five weeks of intensive computerized cognitive training induced a 10% rise in serum BDNF levels in older adults, a significant change that was not observed with equal-duration physical exercise or mindfulness training.[25] In the present study, the BDNF increase in the intervention group (about 80% improvement on average) was greater in magnitude, potentially reflecting the longer training period and high cognitive load demanded by 3D-MOT.

It is well established that aerobic exercise can elevate BDNF, both acutely and with sustained training, and this neurotrophic response is thought to underlie some of exercise's cognitive benefits.[17,26] For instance, a single moderate-intensity exercise session produced a substantially larger immediate surge in serum BDNF in older adults than a similar session of cognitive training or meditation.[17] Over longer timepoints exercise interventions in older adults yield moderate increases in resting BDNF levels.[26] Our results suggest that cognitive training can likewise enhance BDNF, potentially tapping into overlapping neuroplasticity pathways with physical exercise. The increase in BDNF after 3D-MOT indicates that even without physical exertion, engaging in effortful cognitive training may stimulate biological processes associated with brain health and plasticity.

Our findings contribute to a growing body of literature on 3D-MOT training in older adults**,** which has reported mixed outcomes on cognitive performance. Some prior studies have documented significant cognitive gains following similar training, while others found minimal or no transfer effects.[27] Findings from previous 3D-MOT studies with older adults generally support the idea that 3D-MOT can bolster cognitive domains that are vulnerable to aging, possibly by strengthening distributed attention networks or improving information processing speed.[7–9,28] The contrasting cognitive results observed in the present study could be due to differences in the population, as our sample consisted of generally healthy, high-functioning adults over 50, as opposed to those with self-reported cognitive complaints, and perhaps slightly older cohorts in other studies, or differences in the training dose and outcome measures.

On the neuroimaging side, we found no significant changes in white matter FA or MD associated with the 3D-MOT training. However, this null result is not entirely surprising. Detecting structural brain changes over a 3-month period in healthy adults is challenging, especially with a

limited sample. While neuroplasticity is possible at microstructural levels, it likely requires either longer interventions or occurs in subtler forms (*e.g.* synaptic or dendritic changes) that do not manifest as bulk changes in DTI metrics so quickly. Even aerobic exercise interventions, which have more often been associated with structural brain changes, usually span 6-12 months before effects like increased hippocampal volume or white matter integrity improvements are detectable.[29] It is possible that any microstructural modifications, such as increased myelination or connectivity in attention-related tracts, were too diffuse or slight to be captured by voxelwise DTI analysis after just 12 weeks in this small cohort. Future studies should use complementary neuroimaging methods, such as functional MRI or connectivity analyses, which could reveal training-induced neural reorganization, even in the absence of structural change.

4.5.3 Potential mechanisms involved in 3D-MOT training

The finding of increased BDNF in the absence of cognitive change invites discussion of underlying mechanisms. One hypothesis is that BDNF could be part of an early cascade of neuroadaptive responses. Increased BDNF availability may facilitate synaptic modifications that lay the groundwork for future cognitive benefits, even if those benefits did not emerge within the 12-week window in this study. In other words, the brain may have been "primed" by the training at a molecular level, but translating that to better cognition might require either additional training or the occurrence of some external challenge where the reserve can be observed. This idea is supported by a study of combined physical and cognitive training in older adults that found that only the group receiving cognitive stimulation showed an increase in BDNF, and that the degree of BDNF increase mediated their gains in cognitive speed.[18] Results from the exploratory analysis suggest a weak positive correlation between the magnitude of 3D-MOT improvement and the increase in serum BDNF levels. This highlights that participants who

improved most in task performance tended to show greater neurotrophic response. Although preliminary, this aligns with the idea that BDNF upregulation reflects the brain's plastic response to training. It is also possible that 3D-MOT training strengthened existing neural connections rather than creating entirely new ones, resulting in a boost of BDNF, but no change in cognitive performance or structural signatures.

3.5.4 Exploratory benefits in participants with concussion history

Although the intervention did not significantly affect cognitive outcomes in the full sample, an exploratory analysis revealed a potential benefit for participants with a history of concussion. Specifically, adults in the intervention group who had prior mTBI showed greater reductions in repetition errors on verbal fluency tasks compared to those without concussion, and compared to individuals with history of concussion in the control group. Repetition errors on fluency tests (*i.e.* saying the same word more than once when generating words after a category or letter cue) can be interpreted as a lapse in executive control or self-monitoring.[30] The fact that these errors decreased more in the concussed subgroup suggests that 3D-MOT training may have selectively helped those with residual executive dysfunction, a trait that has been associated with having multiple concussions.[31] The present results hint that the heavy demands on attention and working memory from 3D-MOT may have acted as a form of targeted rehabilitation for those latent deficits.

It is important to note that this concussion subgroup analysis was exploratory and based on a three-way interaction in our models. The number of participants with a concussion history was relatively small, and we did not originally stratify the randomization by concussion status. However, it opens an intriguing avenue that 3D-MOT interventions might be useful as a

cognitive support tool for older adults with a history of brain injury, potentially helping to address specific executive function challenges that may persist years after the injury.

