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Women in neurotrauma 2023

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Women in neurotrauma 2023

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Editorial: Women in neurotrauma 2023

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Editorial on the Research Topic
Women in neurotrauma 2023

Introduction

Women in neurotrauma 2023 covers a wide range of areas in neurotrauma research, highlighting the intersection of gender, social determinants of health, and advances in neuroimaging and treatment approaches. The research included focuses primarily on adult and pediatric traumatic brain injury (TBI), but also touches on other neurotrauma-related conditions such as dementia. Furthermore, the goal of this Research Topic was to engage female scientists and clinicians in an effort to reduce gender bias in neurotrauma research.

TBI represents a significant portion of the global injury burden and is a leading cause of morbidity, disability, and mortality across all ages (1). Survivors often face lifelong challenges affecting social relationships, quality of life, work capacity, and societal participation (2). Despite its widespread impact, TBI is often considered a hidden disability, as its consequences are frequently cognitive and psychiatric rather than physical. A major challenge in developing effective treatments, both acutely and in long-term rehabilitation, lies in the heterogeneity of TBI, with varied causes, pathology, patient demographics, and outcomes. While anyone can sustain a TBI, certain groups, like victims of intimate partner violence (IPV), are at higher risk. It is estimated that up to 75% of IPV victims suffer a TBI, often from blows to the head or strangulation (3).

The purpose of this editorial is to summarize and categorize research into: (1) adult neurotrauma, (2) pediatric neurotrauma, (3) advances in neuroimaging, and (4) diversity and public health in neurotrauma care. These topics represent the breadth of research and provide a comprehensive overview of dimensions of neurotrauma. The variety of study types, including systematic or narrative reviews, original research studies, or case reports, further reflects the multifaceted nature of this research area.

Neurotrauma in adults

Rojczyk et al. examined the impact of neuropsychiatric conditions such as posttraumatic stress disorder, depression, and substance use disorders on the odds of

intimated partner violence (IPV) perpetration among male veterans of the Iraq and Afghanistan wars diagnosed with mild TBI (mTBI). Results indicate that veterans with mTBI and psychiatric disorders are significantly more likely to engage in IPV, with aggression associated with microstructural changes in the limbic system, particularly the amygdala-hippocampal complex. This suggests that neurotrauma-related brain abnormalities may contribute to violent behavior and calls for targeted interventions in this vulnerable population.

Molero et al. examined medication use patterns in patients after TBI. The study employed a population-based matched cohort in Sweden to assess prescription rates of non-psychotropic medications before and after injury. Results suggest that TBI patients are more likely to use a wide range of medications compared to a control cohort, with significant use of non-steroidal anti-inflammatory drugs and antibiotics. Furthermore, older patients and women tend to have higher rates of medication use, raising concerns about polypharmacy and its implications for post-TBI care.

Pediatric neurotrauma

Parsons et al. investigated the influence of social determinants of health (SDH) including race, insurance status, and neighborhood opportunity on outcomes after pediatric TBI. The study revealed that Black and Hispanic children are more likely to suffer from severe TBI and experience higher social vulnerability compared to White children. Although no significant differences were observed in mortality or functional outcomes across racial groups, the study highlighted the complex role of SDH in pediatric TBI, suggesting that further research is needed to explore these interactions and their long-term impacts on recovery.

Zeldovich et al. conducted a psychometric evaluation of the German Post-concussion Symptom Inventory (PCSI-SR8) for children aged 8–12 years. The study aimed to validate this self-report instrument for the assessment of post-concussion symptoms in pediatric populations. The research suggests that the inventory reliably captures cognitive, emotional, and physical symptoms associated with pediatric TBI, allowing clinicians to more accurately assess symptom burden. Reference values are provided to facilitate more effective comparisons between TBI patients and children from the general population in future clinical and research settings.

Advancements in neuroimaging

In a narrative review, Kadaba Sridhar et al. investigated the use of structural neuroimaging markers to differentiate normal pressure hydrocephalus (NPH) from Alzheimer's disease (AD), Parkinson's disease (PD), and the effects of chronic traumatic brain injury (cTBI). Given that NPH is a treatable cause of dementia, distinguishing it from AD and PD, which cause irreversible cognitive decline, is crucial. The study reviewed various neuroimaging markers, particularly from MRI studies, and emphasized the need for computational methods to improve the non-invasive diagnosis of these conditions, which will help increase the accuracy of diagnostic techniques aiming to improve treatment outcomes for patients with neurodegenerative diseases.

Harlyjoy et al. presented a case report of a rare life-threatening complication of TBI called traumatic tension pneumocephalus. The study, based in Indonesia, highlighted the barriers to timely management, including patient refusal of surgery and financial constraints. Despite these challenges, the patient eventually underwent emergency neurosurgery and achieved a full recovery. This case underscores the importance of overcoming healthcare access barriers in low- and middle-income countries to improve neurotrauma outcomes.

Diversity and public health in neurotrauma care

In a perspective article, Churchill et al. addressed the persistent gender and racial disparities in leadership, academic publishing, and clinical trial management in the field of neurotrauma. The article highlighted the underrepresentation of women and racial minorities in leadership positions, noting that women are less likely to be invited to publish or serve as principal investigators in clinical trials. The authors called for systemic changes to promote diversity and inclusion, emphasizing that progress in neurotrauma research and practice requires the active participation of underrepresented groups.

Ramsay et al. explored the practices of brain injury physicians regarding firearm injury prevention counseling for TBI patients. Given the elevated risk of suicide and firearm-related injuries in this population, the study found that while most physicians believed in the importance of counseling, only a minority routinely discussed firearm safety with their patients. Moreover, physicians who had received formal training on the Research Topic were significantly more likely to inquire about patients' access to firearms, underscoring the need for better education and training in this area to improve safety outcomes for TBI patients.

Conclusion

Women in neurotrauma 2023 presents a multifaceted view of neurotrauma research, ranging from clinical advances in neuroimaging to the influence of social determinants of health on pediatric and adult neurotrauma outcomes. Key contributions include the identification of risk factors for IPV perpetration among veterans, advances in medication management after TBI, and the development of diagnostic tools for neurodegenerative diseases. The Research Topic emphasizes the importance of addressing gender and racial disparities and advocates for systemic changes to promote diversity in neurotrauma leadership and clinical trials.

Author contributions

LL: Writing – review & editing. ER: Writing – review & editing. AS: Writing – review & editing. MZ: Writing – original draft, Writing – review & editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Firearm injury prevention counseling for patients with traumatic brain injury: a survey of brain injury physicians

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Background: Survivors of traumatic brain injury are at increased risk for firearm-related injuries, including suicide.

Aims: To determine current practices of Brain Injury Medicine (BIM) physicians and their rehabilitation teams in assessing patients' access to firearms and in providing firearm safety education, and the impact of having received training on this topic on physicians' likelihood of inquiring about patients' access to firearms.

Methods: 14-item web-based cross-sectional survey of 86 U.S. physiatrists board-certified in BIM.

Results: 81% of respondents indicated they believe BIM physicians should counsel their patients on firearm safety but only 12.9% reported always doing so. Fifteen percent reported always inquiring about their patients' access to firearms. 88.2% indicated having never received formal training on firearm injury prevention counseling. Physicians who received such training had 7.5 times higher odds of reporting at least sometimes inquiring about patients' access to firearms than those who were not trained [95% confidence interval (1.94, 28.64)]. They also had 5.7 times higher odds for reporting being at least moderately comfortable providing patients firearm safety counseling [95% CI: (1.39, 23.22)].

Conclusion: While most BIM specialists who responded to this survey believe they should counsel patients on firearm safety, few always or usually do so. Moreover, most do not routinely inquire about their patients' access to firearms. The provision of firearm injury prevention training to BIM physicians was strongly associated with an increased likelihood they will inquire about their patients' access to guns and with an improved comfort level in providing counseling on this subject matter.

KEYWORDS

traumatic brain injury, firearms, gun violence, patient safety, brain injury medicine

Introduction

In the United States, firearm-related injuries present a critical public health issue and are a significant contributor to the incidence of traumatic brain injury (TBI) and TBI-related deaths (1, 2). They accounted for 2.2% of adults with TBI presenting to U.S. trauma centers between 2003–2012, a time during which 54.6% of these gunshot injuries were fatal (1). The risk for firearm-related injury and death is increased when firearms are present in one's home. The majority of accidental shooting deaths occur in a home environment, and the presence of a gun increases the potential for altercations to become fatal. Having a gun in the home is also an important risk factor for suicide, even among members of the household without prior history of mental illness or substance abuse (3). As 44 % of U.S. adults live in a home with one or more guns (4), firearms should be viewed as a common household hazard.

Multiple physician organizations have called for measures aimed at the prevention of firearm-related injuries (5). In its position paper on reducing firearm injuries and deaths, the American College of Physicians encouraged doctors to have discussions with their patients regarding the risks associated with having a firearm in their household and the means by which they may reduce these risks (6). Nevertheless, the results of the National Firearms Survey revealed that fewer than 10% of adults residing in a home with a firearm reported having ever discussed the topic with a clinician (7).

Little is known about the practice of Brain Injury Medicine (BIM) physicians regarding their assessment of patients' access to guns and their provision of firearm safety counseling, though they provide care to a patient population at increased risk for both suicide and unintentional death by firearm (8). There are a multitude of factors that likely contribute to this elevated risk among persons with TBI. First, impairments resulting from their injuries may impact their ability to safely use a firearm. These include impairments in mobility, vision, and balance, as well as judgment, executive function, and emotional regulation (9). Another important factor concerns how persons with TBI store their weapons. Safe storage is associated with a lower risk for firearm-related morbidity and mortality (10). Among military service members who own firearms, those with suspected TBI are significantly less likely to practice safe storage than those without suspected TBI (11). A key consideration for those who sustained their injuries from a firearm assault is their risk for revictimization. In a retrospective cohort study of persons treated for nonfatal firearm assault injuries (not limited to TBI) in California, more than 3% sustained one or more additional nonfatal firearm assault injuries and 1% died as a result of a subsequent homicide with a firearm (12).

Far more persons with TBI, however, die by suicide with a firearm. Individuals with a history of TBI are at significantly higher risk for death by suicide than those without such history. Among persons with TBI, risk factors for suicide include suicidal ideation, as well as comorbid depression, substance use disorders, anxiety disorder, and post-traumatic stress disorder. Insomnia may also be an important risk factor (13). Firearms are the most common means of death by suicide among persons with TBI (14). Among firearm suicide cases, the odds of having had a TBI is 23.53 times higher than it is among controls who did not die by suicide (15). It is important to note that nearly 1 in 5 suicides among persons with TBI occur among those with a history of military service (14), and that individuals with a history of such service have the highest rates of firearm suicide (16).

This study serves as a preliminary exploration of the perceptions of the need for and practices providing firearm injury prevention counseling to persons with TBI among BIM physicians. It also aims to determine the associations between having received training in firearm injury prevention on the likelihood of BIM physicians inquiring about patients' access to firearms and on their comfort level providing counseling on this topic.

Methods

This study was submitted for review to the University of Miami Institutional Review Board (IRB ID# 20210668), which determined it met criteria for an exemption. Survey participants were advised that completion of the survey indicated agreement to participate in this study.

Survey development and content

The study team reviewed prior studies evaluating physicians' perceptions of the need for and provision of firearm injury prevention counseling, including the 2020 Council of Academic Family Medicine's Educational Research Alliance survey of family physicians (17), which helped inform this survey's development. No prior published studies were conducted among BIM physicians, and accordingly, this survey's items were created anew.

The survey consisted of 14 questions. Respondents were asked to identify their primary specialty, whether they primarily see adult or pediatric patients, the type of facilities in which they provide care, and the state in which their practice or institution is located. They were asked about their beliefs as to whether BIM physicians should counsel their patients with TBI on firearm safety, their comfort level doing so, their training in providing such education, and their team's current practices regarding inquiry about their patients' access to firearms and in providing firearm injury prevention counseling. Lastly, they were asked to provide any additional topical comments they wished to share.

