INFORMATION PAPER
ON
NEURODEGENERATIVE DISEASES AND TRAUMATIC BRAIN INJURY

TABLE OF CONTENTS

RELEVANCE TO THE DEPARTMENT OF DEFENSE

Research suggests a possible link between sustaining TBIs during military service and developing neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and possibly ALS, but findings are mixed. Biomarkers show promise for earlier detection and improved care for affected service members.

PURPOSE

Considerable research attention has focused on characterizing the relationship between TBI and neurodegenerative disease, with the aim of improving the prevention and treatment of these diseases in populations with high risk of TBI, including military service members and veterans. The purpose of this information paper is to summarize the available evidence on the association of TBI with three common neurodegenerative diseases: Alzheimer's disease, Parkinson's disease, and ALS. A fourth disease, chronic traumatic encephalopathy, is covered in a separate research review.[1]

This information is current as of March 2025 and may be subject to change as new findings become available.

BACKGROUND

The long-term consequences of TBI are especially important to define for warfighters and veterans, who are often exposed to head injury events during their service in the military.[2-4] Research on the relationship between TBI and neurodegenerative disease during the past 5-10 years has focused on three neurodegenerative diseases with cognitive impairment or dementia as a prominent feature: Alzheimer's disease, Parkinson's disease, and ALS. There are multiple reports of an association of a previous history of TBI and Alzheimer's disease, Parkinson's disease, or ALS. However, a common flaw in most of those reports is that TBI history was based on the individual's recall after they were diagnosed with a disease that can impair cognition and, specifically, memory. To more objectively evaluate this relationship, more recent studies have also investigated whether commonly studied biomarkers of neurodegenerative disease can be measured following TBI and whether they could inform the early detection of such diseases in the TBI population. Some researchers interpret the existing data as supporting the suggestion that pathological changes triggered by an earlier TBI can influence the normal aging processes and interact with neurodegenerative disease processes in general, rather than causing a specific disease, such as Alzheimer's disease or Parkinson's disease.[5,6] Additionally, some evidence indicates that the neurodegenerative processes triggered by TBI are distinct from those involved in Alzheimer's disease, Parkinson's disease, and ALS.

ALZHEIMER'S DISEASE

Alzheimer's disease is a progressive neurodegenerative disease characterized by the loss of recent episodic memory, language, visuospatial function, and executive function, as well as neurobehavioral abnormalities later in the disease course.[7] During the mid-to-late stages of the disease, individuals may also experience hallucinations, anxiety, or symptoms of depression.[7-9] Before progression to Alzheimer's disease dementia, patients typically exhibit mild cognitive impairment, which is characterized by cognitive changes that do not interfere with day-to-day activities.[10] To receive a diagnosis of Alzheimer's disease dementia, patients must first meet the criteria for all-cause dementia established by the non-federal entity, National Institute on Aging–Alzheimer's Association (**Table 1**).[11] Patients are then diagnosed with either probable

Alzheimer's disease dementia or possible Alzheimer's disease dementia using additional criteria related to the progression of symptoms and the presence of comorbidities (**Table 2**).[11]

Alzheimer's disease can be further classified as familial (also referred to as young- or early-onset) or sporadic (also referred to as late-onset). Familial Alzheimer's disease is hereditary and very rare (less than 5% of cases), and signs first appear between the ages of 30 to 65.[12] Sporadic Alzheimer's disease is more common, with signs first appearing after age 65, and apolipoprotein E genotype plays an important role in these cases.[12] There are three major human polymorphisms of the APOE gene, which include the ε2, ε3, and ε4 alleles, and the presence of the ε4 allele is one of the most influential risk factors for the development of sporadic Alzheimer's disease; individuals who are homozygous for this allele have an estimated 8-12 times higher risk of Alzheimer's disease.[12-14] The causes of Alzheimer's disease are not known in most people but likely include a combination of age-related changes in the brain, along with genetic, environmental, and lifestyle factors.[15,16] Older age does not cause Alzheimer's disease, but it is the most important known risk factor for the disease. The number of people with Alzheimer's disease doubles about every 5 years beyond age 65 such that one-third of all people age 85 years and older have been diagnosed with Alzheimer's disease.[17]

An area of increasing research and clinical interest in the field of Alzheimer's disease is using diagnostic neuroimaging and biofluid markers to detect the disease before symptoms manifest. While evidence indicates that other neuropathologies also contribute to Alzheimer's disease,[18] the most commonly studied pathologies include neurofibrillary, or tau, tangles[19,20], as well as amyloid-beta (Aβ) plaques, the latter of which can now be therapeutically targeted with recently FDA approved disease-modifying drugs.[21-23] Both of these pathologies result in a loss of neurons that may underlie the clinical manifestations of Alzheimer's disease.[24,25] Amyloid positron emission tomography is one imaging method for detecting Aβ plaque formation; while this method is not recommended for routine use, it can help rule out a diagnosis of Alzheimer's disease in patients with dementia of an unknown cause[10,26] or inform suitability for drug treatment.[27] Tau PET imaging is mostly limited to research settings, but like amyloid PET imaging, it has been FDA approved to help evaluate those with Alzheimer's disease.[28] Studies using these methods indicate that there are several pathological similarities between TBI and Alzheimer's disease, such as Aβ and tau deposition and pronounced cortical thinning.[28-35] Cerebrospinal fluid tests for Aβ, phosphorylated tau, and total tau are also increasingly common in clinical settings and have particularly high accuracy and sensitivity for detecting Alzheimer's disease.[36] Using blood tests to detect these markers—currently done only in research settings—shows great promise for incorporation into clinical practice. Some studies have shown that blood-based biomarkers more accurately identify clinical Alzheimer's disease than primary care physicians or dementia specialists. Additionally, blood tests are not as expensive or invasive as CSF or neuroimaging assessments.[37,38]

Evidence That TBI Is a Risk Factor for Alzheimer's Disease

Many more studies have investigated the link between TBI and Alzheimer's disease than have examined the associations between TBI and either Parkinson's disease or ALS. During the past 30 years, much of this research has linked mild, moderate, and severe TBI to a greater risk of cognitive decline or the development of Alzheimer's disease years after injury.[6,24,39-46] One early study reported that veterans who sustained a moderate TBI during military service had a 2.3 times greater risk of developing Alzheimer's disease than those with no history of head injury, while those with a history of severe TBI had a 4.5 times greater risk.[24,47] Other studies have also

found a link between moderate and severe TBI and higher risk of Alzheimer's disease, cognitive decline, and dementia.[46,48] Some studies have found an association between TBIs incurred later in life with clinical Alzheimer's disease risk, especially among those requiring a higher intensity or duration of TBI care.[49] In one study of approximately 1,200 patients with mild cognitive impairment or Alzheimer's disease, TBI history was associated with an earlier age of onset of cognitive impairment by two or more years.[50] Other studies have linked mild TBI with progressive brain atrophy in regions that are vulnerable to Alzheimer's disease, particularly among individuals with the APOE ε4 allele.[51-53]

Social determinants of health such as ethnicity may play a role. One study of 676 Japanese-American men found no relationship between TBI and subsequent cognitive decline.[54] In a study of 10,000 patients with Alzheimer's disease, onset occurred 2.3 years earlier for non-Hispanic Caucasians and 3.4 years earlier for African Americans in those who had experienced a TBI with loss of consciousness.[55] Among Hispanic women, onset for those who had a TBI with LOC had was 5.8 years earlier than those who did not have a history of TBI with LOC. Hispanic men showed little difference in age of Alzheimer's disease onset, whether or not they had a history of TBI with LOC.[55] While these findings suggest an association between ethnicity or sex and Alzheimer's disease risk following TBI, there are few studies in this area. Additional research is needed to examine the social determinants of health that may link TBI with increased Alzheimer's disease risk.

Military service presents a unique set of factors that may increase the risk of being diagnosed with dementia, including Alzheimer's disease dementia.[56] Studies with veterans have found that those with a history of TBI are 1.2 times more likely to develop mild cognitive impairment[57] and 3.0 times more likely to develop early-onset dementia than those without a history of TBI; the risk for dementia increases with TBI severity.[58] Another study of 112 veterans from the Alzheimer's Disease Neuroimaging Initiative–Department of Defense database observed that those with a history of TBI of any severity had higher CSF levels of $A\beta_{40}$ and $A\beta_{38}$ than those without TBI history, and $A\beta_{40}$ levels were found to have a significant indirect effect on the relationship between TBI and performance on a language test.[59] Another study of 51 veterans who had sustained blast-related mild TBIs and 85 veterans without history of mild TBIs found that differences in CSF $A\beta_{42}$ and total tau levels were more pronounced at older ages, and CSF $A\beta_{42}$ levels were associated with performance on various tests of cognitive function in the mild TBI group.[60] In a study of nearly 10,000 veterans with a TBI, the risk of developing Alzheimer's disease and related dementias was nearly double that of a cohort of 120,000 veterans without a history of TBI who received care at the VA.[61] A study of 88 Vietnam War veterans with a history of TBI found a link between their genetic risk for Alzheimer's disease and levels of certain proteins in their spinal fluid. Veterans with a higher genetic risk for Alzheimer's had lower levels of two proteins, Aβ42 and Aβ40. Lower levels may mean more of a protein called amyloid-beta is building up in the brain. This link was stronger for veterans with more severe TBIs.[62] Collectively, these studies indicate the important contribution of TBI to an increased risk of Alzheimer's disease, as well as its associated neuropathological changes.