4.5.5 Limitations

While this study provides valuable insights, several limitations must be acknowledged. The trial included a relatively small number of participants, which limits statistical power. Small effects on cognition or brain structure may have gone undetected. Moreover, our sample consisted of generally healthy, well-educated older adults, which may not generalize to more cognitively diverse populations. The high baseline cognitive performance in our sample could have led to ceiling effects on some tests, masking potential gains. Further, our control group was a waitlist control. This means the intervention group had a substantial engagement and novelty factor that the control group did not. Although this design helps isolate the effect of doing the training versus doing nothing, it does not rule out placebo effects or general engagement effects. An active control group (*e.g.* doing another type of computer activity, or a 2D visual search task, for instance) would strengthen conclusions about the specificity of 3D-MOT training. Additionally, there are threats to internal validity that should be considered. This study design did not account for confounding lifestyle variables, such as physical activity. Since exercise is known to increase serum BDNF, it is possible that the observed increase was partially influenced by unmeasured changes in participants' activity levels rather than the cognitive training alone. The study was also not powered to assess for potential effect measure modification by sex, meaning the intervention's true effect on outcomes like BDNF may differ between men and women.

4.6 Conclusion

In conclusion, this study demonstrates that 3D-MOT training is an accessible and engaging intervention for older adults that can induce significant neurotrophic effects, in the absence of

overt cognitive and structural changes. Exploratory results suggest that individuals with prior concussions might particularly benefit, highlighting the need to tailor and target cognitive interventions. Overall, the present study contributes to the understanding of how intense perceptual-cognitive exercise can impact the aging brain.

4.7 Chapter 4 References

1. National Institute on Aging. 2024 Report on Cognitive Health and Older Adults. 2024. Retrieved from: www.nia.nih.gov/health/brain-health/cognitive-health-and-older-adults

2. Deary IJ, Corley J, Gow AJ, et al. Age-associated cognitive decline. British Medical Bulletin 2009;92(1):135–152; doi: 10.1093/bmb/ldp033.

3. Salthouse TA. When does age-related cognitive decline begin? Neurobiology of Aging 2009;30(4):507–514; doi: 10.1016/j.neurobiolaging.2008.09.023.

4. Sala G, Aksayli ND, Tatlidil KS, et al. Near and Far Transfer in Cognitive Training: A Second-Order Meta-Analysis. Zwaan R, Verkoeijen P. eds. Collabra: Psychology 2019;5(1):18; doi: 10.1525/collabra.203.

5. Kueider AM, Parisi JM, Gross AL, et al. Computerized Cognitive Training with Older Adults: A Systematic Review. PLOS ONE 2012;7(7):e40588; doi: 10.1371/journal.pone.0040588.

6. Snowden T, Ohlhauser L, Morrison J, et al. A Protocol for Remote Cognitive Training Developed for Use in Clinical Populations During the COVID-19 Pandemic. Neurotrauma Rep 2023;4(1):522–532; doi: 10.1089/neur.2023.0009.

7. Legault I, Allard R, Faubert J. Healthy Older Observers Show Equivalent Perceptual-Cognitive Training Benefits to Young Adults for Multiple Object Tracking. Front Psychol 2013;4:323; doi: 10.3389/fpsyg.2013.00323.

8. Spaner, Musteata, Kenny, et al. 3-Dimensional Multiple Object Tracking Training Can Enhance Selective Attention, Psychomotor Speed, and Cognitive Flexibility in Healthy Older Adults. Ageing Sci Ment Health Stud 2019;3(4):1–12.

9. Musteata, Yoshida, Baranzini, et al. Perceptual-cognitive training can improve cognition in older adults with subjective cognitive decline. Ageing Sci Ment Health Stud 2019;3(6):1–15.

10. van der Laag PJ, Dorhout BG, Heeren AA, et al. Barriers and facilitators for implementation of a combined lifestyle intervention in community-dwelling older adults: a scoping review. Front Public Health 2023;11; doi: 10.3389/fpubh.2023.1253267.

11. Horváth D, Négyesi J, Rácz M, et al. Feasibility of a novel neurofeedback system: a parallel randomized single-blinded pilot study. Sci Rep 2023;13(1):17353; doi: 10.1038/s41598-023-44545-1.

12. Bennett IJ, Madden DJ, Vaidya CJ, et al. Age-related differences in multiple measures of white matter integrity: A diffusion tensor imaging study of healthy aging. Hum Brain Mapp 2009;31(3):378–390; doi: 10.1002/hbm.20872.

13. Cao X, Yao Y, Li T, et al. The Impact of Cognitive Training on Cerebral White Matter in Community-Dwelling Elderly: One-Year Prospective Longitudinal Diffusion Tensor Imaging Study. Sci Rep 2016;6:33212; doi: 10.1038/srep33212.

14. Lövdén M, Schaefer S, Noack H, et al. Spatial navigation training protects the hippocampus against age-related changes during early and late adulthood. Neurobiol Aging 2012;33(3):620.e9-620.e22; doi: 10.1016/j.neurobiolaging.2011.02.013.

15. Wolf G, Cifu D, Baugh L, et al. The effect of hyperbaric oxygen on symptoms after mild traumatic brain injury. Journal of Neurotrauma 2012;29(17):2606–2612; doi: 10.1089/neu.2012.2549.

16. Puderbaugh M, Emmady PD. Neuroplasticity. In: StatPearls StatPearls Publishing: Treasure Island (FL); 2025.

17. Håkansson K, Ledreux A, Daffner K, et al. BDNF Responses in Healthy Older Persons to 35 Minutes of Physical Exercise, Cognitive Training, and Mindfulness: Associations with Working Memory Function. J Alzheimers Dis 2017;55(2):645–657; doi: 10.3233/JAD-160593.

