Long-term risk of cardiovascular disease after traumatic brain injury: screening and prevention

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Traumatic brain injury (TBI) is highly prevalent among individuals participating in contact sports, military personnel, and in the general population. Although it is well known that brain injury can cause neurological and psychiatric complications, evidence from studies on individuals exposed to a single or repetitive brain injuries suggests an understudied association between TBI and the risk of developing chronic cardiovascular diseases and risk factors for cardiovascular disease. Several studies have shown that people without pre-existing comorbidities who sustain a TBI have a significantly higher risk of developing chronic cardiovascular disease, than people without TBI. Similar observations made in military and professional American-style football cohorts suggest causal pathways through which modifiable cardiovascular risk factors might mediate the relationship between brain injury and chronic neurological diseases. A better understanding of cardiovascular disease risk after TBI combined with a proactive, targeted screening programme might mitigate long-term morbidity and mortality in individuals with TBI, and improve their quality of life.

Introduction

Traumatic brain injury (TBI) is a major cause of long-term disability and premature death.[1] This type of injury is highly prevalent among contact sports players, military personnel (eg, due to injuries sustained during conflict), and the general population (eg, due to falls and road traffic incidents).[2] Most studies on TBI have focused on links between single TBI events and chronic neurological and psychiatric consequences (eg, chronic traumatic encephalopathy, Parkinson's disease, and Alzheimer's disease).[3,4] Unfortunately, despite extensive neurologically focused TBI research over the past 50 years, surprisingly little advancement has been made in the reduction of long-term adverse outcomes and mortality.[1,5,6] The recognition of TBI as a chronic condition, rather than an acute sequelae of brain injury, allows for the investigation of non-neurological domains of health;[5] particularly chronic cardiovascular disease, including ischaemic heart disease, heart failure, and stroke. Cardiovascular risk factors (eg, hypertension, hyperlipidaemia, diabetes, obesity, and physical inactivity) have established associations with increased mortality and poor cognitive and other outcomes.[7] TBI has been shown to increase acute cardiovascular disease risk, but associations between TBI, chronic cardiovascular disease, and risk factors for cardiovascular disease have received little attention in comparison with neurological or psychiatric conditions after injury. For example, a report on the long-term consequences of TBI[8] evaluated 1900 studies on TBI in both civilian and military populations. The report reviewed neurocognitive, neurological, and psychiatric outcomes, as well as social functioning, brain tumours, and mortality. Notably, it did not explore any long-term cardiovascular outcomes after TBI. The 2020 *Lancet* Commission on dementia prevention, intervention, and care also recognised TBI as a dementia risk factor, but did not address whether and how cardiovascular risk factors of dementia, such as physical inactivity, obesity, and diabetes, might interact with TBI to contribute to the increased risk of dementia.[9] The 2022, *Lancet Neurology* Commission on traumatic brain injury defined the injury as a systemic disease and highlighted the TBI-related acute extracranial injuries. However, the Commission did not address the long-term risk of non-neurological conditions.[10]

Several studies of general populations, military veterans, and professional American-style football players have investigated the long-term incidence of cardiovascular disease and cardiovascular risk factors in individuals who sustained a TBI. These studies suggest a possible role of TBI in the risk of developing chronic cardiovascular disease and cardiovascular risk factors in individuals who sustained a single or repetitive TBI.[11–31] In this Personal View, we summarise evidence gathered in the past 5 years of the association between TBI and chronic risk of cardiovascular disease and cardiovascular risk factors in the general population, contact sports, and military settings, and identify knowledge gaps requiring further study. We discuss the potential underlying neurobiological mechanisms and propose research plans to further disentangle the chronic multi-organ effects of TBI and the interaction between these systems, particularly in otherwise healthy individuals. We highlight the need to identify markers of cardiovascular disease risk and investigate the safety and efficacy of cardiometabolic therapeutics in individuals who have sustained a TBI.

Long-term cardiovascular manifestations after a TBI

In this section, we review the association between TBI and cardiovascular risks, cardiovascular disease, and mortality. Relevant studies in general populations, military cohorts, and contact sport athletes with specific detail related to study design, TBI exposure and severity, and cardiovascular outcomes are listed in the table. We use the terminology brain injury as an umbrella term

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subsuming both single TBI and repetitive head impacts for clarity of presented information. We acknowledge that there has been ongoing debate on whether repetitive head impacts constitute a brain injury, as they can lead to a mild TBI, but might not cause symptoms after a hit to the head. We therefore additionally clarify injury severity and whether the brain injury was a single TBI or repetitive head impacts for studies in which this information was given.