Evidence That TBI Is Not a Risk Factor for Alzheimer's Disease

While many studies have reported an association between Alzheimer's disease and TBI, several other studies have reported no association. A 2018 meta-analysis of 18 studies comprising more than 3 million patients found no evidence that a previous TBI increased the risk of Alzheimer's disease or Parkinson's disease,[63] and a retrospective study of 933 autopsy-proven cases of

Alzheimer's disease did not find that a previous history of TBI was a risk factor.[64] A systematic review and meta-analysis of 13 cohort studies of veterans found that a history of TBI was not associated with subsequent Alzheimer's disease.[65] One large study did find that a history of TBI was associated with an earlier diagnosis of mild cognitive impairment, but TBI was not significantly associated with progression from mild cognitive impairment to Alzheimer's disease.[66] Additionally, a 2024 prospective study of over 350,000 participants from the United Kingdom Biobank investigating risk factors for young-onset dementia reported that TBI was not one of the environmental factors significantly associated with a higher risk of young-onset dementia,[67] consistent with other studies.[68,69]

A systematic review and meta-analysis of 19 studies was conducted to determine whether contact sport participation is associated with neurodegenerative decline.[70] No significant relationship was observed between contact sport participation and the antemortem diagnosis of neurodegenerative disease or death related to such a diagnosis or cognitive function on the Trail Making Test, which measures visual attention and executive function. A 2024 study found that, while plasma p-tau levels were significantly elevated in an Alzheimer's disease cohort, p-tau levels were not elevated during the first year after moderate to severe TBI and were not associated with imaging features associated with neurodegeneration.[71] A separate study using data from over 4,300 participants aged 65 years or older found no significant association between military employment and cognitive change, dementia risk, or Alzheimer's disease dementia, even after adjusting for TBI history and other potentially confounding factors.[72] One study of over 6 million service members found that, while those who sustained a mild TBI were more likely to receive a diagnosis of memory loss, mild cognitive impairment, Alzheimer's disease, and other dementias, they were not more likely to exhibit earlier dementia onset than those with no mild TBI history.[73] Finally, several studies, including four investigating veterans with military service-related TBIs,[74-77] have observed no significant changes in PET imaging biomarkers of Alzheimer's disease or changes in cortical thickness among individuals with a remote history of TBI after controlling for APOE status, age, and other potentially confounding factors.[78]

There are many potential reasons for these discrepant findings. First, many studies in this area exhibit important methodology concerns. Nearly all studies suggesting that TBI is a risk factor for dementia and Alzheimer's disease are observational studies with low methodological quality.[79,80] Common methodological weaknesses include self-reported TBI,[81,82] poor case definition of TBI, low prevalence of TBI in samples, reverse causality, and not controlling for important confounding factors.[83] In one meta-analysis, only one study exhibited strong methodological rigor (defined as having a prospective design, long follow-up period, medically confirmed TBI, and low risk of reverse causality and bias), and this study observed an increased risk of clinical dementia diagnosis among those with a history of mild to severe TBI.[79] Some studies suggest that the diagnostic criteria used to define subthreshold Alzheimer's disease dementia or mild cognitive impairment could also impact the study findings. For example, one study reported that using a mild cognitive impairment diagnostic scheme that considered neuropsychological findings such as PTSD resulted in stronger observed associations between TBI and Alzheimer's disease biomarkers than a conventional diagnostic method.[84] Across studies, it is difficult to consistently control for lifestyle factors, environmental exposures, comorbidities,[85] and other potentially confounding factors that interact throughout the lifespan to contribute to developing Alzheimer's disease.

Additionally, some studies suggest that multiple non-Alzheimer's disease mechanisms of neurodegeneration may co-occur and influence the association between TBI and dementia,[86-90] which may contribute to inconsistent study results. An analysis of 8,302 male World War II veterans (using data from the National Academy of Sciences-National Research Council's Twins Registry, a non-federal entity) found that among those with a history of TBI, the risk for non-Alzheimer's disease dementia was higher than the risk for Alzheimer's disease.[91] Researchers got the same result when they analyzed 100 twin pairs to control for genetic and shared environmental factors. Another study investigated differences in imaging findings among 1,124 participants, including 343 with Alzheimer's disease and no TBI history; 127 with Alzheimer's disease who had TBI history; 266 cognitively normal adults with TBI; and 388 cognitively normal adults without TBI. The results showed that among those with Alzheimer's disease, TBI was associated with an earlier onset of cognitive symptoms (approximately seven years earlier than those with no TBI history), but those with TBI history exhibited less cortical atrophy in regions commonly associated with Alzheimer's disease,[92] which is consistent with other studies.[93]

Another study found that TBI with LOC was associated with a greater risk of cortical atrophy, but there were no other associations between TBI and other Alzheimer's disease-related pathologies.[94] Finally, another study found that TBI was associated with greater white matter atrophy, while Alzheimer's disease was more associated with atrophy in both white and gray matter regions.[95] The authors concluded that patterns of atrophy post-TBI are more reflective of axonal injury and are distinct from the aging-related patterns of atrophy that more closely resemble Alzheimer's disease pathology.[95] Collectively, these results imply that individuals with both Alzheimer's disease and TBI history exhibit pathological changes in the brain that are distinct from those typically associated with Alzheimer's disease.

Consistent with this conclusion, at the 2019 National Institutes of Health Summit on Alzheimer's disease and Alzheimer's disease-related dementias, national TBI experts determined that TBI is a clinically and pathologically heterogeneous disease and that its associations with Alzheimer's disease are not fully understood.[96] In 2022, a multidisciplinary panel of experts evaluated the Summit conclusions and identified four priorities for accelerating research on the link between TBI and Alzheimer's disease and its related dementias: 1) interdisciplinary collaboration, 2) better characterization of post-traumatic neurodegeneration associated with different lifetime TBI histories, 3) identification of common data elements, and 4) increased support of basic and translational research.[97] Notably, the panel specifically recommended conducting studies evaluating differences in symptom presentation among individuals who develop post-traumatic neurodegeneration, and identifying biomarkers to progressively monitor post-TBI Alzheimer's disease and related pathologies over time.[97]

PARKINSON'S DISEASE

Parkinson's disease is a neurodegenerative disorder characterized by gradual progression and various deficits in motor function.[98] It is much more common after age 60. The most common clinical presentation of Parkinson's disease is a resting tremor in one hand associated with arm swing and shoulder pain.[98] Bradykinesia (slowness of movement) and rigidity are often detectable on the affected side, and there is often reduced facial expression.[99] Gait and balance are progressively affected, resulting in falls.[99,100] Freezing or motor blocks occur, followed by bulbar deterioration, which impairs communication and swallowing.[99] Studies also suggest that more severe forms of Parkinson's disease may involve perceptual challenges, such as difficulties

with visuospatial motion perception related to vestibular dysfunction, such as difficulty perceiving self-motion.[101-103]

The non-federal entity, the International Parkinson and Movement Disorder Society's, diagnostic criteria are intended for research purposes, but can be used to help establish a clinical Parkinson's disease diagnosis.[104] These criteria include the absence of absolute exclusion criteria, the presence of at least two supportive criteria, and no red flags (**Table 3**).[104] Global dementia occurs in approximately 30% of patients, and those with prominent early executive dysfunction and more severe motor signs are particularly at risk.[98] Exposure to pesticides, consumption of dairy products, use of β-antagonists such as propranolol and metoprolol, history of melanoma, depression, participation in contact sports (particularly American football), and TBI have all been associated with an increased risk for Parkinson's disease,[105-107] whereas a reduced risk has been reported in association with smoking, caffeine consumption, higher serum urate concentrations, physical activity, and use of ibuprofen and other analgesic medications.[108]

Parkinson's disease involves the progressive loss of neurons that produce dopamine that are located in regions of the brain that control movement.[99] Thus, the first-line treatment for Parkinson's disease is typically levodopa, a drug that is converted into dopamine in the brain.[109] Enhanced tau protein production and elevated levels of alpha-synuclein (α-synuclein) are thought to underlie the degeneration of affected neurons.[110] Studies suggest various other molecules, including TAR DNA-binding protein 43 and amyloid precursor protein, may be involved in Parkinson's disease pathology, and these proteins are also frequently upregulated following TBI.[111] Similar to research on other neurodegenerative diseases, the development and validation of robust biomarker assessments of these pathological changes, such as α-synuclein aggregation, is an area of increasing research interest, with the goal of accelerating Parkinson's disease diagnosis and treatment initiation.[112,113]

Evidence That TBI Is a Risk Factor for Parkinson's Disease

Several investigators have concluded that TBI, and particularly moderate or severe TBI, is a risk factor for general motor deficits, as well as Parkinson's disease.[39,114-116] One study also showed that Parkinson's disease patients with a history of head injury are more likely to exhibit nonmotor disorders, such as cognitive complaints, depression, and quality of life difficulties, particularly among those with a higher frequency of head injuries.[117] Pooled clinical and neuropathologic data from three prospective cohort studies (n=7,130) indicate that TBI with LOC is associated with progression of Parkinson's disease, but not with dementia, Alzheimer's disease, neuritic plaques, or neurofibrillary tangles.[118] Additionally, studies that were supported by the Michael J. Fox Foundation for Parkinson's Research, a non-federal entity dedicated to accelerating the development of treatments for the disease, have compared the history of head trauma or TBI between individuals with and without Parkinson's disease to investigate this relationship.