18. Nicastri CM, McFeeley BM, Simon SS, et al. BDNF mediates improvement in cognitive performance after computerized cognitive training in healthy older adults. Alzheimers Dement (N Y) 2022;8(1):e12337; doi: 10.1002/trc2.12337.

19. Giza CC, Hovda DA. The new neurometabolic cascade of concussion. Neurosurgery 2014;75 Suppl 4(0 4):S24-33; doi: 10.1227/NEU.0000000000000505.

20. June D, Williams OA, Huang C-W, et al. Lasting consequences of concussion on the aging brain: Findings from the Baltimore Longitudinal Study of Aging. Neuroimage 2020;221:117182; doi: 10.1016/j.neuroimage.2020.117182.

21. Mavroudis I, Kazis D, Petridis FE, et al. The Association Between Traumatic Brain Injury and the Risk of Cognitive Decline: An Umbrella Systematic Review and Meta-Analysis. Brain Sciences 2024;14(12):1188; doi: 10.3390/brainsci14121188.

22. Snowden TM, Hinde AK, Reid HMO, et al. Does Mild Traumatic Brain Injury Increase the Risk for Dementia? A Systematic Review and Meta-Analysis. J Alzheimers Dis 2020;78(2):757–775; doi: 10.3233/JAD-200662.

23. Lysenko-Martin MR, Hutton CP, Sparks T, et al. Multiple Object Tracking Scores Predict Post-Concussion Status Years after Mild Traumatic Brain Injury. J Neurotrauma 2020;37(16):1777–1787; doi: 10.1089/neu.2019.6842.

24. Park DC, Bischof GN. The aging mind: neuroplasticity in response to cognitive training. Dialogues Clin Neurosci 2013;15(1):109–119.

25. Ledreux A, Håkansson K, Carlsson R, et al. Differential effects of physical exercise, cognitive training and mindfulness practice on serum BDNF levels in healthy older adults: a randomized controlled intervention study. J Alzheimers Dis 2019;71(4):1245–1261; doi: 10.3233/JAD-190756.

26. Farrukh S, Habib S, Rafaqat A, et al. Association of exercise, brain-derived neurotrophic factor, and cognition among older women: A systematic review and meta-analysis. Arch Gerontol Geriatr 2023;114:105068; doi: 10.1016/j.archger.2023.105068.

27. Vater C, Gray R, Holcombe AO. A critical systematic review of the Neurotracker perceptual-cognitive training tool. Psychon Bull Rev 2021;28(5):1458–1483; doi: 10.3758/s13423-021-01892-2.

28. Michaels J, Chaumillon R, Mejia-Romero S, et al. Can Three-Dimensional Multiple Object Tracking Training Be Used to Improve Simulated Driving Performance? A Pilot Study in

Young and Older Adults. J Cogn Enhanc 2023;7(1):112–127; doi: 10.1007/s41465-023-00260-3.

29. ten Brinke LF, Bolandzadeh N, Nagamatsu LS, et al. Aerobic Exercise Increases Hippocampal Volume in Older Women with Probable Mild Cognitive Impairment: A 6-Month Randomized Controlled Trial. Br J Sports Med 2015;49(4):248–254; doi: 10.1136/bjsports-2013-093184.

30. Hill BD, Alosco ,Michael, Bauer ,Lyndsey, et al. The Relation of Executive Functioning to CVLT-II Learning, Memory, and Process Indexes. Applied Neuropsychology: Adult 2012;19(3):198–206; doi: 10.1080/09084282.2011.643960.

31. McAllister T, McCrea M. Long-Term Cognitive and Neuropsychiatric Consequences of Repetitive Concussion and Head-Impact Exposure. J Athl Train 2017;52(3):309–317; doi: 10.4085/1062-6050-52.1.14.

Chapter 5

Conclusions

5.1 Dissertation summary

This dissertation explored the long-term effects of mild traumatic brain injury in adults over the age of 50 through a multimodal framework of risk assessment, early detection and prevention. Collectively the findings provide evidence that a history of mTBI increases the risk of later-life neurodegenerative conditions, including dementia, and offer promising insights into potential pathways for early identification (Figure 5.1).

