

# Neuroimaging and advanced research techniques may lead to improved outcomes in military members suffering from traumatic brain injury

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## ABSTRACT

Recent military conflicts in Iraq and Afghanistan have resulted in the significant increase in blast-related traumatic brain injury (TBI), leading to increased Department of Defense interest in its potential long-term effects ranging from the mildest head injuries termed subconcussive trauma to the most debilitating termed chronic traumatic encephalopathy (CTE). Most patients with mild TBI will recover quickly while others report persistent symptoms called postconcussive syndrome. Repeated concussive and subconcussive head injuries result in neurodegenerative conditions that may hinder the injured for years. Fundamental questions about the nature of these injuries and recovery remain unanswered. Clinically, patients with CTE present with either affective changes or cognitive impairment. Genetically, there have been no clear risk factors identified. The discovery that microglia of the cerebral cortex discharged small extracellular vesicles in the injured and adjacent regions to a TBI may soon shed light on the immediate impact injury mechanisms. The combination of neuroimaging and advanced research techniques may, one day, fill critical knowledge gaps and lead to significant TBI research and treatment advancements.

The current understanding of head trauma views concussion and traumatic brain injury (TBI) as injuries that exist along a spectrum, rather than as discrete events. The mildest head injuries are termed subconcussive trauma and the most chronic, debilitating events lead to profound systemic dysregulation known as chronic traumatic encephalopathy (CTE).<sup>1</sup> Subconcussive events are believed to be those injuries that incur brain damage but do not result in noticeable symptoms.<sup>2,3</sup> More severe than subconcussive events are minor TBIs where the head either strikes, or is struck by, an object.<sup>2</sup> During impact to the head, the brain is pushed against the inside of the skull which can cause bruising, bleeding, and tearing of nerve fibers. Although widely varied, symptoms of a concussion can include headache, dizziness, slurred speech and fatigue among many others.<sup>4</sup> Usually, given time and adequate rest, or cessation of at-risk activity, the symptoms of a concussion resolve within 10 days. However, if these symptoms persist, the classification of the injury changes and is dependent on the length of time before symptom resolution. If symptoms linger for longer than 10 days but less than approximately 3 months, the concussion

## Highlights

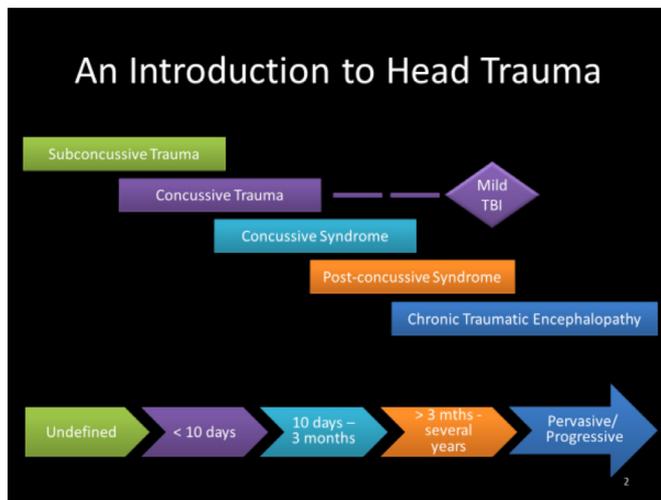
- ▶ Each year, 1 700 000 people in the USA sustain traumatic brain injuries (TBI) from which 52 000 will die. TBI is the contributing factor to 30% of all injury-related deaths in the USA and there are 3.2–5.3 million people in the USA currently living with TBI-related long-term disabilities.
- ▶ Recent military conflicts in Iraq and Afghanistan have resulted in the significant increase in blast-related TBI.
- ▶ Possible links between TBI, post-traumatic stress disorders and suicide are suspected and perhaps even probable.
- ▶ Most patients with mild TBI will recover quickly while others report persistent symptoms called postconcussive syndrome.
- ▶ Repeated concussive and subconcussive head injuries result in neurodegenerative conditions that may hinder the injured for years if not in perpetuity.
- ▶ Genetically, there have been no genes described as clear risk factors, although apolipoprotein E4 carriers have been reported to suffer more severely after TBI.
- ▶ Microglia of the cerebral cortex discharge small extracellular vesicles in the injured and adjacent regions to a TBI which may soon shed light on the immediate impact injury and secondary injury mechanisms.

