The influence of lifelong mild traumatic brain injury on late-life cognition and white matter microstructure in older adults at risk of Alzheimer's disease

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ABSTRACT

Background. The long-term combined effects of mild traumatic brain injury (mTBI) and *APOE* ε4-allele carrier status (*APOE*4+/-), a genetic risk factor of Alzheimer's disease (AD), on later-life cognitive outcomes, Alzheimer's risk based on biomarker levels, and white matter structural integrity in older adults at-risk of AD are not fully understood. Determining these combined effects is crucial to advance our knowledge of the intricate relationship between head injuries, genetic predisposition, and later-life cognition. This knowledge could potentially inform preventive strategies and interventions, providing valuable insights into how certain individuals may be more susceptible to cognitive decline and structural brain changes after mTBI.

Methods. To investigate mTBI effects on late-life neurobehavioural outcomes, cognitively unimpaired adults over age 55 with a parental or multiple-sibling history of AD, from the PREVENT-AD cohort, were included in this study. Participants that self-reported at least one prior mTBI at any point in their life, defined by self-reported loss of consciousness and/or memory gap (n=60, 38.3% *APOE*4+) were demographically matched (age, sex, education) to individuals without self-reported mTBI (n=72, 38.9% *APOE*4+). Cognitive outcomes were evaluated using the Rey Auditory Verbal Learning Test measuring memory, Color-Word Interference Test (CWIT) and Trail Making Test (TMT) both measuring processing speed and executive function. To identify the brain basis of potential cognitive differences between groups, we then sought to determine the extent to which individuals with a history of mTBI showed evidence of preclinical AD, compared to matched controls, based on tau and beta-amyloid PET imaging. In addition, we characterized the extent to which there were group differences in white matter microstructure associated with putative cognitive differences between groups. Further investigation of white matter tracts, focused on bilateral superior longitudinal fasciculus and superior fronto-occipital fasciculus, was conducted using diffusion tensor imaging to evaluate underlying structural differences between groups. Data were analyzed using 2-way ANCOVAs controlling for demographics (sex, age, years of education) and corrected for multiple comparisons.

Results. Significant main effect of prior head injury on executive function and processing speed measures including CWIT word reading, inhibition, and switching tasks (all $p<0.05$ corrected) were observed, whereby individuals with prior mTBI performed worse than controls across both domains. No significant group differences in memory function were identified. These group differences were driven by individuals who were non-carrier of *APOE*4 on all sub-scores of

CWIT, TMT Trail B, and TMT (all $p<0.05$ corrected). AD risk was not influenced by prior mTBI; PET findings revealed that only *APOE*4 carriership, but not mTBI history, was significantly associated with elevated β-amyloid and tau deposition, driven by individuals who did not have a history of head injury. *APOE*4 carriership was associated with significantly higher amyloid and tau biomarker levels compared to non-carriers (all $p<0.05$ corrected). Lastly, DTI findings revealed significantly lower axial diffusivity of the right SFOF in the mTBI group compared to the matched control group. An exploratory analysis of the whole brain revealed that individuals with prior mTBI had decreased axial diffusivity of the left anterior corona radiata but increased axial diffusivity of the left cerebral peduncle compared to controls.

Conclusion. Our findings suggest that prior mTBI impacts late-life cognition in older adults at-risk for AD but depends differentially on *APOE4* carrier status. Specifically, prior mTBI negatively impacts later-life processing speed and executive function. Additionally, prior mTBI does not significantly increase AD-related pathological changes as determined by PET biomarker amyloid and tau accumulation. Examination of group differences in white matter microstructure revealed decreased axial diffusivity of the right SFOF in individuals with prior mTBI compared to matched controls. This reduction in AxD may indicate differences in axonal integrity between groups. These results underscore the complexity of the relationship between prior mTBI and genetic risk of AD on late-life cognitive outcomes, AD pathological changes, and white matter integrity. Taken together, these findings emphasize the need for further research to elucidate the underlying mechanisms and potential long-term consequences of mTBI in the context of at-risk aging.

RÉSUMÉ

Contexte. Les effets combinés à long terme des traumatismes crâniens légers (TCL) et du statut de porteur de l'allèle APOE ε4 (APOE4+/-), un facteur de risque génétique de la maladie d'Alzheimer (MA), sur les résultats cognitifs ultérieurs, le risque d'Alzheimer basé sur les niveaux de biomarqueurs et l'intégrité structurelle de la matière blanche chez les adultes plus âgés à risque de MA ne sont pas entièrement compris. Il est essentiel de déterminer ces effets combinés pour faire progresser nos connaissances sur la relation complexe entre les traumatismes crâniens, les prédispositions génétiques et la cognition au cours de la vie. Ces connaissances pourraient potentiellement éclairer les stratégies et les interventions préventives, en fournissant des informations précieuses sur la manière dont certaines personnes peuvent être plus susceptibles au déclin cognitif et aux changements structurels du cerveau après un traumatisme crânien.

Méthodes. Pour étudier les effets du TCL sur les résultats neurocomportementaux en fin de vie, des adultes cognitivement normaux de plus de 55 ans ayant des antécédents parentaux ou de frères et sœurs multiples de la MA, issus de la cohorte PREVENT-AD, a été inclus dans l'étude. Les participants ayant déclaré avoir subi au moins un TCL à un moment quelconque de leur vie, défini par une perte de conscience et/ou un trou de mémoire (n=60, 38,3 % APOE4+) ont été appariés sur le plan démographique (âge, sexe, éducation) à des personnes n'ayant pas déclaré de traumatisme crânien (n=72, 38,9 % APOE4+). Les résultats cognitifs ont été évalués à l'aide du RAVLT, qui mesure la mémoire, du CWIT et du TMT, qui mesurent tous deux la vitesse de traitement et les fonctions exécutives. Afin d'identifier la base cérébrale des différences cognitives potentielles entre les groupes, nous avons ensuite cherché à déterminer dans quelle mesure les personnes ayant subi un TCL présentaient des signes de MA préclinique, par rapport aux témoins appariés, sur la base de l'imagerie par tomographie par émission de positrons de la protéine tau et de la bêta-amyloïde. En outre, nous avons caractérisé la mesure dans laquelle il y avait des différences de groupe dans la microstructure de la matière blanche associées à des différences cognitives supposées entre les groupes. L'imagerie du tenseur de diffusion a permis d'approfondir l'étude des voies de la substance blanche, en se concentrant sur le faisceau longitudinal supérieur bilatéral et le faisceau fronto-occipital supérieur, afin d'évaluer les différences structurelles sous-jacentes entre les groupes. Les données ont été analysées à l'aide d'ANCOVA à deux voies contrôlant les données démographiques (sexe, âge, années d'études) et corrigées pour les comparaisons multiples.

Résultats. Un effet principal significatif du TCL sur les mesures de la fonction exécutive et de la vitesse de traitement, y compris les tâches de lecture de mots, d'inhibition et de commutation du CWIT (tous les $p<0,05$ corrigés) a été observé, les personnes ayant subi un TCL obtenant de moins bons résultats que les témoins dans les deux domaines. Aucune différence significative entre les groupes n'a été identifiée en ce qui concerne la fonction de mémorisation. Ces différences entre les groupes étaient dues aux individus qui n'étaient pas porteurs de l'APOE4 dans tous les sous-scores du CWIT, du TMT Trail B et du TMT (tous les $p<0,05$ corrigés). Le risque de MA n'a pas été influencé par un TCL; les résultats de la tomographie par émission de positrons ont révélé que seule la carrière APOE4, mais pas les antécédents de TCL, était significativement associée à un dépôt élevé de β-amyloïde et de tau, chez les personnes qui n'avaient pas d'antécédents de TCL. Le portage de l'APOE4 était associé à des niveaux de biomarqueurs amyloïdes et tau significativement plus élevés par rapport aux non-porteurs (tous les $p<0,05$ corrigés). Enfin, les résultats de l'imagerie par résonance magnétique ont révélé une diffusivité axiale du SFOF droit significativement plus faible dans le groupe TCL que dans le groupe témoin apparié. Une analyse exploratoire du cerveau entier a révélé que les individus ayant subi un TCL avaient une diffusivité axiale réduite de la corona radiata antérieure gauche mais une diffusivité axiale accrue du pédoncule cérébral gauche par rapport aux témoins.

Conclusion. Nos résultats suggèrent que le TCL a un impact sur la cognition en fin de vie chez les adultes âgés à risque de MA, mais dépend de manière différentielle du statut de porteur de l'APOE4. Plus précisément, les antécédents de TCL ont un impact négatif sur la vitesse de traitement et les fonctions exécutives à un âge avancé. En outre, un historique de TCL n'augmente pas de manière significative les changements pathologiques liés à la MA, tels que déterminés par l'accumulation d'amyloïde et de tau, biomarqueurs de la TEP. L'examen des différences de groupe dans la microstructure de la matière blanche a révélé une diminution de la diffusivité axiale du SFOF droit chez les personnes ayant subi un TCL par rapport aux témoins appariés. Cette réduction de la diffusivité axiale peut indiquer des différences d'intégrité axonale entre les groupes. Ces résultats soulignent la complexité de la relation entre le TCL et le risque génétique de la MA sur les résultats cognitifs à la fin de la vie, les changements pathologiques de la MA et l'intégrité de la matière blanche. Dans l'ensemble, ces résultats soulignent la nécessité de poursuivre les recherches pour élucider les mécanismes sous-jacents et les conséquences potentielles à long terme des traumatismes crâniens dans le contexte du vieillissement à risque.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
Aβ	Amyloid-beta protein
AD	Alzheimer's Disease
APOE	Apolipoprotein
*APOE*4	Apolipoprotein ε4 allele
AxD	Axial diffusivity
CWIT	Color Word Interference Test, D-KEFS
DTI	Diffusion tensor imaging
MRI	Magnetic resonance imaging
mTBI	Mild traumatic brain injury
PET	Positron emission tomography
PREVENT-AD	Pre-symptomatic Evaluation of Experimental or Novel Treatments for Alzheimer Disease
RAVLT	Rey's Auditory Verbal Learning Test
SFOF	Superior fronto-occipital fasciculus
SLF	Superior longitudinal fasciculus
TBI	Traumatic brain injury
TMT	Trail Making Test

INTRODUCTION

Alzheimer's Disease: A Global Epidemic

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is a leading cause of dementia worldwide, accounting for 60% to 80% of all cases, which currently has no cure.[1] AD is characterized by cognitive impairment, neuropsychiatric, and behavioral changes that can significantly impact the affected individual's quality of life.[2] Additionally, the stigma and lack of understanding surrounding the detrimental progression of AD contribute to the burden experienced by families, caregivers, and the community that surrounds the diagnosed individual. According to the World Health Organization, an estimated 55 million people worldwide are living with dementia, with nearly 10 million new cases each year.[1] In Canada alone, there are currently 747,000 Canadians living with dementia in 2020, with the annual cost of care to be over $10.4 billion to the economy and healthcare system.[3,4] With our aging population, the prevalence of AD is expected to triple by 2050.[5] This presents a significant challenge for healthcare systems globally with both social and economic implications, making this a critical public health issue. Thus, it is essential to focus on AD prevention to reduce the burden of this disease.

Alzheimer's Disease Risk Factors

It is crucial to address the issue of understanding modifiable factors associated with AD, especially among individuals who are most at risk for this illness. Family history of AD is a well-established risk factor for developing the disease. Studies have consistently shown that having a first-degree relative with AD increases the risk of developing the disease two to three-fold compared to individuals without a family history of the disease.[6–8] The exact mechanisms behind this increased risk are not fully understood, but it is likely due to a combination of genetic and environmental factors. Individuals with a family history of AD may carry genetic risk factors that increase their susceptibility to developing the disease. Additionally, individuals with a family history of AD may be exposed to similar environmental risk factors, such as lifestyle habits, social determinants of health or health conditions, that increase their risk of developing the disease.[9,10] By examining how risk factors contribute to the cognitive decline and brain changes associated with AD, we can help promote healthy aging specifically amongst at-risk individuals.

AD is a complex multifactorial disease with a variety of risk factors, both modifiable and nonmodifiable. Nonmodifiable risk factors, such as age, genetics, and family history, cannot be changed; however, modifiable risk factors can be targeted for prevention of AD. Recent

recommendations from the *Lancet* Commission on "Dementia prevention, intervention, and care" emphasizes the importance of identifying and mitigating potentially modifiable risk factors that could prevent or delay 40% of all dementia cases.[9] In that report, the authors identified traumatic brain injury (TBI) as a risk factor for AD, which accounts for 3% population attributable risk, meaning the percent reduction in dementia prevalence if this risk was eliminated.[9] Along with AD and other dementias, TBI is amongst the most common neurological condition that is a major source of mental and physical disability.[11] In Canada, about 200,000 head injuries are reported annually; a statistic that is likely underestimated as many concussion, or mild TBI, diagnoses are unreported.[12] That's one in four adults who end up acquiring a head injury at some point during their lives. As with AD, TBI is a public health concern with a global incidence of up to 69 million persons sustaining a TBI per year, which creates similar socioeconomic burdens to individuals and our society.[13,14] Given the high prevalence, there is an immediate need to address TBI as a potentially modifiable risk factor for AD.

