

ASSOCIATION OF HEAD INJURY WITH MULTIMODAL ALZHEIMER'S  
DISEASE BIOMARKERS AND GENETICS

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## DEDICATION

This thesis is dedicated to my mother, Jennifer Reasoner Dybing. Its completion was driven by the knowledge of how much she would have wanted to see it done.

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Alzheimer's disease (AD) affects over 7 million Americans aged 65 and older and is the seventh-leading cause of death in the United States. AD represents a tremendous social and economic burden, but development of prevention and/or curative strategies has been slow. While much attention is focused on potential pharmacological therapies to stop and/or reverse disease progression, there is growing interest in lifestyle modifications that may lower risk for developing AD. One key lifestyle-related factor that is associated with elevated dementia risk, including AD is head injury (HI), also called concussion or traumatic brain injury (TBI). HI is extremely prevalent, with studies estimating as many as one in four Americans have experienced one. HI is even more prevalent in at-risk populations, including military service members and contact sport athletes. However, the mechanism(s) responsible for the link between HI and AD risk are largely unclear.

While prior work has linked HI to elevated AD biomarkers, particularly amyloid- $\beta$  ( $A\beta$ ) and tau measured using positron emission tomography (PET) and via pathological investigation, the evidence is highly varied and its significance unclear. In this thesis, we utilize multimodal biomarker and genetic tools to investigate potential mechanisms involved in the association of HI with AD risk. Chapter One is a systematic literature review of published studies that assessed whether individuals with HI had higher levels of deposited  $A\beta$  and/or tau as indicated by PET scans. Chapter Two is an original

research report investigating whether AD fluid biomarkers are altered in participants with HI from the Alzheimer’s Disease Neuroimaging Initiative. Chapter Three presents an original research investigation of tau deposition levels in participants with TBI from the National Alzheimer’s Coordinating Center cohort. Finally, Chapter Four is an exploration of whether genetic risk for AD is associated with more severe concussions and/or poorer concussion recovery in student athletes and military service academy students. The complex relationship between HI and dementia risk is not fully characterized, but this body of work elucidates unique and novel associations of AD biomarkers and genetics with HI.

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## LIST OF ABBREVIATIONS

[ <sup>11</sup> C]	carbon-11
[ <sup>11</sup> C]-PiB	Pittsburgh Compound B
[ <sup>18</sup> F]	fluorine-18
[ <sup>18</sup> F]AV-1451	Flortaucipir
[ <sup>18</sup> F]AV-45	Florbetapir
[ <sup>18</sup> F]FBB	Florbetaben
[ <sup>18</sup> F]-MK-6240	Florquinitau
[ <sup>18</sup> F]-NAV4694	Flutafuranol
[ <sup>18</sup> F]-PM-PBB3	Florzolotau
A/T/N	Amyloid- $\beta$ /tau/neurodegeneration
A $\beta$	Amyloid beta
AD	Alzheimer's disease
ADNI	Alzheimer's Disease Neuroimaging Initiative
ADRC	Alzheimer's Disease Research Center
AFR	African genetic ancestry
AIBL	Australian Imaging, Biomarkers and Lifestyle Study of Aging
AMR	Admixed American genetic ancestry
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
APOE	Apolipoprotein E
BESS	Balance Error Scoring System
BLSA	Baltimore Longitudinal Study of Aging

CARE	Concussion Assessment, Research and Education
CERAD	Consortium to Establish a Registry for Alzheimer’s Disease
CN	Cognitively normal
CryoEM	Cryo-electron microscopy
CSF	Cerebrospinal fluid
CTE	Chronic traumatic encephalopathy
DAI	Diffuse axonal injury
DoD	Department of Defense
EAS	East Asian genetic ancestry
EUR	European genetic ancestry
FDA	United States Food & Drug Administration
fMRI	Functional magnetic resonance imaging
FTD	Frontotemporal dementia
GFAP	Glial fibrillary acidic protein
GWAS	Genome wide association study
HABS-HD	Health and Aging Brain Study – Health Disparities
HI	Head injury
HRPO	Human Research Protections Office
IBD	Identical-by-descent
IPV/DV	Intimate partner violence/domestic violence
IRB	Institutional Review Board
LBD	Lewy body dementia
LOC	Loss of consciousness

MCI	Mild cognitive impairment
MMSE	Mini Mental State Exam
MNI	Montreal Neurological Institute
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
MTL	Medial temporal lobe
NA	Not applicable
NACC	National Alzheimer's Coordinating Center
NACCUDSD	NACC Uniform Dataset Diagnosis
NACCETPR	NACC primary etiology
NCAA	National Collegiate Athletic Association
NfL	Neurofilament light chain
OSU TBI-ID	The Ohio State University Traumatic Brain Injury (TBI) Identification Method
p-tau	Phosphorylated tau
PET	Positron Emission Tomography
POSSAD	Possible AD
PROBAD	Probable AD
PRS	Polygenic risk score
PTSD	Post-traumatic stress disorder
ROI	Region of Interest
RTP	Return to play
SAC	Standardized Assessment of Concussion

SAS	South Asian genetic ancestry
SCAT(5)	Sport Concussion Assessment Tool (5 <sup>th</sup> edition)
SCATSEV	Symptom severity score on the SCAT
SCATSYMP	Total number of symptoms score on the SCAT
SCD	Subjective cognitive decline
SD	Standard deviation
SE	Standard error
SNP	Single nucleotide polymorphism
SPM	Statistical Parametric Mapping
SUVR	Standardized uptake value ratio
TBI	Traumatic brain injury
TES	Traumatic encephalopathy syndrome
UCH-L1	Ubiquitin C-terminal hydrolase L1
UDSv4	Uniform Data Set version 4
WM	White matter

## Introduction

Alzheimer's disease (AD) is the seventh-leading cause of death in the United States. It is a progressive neurodegenerative disease characterized by cognitive changes including memory loss, a declining ability to perform activities of daily living like bathing and dressing,<sup>1</sup> and mood and/or behavioral changes.<sup>2,3</sup> AD is the most common type of dementia and is estimated to affect over 7 million Americans over the age of 65.<sup>2,4</sup> Alongside significant numbers of Americans currently suffering from AD, the prevalence of dementia is also increasing, with projections indicating nearly 14 million Americans could be afflicted by AD by 2060, barring breakthroughs in disease prevention and/or treatment.<sup>2</sup> At present, there are no cures for AD, and thus, it represents a significant and growing public health concern.<sup>2</sup>

AD is pathologically defined by the accumulation of extracellular amyloid- $\beta$  (A $\beta$ ) plaques and intracellular neurofibrillary tangles comprised of hyperphosphorylated tau protein. These deposits aggregate in characteristic patterns defined by the Braak and Thal stages respectively,<sup>5,6</sup> and typically appear first in temporal lobe structures such as the hippocampus and entorhinal cortex. Pathology then spreads to other brain regions in a predictable pattern with increasing disease and symptom severity.<sup>5,6</sup> Pathological examination can elucidate the molecular and/or structural brain changes associated with cognitive symptoms in a deceased individual, but in order to diagnose a person with AD in a clinical setting, physicians may use a combination of assessments that measure the patient's cognitive functionality alongside results from biomarker assays.<sup>7,8</sup> Biomarkers are biological indicators of the presence, absence, or state of a disease.<sup>9</sup> In the context of

AD, the most commonly used biomarkers measure A $\beta$  and tau. These biomarkers are specific to AD and can be measured from biofluids, such as cerebrospinal fluid (CSF) and blood, and through neuroimaging techniques.<sup>10-14</sup> Additional biomarkers include glial fibrillary acidic protein (GFAP) and neurofilament light chain (NfL), which are nonspecific for AD but elevate with increasing disease progression and are indicators of neuroinflammation, astrogliosis, and axonal degeneration.<sup>15-17</sup> Recent technological advances have resulted in development of reliable blood-based biomarker assays, permitting less invasive and less expensive capture of fluid biomarker data relative to lumbar puncture for CSF collection.<sup>18</sup>

The most predominant risk factor for AD is advanced age, typically defined as 65 years of age or older.<sup>19, 20</sup> AD is further delineated into two categories based on the age at which an individual is diagnosed.<sup>2</sup> Those diagnosed before the age of 65 are said to have early-onset AD (EOAD), while those diagnosed after the age of 65 have late-onset AD.<sup>21, 22</sup> EOAD is less common, thought to represent between 5-6% of AD cases.<sup>21</sup> Other frequently cited biological risk factors include female sex,<sup>23, 24</sup> racial/ethnic category,<sup>25, 26</sup> and certain genetic loci, most especially the apolipoprotein E (*APOE*) epsilon 4 ( $\epsilon$ 4) allele.<sup>27, 28</sup> However, lifestyle-related risk factors such as concussion/traumatic brain injury (TBI),<sup>22, 29-32</sup> cardiovascular health,<sup>33-35</sup> and smoking,<sup>36, 37</sup> have been attracting greater attention in tandem with increasing efforts to identify non-pharmacological strategies that reduce dementia risk or slow disease progression.<sup>38-40</sup>

In contrast to the aforementioned risk factors, a number of practical preventative factors may lower risk of developing dementia or delay its onset. Studies have found supportive evidence for educational attainment,<sup>41, 42</sup> exercise,<sup>43-45</sup> and dietary patterns like

the Mediterranean diet,<sup>39, 46-48</sup> as potentially beneficial for lowering risk and/or slowing disease progression. However, though initial findings are promising, no lifestyle modification has been definitively proven to prevent or reverse AD.<sup>40, 49</sup>

Similarly, as of today, there are no pharmacological interventions that can cure AD. Some approved medications target problematic symptoms, but do not alter the underlying pathological changes thought to be responsible for said symptomology.<sup>50, 51</sup> Further, though a select number of disease-modifying therapies that clear accumulated A $\beta$  from the brain have been FDA-approved for use in AD, these medications also cannot fully halt or reverse the disease and are associated with potentially serious side effects.<sup>52-56</sup> As such, pursuit of diverse and novel potential methods to address the dementia crisis is extremely necessary, and incorporation of lifestyle modifications such as head injury (HI) prevention has the potential to bring great benefit to patients and the research community.<sup>38</sup> HI is both extremely common and associated with elevated dementia risk, and lowering HI incidence thus represents a promising strategy to alter dementia risk *in vivo* with minimal adverse consequences.

HI, also called concussion, is a type of TBI incurred when an individual sustains a blow or other insult to the brain that results in characteristic symptoms including but not limited to temporary amnesia, loss of consciousness, and/or headache.<sup>57</sup> HI may be acquired via sports participation, motor vehicle accidents, intimate partner/domestic violence (IPV/DV), falls, and other sources.<sup>57-62</sup> Studies have found that nearly one in four Americans has experienced HI, and its prevalence is much higher in contact sport athletes and military servicemembers.<sup>63-66</sup> Importantly, HI may be associated with serious long-term consequences both acutely and long-term, including poor cognitive/psychological

outcomes, risk for neurodegenerative disease, and/or acute mortality.<sup>67-84</sup> As such, HI represents a widespread public health concern, and further study into its adverse consequences and long-term implications is warranted.

Previous reports and meta-analyses have shown a link between exposure to a HI incident and earlier dementia symptom onset,<sup>30-32</sup> as well as increased dementia risk, including a pooled dementia diagnosis odds ratio of 1.81 in individuals with HI (95% CI 1.53-2.14).<sup>85, 86</sup> Though this association has been repeatedly established, the responsible mechanisms remain elusive.<sup>85, 87</sup> Prior research has suggested many potential candidates, including shared underlying genetic commonalities such as *APOE*  $\epsilon$ 4.<sup>74, 88-98</sup> and alterations to pathological processes like A $\beta$  and/or tau deposition.<sup>99-101</sup> However, the evidence is mixed and often contradictory, as other reports have failed to find links between HI and AD biomarkers.<sup>102-110</sup> Similarly, there are other outstanding questions the field has yet to address. For example, there has been limited investigation into genetic influences outside *APOE* that connect HI with AD. In addition, although studies have investigated mostly imaging biomarkers of AD in individuals with HI, it remains to be understood whether fluid-based biomarkers of AD are altered in individuals with HI. Further, the association of HI with neuroimaging biomarkers is disputed. It is also unclear whether a single injury, particularly one incurred years to decades prior to dementia onset, is sufficient to significantly increase AD risk or alter biomarkers in aging adults. The impact of a single HI versus multiple HIs is particularly important to understand when considering that repetitive HI is the primary risk factor for chronic traumatic encephalopathy (CTE), a progressive neurological disorder observed in contact sport athletes and other populations with high HI risk.<sup>76, 111-115</sup>

Despite many previous studies having considered how HI may be associated with AD biomarkers, there is a surprising lack of clarity in the field, likely due to key methodological challenges. First, some reports only considered the relatively acute post-injury period (e.g., HI occurring within the last few years), or utilized younger populations not at risk for AD due to age. Second, some studies only analyzed individuals with normal cognition, but the effects of HI on biomarkers may only be observable in the presence of ongoing cognitive impairment. Third, the majority of previous reports are cross-sectional and/or unimodal, considering only one biomarker at a single point in time. Together, these limitations may partly explain why existing findings are highly heterogeneous. As a result of these methodological challenges, there is insufficient knowledge of what pathological processes are altered in the brain after HI, and the relation of these changes to AD biomarkers and long-term disease risk. Therefore, further research is greatly needed to better characterize changes in the brain associated with HI that contribute to heightened risk for neurodegenerative disease.

In this thesis, we present a systematic literature review and primary research reports that explored alterations to multimodal AD biomarkers, including blood plasma, cerebrospinal fluid, and neuroimaging, in individuals who experienced HI. Further, we assessed whether genetic influences associated with increased AD risk, including and beyond *APOE*, were related to HI severity/recovery. To move the field forward and improve our understanding of the relationship between HI, AD biomarkers and genetics, and risk for neurodegenerative disease, we sought to address many of the aforementioned methodological challenges that contributed to the mixed findings in prior work. First, the participants used in our analyses are predominantly decades out from HI, and the sample

comprises both cognitively normal and impaired older participants either at risk for or already experiencing AD. However, our studies are not limited to aging adults, as we also examined young student athletes. Further, we increased sample size/power and generalizability by utilizing large cohorts of participants combined from many research sites across the country. Another significant strength of our work is our longitudinal strategy for investigating fluid biomarkers, which permits investigation into rates of biomarker change in the context of HI. Thanks to this unique and novel strategy, this thesis reveals a more comprehensive picture of how HI associates with multimodal AD biomarkers and genetics in aging adults.

## **Chapter One: Traumatic brain injury and Alzheimer's Disease biomarkers: A systematic review of findings from amyloid and tau positron emission tomography**

The following chapter is a literature review investigating the association between head injury and elevated tau and/or A $\beta$  deposition on PET in aging adults. Its purpose was to better understand the link between HI and AD neuroimaging biomarkers by searching for consensus among prior studies. Relevant search terms yielded 26 unique studies that investigated aging cohorts using PET radiotracers to quantify tau and/or A $\beta$  in numerous cortical and subcortical regions of interest (ROIs).

Across all studies, the use of different cohorts, radiotracers, and ROIs contributed to mixed findings with no definitive conclusion regarding whether older adults with HI have elevated AD neuroimaging biomarkers. Though sparse, evidence supported a link between HI and elevated tau deposition, particularly in ROIs such as the cingulate gyrus and cuneus/precuneus. Findings were summarized into a number of tables that demonstrate the wide variety of ROIs used and any consensus or disagreement between studies. This review illuminates the sharp lack of clarity in the field regarding potential association of HI and AD biomarkers and comprehensively demonstrates the need for further study using expanded cohorts of aging adults.

## Introduction

Alzheimer's disease (AD) is the most common form of dementia, with approximately 6.7 million Americans currently living with the disease, and this number is expected to grow over the coming decades as the population ages.<sup>116</sup> Worldwide, it is estimated that 152 million people will be living with AD by 2050.<sup>117</sup> There are presently no cures, though recent disease-modifying therapies have become available.<sup>118</sup> AD is conventionally delineated into two categories based on reported age of symptom onset, late-onset AD (onset aged 65 years or older) and early-onset AD (onset before the age of 65).<sup>22</sup> Late-onset AD is more common, representing approximately 95% of all AD cases.<sup>21</sup>

Generally, AD is clinically associated with progressive memory decline and cognitive impairment and is pathologically defined by the presence of neurodegeneration and cortical accumulation of  $\beta$ -amyloid ( $A\beta$ ) as plaques and hyperphosphorylated tau as neurofibrillary tangles (NFTs).<sup>119, 120</sup> A framework for describing AD as a function of the most widely used biomarkers is the A/T/N ( $A\beta$  /tau/neurodegeneration) classification system, which encompasses biomarkers of  $A\beta$ , tau, and neurodegeneration and/or neuronal injury.<sup>121</sup> Recently proposed updates to this framework explore the utility of additional biomarker categories, including inflammation/astrocytic activation ("I"), vascular brain injury ("V), and  $\alpha$ -synuclein ("S"), to better incorporate comorbid pathologies in suspected AD patients. Though this definition of AD is of great utility in a research context, a standardized protocol for assessment and diagnosis of AD in a clinical setting has been developed by the Consortium to Establish a Registry for Alzheimer's

Disease (CERAD).<sup>122, 123</sup> The CERAD battery incorporates clinical and neuropsychological testing, neuroimaging, and pathological assessment when possible.<sup>122,</sup>

123

A $\beta$  and tau accumulate in characteristic patterns in typical AD. A $\beta$  pathology classically deposits in five phases known as Thal stages; this process can begin decades before onset of cognitive symptoms in individuals who will go on to develop AD.<sup>6, 124</sup> Stage 1 is characterized by A $\beta$  deposition in the frontal, temporal, parietal, or occipital neocortex.<sup>6</sup> The allocortex (insula, entorhinal cortex, and CA1 of the hippocampus) is also positive for A $\beta$  deposition in Stage 2.<sup>6</sup> Stage 3 involves A $\beta$  depositions in the diencephalon (thalamus and hypothalamus), striatum (caudate and putamen), and basal forebrain.<sup>6</sup> Stage 4 typically sees A $\beta$  deposition in brainstem nuclei including the substantia nigra, red nucleus, central gray, colliculi, inferior olivary nucleus, and intermediate reticular zone.<sup>6</sup> Finally, Stage 5 is characterized by A $\beta$  deposits in the cerebellum and additional brainstem nuclei (locus coeruleus, pontine, parabrachial, reticulo-tegmental, dorsal tegmental, and raphe nuclei).<sup>6</sup>

Tau deposits in six stages known as Braak stages.<sup>5</sup> In Stage I, tau is predominantly located in the transentorhinal region.<sup>5</sup> In Stage II, lesions extend into the hippocampus and/or entorhinal cortex.<sup>5</sup> In Stage III, tau deposits are found in the fusiform, parahippocampal, and/or lingual gyri.<sup>5</sup> Patients typically begin to show cognitive symptoms in approximately Braak Stage IV; at this stage, tau is present in all regions of Stages I-III but is also found in the inferior temporal gyrus and insula.<sup>5</sup> Stage V is defined with widespread tau deposition in regions that include those in all previous stages, as well as the peristriate area in the occipital lobe and other frontal, superolateral,

and occipital directions.<sup>5</sup> In Stage VI, the final defined stage, tau pathology is found in all stages seen in Stages I to V, both secondary and primary neocortical areas, and the striate area of the occipital lobe.<sup>5</sup>

There are a variety of well-known risk factors for AD, the most well-characterized of which include advanced age, family history, and genetic variations (such as the  $\epsilon 4$  allele of the *APOE* gene).<sup>29</sup> Traumatic brain injury (TBI), also called concussion or head injury, is another frequently cited risk factor for AD. TBI is extremely common; one survey indicated over a quarter (28.9%) of American adults have experienced at least one in their lifetime.<sup>125</sup> Most injuries are thought to be mild, and the diagnostic criteria to establish a diagnosis of mild TBI requires that at least one of the following be present after an injury occurs: loss of consciousness for any period of time, post-traumatic amnesia, confusion, disorientation, or another sign of an altered mental state, or neurological abnormalities such as seizure.<sup>126-129</sup> Common mechanisms for incurring TBIs include the head being struck by or against something or due to a trip, slip, or fall.<sup>125</sup> Sports and recreation, as well as motor vehicle accidents, are also frequent contexts for injury.<sup>125</sup> Additionally, there may be gender-<sup>130-132</sup> and age-based demographic differences in TBI incidence,<sup>79, 125, 133</sup> as well as disparities by racial/ethnic group identification<sup>125, 134</sup> and educational attainment.<sup>125</sup>

Outside the general population, TBIs also occur regularly amongst athletes who play contact sports, as well as military service members.<sup>64, 65</sup> For example, 5-35% of American servicemembers deployed to Iraq and Afghanistan sustained a TBI during deployment.<sup>65</sup> Additionally, TBI has been studied as a risk factor for neurodegenerative disease in the context of the well-documented relationship between repetitive TBI and

chronic traumatic encephalopathy (CTE), a neurodegenerative disease identified frequently in American football players and other populations with high rates of repetitive TBI.<sup>76, 114, 115, 135</sup> Interest in TBI as a risk factor for AD has also been growing due to reports of a link between TBI and earlier onset of AD,<sup>30-32, 136</sup> though there is a lack of consensus in the literature as some studies failed to find such an association.<sup>137, 138</sup> Consequently, less attention has been directed towards understanding the biological underpinnings of the relationship between TBI and AD risk. However, developing technologies, including the widespread use of positron emission tomography (PET) as a tool for *in-vivo* detection and quantification of pathological protein buildup, have better enabled the field to analyze the association of risk factors such as TBI with the spatial and temporal dynamics of protein accumulation in neurodegenerative diseases.

PET is a radiological technique that can be used to visualize the concentrations and distributions of radiolabeled molecules across the body *in vivo*.<sup>139, 140</sup> It is widely used in AD research for the purpose of detection and quantification of pathological changes associated with A $\beta$  and tau, as well as other molecules in the brain. PET uses a small amount of a radioactive tracer that binds to a specific protein target.<sup>141</sup> The tracer emits positrons as a function of radioactive decay, and the positrons are detected by the scanner and computationally mapped back to their place of origin, enabling visualization of both the relative quantity and spatial positioning of the target protein.<sup>141</sup> There are a multitude of different tracers that have been developed to label A $\beta$  and tau. The A $\beta$  tracers employed by studies cited in this review include Pittsburgh Compound B ([<sup>11</sup>C]-PiB), Florbetapir ([<sup>18</sup>F]AV-45), Florbetaben ([<sup>18</sup>F]FBB), <sup>18</sup>F-FPYBF-2, and Flutafuranol ([<sup>18</sup>F]-NAV4694) (Table 1). The tau tracers include Flortaucipir ([<sup>18</sup>F]AV-1451) and

Florquinitalu ( $[^{18}\text{F}]$ -MK-6240) (Table 1). Of the tracers used in the studies included in this review, the U.S. Food and Drug Administration (FDA) has approved  $[^{18}\text{F}]$ Florbetapir (Amyvid),  $[^{18}\text{F}]$ Florbetaben (NeuraCeq), and  $[^{18}\text{F}]$ Flortaucipir (Tauvid).

There is an urgent need to better understand the long-term consequences of TBI, including biological pathways related to AD, as TBI affects many people across many demographics. However, few studies have used A $\beta$ - and tau-PET to detect changes in protein deposition after TBI in individuals at increased risk for AD due to age. These studies are critical in characterizing the effects of TBI on biomarkers and AD risk *in vivo*. The purpose of this review is to synthesize literature that used A $\beta$  and tau-PET to explore associations between TBI and pathological biomarkers in aging populations at risk for AD.

## Methods

### *Eligibility criteria*

We included studies that used tau and/or A $\beta$ -PET in humans to study the impact of TBI in populations either with or at risk for AD due to advancing age. Gray literature (i.e., conference abstracts, meeting reports, etc.) were eligible for inclusion. If a peer-reviewed and published paper was substantially similar to a gray literature report, the gray literature was excluded, and the peer-reviewed paper was included. As this review's purpose is to consider TBI as a risk factor solely for AD, we excluded articles that mainly focused on other neurodegenerative dementias such as CTE. Additional exclusion criteria were: 1) no use of either A $\beta$  or tau PET, 2) not primarily focused on TBI, 3) studies using preclinical models, 4) studies not available in English, and 5) review or meta-analysis articles. Additionally, while articles used varying terminology to describe participants' injuries (e.g., TBI, head injury, concussion), we hereafter exclusively use the term TBI. Finally, we applied an age cutoff to include studies with participants who were on average >40 years of age. In doing so, we avoided studies focused primarily on younger adults or pediatric populations who would not be considered at increased risk for AD due to age.

### *Information sources, search procedure, and study selection*

A medical librarian composed and conducted comprehensive search strategies in MEDLINE (Ovid), Embase (Ovid), and the Cochrane Database of Systematic Reviews on January 9, 2023. The systematic review management tool Covidence removed

duplicate records. 1476 unique citations were initially identified. The research team screened in two stages, first combined title and abstract screening and then full-text review. At each stage of the screening process, two reviewers independently screened each article and conflicts were resolved by consensus. After title and abstract screening, 81 articles were deemed appropriate for full-text review. After full-text review, the research team identified 26 articles that matched the inclusion criteria; data from these articles was then extracted using Covidence. Detailed data on the number of articles excluded during each step of the screening process can be found in Figure 1, and detailed data on the selected articles can be found in Table 1. No additional statistical analyses were performed on the selected citations, chiefly because of large variation in sample sizes across studies and the inability to identify individuals in commonly used datasets (e.g., the Alzheimer's Disease Neuroimaging Initiative (ADNI)) that may have been analyzed in more than one citation.

## Results

### *A $\beta$*

Twenty of the included studies used at least one A $\beta$  tracer. Florbetapir was used in 12 papers, [<sup>11</sup>C]-PiB was used by four, and [<sup>18</sup>F]-FPYBF-2 and [<sup>18</sup>F]-Flutafuranol were each used in one paper. Additionally, one study used both Florbetapir and [<sup>11</sup>C]-PiB, and one used both Florbetapir and Florbetaben. The regions which had the strongest supportive evidence for increased A $\beta$  tracer uptake after TBI were the cingulate gyrus and cuneus/precuneus. Commonly identified limitations of the citations were small sample size, limited clinical detail about TBI, recall bias, the potential for biased recruitment strategies, and an inability to establish causation due to cross-sectional study designs.

### Evidence for limbic A $\beta$ deposition

Four articles analyzed A $\beta$  tracer uptake in limbic regions of interest (ROIs), including the medial temporal lobe (MTL)/hippocampus, temporal pole, and entorhinal cortex (Table 2).<sup>109, 142-144</sup> In the hippocampus, one paper found evidence for altered Florbetapir uptake at multiple post-injury timepoints,<sup>142</sup> while a paper using [<sup>11</sup>C]-PiB found no change.<sup>144</sup> Additionally, one study suggested there may be increased Florbetapir in the temporal pole of TBI cases,<sup>143</sup> but another found no change in the temporal pole or entorhinal cortex.<sup>109</sup>

### Evidence for subcortical or white matter A $\beta$ deposition

Seven articles investigated A $\beta$  tracer uptake in subcortical ROIs, including the thalamus, globus pallidus, caudate and putamen (striatum), and cerebellum; the corpus callosum and global white matter (WM) analyses were also included in this category (Table 3).<sup>142-148</sup> Four papers using different A $\beta$  tracers (Florbetapir,<sup>142</sup> [<sup>11</sup>C]-PiB,<sup>144, 148</sup> and [<sup>18</sup>F]-FPYBF-2<sup>146</sup>) reported no significant differences in thalamic A $\beta$  burden in TBI. Additionally, there was no significant difference in [<sup>18</sup>F]-FPYBF-2 binding in the globus pallidus.<sup>146</sup> In the striatum (caudate and putamen), two studies found some evidence of altered Florbetapir uptake, with the caveat that alterations were time-dependent<sup>74</sup> and potentially related to more severe diagnoses and/or higher *APOE*  $\epsilon$ 4 allele frequency in the TBI group.<sup>147</sup> Similarly, another study showed significantly higher [<sup>11</sup>C]-PiB distribution volume ratios in the striatum of TBI patients relative to controls.<sup>148</sup> However, two papers using [<sup>11</sup>C]-PiB<sup>144</sup> and [<sup>18</sup>F]-FPYBF-2<sup>146</sup> both found no evidence for altered tracer binding in the striatum of TBI cases relative to non-TBI. Next, of the four papers that examined cerebellar ROIs, three found evidence for altered Florbetapir and [<sup>11</sup>C]-PiB binding,<sup>143-145</sup> while another found no change in Florbetapir binding in TBI relative to controls.<sup>147</sup> Two studies investigated A $\beta$  burden in the global WM (using [<sup>18</sup>F]-FPYBF-2<sup>146</sup> and [<sup>11</sup>C]-PiB<sup>148</sup>) but saw no difference between focal TBI patients and controls. Finally, one study saw elevated Florbetapir in the corpus callosum of TBI patients,<sup>145</sup> but another reported no change using [<sup>18</sup>F]-FPYBF-2.<sup>146</sup>

## Evidence for cortical A $\beta$ deposition

Twenty articles assessed at least one measure of cortical A $\beta$  tracer uptake, including global A $\beta$  status/burden, cortical lobes, the cingulate gyrus, and cuneus/precuneus (Table 4).<sup>103-110, 142-153</sup> 14 papers assessed a global cortical ROI, and five found evidence for altered uptake of [<sup>11</sup>C]-PiB or Florbetapir.<sup>147-151</sup> However, nine papers saw no change in global uptake of [<sup>11</sup>C]-PiB, Florbetapir, Florbetaben, or [<sup>18</sup>F]-NAV4694 in TBI patients.<sup>103-108, 110, 152, 153</sup>

Many papers considered individual lobar ROIs. In the frontal lobe, four found evidence for altered Florbetapir uptake,<sup>143, 145, 147, 150</sup> which might have been related to ongoing cognitive impairment<sup>147</sup> and/or multiple injuries.<sup>150</sup> Three additional papers using Florbetapir,<sup>29</sup> [<sup>11</sup>C]-PiB,<sup>31</sup> and [<sup>18</sup>F]-FPYBF-2<sup>146</sup> found no change. In the parietal lobe, two studies observed altered Florbetapir uptake in TBI, albeit in opposing directions where one showed lowered uptake<sup>145</sup> and another elevated uptake.<sup>147</sup> However, five additional studies saw no differences.<sup>109, 142, 143, 146, 150</sup>

Temporal lobe ROIs were examined by the same seven papers that studied parietal ROIs. Similar to the parietal lobe, four reports noted altered A $\beta$  tracer uptake in TBI cases,<sup>143, 145-147</sup> with comorbid post-traumatic stress disorder (PTSD)<sup>145</sup> and more severe injuries (diffuse axonal injury, or DAI)<sup>146</sup> as potential contributing factors. However, three papers saw no change in uptake.<sup>142, 150, 154</sup> In the occipital lobe, results were similarly split. Two studies using Florbetapir<sup>29,30</sup> and one using [<sup>18</sup>F]-FPYBF-2<sup>34</sup> found altered A $\beta$  deposition.<sup>142, 143, 146</sup> Two studies using Florbetapir<sup>35,40</sup> and one using [<sup>11</sup>C]-PiB<sup>144</sup> found no change in TBI cases.<sup>144, 147, 150</sup>

Seven papers investigated the cingulate gyrus. In the anterior cingulate, two studies from the same group showed elevated Florbetapir uptake,<sup>143, 145</sup> while three papers from other groups saw no change.<sup>142, 144, 150</sup> In the posterior cingulate, four studies observed altered A $\beta$  tracer uptake,<sup>143-145, 150</sup> but three did not.<sup>142, 147, 154</sup> Finally, ROIs of the cuneus and/or precuneus were analyzed in seven studies, of which five showed altered tracer uptake<sup>142-145, 147</sup>, albeit in an inconsistent pattern. Though four of the five showed elevated uptake,<sup>143-145, 147</sup> a case report suggested there was evidence of lowered A $\beta$ .<sup>142</sup> Furthermore, two additional studies found no change in cuneus/precuneus A $\beta$  deposition in TBI.<sup>109, 150</sup>

### *Tau*

Of the 10 papers which used a tau tracer, eight utilized Flortaucipir and two used [<sup>18</sup>F]-MK-6240. The regions with most concordant evidence for elevated tracer uptake in TBI patients were the MTL and entorhinal cortex, precuneus, and cortical lobes. The major limitations described were a small number of participants with TBI, a paucity of clinical detail, and the potential for recall bias.

### Evidence for limbic tau deposition

Six papers examined tau deposition in at least one limbic ROI, including the MTL/hippocampus, entorhinal cortex, and temporal pole (Table 5).<sup>105, 152, 155-158</sup> In a MTL/hippocampus composite, there was no evidence for altered Flortaucipir uptake.<sup>155</sup> However, results from three studies of non-composite MTL/hippocampus ROIs

suggested elevated Flortaucipir binding in TBI.<sup>152, 156, 158</sup> In the entorhinal cortex, one study saw no cross-sectional or longitudinal changes to Flortaucipir uptake in TBI-exposed participants<sup>105</sup>, while another paper observed elevated Flortaucipir in the transentorhinal cortex of TBI participants.<sup>156</sup> Finally, two studies showed elevated Flortaucipir SUVR in the temporal pole of TBI participants.<sup>156, 157</sup>

### Evidence for cortical and/or subcortical tau deposition

Ten papers analyzed tau tracer binding in at least one cortical and/or subcortical ROI, including composite (mesial-temporal, temporoparietal, metatemporal, and neocortex) ROIs, cortical lobes, cingulate gyrus, precuneus, insula, basal ganglia, and substantia nigra (Table 6).<sup>102-105, 152, 155-159</sup> In composite ROIs, two reports observed elevated [<sup>18</sup>F]-MK-6240 binding in AD cases compared to controls, but no change in TBI patients.<sup>102, 104</sup> Intriguingly, controls demonstrated higher SUVRs than TBI cases.<sup>104</sup> Another paper also showed no difference in Flortaucipir binding between TBI and non-TBI participants in mesial-temporal, temporoparietal, and neocortex composites.<sup>103</sup>

Of the three studies that considered frontal lobe/gyrus ROIs, all found elevated Flortaucipir uptake in TBI,<sup>152, 157, 158</sup> which authors hypothesized could be related to cognitive impairment<sup>152</sup> and/or comorbid PTSD.<sup>157</sup> Similarly, four studies demonstrated altered Flortaucipir uptake in temporal ROIs,<sup>152, 156-158</sup> although another reported neither cross-sectional nor longitudinal changes in a temporal composite.<sup>105</sup> Next, five studies saw consistent evidence for elevated Flortaucipir SUVRs in parietal ROIs of TBI

cases.<sup>152, 156-159</sup> Similarly, four reports of occipital ROIs found elevated Flortaucipir in TBI participants,<sup>155, 156, 158, 159</sup> though one study reported no differences.<sup>157</sup>

Five papers showed elevated Flortaucipir in the cuneus/precuneus of TBI participants relative to controls.<sup>152, 156-159</sup> Multiple injuries<sup>159</sup> and comorbid PTSD<sup>157</sup> were discussed as potential contributing factors. Only one paper investigated the insula but found higher Flortaucipir SUVR in TBI participants relative to controls.<sup>157</sup> Similarly, two studies reported elevated Flortaucipir SUVRs in the basal ganglia of TBI participants.<sup>157, 158</sup> Finally, the same group observed elevated Flortaucipir in both the substantia nigra<sup>158</sup> and cingulate gyrus<sup>159</sup> of TBI cases.

## Discussion

Findings from the current body of literature are incongruent regarding an association between TBI and A $\beta$  and/or tau deposition on PET in older adults at risk for AD. The areas with most concordant evidence for elevated A $\beta$  deposition in TBI patients were the cingulate gyrus and the cuneus/precuneus. However, findings were mixed in most limbic, cortical, and subcortical ROIs. Many studies reported at least some evidence for altered A $\beta$  deposition in TBI, but the patterns were inconsistent and other studies saw no change.

Studies of tau deposition were generally in better agreement than the A $\beta$  studies. This may be a consequence of fewer tau tracers being available, as Flortaucipir was used in all but two reports, but five A $\beta$  tracers were employed. In limbic ROIs, there was fairly consistent evidence for elevated tau in the MTL/hippocampus and temporal pole of TBI participants. In cortical composite ROIs, results were mixed, with some studies finding elevated tracer binding in TBI and others finding no change. Consensus was improved when individual lobes/gyri were considered, which suggests greater utility of cortical parcellations as opposed to composite ROIs. In the cortical lobes, most reports saw increased SUVRs in TBI. Jointly, these studies suggest there may be elevated cortical tau in older individuals with TBI history.

There was also concordant evidence for increased tau in the cingulate, insula, basal ganglia, and substantia nigra of TBI cases, though these ROIs were subject to limited analysis and require confirmatory replications. Similarly, in the precuneus, five

studies showed elevated tau in TBI. Together, these papers suggest the precuneus may be vulnerable to pathological A $\beta$  and tau deposition in older adults with TBI history.

Though currently-available PET tracers may not be highly sensitive to early Thal Stage amyloid deposition, the findings from studies in this review are somewhat consistent with an AD-like pattern of early A $\beta$  deposition in showing the strongest evidence for elevated A $\beta$  in the cuneus/precuneus and cingulate gyrus.<sup>6</sup> Similarly, increased tau SUVRs in the MTL and entorhinal cortex, precuneus, and cortical lobes of TBI cases is also relatively consistent with an AD-like pattern of tau deposition based on the Braak stages. However, the ROIs with higher A $\beta$  deposition tended to reflect early Thal stages, but the ROIs with elevated tau represented nearly all the Braak stages. For example, there was elevated tau in early-depositing regions such as the entorhinal cortex, which typically shows tau in Braak Stage I, but there was also elevated tau in later-depositing regions like the cortical lobes, which typically demonstrate widespread tau only in Stages V and VI.<sup>5</sup> Though the evidence is not conclusive, these patterns suggest TBI in older adults may be associated with AD-like A $\beta$  deposition, but a more unique pattern of tau deposition. This raises the question of whether elevated tau is consistent with AD or another neurodegenerative disease, such as CTE,<sup>160-162</sup> which will be discussed later.

The largely contradictory nature of the findings highlights the need for confirmatory replications in large prospective datasets to better understand the relationship between TBI and AD-related protein deposition. Several key factors likely contributed to inconsistency between studies. First, there is significant participant-level heterogeneity, including differing TBI severity, time since injury, mechanisms of injury,

and comorbid diagnoses such as PTSD or cognitive impairment. Similarly, there is substantial methodological variation between studies, including inclusion/exclusion criteria, radiotracer and ROI selection, and analysis pipelines.

Variations in injury severity, both between participants in the same study and between samples enrolled across studies, likely contributed to the inconsistency of the findings. Only one study explicitly investigated DAI, but patients with DAI may have showed different patterns of A $\beta$  deposition compared to focal injury patients.<sup>146</sup> Specifically, there was increased A $\beta$  tracer binding in the WM of DAI patients compared to focal injuries.<sup>146</sup> As DAI by definition is associated with widespread WM damage, this finding is logical; however, off-target WM binding is a known issue and may contribute to false positive findings.<sup>163-165</sup> Nonetheless, there was also widespread variation in injury severity across studies that did not consider DAI. Some studies utilized cohorts with only self-reported TBI, like ADNI (participants would likely be classified as mild TBI),<sup>143, 145, 152, 154</sup> while others included moderate to severe TBI.<sup>142, 144</sup> This variation limits the validity of direct comparison between studies, as injury severity may be associated with differences in protein deposition.<sup>152, 166</sup> However, additional investigation of whether severe injuries are associated with greater protein load is needed to clarify if this is a meaningful confounding variable.

Next, the chronicity/acuity of TBI relative to the time of imaging is another likely contributor to the ambiguity of the findings. Previous studies have demonstrated changes in A $\beta$  levels in biofluids, on imaging, and upon pathological examination acutely after TBI, particularly in severely injured individuals with short survival time.<sup>167-174</sup> Additional evidence of acute post-TBI biomarker changes comes from sports medicine, where

biofluid biomarkers to aid in TBI evaluation have been investigated. There is evidence of acute alterations in glial fibrillary acidic protein (GFAP), ubiquitin C-terminal hydrolase L1 (UCH-L1), and neurofilament light chain (NFL) after TBI.<sup>175-178</sup> However, there is little longitudinal data beyond the injury recovery period, and limited evidence of acute changes on tau- or A $\beta$ -PET that could be detectable years after injury.<sup>179, 180</sup>

Additionally, biofluid protein levels return to baseline relatively quickly, which does not support the presence of long-term associations between TBI and protein deposition on PET.<sup>167, 175, 176, 179</sup> As such, in older participants with remote TBI history, biomarkers may have returned to pre-injury levels before participants undergo PET scans for AD biomarkers. Furthermore, most studies included in this review did not measure any fluid biomarkers, so persistent changes to fluid biomarkers could not be assessed to indicate whether concurrent PET changes are expected. Together, it is unclear whether alterations in AD-related protein levels after TBI are detectable on PET years or decades after injury. That evidence notwithstanding, many studies covered in this review lacked the necessary clinical detail to even consider time since injury as a factor. In studies that did characterize time since injury, there were widely varying injury-to-imaging intervals. For example, some participants were >15 years out from their TBI,<sup>48</sup> while others were assessed only weeks to months after injury.<sup>142</sup> This discrepancy limits the utility of direct comparison between studies and likely contributes to the uncertainty of the findings.

Along the same lines, varying mechanisms of injury are another plausible contributing factor to the inconsistency. Many studies could not identify mechanisms of injury, and in others, mechanisms were widely variable, encompassing military service, car accidents, sports participation, and others. This is a significant limitation, as each

mechanism of injury may impact the brain in unique ways. For example, TBI resulting from blast exposure may affect the entirety of the brain and body, whereas blunt-force TBIs often result in localized damage.<sup>66, 181</sup> If these injuries are reflected in differential tau and/or A $\beta$  deposition patterns, this could partly explain why studies found such widespread results. To improve coherence, it could be informative to compare PET findings from participants whose TBI(s) occurred through similar mechanisms. This would be most feasible for injuries incurred due to sports, military service, or falls, as these are prominently discussed in the literature.<sup>64, 79, 182-184</sup> However, another important mechanism for incurring TBI is intimate partner/domestic violence (IPV/DV).<sup>61</sup> Consideration of IPV/DV raises concerns related to demographic differences in mechanism of injury, as the prevalence of TBIs resulting from IPV/DV may have sex-, age- and/or racial/ethnic group differences.<sup>62</sup> These demographic confounds could represent another source of bias if not carefully controlled. None of the analyzed studies explicitly discussed IPV/DV, but there may be similar demographic confounds in other sources of TBI, like military service or sports participation, that were part of this review.<sup>130-132, 134, 185</sup> Future studies should thoroughly document mechanisms of injury whenever possible, as meta-analyses between participants with similar injury mechanisms may result in improved consensus.

Furthermore, we cannot exclude the possibility that altered protein deposition on PET represents chronic traumatic encephalopathy (CTE) rather than AD in some older adults with TBI. This possibility is of particular concern for participants with numerous injuries, as repetitive TBI is the most significant risk factor for CTE.<sup>76, 112, 115</sup> CTE is characterized pathologically by hyperphosphorylated tau inclusions in the sulcal depths

around blood vessels in the brain.<sup>111, 113, 115</sup> CTE and AD also show near-inverse patterns of tau accumulation.<sup>160-162</sup> While tau in AD spreads according to the Braak stages and does not diffusely reach the neocortex until later in the disease,<sup>5</sup> tau in CTE tends to originate in the neocortex and spread interiorly in later disease stages.<sup>111, 113, 115, 160</sup> In this review, studies frequently observed elevated tau in the MTL and entorhinal cortex, which is consistent with early tau deposition in AD. However, there was also elevated tau in the precuneus and throughout the cortical lobes, which cannot be specifically attributed to either AD or CTE. CTE can only definitively be diagnosed post-mortem, though a differential diagnosis may be established based on both the distribution and magnitude of tau tracer binding in suspected CTE patients, as well as clinical symptoms and history of brain injury exposure.<sup>186, 187</sup> However, it is impossible to distinguish what unique tau fold isoforms are present solely based on a positive tau-PET scan. Work from cryo-electron microscopy has demonstrated that tau folds differently in CTE as opposed to AD,<sup>188</sup> but affinities of the available tau radiotracers to these disease-specific tau conformations is unclear. Some reports have attempted to clarify whether radiotracers have higher affinities for specific tau conformations, but more work is needed, as there is currently no known tau tracer that binds only to CTE-type tau and not AD-type tau.<sup>189, 190</sup> A number of tau-PET tracers have been evaluated and compared head-to-head for use in non-AD dementias, including suspected CTE.<sup>189, 190</sup> These tracers, including florzolotau ([<sup>18</sup>F]-PM-PBB3), [<sup>18</sup>F]-PI-2620, and [<sup>18</sup>F]-CBD-2115, may be more optimized for use in suspected CTE than previous-generation tracers such as Flortaucipir, but none are specific particularly to CTE pathology.<sup>189-195</sup> As such, the inability to determine whether a positive tau-PET scan is consistent with CTE, AD pathology, or some combination of

AD, CTE, and/or other neurodegenerative diseases is challenging, particularly when mixed pathology is suspected. These limitations further prevent a definitive statement of whether the evidence supports a link between TBI and AD-related protein deposition in older adults.

Though a CTE diagnosis cannot be made without pathological examination, some comorbid conditions that can be diagnosed during life, like PTSD or cognitive impairment, may also be associated with protein deposition in individuals with TBI. PTSD is of particular interest, given that PTSD rates are high in military servicemembers<sup>196</sup> and survivors of IPV/DV,<sup>197</sup> populations that also have high prevalence of TBI.<sup>62, 182, 183</sup> Potential associations of PTSD with A $\beta$  and tau are even more intriguing given that studies cited in this review found conflicting evidence for altered tau and/or A $\beta$  deposition in participants with PTSD.<sup>110, 145</sup> Additionally, animal and human studies have found mixed evidence for associations between PTSD alone and AD biomarkers,<sup>198-200</sup> and PTSD has also been linked to risk for cognitive impairment and dementia.<sup>72, 82, 201-203</sup> Though conflicting, the evidence to date indicates there may be unique effects of PTSD on AD biomarkers independent of TBI. However, particularly in veteran populations, which were the only population with PTSD included in studies cited by this review, it may be challenging to identify unique effects of TBI on AD biomarkers due to high comorbidity of PTSD. As such, in individuals with PTSD and TBI where there is evidence for alterations to AD biomarkers, it is near-impossible to determine whether those changes are specifically attributable to TBI. PTSD as a comorbid diagnosis alongside TBI thereby contributes to the difficulty of directly comparing studies and likely also contributed to ambiguity in the findings.