TBI in the general population

Several general population studies have shown a heightened risk of long-term cardiovascular and metabolic disease beyond the acute phase (after 6 months) of a single TBI. All these studies were retrospective, used national or local registries, and were predominantly done in individuals with pre-existing cardiovascular conditions. For example, in a study by Lu and colleagues, which enrolled individuals with all TBI severities, with pre-existing cardiovascular risk factors and cardiovascular disease, TBI was an independent risk factor for myocardial dysfunction, defined as cardiac dysrhythmias, ischaemic heart disease, and heart failure.[11] Another study found that individuals who sustained a TBI who had been age-matched and sex-matched with people without a TBI, who had previous cardiovascular risk factors (but without previous myocardial dysfunction at baseline), had a significantly higher risk of ischaemic heart disease within 5 years after brain injury.[14] In a 10-year study of 400 individuals with moderate to severe TBI and pre-existing cardiovascular and medical conditions, the most common self-reported cardiovascular risk factors were hypertension, hypercholesterolaemia, and diabetes.[13] Although these studies are offering evidence of elevated cardiovascular risk subsequent to a single TBI, the inclusion of individuals with pre-existing medical comorbidities makes it difficult to determine the timing of incident cardiovascular disease and cardiovascular risk factors subsequent to brain injury. A few studies have included populations without pre-existing medical and cardiovascular comorbidities to measure the incidence, rather than prevalence, and to better refine the order and timing of cardiovascular disease and other risk factors in individuals with TBI. For example, a study of concussion survivors without pre-existing diagnoses showed that cardiovascular, endocrinological, and neuropsychiatric comorbidities occurred at a significantly higher incidence within 5 years after concussive TBI, compared with healthy individuals who were matched in terms of age, race, and sex and didn't have a TBI exposure.[15] A subsequent study was done in 4351 individuals with mild TBI and 4351 individuals with moderate to severe TBI, without any previous cardiovascular disease or cardiovasular risk factors, and 4351 individuals without a TBI matched according to age, sex, and race, who were followed up for up to 10 years. The study showed similar results, with a higher rate of cardiovascular disease after both mild and moderate to severe TBI compared with the control group, across all age groups.[17] Mild TBI in individuals aged 41–60 years was associated with higher risk of long-term cardiovascular disease compared with their matched unexposed controls (figure 1). These results support the hypothesis that other mechanisms, rather than the injury severity alone, might be driving the risks for cardiovascular disease. The retrospective nature of this study precluded an examination of psychosocial stress and lifestyle changes both before and after the injury, which could have a role in cardiovascular disease risk in this age group. Future studies should explore these factors and whether follow-up should differ by TBI severity.[31]

Cardiovascular risk factors and events become increasingly common with age, underscoring the importance of accounting for age in evaluating the effects of TBI. Many studies of TBI and subsequent cardiovascular disease had not stratified individuals by age. For example, Hammond and colleagues reported higher incidence of newly diagnosed hypertension and hypercholesterolemia in individuals older than 50 years with moderate to severe TBI compared with the incidence of those risk factors in TBI patients younger than 50 years.[13] However, in a 10-year study of people without any known cardiovascular or neuropsychiatric conditions who sustained TBI, individuals as young as 18–40 years were more likely to develop hypertension, hyperlipidaemia, obesity, and diabetes within 3–5 years after brain injury (figure 1) compared with individuals in the control group, who were frequency matched in terms of age, sex, and race.[17] Other studies have shown that individuals younger than 30 years with TBI were at a higher risk of cardiovascular and cerebrovascular events compared with the general population, matched on the basis of age, sex, and age-adjusted Charlson comorbidity index score.[14] Furthermore, a higher rate of long-term cardiovascular autonomic dysfunction has been noted after moderate to severe TBI in a group of young patients (mean age of 33 years) compared with healthy unexposed individuals.[32]

In otherwise healthy individuals with TBI, both mild and moderate to severe injuries conferred significantly higher risk of cardiovascular disease in the chronic phase of TBI compared with age-matched, race-matched, and sex-matched unexposed control groups.[17]

Following the publication of several studies on the long-term risk of ischaemic stroke in the acute phase of TBI,[33] the long-term risk of ischemic stroke is gaining increasing attention.[16,19] A retrospective study, which included individuals with pre-existing medical comorbidities, showed that moderate to severe TBI was a stronger risk factor than mild TBI for ischaemic stroke.[16] Another study of individuals who sustained a TBI who were followed up for a median of 20 years, showed that the risk of stroke was higher for moderate to severe TBI

	Demographic characteristics	Study sample design	Single or multiple brain injuries	Pre-existing comorbidities included in the study	Outcome	Comparator	Key findings
Studies of general populations exposed to brain injury							
Lu et al (2017)[11]	Civilian, mean age 40 years, n=26 860	Design: retrospective cohort of national database; exposure: mTBI and msTBI	Single	Diabetes, dyslipidaemia, hypertension, peripheral vascular disease, cerebrovascular disease, respiratory disease, peptic ulcer, chronic liver disease, chronic kidney disease, rheumatological disease, and cancer	Myocardial dysfunction	Controls matched by age, sex, and index day	TBI was associated with increased risk of myocardial dysfunction
Kumar et al (2018)[12]	Civilian, non-athletes older than 50 years; mean age 66 years; n=2134	Design: cross-sectional analysis of a prospective cohort study; exposure: msTBI	Unknown	No patient was excluded based on preexisting comorbidities	Prevalence of 45 comorbidity categories	None	Hypertensive disease, respiratory disease, and fluid and electrolytes imbalances had the highest prevalence in the entire cohort; prevalence of CVD was positively associated with increasing age
Hammond et al (2019)[13]	Civilian non-athletes, mean age 37 years, n=404	Design: retrospective cohort with self-administered questionnaire; exposure: msTBI	Single	Cardiovascular, neurological, endocrine, psychiatric, respiratory, gastrointestinal, genitourinary, musculoskeletal or rheumatological diseases, and cancer	44 health comorbidities	None	Most common post-TBI comorbidities at 10 years were back pain, depression, hypertension, anxiety, hyperlipidaemia, sleep disorders, and diabetes
Eric Nyam et al (2019)[14]	Civilian non-athletes, n=48 633, mean age not reported	Design: retrospective cohort; exposure: any TBI severity	Single	Hypertension, diabetes, COPD, renal disease, and liver disease	Major adverse cardiovascular and cerebrovascular events, including CAD, heart failure, arrhythmia, ischaemic and haemorrhagic stroke, and death	Controls matched by age, sex, and Charlson comorbidity index	Individuals with TBI had a significant increased risk of major adverse cardiovascular events (HR 1·72), ischaemic stroke (HR 2·1), haemorrhagic stroke (HR 6·0), and death (HR 3·1)
Izzy et al (2021)[15]	Civilian non-athletes, median age 31 years, n=9205	Design: retrospective cohort; exposure: mTBI	Single	None	CVD, endocrine, neurological, and psychiatric comorbidities	Controls matched by age, sex, and race	Individuals with a concussion had higher risk of hypertension (HR 1·7), obesity (HR 1·7), and diabetes (HR 1·8)
Vadlamani et al(2020)[16]	Civilian non-athlete individuals >65 years, n=132	Design: retrospective cohort; exposure: mTBI and msTBI	Single	Myocardial infarction, dementia, anaemia, chronic kidney disease, congestive heart failure, diabetes, depression, hypertension, ischaemic heart disease, and stroke	Ischaemic stroke and depression	None	High TBI severity was associated with increased risk of ischaemic stroke compared with low TBI severity (HR 6·7)
Izzy et al (2022)[17]	Civilian non-athletes, median age 47 years, n=4351	Design: retrospective cohort; exposure: mTBI and msTBI	Single	None	CVD, endocrine, neurological, and psychiatric comorbidities	Controls matched by age, sex, and race frequency	Cardiometabolic diseases including hypertension (HR 2·5), DM (HR 1·9), and neuropsychiatric comorbidities were more prevalent in mTBI and msTBI; post-TBI comorbidities were associated with higher mortality
Korkmaz et al (2022) [18]	Civilian non-athletes, mean age 31 years, n=60	Design: case-control: msTBI	Single	None	Insulin resistance	Controls matched by age, sex, and BMI	Insulin resistance was more common in the TBI group
Sperl et al (2022)[19]	Civilian, non-athletes, median age 54 years, n=1410	Design: retrospective cohort; exposure: possible, probable, or definite TBI	Single	No patient was excluded based on preexisting comorbidities	Ischaemic and haemorrhagic stroke	Age and sex matched	msTBI was associated with significant risk (HR 2·20) of stroke

