Traumatic brain injury under-recognized as a risk factor for cardiovascular disease, says new study

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Traumatic brain injury (TBI) is a leading cause of long-term disability and premature death, especially among military personnel and those playing contact sports. Substantial research has examined acute and

chronic neurological consequences of TBI; however, non-neurological conditions associated with TBI are understudied.

A new review paper by investigators from Mass General Brigham presents key findings on long-term associations between TBI and cardiovascular disease, highlighting that nervous system dysfunction, neuroinflammation, changes in the brain-gut connection, and post-injury comorbidities may elevate risk of both cardiovascular and cognitive dysfunction in TBI survivors compared to the general population.

The review, published in *The Lancet Neurology*, emphasizes the need for future cardiovascular research, surveillance and intervention in TBI survivors.

"Despite decades of extensive traumatic brain injury focused research, surprisingly, there has been minimal progress in mitigating long-term outcomes and mortality following injuries. The cardiovascular effects of TBI may be a missing link in advancing our efforts to improve long-term quality of life and reducing mortality rates in TBI patients," said first author Saef Izzy, MD, MBChB, of the Stroke and Cerebrovascular Center of Brigham and Women's Hospital.

"We have the opportunity to identify and improve targeted screening for high-risk popualtions, build preventative care strategies and improve outcomes for survivors of TBI."

Existing research has identified a strong link between TBI and neurological conditions, such as Alzheimer's disease and dementia. However, the mechanisms driving neurological disease after TBI remain poorly understood, despite decades of research. Izzy and co-authors from Spaulding Rehabilitation Hospital, Massachusetts General Hospital, Brigham and Women's Hospital and elsewhere suggest that non-neurological effects of TBI, such as cardiovascular, cardiometabolic and

endocrine dysfunction, may act as intermediaries contributing to neurological disease decades after TBI.

For example, hypertension, hyperlipidemia, diabetes and hypopituitarism can negatively affect cognitive function and are established risk factors for dementia. These cardiometabolic risk factors have also been found to be more prevalent in those with a history of TBI, as demonstrated in over a dozen studies on military personnel, athletes and the general patient population, which are summarized by the authors of the review.

There are many potential links between TBI and cardiovascular and cognitive dysfunction. Neuroinflammatory pathways triggered by TBI could predispose individuals to atherosclerosis. Weight gain and sleep disturbances after an injury could pose independent or additive risks. Disruptions to connections between the nervous and gastrointestinal systems could throw off the balance of microbes in the gut, contributing to cognitive and cardiovascular effects.

Investigators are actively pursuing research related to the role of the gut microbiome and are also working to create new models of TBI to further study the biological mechanisms underlying cardiovascular disease.

It remains unclear how single versus repetitive injuries, age at injury, TBI severity, and other comordibities impact cardiovascular risk. This is in part due to methodological limitations to current research, such as retrospective study designs and reliance on self-reported health data. Prospective studies can clarify what risk factors and biomarkers may be most relevant to cardiovascular dysfunction post-TBI.

"This review is a clarion call to conduct better assessments and earlier intervention for survivors of TBI who may have increased cardiovascular risk. It calls for new or expanded datasets that capture, over time,

changes in biomarkers and targets associated with cardiovascular disease ," said corresponding author Ross Zafonte, DO, President of Spaulding Rehabilitation Network and Chief of the Departments of Physical Medicine and Rehabilitation at Massachusetts General Hospital and Brigham and Women's Hospital. Zafonte is also the principal investigator of the Football Players Health Study at Harvard.

"There is a growing recognition that many systems interact to produce multilevel dysfunction after TBI, with a series of nuanced comorbidities. Clinicians can begin to treat some of these conditions, and in the future, management guidelines can more directly address the cardiovascular health of TBI survivors," Zafonte concluded.

Mass General Brigham co-authors include Farid Radmanesh (Brigham and Women's Hospital) and Meagan Wasfy (Massachusetts General Hospital). Additional co-authors include Rachel Grashow, Patrick Chen, Herman Taylor, Rita Formisano, Fiona Wilson, and Aaron Baggish.

More information: Izzy, S et al, Long-term risk of cardiovascular disease after traumatic brain injury: an opportunity for proactive screening and prevention, *Lancet Neurology* (2023). DOI: 10.1016/S1474-4422(23)00241-7. www.thelancet.com/journals/lan … (23)00241-7/fulltext

Provided by Mass General Brigham