Prior head injuries: A modifiable risk factor for Alzheimer's Disease

It has been well documented that moderate to severe TBI contributes to accelerated cognitive aging and earlier onset of dementia.[15–19] However, less is known about the long-term impacts of mild TBI (mTBI), which is the most common form of head injury, especially to individuals at-risk of AD. MTBI is a form of brain injury caused by an external force, such as a blow to the head or a jolt to the body.[20] And mTBI is characterized by less severe symptoms: brief or no loss of consciousness, and a generally quicker recovery compared to the more pronounced symptoms, extended loss of consciousness, and potential long-term impairments associated with moderate to severe TBI.[11,13,17] It is known that even mTBI affects structure and function of the brain,[21] and if left untreated, there may be long-term impacts that may potentially lead to neurodegenerative diseases.[22,23]

Cognitive outcomes of mTBI can vary widely depending on the severity and location of the injury, but some common effects include deficits in attention, processing speed, memory, and executive function.[23] Reduced cognitive abilities immediately after a head injury has been extensively studies amongst athletes, military personnel, and other populations at high risk for mTBI. One study found that college football players with a history of mTBI had significantly worse performance on tests of processing speed and working memory compared to players without

a history of mTBI.[13] However, there is currently no consensus on the impact of mTBI on later-life cognitive outcomes, especially in the population of older adults at-risk for AD.[24]

Moreover, previous research indicates that individuals with a history of moderate to severe TBI and post-mortem studies of those with repetitive mild TBIs may develop chronic traumatic encephalopathy.[16,25] This condition is characterized by an abnormal increase in tau deposition, a protein that also accumulates in AD.[26–28] Prior studies have established a link between moderate to severe TBI to the accumulation of amyloid-β (Aβ) and tau, both considered markers of AD.[26,28–36] The presence of these abnormal protein aggregates is indicative of underlying pathological changes and suggests a potential link between mTBI and the development or progression of AD. The deposition of both beta-amyloid and tau have been linked to AD, with biomarker aggregates throughout the deep and subcortical white matter.[34,35]

Apolipoprotein E: A genetic risk factor in AD and mTBI

The apolipoprotein E (*APOE*) gene is identified as a major genetic risk factor for AD. The mechanism by which *APOE* genotype affects AD risk is not fully understood, but it is believed to be related to its role in cholesterol metabolism and transport.[37] Evidently, the *APOE* ε4 (*APOE*4) allele, a known genetic risk factor for AD, has been found to interact with mTBI, resulting in increased amyloid-beta deposition and neuroinflammation.[30,31,33] This raises the possibility that mTBI, particularly in individuals carrying the *APOE* e4 allele, may accelerate the accumulation of AD-related biomarkers and contribute to the development of AD pathology.

The *APOE*4 allele has been found to increase the risk of AD, while the *APOE*2 allele has a protective effect on the risk of developing AD.[38] Studies have shown that individuals with the *APOE*4 allele have higher levels of beta-amyloid in the brain and are more likely to develop AD, even though not all individuals with *APOE*4 develop AD.[39–41] There is a notable distinction between AD and cognitive decline, particularly evident in the poor correlation observed between cognition and biomarker deposition. The Rush Memory and Aging Project study revealed that only 25% of the variance in cognition is explained by the presence of amyloid and tau biomarkers.[42] Notably, this link between biomarkers and cognition is weakest in older individuals, highlighting the complexity of factors influencing cognitive decline beyond the traditional biomarker-centric understanding of AD. Some research has shown that carriers of *APOE*4 have worse recovery and increased cognitive impairment post-injury.[43] However, the association between *APOE*4 carriership and post-concussive cognitive function is controversial. In another observational study,

a contrasting result emerged in children, where individuals post-mTBI who were carriers of *APOE*4 had better cognitive and functional recovery than their non-carrier counterparts.[38] This suggests that the *APOE*4 allele may confer a protective effect in certain situations. Although the consensus of the contributing factor of *APOE*4 on mTBI sequelae are not fully understood, experimental and epidemiological brain injury studies support the important role of the *APOE* gene on the outcomes after brain injury.[37]

Problem Statement

It remains unclear how lifelong mTBI contributes to late-life cognition in adults at-risk of AD. Understanding the risk factors leading to AD is a high priority: prior head injury may be a risk factor for neurodegeneration and there is controversial evidence of an association between prior head injuries and accumulation of AD-related biomarkers. Understanding the impact of mTBI on the potential development of preclinical AD is important for elucidating the role of mTBI in disease pathogenesis. Prior findings highlight the need for further research to determine the extent to which mTBI may be associated with the development or progression of AD. Additionally, individuals with *APOE*4 allele, a genetic risk factor of AD, may also susceptible to worse cognitive outcomes post-injury, however this question has not been fully addressed.[25,44,45] Thus, this highlights the importance of understanding the interaction between prior head injury and *APOE*4 status on accelerated cognitive decline and AD pathological changes among those who are already at-risk of AD. By gaining a better understanding of this relationship, novel strategies for early detection, prevention, and treatment of AD can be developed.

BACKGROUND

AD is a progressive neurodegenerative disorder that affects brain structure and function, impacting cognitive abilities including memory, attention, social, language, visuospatial and executive function.[2] The pathological basis of AD involves the accumulation of beta-amyloid plaques and tau protein tangles in the brain, which disrupt the communication between nerve cells and eventually lead to cell death.[34,46] These changes leads to the degeneration of specific brain regions, including the hippocampus, the parietal cortex, and the temporal cortex, which are crucial for memory consolidation and retrieval.[47,48] Additionally, neuroimaging studies have shown that the damage caused by AD is often more severe in white matter tracts that connect these regions, such as the cingulum, the fornix, and the uncinate fasciculus.[49] These white matter changes are associated with cognitive decline, including memory impairment.[49,50] It's important to acknowledge that our understanding of the complexity of AD pathogenesis is evolving, and researchers are exploring various factors, including lifestyle factors (i.e., diet, physical activity, sleep, etc.) on an individual and on a population level, to gain a more comprehensive understanding.

AD is typically diagnosed based on cognitive and behavioural symptoms coupled with objective signs converging across the clinical history, standardized cognitive and behavioural measures integrated into a comprehensive neurobehavioural status exam. Neuroimaging is used to rule out secondary causes of these changes, but currently does not make the diagnosis. Early detection of AD is critical for effective interventions, and there is increasing interest in identifying individuals in the preclinical stage of the disease when interventions are most likely to have the largest impact of prevention and/or neuroprotection. Preclinical AD is characterized by the abnormal accumulation of Aβ plaques and tau in the brain, which can be detected through imaging techniques such as positron emission tomography (PET) scans, before the onset of noticeable clinical symptoms.[46] Prior work has shown that repetitive mTBI can result in the accumulation of hyperphosphorylated tau detectable with PET imaging.[51] In this preclinical stage, individuals do not show evidence of cognitive or behavioural change, nor do they have any functional change that impedes their daily living. Early identification of AD and intervention at this interval is crucial to delay or prevent the onset of dementia.

Post-injury symptoms following mTBI is known to affect various cognitive abilities, including attention, memory, processing speed, and executive function.[52] There is converging

evidence that links the effects of mTBI with cognitive function are thought to result in part from the disruption of white matter tracts that connect different brain regions, such as the corpus callosum, the cingulum, and the frontal and temporal lobes.[53,54] White matter and grey matter have distinct compositions and structures, contributing to their varying sensitivities to head injuries. White matter consists of myelinated axons, which are nerve fibers responsible for transmitting signals between different brain regions. These axons are vulnerable to shearing forces during head trauma, leading to axonal injury or damage. The long, extended nature of white matter tracts makes them more susceptible to rotational forces, causing shearing and stretching of axons. In contrast, grey matter primarily comprises neuronal cell bodies, dendrites, and synapses. While grey matter can also be affected by head injuries, it is generally less susceptible to shearing forces due to its denser, more compact structure.[55,56] Grey matter injuries often result from direct impact or contact, as seen in focal contusions or coup-contrecoup injuries. The differential vulnerability of white and grey matter is also influenced by their respective roles in information processing. White matter facilitates communication between different brain regions, making it crucial for integrated cognitive functions. Disruptions in white matter connectivity can lead to cognitive deficits observed in conditions including TBI. Overall, the distinct anatomical and compositional features of white and grey matter contribute to the relative sensitivity of white matter to shearing forces, making it more prone to injury in the context of head trauma.

Specifically, the bilateral tracts of interest are the superior longitudinal fasciculus (SLF) and superior frontal occipital fasciculus (SFOF), which are long association tracts in the brain that connect the frontal to the parietal and occipital lobes.[57,58] These white matter tracts run longitudinally, which is thought to be an orientation most susceptible to injury post-mTBI, due to the mechanism of injury.[59] In TBI, the mechanism of injury involves either direct or indirect impact causing a sudden acceleration and deceleration of the brain to collide with the skull. Integrity of SLF is associated with attentional skills and plays a role in visuospatial ability, perceptual organization, and working memory.[60] SFOF is critical to semantic language processing and visual switching tasks.[61] Our focus on the SLF and SFOF tracts are due to the associated cognitive functions that have been shown to be significantly impaired post-TBI across cognitive domains specifically working memory, processing speed, inhibitory control, and attention.[18,24,61–63] Neuroimaging studies have shown that mTBI can cause axonal damage, microstructural changes, and alterations in white matter connectivity.[64–66] These changes are associated with cognitive

impairment and can lead to persistent cognitive deficits even after the resolution of early post-concussive symptoms.

Diffusion tensor imaging (DTI) measures the diffusion of water molecules in tissues which can non-invasively quantify white matter integrity and grossly characterize structural features, including axonal membrane status, myelin sheath thickness, number of intracellular neurofilaments and microtubules, axonal packing density, and inflammation or edema. The three diffusivity parameters ($\lambda 1$, $\lambda 2$, and $\lambda 3$) are used to describe water diffusivity, which can be further characterized as parallel ($\lambda 1$) and perpendicular ($\lambda 2$ and $\lambda 3$) components to the axonal tract. Axial diffusivity (AxD) describes the mean diffusion coefficient of water molecules diffusing parallel to the tract within the voxel of interest: $\lambda \| \equiv \lambda 1 > \lambda 2, \lambda 3$. AxD measures directionality of water only along the primary axis of the longitudinal eigenvalue in comparison to a summative average of two and three eigenvalues, referencing radial and mean diffusivity respectively.[67–69] Nir et al. noted that AxD is more sensitive to the subtle differences presented in older adults with mild cognitive impairment compared to fractional anisotropy.[70] Based on our study's main objectives, we focused on AxD over other DTI metrics, such as fractional anisotropy, as it is sensitive to axonal damage or alterations in fiber structure that could be susceptible to damage post-TBI. As our primary measure, AxD provides information about the integrity and organization of axons, which is key in revealing potential alterations related to axonal damage or directional changes within white matter tracts of interest.[53,54,64,66] Understanding how prior mTBI impacts white matter integrity of older adults could help reveal underlying mechanisms of cognitive differences between those with and those without a history of prior head injury. Particularly, demyelination of both the SLF and SFOF tracts has been linked to cognitive decline.[71] Investigating these specific tracts allows for a targeted exploration of the regions associated with cognitive deficits post-mTBI. While examining global white matter tracts provides a data-driven examination, a focused analysis on SLF and SFOF aligns with the hypothesis that certain tracts may be more vulnerable or critical to mTBI-related cognitive outcomes, offering a nuanced understanding of the intricate relationship between mTBI, specific white matter tracts, and cognitive function.

Overall, prior research suggests that concussion history is a crucial consideration in assessing cognitive health and risk for AD, and further research is needed to better understand the long-term effects of post-concussion symptoms and the neural mechanisms underlying concussion risk.[17,31,32] It is also essential to conduct larger, more robust studies to better understand the

relationship between concussion and late-life cognitive health.[72,73] Thus, the current study not only aims to examine the impacts of mTBI on individuals at-risk of AD, but also the interaction with AD risk, specifically the contribution of being a carrier of the genetic risk factor, *APOE*4 allele. These results could inform interventions by identifying the group of individuals who are most at risk for long term sequela of mTBI and thus stand most to benefit from targeted dementia prevention.

Rational for the Study

There is evidence to suggest that prior moderate and severe head injuries may be associated with negative long-term effects on cognition, biomarker accumulation, brain structure and clinical outcomes. However, the exact contributions by which mild TBI may increase the risk of cognitive impairment are not fully understood. The mechanism of injury may lead to shearing, axonal damage, and degradation of the white matter structural integrity; as such, Berginström et al. found that TBI patients more commonly presented white matter hyperintensities than the control group.[74] Damage to the brain's white matter may trigger a cascade of neuroinflammation, which is now understood to contribute to AD pathogenesis.[75,76] Although, most supporting evidence of progressive cognitive decline and dementia are linked with moderate and severe TBI, there is growing evidence to support that even mild TBI may contribute to long-term cognitive outcomes. Santhanam et al. reported significant cortical thinning in many regions, including bilateral parietal and left frontal and temporal cortices, in older adults with prior mTBI, which are also seen in patients with AD.[77] However, particular to individuals who are already at-risk of AD, not much is known about how mild TBI may disrupt the structural integrity of the brain and how mild TBI contributes to cognitive decline. The presence of the *APOE*4 gene, a genetic risk factor for AD, may further increase the susceptibility of individuals to worse cognitive outcomes post-injury.[78,79] Thus, it may be critical to understand how mild TBI impacts the brain's white matter, which may lead to impaired communication between brain regions and potentially contributing to cognitive decline over time, in older adults at-risk for AD. AD prevention is important and targeting risk factors can help reduce the incidence of AD.