In one Michael J. Fox Foundation-funded study comparing twins, the twin who had a prior head injury was more likely to be diagnosed with Parkinson's disease.[119] Three meta-analyses of several published studies have since confirmed this result, finding that TBI (including mild TBI) is associated with a higher risk of developing Parkinson's disease.[120-122] In one large retrospective study, researchers used the medical records of 325,870 veterans, half of whom had a mild, moderate, or severe TBI. At the beginning of the study, none had a Parkinson's disease diagnosis.[123] During the follow-up (average follow-up was 4.6 years), 1,462 veterans were

diagnosed with Parkinson's disease, and 949 of them had a TBI.[123] After adjusting for age, medical conditions, and other factors, the researchers found that mild TBI increased the risk for Parkinson's disease by 56%, and moderate to severe TBI increased the risk for Parkinson's disease by 83%.[123]

Other studies support these findings, showing that TBI severity, frequency, and timing influence Parkinson's disease risk. One study supported by the same foundation used medical records from over 52,000 individuals with TBI and over 113,000 controls who had a non-TBI trauma. Researchers observed that TBI was associated with a 44% increased risk of developing Parkinson's disease during the subsequent 5 to 7 years of the study, and the risk was higher in those with more severe or recurrent injuries.[124] An unmatched case-control study of 379 neurologist-confirmed Parkinson's disease patients and 230 controls found a significant effect of age at the time of the first head injury.[125] For every five years earlier the first head injury with LOC occurred, the odds for Parkinson's disease was 1.37 times higher, suggesting that head injury earlier in life significantly increases the risk of Parkinson's disease.[125] In one small study, 25 Parkinson's disease patients with a history of mild to moderate TBI had significantly greater declines in overall cognition over a two-year period than 25 matched Parkinson's disease controls[126]; collectively, these findings suggest that a history of TBI may not only increase Parkinson's disease risk but also accelerate Parkinson's disease progression.

Interestingly, other studies suggest that comorbid neuropsychological conditions commonly observed in individuals with TBI may influence Parkinson's disease risk. One study examined the risk of developing Parkinson's disease following TBI and PTSD by comparing the medical records of 176,871 veterans diagnosed with Parkinson's disease to those of 707,484 randomly selected veterans with no history of Parkinson's disease.[127] The overall prevalence of mild TBI, moderate to severe TBI, and PTSD in the study cohort was 0.65%, 0.69%, and 5.5%, respectively. The results suggest a positive interaction with comorbid PTSD and TBI in dual-risk factor analyses, with a significant 2.69-fold (mild TBI) and 3.70-fold (moderate to severe TBI) excess relative risk of Parkinson's disease in veterans with TBI when compared with veterans with PTSD but no TBI history. Additionally, there was a 2.17- to 2.80-fold excess risk when PTSD was absent. These findings are consistent with a 2023 case-control study of over 71,000 veterans with Parkinson's disease and over 280,000 controls, which observed that both TBI and PTSD were associated with increased Parkinson's disease risk.[128] Additionally, chronic pain and migraine had a synergistic effect on the association of TBI and PTSD with Parkinson's disease risk.[128] In a separate study of 114 veterans, those who had a combat-related mild TBI within the last seven years had subtle premature cognitive decline that signified the eventual onset of Parkinson's disease.[129] Together, these studies provide some evidence of factors commonly associated with TBI—such as PTSD, chronic pain, and military service—that may impact the development or progression of Parkinson's disease.

Evidence That TBI Is Not a Risk Factor for Parkinson's Disease

Other studies have not found an association between TBI and Parkinson's disease.[130] In a cross-sectional cohort study of 120 older adults (60-85 years; 60% men), a history of TBI or the number of TBIs was not significantly related to an increased risk of Parkinson's disease.[131] A systematic review of 65 studies identified five studies with low risk of bias, four of which did not find a significant association between mild TBI and Parkinson's disease.[132] Although the fifth study did find an association, the estimated odds ratio decreased with increasing latency between the TBI and Parkinson's disease diagnosis, suggesting reverse causality. In a nested case-

controlled population-based analysis of 918 participants, neither the severity nor the number of TBIs were found to be associated with subsequent Parkinson's disease.[133] A meta-analysis of 18 studies that included 3,263,207 patients did not find that a history of TBI was associated with the development of subsequent neurodegenerative diseases, including Parkinson's disease.[63] Collectively, most but not all studies support an association between TBI and developing Parkinson's disease. Like studies on the link between Alzheimer's disease and TBI, methodological concerns and unknown underlying mechanisms may contribute to the discrepant findings among studies on the risk of Parkinson's disease after TBI.

AMYOTROPHIC LATERAL SCLEROSIS

ALS is a rapidly progressing disease primarily affecting discrete groups of neurons that control movement.[134] While available treatments may slow its progression, there is no cure, and the disease is always fatal. It usually affects people between the ages of 40 and 70, and the disease begins with muscle twitching and weakness in a limb, or slurred speech. Eventually, it affects muscles needed to move, speak, eat, and breathe; in later stages it is associated with cognitive and behavioral changes.[134,135] ALS can be diagnosed using the El Escorial criteria, which describes three categories of ALS–definite, probable, and possible ALS–that differ in the number of signs observed in independent body parts (**Table 4**).[136] The El Escorial criteria have long been considered the gold standard for diagnosing ALS. However, some evidence suggests the newer Awaji criteria may have higher diagnostic accuracy and could allow earlier ALS diagnosis.[137] The median duration of survival following symptom onset is approximately 2-4 years, but 10-20% of ALS patients live longer than 10 years after their diagnosis, indicating that ALS is a considerably heterogeneous condition.[138] While the risk factors influencing survival following ALS diagnosis are not fully understood, some evidence suggests that indicators of poor prognosis include an older age of onset, bulbar onset (involving speech or swallowing problems), aggressive progression between office visits, low body mass index, concurrent frontotemporal dementia, dyspnea (difficulty breathing) at the time of diagnosis, and a rapid decline on pulmonary function tests.[138,139]

There are two forms of ALS: sporadic and familial. Most cases of ALS are sporadic, but ALS is familial in 5-10% of people.[140] Family members of people with sporadic ALS are at an increased risk for the disease, but the overall risk is very low. ALS can develop at any age, but symptoms most commonly arise between the ages of 55 and 75 years.[140] Additionally, some studies suggest that ALS is significantly more common among military service members than in the general population.[141,142] One study showed that veterans are nearly 60% more likely to develop ALS than the general population.[143] Indeed, based on these data, ALS is now considered a service-linked disease, which allows veterans to receive care for ALS in the Department of Veterans Affairs.[144] Smoking is one of the most well-established lifestyle risk factors for ALS, increasing risk by more than 40% among people who have smoked cigarettes.[145] Some studies have suggested that people with a history of electric shock or exposure to electromagnetic fields are more likely to develop ALS. The risk is higher for those in professions related to electricity, such as electricians, train drivers, and people operating electric equipment (like welders or carpenters).[146,147]

Pathologically, sporadic ALS is commonly associated with brain and spinal cord accumulation of TAR DNA-binding protein 43, a protein involved in regulating gene expression[148]; indeed, evidence of TDP-43 accumulation has been reported in up to 97% of all ALS cases.[149] Thus, increased understanding of the mechanisms involved in ALS-associated TDP-43 pathology could

help identify new therapies. ALS also involves damage to cells caused by unstable molecules called free radicals, which can be targeted with recently FDA-approved treatments.[150] Another FDA-approved treatment may slow ALS progression by protecting neurons from overstimulation.[151]

Evidence That TBI Is a Risk Factor for ALS

Few studies have directly evaluated the relationship between TBI and ALS. Some studies have reported that the risk of ALS is higher in those who play varsity and professional contact sports such as soccer and football, which may be attributable to physical activity or to other factors such as head trauma.[152-156] One study found that the mortality from ALS among National Football League players was nearly four times higher than that in the general population, suggesting the potential contribution of exposure to repetitive head impacts.[153] While some studies suggest that people who are very physically active and regularly engage in strenuous exercise are more likely to develop ALS,[157] others have not found that ALS risk is significantly altered for people who engage in recreational sports.

Some studies support a potential association between TBI and ALS. A 2019 study found that the prevalence of ALS was about four times higher among military service members who were deployed to post-9/11 wars than those deployed in the Gulf War.[158] While it remains unclear why, members of the post-9/11 military often were exposed to chemicals and heavy metals—particularly manganese, mercury, and zinc—as well as formaldehyde and pesticides, all of which may play a role. Strenuous physical conditions and trauma may also have influenced this finding. In 2024, one meta-analysis of 60 studies including over 8,800 patients reported that CSF levels of neurofilament light, a potential biomarker of axonal injury following TBI, showed high diagnostic accuracy for distinguishing individuals with ALS from controls. The study also found that higher levels were linked to more severe ALS symptoms and faster disease progression.[159]

Other studies have directly linked TBI with an increased risk for ALS. An early study found that veterans who died from ALS were exposed to more trauma before and during their service than veterans who died from other causes.[160] A larger study of veterans reported that individuals who had sustained a TBI up to 15 years before the study were more likely to receive an ALS diagnosis than those with no TBI history, and this association was strongest among those with the APOE ε4 allele.[161] One study reported an increased risk of ALS only for those who had sustained multiple head injuries, including at least one such injury in the past 10 years. This group had an 11-fold higher risk of ALS than those with no history of head injury.[162] Another meta-analysis of 14 independent studies found a 38% greater likelihood of developing ALS among those with a history of any TBI, which increased to 69% among those with severe head injuries.[163]

Evidence That TBI Is Not a Risk Factor for ALS

Several studies have reported no association between TBI and ALS. One of these studies observed no significant differences in the rate of functional decline between individuals with ALS who sustained a head injury and those who did not, as well as no significant differences in the presence of TDP-43 or tau pathology among a cohort of autopsy-confirmed ALS cases.[164] A Finnish study of more than 40,000 individuals with moderate or severe TBI found that, while these injuries were associated with a risk for future dementia, they were not associated with a risk for ALS or Parkinson's disease.[165] One meta-analysis of four studies investigating the association between ALS and TBI observed that three reported no significant association and the

fourth reported that a significant association was observed only within the first year following TBI, which may have been due to early-stage ALS contributing to motor dysfunction and a higher risk of falls.[166] Another study showed similar results, reporting a significant association between severe TBI and ALS only within the first year following TBI.[167] Together, these studies indicate that more research is needed to improve our understanding of the relationship between TBI and ALS incidence and progression. In particular, some researchers propose additional preclinical and clinical studies to clarify the mechanistic interactions between TBI and ALS and the contribution of time elapsed since injury to ALS risk.[168,169]

CONCLUSION

Many studies have demonstrated associations between TBI and the incidence or accelerated progression of neurodegenerative diseases, particularly Alzheimer's disease and Parkinson's disease. Most studies have observed stronger associations between TBI and neurodegenerative diseases among those who have sustained more—or more severe—TBIs. While these findings have begun to provide insight into the specific aspects of TBI that may confer an increased risk of developing a neurodegenerative disease, there are some discrepancies among studies, and several unknowns remain. For example, few studies have evaluated how the mechanism of injury, specific injury features, the presence of common TBI comorbidities, and the timing of the injury contribute to the risk of neurodegenerative disease following TBI. More long-term studies are needed to clarify these connections.