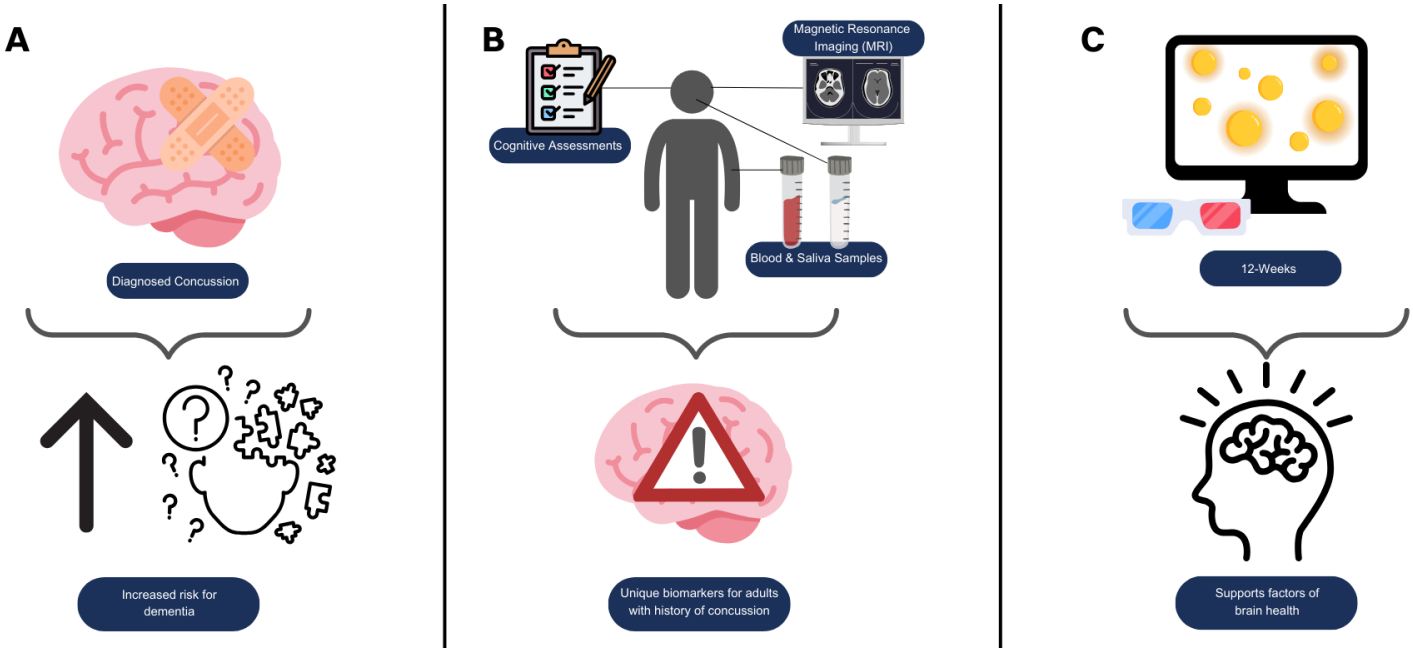


Figure 5.1. *Summary of key findings within this dissertation.*

(A) The first study, presented in chapter 2, presents a systematic review and meta-analysis highlighting that adults with a diagnosed concussion are nearly 2x more likely to be diagnosed with dementia later in life, compared to adults without. (B). The second study highlights how using a combination of measures to assess brain health may create a unique set of biomarkers,

specifically tailored for adults with a history of concussion. (C). The third study presents a small intervention study, in which 12 weeks of 3D-MOT training was associated with increased levels of BDNF, a measure of neuroplasticity.

5.2 Summary of key findings

Chapter two, a systematic review and meta-analysis, found evidence that having a history of a diagnosed mTBI is a risk for developing dementia later in life. A pooled odds ratio of 1.96 indicated that individuals with a history of mTBI were nearly twice as likely to be diagnosed with dementia compared to those without. Neuroimaging and neuropsychiatric findings included studies that further supported this association by revealing subtle yet persistent alterations in brain structure and function. While the review affirmed a significant association between mTBI and dementia, it also highlighted heterogeneity in study quality, methods of mTBI classification, and the role of repetitive injury.

Chapter three extended the prior findings by comparing cognitive, neuroimaging, and biomarker profiles in older adults with and without a history of concussion, and other concussion-related metrics. While traditional neuropsychological comparisons showed few group-level cognitive differences, advanced biomarker and neuroimaging analyses uncovered subtle yet meaningful biological signatures of past injury. Specifically, individuals with a history of concussion exhibited lower levels of NfL compared to non-injured groupings, however, higher levels within the concussion groupings correlated with poorer verbal fluency and decreased white matter integrity on diffusion tensor imaging DTI. These findings suggest that even in the absence of overt cognitive decline, biological and microstructural changes may signal latent damage or diminished neural reserve. This study underscores the value of multimodal methodologies for detecting concussion sequelae that would be missed using behavioral assessments alone.

Chapter four addressed the critical issue of prevention by implementing a cognitive training intervention that may uniquely benefit adults with a history of concussion. While participants in the intervention group did not exhibit significant improvements in measures of cognition compared to controls, there was preliminary evidence of increased BDNF levels post-intervention, aligning with previous findings that aerobic exercise and cognitive engagement can promote neurotrophic support. However, structural MRI outcomes did not reveal significant changes following the intervention, possibly due to the relatively short duration or limited sample size. These findings contribute to the growing literature suggesting that while cognitive training may modulate neurobiological factors, translating these changes into measurable structural or cognitive outcomes remains a challenge.

5.3 Integrated summary of results

Taken together, these studies paint a complex picture of concussion as a chronic, multifaceted condition with effects that may persist below the threshold of clinical diagnosis. While the second chapter suggests that concussion is a long-term risk factor for dementia, the third and fourth chapters reveal how these risks may manifest biologically before becoming behaviorally apparent. The lack of group-level cognitive deficits in chapter 2 highlight the importance of looking beyond standard cognitive tests to identify at-risk individuals. The convergent findings of elevated NfL and pTau-217 with decreased measures of white matter integrity when controlling for the number of concussions that someone has sustained, support a model in which concussion leads to persistent neurobiological disruption that may accelerate age-related degeneration. Importantly, this dissertation also underscores the potential for intervention. Although the 3D-MOT intervention in chapter four did not yield generalized cognitive improvements, the rise in BDNF and selective executive function benefits in participants with

prior concussion suggest that the aging brain retains plasticity, and that this plasticity may be especially malleable in individuals with injury-related vulnerabilities. Figure 5.2 provides a walkthrough of key results in a generalized format, designed for study participants.