Research Aims

The primary goal of the proposed research is to determine the extent to which prior head injuries influence late-life cognitive outcomes, and whether *APOE*4 carrier status engenders differential risk of late-life cognitive function. The secondary goals of this study are to determine

the extent to which putative cognitive differences are associated with group differences in AD biomarker status or white matter structural integrity in older adults at-risk of AD. Our goal is to increase our understanding of the contributions of modifiable (mTBI) and non-modifiable (*APOE*4 carriership) risk factors of AD, specifically, in individuals at a higher risk for AD. We hypothesize that a prior history of mTBI will be associated with lower executive function, memory function and processing speed, higher levels of AD-related pathological changes, and decreased white matter structural integrity, specifically in the SLF and SFOF tracts as indexed by diffusion tensor imaging. Specifically, we expected to identify decreased AxD of the white matter tracts of interest, which would indicate chronic axonal injury and disorganization of axons in individuals with a history of mTBI compared to matched controls. Finally, we hypothesized that carriers of *APOE4* would show diminished late-life cognition and increased biomarker accumulation compared to non-carriers.

The specific aims of the research are to:

1. To examine the effect of lifelong mTBI on objective measures of cognitive function, and the extent to which being a carrier for *APOE*4 allele influences this potential interaction in older adults at risk for AD.
2. To assess the impact of prior mTBI and *APOE*4 carriership on amyloid-beta and tau deposition levels in later life, and to determine the potential influence of prior mTBI on AD risk in explaining cognitive differences observed between the groups.
3. To assess for group differences in white matter integrity of tracts related to affected cognitive outcomes due to mTBI, and to examine the impact of prior mTBI on white matter microstructure in older adults at-risk of AD.

METHODS

Participants

To investigate mTBI effects on late-life neurobehavioural outcomes, the PREVENT-AD (Pre-symptomatic Evaluation of Experimental or Novel Treatments for Alzheimer Disease) cohort from the Data Release v6.0 was analyzed. Participants were cognitively unimpaired adults over age 55 with a parental or multiple-sibling history of AD. Recruitment of these participants into the longitudinal PREVENT-AD cohort, and the inclusion and exclusion criteria, are described by Tremblay-Mercier et al.[7] Participants underwent serial comprehensive neuropsychological assessment, including tests of memory, executive functions, attention, and processing speed. All participants had genetic testing for *APOE* status. Additionally, subset of these participants had neuroimaging data including magnetic resonance imaging (MRI) for analyses of white matter microstructure and PET imaging for Aβ and tau levels.

The subsample included in this study met all the criteria for the 2017 cohort and were not excluded from further follow-up. Participants were excluded if they had less than 6 years of formal education, cognitive disorders at the time of recruitment, medication affecting cognition, and/or suffered a moderate or severe TBI (defined below). Inclusion criteria for the mTBI group consists of participants who self-reported at least one prior head injury with either loss of consciousness of less than 30 minutes, acute memory loss, or altered mental state during injury onset. The control group was demographically matched based on age, sex, and years of education, and only included participants who reported no prior head injury during their lifetime. Participants were also categorized into either carriers or non-carriers of *APOE*4 allele. Participants were excluded if they had two copies of the *APOE*4 allele (mTBI, n = 0; control, n = 6), which is more strongly associated with AD risk, or are carriers of the *APOE*2 allele (mTBI, n = 9; control, n = 20), which may have protective properties.[80] Therefore, participants deemed "at-risk" are carriers of *APOE*4 (heterozygous for ε4/ ε3 alleles), and participants deemed "not-at-risk" are non-carriers of *APOE*4 (homozygous for ε3/ε3 alleles).

Mild Traumatic Brain Injury (mTBI)

Participants in the PREVENT-AD cohort were asked to complete a self-reported retrospective assessment of lifelong head injury. A questionnaire was distributed to all participants to provide details on prior, up to a maximum of five, head injuries and included the following information: 1) the mechanism of the head injury; 2) whether they were "knocked out" or

experienced a loss of consciousness, and if so for how long (<30 minutes, 30 minutes to 24 hours, 24 hours or more); 3) whether they experienced altered mental state (e.g., dazed) or memory gap; and 4) the age at which they suffered the head injury. [See Appendix A for self-reported survey used] Out of the total cohort of 339 participants, 115 identified as having suffered at least one head injury in the past. This is an over representative in comparison to the general statistic of 19% of Canadians reporting at least one prior head injury, inclusive of all age ranges.[81,82]

The following definition from the Mild Traumatic Brain Injury Committee of the American Congress of Rehabilitation Medicine was used to define our mTBI group.[83]

> Traumatically induced physiological disruption of brain function, as manifested by at least one of the following:
>
> 1. Any period of loss consciousness
> 2. Any loss of memory for events immediately before/after the accident
> 3. Any alteration in mental state at the time of accident (e.g., feeling dazed, disorientated, confused)
> 4. Focal neurological deficits that may or may not be transient.
>
> Severity of mTBI injury does not exceed:
>
> - loss of consciousness =/< 30 minutes
> - After 30 minutes, initial Glasgow Coma Scale of 13 to 15
> - Post-traumatic amnesia < 24 h

Based on the above criteria, participants who had indicated at least one prior head injury which included a loss of consciousness for less than 30 minutes *and/or* memory loss were kept in this study. This definition of mTBI is currently most commonly used in retrospective studies,[24] and is consistent with American Congress of Rehabilitation Medicine, World Health Organization Collaborating Center Task Force on Mild Traumatic Brain Injury, and Mayo Classification System.[84] Participants who reported one or more prior head injury with no history of loss of consciousness and/or memory loss at any point in time (n = 39) were excluded from this study. We had no access to medical records nor any ability to follow up with the participant to clarify any details on their self-report of prior head injuries. Choosing a more restrictive definition of mTBI excluded potential false negatives between the mTBI and control groups. The range of age, years of education, sex, and *APOE* status were all considered when selecting a matched control group that was age and demographically matched to the mTBI group. Participants who had missing

data or incomplete measures of cognitive outcomes, genetic testing, and demographic information that was collected within the PREVENT-AD Data Release v6.0 were excluded (n = 8). Table 1 outlines the demographic details of the two groups being compared in this study, those who did report at least one prior head injury with a loss of consciousness and/or memory gap (n = 60) and those who did not report any prior head injuries (n = 72). There were no significant group differences in demographic criteria, using $p < 0.05$ for significance level.

Table 1. Participant demographic information and clinical characteristics for individuals included in the analysis of late-life cognitive function. MTBI was defined as the presence of at least one prior head injury with loss of consciousness and/or memory gap.

	mTBI (n = 60)	**Controls (n = 72)**
Age		
Mean ± SD (yrs)	68.3 ± 5.5	67.1 ± 4.5
Range (yrs)	min. 58, max. 85.7	min. 57.9, max. 79.5
Sex		
Female — no.(%)	36 (60.0%)	59 (81.9%)
Male — no.(%)	24 (40.0%)	13 (18.1%)
Education, years of		
Mean ± SD (yrs)	15.4 ± 3.8	15.7 ± 3.4
Range (yrs)	min. 7, max. 29	min. 7, max. 27
***APOE*4 carrier status**		
***APOE*4+ — no.(%)**	23 (38.3%)	28 (38.9%)
***APOE*4- — no.(%)**	37 (61.7%)	44 (61.1%)
Characteristics of prior mTBI		
Number of mTBI – mean ± sd	1.8 ± 0.9	0
Single occurrence – no.	25	0
Multiple occurrence – no.	35[a]	0
Age of last mTBI – mean ± sd	35.9 ± 19.7	--
Range (yrs)	min. 8, max. 70	--
Time from last injury – mean ± sd	32.2 ± 19.3	--
Range (yrs)	min. 2.7, max. 68.5	--

Note: All participants in this subset were included in subsequent analyses for aims 2 and 3, where participants in the PET and DTI analyses each represent a subsample of individuals, due to incomplete neuroimaging data, as examined in the primary cognitive analyses, as described here in Table 1.

[a]Within the mTBI group, participants could report up to 5 prior mTBI and were composed of those who reported 2 prior mTBI (n = 28), reported 3 prior mTBI (n = 3), reported 4 prior mTBI (n = 2), and reported 5 prior mTBI (n = 2).

Neuropsychological Measures

Episodic memory was measured using the Rey Auditory Verbal Learning Test (RAVLT). Specifically, outcomes of interest included immediate and delayed recall. Executive functions, specifically inhibitory control, cognitive flexibility, and task-switching, were measured using the Color-Word Interference Test (CWIT) task (inhibition and switching trials) and the Trail Making Test (TMT) Part B. Processing speed was measured using Color-Word Interference Test (CWIT) colour naming and word reading trials and Trail Making Test (TMT) Part A.

Rey Auditory Verbal Learning Test (RAVLT)

The Rey Auditory Verbal Learning Test (RAVLT) is a widely used and well validated task to assess supraspan episodic memory.[85,86] RAVLT is sensitive to early verbal memory deficits in the context of AD.[85,87,88] RAVLT consists of word recall over five learning trials, recall of a distractor list, recall of initial list after the distractor, 30-minutes delayed recall, and recognition of words on initial list by circling target words from a paragraph of words from both lists. The initial list (List A) of 15 words was read out loud to the participant, and immediately asked the participant to recall as many words as possible he/she remembers over 5 consecutive trials (Trials 1 to 5). After, a new list (List B) of 15 different words is read and asked to be recalled immediately (Trial 6). After the List B trial, the participant is asked to recall words from List A (Trial 7). After 30-minutes from the completion of List B recall, the participant is asked to recall words from List A (Trial 8). The total number of correctly recalled words from List A reflect scores of immediate (Trial 7) and delayed recall (Trial 8).

Color-Word Interference Test (CWIT)

Delis-Kaplan Executive Function System Color-Word Interference Test (CWIT) is a validated measure examining a range of executive functions including verbal processing speed, inhibitory control, and cognitive flexibility.[89] CWIT consists of four sections and performance is measured by completion time for each section: color naming, word reading, inhibition, and switching. For colour naming, a series of red, green, and blue squares is presented to the participant to say the names of the colours as quickly as possible without making mistakes. For word reading, a series of the words “red,” “green,” and “blue” in black ink is presented to the participant to read out load as quickly as possible without making mistakes. For inhibition, a series of the words “red,” “green,” and “blue” but printed incongruently in red, green, or blue ink, is presented to the participant to say the colour of the ink as quickly as possible without making mistakes. For

switching, a series of the words “red,” “green,” and “blue” in red, green, or blue ink, but half of these words are enclosed in a box. Participant were asked to say the color of the ink the word is printed (same as the inhibition trial), but to read the word aloud when the word appeared inside the box, as quickly as possible without making mistakes. Raw scores were based on completion time in each section. Normative data obtained using age-adjusted scaled scores from the test manual were used to compare between groups, so that higher the score meant better performance.

Trail Making Test (TMT)

Trail Making Test Part A (TMT-A) measures visual attention and processing speed, whereas, Part B (TMT-B) additionally involves a measure of executive control, task switching, which was originally created by Ralph Reiten in 1944.[90] Part A consists of 25 circles on a page with numbers 1 to 25 inside each circle. Participants draw a line in ascending numerical order in a connect-the-dots fashion as quickly as possible. Part B consists of 25 circles on a page containing numbers 1 to 13 and letters A to L. Participants were asked to start at 1, and alternate in ascending order between numbers and letters, as such: 1-A-2-B-3-C-4-D-5-E-6-F-7-G-8-H-9-I-10-J-11-K-12-L-13. Performance was based on completion time separately for both TMT-A and TMT-B. Derived scores can be calculated using completion time for TMT-A and TMT-B to get the difference (B – A) and ratio (B/A), as measures of executive functioning.[91] Both raw and derived scores are reported, where lower raw scores and higher derived scores correspond to better performance.

Neuroimaging Measures

A subset of participants above also underwent Positron Emission Tomography (PET) to assess Aβ and tau deposition, and DTI using MRI to assess white matter microstructure.

PET Imaging Acquisition

To investigate the relationship between prior mTBI and the burden of Aβ and tau deposition, a subset of the PREVENT-AD participants who underwent PET imaging for both biomarkers were analyzed (n = 31 mTBI group, and n = 60 control group; 4 participants were excluded due to missing Aβ PET scan and/or demographic data). ^{18}F-NAV4694 and ^{18}F-AV1451 (flortaucipir) were used to access for Aβ and tau deposition, respectively, and scans were preprocessed using a standard pipeline (https://github.com/villeneuvelab/vlpp).[92] Based on regions of the Desikan-Killiany atlas, standardized uptake value ratios (SUVRs) were calculated for each region of the whole cerebellum gray matter, as the negative control region, for Aβ PET scans[93]

and the inferior cerebellar gray matter for tau PET.[36] Cutoffs for biomarker positivity was determined by identifying individuals in the high risk category for global Aβ SUVR (≥1.55) and entorhinal tau SUVR (≥1.22).[94,95] Preclinical AD is characterized by both Aβ plaques and pathologic tau deposition at an elevated level (A+T+); biomarker positivity of only Aβ (A+T-) is considered amyloid pathological change and only tau (A-T+) is considered as non-AD pathologic change.[34] We reported the number of individuals with biomarker positivity and included these individuals in subsequent PET imaging analyses due to unwanted reduction in statistical power (see Table 2).