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	Demographic characteristics	Study sample design	Single or multiple brain injuries	Pre-existing comorbidities included in the study	Outcome	Comparator	Key findings
(Continued from previous page)							
Studies of populations exposed to military related brain injury							
Stewart et al (2022)[20]	US veterans serving after Sept 11, 2001, median age 27 years, n=1 559 928	Design: retrospective cohort; exposure: mTBI, msTBI, or penetrating TBI	Both	Hypertension, diabetes, obesity, kidney disease, hyperlipidaemia, obstructive sleep apnoea, insomnia, depression, PTSD, anxiety, and substance use disorder	Composite endpoint of CVD: CAD, stroke, peripheral arterial disease, and cardiovascular death	Non-TBI controls	TBI exposure increases risk of CVD with an increasing effect estimate with higher TBI severity (mTBI HR 1·62, msTBI HR 2·6, penetrating TBI HR 4)
Howard et al (2022)[21]	Veterans serving during the war operations in Iraq and Afghanistan after 2001, median age 27 years, n=2 516 189	Design: retrospective cohort; exposure: mTBI and msTBI	Not reported	Not reported	All-cause mortality and mortality rate from CVD	Non-TBI and civilian controls	Moderate-severe TBI associated with the highest all-cause mortality, including CVD and other causes (33·6% of total excess deaths) compared with non-exposed veterans
Kornblith et al (2022)[22]	Military veterans, mean age 67 years, n=97 708	Design: retrospective cohort; exposure: mTBI and msTBI	Unknown	Diabetes, obesity, smoking, hypertension, hypercholesterolaemia, Depression, PTSD, CAD, CVD, stroke and transient ischemic attacks	Dementia	Controls matched by age, sex, and race	Individuals with TBI were more likely to have CVD compared with control (36% *vs* 24%); both TBI and CVD increased risk of dementia in an additive way (HR 2·5)
Clark et al (2023)[23]	US veterans, age equally represented by decade, n=16 452	Design: observational cohort; exposure: positive TBI screen, no confirmed TBI, and confirmed TBI	Not reported	Not reported	Self-reported cardiometabolic conditions (hypertension, stroke, TIA, heart attack, CAD, peripheral vascular disease, pulmonary embolism, heart failure, CHF, diabetes, and obesity)	Veterans without TBI	Veterans who screened positive for TBI (regardless of whether they were diagnosed with TBI) were at higher risk for stroke (OR 3·4) and cardiometabolic conditions (OR 1·2) compared with screen negative controls
Lendvai et al (2023)[24]	Veterans serving during the war operations in Iraq and Afghanistan after 2001, mean age 34 years, n=734	Design: retrospective cohort; exposure: blast exposure, combat blast, and blast-related TBI	Not reported	Not reported	Obesity, glucose dysregulation, and cardiometabolic syndrome	None	No significant association between blast exposure, close blast exposure, and blast-TBI with metabolic disorders (RR 0·7–1·5)
Gardner et al (2023)[25]	US Veterans, mean age 66 years, n=285 417	Design: retrospective cohort; exposure: mTBI or msTBI	Not reported	Hypertension , CAD, diabetes, CVD, depression epilepsy, PTSD reported at TBI index or within 2 years before injury	History of hypertension, CAD, diabetes, CVD, depression, and PTSD	Veterans without TBI	Comorbidities and TBI together increased risk of dementia (HR 1·08–1·37); all comorbidities were more prevalent in veterans with TBI (5·7–21·5% higher) than in controls

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than for mild and concussive TBI after adjusting for pre-existing conditions using the Charlson comorbidity index.[19] A systematic review of all stroke events in acute and chronic phases of TBI showed an increased risk of stroke after both mild and moderate to severe TBI.[34] The extent to which the severity of injury affects cardiovascular risk factors, such as long-term risk of ischaemic stroke, requires further investigation.