has become a concussive syndrome.<sup>5,6</sup> If symptoms persist for longer than 3 months, up to and including several years, the injury is no longer seen as a single episodic event and is termed postconcussive syndrome.<sup>6,7</sup> If the symptoms become pervasive and/or permanent, this chronic outgrowth of head trauma is known as CTE.<sup>7</sup> Currently, the only definitive diagnosis for CTE is a postmortem examination of brain tissue.<sup>1</sup> Most tragically, the clinical features of CTE often mirror characteristic of Parkinson's disease and Alzheimer's disease, and like these two devastating conditions there is no known cure for the malady of CTE.<sup>8–11</sup> A graphical depiction of the spectrum of head trauma can be found in [figure 1](#) and [table 1](#).

The constellation of symptoms after a concussion or head trauma is both complex and problematic. Proper diagnosis, treatment, and prediction

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**Figure 1** The spectrum of traumatic brain injury (TBI).

of outcomes after any gradation of head injury are difficult and prone to significant error and subjective bias.<sup>1</sup> Due to the heterogeneity of symptom presentation and the disparate factors underlying pathology, in addition to probable genetic precursors (eg, apolipoprotein E<sup>12-14</sup> and allelic inheritance), accurate assessment of injury, severity, and recovery is nearly impossible at this juncture.<sup>11</sup>

Despite the greater awareness and pronounced increase in funding of research into TBIs, TBI still imposes a significant societal burden in terms of lost work time,<sup>15 16</sup> medical care costs,<sup>17 18</sup> and neuropsychiatric complications.<sup>19 20</sup> Each year in the USA, at least 1 692 000 people sustain TBI. This includes 52 000 deaths, 275 000 hospitalizations, and 1 365 000 patients treated and released from an emergency department.<sup>21</sup> TBI is a contributing factor to 30% of all injury-related deaths in the USA. It is estimated that 3 200 000–5 300 000 persons currently live with long-term physical and neuropsychiatric disabilities attributable to TBI.<sup>22</sup> Even with the increased focus on the assessment of TBI of all severities, much work remains to be done to fully

elucidate the various causes and outcomes along the spectrum of injuries. After the publication of the preceding work, significant cross-modal, multicenter studies in TBI risk factors, etiology, assessment and outcomes have been undertaken, with varying degrees of success.<sup>23</sup> Researchers are increasingly skeptical of the discovery of the ‘magic bullet’, one-size-fits-all biomarker of neuronal or systemic damage as a clear, indisputable indicator of TBI. Current studies are shifting the onus towards the formulation of the aforementioned ‘trauma panel’: a compendium of proteins or biomarkers whose dysregulation and presence in cerebral spinal fluid or the peripheral blood may be indicative of a level of central nervous system disruption, neuronal damage or systemic loss of homeostatic balance. Recently, the Food and Drug Administration approved a ‘concussion test’ via peripheral blood draw that assesses the presence/level of a pair of proteins in the peripheral blood: glial fibrillar acidic protein and ubiquitin carboxy-terminal hydrolase L1 at 12 hours after a suspected injury.<sup>24–27</sup> This is exciting news because we specifically highlighted these proteins, among others, earlier in our work.<sup>28</sup> However, this is only one of many steps that need to be undertaken to paint a fuller picture of this troubling disease/condition.