Diffusion Tensor Imaging (DTI) Imaging

Acquisition. Participants were imaged in a 3T MRI scanner (Siemens Tim Trio) with a standard 12-channel head receiver coil; MRI protocol included t1-weighted (t1w) ADNI Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) protocol, fluid attenuated inversion recovery (FLAIR), and 65-direction diffusion weighted imaging (dwi65). T1w images were acquired with field-of-view (FOV) = 256 × 256 acquisition matrix, 1 mm slice thickness, 1 x 1 mm in-plane resolution, repetition time/echo time = 2300/30 ms, and flip angle = 9°. FLAIR images were acquired with FOV = 256 × 256 acquisition matrix, 1 mm slice thickness, 1 x 1 mm in-plane resolution, repetition time/echo time = 2300/30 ms, and inversion time = 1800 ms. The dwi65 images were acquired with FOV = 96 × 96 acquisition matrix, 65 volumes, 2 mm slice thickness, 2 x 2 mm in-plane resolution, repetition time/echo time = 9300/92 ms. Structural scans were first reviewed by an MRI technologist; if abnormalities were identified, they were then reviewed by a neuroradiologist and excluded from the PREVENT-AD cohort.

Preprocessing. To investigate the impact of prior mTBI on white matter microstructure, a subset of all available PREVENT-AD participants from the first aim (total n = 93; where n = 42 mTBI group, and n = 51 control group) with an MRI scan, collected within the same year as the head injury survey, containing the dwi65 sequence were included in this study (see Table 3). From the raw NIfTI file, only eddy corrections were applied and not the mean diffusion map due to the varied distortion between participants' MRI scans. Using FSL, the DTIFit toolbox was used to create maps for the following DTI metrics: fractional anisotropy (FA), axial diffusivity (AxD), and radial diffusivity (RD).[96] Diffusivity along the principal axis (λ_1) is the AxD, and averaged diffusivities along the two minor axes (λ_2 and λ_3) is the RD.[67] FA is calculated by square root the sum of squares of the three eigenvalues, and the dominating direction of water flow along the three

axes will indicate either linear ($\lambda_1 >> \lambda_2 \sim \lambda_3$), planar ($\lambda_1 \sim \lambda_2 >> \lambda_3$), or spherical ($\lambda_1 \sim \lambda_2 \sim \lambda_3$) cases.[67] These are quantitative assessments of the degree of restriction of water movement within the white matter membranes, and prior studies have reported high sensitivity to detect neurodegenerative pathology. Based on our main objectives, only AxD map was considered. Negative values indicated lower relative AxD. TBSS analysis was applied to orientate AxD into standard space (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS/UserGuide).[97] JHU-atlas was applied through FSLmaths to get AxD values by parcellation. The JHU white matter tractography atlas probabilistically identified 20 structures.[98–100]

Table 2. PET analyses: demographic and clinical characteristics between groups.

	mTBI (n = 31)	Controls (n = 60)
Age		
Mean ± SD (yrs)	68.6 ± 4.9	68.9 ± 4.7
Range (yrs)	min. 59.7, max. 78.4	min. 61.4, max. 79.5
Sex		
Female — no.(%)	21 (67.7%)	47 (78.3%)
Male — no.(%)	10 (32.3%)	13 (21.7%)
Education, years of		
Mean ± SD (yrs)	15.1 ± 3.6	15.0 ± 3.3
Range (yrs)	min. 7, max. 24	min. 7, max. 23
***APOE* status**		
***APOE*4+ — no.(%)**	15 (48.4%)	19 (31.7%)
***APOE*4- — no.(%)**	16 (51.6%)	41 (68.3%)
PET imaging, Mean ± SD		
Global Aβ SUVR	1.356 ± 0.384	1.347 ± 0.354
entorhinal tau SUVR	1.058 ± 0.099	1.073 ± 0.149
AT profile[a]		
A-T- — no.(%)	24 (77.4%)	47 (78.3%)
A+T- — no.(%)	4 (12.9%)	4 (6.7%)
A-T+ — no.(%)	2 (6.5%)	2 (3.3%)
A+T+ — no.(%)	1 (3.2%)	7 (11.7%)

Note: All participants in the PET analysis are a subset of those with cognitive tests data that had also undergone PET imaging. The mTBI definition and categorization of APOE4 carriership remained consistent with the previous aim.

a Based on the ATN-framework for AD pathology, where preclinical AD is determined by Aβ positivity (A+) and tau positivity (T+).46

Table 3. White matter analyses: demographic and clinical characteristics of the PREVENT-AD sample.

	mTBI (n = 42)	Controls (n = 51)
Age		
Mean ± SD (yrs)	68.5 ± 5.1	67.1 ± 4.3
Range (yrs)	min. 58, max. 79.5	min. 57.9, max. 78
Sex		
Female — no.(%)	28 (66.7%)	40 (78.4%)
Male — no.(%)	14 (33.3%)	11 (21.6%)
Education, years of		
Mean ± SD (yrs)	15.4 ± 3.8	15.7 ± 3.4
Range (yrs)	min. 7, max. 29	min. 7, max. 27
***APOE* status**		
***APOE*4+ — no.(%)**	16 (38.1%)	18 (35.3%)
***APOE*4- — no.(%)**	26 (61.9%)	33 (64.7%)

Note: All participants included in DTI analyses are a subset of those with cognitive tests data that had also undergone MRI imaging. The mTBI definition and categorization of APOE4 carriership remained consistent across all aims.

Data Analysis

Statistical analyses were performed with both R Version 2023.06.1+524 (Posit Software, 2022) and JASP Version 0.16 (JASP Team, 2021). Analyses were conducted after carefully verifying that the underlying assumptions of the parametric test were satisfied. The Shapiro-Wilk test was performed to ensure the samples were normally distributed. Levene's test of sphericity was conducted to ensure the homogeneity of variances within each group.

Examining potential interactions between lifelonng mTBI and *APOE*4 carriership

To compare group means, analyses of covariance (ANCOVA) was the chosen method to conduct the analyses between the main effects of 1) presence of prior head injury and 2) *APOE*4 allele carriership, while controlling for age, sex, and years of education as covariates of non-interest. This analysis was carried out for the first two aims, whereby all three demographic covariates were used consistently across all cognitive and biomarker analyses. For Aim 1, we examine the effects of prior mTBI on cognitive outcomes where the dependent variables of interest were the sub-measures of each cognitive test, as aforementioned the RAVLT, CWIT, and TMT. To assess whether there was an interaction effect between having a history of mTBI and having the genetic risk factor, based on *APOE*4 carriership, we employed 2x2 ANCOVAs to evaluate this effect on later life cognitive performance on the RAVLT, CWIT, and TMT. These standardized neuropsychological tests measure different domains of executive functioning skills, including episodic memory (i.e., immediate and delayed recall), processing speed, inhibition, and cognitive flexibility.[85,91,101,102] We conducted an ANCOVA to assess the impact of prior mTBI and APOE4 carriership on each sub-test, while controlling for age, sex, and years of education. For Aim 2, the dependent variables of interest were levels of global Aβ SUVR and entorhinal tau SUVR measured by PET imaging. The standard cut-off for high risk was used to determine biomarker positivity for these individuals.[94,95]

All significant main effects of each ANCOVA test were reported with F statistic and partial Eta-squared to explain the effect size to provide a focused measure of the unique contribution of the independent variables to the variance in the dependent variable, while controlling for the covariates. For effect sizes, partial Eta-squared is reported for ANCOVAs, indicating small ($\eta_p^2 \geq 0.01$), moderate ($\eta_p^2 \geq 0.06$), or strong ($\eta_p^2 \geq 0.14$) effects.[103] Bonferroni corrections were applied to correct for multiple comparisons ($\alpha = .01$) and reporting significant group differences ($p < .05$) with effect size (Cohen's d).[103] Planned post-hoc comparisons were conducted to further

investigate the potential interaction effects between mTBI history and *APOE*4 carriership, reporting only significant interactions with effect sizes. For effect sizes, Cohen's d is reported for t-tests, indicating small ($d \geq 0.2$), moderate ($d \geq 0.5$), or strong ($d \geq 0.8$) effects.[103]

Characterizing the relationship between prior mTBI and biomarker levels

We wanted to see if prior mTBI contributed to increased accumulation of the two AD biomarkers, Aβ and tau, compared to those without a prior mTBI. Due to small sample sizes in each category, Fisher's exact test was employed to test whether the distribution of biomarker positive individuals was significantly different between groups. The association between groups of individuals that were biomarker positive and negative was assessed for statistical significance ($p < .05$) with odds ratio, to quantify the strength and direction of the relationship between two variables, and 95% confidence interval, to indicate the level of certainty.

Exploratory analyses of the global effects of mTBI on white matter microstructure

The purpose of this global analyses was to contribute to the current lack of consensus of affected tracts post mTBI, due to the non-focal mechanism of injury with potentially more diffuse consequences. Assumption checks for normality and equality of variances in the data were conducted priorly to determine the appropriate analytic method. Welch's t-test was the chosen method, due to unequal sample sizes, to initially assess for group differences in AxD between individuals with and without a prior mTBI. For effect sizes, Cohen's d is reported for t-tests, indicating small ($d \geq 0.2$), moderate ($d \geq 0.5$), or strong ($d \geq 0.8$) effects.[103] Additionally, an exploratory analysis of all white matter tracts defined by the JHU-parcellated atlas was conducted to uncover potential group differences in AxD values. All tracts with significant group differences were then further examined using multiple linear regression to access the contribution of having a history of mTBI on later life white matter microstructure (as defined by the metrics of AxD), while controlling for age, sex, years of education, and genetics (i.e. *APOE*4 carriership). Bonferroni corrections were applied to correct for multiple comparisons ($\alpha = .01$) and adjusted p-values are reported with effect size (R-squared). For effect sizes, R-squared is reported for each linear regression model to explain small ($R^2 \geq 0.02$), medium ($R^2 \geq 0.13$), or large ($R^2 \geq 0.26$) proportion of the variance in the dependent variable.[80]

RESULTS

The influence of mTBI on late life cognitive function

Table 4 displays the following main effects, for which significance survived Bonferroni correction for multiple comparisons. Planned post-hoc comparisons were carried out to assess significance between the interacting variables, which individualized data and specific group significant differences has been visualized (see Figures 1 to 5).

Measures of processing speed were the completion time for each of these sub-tests: CWIT colour naming, CWIT word reading, and TMT Trial A. For CWIT colour naming, the interaction effect [$F(1,123) = 5.426$, $p = 0.021$, $\eta_p^2 = 0.042$] between prior mTBI and *APOE*4 carrier status was driven by non-carriers of *APOE*4, where *APOE*4- individuals in the control group performed better than *APOE*4- individuals in the mTBI group ($t = 2.780$, $p_{bonf} = 0.038$). For CWIT word reading, there was a main effect of prior mTBI [$F(1,125) = 4.147$, $p = 0.044$, $\eta_p^2 = 0.032$] where the controls performed better than those with a history of mTBI ($t = 2.036$, $d = 0.377$, $p_{bonf} = 0.044$), where this difference was further driven by *APOE4*- individuals ($t = 3.088$, $p_{bonf} = 0.015$). For TMT Trail A, the interaction effect [$F(1,125) = 4.082$, $p = 0.045$, $\eta_p^2 = 0.032$] between prior mTBI and *APOE*4 carrier status did not survive statistical significance after Bonferroni correction in post-hoc comparisons.

Measures of executive functioning skills, specifically inhibition and cognitive flexibility, were measured by the completion time for CWIT inhibition, CWIT switching, and TMT Trail B. Additionally, the derived score of the difference in completion time between TMT Trail A and B was used to isolate the outcome measure corresponding to cognitive flexibility. For CWIT inhibition time, there was both the main effect of prior mTBI [$F(1,125) = 5.898$, $p = 0.017$, $\eta_p^2 = 0.045$] and an interaction effect [$F(1,125) = 5.068$, $p = 0.026$, $\eta_p^2 = 0.039$], where the control group performed better than the mTBI group ($t = 2.429$, $d = 0.427$, $p_{bonf} = 0.017$) driven by the difference of scores among the *APOE*4- individuals ($t = 3.745$, $p_{bonf} = 0.002$). Similarly, for CWIT switching time, the main effect of head injury [$F(1,125) = 5.103$, $p = 0.026$, $\eta_p^2 = 0.039$] and the interaction effect [$F(1,125) = 4.520$, $p = 0.035$, $\eta_p^2 = 0.035$] was found, where the controls out performed individuals with prior mTBI ($t = 2.259$, $d = 0.395$, $p_{bonf} = 0.026$) driven by *APOE*4- individuals ($t = 3.508$, $p_{bonf} = 0.004$). For TMT Trail B, the interaction effect [$F(1,125) = 10.953$, $p = 0.001$, $\eta_p^2 = 0.081$] between prior mTBI and *APOE*4 carrier status was driven by *APOE*4- individuals, where those without prior mTBI out performed those with a history of mTBI ($t = 3.419$, $p_{bonf} = 0.005$).