Data from the general population highlight the importance of: (1) determining cardiovascular disease risk in individuals diagnosed with TBI, with and without pre-existing comorbidities; (2) proactively screening young people with TBI for cardiovascular disease; and (3) further research on age, TBI severity, and other predictors of chronic cardiovascular disease after a TBI. Considering that these disorders predominantly emerge within 3–5 years after a single brain injury, and that these factors are associated with increased mortality,[17] medical care providers should be proactive in the surveillance and treatment of cardiovascular disease in individuals who sustained TBI. Given the accumulating evidence, occupationally defined populations at risk for TBIs are also of interest in studies that link brain injury and non-neurological chronic health risks.

TBI in military settings

A few investigations into the relationship between combat exposure with the long-term risk of cardiovascular disease and risk factors have explored the specific role of TBI,[35–38] although most studies described only cardiovascular risk

	Demographic characteristics	Study sample design	Single or multiple brain injuries	Pre-existing comorbidities included in the study	Outcome	Comparator	Key findings
(Continued from previous page)							
Studies of populations exposed to sport-related brain injury							
Brett et al (2022)[26]	Former professional football players, mean age=65 years, n=979	Design: cross sectional; exposure: mTBI	Multiple	Hypertension, hyperlipidaemia, smoking, obstructive sleep apnoea, diabetes, and COPD	Ischemic stroke	None	Prevalence of ischaemic stroke was lower than in the general population but history of ten or more concussions were associated with significantly increased rate of stroke
MacKay et al (2019)[27]	Former soccer players, age > 40 years n=7676	Design: retrospective cohort; exposure: undefined	Not reported	Not reported	Mortality due to neurodegenerative disease, ischaemic heart disease, cancer, and respiratory disease	Controls matched by age, sex, and degree of social deprivation	Former soccer players had lower mortality secondary to ischaemic heart disease (HR 0·8)
Grashow et al (2023)[28]	Former professional football players, mean age 51 years, n=4168	Design: survey; exposure: mTBI exposure	Multiple	Smoking	Post-career hypertension	None	Association between concussion symptoms burden during years of active play and post-career hypertension
Memmini et al (2021)[29]	Young hockey players, mean age=16 years, n=15	Design: case-control; exposure: concussion	Single and multiple	None	Measures of heart rate variability	Age, BMI, and years of experience matched controls	Athletes with two or more concussions had a higher risk of dysautonomia
Harrison et al (2022) [30]	Young hockey players, mean age=16 years, n=16	Design: case-control; exposure: concussion	Not reported	None	Measures of heart rate variability	Age and BMI matched controls	Athletes with prior concussion had elevated heart rate variability during completing a cognitive task at rest, and while completing a cognitive task after a bout of submaximal aerobic exercise

CAD=coronary artery disease. COPD=chronic obstructive pulmonary disease. CVD=cardiovascular disease. HR=hazard ratio. mTBI=mild traumatic brain injury. msTBI=moderate or severe traumatic brain injury. PTSD=post traumatic stress disorder. TIA=transient ischaemic attack.

Table: **Studies on the risk of cardiovascular disease in populations exposed to single or repetitive brain injuries**

in military cohorts without specific consideration of the role of TBI. For example, a meta-analysis of data from military cohorts suggested an increased prevalence of dyslipidaemia, obesity, and hypertension in military personnel.[35] Similarly, another meta-analysis suggested an increased risk of cardiovascular risk factors and coronary artery disease-related deaths in individuals with combat exposure and related traumatic injury compared with unexposed control population.[36] Neither study included information about brain injury exposure.[36] However, a study by Johnson and colleagues,[39] who compared data from veterans with and without combat exposure, and a study by Shresta and colleagues,[40] who compared data from active duty personnel with data from the US civilian population, did not identify an increased risk of cardiovascular risk factors in the military. Limitations in both studies include the retrospective review of health surveys and heterogeneity in years of service (these studies included mostly veterans serving in the Korean War or the Vietnam War). Healthy worker bias—whereby occupational cohorts tend to be healthier on average than the general population—might also contribute to disparate findings.

Studies of military cohorts, which include data on specific exposures to TBI, can closely investigate how the wartime experience might increase risk for chronic cardiovascular dysfunction. Military personnel can receive a wide range of traumatic injuries when deployed to a combat zone.[41] Several studies documented the link between combat exposure and risk of cardiovascular risk factors. Examples include an observational cohort study, in which data from combat-exposed personnel were compared with data from non-combat-exposed veterans,[38] and a cross-sectional national health interview survey study that compared data from combat-exposed veterans with data from non-veterans respondents.[37] The intensity of combat exposure has also been shown to be associated with the risk of hypertension, coronary artery disease, and diabetes.[42] Both single and repetitive head injuries might be contributors to the increased cardiovascular disease risk, given the high risk of TBI during combat exposure and training.[43] However, studies that compared military cohorts with combat exposure with those without did not specifically capture the TBI severity and number of head injuries in their evaluations of long-term risk of cardiovascular disease. Instead, measures of military exposure encompassed conditions unique to military service, including pre-existing general health status and fitness, lifestyle, environmental factors, and psychiatric disease. Polytrauma can result