These new discoveries and the renewed focus on the course and impact of TBI have laid the groundwork for some truly novel experimental approaches and collaborative efforts. Perhaps some of the most fertile and untapped territory, however, is the design and implementation of head injury studies focusing on armed services personnel currently deployed, or returning from deployment, in the Middle East and other combat zones. Significant numbers of men and women in uniform sustain TBI resulting from, and in conjunction with, injuries sustained in combat. In contrast to even some of the most rigorously designed multicenter studies of head trauma in academic centers, inclusion criteria for a TBI study involving armed services personnel would be relatively straightforward. Postacute and rehabilitation care provided to uniformed service members by the military could be more centralized which would significantly aid in data collection and patient stratification. The significance of focusing on those returning from combat deployment is readily apparent: they suffer the worst injuries/TBIs (with the possible exception

**Table 1** Syndrome clinical manifestations

Timeline	Syndromes	Clinical manifestations		Source
		Type	Symptom	
Undefined <10 days	Subconcussive trauma	Typically undiagnosed	Accumulative effect	43–46
	Concussive trauma	Somatic symptoms	Headache, dizziness, nausea, vomiting, slurred speech imbalance, vacant stare, disorientation, or delayed response	47–53
		Cognitive symptoms	Confusion, temporary loss of consciousness, or poor concentration and attention	47–53
10 days to 3 months	Concussive syndrome	Somatic symptoms	Headache, visual disturbance, dizziness, nausea, vomiting, gait balance control difficulties, photophobia, and phonophobia	54–60
		Cognitive symptoms	Fatigue, drowsiness, difficulty concentrating, cognitive slowing, motor planning	54–60
>3 months to several years	Postconcussive syndrome	Somatic symptoms	Headache, visual disturbance, dizziness, nausea, vomiting, balance difficulties, photophobia, and phonophobia	48 52 61 62
		Cognitive symptoms	Fatigue, drowsiness, difficulty concentrating, cognitive slowing	48 52 61 62
		Sleep symptoms	Difficulty sleeping or sleeping more or less than usual	48 52 61 62
		Emotional symptoms	More emotional, sad, or irritable	48 52 61 62
Pervasive/progressive	Chronic traumatic encephalopathy	Somatic symptoms	Unsteady gait, slow muscular movements, hesitant speech, hand or head tremors	63–70
		Cognitive symptoms	Mental confusion and short-term memory loss	63–70
		Behavioral symptoms	Irritability, impulsivity, aggression, depression, suicidal tendencies	63–70

of athletes in contact and combat sports), have the most difficult to diagnose and triage combination of symptoms, and exhibit the poorest outcomes.<sup>29,30</sup> Additionally, links and potential cross-pollination with post-traumatic stress disorder (PTSD)<sup>31,32</sup> and the societal impact have been acknowledged and require further study. Well-designed and implemented studies with proper triage, outcome assessments and multidisciplinary approaches will elucidate previously unknown linkages between TBI and various ailments (PTSD, neuropsychiatric dysregulation, and so on) and facilitate applicable conclusions and treatments to the general populace and/or other at-risk groups (contact and combat sports participants).

We are on the cusp of a new age in TBI research and treatment and we believe that a proteomic and genomic approach to the study of this disease is vital to the discovery of its cure and treatment. Overall, there is a paucity of serum diagnostic, predictive and prognostic biomarkers in TBI and CTE to help in the early identification, predictions for response to treatment, and aid in treatment selection. There is thus an urgent need to identify novel blood-based biomarkers, that is, liquid biopsy for TBI and CTE. Liquid biopsies offer a rapid and minimally invasive technique to detect and evaluate these injuries and their progression. By analyzing those biomolecules (miRNA, mRNA, mDNA and proteins) that circulate in the potentially injured individual's serum/plasma and other body fluids, a liquid biopsy can be developed to easily and quickly diagnose if a service member on a battlefield or athlete in their arena has suffered a potential life-challenging injury, allowing leaders to know whether they can be put back into the arena or removed from this theater.

Recent investigations have shown that exosomes, membrane-bound nanovesicles (30–150 nm) released from cells, play an important role in physiologic processes and intercellular communication.<sup>33,34</sup> The role of exosomes in brain disease including TBI is still in its infancy but may hold promise as biomarkers as well as drug targets. Exosomes are excellent targets for liquid biopsy as they are easily detected in the serum and are stable at room temperature for hours.<sup>35–38</sup> Recent studies in cancer have suggested that specific exosomal miRNAs can serve as biomarkers and have also only begun to be investigated for their diagnostic, prognostic and theranostic properties.