Study participants and invitation methods

Electronic invitations to participate were sent to physicians board-certified in the subspecialty of Brain Injury Medicine identified via a search of the American Board of Physical Medicine and Rehabilitation (ABPMR)'s website (18). Physicians located outside of the U.S. and its territories were excluded. At the time the survey was conducted, 667 physicians nationwide met the inclusion criteria. The physicians for whom the study team was able to locate an email address received an invitation to participate, with the survey link, via email, using REDCap distribution tools. A reminder email was sent eight days following the initial invitation to those who had not yet responded.

Of the BIM physicians for whom an email address was not located, the majority had messaging enabled on the Doximity messaging platform, through which the study team sent them invitations to participate along with the survey link. Doximity is an online community which enables secure electronic messaging between health care professionals (19). These individuals did not receive a reminder invite, as whether they responded could not be tracked.

Participants did not receive an incentive to respond. The survey remained open for a two-week period in August 2021.

TABLE 1 Characteristics of responding physicians.

Characteristic	# of Respondents Selecting Option
Primary specialty – Physical Medicine & Rehabilitation ($n=86$)	86 (100%)
Primary patient population by age group ($n=86$)	
Adults	72 (83.7%)
Children	12 (14.0%)
Approximately equal numbers of children and adults	2 (2.3%)
Type of facility/facilities in which they provide care ($n=86$)	
Academic medical center	56 (65.1%)
Community hospital	26 (30.2%)
Multispecialty group	12 (14.0%)
Veterans Affairs Medical Center	8 (9.3%)
Private office	7 (8.1%)
Military healthcare facility	0 (0%)
Location of practice/institution – top 5 responses ($n=86$)	
Texas	13 (15.1%)
California	9 (10.5%)
Florida	6 (7.0%)
New York	6 (7.0%)
Ohio	6 (7.0%)

Data collection

Survey data were collected and managed using REDCap electronic data capture tools hosted at the University of Miami. REDCap (Research Electronic Data Capture) is a secure web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to standard statistical packages, and (4) procedures for data integration and interoperability (20, 21).

Missing data

Participants had the option of not responding to items on the survey. All but two items received at least 84 responses. Participants who did not respond to a question were excluded from the sample size for that item.

Statistical methods

The frequency of inquiring about patients' access to firearms was coded as one of three options: always/usually, sometimes, and rarely/never. The participants' level of comfort in providing firearm safety counseling was categorized as high (7 – 10), moderate (4 – 6), or low (0–3). Fisher's exact test and ordinal logistical regression were used to examine the association of receiving training in firearm injury prevention with the reported frequency of inquiring about patients' access to firearms and comfort levels providing firearm safety counseling. The proportional odds assumption was checked and not violated. All analyses were conducted using SAS version 9.4.

Results

Responses were received from 86 U.S. BIM physicians, all physiatrists, practicing in 30 states and Puerto Rico. Table 1 summarizes participant characteristics, and Table 2 displays the

TABLE 2 Fisher's test contigency tables for associations with training in firearm injury prevention.

		Formal training in firearm injury prevention		
	n	Yes ($n=10$)	No ($n=75$)	*p*-value
Frequency of inquiring about patients' access to firearms	86			
Always/Usually	20	6 (60.0%)	13 (17.3%)	0.007
Sometimes	28	3 (30.0%)	25 (33.3%)	1.0000
Rarely/Never	38	1 (10.0%)	37 (49.4%)	0.021
Comfort (on scale from 1 to 10) providing firearm safety counseling*	84			
High (7–10)	27	7 (70.0)	20 (27.4)	0.012
Moderate (4–6)	36	2 (20.0)	34 (46.6)	0.175
Low (0–3)	21	1 (10.0)	19 (26.0)	0.438

*Participants were asked, "On a scale of 0–10, how comfortable are you in counseling patients on firearm safety? (0 = not at all comfortable, 10 = very comfortable)."

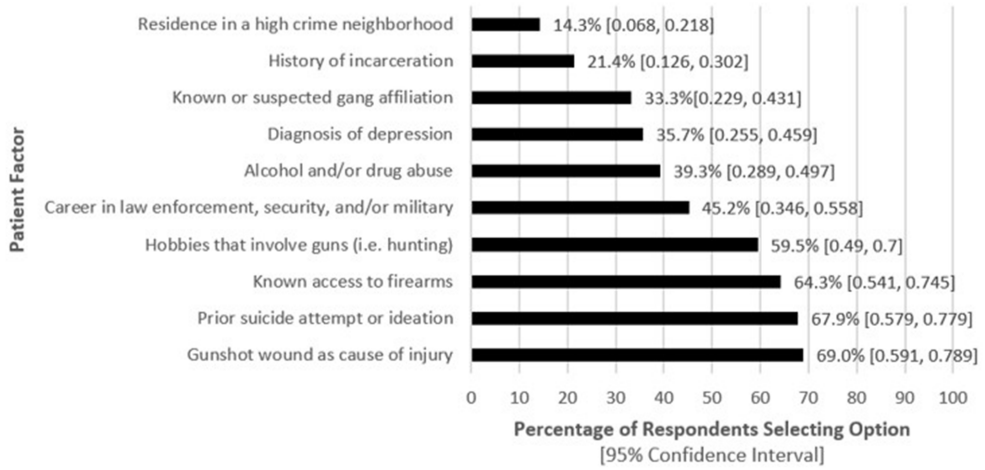

FIGURE 1
Patient factors reported by physician respondents that increase the likelihood they will counsel TBI patients on firearm safety (*n* = 84).

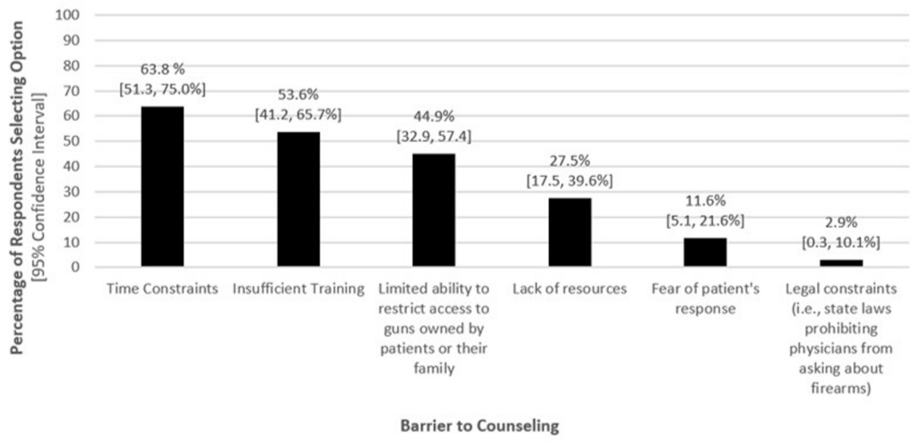

FIGURE 2
Self-reported factors preventing physicians from counseling TBI patients on firearm safety (*n* = 69).

distribution of responses on items pertaining to the frequency with which the physicians' teams inquire about their patients' access to guns and with which they provide counseling on firearm injury prevention. Of note, 81% of respondents agreed that BIM physicians should counsel their patients on firearm injury prevention, but only 12.9% reported always doing so, 95% CI [6.6, 22%]. 15% reported always inquiring about access to firearms among their patients with TBI, 95% CI [8.3, 24.4%].

Respondents reported several patient factors increase their likelihood of inquiring about their access to firearms, with the most common being gunshot wound as the cause of injury (69%) and prior suicide attempts or ideation (67.9%), with 95% CIs of [58, 78.7%] and [56.8, 77.6%], respectively. These results are shown in Figure 1.

Figure 2 illustrates factors that reportedly prevent the respondents and/or their team from providing this counseling, with time constraints and insufficient training each selected by more than half of the respondents as barriers.

88.2% of survey participants indicated having never received formal training on firearm injury prevention or counseling, 95% CI [79.4, 94.2%]. Physicians who received training in firearm injury prevention had 7.5 times higher odds of reporting at least sometimes inquiring about patients' access to firearms than those who did not receive training, 95% CI [1.94, 28.64]. They also had 5.7 times higher odds for reporting at least moderate comfort levels (4 or higher on a 0–10 scale) providing firearm safety counseling than those who did not, 95% CI [1.39, 23.22].

70% of respondents reported having asked a friend or family member of a patient with TBI to remove a firearm from the home, 95% CI [59.7, 80%]. 14% of respondents indicated having had a patient with TBI die by suicide by firearm, 95% CI [7.4, 23.11%].

Twenty-eight respondents provided additional comments. Three comments underscored the need for more training on this topic, while two addressed why they felt the topic often gets neglected in clinical

settings. Seven comments pertained to the respondents' personal criteria for deciding to whom such education should be provided.

Discussion

Most surveyed believe BIM specialists should counsel patients on firearm safety, but the majority do not often or always do so. Additionally, most do not routinely inquire about the presence of firearms in their patients' homes. Respondents reported being more likely to counsel patients with conditions known to increase the risk for suicide among persons with TBI (e.g., depression, substance use disorders, and/or a prior suicide attempt or ideation (13)). Many BIM physicians also reported being more likely to provide such counseling to those whose careers and/or hobbies involve firearms. Importantly, many respondents indicated being more likely to provide such counseling to patients who had sustained firearm-related TBIs. This group may be particularly high-risk for subsequent firearm-related injuries. Survivors of firearm injuries are at significantly elevated risk of carrying firearms and of higher levels of post-traumatic stress disorder symptoms when compared to survivors of other mechanisms of traumatic injuries (22). Moreover, survivors of firearm assaults are at increased risk for recurrent assaultive firearm injury and death (12).

Most BIM physicians surveyed reported having asked a friend or family member of a patient with a TBI to remove firearms from the home. It is noted that some states have legal barriers to the temporary transfer of a firearm to a friend or family member, including the potential need for a background check or completion of safety training certification by the individual to whom it is being transferred (23).

Only two respondents, both practicing in Florida, indicated that state laws prevent them from counseling patients about firearm safety. Florida passed the Firearm Owners' Privacy Act in 2011, which prohibited physicians from routinely inquiring about their patients' ownership of firearms, but the U.S. Court of Appeals overturned it in 2017 (24). A subsequent survey of faculty physicians at the University of Florida revealed that many were not aware that the restrictions on physicians discussing firearms with their patients had been ruled unconstitutional and were no longer in effect (25).

Resources, such as pamphlets or web applications, that educate patients and caregivers about the impact of sequelae of TBI on one's ability to safely store, load, and utilize a firearm, may allow health care teams to provide recommendations to mitigate one's risk of firearm-related injury without the time burden that providing one-on-one counseling entails. Moreover, such materials are likely to receive a neutral or positive response from patients and their family members (26–28). It is noted that educational resources on this topic have been made available by the Department of Veterans Affairs, including an informative website and a toolkit addressing safe firearm storage (29, 30).

More extensive counseling on firearm safety may be necessary for patients at highest risk for firearm-related suicide or injuries, and it is vital to address physicians' lack of training and comfort in providing this education. A prior study found that family physicians who received formal training on firearm safety counseling reported greater comfort in asking their patients about firearms (17). A survey of North Carolina physicians revealed that few had attended continuing medical education events on gun violence, but participation in such events was strongly associated with providing patient firearm counseling often or very often (31). Accordingly, the development of educational programs for health care professionals caring for persons with TBI addressing firearm injury prevention may be an appropriate strategy to improve their training and comfort in the provision of this education and the likelihood they will provide it.