Potential effects of concurrent cognitive impairment on the ambiguity of the findings also cannot be discounted, but as with many previously discussed confounding variables, associations are very difficult to identify. Nine of the cited studies did not include any impaired participants (e.g.,<sup>39,40</sup>) (Table 1). In the remaining 17 studies that included impaired individuals, there were multiple levels of impairment (e.g.,<sup>152,51</sup>) (Table 1). For example, some participants were impaired due to AD, while others who did not meet criteria for AD were classified as mild cognitive impairment, in line with clinical guidance for diagnosing AD.<sup>204</sup> Additionally, it is possible that impairment in some participants is due to a non-AD dementia (potentially CTE, as discussed earlier).<sup>205,</sup><sup>206</sup> Finally, some participants were acutely impaired as a consequence of their TBI, as opposed to AD or another dementia (e.g.,<sup>142,50</sup>). Unless impaired participants are carefully matched based on diagnosis and reasons for impairment, comparison of AD protein deposition on PET has little value, particularly in the context of TBI where misdiagnosis is of concern.<sup>205, 206</sup> As such, it is incredibly challenging to parse out the relationship between cognitive impairment and changes to A $\beta$ - and/or tau-PET in older adults with TBI history when participants with widely varying diagnoses are combined for analysis. Too much of the variability in PET findings could be attributed to variation in cognitive status as opposed to TBI, which prevents the establishment of reliable conclusions.

Next, methodological differences across studies almost certainly contribute to the mixed findings. Participant recruitment and inclusion/exclusion criteria are a critical point in which bias can be introduced into studies. For example, in some cohorts, particularly those whose primary focus is aging or AD and not TBI, participants with severe TBI history may be excluded from the sample during the medical history

screening.<sup>207</sup> This exclusion criterion could bias the findings in favor of lower associations between TBI and protein deposition.

Another important methodological element which introduces variability is the challenge of comparing studies that used different tau and A $\beta$  tracers, as each tracer may produce unique findings. Previous studies indicate A $\beta$  tracers have only slight variability of sensitivity and specificity in AD, which suggests this concern may be minimal.<sup>208, 209</sup> However, tau exists as two isomers, 3R and 4R, identified based on the number of microtubule-binding repeats present,<sup>210</sup> and currently available tau tracers may bind with distinct affinities to these isomers.<sup>190</sup> Additionally, cryo-EM studies have identified unique tau folds specific to certain diseases, such as CTE, to which the sensitivity of tau tracers has not yet been conclusively determined.<sup>188, 211, 212</sup> Though differential tracer binding may explain some variability in the findings, only two tau tracers were used, and results from tau studies were more consistent than the A $\beta$  studies, where five different tracers were used. This suggests radiotracer selection may indeed impact the findings and replicability of studies, as coherence seemingly improved when studies used the same tracer.

Similarly, ROI selection and definition may have contributed to the discrepancy in the results. As noted in the results, studies that used summary or global ROIs were challenging to compare to studies that used individual lobar or gyrus ROIs, which may have also resulted in differing conclusions (Table 6). Use of summary or global ROIs severely limits consideration of regional changes to protein deposition, as the summarization of information results in the loss of nuances between smaller parcellated brain regions. Additionally, summary ROIs limit the ability to detect localized tau and/or

A $\beta$  deposits, which is especially concerning given that tau deposits in CTE may be confined to specific regions.<sup>111, 113, 115</sup> Outside the use of summary ROIs, variation could also have been introduced if labs used different segmentation methods to identify ROIs. For example, a lab using Freesurfer could generate different results than a lab using SPM (or any other image processing suite) if ROI boundaries are defined slightly differently.<sup>213-215</sup> ROI selection and definition may be specific to image processing and analysis pipelines, which represents another opportunity for variability to be introduced across studies.

Unique image processing and analytical pipelines utilized by separate labs can introduce significant variation in findings, even if the exact same dataset is analyzed. This failure to replicate phenomenon has been demonstrated previously in neuroimaging modalities, particularly in fMRI.<sup>216</sup> As neuroimaging and most scientific fields in general face a replication crisis, the impact of image processing and analysis pipelines on diverging results cannot be ignored. This is a highly probable source of variability in the included studies and is emphasized by the observation that findings from studies published by the same group (and thereby using the same or substantially similar methods) tended to share more similar findings than did the whole body of literature.<sup>32,145, 156,54</sup> Careful documentation of methods, in addition to potential adoption of standardized pipelines, is necessary to improve replicability across multiple labs.

Considering the numerous potential sources for variation between studies, it is not surprising that there is little concordance in the field regarding an association of TBI with AD-related protein deposition on PET. Given the contrasting nature of the findings and the wide variation in methods used, there is not enough evidence to conclusively state

whether an association exists between TBI and A $\beta$  and/or tau deposition in older individuals, though there was more consistent evidence for elevated tau. Such associations may be present, as many of the included studies suggest, but the evidence is far from consistent and additional data and replications are needed.

Moving forward, analyses of new and/or expanded samples will be of significant value, but replications in smaller datasets that have been previously analyzed may identify major methodological contributors to discrepancies in the results. Significant attention should be devoted to improving standardization and alignment of PET processing and analysis pipelines, so it is easier to determine whether there is consistent signal in the data or whether findings are spurious or coincidental. This is especially important when investigating associations with a small effect size and wide variation between participants, such as the association of TBI with A $\beta$  and/or tau deposition in older individuals.

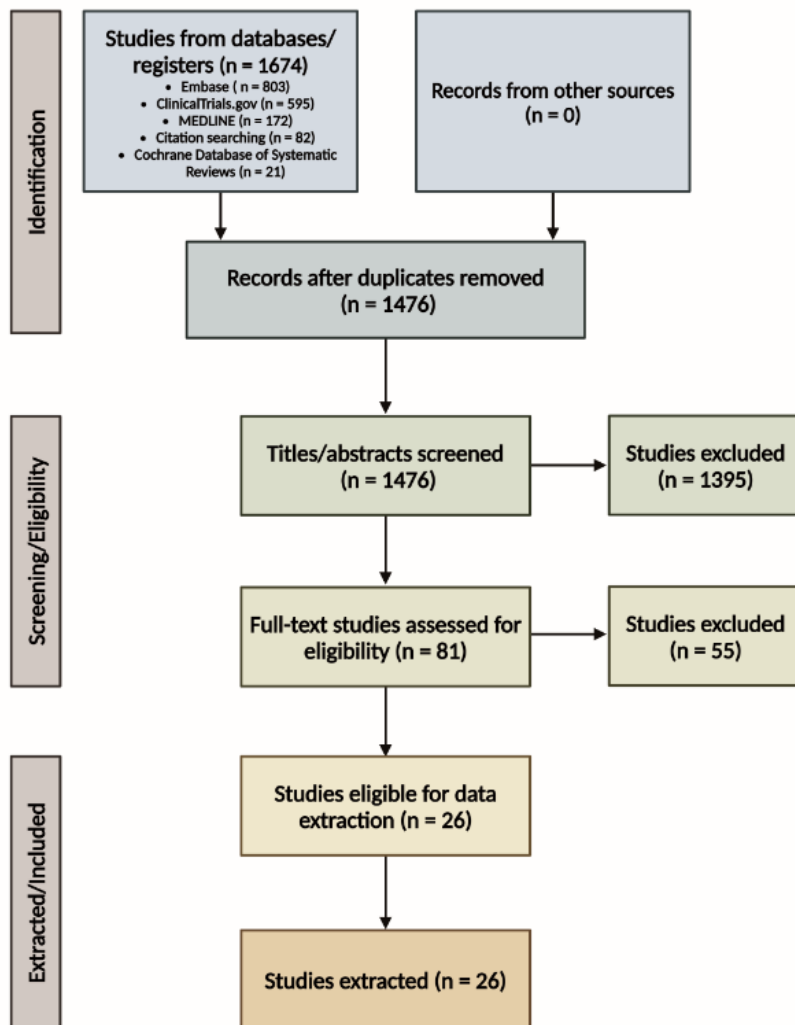


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)<sup>217</sup> flow diagram. Created with BioRender.com.

<u>Article</u>	<u>Total subjects</u>	<u>Pathology imaged</u>	<u>Tracer(s)</u>	<u>Subject sources</u>	<u>Injury/cognition breakdown</u>	<u>Cognitive statuses</u>
Asken et al., 2021	134	Amyloid	Florbetapir (92.5%), [ <sup>11</sup> C]-PiB (7.5%)	UCSF Memory and Aging Center Hillblom Aging Network	48 mTBI (31 with 1 TBI, 17 with 2+), 86 non-TBI	CN
Hong et al., 2014	49	Amyloid	[ <sup>11</sup> C]-PiB	Convenience sample of patients with TBI from neuroscience referrals center and age-matched controls, and pathological validation in tissue from Glasgow TBI Archive	15 moderate to severe TBI, 11 healthy controls, 16 TBI pathology samples, 7 control tissue samples	CN and impaired
James et al., 2021	499	Amyloid	Florbetapir	Insight 46 (sub-study of National Survey of Health & Development, UK)	80 with LOC HI > 15 years prior, 104 at least 1 HI at any time, 315 without HI	CN
Kawai et al., 2013	12	Amyloid	[ <sup>11</sup> C]-PiB	Patients referred to Kagawa University Hospital for assessment of impairment after TBI	9 with severe TBI, 3 with moderate TBI	CN and impaired
Munro et al., 2019	61	Amyloid	Florbetapir	Dallas Lifespan Brain Study	-	CN
Wang et al., 2017	90	Amyloid	Florbetapir	ADNI	45 with mTBI (8 normal, 10 preclinical AD, 17 MCI due to AD, 10 AD), 45 controls	CN and impaired
Weiner et al., 2017	180	Amyloid	Florbetapir	Vietnam Veterans identified by VA records (ADNI-DOD)	TBI only (22), PTSD only (63), both TBI + PTSD (32), and controls (63)	CN and impaired
Gatson et al., 2016	2	Amyloid	Florbetapir	Two clinic patients who had MVA	Both severe TBI and impaired	Case report
Mielke et al., 2014	589	Amyloid	[ <sup>11</sup> C]-PiB	Mayo Clinic Study on Aging (MCSA)	448 CN (74 TBI), 141 MCI (25 TBI)	CN and impaired

Mohamed et al., 2018	164	Amyloid	Florbetapir	ADNI-DOD Vietnam War veterans	57 control, 21 TBI, 57 PTSD, 29 TBI + PTSD	CN
Mohamed et al., 2022	241	Amyloid	Florbetapir	ADNI	19 TBI + CDR > 0.5, 22 TBI and CDR = 0, 100 without TBI and CDR > 0.5, 100 without TBI and CDR = 0	CN and impaired
Schneider et al., 2019	329	Amyloid	Florbetapir	Atherosclerosis Risk in Communities-Positron Emission Tomography (ARIC-PET) Study	81 with HI, 248 without HI	CN
Scott et al., 2016	28	Amyloid	[ <sup>11</sup> C]-PiB	9 clinic patients, recruited at least 11 months after their injury	9 with TBI, 9 controls, 10 with AD	CN and impaired
Tateno et al., 2015	1	Amyloid	Florbetapir	Clinic patient struck by a vehicle	1 with prior HI	Impaired
Ubukata et al., 2020	70	Amyloid	[ <sup>18</sup> F]-FPYBF-2	Recruited from outpatient clinic of neuropsychology unit at Dept. of Psychiatry & Department of Neurosurgery, Kyoto University Hospital	20 chronic TBI patients, 50 controls	CN
Yang et al., 2015	27	Amyloid	Florbetapir	TBI patients treated for acute TBI at Taipei Medical University Hospital or TMU-Shuang Ho Hospital	27 mTBI (6 with cognitive impairment/dementia), 10 controls	CN and impaired
Dore et al., 2022	70	Amyloid and tau	Florbetapir, Flortaucipir	Vietnam War veterans from Australian Imaging Biomarkers and Lifestyle Study of Aging-Veterans Study (AIBL-VETS)	40 TBI, 30 controls	CN
Hicks et al., 2022	146	Amyloid and tau	[ <sup>18</sup> F]-NAV4694,	Longitudinal head injury outcome study	87 TBI, 59 control	CN

			[ <sup>18</sup> F]-MK-6240	from admissions to inpatient rehabilitation program at Epworth HealthCare (Melbourne, AUS)		
Weiner et al., 2022	289	Amyloid and tau	Florbetapir, Flortaucipir	ADNI-DOD Vietnam War veterans	Baseline: 71 control, 81 PTSD, 43 TBI, 94 TBI + PTSD Longitudinal: 60 control, 63 PTSD, 37 TBI, 65 TBI + PTSD	CN and impaired
Risacher et al., 2021	752	Amyloid and tau	Florbetapir, Florbetaben, Flortaucipir	ADNI and Indiana Memory and Aging Study (IMAS)	302 impaired, 450 CN 63 with HI (38 CN, 25 impaired)	CN and impaired
Rowe et al., 2019	128	Tau	[ <sup>18</sup> F]MK-6240	-	70 controls, 8 MCI, 10 AD, 4 other dementia, 36 remote TBI	CN and impaired
Gorgoraptis et al., 2019	32	Tau	Flortaucipir	19 TBI from Institute of Health and Wellbeing, Head Injury Research Group, University of Glasgow; 2 TBI from clinic at Imperial College Healthcare NHS Trust	21 TBI, 11 control	CN and impaired
Mohamed et al., 2019	80	Tau	Flortaucipir	ADNI-DOD Vietnam War veterans	21 control, 10 TBI, 32 PTSD, 17 TBI + PTSD	CN and impaired
Mohamed et al., 2022	120	Tau	Flortaucipir	ADNI	10 TBI + CDR > 0.5, 10 TBI and CDR = 0, 50 without TBI and CDR > 0.5, 50 without TBI and CDR = 0	CN and impaired
Mountz et al., 2017	13	Tau	Flortaucipir	-	7 chronic TBI, 6 control	CN
Mountz et al., 2018	34	Tau	Flortaucipir	-	27 TBI (all impaired), 7 non-TBI controls	CN and impaired

Table 1. Characteristics of included studies.

<b>Article</b>	<b>Medial temporal lobe/hippocampus</b>	<b>Temporal pole</b>	<b>Entorhinal cortex</b>
Asken et al., 2021	-	-	-
Hong et al., 2014	-	-	-
Gatson et al., 2016	x	-	-
James et al., 2021	-	-	-
Kawai et al., 2013	-	-	-
Mielke et al., 2014	-	-	-
Mohamed et al., 2018	-	-	-
Mohamed et al., 2022	-	x	-
Munro et al., 2019	-	-	-
Schneider et al., 2019	-	-	-
Scott et al., 2016	NS	-	-
Tateno et al., 2015	-	-	-
Ubukata et al., 2020	-	-	-
Wang et al., 2017	-	NS	NS
Weiner et al., 2017	-	-	-
Yang et al., 2015	-	-	-
Dore et al., 2022	-	-	-
Hicks et al., 2022	-	-	-
Weiner et al., 2022	-	-	-
Risacher et al., 2021	-	-	-

Table 2. Amyloid deposition in limbic regions (- = not studied; NS = not significant, x = significant).

Article	Thalamus	Globus pallidus	Caudate	Putamen	Cerebellum	White matter	Corpus callosum
Asken et al., 2021	-	-	-	-	-	-	-
Hong et al., 2014	NS	-	x	x	-	NS	-
Gatson et al., 2016	NS	-	x	x	-	-	-
James et al., 2021	-	-	-	-	-	-	-
Kawai et al., 2013	-	-	-	-	-	-	-
Mielke et al., 2014	-	-	-	-	-	-	-
Mohamed et al., 2018	-	-	-	-	x	-	x
Mohamed et al., 2022	-	-	-	-	x	-	-
Munro et al., 2019	-	-	-	-	-	-	-
Schneider et al., 2019	-	-	-	-	-	-	-
Scott et al., 2016	NS	-	NS	NS	x	-	-
Tateno et al., 2015	-	-	-	-	-	-	-
Ubukata et al., 2020	NS	NS	NS	NS	-	x	NS
Wang et al., 2017	-	-	-	-	-	-	-
Weiner et al., 2017	-	-	-	-	-	-	-
Yang et al., 2015	-	-	x	x	NS	-	-
Dore et al., 2022	-	-	-	-	-	-	-
Hicks et al., 2022	-	-	-	-	-	-	-
Weiner et al., 2022	-	-	-	-	-	-	-
Risacher et al., 2021	-	-	-	-	-	-	-

Table 3. Amyloid deposition in subcortical regions.

Article	Global amyloid status/burden	Frontal lobe	Parietal lobe	Temporal lobe	Occipital lobe	Ant. cingulate	Post. cingulate	Pre/cuneus
Asken et al., 2021	NS	-	-	-	-	-	-	-
Hong et al., 2014	x	-	-	-	-	-	-	-
Gatson et al., 2016	-	NS	NS	NS	x	NS	NS	x
James et al., 2021	NS	-	-	-	-	-	-	-
Kawai et al., 2013	NS	-	-	-	-	-	-	-
Mielke et al., 2014	x	-	-	-	-	-	-	-
Mohamed et al., 2018	-	x	x	x	-	x	x	x
Mohamed et al., 2022	-	x	NS	x	x	x	x	x
Munro et al., 2019	NS	-	-	-	-	-	-	-
Schneider et al., 2019	x	x	NS	NS	NS	NS	x	NS
Scott et al., 2016	-	NS	-	-	NS	NS	x	x
Tateno et al., 2015	x	-	-	-	-	-	-	-
Ubukata et al., 2020	-	NS	NS	x	x	-	-	-
Wang et al., 2017	-	-	NS	NS	-	-	NS	NS
Weiner et al., 2017	NS	-	-	-	-	-	-	-
Yang et al., 2015	x	x	x	x	NS	-	NS	x
Dore et al., 2022	NS	-	-	-	-	-	-	-
Hicks et al., 2022	NS	-	-	-	-	-	-	-
Weiner et al., 2022	NS	-	-	-	-	-	-	-
Risacher et al., 2021	NS	-	-	-	-	-	-	-

Table 4. Amyloid deposition in cortical regions.

<b>Article</b>	<b>Medial temporal lobe/hippocampus</b>	<b>Temporal pole</b>	<b>Entorhinal cortex</b>
Dore et al., 2022	-	-	-
Hicks et al., 2022	-	-	-
Weiner et al., 2022	-	-	NS
Risacher et al., 2021	x	-	-
Gorgoraptis et al., 2019	NS	-	-
Mohamed et al., 2019	-	x	-
Mohamed et al., 2022	x	x	x
Mountz et al., 2017	x	-	-
Mountz et al., 2018	-	-	-
Rowe et al., 2019	-	-	-

Table 5. Tau deposition in limbic regions.

Article	Brain Regions												
	Substantia nigra	Basal ganglia	Insula	Precuneus	Cingulate gyrus	Occipital lobe	Parietal lobe	Temporal lobe	Frontal lobe	Rest of neocortex composite (dorsolateral and ventrolateral prefrontal, orbitofrontal, gyrus rectus, superior temporal and anterior cingulate)	Meta-temporal composite (entorhinal cortex, hippocampus proper, parahippocampus, amygdala, fusiform, inferior and middle temporal gyri, temporo-occipital region, angular gyrus)	Temporoparietal composite (inferior and middle temporal, fusiform, supramarginal and angular gyri, posterior cingulate/precuneus, superior and inferior parietal, lateral occipital)	Mesial-temporal composite (entorhinal cortex, hippocampus, parahippocampus, amygdala)
Dore et al., 2022	-	-	-	-	-	-	-	-	-	NS	-	NS	NS
Hicks et al., 2022	-	-	-	-	-	-	-	-	-	x	x	x	x
Weiner et al., 2022	-	-	-	-	-	-	-	NS	-	-	-	-	-
Risacher et al., 2021	-	-	-	x	-	-	x	x	x	-	-	-	-
Gorgoraptis et al., 2019	-	-	-	-	-	x	-	-	-	-	-	-	-
Mohamed et al., 2019	-	x	x	x	-	NS	x	x	x	-	-	-	-

Mohamed et al., 2022	-	-	-	-	-	x	x	x	-	x	-	-	
Mountz et al., 2017	-	-	-	-	x	x	x	x	-	x	-	x	x
Mountz et al., 2018	-	-	-	-	-	-	x	x	x	x	-	-	-
Rowe et al., 2019	x	x	-	-	-	-	-	-	-	-	-	-	-

Table 6. Tau deposition in cortical and sub-cortical regions.

## **Chapter Two: History of head injury is not associated with Alzheimer's disease fluid biomarkers in older adults**

The following chapter is an original research report exploring biofluid biomarkers of AD in participants with HI from the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset. Utilizing a novel strategy comprised of both cross-sectional and longitudinal analyses, we assessed eight biofluid biomarkers collected from both cerebrospinal fluid (CSF) and blood plasma to explore whether cognitively normal and/or impaired participants who self-report having HI would demonstrate altered biomarker profiles compared to those without HI. This novel study included multiple markers of amyloid, tau, and neurofilament light chain.

In a total of 2,511 participants, 100 had HI history. Across all biomarkers, there were no consistent baseline cross-sectional or longitudinal differences in participants with HI compared to those without HI. Of the covariates included in the models, increasing age and cognitive impairment were associated with worsened biomarker signatures, whereas participant sex and ethnicity did not demonstrate an easily interpretable pattern of associations. In sum, our report did not reveal strong evidence for an association of HI with AD fluid biomarkers in ADNI participants.

## Introduction

Alzheimer's disease (AD) is the most common form of dementia, and over 150 million people worldwide are predicted to be diagnosed with AD by 2050.<sup>117</sup> AD is a continuum of increasing pathological and symptom severity that incorporates preclinical and prodromal stages, such as subjective cognitive decline (SCD) and mild cognitive impairment (MCI), before the dementia stage.<sup>116</sup> AD is pathologically defined by the presence of extracellular amyloid plaques and intracellular tau neurofibrillary tangles that deposit in characteristic Thal and Braak stages with increasing disease progression.<sup>5, 6</sup>

A multitude of well-characterized biological and potentially modifiable lifestyle-related risk factors affect one's individual risk for AD. Biological risk factors include advanced age, female sex, and the presence of one or more *APOE*  $\epsilon$ 4 allele(s).<sup>116, 218</sup> Head injury (HI), also known as concussion, is a type of traumatic brain injury (TBI) that is a potentially modifiable risk factor for AD, and there would be a 3% reduction in dementia prevalence if head injuries were completely eliminated.<sup>219</sup> However, the mechanisms mediating the link between HI and AD are not well understood. Molecular changes in the brain after HI are complex and can lead to neuronal dysfunction.<sup>220, 221</sup> Acute changes in the brain following HI include rapid, uncontrolled neuronal depolarization, release of excitatory neurotransmitters, alterations to ionic concentrations, diminished cerebral blood flow, and an increased demand for glucose.<sup>220, 221</sup> These physiological changes may be associated with neuropsychiatric symptoms in the injured individual, such as headache, memory interruptions, sleep disruption, depression, and anxiety.<sup>220, 221</sup> Additionally, upregulation of proteins associated with neurodegeneration, such as

amyloid- $\beta$  ( $A\beta$ ) and hyperphosphorylated tau, have been observed in both animal models and human TBI patients, suggesting HI may induce neurodegenerative processes in the brain that contribute to long-term dementia risk.<sup>87, 222-226</sup> Further, individuals who experience repetitive injuries may be at risk for different long-term outcomes than individuals with only one injury. Repetitive injuries, particularly those observed in professional athletes such as American football players or boxers, have been strongly linked to the development of chronic traumatic encephalopathy (CTE), a neurodegenerative disease characterized by behavioral dysregulation, changes in memory, attention, and executive functioning, and a unique pattern of hyperphosphorylated tau deposition in sulcal depths.<sup>76, 112-115, 227</sup> While there may be differential effects of single injuries versus multiple injuries on AD or CTE risk, there is little data available to examine this question.

Prior studies have reported that HI is associated with increased risk for AD, earlier disease onset, and increased deposition of both  $A\beta$  and tau on positron emission tomography (PET).<sup>30-32, 136, 143, 152, 156, 157</sup> However, there is a lack of consensus in the literature, as other studies found no relationships.<sup>103-110</sup> Potential reasons for this lack of clarity may include separate strategies for HI ascertainment in different cohorts, large variations in sample size, samples consisting of young vs older adults, among other reasons. As such, greater investigation into the possibility of HI-associated biomarker changes in older adults at risk for AD is needed to clarify whether such associations exist and thereby represent a mechanistic explanation behind HI as a risk factor for AD.

Phosphorylated tau (pTau) and  $A\beta$  are AD-specific biomarkers that can be precisely measured in biofluid samples, including cerebrospinal fluid (CSF) and blood

plasma, thus offering an in-vivo method for detecting and tracking changes associated with AD.<sup>12</sup> With the advantages of being more accessible and less expensive than neuroimaging biomarkers like PET, fluid biomarkers also exhibit characteristic changes in patients with AD and can be used for diagnosis and disease staging.<sup>12</sup> However, it is important to consider that plasma levels of A $\beta$  may reflect peripheral alongside central nervous system (CNS) amyloid processes.<sup>228</sup> As such, plasma A $\beta$  levels may not exclusively reflect CNS A $\beta$  deposition. The canonical AD biomarker signature is characterized by decreased A $\beta$  and increased pTau in both CSF and plasma, and this signature is robust for detecting and diagnosing AD.<sup>229</sup> In addition to AD pathology-specific biomarkers, other biomarkers can be used to capture a more complete picture of ongoing pathology. For example, neurofilament light chain (NfL) is a non-specific neurodegeneration biomarker that is elevated in patients with AD.<sup>230, 231</sup> Additionally, use of biomarker ratios in CSF and blood plasma, such as A $\beta_{42/40}$ , is becoming commonplace, as these measures improve diagnostic accuracy and have high concordance with PET findings.<sup>12, 232, 233</sup>

Intriguingly, HI has been linked to both acute and chronic changes in AD biomarkers such as A $\beta$  and tau,<sup>179, 234-236</sup> though fluid biomarker evidence from older adults is limited as most previous reports concentrated on the relatively acute post-injury phase or studied younger adults who were not at substantial risk for AD due to advanced age.<sup>172, 175, 176, 178, 237</sup> Additionally, there is little data examining HI and longitudinal AD fluid biomarkers.<sup>106, 108</sup> Therefore, the goal of this study was to characterize AD biomarker patterns in CSF and blood plasma in individuals with self-reported history of HI from the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset. We

hypothesized participants with HI would show a worsened AD-like biomarker signature, and the associations between HI and biomarkers would be most pronounced in individuals with cognitive impairment.

## Methods

### *ADNI participants*

Data used in the preparation of this article were obtained from ADNI (<http://adni.loni.usc.edu>). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). For up-to-date information, see [www.adni-info.org](http://www.adni-info.org). See supporting information, <http://adni.loni.usc.edu>, and previous reports<sup>238-246</sup> for more details. Written informed consent was obtained from all participants in ADNI.

To identify participants with HI, we searched the medical history database ("RECMHIST") for entries including the key words/phrases "hit head," "TBI," "traumatic brain injury," "head injury," and "concussion," as described previously.<sup>152</sup> These search terms returned 159 instances of HI from a total of 102 participants. 57 of the reported injuries were the result of participants reporting more than one HI. There were therefore 102 participants who self-reported HI history. The most common causes of HI were sports/athletic activities, falls, and motor vehicle accidents. Two participants had no data past the screening visit and were removed, leaving 100 participants with HI in the sample. There were 2,411 participants who did not report a HI, for a total of 2,511 participants. The mean number of participants with at least one biomarker measurement

for each biomarker modality was 1,178, and participants had an average of 2 measurements per biomarker (*Appendix A, Table 1*). Follow-up for all biomarkers was calculated relative to the participant's first-ever study visit. For example, if a participant had only CSF data collected at baseline, followed by both CSF and blood plasma at 36 months, the blood plasma data would be recorded as the 36-month measurement. Further, the sample included participants from ADNI 1, ADNI GO, ADNI 2, and ADNI 3.

Participants were grouped based on HI history (1 = history of HI, 2 = no HI) and cognitive status (1 = cognitively normal (CN), 2 = cognitively impaired). In the ADNI study, a clinical diagnosis/cognitive status is obtained based on cognitive symptoms, cognitive scores, and clinical assessment.<sup>247</sup> Participants with subjective cognitive decline/complaints were included in the CN group. Patients with a diagnosis of MCI or AD were included in the cognitively impaired group. As cognitive status could change between study visits, this grouping was repeated for every study visit. Due to limited sample size particularly in the HI group, we did not conduct additional stratification between impaired participants (e.g., mild cognitive impairment (MCI) versus AD).

### *Biomarker assays*

Biomarker collection and sample processing procedures have been described previously.<sup>240</sup> From cerebrospinal fluid samples, we analyzed data from the Roche Elecsys immunoassays of A $\beta$ <sub>40</sub>, A $\beta$ <sub>42</sub>, total tau, and pTau-181. We also calculated and analyzed the A $\beta$ <sub>42/40</sub> ratio from these data. In blood plasma, we analyzed the raw A $\beta$ <sub>42/40</sub> ratio calculated by the Bateman group,<sup>248</sup> as well as the Simoa assays of pTau-181 and NfL.<sup>11, 249</sup> One outlying data point, defined as a data point falling more than three

standard deviations from the mean of all other data points, was removed for the analysis of plasma pTau-181.

### *Data organization*

Other potential risk factors included common demographic variables (sex, race, ethnicity, years of education, and *APOE* genotype ( $\epsilon 4$  carrier vs non-carrier)). We calculated participants' precise age at each study visit by subtracting the date of the visit from participants' date of birth and dividing it by 365.25. As ADNI reports only birth month and year, age may be miscalculated by ~30 days. If there was no recorded date for a visit, any biomarker measurements from that visit were excluded (*Appendix A, Table 2*). If a study visit had biomarker measurements but no cognitive status, we inferred cognitive status based on previous and subsequent visits (if available). 27 cognitive statuses were inferred (*Appendix A, Table 3*), none of which represented a diagnostic conversion (e.g., the participant was either previously CN and remained as such or was impaired and remained as such). Biomarker measurements outside the limit of detection (those that contained  $<$  or  $>$ ) were also removed (*Appendix A, Table 4*).

### *Statistical analyses*

Demographic and neuropsychological variables were compared between groups via Chi-square tests (for dichotomous variables) or two-way ANCOVAs using SPSS 29.0.1.0. Age, sex, and years of education were included as covariates where appropriate. A  $p$ -value  $< 0.05$  was considered significant for all comparisons. Cross-sectional analyses were performed using two-way ANCOVAs where biomarker measures were dependent

variables and HI and cognitive status, and the interaction between HI and cognitive status were independent variables. As the data were not normally distributed for all biomarkers except the CSF and plasma A $\beta$ 42/40 ratios (*Appendix A, Figure 1*), a log transformation was performed (*Appendix A, Figure 2*). Covariates included age, sex, race, ethnicity, education, and *APOE*  $\epsilon$ 4 carrier status. For longitudinal analyses, random slope and random intercept linear mixed effects models (LMEMs) were generated via the nlme package in R 2023.12.0.<sup>250</sup> The biomarker measurement was the dependent variable, and fixed effects were age, HI (yes or no), and the interaction between age and HI. Covariates included cognitive status, sex, race, ethnicity, years of education, and *APOE* genotype ( $\epsilon$ 4 carrier vs non-carrier). Random effects were age and participant ID number (RID). LMEMS were optimal for this analysis due to their robust nature in the presence of missing data and their flexibility to incorporate multiple fixed effects, random effects, and covariates.<sup>251, 252</sup> Post-hoc tests for significant main/interaction effects or covariates were performed using the emmeans() function with Tukey adjustment or via separate linear regressions outside the mixed effects model for continuous variables.

## Results

### *Demographics, clinical measures, and cognitive performance (Table 7)*

Table 7 presents the baseline demographics and neuropsychological performance of the included participants. Impaired participants had fewer years of education than CN participants ( $p = 0.015$ ), higher frequency of *APOE*  $\epsilon 4$  positivity ( $p < 0.001$ ) and performed worse on all baseline cognitive measures than CN participants ( $p < 0.001$  for all cognitive tests). Sex and ethnicity (proportion of non-Hispanic white participants) were significantly different between groups. The CN-non-HI group had a lower proportion of non-Hispanic white participants. The impaired groups had lower proportions of female participants than expected, while the CN-non-HI group had a higher proportion of female participants. There were no other significant differences based on HI history, nor any significant interactions between cognitive status and HI history. The average number of study visits for participants with HI was 6.96, and the average number of study visits for participants without HI was 5.45.

### *Baseline cross-sectional biomarker analyses (Appendix A, Tables 5-7)*

There were no significant differences between HI and non-HI participants for any biomarker (Panel A of Figures 2-3, 5-9) besides CSF  $A\beta_{42/40}$  ratios, where HI participants had higher ratios than non-HI participants ( $p = 0.004$ ) (Figure 4a). There were no other significant differences between HI and non-HI participants for any other biomarker. CN participants had higher CSF  $A\beta_{42}$  levels ( $p < 0.001$ ) and CSF  $A\beta_{42/40}$  ratios ( $p = 0.004$ ) than impaired participants, while impaired participants had higher CSF pTau-181, CSF

total tau, and plasma NfL levels ( $p < 0.001$  for all comparisons). Age was a significant covariate for all biomarkers except plasma  $A\beta_{42/40}$  ratios. Sex was a significant covariate for CSF  $A\beta_{40}$ , CSF pTau-181, CSF total tau, plasma NfL, and plasma pTau-181. *APOE*  $\epsilon 4$  status was a significant covariate for CSF  $A\beta_{42}$ , CSF  $A\beta_{42/40}$ , CSF pTau-181, CSF total tau, and plasma pTau-181. Education was a significant covariate for CSF pTau-181, CSF total tau, and plasma pTau-181. Ethnicity was a significant covariate for plasma  $A\beta_{42/40}$  ratios. All log-transformed biomarkers had similar results (*Appendix A, Table 6*).

As we observed that sex was a significant covariate for multiple biomarkers, we performed two-way ANCOVAs that tested biomarker levels as function of HI and sex with covariates of age, cognition, race, ethnicity, education, and *APOE*  $\epsilon 4$  carriership (*Appendix A, Table 7*). Female participants had higher CSF pTau-181 ( $p = 0.01$ ) and CSF total tau ( $p = 0.005$ ) than male participants, but there were no other significant differences by sex, and there were no significant interactions between HI and sex.

#### *Longitudinal biomarker analyses (Appendix A, Tables 8-17 and Figure 3)*

There were no main effects of HI history, nor any interactions between HI history and age, for any biomarker (Panel B of Figures 2-9). Age was positively associated with CSF pTau-181, CSF total tau, plasma NfL, and plasma pTau-181 levels ( $p < 0.001$  for all comparisons), and negatively associated with CSF  $A\beta_{42}$  levels and CSF  $A\beta_{42/40}$  ratios ( $p < 0.001$  for all comparisons). CN participants had higher CSF  $A\beta_{40}$  ( $p = 0.0734$ ), CSF  $A\beta_{42}$  ( $p < 0.0001$ ), and CSF  $A\beta_{42/40}$  ( $p < 0.0001$ ) ratios than impaired participants, while impaired participants had higher CSF pTau-181, CSF total tau, plasma NfL, and plasma pTau-181 than CN participants ( $p < 0.0001$  for all comparisons). Female participants had

higher CSF  $A\beta_{40}$  ( $p = 0.0314$ ), CSF  $A\beta_{42}$  ( $p = 0.0156$ ), CSF pTau-181 ( $p = 0.0057$ ), CSF total tau ( $p = 0.0001$ ), and plasma NfL ( $p = 0.0008$ ) than male participants, while male participants had higher plasma pTau-181 ( $p = 0.0191$ ) than female participants. Non-Hispanic/Latino participants trended towards higher CSF pTau-181 ( $p = 0.0786$ ) and CSF total tau ( $p = 0.0871$ ) than Hispanic/Latino participants, while Hispanic/Latino participants had higher plasma  $A\beta_{42/40}$  ratios ( $p = 0.0086$ ) than non-Hispanic/Latino participants. Educational attainment was negatively associated with CSF pTau-181 ( $p < 0.001$ ) and CSF total tau ( $p = < 0.001$ ). *APOE*  $\epsilon 4$  noncarriers had higher CSF  $A\beta_{42}$  ( $p < 0.0001$ ) and CSF  $A\beta_{42/40}$  ratios ( $p < 0.0001$ ) than  $\epsilon 4$  carriers, while  $\epsilon 4$  carriers had higher CSF pTau-181 ( $p < 0.0001$ ), CSF total tau ( $p < 0.0001$ ), plasma NfL ( $p = .0006$ ), and plasma pTau-181 ( $p < 0.0001$ ).

As we observed that sex was a significant covariate for multiple biomarkers, we ran additional linear mixed effects models to test for significant interactions of HI and sex. Age, HI, and sex were fixed effects with covariates of cognition, race, ethnicity, years of education, and *APOE*  $\epsilon 4$  carriership (*Appendix A, Table 9*). Random effects were age and participant ID number (RID). There was an interaction between age and sex only on plasma NfL levels ( $p = 0.0355$ ), but there were no significant interactions between HI and sex on biomarker levels, nor were there any three-way interactions between age, HI, and sex.

## Discussion

Our findings do not support an association between AD biofluid biomarkers and self-reported history of HI in aging participants from the ADNI cohort. Consistent main effects of age and cognitive impairment indicated a pattern of worsened AD-like biomarker signatures in impaired participants with increasing age.

Previous studies have shown that biofluid A $\beta$  levels drop in AD,<sup>12</sup> whereas phosphorylated tau isoforms, including pTau-181, increase.<sup>253, 254</sup> NfL levels also tend to increase in AD, though NfL is not an AD-specific marker.<sup>25, 26</sup> In our analyses, age was positively associated with CSF pTau-181, CSF total tau, plasma NfL, and plasma pTau-181 levels, but negatively associated with CSF A $\beta$ <sub>42</sub> and CSF A $\beta$ <sub>42/40</sub> ratios. Additionally, CN participants had higher CSF A $\beta$ <sub>40</sub>, CSF A $\beta$ <sub>42</sub>, and CSF A $\beta$ <sub>42/40</sub> ratios than impaired participants, while impaired participants had higher CSF pTau-181, CSF total tau, plasma NfL, and plasma pTau-181 than CN participants. These findings are concordant with prior literature and indicate a pattern of worsened AD-like biomarker signatures with increasing age and in cognitively impaired participants relative to those without impairment.

We only observed one significant difference in biomarker levels, where HI participants had higher CSF A $\beta$ <sub>42/40</sub> ratios than non-HI participants. This finding was in the opposite direction that we anticipated, as higher A $\beta$ <sub>42/40</sub> ratios are indicative of less AD pathology, suggesting HI participants have lower deposited amyloid than participants without HI. However, as the remainder of the analyses were nonsignificant, our findings do not support a main effect of HI on AD fluid biomarkers. In the context of prior

literature, this result is relatively unsurprising. One study examining plasma biomarkers in veterans with history of concussion also did not observe any changes in plasma amyloid levels<sup>53</sup>, and numerous reports found no association between cognition and plasma tau in individuals with HI history.<sup>255-257</sup> Oppositely, some studies observed alterations to fluid pTau levels in participants with history of concussion<sup>177, 234, 258, 259</sup> but those samples included more severe injuries<sup>258</sup> or former professional athletes who experienced repetitive concussions during their careers.<sup>177, 234</sup> This raises the question of whether elevated pTau in individuals with history of repetitive injuries may be more likely to indicate chronic traumatic encephalopathy (CTE) as opposed to AD.<sup>260, 261</sup> Alternatively, as numerous studies have noted associations between HI and elevated amyloid and/or tau deposition on PET,<sup>149, 152, 156-158, 262, 263</sup> HI may be associated with an increase in cortical amyloid and/or tau deposition during the post-injury period.<sup>136, 169, 223, 264-267</sup> Similarly, there is mixed data from sports concussion studies regarding whether NfL levels are altered either during acute recovery from concussion, or in the years following concussion. One study found no evidence for NfL changes in the hours/days after concussion;<sup>175</sup> however, other studies suggested NfL is elevated in the immediate post-injury period<sup>178</sup> and may remain elevated even 5 years after injury.<sup>172</sup> However, two reports that examined the association of TBI with NfL studied professional athletes with high risk for repetitive concussion, which again raises the question of whether elevated NfL in these populations is related to CTE pathology rather than AD,<sup>172, 178</sup> and also whether a single remote incidence of HI would be sufficient to result in chronic changes to NfL.

In our initial analyses where participant sex was included as a covariate, we observed that sex was a significant covariate for multiple biomarkers both at baseline and upon longitudinal analysis. Specifically, female participants had higher longitudinal CSF A $\beta$ <sub>40</sub>, A $\beta$ <sub>42</sub>, pTau-181, total tau, and plasma NfL, while male participants had higher plasma pTau-181. However, when we performed subsequent analyses testing for main effects of sex in combination with HI on biomarker levels both cross-sectionally and longitudinally, we found no significant interactions between sex and HI for any biomarker. Extensive literature suggests women are at higher risk for AD,<sup>23, 268, 269</sup> though the presence of sex differences in biofluid and imaging-based AD biomarkers is not definitive.<sup>269</sup> Our results are similarly unclear, as female participants had more favorable CSF A $\beta$  levels, but less favorable CSF tau levels. Additionally, male participants had less favorable plasma pTau levels compared to female participants. Interpretation of these findings is challenging, as there is no clear pattern to implicate either female or male sex as being associated with poorer AD biofluid biomarker profiles in this analysis.

Prior literature has also suggested educational attainment may be protective against AD (see <sup>41</sup> for review). Our results indicated that educational attainment was negatively associated with both CSF pTau-181 and total tau levels, which is concurrent with prior reports of a potential protective effect of educational attainment against AD biomarkers. However, no such relationship between educational attainment and biomarker levels was observed for any A $\beta$  biomarker, nor for any plasma biomarker. Hence, our data suggest higher educational attainment may be associated with lower CSF tau, but our findings do not definitively support a protective effect of educational attainment on all AD biomarkers.

We also observed associations between ethnicity and AD biofluid biomarkers. Non-Hispanic/Latino participants trended towards higher CSF pTau-181 and total tau, while Hispanic/Latino participants had higher plasma A $\beta$ <sub>42/40</sub> ratios. This pattern suggests non-Hispanic/Latino participants have worsened AD biomarker signatures compared to those of Hispanic/Latino backgrounds. There have been few reports investigating AD fluid biomarkers in Hispanic/Latino populations with which to compare our findings, but work from the Health & Aging Brain Study—Health Disparities (HABS-HD) cohort<sup>270</sup> has suggested AD biomarkers do indeed differ between Mexican-Americans and non-Hispanic Whites.<sup>270-274</sup> However, much more work is needed to characterize AD fluid biomarkers in diverse populations to establish whether true differences exist between participants of different ethnic backgrounds, as in our study the Hispanic population did not solely contain Mexican-American individuals.

Similarly, additional research into the temporal kinetics of biofluid biomarker levels after brain injury will be necessary to clarify if/how biomarkers change in response to HI, how long these changes persist, and their implications for long-term AD/dementia risk.<sup>176, 275</sup> For example, levels of GFAP, NfL, and UCH-L1 may be increased in athletes following concussion,<sup>172, 175-178, 235, 275-277</sup> but it is unclear how long these biomarkers remain elevated before returning to pre-injury levels. Our findings indicate that AD-specific biomarkers may not be significantly elevated in adults with far-remote injuries. Additionally, future studies specifically examining important covariates such as sex, educational attainment, and ethnicity will also be necessary to clarify whether these covariates are associated with any/all biofluid biomarkers in the context of HI.

### *Limitations & future directions*

Our study has a number of limitations, chief of which is low power due to limited availability of participants with HI. The ADNI medical history battery does not ask about HI history, so probable underreporting of HI incidence likely limited the number of participants available for analysis. This is evidenced by prior work that indicates up to 25% of American adults may have experienced a concussion in their lifetime, whereas only approximately 4% of participants in ADNI self-reported history of HI.<sup>63</sup> An additional consequence of not directly asking about HI is a lack of clinical detail if a participant does report HI. Participants may not offer information about when the HI occurred, the mechanism of injury, or whether consciousness was lost. This precludes analysis of time since injury or mechanism of injury as a factor, and participants also cannot be stratified based on loss of consciousness as an indicator of injury severity for the purpose of sub-group analyses. As the severity of an injury could plausibly affect the extent and/or duration of biomarker changes after head injury, this lack of clinical detail is a hindrance towards improving our understanding of the association of HI with dementia biomarkers.<sup>87</sup> Furthermore, reliance on self-report of HI introduces the possibility of recall bias, as participants who have experienced HI but did not volunteer that information would erroneously be included in the non-HI group. In the future, we plan to replicate this analysis using participants from datasets with better HI ascertainment, like the Indiana Memory and Aging Study (IMAS).

Another limitation is the lack of extensive longitudinal data for some participants. Future replications using datasets with greater longitudinal follow-up will be beneficial. Furthermore, lack of diversity in the cohort is a limitation. As ADNI is comprised mainly

of participants who are highly educated and of European descent, our findings may not generalize to other populations.

Furthermore, it is possible that there are differences between participants who remain in the study for an extended period and those who leave the study early due to mortality, voluntary withdrawal, or some other reason. Such potential group differences may bias the results, and future studies with larger longitudinal samples and consistent biomarker measurements are warranted. In a separate sensitivity analysis comparing participants with only a single baseline biomarker measurement to those with two or more measurements, some differences were observed in the proportion of participants who were cognitively normal versus impaired, as well as the proportion of participants with and without HI. However, the differences were inconsistent. For example, the group with two or more measurements had a higher proportion of cognitively normal individuals for baseline analyses of CSF  $A\beta_{40}$ , the CSF  $A\beta_{42/40}$  ratio, CSF total tau, and plasma NfL. However, the group with only one measurement had a higher proportion of cognitively normal participants for baseline analyses of CSF  $A\beta_{42}$ , CSF pTau, and plasma pTau. The group with two or more measurements also had a higher proportion of HI participants than the single measurement group for baseline analyses of plasma pTau and NfL. Given these mixed findings, it is challenging to estimate the level of bias that differences due to drop out may have had on our findings. As we did not observe significant relationships between HI and biomarkers in our principal analysis, these group differences are not likely causing false positivity in this sample. However, the participants may have other fundamental differences that the data cannot capture, and this is a limitation of our analysis.

