

# The neurological risks of playing association football

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## Abstract

### Aims:

The present study aims to provide a narrative review of the literature surrounding concussion and head injury in football and its clarity in evaluating the risk of long-term neurological disease.

### Findings:

Epidemiological studies have shown correlations between participation in professional football and increased incidence of neurodegenerative disease and there have been reports of chronic traumatic encephalopathy (CTE) in the brains of former players in autopsy. These findings have been assumed by some to be the result of repetitive brain injury from head injuries and/or from heading the ball over a player's career. Data linking increased heading exposure with dementia is conflicting, and studies are limited by the reliance on retrospection and undocumented reports of concussion. It remains unclear whether CTE is unique to sportsmen or a variant of dementia pathology endemic in the population.

### Conclusions:

Although logically appealing, there is no current evidence that heading is the cause of neurodegeneration amongst footballers and risks should be balanced by the protective mental and physical benefits of the sport. Physicians have an important role in providing balanced views in this emotive and controversial area.

## Keywords

Association football, heading, neurodegenerative disorder, concussion, head trauma, dementia, chronic traumatic encephalopathy, traumatic brain injury, sub-concussive impact

players. Physicians have an important role in this debate. The public health issues concerning the safety of football regarding neurocognitive function, as well as the future of football as a recreational and professional game, are emotive areas which neurologists and general practitioners, with their extensive experience of neurological disease, can provide crucial expertise.

In this article, the authors look at the current evidence linking dementia to football and will give their opinion regarding the risks of football, and the role of physicians in making specific recommendations about football participation at all levels, the safety of heading, and management of head injury and its complications in football.

## Methods

Articles were obtained via manual searching of databases (Web of Science, PubMed, Google Scholar) using keywords. Articles were selected based on relevance to the topic as well as the quality of the investigative methods. Articles were also obtained from the reference section of selected papers. Articles were approved for inclusion by two investigators (OCC and NIH) and any disagreements were resolved via discussion.

## Evidence that football causes dementia in players

### *The link between dementia and traumatic brain injury*

There is increasing evidence that patients who have had a non-sports-related severe traumatic brain injury (TBI) have an increased risk of dementia.<sup>1</sup> This relationship, however, is generally assumed to be present and the effects of all-cause neurodegeneration and other psychological factors are often overlooked. It is also generally accepted that in the one sport where the causation of head injury is the aim of the sport,

## Introduction

There has been increasing concern about the risk of dementia in footballers. This has been driven by numerous high-profile cases, including five members of the 1966 England world cup winning team, but these concerns apply to youth, amateur, and professional

boxing, that multiple severe blows to the head cause dementia pugilistica which is a dementia syndrome with typical neurological features including an akinetic rigid syndrome.<sup>2</sup>

### Footballers are at risk of head injury

Head injuries accounted for two percent of football-related injuries, following lower limb injuries and upper limb injuries, in 23 European teams over seven consecutive seasons.<sup>3</sup> Severe head injury in football is uncommon but there have been high profile cases such as Ryan Mason, an England international player, who suffered a career-ending skull fracture/traumatic brain injury (TBI) in 2017. Mild TBI (mTBI)/concussion is more frequent and the incidence seems to be higher amongst female football players at the secondary and collegiate levels.<sup>4</sup> However, the incidence of concussion is likely underestimated compared to that seen in many other contact sports (such as Rugby) due to a combination of less rigorous pitchside assessment and downplaying of symptoms to avoid being prevented from returning to play. In addition, football's unique feature of heading the ball, both in practice and match situations, exposes players to repeated head impacts over the course of their playing career.

### Chronic traumatic encephalography (CTE) may be due to repeated head impacts

CTE describes dementia-related pathology that has been putatively associated with repetitive head impacts (RHI)

although there is increasing evidence from human pathological studies and animal models to suggest a causal link.<sup>5</sup> CTE produces progressive, neuropsychiatric, cognitive and motor dysfunction. Pathologically CTE is characterized by the presence of neurofibrillary tangles (NFT) of microtubule-associated hyperphosphorylated tau protein surrounding small vessels in the depths of cortical sulci, thorned astrocytes and abnormal deposits of TDP-43.<sup>6</sup> The pathology of CTE differs from Alzheimer's disease (AD) predominantly in the distribution and progression of NFTs across the cortical layers, which typically appear around small blood vessels.<sup>7</sup> In advanced CTE, widespread tau pathology dominates, however in older cases it can become more difficult to distinguish CTE from other neurodegenerative diseases due to the presence of multiple pathologies. Development of NFTs has been suggested to be the cause of cerebral atrophy, seen particularly in the superficial layers of the frontal and temporal cortices, reduced brain mass and widening of cortical sulci seen in CTE diagnosed patient's post-mortem. However, there have been cases of CTE with no demonstration of cortical atrophy, contusion, haemorrhage or infarct.<sup>8</sup>