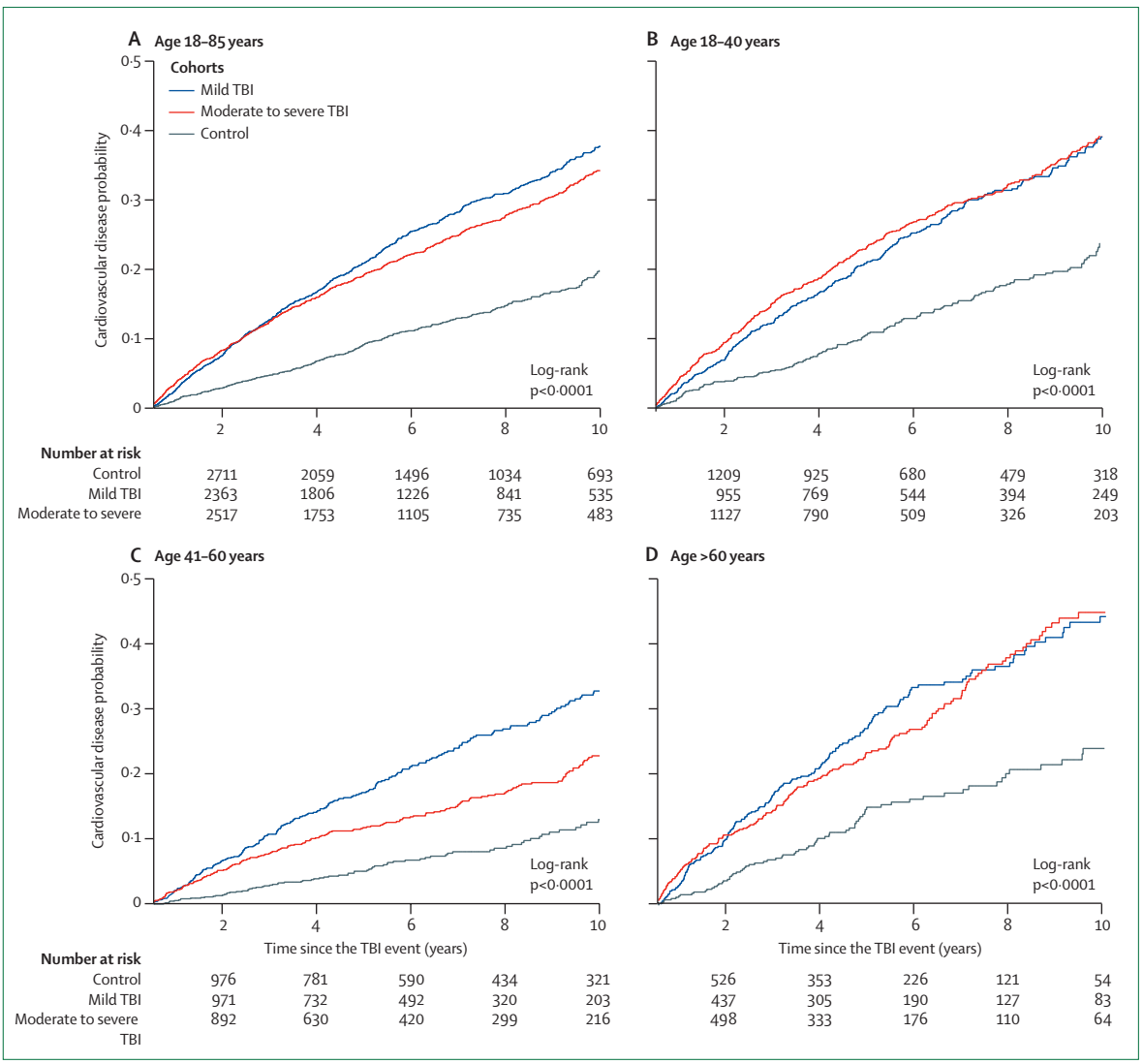

***Figure 1*: Cumulative incidence of cardiovascular disease after a TBI, stratified by age and TBI severity**
The data shown in (A) were obtained from a hospital-based patient cohort of 4351 patients who sustained a mild TBI, and 4351 individuals with moderate to severe TBI, with no prior clinical comorbidities, and 4351 frequency-matched controls by age, race, and gender who were unexposed to TBI. Participants were followed-up for up to 10 years. Data are shown stratified by age (B) 18–40 years, (C) 41–60 years, and (D) 61 years and older.[17] The composite cardiovascular disease category included hypertension, coronary artery disease, hyperlipidaemia, and obesity. The log-rank test compared mild TBI and moderate to severe TBI groups with age, race, and gender matched controls.

in systemic inflammatory response and disabilities that can eventually lead to cardiovascular disease, and future studies will need to isolate the effect of TBI from other adverse exposures related to combat and training. Furthermore, the interplay between behavioural and psychiatric disease in military populations is an important factor that might complicate efforts to identify causal pathways between TBI, neuropsychiatric disease, and cardiovascular dysfunction. For example, post-traumatic stress disorder and depression, which are commonly seen in military personnel, have been shown to be associated with cardiovascular risk factors.[44,45]

Several studies in military cohorts have evaluated the direct effect of brain injury on risk of chronic cardiovascular disease and cardiovascular mortality. Stewart and colleagues did a large retrospective analysis of military veterans who served during the war operations in Iraq and Afghanistan after 2001, that investigated the effect of TBI on the subsequent development of cardiovascular disease in predominantly young (<35 years at the index date), White male military members without history of TBI.[20] This study found that TBI exposure (mild, moderate to severe, and penetrating brain injury) was associated with increased risk of cardiovascular disease measured as a composite of coronary artery disease, stroke, and peripheral vascular disease.[20] Additionally, veterans exposed to mild and moderate to severe TBI were at higher risk of death

caused by cardiovascular disease compared with those who where not exposed to TBI. Similarly, Howard and colleagues reported an increase in cardiovascular disease-related mortality in US veterans who served during the war operations in Iraq and Afghanistan after 2001, compared with non-exposed individuals.[21]

These results highlight the importance of determining the link between TBI and cardiovascular disease risk in veterans. Longitudinal studies should be done to further disentangle the effects of military, combat, and TBI exposure on cardiovascular health and to assess the interaction between other physiological, behavioural, and psychiatric confounders.