Finally, though studies from sports medicine have been helpful in illuminating acute post-concussion changes in relevant fluid biomarker levels, the majority of reports suggest that fluid biomarker levels return to their pre-injury baseline in a matter of days to weeks.<sup>172, 175-178, 235, 275-277</sup> The time elapsed between HI and biomarker data capture in the participants included in our analysis is therefore a significant limitation of our study, as it is plausible that no biofluid biomarkers remain elevated long enough to be captured in aging cohorts such as ADNI. This may represent a potential explanation for why we did not observe significant changes in biomarker levels between participants with and without HI. Future studies measuring fluid biomarkers in older adults immediately following incidents of HI, such as those incurred by falls, could prove useful in illuminating the temporal dynamics of fluid biomarker changes after HI and their relevance to risk for developing dementia.

	Head injury (n = 100)		No head injury (n = 2,411)		Total n participants	HI p-value	DX p-value	DX by HI p-value
<i>Baseline characteristics</i>	<i>CN (n = 33)</i>	<i>Cognitively impaired (n = 67)</i>	<i>CN (n = 896)</i>	<i>Cognitively impaired (n = 1515)</i>		-	-	-
Age (SD)	71.96 (6.57)	72.40 (7.55)	72.23 (6.71)	73.45 (7.79)		0.414	0.300	0.624
Years of education (SE)	16.85 (2.65)	16.16 (2.97)	16.49 (2.50)	15.75 (2.79)		0.186	<b>0.015</b>	0.934
% female (n)*	42.4 (14)	29.9 (20)	57.5 (515)	42.9 (650)		< <b>0.001</b> (Pearson Chi-Square = 57.792, likelihood ratio = 58.181)		
% Non-Hispanic White (n)*	97.0 (32)	100.0 (67)	93.5 (832)	95.8 (1443)	2,497 (99.44%), 14 missing (6 CN-non-HI, 8 Impaired-non-HI)	<b>0.032</b> (Pearson Chi-Square = 8.800, likelihood ratio = 11.814)		
% APOE ε4 positive (n)*	31.0 (9)	51.7 (30)	30.5 (236)	54.7 (740)	2,215 (88.21%), 296 missing (4 CN-HI, 9 Impaired-HI, 122 CN-non-HI, 161 Impaired-non-HI)	< <b>0.001</b> (Pearson Chi-Square = 119.531, likelihood ratio = 122.000)		
Diagnostic status (CN, SCD, EMCI, LMCI, AD)*	23 CN, 10 SCD	26 EMCI, 31 LMCI, 10 AD	534 CN, 360 SCD	424 EMCI, 665 LMCI, 415 AD	2,498 (99.48%), 13 missing (2 CN-non-HI, 9 Impaired-non-HI)	< <b>0.001</b> (Pearson Chi-Square = 2511.710, likelihood ratio = 3303.266)		
CDR – Global (SE) <sup>+</sup>	0.00 (0.00)	0.54 (0.17)	0.002 (0.03)	0.57 (0.20)	2,510 (99.96%), 1 missing (Impaired-non-HI)	0.540	< <b>0.001</b>	0.496
CDR – Sum of Boxes (SE) <sup>+</sup>	0.02 (0.09)	1.93 (1.63)	0.04 (0.16)	2.31 (1.76)	2,510 (99.96%), 1 missing (Impaired-non-HI)	0.262	< <b>0.001</b>	0.269
MoCA Total Score (SE) <sup>+</sup>	26.41 (1.97)	21.77 (3.89)	25.92 (2.59)	21.78 (4.40)	1,585 (63.12%), 926 missing (16 CN-HI,	0.992	< <b>0.001</b>	0.792

					23 Impaired- HI, 248 CN-non-HI, 639 Impaired- non-HI)			
MMSE Total Score (SE) <sup>+</sup>	28.97 (0.81)	27.18 (2.68)	29.07 (1.13)	26.38 (2.79)	2,480 (98.77%), 31 missing (14 CN- non-HI, 17 Impaired- non-HI)	0.270	<b>&lt;0.001</b>	0.077
Trails Making A [seconds] (SE) <sup>+</sup>	34.27 (10.95)	42.77 (23.98)	33.34 (11.77)	47.92 (27.42)	2,398 (95.50%), 113 missing (3 CN-HI, 5 Impaired- HI, 29 CN- non-HI, 76 Impaired- non-HI)	0.480	<b>&lt;0.001</b>	0.265
Trails Making B [seconds] (SE) <sup>h+</sup>	85.13 (44.95)	123.92 (78.21)	80.78 (39.90)	136.31 (80.09)	2,353 (93.71%), 158 missing (3 CN-HI, 7 Impaired- HI, 32 CN- non-HI, 116 Impaired- non-HI)	0.874	<b>&lt;0.001</b>	0.316
Animal Fluency Score (SE) <sup>+</sup>	22.07 (5.56)	17.03 (5.02)	20.98 (5.40)	15.88 (5.60)	2,407 (95.86%), 104 missing (3 CN-HI, 5 Impaired- HI, 29 CN- non-HI, 67 Impaired- non-HI)	0.135	<b>&lt;0.001</b>	0.970
RAVLT – Immediate Recall (SE) <sup>+</sup>	46.87 (10.12)	32.00 (11.64)	45.64 (10.12)	31.34 (11.07)	2,402 (95.66%), 109 missing (3 CN-HI, 5 Impaired- HI, 32 CN- non-HI, 69 Impaired- non-HI)	0.285	<b>&lt;0.001</b>	0.655
RAVLT – Delayed Recall (SE) <sup>+</sup>	8.07 (3.67)	3.37 (3.46)	7.79 (4.00)	3.04 (3.71)	2,405 (95.78%), 106 missing (3 CN-HI, 5 Impaired- HI, 31 CN-	0.420	<b>&lt;0.001</b>	0.947

					non-HI, 67 Impaired- non-HI)			
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Table 7. Baseline demographics and neuropsychological performance of included participants (HI = head injury, DX = diagnosis, SD = standard deviation, SE = standard error, n = number of participants, APOE = Apolipoprotein E, CN = cognitively normal, SCD = subjective cognitive decline, EMCI = early mild cognitive impairment, LMCI = late mild cognitive impairment, AD = Alzheimer's disease, CDR = Clinical Dementia Rating, MoCA = Montreal Cognitive Assessment, MMSE = Mini Mental State Examination, RAVLT = Rey's Auditory Verbal Learning Test, ANOVA = analysis of variance).

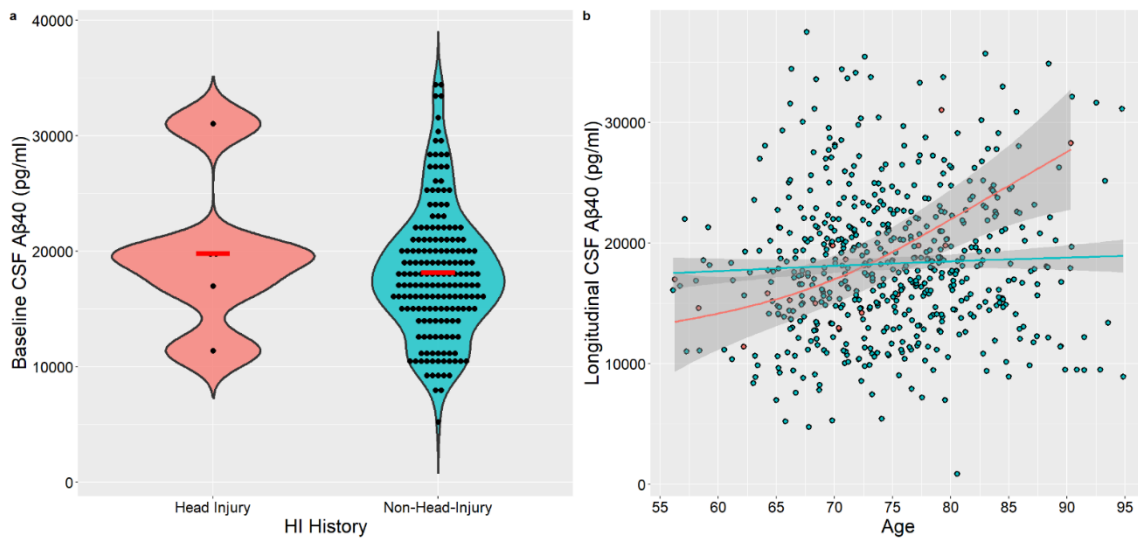


Figure 2. Cerebrospinal fluid (CSF) amyloid- $\beta_{40}$  ( $A\beta_{40}$ ) analyzed cross-sectionally at baseline (a) and longitudinally (b) (red = HI, blue = non-HI; red crossbar = mean). There were 568 participants with at least one measurement, the average number of measurements per participant was 1.62, and the total number of datapoints was 921.

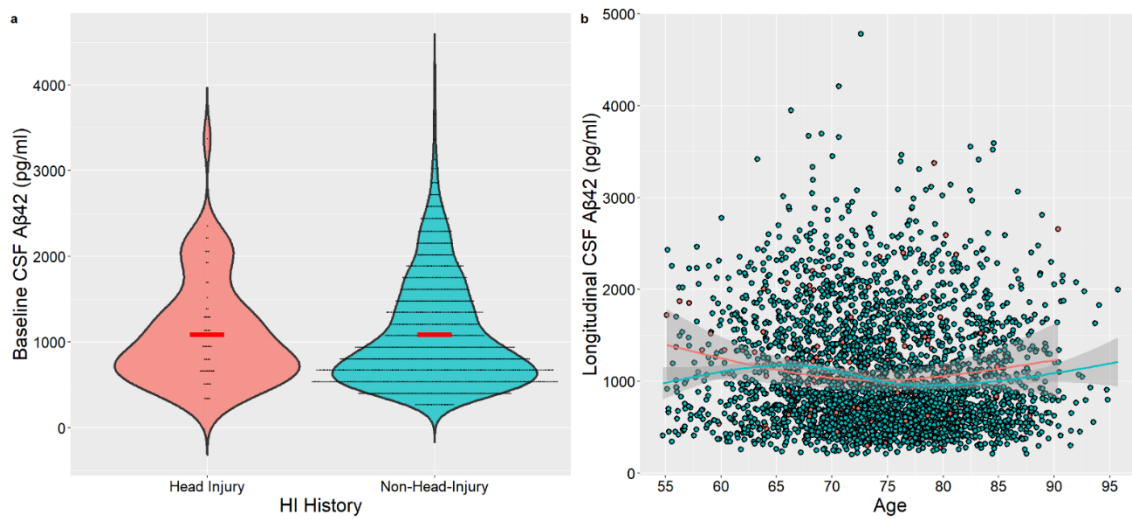


Figure 3. Cerebrospinal fluid (CSF) amyloid- $\beta_{42}$  ( $A\beta_{42}$ ) analyzed cross-sectionally at baseline (a) and longitudinally (b) (red = HI, blue = non-HI; red crossbar = mean). There were 1,660 participants with at least one measurement, the average number of measurements per participant was 1.89, and the total number of datapoints was 3,153.

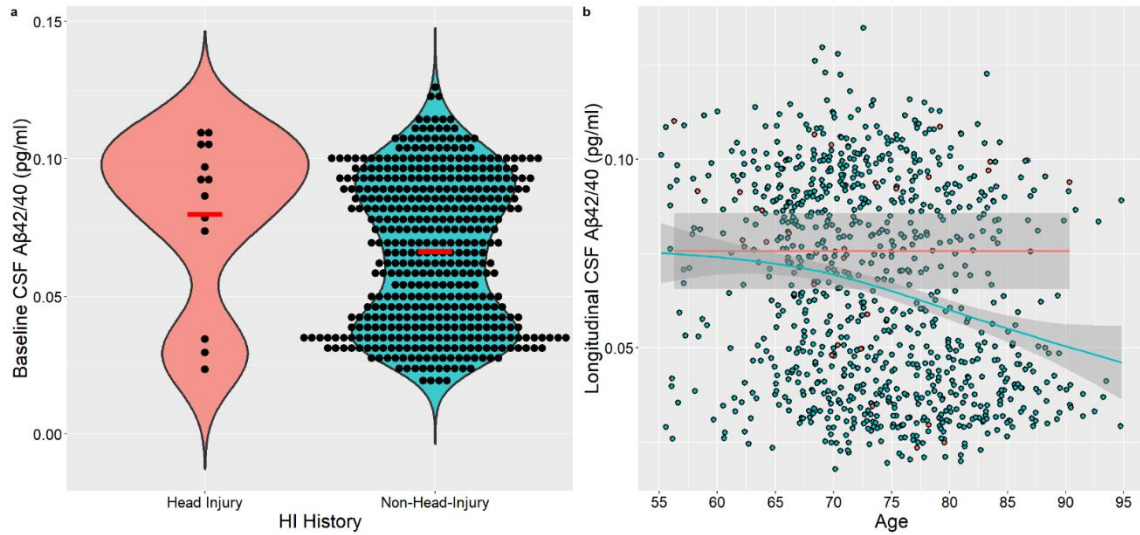


Figure 4. Cerebrospinal fluid (CSF) amyloid- $\beta_{42}$ /amyloid- $\beta_{40}$  ( $A\beta_{42/40}$ ) ratios analyzed cross-sectionally at baseline (a) and longitudinally (b) (red = HI, blue = non-HI; red crossbar = mean). There were 568 participants with at least one measurement, the average number of measurements per participant was 1.62, and the total number of datapoints was 918.

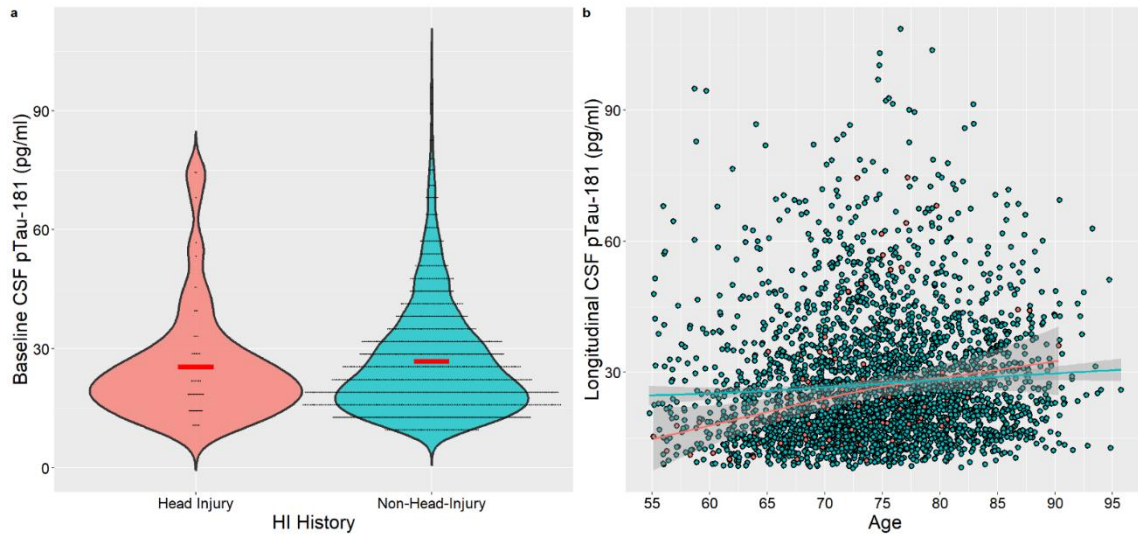


Figure 5. Cerebrospinal fluid (CSF) phosphorylated tau (pTau)-181 ratios analyzed cross-sectionally at baseline (a) and longitudinally (b) (red = HI, blue = non-HI; red crossbar = mean). There were 1,650 participants with at least one measurement, the average number of measurements per participant was 1.89, and the total number of datapoints was 3,133.

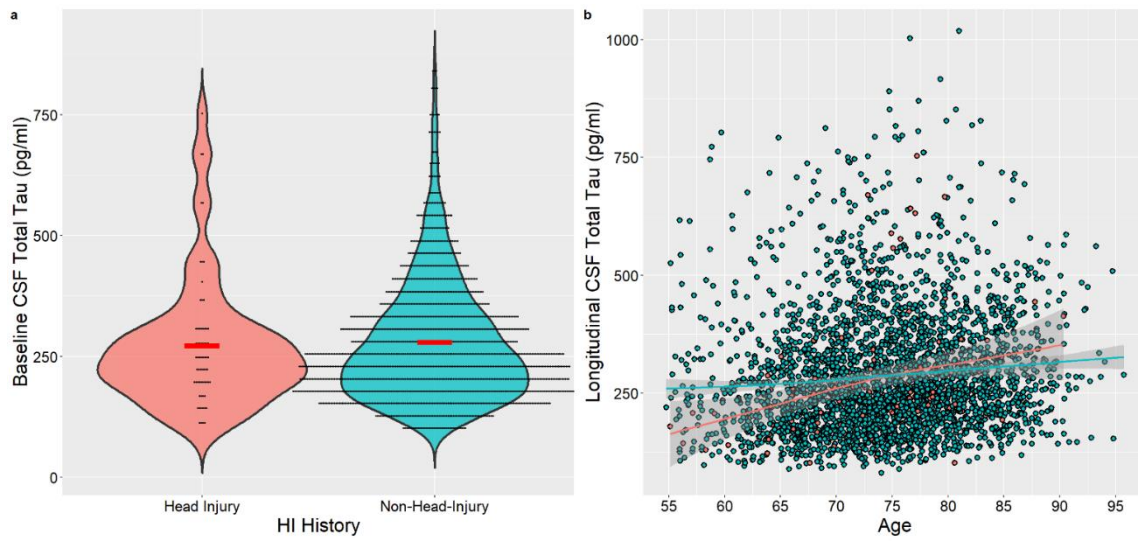


Figure 6. Cerebrospinal fluid (CSF) total tau analyzed cross-sectionally at baseline (a) and longitudinally (b) (red = HI, blue = non-HI; red crossbar = mean). There were 1,653 participants with at least one measurement, the average number of measurements per participant was 1.89, and the total number of datapoints was 3,145.

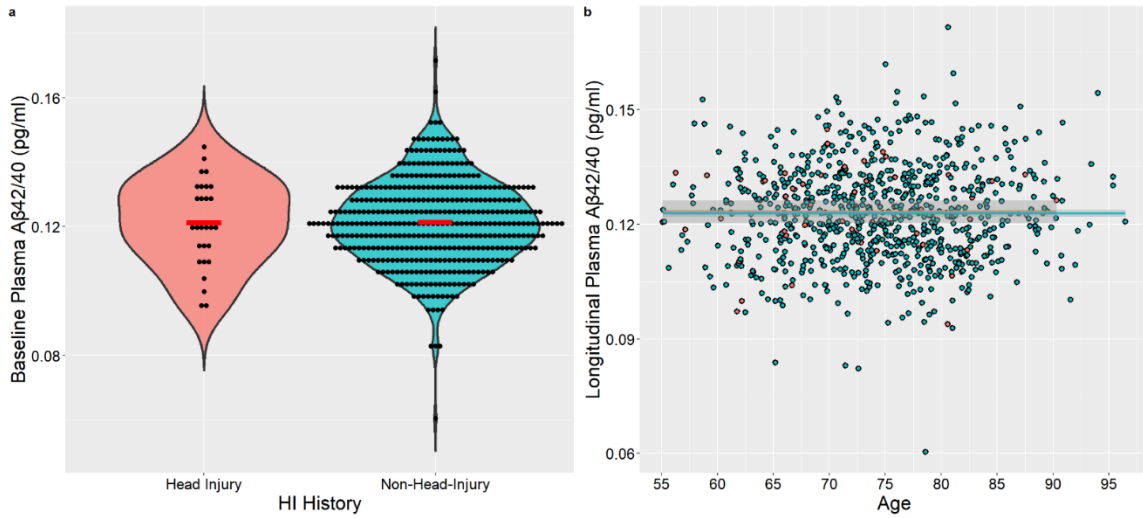


Figure 7. Blood plasma amyloid- $\beta_{42}$ /amyloid- $\beta_{40}$  ( $A\beta_{42/40}$ ) ratios analyzed cross-sectionally at baseline (a) and longitudinally (b) (red = HI, blue = non-HI; red crossbar = mean). There were 550 participants with at least one measurement, the average number of measurements per participant was 1.52, and the total number of datapoints was 836.

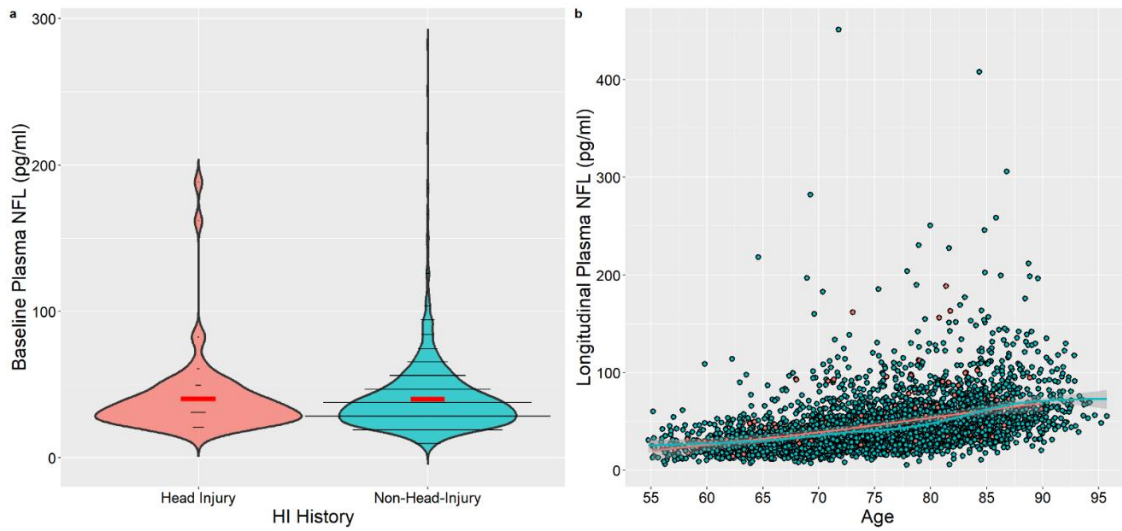


Figure 8. Blood plasma neurofilament light chain (NfL) analyzed cross-sectionally at baseline (a) and longitudinally (b) (red = HI, blue = non-HI; red crossbar = mean). There were 1,583 participants with at least one measurement, the average number of measurements per participant was 2.70, and the total number of datapoints was 4,278.

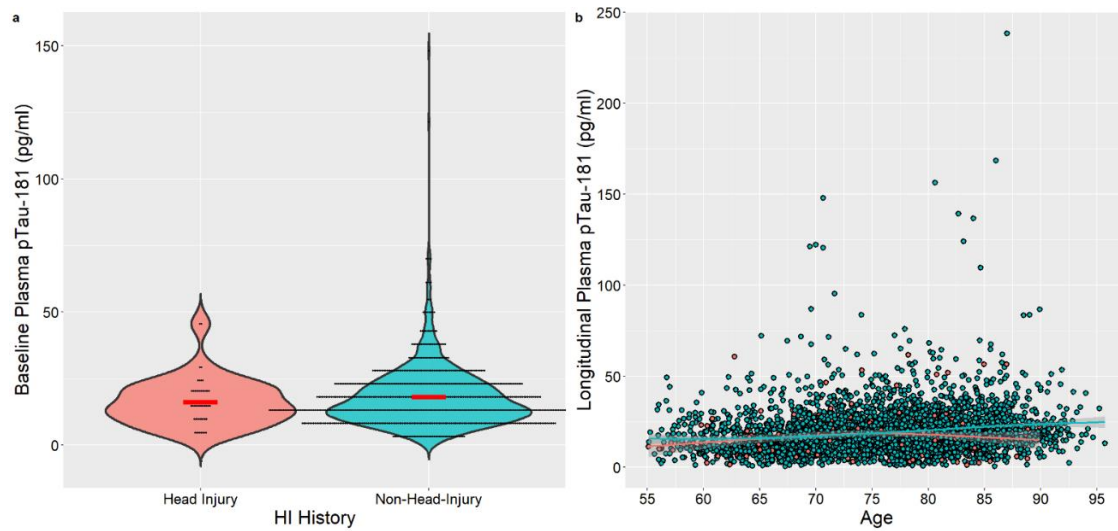


Figure 9. Blood plasma phosphorylated tau (pTau)-181 analyzed cross-sectionally at baseline (a) and longitudinally (b) (red = HI, blue = non-HI; red crossbar = mean). There were 1,190 participants with at least one measurement, the average number of measurements per participant was 3.11, and the total number of datapoints was 3,700.

### **Chapter Three: Traumatic brain injury is associated with tau on positron emission tomography in individuals with dementia due to Alzheimer's disease**

The following chapter is an original research report investigating levels of tau deposition via positron emission tomography (PET) in individuals from the National Alzheimer's Coordinating Center (NACC) dataset. We used analyses of covariance to assess whether traumatic brain injury (TBI) and cognition were independently and/or interactively associated with tau in this cohort. This chapter builds upon previous work, highlighted in Chapter 1, in investigating whether TBI is linked to higher tau levels in older adults. Here, we observed that in individuals with dementia due to AD, participants with history of TBI had elevated tau deposition compared to individuals without TBI in multiple key regions of interest. Further, we performed a novel investigation of whether age at TBI was associated with tau levels. Critically, in participants with dementia, those whose injuries occurred before the age of 18 had higher tau than those whose injuries took place after the participant turned 18. This finding has critical public health implications and emphasizes the urgent need for improved TBI prevention methods and/or management strategies during youth, especially for athletes in contact sports where TBI is prevalent; however, the sample sizes are small and additional studies are needed.

In sum, this report demonstrates that TBI history may be associated with elevated tau levels in older adults with dementia. Additionally, injuries incurred during childhood may have important implications for brain health later in life, and the relationship between early-life TBI and later-life dementia risk thus demands further study.

## Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease that is clinically characterized by increasing difficulties with memory and other cognitive processes, a decline in the ability to perform activities of daily living such as bathing and dressing, and behavioral changes including aggression, confusion, and depression.<sup>2, 3, 278</sup> Pathologically, AD is distinguished predominantly by the presence of accumulated amyloid- $\beta$  (A $\beta$ ) in the form of extracellular amyloid plaques, and hyperphosphorylated tau in the form of intracellular neurofibrillary tangles.<sup>3, 12, 278</sup> There are several unalterable risk factors for AD, including advanced age, female sex, and genetic variations such as the  $\epsilon$ 4 allele of the Apolipoprotein E (*APOE*) gene.<sup>23, 29, 278-280</sup> However, modifiable risk factors, such as poor cardiovascular health, lack of sleep, poor diet, environmental pollutant exposure, and concussion have been gaining increased attention as potential opportunities to modify/reduce dementia risk via lifestyle interventions.<sup>38, 39, 47, 48, 85, 87, 281-287</sup>

Concussions are a common type of traumatic brain injury (TBI) that are often incurred via traumatic impacts to the head.<sup>32, 59, 79, 104, 133, 288, 289</sup> Examples of settings where concussion/TBI may occur include sports participation, motor vehicle accidents, interpersonal violence, military service, and falls, with the latter being particularly relevant to aging adults.<sup>58, 62, 63, 79, 182, 290</sup> TBI represents a significant economic and social burden and is a growing public health crisis. It is estimated that approximately 1 in 4 American adults has experienced at least one TBI in their lifetime, while rates are significantly higher in military servicemembers and other at-risk populations.<sup>63-66, 133, 182-</sup>

184, 290-292 Importantly, TBI has been repeatedly linked to increased risk for AD as well as other neurodegenerative diseases such as chronic traumatic encephalopathy (CTE), for which the largest single risk factor is exposure to multiple head injuries over the course of one's life.<sup>76, 85, 87, 114, 281, 293-296</sup>

Though an association has been established between TBI and elevated risk for dementia, the biological underpinnings of this relationship are poorly understood. For example, numerous studies have linked TBI history to elevated AD biomarkers, including A $\beta$  and tau, using positron emission tomography (PET).<sup>99, 181, 186, 281, 297-299</sup> These studies suggest the link between TBI and dementia could be a consequence of elevated pathological protein deposition, though other papers failed to find such associations.<sup>104, 110, 300, 301</sup> Thus, as the evidence has been mixed to date, it is critically important to continue to investigate potential mechanisms for the association between TBI dementia in expanded datasets and additional participant populations to bring further clarity to the field.

Many well-established methodological challenges likely contributed to the mixed findings in prior studies. Most reports utilized different PET radiotracers, examined different brain regions of interest, and/or studied unique participant populations.<sup>99</sup> Further, in some large aging/dementia-focused cohorts, TBI data is not extensively collected, and thus some datasets may have limited utility for exploring the relationship between TBI and dementia. However, use of the Uniform Data Set version 4 (UDSv4) by the National Alzheimer's Coordinating Center (NACC), which incorporates data from Alzheimer's Disease Research Centers (ADRCs) across the United States, results in consistent capture of some relevant TBI data in a large cohort of primarily older adults

with and without cognitive impairment.<sup>302, 303</sup> As such, the NACC dataset is highly appealing for use in investigating whether TBI is associated with AD neuroimaging biomarkers.

Therefore, the purpose of our study was to examine the relationship between history of TBI and tau on PET in older adult participants from the NACC cohort. Using this expanded sample of participants with improved clinical capture of TBI data, we sought to determine whether certain brain regions, particularly those associated with memory, demonstrated elevated tau deposition in participants with TBI history.

## Methods

### *Participants*

The NACC dataset was chosen for this project because participants are asked whether they have had a TBI, and if so, additional questions are asked related to the date of the injury, loss of consciousness, and other important clinical features. Additionally, as the NACC dataset represents the combined national ADRC database, it includes a large sample size of participants who received tau PET scans. There were 850 cross-sectional tau PET scans in the dataset upon project initiation. 91 scans were excluded from participants with no completed clinical visits. Next, as scanning began in 2021, 10 scans were excluded from participants with no matching study visits later than 2019. Finally, 20 participants without a cognitive diagnosis were removed, leaving 729 scans for analysis. Tau PET data were then matched to clinical data from the study visit closest in time to the scan. For participants with only one study visit, the scan and study visit dates were occasionally far apart (e.g., >2 years). To assess the impact of time between study visit and scan, we performed a sensitivity analysis, described below in the Statistics section. We did not see significant differences in tau deposition when the aforementioned scans were excluded, and thus all scans were subsequently included in our analyses.

The history of TBI was determined via the “TBI” variable in the UDS. In the full dataset of 729 scans, 132 participants reported history of TBI, 604 participants had no history of TBI, and 13 participants with unknown TBI status were included in the non-TBI group.

At each ADRC, diagnosis of a participant is made by either a consensus panel or a physician, usually the physician that examined the participant. Using the UDS Clinician Diagnosis Form, participants are diagnosed according to cognitive status: normal, impaired-not-mild cognitive impairment (MCI), MCI, or dementia. Clinicians also record the suspected cause of the impairment as primary, contributing, or non-contributing. Four variables were used to establish cognitive status/clinical diagnosis at each study visit for our analysis, including the NACC Uniform Dataset Diagnosis, Probable AD, Possible AD, and Primary Etiology. Participants were classified as either cognitively normal (CN), mild cognitive impairment (MCI), or Alzheimer's disease (AD). 408 participants were CN, 175 participants had a diagnosis of MCI, and 146 participants had a diagnosis of AD. 20 participants had NA/not applicable as their cognitive status, indicating a diagnosis of a dementia other than AD. These were removed from the sample, as we wanted to analyze only participants with Alzheimer's disease dementia.

We analyzed baseline scores on cognitive assessments including animal and vegetable naming, where participants are asked to name as many items in a category in a defined period of time (usually 1 minute),<sup>304</sup> parts A and B of the Trail Making Test, which assesses executive function in the form of visual scanning and drawing connections between points,<sup>305</sup> the Montreal Cognitive Assessment (MoCA), a comprehensive clinical screener for cognitive impairment,<sup>306</sup> the Multilingual Naming Test (MINT), which assesses naming impairments in MCI and dementia,<sup>307</sup> and the Sum of Boxes and Global scores from the Clinical Dementia Rating (CDR) scale, which stages the severity of cognitive impairment/dementia.<sup>308</sup> Data points were removed as outliers if they were 3 standard deviations above or below the mean score on each test.

To perform a secondary analysis examining the impact of time since injury on tau deposition, we used 99 scans from participants who had a TBI and whose medical history included the year in which the TBI occurred. The elapsed time between TBI and scan was calculated by subtracting the scan date from the TBI date and dividing it by 365.25, assuming each injury happened on January 1 of the TBI year. Participants were categorized based on the length of time since TBI: 1-5yrs (n = 13), 5-10yrs (n = 14), and 10+ yrs (n = 72).

The approximate age of participants at the time of TBI was calculated by subtracting the year of injury from participants' year of birth. Participants were then sorted into juvenile (injuries incurred under the age of 18; n = 27) versus adult injuries (injuries at 18 years of age or older; n = 72).

In an additional secondary analysis to assess loss of consciousness (LOC), participants were filtered based on the "TBIWOLOS" variable, where 1 or 2 indicated LOC, and 0 or 9 indicated no or unknown LOC. Of 132 scans from participants with TBI, three participants with "NA" cognitive status were removed, leaving 129 participants of whom 49 reported LOC.

### *Tau scans*

Detailed documentation regarding scan protocols and image processing has been previously described and can be found on the NACC website (<https://scan.naccdata.org/>). Briefly, NACC uses MRI-free processing as many PET scans do not have an associated MRI. Information regarding this protocol is available via the SCAN website ([https://files.alz.washington.edu/scan/UCBerkeley\\_SCAN\\_Tau\\_MRIfree\\_Methods.pdf](https://files.alz.washington.edu/scan/UCBerkeley_SCAN_Tau_MRIfree_Methods.pdf)).

The dataset includes scans using the tau tracers  $^{18}\text{F}$ -Flortaucipir and  $^{18}\text{F}$ -MK-6240. Scans are linearly registered to a Montreal Neurological Institute (MNI) template, then spatially normalized in a nonlinear fashion to a tracer-specific PET template. Templates are based on the Desikan-Killiany atlas. Within selected regions of interest (ROIs), the mean intensity is quantified, and intensity is then normalized in relation to the inferior cerebellar gray matter to generate standardized uptake value ratios (SUVRs).

### *Statistics*

Demographic and neuropsychological variables were compared between groups via Chi-square tests (for categorical variables) or two-way ANCOVAs using SPSS 29.0.1.0. Age, sex, and years of education were included as covariates where appropriate. A p-value  $< 0.05$  was considered significant for all comparisons.

For our primary analysis, we ran two-way ANCOVAs using R 2024.12.0. Tau SUVRs in each ROI were the dependent variable, and TBI status (yes or no) and cognitive status (cognitively normal, mild cognitive impairment (MCI) or dementia) were the independent variables. We tested the main effects and interaction of TBI and cognitive status. Covariates included sex, race, participants' age at the tau PET scan, years of education, Hispanic/Latino ethnicity, and *APOE* genotype. We did not correct for multiple comparisons due to the small number of ROIs being analyzed and the high interrelatedness of measurements between ROIs in close physical proximity (tests of individual ROIs are not independent). We performed a sensitivity analysis to assess whether large intervals between visit and scan dates would influence the results. 115 ROIs were analyzed in three ways: using all scans ( $n = 729$ ), using scans with less than

730 days between visit and scan (n = 725), and using scans with less than 365 days between visit and scan (n = 698). We did not observe a significant influence of scans with large intervals (*Appendix B, Text 1*), so all scans were used in subsequent analyses. The bilateral entorhinal cortex, amygdala, fusiform gyrus, cuneus and precuneus, and inferior and middle temporal gyri were chosen as the ROIs of interest based on prior work indicating relatively concordant evidence for elevated tau deposition in these areas in older adults with head injury history.<sup>99</sup> A pre-calculated meta-temporal composite ROI was also analyzed.

As a secondary analysis, we analyzed ROIs that were previously associated with chronic traumatic encephalopathy (CTE) or traumatic encephalopathy syndrome (TES)<sup>81</sup>, including the precuneus, cuneus, and frontal lobe ROIs such as the caudal middle frontal gyrus, lateral orbitofrontal gyrus, medial orbitofrontal gyrus, rostral middle frontal gyrus and superior frontal gyrus. The purpose was to assess whether regions that have previously demonstrated elevated tau in the context of CTE/TES would be more strongly associated with TBI status as opposed to memory-associated areas. Additional secondary analyses included investigation of time since injury, pediatric vs. adult injuries, and loss of consciousness as main effects alongside cognitive status.

Finally, to reduce heterogeneity in the underlying pathophysiology and increase the relative proportion of individuals with suspected AD pathology, we repeated our analysis but only included the 229 participants with at least one copy of *APOE* ε4, 35 of whom had a history of TBI. We subsequently investigated only participants that were amyloid-positive as indicated via Centiloid readings >0 on amyloid-PET scan. Here, there were 319 participants, 55 of whom had a history of TBI.

## Results

### *Demographics (Table 8)*

Male participants were generally more likely to report TBI than female participants. The cognitively normal participants had lower *APOE*  $\epsilon 4$  positivity than participants with MCI or AD, participants with AD generally performed worse than both CN and MCI participants on baseline neuropsychological tests ( $p > 0.001$  for all comparisons), as expected.

### *Tau by TBI and diagnosis (Table 9)*

Participants with dementia and TBI had higher SUVRs than those without TBI in the right entorhinal cortex ( $p = 0.0170$ ) (Figure 10a), left fusiform gyrus ( $p = 0.0016$ ) (Figure 10b), and right fusiform gyrus ( $p = 0.0119$ ) (Figure 10c).

TBI was not associated with tau in the left entorhinal cortex, bilateral cuneus, precuneus, inferior temporal gyrus, middle temporal gyrus, amygdala, or meta-temporal ROI, and there were no interactions between TBI and diagnosis. TBI was also not associated with tau in any frontal lobe ROI, and there were no interactions between TBI and diagnosis.

### *Consideration of possible modifying factors – loss of consciousness, time since injury, and age group at injury (pediatric vs. adult)*

Neither time since injury (*Appendix B, Table 1*) nor loss of consciousness (*Appendix B, Table 2*) were associated with tau SUVRs. In participants whose injuries

occurred before the age of 18 (juvenile) and those whose injuries occurred when they were over 18 (adult), there were no differences in SUVRs by age at injury alone (*Appendix B, Table 3*). However, in participants with dementia, those with juvenile injuries had higher SUVRs in the right inferior temporal gyrus than those with adult injuries ( $p = 0.0046$ ) (Figure 11a). The same interaction was observed in the right middle temporal gyrus ( $p = 0.0008$ ) (Figure 11b).

In the subgroup of participants who were *APOE*  $\epsilon 4$ -positive, there were no relationships between TBI and tau deposition, nor any interaction between TBI and diagnosis on tau deposition, for any ROI (Table 10). Similarly, in participants who were amyloid-positive, there were also no relationships between TBI and tau deposition, nor any interaction between TBI and diagnosis on tau deposition, for any ROI (Table 11).

## Discussion

In the full sample, we observed significant interactions between diagnosis and TBI in the right entorhinal cortex and bilateral fusiform gyrus. In participants with dementia, those with TBI had higher tau SUVRs than those without TBI. Additionally, in participants with AD, those with juvenile injuries had higher tau SUVRs than participants whose injuries occurred during adulthood in the right inferior temporal gyrus and right middle temporal gyrus. These findings are congruent with prior work that demonstrated elevated tau deposition in aging individuals with TBI history,<sup>156, 158, 159, 309</sup> especially in showing a relationship between TBI and tau deposition in individuals with AD.<sup>297</sup>

However, a number of other reports found no evidence for elevated tau in TBI,<sup>103, 105</sup> and our results similarly showed no differences in tau SUVRs between participants with and without TBI in a number of areas, including the cuneus, precuneus, and meta-temporal ROI. Additionally, time since injury was not associated with tau, nor was loss of consciousness. Finally, there was no difference in tau between participants with and without TBI in frontal lobe ROIs, where prior papers have suggested there may be elevated tau in CTE/TES (traumatic encephalopathy syndrome).<sup>81</sup> Together, our findings provide some support for elevated tau in older adults with TBI history, but more work is necessary to clarify discrepancies in the conclusions from prior work.

In the full sample of participants, we observed occasional non-significant trends in MCI participants, where those without TBI had higher tau than those with TBI. To make sense of this, we repeated the analyses first using the subset of participants with at least one copy of the *APOE*  $\epsilon 4$  allele, then using the subset that were amyloid-positive.

These analyses resulted in a significantly decreased sample size, and in both cases there were no longer any significant relationships between TBI, diagnosis, and tau deposition, even for participants with AD as we observed in the full sample. This null finding, though it may be partly due to small sample size, suggests that the trend in the full data may be a function of heterogeneity with respect to disease pathology in the MCI group, specifically MCI participants that have non-AD etiology. While we were able to filter only participants with dementia due to AD, the underlying etiology responsible for impairment in participants with MCI was not defined. As such, the full MCI sample likely included a number of participants whose impairment was not due to AD pathology, but the dementia group only contained participants clinically diagnosed with AD. This heterogeneity likely explains why there were no significant differences in our subsequent analyses of only *APOE*  $\epsilon$ 4-positive and amyloid-positive participants. Our findings are consistent with prior research that has shown stronger evidence for elevated tau in individuals with TBI specifically in participants with dementia.<sup>297</sup>

Our observation of higher tau in participants with dementia and childhood injuries compared to those with adult injuries in temporal lobe gyri is intriguing, though this analysis was hindered by small sample size. There has been very little prior investigation into potential differences in long-term prognosis between individuals who incur a TBI during childhood and those injured as adults. Studies of acute TBI recovery have been mixed, with a 2017 literature review suggesting children may take longer to recover from TBI than adults,<sup>310</sup> but other studies finding no difference in recovery.<sup>84</sup> There is strong evidence that early-life TBI may have long-term effects on developmental trajectories and risk for psychiatric disorders.<sup>311-316</sup> Our finding of elevated tau in participants with

dementia who had a TBI during childhood warrants additional investigation into whether injuries in childhood versus adulthood differentially impact risk for dementia or levels of protein accumulation in individuals with AD.

We did not observe significant relationships between TBI history and tau levels in frontal lobe ROIs where prior studies have suggested there may be preferential tau deposition in chronic traumatic encephalopathy (CTE).<sup>113, 317, 318</sup> This analysis was exploratory in nature, and the negative findings are unsurprising, particularly considering that repetitive TBI is the predominant risk factor for CTE, and it is unlikely that any of the participants included in our study had repetitive TBIs. Further, the NACC cohort is not intended to capture CTE patients; the cohort is focused on other forms of dementia such as AD, Lewy Body Dementia (LBD), and frontotemporal dementia (FTD). Therefore, it was unlikely that our investigation of frontal ROIs would show a consistent pattern of elevated tau in participants with TBI.

Our study has a number of limitations, primarily the lack of clinical detail about participants' injuries. This paucity of detail prevents sub-group studies that could examine potential confounding variables such as injury severity or mechanism of injury. Additionally, limited longitudinal data prevents a thorough investigation into whether TBI is associated with a faster rate of tau deposition. Further, at the time of analysis, we combined raw SUVR data collected via two separate radiotracers. In the future we plan to analyze the data after performing two rank-based inverse normal transformations to account for differences in SUVR values between the tracers. Finally, the limited number of participants with TBI limited our ability to perform sub-analyses investigating whether TBI was differentially associated with tau deposition based on sex, race/ethnicity, and

other demographic factors. Going forward, the field would benefit from the addition of further questions related to TBI in the medical history battery of large aging cohorts, particularly those with advanced neuroimaging. There are existing validated questionnaires that have been designed for this purpose and could be incorporated into existing batteries, including the Ohio State University TBI Identification Method.<sup>319</sup> In addition, greater capture of longitudinal data will significantly benefit the field, as investigation of longitudinal changes in protein deposition might help explain why we observed associations of TBI with tau levels only once participants had progressed to dementia.

Together, our findings provide some evidence for a relationship between TBI, diagnosis, and tau deposition via PET scan in temporal lobe regions of interest, specifically the right entorhinal cortex and bilateral fusiform gyrus. In participants with dementia, those with TBI had higher tau SUVRs than those without TBI. Further, we observed a relationship between age at injury and tau deposition in participant with AD< where those whose injuries occurred before the age of 18 had elevated tau deposition compared to those whose injuries took place after the age of 18. These findings point to the importance of continued exploration into the association between TBI and elevated pathological protein deposition in dementia such as AD, and demonstrate the need for expanded investigation of the role of age at injury in the relationship between TBI and tau deposition.