Limitations

Among this study's limitations is the lack of responses from physicians practicing in the states with the highest estimated average household firearm ownership rates (Montana, Wyoming, Alaska, Idaho, and West Virginia) (32). This is likely secondary to a dearth of physicians meeting inclusion criteria in those states, as there were only 3 physicians board-certified in BIM in those states combined at the time this study was conducted (18). Nevertheless, this may impact the generalizability of the findings.

Potentially important physician characteristics, such as age, gender, and gun ownership, were not inquired about. There is evidence that physicians who own firearms may be more likely to counsel patients about firearm safety (33).

Lastly, BIM physicians often provide care within multidisciplinary rehabilitation teams, and some may be unaware of the screening and counseling provided by other team members.

Conclusion

Individuals with TBI have a significantly higher risk of firearm-related death. Although most surveyed BIM physicians believe they should offer firearm injury prevention counseling to their patients, they perceive barriers to doing so. Only a small minority (less than 12%) have received firearm safety training, but those who have are more likely to inquire about firearm access and feel comfortable educating patients on this matter. Creating firearm injury prevention training programs for rehabilitation professionals caring for persons with TBI, along with educational resources for patients and caregivers, could enhance awareness and prevent firearm-related injuries in this vulnerable group.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by University of Miami Miller School of Medicine. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because exempt (low risk, survey of physicians).

Author contributions

IR, NM-C, and LS contributed to the conception and design of the survey and study. IR, NM-C, OA, and LS wrote sections of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

LS holds stock in Doximity. This platform was used to make contact with brain injury specialists for whom we were unable to locate an email address, though ultimately, we received only one survey response via this method.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1237095/full#supplementary-material

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Psychometric evaluation and reference values for the German Postconcussion Symptom Inventory (PCSI-SR8) in children aged 8–12 years

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Background: Post-concussion symptoms (PCS) are a common consequence of pediatric traumatic brain injury (pTBI). They include cognitive, emotional, and physical disturbances. To address the lack of age-adapted instruments assessing PCS after pTBI, this study examines the psychometric properties of the German 17-item post-TBI version of the Postconcussion Symptom Inventory (PCSI-SR8) in children aged 8–12 years. The study also aims to establish reference values based on data from a pediatric general population sample to better estimate the prevalence and clinical relevance of PCS after pTBI in clinical and research settings.

Methods: A total of 132 children aged 8–12 years from a post-acute TBI sample and 1,047 from a general population sample were included in the analyses. The questionnaire was translated from English into German and linguistically validated using forward and backward translation and cognitive debriefing to ensure comprehensibility of the developed version. Reliability and validity were examined; descriptive comparisons were made with the results of the English study. Measurement invariance (MI) analyses between TBI and general population samples were conducted prior to establishing reference values. Factors contributing to the total and scale scores of the PCSI-SR8 were identified using regression analyses. Reference values were calculated using percentiles.

Results: Most children (TBI: 83%; general population: 79%) rated at least one symptom as "a little" bothersome. The German PCSI-SR8 met the psychometric assumptions in both samples and was comparable to the English version. The

four-factor structure comprising physical, emotional, cognitive, and fatigue symptoms could be replicated. The MI assumption was retained. Therefore, reference values could be provided to determine the symptom burden of patients in relation to a comparable general population. Clinical relevance of reported symptoms is indicated by a score of 8, which is one standard deviation above the mean of the general population sample.

Conclusion: The German version of the PCSI-SR8 is suitable for assessment of PCS after pTBI. The reference values allow for a more comprehensive evaluation of PCS following pTBI. Future research should focus on validation of the PCSI-SR8 in more acute phases of TBI, psychometric examination of the pre-post version, and child-proxy comparisons.

KEYWORDS

pediatric traumatic brain injury, post-concussion symptoms, patient-reported outcome measure (PROM), Postconcussion Symptom Inventory (PCSI), reference values

1. Introduction

Pediatric traumatic brain injury (pTBI) is a significant condition with a wide range of incidence worldwide (47–280 per 100,000). The highest rates are reported in Australia and the lowest in Northern Europe (1). In Germany, TBI accounts for 45–80% of all accidental deaths and affects approximately 580 per 100,000 children and adolescents up to the age of 16 (2). While most of the cases are classified as "mild" according to the Glasgow Coma Scale (1, 3) (GCS ≥ 13), approximately one-third of those affected report cognitive, somatic, and/or emotional disturbances, collectively referred to as post-concussion symptoms (PCS) (4). While most symptoms resolve within the first month after the injury, in some cases, PCS may persist for longer (5), affecting the daily lives of patients and their families (6, 7).

To better capture the individual's perspective on symptom burden, assessment of PCS is often based on self-report (6). Two patient-reported outcome measures (PROMs) listed in the Common Data Elements (CDE) recommendations (8) to measure PCS are the Rivermead Post-Concussion Symptoms Questionnaire (RPQ) (9) for adults and the Postconcussion Symptoms Inventory (PCSI) (10, 11) for children and adolescents.

While the RPQ is available in an age-independent version (16 items), the age-adjusted PCSI consists of three self-report forms and one proxy form. The self-report forms are the PCSI-SR5 (5–7 years; 5 items), the PCSI-SR8 (8–12 years; 17 items), and the PCSI-SR13 (13–18 years; 21 items). The 20-item proxy version (PCSI-P; suitable for ages 5–18) can be used when children and adolescents are unable to complete the questionnaires themselves, to obtain the opinions of caregivers, or to supplement self-reports (11). The items apply a Guttman scale, which differs according to the age version. For children up to 12 years of age, three response categories are used (0: "No", 1: "A little", 2: "A lot"). For adolescents and the proxy version, a seven-point scale ranging from 0 to 6 with three anchors (0: "Not a problem", 3: "Moderate problem", 6: "Severe problem") is utilized. All versions refer to two occasions: before (pre version) and after (post version) TBI. The interpretation is based on the Retrospective Adjusted Post-Injury Difference (RAPID) score, which determines clinically significant changes before and after injury. Improvement or worsening of symptom burden is defined as an 80% change that is deemed clinically relevant. In younger children, it is often difficult to obtain reliable self-reported information about pre-TBI symptom experience, especially if the TBI occurred in early childhood. In this case, only the post version can be used (11).

To date, only one instrument for assessing PCS after pTBI has been validated in the German-speaking context, the RPQ in adolescents (13–17 years of age) (12). Validation of the proxy version for younger children (i.e., aged 8–12 years) is currently ongoing. Thus, there is still a need for an age-appropriate German version of the PCSI, since the RPQ was primarily designed to assess PCS in adults (9).

Interpretation of values obtained from PROMs can be challenging. Often, there are no suitable normative or reference data from a comparable general population that can be used to determine the clinical relevance of self-reported symptoms. For the post-TBI version of the PCSI, no such reference data are available either in English- or German-speaking countries. Given the relatively high prevalence of symptoms comparable to PCS in the general pediatric population (13), establishing reference data would facilitate understanding of the clinical relevance and intensity of reported PCS, thus helping clinicians to focus on potentially affected areas.

To fill these gaps, the present study aims to investigate the psychometric properties of the newly translated German post-TBI version of the PCSI-SR8 and to provide reference values for the interpretation of the scores in clinical practice and research.

2. Materials and methods

2.1. Participants – TBI sample

Participants were recruited from hospital registers in Germany between January 2019 and January 2022. Inclusion criteria for the core study were age 8–17 years, diagnosis of TBI at least three months but no more than ten years prior to study enrolment, formal GCS score or clinically diagnosed TBI severity, outpatient status or being at the beginning of hospital discharge, and ability to understand and respond to the questions. Exclusion criteria were current vegetative state (i.e., minimally conscious according to the GCS), spinal cord injury, severe

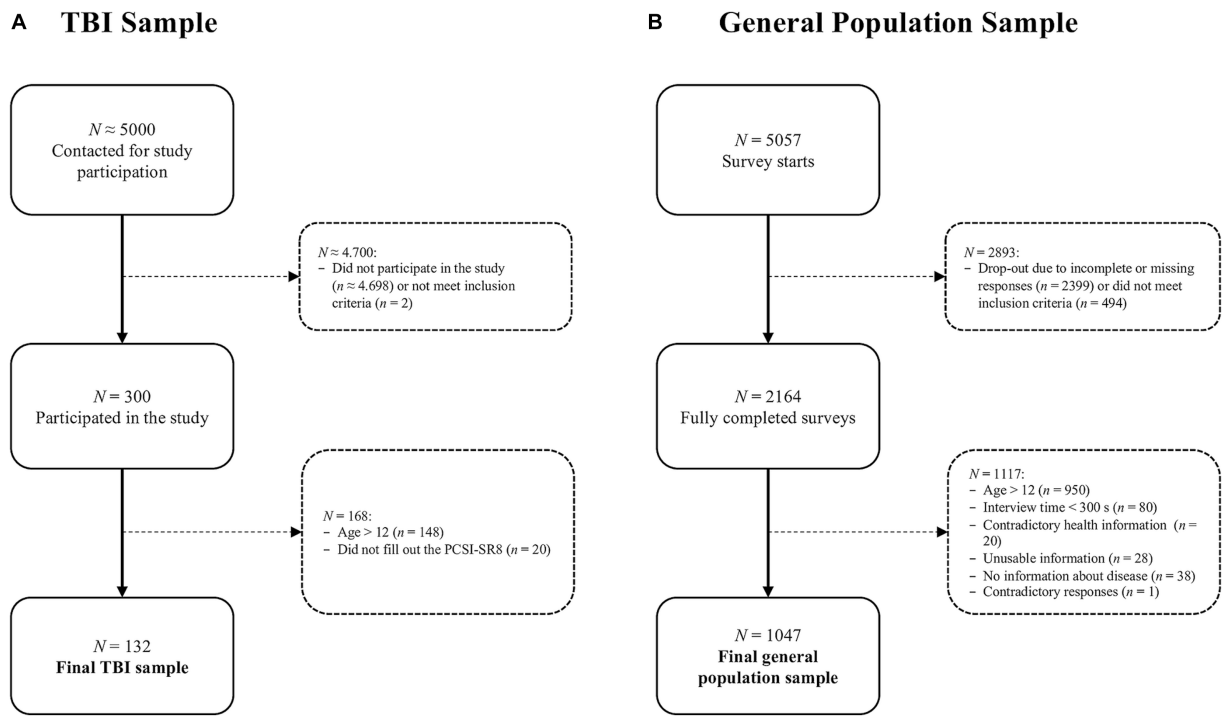

FIGURE 1
Sample composition: **(A)** TBI sample, **(B)** general population sample.

premorbid mental illness (e.g., psychosis, autism, etc.), epilepsy, terminal illness, or very severe polytrauma. Those who met the inclusion criteria were invited by postal mail to participate in the study (approx. 5,000 invitations). Children, adolescents, and their families were informed of the purpose and procedures of the study. Participants and/or their parents or legal guardians provided written informed consent and medical record release forms. The interviews were conducted in person, either online or offline. From a total of 300 participants aged 8–17 years, 152 children aged 8–12 years were recruited. Overall, 132 children completed the PCSI-SR8. For more details on sample composition, see Figure 1A – TBI sample.

2.2. Participants – general population sample

Participants were recruited and surveyed online from March 2022 to April 2022 using the databases of two Germany-based market research agencies.[1] In the first phase, agencies used information in the database to identify and contact parents of children ages 8 to 17. Recruitment was conducted through email invitations, phone notifications, banners, and messages on panel community pages to engage people with a variety of motivations to participate in the study. They were informed of the purpose of the data assessment and the privacy policy and were asked to explicitly consent to the assessment of sensitive information (i.e., their children's health data). After providing sociodemographic information, parents were asked whether their child had experienced a TBI or had a serious life-threatening condition. If so, participation in the study was terminated. All other parents were redirected to the socio-demographic questions and then asked if the child was available at the present time. If not, the questionnaire could be completed later; if yes, the child was invited and after a question about readiness to begin, which had to be confirmed, the pediatric questionnaires were presented. Participants received incentives in the form of tokens or certificates.