TBI in contact sports

Despite their good health, epidemiological research has shown an increased risk of cardiovascular disease and risk factors among collegiate professional American-style football players and participants in other sports that put players at risk for repetitive head impacts.[46–50] A National Institute for Occupational Safety and Health study of American-style football players showed that the risk of death from cardiovascular disease was 52% higher for players than in the general population.[51] Nguyen and colleagues also reported elevated cardiovascular disease mortality in National Football League players compared with Major League Baseball players.[52] Several observational studies showed higher rates of chronic cardiometabolic conditions, including sleep apnoea, impaired glucose tolerance, left ventricular hypertrophy, and hypertension among American style footballers, which raises concerns about the long-term health of elite athletes.[53] These conditions might emerge due to factors including genetic predisposition, large body habitus of athletes, weight gain after ending sports careers, and lifestyle choices (eg, dietary habits, repetitive isometric exercise, and surreptitious use of cardiotoxic performance-enhancing drugs). However, the interplay of these factors is expected to be intricate and multifaceted; the relative contributions of these factors to the risk of cardiovascular disease in contact sports remain uncertain.[53] Post-career players aged 25–30 years were shown to have significantly higher prevalence of hypertension and diabetes compared with the general US population.[54] Furthermore, long-term cardiovascular autonomic dysfunction, such as measures of heart rate variability, have also been diagnosed even in healthy adolescent hockey players after concussive injury.[29,30] These small case-control studies also reported that repetitive head impacts might be associated with pronounced cardiovascular autonomic dysregulation and potentially exercise intolerance; however, these findings need to be validated in large longitudinal cohort studies.

Few sport-related studies have carefully evaluated the effect of TBI burden (severity and number of events) on the risk of chronic cardiovascular disease in athletes. A study of former professional football players showed that higher cumulative burden of concussion was associated with increased risk of stroke.[26] Furthermore, another study investigated the relationship between concussion symptom burden and hypertension later in life in a cohort of 4168 former professional American-style football players.[28] The authors found a significant dose–response association between burden of concussion symptoms during years of active play and the odds of post-career hypertension, even after adjusting for hypertension risk factors including older age, self-identified race, smoking, diabetes, and high BMI. However, the type of sport might be an important consideration in evaluating associations between brain injury and cardiovascular disease. In contrast to former American-style football players, a study by Mackay and colleagues reported lower ischaemic heart disease mortality among Scottish former professional soccer players, but also higher neurodegenerative disease mortality compared with age-matched controls.[27] Reduced cardiovascular disease mortality could be related to the players' health behaviours and lifestyle, including engaging in higher levels of strenuous aerobic exercise and training on a regular basis for several years, and fewer cardiovascular disease risk factors such as unhealthy diet, obesity, smoking, and drug abuse, compared with the general population. These results question whether individual sports have distinct injury mechanisms, which might differentially contribute to cardiovascular disease risk. Thereby, the studies underscore the need for better elucidation of pathophysiological pathways to mitigate chronic cardiovascular disease risks after injury.

Effects of TBI on extracranial organ systems—potential mechanisms

Brain injury has been associated with acute cardiovascular dysfunction, including autonomic heart–brain axis dysregulation, imbalances between the sympathetic and parasympathetic nervous systems, and excessive catecholamine release.[55,56] However, the mechanisms that link TBI to increased long-term risk of cardiovascular disease are probably multifactorial and involve risk factors from the pre-injury, injury, and post-injury phases of the disease (figure 2). Plausible links between TBI and cardiovascular dysfunction might include a combination of: alterations in neurobiological mechanisms (chronic autonomic system dysfunction, neuroinflammation, and brain-gut axis changes); the emergence of other medical comorbidities after injury; and subsequent behavioural and lifestyle changes that put patients at higher risk of cardiovascular disease.

Biological changes resulting from TBI, such as neuroinflammation-mediated pathways, might predispose individuals to atherosclerosis and other cardiovascular diseases.[57] Long-term multisystem effects of TBI might also be related to autonomic nervous system dysfunction, which is associated with cardiac and endocrine sequelae, with increased mortality after moderate to severe TBI.[58,59]