		Non-TBI (n = 600)			TBI (n = 129)			TBI p-value	Diagnosis p-value	TBI*Diagnosis p-value
		CN (n = 342)	MCI (n = 132)	Dementia (n = 126)	CN (n = 66)	MCI (n = 43)	Dementia (n = 20)			
<u>Sex (%)</u>	Male	101 (29.5)	71 (53.8)	59 (46.8)	38 (57.6)	31 (72.1)	12 (60.0)	Pearson chi-square value 55.310, $p < 0.001$		
	Female	241 (70.5)	61 (46.2)	67 (53.2)	28 (42.4)	12 (27.9)	8 (40.0)			
<u>Age at scan (SE)</u>		71.41 (9.48)	72.97 (7.76)	70.67 (8.99)	69.71 (9.20)	71.06 (7.84)	69.05 (7.81)	0.074	0.251	0.997
<u>Education (SE)</u>		16.34 (2.33)	16.24 (2.83)	16.31 (2.56)	16.17 (2.56)	16.07 (3.04)	16.75 (2.57)	0.729	0.389	0.562
<u>Race (%)</u>	White	282 (82.5)	112 (84.8)	119 (94.4)	57 (86.4)	35 (81.4)	19 (95.0)	Pearson chi-square value 29.785, $p = 0.232$		
	Black/African American	39 (11.4)	16 (12.1)	4 (3.2)	5 (7.6)	6 (14.0)	1 (5.0)			
	Other	21 (6.1)	4 (3.0)	3 (2.4)	4 (6.1)	2 (4.7)	0			
<u>Hispanic (%)</u>	Not Hispanic or Latino	309 (90.4)	127 (96.2)	124 (98.4)	63 (95.5)	41 (95.3)	20 (100.0)	Pearson chi-square value 16.174, $p = 0.095$		
	Hispanic or Latino	29 (8.5)	5 (3.8)	2 (1.6)	3 (4.5)	2 (4.7)	0			
	Unknown	4 (1.2)	0	0	0	0	0			
<u>APOE ε4 positive: 3/4, 4/4, and 2/4 (%)</u>		97 (28.4)	52 (39.4)	49 (38.9)	15 (22.7)	13 (30.2)	6 (30.0)	Pearson chi-square value 10.872, $p = 0.054$		
<u>APOE genotype (%)</u>	3/3	162 (47.4)	39 (29.5)	30 (23.8)	35 (53.0)	14 (32.6)	8 (40.0)	Pearson chi-square value 76.908, $p < 0.001$ . Impaired groups have higher ε4 positivity		
	3/4	81 (23.7)	37 (28.0)	39 (31.0)	9 (13.6)	10 (23.3)	4 (20.0)			
	2/3	33 (9.6)	4 (3.0)	7 (5.6)	6 (9.1)	3 (7.0)	1 (5.0)			
	4/4	9 (2.6)	15 (11.4)	10 (7.9)	6 (9.1)	2 (4.6)	2 (10.0)			
	2/4	7 (2.0)	0	0	0	1 (2.3)	0			

	2/2	1 (0.3)	1 (0.8)	0	0	0	0			
	Unkno wn	49 (14.3)	36 (27.3)	40 (31.7)	10 (15.2)	13 (30.2)	5 (25.0)			
<u>Animal Fluency (SE)</u>		21.59 (5.23)	17.36 (5.17)	12.11 (5.61)	21.48 (5.43)	18.40 (5.45)	13.15 (5.56)	0.412	< <b>0.001</b> (CN > MCI > AD)	0.564
<u>Vegetable Fluency (SE)</u>		14.90 (4.07)	11.33 (3.89)	7.07 (4.03)	14.08 (3.56)	10.93 (4.23)	6.80 (3.17)	0.665	< <b>0.001</b> (CN > MCI > AD)	0.949
<u>Trails A (SE)</u>		30.36 (13.43)	39.33 (17.98)	64.87 (43.44)	29.55 (9.25)	39.39 (19.64)	48.94 (20.20)	0.09	< <b>0.001</b> (CN > MCI > AD)	0.067
<u>Trails B (SE)</u>		94.65 (126.36)	182.06 (245.32)	493.48 (416.76)	131.24 (232.86)	142.79 (155.91)	336.79 (355.94)	0.131	< <b>0.001</b> (CN > AD, MCI > AD)	<b>0.024</b>
<u>MOCA total score (SE)</u>		26.56 (2.41)	22.13 (3.46)	16.00 (6.33)	26.60 (2.41)	22.75 (3.96)	16.21 (6.86)	0.782	< <b>0.001</b> (CN > MCI > AD)	0.659
<u>MINT total score (SE)</u>		30.48 (1.89)	28.43 (3.69)	24.95 (7.13)	30.43 (2.48)	29.50 (2.41)	24.37 (8.45)	0.836	< <b>0.001</b> (CN > MCI > AD)	0.331
CDR SB (SE)		0.13 (0.30)	1.30 (0.96)	5.15 (3.13)	0.29 (0.61)	1.29 (1.02)	5.20 (2.51)	0.689	< <b>0.001</b> (CN > MCI > AD)	0.854
CDR Global (SE)		0.06 (0.17)	0.44 (0.17)	0.93 (0.53)	0.10 (0.20)	0.45 (0.18)	0.83 (0.37)	0.522	< <b>0.001</b> (CN > MCI > AD)	0.184

Table 8. Demographics and neuropsychological characteristics of included participants (TBI = traumatic brain injury, SD = standard deviation, SE = standard error, n = number of participants, APOE = Apolipoprotein E, CN = cognitively normal, MCI = mild cognitive impairment, CDR = Clinical Dementia Rating, MoCA = Montreal Cognitive Assessment, MINT = Multilingual Naming Test).

<u>Region of Interest</u>	<u>Hemisphere</u>	<u>Group SUVR means (SE)</u>	<u>TBI p-value</u>	<u>Diagnosis p-value</u>	<u>TBI*Diagnosis p-value</u>	<u>Post-hoc tests</u>
Entorhinal cortex	L	CN non-TBI 1.20 (0.09) CN TBI 1.20 (0.10) MCI non-TBI 1.47 (0.10) MCI TBI 1.35 (0.11) AD non-TBI 1.53 (0.10) AD TBI 1.63 (0.12)	0.1735	< <b>0.0001</b>	0.0574	
	R	CN non-TBI 1.24 (0.10) CN TBI 1.23 (0.11) MCI non-TBI 1.50 (0.10) MCI TBI 1.41 (0.11) AD non-TBI 1.53 (0.11) AD TBI 1.72 (0.13)	0.4288	< <b>0.0001</b>	<b>0.0161</b>	AD Non-TBI 1.53 (SE 0.105), AD TBI 1.72 (SE 0.127); difference 0.1984 (SE 0.0830), p = 0.0170
Fusiform gyrus	L	CN non-TBI 1.18 (0.10) CN TBI 1.18 (0.11) MCI non-TBI MCI TBI 1.39 (0.12) AD non-TBI 1.66 (0.11) AD TBI 1.93 (0.13)	0.7121	< <b>0.0001</b>	<b>0.0127</b>	AD Non-TBI 1.66 (SE 0.107), AD TBI 1.93 (SE 0.130); difference 0.2689 (SE 0.0849), p = 0.0016
	R	CN non-TBI 1.17 (0.10) CN TBI 1.17 (0.11) MCI non-TBI 1.38 (0.10) MCI TBI 1.34 (0.11) AD non-TBI 1.63 (0.10) AD TBI 1.84 (0.13)	0.9205	< <b>0.0001</b>	<b>0.037</b>	AD Non-TBI 1.63 (SE 0.1033), AD TBI 1.84 (SE 0.1254); difference 0.20617 (SE 0.0817), p = 0.0119
Cuneus	L	CN non-TBI 1.06 (0.08) CN TBI 1.06 (0.09) MCI non-TBI 1.18 (0.08) MCI TBI 1.16 (0.09) AD non-TBI 1.41 (0.09) AD TBI (1.43 0.10)	0.2716	< <b>0.0001</b>	0.8645	
	R	CN non-TBI 1.05 (0.09) CN TBI 1.04 (0.10) MCI non-TBI 1.14 (0.09) MCI TBI 1.11 (0.10)	0.0859	< <b>0.0001</b>	0.8185	

		AD non-TBI 1.43 (0.09) AD TBI 1.37 (0.11)				
Precuneus	L	CN non-TBI 0.99 (0.11) CN TBI 0.97 (0.12) MCI non-TBI 1.17 (0.12) MCI TBI 1.16 (0.13) AD non-TBI 1.59 (0.12) AD TBI 1.61 (0.14)	0.4084	< <b>0.0001</b>	0.9270	
	R	CN non-TBI 0.98 (0.11) CN TBI 0.97 (0.12) MCI non-TBI 1.16 (0.11) MCI TBI 1.11 (0.12) AD non-TBI 1.56 (0.11) AD TBI 1.54 (0.14)	0.1652	< <b>0.0001</b>	0.9270	
Inferior temporal gyrus	L	CN non-TBI 1.35 (0.11) CN TBI 1.34 (0.12) MCI non-TBI 1.55 (0.12) MCI TBI 1.51 (0.13) AD non-TBI 1.87 (0.12) AD TBI 2.08 (0.14)	0.6466	< <b>0.0001</b>	0.0776	
	R	CN non-TBI 1.27 (0.11) CN TBI 1.28 (0.12) MCI non-TBI 1.48 (0.11) MCI TBI 1.43 (0.12) AD non-TBI 1.79 (0.11) AD TBI 1.93 (0.14)	0.5690	< <b>0.0001</b>	0.2506	
Middle temporal gyrus	L	CN non-TBI 1.23 (0.10) CN TBI 1.23 (0.11) MCI non-TBI 1.38 (0.10) MCI TBI 1.38 (0.11) AD non-TBI 1.71 (0.11) AD TBI 1.81 (0.13)	0.4815	< <b>0.0001</b>	0.4912	
	R	CN non-TBI 1.21 (0.10) CN TBI 1.22 (0.11) MCI non-TBI 1.35 (0.11) MCI TBI 1.34 (0.12) AD non-TBI 1.69 (0.11)	0.4236	< <b>0.0001</b>	0.5887	

		AD TBI 1.79 (0.13)				
Amygdala	L	CN non-TBI 0.97 (0.10) CN TBI 0.95 (0.11) MCI non-TBI 1.29 (0.10) MCI TBI 1.15 (0.11) AD non-TBI 1.44 (0.10) AD TBI 1.46 (0.13)	0.1165	< <b>0.0001</b>	0.1785	
	R	CN non-TBI 0.96 (0.10) CN TBI 0.95 (0.11) MCI non-TBI 1.27 (0.10) MCI TBI 1.16 (0.11) AD non-TBI 1.42 (0.10) AD TBI 1.50 (0.12)	0.2440	< <b>0.0001</b>	0.1180	
Meta-temporal		CN non-TBI 1.22 (0.09) CN TBI 1.22 (0.10) MCI non-TBI 1.41 (0.10) MCI TBI 1.38 (0.11) AD non-TBI 1.69 (0.10) AD TBI 1.85 (0.12)	0.6104	< <b>0.0001</b>	0.1213	
Caudal middle frontal gyrus	L	CN non-TBI 0.96 (0.10) CN TBI 0.95 (0.11) MCI non-TBI 1.12 (0.10) MCI TBI 1.14 (0.11) AD non-TBI 1.48 (0.11) AD TBI 1.50 (0.13)	0.6507	< <b>0.0001</b>	0.8548	
	R	CN non-TBI 0.94 (0.10) CN TBI 1.96 (0.11) MCI non-TBI 1.10 (0.11) MCI TBI 1.08 (0.12) AD non-TBI 1.48 (0.11) AD TBI 1.49 (0.13)	0.5265	< <b>0.0001</b>	0.8798	
Lateral orbitofrontal gyrus	L	CN non-TBI 1.11 (0.06) CN TBI 1.13 (0.07) MCI non-TBI 1.19 (0.07) MCI TBI 1.16 (0.07) AD non-TBI 1.39 (0.07)	0.7932	< <b>0.0001</b>	0.5725	

		AD TBI 1.40 (0.08)				
	R	CN non-TBI 1.13 (0.06) CN TBI 1.15 (0.07) MCI non-TBI 1.21 (0.07) MCI TBI 1.18 (0.07) AD non-TBI 1.41 (0.07) AD TBI 1.43 (0.08)	0.8180	< <b>0.0001</b>	0.6270	
Medial orbitofrontal gyrus	L	CN non-TBI 0.96 (0.06) CN TBI 0.96 (0.07) MCI non-TBI 1.06 (0.06) MCI TBI 1.02 (0.07) AD non-TBI 1.22 (0.07) AD TBI 1.24 (0.08)	0.3612	< <b>0.0001</b>	0.5003	
	R	CN non-TBI 0.95 (0.06) CN TBI 0.94 (0.07) MCI non-TBI 1.05 (0.07) MCI TBI 1.00 (0.07) AD non-TBI 1.20 (0.07) AD TBI 1.22 (0.08)	0.3147	< <b>0.0001</b>	0.5369	
Rostral middle frontal gyrus	L	CN non-TBI 0.98 (0.08) CN TBI 0.98 (0.09) MCI non-TBI 1.09 (0.09) MCI TBI 1.06 (0.09) AD non-TBI 1.33 (0.09) AD TBI 1.29 (0.11)	0.2150	< <b>0.0001</b>	0.7403	
	R	CN non-TBI 0.97 (0.09) CN TBI 0.98 (0.10) MCI non-TBI 1.07 (0.09) MCI TBI 1.4 (0.10) AD non-TBI 1.34 (0.09) AD TBI 1.30 (0.11)	0.2615	< <b>0.0001</b>	0.7194	
Superior frontal gyrus	L	CN non-TBI 0.91 (0.07) CN TBI 0.88 (0.08) MCI non-TBI 1.02 (0.07) MCI TBI 0.99 (0.08) AD non-TBI 1.21 (0.07)	0.2260	< <b>0.0001</b>	0.9590	

		AD TBI 1.20 (0.09)				
	R	CN non-TBI 0.89 (0.07) CN TBI 0.87 (0.08) MCI non-TBI 1.00 (0.07) MCI TBI 0.96 (0.08) AD non-TBI 1.19 (0.07) AD TBI 1.19 (0.09)	0.2553	< <b>0.0001</b>	0.8576	

Table 9. Full results from ANCOVA analyses of tau SUVRs by TBI status and cognition (SUVR = standardized uptake value ratio, SE = standard error, L = left, R = right, MCI = mild cognitive impairment, ANCOVA = analysis of covariance, TBI = traumatic brain injury).

<u>Region of Interest</u>	<u>Hemisphere</u>	<u>Group SUVR means (SE)</u>	<u>TBI p-value</u>	<u>Diagnosis p-value</u>	<u>TBI*Diagnosis p-value</u>
Entorhinal cortex	L	CN non-TBI 1.18 (0.18) CN TBI 1.14 (0.21) MCI non-TBI 1.59 (0.19) MCI TBI 1.50 (0.21) AD non-TBI 1.54 (0.19) AD TBI 1.32 (0.25)	0.1793	< <b>0.0001</b>	0.6862
	R	CN non-TBI 1.23 (0.20) CN TBI 1.26 (0.22) MCI non-TBI 1.61 (0.20) MCI TBI 1.63 (0.23) AD non-TBI 1.57 (0.20) AD TBI 1.39 (0.27)	0.7883	< <b>0.0001</b>	0.6555
Fusiform gyrus	L	CN non-TBI 0.94 (0.19) CN TBI 0.92 (0.21) MCI non-TBI 1.24 (0.20) MCI TBI 1.49 (0.22) AD non-TBI 1.51 (0.20) AD TBI 1.55 (0.26)	0.5851	< <b>0.0001</b>	0.3535
	R	CN non-TBI 0.98 (0.18) CN TBI 1.01 (0.20) MCI non-TBI 1.32 (0.19) MCI TBI 1.44 (0.21) AD non-TBI 1.56 (0.19) AD TBI 1.60 (0.25)	0.7440	< <b>0.0001</b>	0.8650
Cuneus	L	CN non-TBI 0.96 (0.13) CN TBI 1.09 (0.14) MCI non-TBI 1.02 (0.13) MCI TBI 1.04 (0.15) AD non-TBI 1.03 (0.13) AD TBI 0.91 (0.17)	0.5594	0.4298	0.1989
	R	CN non-TBI 0.93 (0.15) CN TBI 1.07 (0.17) MCI non-TBI 1.01 (0.16) MCI TBI 0.98 (0.18) AD non-TBI 1.05 (0.16)	0.7290	0.2190	0.3540

		AD TBI 0.97 (0.20)			
Precuneus	L	CN non-TBI 1.01 (0.19) CN TBI 1.07 (0.22) MCI non-TBI 1.14 (0.20) MCI TBI 1.23 (0.23) AD non-TBI 1.10 (0.20) AD TBI 0.98 (0.26)	0.7390	0.1820	0.6560
	R	CN non-TBI 1.05 (0.20) CN TBI 1.12 (0.23) MCI non-TBI 1.20 (0.21) MCI TBI 1.24 (0.24) AD non-TBI 1.19 (0.21) AD TBI 1.15 (0.28)	0.6880	0.1100	0.9010
Inferior temporal gyrus	L	CN non-TBI 1.10 (0.21) CN TBI 1.13 (0.24) MCI non-TBI 1.43 (0.22) MCI TBI 1.61 (0.25) AD non-TBI 1.74 (0.22) AD TBI 1.68 (0.29)	0.8371	< <b>0.0001</b>	0.6046
	R	CN non-TBI 1.11 (0.20) CN TBI 1.20 (0.23) MCI non-TBI 1.46 (0.21) MCI TBI 1.58 (0.24) AD non-TBI 1.79 (0.21) AD TBI 1.69 (0.28)	0.9170	< <b>0.0001</b>	0.6540
Middle temporal gyrus	L	CN non-TBI 0.99 (0.19) CN TBI 1.04 (0.22) MCI non-TBI 1.24 (0.20) MCI TBI 1.40 (0.23) AD non-TBI 1.55 (0.20) AD TBI 1.48 (0.26)	0.8101	< <b>0.0001</b>	0.6192
	R	CN non-TBI 0.97 (0.20) CN TBI 1.09 (0.22) MCI non-TBI 1.24 (0.20) MCI TBI 1.30 (0.23) AD non-TBI 1.61 (0.21)	0.9867	< <b>0.0001</b>	0.7744

		AD TBI 1.56 (0.27)			
Amygdala	L	CN non-TBI 0.87 (0.18) CN TBI 0.78 (0.20) MCI non-TBI 1.30 (0.18) MCI TBI 1.19 (0.20) AD non-TBI 1.49 (0.18) AD TBI 1.19 (0.24)	0.0770	< <b>0.0001</b>	0.5852
	R	CN non-TBI 0.86 (0.17) CN TBI 0.81 (0.19) MCI non-TBI 1.28 (0.18) MCI TBI 1.23 (0.20) AD non-TBI 1.48 (0.18) AD TBI 1.15 (0.23)	0.1542	< <b>0.0001</b>	0.3276
Meta-temporal		CN non-TBI 1.02 (0.18) CN TBI 1.06 (0.20) MCI non-TBI 1.33 (0.19) MCI TBI 1.45 (0.21) AD non-TBI 1.61 (0.19) AD TBI 1.55 (0.24)	0.9169	< <b>0.0001</b>	0.7012
Caudal middle frontal gyrus	L	CN non-TBI 1.07 (0.17) CN TBI 1.13 (0.19) MCI non-TBI 1.15 (0.18) MCI TBI 1.25 (0.20) AD non-TBI 1.10 (0.18) AD TBI 1.14 (0.23)	0.3690	0.5090	0.9380
	R	CN non-TBI 1.11 (0.19) CN TBI 1.22 (0.21) MCI non-TBI 1.24 (0.20) MCI TBI 1.25 (0.22) AD non-TBI 1.17 (0.20) AD TBI 1.32 (0.26)	0.2600	0.3190	0.7930
Lateral orbitofrontal gyrus	L	CN non-TBI 1.14 (0.10) CN TBI 1.23 (0.12) MCI non-TBI 1.24 (0.11) MCI TBI 1.29 (0.12) AD non-TBI 1.17 (0.11)	0.0690	0.0773	0.9130

		AD TBI 1.27 (0.14)			
	R	CN non-TBI 1.14 (0.11) CN TBI 1.21 (0.13) MCI non-TBI 1.21 (0.12) MCI TBI 1.23 (0.13) AD non-TBI 1.19 (0.12) AD TBI 1.28 (0.15)	0.2190	0.2950	0.8330
Medial orbitofrontal gyrus	L	CN non-TBI 0.97 (0.11) CN TBI 1.11 (0.12) MCI non-TBI 1.10 (0.11) MCI TBI 1.10 (0.12) AD non-TBI 1.05 (0.11) AD TBI 0.98 (0.14)	0.2880	<b>0.0389</b>	0.2149
	R	CN non-TBI 0.99 (0.11) CN TBI 1.12 (0.12) MCI non-TBI 1.12 (0.11) MCI TBI 1.11 (0.13) AD non-TBI 1.07 (0.11) AD TBI 1.01 (0.15)	0.3148	<b>0.0342</b>	0.2246
Rostral middle frontal gyrus	L	CN non-TBI 1.14 (0.15) CN TBI 1.14 (0.17) MCI non-TBI 1.23 (0.15) MCI TBI 1.25 (0.17) AD non-TBI 1.19 (0.16) AD TBI 1.33 (0.20)	0.4140	0.2110	0.7530
	R	CN non-TBI 1.18 (0.16) CN TBI 1.16 (0.18) MCI non-TBI 1.28 (0.17) MCI TBI 1.24 (0.19) AD non-TBI 1.25 (0.17) AD TBI 1.44 (0.22)	0.5794	0.1632	0.4487
Superior frontal gyrus	L	CN non-TBI 0.99 (0.11) CN TBI 1.07 (0.13) MCI non-TBI 1.07 (0.12) MCI TBI 1.15 (0.13) AD non-TBI 1.04 (0.12)	0.2310	0.2320	0.6870

		AD TBI 1.02 (0.15)			
	R	CN non-TBI 1.02 (0.12) CN TBI 1.09 (0.13) MCI non-TBI 1.11 (0.12) MCI TBI 1.17 (0.13) AD non-TBI 1.08 (0.12) AD TBI 1.10 (0.16)	0.2480	0.1210	0.9310

Table 10. Full results from ANCOVA analyses of tau SUVRs by TBI status and cognition including *APOE*  $\epsilon 4$ -positive participants (SUVR = standardized uptake value ratio, SE = standard error, L = left, R = right, MCI = mild cognitive impairment, ANCOVA = analysis of covariance, TBI = traumatic brain injury).

<u>Region of Interest</u>	<u>Hemisphere</u>	<u>Group SUVR means (SE)</u>	<u>TBI p-value</u>	<u>Diagnosis p-value</u>	<u>TBI*Diagnosis p-value</u>
Entorhinal cortex	L	CN non-TBI 1.32 (0.12) CN TBI 1.25 (0.16) MCI non-TBI 1.65 (0.13) MCI TBI 1.53 (0.14) AD non-TBI 1.69 (0.13) AD TBI 1.73 (0.16)	0.4286	< <b>0.0001</b>	0.5260
	R	CN non-TBI 1.36 (0.13) CN TBI 1.28 (0.17) MCI non-TBI 1.66 (0.14) MCI TBI 1.61 (0.15) AD non-TBI 1.67 (0.14) AD TBI 1.83 (0.17)	0.8940	< <b>0.0001</b>	0.2680
Fusiform gyrus	L	CN non-TBI 1.24 (0.14) CN TBI 1.19 (0.18) MCI non-TBI 1.52 (0.14) MCI TBI 1.58 (0.16) AD non-TBI 1.87 (0.15) AD TBI 2.04 (0.18)	0.2822	< <b>0.0001</b>	0.3965
	R	CN non-TBI 1.20 (0.13) CN TBI 1.16 (0.17) MCI non-TBI 1.47 (0.14) MCI TBI 1.47 (0.15) AD non-TBI 1.80 (0.14) AD TBI 1.93 (0.17)	0.5324	< <b>0.0001</b>	0.5292
Cuneus	L	CN non-TBI 1.08 (0.12) CN TBI 1.04 (0.15) MCI non-TBI 1.24 (0.12) MCI TBI 1.24 (0.14) AD non-TBI 1.54 (0.12) AD TBI 1.46 (0.15)	0.3857	< <b>0.0001</b>	0.8345
	R	CN non-TBI 1.09 (0.13) CN TBI 1.05 (0.16) MCI non-TBI 1.20 (0.13) MCI TBI 1.18 (0.15) AD non-TBI 1.60 (0.13)	0.1092	< <b>0.0001</b>	0.5101

		AD TBI 1.42 (0.16)			
Precuneus	L	CN non-TBI 0.96 (0.15) CN TBI 0.89 (0.19) MCI non-TBI 1.22 (0.16) MCI TBI 1.29 (0.18) AD non-TBI 1.75 (0.16) AD TBI 1.59 (0.19)	0.7021	< <b>0.0001</b>	0.4122
	R	CN non-TBI 0.95 (0.15) CN TBI 0.92 (0.19) MCI non-TBI 1.21 (0.15) MCI TBI 1.18 (0.18) AD non-TBI 1.71 (0.16) AD TBI 1.52 (0.19)	0.2909	< <b>0.0001</b>	0.5709
Inferior temporal gyrus	L	CN non-TBI 1.41 (0.15) CN TBI 1.35 (0.19) MCI non-TBI 1.68 (0.16) MCI TBI 1.67 (0.18) AD non-TBI 2.09 (0.16) AD TBI 2.19 (0.20)	0.8904	< <b>0.0001</b>	0.7169
	R	CN non-TBI 1.29 (0.15) CN TBI 1.27 (0.19) MCI non-TBI 1.57 (0.15) MCI TBI 1.53 (0.17) AD non-TBI 1.97 (0.15) AD TBI 2.02 (0.19)	0.9040	< <b>0.0001</b>	0.8590
Middle temporal gyrus	L	CN non-TBI 1.26 (0.13) CN TBI 1.24 (0.17) MCI non-TBI 1.45 (0.14) MCI TBI 1.48 (0.16) AD non-TBI 1.88 (0.14) AD TBI 1.88 (0.17)	0.9069	< <b>0.0001</b>	0.9328
	R	CN non-TBI 1.20 (0.14) CN TBI 1.23 (0.18) MCI non-TBI 1.39 (0.15) MCI TBI 1.37 (0.17) AD non-TBI 1.83 (0.15)	0.7939	< <b>0.0001</b>	0.9491

		AD TBI 1.84 (0.18)			
Amygdala	L	CN non-TBI 1.04 (0.12) CN TBI 0.85 (0.15) MCI non-TBI 1.41 (0.12) MCI TBI 1.27 (0.14) AD non-TBI 1.56 (0.12) AD TBI 1.50 (0.15)	0.0614	< <b>0.0001</b>	0.6428
	R	CN non-TBI 1.02 (0.12) CN TBI 0.87 (0.15) MCI non-TBI 1.39 (0.12) MCI TBI 1.28 (0.14) AD non-TBI 1.53 (0.12) AD TBI 1.55 (0.15)	0.2872	< <b>0.0001</b>	0.4543
Meta-temporal		CN non-TBI 1.25 (0.13) CN TBI 1.22 (0.16) MCI non-TBI 1.50 (0.13) MCI TBI 1.49 (0.15) AD non-TBI 1.86 (0.13) AD TBI 1.93 (0.16)	0.9113	< <b>0.0001</b>	0.7797
Caudal middle frontal gyrus	L	CN non-TBI 1.01 (0.14) CN TBI 0.95 (0.17) MCI non-TBI 1.21 (0.14) MCI TBI 1.31 (0.16) AD non-TBI 1.68 (0.14) AD TBI 1.57 (0.17)	0.9840	< <b>0.0001</b>	0.3890
	R	CN non-TBI 0.93 (0.14) CN TBI 0.95 (0.18) MCI non-TBI 1.12 (0.15) MCI TBI 1.11 (0.17) AD non-TBI 1.61 (0.15) AD TBI 1.51 (0.18)	0.6136	< <b>0.0001</b>	0.7626
Lateral orbitofrontal gyrus	L	CN non-TBI 1.06 (0.08) CN TBI 1.06 (0.11) MCI non-TBI 1.15 (0.09) MCI TBI 1.15 (0.10) AD non-TBI 1.42 (0.09)	0.7603	< <b>0.0001</b>	0.7726

		AD TBI 1.36 (0.11)			
	R	CN non-TBI 1.06 (0.09) CN TBI 1.07 (0.11) MCI non-TBI 1.16 (0.09) MCI TBI 1.15 (0.10) AD non-TBI 1.42 (0.09) AD TBI 1.38 (0.11)	0.8175	< <b>0.0001</b>	0.9002
Medial orbitofrontal gyrus	L	CN non-TBI 0.93 (0.08) CN TBI 0.86 (0.10) MCI non-TBI 1.04 (0.08) MCI TBI 1.02 (0.09) AD non-TBI 1.26 (0.08) AD TBI 1.22 (0.10)	0.4310	< <b>0.0001</b>	0.8883
	R	CN non-TBI 0.92 (0.08) CN TBI 0.86 (0.10) MCI non-TBI 1.03 (0.09) MCI TBI 0.99 (0.10) AD non-TBI 1.23 (0.09) AD TBI 1.19 (0.10)	0.4272	< <b>0.0001</b>	0.9831
Rostral middle frontal gyrus	L	CN non-TBI 0.89 (0.10) CN TBI 0.89 (0.14) MCI non-TBI 1.03 (0.11) MCI TBI 1.02 (0.13) AD non-TBI 1.35 (0.12) AD TBI 1.22 (0.14)	0.4410	< <b>0.0001</b>	0.5708
	R	CN non-TBI 0.86 (0.11) CN TBI 0.89 (0.14) MCI non-TBI 0.98 (0.12) MCI TBI 0.94 (0.14) AD non-TBI 1.33 (0.12) AD TBI 1.22 (0.15)	0.4645	< <b>0.0001</b>	0.6112
Superior frontal gyrus	L	CN non-TBI 0.92 (0.09) CN TBI 0.86 (0.12) MCI non-TBI 1.05 (0.09) MCI TBI 1.04 (0.11) AD non-TBI 1.31 (0.10)	0.3720	< <b>0.0001</b>	0.6750

		AD TBI 1.21 (0.12)			
	R	CN non-TBI 0.88 (0.09) CN TBI 0.84 (0.12) MCI non-TBI 1.01 (0.10) MCI TBI 0.97 (0.11) AD non-TBI 1.26 (0.10) AD TBI 1.18 (0.12)	0.3510	<b>&lt; 0.0001</b>	0.8950

Table 11. Full results from ANCOVA analyses of tau SUVRs by TBI status and cognition including amyloid-positive participants (SUVR = standardized uptake value ratio, SE = standard error, L = left, R = right, ANCOVA = analysis of covariance, TBI = traumatic brain injury).

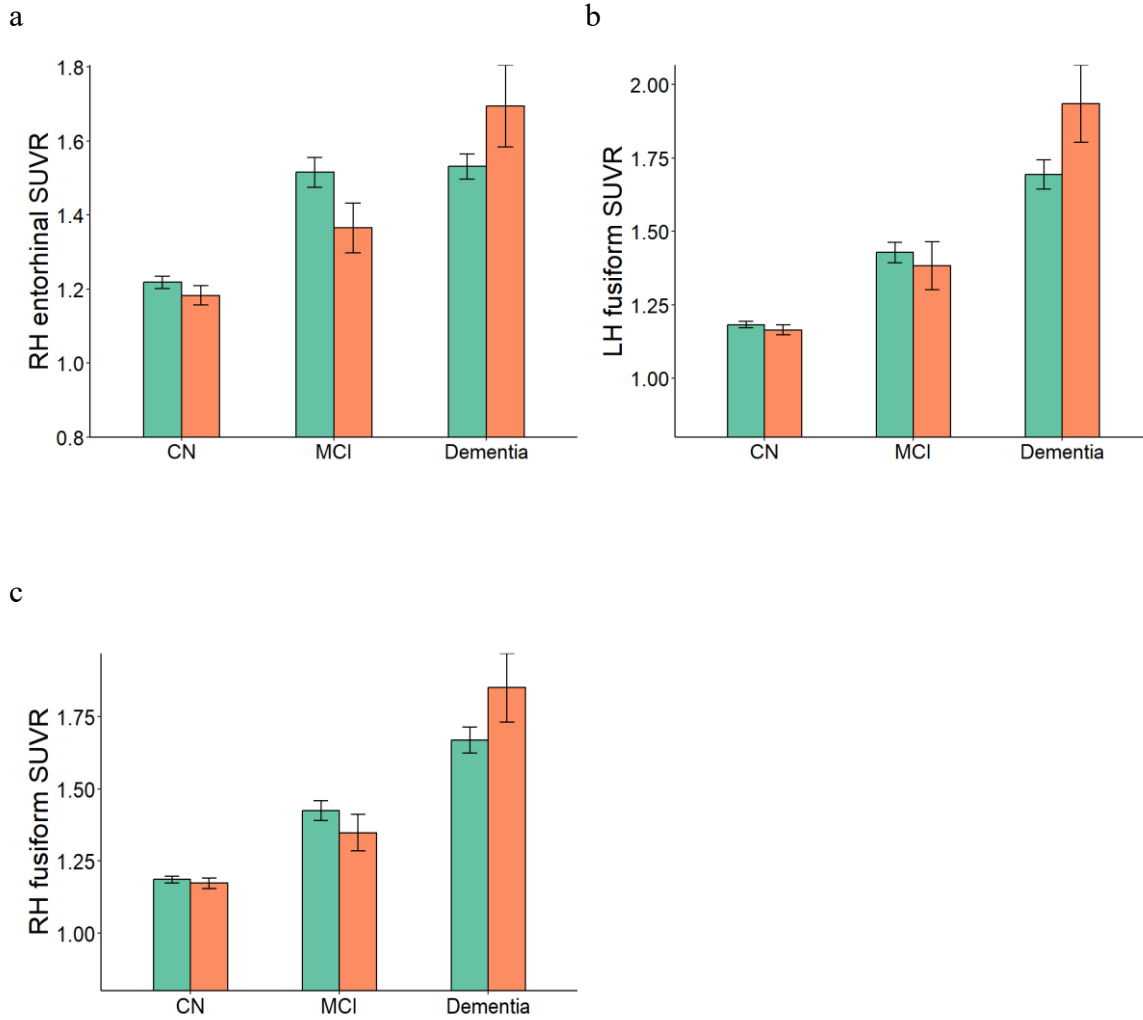


Figure 10. Tau standardized uptake value ratios (SUVRs) in the full sample of participants in the right entorhinal cortex (a), left fusiform gyrus (b), and right fusiform gyrus (c) (RH = right hemisphere, LH = left hemisphere, SUVR = standardized uptake value ratio, CN = cognitively normal; MCI = mild cognitive impairment; green = non-TBI; orange = TBI).

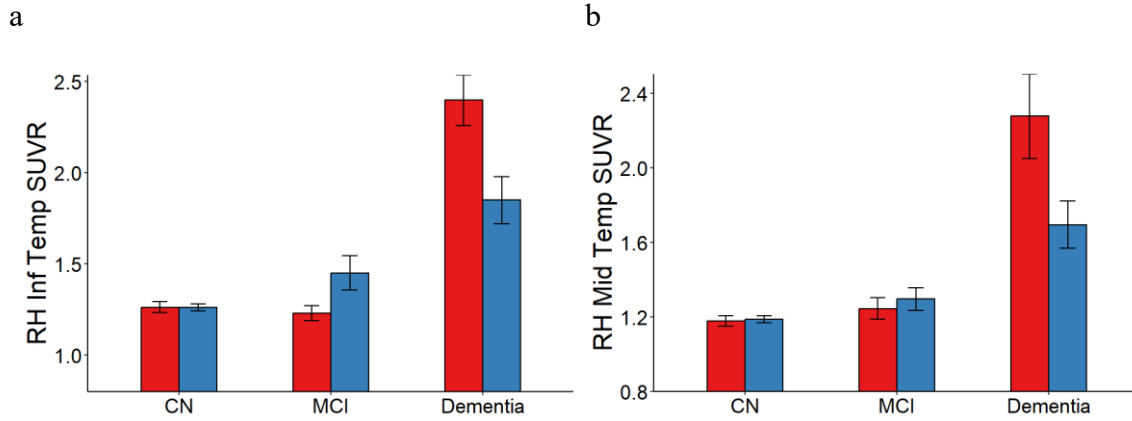


Figure 11. Tau standardized uptake value ratios (SUVRs) of injured participants whose TBI occurred before vs after the age of 18 in the right inferior temporal gyrus (a) and right middle temporal gyrus (b) (RH = right hemisphere, Inf Temp = inferior temporal gyrus, Mid Temp = middle temporal gyrus, SUVR = standardized uptake value ratio, CN = cognitively normal; MCI = mild cognitive impairment; red = TBI before age 18; blue = TBI after age 18).

## **Chapter Four: Association of Alzheimer’s disease polygenic risk score with concussion severity and recovery metrics**

The following chapter is an original research report examining associations between AD genetic risk and measures of concussion severity and recovery using data from the Concussion Assessment, Research, and Education (CARE) Consortium, a jointly-funded project from the National Collegiate Athletic Association (NCAA) and United States Department of Defense (DoD).

In this chapter, we transition from studying remote concussion, where injuries were incurred years to decades prior to assessment, to a focus on the acute post-injury period. The injury severity/recovery metrics analyzed in this report were collected within 24-48 hours following participants’ injuries. Rapid capture of this data is a necessity because brain changes after concussion often completely resolve in the days to weeks following injury. As a result, it is challenging to assess the association of AD genetic risk with concussion severity and recovery in cohorts with remote injuries such as ADNI.

Further, the participant population is comprised of young adults who are either collegiate NCAA student athletes or students at the United States Military Service Academies. This is in contrast to prior chapters, all of which concentrated on aging adults whose injuries predominantly occurred decades before their entry into an aging and/or dementia-focused study. Concentration on acute post-injury symptomology and recovery in younger individuals permits a more comprehensive investigation into mechanisms explaining how and why head injuries may lead to elevated risk for poor later-life outcomes such as AD.

Additionally, this chapter contains primarily genetic analyses, as opposed to the concentration on biomarkers in all prior chapters. This work thus expands the scope of the overall thesis from a sole investigation of the remote consequences of concussion on AD biomarkers to also include a limited investigation into the contribution of genetics to the association between concussion and dementia risk. Though many prior reports have linked *APOE* genotype to poor concussion recovery, little to no investigation of polygenic risk has occurred. There is thus a gap in the literature concerning the role of genetics beyond *APOE* in concussion recovery and the concussion-dementia relationship.

Using data collected by the CARE Consortium, we calculated AD polygenic risk scores (PRS) and tested their association with a number of concussion outcome metrics, such as the time an athlete took to recover and participants' scores on cognitive and balance tests. We also assessed whether the outcome metrics were associated with *APOE* genotype. Further, the impacts of sex, race, loss of consciousness following the injury, and other key variables were also investigated. After extensive analysis, we found that a one-standard deviation increase in AD PRS was associated with a slightly longer recovery time (~9.89 hours) after concussion, meaning that athletes with higher genetic risk for AD may take longer to recover after being concussed. However, as the majority of other analyses were insignificant, we concluded that there is no strong evidence for an association of AD genetic risk with concussion severity or recovery in this sample.

## Introduction

Sport-related concussions are a serious public health concern, with an annual occurrence of 1.6 to 3.8 million in the United States.<sup>59, 289, 320</sup> Outside of acute consequences, such as inability to participate in athletic competition and/or academic difficulties<sup>321-324</sup>, concussions can be associated with long-term consequences, especially when multiple injuries are incurred.<sup>73, 322, 325-329</sup> Concussion has also been linked to elevated risk for neurodegenerative diseases like Alzheimer's disease (AD).<sup>38, 330, 331</sup> However, there have been limited opportunities to examine associations between concussion incurred during the early decades of life and later dementia risk, as longitudinal clinical studies can be costly and challenging.<sup>332, 333</sup> Additionally, dementia research cohorts are often overwhelmingly white and highly educated<sup>334, 335</sup>, making it difficult to investigate diverse populations. The Concussion Assessment, Research and Education (CARE) Consortium was designed to address many of these limitations, and its mission is to expand and improve concussion diagnosis, treatment, and prevention.<sup>184</sup> The CARE dataset is ethnically and racially diverse, and includes non-military NCAA collegiate athletes, Military Service Academy students, and Military Service Academy NCAA-student athletes.<sup>184</sup>

Previous reports have suggested concussion severity and/or recovery may be influenced by genetic factors. Specifically, the  $\epsilon 4$  allele of the Apolipoprotein E (*APOE*) gene, also known as *APOE*  $\epsilon 4$ , is associated with higher likelihood of unfavorable outcome, such as reduced cognitive functioning, after concussion.<sup>74, 92-94, 96, 336-338</sup> *APOE* plays a critical role in restoration of the blood brain barrier, regulating inflammation, and

clearing waste products after brain injury. Evidence suggests that *APOE*  $\epsilon$ 4 is less effective in these mechanisms than the neutral *APOE*  $\epsilon$ 3 allele<sup>95, 97, 339-343</sup>, which represents a potential mechanism to explain previously observed associations between *APOE*  $\epsilon$ 4 and poorer concussion recovery. Importantly, *APOE*  $\epsilon$ 4 also contributes to elevated risk for AD<sup>218</sup>, a progressive neurodegenerative disorder that clinically presents with loss of memory, cognitive function, and behavioral changes. AD is pathologically characterized by extracellular amyloid- $\beta$  plaques, intracellular neurofibrillary tau tangles, and neurodegeneration.<sup>5, 6</sup> In addition to *APOE*  $\epsilon$ 4, a myriad of other genetic variants contribute to risk for AD.<sup>279</sup> The overall disease risk of an individual genomic profile can be summarized as a polygenic risk score (PRS), a weighted sum of the risk alleles present in an individual.<sup>344-346</sup> PRS are widely used in both genetic and neurodegenerative disease research.<sup>344-346</sup>

The previously described association of *APOE*  $\epsilon$ 4 with elevated risk for both AD and poor concussion prognosis raises the question of whether additional genetic links may exist. However, previous research has concentrated on *APOE*  $\epsilon$ 4<sup>74, 92-94, 96, 336, 337</sup>, and other genes are under-investigated. Therefore, we sought to characterize associations of AD PRS and *APOE* genotype with concussion severity and recovery metrics to assess whether young adult individuals with high genetic risk for AD would experience poorer concussion recovery and/or more severe injuries.

## Methods

### *Study Sample*

This study utilized data collected from participants in the multi-site Concussion Assessment, Research, and Education (CARE) Consortium established by the National Collegiate Athletic Association (NCAA) and US Department of Defense (DoD), protocols of which have been described in previous reports.<sup>184</sup> The study has enrolled over 20,000 participants, though not all incurred an injury while in the study. Upon initiation of this project, there were 1,917 recorded concussions in the dataset. Information on these injuries was identified from the “CARE\_Injuries\_2022\_06\_28” data file, and a description of the methods used to detect, diagnose, and evaluate these injuries can be found in prior reports.<sup>184</sup> Briefly, NCAA student athletes and Military Service Academy students recruited from participating institutions complete a baseline test battery incorporating demographics, medical history, cognitive performance, and other variables. If at any time point a participant is suspected of having suffered a concussion, evaluation and diagnosis are made by on-site research and medical personnel. Injured participants are then assessed at five timepoints: within 6 hours of the injury, again at 24-48 hours post-injury, once asymptomatic and cleared to initiate return to play protocols, when fully cleared to return to play, and finally approximately 6 months after the injury. Until participants are cleared to return to activity, symptoms are documented daily for up to 14 days then once weekly thereafter. Tests conducted at each post-injury timepoint include the Sport Concussion Assessment Tool (SCAT) for symptomology and symptom severity, the Standardized Assessment of Concussion (SAC) to assess cognitive

performance, the Balance Error Scoring System as a measure of postural stability, and many others. The DoD Human Research Protections Office (HRPO) reviewed and approved all site-level Institutional Review Board (IRB) protocols, and participant consent and site-level IRB approval were also obtained.

Of the 1,917 injuries identified at the beginning of this study, 304 did not have associated outcome measures and were removed. Furthermore, 573 concussions did not have corresponding genetic data and were excluded. Also, only participants' first injury in the study was considered, thus, 107 repeat injuries were removed due to concern over the introduction of bias on the outcomes and bias due to multiple instances of the same PRS.

We also wanted to remove first- or second-degree relatives from the sample. To do so, we employed the pi-hat identical-by-descent (IBD) estimate from the PLINK software package.<sup>347</sup> Higher pi-hat values represent greater genetic similarity, and we used a threshold of 0.2 to indicate first- or second-degree relatives.<sup>347</sup> In our sample, two pairs of participants had pi-hat > 0.2, and one from each pair was randomly removed. This left 931 non-related injured participants for analysis.

### *Participant stratifications and subgroup analyses*

Some reports have suggested there may be sex differences in concussion severity and recovery.<sup>130-132</sup> Similarly, studies have suggested that loss of consciousness (LOC) may be used as a proxy for more severe injury, which can impact recovery trajectories.<sup>348,</sup><sup>349</sup> Therefore, when significant associations were observed between PRS and outcomes in the full participant sample, we intended to further examine the relationships for

differential effects based on sex or LOC by stratifying participants on these variables. Participants were subdivided into four groups: females with loss of consciousness (F LOC+), females without loss of consciousness (F LOC-), males with loss of consciousness (M LOC+), and males without loss of consciousness (M LOC-) (Figure 1). The lack of signal in most of our analyses resulted in this subgrouping being utilized for analysis only once, though we also utilized this subgrouping in our baseline assessments of demographic and neuropsychological variables to establish whether sex- and/or severity-specific effects were visible immediately after injury. A consort diagram of the participant selection process is available as Figure 12.

We also elected to analyze outcomes with participants stratified by genetically-determined ancestry, principally to assess the transferability of the European-derived PRS to non-European CARE participants. To determine genetic ancestry, genome-wide association study (GWAS) data from the CARE participants was compared to 1000Genomes Reference data using plink multidimensional scaling, which clusters participants into ancestral groups including European (EUR), East Asian (EAS), African (AFR), South Asian (SAS), and admixed Americans (AMR).<sup>350, 351</sup> The majority of our sample was EUR (731 participants), and the second-largest ancestry group was AFR (135 participants).

Finally, we also elected to perform subgroup analyses based on whether an individual came into the study as a military or civilian participant. This stratification was exploratory, and intended to ascertain whether the selected PRS performed differently in certain groups of participants. If differential associations between PRS and outcomes

were observed in the military or civilian subgroups, this would prompt further consideration of whether the chosen PRS was appropriate for this sample.

#### *Determining polygenic risk score and APOE genotype*

To calculate AD PRS, we selected a published score<sup>352</sup> comprised of 39 single-nucleotide polymorphisms (SNPs) and used it to calculate PRS in our participants. However, this score was derived entirely from individuals of European ancestry, and the CARE study sample is more diverse. While searching for a PRS to apply in this study, we were unable to identify a PRS that matched the demographics of the CARE study. We therefore selected this score principally because of the large sample size (over 400,000) from which it was derived<sup>352</sup>, with the caveat that subgroup analyses would be performed in the CARE sample based on genetically-derived ancestry to assess the transferability of the PRS to diverse participants in CARE.

Once calculated, PRS were transformed to z-scores. The CARE data was missing 2 alleles from the original PRS: rs2732703 (a duplicated variant with different weights for *APOE*  $\epsilon$ 4 carriers and non-carriers) and rs616338. We therefore calculated the PRS from 37 SNPs in our participants. There were several instances where a participant did not have available data for one or more SNP(s). There are two analytical strategies for addressing this: the missing SNP can be ignored and the PRS calculated without it, or the value of the missing SNP can be substituted with the mean from all other participants on that SNP. To compare these methods, we performed a sensitivity analysis and did not identify significant differences between these strategies (*Appendix C, Figures 1a-d*). We therefore chose to use the ignored missing values strategy for all further analyses. Table 2

of Appendix C lists how many participants were missing data for each SNP. The average number of missed SNPs per participant in our study sample was 2.48.

We also wanted to investigate recovery/severity outcomes as a function of *APOE* genotype. As we had limited power, we split participants into *APOE*  $\epsilon 3/\epsilon 3$ ,  $\epsilon 2$  carriers, and  $\epsilon 4$  carriers rather than considering every possible *APOE* genotype. Due to limited power, we chose not to further stratify participants. Of the 931 participants, 10 did not have available *APOE* genotypes and 21 were *APOE*  $\epsilon 2/\epsilon 4$ . The  $\epsilon 2/\epsilon 4$  participants were excluded given the small number and potential for confounding if included in either the  $\epsilon 2$  or  $\epsilon 4$  carrier group. Therefore, 900 total participants were included.

#### *Selection of outcome metrics*

There is a significant amount of data concerning both concussion severity and recovery generated through the CARE Consortium<sup>184</sup>; we examined six key metrics. These were the injury to asymptomatic interval, the injury to RTP interval, SCAT symptom severity and total symptom scores, and total scores on the SAC and BESS.