Recently, using diffusion tensor imaging (DTI), blast-related TBI was shown to involve traumatic axonal injury.<sup>39</sup> DTI is an advanced form of MRI that is sensitive to axonal injury. Using DTI, axonal abnormalities have been found in US military personnel with blast-related mild TBI (mTBI). Substantial numbers of abnormalities were found in regions of the brain not known to be commonly injured in civilian cases of mTBI but predicted to be vulnerable to blast on the basis of computational simulations. Our goal is using these types of technologies to understand the biomolecules' molecular pathways and mechanisms to fully understand the individuals' injury and to decide on the proper course of treatment. Also, because DTI and, one day soon, liquid biopsies will be performed relatively quickly using MRI scanners positioned at sports stadiums and US military facilities and civilian hospitals, these assessments may be useful in diagnosis, triage, and treatment.

It is also vitally important to be aware of the potential for unforeseen impact as the efficacy of TBI assessment improves. While the benefits of injury treatment, and especially prevention, are self-evident, there are potential pitfalls with implementation of protocols designed to minimize risk. With the increased awareness of the dangers of concussion in the pediatric population, enrollment in youth football and other contact sports is declining precipitously.<sup>40–42</sup> Armed services personnel experience

a wide array of injuries while performing tasks essential to their duties.<sup>32</sup> Links between TBI and PTSD are suspected and perhaps even probable. Yet, the mechanistic underpinnings of how exactly the dysregulation caused by concussive events leads to the behaviors observed in post-traumatic stress have yet to be elucidated. Discovery of a panel of definitive trauma-specific biomarkers could, and would, lead to a fuller understanding of etiology and progression. However, great care must be taken in how to use our burgeoning knowledge. Removal from participation in contact sports based on a likelihood of injury could be problematic. Determinations of ineligibility for enlistment in the armed services or imposed limitations in scope of service or in specific roles that result from pre-emptive testing could have profound negative effects on the culture of service and sacrifice inherent in our military. The costs in manpower and personnel have the potential to be significant. Therefore, we must tread carefully in how we use and implement the knowledge that we acquire through the advancements in our methodologies.

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#### REFERENCES

- Elder GA, Ehrlich ME, Gandy S. Relationship of traumatic brain injury to chronic mental health problems and dementia in military veterans. *Neurosci Lett* 2019;707:134294.
- Iverson GL, Luoto TM, Karhunen PJ, 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;78:615–25.
- Shin N, Kim H-G, Shin HJ, Kim S, Kwon HH, Baek H, Yi M-H, Zhang E, Kim J-J, Hong J, et al. Uncoupled endothelial nitric oxide synthase enhances p-tau in chronic traumatic encephalopathy mouse model. *Antioxid Redox Signal* 2019;30:1601–20.
- Mallott JM, Palacios EM, Maruta J, Ghajar J, Mukherjee P. Disrupted white matter microstructure of the cerebellar peduncles in scholastic athletes after concussion. *Front Neurol* 2019;10:518.
- Mares C, Dagher JH, Harissi-Dagher M. Narrative review of the pathophysiology of headaches and photosensitivity in mild traumatic brain injury and concussion. *Can J Neurol Sci* 2019;46:14–22.
- Asselstine J, Kristman VL, Armstrong JJ, Dewan N. The Rivermead Post-Concussion questionnaire score is associated with disability and self-reported recovery six months after mild traumatic brain injury in older adults. *Brain Inj* 2020;34:195–202.
- Goetzl EJ, Ledreux A, Granholm A-C, Elahi FM, Goetzl L, Hiramoto J, Kapogiannis D. Neuron-Derived exosome proteins may contribute to progression from repetitive mild traumatic brain injuries to chronic traumatic encephalopathy. *Front Neurosci* 2019;13:452.
- Adams JW, Alvarez VE, Mez J, Huber BR, Tripodis Y, Xia W, Meng G, Kubilus CA, Cormier K, Kiernan PT, et al. Lewy body pathology and chronic traumatic