To ensure data quality, participants who provided inconsistent or unusable information (e.g., children attending vocational school, which is not possible according to the German school system), those with inconsistent responses (e.g., no health problems but a comment in the text box), and those who completed the survey in less than five minutes (i.e., the time required to click through the survey without paying attention to the questions) were excluded. A total 1,047 children aged 8–12 years were included in the analyses from 2,164 completed surveys of children and adolescents. For more details on sample composition, see Figure 1B – General population sample.

2.2.1. Ethical approval

Both studies have been conducted in accordance with all relevant German laws including but not limited to the ICH Harmonized Tripartite Guideline for Good Clinical Practice ("ICH GCP") and the World Medical Association's Declaration of Helsinki ("Ethical Principles for Medical Research Involving Human Subjects"). The Ethics Committee of the University Medical Center in Goettingen has approved the studies (application number 19/4/18).

1 Dynata: https://www.dynata.com; respondi: https://www.respondi.com; last access 23.07.2023.

2.3. Materials and measures

Sociodemographic and health-related information was collected for both the TBI and general population samples. Participants of the TBI sample or their proxies also completed additional questionnaires measuring health-related quality of life (HRQoL), PCS, anxiety, and depression, which were used in psychometric analyses (see the description of the questionnaires for more details).

2.3.1. Sociodemographic and health-related information

Sociodemographic data comprised age, gender, and school participation. In the TBI sample, health-related information comprised information on health status reported by parents (i.e., presence of chronic health complaints, neurological disorders, and/or developmental health conditions), TBI severity (mild, moderate, severe), time since TBI, and functional recovery/disability status as measured by the King's Outcome Scale for Childhood Head Injury (KOSCHI) (14). The KOSCHI score includes the following categories: (1) dead, (2) vegetative state, (3a) lower severe disability, (3b) upper severe disability, (4a) lower moderate disability, (4b) upper moderate disability, (5a) good recovery, and (5b) intact recovery.

In the general population sample, information on health status was based on the parental report. It consisted of nine categories, with multiple answers allowed: central nervous system disease; alcohol and/or psychotropic substance abuse; active or uncontrolled systemic disease; psychiatric disorders; severe sensory deficits; use of psychotropic drugs or other medications; intellectual disability or other neurobehavioral disorders; pre, peri-, and postnatal problems; other. If at least one was endorsed, a participant was considered to have at least one chronic health condition.

2.3.2. Postconcussion Symptom Inventory – self report (PCSI-SR8)

The PCSI-SR8 has been translated into German largely in accordance with translation and linguistic validation guidelines (15). Two staff members of the Institute of Medical Psychology and Medical Sociology at the University Medical Center Goettingen independently translated the English version of the PCSI-SR8 into German. With support of a language coordinator (NvS), the two German translations were harmonized. A backward translation into English was then performed by an independent professional translator. The next step was to compare the backward translation with the original English version and, if possible, bring the item wording closer to English. One of the lead developers of the original version of the PCSI (GG) was consulted about any necessary deviations in the wording of individual items resulting from the translation process. The final German version of the PCSI-SR8 was subjected to a cognitive debriefing (CD) with a total of three children aged 8–9 years (one female child after TBI, one female and one male child without TBI). The CD was used to check the comprehensibility of the instructions and the individual items. After evaluating and discussing the CD, no further adjustments were made. In the present study, only PCSI-SR8 post-TBI version was used.

For the general population, the questionnaire was adapted by removing the reference to the TBI. The only change was to the instruction, which was rephrased as follows: "We would like to know if you have any of these complaints at the present time (yesterday and today)." Since there was no further explicit reference to injury, the wording of the items and response categories remained the same.

2.3.3. Rivermead Post-Concussion Symptoms Questionnaire (RPQ) – proxy report

The RPQ (9) is a PROM that assesses 16 PCS rated on a five-point Likert-type scale (from 0: "No problem at all" to 4 "A severe problem"). Although the original scoring included only the total score, there is evidence that the RPQ provides multidimensional assessment of the PCS in adults (16) and adolescents (12). Therefore, in addition to the total score, three scale-scores were used, including somatic (9 items), cognitive (3 items), and emotional (4 items) symptoms. For the calculation of the total and scale scores, values of 1, indicating no more problems with symptoms than before TBI, were treated as 0. Higher score values indicate higher symptom burden. Because the wording of the RPQ items is not age-appropriate for the present study age group, proxies were asked to rate the severity of the children's symptoms.

2.3.4. Quality of life after brain injury for kids and adolescents (QOLIBRI-Kid/ADO) – self report

The QOLIBRI-KID/ADO (17) is a PROM assessing TBI-related HRQoL in children and adolescents. The final version of the questionnaire comprises 35 items with a five-point response format (from 1: "Not at all" to 5: "Very") forming six scales (Cognition, Self, Daily Life & Autonomy, Social Relationships, Emotions, and Physical Problems). The total score depicting average values of the scales is transformed in a 0–100 scale with higher values associated with better HRQoL.

2.3.5. Generalized anxiety disorder 7 (GAD-7) – proxy report

The GAD-7 (18) assesses anxiety symptoms using seven items applying a five-point response scale (from 0: "Not at all" to 3: "Nearly every day"). The total score is calculated as a sum of the items and ranges from 0 (no anxiety) to 21 (anxiety symptoms experienced nearly every day). For the present study, proxy-reported GAD-7 was used since the questionnaire had not been yet validated for administration in children aged 8–12 years.

2.3.6. Patient health questionnaire 9 (PHQ-9) – proxy report

The PHQ-9 (19) measures symptoms of major depression with nine items using a five-point response scale (from 0: "Not at all" to 3: "Nearly every day"). The total score ranges from 0 (no depression) to 27 (depressive symptoms reported nearly every day). For the same reasons as for the GAD-7, the PHQ-9 was also completed by proxies.

2.4. Statistical analyses

2.4.1. Missing values

To preserve information, missing values in the questionnaires at the scale or total score level were replaced with the scale or total score means, respectively, if more than two-thirds of the responses were available. This resulted in the substitution of five scores for the PCSI-SR8, seven for the RPQ, twelve for the QOLIBRI-KID/ADO, and one value for the PHQ-9.

2.4.2. Psychometric properties of the PCSI-SR8 and its general-population-adapted version

For the TBI and the general population versions of the PCSI-SR8, we first examined items by providing endorsement rates (*n*, %) per response category (additionally stratified by TBI severity for the TBI sample only). The proportions of items rated as at least "a little" bothersome were reported for both samples and compared to those reported in the original English validation study (11). Then, internal consistency was assessed using Cronbach's alpha on the scale level, supplemented by the McDonald's ω (0.70–0.95 considered good–excellent, respectively) (20). Corrected-item-total correlations (CITC) were calculated to examine associations between the items with the respective scales. Values greater or equal to 0.30 corresponding to a medium effect (21) were considered acceptable.

For the TBI sample only, convergent and divergent validity were examined using Spearman correlation coefficients. For convergent validity, we used the proxy version of the RPQ, expecting correlations $r_S \geq 0.50$ corresponding to a large effect size (21) at the total and scale scores level. For divergent validity, we used total scores of the QOLIBRI-KID/ADO, GAD-7, and PHQ-9, with values $|0.30| \leq r_S < |0.50|$ considered acceptable. At the same time, correlation coefficients provide information about the direction of the associations allowing for testing of construct validity. We expected positive relationships with the questionnaires measuring symptom burden (i.e., RPQ, PHQ-9, and GAD-7) and negative associations with the QOLIBRI-KID/ADO, indicating that higher PCS severity is associated with reduced HRQoL.

Finally, we examined the factorial structure in both samples using confirmatory factor analysis (CFA) with robust weighted least squares estimators (WLSMV) for ordinal items (22). We estimated a four-factor model consisting of physical (8 items), emotional (3 items), cognitive (4 items), and fatigue (2 items) symptoms. The goodness of the model fit was evaluated simultaneously using multiple fit indices, with the desired values given in parentheses: the χ^2-test value ($p > 0.05$), ratio of χ^2 value and degrees of freedom ($\chi^2/df \leq 2$) (23), comparative fit index (CFI ≥ 0.95) (24), Tucker-Lewis index (TLI ≥ 0.95) (24), root mean square error of approximation (excellent fit RMSEA <0.05; mediocre fit 0.05 ≤ RMSEA <0.10) (25, 26) including 90% confidence interval ($CI_{90\%}$), and standardized root mean square residual (SRMR <0.08) (24). To provide robust results, scaled values were obtain for all fit indices except the SRMR (not computable). Where available, the results from the original English PCSI-SR8 study (11) have been provided to allow for a direct comparison.

2.4.3. Reference values for the PCSI-SR8

2.4.3.1. Measurement invariance analyses

Ensuring that the same latent construct of PCS is measured in the general population sample as in the TBI sample is necessary to provide reference values. Therefore, we conducted measurement invariance (MI) testing. We used a CFA framework and estimated three models with imposing parameter constraints following approach suitable for ordinal data (27, 28). First, the baseline model was estimated to account for (1) configural MI. Then, equality of (2) thresholds between the groups was assumed. Finally, equality of (3) thresholds and loadings between the samples was tested. The models were compared using scaled χ^2 difference test, with a non-significant result ($p > 0.05$) suggesting no difference between the models tested and thus no violation of the MI assumption. In addition, differences in fit indices were considered with ΔCFI <0.01 (29) and ΔRMSEA ≤0.01 (30) indicating model equivalence. Maintaining this assumption would imply that differences between TBI and general population samples are due solely to differences in the experience of PCS and that meaningful comparisons can be made.

2.4.3.2. Regression analyses

Regression analyses were used to examine the potential effects of other factors for possible further stratification of the reference values. Negative binomial models were estimated to account for the distribution of the PCSI-SR8 scores. We used the PCSI-SR8 total and scale scores as dependent variables and sex, age, and health status as covariates. Second order interactions between covariates were also included in the model.

2.4.3.3. Reference values

Reference values were calculated using percentiles. Percentiles represent the value below which a certain percentage of observations fall. This information helps to determine whether a post-TBI child's PCSI-SR8 score is below, at, or above the reference population score. The following percentiles were provided: 2.5, 5, 16, 30, 40, 50, 60, 70, 85, 95, and 97.5%. Values that exceed the reference mean (i.e., 50%) by one standard deviation, corresponding to the 85th percentile (rounded up to the next integer) for normally distributed data, were considered clinically relevant. Examples of interpretation are provided in the results section.

2.4.3.4. Software

All analyses were carried out with R version 4.2.3 (31) under application of the packages table1 (32) for descriptive statistics, psych (33) for psychometric analyses, and lavaan (34) for the CFA and the MI analyses. The α-level was set at 5%. Bonferroni correction (i.e., $\alpha_{adj} = 0.05/4 = 0.0125$) was applied for multiple scale comparisons where appropriate.

3. Results

3.1. Sample characteristics

The TBI sample included $N = 132$ children (59.8% male) with a mean age of 10.7 ± 1.40 years. The majority reported no chronic health conditions (59.8%). Most suffered a TBI due to a fall (68.2%) without loss of consciousness (74.2%) with the injury having occurred on average 4.49 ± 2.63 years ago. In most cases, the TBI was classified as mild (72.0%) with no lesions present (74%). At the time of study entry, most participants had fully recovered from the injury (88.6%) according to the KOSCHI score. A descriptive comparison to the study investigating psychometric properties of the PCSI-SR8 (11) revealed some differences in the sample composition. The participants of the original English study rather sustained a sport related TBI (41.0%) classified as mild (100%) and were at an early stage of the injury with the mean of 11.3 ± 2.63 days. The general population sample consisted of $N = 1{,}047$ children (50.0% male) with a mean age of 10.0 ± 1.42 years. Most of the children had no chronic health conditions (88.3%). For more details, see Table 1.