First, the injury to return to play (RTP) interval, also called days to RTP or simply RTP, represents the length of time an individual takes to be medically cleared for full participation in sports/physical activity after a concussion.<sup>353, 354</sup> This is thought to typically occur within one month of injury<sup>60, 322, 355-359</sup>, but may vary depending on factors like age<sup>360, 361</sup> and sex.<sup>131, 132, 362, 363</sup> Athletes enrolled in the CARE Consortium initiated the RTP protocol at the discretion of staff and were not necessarily entirely asymptomatic when the protocol was initiated.<sup>364</sup> Though the international consensus group on concussion in sport defined normal recovery to be <28 days [6], a previous report from

the CARE Consortium suggested 80% of CARE participants RTP within 24 days.<sup>354</sup> Therefore, we used <24 days as the definition of normal RTP in this study. We also considered the injury to asymptomatic interval, which tracks how long a participant remains symptomatic after an injury.<sup>354, 359</sup> In previous studies by the CARE team, 80% of participants were found to be asymptomatic by day 14 after concussion.<sup>354</sup>

The Sport Concussion Assessment Tool (5th edition) (SCAT5) is one of the most commonly used tests to evaluate concussion. The SCAT5 incorporates elements such as reading, memory, balance, and gait.<sup>365</sup> Individuals self-report 22 concussion symptoms on a 7-point Likert scale, ranging from 0 (none) to 6 (severe).<sup>365, 366</sup> This generates a score out of 22 reflecting the total number of symptoms experienced by the individual (SCAT5 total symptoms score) and a score out of 132 indicating the severity of the present symptoms (SCAT5 symptom severity score).<sup>366</sup> The SCAT5 incorporates the BESS and SAC (described below); from this test we utilized only the SCAT5 symptom severity and total symptoms scores.

Another validated and widely used test for assessing concussions is the Balance Error Scoring System (BESS), which consists of 3 stances performed on both a firm and a foam surface with the eyes closed.<sup>367</sup> Participants are scored from 0 to 30 based on the number of errors made within 20-second trials, with higher scores indicating greater postural instability.<sup>367</sup> Errors include opening the eyes or falling out of the stance, among others.<sup>367</sup> The BESS can identify balance deficits/postural instability in concussed individuals.<sup>368-370</sup>

Finally, the Standardized Assessment of Concussion (SAC) is a brief screening tool to assess cognition in suspected concussion through four domains (orientation,

immediate memory, concentration, and delayed recall).<sup>371</sup> Participants receive a total score out of 30, where lower scores indicate poorer performance.<sup>371</sup>

### *Statistical analyses*

Statistical tests were performed using RStudio 2023.12.0 and SPSS 29.0.1.0. A  $p$ -value  $< 0.05$  was considered significant for all comparisons. Demographic comparisons were performed in SPSS using chi-square tests or one-way ANOVAs with Tukey post-hoc tests. Chi-square tests were used to determine the expected number of participants in each category relative to the actual number of participants in each category. If the homogeneity of variance assumption was violated (indicated by a significant Levene statistic), the Welch test was used in place of ANOVA and post-hoc tests were performed using the Games-Howell method. When testing the association of AD PRS with selected outcomes, we performed linear regressions using the `lm()` function in R. When testing differences in selected outcomes by *APOE* genotype, t-tests were performed using the `t_test()` function in R or one-way ANOVAs using SPSS. We also replicated our analyses of the outcomes by PRS and *APOE* genotype in the full sample with covariates of genetic ancestry, sex, LOC status, and participant origin (military vs. civilian).

## Results

### *Demographic & neuropsychological variables*

Participant characteristics are summarized in Table 12 and Table 1 of Appendix C. We analyzed participants' baseline demographics and neuropsychological characteristics using the first available test values obtained within 24-48 hours following the injury (Table 12). F LOC- participants were younger (19.849 years) than M LOC- participants (20.196 years) (mean difference = -0.347 years,  $p < 0.001$ , 95% CI [-0.572, -0.121]). Additionally, F LOC- participants had higher SCAT total symptoms scores (10.276) than M LOC+ participants (5.333) (mean difference = 4.942,  $p = 0.028$ ,  $\eta^2 = 0.018$ , 95% CI [0.385, 9.500]). Furthermore, F LOC- participants took longer to become asymptomatic (12.521 days) than M LOC- participants (9.541 days) (mean difference 2.980,  $p = 0.014$ , 95% CI [0.431, 5.530]).

The chi-square test of self-reported ancestry was significant ( $\chi^2$  (21, N = 931) = 36.064,  $p = 0.022$ , Cramer's V = 0.114). There were fewer Black/African American F LOC- participants and more Black/African American M LOC- participants than anticipated. The chi-square test of genetic ancestry was also significant ( $\chi^2$  (3, N = 866) = 16.067,  $p = 0.001$ , Cramer's V = 0.136). In the F LOC- group, there were more European participants but fewer African participants than anticipated. Conversely, in the M LOC- group, there were fewer European participants but more African participants than anticipated. The chi-square test of *APOE* genotype was not significant ( $\chi^2$  (12, N = 931) = 17.950,  $p = 0.117$ ), and there were no additional differences in the outcomes.

*Concussion recovery (injury to RTP and injury to asymptomatic intervals) as a function of PRS*

We assessed the number of days a participant took to return to play (injury to RTP interval/RTP) by AD PRS using linear regression (Table 13). We divided the participants into two categories: normal (<24 days) and long (>24 days) RTP.<sup>354</sup> We found a relationship between PRS and RTP in the normal RTP category, where higher PRS was associated with a longer injury to RTP interval ( $\beta = 0.412$ ,  $SE = 0.182$ , 95% CI [0.055, 0.769],  $t\text{-value} = 2.267$ ,  $p = 0.024$ ) (Figure 13a). There was no relationship in the long RTP category ( $p = 0.778$ ) (Figure 13b). When we replicated this analysis while covarying for genetic ancestry, sex, LOC status, and military vs. civilian origin, the relationship between PRS and RTP in the normal RTP category was no longer significant ( $p = 0.054$ ) (Appendix C, Table 3).

Since there was a significant relationship between PRS and RTP in the whole normal RTP group, we analyzed the injury to RTP interval by PRS in each participant subgroup (Appendix C, Figures 2a-d). There was no relationship in the F LOC+ group ( $p = 0.576$ ), the M LOC+ group ( $p = 0.477$ ), or the M LOC- group ( $p = 0.16$ ), and the F LOC- group approached significance ( $p = 0.067$ ) (Table 13).

We then assessed the injury to asymptomatic interval as a function of PRS with participants split into normal and long RTP subsets (Table 13). This was done rather than splitting based on the normal injury to asymptomatic interval (<14 days, as defined previously) so that the results could be directly compared with the RTP analysis. The relationship approached significance in the normal RTP group ( $p = 0.062$ ) (Figure 13c) but was not significant in the long RTP group ( $p = 0.664$ ) (Figure 13d).

### *Concussion severity outcomes as a function of PRS*

Linear regressions were used to assess the impact of AD PRS on concussion severity outcomes (BESS and SAC total scores, SCAT 5 symptom severity score (SCATSEV) and total number of symptoms (SCATSYMP)) (Table 13). No significant relationships were identified in the full data (BESS  $p = 0.502$ ; SAC  $p = 0.546$ ; SCATSEV  $p = 0.688$ ; SCATSYMP  $p = 0.580$ ) (Figures 14a-d).

Similarly, there were no associations in the normal RTP subset (BESS  $p = 0.580$ ; SAC  $p = 0.937$ ; SCATSEV  $p = 0.746$ ; SCATSYMP  $p = 0.969$ ) (*Appendix C, Figures 3a-d*) (Table 2). There were also no significant relationships in the long RTP subset (BESS  $p = 0.645$ ; SAC  $p = 0.117$ ; SCATSEV  $p = 0.465$ ; SCATSYMP  $p = 0.578$ ) (*Appendix C, Figures 4a-d*) (Table 13).

### *Concussion recovery & severity across APOE genotypes*

We used ANOVA tests to assess concussion recovery & severity by *APOE* genotype ( $\epsilon 3/\epsilon 3$  vs.  $\epsilon 2$  carriers,  $\epsilon 3/\epsilon 3$  vs.  $\epsilon 4$  carriers) (Table 14). Participants were divided based on whether they were a military or civilian participant. There were no differences between  $\epsilon 3/\epsilon 3$  participants compared to  $\epsilon 2$  carriers or  $\epsilon 4$  carriers in either the military or civilian subgroups. There were also no significant differences when this analysis was repeated in only participants of European genetic ancestry (Table 14). Upon replicating these tests with covariates of genetic ancestry, sex, LOC status, and military vs. civilian origin, there were no significant differences (*Appendix C, Table 4*).

### *Frequency of long vs. normal RTP by APOE genotype*

We performed a chi-square analysis of RTP category by *APOE* genotype in military and civilian participants to test whether the frequency with which participants fell into the long RTP category was associated with *APOE* genotype. There were no significant findings in either civilian ( $\epsilon3/\epsilon3$  vs  $\epsilon2$ :  $\chi^2$  (1, N = 494) = 0.534,  $p$  = 0.465;  $\epsilon3/\epsilon3$  vs  $\epsilon4$ :  $\chi^2$  (1, N = 579) = 0.228,  $p$  = 0.633) or military ( $\epsilon3/\epsilon3$  vs  $\epsilon2$ :  $\chi^2$  (1, N = 163) = 1.192,  $p$  = 0.275;  $\epsilon3/\epsilon3$  vs  $\epsilon4$ :  $\chi^2$  (1, N = 212) = 0.946,  $p$  = 0.331) participants.

### *Outcomes by PRS in European and African genetic ancestry*

The selected PRS was derived entirely from individuals of European ancestry, but the CARE dataset is ethnically and racially heterogeneous.<sup>184</sup> As such, we performed a subgroup analysis in the CARE participants of European ancestry, as the European-derived PRS may translate better to this subgroup than participants of other ancestries. We therefore used linear regressions to look for associations of PRS and outcome measures with participants divided based on genetic ancestry (African or European). There were no relationships in European participants (BESS  $p$  = 0.290; normal RTP  $p$  = 0.108; long RTP  $p$  = 0.860; SAC  $p$  = 0.673; SCATSEV  $p$  = 0.718; SCATSYMP  $p$  = .759) (Figures 15a-f). In individuals with African genetic ancestry, higher AD PRS was associated with lower SCAT total number of symptoms (SCATSYMP) ( $\beta$  = -1.796, SE = 0.794, 95% CI [-3.386, -0.205], t-ratio = -2.260,  $p$  = 0.028) (Figure 16). There were no other significant differences (BESS  $p$  = 0.163; normal RTP  $p$  = 0.221; long RTP  $p$  = 0.446; SAC  $p$  = 0.715; SCATSEV  $p$  = 0.144) (*Appendix C, Figures 5a-e*).

## Discussion

Our preliminary results identified that an increase in AD PRS was associated with a slight increase to the injury to RTP interval in participants who took 24 days or less to RTP. However, as the remaining analyses and metrics were generally nonsignificant, and this difference was no longer significant with the addition of covariates, our findings generally indicate that NCAA student athletes and Military Service Academy students with high genetic risk for AD are unlikely to experience worse concussions or poorer recovery than those with lower genetic risk.

Participants in the F LOC- group were 0.35 years (approximately 4.2 months) younger than participants in the M LOC- group. However, though this was statistically significant, a four-month age difference is unlikely to be clinically meaningful. Similarly, there was little evidence for an initial difference in injury or symptom severity between the groups. While the F LOC- group took longer to become asymptomatic than the M LOC- group, and the M LOC+ group demonstrated fewer symptoms on the SCAT5 than the F LOC- group, there was no consistent pattern of findings that suggested worse initial injury severity or recovery trajectories between the groups. Similarly, significant chi-square tests of both self-reported race/ethnicity and genetically derived ancestry are likely related to demographic differences in sports participation in the CARE Consortium, as described previously.<sup>372</sup> These significant tests are unlikely to represent clinically meaningful differences between groups on concussion severity and/or recovery.

Intriguingly, though the 21 *APOE*  $\epsilon 2/\epsilon 4$  participants were excluded, 20 of these participants belonged to the M LOC- group while only one belonged to the F LOC-

group. This is curious given that the *APOE* gene is located on chromosome 19 and is thus not expected to exhibit sex differences in prevalence. Furthermore, it was surprising that we found no associations between *APOE* genotype and concussion severity/recovery. Multiple previous reports have found *APOE*  $\epsilon 4$  to be associated with poorer concussion outcomes;<sup>88, 90-98, 373</sup> however, this is not a definitive relationship, as other studies have not identified a clear influence of *APOE*  $\epsilon 4$  on either injury severity or recovery.<sup>88, 98</sup> Our null finding may be a consequence of low power, but could also indicate our chosen recovery/severity metrics are not sensitive to identify *APOE*-associated differences in concussion severity and/or recovery. However, replications are needed to further explore these possibilities.

We observed a relationship between PRS and the injury to RTP interval in participants who took 24 days or less to return to play after an injury where higher AD PRS was associated with elevated recovery time. For every 1 standard deviation increase in PRS, the injury to RTP interval increased by 0.4121 days (9.89 hours). However, this relationship was no longer significant when the model was replicated with the addition of covariates for genetic ancestry, LOC status, sex, and military vs. civilian participant origin. Furthermore, the adjusted  $R^2$  value of the regression between AD PRS and the injury to RTP interval was 0.00585, indicating AD PRS only explained 0.585% of the variability in RTP. Additionally, there was no relationship between AD PRS and either the injury to asymptomatic or RTP intervals in the long (>24 days) RTP category. However, the long RTP group had fewer datapoints and numerous extremely long (100+ days) injury to RTP and/or asymptomatic intervals, both of which may partly contribute to the null finding in that group. Last, upon subgroup analyses based on sex and LOC

status of the injury to RTP interval within the normal RTP group, there were no significant relationships. Together, our results do not provide compelling evidence for an association between AD PRS and concussion recovery metrics.

Upon subgroup analyses based on genetic ancestry, we observed that higher PRS was associated with a lower SCAT total number of symptoms in individuals with African genetic ancestry, which was intriguing given that we would have expected higher AD genetic risk to be associated with more concussion symptoms. However, the  $R^2$  value was very small (multiple  $R^2 = 0.081$ , adjusted  $R^2 = 0.0651$ ), indicating very little variance in the number of concussion symptoms can be attributed to PRS. Additionally, since the PRS was derived from European participants only, this finding in African genetic ancestry participants must be interpreted with significant caution.

Along these lines, the main limitation of our study is that the selected PRS may not have been an optimal choice. We primarily chose this score because it was generated from a large sample size, but this population was entirely European.<sup>352</sup> The CARE dataset is not homogeneous (Table 12)<sup>184</sup>, and prior reports have identified poor transferability of European scores into African ancestry populations.<sup>374, 375</sup> However, as we could not identify a PRS that was reflective of the CARE demographics, we performed subgroup analyses based on ancestry to assess the PRS in CARE participants of European ancestry only, as well as the transferability of the chosen PRS to diverse CARE participants. The lack of significant associations in the European ancestry subsample suggests that the selected PRS was acceptable for use in this study, though these analyses should ideally be replicated using a PRS more reflective of the CARE sample once such a score is available.

Another limitation is that the injury to RTP interval does not capture all dimensions of concussion recovery. Our method assumes that the interval is solely reflective of continued concussion symptomology, which may be an incorrect assumption in some cases. Recovery is a multi-factorial process, and many variables that can affect recovery trajectories were not considered here. For example, if an athlete suffered a simultaneous concussion and musculoskeletal injury, the injury to RTP interval could be influenced by the musculoskeletal injury, but we would be unable to distinguish this. Also, we did not consider psychological effects on recovery, but this is a critical future direction. Previous reports have identified relationships between concussion and psychological health in the form of anxiety/depression<sup>67, 68, 71, 376-378</sup>, particularly in individuals with persistent post-concussive symptoms.<sup>70, 75, 77, 379</sup> Additionally, somatization is the biggest factor influencing concussion recovery.<sup>69</sup> As such, future studies would benefit by incorporating psychological test scores alongside physical recovery measures when assessing concussion recovery/severity in the context of genetic risk for neurodegenerative disease. An important future direction will be investigating PRS-associated neuroimaging changes in this cohort, such as white matter (WM) damage using diffusion tensor imaging (DTI). Reports from the CARE Consortium and other studies have noted WM changes, such as worsened myelin integrity, in concussed athletes/military servicemembers<sup>380-386</sup>, but few studies have examined whether concussion-associated WM damage is exacerbated in individuals with high genetic risk for neurodegenerative disease. One study found limited evidence for altered fractional anisotropy (FA) in the cingulum of *APOE*  $\epsilon 4$  carriers with concussion/mild traumatic brain injury<sup>90</sup>, while another observed that military veterans who are *APOE*  $\epsilon 4$  carriers

may be more vulnerable to WM abnormalities after blast exposure.<sup>89</sup> This evidence is supportive of a link between AD genetic risk and WM changes after concussion, but fewer explorations into lesser-known AD risk genes using summary tools like PRS have been reported.

Finally, though we excluded repeated injuries from this analysis, investigating the effects of AD genetic risk on recovery after multiple injuries is an important next step. Though we did not identify consistent links between AD genetic risk and recovery/severity in the first injury exposure, it is possible that AD genetic risk may be more strongly associated with severity/recovery in the context of multiple injuries. We will investigate this possibility in future studies. Exploration into potential effects of sub-concussive injuries may also offer intriguing information particularly in the context of inter-sport differences in head injury exposure. However, it may prove challenging to establish protocols and standards to facilitate the capture of data on sub-concussive and/or asymptomatic brain injuries.

	F LOC+	F LOC-	M LOC+	M LOC-	N (%)	Levene statistic (p)	ANOVA F/Welch statistic	P-value
Number of participants	15	341	24	551	931	-	-	-
Military participants (%)	0 (0)	70 (20.528)	12 (50)	176 (31.942)	258 (27.712)	-	-	-
Civilian participants (%)	15 (100)	271 (79.472)	12 (50)	375 (68.058)	673 (72.288)	-	-	-
Avg. PRS z-score (SD)	-0.073 (0.542)	-0.004 (1.026)	0.045 (1.112)	0.003 (0.991)	931	2.006 (0.112)	0.046	0.987
<i>APOE genotype</i>								
ε3/ε3	9	206	13	320	548 (58.861)	$\chi^2 (12, N = 931) = 17.950, p = 0.117$		
ε2 carrier	2	44	2	61	109 (11.708)			
ε4 carrier	4	89	8	142	243 (26.101)			
ε2/ε4 (excluded)	0	1	0	20	21 (2.256)			
Missing	0	1	1	8	10 (1.074)			
<i>Self-reported race/ethnicity (%)</i>								
Non-Hispanic white	10 (66.667)	213 (62.463)	17 (70.833)	320 (58.076)	560 (60.150)	$\chi^2 (21, N = 931) = 36.064, p = \mathbf{0.022}$  <i>F LOC- Black/African American (expected 49)</i>  <i>M LOC- Black/African American (expected 79)</i>		
Black/African American	2 (13.333)	23 (6.745)	4 (16.667)	104 (18.874)	133 (14.286)			
Hispanic white	1 (6.667)	14 (4.106)	0	18 (3.267)	33 (3.545)			
Asian	0 (0)	8 (2.346)	0	9 (1.633)	17 (1.826)			
Multiple races	2 (13.333)	34 (9.971)	0	39 (7.078)	75 (8.056)			
Hawaiian/Pacific Islander	0	3 (0.880)	0	2 (0.363)	5 (0.537)			
Native American/Indian/Alaskan	0	0	0	1 (0.181)	1 (0.107)			
Skipped	0	46 (13.490)	3 (12.500)	58 (10.526)	107 (11.493)			
<i>Genetic ancestry</i>								
European/EUR	12	280	20	419	731 (78.518)	$\chi^2 (3, N = 866) = 16.067, p = \mathbf{0.001}$  <i>F LOC- (expected 261 EUR, 48 AFR)</i> <i>M LOC- (expected 440 EUR, 81 AFR)</i>		
African/AFR	1	29	3	102	135 (14.501)			
<i>Outcomes</i>								
Avg. age at injury (SD)	20.351 (1.623)	19.849 (1.117)	19.837 (1.024)	20.196 (1.354)	931	4.866 ( <b>0.002</b> )	6.026 <sup>a</sup>	<b>0.002<sup>a</sup></b> (F LOC- vs. M LOC-; $p < \mathbf{0.001}$ )

Avg. days to RTP (SD)	17.500 (10.455)	23.627 (23.483)	20.038 (21.632)	20.270 (26.109)	931	1.478 (0.219)	1.433	0.232
Avg. days to asymptomatic (SD)	9.740 (5.264)	12.521 (16.502)	10.365 (20.362)	9.541 (7.812)	857	<b>7.689</b> ( <b>&lt;0.001</b> )	2.938 <sup>a</sup>	<b>0.045<sup>a</sup></b> (F LOC- vs M LOC-; <i>p</i> = <b>0.014</b> ).
Avg. SCAT # of symptoms (SD) ( <i>n</i> )	9.444 (4.475) (9)	10.276 (5.936) (225)	5.333 (6.527) (12)	9.609 (6.013) (225)	471	0.672 (0.569)	2.805	<b>0.039</b> (F LOC- vs M LOC+; <i>p</i> = <b>0.028</b> )
Avg. SCAT symptom severity score (SD) ( <i>n</i> )	19.333 (12.708) (9)	22.907 (20.238) (225)	10.667 (17.201) (12)	20.609 (19.419) (225)	471	1.201 (0.309)	1.784	0.149
Avg. BESS total score (SD) ( <i>n</i> )	12.267 (5.561) (15)	14.331 (7.715) (323)	13.957 (7.601) (23)	14.767 (7.451) (527)	888	0.682 (0.563)	0.744	0.526
Avg. SAC total score (SD) ( <i>n</i> )	25.067 (6.734) (15)	26.952 (2.080) (336)	26.708 (2.156) (24)	26.762 (2.405) (543)	918	12.628 ( <b>&lt;0.001</b> )	0.866 <sup>a</sup>	0.466

<sup>a</sup> Welch statistic & Welch test p-value reported due to significant Levene statistic

Table 12. Baseline demographic & neuropsychological characteristics (at first available post-injury assessment) of included participants (F LOC+ = female participants with loss of consciousness (LOC); F LOC- = female participants without LOC; M LOC+ = male participants with LOC; M LOC- = male participants without LOC; n = number of participants; AD = Alzheimer's disease; PRS = polygenic risk score; SD = standard deviation; RTP = return to play; SCAT = Sport Concussion Assessment Tool; BESS = Balance Error Scoring System; SAC = Standardized Assessment of Concussion).

Analysis	Estimate ( $\beta$ )	Standard error (SE)	T value	P	R <sup>2</sup>
PRS & days to normal RTP ( <i>fig. 2a</i> )	0.412	0.183	2.267	<b>0.024</b>	Mult. 0.007 Adj. 0.006
PRS & days to long RTP ( <i>fig. 2b</i> )	0.757	2.682	0.282	0.778	Mult. 0.000 Adj. -0.004
PRS & days to asymptomatic in normal RTP ( <i>fig. 2c</i> )	0.293	0.157	1.869	0.062	Mult. 0.005 Adj. 0.004
PRS & days to asymptomatic in long RTP ( <i>fig. 2d</i> )	-0.635	1.458	-0.435	0.664	Mult. 0.001 Adj. -0.004
Full data; PRS & BESS ( <i>fig. 3a</i> )	0.169	0.252	0.672	0.502	Mult. 0.001 Adj. -0.001
Full data; PRS & SAC ( <i>fig. 3b</i> )	0.048	0.080	0.603	0.546	Mult. 0.000 Adj. -0.001
Full data; PRS & SCATSEV ( <i>fig. 3c</i> )	-0.356	0.885	-0.402	0.688	Mult. 0.000 Adj. -0.002
Full data; PRS & SCATSYMP ( <i>fig. 3d</i> )	-0.150	0.269	-0.553	0.580	Mult. 0.001 Adj. -0.002
EUR; PRS & BESS ( <i>fig. 4a</i> )	0.310	0.293	1.059	0.290	Mult. 0.002 Adj. 0.000
EUR; PRS & normal RTP ( <i>fig. 4b</i> )	0.329	0.204	1.612	0.108	Mult. 0.005 Adj. 0.003
EUR; PRS & long RTP ( <i>fig. 4c</i> )	-0.548	3.097	-0.177	0.860	Mult. 0.000 Adj. -0.006
EUR; PRS & SAC ( <i>fig. 4d</i> )	0.038	0.091	0.423	0.673	Mult. 0.000 Adj. -0.001
EUR; PRS & SCATSEV ( <i>fig. 4e</i> )	0.356	0.987	0.361	0.718	Mult. 0.000 Adj. -0.002
EUR; PRS & SCATSYMP ( <i>fig. 4f</i> )	0.093	0.303	0.307	0.759	Mult. 0.000 Adj. -0.002
AFR; PRS & SCATSYMP ( <i>fig. 5</i> )	-1.796	0.794	-2.26	<b>0.028</b>	Mult. 0.081 Adj. 0.065
PRS & days to normal RTP, F LOC+ ( <i>supp. fig. 2a</i> )	-1.795	3.111	-0.577	0.576	Mult. 0.029 Adj. -0.059
PRS & days to normal RTP, F LOC- ( <i>supp. fig. 2b</i> )	0.554	0.301	1.841	0.067	Mult. 0.014 Adj. 0.010
PRS & days to normal RTP, M LOC+ ( <i>supp. fig. 2c</i> )	0.793	1.090	0.727	0.477	Mult. 0.030 Adj. -0.027
PRS & days to normal RTP, M LOC- ( <i>supp. fig. 2d</i> )	0.329	0.233	1.409	0.16	Mult. 0.005 Adj. 0.002
Normal RTP; PRS & BESS ( <i>supp. fig. 3a</i> )	0.153	0.277	0.553	0.58	Mult. 0.001 Adj. -0.001
Normal RTP; PRS & SAC ( <i>supp. fig. 3b</i> )	-0.007	0.094	-0.079	0.937	Mult. 0.000 Adj. -0.001
Normal RTP; PRS & SCATSEV ( <i>supp. fig. 3c</i> )	0.308	0.955	0.324	0.746	Mult. 0.003 Adj. -0.003
Normal RTP; PRS & SCATSYMP ( <i>supp. fig. 3d</i> )	0.012	0.297	0.039	0.969	Mult. 0.000 Adj. -0.003
Long RTP; PRS & BESS ( <i>supp. fig. 4a</i> )	0.266	0.576	0.461	0.645	Mult. 0.001 Adj. -0.004
Long RTP; PRS & SAC ( <i>supp. fig. 4b</i> )	0.235	0.149	1.573	0.117	Mult. 0.011 Adj. 0.007
Long RTP; PRS & SCATSEV ( <i>supp. fig. 4c</i> )	-1.397	1.906	-0.733	0.465	Mult. 0.005 Adj. -0.004
Long RTP; PRS & SCATSYMP ( <i>supp. fig. 4d</i> )	-0.291	0.523	-0.557	0.578	Mult. 0.003 Adj. -0.006
AFR; PRS & BESS ( <i>supp. fig. 5a</i> )	-0.849	0.605	-1.402	0.163	Mult. 0.015 Adj. 0.008

AFR; PRS & normal RTP ( <i>supp. fig. 5b</i> )	0.645	0.523	1.232	0.221	Mult. 0.015 Adj. 0.005
AFR; PRS & long RTP ( <i>supp. fig. 5c</i> )	3.203	4.136	0.774	0.446	Mult. 0.023 Adj. -0.016
AFR; PRS & SAC ( <i>supp. fig. 5d</i> )	0.085	0.232	0.366	0.715	Mult. 0.001 Adj. -0.007
AFR; PRS & SCATSEV ( <i>supp. fig. 5e</i> )	-4.026	2.719	-1.481	0.144	Mult. 0.036 Adj. 0.020

Table 13. Summary of outcomes of linear regression analyses (PRS = polygenic risk score; RTP = return to play; BESS = balance error scoring system; SAC = standardized assessment of concussion; SCATSEV = symptom severity score on the sport concussion assessment tool (SCAT); SCATSYMP = total number of symptoms score on the SCAT; EUR = participants of European genetic ancestry; AFR = participants of African genetic ancestry; F LOC+ = female participants with loss of consciousness (LOC); F LOC- = female participants without LOC; M LOC+ = male participants with LOC; M LOC- = male participants without LOC).

Analysis	n $\epsilon 3/\epsilon 3$	n $\epsilon 2$ or $\epsilon 4$	<i>p</i>
<i>APOE <math>\epsilon 3/\epsilon 3</math> vs. <math>\epsilon 2</math> carriers; military vs. civilian</i>			
BESS; Civilian	397	74	0.646
BESS; Military	131	27	0.963
Days to RTP; Civilian; normal RTP (<24 days)	316	58	0.174
Days to RTP; Civilian; long RTP (>24 days)	98	22	0.383
Days to RTP; Military; normal RTP	101	19	0.839
Days to RTP; Military; long RTP	33	10	0.226
SAC; Civilian	407	80	0.441
SAC; Military	134	29	0.372
SCATSEV; Civilian	249	50	0.140
SCATSEV; Military	31	5	0.744
SCATSYMP; Civilian	249	50	0.445
SCATSYMP; Military	31	5	0.774
<i>APOE <math>\epsilon 3/\epsilon 3</math> vs. <math>\epsilon 4</math> carriers; military vs. civilian</i>			
BESS; Civilian	397	154	0.074
BESS; Military	131	76	0.097
Days to RTP; Civilian; normal RTP (<24 days)	316	129	0.932
Days to RTP; Civilian; long RTP (>24 days)	98	36	0.876
Days to RTP; Military; normal RTP (<24 days)	101	54	0.891
Days to RTP; Military; long RTP (>24 days)	33	24	0.545
SAC; Civilian	407	161	0.646
SAC; Military	134	78	0.353
SCATSEV; Civilian	249	102	0.743
SCATSEV; Military	31	21	0.216
SCATSYMP; Civilian	249	102	0.943
SCATSYMP; Military	31	21	0.181
<i><math>\epsilon 3/\epsilon 3</math> vs. <math>\epsilon 2</math> or <math>\epsilon 4</math>; EUR ancestry only</i>			
BESS $\epsilon 3/\epsilon 3$ vs $\epsilon 2$	423	82	0.767
BESS $\epsilon 3/\epsilon 3$ vs $\epsilon 4$	423	169	0.670
Days to RTP $\epsilon 3/\epsilon 3$ vs $\epsilon 2$ ; normal RTP (<24 days)	336	61	0.548
Days to RTP $\epsilon 3/\epsilon 3$ vs $\epsilon 2$ ; long RTP (>24 days)	104	27	0.986
Days to RTP $\epsilon 3/\epsilon 3$ vs $\epsilon 4$ ; normal RTP (<24 days)	336	133	0.613
Days to RTP $\epsilon 3/\epsilon 3$ vs $\epsilon 4$ ; long RTP (>24 days)	104	47	0.225
SAC $\epsilon 3/\epsilon 3$ vs $\epsilon 2$	435	88	0.801
SAC $\epsilon 3/\epsilon 3$ vs $\epsilon 4$	435	175	0.700
SCATSEV $\epsilon 3/\epsilon 3$ vs $\epsilon 2$	229	45	0.057
SCATSEV $\epsilon 3/\epsilon 3$ vs $\epsilon 4$	229	93	0.222
SCATSYMP $\epsilon 3/\epsilon 3$ vs $\epsilon 2$	229	45	0.624
SCATSYMP $\epsilon 3/\epsilon 3$ vs $\epsilon 4$	229	93	0.193

Table 14. Results from ANOVAs of outcomes by apolipoprotein E (*APOE*) genotype ( $\epsilon 3/\epsilon 3$  vs  $\epsilon 2$  or  $\epsilon 4$  carriers), participant type (military or civilian origin), and in participants of European (EUR) genetic ancestry (BESS = balance error scoring system; RTP = return to play; SAC = standardized assessment of concussion; SCATSEV = symptom severity score on the sport concussion assessment tool (SCAT); SCATSYMP =

total number of symptoms score on the SCAT; EUR = participants of European genetic ancestry).

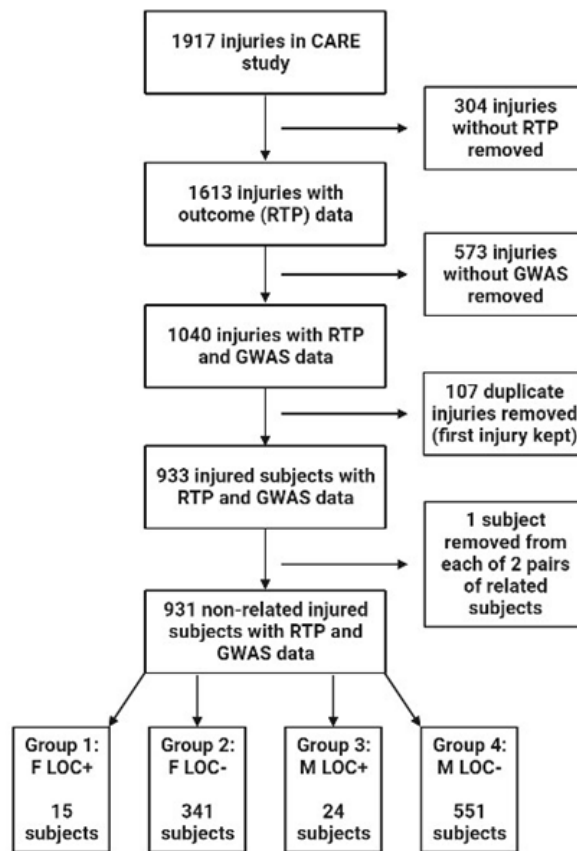


Figure 12. A consort diagram detailing the cohort of Concussion Assessment, Research and Education (CARE) Consortium participants used in this study (created with BioRender.com) (RTP = return to play; GWAS = genome-wide association study; F LOC+ = female participants with loss of consciousness (LOC); F LOC- = female participants without LOC; M LOC+ = male participants with LOC; M LOC- = male participants without LOC).

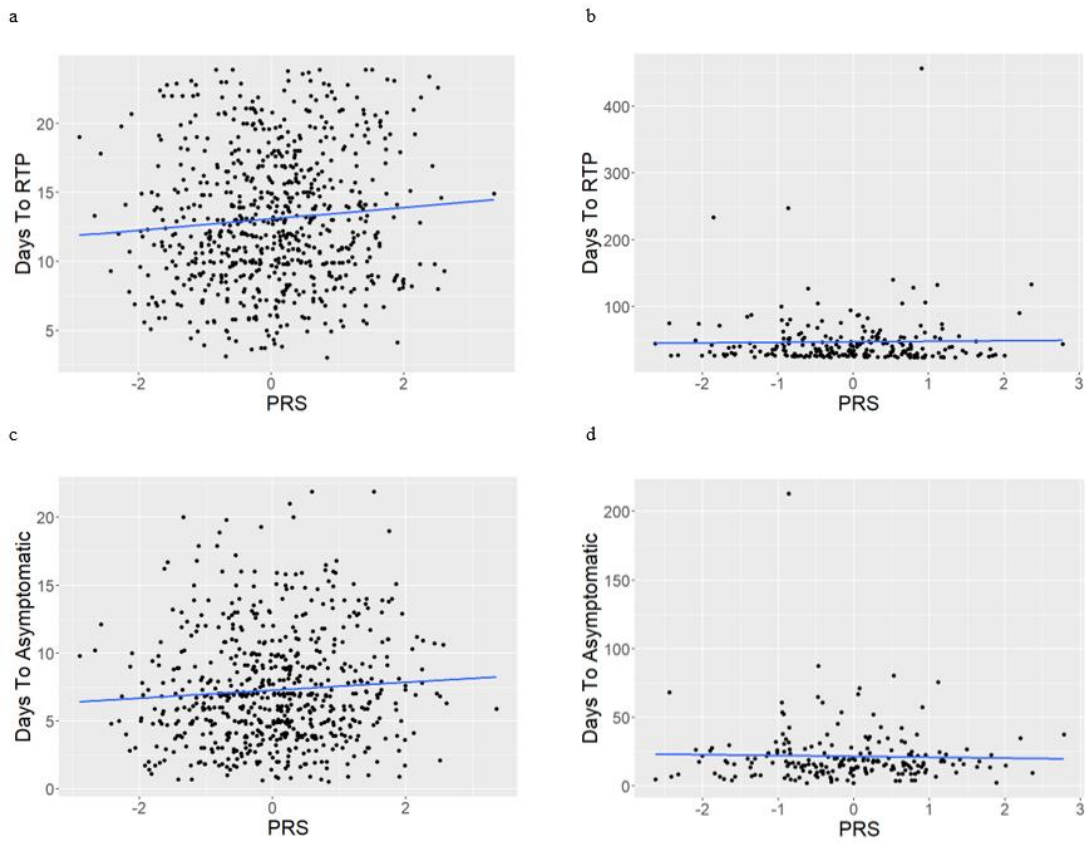


Figure 13. Concussion recovery measures as a function of polygenic risk score (PRS). Number of days to return to play (RTP) by PRS in normal (<24 days) (a) and long (>24 days) (b) RTP categories, and number of days to asymptomatic in normal RTP participants (c) and long RTP participants (d).

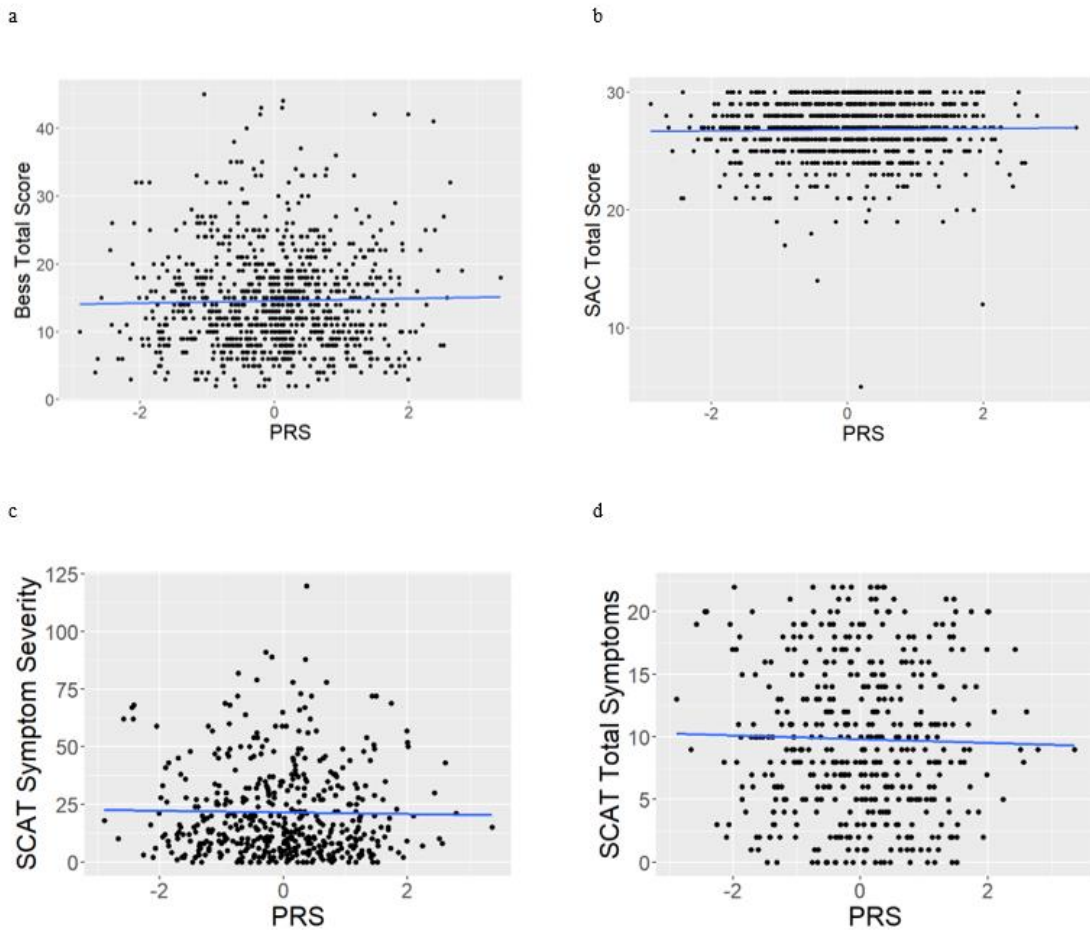


Figure 14. Alzheimer's disease (AD) polygenic risk score (PRS) and severity outcome measures in the full dataset (Balance error scoring system (BESS) (a) and standardized assessment of concussion (SAC) (b) total scores, and sport concussion assessment tool (SCAT) symptom severity score (SCATSEV) (c) and total number of symptoms (SCATSYMP) (d)).

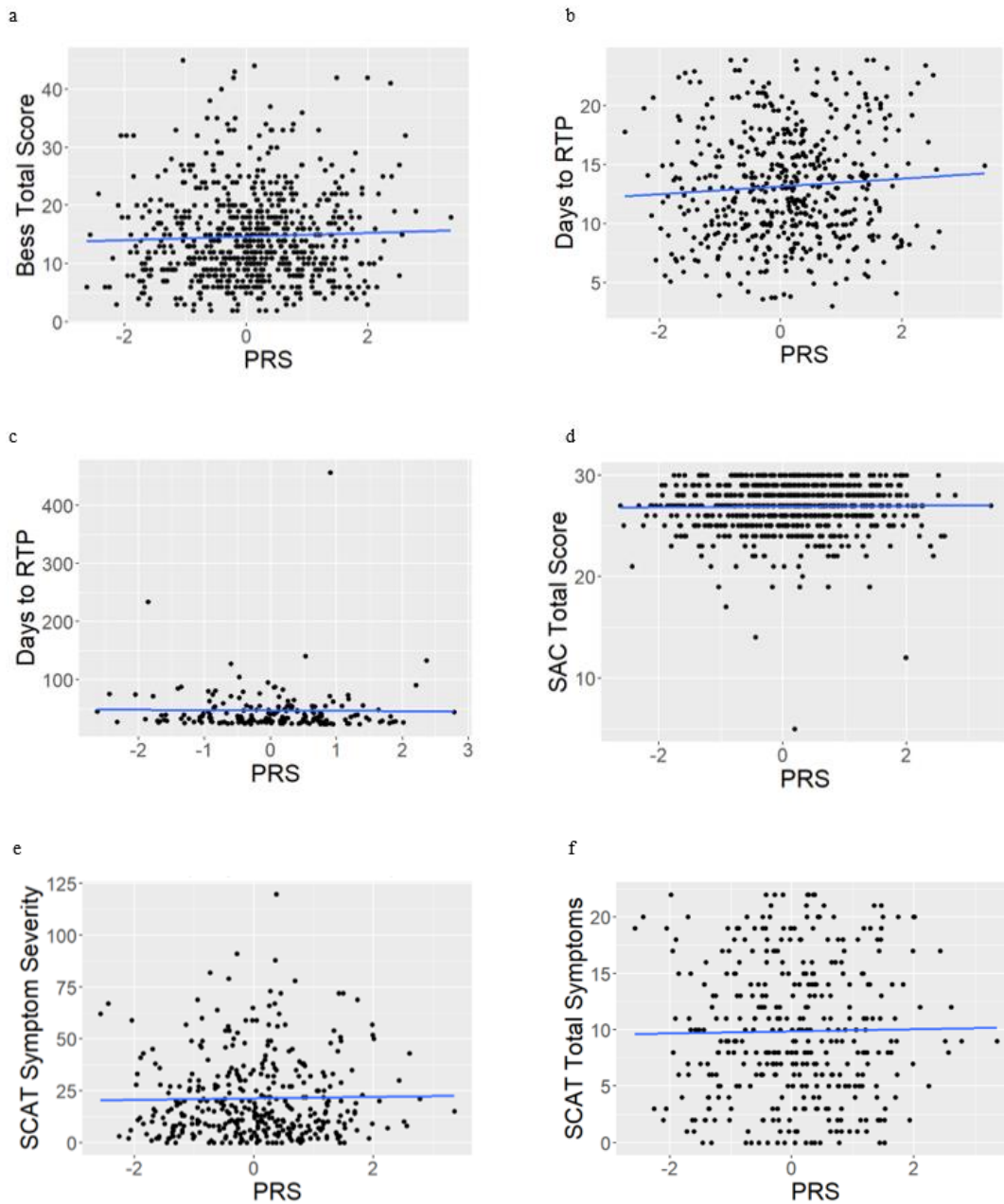


Figure 15. Outcome measures (balance error scoring system (BESS) total score (a), days to return to play (RTP) in normal (<24 days) subset (b), days to RTP in long (>24 days) subset (c), total score on standardized assessment of concussion (SAC) (d), sport concussion assessment tool (SCAT) symptom severity score (e), and SCAT total number

of symptoms (f) as a function of Alzheimer's disease (AD) polygenic risk score (PRS) in participants with European genetic ancestry.

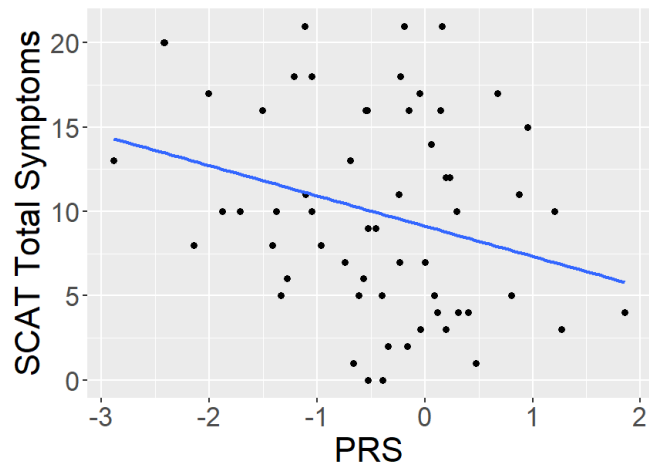


Figure 16. In individuals with African genetic ancestry, higher Alzheimer’s disease (AD) polygenic risk score (PRS) was associated with lower sport concussion assessment tool (SCAT) total number of symptoms (SCATSYMP) ( $p = 0.0276$ ).