Additionally, within the mTBI group, *APOE*4+ individuals performed better than *APOE*4- individuals ($t = 3.191$, $p_{bonf} = 0.011$) because they had a lower time score. To better assess the cognitive flexibility component of TMT Trail B, a derived score was calculated by subtracting the difference between completion time on Trial A from Trail B. For the difference score of TMT, the interaction effect [$F(1,125) = 5.721$, $p = 0.018$, $\eta_p^2 = 0.044$] between prior mTBI and *APOE*4 carrier status was driven by *APOE*4- individuals, where those without prior mTBI out performed those with a history of mTBI ($t = 2.834$, $p_{bonf} = 0.032$).

In summary, we found a significant main effect of prior mTBI on late-life cognition, where individuals with prior mTBI performed worse than individuals in the control group, on three sub-scores of CWIT: word reading, inhibition, and switching. Although there was no main effect of *APOE*4 carriership, we found significant interaction effect between having a history of mTBI and *APOE*4 carrier status over all four sub-scores of CWIT, raw scores of TMT trail A and B, and derived difference score of TMT. Due to significant differences in the ANCOVA, post-hoc tests were conducted, with a Bonferroni-corrected alpha level of 0.05 to assess the specific statistically significant interaction between the two independent variables of interest (see Figures 1 to 5). This revealed that the difference of scores between the control and mTBI groups were driven by individuals who are non-carriers of *APOE*4.

Table 4. Summary of results from ANCOVA analyses of cognitive measures considering both prior mTBI and *APOE*4 status.

		Group	*APOE4-* (mean ± SD)	*APOE4+* (mean ± SD)	F (p-value) *APOE* effect	F (p-value) group effect	F (p-value) interaction effect
RAVLT	Immediate recall	mTBI	10.054 ± 3.266	9.174 ± 2.933	0.955 (0.330)	0.270 (0.604)	0.578 (0.448)
		Controls	10.386 ± 2.919	10.250 ± 3.216			
	Delayed recall	mTBI	8.865 ± 3.831	7.957 ± 3.404	0.904 (0.343)	1.299 (0.257)	0.211 (0.647)
		Controls	9.558 ± 3.232	9.143 ± 2.864			
CWIT	Colour naming[a]	mTBI	32.568 ± 4.174	31.478 ± 4.337	0.963 (0.328)	1.273 (0.261)	5.426 (0.021)*
		Controls	29.477 ± 4.151	32.115 ± 4.493			
	Word reading[a]	mTBI	25.568 ± 4.259	24.826 ± 5.114	0.562 (0.455)	4.147 (0.044)*	3.321 (0.071)
		Controls	22.500 ± 2.977	24.500 ± 4.418			
	Inhibition[a]	mTBI	66.486 ± 15.884	60.609 ± 16.062	0.004 (0.952)	5.898 (0.017)*	5.068 (0.026)*
		Controls	54.636 ± 8.678	60.286 ± 12.690			
	Switching[a]	mTBI	70.459 ± 14.719	64.565 ± 17.786	0.262 (0.610)	5.103 (0.026)*	4.520 (0.035)*
		Controls	57.182 ± 11.417	63.821 ± 14.609			
TMT	Trail A[a]	mTBI	43.432 ± 13.226	35.609 ± 12.176	2.309 (0.131)	0.001 (0.974)	4.082 (0.045)*
		Controls	38.023 ± 11.748	39.214 ± 9.267			
	Trail B[a]	mTBI	86.351 ± 21.274	68.870 ± 19.139	2.085 (0.151)	0.999 (0.320)	10.953 (0.001)*
		Controls	69.795 ± 19.139	76.000 ± 18.746			
	Difference (B-A)	mTBI	42.919 ± 17.922	33.261 ± 13.952	0.301 (0.584)	1.368 (0.244)	5.721 (0.018)*
		Controls	31.773 ± 13.148	36.786 ± 16.100			

*Significant results and adjusted for comparing 4 subgroups, $p < 0.05$ corrected

[a]Raw scores are of time in seconds taken to complete each sub-test task, where shorter completion time, or lower the score, corresponds to better performance.

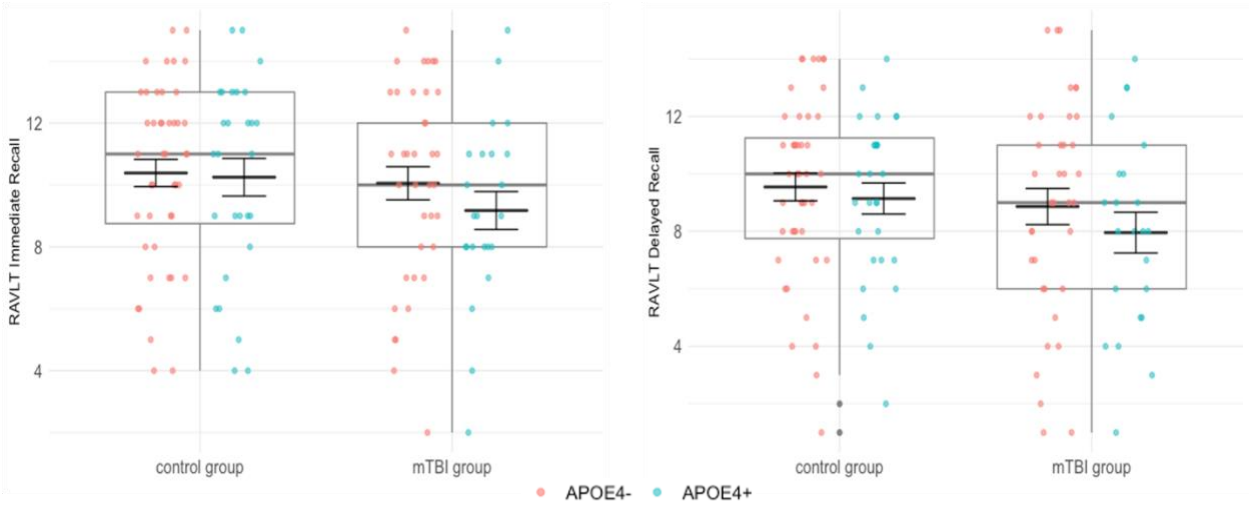

Figure 1. Cognitive domain: Memory.

Prior mTBI had no statistically significant effect on immediate (graph on the left) or delayed memory (graph on the right), nor did *APOE*4 carriership affect this relationship.

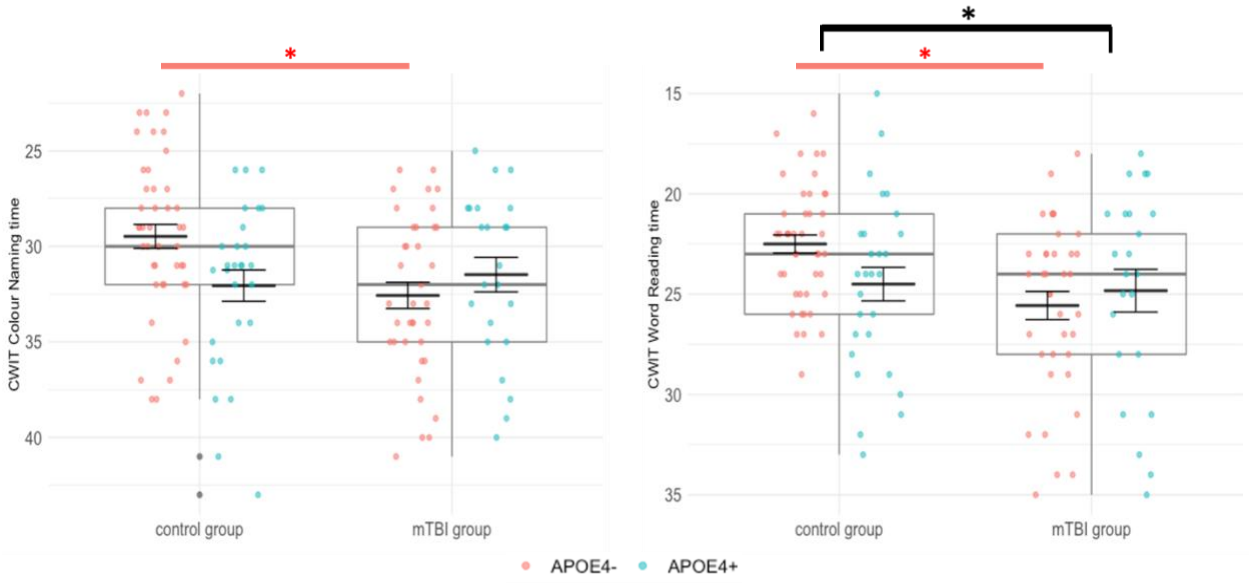

Figure 2. Cognitive domain: Processing speed measured by CWIT.

The graph on the right shows a significant difference in the main effect of prior mTBI for word reading time (*adjusted p-value < 0.05), marked by the black bar. For both colour naming and word reading time, significant difference found in the interaction term was driven by APOE4- individuals, where individuals in the control group performed better than those in the mTBI group (*adjusted p-value < 0.05), marked by the red bar.

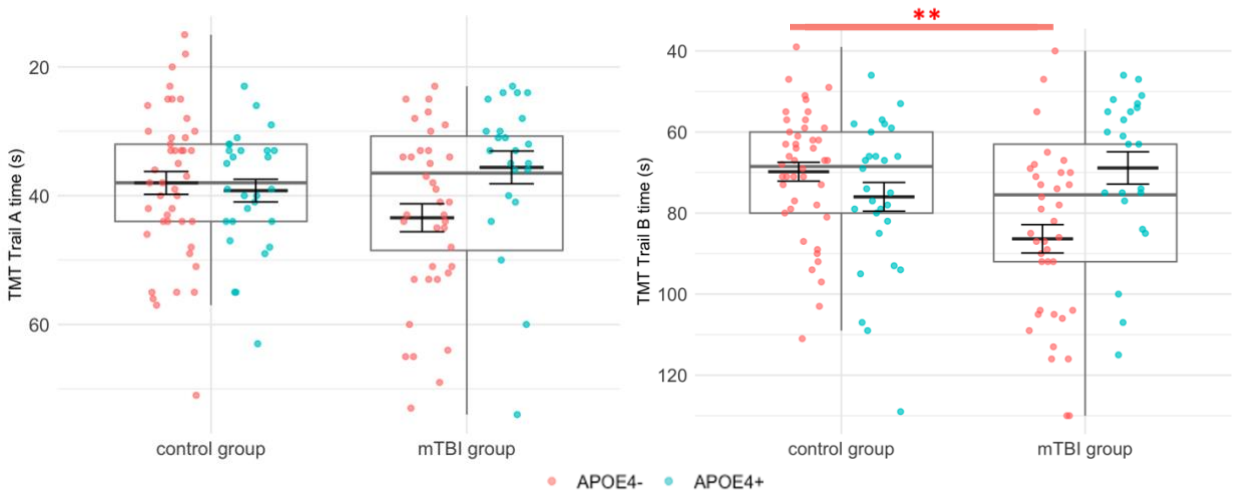

Figure 3. Cognitive domain: processing speed measured by TMT.

While no statistically significant difference was observed in processing speed between the mTBI and control groups overall, among individuals without the *APOE*4-, those with a history of prior head injury performed significantly worse than the control group on the TMT Trail B (**adjusted p-value < 0.01), marked by the red bar. Additionally, amongst the mTBI group, *APOE*4+ performed better than *APOE*4- individuals (*adjusted p-value < 0.05).

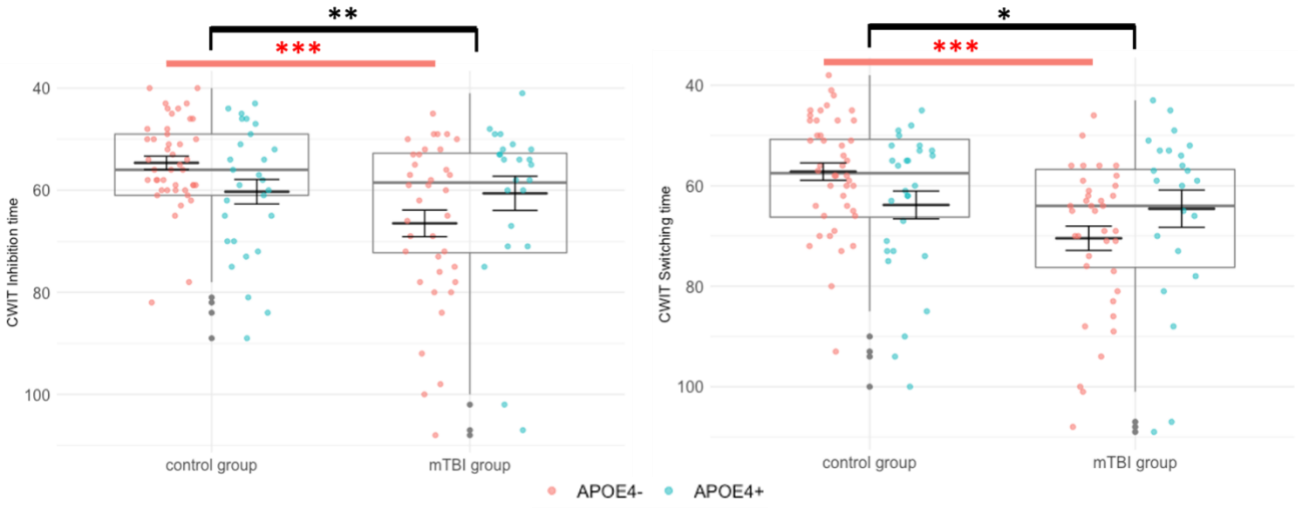

Figure 4. Cognitive domain: Executive functioning measured by CWIT.