Chapter 2

Start here!

Have you been diagnosed with a concussion?

Great news! However, there are many things that can influence your risk for dementia. Some things that can increase your risk include genetic predisposition, obesity, and social isolation.

It turns out that having a history of diagnosed concussion may increase your risk for dementia nearly 2x.

No

Yes

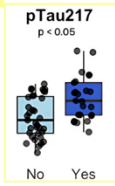
Chapter 3

Have you played contact sports?

No

Yes

Great news! When considering head hits as a risk factor for dementia, your risk is low. You likely have typical cognitive performance, neuroimaging markers and levels of blood-based biomarkers.



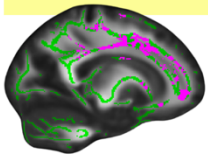
You may have increased levels of pTau-217, a protein linked to Alzheimer's pathology, even if you've never had a diagnosed concussion.

Do you think that you've had a concussion, even if it wasn't diagnosed?

No

Yes

You may have lower levels of NfL, which on it's own might sound like a good thing, but within this group, individuals with higher NfL tended to perform worse on cognitive tasks and had reduced white matter integrity (pink areas) throughout the brain.

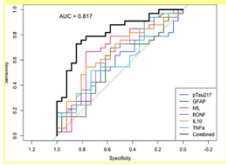


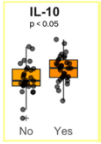
Have you experienced multiple concussions?

No

Yes

Based on the levels of blood biomarkers you have, we can fairly acurately predict that you have sustained multiple concussions!





Having multiple concussions was associated with elevated IL-10, which may reflect a chronic immune response in the brain.

Chapter 4

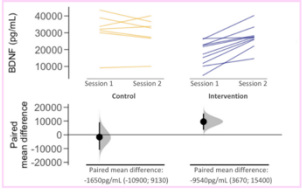
Were you asssigned to the 3D-MOT intervention group?

That's ok! Being a part of the waitlist control group is a very important job. By continuing your regular daily routine, we can compare differences in results to the intervention group.

No

Yes

3D-MOT training led to a significant increase in BDNF, a growth factor that supports brain repair and learning.

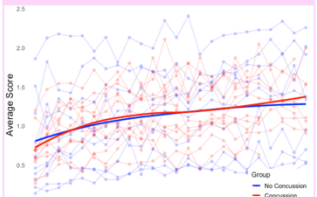


Have you experienced a concussion?

No

Yes

In task performance improved by an average of 118%, regardless of if you have had a concussion or not!



3D-MOT training was associated with less errors on a verbal memory, and might be a good intervention choice for people with a history of concussion.

Figure 5.2. *Decision-tree style infographic summarizing key findings from Chapters 2, 3, and 4 from the participant's perspective.*

The flow chart is designed to walk study participants through a generalized map of what we have learned in this study so far. The infographic is designed to communicate individual-level implications of study findings in an accessible, visually guided format.

5.4 Limitations

While this dissertation advances our understanding of the long-term effects of concussion in older adults, several limitations should be considered when interpreting the findings. One confounding factor in this study is that the accepted definition of concussion changed during the middle of the study period.[10] For the purpose of continuity, we did not update the definition of concussion and continued working with the 2014 International Collaboration on mTBI Prognosis definition. The 2023 concussion definition differs from previous versions by establishing a structured, operationalized framework that requires specific combinations of clinical signs, symptoms, and objective findings like biomarkers for a more precise diagnosis. This change in definition is timely, but adds complexity to on-going studies. We are hopeful that the new definition provides clarity for physicians, allowing mTBI survivors to get a proper diagnosis. Although the multimodal approach is a clear strength of this work, the sample sizes in both chapters three and four were relatively small. This limits the ability to detect subtle effects and to perform subgroup analyses that might reveal individual differences in vulnerability or responsiveness. For instance, it remains unknown whether sex, age at injury, or time since injury may have moderated the observed outcomes. A larger cohort would have permitted a more nuanced exploration of these interactions. In chapter four, while the increase in serum BDNF following cognitive training is encouraging, the intervention lacks an active control condition.

This limits our ability to disentangle the effects of cognitive engagement from nonspecific factors such as expectancy, task novelty, or social interaction. Furthermore, while BDNF is a widely studied neuroplasticity marker, it is influenced by numerous factors including circadian rhythms, stress, and physical activity levels. The interpretation of BDNF changes in isolation, without parallel neuroimaging or functional data, warrants caution.

Together, these limitations do not diminish the value of the findings, but rather emphasize the need for future research to move beyond isolated methodologies toward larger, prospective, and multimodal investigations that can capture the complex and heterogeneous nature of brain injury and aging.