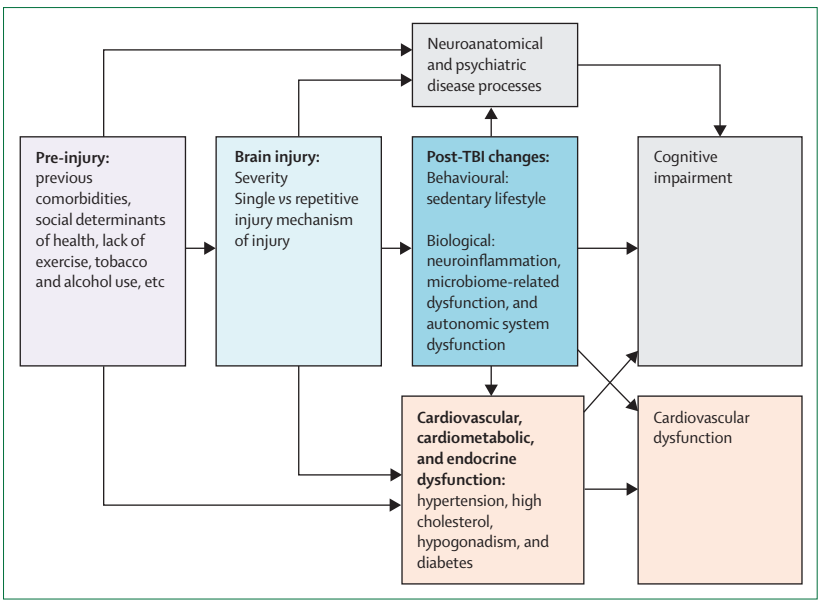

Figure 2: **Potential mechanisms underlying how pre-injury factors and brain injury could lead to cognitive and cardiovascular dysfunction**

Another possible explanation is the disruption to the bidirectional brain–gut axis after TBI resulting in gastrointestinal dysfunction, including dysmotility, food intolerance, and gastroparesis, and increased gut mucosal permeability.[60] Gut microbial dysbiosis has been linked to alterations in peripheral and central immune responses, which can affect neurogenesis after TBI.[61] Thus, the gut microbial dysbiosis could be a research focus and ultimately a potential therapeutic target. New research findings should motivate the creation of new TBI models that allow investigation of underlying biological mechanisms of cardiovascular disease and risk factors.

Individuals who sustained a TBI are at risk for modifiable cardiovascular risk factors such as weight gain, sleep disturbances, and reduction in functional health post-injury, which could interact with neurobiological mechanisms and have a role in increasing cardiovascular disease after injury.[5,62,63] Moreover, the established cardiovascular risk factors, such as hypertension, diabetes, hyperlipidaemia, obesity, sleep disorder, physical inactivity, unhealthy lifestyle, and smoking, might have been present (or not diagnosed) before injury, or diagnosed in the acute or subacute phase of TBI. These factors could contribute to the cardiovascular disease risk after TBI. However, the directionality and magnitude of the effects attributable to each risk factor for cardiovascular disease in individuals with brain injuries are largely unknown. For example, a large population-based study showed that people who sustained a severe TBI had a higher rate of new-onset cardiovascular disease and cardiovascular risk factors, compared with individuals with orthopaedic trauma or spinal cord injury, suggesting that immobility secondary to trauma might not explain the entire risk difference.[64]

TBI can also cause behavioural and subsequent lifestyle changes, such as inability to work, unhealthy diet, increased alcohol intake, and drugs misuse, which might contribute to the increased risk of cardiovascular disease, in combination with or independent of other pathways. Psychosocial determinants of health, including discrimination based on disability, sex, or race, as well as mood disorders, socioeconomic status, and social isolation, are also associated with cardiometabolic disorders.[65] Therefore, these factors might also have a role in the increased risk for cardiovascular disease after a TBI. Another possible interaction with chronic cardiovascular disease might be due to the use or misuse of some medications, generally prescribed for post-traumatic epilepsy,[66] neuropsychiatric disorders, and chronic pain, such as antidepressants,[67] antipsychotics,[68] and non-steroidal anti-inflammatory drugs.[69] Differences in cardiovascular disease risk depending on TBI severity (eg, mild, moderate to severe) might be attributed to different pathophysiological pathways. Such changes, in concert with post-injury behavioural and lifestyle changes, might act synergistically to affect cardiovascular risk. Lastly, isolated TBI and repetitive head impacts have distinct injury mechanisms, which might contribute to cardiovascular disease risk in different ways.

The role of cardiovascular risk factors in brain injury and chronic neurological disease

The association between TBI, cardiovascular disease, and cardiovascular disease risk factors suggests potential causal pathways via which cardiovascular risk factors could act as intermediaries between brain injury and chronic neurological diseases, including dementia and other neurodegenerative diseases (figure 2). Cardiovascular,[70] metabolic,[71] and endocrine[72] dysfunction including hypertension, hyperlipidaemia, obesity, diabetes, and hypopituitarism adversely affect cognitive function,[73–77] and are well established risk factors for dementia.[78–81] In parallel, the social determinants of health, including discrimination[82] and poverty,[83] have been linked to risk of cardiovascular disease and dementia. The 2020 *Lancet* Commission on dementia prevention, intervention, and care identified several modifiable risk factors including TBI, physical inactivity, infrequent social contact, and cardiovascular risk factors.[9] However, few studies have systematically explored the extent to which these factors play a role in the causal pathway between brain injury and severity of cognitive impairment.

Importantly, studies of people who did not sustain a brain injury have shown that dementia risk can be mitigated by alleviating cardiovascular risk factors such as diabetes, hypertension, hyperlipidaemia, and sleep apnoea.[84] Two studies have investigated the effect of cardiometabolic interventions in prevention of cognitive impairment in individuals who sustained a brain injury. In one study of 28 815 individuals with concussion, use of statins was associated with a decreased risk of subsequent

dementia.[85] Another study of electronic data from veterans in the USA showed that use of angiotensin-converting enzyme inhibitors in combination with statins was associated with lower risk of dementia and later age of onset for dementia in individuals with a history of multiple TBIs, compared with those who took statins alone or didn't take any of the studied angiotensin-converting enzyme inhibitors after TBI.[86] This change in risk might be due to the potential effect of statins on trauma-induced neuroinflammation,[87] amyloid β aggregation, and brain oedema.[88] Statins have also been shown to increase cerebral blood flow, which might underlie the association between their use and reduced risk of dementia.[88] Future studies should be designed to provide critical insight into whether and how cardiometabolic risk factors mediate the TBI–cognitive impairment relationship and to test cardiometabolic interventions,[89–91] which might help reduce the risk of cognitive decline and dementia in individuals with TBI.