Achieving a better understanding of the relationship between TBI and neurodegenerative disease has important potential clinical implications. The FDA has recently approved several drugs for treatment. While these drugs do not halt or reverse disease progression, they may slow its progression if applied early. As novel therapies emerge, studying biofluid and neuroimaging biomarkers may lead to early detection and treatment of neurogenerative diseases (particularly Alzheimer's disease) among those with TBI history. While the exact factors underlying the association between TBI and neurodegenerative disease are unknown, some investigators postulate that this relationship involves the cascade of pathological processes triggered by TBI. These pathologies can worsen the harmful buildup of proteins that characterizes neurodegenerative diseases. Researchers believe that further study could reveal new ways to detect these problems earlier.[111,170-172] Thus, an improved understanding of the pathological link between TBI and neurodegenerative diseases could help support more widespread incorporation of TBI history into clinical decision-making schemes (including criteria for when to obtain biomarker data) for managing neurodegenerative diseases.

IMPACT TO THE WARFIGHTER

- While it is unlikely that warfighters will be diagnosed with Alzheimer's disease, Parkinson's disease, or ALS during their time in service, understanding the risks associated with different cumulative operational exposures is necessary to develop prevention strategies.
- Some studies suggest that individuals who sustain a mild TBI during their military service have a greater risk of developing Alzheimer's disease and Parkinson's disease than those with no history of head injury. However, this finding is not universal, emphasizing that factors beyond TBI also play a role in one's risk for these diseases.

- The relationship between TBIs sustained during military service and ALS is unclear, and there have been few studies in this area. More research is needed to investigate the relationship between TBI, and the development of ALS.
- As our understanding of the relationship between TBI and neurodegenerative disease improves, novel biomarkers may be developed to allow the early detection of these diseases in individuals with TBI well before symptoms arise. Military and VA clinicians may then be more likely to incorporate these biomarkers, as well as TBI history, into decision-making schemes when considering individuals for FDA-approved treatments for neurodegenerative disease.

Prepared by:

Clinical Translation Office
Traumatic Brain Injury Center of Excellence
dha.ncr.TBICoEResearch@health.mil

DISCLAIMER

TABLES

Table 1: National Institute on Aging–Alzheimer's Association Criteria for All-Cause Dementia[11]

CRITERIA
1. Cognitive or behavioral symptoms interfere with one's ability to function at work or perform usual activities.
2. Cognitive or behavioral symptoms represent a decline from previous levels of functioning.
3. Cognitive or behavioral symptoms are not explained by a major psychiatric disorder.
4. Cognitive impairment is detected through a combination of a) history-taking from the and a knowledgeable informant and (b) an objective cognitive assessment.
5. Cognitive or behavioral impairment involves **at least two** of the following domains: a) **Impaired ability to learn and remember new information**: Individuals ask repetitive questions or have repetitive conversations, misplace personal belongings, forget appointments or events, or get lost on a familiar route. b) **Impaired reasoning and handling of complex tasks (poor judgement)**: Individuals have a poor understanding of safety risks, an inability to manage finances, poor decision-making, or an inability to plan complex or sequential activities. c) **Impaired visuospatial abilities**: Individuals are unable to recognize faces or common objects or find objects in direct view (despite good visual function), operate simple instruments, or dress themselves. d) **Impaired language functions**: Individuals have difficulty with word finding; hesitate during speech; or exhibit speech, spelling, or writing errors. e) **Changes in personality or behavior**: Individuals exhibit uncharacteristic mood fluctuations (including agitation), impaired motivation, apathy, social withdrawal, or compulsive or socially unacceptable behaviors.

Table 2: National Institute on Aging–Alzheimer's Association Criteria for Probable and Possible Alzheimer's Disease Dementia[11]

CRITERIA FOR PROBABLE ALZHEIMER'S DISEASE
1. An insidious onset of months to years (rather than a rapid onset of hours to days) 2. A clear history of worsening 3. An amnestic presentation (involving impaired learning and recall) or a non-amnestic presentation (involving impaired language, visuospatial function, or executive function) 4. No evidence of other concomitant neurologic diseases (e.g., cerebrovascular disease, Lewy body dementia)
CRITERIA FOR POSSIBLE ALZHEIMER'S DISEASE
Patients meet the other core clinical criteria for Alzheimer's disease, but there is 1) evidence of another concomitant neurologic disease or 2) there is an atypical disease course.

Table 3: International Parkinson and Movement Disorder Society's Diagnostic Criteria for Parkinson's Disease[104]

TYPE OF CRITERIA	EXAMPLES
Absolute Exclusion Criteria	Unequivocal cerebellar abnormalities; diagnosis of behavioral variant frontotemporal dementia; normal functional neuroimaging of the presynaptic dopaminergic systems; absence of observable response to high-dose levodopa despite moderate to severe disease
Supportive Criteria	Clear and dramatic beneficial response to dopaminergic therapy; presence of levodopa-induced dyskinesia; rest tremor of a limb; presence of olfactory loss or cardiac sympathetic denervation
Red Flags	Rapid progression of gait impairment within five years of onset; complete absence of progression of motor symptoms over five years unless stability is related to treatment; early bulbar dysfunction; severe autonomic failure during the first five years of disease

Table 4: El Escorial Criteria for the Diagnosis of ALS[136]

ALS SUBTYPE	CRITERIA
Definite ALS	Upper and lower motor neuron signs observed in the bulbar region and at least two spinal regions or in three spinal regions
Probable ALS	Upper and lower motor neuron signs observed in two independent body regions
Possible	Upper and lower motor neuron signs observed in one body region or upper motor neuron signs in two body regions

REFERENCES

1. Traumatic Brain Injury Center of Excellence. Research review on chronic traumatic encephalopathy. Updated 2023. Available from: health.mil/CTE-TBICoEResearchReview
2. French LM. Military traumatic brain injury: An examination of important differences. Ann N Y Acad Sci. 2010;1208:38-45. doi:10.1111/j.1749-6632.2010.05696.x
3. Kong LZ, Zhang RL, Hu SH, Lai JB. Military traumatic brain injury: A challenge straddling neurology and psychiatry. Mil Med Res. 2022;9(1):2. doi:10.1186/s40779-021-00363-y
4. Lindberg MA, Moy Martin EM, Marion DW. Military traumatic brain injury: The history, impact, and future. J Neurotrauma. 2022;39(17-18):1133-1145. doi:10.1089/neu.2022.0103
5. Griesbach GS, Masel BE, Helvie RE, Ashley MJ. The impact of traumatic brain injury on later life: Effects on normal aging and neurodegenerative diseases. J Neurotrauma. 2018;35(1):17-24. doi:10.1089/neu.2017.5103
6. Perry DC, Sturm VE, Peterson MJ, et al. Association of traumatic brain injury with subsequent neurological and psychiatric disease: A meta-analysis. J Neurosurg. 2016;124(2):511-26. doi:10.3171/2015.2.jns14503
7. Zhang J, Zhang Y, Wang J, Xia Y, Zhang J, Chen L. Recent advances in Alzheimer's disease: Mechanisms, clinical trials and new drug development strategies. Signal Transduct Target Ther. 2024;9(1):211. doi:10.1038/s41392-024-01911-3
8. Huang YY, Gan YH, Yang L, Cheng W, Yu JT. Depression in Alzheimer's Disease: Epidemiology, mechanisms, and treatment. Biol Psychiatry. 2024;95(11):992-1005. doi:10.1016/j.biopsych.2023.10.008
9. Ismail Z, Creese B, Aarsland D, et al. Psychosis in Alzheimer disease—mechanisms, genetics and therapeutic opportunities. Nat Rev Neurol. 2022;18(3):131-144. doi:10.1038/s41582-021-00597-3
10. Budson AE, Solomon PR. New diagnostic criteria for Alzheimer's disease and mild cognitive impairment for the practical neurologist. Pract Neurol. 2012;12(2):88-96. doi:10.1136/practneurol-2011-000145
11. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7(3):263-9. doi:10.1016/j.jalz.2011.03.005
12. Liu E, Zhang Y, Wang JZ. Updates in Alzheimer's disease: From basic research to diagnosis and therapies. Transl Neurodegener. 2024;13(1):45. doi:10.1186/s40035-024-00432-x
13. Fernández-Calle R, Konings SC, Frontiñán-Rubio J, et al. APOE in the bullseye of neurodegenerative diseases: Impact of the APOE genotype in Alzheimer's disease pathology and brain diseases. Mol Neurodegener. 2022;17(1):62. doi:10.1186/s13024-022-00566-4

14. Maiti TK, Konar S, Bir S, Kalakoti P, Bollam P, Nanda A. Role of apolipoprotein E polymorphism as a prognostic marker in traumatic brain injury and neurodegenerative disease: A critical review. Neurosurg Focus. 2015;39(5):E3. doi:10.3171/2015.8.focus15329

15. Armstrong RA. Risk factors for Alzheimer's disease. Folia Neuropathol. 2019;57(2):87-105. doi:10.5114/fn.2019.85929

16. Merritt VC, Maihofer AX, Gasperi M, et al. Genome-wide association study of traumatic brain injury in U.S. military veterans enrolled in the VA million veteran program. Mol Psychiatry. 2024;29(1):97-111. doi:10.1038/s41380-023-02304-8

17. DeKosky ST, Kaufer DI, Hamilton RL, Wolk DA, and Lopez OL. The Dementias. In: Bradley WG, Daroff RB, Fenichel GM, and Jankovic J., eds. Neurology in Clinical Practice. Elsevier; 2008:1855-1907:chap 70.