- encephalopathy associated with contact sports. *J Neuropathol Exp Neurol* 2018;77:757–68.
- 9 Cummings J, Ballard C, Tariot P, Owen R, Foff E, Youakim J, Norton J, Stankovic S. Pimavanserin: potential treatment for Dementia-Related psychosis. *J Prev Alzheimers Dis* 2018;5:253–8.
  - 10 Edlow BL, Keene CD, Perl DP, Iacono D, Folkert RD, Stewart W, Mac Donald CL, Augustinack J, Diaz-Arrastia R, Estrada C, et al. Multimodal characterization of the late effects of traumatic brain injury: a methodological overview of the late effects of traumatic brain injury project. *J Neurotrauma* 2018;35:1604–19.
  - 11 A Armstrong R. Risk factors for Alzheimer's disease. *Folia Neuropathol* 2019;57:87–105.
  - 12 Yousuf A, Khurshed N, Rasool I, Kundal V, Jeelani H, Afroze D. Genetic variation of APOE gene in ethnic Kashmiri population and its association with outcome after traumatic brain injury. *J Mol Neurosci* 2015;56:597–601.
  - 13 Tanriverdi F, Taheri S, Ulutabanca H, Caglayan AO, Ozkul Y, Dundar M, Selcuklu A, Unluhizarci K, Casanueva FF, Kelestimur F. Apolipoprotein E3/E3 genotype decreases the risk of pituitary dysfunction after traumatic brain injury due to various causes: preliminary data. *J Neurotrauma* 2008;25:1071–7.
  - 14 Mauri M, Sinforiani E, Bono G, Cittadella R, Quattrone A, Boller F, Nappi G. Interaction between apolipoprotein epsilon 4 and traumatic brain injury in patients with Alzheimer's disease and mild cognitive impairment. *Funct Neurol* 2006;21:223–8.
  - 15 Dewan MC, Mummaledy N, Wellons JC, Bonfield CM. Epidemiology of global pediatric traumatic brain injury: qualitative review. *World Neurosurg* 2016;91:497–509.
  - 16 Majdan M, Plancikova D, Maas A, Polinder S, Feigin V, Theadom A, Rusnak M, Brazinova A, Haagsma J. Years of life lost due to traumatic brain injury in Europe: a cross-sectional analysis of 16 countries. *PLoS Med* 2017;14:e1002331.
  - 17 Pavlov V, Thompson-Leduc P, Zimmer L, Wen J, Shea J, Beyhaghi H, Toback S, Kirson N, Miller M. Mild traumatic brain injury in the United States: demographics, brain imaging procedures, health-care utilization and costs. *Brain Inj* 2019;33:1151–7.
  - 18 van Dijk JTJM, Dijkman MD, Ophuis RH, de Ruiter GCW, Peul WC, Polinder S. In-hospital costs after severe traumatic brain injury: a systematic review and quality assessment. *PLoS One* 2019;14:e0216743.
  - 19 Yoo HS, Kim YW, Kim NY. Drug-induced parkinsonism manifesting as gait freezing in a patient with traumatic brain injury: a case report. *Clin Neuropharmacol* 2019;42:94–6.
  - 20 Clay FJ, Kuriakose A, Lesche D, Hicks AJ, Zaman H, Azizi E, Ponsford JL, Jayaram M, Hopwood M. Klüver-Bucy syndrome following traumatic brain injury: a systematic synthesis and review of pharmacological treatment from cases in adolescents and adults. *J Neuropsychiatry Clin Neurosci* 2019;31:6–16.
  - 21 Taylor CA, Bell JM, Breiding MJ, Xu L. Traumatic Brain Injury-Related Emergency Department Visits, Hospitalizations, and Deaths - United States, 2007 and 2013. *MMWR Surveill Summ* 2017;66:1–16.
  - 22 Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: global burden of disease study. *Lancet* 1997;349:1436–42.
  - 23 Yue JK, Vassar MJ, Lingsma HF, Cooper SR, Okonkwo DO, Valadka AB, Gordon WA, Maas AIR, Mukherjee P, Yuh EL, et al. Transforming research and clinical knowledge in traumatic brain injury pilot: multicenter implementation of the common data elements for traumatic brain injury. *J Neurotrauma* 2013;30:1831–44.
  - 24 Papa L, Zonfrillo MR, Welch RD, Lewis LM, Braga CF, Tan CN, Ameli NJ, Lopez MA, Haessler CA, Mendez Giordano D, et al. Evaluating glial and neuronal blood biomarkers GFAP and UCH-L1 as gradients of brain injury in concussive, subconcussive and non-concussive trauma: a prospective cohort study. *BMJ Paediatr Open* 2019;3:e000473.