5.5 Future directions

This dissertation lays the groundwork for a deeper understanding of the long-term effects of concussion on brain health in older adults. Importantly, the work presented in chapters three and four is part of a broader, ongoing longitudinal study funded through 2027. This extended support will enable the recruitment of a significantly larger and more diverse sample, allowing for more robust statistical modeling and finer-grained analysis of individual differences in injury history, biomarker profiles, and intervention response. This larger study includes an a-priori power analysis, to ensure it is adequately powered to detect small to medium effect sizes. The increased sample size will enhance the power to detect subtle associations and permit more comprehensive subgroup analyses, including the effects of age at injury, time since last concussion and sex. Moreover, the ongoing study's longitudinal design will allow for tracking of biomarker, structural, and cognitive changes over eighteen months. This is a critical next step in establishing whether the subtle differences observed in this dissertation serve as early predictors of cognitive decline or markers of resilience. Repeated measures of blood biomarkers and MRI, paired with

cognitive assessments, will help us better understand aging pathways in adults with histories of concussion. Further, we plan to use linear mixed effects models to analyze trajectories of change over time. This approach is ideal as it can handle missing data from participant drop-out and allows us to model individual differences in the rate of change for our key biomarker and cognitive outcomes. The larger sample size will permit testing for potential interactions, for instance, "concussion history x sex" in our models. This will allow us to investigate whether the pathways linking concussion to long-term outcomes differ between men and women, a question this dissertation was not powered to answer. By incorporating these analytic considerations, our future work will be able to build upon these foundational findings with greater statistical power and methodological rigor.

5.6 General References (Chapters 1 & 5)

1. Menon DK, Schwab K, Wright DW, et al. Position Statement: Definition of Traumatic Brain Injury. Archives of Physical Medicine and Rehabilitation 2010;91(11):1637–1640; doi: 10.1016/j.apmr.2010.05.017.

2. Malec JF, Brown AW, Leibson CL, et al. The Mayo Classification System for Traumatic Brain Injury Severity. Journal of Neurotrauma 2007;24(9):1417–1424; doi: 10.1089/neu.2006.0245.

3. Champagne AS, Yao X, McFaull SR, et al. Self-reported concussions in Canada: A cross-sectional study. Health Rep 2023;34(6):17–28; doi: 10.25318/82-003-x202300600002-eng.

4. Balabandian M, Noori M, Lak B, et al. Traumatic brain injury and risk of Parkinson's disease: a meta-analysis. Acta Neurol Belg 2023;123(4):1225–1239; doi: 10.1007/s13760-023-02209-x.

5. Scholten AC, Haagsma JA, Andriessen TMJC, et al. Health-related quality of life after mild, moderate and severe traumatic brain injury: patterns and predictors of suboptimal functioning during the first year after injury. Injury 2015;46(4):616–624; doi: 10.1016/j.injury.2014.10.064.

6. Scholten AC, Haagsma JA, Cnossen MC, et al. Prevalence of and Risk Factors for Anxiety and Depressive Disorders after Traumatic Brain Injury: A Systematic Review. Journal of Neurotrauma 2016;33(22):1969–1994; doi: 10.1089/neu.2015.4252.

7. Dewan MC, Rattani A, Gupta S, et al. Estimating the global incidence of traumatic brain injury. J Neurosurg 2019;130(4):1080–1097; doi: 10.3171/2017.10.JNS17352.

8. Leo P, McCrea M. Epidemiology. In: Translational Research in Traumatic Brain Injury. (Laskowitz D, Grant G. eds). Frontiers in Neuroscience CRC Press/Taylor and Francis Group: Boca Raton (FL); 2016.

9. Kristman VL, Borg J, Godbolt AK, et al. Methodological issues and research recommendations for prognosis after mild traumatic brain injury: results of the International

Collaboration on Mild Traumatic Brain Injury Prognosis. Arch Phys Med Rehabil 2014;95(3 Suppl):S265-277; doi: 10.1016/j.apmr.2013.04.026.

10. Silverberg ND, Iverson GL, Cogan A, et al. The American Congress of Rehabilitation Medicine Diagnostic Criteria for Mild Traumatic Brain Injury. Archives of Physical Medicine and Rehabilitation 2023;104(8):1343–1355; doi: 10.1016/j.apmr.2023.03.036.

11. Henry LC, Elbin RJ, Collins MW, et al. Examining Recovery Trajectories After Sport-Related Concussion With a Multimodal Clinical Assessment Approach. Neurosurgery 2016;78(2):232–241; doi: 10.1227/NEU.0000000000001041.

12. Collins MW, Grindel SH, Lovell MR, et al. Relationship between concussion and neuropsychological performance in college football players. JAMA 1999;282(10):964–970; doi: 10.1001/jama.282.10.964.

13. Karen Barlow. Postconcussion Syndrome. Sage Publications 2016;31(1):57–67; doi: 10.1177/0883073814543305.

14. Ryan LM, Warden DL. Post concussion syndrome. Int Rev Psychiatry 2003;15(4):310–316; doi: 10.1080/09540260310001606692.

15. Broshek DK, Pardini JE, Herring SA. Persisting symptoms after concussion: Time for a paradigm shift. PM R 2022;14(12):1509–1513; doi: 10.1002/pmrj.12884.

16. Prince M, Guerchet M, Prina M. The Global Impact of Dementia 2013-2050. Alzheimer's Disease International: London; 2013.

17. Statistics Canada. Population Estimates on July 1, by Age and Gender. 2024 Available from: https://www150.statcan.gc.ca/n1/en/catalogue/1710000501 [Last accessed: 2/5/2025]. doi: 10.25318/1710000501

18. United States Census Bureau.An Aging World: 2015. 2015. Available from: https://www.census.gov/library/publications/2016/demo/P95-16-1.html [Last accessed: 2/5/2025].