18. Boyle PA, Yu L, Leurgans SE, et al. Attributable risk of Alzheimer's dementia attributed to age-related neuropathologies. Ann Neurol. 2019;85(1):114-124. doi:10.1002/ana.25380

19. Vogel JW, Young AL, Oxtoby NP, et al. Four distinct trajectories of tau deposition identified in Alzheimer's disease. Nat Med. 2021;27(5):871-881. doi:10.1038/s41591-021-01309-6

20. Martin SP, Leeman-Markowski BA. Proposed mechanisms of tau: Relationships to traumatic brain injury, Alzheimer's disease, and epilepsy. Front Neurol. 2023;14:1287545. doi:10.3389/fneur.2023.1287545

21. Shcherbinin S, Evans CD, Lu M, et al. Association of amyloid reduction after Donanemab treatment with tau pathology and clinical outcomes: The TRAILBLAZER-ALZ randomized clinical trial. JAMA Neurol. 2022;79(10):1015-1024. doi:10.1001/jamaneurol.2022.2793

22. Sims JR, Zimmer JA, Evans CD, et al. Donanemab in early symptomatic Alzheimer disease: The TRAILBLAZER-ALZ 2 randomized clinical trial. JAMA. 2023;330(6):512-527. doi:10.1001/jama.2023.13239

23. Van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in early Alzheimer's disease. N Engl J Med. 2023;388(1):9-21. doi:10.1056/NEJMoa2212948

24. Alzheimer's Association. Traumatic brain Injury. Accessed February 27, 2023. Available from: https://www.alz.org/alzheimers-dementia/what-is-dementia/related_conditions/traumatic-brain-injury

25. Jack CR, Jr., Bennett DA, Blennow K, et al. A/T/N: An unbiased descriptive classification scheme for Alzheimer disease biomarkers. Neurology. 2016;87(5):539-47. doi:10.1212/wnl.0000000000002923

26. Vives-Rodriguez AL, Schiloski KA, Marin A, et al. Impact of amyloid PET in the clinical care of veterans in a tertiary memory disorders clinic. Alzheimers Dement (N Y). 2022;8(1):e12320. doi:10.1002/trc2.12320

27. Turk KW, Knobel MD, Nothern A, et al. An interprofessional team for disease-modifying therapy in Alzheimer disease implementation. Neurol Clin Pract. 2024;14(6):e200346. doi:10.1212/cpj.0000000000200346

28. 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 (PET). medRxiv. 2023;11.30.23298528. doi:10.1101/2023.11.30.23298528

29. Mohamed AZ, Nestor PJ, Cumming P, Nasrallah FA. Traumatic brain injury fast-forwards Alzheimer's pathology: Evidence from amyloid positron emission tomorgraphy imaging. J Neurol. 2022;269(2):873-884. doi:10.1007/s00415-021-10669-5

30. Rostowsky KA, Irimia A. Acute cognitive impairment after traumatic brain injury predicts the occurrence of brain atrophy patterns similar to those observed in Alzheimer's disease. Geroscience. 2021;43(4):2015-2039. doi:10.1007/s11357-021-00355-9

31. D'Souza GM, Churchill NW, Guan DX, et al. The relationship between history of traumatic brain injury and longitudinal changes in cortical thickness among patients with Alzheimer's disease. J Prev Alzheimers Dis. 2024;11(5):1348-1354. doi:10.14283/jpad.2024.86

32. Flavin WP, Hosseini H, Ruberti JW, Kavehpour HP, Giza CC, Prins ML. Traumatic brain injury and the pathways to cerebral tau accumulation. Front Neurol. 2023;14:1239653. doi:10.3389/fneur.2023.1239653

33. Friberg S, Lindblad C, Zeiler FA, et al. Fluid biomarkers of chronic traumatic brain injury. Nat Rev Neurol. 2024;20(11):671-684. doi:10.1038/s41582-024-01024-z

34. Barker S, Paul BD, Pieper AA. Increased risk of aging-related neurodegenerative disease after traumatic brain injury. Biomedicines. 2023;11(4). doi:10.3390/biomedicines11041154

35. Turner M, Belli A, Castellani RJ. Changes in brain structure and function in a multisport cohort of retired female and male athletes, many years after suffering a concussion: Implications for neuroplasticity and neurodegenerative disease pathogenesis. J Alzheimers Dis Rep. 2024;8(1):501-516. doi:10.3233/adr-240021

36. Self WK, Holtzman DM. Emerging diagnostics and therapeutics for Alzheimer disease. Nat Med. 2023;29(9):2187-2199. doi:10.1038/s41591-023-02505-2

37. Palmqvist S, Tideman P, Mattsson-Carlgren N, et al. Blood biomarkers to detect Alzheimer disease in primary care and secondary care. JAMA. 2024;332(15):1245-1257. doi:10.1001/jama.2024.13855

38. Meyer MR, Kirmess KM, Eastwood S, et al. Clinical validation of the PrecivityAD2 blood test: A mass spectrometry-based test with algorithm combining %p-tau217 and Aβ42/40 ratio to identify presence of brain amyloid. Alzheimers Dement. 2024;20(5):3179-3192. doi:10.1002/alz.13764

39. Brett BL, Gardner RC, Godbout J, Dams-O'Connor K, Keene CD. Traumatic brain injury and risk of neurodegenerative disorder. Biol Psychiatry. 2022;91(5):498-507. doi:10.1016/j.biopsych.2021.05.025

40. Bray MJC, Richey LN, Bryant BR, et al. Traumatic brain injury alters neuropsychiatric symptomatology in all-cause dementia. Alzheimers Dement. 2021;17(4):686-691. doi:10.1002/alz.12225

41. Xu J, Chen Y, Shi Y, et al. Associations between neuroinflammation-related conditions and Alzheimer's disease: A study of US insurance claims data. J Alzheimers Dis. 2024;99(2):739-752. doi:10.3233/jad-231286

42. Snowden TM, Hinde AK, Reid HMO, Christie BR. Does mild traumatic brain injury increase the risk for dementia? A systematic review and meta-analysis. J Alzheimers Dis. 2020;78(2):757-775. doi:10.3233/jad-200662

43. Graham A, Livingston G, Purnell L, Huntley J. Mild traumatic brain injuries and future risk of developing Alzheimer's disease: Systematic review and meta-analysis. J Alzheimers Dis. 2022;87(3):969-979. doi:10.3233/jad-220069

44. Mielke MM, Ransom JE, Mandrekar J, Turcano P, Savica R, Brown AW. Traumatic brain injury and risk of Alzheimer's disease and related dementias in the population. J Alzheimers Dis. 2022;88(3):1049-1059. doi:10.3233/jad-220159

45. De Guise E, Soucy B, Joubert S, Correa JA, Dagher JH. Risk factors for Alzheimer disease development after traumatic brain injury: A preliminary study. Alzheimer Dis Assoc Disord. 2022;36(4):354-358. doi:10.1097/wad.0000000000000481

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

47. Plassman BL, Havlik RJ, Steffens DC, et al. Documented head injury in early adulthood and risk of Alzheimer's disease and other dementias. Neurology. 2000;55(8):1158-66. doi:10.1212/wnl.55.8.1158

48. Zhang J, Zhang Y, Zou J, Cao F. A meta-analysis of cohort studies: Traumatic brain injury and risk of Alzheimer's disease. PLoS One. 2021;16(6):e0253206. doi:10.1371/journal.pone.0253206

49. Yashkin AP, Gorbunova GA, Tupler L, Yashin AI, Doraiswamy M, Akushevich I. Differences in risk of Alzheimer's disease following later-life traumatic brain injury in veteran and civilian populations. J Head Trauma Rehabil. 2023;38(6):E384-e393. doi:10.1097/htr.0000000000000865

50. Li W, Risacher SL, McAllister TW, Saykin AJ. Traumatic brain injury and age at onset of cognitive impairment in older adults. J Neurol. 2016;263(7):1280-5. doi:10.1007/s00415-016-8093-4

51. Gan S, Sun Y, Liu K, et al. APOE ε4 allele status modulates the spatial patterns of progressive atrophy in the temporal lobes after mild traumatic brain injury. Alzheimers Dement (Amst). 2024;16(1):e12550. doi:10.1002/dad2.12550

52. Aldrich G, Evans JE, Davis R, et al. APOE4 and age affect the brain entorhinal cortex structure and blood arachidonic acid and docosahexaenoic acid levels after mild TBI. Sci Rep. 2024;14(1):29150. doi:10.1038/s41598-024-80153-3

53. Logue MW, Miller MW, Sherva R, et al. Alzheimer's disease and related dementias among aging veterans: Examining gene-by-environment interactions with post-traumatic stress

disorder and traumatic brain injury. Alzheimers Dement. 2023;19(6):2549-2559. doi:10.1002/alz.12870

54. Chosy EJ, Gross N, Meyer M, et al. Brain injury and later-life cognitive impairment and neuropathology: The Honolulu-Asia Aging Study. J Alzheimers Dis. 2020;73(1):317-325. doi:10.3233/jad-190053

55. Bailey KC, Burmaster SA, Schaffert J, et al. Associations of race-ethnicity and history of traumatic brain injury with age at onset of Alzheimer's disease. J Neuropsychiatry Clin Neurosci. 2020;32(3):280-285. doi:10.1176/appi.neuropsych.19010002