Other gross manifestations include cavum septum pellucidum, dilation of the lateral and third ventricles and atrophy of the hippocampus, brainstem structures and the cerebellum. CTE symptoms include, but are not limited to headaches, depression, short-term memory loss, aggression, and irritability (Table 1).<sup>9</sup> The age of onset of CTE is said to be different from other neurodegenerative disorders with symptoms generally beginning to present a decade after the traumatic injuries. The

**Table 1.** Proposed summary of clinical symptoms of each stage of CTE progression.<sup>6</sup>

Symptom	Stage I (very mild)	Stage II (mild)	Stage III (moderate)	Stage IV (severe)
Headaches	x	x	x	x
Lack of concentration	x	x	x	x
Depression		x	x	x
Explosivity		x	x	x
Short-term memory loss		x	x	x
Executive dysfunction			x	x
Visuospatial abnormalities			x	x
Aggression			x	x
Severe memory loss				x
Paranoia				x
Suicidality				x

mean age of behavioural/mood symptom onset was 46.28 and the age of cognitive symptom onset was 53.28 in data collected from 211 CTE diagnosed patients in a recent publication.<sup>10</sup> This compares to AD which has an average age of symptom onset of 60, however, the onset of pathological insult is said to begin much earlier.

### *Dementia occurs in footballers*

There are numerous case studies in football players with dementia, the most well-known being that of Jeff Astle who died aged 59 years, just five years after being diagnosed with dementia which was later confirmed to be CTE in autopsy. The death of such a celebrated player led to a legal inquiry linking heading with the neurodegenerative disease for the first time. The largest scale study of association football players was carried out in 2019, which reviewed the medical records of 7676 deceased professional football players from the Scottish National League.<sup>11</sup> The study reported that mortality where the neurodegenerative disease was a primary or contributory cause was 2.9% in former players compared to 1.0% in matched controls. Prescription of dementia-related medication was also higher in former players than controls. CTE was also found to be a common co-morbidity in a recent study of 11 former football and rugby players.<sup>12</sup> Mixed pathologies were reported, including fenestrations ( $N=2$ ) and cavum septum pellucidum ( $N=3$ ), TDP-43 ( $N=4$ ) and cerebral amyloid angiopathy ( $N=4$ ). Suggesting that RHIs results in mixed pathologies reminiscent of AD, and CTE may represent a pattern of pathology rather than a specific diagnosis.

The clinical data over four decades of a group of 14 retired football players with dementia was analyzed in a 2017 study by Ling *et al.*<sup>13</sup> All participants in the study developed cognitive impairments with a mean age of onset of 63 years, despite six cases only experiencing one concussive episode throughout their careers. Four cases had pathologically confirmed CTE, with concomitant pathologies including AD ( $N=6$ ), TDP-43 ( $N=6$ ) and cerebral amyloid angiopathy ( $N=5$ ). The small sample size of this study prevents it from providing conclusive evidence but does imply that there is a correlation between exposure to RHIs and CTE pathology.

### *Concussion occurs in footballers*

Concussion is a neurological syndrome caused by a blow or acceleration/deceleration. Criteria for medical concussion can be defined as an immediate and transient alteration in brain function, including alteration of mental status or level of consciousness. The overall mean number of concussions suffered by a typical footballer is one concussion per team every second season.<sup>3</sup> Most

cases of concussion in footballers occur when there is player-to-player contact or contact of the player with the goal woodwork or pitch barriers. This differs from the act of heading the ball which has been described as a sub-concussive impact without overt neurological symptoms. Heading a football causes mean head accelerations of less than 10 g while the minimum values for a sport-related concussion are 40–60 g.<sup>14</sup> A recent study of ball mechanics has suggested that it is in fact the speed of the ball that determines its force, rather than the mass or stiffness.<sup>15</sup> This contradicts the theory that the heavier leather balls used up until the late 1980s, were the cause of brain injury and instead implies that newer, faster plastic balls might be more damaging. The study suggested that goal kicks produce the highest heading ball speeds and replacement with throws for example may improve heading safety.