19. Irwin K, Sexton C, Daniel T, et al. Healthy Aging and Dementia: Two Roads Diverging in Midlife? Front Aging Neurosci 2018;10:275; doi: 10.3389/fnagi.2018.00275.

20. Arvanitakis Z, Shah RC, Bennett DA. Diagnosis and Management of Dementia: Review. JAMA 2019;322(16):1589–1599; doi: 10.1001/jama.2019.4782.

21. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7(3):270–279; doi: 10.1016/j.jalz.2011.03.008.

22. Alzheimer's Association. Alzheimer's Disease Facts and Figures. 2024. Available from: https://www.alz.org/alzheimers-dementia/facts-figures [Last accessed: 2/5/2025].

23. Jansen WJ, Ossenkoppele R, Knol DL, et al. Prevalence of Cerebral Amyloid Pathology in Persons Without Dementia: A Meta-analysis. JAMA 2015;313(19):1924–1938; doi: 10.1001/jama.2015.4668.

24. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. The Lancet 2020;396(10248):413–446; doi: 10.1016/S0140-6736(20)30367-6.

25. Stern Y, Arenaza-Urquijo EM, Bartrés-Faz D, et al. Whitepaper: Defining and investigating cognitive reserve, brain reserve, and brain maintenance. Alzheimers Dement 2020;16(9):1305–1311; doi: 10.1016/j.jalz.2018.07.219.

26. Crane PK, Gibbons LE, Dams-O'Connor K, et al. Association of Traumatic Brain Injury With Late-Life Neurodegenerative Conditions and Neuropathologic Findings. JAMA Neurol 2016;73(9):1062–1069; doi: 10.1001/jamaneurol.2016.1948.

27. Sivanandam TM, Thakur MK. Traumatic brain injury: a risk factor for Alzheimer's disease. Neurosci Biobehav Rev 2012;36(5):1376–1381; doi: 10.1016/j.neubiorev.2012.02.013.

28. Barnes DE, Kaup A, Kirby KA, et al. Traumatic brain injury and risk of dementia in older veterans. Neurology 2014;83(4):312–319; doi: 10.1212/WNL.0000000000000616.

29. Nordström A, Nordström P. Traumatic brain injury and the risk of dementia diagnosis: A nationwide cohort study. PLoS Med 2018;15(1):e1002496; doi: 10.1371/journal.pmed.1002496.

30. Barnes DE, Byers AL, Gardner RC, et al. Association of Mild Traumatic Brain Injury With and Without Loss of Consciousness With Dementia in US Military Veterans. JAMA Neurology 2018;75(9):1055–1061; doi: 10.1001/jamaneurol.2018.0815.

31. Lee Y-K, Hou S-W, Lee C-C, et al. Increased risk of dementia in patients with mild traumatic brain injury: a nationwide cohort study. PLoS One 2013;8(5):e62422; doi: 10.1371/journal.pone.0062422.

32. Johnson VE, Stewart W, Smith DH. Widespread τ and amyloid-β pathology many years after a single traumatic brain injury in humans. Brain Pathol 2012;22(2):142–149; doi: 10.1111/j.1750-3639.2011.00513.x.

33. Mortamais M, Ash JA, Harrison J, et al. Detecting Cognitive Changes in Preclinical Alzheimer's Disease: A Review of Its Feasibility. Alzheimer's and Dementia 2017;13(4):468–492; doi: 10.1016/j.jalz.2016.06.2365.

34. Salthouse TA. Why Are There Different Age Relations in Cross-Sectional and Longitudinal Comparisons of Cognitive Functioning? Current Directions in Psychological Science 2014;23(4):252–256; doi: 10.1177/0963721414535212.

35. Alexander GE, Bergfield KL, Chen K, et al. Gray matter network associated with risk for Alzheimer's disease in young to middle-aged adults. Neurobiology of Aging 2012;33(12):2723–2732; doi: 10.1016/j.neurobiolaging.2012.01.014.

36. Irwin K, Sexton C, Daniel T, et al. Healthy Aging and Dementia: Two Roads Diverging in Midlife? Frontiers in Aging Neuroscience 2018;10(SEP):275; doi: 10.3389/fnagi.2018.00275.

37. Westlye LT, Reinvang I, Rootwelt H, et al. Effects of APOE on brain white matter microstructure in healthy adults. Neurology 2012;79(19):1961–1969; doi: 10.1212/WNL.0b013e3182735c9c.

38. Persson J, Lind J, Larsson A, et al. Altered brain white matter integrity in healthy carriers of the APOE epsilon4 allele: a risk for AD? Neurology 2006;66(7):1029–1033; doi: 10.1212/01.wnl.0000204180.25361.48.

39. Tremblay S, Henry LC, Bedetti C, et al. Diffuse white matter tract abnormalities in clinically normal ageing retired athletes with a history of sports-related concussions. Brain 2014;137(11):2997–3011; doi: 10.1093/brain/awu236.

40. Monti JM, Voss MW, Pence A, et al. History of mild traumatic brain injury is associated with deficits in relational memory, reduced hippocampal volume, and less neural activity later in life. Front Aging Neurosci 2013;5:41; doi: 10.3389/fnagi.2013.00041.