56. Raza Z, Hussain SF, Ftouni S, et al. Dementia in military and veteran populations: A review of risk factors-traumatic brain injury, post-traumatic stress disorder, deployment, and sleep. Mil Med Res. 2021;8(1):55. doi:10.1186/s40779-021-00346-z

57. Akhanemhe R, Stevelink SAM, Corbett A, et al. Is lifetime traumatic brain injury a risk factor for mild cognitive impairment in veterans compared to non-veterans? Eur J Psychotraumatol. 2024;15(1):2291965. doi:10.1080/20008066.2023.2291965

58. Kennedy E, Panahi S, Stewart IJ, et al. Traumatic brain injury and early onset dementia in post 9-11 veterans. Brain Inj. 2022;36(5):620-627. doi:10.1080/02699052.2022.2033846

59. Howard E, Moody JN, Prieto S, Hayes JP. Higher cerebrospinal fluid levels of amyloid-β40 following traumatic brain injury relate to confrontation naming performance. J Alzheimers Dis. 2024;100(2):539-550. doi:10.3233/jad-240254

60. Li G, Iliff J, Shofer J, et al. CSF β-amyloid and tau biomarker changes in veterans with mild traumatic brain injury. Neurology. 2024;102(7):e209197. doi:10.1212/wnl.0000000000209197

61. Albrecht JS, Gardner RC, Wiebe D, Bahorik A, Xia F, Yaffe K. Comparison groups matter in traumatic brain injury research: An example with dementia. J Neurotrauma. 2022;39(21-22):1518-1523. doi:10.1089/neu.2022.0107

62. Moody JN, Howard E, Nolan KE, Prieto S, Logue MW, Hayes JP. Traumatic brain injury and genetic risk for Alzheimer's disease impact cerebrospinal fluid β-amyloid levels in Vietnam War veterans. Neurotrauma Rep. 2024;5(1):760-769. doi:10.1089/neur.2024.0048

63. Huang CH, Lin CW, Lee YC, et al. Is traumatic brain injury a risk factor for neurodegeneration? A meta-analysis of population-based studies. BMC Neurol. 2018;18(1):184. doi:10.1186/s12883-018-1187-0

64. Jellinger KA. Blunt Traumatic Brain Injury and Alzheimer Pathology. Dement Geriatr Cogn Disord. 2022;51(5):428-433. doi:10.1159/000527686

65. Leung KK, Carr FM, Russell MJ, Bremault-Phillips S, Triscott JAC. Traumatic brain injuries among veterans and the risk of incident dementia: A systematic review & meta-analysis. Age Ageing. 2022;51(1). doi:10.1093/ageing/afab194

66. LoBue C, Woon FL, Rossetti HC, Hynan LS, Hart J, Cullum CM. Traumatic brain injury history and progression from mild cognitive impairment to Alzheimer disease. Neuropsychology. 2018;32(4):401-409. doi:10.1037/neu0000431

67. Hendriks S, Ranson JM, Peetoom K, et al. Risk factors for young-onset dementia in the UK Biobank. JAMA Neurol. 2024;81(2):134-142. doi:10.1001/jamaneurol.2023.4929

68. Son S, Speechley M, Zou GY, et al. Potentially modifiable dementia risk factors in Canada: An analysis of Canadian Longitudinal Study on Aging with a multi-country comparison. J Prev Alzheimers Dis. 2024;11(5):1490-1499. doi:10.14283/jpad.2024.105

69. Schaffert J, LoBue C, Chiang HS, Peters ME, Hart J, Jr., Cullum CM. Traumatic brain injury characteristics are not related to neurocognitive decline in older adults: A nationwide longitudinal cohort study. Arch Clin Neuropsychol. 2024;39(3):325-334. doi:10.1093/arclin/acae003

70. Monsour MA, Wolfson DI, Jo J, Terry DP, Zuckerman SL. Is contact sport participation associated with chronic traumatic encephalopathy or neurodegenerative decline? A systematic review and meta-analysis. J Neurosurg Sci. 2023;doi:10.23736/s0390-5616.22.05895-7

71. Graham N, Zimmerman K, Heslegrave AJ, et al. Alzheimer's disease marker phospho-tau181 is not elevated in the first year after moderate-to-severe TBI. J Neurol Neurosurg Psychiatry. 2024;95(4):356-359. doi:10.1136/jnnp-2023-331854

72. Power MC, Murphy AE, Gianattasio KZ, et al. Association of military employment with late-life cognitive decline and dementia: A population-based prospective cohort study. Mil Med. 2023;188(5-6):e1132-e1139. doi:10.1093/milmed/usab413

73. Belding JN, Bonkowski J, Englert R, Grimes Stanfill A, Tsao JW. Associations between concussion and more severe TBIs, mild cognitive impairment, and early-onset dementia among military retirees over 40 years. Front Neurol. 2024;15:1442715. doi:10.3389/fneur.2024.1442715

74. Cummins TL, Doré V, Feizpour A, et al. Tau, β-amyloid, and glucose metabolism following service-related traumatic brain injury in Vietnam War veterans: The Australian Imaging Biomarkers and Lifestyle Study of Aging-Veterans Study (AIBL-VETS). J Neurotrauma. 2023;40(11-12):1086-1097. doi:10.1089/neu.2022.0172

75. Hayes JP, Pierce ME, Brown E, et al. Genetic risk for Alzheimer disease and plasma tau are associated with accelerated parietal cortex thickness change in middle-aged adults. Neurol Genet. 2023;9(1):e200053. doi:10.1212/nxg.0000000000200053

76. Weiner MW, Harvey D, Landau SM, et al. Traumatic brain injury and post-traumatic stress disorder are not associated with Alzheimer's disease pathology measured with biomarkers. Alzheimers Dement. 2023;19(3):884-895. doi:10.1002/alz.12712

77. Marcolini S, Rojczyk P, Seitz-Holland J, Koerte IK, Alosco ML, Bouix S. Posttraumatic stress and traumatic brain injury: Cognition, behavior, and neuroimaging markers in Vietnam veterans. J Alzheimers Dis. 2023;95(4):1427-1448. doi:10.3233/jad-221304

78. Vanderlinden G, Michiels L, Koole M, et al. Tau imaging in late traumatic brain injury: A [(18)F]MK-6240 positron emission tomography study. J Neurotrauma. 2024;41(3-4):420-429. doi:10.1089/neu.2023.0085

79. Hicks AJ, James AC, Spitz G, Ponsford JL. Traumatic brain injury as a risk factor for dementia and Alzheimer disease: Critical review of study methodologies. J Neurotrauma. 2019;36(23):3191-3219. doi:10.1089/neu.2018.6346

80. Clem MA, LoBue C, Schaffert J, Cullum CM. Traumatic brain injury and risk of incident dementia: Forensic applications of current research. Arch Clin Neuropsychol. 2024;40(2):289-301. doi:10.1093/arclin/acae076

81. Sugarman MA, McKee AC, Stein TD, et al. Failure to detect an association between self-reported traumatic brain injury and Alzheimer's disease neuropathology and dementia. Alzheimers Dement. 2019;15(5):686-698. doi:10.1016/j.jalz.2018.12.015

82. Wilmoth K, LoBue C, Clem MA, et al. Consistency of traumatic brain injury reporting in older adults with and without cognitive impairment. Clin Neuropsychol. 2018;32(3):524-529. doi:10.1080/13854046.2017.1378371

83. Raymont V, Thayanandan T. What do we know about the risks of developing dementia after traumatic brain injury? Minerva Med. 2021;112(2):288-297. doi:10.23736/s0026-4806.20.07084-6

84. Ly MT, Adler J, Ton Loy AF, Edmonds EC, Bondi MW, Delano-Wood L. Comparing neuropsychological, typical, and ADNI criteria for the diagnosis of mild cognitive impairment in Vietnam-era veterans. J Int Neuropsychol Soc. 2024;30(5):439-447. doi:10.1017/s135561772301144x

85. Scambray KA, Nguyen HL, Sajjadi SA. Association of vascular and degenerative brain pathologies and past medical history from the National Alzheimer's Coordinating Center Database. J Neuropathol Exp Neurol. 2023;82(5):390-401. doi:10.1093/jnen/nlad020

86. Janković T, Pilipović K. Single versus repetitive traumatic brain injury: Current knowledge on the chronic outcomes, neuropathology and the role of TDP-43 proteinopathy. Exp Neurobiol. 2023;32(4):195-215. doi:10.5607/en23008

87. Saltiel N, Tripodis Y, Menzin T, et al. Relative contributions of mixed pathologies to cognitive and functional symptoms in brain donors exposed to repetitive head impacts. Ann Neurol. 2024;95(2):314-324. doi:10.1002/ana.26823

88. Smolen P, Dash PK, Redell JB. Traumatic brain injury-associated epigenetic changes and the risk for neurodegenerative diseases. Front Neurosci. 2023;17:1259405. doi:10.3389/fnins.2023.1259405

89. Asken BM, Tanner JA, Vandevrede L, et al. Linking type and extent of head trauma to cavum septum pellucidum in older adults with and without Alzheimer disease and related dementias. Neurology. 2024;102(7):e209183. doi:10.1212/wnl.0000000000209183

90. Raji CA, Meysami S, Porter VR, Merrill DA, Mendez MF. Diagnostic utility of brain MRI volumetry in comparing traumatic brain injury, Alzheimer disease and behavioral variant frontotemporal dementia. BMC Neurol. 2024;24(1):337. doi:10.1186/s12883-024-03844-4

91. Plassman BL, Chanti-Ketterl M, Pieper CF, Yaffe K. Traumatic brain injury and dementia risk in male veteran older twins-Controlling for genetic and early life non-genetic factors. Alzheimers Dement. 2022;18(11):2234-2242. doi:10.1002/alz.12571

92. D'Souza GM, Churchill NW, Guan DX, et al. Interaction of Alzheimer disease and traumatic brain injury on cortical thickness. Alzheimer Dis Assoc Disord. 2024;38(1):14-21. doi:10.1097/wad.0000000000000607