TABLE 1 Sample characteristics of the TBI and general population samples in the present study and comparison with the sample used in the original English validation study.

Variable	Group/value	TBI sample (*N* = 132)	General population sample (*N* = 1,047)	Original English study[1] (*N* = 315)
Sex	Male	79 (59.8%)	524 (50.0%)	n.a.
	Female	53 (40.2%)	523 (50.0%)	n.a.
Age (years)	*M* (*SD*)	10.7 (1.41)	10.0 (1.42)	n.a.
	Md [*Min*, *Max*]	10.5 [8.00, 12.9]	10.0 [8.00, 12.0]	n.a.
Education	None	13 (9.8%)	0 (0%)	n.a.
	Nursery	36 (27.3%)	n.a.	n.a.
	Primary school	55 (41.7%)	556 (53.1%)	n.a.
	Special school	1 (0.8%)	47 (4.5%)	n.a.
	Secondary school	11 (8.3%)	236 (22.5%)	n.a.
	Preparatory high school	2 (1.5%)	193 (18.4%)	n.a.
	Missing	14 (10.6%)	15 (1.4%)	n.a.
Integration assistance	Yes	1 (0.8%)	145 (13.8%)	n.a.
	No	127 (96.2%)	902 (86.2%)	n.a.
	Missing	4 (3.0%)	0 (0%)	n.a.
Chronic health conditions[2]	One and more	79 (59.8%)	122 (11.7%)	-
	None	53 (40.2%)	925 (88.3%)	-
Injury cause	Sports	n.a.	-	130 (41%)
	Fall	90 (68.2%)	-	83 (26%)
	Road traffic/Motor vehicle	17 (12.9%)	-	40 (13%)
	Crash with an object	3 (2.3%)	-	-
	Other	22 (16.6%)	-	58 (18%)
	Missing/not reported	0 (0%)	-	4 (1%)
Loss of consciousness	No	98 (74.2%)	-	192 (61%)
	Yes	33 (25.0%)	-	89 (28%)
	Missing	1 (0.8%)	-	34 (11%)
Time since injury	*M* (*SD*)	4.49 (2.63)[3]	-	11.3 (7.4)[4]
TBI severity	Mild	95 (72.0%)	-	315 (100%)
	Moderate	11 (8.3%)	-	-
	Severe	26 (19.7%)	-	-
Lesions	No	97 (73.5%)	-	n.a.
	Yes	34 (25.8%)	-	n.a.
	Missing	1 (0.8%)	-	n.a.
Recovery (KOSCHI)	4a	3 (2.3%)	-	n.a.
	4b	2 (1.5%)	-	n.a.
	5a	10 (7.6%)	-	n.a.
	5b	117 (88.6%)	-	n.a.

[1]Values obtained from the original validation study by Sady et al. (11). Sex was reported without age stratification and thus cannot be provided. Age was reported in groups only (i.e., 8–12 years).
[2]Presence of chronic health conditions is based on parental report and includes at least one health problem from the following lists: presence of chronic health complaints, neurologic disorders, and/or developmental health conditions (TBI sample) and central nervous system disease, alcohol and/or psychotropic substance abuse, active or uncontrolled systemic disease, psychiatric disorders, severe sensory deficits, use of psychotropic drugs or other medications, intellectual disability or other neurobehavioral disorders, pre, peri-, and postnatal problems, other (general population sample).
[3]Time since injury in years.
[4]Time since injury in days.
n.a., information is not available or not collected in this form; —, information is not relevant for this sample; *N*, absolute frequencies %:, relative frequencies; *M*, mean; *SD*, standard deviation; *Md*, median; *Min*, minimum; *Max*, maximum; TBI, traumatic brain injury; KOSCHI, King's Outcome Scale for Closed Head Injury (4a: lower moderate disability; 4b: upper moderate disability; 5a: good recovery; 5b: intact recovery). Values may not add up to 100% due to rounding.

3.2. Response patterns

Overall, most children (TBI: 83%; general population: 79%) rated at least one symptom as "a little" bothersome, including 24 and 17%, respectively, who rated at least one symptom as "very" bothersome. Analysis of item response patterns revealed that participants in both the TBI and general population samples were less likely to report the maximum level of PCS (i.e., the "a lot" category was selected less frequently for all items). Frequencies in

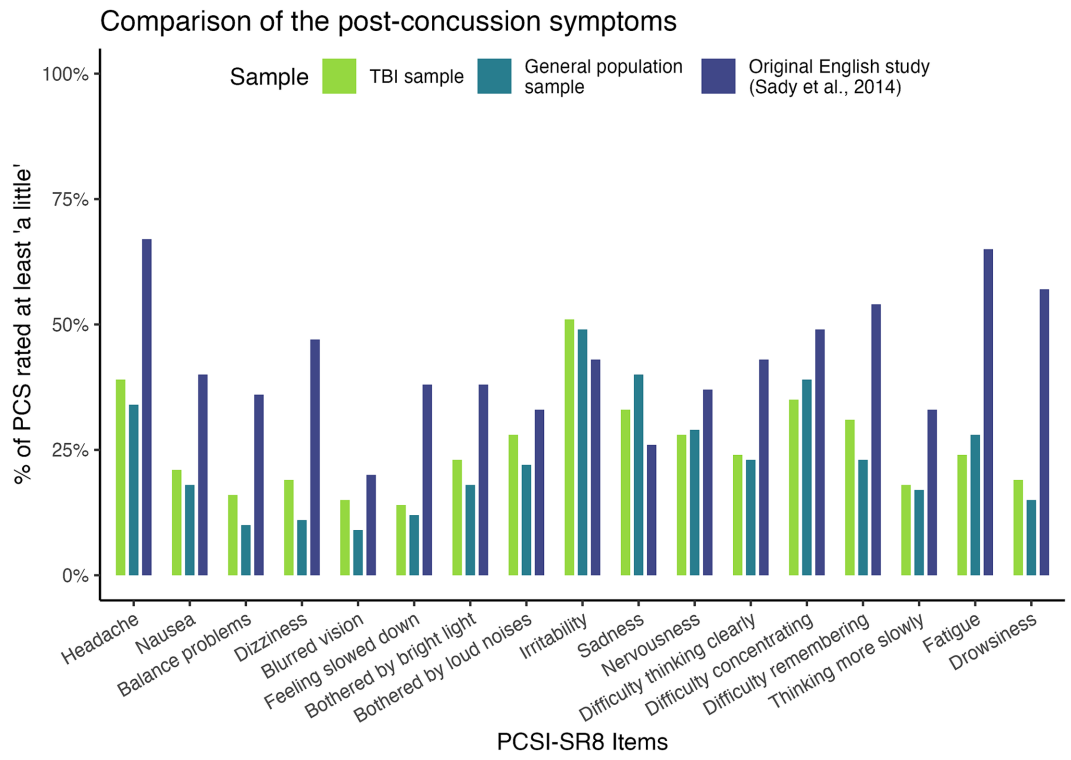

FIGURE 2
Proportions of PCS rated as at least "a little".

this category ranged from 3% (*Difficulty remembering*) to 6% (*Headaches*) in the TBI sample and from 0.4% (*Feeling slowed down*) to 2.8% (*Irritability*) in the general population sample. When TBI severity groups were examined separately, no systematic differences in the distribution of responses due to group size were observed, at least on a descriptive basis. However, participants in the mild TBI subsample were more likely to endorse emotional and fatigue items, whereas participants in the severe TBI subsample tended to rate physical and cognitive symptoms more highly. Comparison with the response patterns of the original English study sample showed a higher frequency of "a lot" responses, particularly for symptoms such as *Headache* (28%) and *Fatigue* (23%), and less frequently reported symptoms such as *Blurred vision* (2%) or *Nervousness* (6%). For a detailed overview, see Supplementary Table S1.

Figure 2 provides an overview of symptoms rated as at least "a little." We found a trend toward more bothersome PCS in the acute mild TBI sample used to validate the English version of the PCSI-SR8, followed by the post-acute TBI sample used in the present study and the general population sample in all scales except the emotional symptom scale. For emotional symptoms (particularly irritability and sadness), both our TBI sample and the general population sample were more likely to be bothered.

3.3. Reliability

Table 2 provides reliability coefficients for the PCSI-SR8 in the TBI and general population samples and for the original English study. Cronbach's α and McDonald's ω ranged from α = 0.69 and ω = 0.73 (Emotional scale) to α = 0.90 and ω = 0.91 (Total score) in the TBI sample and from α = 0.66 and ω = 0.68 (Emotional scale) to α = 0.89 and ω = 0.90 (Total score) in the general population sample. The Cronbach's α values were comparable to those reported in the original study. The omission of none of the items resulted in exceeding the initial Cronbach's α of the respective scale. The CITCs were above 0.40 in both samples.

3.4. Validity

3.4.1. Factorial validity

Goodness of fit indices indicated replicability of the original four-factor structure with χ^2 (113) = 16.31, p = 0.397, χ^2/df = 1.03, CFI = 0.99, TLI = 0.99, RMSEA [90% CI] = 0.015 [0.000, 0.047], SRMR = 0.076 (TBI sample) and χ^2 (113) = 272.11, χ^2/df = 2.41, CFI = 0.99, TLI = 0.98, RMSEA [90% CI] = 0.037 [0.031, 0.042], SRMR = 0.042 (see Table 3).

3.4.2. Convergent, divergent, and construct validity

Figure 3 shows a correlation matrix for the PCSI-SR8, RPQ, QOLIBRI-KID/ADO, GAD-7 and PHQ-9 based on data from the TBI sample. The PCSI-SR8 total and scale scores showed low to moderate positive correlations with the proxy-reported RPQ total and scale scores ranging from 0.13 (Emotional scales) to 0.35 (Total scores). Similarly, low to medium positive associations were observed between

TABLE 2 Results of reliability analyses.

		TBI sample				General population sample				Original English version[1]
Scale	Item	Cronbach's α	McDonald's ω	Cronbach's α if item omitted	CITC	Cronbach's α	McDonald's ω	Cronbach's α if item omitted	CITC	Cronbach's α
Physical	Headache	**0.79**	**0.83**	**0.78**	**0.45**	**0.85**	**0.86**	**0.84**	**0.51**	**0.81**
	Nausea			**0.75**	**0.65**			**0.83**	**0.58**	
	Balance problems			**0.76**	**0.61**			**0.82**	**0.66**	
	Dizziness			**0.76**	**0.62**			**0.82**	**0.65**	
	Blurred vision			**0.75**	**0.65**			**0.83**	**0.57**	
	Feeling slowed down			**0.76**	**0.56**			**0.83**	**0.57**	
	Sensitivity to light			**0.79**	**0.42**			**0.83**	**0.58**	
	Sensitivity to noise			**0.77**	**0.55**			**0.84**	**0.52**	
Emotional	Irritability	0.69	**0.73**	**0.66**	**0.55**	0.66	0.68	**0.64**	**0.42**	0.62
	Sadness			**0.66**	**0.56**			**0.48**	**0.53**	
	Nervousness			**0.44**	**0.74**			**0.56**	**0.47**	
Cognitive	Difficulty thinking clearly	**0.73**	**0.80**	**0.65**	**0.66**	**0.79**	**0.84**	**0.70**	**0.66**	**0.84**
	Difficulty concentrating			**0.70**	**0.57**			**0.74**	**0.57**	
	Difficulty remembering			**0.69**	**0.57**			**0.77**	**0.52**	
	Thinking more slowly			**0.65**	**0.67**			**0.72**	**0.61**	
Fatigue	Fatigue	**0.74**	**0.74**	-	-	**0.76**	**0.76**	-	-	**0.79**
	Drowsiness			-	-			-	-	
Total		**0.90**	**0.91**	-	-	**0.89**	**0.90**	-	-	**0.90**

[1]Values obtained from the original validation study by Sady et al. (11).