### *Footballers with concussions get symptoms and abnormalities on testing*

Early observations of neuropsychological abnormalities in football players made by Tysvaer's group found that out of 37 former players of the national Norwegian team, 81% demonstrated mild to severe deficits in attention, concentration, memory and judgment using the Wechsler Adult Intelligence Scale. Computed tomography analysis of the former players ( $N=33$ ) showed cerebral atrophy in a third of cases, of which those who categorized themselves as 'headers' (i.e. proficient and frequent headers of the ball) showed significantly higher levels when compared to 'non-headers'.<sup>16</sup> Surprisingly, EEG abnormalities were identified more frequently in 'non-headers'. They attributed this to non-headers being less skilled and less adept at bracing the neck muscles when heading the ball, thus causing more internal damage. This has critical implications for children and adolescents who have not yet developed heading techniques and are therefore more susceptible to structural damage.

White matter microstructural abnormalities and lower memory scores were reported with a threshold of 1800 headers per year in amateur footballers ( $N=37$ ) by Lipton *et al.*,<sup>17</sup> however this was not determined to be linked with incidence of concussions. A more recent study found increased mean diffusivity and radial diffusivity in the genu and body of the corpus callosum following acute concussion in collegiate level athletes.<sup>18</sup> Indicative of white matter destruction, specifically tissue microarchitectures and de-myelination which persisted once athletes became asymptomatic. The concussed group ( $N=82$ ) however, were athletes from multiple contact sports of which only 25 were football players. Studies with a direct focus on football as a risk factor for neurological impairments are lacking and are inconsistent in findings (Table 2).

**Table 2.** Summary of key studies evaluating participation in association football as a risk factor for neurological impairment.

Author and year	N	Research question/aims	Reported findings	Explanation
Wu <i>et al.</i> (2020) <sup>18</sup>	82	To study longitudinal recovery trajectories of white matter after sports-related concussion using diffusion tensor imaging (DTI)	Concussed athletes have higher DTI-derived mean diffusivity. Greater diffusivity was associated with worse clinical outcome.	Abnormalities in white matter are the result of pathophysiological changes such as axonal swelling, de-myelination that occur following concussive episodes and repetitive mTBI.
Mackay <i>et al.</i> (2019) <sup>11</sup>	7676	To characterise neurodegenerative disease in former professional football players	All-cause mortality was lower in former players than controls. Mortality with neurodegenerative disease as a primary or contributory cause was 2.9% vs. 1% in matched controls. Former players were more likely to be prescribed dementia-related medication.	Participation in association football is a risk factor for neurodegenerative disease and is associated with dementia in old age. Lower all-cause mortality rates are reflective of higher levels of physical activity and lower obesity levels.
Lee <i>et al.</i> (2019) <sup>12</sup>	7	To assess the neuropathologies of former soccer and rugby players with dementia as a co-morbidity.	Five of seven former soccer players with clinically diagnosed AD had CTE pathology. P-tau pathology was present in all cases and cavum septum pellucidum was present in four.	Mixed pathologies may reflect an older patient cohort and be responsible for the range of clinical diagnoses. CTE dementia may represent a pattern of pathology rather than a diagnosis.
Ling <i>et al.</i> (2017) <sup>13</sup>	14	To analyse the concussive history of a cohort of retired football players and examine the brain pathology post-mortem.	12 cases died from advanced neurodegenerative disease. Of six cases examined, four met the NINDS diagnostic criteria for CTE.	Pathologies are supportive of history of concussion (N=6) and repetitive trauma from heading the ball.
Tysvaer (1992) <sup>16</sup>	106	To provide a clinical and neuropsychological investigation of minor head trauma in soccer players	One-third of players showed central cerebral atrophy and 81% showed mild to severe neuropsychological impairment. Typical 'non-headers' had higher EEG abnormalities than 'headers'.	EEG abnormalities in non-headers are due to inferior heading technique and ability to brace neck muscles during heading compared to typical 'headers'.