93. Mueller SG. Traumatic brain injury and post-traumatic stress disorder and their influence on development and pattern of Alzheimer's disease pathology in later life. J Alzheimers Dis. 2024;98(4):1427-1441. doi:10.3233/jad-231183

94. Gibbons LE, Power MC, Walker RL, et al. Association of traumatic brain injury with late life neuropathological outcomes in a community-based cohort. J Alzheimers Dis. 2023;93(3):949-961. doi:10.3233/jad-221224

95. Graham NSN, Cole JH, Bourke NJ, Schott JM, Sharp DJ. Distinct patterns of neurodegeneration after TBI and in Alzheimer's disease. Alzheimers Dement. 2023;19(7):3065-3077. doi:10.1002/alz.12934

96. Dams-O'Connor K, Bellgowan PSF, Corriveau R, et al. Alzheimer's Disease-Related Dementias Summit 2019: National research priorities for the investigation of traumatic brain injury as a risk factor for Alzheimer's disease and related dementias. J Neurotrauma. 2021;38(23):3186-3194. doi:10.1089/neu.2021.0216

97. Dams-O'Connor K, Awwad HO, Hoffman S, et al. Alzheimer's Disease-Related Dementias Summit 2022: National research priorities for the investigation of post-traumatic brain injury Alzheimer's disease and related dementias. J Neurotrauma. 2023;40(15-16):1512-1523. doi:10.1089/neu.2022.0514

98. Jankovic J, Shannon KM. Movement Disorders. In: Bradley WG, Daroff RB, Fenichel GM, and Jankovic J, eds. Neurology in Clinical Practice. Elsevier; 2008:2087-2096:chap 75.

99. Bloem BR, Okun MS, Klein C. Parkinson's disease. Lancet. 2021;397(10291):2284-2303. doi:10.1016/s0140-6736(21)00218-x

100. Ilmaniemi S, Tolppanen AM, Herukka SK, Hartikainen P, Hartikainen S. Incidence and outcomes of head injuries in people with and without Parkinson disease. Eur J Neurol. 2023;30(6):1648-1657. doi:10.1111/ene.15782

101. Beylergil SB, Gupta P, ElKasaby M, Kilbane C, Shaikh AG. Does visuospatial motion perception correlate with coexisting movement disorders in Parkinson's disease? J Neurol. 2022;269(4):2179-2192. doi:10.1007/s00415-021-10804-2

102. Beylergil SB, Petersen M, Gupta P, Elkasaby M, Kilbane C, Shaikh AG. Severity-dependent effects of Parkinson's disease on perception of visual and vestibular heading. Mov Disord. 2021;36(2):360-369. doi:10.1002/mds.28352

103. Balta Beylergil S, Skelly P, Quagraine I, Kilbane C, Ghasia FF, Shaikh AG. Navigating visual challenges: How Parkinson's disease alters cognitive priorities in visual search. Mov Disord. 2024;39(9):1630-1635. doi:10.1002/mds.29907

104. Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord. 2015;30(12):1591-601. doi:10.1002/mds.26424

105. Campdelacreu J. Parkinson disease and Alzheimer disease: Environmental risk factors. Neurologia (Barcelona, Spain). 2014;29(9):541-9. doi:10.1016/j.nrl.2012.04.001

106. Saengphatrachai W, Praditukrit K, Owattanapanich W, Pitakpatapee Y, Srivanitchapoom P. The association between developing Parkinson's disease and β-Adrenoceptor acting agents use: A systematic review and meta-analysis. J Neurol Sci. 2021;430:120009. doi:10.1016/j.jns.2021.120009

107. Bruce HJ, Tripodis Y, McClean M, et al. American football play and Parkinson disease among men. JAMA Netw Open. 2023;6(8):e2328644. doi:10.1001/jamanetworkopen.2023.28644

108. Ascherio A, Schwarzschild MA. The epidemiology of Parkinson's disease: Risk factors and prevention. Lancet Neurol. 2016;15(12):1257-1272. doi:10.1016/s1474-4422(16)30230-7

109. Orayj K, Lane E. Patterns and determinants of prescribing for Parkinson's disease: A systematic literature review. Parkinsons Dis. 2019;2019:9237181. doi:10.1155/2019/9237181

110. Sharma A, Muresanu DF, Castellani RJ, et al. Mild traumatic brain injury exacerbates Parkinson's disease induced hemeoxygenase-2 expression and brain pathology: Neuroprotective effects of co-administration of TiO(2) nanowired mesenchymal stem cells and cerebrolysin. Prog Brain Res. 2020;258:157-231. doi:10.1016/bs.pbr.2020.09.010

111. Delic V, Beck KD, Pang KCH, Citron BA. Biological links between traumatic brain injury and Parkinson's disease. Acta Neuropathol Commun. 2020;8(1):45. doi:10.1186/s40478-020-00924-7

112. Gibbons CH, Levine T, Adler C, et al. Skin biopsy detection of phosphorylated α-synuclein in patients with synucleinopathies. JAMA. 2024;331(15):1298-1306. doi:10.1001/jama.2024.0792

113. Hall S, Orrù CD, Serrano GE, et al. Performance of αSynuclein RT-QuIC in relation to neuropathological staging of Lewy body disease. Acta Neuropathol Commun. 2022;10(1):90. doi:10.1186/s40478-022-01388-7

114. Jenkins PO, Roussakis AA, De Simoni S, et al. Distinct dopaminergic abnormalities in traumatic brain injury and Parkinson's disease. J Neurol Neurosurg Psychiatry. 2020;91(6):631-637. doi:10.1136/jnnp-2019-321759

115. Corrigan F, Wee IC, Collins-Praino LE. Chronic motor performance following different traumatic brain injury severity—A systematic review. Front Neurol. 2023;14:1180353. doi:10.3389/fneur.2023.1180353

116. Coppel D, Barber J, Temkin NR, Mac Donald CL. Longitudinal assessment of selective motor dysfunction in service members with combat-related mild TBI. Mil Med. 2024;doi:10.1093/milmed/usae400

117. Jones JD, Timblin H, Baxter F. Cumulative effect of head injuries on nonmotor outcomes in Parkinson's disease. J Neuropsychiatry Clin Neurosci. 2023;35(2):165-170. doi:10.1176/appi.neuropsych.21100257

118. Crane PK, Gibbons LE, Dams-O'Connor K, et al. Association of traumatic brain injury with late-life neurodegenerative conditions and neuropathologic findings. JAMA Neurol. 2016;73(9):1062-9. doi:10.1001/jamaneurol.2016.1948

119. Goldman SM, Tanner CM, Oakes D, Bhudhikanok GS, Gupta A, Langston JW. Head injury and Parkinson's disease risk in twins. Ann Neurol. 2006;60(1):65-72. doi:10.1002/ana.20882

120. Jafari S, Etminan M, Aminzadeh F, Samii A. Head injury and risk of Parkinson disease: A systematic review and meta-analysis. Mov Disord. 2013;28(9):1222-9. doi:10.1002/mds.25458

121. Balabandian M, Noori M, Lak B, Karimizadeh Z, Nabizadeh F. Traumatic brain injury and risk of Parkinson's disease: A meta-analysis. Acta Neurol Belg. 2023;123(4):1225-1239. doi:10.1007/s13760-023-02209-x

122. Khan N, Romila L, Ciobica A, Burlui V, Kamal FZ, Mavroudis I. Mild traumatic brain injury as a risk factor for parkinsonism, tics, and akathisia: A systematic review and meta-analysis. Life (Basel). 2023;14(1). doi:10.3390/life14010032

123. Gardner RC, Byers AL, Barnes DE, Li Y, Boscardin J, Yaffe K. Mild TBI and risk of Parkinson disease: A Chronic Effects of Neurotrauma Consortium Study. Neurology. 2018;90(20):e1771-e1779. doi:10.1212/wnl.0000000000005522

124. Gardner RC, Burke JF, Nettiksimmons J, Goldman S, Tanner CM, Yaffe K. Traumatic brain injury in later life increases risk for Parkinson disease. Ann Neurol. 2015;77(6):987-95. doi:10.1002/ana.24396

125. Taylor KM, Saint-Hilaire MH, Sudarsky L, et al. Head injury at early ages is associated with risk of Parkinson's disease. Parkinsonism Relat Disord. 2016;23:57-61. doi:10.1016/j.parkreldis.2015.12.005

126. Schiehser DM, Filoteo JV, Litvan I, Pirogovsky-Turk E, Lessig SL, Song DS. Cognitive functioning in individuals with Parkinson's disease and traumatic brain injury: A longitudinal study. Parkinsonism Relat Disord. 2016;30:58-61. doi:10.1016/j.parkreldis.2016.05.024

127. White DL, Kunik ME, Yu H, et al. Post-traumatic stress disorder is associated with further increased Parkinson's disease risk in veterans with traumatic brain injury. Ann Neurol. 2020;88(1):33-41. doi:10.1002/ana.25726

128. Scott GD, Neilson LE, Woltjer R, Quinn JF, Lim MM. Lifelong association of disorders related to military trauma with subsequent Parkinson's disease. Mov Disord. 2023;38(8):1483-1492. doi:10.1002/mds.29457

129. Nejtek VA, James RN, Salvatore MF, Alphonso HM, Boehm GW. Premature cognitive decline in specific domains found in young veterans with mTBI coincide with elder

normative scores and advanced-age subjects with early-stage Parkinson's disease. PLoS One. 2021;16(11):e0258851. doi:10.1371/journal.pone.0258851

130. Polimanti R, Chen CY, Ursano RJ, et al. Cross-phenotype polygenic risk score analysis of persistent post-concussive symptoms in U.S. army soldiers with deployment-acquired traumatic brain injury. J Neurotrauma. 2017;34(4):781-789. doi:10.1089/neu.2016.4550