## Chapter Five: Implications of Findings and Future Directions

### *Summary and Implications*

The principal aim of this thesis was to study the association between head injury (HI) and risk for Alzheimer's disease (AD), in particular by evaluating the impact of HI on ADRD biomarkers. This work targets an important knowledge gap in the field, as our understanding of the mechanisms behind the link between HI and dementia is insufficient. As HI is a common injury affecting as many as one in four Americans, improving our understanding of its long-term consequences related to neurodegeneration will be critical to addressing the growing dementia crisis. To approach this knowledge gap, we utilized a multimodal approach that explored how AD biomarkers and genetic risk were correlated with HI both acutely and remotely. Specifically, we investigated AD biofluid and neuroimaging biomarkers in aging adults with HI and examined whether AD genetics contributed to concussion recovery and/or severity in young adult athletes and military service academy students. In doing so, we demonstrated that HI may have unique associations with dementia biomarkers and genetics.

In Chapter One, we presented a systematic literature review that demonstrated highly mixed findings regarding an association of head injury with elevated amyloid and/or tau deposition on PET. That review pointed to key regions of interest, such as the cuneus, precuneus, and temporal lobes, as likely to demonstrate elevated protein deposition in individuals with HI, particularly for tau. The review also highlighted a number of challenges in the field that likely contributed to the mixed findings, including use of a multitude of different ROIs, unique imaging processing pipelines, and

differences in participant characteristics across many studies. In sum, the review demonstrated the need for continued exploration of advanced neuroimaging biomarkers in older adults either at risk for or living with dementia in the context of HI.

In Chapter Two, we presented a novel analysis of biofluid biomarkers from participants in the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort who reported history of HI. Using 2,511 cognitively normal and impaired participants, of whom 100 had HI history, we cross-sectionally and longitudinally assessed cerebrospinal fluid (CSF) and blood plasma biomarker levels. We found no consistent differences in tau, amyloid- $\beta$  (A $\beta$ ), or neurofilament light chain (NfL) as a consequence of HI, either cross-sectionally or longitudinally. Though a null finding, this report is one of the first of its kind to study biofluid biomarkers in older adults with remote HI.

The absence of an association between fluid biomarkers and HI in our study is in line with prior studies that characterized the temporal dynamics of fluid biomarkers after sports-related concussion. For example, glial fibrillary acidic protein (GFAP), ubiquitin C-terminal hydrolase-L1 (UCH-L1), NfL, and tau have been studied as potential concussion biomarker candidates.<sup>175, 176</sup> Reports observed that GFAP levels peaked 20 hours after injury and declined over 72 hours, while UCH-L1 peaked at 8 hours and declined over 48 hours.<sup>175</sup> Similarly, tau levels increased and fell within 24-48 hours of injury, while NfL levels were unchanged across the study duration.<sup>176</sup> These reports suggest that while fluid biomarkers may be useful for detecting and diagnosing concussion in the immediate hours to days following injury, they are less likely to be of use in remote HI because elevated levels do not persist for an extended period of time. As

such, fluid biomarkers may not be the optimal modality for identifying long-term mechanisms after HI that contribute to elevated dementia risk.

However, the findings from prior work and our study are only relevant to the limited number of biomarkers whose immediate temporal dynamics after concussion have been characterized. Only a few reports have explored fluid biomarkers after HI either acutely or remotely, and these studies concentrated on a limited number of relevant biomarkers. There has been even less analysis of the post-injury temporal dynamics of dementia-specific biomarkers like A $\beta$ , particularly in aging cohorts. As such, replication using additional biomarkers and in diverse cohorts covering the full spectrum from acute to remote HI, is strongly needed to confirm the lack of association observed in our report.

It is also probable that there are biomarkers that remain altered for an extended duration post-concussion but have not yet been identified. For example, previous work has indicated that neuroinflammation may persist for months to years after injury.<sup>387, 388</sup> Further, as neuroinflammation is gaining prominence as a potentially significant contributor to dementia risk and progression,<sup>389</sup> it is possible that shared neuroinflammatory mechanisms may contribute to the link between HI and dementia.<sup>388</sup> Though NfL levels did not demonstrate alterations after concussion either in the acute period<sup>176</sup> or the remote period, as we demonstrated in Chapter Two, neuroinflammatory biomarkers such as NfL or GFAP remain a promising future avenue of research. Greater attention should be devoted to understanding the neuroinflammatory response after concussion and its relation to long-term prognosis and risk for adverse outcomes such as dementia.

Next, in Chapter Three we investigated whether traumatic brain injury (TBI) and cognition were either independently and/or interactively related to cross-sectional tau deposition using positron emission tomography (PET) scans from older adults in the National Alzheimer's Coordinating Center (NACC) cohort. We found significant associations between TBI and tau specifically in participants with dementia, where individuals with TBI had elevated tau in the bilateral entorhinal cortex, bilateral fusiform gyrus, left inferior temporal gyrus, left amygdala, and meta-temporal regions of interest (ROIs). Further, adults with dementia whose injuries occurred before the age of 18 had elevated tau compared to participants with injuries incurred after 18 in the right inferior temporal gyrus, right middle temporal gyrus, and meta-temporal ROIs. Prior studies contain highly conflicting results regarding an association of TBI with tau deposition in these brain regions, as some studies have also seen higher tau deposition in older adults with history of TBI in similar temporal regions, while other work has identified higher tau in other ROIs, or no elevated tau deposition.<sup>99</sup> Our study thus adds yet another datapoint to a highly incongruous body of work. Importantly, we also expanded on prior findings emphasizing the need for additional focus on TBI reduction particularly early in life by showing that age of injury may be related to tau deposition, though low sample size is a consideration.<sup>390-392</sup> However, we plan to repeat this analysis using rank-based inverse normal transformations to account for any differences in SUVRs derived from two separate tau-PET radiotracers, and this will be critical to bolster these findings.

Our study also supports existing work in showing that PET imaging, particularly tau, is a promising modality for identifying HI-associated pathological changes in the context of dementia. However, further work is needed to fully characterize what areas of

the brain best reflect these alterations, as our report demonstrates.<sup>99</sup> For example, in our study we identified the entorhinal cortex, fusiform gyrus, inferior temporal gyrus, and amygdala as being associated with higher tau in participants with HI compared to those without HI. These ROIs are intriguing because temporal structures are some of the first to develop tau pathology in AD.<sup>5</sup> As such, our observation of elevated tau in these regions only in participants with dementia suggests that exacerbation of tau pathology in individuals with HI may only become evident once the brain has suffered significant insult due to the underlying ADRD disease process. In other words, the effects of HI on tau deposition may be masked until individuals are in the dementia stages, an observation that is consistent with prior reports.<sup>297</sup> This strongly suggests that elevated risk for cognitive impairment/dementia after HI may in part be mediated by mechanisms related to tau deposition.

Finally, in Chapter Four we conducted a highly novel study investigating whether genetic risk for AD was associated with concussion severity/recovery in young adults from the Concussion Assessment, Research, and Education (CARE) Consortium. In this report, we calculated AD polygenic risk scores (PRS) and correlated them with a number of metrics of concussion severity and recovery. We also searched for relationships between concussion severity/recovery and apolipoprotein E (*APOE*) genotypes, loss of consciousness, participant race, and other important factors. Our predominant finding was that a one-standard deviation (SD) increase in PRS was associated with a slightly elevated duration of time needed for a participant to recover and be cleared to return to play/practice after being concussed. The extension in recovery time was approximately ten hours per SD increase in PRS.

Though the majority of other tests in this report were insignificant, this was the first study to assess polygenic indicators of AD genetic risk in the context of concussion recovery outcomes, and the findings have important implications for young athletes and the field of sports medicine.

We showed that young adults with higher genetic risk for AD are unlikely to experience more severe concussions or require extensively extended recovery time compared to their peers with lower genetic risk. This observation may be reassuring for athletes with known family history and/or strong genetic risk factors for AD. However, the findings from our study are only applicable to the acute recovery period. We cannot extend the results to speculate on whether AD genetic risk is implicated in long-term concussion outcomes, such as risk of developing chronic traumatic encephalopathy (CTE). CTE is a highly complex disease, and it is likely that genetics play a role to some extent in its pathophysiology.<sup>393</sup> Specifically, evidence suggests that the  $\epsilon 4$  allele of the *APOE* gene may be linked to tau burden in CTE.<sup>394</sup> *APOE*  $\epsilon 4$  is associated with greater risk for AD<sup>28, 218</sup> and poorer recovery from concussion,<sup>74, 88-96, 98, 338, 373</sup> which provides evidence of the interrelatedness of genetic influences on both concussion recovery and risk for neurodegenerative diseases. However, the complex interrelationship and probable shared pathological mechanisms between AD and CTE in aging individuals with concussion history has yet to be fully characterized.<sup>205</sup> Our report sheds light on the influence of AD genetics with acute concussion outcomes, but also demonstrates the necessity of future reports to better characterize the relationship between AD genetics and long-term concussion-related consequences, such as development of AD or CTE.

As prior work has accumulated into highly conflicting opinions regarding the association between HI and AD biomarkers and/or genetics, the gap in our understanding of the mechanisms mediating the relationship between HI and AD persists. However, this thesis contributes significantly to the field through its presentation of multimodal analyses that reveal new information about the association between HI and dementia. Specifically, this body of work did not find evidence of a relationship between remote HI and AD fluid biomarkers, but does provide supportive evidence for an association between HI and tau deposition on PET, particularly in individuals already experiencing cognitive impairment/dementia due to AD. These findings are intriguing and have a number of important implications for the field, but additional studies are greatly warranted.

#### *Inherent Limitations and Challenges*

This work has a number of important limitations, chief among which is the small number of individuals with HI history. The number of participants whose injuries have documented clinical information is even smaller, particularly in datasets where HI history is not included as a line of inquiry in the medical history battery. Low sample size and detail significantly hinders investigation into the influence of factors such as time since injury or injury severity on AD biomarkers. The number of participants with longitudinal neuroimaging data is similarly insufficient. Longitudinal investigation into rates of tau deposition in individuals with HI would be incredibly illuminating; cross-sectional analyses can indicate whether tau levels are different at a static moment in time, but longitudinal analysis would permit investigation into rates of change in tau and other AD

biomarkers. As such, this will be a critical future area of investigation once more data is available.

While there are no practical strategies to retroactively bolster datasets that have limited HI ascertainment, implementation of the Uniform Dataset Version 4 (UDS-4) may enable future collection of more detailed clinical HI data. For example, the UDS-4 contains questions that ask about the presence of traumatic brain injury as either a primary, contributing, or non-contributing cause of ongoing cognitive impairment. Likewise, the UDS-4 also contains options for physicians to select traumatic encephalopathy syndrome (TES) and/or chronic traumatic encephalopathy (CTE) as diagnoses. Additionally, some universities/research groups have also developed specialized questionnaires that assess lifetime history of HI, including The Ohio State University Traumatic Brain Injury (TBI) Identification Method (OSU TBI-ID)<sup>319</sup> and the Boston Assessment of Traumatic Brain Injury–Lifetime (BAT-L), the latter of which was designed for use in military servicemembers.<sup>395</sup> The addition of one of these pre-existing questionnaires to the medical history battery of large aging-focused cohorts such as ADNI would enable more robust investigations into the relationship of HI with lifetime dementia risk and biomarkers in older adults.

Similarly, other large cohorts with better HI ascertainment protocols could serve as models for collecting HI data in more detail or may represent replication cohorts to test the findings presented in this work. For example, the Health and Aging Brain Study – Health Disparities (HABS-HD) study lists TBI with loss of consciousness (LOC) as one of its exclusion criteria, indicating that prospective participants in that study would be directly asked about their history of brain injury. Presumably, participants who had TBI

but without LOC would be included in the dataset, and that population of subjects could thus be studied.<sup>270</sup> Another example is the Baltimore Longitudinal Study of Aging (BLSA), from which studies of concussion in aging adults have been published.<sup>296</sup> Similar to ADNI, the BLSA relies on self-reported HI, but could be used in a replication study. Finally, the Australian Imaging, Biomarkers and Lifestyle Study of Aging (AIBL) has been used to examine the impact of HI in older adults and could also represent a potential replication cohort.<sup>83</sup>

Another primary limitation of the studies in this dissertation is that many aging/dementia-focused cohorts have historically included low numbers of minority participants, so findings using these cohorts may be inapplicable to the general population. Though lack of diversity and low power can both be somewhat addressed through the combination of multiple cohorts in a single study, this strategy introduces new challenges of data harmonization. Harmonization of multimodal data brings even more complexity. For example, there is significant variation in neuroimaging techniques and/or processing pipelines, whereas there are a limited number of select biofluid biomarker assays that may be commonly used across multiple large cohort studies. Different strategies are thus needed to combine imaging data versus biofluid data. In the context of PET imaging, the use of different radiotracers, regions of interest, processing pipelines, and other methodological variation between cohorts and/or study sites increases the difficulty of combining studies for meta-analysis. If two neuroimaging studies use different methods to ask similar research questions, contrasting findings become difficult to interpret because incongruence in the findings may be a result of methodological variation as opposed to variance in the data. Future development of

standardized neuroimaging pipelines may aid in addressing this replication crisis, but until such pipelines are developed and implemented, the field will likely continue to be plagued by contrasting findings.

Similar issues of heterogeneity are introduced via the head injuries themselves. Individuals can suffer a head injury in a wide variety of ways, resulting in difficulty generalizing findings from one individual to another, let alone across cohorts. For example, if a cohort is comprised predominantly of participants who were injured via sports participation, such as the CARE dataset, findings from that study may not be extendable to a cohort of older military servicemembers/veterans, such as ADNI-DoD. Furthermore, even within a single mechanism of injury (e.g., a cohort solely comprised of athletes, or even more specific, a cohort comprised of athletes from one sport), inter-subject variability precludes generalization of results across individuals. For example, if designing a study to investigate concussions in professional American football players, individuals who play different positions (e.g., quarterback vs. linebacker) may become concussed in different ways. Consequently, it is difficult to develop a study of concussion that would be adequately powered and simultaneously able to generalize to the larger US population. Furthermore, following such a cohort and capturing adequate clinical detail about participants' injuries would require a significant investment of both time and financial resources. As such, the issue of subject and cohort heterogeneity is a significant barrier to illuminating the relationship between concussion and risk for neurodegenerative diseases.

### *New Research Questions and Future Directions*

This thesis addresses a number of important unanswered questions in the field, but each report generates many additional questions to be addressed in future research. For example, we did not observe any changes in fluid biomarkers of tau in adults with remote HI, but studies of acute concussion have shown transient alterations to biofluid tau levels after injury. This suggests HI may induce transient changes in tau production as indicated by the acute rise in biofluid tau levels, but may not consistently generate long-term elevations. Alternatively, we observed higher deposited tau in the brains of older adults with dementia, which may suggest that HI increases susceptibility to tau deposition later in life, particularly in the context of ADRD.

Candidate biomarkers to capture brain changes in both acute and remote HI could be identified by exploring neuroimaging biomarkers outside A $\beta$  and tau. This is a planned future direction to build upon Chapter Four of this thesis, where we identified a relationship between AD genetic risk and concussion recovery time in CARE participants. In line with fluid biomarkers that demonstrate transient changes after concussion, prior reports have noted white matter (WM) changes on diffusion tensor imaging (DTI) in concussed athletes/military servicemembers,<sup>380-386</sup> including higher mean diffusivity (MD; indicative of worsened myelin integrity)<sup>381, 382</sup> and correlations between axonal integrity (AxD), clinical outcomes (Brief Symptom Inventory and SCAT symptom severity score), and elevated recovery time.<sup>382</sup> Additionally, one study outside CARE investigated an effect of *APOE* genotype on DTI metrics in concussed individuals and found limited evidence for altered fractional anisotropy (FA) in the cingulum of *APOE*  $\epsilon$ 4 carriers.<sup>90</sup> Another study observed that *APOE*  $\epsilon$ 4 carriers may be more

vulnerable to WM abnormalities after blast exposure.<sup>89</sup> These findings support a potential link between AD genetic risk and WM changes after concussion, as *APOE* ε4 is a known risk allele for both AD<sup>218</sup> and poor concussion prognosis.<sup>74, 92-94, 96, 336-338</sup> These reports demonstrate that studying the effects of HI on WM may help identify methods to track remote brain changes associated with HI, and similarly, the combination of genetics and neuroimaging may prove useful in understanding the link between HI and dementia. However, there has been little exploration into lesser-known risk genes using summary tools like PRS, and our future research will address this important knowledge gap.

Our planned analysis also addresses another important outstanding question, which is whether/to what extent comorbid conditions like cardiovascular disease are involved in the association between concussion and dementia. WM changes are common in AD,<sup>396</sup> but numerous studies have also linked cardiovascular risk factors to white matter hyperintensities (WMH).<sup>34, 397-400</sup> Intriguingly, some evidence indicates concussion may increase risk for cardiovascular disease (CVD), suggesting CVD risk factors could play a role in the link between concussion and risk for neurodegenerative disease (see <sup>401</sup> for review). Additionally, prior studies have applied coronary artery disease (CAD) risk scores to individuals with AD and found CAD risk to be associated with declining brain volume.<sup>402</sup> Links between concussion and risk for CVD have been repeatedly reported in the literature,<sup>401, 403-405</sup> but no study has simultaneously explored both CVD and AD genetic risk while investigating WM damage after concussion. As such, further investigation into potential interactions between AD and CVD genetic risk on WM is strongly warranted.<sup>282, 406</sup> Therefore, our future research will search for interactive effects between AD and CVD genetic risk scores on WM damage in

concussed CARE participants. Results from this study will aid in determination of what post-injury changes in the brain are visible on neuroimaging and may contribute to elevated long-term dementia risk.

Next, the injury ‘threshold’ that is required to establish higher risk for altered AD biomarkers and/or dementia has not been fully characterized. To better understand why head injuries are linked to neurodegenerative disease, the impact of variables such as age at injury, injury severity, mechanisms of injury, and/or comorbid conditions on AD risk, biomarkers, and/or disease progression must be studied in greater detail. For example, a number of prior reports have demonstrated that individuals with HI experience earlier onset of AD, but few have studied whether age at injury is associated with age at disease onset.<sup>407-410</sup> Similarly, the number of injuries an individual incurs plays a demonstrable role in risk for neurodegenerative disease. Along with conferring greater risk for AD, repetitive HI is the main risk factor for CTE, a neurodegenerative disease observed in populations at high risk for HI such as professional football players or boxers. There are many similarities between CTE and AD, and the level of risk for either disease that is conferred by a single HI is unclear. For example, one of the diagnostic criteria required to diagnose traumatic encephalopathy syndrome (TES), the clinical syndrome associated with suspected CTE pathology, is “substantial exposure” to repetitive HI.<sup>227</sup> However, the definition of substantial exposure is extremely broad and must be considered on a case-by-case basis.<sup>227</sup> As a result, it is difficult to determine whether there is a threshold (defined either by number of injuries, injury severity, or some other quantifying metric) above which risk for CTE is a more predominant concern than risk for AD.

Further, cryo-electron microscopy (cryoEM) studies have demonstrated unique tau isoforms in pathologically-confirmed CTE cases,<sup>188</sup> but the mechanisms responsible for this unique pathology, as well as factors that determine whether tau takes on a CTE- vs AD-like fold, are undetermined.<sup>188</sup> A tau radiotracer that could differentiate between disease-specific isoforms would benefit research into the distinctions between CTE and AD, and would enable easier differential diagnoses of AD vs CTE *in vivo*. Currently, a differential diagnosis can be made based on medical history, tau deposition patterns, symptomology, etc., but CTE can only be confirmed via autopsy. *In vivo* methods to image and diagnose CTE-like tau would permit studies comparing the course of CTE with other dementias such as AD, and may also offer patients and their families a greater ability to anticipate the needs of individuals as they progress through the disease course.

Furthermore, disease-specific radiotracers could clear up a significant proportion of the uncertainty summarized in Chapter One regarding whether HI associates with elevated protein deposition in AD. If participants with CTE-like tau could be identified *in vivo*, they could be excluded from studies whose sole purpose is to characterize the association of HI with protein deposition in AD. Though no currently existing radiotracer binds exclusively to CTE-like tau, a number of tracers have been evaluated for use in suspected CTE cases.<sup>189</sup> The tracers showing the most potential utility are MK-6240 and PI-2620, but additional research and development will be necessary to confirm what tau isoforms these tracers are labeling, and whether they can be used to specifically target CTE pathology.<sup>189</sup> Greater specificity of future tau tracers may in part depend on identification of cryptic sites in tau fibrils that have been shown to play a role in preferential binding of tracers to disease-specific tau isoforms.<sup>411</sup>

Based on the work presented in this dissertation and that of prior studies, it is evident that development of strategies to lower overall HI incidence and/or modulate risk for AD after HI will be crucial. The need to determine why HI leads to higher risk for dementia would be less urgent if head injury was less prevalent in the US and across the world. Particularly in the US, youth participation in contact sports such as football remains a significant source of HI among the general population. Furthermore, high-risk groups like military servicemembers and professional contact sport athletes accept dramatic rates of HI as part of their job description, though this unfortunately contributes to greater risk for poor long-term outcomes like TES/CTE. Therefore, lowering HI prevalence could lessen the consequential risk for neurodegenerative diseases across both the general population and special groups.

Some reports have indicated physical therapy/conditioning techniques may be useful for concussion prevention and/or recovery,<sup>412, 413</sup> while others support education efforts to target concussion reduction.<sup>414, 415</sup> Similarly, introduction of policies in contact sports that aim to reduce collisions between players and/or lower the impact of player collisions through use of protective gear are effective strategies to lower concussion incidence.<sup>416, 417</sup> Though some pushback against methods to reduce concussion has slowed progress,<sup>418, 419</sup> the most effective way to address the link between HI and dementia is to prevent the occurrence of HI in the first place. Moving forward, devoting greater resources toward development of innovative strategies to reduce brain injury rates will provide great benefit not just to athletes, but also military service members, civilians with head injuries, and all others who have a vested interest in stopping and/or preventing dementia.

### *Concluding Remarks*

In summary, this dissertation highlighted an association between HI and elevated levels of deposited tau in older adults with cognitive impairment, but there was no such link with fluid biomarkers. We also demonstrated that AD genetic risk was associated with slightly elongated recovery time in NCAA student athletes and military service academy students. Our work emphasizes the need for neuroimaging, particularly tau-PET, to be prominently involved in future exploration of head injury as a risk factor for neurodegenerative diseases including AD and CTE/TES. Taken together, this thesis exemplifies the complex interplay between head injury, genetics, and multimodal biomarkers of neurodegenerative diseases, and conclusively illustrates the need for additional research to better characterize both acute and remote *in vivo* changes after HI that contribute to altered biomarkers and disease risk.

## Appendix A

### Text A-1. ADNI

ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a \$60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California-San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 subjects but ADNI has been followed by ADNI-GO and ADNI-2. To date these three protocols have recruited over 1500 adults, ages 55 to 90, to participate in the research, consisting of cognitively normal older individuals, people with early or late MCI, and people with early AD. The follow

up duration of each group is specified in the protocols for ADNI-1, ADNI-2 and ADNI-GO. Subjects originally recruited for ADNI-1 and ADNI-GO had the option to be followed in ADNI-2.

<b>Biomarker</b>	<b># participants with at least 1 measurement</b>	<b>Mean # measurements per participant</b>	<b>Total # datapoints</b>
CSF A $\beta$ 40	568	1.62	921
CSF A $\beta$ 42	1660	1.89	3153
CSF A $\beta$ 42/40	568	1.62	918
CSF pTau-181	1650	1.89	3133
CSF Total Tau	1653	1.89	3145
Plasma A $\beta$ 42/40	550	1.52	836
Plasma NfL	1583	2.70	4278
Plasma pTau-181	1190	3.11	3700

Table A-1. Number of participants per biomarker modality, average number of biomarker measurements per participant, and total number of data points for each biomarker.

	BL	M06	M12	M18	M24	M36	M48	M60	M72	M84	M96	M108	M120	M132	M144	M156	M168	M180	M192
CSF A $\beta$ 40	0	0	0	0	0	1	0	0	3	1	3	1	2	0	1	0	0	0	0
CSF A $\beta$ 42/40	0	0	0	0	0	1	0	0	3	1	3	1	2	0	1	0	0	0	0
CSF A $\beta$ 42	0	0	1	0	0	1	0	0	3	1	3	1	2	0	1	0	0	0	0
CSF pTau	0	0	1	0	0	1	0	0	3	1	3	1	2	0	1	0	0	0	0
CSF Tau	0	0	1	0	0	1	0	0	3	1	3	1	2	0	1	0	0	0	0
Plasma raw A $\beta$ 42/40	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Plasma NfL	0	0	3	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Plasma pTau 181	0	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Table A-2. Number of biomarker measurements excluded when there was no recorded date available for a study visit.

	BL	M06	M12	M18	M24	M36	M48	M60	M72	M84	M96	M108	M120	M132	M144	M156	M168	M180	M192
CSF A $\beta$ 40	0	0	0	0	0	1	0	0	3	1	3	1	2	0	1	0	0	0	0
CSF A $\beta$ 42/40	0	0	0	0	0	1	0	0	3	1	3	1	2	0	1	0	0	0	0
CSF A $\beta$ 42	0	0	1	0	0	1	0	0	3	1	3	1	2	0	1	0	0	0	0
CSF pTau	0	0	1	0	0	1	0	0	3	1	3	1	2	0	1	0	0	0	0
CSF Tau	0	0	1	0	0	1	0	0	3	1	3	1	2	0	1	0	0	0	0
Plasma raw A $\beta$ 42/40	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Plasma NfL	0	0	3	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Plasma pTau 181	0	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Table A-3. Number of cognitive statuses that were inferred based on previous/subsequent visits if a study visit had biomarker measurements but no associated cognitive status.

<b>Biomarker</b>	<b>Outside detection value</b>	<b># datapoints removed</b>	<b>Total removed from biomarker</b>
CSF A $\beta$ 40	<200, >1700	0	0
CSF A $\beta$ 42	<200, >1700	3, 1	4
CSF A $\beta$ 42/40	N/A	N/A	N/A
CSF pTau-181	<8, >120	21, 2	23
CSF Total Tau	<80, >1300	11, 1	12
Plasma A $\beta$ 42/40	N/A	0	0
Plasma NfL	<lloq, <LOD	35, 3	38
Plasma pTau-181	N/A	0	0

Table A-4. Number of biomarker measurements excluded when the measurement was outside the limit of detection (measurements that contained < or >).

	Head injury (n = 100)		No head injury (n = 2,411)		HI p-value	DX p-value	DX by HI p-value	Covariate p-values
	CN (n = 33)	Impaired (n = 67)	CN (n = 896)	Impaired (n = 1515)				
					-	-	-	-
<b>CSF Aβ40 (SD)<sup>a</sup></b>	21236.67 (8506.15)	17703.33 (4200.40)	18760.08 (5410.35)	17465.10 (5620.53)	0.375	0.295	0.606	Age <0.001 Sex 0.017 Education 0.326 Race 0.066 Ethnicity 0.144 APOE ε4 status 0.294
<b>CSF Aβ42 (SD)<sup>b</sup></b>	1301.32 (712.58)	1000.32 (550.25)	1344.63 (659.63)	933.38 (554.93)	0.472	<0.001 (CN>Imp, mean difference 275.557)	0.910	Age <0.001 Sex 0.158 Education 0.889 Race 0.610 Ethnicity 0.222 APOE ε4 status <0.001
<b>CSF Aβ42/40 (SD)<sup>a</sup></b>	0.1053 (0.0072)	0.0697 (0.033)	0.0717 (0.025)	0.0559 (0.026)	0.004 (HI>non-HI; mean difference 0.022)	0.004 (CN>Imp, mean difference 0.023)	0.134	Age <0.001 Sex 0.369 Education 0.529 Race 0.208 Ethnicity 0.788 APOE ε4 status <0.001
<b>CSF pTau 181 (SD)<sup>c</sup></b>	20.66 (6.94)	28.29 (16.17)	21.47 (9.23)	30.02 (15.36)	0.527	<0.001 (CN<Imp, mean difference 6.927)	0.957	Age <0.001 Sex <0.001 Education 0.002 Race 0.882 Ethnicity 0.081

								APOE ε4 status <b>&lt;0.001</b>
<b>CSF total tau (SD)<sup>d</sup></b>	230.11 (73.59)	297.20 (150.61)	235.81 (87.53)	306.17 (135.96)	0.773	<b>&lt;0.001</b> (CN<Imp, mean difference 59.693)	0.873	Age <b>&lt;0.001</b> Sex <b>&lt;0.001</b> Education <b>0.003</b> Race 0.903 Ethnicity 0.077 APOE ε4 status <b>&lt;0.001</b>
<b>Plasma Aβ42/40 (SD)<sup>e</sup></b>	0.1236 (0.01)	0.1199 (0.01)	0.1215 (0.01)	0.1213 (0.01)	0.739	0.553	0.565	Age 0.708 Sex 0.409 Education 0.339 Race 0.517 Ethnicity <b>0.028</b> APOE ε4 status 0.620
<b>Plasma NfL (SD)<sup>f</sup></b>	36.56 (30.05)	42.46 (25.84)	34.55 (20.90)	42.79 (23.82)	0.213	<b>0.007</b> (CN<Imp, mean difference 7.569)	0.535	Age <b>&lt;0.001</b> Sex <b>0.010</b> Education 0.743 Race 0.554 Ethnicity 0.903 APOE ε4 status 0.373
<b>Plasma pTau 181 (SD)<sup>g</sup></b>	13.84 (6.32)	17.16 (9.95)	15.72 (12.92)	19.28 (11.35)	0.322	0.230	0.902	Age <b>&lt;0.001</b> Sex 0.110 Education <b>0.030</b> Race 0.916 Ethnicity 0.808 APOE ε4 status <b>&lt;0.001</b>

<sup>a</sup>410 participants (3 CN-HI, 6 Impaired-HI, 254 CN-non-HI, 147 Impaired-non-HI)

<sup>b</sup>1560 participants (18 CN-HI, 45 Impaired-HI, 553 CN-non-HI, 944 Impaired-non-HI)

<sup>c</sup>1553 participants (18 CN-HI, 45 Impaired-HI, 549 CN-non-HI, 941 Impaired-non-HI)

<sup>d</sup>1556 participants (18 CN-HI, 45 Impaired-HI, 551 CN-non-HI, 942 Impaired-non-HI)

<sup>e</sup>450 participants (10 CN-HI, 18 Impaired-HI, 175 CN-non-HI, 247 Impaired-non-HI)

<sup>f</sup>1454 participants (24 CN-HI, 44 Impaired-HI, 459 CN-non-HI, 927 Impaired-non-HI)

<sup>g</sup>877 participants (15 CN-HI, 35 Impaired-HI, 275 CN-non-HI, 552 Impaired-non-HI)

Table A-5. Full results from baseline cross-sectional biomarker two-way ANCOVAs

testing HI and cognition as main effects.

	Head injury (n = 100)		No head injury (n = 2,411)		HI p-value	DX p-value	DX by HI p-value	Covariate p-values
	<i>CN (n = 33)</i>	<i>Impaired (n = 67)</i>	<i>CN (n = 896)</i>	<i>Impaired (n = 1515)</i>	-	-	-	-
<b>CSF Aβ40 (SD)</b>	4.3059 (0.16193)	4.2369 (0.11060)	4.2547 (0.12956)	4.2181 (0.15017)	0.362	0.367	0.798	Age < <b>0.001</b> Sex <b>0.022</b> Education 0.480 Race <b>0.034</b> Ethnicity 0.260 APOE ε4 status 0.573
<b>CSF Aβ42 (SD)</b>	3.0611 (0.21723)	2.9384 (0.23614)	3.0752 (0.22159)	2.9053 (0.23183)	0.325	< <b>0.001</b>	0.889	Age < <b>0.001</b> Sex 0.055 Education 0.838 Race 0.940 Ethnicity 0.630 APOE ε4 status < <b>0.001</b>
<b>CSF pTau 181 (SD)</b>	1.2920 (0.14672)	1.3937 (0.22075)	1.2973 (0.16935)	1.4245 (0.21526)	0.524	< <b>0.001</b>	0.876	Age < <b>0.001</b> Sex < <b>0.001</b> Education <b>0.003</b> Race 0.291 Ethnicity <b>0.007</b> APOE ε4 status < <b>0.001</b>
<b>CSF total tau (SD)</b>	2.3395 (0.14775)	2.4266 (0.19862)	2.3452 (0.15288)	2.4456 (0.18793)	0.705	<b>0.001</b>	0.981	Age < <b>0.001</b> Sex < <b>0.001</b> Education <b>0.007</b> Race 0.143 Ethnicity <b>0.009</b> APOE ε4 status < <b>0.001</b>
<b>Plasma NfL (SD)</b>	1.4948 (0.21142)	1.5856 (0.17584)	1.4916 (0.19134)	1.5790 (0.21044)	0.146	< <b>0.001</b>	0.821	Age < <b>0.001</b> Sex <b>0.005</b> Education 0.590 Race 0.772 Ethnicity 0.838 APOE ε4 status <b>0.014</b>
<b>Plasma pTau 181 (SD)</b>	1.0912 (0.23025)	1.1588 (0.27645)	1.1031 (0.29248)	1.2138 (0.26272)	0.486	0.160	0.603	Age < <b>0.001</b> Sex 0.208 Education 0.079



	Head injury (n = 100)		No head injury (n = 2,411)		HI p-value	Sex p-value	Sex by HI p-value	Covariate p-values
	Male	Female	Male	Female				
CSF A $\beta$ 40 (SD) <sup>a</sup>	19334.00 (7449.33)	18315.00 (3347.50)	17666.02 (5297.25)	18794.91 (5652.25)	0.489	0.876	0.533	Age < <b>0.001</b> Dx 0.063 Education 0.35 Race 0.073 Ethnicity 0.146 APOE $\epsilon$ 4 status 0.300
CSF A $\beta$ 42 (SD) <sup>b</sup>	1075.57 (651.82)	1109.44 (526.08)	1032.41 (608.73)	1142.68 (643.30)	0.626	0.793	0.383	Age < <b>0.001</b> Dx < <b>0.001</b> Education 0.891 Race 0.628 Ethnicity 0.220 APOE $\epsilon$ 4 status < <b>0.001</b>
CSF A $\beta$ 42/40 (SD) <sup>a</sup>	0.0812 (0.034)	0.0820 (0.033)	0.0648 (0.027)	0.0669 (0.027)	<b>0.013</b>	0.811	0.981	Age < <b>0.001</b> Dx < <b>0.001</b> Education 0.458 Race 0.182 Ethnicity 0.784 APOE $\epsilon$ 4 status < <b>0.001</b>
CSF pTau 181 (SD) <sup>c</sup>	24.54 (12.17)	29.48 (18.53)	26.39 (13.12)	27.40 (14.99)	0.842	<b>0.010</b>	0.219	Age < <b>0.001</b> Dx < <b>0.001</b> Education <b>0.002</b> Race 0.859 Ethnicity 0.081 APOE $\epsilon$ 4 status < <b>0.001</b>
CSF total tau (SD) <sup>d</sup>	262.63 (114.27)	311.13 (172.82)	273.55 (116.08)	287.47 (133.85)	0.862	<b>0.005</b>	0.252	Age < <b>0.001</b> Dx < <b>0.001</b> Education <b>0.003</b> Race 0.920 Ethnicity 0.077 APOE $\epsilon$ 4 status < <b>0.001</b>

<b>Plasma A<math>\beta</math>42/40 (SD)<sup>e</sup></b>	0.1217 (0.014)	0.1196 (0.011)	0.1206 (0.013)	0.1221 (0.013)	0.931	0.927	0.606	Age 0.712 Dx 0.835 Education 0.367 Race 0.501 Ethnicity <b>0.027</b> APOE $\epsilon$ 4 status 0.579
<b>Plasma NfL (SD)<sup>f</sup></b>	41.53 (31.20)	37.80 (15.87)	39.99 (21.68)	40.15 (24.89)	0.518	0.924	0.295	Age < <b>0.001</b> Dx < <b>0.001</b> Education 0.702 Race 0.527 Ethnicity 0.903 APOE $\epsilon$ 4 status 0.386
<b>Plasma pTau 181 (SD)<sup>g</sup></b>	15.99 (8.79)	16.67 (10.22)	19.00 (13.35)	17.16 (10.37)	0.634	0.715	0.248	Age < <b>0.001</b> Dx <b>0.004</b> Education <b>0.027</b> Race 0.945 Ethnicity 0.795 APOE $\epsilon$ 4 status < <b>0.001</b>

<sup>a</sup>410 participants (5 Male-HI, 4 Female-HI, 181 Male-non-HI, 220 Female-non-HI)

<sup>b</sup>1560 participants (43 Male-HI, 20 Female-HI, 779 Male-non-HI, 718 Female-non-HI)

<sup>c</sup>1553 participants (42 Male-HI, 20 Female-HI, 778 Male-non-HI, 712 Female-non-HI)

<sup>d</sup>1556 participants (43 Male-HI, 20 Female-HI, 779 Male-non-HI, 714 Female-non-HI)

<sup>e</sup>450 participants (21 Male-HI, 7 Female-HI, 206 Male-non-HI, 216 Female-non-HI)

<sup>f</sup>1454 participants (47 Male-HI, 21 Female-HI, 745 Male-non-HI, 641 Female-non-HI)

<sup>g</sup>877 participants (37 Male-HI, 13 Female-HI, 420 Male-non-HI, 407 Female-non-HI)

Table A-7. Full results from baseline cross-sectional biomarker two-way ANCOVAs testing HI and sex as main effects.

Biomarker	Age F statistic ( $\beta$ )	Age p-value	HI F statistic	HI p-value	Age:HI interaction	Age:HI interaction n-value	Covariate F statistics	Covariate p-values
CSF A $\beta$ 40	1.847 (-32.600)	0.1750	0.282	0.5959	0.293	0.5886	DXGrp 4.491 Sex 3.902 Race 2.335 Ethnicity 0.675 Education 0.639 APOE $\epsilon$ 4 status 2.342	DXGrp <b>0.0348</b> (CN>Impaired, $p = 0.0734$ ) Sex <b>0.0488</b> (Female>Male, $p = 0.0314$ ) Race 0.0547 Ethnicity 0.5095 Education 0.4245 APOE $\epsilon$ 4 status 0.1265
CSF A $\beta$ 42	119.965 (-14.757)	<.0001 (estimate = -6.845, SE = 1.415, t-value = -4.839, $p = <.001$ )	0.141	0.7077	0.000	0.9842	DXGrp 76.017 Sex 4.185 Race 0.753 Ethnicity 0.119 Education 2.405 APOE $\epsilon$ 4 status 361.586	DXGrp <.0001 (CN>Impaired, $p = <.0001$ ) Sex <b>0.0410</b> (Female>Male, $p = 0.0156$ ) Race 0.6074 Ethnicity 0.8881 Education 0.1212 APOE $\epsilon$ 4 status <.0001 (e4 negative>e4 positive, $p = <.0001$ )
CSF A $\beta$ 42/40	62.123 (-0.002)	<.0001 (estimate = -0.0008311, SE = 0.0001157, t-value = -7.184, $p = <.001$ )	1.382	0.2404	2.502	0.1146	DXGrp 42.647 Sex 2.557 Race 1.178 Ethnicity 0.323 Education 0.990 APOE $\epsilon$ 4 status 191.262	DXGrp <.0001 (CN>Impaired, $p = <.0001$ ) Sex 0.1104 Race 0.3194 Ethnicity 0.7238 Education 0.3202 APOE $\epsilon$ 4 status <.0001 (e4 negative>e4 positive, $p = <.0001$ )
CSF pTau 181	91.515 (0.489)	<.0001 (estimate = 0.18486, SE = 0.03446, t-value = 5.365, $p <.001$ )	0.034	0.8541	0.556	0.4559	DXGrp 60.112 Sex 12.780 Race 1.501 Ethnicity 3.244 Education 16.895 APOE $\epsilon$ 4 status 188.077	DXGrp <.0001 (Impaired>CN, $p = <.0001$ ) Sex <b>0.0004</b> (Female>Male, $p = 0.0057$ ) Race 0.1739 Ethnicity <b>0.0393</b> (Hisp/Lat<Not Hisp/Lat, $p = 0.0786$ ) Education <.0001 (estimate = -

								0.55158, SE = 0.09461, t-value = -5.83, p = <.001) APOE ε4 status <.0001 (e4 negative<e4 positive, p = <.0001)
<b>CSF total tau</b>	139.167 (5.300)	<.0001 (estimate = 2.0248, SE = 0.3084, t-value = 6.566, p <.001)	0.001	0.9775	0.666	0.4147	DXGrp 56.255 Sex 22.068 Race 1.950 Ethnicity 3.195 Education 13.155 APOE ε4 status 157.007	DXGrp <.0001 (Impaired>CN, p = <.0001) Sex <.0001 (Female>Male, p = 0.0001) Race 0.0696 Ethnicity <b>0.0412</b> (Hisp/Lat<Not Hisp/Lat, p = 0.0871) Education <b>0.0003</b> (estimate = -5.0982, SE = 0.8487, t-value = -6.007, p = <.001) APOE ε4 status <.0001 (e4 negative<e4 positive, p = <.0001)
<b>Plasma Aβ42/40</b>	0.75 (0.000)	0.3884	0.13	0.7164	0.00	0.9722	DXGrp 0.00 Sex 2.50 Race 1.75 Ethnicity 4.38 Education 0.07 APOE ε4 status 0.47	DXGrp 0.9455 Sex 0.1145 Race 0.1219 Ethnicity <b>0.0130</b> (Hisp/Lat>Not Hisp/Lat, p = 0.0086) Education 0.7950 APOE ε4 status 0.4942
<b>Plasma NFL</b>	463.068 (1.450)	<.0001 (estimate = 1.46337, SE = 0.05006, t-value = 29.23, p <.001)	2.111	0.1464	0.001	0.9775	DXGrp 102.095 Sex 9.791 Race 1.728 Ethnicity 0.163 Education 0.222 APOE ε4 status 11.898	DXGrp <.0001 (Impaired>CN, p = <.0001) Sex <b>0.0018</b> (Female>Male, p = 0.0008) Race 0.1107 Ethnicity 0.8497 Education 0.6379 APOE ε4 status <b>0.0006</b> (e4 negative<e4 positive, p = .0006)
<b>Plasma pTau 181</b>	60.390 (0.377)	<.0001 (estimate = 0.29064,	0.191	0.6620	0.079	0.7783	DXGrp 64.553 Sex 4.022	DXGrp <.0001 (Impaired>CN, p = <.0001)

		<i>SE = 0.02765, t-value = 10.510, p = &lt;.001)</i>					Race 1.041 Ethnicity 0.066 Education 3.712 APOE ε4 status 64.588	Sex <b>0.0451</b> ( <i>Female&lt;Male, p = 0.0191</i> ) Race 0.3968 Ethnicity 0.9365 Education 0.0543 APOE ε4 status <b>&lt;.0001</b> ( <i>e4 negative&lt;e4 positive, p = &lt;.0001</i> )
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Table A-8. Full ANOVA table results from longitudinal linear mixed effects models testing main effects of HI and age and their interaction.

Biomarker	Age F statistic (p value) [ $\beta$ ]	HI F statistic (p value)	Sex F statistic (p value)	Age:HI interaction F statistic (p)	Age:Sex interaction F statistic (p)	HI:Sex interaction F statistic (p)	Age:HI:Sex interaction F statistic (p)	Covariate F statistics (p values)
CSF A $\beta$ 40	1.81 (0.1794) [29.302]	0.282 (0.5955)	4.876 <b>(0.0277)</b>	0.295 (0.5872)	1.067 (0.3023)	0.561 (0.4541)	0.426 (0.5145)	DXGrp 3.483 (0.0629) Race 2.324 (0.0556) Ethnicity 0.665 (0.5146) Education 0.642 (0.4232) APOE $\epsilon$ 4 status 2.329 (0.1276)
CSF A $\beta$ 42	120.069 <b>(&lt;0.0001)</b> [-13.647]	0.141 (0.7078)	7.633 <b>(0.0058)</b>	0.000 (0.9831)	1.870 (0.1717)	0.775 (0.3787)	0.000 (0.9980)	DXGrp 72.320 <b>(&lt;0.0001)</b> Race 0.752 (0.6082) Ethnicity 0.118 (0.8883) Education 2.405 (0.1212) APOE $\epsilon$ 4 status 361.180 <b>(&lt;0.0001)</b>
CSF A $\beta$ 42/40	61.243 <b>(&lt;0.0001)</b> [-0.002]	1.359 (0.2442)	0.853 (0.3562)	2.482 (0.1161)	0.139 (0.7096)	0.129 (0.7201)	0.075 (0.7841)	DXGrp 44.079 <b>(&lt;0.0001)</b> Race 1.167 (0.3243) Ethnicity 0.326 (0.7217) Education 0.980 (0.3227) APOE $\epsilon$ 4 status 190.423 <b>(&lt;0.0001)</b>

<b>CSF pTau 181</b>	91.273 ( <b>&lt;0.0001</b> ) [0.491]	0.033 (0.8552)	8.875 ( <b>0.0029</b> )	0.557 (0.4557)	0.026 (0.8728)	1.507 (0.2198)	0.000 (0.9920)	DXGrp 63.982 ( <b>&lt;0.0001</b> ) Race 1.500 (0.1743) Ethnicity 3.244 ( <b>0.0393</b> ) Education 16.883 ( <b>&lt;0.0001</b> ) APOE ε4 status 188.074 ( <b>&lt;0.0001</b> )
<b>CSF total tau</b>	138.841 ( <b>&lt;0.0001</b> ) [5.066]	0.001 (0.9759)	16.612 ( <b>&lt;0.0001</b> )	0.665 (0.4150)	0.060 (0.8061)	1.050 (0.3056)	0.020 (0.8865)	DXGrp 61.604 ( <b>&lt;0.0001</b> ) Race 1.947 (0.0701) Ethnicity 3.193 ( <b>0.0413</b> ) Education 13.145 ( <b>0.0003</b> ) APOE ε4 status 156.913 ( <b>&lt;0.0001</b> )
<b>Plasma Aβ42/40</b>	0.74 (0.3890) [0.000]	0.13 (0.7167)	2.50 (0.1146)	0.00 (0.9723)	0.06 (0.8051)	0.36 (0.5501)	0.56 (0.4551)	DXGrp 0.00 (0.9885) Race 1.74 (0.1228) Ethnicity 4.37 ( <b>0.0131</b> ) Education 0.07 (0.7952) APOE ε4 status 0.47 (0.4947)
<b>Plasma NFL</b>	460.266 ( <b>&lt;0.0001</b> ) [1.642]	2.113 (0.1462)	4.965 ( <b>0.0260</b> )	0.001 (0.9821)	4.425 ( <b>0.0355</b> )	0.130 (0.7182)	0.213 (0.6442)	DXGrp 106.584 ( <b>&lt;0.0001</b> ) Race 1.714 (0.1139) Ethnicity 0.165 (0.8477)

								Education 0.245 (0.6205) APOE ε4 status 11.857 <b>(0.0006)</b>
<b>Plasma pTau 181</b>	60.159 <b>(&lt;0.0001)</b> [0.323]	0.187 (0.6658)	7.913 <b>(0.0050)</b>	0.077 (0.7816)	0.261 (0.6097)	0.737 (0.3908)	0.173 (0.6778)	DXGrp 60.546 <b>(&lt;0.0001)</b> Race 1.035 (0.4008) Ethnicity 0.066 (0.9383) Education 3.700 (0.0547) APOE ε4 status 64.453 <b>(&lt;0.0001)</b>

Table A-9. Full ANOVA table results from longitudinal linear mixed effects models testing main effects of HI, age, and sex, and their three-way interaction.