Identifying cardiovascular risk factors after injury could guide clinicians in screening TBI survivors and identify high-risk individuals for cardiovascular testing, early treatment, and follow-up. Characterising the long-term cardiovascular outcomes after a TBI, and identifying biological and psychosocial risk factors through well designed longitudinal studies or established community initiatives, such as TRACK-TBI,[92] CENTER-TBI, the Jackson Heart Study,[93] the Framingham heart study, National Institute on Disability, Independent Living, and Rehabilitation Research Traumatic Brain Injury Model Systems,[5] and veteran cohort studies, such as LIMBIC CENC,[94] is a highly encouraged next step.

Knowledge gaps

The accumulation of literature over the last decade suggests an increased burden of cardiovascular disease in the chronic phase of TBI. The contributions of single versus repetitive injury, age, and TBI severity remain uncertain as, for example, some studies did not include young TBI survivors.[12,22] Several methodological limitations exist in published studies that limit the drawing of clear conclusions. For example, the interpretation of existing literature is affected by: case ascertainment bias, given the retrospective design of the studies with diagnoses based on either International Statistical Classification of Diseases and Related Health Problems coded data or self-report;[13,46] lead time bias, given variable follow-up durations; recall bias, specifically as pertaining to exposure; and confounding bias, due to the presence of pre-existing cardiovascular disease and cardiovascular risk factors. Another area that requires further investigation is the suboptimal determination of the number of head impacts—isolated TBI is not uncommon in military, and isolated mild TBI is common in contact sport athletes. Both populations are at risk of combined exposure to a single and repetitive injuries, the effects of which on cardiovascular disease require further investigation. Additional population-specific factors might be relevant to cardiovascular disease risk (eg, the use of steroids or pain medications and obesity in some contact sport athletes, as well as deployment duration and exposure to toxins in military service members). The implications of these exposure patterns for cardiovascular disease risk after brain injury are not addressed in the published studies and underscore the need for prospective studies.

Conclusions and future directions

TBI might be an underrecognised risk factor for cardiovascular disease in contact sports, military personnel, and the general population. Understanding the long-term cardiovascular disease risk after a TBI, combined with a targeted screening programme for cardiovascular risk factors might enhance the quality of life of individuals with TBI, but could also mitigate the risks for specific secondary neurological diseases. Investigation of cardiovascular disease and cardiovascular risk factors after different severities and endophenotypes of TBI should therefore be the focus of future mechanistic and longitudinal studies to unravel the pathophysiology and chronic multi-organ effects of TBIs. Development of quantifiable measures of cardiovascular disease risk and other multisystemic effects after a TBI, including potential biomarkers of TBI exposure, would delineate the linkage between short-term and long-term comorbidities, identify individuals with TBI at risk cardiovascular disease, and improve the prediction accuracy of existing TBI outcome

Search strategy and selection criteria

An extensive non-systematic review of the literature published between Jan 1, 2001, and June 18, 2023, was done with the use of MEDLINE PubMed. The literature search used a combination of the following medical subject heading terms: ("TBI", "concussion", "head trauma", "brain injury", "head injury", "post-TBI", " post-concussion", "neurotrauma", "military", "veterans", "combat", "NFL", "field-based athlete", "baseball', "field hockey", "rugby", or "soccer") with cardiovascular disease terms ("cardiovascular disease", "CVD", "cardiovascular disease risk factors", "hypertension", "blood pressure", "hyperlipidemia", coronary heart disease", "stroke", "obesity", "peripheral vascular disease", "diabetes", or "BMI"); and with outcome terms ("medical health", "long-term outcomes", "chronic comorbidities", "chronic diseases", or "recovery"). 26 335 articles were retrieved in total. The inclusion criteria identified any articles that investigated the risk of cardiovascular disease, cardiovascular disease risk factors, and cerebrovascular disease in the chronic phase of traumatic brain injury (including community, military, or sport-related brain trauma), regardless of the timing of disease occurrence with respect to brain injury (traumatic brain injury or repetitive head impact). We only included articles published in English. We also searched references of relevant articles. Preclinical studies were excluded, unless identified as highly translational. All identified articles that met the criteria for inclusion in this Personal View are discussed in the manuscript. Articles that investigated the risk of cardiovascular disease, cardiovascular disease risk factors, and cerebrovascular disease in the chronic phase of traumatic brain injury (including community, military, or sport-related brain trauma), regardless of the timing of disease occurrence with respect to brain injury (traumatic brain injury or repetitive head impact) and are also listed in the table.

models. Such measures would also help in designing future surveillance algorithms, preventive strategies, and interventional studies, to assess whether targeting cardiovascular risk factors after TBI would reduce mortality and improve recovery after the injury. Finally, prospective studies should evaluate modifiable risk factors, assess additive or synergistic effects on outcomes, and explore the interaction between biological and social determinants of health after a TBI. Overall, the identification of non-psychiatric and non-neurological comorbidities after a TBI might reduce morbidity through the novel application of established cardiovascular interventions for individuals who sustained a TBI, while focusing medical surveillance on subgroups at increased risk for cognitive impairment after brain injury.

Contributors

SI, RG, FR, PC, MW, AB, and RZ conceptualised and designed the Personal View. SI, RG, FR, PC, and RZ did the literature search and data acquisition. All authors contributed to interpretation of data, drafting, and critical revision of the manuscript, and approved the manuscript for publication.

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