  - 25 Joseph JR, Swallow JS, Willsey K, Lapointe AP, Khalatbari S, Korley FK, Oppenlander ME, Park P, Szerlip NJ, Broglio SP. Elevated markers of brain injury as a result of clinically asymptomatic high-acceleration head impacts in high-school football athletes. *J Neurosurg* 2018:1–7.
  - 26 Lugones M, Parkin G, Bjelosevic S, Takagi M, Clarke C, Anderson V, Ignjatovic V. Blood biomarkers in paediatric mild traumatic brain injury: a systematic review. *Neurosci Biobehav Rev* 2018;87:206–17.
  - 27 Lewis LM, Schloemann DT, Papa L, Fucetola RP, Bazarian J, Lindburg M, Welch RD. Utility of serum biomarkers in the diagnosis and stratification of mild traumatic brain injury. *Acad Emerg Med* 2017;24:710–20.
  - 28 Moyron RB, Wall NR. Differential protein expression in exosomal samples taken from trauma patients. *Proteomics Clin Appl* 2017;11:1700095.
  - 29 Glaser J, Vasquez M, Cardarelli C, Galvagno S, Stein D, Murthi S, Scalea T. Through the looking glass: early non-invasive imaging in TBI predicts the need for interventions. *Trauma Surg Acute Care Open* 2016;1:e000019.
  - 30 Kehoe A, Smith JE, Bouamra O, Edwards A, Yates D, Lecky F. Older patients with traumatic brain injury present with a higher GCS score than younger patients for a given severity of injury. *Emerg Med J* 2016;33:381–5.
  - 31 Hoffman AN, Lam J, Hovda DA, Giza CC, Fanselow MS. Sensory sensitivity as a link between concussive traumatic brain injury and PTSD. *Sci Rep* 2019;9:13841.
  - 32 Shackelford JL, Smith LS, Farrell CT, Neils-Strunjas J. Interrelationships among resilience, posttraumatic stress disorder, traumatic brain injury, depression, and academic outcomes in student military veterans. *J Psychosoc Nurs Ment Health Serv* 2019;57:35–43.
  - 33 Johnstone RM. Exosomes biological significance: a Concise review. *Blood Cells Mol Dis* 2006;36:315–21.
  - 34 van Niel G, Porto-Carreiro I, Simoes S, Raposo G. Exosomes: a common pathway for a specialized function. *J Biochem* 2006;140:13–21.
  - 35 Aspe JR, Diaz Osterman CJ, Jutzy JMS, Deshields S, Whang S, Wall NR. Enhancement of gemcitabine sensitivity in pancreatic adenocarcinoma by novel exosome-mediated delivery of the Survivin-T34A mutant. *J Extracell Vesicles* 2014;3:23244. [Epub ahead of print: 17 Apr 2014].
  - 36 Khan S, Bennis HF, Wall NR. The emerging role of exosomes in survivin secretion. *Histol Histopathol* 2015;30:43–50.
  - 37 Khan S, Jutzy JMS, Aspe JR, McGregor DW, Neidigh JW, Wall NR. Survivin is released from cancer cells via exosomes. *Apoptosis* 2011;16:1–12.
  - 38 Valenzuela MMA, Ferguson Bennis HR, Gonda A, Diaz Osterman CJ, Hibma A, Khan S, Wall NR. Exosomes secreted from human cancer cell lines contain inhibitors of apoptosis (IAP). *Cancer Microenviron* 2015;8:65–73.
  - 39 Mac Donald CL, Johnson AM, Cooper D, Nelson EC, Werner NJ, Shimony JS, Snyder AZ, Raichle ME, Witherow JR, Fang R, et al. Detection of blast-related traumatic brain injury in U.S. military personnel. *N Engl J Med* 2011;364:2091–100.
  - 40 Champagne AA, Distefano V, Boulanger M-M, Magee B, Coverdale NS, Gallucci D, Guskiewicz K, Cook DJ. Data-informed intervention improves football technique and reduces head impacts. *Med Sci Sports Exerc* 2019;51:2366–74.
  - 41 Sandmo SB, Andersen TE, Koerte IK, Bahr R. Head impact exposure in youth football-Are current interventions hitting the target? *Scand J Med Sci Sports* 2020;30:193–8.
  - 42 Sarmiento K, Thomas KE, Daugherty J, Waltzman D, Haarbauer-Krupa JK, Peterson AB, Haileyesus T, Breiding MJ. Emergency Department Visits for Sports- and Recreation-Related Traumatic Brain Injuries Among Children - United States, 2010–2016. *MMWR Morb Mortal Wkly Rep* 2019;68:237–42.