	<u>Value</u>	<u>Std. Error</u>	<u>DF</u>	<u>t-value</u>	<u>p-value</u>
<b>(Intercept)</b>	20634.655	12510.3261	502	1.64940984	0.09968927
<b>Age</b>	-32.599812	148.793138	343	-0.2190949	0.82670647
<b>Head injury</b>	-6998.1945	11064.6463	502	-0.6324824	0.52735965
<b>Diagnostic group</b>	-702.37152	391.07323	343	-1.7960102	0.07337283
<b>Sex</b>	1066.04642	494.021611	502	2.15789431	<b>0.03140963</b>
<b>Asian</b>	-1654.557	6310.2102	502	-0.2622031	0.79327239
<b>Black or African American</b>	-681.58412	5841.19816	502	-0.1166857	0.90715581
<b>White</b>	1968.48834	5705.84883	502	0.34499483	0.73024276
<b>More than one race</b>	-1232.7543	5980.94373	502	-0.2061137	0.83678568
<b>Not Hispanic or Latino</b>	479.733459	1410.46495	502	0.34012434	0.73390516
<b>Unknown ethnicity</b>	4789.35901	4113.19356	502	1.16438941	0.2448193
<b>Education</b>	-81.922761	101.614469	502	-0.8062116	0.42050261
<b>APOE e4 positive</b>	-748.85432	490.455938	502	-1.5268534	0.12742726
<b>Age/Head injury interaction</b>	81.9201315	151.318637	343	0.54137503	0.58860057

Table A-10. Coefficients (summary) table from longitudinal linear mixed-effects model analysis of cerebrospinal fluid (CSF) amyloid- $\beta$ 40 (A $\beta$ 40).

	<u>Value</u>	<u>Std.Error</u>	<u>DF</u>	<u>t-value</u>	<u>p-value</u>
<b>(Intercept)</b>	2016.94033	608.606485	1805	3.3140303	0.00093781
<b>Age</b>	-14.75733	6.17287324	1805	-2.3906744	<b>0.0169194</b>
<b>Head injury</b>	-6.2791712	465.104091	1592	-0.0135006	0.98923012
<b>Diagnostic group</b>	-98.685377	17.7422955	1805	-5.5621538	<b>3.0634E-08</b>
<b>Sex</b>	67.0801165	27.7134072	1592	2.4204933	<b>0.01561074</b>
<b>Asian</b>	401.433046	404.65182	1592	0.99204557	0.32132605
<b>Native Hawaiian or Other Pacific Islander</b>	552.865915	544.511298	1592	1.01534333	0.31009648
<b>Black or African American</b>	290.236928	393.607613	1592	0.73737631	0.4610022
<b>White</b>	301.161923	387.467353	1592	0.77725754	0.43712232
<b>More than one race</b>	272.840381	407.800853	1592	0.66905299	0.50355868
<b>Unknown race</b>	132.275581	484.498423	1592	0.2730155	0.78487671
<b>Not Hispanic or Latino</b>	72.4661905	80.5622216	1592	0.89950586	0.36851931
<b>Unknown ethnicity</b>	42.01673	201.533505	1592	0.20848509	0.8348769
<b>Education</b>	2.66666452	5.1529026	1592	0.51750726	0.604874
<b>APOE e4 positive</b>	-522.15108	27.4594553	1592	-19.015347	<b>8.1368E-73</b>
<b>Age/Head injury interaction</b>	-0.125385	6.31060331	1805	-0.0198689	0.98415012

Table A-11. Coefficients (summary) table from longitudinal linear mixed-effects model analysis of cerebrospinal fluid (CSF) amyloid- $\beta$ 42 (A $\beta$ 42).

	<u>Value</u>	<u>Std.Error</u>	<u>DF</u>	<u>t-value</u>	<u>p-value</u>
<b>(Intercept)</b>	0.22765753	0.05284401	502	4.30810503	<b>1.9817E-05</b>
<b>Age</b>	-0.0019011	0.00063994	340	-2.9706982	<b>0.00318265</b>
<b>Head injury</b>	-0.0798858	0.04711481	502	-1.6955569	0.09058989
<b>Diagnostic group</b>	-0.0067217	0.00142905	340	-4.7036142	<b>3.7226E-06</b>
<b>Sex</b>	-0.0007196	0.00205209	502	-0.3506858	0.72597121
<b>Asian</b>	0.00200712	0.02609661	502	0.0769111	0.93872491
<b>Black or African American</b>	-0.0002634	0.02399443	502	-0.0109758	0.99124714
<b>White</b>	-0.0071988	0.0234287	502	-0.3072631	0.75877057
<b>More than one race</b>	-0.0130293	0.02459761	502	-0.5296978	0.59655562
<b>Not Hispanic or Latino</b>	-0.0047334	0.00591477	502	-0.8002712	0.42393225
<b>Unknown ethnicity</b>	-0.0063214	0.01742118	502	-0.3628549	0.71686598
<b>Education</b>	0.00038158	0.00042345	502	0.90113307	0.36794969
<b>APOE e4 positive</b>	-0.0281755	0.0020398	502	-13.81289	<b>5.1742E-37</b>
<b>Age/Head injury interaction</b>	0.00102913	0.00065058	340	1.58186356	0.11461047

Table A-12. Coefficients (summary) table from longitudinal linear mixed-effects model analysis of cerebrospinal fluid (CSF) amyloid- $\beta$ 42/40 (A $\beta$ 42/40).

	<u>Value</u>	<u>Std.Error</u>	<u>DF</u>	<u>t-value</u>	<u>p-value</u>
<b>(Intercept)</b>	-18.446127	15.6695267	1585	-1.1771975	0.23929344
<b>Age</b>	0.48892344	0.17682418	1468	2.76502591	<b>0.00576307</b>
<b>Head injury</b>	10.2245939	12.9867208	1585	0.78731144	0.43121728
<b>Diagnostic group</b>	2.04051175	0.35374481	1468	5.76831565	<b>9.7484E-09</b>
<b>Sex</b>	1.84076076	0.66547794	1585	2.76607332	<b>0.00573942</b>
<b>Asian</b>	7.18408657	9.23181555	1585	0.77818784	0.43657443
<b>Native Hawaiian or Other Pacific Islander</b>	-8.4658627	12.2519812	1585	-0.6909791	0.48967987
<b>Black or African American</b>	3.08256678	8.9189794	1585	0.34561878	0.72967509
<b>White</b>	5.40703488	8.759128	1585	0.61730287	0.53712364
<b>More than one race</b>	-0.0042129	9.25218223	1585	-0.0004553	0.99963675
<b>Unknown race</b>	2.89623055	11.3105907	1585	0.2560636	0.79793496
<b>Not Hispanic or Latino</b>	4.1659289	1.92926686	1585	2.15933264	0.03097398
<b>Unknown ethnicity</b>	0.79261367	4.91922968	1585	0.16112557	0.87201504
<b>Education</b>	-0.4009366	0.12544809	1585	-3.196036	<b>0.00142075</b>
<b>APOE e4 positive</b>	9.02010904	0.65788011	1585	13.7108705	<b>1.6245E-40</b>
<b>Age/Head injury interaction</b>	-0.1349428	0.18093688	1468	-0.7458005	0.45590732

Table A-13. Coefficients (summary) table from longitudinal linear mixed-effects model analysis of cerebrospinal fluid (CSF) phosphorylated Tau-181 (pTau-181).

	<u>Value</u>	<u>Std.Error</u>	<u>DF</u>	<u>t-value</u>	<u>p-value</u>
<b>(Intercept)</b>	-196.4577	140.585642	1587	-1.3974236	0.16248154
<b>Age</b>	5.29950238	1.59676179	1477	3.31890606	<b>0.00092571</b>
<b>Head injury</b>	96.1008374	117.148706	1587	0.82033205	0.41215004
<b>Diagnostic group</b>	19.4878417	3.45551244	1477	5.6396387	<b>2.0388E-08</b>
<b>Sex</b>	24.1034929	6.02549143	1587	4.00025345	<b>6.6186E-05</b>
<b>Asian</b>	63.5056681	81.9485878	1587	0.77494524	0.43848746
<b>Native Hawaiian or Other Pacific Islander</b>	-85.407443	109.942403	1587	-0.7768381	0.43737009
<b>Black or African American</b>	22.5202571	79.0409503	1587	0.28491885	0.77574349
<b>White</b>	51.1587877	77.6118117	1587	0.6591624	0.50988712
<b>More than one race</b>	-2.1839526	82.1451617	1587	-0.0265865	0.97879288
<b>Unknown race</b>	26.7675029	100.122574	1587	0.26734733	0.78923649
<b>Not Hispanic or Latino</b>	36.7697592	17.3861332	1587	2.11489	0.03459484
<b>Unknown ethnicity</b>	0.71017758	44.333875	1587	0.01601885	0.98722137
<b>Education</b>	-3.1857624	1.13456241	1587	-2.8079217	<b>0.00504726</b>
<b>APOE e4 positive</b>	74.6616675	5.96033048	1587	12.5264308	<b>2.1377E-34</b>
<b>Age/Head injury interaction</b>	-1.3329418	1.63362595	1477	-0.8159406	0.41466567

Table A-14. Coefficients (summary) table from longitudinal linear mixed-effects model analysis of cerebrospinal fluid (CSF) total tau.

	<u>Value</u>	<u>Std.Error</u>	<u>DF</u>	<u>t-value</u>	<u>p-value</u>
<b>(Intercept)</b>	0.13183656	0.01790589	538	7.36274933	<b>6.7974E-13</b>
<b>Age</b>	5.3227E-05	0.00021183	283	0.2512673	0.8017898
<b>Head injury</b>	-0.0015785	0.01583403	538	-0.09969	0.92062755
<b>Diagnostic group</b>	0.00048308	0.00089135	283	0.54196643	0.58826809
<b>Sex</b>	0.00096815	0.00090351	538	1.07154293	0.28440582
<b>Asian</b>	-0.0022627	0.00967201	538	-0.2339439	0.81511752
<b>Black or African American</b>	-0.001292	0.00914016	538	-0.1413547	0.88764263
<b>White</b>	-0.005719	0.00883915	538	-0.6470036	0.51790553
<b>More than one race</b>	-0.0040043	0.00968375	538	-0.4135088	0.67939864
<b>Unknown race</b>	0.01054559	0.01547177	538	0.68160197	0.49578397
<b>Not Hispanic or Latino</b>	-0.0078873	0.00265203	538	-2.9740398	<b>0.00307091</b>
<b>Unknown ethnicity</b>	-0.0098502	0.00765313	538	-1.2870794	0.1986201
<b>Education</b>	3.8788E-05	0.00017387	538	0.22308918	0.82355077
<b>APOE e4 positive</b>	-0.000639	0.00093326	538	-0.6847511	0.4937959
<b>Age/Head injury interaction</b>	7.6579E-06	0.00021974	283	0.03484946	0.97222435

Table A-15. Coefficients (summary) table from longitudinal linear mixed-effects model analysis of blood plasma amyloid- $\beta$ 42/40 (A $\beta$ 42/40).

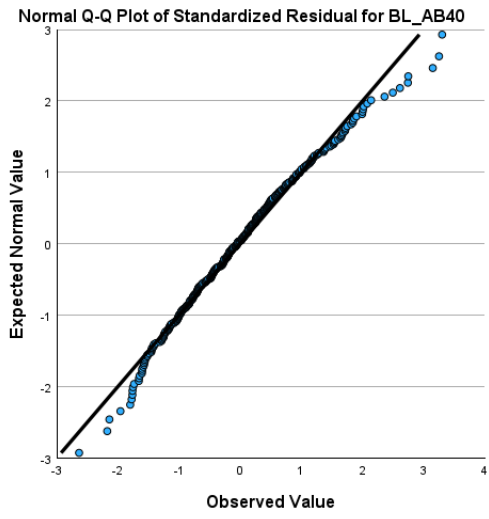
	<u>Value</u>	<u>Std.Error</u>	<u>DF</u>	<u>t-value</u>	<u>p-value</u>
<b>(Intercept)</b>	-53.661715	23.0784171	2692	-2.3251904	<b>0.02013576</b>
<b>Age</b>	1.45018249	0.27173771	2692	5.33669947	<b>1.0254E-07</b>
<b>Head injury</b>	-4.3169304	19.9049478	1570	-0.2168773	0.82833218
<b>Diagnostic group</b>	8.62573747	0.9272506	2692	9.30248785	<b>2.7535E-20</b>
<b>Sex</b>	3.32092923	0.9846672	1570	3.37264128	<b>0.00076261</b>
<b>Asian</b>	-14.012427	12.4849001	1570	-1.12235	0.26188528
<b>Native Hawaiian or Other Pacific Islander</b>	-29.690747	17.0927442	1570	-1.7370381	0.08257658
<b>Black or African American</b>	-23.458485	12.1591164	1570	-1.9292919	0.05387466
<b>White</b>	-17.656679	11.9370227	1570	-1.4791526	0.13930013
<b>More than one race</b>	-18.569971	12.6244422	1570	-1.4709538	0.14150401
<b>Unknown race</b>	-24.108257	14.0205788	1570	-1.7194909	0.08572213
<b>Not Hispanic or Latino</b>	1.505501	2.77771331	1570	0.54199294	0.58790028
<b>Unknown ethnicity</b>	-0.2917959	7.87603509	1570	-0.0370486	0.97045098
<b>Education</b>	-0.0410096	0.17892346	1570	-0.2292018	0.81874191
<b>APOE e4 positive</b>	3.35400707	0.97328619	1570	3.44606459	<b>0.00058381</b>
<b>Age/Head injury interaction</b>	0.00788258	0.27978272	2692	0.02817392	0.97752553

Table A-16. Coefficients (summary) table from longitudinal linear mixed-effects model analysis of blood plasma neurofilament light chain (NfL).

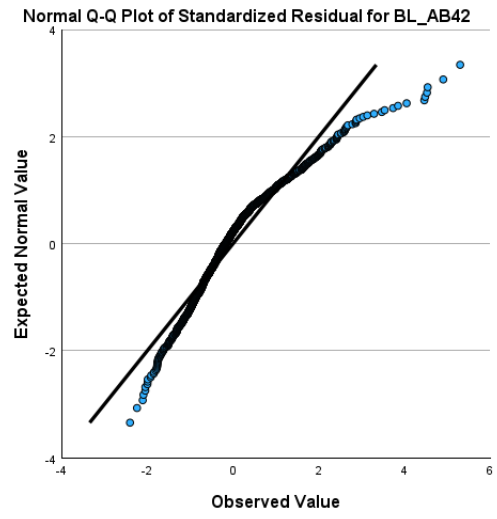
	<u>Value</u>	<u>Std.Error</u>	<u>DF</u>	<u>t-value</u>	<u>p-value</u>
<b>(Intercept)</b>	-13.793179	14.8483323	2507	-0.9289379	0.35301069
<b>Age</b>	0.37716201	0.16698525	2507	2.25865468	<b>0.02399047</b>
<b>Head injury</b>	4.28724009	12.5548323	1177	0.34148127	0.73280226
<b>Diagnostic group</b>	3.22288238	0.53652192	2507	6.00699102	<b>2.1646E-09</b>
<b>Sex</b>	-1.4349217	0.61142474	1177	-2.3468492	<b>0.01909798</b>
<b>Asian</b>	-0.2501229	8.47398109	1177	-0.0295166	0.97645761
<b>Native Hawaiian or Other Pacific Islander</b>	-7.9954197	10.6218337	1177	-0.7527344	0.45176005
<b>Black or African American</b>	2.82543381	8.30957321	1177	0.34002153	0.73390098
<b>White</b>	2.39148419	8.18103472	1177	0.2923205	0.7700931
<b>More than one race</b>	-0.2928822	8.57342609	1177	-0.0341616	0.97275405
<b>Unknown race</b>	-3.2418232	9.63473914	1177	-0.3364723	0.73657468
<b>Not Hispanic or Latino</b>	0.53089796	1.639331	1177	0.32385038	0.74610885
<b>Unknown ethnicity</b>	0.6439274	5.01050516	1177	0.12851546	0.89776302
<b>Education</b>	-0.1569585	0.11366847	1177	-1.3808442	0.16758899
<b>APOE e4 positive</b>	4.82914685	0.60051973	1177	8.04161235	<b>2.1452E-15</b>
<b>Age/Head injury interaction</b>	-0.0485126	0.17233539	2507	-0.2815009	0.77834949

Table A-17. Coefficients (summary) table from longitudinal linear mixed-effects model analysis of blood plasma phosphorylated Tau-181 (pTau-181).

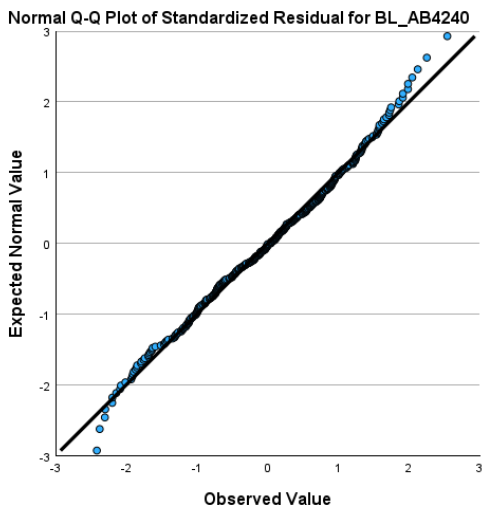
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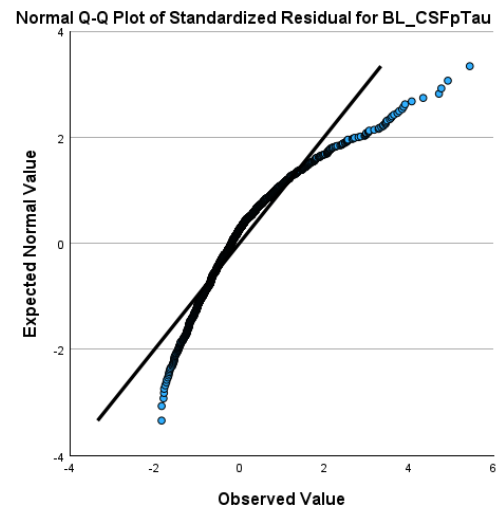
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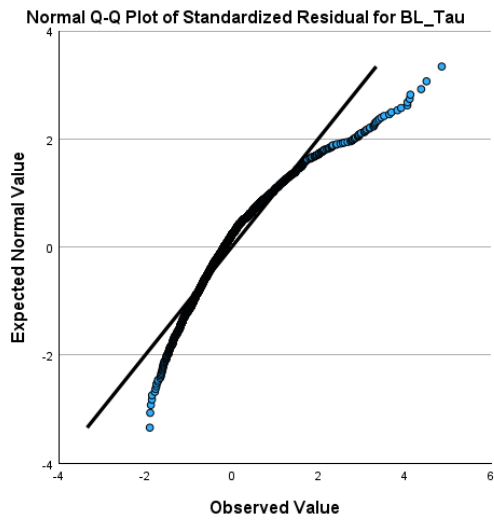
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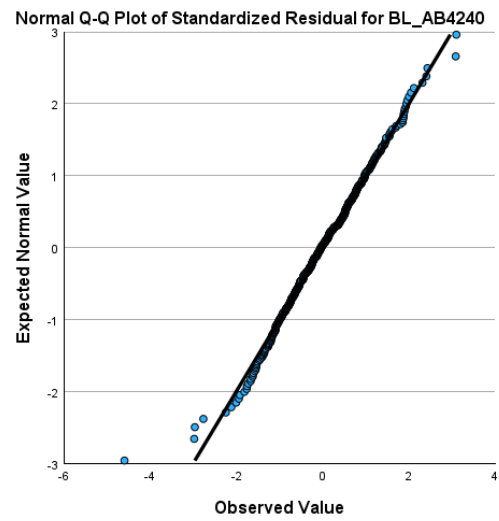
d



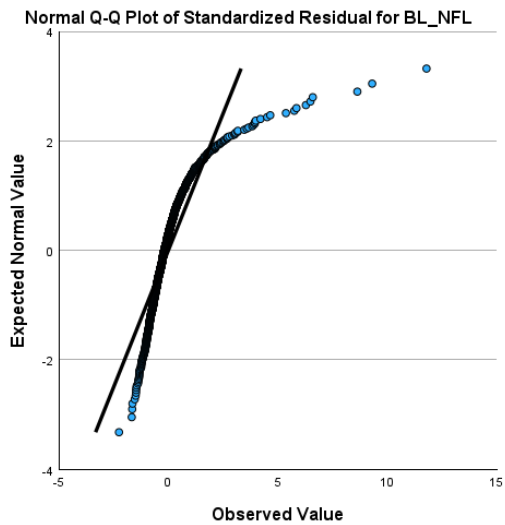
e



f



g



h

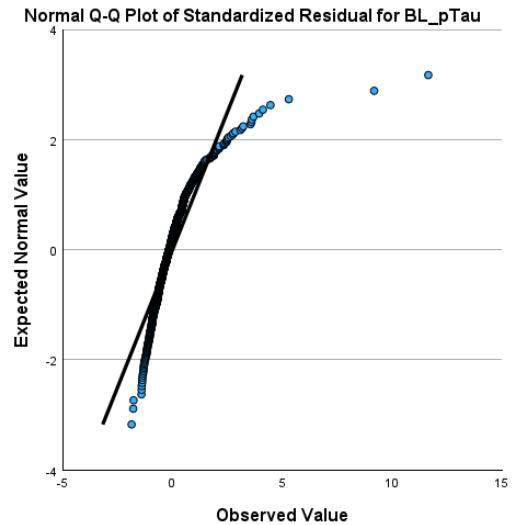
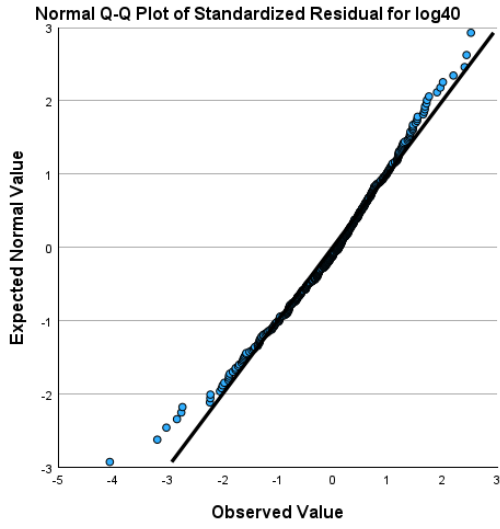
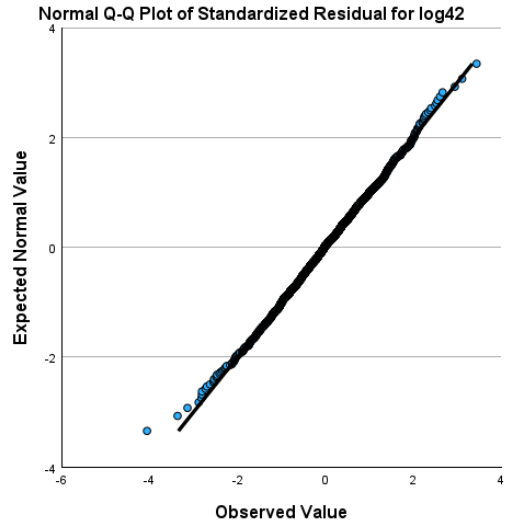


Figure A-1. Residual QQ plots from baseline cross-sectional two-way ANCOVA analyses of cerebrospinal fluid (CSF) amyloid- $\beta$ 40 ( $A\beta$ 40) (a), CSF amyloid- $\beta$ 42 ( $A\beta$ 42) (b), CSF amyloid- $\beta$ 42/40 ( $A\beta$ 42/40) (c), CSF pTau-181 (d), CSF total tau (e), plasma amyloid- $\beta$ 42/40 ( $A\beta$ 42/40) (f), plasma neurofilament light chain (NfL) (g), and plasma pTau-181 (h).

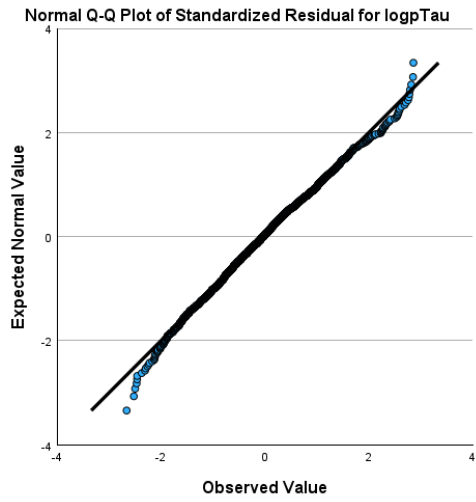
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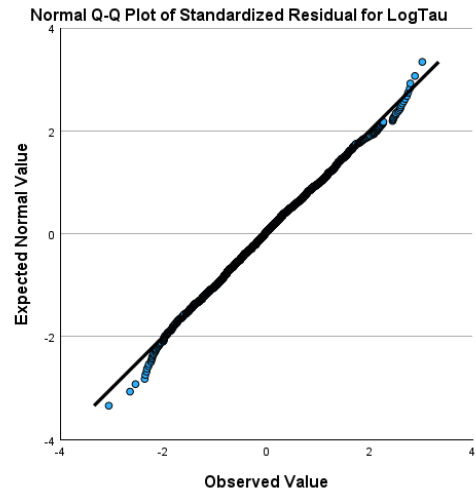
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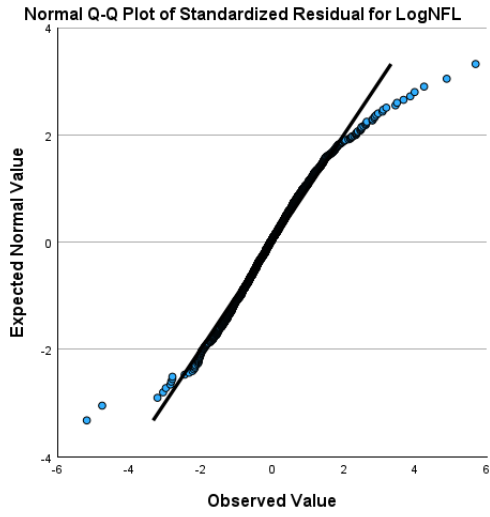
c



d



e



f

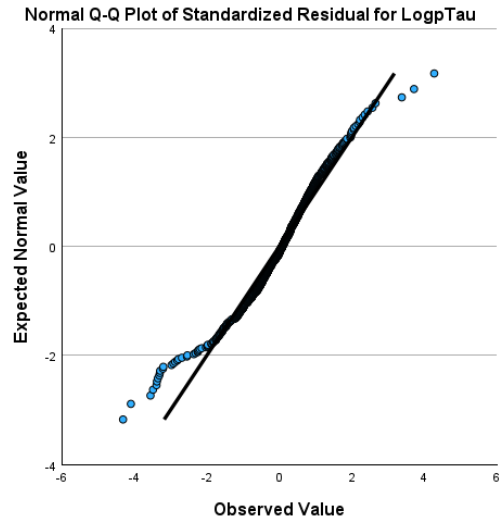
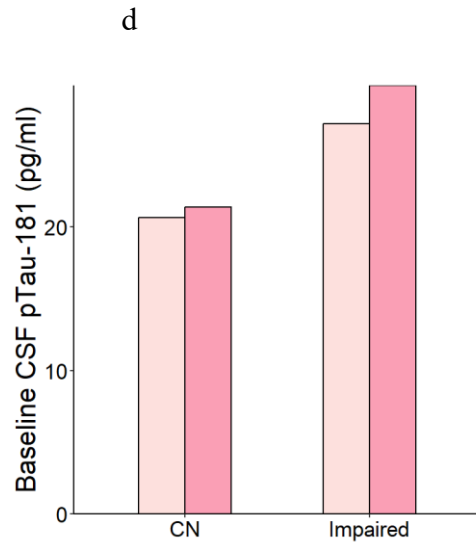
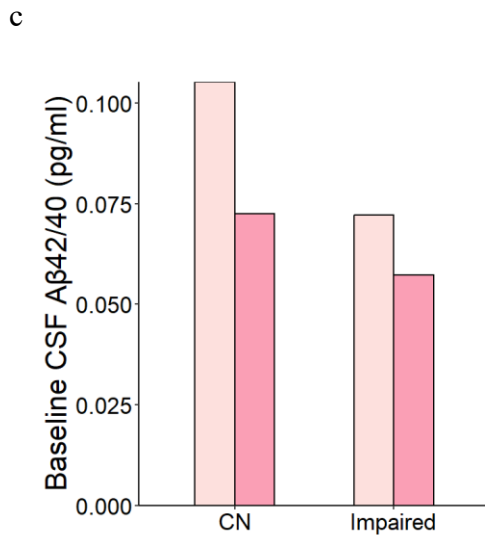
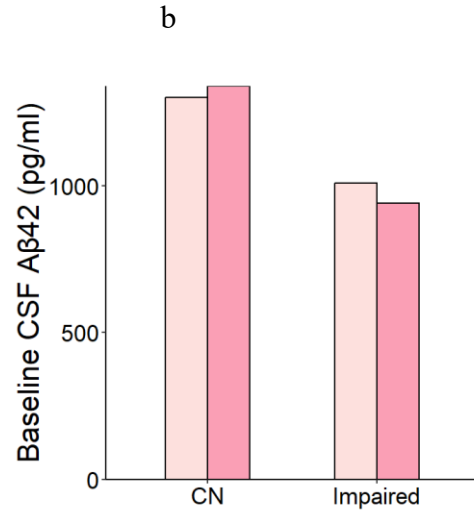
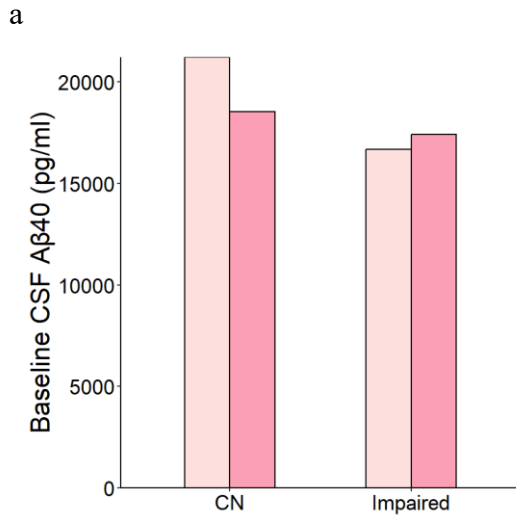


Figure A-2. Residual QQ plots from baseline cross-sectional two-way ANCOVA analyses of log-transformed cerebrospinal fluid (CSF) amyloid- $\beta$ 40 ( $A\beta$ 40) (a), CSF amyloid- $\beta$ 42 ( $A\beta$ 42) (b), CSF pTau-181 (c), CSF total tau (d), plasma neurofilament light chain (NfL) (e), and plasma pTau-181 (f).



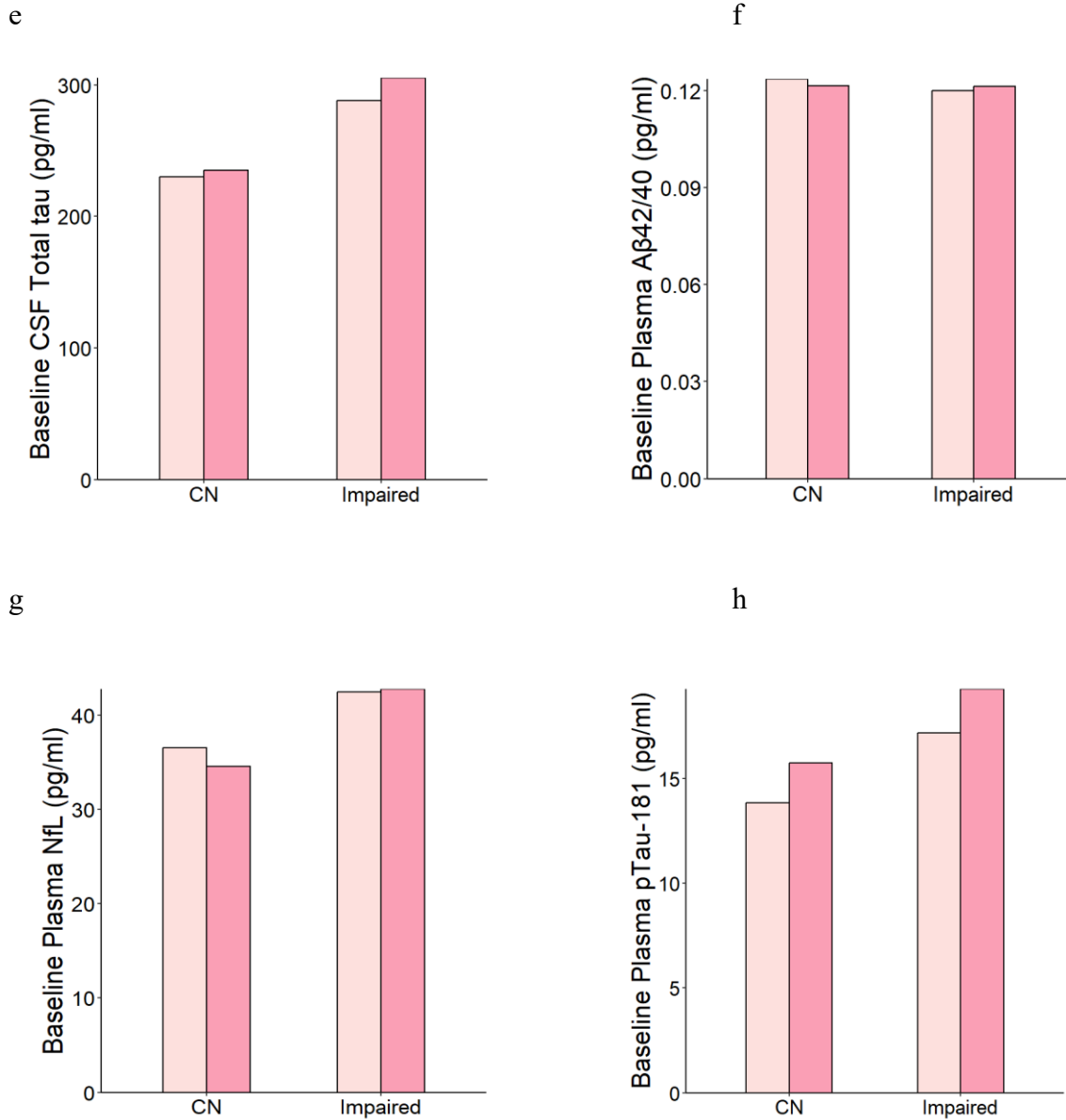


Figure A-3. Cerebrospinal fluid (CSF) amyloid- $\beta$ 40 (A $\beta$ 40) (a), CSF amyloid- $\beta$ 42 (A $\beta$ 42) (b), CSF amyloid- $\beta$ 42/40 (A $\beta$ 42/40) (c), CSF pTau-181 (d), CSF total tau (e), plasma amyloid- $\beta$ 42/40 (A $\beta$ 42/40) (f), plasma neurofilament light chain (NfL) (g), and plasma pTau-181 (h) analyzed cross-sectionally at baseline based on head injury and cognition (light pink = head injury; dark pink = non-head injury).

## Appendix B

Text B-1. Sensitivity analysis to assess whether including scans with large intervals between visit and scan would significantly influence the results.

For participants with only one completed study visit, the scan and study visit dates were sometimes very far apart. A variable, “Interval”, was created to classify scans based on the time between scan and study visit. Scans were divided into categories: those with an interval of less than 365 days ( $n = 715$ ), those with an interval of 365 to 730 days ( $n = 30$ ), and those with an interval greater than 730 days ( $n = 4$ ). To perform our sensitivity analysis, out of 162 total regions of interest (ROIs), we removed 47 that included areas known to demonstrate off-target binding of tau radiotracers (e.g., caudate, pallidum, putamen, thalamus), white matter regions (corpus callosum, cortical white matter), ventricles and vessels, and cerebellar regions. This left a total of 115 ROIs.

We ran two-way ANCOVAs using R 2024.12.0. Tau in each individual brain region was the dependent variable, and TBI status (yes or no) and cognitive status (cognitively normal, mild cognitive impairment (MCI) or dementia) were the independent variables. We tested the main effects and the interaction of TBI and cognitive status. Covariates included sex, race, the age of the participant on the day of the tau scan, years of education, Hispanic/Latino (yes, no, or unknown), and *APOE* genotype. We applied false discovery rate (FDR) multiple testing correction. The data were analyzed in three ways: using all scans ( $n = 729$ ), using scans with less than 730 days

between visit and scan ( $n = 725$ ), and using scans with less than 365 days between visit and scan ( $n = 698$ ).

When all scans were included, the cortical pericalcarine ROI ( $p = 0.0169$ ) and right hemisphere (RH) pericalcarine ROI ( $p = 0.0085$ ) showed significant differences between TBI and non-TBI participants before correction. The TBI group had lower right hemisphere pericalcarine SUVRs (mean = 1.0483) than the non-TBI group (mean = 1.1179) ( $t = 2.6989$ ,  $df = 747$ ,  $p = 0.0071$ ). The TBI group also had lower cortical pericalcarine SUVRs (mean = 1.0530) than the non-TBI group (mean = 1.1118) ( $t = 2.4776$ ,  $df = 747$ ,  $p = 0.01345$ ). Neither region maintained significance after correction. The pattern was consistent when comparing only the scans with less than 730 days between scan and visit, and when comparing the scans with less than 365 days between scan and visit. The cortex pericalcarine and right hemisphere pericalcarine ROIs showed significant differences in tau SUVRs before correction but no longer were significant after correction. In all three analysis iterations, there were significant interactions between TBI and cognitive diagnosis for eight ROIs encompassing the parahippocampal gyrus, entorhinal cortex, and fusiform gyrus, but none survived correction. In sum, no ROI showed significant differences in tau between TBI and non-TBI participants, nor were there any significant interactions between TBI and cognitive diagnosis, after FDR correction. Further, we did not observe a significant influence of scans with large intervals on the results.

<u>Region of Interest</u>	<u>Hemisphere</u>	<u>Time since TBI p-value</u>	<u>Diagnosis p-value</u>	<u>Time since TBI*Diagnosis p-value</u>
Entorhinal cortex	L	0.5708	< <b>0.0001</b>	0.4269
	R	0.5527	< <b>0.0001</b>	0.1496
Fusiform gyrus	L	0.4620	< <b>0.0001</b>	0.1950
	R	0.5040	< <b>0.0001</b>	0.1360
Inferior temporal gyrus	L	0.1930	< <b>0.0001</b>	0.4240
	R	0.2200	< <b>0.0001</b>	0.2400
Middle temporal gyrus	L	0.1020	< <b>0.0001</b>	0.1990
	R	0.1562	< <b>0.0001</b>	0.0906
Amygdala	L	0.7742	< <b>0.0001</b>	0.8377
	R	0.6876	< <b>0.0001</b>	0.2479
Meta-temporal		0.2500	< <b>0.0001</b>	0.1830

Table B-1. Results of two-way ANCOVAs analyzing the main effects of cognition and time since injury, and their interaction, on tau levels.

<b><u>Region of Interest</u></b>	<b><u>Hemisphere</u></b>	<b><u>LOC p-value</u></b>	<b><u>Diagnosis p-value</u></b>	<b><u>LOC*Diagnosis p-value</u></b>
Entorhinal cortex	L	0.1098	< <b>0.0001</b>	0.6653
	R	0.1470	< <b>0.0001</b>	0.5490
Fusiform gyrus	L	0.9640	< <b>0.0001</b>	0.9990
	R	0.9640	< <b>0.0001</b>	0.9660
Inferior temporal gyrus	L	0.5450	< <b>0.0001</b>	0.6400
	R	0.7740	< <b>0.0001</b>	0.6560
Middle temporal gyrus	L	0.5080	< <b>0.0001</b>	0.7200
	R	0.7016	< <b>0.0001</b>	0.3732
Amygdala	L	0.8641	< <b>0.0001</b>	0.6182
	R	0.9346	< <b>0.0001</b>	0.5965
Meta-temporal		0.6750	< <b>0.0001</b>	0.9430

Table B-2. Results of two-way ANCOVAs analyzing the main effects of cognition and loss of consciousness (LOC; yes or no) and the interaction of cognition and LOC on tau levels.

<u>Region of Interest</u>	<u>Hemisphere</u>	<u>Pediatric vs. adult p-value</u>	<u>Diagnosis p-value</u>	<u>Pediatric vs. adult*Diagnosis p-value</u>	<u>Post-hoc</u>
Entorhinal cortex	L	0.4297	< <b>0.0001</b>	0.6112	
	R	0.3731	< <b>0.0001</b>	0.3980	
Fusiform gyrus	L	0.6690	< <b>0.0001</b>	0.2700	
	R	0.5859	< <b>0.0001</b>	0.1511	
Inferior temporal gyrus	L	0.7870	< <b>0.0001</b>	0.1050	
	R	0.6805	< <b>0.0001</b>	<b>0.0099</b>	Dementia juvenile 2.25 (SE 0.212), dementia adult 1.72 (SE 0.169), difference 0.532018 (SE 0.182), p = 0.0046
Middle temporal gyrus	L	0.9240	< <b>0.0001</b>	0.3050	
	R	0.5204	< <b>0.0001</b>	<b>0.0064</b>	Dementia juvenile 2.17 (SE 0.178), dementia adult 1.64 (SE 0.142), difference 0.5322 (SE 0.1534), p = 0.0008
Amygdala	L	0.9357	< <b>0.0001</b>	0.7564	
	R	0.7721	< <b>0.0001</b>	0.5125	
Meta-temporal		0.8370	< <b>0.0001</b>	0.0770	

Table B-3. Results of two-way ANCOVAs analyzing the main effects of cognition and age at injury (juvenile/under 18 vs adult/over 18) and the interaction of cognition and age at injury on tau levels.

## Appendix C

	FLOC+	FLOC-	MLOC+	MLOC-	N (%)
Total number of participants	15	341	24	551	931
<i>Sport</i>					
Baseball	-	-	1	21	22
Basketball	1	35	-	18	54
Beach volleyball	-	1	-	-	1
Boxing	-	-	-	2	2
Cheerleading	-	17	-	4	21
Cross country/track	-	6	-	31	37
Diving	-	11	-	6	17
Fencing	-	2	-	1	3
Field event	-	6	-	2	8
Field hockey	1	16	-	-	17
Football	-	-	5	262	267
Golf	-	2	-	-	2
Gymnastics	3	12	-	5	20
Ice hockey	-	-	-	15	15
Lacrosse	-	24	2	29	55
Rowing/crew	-	7	-	-	7
Rugby	-	11	2	13	26
Soccer	7	59	5	50	121
Softball	-	23	-	-	23
Sprint football	-	-	-	1	1
Swimming	-	12	-	7	19
Tennis	-	5	1	4	10
Track/field	3	-	-	-	3
Volleyball	-	39	-	5	44
Water polo	-	18	-	8	26

Wrestling	-	-	1	22	23
Blank/military student	-	35	7	45	87

Table C-1. Number of participants in the sample of 931, subdivided by sport participation.

rsID	# participants missing SNP in full GWAS (n = 4108)	# participants missing SNP in study sample (n = 931)
rs4844610	43	9
rs876461	104	21
rs6733839	46	12
rs10933431	1481	315
rs4351014	390	88
rs9275152	57	9
rs143332484	0	0
rs75932628	2	1
rs9381040	16	3
rs9381564	340	85
rs1859788	1073	252
rs56402156	0	0
rs73223431	50	12
rs9331896	26	7
rs34674752	320	79
rs34173062	890	210
rs7920721	120	22
rs3740688	122	31
rs1582763	183	48
rs3851179	6	2
rs11218343	12	5
rs17125924	109	21
rs11623019	200	48
rs593742	720	160
rs117618017	798	210
rs7185636	993	205
rs4985556	484	119
rs12444183	94	18
rs3935877	270	57
rs72824905	40	12
rs72835061	84	19
rs75511804	0	0
rs4311	18	2
rs3752231	286	76
rs12459419	48	8
rs6024870	135	34
rs2154481	477	113

Table C-2. Number of participants from full GWAS sample (n = 4108) and the subsample of participants in this project (n = 931) who had missing data for 37 included alleles (excluded alleles: rs2732703 (duplicated), rs616338). In the full GWAS sample, the average number of missed SNPs for a participant was 2.44, and in the study sample the average number of missed SNPs for a participant was 2.48.