## Evidence against football causing dementia

### *The problem of CTE*

So far there are only a handful of cases of CTE occurring in footballers. Secondly, it is far from clear whether CTE is unique to sportsmen or whether it is a naturally occurring variant of other dementia pathology endemic in the population. Preliminary data has shown CTE pathology in individuals with no known history of mTBI.<sup>19,20</sup> Recall bias may be an issue, as it is very common for concussions to go undocumented and forgotten. But the prevalence of CTE pathology in non-athletes and non-concussed individuals has yet to be explored in well-designed large-scale studies. Identifying appropriate

controls for cases of CTE is not straightforward and the extent to which tau pathology can be found in elderly healthy brains may help to improve this problem.

### *Conceptual confusion*

It has been assumed that concussion causes brain alterations that may lead to brain damage and subsequently cause dementia. While this may turn out to be the case, there are currently no studies in any sport that have definitively shown this chain of causation. The assumption of causality may arise from conceptual errors that are common in the field of sports medicine.

The first is that of the concept of the concussion itself. Current guidelines in sport mean that any injury with

neurological symptoms is assumed to be a brain injury (concussion). This may well be the safest course of action practically on the sports field, but there is currently no objective way to validate this and the presence of many mimics and the lack of certainty about the underlying pathophysiological processes generate false assumptions and mar consistent data collection in research.

The next issue is the second impact syndrome. Second impact syndrome is said to occur if a head injury occurs when the neurological environment is still in a vulnerable state of oedema after an initial injury, resulting in a far more extensive brain injury and death. However, this condition is incredibly rare, and most cases have occurred in adolescent athletes. Historically this was a driving factor in the development of concussion protocols to remove concussed players from the field of play. More recent motivation is the consistent finding that the risk of further mTBI is significantly raised until symptoms have resolved. Guidelines on return to play in the American Academy of Neurology state that athletes should be 'prohibited to return to play/practice (contact-risk activity) until a licensed healthcare provider has judged that the concussion has resolved, and the athlete is asymptomatic (using the Post-Concussion Symptom Scale or Graded Symptom Checklist) off medication'.<sup>21</sup> This has led to an assumption that preventing a premature return to play protects against brain damage and dementia, embedding the assumption that concussion causes dementia.

The second is that prolonged symptoms following concussion represent permanent brain damage. There is some evidence that biomarkers of neuronal damage are higher in athletes with prolonged symptoms after concussion.<sup>22</sup> However, prolonged symptoms after concussion may not be due to brain injury and other factors need to be considered. Migraine, vestibular and psychological factors can be difficult to distinguish from symptoms due to brain damage after injury and conflating all neurological symptoms with brain injury is probably incorrect.

### *Dementia has not been shown to be linked to players at risk*

Whilst the study of Mackay *et al.*<sup>11</sup> did show an increased risk of dementia in footballers the same study showed that dementia-related medication was prescribed less frequently to goalkeepers than outfield players. This may reflect the well-documented increased incidence of concussion in outfield players to goalkeepers and could support the argument that increased rates of heading the ball lead to a higher incidence of dementia-related disorders later in life. However, analysis of cases based on player position showed no significant difference in mortality between goalkeepers and outfield players where the neurodegenerative disease was listed as the primary

cause. In principle, this may contradict the theory that heading the ball is the primary cause of the progression as it is rare for goalkeepers to head the ball. However, this subgroup analysis was limited by low numbers of goalkeepers and the absence of evidence should not be taken as negative evidence against this theory.

### *Inconclusive evidence linking mTBI and dementia*

In the general population, the evidence linking mTBI with dementia is lacking and most authorities maintain that the evidence for mTBI as a risk factor for dementia is far from being conclusive. No significant association was drawn between mTBI with or without loss of consciousness in a meta-analysis of risk factors for AD in adults.<sup>23</sup> Head injury without loss of consciousness was associated with dementia, but head injury with loss of consciousness was not in another often-cited study.<sup>24</sup> Loss of consciousness is a widely accepted hallmark of brain injury. Similarly, a large-scale neuropathological examination of 7130 subjects found no association between TBI with loss of consciousness and AD pathology but did find an increase in Parkinson's disease and Lewy body aggregation.<sup>25</sup>

The lack of conclusiveness of the aforementioned studies of dementia as a direct result of head trauma leads us to believe that other risk factors may be at play. Opiate use has been linked previously to amyloid precursor protein-positive axonal abnormalities.<sup>26</sup> Mental health problems are also a risk factor for prolonged health problems after sport-related concussion and the nature of symptoms seen in many ex-players could convincingly reflect a functional cognitive disorder confused with early-onset dementia. Performance validity failure in neuropsychological testing is relatively common and factors such as fatigue, pain and memory impairment can divert attention towards or away from symptoms and further distort results.