CITC, corrected item-total correlations. The values printed in **bold** are within the permissible cut-off values (Cronbach's α and McDonald's ω: ≥ 0.70, Cronbach's α if item omitted does not exceed Cronbach's α; CITC: ≥ 0.30). Cronbach's α if item omitted and CITC are reported for scales with k > 2 items.

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TABLE 3 Factorial validity.

Sample	χ^2 (df)	*p*	χ^2/df	CFI	TLI	RMSEA [90% CI]	SRMR
TBI sample	16.31 (113)	**0.397**	**1.03**	**0.99**	**0.99**	**0.015 [0.000, 0.047]**	**0.076**
General population sample	272.11 (113)	**<0.001**	2.41	**0.99**	**0.98**	**0.037 [0.031, 0.042]**	**0.042**
Original English version[1]	n.a.	n.a.	2.10	**0.97**	n.a.	**0.065** [n.a., n.a.]	n.a.

[1]Values obtained from the original validation study by Sady et al. (11). n.a., information is not available;
χ^2, chi-square statistics; *df*, degrees of freedom (cut-off: ≤ 2); *p*, value of *p*; CFI, Comparative Fit Index (cut-off: > 0.95); TLI, Tucker-Lewis Index (cut-off: > 0.95); RMSEA [90%CI], root mean square error of approximation with 90% confidence interval (cut-off: < 0.06); SRMR, Standardized Root Mean Square Residual (cut-off: < 0.08). Values in **bold** are within acceptable range.

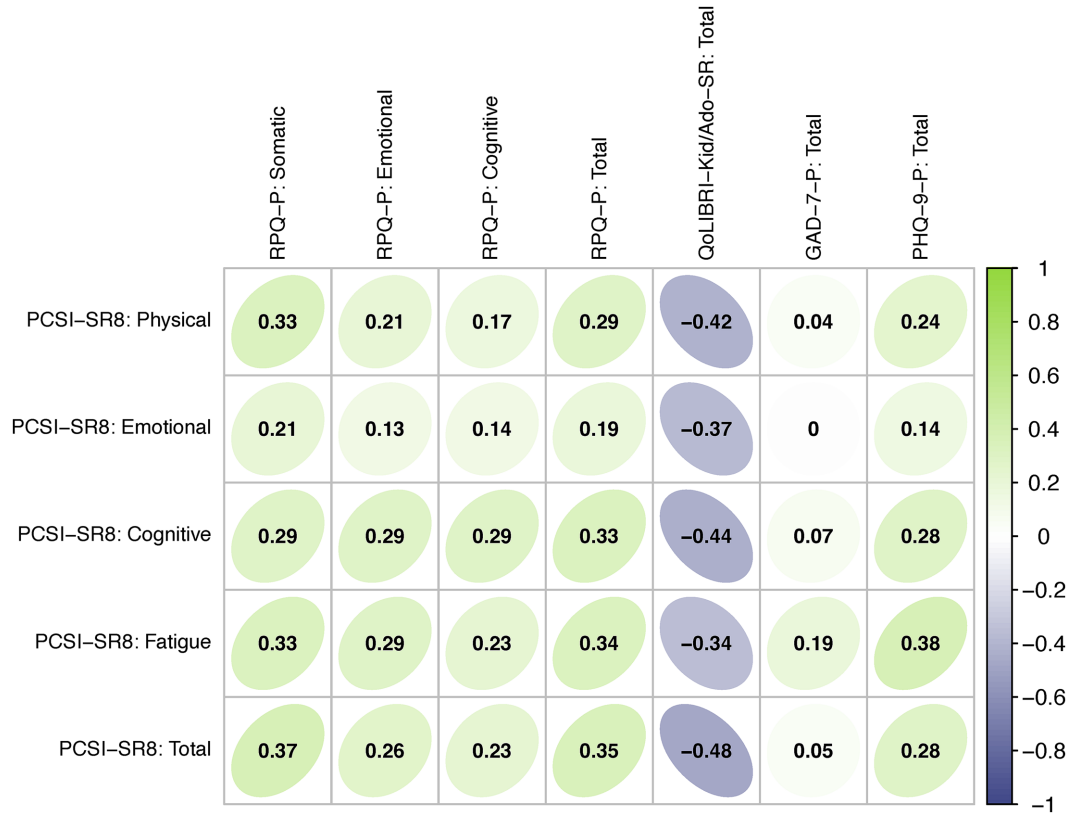

FIGURE 3
Convergent and divergent validity: Spearman correlations between PROMs. Green shading indicates positive correlations, purple shading indicates negative coefficients.

the PCSI-SR8 total and scale scores and the proxy-reported PHQ-9 (0.14 for Emotional scale to 0.38 Fatigue scale) and GAD-7 (< 0.01 for Emotional scale to 0.19 Fatigue scale) total scores. Correlations between the PCSI-SR8 total and scale scores and the QOLIBRI-KID/ADO total score were low to medium and negative (−0.34 for Fatigue scale to −0.48 Total score).

3.5. Measurement invariance

The MI analyses demonstrated no significant differences between the models with increased constraints, indicating the comparability of the TBI and general population samples in assessing PCS using the PCSI-SR8. For details, see Table 4.

3.6. Regression analyses

Regression analyses revealed that only health status was significantly associated with PCSI-SR8 total and scale scores (see Table 5). The second-order interaction analyses showed a significant interaction between age and health status only in the Emotional scale. For details, see Supplementary Table S2. These results suggest that reference values should be stratified by health

TABLE 4 Measurement invariance analyses.

Samples	Constraints	χ^2 (df)	*p*	χ^2/df	CFI	TLI	RMSEA [90% CI]	SRMR	χ^2 (df)	$\Delta\chi^2$	Δ df	*p*
General population vs. TBI sample	Baseline	356.43 (226)	**<0.001**	**1.58**	**0.99**	**0.99**	**0.031 [0.025, 0.037]**	**0.045**	-	-	-	-
	Thresholds	356.43 (226)	**<0.001**	**1.58**	**0.99**	**0.99**	**0.031 [0.025, 0.037]**	**0.045**	234.09 (226)	-	-	-
	Thresholds and loadings	366.35 (239)	**<0.001**	**1.53**	**0.99**	**0.99**	**0.030 [0.024, 0.036]**	**0.045**	247.86 (239)	16.657	13	0.216

χ^2, scaled chi-square statistics; df, scaled degrees of freedom; *p*, value of *p*; χ^2/df, scaled ratio (cut-off: ≤ 2); CFI, scaled Comparative Fit Index (cut-off: > 0.90); TLI, scaled Tucker-Lewis Index (cut-off: > 0.95); RMSEA [90%CI], scaled root mean square error of approximation with 90% confidence interval (cut-off: < 0.06); SRMR, scaled Standardized Root Mean Square Residual (cut-off: < 0.08). Values in bold indicate at least satisfactory/mediocre model fit according to the respective cut-offs and/or are within acceptable range. Only threshold and threshold and loadings models were compared due to identical test values (i.e., χ^2 and *df*), in baseline and threshold models.

TABLE 5 Results of negative binomial regression analyses.

	Variable	Reference Group	Estimate	S.E.	*z*	*p*
Total score	(Intercept)	-	2.22	0.26	8.44	**<0.001**
	Age	-	−0.02	0.02	−0.80	0.421
	Male	Female	−0.12	0.07	−1.66	0.097
	No chronic health complaints	At least one chronic health complaint	−0.57	0.11	−5.40	**<0.001**
Physical	(Intercept)	-	1.14	0.36	3.14	**0.002**
	Age	-	−0.02	0.03	−0.53	0.596
	Male	Female	−0.13	0.10	−1.33	0.185
	No chronic health complaints	At least one chronic health complaint	−0.58	0.14	−4.04	**<0.001***
Emotional	(Intercept)	-	0.91	0.23	3.94	**<0.001**
	Age	-	−0.03	0.02	−1.15	0.250
	Male	Female	−0.13	0.06	−2.15	**0.032**
	No chronic health complaints	At least one chronic health complaint	−0.39	0.09	−4.46	**<0.001***
Cognitive	(Intercept)	-	1.06	0.33	3.16	**0.002**
	Age	-	−0.02	0.03	−0.74	0.461
	Male	Female	−0.09	0.09	−1.02	0.306
	No chronic health complaints	At least one chronic health complaint	−0.78	0.13	−6.13	**<0.001***
Fatigue	(Intercept)	-	−0.46	0.42	−1.08	0.281
	Age	-	0.02	0.04	0.41	0.681
	Male	Female	−0.07	0.11	−0.61	0.540
	No chronic health complaints	At least one chronic health complaint	−0.48	0.16	−2.98	**0.003***

Estimate, regression coefficient; S.E., standard error; *z*, *z*-value; *p*, value of *p*; values in bold are significant at 5%. Covariates additionally marked with an asterisk (*) are significant at 1.25% (adjusted significance level after Bonferroni correction: $\alpha_{adj} = 0.05/4 = 0.0125$).

status (i.e., no chronic health complaints vs. at least one chronic health complaint). However, in view of the relatively small number of participants from general population samples with any health conditions ($n = 122$), and thus the potential impact on the generalizability of the results, we decided to exclude this subgroup from the calculation of reference values.

3.7. Reference values

Table 6 provides reference values for the PCSI-SR8 total and scale scores. The following examples illustrate how this table can be used to interpret a patient's score after pediatric TBI. Suppose a child after a TBI scores 5 on the PCSI-SR8 total score. Compared to a general population

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TABLE 6 Reference values.

		Low symptoms severity		−1 *SD*			*Md*			+1 *SD*		High symptoms severity
Scale	*N*	2.5%	5%	16%	30%	40%	50%	60%	70%	85%	95%	97.5%
Total	925	0	0	0	1	2	3	3	4	8	14	17
Physical		0	0	0	0	0	0	1	1	3	7	8
Emotional		0	0	0	0	1	1	1	2	3	3	4
Cognitive		0	0	0	0	0	0	1	1	2	4	5
Fatigue		0	0	0	0	0	0	0	0	1	2	3

N: absolute frequencies ($n = 122$ participants from the general population sample suffering at least from one chronic health condition are excluded); 50% percentiles represent 50% of the distribution corresponding to the median (*Md*); *SD*, standard deviation (corresponding to the cut-offs of the normal distribution); values from −1 standard deviation (16%) to +1 standard deviation (85%, round up to the next integer) are within the normal range (i.e., not clinically relevant symptom severity); values below 16% indicate low symptoms severity (i.e., absence of PCSI-SR8 symptoms) and values above 85% indicate high symptom severity (i.e., presence of clinically relevant PCSI-SR8 symptoms).

sample, his or her score falls between the 70th and 80th percentiles. The score can be considered average and there is no evidence of clinical relevance of the reported symptom burden. If a child after a TBI scores 15 on the PCSI-SR8 total score, his or her score falls between the 95th and 97.5th percentiles of the general population sample and is therefore above average. The symptom burden can be considered clinically relevant and further diagnosis and treatment is highly indicated. The PCSI-SR8 scale scores can be handled in a similar manner. In this case, a specific symptom domain (e.g., emotional or physical) can be examined for clinical relevance to further refine possible areas of concern.

Alternatively, a cut-off of 8 can be used to determine the clinical relevance of the reported symptom burden, which represents the upper limit of one standard deviation above the mean. Scores above this level are considered clinically relevant (i.e., less likely to be reported by the healthy reference population). The same applies for the scale scores. A score of 3 can be used for the Physical and Emotional scales, a score of 2 for the Cognitive scale, and a score of 1 for the Fatigue scale.

4. Discussion

The aim of the present study was to investigate the psychometric properties of the age-adapted German version of the PROM for measuring PCS in children aged 8–12 years after TBI (i.e., PCSI-SR8) and to provide reference values for the interpretation of individual patient scores. Our results indicate that the German translation of the PCSI-SR8 is psychometrically comparable to the original English version and can be used for the assessment of PCS after pTBI. The reference values provided allow for an easy interpretation of the PCSI-SR8 scores at the total and scale score level and help to determine the clinical relevance of the PCS exposure. However, some of the results deserve special attention and are discussed in more detail below.