Analysis	Estimate (β)	Standard error (SE)	T value	P	R <sup>2</sup>	Covariate F value (p)
PRS & days to normal RTP	0.349	0.180	1.935	0.054	Mult. 0.062 Adj. 0.050	<u>Ancestry</u> 1.564 (0.182) <u>Sex</u> 1.327 (0.250) <u>LOC</u> 2.001 (0.136) <u>Mil vs. Civ</u> 28.801 (< <b>0.001</b> ) (mil>civ; estimate = 2.210, SE = 0.413)
PRS & days to long RTP	0.013	2.790	0.005	0.996	Mult. 0.024 Adj. -0.012	<u>Ancestry</u> 1.444 (0.231) <u>Sex</u> 0.011 (0.916) <u>LOC</u> 0.077 (0.926) <u>Mil vs. Civ</u> 0.772 (0.381)
PRS & days to asymptomatic	-0.337	0.413	-0.816	0.415	Mult. 0.053 Adj. 0.043	<u>Ancestry</u> 2.684 ( <b>0.030</b> ) (EAS>EUR, estimate = 5.297, SE = 1.76) <u>Sex</u> 10.044 ( <b>0.002</b> ) (female>male, estimate = 3.360, SE = 0.872) <u>LOC</u> 0.1065 (0.899) <u>Mil vs. Civ</u> 25.9778 (< <b>0.001</b> ) (mil>civ; estimate = 4.750, SE = 0.932)
PRS & BESS total score	0.124	0.251	0.495	0.621	Mult. 0.047 Adj. 0.037	<u>Ancestry</u> 0.751 (0.557) <u>Sex</u> 0.905 (0.342) <u>LOC</u> 13.170 (< <b>0.001</b> ) (no LOC>unknown LOC status; estimate = 3.460, SE = 0.752) <u>Mil vs. Civ</u> 12.607 (< <b>0.001</b> ) (mil>civ; estimate = 2.00, SE = 0.563)
PRS & SAC total score	0.001	0.080	0.018	0.986	Mult. 0.040 Adj. 0.030	<u>Ancestry</u> 1.413 (0.540) <u>Sex</u> 0.148 (0.228) <u>LOC</u> 12.288 (< <b>0.001</b> ) (LOC & no LOC<unknown; estimates = 1.805 & 1.158, SE = 0.444 & 0.242) <u>Mil vs. Civ</u> 7.011 ( <b>0.008</b> ) (mil>civ; estimate = 0.474, SE = 0.179)
PRS & SCATSYMP	-0.137	0.273	-0.503	0.615	Mult. 0.019 Adj. 0.002	<u>Ancestry</u> 0.386 (0.763) <u>Sex</u> 2.494 (0.115) <u>LOC</u> 2.351 (0.096) <u>Mil vs. Civ</u> 0.057 (0.812)
PRS & SCATSEV	-0.202	0.895	-0.226	0.821	Mult. 0.020 Adj. 0.003	<u>Ancestry</u> 0.874 (0.454) <u>Sex</u> 2.600 (0.108) <u>LOC</u> 1.776 (0.171) <u>Mil vs. Civ</u> 0.357 (0.551)

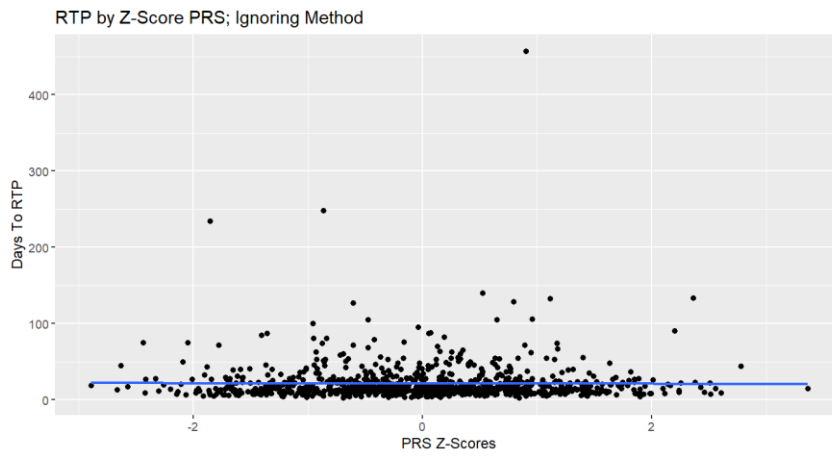
Table C-3. Summary of outcomes of linear regression analyses with covariates (PRS = polygenic risk score; RTP = return to play; BESS = balance error scoring system; SAC = standardized assessment of concussion; SCATSEV = symptom severity score on the sport concussion assessment tool (SCAT); SCATSYMP = total number of symptoms score on the SCAT; LOC = loss of consciousness; Mil = participant of military origin; Civ = participant of civilian origin, EAS = East Asians, EUR = Europeans, AFR = Africans, AMR = Admixed Americans, SAS = South Asians).

Analysis	n participants	F value (p)	Covariate F value (p)
Normal RTP	417 $\epsilon 3/\epsilon 3$ 77 $\epsilon 2$ carriers 183 $\epsilon 4$ carriers	1.099 (0.334)	<u>Ancestry</u> 0.588 (0.443) <u>Sex</u> 7.989 ( <b>0.005</b> ) <u>LOC</u> 3.270 (0.071) <u>Mil vs. Civ</u> 27.242 ( <b>&lt;0.001</b> )
Long RTP	131 $\epsilon 3/\epsilon 3$ 32 $\epsilon 2$ carriers 60 $\epsilon 4$ carriers	0.107 (0.899)	<u>Ancestry</u> 2.226 (0.137) <u>Sex</u> 0.057 (0.811) <u>LOC</u> 0.084 (0.773) <u>Mil vs. Civ</u> 0.591 (0.443)
Time to asymptomatic	508 $\epsilon 3/\epsilon 3$ 98 $\epsilon 2$ carriers 221 $\epsilon 4$ carriers	0.186 (0.831)	<u>Ancestry</u> 5.972 ( <b>0.015</b> ) <u>Sex</u> 14.622 ( <b>&lt;0.001</b> ) <u>LOC</u> 0.047 (0.828) <u>Mil vs. Civ</u> 23.198 ( <b>&lt;0.001</b> )
BESS total score	528 $\epsilon 3/\epsilon 3$ 101 $\epsilon 2$ carriers 230 $\epsilon 4$ carriers	0.089 (0.915)	<u>Ancestry</u> 1.448 (0.229) <u>Sex</u> 0.970 (0.325) <u>LOC</u> 7.008 ( <b>0.008</b> ) <u>Mil vs. Civ</u> 14.529 ( <b>&lt;0.001</b> )
SAC total score	541 $\epsilon 3/\epsilon 3$ 109 $\epsilon 2$ carriers 238 $\epsilon 4$ carriers	0.104 (0.901)	<u>Ancestry</u> 0.365 (0.546) <u>Sex</u> 3.091 (0.079) <u>LOC</u> 23.366 ( <b>&lt;0.001</b> ) <u>Mil vs. Civ</u> 6.555 ( <b>0.011</b> )
SCATSYMP	280 $\epsilon 3/\epsilon 3$ 55 $\epsilon 2$ carriers 123 $\epsilon 4$ carriers	0.396 (0.673)	<u>Ancestry</u> 0.189 (0.664) <u>Sex</u> 2.024 (0.155) <u>LOC</u> 4.255 ( <b>0.040</b> ) <u>Mil vs. Civ</u> 0.018 (0.895)
SCATSEV	280 $\epsilon 3/\epsilon 3$ 55 $\epsilon 2$ carriers 123 $\epsilon 4$ carriers	1.336 (0.264)	<u>Ancestry</u> 0.046 (0.830) <u>Sex</u> 1.336 (0.248) <u>LOC</u> 2.058 (0.152) <u>Mil vs. Civ</u> 0.584 (0.445)

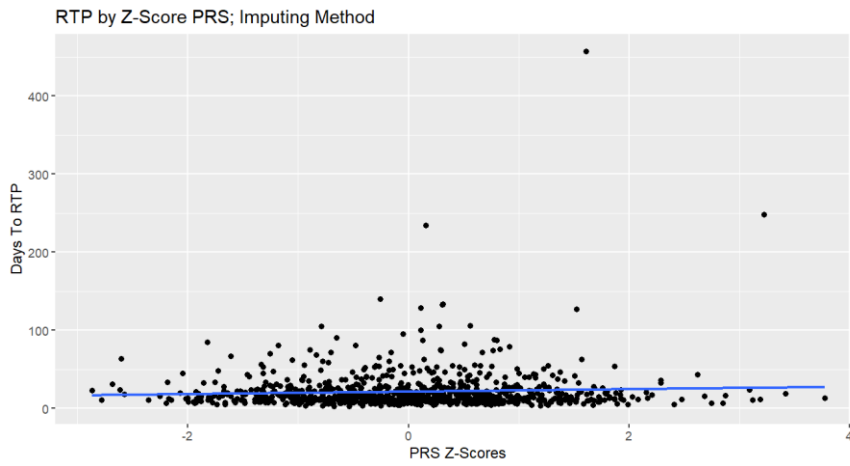
Table C-4. Results from ANOVAs of outcomes by apolipoprotein E (*APOE*) genotype ( $\epsilon 3/\epsilon 3$  vs  $\epsilon 2$  carriers vs  $\epsilon 4$  carriers), with covariates of sex (male vs. female), loss of consciousness (LOC) status, participant type (military or civilian origin), and genetic ancestry (BESS = balance error scoring system; RTP = return to play; SAC = standardized assessment of concussion; SCATSEV = symptom severity score on the sport concussion assessment tool (SCAT); SCATSYMP = total number of symptoms

score on the SCAT, Mil = participant of military origin; Civ = participant of civilian origin, EAS = East Asians, EUR = Europeans, AFR = Africans, AMR = Admixed Americans, SAS = South Asians).

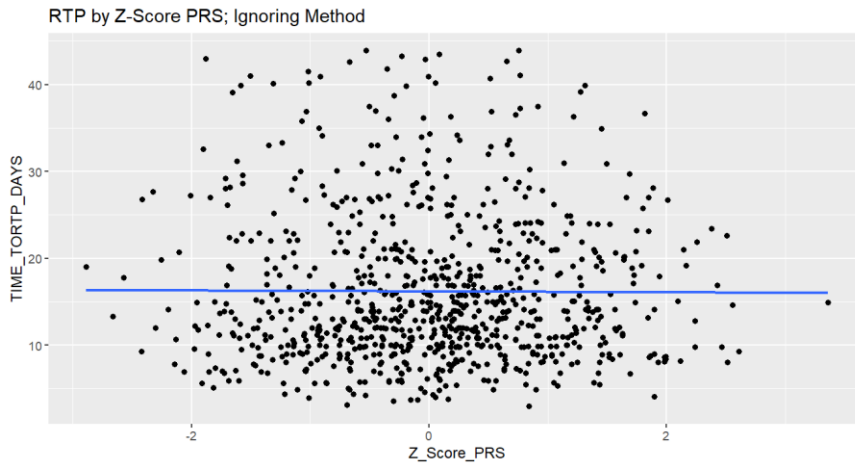
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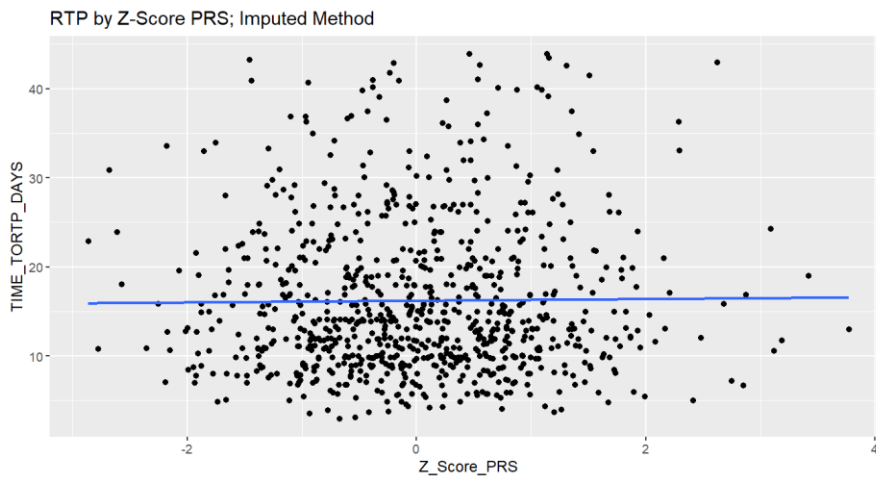
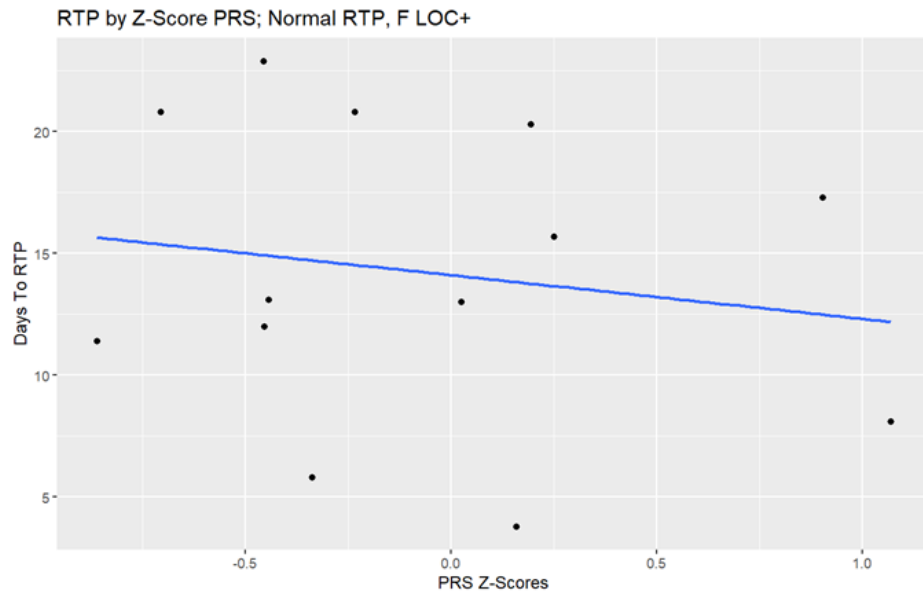


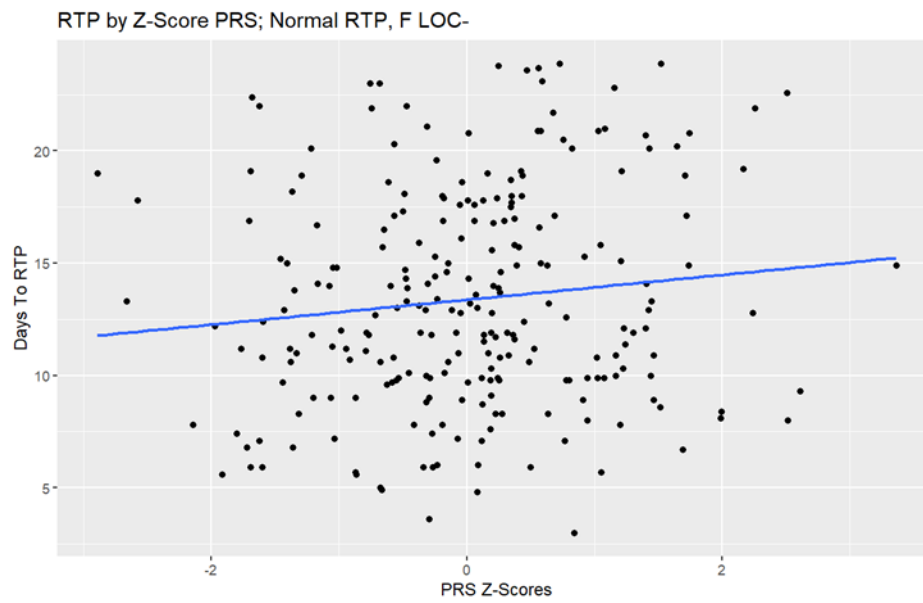
Figure C-1. Sensitivity analysis of missing SNP data handling methods. In (a) and (b), linear regressions to test the relationship between RTP and AD PRS were performed on the full 931 participants using two methods for handling missing SNP data: the ignoring method (PRS value of missing SNP is replaced with 0) (a) and the mean substitution method (PRS value of missing SNP is replaced with the mean score for that SNP from all other participants) (b). For the ignoring method, there was no significant relationship ( $p = 0.8152$ ). The relationship approached significance using the mean substitution method ( $p$

= 0.05314). These tests were repeated using a subsample of participants with outliers removed by R (c and d). There were no significant relationships using the ignoring method ( $p = 0.8605$ ) (c) or the mean substitution method ( $p = 0.7352$ ) (d).

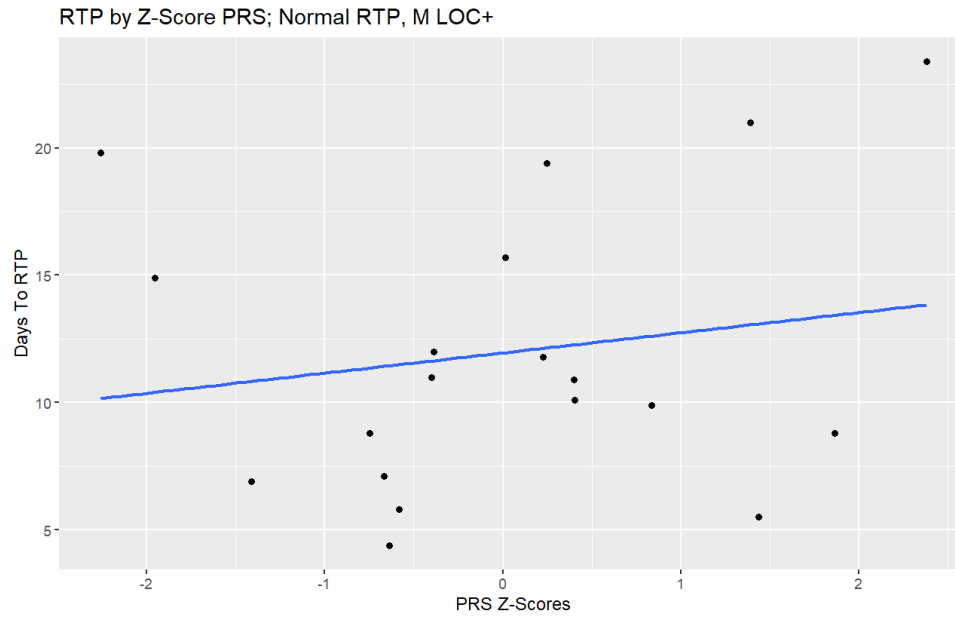
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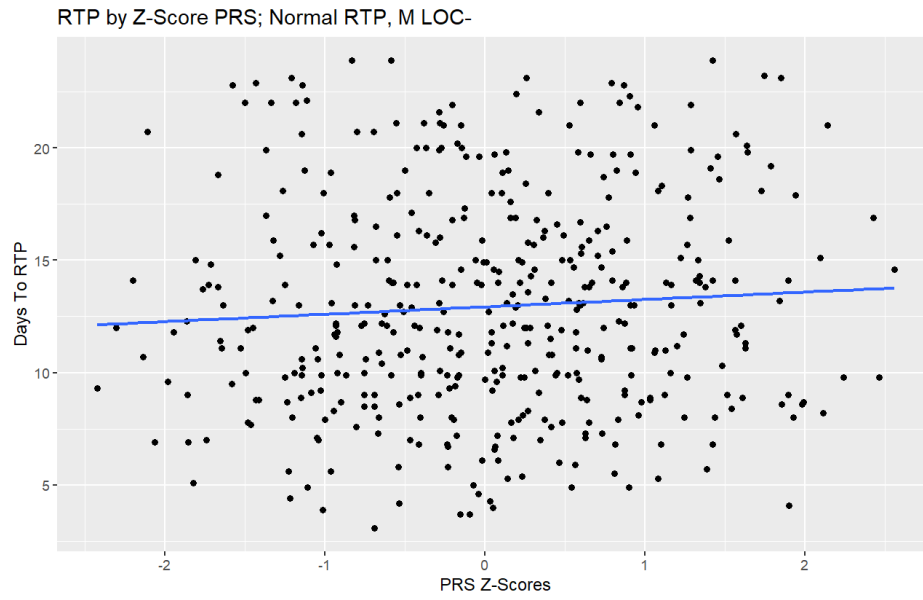
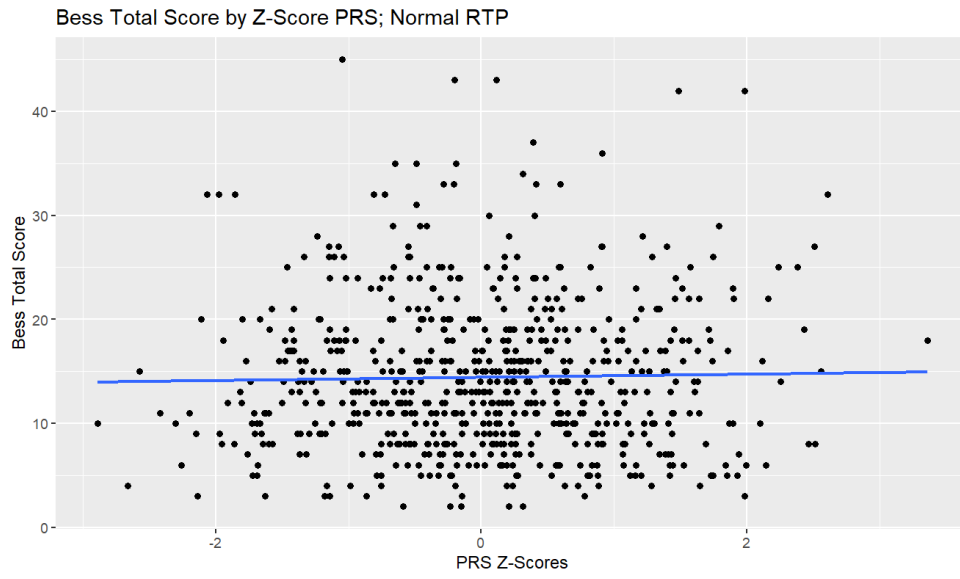
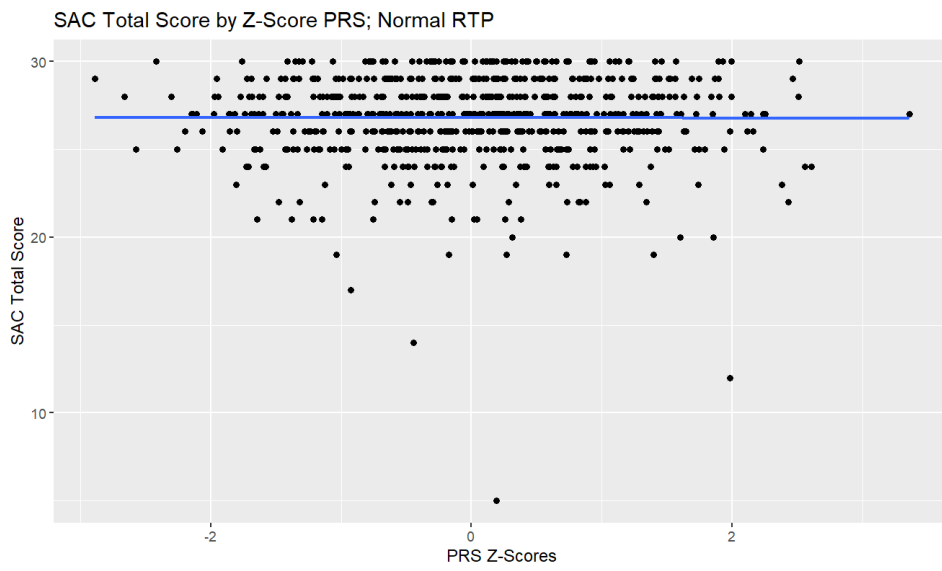


Figure C-2. AD PRS & normal RTP interval in F LOC+ (a), F LOC- (b), M LOC+ (c), and M LOC- (d) participant subgroups.

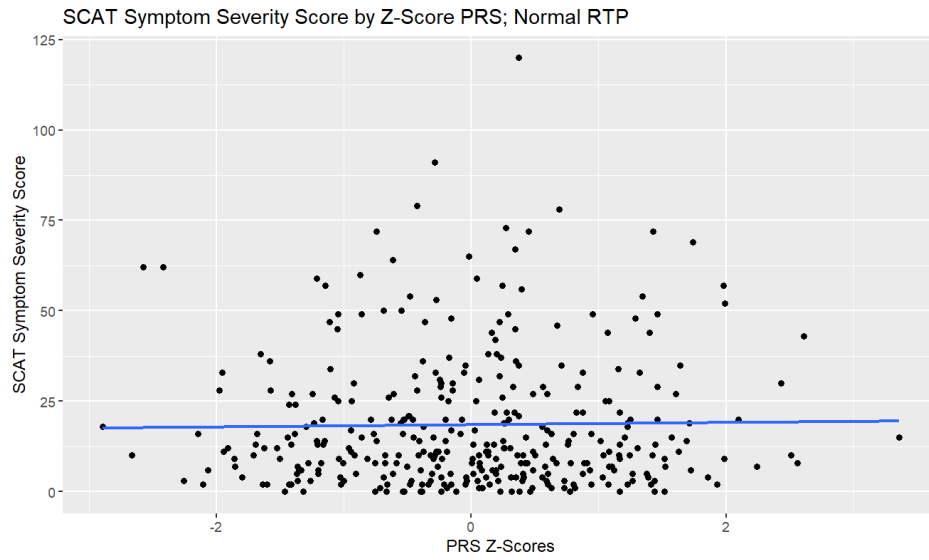
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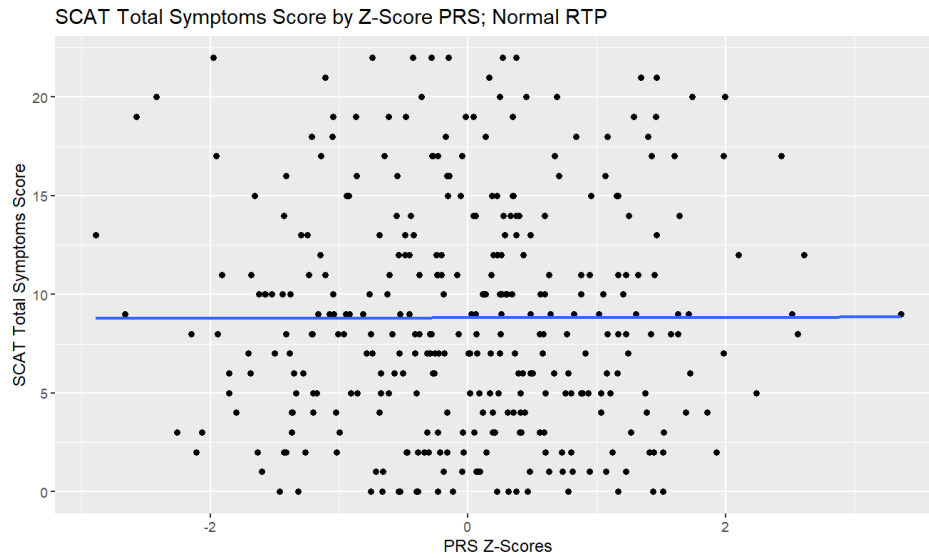
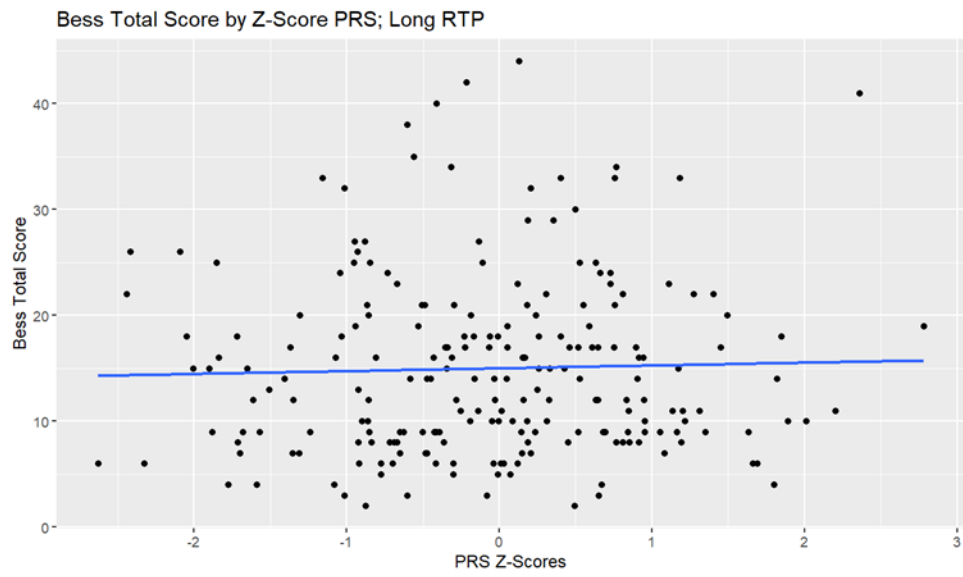
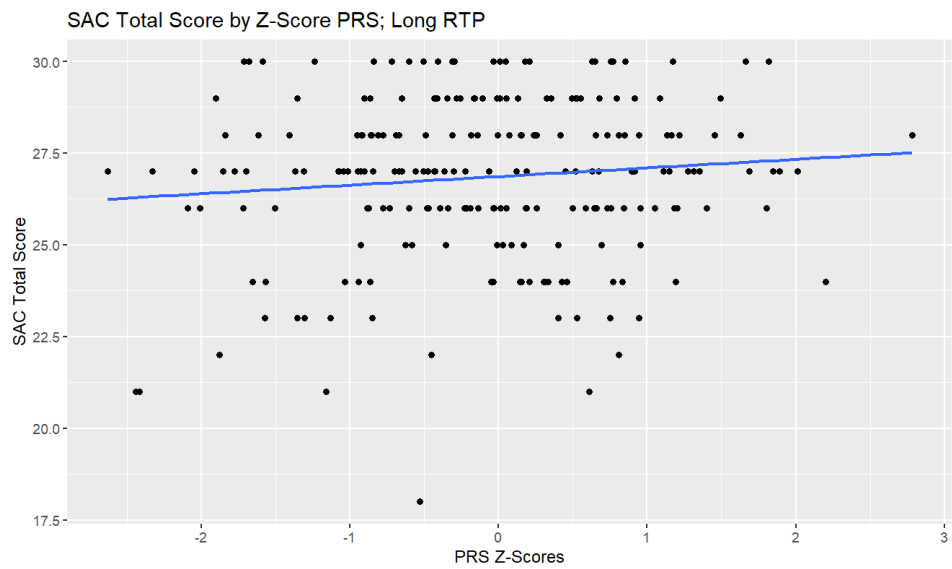


Figure C-3. AD PRS & total scores on BESS ( $p = 0.58$ ) (a), total scores on SAC ( $p = 0.937$ ) (b), SCAT symptom severity scores (SCATSEV;  $p = 0.746$ ) (c), and SCAT total number of symptom scores (SCATSYMP;  $p = 0.969$ ) (d) in normal RTP (<24 days) data subset.

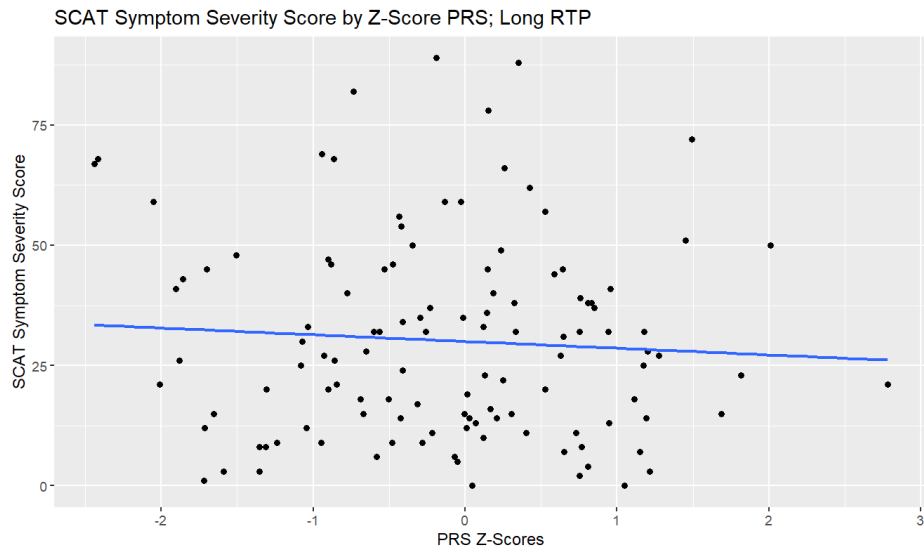
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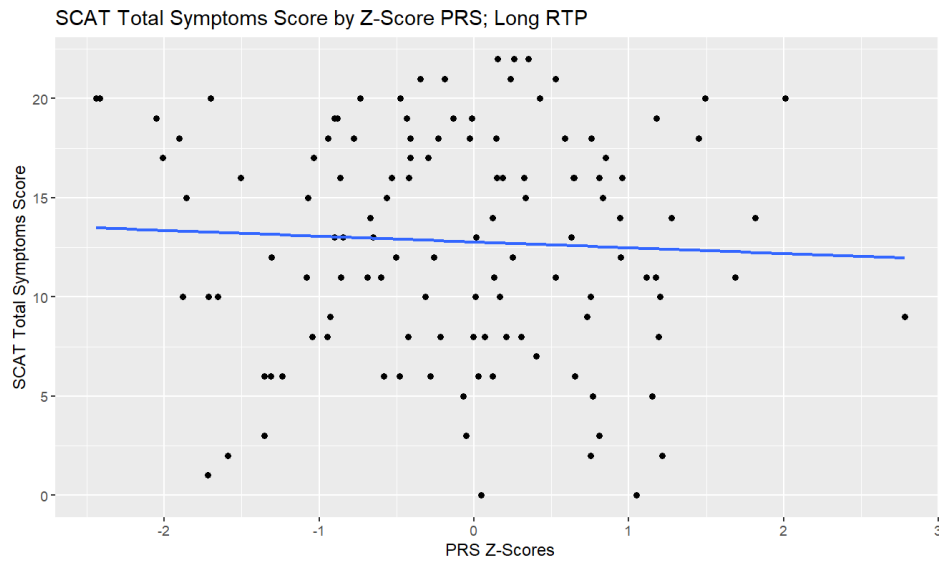
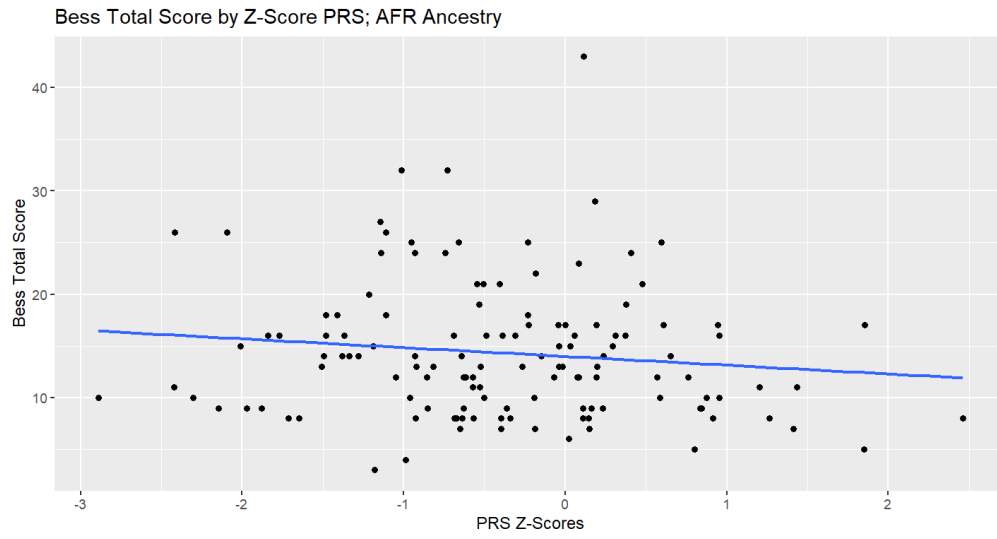
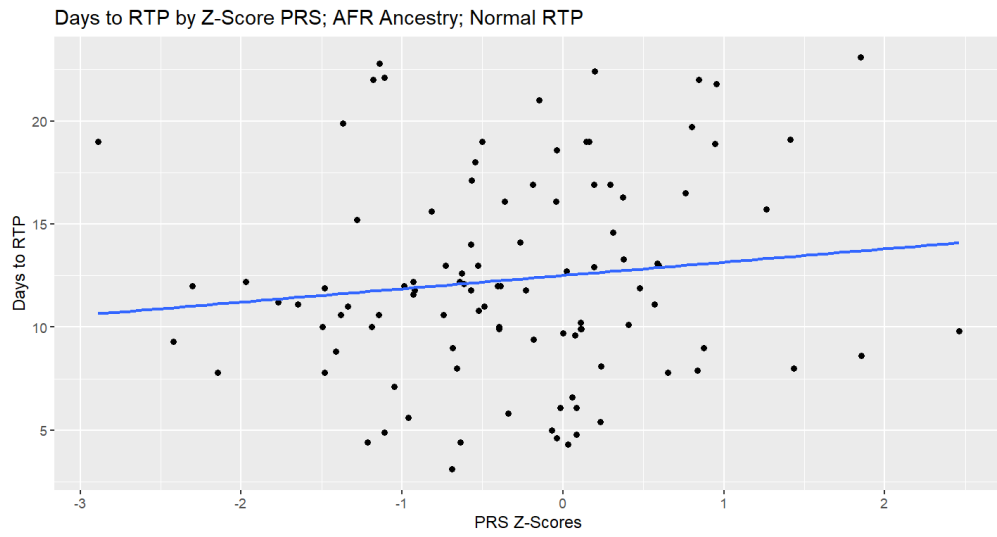


Figure C-4. AD PRS & total scores on BESS ( $p = 0.645$ ) (a), total scores on SAC ( $p = 0.117$ ) (b), SCAT symptom severity scores (SCATSEV;  $p = 0.465$ ) (c), and SCAT total number of symptom scores (SCATSYMP;  $p = 0.578$ ) (d) in long RTP (>24 days) data subset.

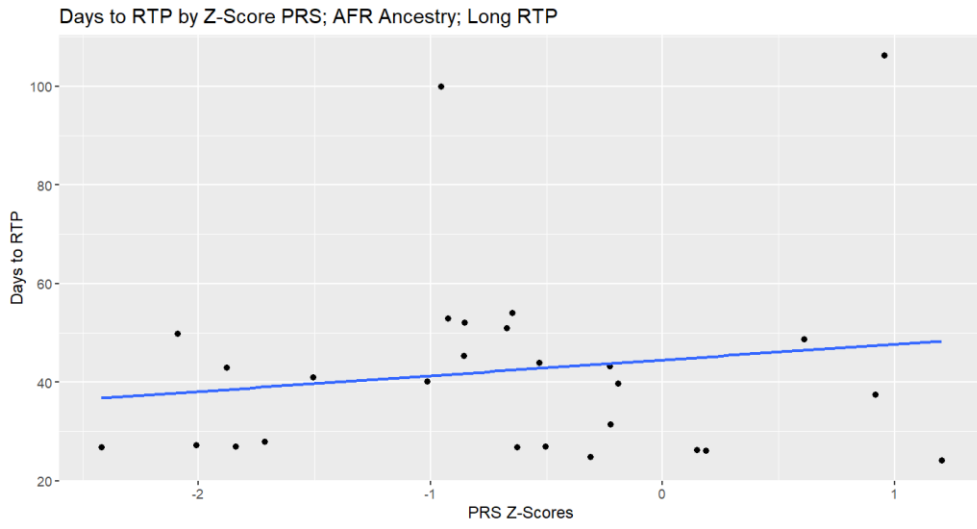
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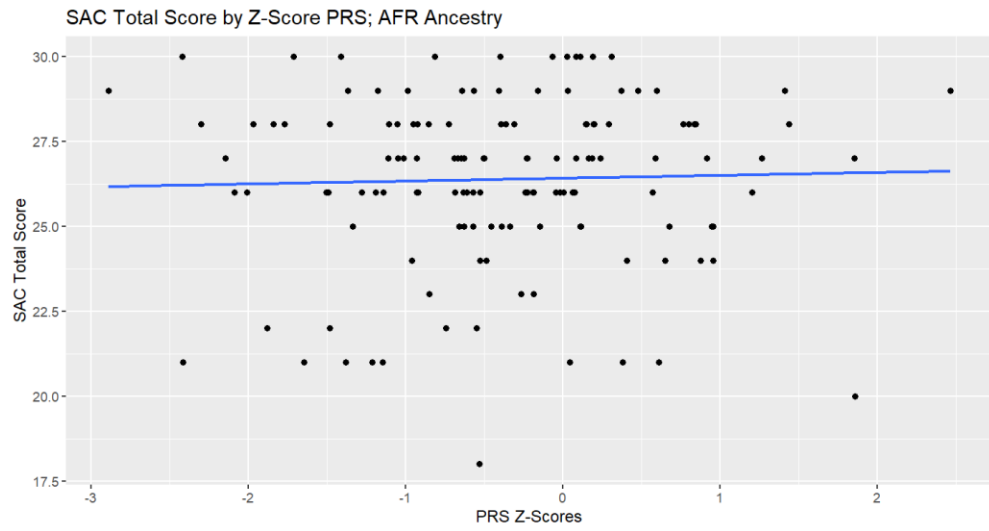
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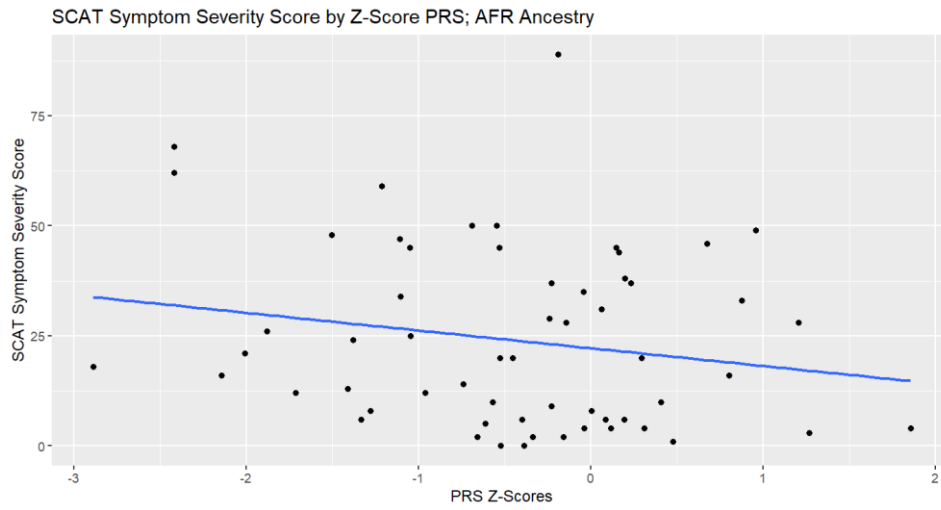


Figure C-5. AD PRS and total scores on BESS ( $p = 0.163$ ) (a), days to normal RTP ( $p = 0.221$ ) (b), days to long RTP ( $p = 0.446$ ) (c), total scores on SAC ( $p = 0.715$ ) (d), and SCAT symptom severity scores (SCATSEV;  $p = 0.144$ ) (e) in participants of African genetic ancestry.

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## Curriculum Vitae

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### **Education**

Indiana University

PhD in Medical Neuroscience, December 2025

Indianapolis, IN. Dissertation: *Association of Head Injury with Multimodal Alzheimer's Disease Biomarkers and Genetics*. Advisors: Andrew J. Saykin, PsyD and Shannon L. Risacher, PhD

Western Washington University

BS in Behavioral Neuroscience, June 2021

### **Research and Training Experience**

Graduate Student, Laboratory of Drs. Andrew J. Saykin and Shannon L. Risacher, April 2022 – December 2025

Stark Neurosciences Research Institute, Indiana University School of Medicine  
Indianapolis, IN  
Head injury and Alzheimer's disease biomarkers

Rotation Student, Laboratory of Dr. Xiaoming Jin, January 2022 – March 2022

Stark Neurosciences Research Institute, Indiana University School of Medicine  
Indianapolis, IN  
Mouse models of posttraumatic epilepsy

Rotation Student, Laboratory of Dr. Nian Wang, October 2021 – December 2021

Stark Neurosciences Research Institute, Indiana University School of Medicine  
Indianapolis, IN  
Diffusion MRI in mouse models of Alzheimer's disease

Undergraduate Research Assistant, Laboratory of Dr. Jaqueline Rose, September 2018 – June 2021

Behavioral Neuroscience Program, Western Washington University  
Molecular mechanisms of learning and memory in *C. elegans*

### **Honors, Awards, and Fellowships**

Ruth L. Kirschstein Predoctoral Individual National Research Service Award Predoctoral Fellowship, August 2025 (Declined)

National Institute on Aging/National Institute of Neurological Disorders and Stroke

Award ID: F31NS139600

Project Title: Association of Head Injury With Multi-modal AD Neuroimaging Biomarker Changes

Indiana University Elite 50 Award, March 2025

Larry Kays Fellowship, March 2025

Medical Neuroscience Graduate Program, Stark Neurosciences Research Institute,  
Indiana University School of Medicine

Ruth L. Kirschstein Predoctoral Institutional National Research Service Award  
Predoctoral Fellowship, August 2022

National Institute on Aging

Award ID: AG071444

Project Title: Training Grant on Alzheimer's Disease and ADRD at Indiana  
University

Indiana University-Purdue University Indianapolis Graduate University Fellowship,  
August 2021

## **Publications, Presentations, and Abstracts**

### Published Manuscripts

Dybing KM, McAllister TW, Wu YC, McDonald BC, Broglio SP, Mihalik JP, Guskiewicz KM, Goldman JT, Jackson JC, Saykin AJ, Risacher SL, Nudelman KNH. Association of Alzheimer's Disease Polygenic Risk Score with Concussion Severity and Recovery Metrics. *Sports Med.* 2025 Jun;55(6):1487-1503. doi: 10.1007/s40279-024-02150-w Epub 2025 Jan 16. PMID: 39821585; PMCID: PMC12152024.

Dybing KM, Vetter CJ, Dempsey DA, Chaudhuri S, Saykin AJ, Risacher SL. Traumatic Brain Injury and Alzheimer's Disease Biomarkers: A Systematic Review of Findings from Amyloid and Tau Positron Emission Tomography. *J Neurotrauma.* 2025 Mar;42(5-6):333-348. doi: 10.1089/neu.2024.0055 Epub 2024 Dec 6. PMID: 39639808; PMCID: PMC11971548.

### Manuscripts in Preparation

Dybing KM, Gao S, Risacher SL, Saykin AJ. (2025). History of head injury is not associated with Alzheimer's disease fluid biomarkers in older adults. Under revision at *Journal of Alzheimer's Disease*.

Dybing KM, Risacher SL, Saykin AJ. (2025). Traumatic brain injury is associated with tau positron emission tomography in individuals with dementia due to Alzheimer's disease. In preparation.

## Abstracts and Presentations

Dybing KM. (2024). Association of Alzheimer's disease polygenic risk score with concussion severity and recovery metrics. Oral presentation, 2024 Fall Indiana Alzheimer's Disease Research Symposium, Indianapolis, IN.

Dybing KM. (2023). Association of Alzheimer's disease polygenic risk score with concussion severity and recovery metrics. Oral presentation, Care-Saltos Integrated (CSI) Study Investigator Meeting, Rosemont, IL.

Dybing KM, Saykin AJ, Risacher SL. (2023). Impact of self-reported history of head injury on Alzheimer's disease biomarker profiles. Poster abstract & presentation, Alzheimer's Association International Conference (AAIC), Amsterdam, NL.

Dybing KM, Gao S, Risacher SL, Saykin AJ. (2023). Head injury is associated with Alzheimer's Disease fluid biomarkers. Poster abstract & presentation, 2023 Big Ten Neurosciences Annual Meeting, Indianapolis, IN, USA.

Maharjan S, Dybing KM, Wang N. (2022). Diffusion MRI in a transgenic mouse model of Alzheimer's disease. Poster abstract, 2022 ISMRM-ESMRMB & ISMRT Meeting, London, UK.