  - 43 Johnson B, Neuberger T, Gay M, Hallett M, Slobounov S. Effects of subconcussive head trauma on the default mode network of the brain. *J Neurotrauma* 2014;31:1907–13.
  - 44 Harris SA, Chivers PT, McIntyre FL, Piggott B, Bulsara M, Farrington FH. Exploring the association between recent concussion, subconcussive impacts and depressive symptoms in male Australian football players. *BMJ Open Sport Exerc Med* 2020;6:e000655.
  - 45 Rose SC, Yeates KO, Fuerst DR, Ercole PM, Nguyen JT, Pizzimenti NM. Head impact burden and change in neurocognitive function during a season of youth football. *J Head Trauma Rehabil* 2019;34:87–95.
  - 46 Tsushima WT, Ahn HJ, Siu AM, Yoshinaga K, Choi SY, Murata NM. Effects of repetitive subconcussive head trauma on the neuropsychological test performance of high school athletes: a comparison of high, moderate, and low contact sports. *Appl Neuropsychol Child* 2019;8:223–30.
  - 47 Kushner D. Mild traumatic brain injury: toward understanding manifestations and treatment. *Arch Intern Med* 1998;158:1617–24.
  - 48 Richey LN, Rao V, Roy D, Narapareddy BR, Wigh S, Bechtold KT, Sair HI, Van Meter TE, Falk H, Leoutsakos J-M, et al. Age differences in outcome after mild traumatic brain injury: results from the HeadSMART study. *Int Rev Psychiatry* 2020;32:22–30.
  - 49 Zasler N, Haider MN, Grzibowski NR, Leddy JJ. Physician medical assessment in a multidisciplinary concussion clinic. *J Head Trauma Rehabil* 2019;34:409–18.
  - 50 Rose SC, Yeates KO, Nguyen JT, McCarthy MT, Ercole PM, Pizzimenti NM. Neurocognitive function and head impact burden over two seasons of youth tackle football. *J Neurotrauma* 2019;36:2803–9.
  - 51 Chen J, Oddson B, Gilbert HC. Differential effect of recurrent concussions on symptom clusters in sport concussion assessment tool. *J Sport Rehabil* 2019;28:735–9.
  - 52 Corwin DJ, Arbogast KB, Haber RA, Pettijohn KW, Zonfrillo MR, Grady MF, Master CL. Characteristics and outcomes for delayed diagnosis of concussion in pediatric patients presenting to the emergency department. *J Emerg Med* 2020;59:795–804.
  - 53 Lumba-Brown A, Teramoto M, Bloom OJ, Brody D, Chesnut J, Clugston JR, Collins M, Gioia G, Kontos A, Lal A, et al. Concussion guidelines step 2: evidence for subtype classification. *Neurosurgery* 2020;86:2–13.
  - 54 Brenner LA, Forster JE, Stearns-Yoder KA, Stamper CE, Hoisington AJ, Brostow DP, Mealer M, Wortzel HS, Postolache TT, Lowry CA. Evaluation of an immunomodulatory probiotic intervention for veterans with co-occurring mild traumatic brain injury and posttraumatic stress disorder: a pilot study. *Front Neurol* 2020;11:1015.
  - 55 Eman Abdulle A, van der Naalt J. The role of mood, post-traumatic stress, post-concussive symptoms and coping on outcome after MTBI in elderly patients. *Int Rev Psychiatry* 2020;32:3–11.
  - 56 Gasquoine PG. Historical perspectives on evolving operational definitions of concussive brain injury: from Railway spine to sport-related concussion. *Clin Neuropsychol* 2020;34:278–95.
  - 57 Heslot C, Cogné M, Guillouët E, Perdrieau V, Lefevre C, Glize B, Bonan I, Azouvi P. Management of unfavorable outcome after mild traumatic brain injury: review of physical and cognitive rehabilitation and of psychological care in post-concussive syndrome. *Neurochirurgie* 2020. [Epub ahead of print: 10 Oct 2020].
  - 58 Mehrolhassani N, Movahedi M, Nazemi-Rafi M, Mirafzal A. Persistence of post-concussion symptoms in patients with mild traumatic brain injury and no psychiatric history in the emergency department. *Brain Inj* 2020;34:1350–7.
  - 59 Mercier LJ, Fung TS, Harris AD, Dukelow SP, Debort CT. Improving symptom burden in adults with persistent post-concussive symptoms: a randomized aerobic exercise trial protocol. *BMC Neurol* 2020;20:46.