4.1. Psychometric properties and comparability with the original English version

The German version of the PCSI-SR8 adapted both positive and negative qualities of the original version. For example, while the reliability coefficients of the Physical, Cognitive, Fatigue, and Total scales indicated good internal consistency, the Emotional scale was the one with values below 0.70 in both TBI and general population samples. This was also the case in the analyses of the original English version reported by Sady et al. (11), where the Emotional scale had the lowest reliability. According to a systematic review of psychometric studies on instruments assessing PCS in student athletes (10), the reliability of instruments used in children aged 5–12 years has not been systematically reported. Therefore, it is challenging to conclude whether the lower internal consistency of the Emotional scale is a maladaptive psychometric characteristic of the PCSI-SR8 or whether this also applies to other questionnaires. A possible explanation could be that children experience challenges in reporting their internalized emotional state, which has been discussed in the literature (35–37).

The results of the correlation analyses indicated the expected direction (i.e., positive associations with scales that measure symptom burden and negative associations with self-reported TBI-specific HRQoL). However, the correlations between some constructs – particularly with an alternative measure, the RPQ, to assess PCS – were rather low. This finding may be explained by the use of proxy reports in assessing depression, anxiety, and PCS using the RPQ. Although proxy reports are commonly used to assess children's health, they often tend to distort the true condition (38). Specifically, ratings of emotional symptoms show poor parent–child agreement, whereas ratings of physical symptoms do concur (39, 40). Furthermore, parents' unawareness of certain emotional symptoms or children's unwillingness or inability to verbalize certain symptoms could affect the quality of the assessment (35, 37, 41). Particularly in the assessment of PCS, which is characterized by a relatively high number of non-directly observable emotional symptoms, child-proxy concordance tends to be moderate (10, 41, 42). A recent study assessing PCS in adolescents aged 13–17 years using both the self-report and proxy-report versions of the RPQ found poor to moderate agreement between ratings (12). The use of the PCSI-P version may have resulted in higher correlations due to greater item concordance between the PCSI-SR8 and the PCSI-P compared to the RPQ. However, the intent was to administer an instrument other than the PCSI, but generally measuring the same construct, to test for convergent validity. The need to treat proxy information with caution, especially in the post-acute phase of injury when awareness of symptom burden may have dissipated

over time, and to interview children whenever possible is reinforced by the results of the current study.

4.2. Reference values and symptom burden in general population samples

Based on parental report, 11.7% of children in the general population sample had at least one chronic health condition. Health status was the only significant factor contributing to the PCSI-SR8 total and scale scores (i.e., the presence of chronic health conditions was positively associated with symptom burden). This provides an indication of the impact of general health on the development of PC-related symptoms. Given the relatively small sample size of this group, we were not able to stratify the reference values according to the health status. However, this would be a very important point as children with TBI may also have suffered from premorbid conditions. In our study, 40.2% of the children had at least one chronic health condition, as reported by their parents. It is known from adult research (43) that general population samples with at least one chronic health condition are more likely to report PC-like symptoms than those without any chronic conditions. Moreover, some studies in adult context suggest that the development of PCS is TBI independent and is rather associated with the general health state [e.g., (44, 45)]. In the pediatric context, young uninjured athletes aged 9–12 years reported overall increased levels of drowsiness, nervousness, and feeling tired or less able to concentrate (endorsement of the "a little" category ranged from 10 to 27%) (13). However, those with a history of concussion were significantly more affected by cognitive and fatigue symptoms than children without a TBI. In the present study, a history of TBI was one of the exclusion criteria for the general population sample. Therefore, this information could not be included in the reference values. Further investigation of children with chronic health conditions, including concussion history, in general population samples is highly recommended to better determine the clinical relevance of reported PCS after TBI. Finally, given that children between 8 and 12 years of age often experience a prepubertal phase, symptoms such as fatigue (46) or mental health issues (47) may occur. Knowledge of this is therefore crucial for the differential diagnosis and subsequent treatment of PCS.

In summary, the provided reference values should serve as an ideal health norm for the screening of PCS in children after TBI in Germany in order to obtain information for a screening diagnosis. Finally, we recommend that scale scores should always be considered when interpreting symptom burden using the reference values provided. In some cases, a clinical cut-off according to the total score may be in the normal range, but the scale score may exceed levels acceptable for the non-clinical population.

4.3. Strengths and limitations

The main strength of the present study is that it is the first study to perform psychometric analyses of an age-adjusted PROM to assess PCS after TBI in children aged 8–12 years and to provide reference values from the general population in Germany. However, there are some limitations to be noted.

First, our sample size of individuals after TBI was relatively small, which may limit the generalizability of the findings. Despite a relatively large pool of families contacted, the response rate was rather low, which might have had several reasons. This limitation has already been exhaustively discussed by von Steinbuechel et al. (17). In addition, our sample consisted of children who had sustained TBI relatively long ago. Therefore, validation of the German PCSI-SR8 at more acute stages after injury, similar to the investigation by Sady et al. (11), is highly indicated. Furthermore, PCS are most common after mild to moderate TBI. Although comparable symptoms are often reported after moderate and severe TBI (9), they are not necessarily due to the brain injury but may have other causes (e.g., extracranial injury or polytrauma). Although our sample consisted predominantly of injuries classified as mild (72%), the absolute number of participants would not be sufficient to perform robust analyses. Therefore, we would strongly recommend further validation of the PCSI-SR8 within different TBI severity groups. Finally, the translated and original versions were only compared descriptively using goodness-of-fit indices according to the respective cut-offs. For further validation of the PCSI-SR8, direct comparisons between language versions (e.g., using MI analyses) would be beneficial to provide evidence of the comparability of the PCS assessment. This would allow data aggregation between language samples and the conduct of multi-center, multi-lingual studies. The same is also applicable to TBI severity groups: MI analyses would provide further evidence that the construct of PCS captured by the PCSI-SR8 is measured equally across the full spectrum of TBI severity, suggesting that differences in questionnaire scores correspond to true differences in experienced symptom burden.

Second, as already stated above, we used proxy measures of mental health (i.e., PHQ-9 and GAD-7) and PCS (i.e., the RPQ) rather than self-report measures, which may have influenced the results of divergent and convergent validity. Because proxy ratings may not fully capture symptom burden, especially when measuring mental and emotional state, further validation of the PCSI-SR8 using self-report information is warranted. Finally, we collected data from the general pediatric population through an online survey, which may have limited the generalizability of our findings to individuals who have access to the Internet and are willing to participate in online surveys. In addition, the exclusion of children with chronic health conditions may have limited the generalizability of our findings to the broader population of children after TBI, and further research is needed to better understand the impact of chronic health conditions on PCS.

4.4. Outlook

Further studies to validate the German version of the PCSI should focus on more acute TBI samples, concordance with PCSI-P results, and validation of the pre-post version. For the latter, it would be also beneficial to collect data from TBI populations who have recently sustained a TBI to avoid recall and memory bias. In addition, detailed comparisons between the PCSI-SR8 and the RPQ would provide more insight into the potential benefits of age-adjusted PCS assessments after TBI.

Data availability statement

The data presented in this study are available upon request from the corresponding author. Data are not publicly available for privacy reasons. R scripts are available from GitHub https://github.com/mzeldovich/Project-Reference-values (last access on 23.07.23). The R-Shiny application with reference values is available at https://reference-values.shinyapps.io/Tables_Reference_values/ (tab PCSI-SR8; last access on 23.07.23).

Ethics statement

Both studies involving humans were approved by Ethics Committee of the University Medical Center in Goettingen (application number 19/4/18). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

MZ: Conceptualization, Funding acquisition, Fromal analysis, Software, Writing - original draft, Writing - review & editing. LK: Data curation, Formal analysis, Software, Writing – original draft. DT: Investigation, Writing – review & editing. UK: Writing – review & editing. JA-L: Writing – review & editing. GG: Writing – review & editing. KB: Writing – review & editing. IK: Investigation, Writing – review & editing. AB: Writing – review & editing. MR: Investigation, Writing – review & editing. MK: Investigation, Writing – review & editing. NS: Conceptualization, Funding acquisition, Investigation, Writing – review & editing. KC: Data curation, Investigation, Project administration, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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Corrigendum: Psychometric evaluation and reference values for the German Postconcussion Symptom Inventory (PCSI-SR8) in children aged 8–12 years

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pediatric traumatic brain injury, post-concussion symptoms, patient-reported outcome measure (PROM), Postconcussion Symptom Inventory (PCSI), reference values

A corrigendum on
Psychometric evaluation and reference values for the German Postconcussion Symptom Inventory (PCSI-SR8) in children aged 8–12 years

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In the published article, there was an error in Table 5 as published. There was an error in the sixth column containing the test statistic (t) and subsequently in the table footer (t, t-value). The statistic should be z (z-value). The corrected Table 5 and its caption Results of negative binomial regression analyses appear below.

In the published article, there was an error in Supplementary Table S2. There was an error in the sixth column containing the test statistic (t) and subsequently in the table footer (t, t-value). The statistic should be z (z-value).

In the published article, there was an error in the Funding statement. The names of two funding organizations were misspelled (i.e., Senckenbergische Stiftung instead of Dr. Senckenbergische Stiftung and Christ'sche Stiftungen instead of Dr. Christ'sche Stiftungen). The correct Funding statement appears below.

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The authors apologize for these errors and state that this does not change the scientific conclusions of the article in any way. The original article has been updated.

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TABLE 5 Results of negative binomial regression analyses.

	Variable	Reference group	Estimate	S.E.	*z*	*p*
Total score	(Intercept)	-	2.22	0.26	8.44	**<0.001**
	Age	-	−0.02	0.02	−0.80	0.421
	Male	Female	−0.12	0.07	−1.66	0.097
	No chronic health complaints	At least one chronic health complaint	−0.57	0.11	−5.40	**<0.001**
Physical	(Intercept)	-	1.14	0.36	3.14	**0.002**
	Age	-	−0.02	0.03	−0.53	0.596
	Male	Female	−0.13	0.10	−1.33	0.185
	No chronic health complaints	At least one chronic health complaint	−0.58	0.14	−4.04	**<0.001***
Emotional	(Intercept)	-	0.91	0.23	3.94	**<0.001**
	Age	-	−0.03	0.02	−1.15	0.250
	Male	Female	−0.13	0.06	−2.15	**0.032**
	No chronic health complaints	At least one chronic health complaint	−0.39	0.09	−4.46	**<0.001***
Cognitive	(Intercept)	-	1.06	0.33	3.16	**0.002**
	Age	-	−0.02	0.03	−0.74	0.461
	Male	Female	−0.09	0.09	−1.02	0.306
	No chronic health complaints	At least one chronic health complaint	−0.78	0.13	−6.13	**<0.001***
Fatigue	(Intercept)	-	−0.46	0.42	−1.08	0.281
	Age	-	0.02	0.04	0.41	0.681
	Male	Female	−0.07	0.11	−0.61	0.540
	No chronic health complaints	At least one chronic health complaint	−0.48	0.16	−2.98	**0.003***

Estimate: regression coefficient; S.E.: standard error; *z*: *z*-value; *p*: *p*-value; values in bold are significant at 5%. Covariates additionally marked with an asterisk (*) are significant at 1.25% (adjusted significance level after Bonferroni correction: $\alpha_{adj} = 0.05/4 = 0.0125$).