On a group level, controls performed significantly better than individuals with prior mTBI on both CWIT inhibition (**adjusted p-value < 0.01) and switching (*adjusted p-value < 0.05), marked by the black bar. For both sub-tests of CWIT, this group difference is driven by *APOE*4- individuals for both inhibition (***adjusted p-value < 0.001) and switching (***adjusted p-value < 0.001) time, marked by the red bar.

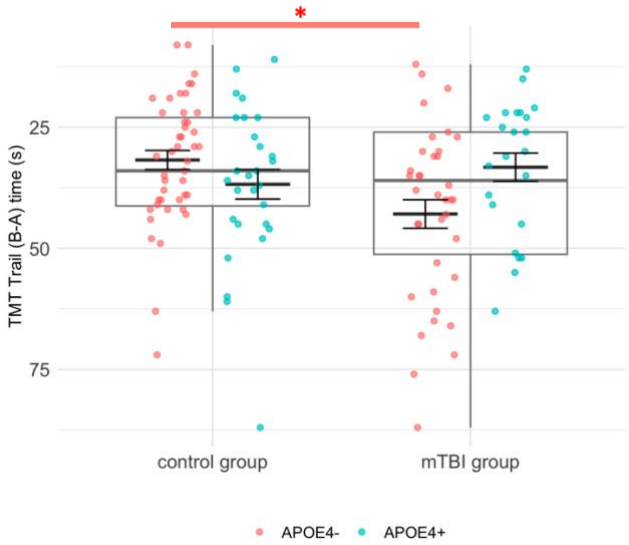

Figure 5. Cognitive domain: Cognitive flexibility measured by derived scores of TMT.

Only statistical differences were found amongst *APOE*4- individuals, where those with a prior head injury performed significantly worse than the control group (*adjusted p-value < 0.05). On a group level, there was no statistical difference between the mTBI and control group. Derived score of TMT was calculated by taking the difference between the completion time between Trail B and A, where greater time difference indicates lower cognitive flexibility.

The influence of Prior mTBI on AD PET Biomarker Positivity

Descriptive statistics of this group were carried out to characterize group differences in AD biomarker status based on global Aβ SUVRs and entorhinal tau SUVRs. Table 5 displays the number of individuals who fall above the cut-off points for biomarker positivity. To assess whether the distribution of Aβ and tau biomarker positive differs significantly between groups, a Fisher's exact test was used. For Aβ positivity, the p-value was 1.00 with the odds ratio 0.8581 and 95% confidence interval of 0.2105 to 3.0440. For tau positivity, the p-value was 0.7448 with the odds ratio 0.6103 and 95% confidence interval of 0.0983 to 2.7124. Thus, there was no significant difference between groups for Aβ and tau biomarker positivity.

Table 5. Number of participants in each cut-off of Aβ and tau SURVs, based on the presence of a self-reported prior head injury.

Cut-off SUVR category	mTBI (n=31)	Controls (n=60)	Ficher's Exact p-value
Aβ positivity—high risk (>1.55)	5	11	1.0000
Tau positivity—high risk (≥1.22)	3	9	0.7448

Prior mTBI and APOE4 carriership on beta-Amyloid and Tau Accumulation

To assess the influence of history of mTBI and genetic risk based on *APOE*4 carriership on global Aβ SUVRs and entorhinal tau SUVRs, we employed 2x2 ANCOVAs. We conducted an ANCOVA to assess the impact of prior mTBI and APOE4 carriership on biomarker levels, controlling for age, sex, and years of education. Table 6 displays the following main effects, for which significance survived Bonferroni correction for multiple comparisons, and post-hoc comparisons were carried out to assess significance between the interacting variables. The values for Aβ SUVRs were log10 transformed based on a significant Shapiro-Wilk test of normality ($p < 0.001$).

On a group level, history of mTBI did not contribute to the difference in Aβ nor tau deposition compared to the control group, measured by PET imaging. However, there was a significant main effect of *APOE*4 carriership on Aβ [$F(1,84) = 5.563$, $p = 0.008$, $\eta_p^2 = 0.082$] and tau [$F(1,84) = 6.806$, $p = 0.011$, $\eta_p^2 = 0.075$], where *APOE4* carriers had a significantly higher levels of both AD biomarkers. Due to significant differences in the ANCOVA, post-hoc tests were

conducted, with a Bonferroni-corrected alpha level of 0.05. Significant differences for both biomarker deposition levels were found to be driven by the main effect of *APOE*4 carriership, where individuals who are *APOE*4+ have elevated Aβ ($t = 2.735$, $d = 0.616$, $p_{bonf} = 0.008$) and tau ($t = 2.609$, $d = 0.568$, $p_{bonf} = 0.011$). Specifically, this difference is driven by individuals in the control group, where *APOE*4+ individuals had elevated Aβ ($t = 3.696$, $p_{bonf} = 0.002$) and tau ($t = -2.767$, $p_{bonf} = .04$). Figure 4 displays the individualized data to compare based on history of mTBI and *APOE*4 carrier status with significant post-hoc comparisons for the interaction in both Aβ and tau, shown in purple.

Table 6. Results of the ANCOVAs assessing potential differences in AD biomarker accumulation between groups and under the condition of APOE4 carriership.

Biomarker	Group	*APOE*4- (mean ± SD)	*APOE*4+ (mean ± SD)	F (p-value) *APOE* effect	F (p-value) group effect	F (p-value) interaction effect
$Log_{10}(A\beta)$	mTBI	0.112 ± 0.107	0.126 ± 0.103	7.481 (0.008)*	0.407 (0.525)	3.242 (0.075)
	Controls	0.089 ± 0.058	0.181 ± 0.122			
Tau	mTBI	1.047 ± 0.133	1.042 ± 0.087	6.806 (0.011)*	0.723 (0.397)	0.622 (0.432)
	Controls	1.131 ± 0.167	1.076 ± 0.111			

*Significant results and adjusted for comparing 4 subgroups, $p < 0.05$ corrected

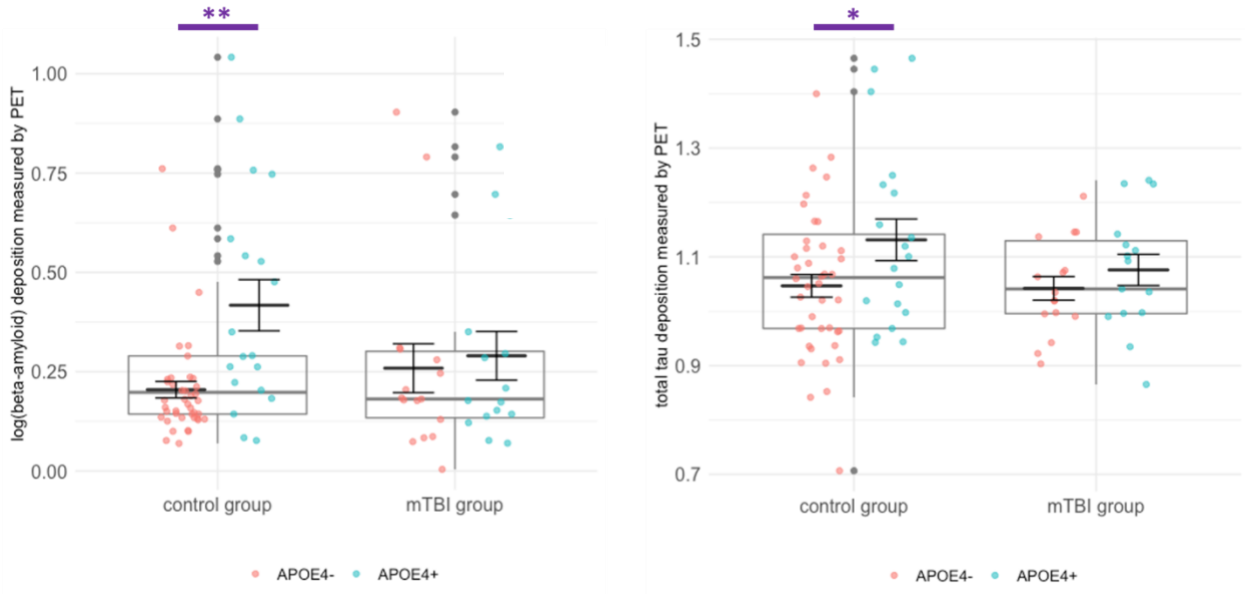

Figure 6. Bar graphs: group differences of total beta-amyloid and entorhinal tau SUVR

Significant difference in the main effect of *APOE*4 carriership in both Aβ (graph on the left) and tau (graph on the right) deposition levels are driven by the control group. Statistical significance upon post-hoc comparisons are marked by the purple bar for Aβ (**adjusted p-value < 0.01) and tau (*adjusted p-value < 0.05).

Effect of lifelong mTBI on late-life white matter microstructure

Prior studies have shown that long tracts are most susceptible to damage during head injury, particularly tracts along the base of the skull.[104] Our study focused on examining these tracts of interest: the bilateral SLF and SFOF. We found that individuals with prior mTBI compared to the controls had an overall reduced AxD in all the tracts of interest. Right SLF [$t_{Welch}(90.991) = -1.896$, $p = 0.061$, $d = -0.392$], left SLF [$t_{Welch}(90.759) = -1.153$, $p = 0.252$, $d = -0.237$], right SFOF [$t_{Welch}(86.359) = -2.818$, $p = 0.006$, $d = -0.575$], and left SFOF [$t_{Welch}(90.798) = -1.541$, $p = 0.127$, $d = -0.317$]. However, only the difference in AxD of the right SFOF was found statistically significant between groups.

Given that the mechanism of a mTBI is non-focal, we then conducted a secondary whole-brain exploratory examination of the diffusion property on the primary axis, AxD, for all tracts in a between group analyses. This approach was applied as a discovery strategy and to aid future meta-analytic work given that there is a lack of prior studies that systematically assess the long-term effects of mTBI on white matter microstructure in older adults, especially in those with a familial link to AD. Compared to the control group, the mTBI group showed significantly reduced AxD in the left anterior corona radiata [$t_{Welch}(89.034) = -2.031$, $p = 0.045$, $d = -0.422$], but a significantly increased AxD in the left cerebral peduncle [$t_{Welch}(90.242) = 2.392$, $p = 0.019$, $d = 0.496$]. These results highlight the potential impact of the mechanism of injury from prior mTBI on surrounding white matter tracts and specifically brain regions along the cranial base of the skull. Table 7 outlines the descriptive statistics of the group means in AxD of the four tracts-of-interest and only the tracts that showed significant group difference from the exploratory analyses.

To model the impact of having a prior mTBI on the above group differences in AxD of the identified white matter tracts, multiple linear regressions were run while controlling for age, sex, years of education, and *APOE*4 carriership. Multiple linear regression was used to test if the history of mTBI significantly predicted AxD of the right SFOF, left anterior corona radiata, and left cerebral peduncle. Covariates were included in the model to control for potential confounding factors, and the adjusted coefficients reflect the unique contribution of each variable to the dependent variable. It was found that prior mTBI significantly predicted AxD of the right SFOF ($\beta_{adj} = -0.6795$, $SE = 0.1806$, $p = 0.0089$), left anterior corona radiata ($\beta_{adj} = -0.3784$, $SE = 0.2198$, $p = 0.0887$), and left cerebral peduncle ($\beta_{adj} = 0.4676$, $SE = 0.2026$, $p = 0.0234$). Thus, each coefficient indicates the average change in the dependent variable for the mTBI group compared

to the control group. There was no significant contribution of any covariates to any of these regression models. Assumptions of linearity, independence, and homoscedasticity were checked. Residual analysis indicated no apparent patterns or violations of assumptions. See below for the following models for each multiple linear regression analyses.

The overall regression of right SFOF was not significant [$F(5,87) = 1.708$, $p = 0.1413$, $R^2 = 0.0894$] and adjusted p-value of 0.0534 after Bonferroni correction ($\alpha = 0.01$). Equation of this regression model:

AxD of the right SFOF = 0.821403 – 0.483340*(presence of prior mTBI) – 0.002799*(age) + 0.036499*(sex) – 0.029630*(years of education) – 0.045410*(*APOE*4 carrier status)

The overall regression of left anterior corona radiata was not significant [$F(5,87) = 1.221$, $p = 0.3063$, $R^2 = 0.06555$] and adjusted p-value of 0.5320 after Bonferroni correction ($\alpha = 0.01$). Equation of this regression model:

AxD of the left anterior corona radiata = 1.063454 – 0.378440*(presence of prior mTBI) – 0.010988*(age) – 0.307792*(sex) – 0.003881*(years of education) – 0.117826*(*APOE*4 carrier status)

The overall regression of left cerebral peduncle was not significant [$F(5,87) = 1.214$, $p = 0.3095$, $R^2 = 0.06521$] and adjusted p-value of 0.1405 after Bonferroni correction ($\alpha = 0.01$). Equation of this regression model:

AxD of the left cerebral peduncle = 0.700937 + 0.467615*(presence of prior mTBI) – 0.012706*(age) + 0.108781*(sex) – 0.001593*(years of education) – 0.077809*(*APOE*4 carrier status)

Table 7. Descriptive statistics of the AxD values from DTI data comparing individuals with and without a history of mTBI.