41. Devanarayan V, Doherty T, Charil A, et al. Plasma pTau217 predicts continuous brain amyloid levels in preclinical and early Alzheimer's disease. Alzheimers Dement 2024;20(8):5617–5628; doi: 10.1002/alz.14073.

42. Ashton NJ, Brum WS, Di Molfetta G, et al. Diagnostic Accuracy of a Plasma Phosphorylated Tau 217 Immunoassay for Alzheimer Disease Pathology. JAMA Neurology 2024;81(3):255–263; doi: 10.1001/jamaneurol.2023.5319.

43. Mattsson N, Cullen NC, Andreasson U, et al. Association between Longitudinal Plasma Neurofilament Light and Neurodegeneration in Patients with Alzheimer Disease. JAMA Neurology 2019;76(7):791–799; doi: 10.1001/jamaneurol.2019.0765.

44. Zetterberg H, Bendlin BB. Biomarkers for Alzheimer's disease—preparing for a new era of disease-modifying therapies. Molecular Psychiatry 2020; doi: 10.1038/s41380-020-0721-9.

45. Plantone D, Pardini M, Righi D, et al. The Role of TNF-α in Alzheimer's Disease: A Narrative Review. Cells 2023;13(1):54; doi: 10.3390/cells13010054.

46. Elahi FM, Casaletto KB, La Joie R, et al. Plasma biomarkers of astrocytic and neuronal dysfunction in early- and late-onset Alzheimer's disease. Alzheimer's & Dementia 2020;16(4):681–695; doi: 10.1016/j.jalz.2019.09.004.

47. Pereira JB, Janelidze S, Smith R, et al. Plasma GFAP is an early marker of amyloid-β but not tau pathology in Alzheimer's disease. Brain 2021;144(11):3505–3516; doi: 10.1093/brain/awab223.

48. Shen XN, Niu LD, Wang YJ, et al. Inflammatory markers in Alzheimer's disease and mild cognitive impairment: A meta-analysis and systematic review of 170 studies. Journal of Neurology, Neurosurgery and Psychiatry 2019;90(5):590–598; doi: 10.1136/jnnp-2018-319148.

49. Pedrini S, Gupta VB, Hone E, et al. A blood-based biomarker panel indicates IL-10 and IL-12/23p40 are jointly associated as predictors of β-amyloid load in an AD cohort. Sci Rep 2017;7(1):14057; doi: 10.1038/s41598-017-14020-9.

50. Álvarez A, Cacabelos R, Sanpedro C, et al. Serum TNF-alpha levels are increased and correlate negatively with free IGF-I in Alzheimer disease. Neurobiology of Aging 2007;28(4):533–536; doi: 10.1016/j.neurobiolaging.2006.02.012.

51. Shahim P, Pham DL, van der Merwe AJ, et al. Serum NfL and GFAP as biomarkers of progressive neurodegeneration in TBI. Alzheimers Dement 2024;20(7):4663–4676; doi: 10.1002/alz.13898.

52. Shahim P, Politis A, van der Merwe A, et al. Time course and diagnostic utility of NfL, tau, GFAP, and UCH-L1 in subacute and chronic TBI. Neurology 2020;95(6):e623–e636; doi: 10.1212/WNL.0000000000009985.

53. Chaban V, Clarke GJB, Skandsen T, et al. Systemic Inflammation Persists the First Year after Mild Traumatic Brain Injury: Results from the Prospective Trondheim Mild Traumatic Brain Injury Study. J Neurotrauma 2020;37(19):2120–2130; doi: 10.1089/neu.2019.6963.

54. Hill NTM, Mowszowski L, Naismith SL, et al. Computerized cognitive training in older adults with mild cognitive impairment or dementia: A systematic review and meta-analysis. American Journal of Psychiatry 2017;174(4):329–340; doi: 10.1176/appi.ajp.2016.16030360.

55. Bahar-Fuchs A, Clare L, Woods B. Cognitive training and cognitive rehabilitation for mild to moderate Alzheimer's disease and vascular dementia. Cochrane Database of Systematic Reviews 2013;2013(6); doi: 10.1002/14651858.CD003260.pub2.

56. Musteata S, Yoshida K, Baranzini D, et al. Perceptual-Cognitive Training Can Improve Cognition in Older Adults with Subjective Cognitive Decline. Research Open 2019;3(6):1–15.

57. Spaner CR, Musteata S, Kenny RA, et al. 3-Dimensional Multiple Object Tracking Training Can Enhance Selective Attention , Psychomotor Speed , and Cognitive Flexibility in Healthy Older Adults. Research Open 2019;3(4).

58. Chandler MJ, Parks AC, Marsiske M, et al. Everyday Impact of Cognitive Interventions in Mild Cognitive Impairment: a Systematic Review and Meta-Analysis. Neuropsychology Review 2016;26(3):225–251; doi: 10.1007/s11065-016-9330-4.

59. Legault I, Allard R, Faubert J. Healthy Older Observers Show Equivalent Perceptual-Cognitive Training Benefits to Young Adults for Multiple Object Tracking. Front Psychol 2013;4:323; doi: 10.3389/fpsyg.2013.00323.

60. Snowden T, Ohlhauser L, Morrison J, et al. A Protocol for Remote Cognitive Training Developed for Use in Clinical Populations During the COVID-19 Pandemic. Neurotrauma Rep 2023;4(1):522–532; doi: 10.1089/neur.2023.0009.