Population-based cohort studies suggest that the risk of dementia is slightly higher in those with a history of TBI, particularly in the first six months after injury.<sup>27</sup> This high initial incidence could easily be attributed to direct cognitive impairment due to TBI or a result of reverse causality. Even so, if the findings are true this would account for less than 1 additional case of dementia per 100 at the age of 70. Research is further limited by the inherent difficulties in knowing every neurotraumatic episode that an individual has ever experienced, commonly known as 'recall bias'. Pathological examination is also restricted to an autopsy, so the progression of the disease cannot be followed.

### **Conclusions**

There are a number of conclusions to be drawn from the current evidence.

1. There is currently no direct evidence that head injuries in contact sport are associated with transient acute neurological symptoms suggesting brain dysfunction and or heading footballs leads to permanent brain damage.
2. Although there is evidence for an increased risk of dementia (and other neurodegenerative diseases) in professional footballers, the mechanisms underlying this are unclear and although logically appealing there is no current evidence that head injury or heading the football are direct causes. Although CTE pathological changes do occur in footballers, the incidence of this pathology in this group and in control populations is not currently known.
3. While there is evidence that returns to play protocols protect athletes from further acute (and potentially more severe) injuries, there is no evidence that they protect against long-term neurocognitive problems suffered by footballers such as dementia.
4. Any risks of neurocognitive decline in later life in footballers must be balanced by the physical and mental health benefits of playing that have been clearly demonstrated. The authors of this paper, therefore, do not feel that there is currently enough evidence to change the rules of the game to stop heading in players with the capacity to take a view about the risks, whereas, in children under the age of 16, a heading ban in games and in training may be the more ethically correct advice.
3. Return to play protocols protects athletes from further acute brain injury, but there is no evidence that they protect against long-term neurocognitive problems.
4. Doctors should advocate gold standard management of acute head injuries in football but should also provide a balanced view that takes into account the physical and mental health benefits of playing football before advocating rule changes to the game.

### Declarations


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### References

1. Graham NS and Sharp DJ. Understanding neurodegeneration after traumatic brain injury: from mechanisms to clinical trials in dementia. *J Neurol Neurosurg Psychiatry* 2019; 90(11): 1221–1233.
2. Martland HS. Punch drunk. *J Am Med Assoc* 1928; 91(15): 1103–1107.
3. Ekstrand J, Häggglund M and Waldén M. Injury incidence and injury patterns in professional football: the UEFA injury study. *Br J Sports Med* 2011; 45(7): 553–558.
4. Gessel LM, Fields SK, Collins CL, Dick RW and Comstock RD. Concussions among United States high school and collegiate athletes. *J Athl Train* 2007; 42(4): 495–503.
5. Tagge CA, Fisher AM, Minaeva OV, et al. Concussion, microvascular injury, and early tauopathy in young athletes after impact head injury and an impact concussion mouse model. *Brain* 2018; 141(2): 422–458.
6. McKee AC, Stern RA, Nowinski CJ, et al. The spectrum of disease in chronic traumatic encephalopathy. *Brain* 2013; 136(Pt 1): 43–64.
7. Turner RC, Lucke-Wold BP, Robson MJ, Lee JM and Bailes JE. Alzheimer's disease and chronic traumatic encephalopathy: distinct but possibly overlapping disease entities. *Brain Inj* 2016; 30(11): 1279–1292.
8. Omalu BI, DeKosky ST, Minster RL, Kamboh MI, Hamilton RL and Wecht CH. Chronic traumatic encephalopathy in a national football league player. *Neurosurgery* 2005; 57(1): 128–134; discussion –34.
9. McKee AC, Cairns NJ, Dickson DW, et al. The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy. *Acta Neuropathol* 2016; 131(1): 75–86.

This is a rapidly evolving field and ongoing epidemiological studies in combination with the use of advanced biomarkers of brain injury including imaging (DTI, tau PET), fluid (CSF, blood and saliva) and careful neuropsychological testing may help to clarify some of the current controversies. Doctors have an important role both in clarifying the current state of evidence regarding the relationship between football and dementia, but also in directing future research. Decisions about rule changes in sport are made by governing bodies under huge public pressure and following the science is only one aspect of the decision-making process in this emotive and controversial area.