	Group	N	Mean	SD	SE
Tracts-of-interest					
SLF, right	mTBI	42	-0.211	0.889	0.137
	controls	51	0.174	1.071	0.150
SLF, left	mTBI	42	-0.103	0.881	0.136
	controls	51	0.137	1.130	0.158
SFOF, right	mTBI	42	-0.320	0.629	0.097
	controls	51	0.152	0.976	0.137
SFOF, left	mTBI	42	-0.022	0.780	0.120
	controls	51	0.262	0.996	0.139
Tracts from exploratory analyses that yielded significant group differences					
Anterior corona radiata, left	mTBI	42	-0.275	0.996	0.154
	controls	51	0.156	1.045	0.146
Cerebral peduncle, left	mTBI	42	0.280	0.881	0.136
	controls	51	-0.181	0.979	0.137

Note: superior longitudinal fasciculus = SLF, and superior fronto-occipital fasciculus = SFOF.

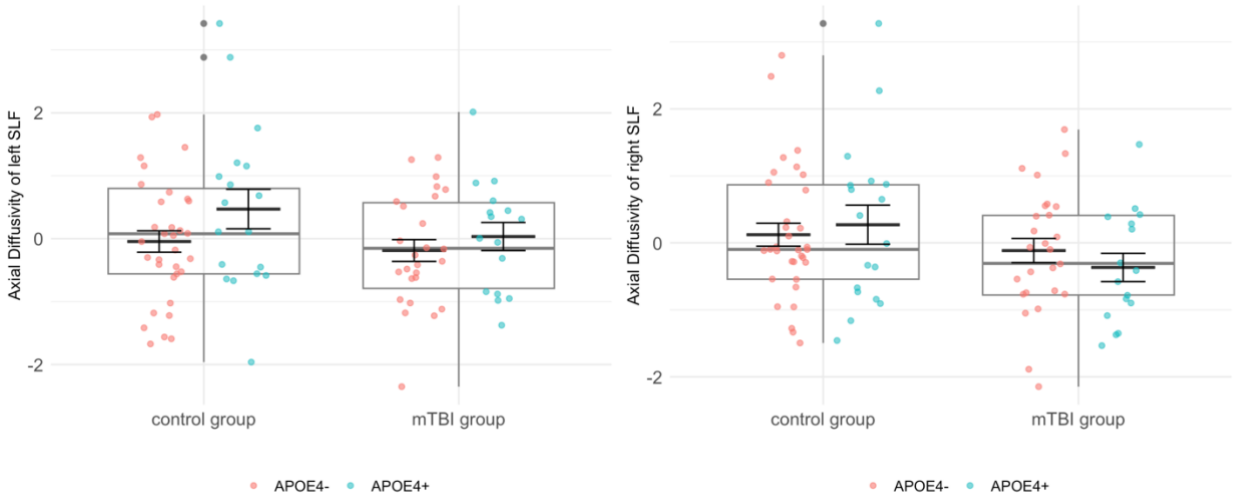

Figure 7. Bar graphs: group differences in AxD of the left and right SLF

From our initial tract-of-interest analyses, neither left (p = 0.252) nor right (p = 0.061) SLF showed statistically significant difference between groups using a significance level of $p < 0.05$ uncorrected. Overall, individuals with prior mTBI showed lower AxD in both left and right SLF compared to controls.

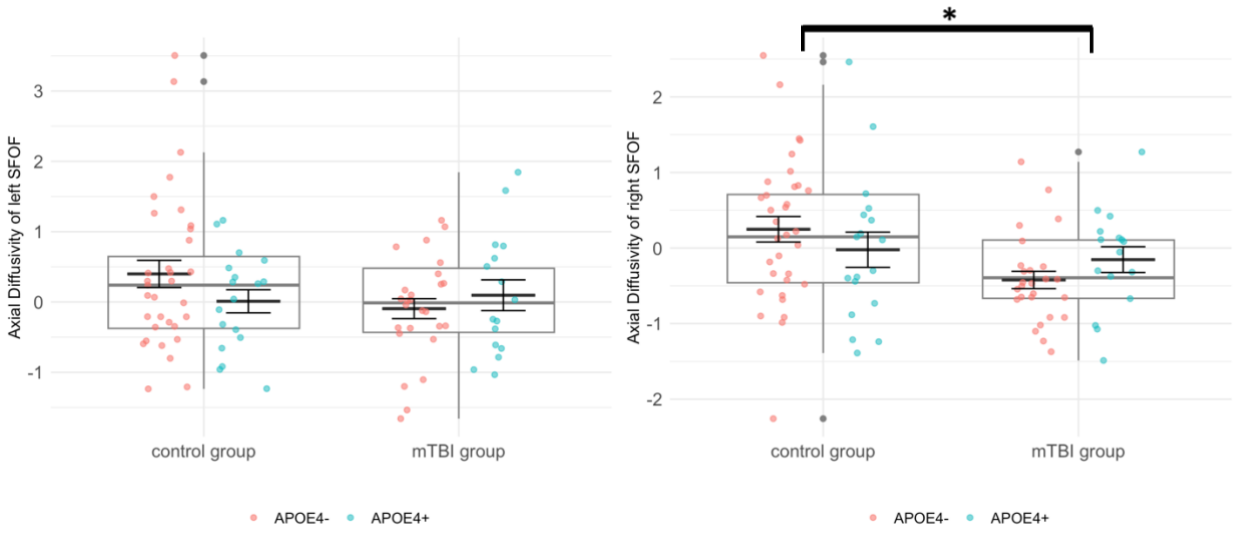

Figure 8. Bar graphs: group differences in AxD of the left and right SFOF.

From our initial tract-of-interest analyses, only the right SFOF (p = 0.006) showed statistically significant difference between groups is marked by the black bar, whereas the left SFOF was not (p = 127) using a significance level of $p < 0.05$ uncorrected. Overall, individuals with prior mTBI showed lower AxD in both left and right SFOF compared to individuals in the control group.

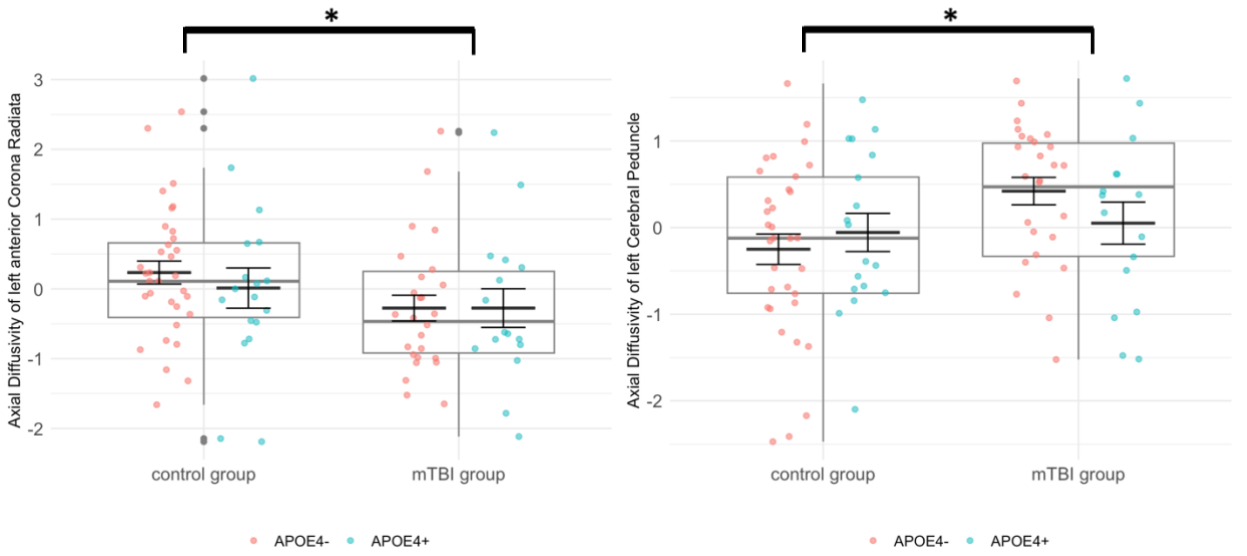

Figure 9. Bar graphs: group differences in AxD of the left anterior corona radiata and left cerebral peduncle.

From our additional exploratory analyses, the AxD of the left anterior corona radiata was significantly reduced ($p = 0.045$) but the AxD of the left cerebral peduncle was significantly elevated ($p = 0.019$) in individuals with mTBI compared to those in the control group. These group differences are marked by a black bar using a significance level of $p < 0.05$ uncorrected.

DISCUSSION

Our findings suggest that prior mTBI across the lifespan is associated with diminished late-life cognitive function in older adults at-risk for AD. Further, this relationship is differentially influenced depending on the presence of the genetic risk factor *APOE*4. On a group level, individuals with at least one self-reported mTBI, defined by loss of consciousness and/or memory gap following head injury, performed significantly worse on tests of inhibition and task switching components of executive functioning compared to age- and education-matched controls. These findings were congruent with our hypothesis that prior mTBI negatively influences late-life cognition in older adults at risk for AD. Examining the interaction between *APOE*4 carrier status and the presence of prior mTBI, revealed that individuals without a history of mTBI who were *APOE*4 carriers performed worse on a test of processing speed (CWIT colour naming). However, we identified a surprising interaction of *APOE*4 status that differed between the mTBI and control groups. Amongst *APOE*4 carriers in the mTBI group, individuals who were *APOE*4 carriers performed significantly faster on tests of processing speed (TMT-A and TMT-B) compared to non-*APOE*4 carriers. This finding suggests that *APOE*4 has a differential effect on cognition in individuals with and without a history of mTBI. Specifically, these results are in line with other studies revealing greater neurocognitive variability post-injury in *APOE*4 carriers than non-carriers.[43,45] One hypothesis draws to *APOE*4 altering repair mechanisms leading to increased cerebral edema and brain inflammation post-injury.[105] Finally, among individuals who were non-carriers of *APOE*4, the control group performed better than the mTBI group on multiple cognitive outcomes including processing speed, inhibition, and switching. These results raise interesting questions about the circumstances in which *APOE4* carriership confers cognitive risk and benefit. Future studies should investigate the potential context under which *APOE*4 carriership might provide potential protective benefits following mTBI on recovery and long-term cognitive outcomes.

Considering our two key findings, the first being that mTBI adversely impacts specific cognitive domains in late-life and the second revealing a potentially beneficial influence of *APOE*4 on cognition after mTBI, it is imperative to contextualize these results within existing literature and consider potential mechanisms underlying these effects. For the first finding, the observed impact of mTBI on cognitive domains aligns with the prior literature on TBI across diverse populations and injury severities. The preferential impact on memory, processing speed, and

cognitive flexibility suggests a pattern consistent with the known consequences of head injuries, specifically those that are retrospectively self-reported.[106] A scoping review found long-term cognitive consequences of mTBI in adults, revealing persistent cognitive deficits in episodic memory and processing speed even years after the initial injury.[22] Additionally, Li et al. reported earlier age at onset of mild cognitive impairment for individuals with history of mTBI compared to those without.[107] Thus, this highlights the importance of longitudinal studies and examining aging populations to understand the contributions of prior mTBI on accelerated cognitive decline.

Prior meta-analyses on the influence of *APOE*4 carriership on cognition following traumatic brain injury is controversial, with most studies support an association with diminished cognitive functioning, with a few important exceptions.[25,37,38,44,45,78,79,108] Our finding of the beneficial influence of *APOE*4 on later life cognition following prior mTBI echoes the findings of Terrell et al. who looked at a longitudinal cohort of college athletes.[109] Furthermore, Noé et al. found patients who were *APOE*4 carriers had a faster trajectory of verbal memory recovery following post-traumatic amnesia from a moderate to severe TBI.[110] Son et al. also found the protective influence of *APOE*4 carriership on global cognitive recovery at 18 and 36 months following TBI compared to non-carriers.[111] These finding align with studies indicating a neuroprotective role of *APOE*4 in certain contexts, and not the expected determinant role on post-injury cognitive outcomes.[44] Potential mechanisms, such as cholesterol metabolism or neuroinflammation, may play a role in shaping cognitive trajectories or brain reorganization post-mTBI. One proposed mechanism involves cholesterol metabolism, where *APOE*, a lipid transport protein, is known to play a crucial role in cholesterol homeostasis in the brain.[38,112,113] *APOE*4 carriers exhibit altered cholesterol metabolism, which may impact synaptic function and slower rebuild of damaged myelin. This may be conversely beneficial than a rapid rebuild in non-carriers of *APOE*4. Moreover, in the context mTBI recovery, a balanced inflammatory response is crucial. Adequate cholesterol metabolism may contribute to the resolution of inflammation and the promotion of healing. Neuroinflammation is characterized by the activation of microglia and release of pro-inflammatory cytokines that plays a significant role in the aftermath of mTBI.[114] As such, *APOE*4 could modulate neuroinflammatory responses by prolonging its duration. Future research should delve into these mechanisms, considering factors like survivorship bias within our sample, to enhance the robustness and generalizability of our claims. Our results provide a

foundation for further investigation in understanding the intricate interplay between *APOE*4 carriership, history of mTBI, and late-life cognitive outcomes.