131. Joyce JM, Monchi O, Ismail Z, et al. The impact of traumatic brain injury on cognitive and neuropsychiatric symptoms of Parkinson's disease. Int Rev Psychiatry. 2020;32(1):46-60. doi:10.1080/09540261.2019.1656177

132. Marras C, Hincapié CA, Kristman VL, et al. Systematic review of the risk of Parkinson's disease after mild traumatic brain injury: Results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. Arch Phys Med Rehabil. 2014;95(3 Suppl):S238-44. doi:10.1016/j.apmr.2013.08.298

133. Hasan S, Mielke MM, Turcano P, Ahlskog JE, Bower JH, Savica R. Traumatic brain injury preceding clinically diagnosed α-synucleinopathies: A case-control study. Neurology. 2020;94(8):e764-e773. doi:10.1212/wnl.0000000000008995

134. Factor-Litvak P, Al-Chalabi A, Ascherio A, et al. Current pathways for epidemiological research in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. 2013;14 Suppl 1(Suppl 1):33-43. doi:10.3109/21678421.2013.778565

135. Polverino M, Sampaolo S, Capuozzo A, et al. Respiratory function changes as early signs of amyotrophic lateral sclerosis. Respiration. 2023;102(11):919-923. doi:10.1159/000533870

136. Brooks BR, Miller RG, Swash M, Munsat TL. El Escorial revisited: Revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord. 2000;1(5):293-9. doi:10.1080/146608200300079536

137. Costa J, Swash M, de Carvalho M. Awaji criteria for the diagnosis of amyotrophic lateral sclerosis:a systematic review. Arch Neurol. 2012;69(11):1410-6. doi:10.1001/archneurol.2012.254

138. Chiò A, Logroscino G, Hardiman O, et al. Prognostic factors in ALS: A critical review. Amyotroph Lateral Scler. 2009;10(5-6):310-23. doi:10.3109/17482960802566824

139. Su WM, Cheng YF, Jiang Z, et al. Predictors of survival in patients with amyotrophic lateral sclerosis: A large meta-analysis. EBioMedicine. 2021;74:103732. doi:10.1016/j.ebiom.2021.103732

140. Wexler M. Causes of ALS. Accessed February 27, 2023. Available from: https://alsnewstoday.com/causes-of-als/

141. Tai H, Cui L, Shen D, Li D, Cui B, Fang J. Military service and the risk of amyotrophic lateral sclerosis: A meta-analysis. J Clin Neurosci. 2017;45:337-342. doi:10.1016/j.jocn.2017.08.035

142. McKay KA, Smith KA, Smertinaite L, Fang F, Ingre C, Taube F. Military service and related risk factors for amyotrophic lateral sclerosis. Acta Neurol Scand. 2021;143(1):39-50. doi:10.1111/ane.13345

143. Schwartzenburg J, Juncker M, Reed R, Desai S. Increased ISGylation in cases of TBI-exposed ALS veterans. J Neuropathol Exp Neurol. 2019;78(3):209-218. doi:10.1093/jnen/nly129

144. United States Department of Veteran Affairs. VA ALS System of Care. Updated 2024. Available from: https://www.va.gov/health/als.asp

145. Wang H, O'Reilly EJ, Weisskopf MG, et al. Smoking and risk of amyotrophic lateral sclerosis: A pooled analysis of 5 prospective cohorts. Arch Neurol. 2011;68(2):207-13. doi:10.1001/archneurol.2010.367

146. Zhou H, Chen G, Chen C, Yu Y, Xu Z. Association between extremely low-frequency electromagnetic fields occupations and amyotrophic lateral sclerosis: A meta-analysis. PLoS One. 2012;7(11):e48354. doi:10.1371/journal.pone.0048354

147. Wang MD, Little J, Gomes J, Cashman NR, Krewski D. Identification of risk factors associated with onset and progression of amyotrophic lateral sclerosis using systematic review and meta-analysis. Neurotoxicology. 2017;61:101-130. doi:10.1016/j.neuro.2016.06.015

148. Tamaki Y, Urushitani M. Molecular dissection of TDP-43 as a leading cause of ALS/FTLD. Int J Mol Sci. 2022;23(20). doi:10.3390/ijms232012508

149. Ling SC, Polymenidou M, Cleveland DW. Converging mechanisms in ALS and FTD: Disrupted RNA and protein homeostasis. Neuron. 2013;79(3):416-38. doi:10.1016/j.neuron.2013.07.033

150. Tzeplaeff L, Wilfling S, Requardt MV, Herdick M. Current state and future directions in the therapy of ALS. Cells. 2023;12(11). doi:10.3390/cells12111523

151. Blair HA. Tofersen: First approval. Drugs. 2023;83(11):1039-1043. doi:10.1007/s40265-023-01904-6

152. Russell ER, Mackay DF, Stewart K, MacLean JA, Pell JP, Stewart W. Association of field position and career length with risk of neurodegenerative disease in male former professional soccer players. JAMA Neurol. 2021;78(9):1057-1063. doi:10.1001/jamaneurol.2021.2403

153. Daneshvar DH, Mez J, Alosco ML, et al. Incidence of and mortality from amyotrophic lateral sclerosis in National Football League athletes. JAMA Netw Open. 2021;4(12):e2138801. doi:10.1001/jamanetworkopen.2021.38801

154. Bellomo G, Piscopo P, Corbo M, et al. A systematic review on the risk of neurodegenerative diseases and neurocognitive disorders in professional and varsity athletes. Neurol Sci. 2022;43(12):6667-6691. doi:10.1007/s10072-022-06319-x

155. Feddermann-Demont N, Junge A, Weber KP, Weller M, Dvořák J, Tarnutzer AA. Prevalence of potential sports-associated risk factors in Swiss amyotrophic lateral sclerosis patients. Brain Behav. 2017;7(4):e00630. doi:10.1002/brb3.630

156. Ramsay D, Miller A, Baykeens B, Hassan H, Gentleman S. Football (Soccer) as a probable cause of long-term neurological impairment and neurodegeneration: A narrative review of the debate. Cureus. 2023;15(1):e34279. doi:10.7759/cureus.34279

157. Zheng X, Wang S, Huang J, et al. Physical activity as risk factor in amyotrophic lateral sclerosis: A systematic review and meta-analysis. J Neurol. 2023;doi:10.1007/s00415-022-11555-4

158. Sagiraju HKR, Zivkovic S, VanCott AC, et al. Amyotrophic Lateral sclerosis among veterans deployed in support of post-9/11 U.S. conflicts. Mil Med. 2020;185(3-4):e501-e509. doi:10.1093/milmed/usz350

159. Shahim P, Norato G, Sinaii N, et al. Neurofilaments in sporadic and familial amyotrophic lateral sclerosis: A systematic review and meta-analysis. Genes (Basel). 2024;15(4). doi:10.3390/genes15040496

160. Kurtzke JF, Beebe GW. Epidemiology of amyotrophic lateral sclerosis: 1. A case-control comparison based on ALS deaths. Neurology. 1980;30(5):453-62. doi:10.1212/wnl.30.5.453

161. Schmidt S, Kwee LC, Allen KD, Oddone EZ. Association of ALS with head injury, cigarette smoking and APOE genotypes. J Neurol Sci. 2010;291(1-2):22-9. doi:10.1016/j.jns.2010.01.011

162. Chen H, Richard M, Sandler DP, Umbach DM, Kamel F. Head injury and amyotrophic lateral sclerosis. Am J Epidemiol. 2007;166(7):810-6. doi:10.1093/aje/kwm153

163. Liu G, Ou S, Cui H, et al. Head injury and amyotrophic lateral sclerosis: A meta-analysis. Neuroepidemiology. 2021:1-9. doi:10.1159/000510987

164. Fournier CN, Gearing M, Upadhyayula SR, Klein M, Glass JD. Head injury does not alter disease progression or neuropathologic outcomes in ALS. Neurology. 2015;84(17):1788-95. doi:10.1212/wnl.0000000000001522

165. Raj R, Kaprio J, Korja M, Mikkonen ED, Jousilahti P, Siironen J. Risk of hospitalization with neurodegenerative disease after moderate-to-severe traumatic brain injury in the working-age population: A retrospective cohort study using the Finnish national health registries. PLoS Med. 2017;14(7):e1002316. doi:10.1371/journal.pmed.1002316

166. Turner MR, Abisgold J, Yeates DG, Talbot K, Goldacre MJ. Head and other physical trauma requiring hospitalisation is not a significant risk factor in the development of ALS. J Neurol Sci. 2010;288(1-2):45-8. doi:10.1016/j.jns.2009.10.010

167. Peters TL, Fang F, Weibull CE, Sandler DP, Kamel F, Ye W. Severe head injury and amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. 2013;14(4):267-72. doi:10.3109/21678421.2012.754043

168. Franz CK, Joshi D, Daley EL, et al. Impact of traumatic brain injury on amyotrophic lateral sclerosis: From bedside to bench. J Neurophysiol. 2019;122(3):1174-1185. doi:10.1152/jn.00572.2018

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

170. Masi M, Biundo F, Fiou A, Racchi M, Pascale A, Buoso E. The labyrinthine landscape of APP processing: State of the art and possible novel soluble APP-related molecular players in traumatic brain injury and neurodegeneration. Int J Mol Sci. 2023;24(7). doi:10.3390/ijms24076639

171. Lillian A, Zuo W, Laham L, Hilfiker S, Ye JH. Pathophysiology and neuroimmune interactions underlying Parkinson's disease and traumatic brain injury. Int J Mol Sci. 2023;24(8). doi:10.3390/ijms24087186

172. Chiu LS, Anderton RS. The role of the microbiota-gut-brain axis in long-term neurodegenerative processes following traumatic brain injury. Eur J Neurosci. 2023;57(2):400-418. doi:10.1111/ejn.15892