### Key points

1. While there is an indication that professional footballers have a higher incidence of dementia than the general population, there is no current evidence that repetitive concussive injuries or heading leads to permanent alterations in brain functioning.
2. CTE pathology is a tau-related pathology not restricted to sportsmen and women and maybe a variant of dementia in normal ageing brains.

10. Alosco ML, Mez J, Tripodis Y, et al. Age of first exposure to tackle football and chronic traumatic encephalopathy. *Ann Neurol* 2018; 83(5): 886–901.
11. Mackay DF, Russell ER, Stewart K, MacLean JA, Pell JP and Stewart W. Neurodegenerative disease mortality among former professional soccer players. *N Engl J Med* 2019; 381(19): 1801–1808.
12. Lee EB, Kinch K, Johnson VE, Trojanowski JQ, Smith DH and Stewart W. Chronic traumatic encephalopathy is a common co-morbidity, but less frequent primary dementia in former soccer and rugby players. *Acta Neuropathol* 2019; 138(3): 389–399.
13. Ling H, Morris HR, Neal JW, et al. Mixed pathologies including chronic traumatic encephalopathy account for dementia in retired association football (soccer) players. *Acta Neuropathol* 2017; 133(3): 337–352.
14. Naunheim RS, Standeven J, Richter C and Lewis LM. Comparison of impact data in hockey, football, and soccer. *J Trauma* 2000; 48(5): 938–941.
15. Tierney GJ, Power J and Simms C. Force experienced by the head during heading is influenced more by speed than the mechanical properties of the football. *Scand J Med Sci Sports* 2021; 31: 124–131.
16. Tysvaer AT. Head and neck injuries in soccer. Impact of minor trauma. *Sports Med* 1992; 14(3): 200–213.
17. Lipton ML, Kim N, Zimmerman ME, et al. Soccer heading is associated with white matter microstructural and cognitive abnormalities. *Radiology* 2013; 268(3): 850–857.
18. Wu Y-C, Harezlak J, Elsaid NMH, et al. Longitudinal white-matter abnormalities in sports-related concussion. *A Diffusion MRI Study* 2020; 95(7): e781–ee92.
19. Iverson GL, Luoto TM, Karhunen PJ and Castellani RJ. Mild chronic traumatic encephalopathy neuropathology in people with no known participation in contact sports or history of repetitive neurotrauma. *J Neuropathol Exp Neurol* 2019; 78(7): 615–625.
20. Ling H, Holton JL, Shaw K, Davey K, Lashley T and Revesz T. Histological evidence of chronic traumatic encephalopathy in a large series of neurodegenerative diseases. *Acta Neuropathol* 2015; 130(6): 891–893.
21. Giza CC, Kutcher JS, Ashwal S, et al. Summary of evidence-based guideline update: evaluation and management of concussion in sports: report of the guideline development subcommittee of the American academy of neurology. *Neurology* 2013; 80(24): 2250–2257.
22. Shahim P, Zetterberg H, Tegner Y and Blennow K. Serum neurofilament light as a biomarker for mild traumatic brain injury in contact sports. *Neurology* 2017; 88(19): 1788–1794.
23. Xu W, Tan L, Wang H-F, et al. Meta-analysis of modifiable risk factors for Alzheimer’s disease. *J Neurol Neurosurg Psychiatry* 2015; 86(12): 1299–1306.
24. Li Y, Li Y, Li X, et al. Head injury as a risk factor for dementia and Alzheimer’s disease: a systematic review and meta-analysis of 32 observational studies. *PLOS ONE* 2017; 12(1): e0169650.
25. Crane PK, Gibbons LE, Dams-O’Connor K, et al. Association of traumatic brain injury with late-life neurodegenerative conditions and neuropathologic findings. *JAMA Neurol* 2016; 73(9): 1062–1069.
26. Ryu J, Horkayne-Szakaly I, Xu L, et al. The problem of axonal injury in the brains of veterans with histories of blast exposure. *Acta Neuropathol Commun* 2014; 2():153.
27. Fann JR, Ribe AR, Pedersen HS, et al. Long-term risk of dementia among people with traumatic brain injury in Denmark: a population-based observational cohort study. *Lancet Psychiatry* 2018; 5(5): 424–431.