Given the difference in late-life cognitive outcomes following mTBI, we next sought to address whether mTBI would be associated with an increased rate of preclinical AD compared to controls as a potential mechanism underlying these effects. Prior research on moderate and severe TBI have shown potentially increased deposition of Alzheimer's disease-related proteins in the brain.[26,30,31,33] To further investigate the effects of mTBI as a risk factor for late-life tau and amyloid accumulation, we examined whether past mTBI was associated with abnormal accumulation of AD biomarkers. Contrary to our hypothesis, we did not detect significant group differences. Thus, our findings do not suggest that the diminished late-life cognitive outcomes following lifelong mTBI that we observed were due to increased accumulation of AD-related pathological changes. However, we found that *APOE*4 carriership was significantly associated with increased brain Aβ and tau levels but only amongst individuals in the control group, but not those in the mTBI group. Amongst only the control group, *APOE4* carriers had significantly higher levels of Aβ and tau deposition compared to non-carriers. In contrast, amongst individuals living with a history of prior mTBI, *APOE*4 carriership was not associated with Aβ nor tau deposition above cutoff. While *APOE*4 is generally considered a risk factor for AD and is associated with an increased deposition of Aβ plaques and altered tau pathology, studies on the specific effects of *APOE*4 following TBI have yielded mixed results.[78,115,116] Some studies suggest that *APOE*4 may exacerbate the accumulation of Aβ and tau after TBI, potentially increasing the risk of developing AD-like pathology.[43,79] Other studies propose a more nuanced perspective, indicating that *APOE*4 may influence the response to TBI in a bidirectional manner, with both detrimental and, in some cases, potentially protective effects.[117] In a retrospective autopsy study, patients lacking the *APOE*4 allele were subject to greater risk of AD pathology following severe TBI.[118] Thus, prior mTBI contributes to late-life cognitive decline that is likely independent from accumulation of underlying AD pathology indexed by Aβ and tau deposition among older adults who are at a higher risk for AD.

We aimed to address the question whether late-life decline in cognition following mTBI may be due increased accumulation of AD pathology, a finding previously reported in more severe head injuries.[28] However, we did not find evidence of increased by AD risk following mTBI, as defined by the sensitive measurement of amyloid and tau using in-vivo PET biomarker imaging.

The absence of a direct association with AD biomarkers suggests that an alternative mechanism, distinct from neurodegenerative change, underlies the observed cognitive disparities between the two groups that we observed. Thus, this finding prompts further exploration into non-AD-related factors contributing to cognitive outcomes post-mTBI. Future investigations should probe alternative mechanisms, such as inflammation, synaptic dysfunction, or neurodegenerative processes, to comprehensively understand the nuanced interplay between mTBI and late-life cognitive function. Post-injury, the brain experiences inflammatory responses, involving immune cells and signaling molecules, which chronic inflammation has been linked to neurodegenerative processes and cognitive decline.[119] Synaptic dysfunction could be disrupted following mTBI, affecting communication between neurons, which these alterations could then impact memory, learning, and other cognitive functions.[120] These nuanced perspective acknowledges the multifaceted nature of cognitive outcomes and reinforces the need for a broader exploration of potential mechanisms beyond traditional AD pathways.

Lastly, we evaluated the impact of prior mTBI on white matter microstructure to understand the potential long-term structural effects of injury as a potential mechanism underlying accelerated cognitive decline in individuals with prior mTBI. Prior work has shown the significance of DTI metrics in predicting the likelihood of white matter injury.[104] A study using a mouse model found a significantly reduced AxD from injury onset to 4 days post-injury, but a pseudo-normalization of AxD up to 4 weeks after injury, which all changes corresponded to demyelination of the axons.[121] Palacios et al. found higher AxD in mTBI patients at both two weeks and six months post-injury compared to controls, with a decrease in AxD within the mTBI group between the two timepoints.[122] Thus, measures of DTI are differentially affected based on temporal features since brain injury. Several computational neuroimaging studies have examined how brain tissue responds to mechanical force, and found negative impacts on white matter microstructure, while considering both isotropic and anisotropic definitions.[123] Whole brain white matter is considered anisotropic where diffusion varies in direction due to various white matter tracts, which locally, can be defined as isotropic with an uniform direction. These studies aim to characterize how different representations of white matter influence computational models, providing insights into the structural mechanics of the brain, organization, and connectivity of brain white matter tracts.[54,124] In this study, we focused on the isotropic model of white matter because we were specifically interested in examining the SLF and SFOF tracts, both with defined

directionality. Therefore, direction-dependent variations of the anisotropic model are not accounted for when considering only AxD, but AxD was prioritized because it provides more specific information about the alterations in the primary direction of diffusion within the tracts. It allows for a more detailed examination of axonal integrity, which is crucial in investigating conditions such as TBI where axonal damage is a key concern.

Of the tracts of interest, the mTBI group had significantly reduced AxD in the right SLF and right SFOF compared to the control group. Lower AxD is considered to be an indicator of axonal injury, reduced axonal caliber, or less coherent orientation of axons.[125] Prior meta-analysis showed that diffusion-related alterations following axonal injury marked by the reduction in anisotropy and diffusion, specifically in the axial direction.[126] Farbota et al. noted findings of long-term progressive white matter deterioration several years post-injury.[127] Additional evidence suggests that TBI may induce long-term neurodegenerative processes in the form of progressive axonal degeneration, persisting beyond the time of injury and contributing to the development of AD-like pathological changes.[128] Both the right SLF and right SFOF are association fibers with along the rostral-caudal axis, located in close proximity to each other. Indication of axonal injury may underlie cognitive deficits related to the role of SLF in attention and the role of SFOF in processing speed.[57,61] However, our findings did not support the association between SLF and SFOF axonal integrity and cognitive function. These white matter tracts have linked to higher susceptibility to injury in various populations, including military personnel, athletes, and across all ages.[129] This shared vulnerability of these specific tracts underscores their relevance in guiding targeted interventions and rehabilitation strategies. While additional research is needed for a complete understanding of the long-term effects of mTBI on white matter microstructure and cognitive outcomes, these findings contribute to the current knowledge, providing insights into the potential adverse consequences of mTBI on the cognitive abilities of older adults at risk for AD in later life.

In addition to hypothesis-driven ROI-based analyses, we performed whole-brain investigation of white matter microstructure. We found that individuals with prior mTBI had significantly reduced AxD in the left anterior corona radiata, but an elevated AxD in the left cerebral peduncle compared to controls. Clinical correlation has shown that corona radiata supports cognitive and sensorimotor systems.[61] In a meta-analytic review, Eierud et al. noted that decreased AxD is an indication of acute injury seen a few months post-mTBI, followed by

increased AxD in the chronic stage after brain injury.[130] The cerebral peduncle is also associated with descending corticospinal tracts important for motor movements and processing proprioceptive information for balance and posture.[131] Located at the intersection of the middle and posterior cranial fossa, the cerebral peduncle sits above the bony protuberance of the posterior clinoid process, located at the superior lateral aspect of the dorsum sellae.[132] A systematic review summarized deficits of the Kernohan-Woltman notch phenomenon caused by compression to the cerebral peduncle post-TBI.[133] This underlines this highly susceptible brain region to damage after post-TBI, leading these common post-concussive symptoms of proprioceptive difficulties.[134,135] Evidently, our results align with the current literature on the differential effects on AxD given the long-term impact of mTBI on white matter microstructure. Our exploratory analyses underscored the complexity of the non-focal mechanism of injury mTBI poses. Thus, further studies should investigate the clinical relevance of the directionality of DTI-derived metrics to help inform the impacts of prior head injury as a potentially modifiable risk factor of AD.

Future directions could address the impacts of mTBI and APOE4 carriership on later-life cognition, AD risk based on biomarker accumulation, and white matter integrity in a longitudinal design that integrates repeated cognitive and brain structural measures over time. This current study was cross sectional, and thus the influence of temporal features, such as cognitive trajectories over time or white matter changes acutely compared to the chronic state could not be addressed. Moreover, additional investigations should address potential confounds and interaction effects between modifiable lifestyle factors (e.g., exercise, sleep, etc.) that may have influence both acute and chronic post-injury recovery. This broader exploration may unveil additional dimensions influencing the observed outcomes, and, enhancing the overall understanding of the complex interplay between mTBI, white matter integrity, and cognitive consequences in later-life. The current findings underscore the need for health policy aimed at promoting prevention of head injury to enhance late-late cognitive outcomes. Understanding how this process interacts with other modifiable lifestyle factors would help to further strengthen and focus dementia prevention efforts.

Limitations

The accuracy of retrospective self-reported head injury is potentially confounded by recall bias, and there are no hospital records to confirm diagnosis or specify severity by excluding the possibility of acute structural changes at the time of injury. There is likely heterogeneity in the head injuries reported, but participants were screened out from the PREVENT-AD cohort based

on adverse MRI results, which could include moderate to severe TBI patients or those with identified infarcts. In addition, there is a survivorship effect due to the PREVENT-AD cohort eligibility criteria, which includes only cognitively unimpaired individuals at the time of recruitment thus excluding all individuals with more severe cognitive impairment or earlier conversion to mild cognitive impairment and dementia. Additionally, the control group defined in this study is still composed of patients identified as at-risk of AD based on first degree family member with AD diagnoses. Ideally, a third control group of older adults without a family history of AD would help to dissociate the potential influence of AD risk on outcomes. Individuals who fail to recognize and report a potential head injury that may have occurred in their life might have been absorbed in the control group, thus increasing the heterogeneity of the groups and the risk of Type II errors. Misreporting head injuries is a limitation, especially under-reporting as evidence by observational studies on the incidence of mTBI; however, to account for over-reporting mTBIs, we only included individuals who acquired a mTBI with the presences of brief loss of consciousness and/or memory gap at the time of the injury. These are potential confounders that would bias our results towards the null hypothesis.

About 60% of AD diagnoses are female, which may influence volunteerism and contribute to over-representation in aging research, including the PREVENT-AD cohort.[136] There are sex differences in neuropsychological measures and risk prevalence for neurodegenerative diseases, and potentially in reporting of mTBI. The primarily female sample in the current study limits the generalizability of our findings. Additionally, alterations in white matter due to prior mTBI needs to be further explored, such as the interaction between mTBI and microvascular changes, to address the critical need to understand early biomarkers of AD.

CONCLUSION

In addressing the first aim, our study delves into examining the impact of mTBI on objective measures of cognitive function, with a specific focus on elucidating how being a carrier of the *APOE*4 allele influences this interaction. The expected contribution of this investigation is twofold. Firstly, it aims to provide valuable insights into the specific cognitive domains that bear the impact of mTBI. Secondly, it seeks to unravel the intricate interplay between genetic factors, particularly *APOE*4, and the consequences of mTBI on cognitive function among older adults. By achieving these objectives, our study will significantly enhance our understanding of the nuanced relationships between mTBI, genetic factors, and late-life cognitive outcomes.

In the pursuit of the second aim, our research endeavors to unravel the influence of mTBI and *APOE*4 carriership on the levels of amyloid-beta and tau deposition – biomarkers that are associated with AD pathology. The overarching goal is to assess the extent to which prior head injury correlates with abnormal accumulation of these AD-related biomarkers. By deepening our understanding of the relationships between mTBI and the accrual of AD-related pathology, this study will advance knowledge of the underlying processes involved in AD development. Furthermore, it holds promise for unveiling new avenues in AD prevention or intervention strategies.

The last aim of our study is centered on exploring the enduring impact of prior mTBI on white matter microstructure in older adults at risk of AD. Additionally, it aims to assess whether differences in white matter integrity drive group disparities in cognitive outcomes, which we did not identify. Future directions should further investigate the potential link between changes in white matter microstructure and cognitive function, as it will furnish valuable insights into the neurobiological mechanisms underlying cognitive decline post-mTBI.

To conclude, our multifaceted investigation into the repercussions mTBI and its interaction with genetic factors such as the *APOE*4 allele has illuminated critical insights into the complex dynamics of cognitive function, biomarker accumulation, and white matter integrity in older adults at-risk of AD. The evidence gleaned from our study indicates that while mTBI may adversely affect certain cognitive domains in later life, the presence of the *APOE*4 allele confers a unique cognitive resilience following such injuries. Contrary to expectations, our findings reveal that mTBI does not significantly escalate the risk of AD, as determined by biomarker accumulation, yet instigates distinct alterations in the AxD of specific white matter tracts. These results contribute

substantially to the current knowledge landscape by refining our understanding of the nuanced interplay between mTBI, genetic factors, and cognitive outcomes. This study offers a comprehensive investigation of the intricacies of AD-related biomarkers and white matter integrity post-mTBI, providing a foundation for future research avenues and potentially influencing preventive and interventional strategies for cognitive decline in at-risk populations.

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APPENDIX A

Head injury questionnaire given to PREVENT-AD participants:

You indicated that you have suffered a head injury. Please share some details about that incident in the following table. If you have had more than one injury, there is space to fill out the details of these injuries. If not, you may leave the additional fields blank.

	What was the cause of the injury? (Car accident, Other vehicle accident, Sports accident, Playground accident, Fall, hit by something, Shaken violently, Fight, Gunshot, Explosion, Other)	Were you knocked out or did you lose consciousness? If yes, for how long?				Were you dazed or did you have a gap in your memory from your injury?		How old were you?
		No	Yes – for less than 30 minutes	Yes – for 30 minutes to 24 hours	Yes – for more than 24 hours	No	Yes	
Head Injury #1								
Head Injury #2								
Head Injury #3								
Head Injury #4								
Head Injury #5								