- 60 Pitt W, Chou L-S. A case-control study of gait balance control in veterans with chronic symptoms following mTBI. *Gait Posture* 2020;76:188–92.
- 61 Morgan CD, Zuckerman SL, Lee YM, King L, Beaird S, Sills AK, Solomon GS. Predictors of postconcussion syndrome after sports-related concussion in young athletes: a matched case-control study. *J Neurosurg Pediatr* 2015;15:589–98.
- 62 Goreth MB, Palokas M. Association between premorbid neuropsychological conditions and pediatric mild traumatic brain injury/concussion recovery time and symptom severity: a systematic review. *JBI Database System Rev Implement Rep* 2019;17:1464–93.
- 63 Stein TD, Alvarez VE, McKee AC. Chronic traumatic encephalopathy: a spectrum of neuropathological changes following repetitive brain trauma in athletes and military personnel. *Alzheimers Res Ther* 2014;6:4.
- 64 Kelley CM, Perez SE, Mufson EJ. Tau pathology in the medial temporal lobe of athletes with chronic traumatic encephalopathy: a chronic effects of neurotrauma Consortium study. *Acta Neuropathol Commun* 2019;7:207.
- 65 Cantu R, Budson A. Management of chronic traumatic encephalopathy. *Expert Rev Neurother* 2019;19:1015–23.
- 66 Stern RA, Adler CH, Chen K, Navitsky M, Luo J, Dodick DW, Alosco ML, Tripodis Y, Goradia DD, Martin B, *et al.* Tau positron-emission tomography in former national football League players. *N Engl J Med* 2019;380:1716–25.
- 67 Robinson ME, McKee AC, Salat DH, Rasmusson AM, Radigan LJ, Catana C, Milberg WP, McGlinchey RE. Positron emission tomography of tau in Iraq and Afghanistan veterans with blast neurotrauma. *Neuroimage Clin* 2019;21:101651.
- 68 Iverson GL, Gardner AJ. Risk for Misdiagnosing chronic traumatic encephalopathy in men with anger control problems. *Front Neurol* 2020;11:739.
- 69 Ledreux A, Pryhoda MK, Gorgens K, Shelburne K, Gilmore A, Linseman DA, Fleming H, Koza LA, Campbell J, Wolff A, *et al.* Assessment of long-term effects of sports-related concussions: biological mechanisms and exosomal biomarkers. *Front Neurosci* 2020;14:761.
- 70 Spencer KR, Foster ZW, Rauf NA, Guilderson L, Collins D, Averill JG, Walker SE, Robey I, Cherry JD, Alvarez VE, *et al.* Neuropathological profile of long-duration amyotrophic lateral sclerosis in military veterans. *Brain Pathol* 2020;30:1028–40.