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Traumatic tension pneumocephalus: a case report and perspective from Indonesia

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Traumatic tension pneumocephalus is a rare and life-threatening complication of traumatic brain injury necessitating prompt diagnosis and neurosurgical treatment. Nevertheless, various possibilities for impedance in timely management, including patient-related barriers are commonly experienced in low-and middle-income countries setting. Here we presented a delay of management in traumatic tension pneumocephalus case due to initial refusal for emergency surgery. A 59-year-old male presented to the emergency department following a motorcycle accident fully alert with no neurological deficit. He acknowledged clear nasal discharge within 1 h after the initial trauma, but no rhinorrhea or otorrhea was present during physical examination. Head CT revealed extensive pneumocephalus with "Mount Fuji sign," anterior skull base fracture, and frontal sinus fracture. The patient initially refused immediate surgical intervention due to excellent clinical condition and financial scare. Acute decrease of consciousness occurred 40 h post-trauma: GCS of 6 with slight dilatation of both pupils (4 mm) and sluggish pupillary reflex. Emergency bifrontal craniotomy, subdural air drainage, and dura mater tear repair were performed afterwards. Postoperative care was uneventful, with rapid improvement of consciousness and follow-up head CT showing minimal subdural fluid collection and absence of remaining pneumocephalus. The patient was discharged from the hospital after 7 days with GCS of 15 and GOS of 5, proving the importance of overcoming barriers for delay in delivering neurotrauma care in low-and middle-income countries.

KEYWORDS

tension pneumocephalus, traumatic brain injury, LMIC, Indonesia, global neurosurgery

Introduction

Pneumocephalus is defined as pathological air collection in the cranial cavity. The air accumulation can reside in the epidural, subdural, subarachnoid, intraparenchymal, or intraventricular spaces (1–5). Etiological factors comprised of head injury, intracranial infection, and craniofacial operative procedures, including but not limited to neurosurgical and otorhinolaryngology interventions (3, 6). A report of 295 cases shows that the most common cause for pneumocephalus is trauma, accounting for 75% of the study population (7). Traumatic pneumocephalus is considered an uncommon pathology in traumatic brain injury (TBI) group, having its incidence contributing only to 0.5–9.7% of all TBI cases, and is primarily self-limiting (3, 4, 8). Nevertheless, complication could

occur when the intracranial air collection generates significant increase in intracranial pressure (ICP), causing subsequent neurological deterioration (3, 4, 9). This emergency is identified as traumatic tension pneumocephalus, a serious complication that could lead to progressive brain compression, brain oxygen supply reduction, and brain herniation (6). Traumatic tension pneumocephalus requires urgent diagnosis and intervention, with predominantly good outcome if managed timely (8). Diagnostic and treatment delays will bring about poor neurologic outcomes and mortality (1, 9).

Immediate access to medical service for TBI is one of the unmet global neurosurgical necessities, with even greater delays in low- and middle-income countries (LMICs) due to social, cultural, financial, infrastructure, and disparity of resources issues (10, 11). According to the Global Burden of Disease study in 2017, trauma causes 4.5 million deaths and 759 per 100,000 individuals living with disability worldwide, with majority of those residing in LMICs (12, 13). It is estimated that the global incidence of TBI reached 69 million each year, and the South East Asia region is regarded as its largest contributor with the annual incidence of 18.3 million cases (14). This report examines a traumatic tension pneumocephalus case from Indonesia, the highest populated LMIC in South East Asia, providing further insight on the issues encountered during management of a rare TBI presentation in a developing country.

Case

A 59-year-old male was admitted to a type 1 emergency department of a secondary-care hospital two hours after a motorcycle accident. He was admitted straight from the accident site by private-owned vehicle of a passerby, fully alert (Glasgow Coma Scale [GCS] of 15) without any neurological deficit and motor score of 5 in all extremities. The patient reported a history of rhinorrhea in the first hour after the accident, but no cerebrospinal fluid was visible in the nasal cavity or auditory canal. Vital signs, other physical examinations, and laboratory results were within normal range.

Computerized tomography (CT) imaging of the head revealed extensive pneumocephalus with "Mount Fuji sign," together with fractures of the anterior skull base and frontal sinus anterior–posterior wall. Smaller diffuse bubbles were also present throughout the posterior part of the interhemispheric space (Figure 1).

The on-call neurosurgeon assessed the case as a tension pneumocephalus indicated for emergency craniotomy. Patient initially refused neurosurgical intervention and hospital care due to excellent clinical condition and financial scare, but eventually agreed to be admitted for a 48-h post-trauma monitoring. Clinical deterioration occurred 40 h after trauma. He became lethargic and had widened pulse pressure, which in the next 30 min progressed into unresponsiveness (GCS of 6), slight dilatation of both pupils (4 mm), and sluggish pupillary reflex.

Emergency bifrontal craniotomy was carried out immediately. Initial intraoperative findings were subdural air collection and dura mater tear in the anterior skull base. Consequent subdural air drainage and repair of the dura mater were performed.

The patient regained consciousness rapidly and was fully alert the day after surgery. He had an uneventful recovery and was discharged from the hospital after 7 days, with discharge GCS of 15 and Glasgow Outcome Score (GOS) of 5. A follow-up head CT scan showed thin subdural collection and minimal remains of pneumocephalus in the frontal region (Figure 2). Timeline of the case is illustrated in Figure 3.

Discussion

Efforts to deliver optimal treatment for neurotrauma cases in LMICs are often met with a myriad of challenges, including patient-related barriers (10). This report presents a delay of definitive treatment for traumatic tension pneumocephalus encountered in a hospital with type 1 emergency care due to patient's initial reluctance to undergo immediate neurosurgical intervention. The main pathology in this case is identified at an early stage through proper imaging modalities available at the hospital. Pneumocephalus is most easily diagnosed through a head CT scan, where air appears darker than CSF, with attenuation values of-1000 Hounsfield units (8, 9, 15). If the air resides in subdural space, extends downward to the interhemispheric fissure, and separates both frontal lobes anteriorly, it will show a unique appearance referred to as the "Mount Fuji sign." This bilateral compression of the frontal lobe had been associated with tension pneumocephalus (1, 2, 8, 9). The case depicted in this report exhibited the pathognomonic "Mount Fuji sign" on head CT scan, making tension pneumocephalus a definite diagnosis.

Identification of underlying disease at earlier stage significantly aids correct planning for patient's management. Patients with

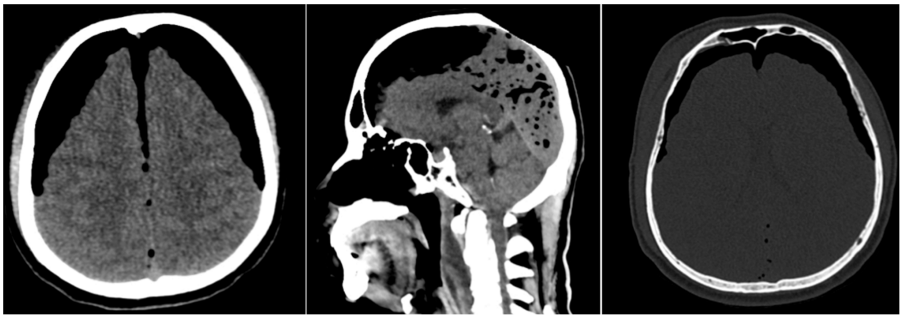

FIGURE 1
Emergency CT scan showed tension pneumocephalus with "Mount Fuji sign," diffuse air bubbles, anterior skull base fracture, and frontal sinus fracture.

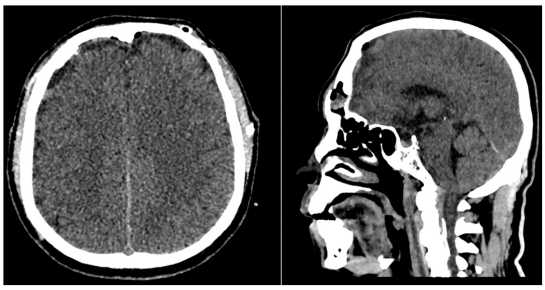

FIGURE 2
The follow-up head CT scan showed thin subdural collection and minimal remains of pneumocephalus.

untreated tension pneumocephalus are at great risk for further complications due to progressive brain compression (2, 5, 6, 16). Spectrum of neurological deterioration ranges from altered mental status and lethargy (from reduced oxygen supply), stupor and coma (from brain herniation), to death of the patient (2, 4, 6, 8, 16). In delayed or slow-progressing cases, it is important to recognize early signs of increased ICP, including headache, nausea, and vomiting (8, 16). More significant changes such as agitation, delirium, decreased vision, pupillary changes, or evidence of Cushing reflex should be noted as well (8, 9, 16). In his initial state, the patient presented in this report did not exhibit any neurological deficits, which contributes to his refusal for emergency surgical intervention despite being given thorough explanation by the on call neurosurgeon. Lack of comprehension regarding course of the disease and importance of treatment, paired with patient's financial instability, are common socioeconomic issues causing hesitance to receive medical care in LMICs (11, 17). Considering the imminent life threat identified through head CT, the neurosurgeon persuaded the patient to agree to a 48-h hospital admission for monitoring. As anticipated, the patient then experienced the predicted clinical deteriorations due to ICP raise in the form of lethargy and widened pulse pressure, which rapidly progressed into loss of consciousness and slightly dilated pupils. The 40-h delayed neurological decline provides the patient's family the conviction required to finally opt for surgery. Fortunately, urging for hospitalization, instead of allowing the patient to be discharged from medical care earlier on, saves significant amount of preparation time required for emergency neurosurgical procedure.

Urgent surgical decompression is mandatory for tension pneumocephalus (1, 2, 5, 6). Various surgical options are available, including craniotomy, burr hole, endoscopy, and ventriculostomy (2, 5, 9, 16). Irrespective of the procedure, emergent evacuation of compressive intracranial air is crucial for optimal outcome (5, 6). If possible, identification and repair of the dura mater defect is considered as definitive treatment that should be performed as well, and could also be achieved through endoscopic endonasal procedure (1, 9, 16, 18, 19). In this patient's case, bifrontal craniotomy, subdural air drainage, and definitive closure of the dura mater defect, were the chosen course of action. Despite considerable hours of delay, the procedure proved to be effective, enabling the patient to be discharged from hospital care 7 days after initial trauma with GCS of 15 and GOS of 5.

This case report shows the significance of patient-related issues in LMICs. Despite attaining the global neurotrauma proposed standard of 4-h window and Lancet Commission of Global Surgery recommendation of 2 hours access to care, added with availability of sufficient diagnostic measures, hospital facilities, and neurosurgeon, the patient still experienced a 40-h delay due to initial refusal for surgery (20, 21). It is important to note that previous accounts of traumatic tension pneumocephalus cases had described the outcome of mortality in absence of neurosurgical intervention (1–4, 6).

Delays in providing best neurotrauma care in LMICs is highly influenced by patient-related barriers (10, 11, 17). Presence of stigma and traditional beliefs concerning disease processes, absence of health education and social support, together with possibility of patient's financial detriments due to seeking care, are few of the main problems encountered in daily medical practice of developing countries, including Indonesia (11, 17, 22). Limited understanding of medical problems where certain perspective that the disease contracted does not have significant negative impact on patients' lives results in reluctance for receiving medical care (23). The fact that current demography of LMICs TBI patients are dominated by breadwinners of the family consequently adds additional hindrance, since hospitalization would result in income regression and unemployment (12, 13, 17, 24). A survey involving Indonesian neurosurgeons found that 27.3% of its participants regarded TBI as the worst cause for economic hardship among patients. Even though public neurosurgical centers in Indonesia are mandated by legislation to provide healthcare at minimum or zero cost, seeking healthcare would put the poverty-ridden population under serious financial burden due to transportation costs and caregiving expenses (17).

Being the world's largest archipelagic country, geography-related issues become the most notable reason for delay in reaching care in Indonesia, which expands through 1,892,410.09 km^2, 17,001 islands, and 37 provinces, with a population of 275,773,000 people. Population density differs highly, where 56% of the citizens live on Java Island (geographically occupies only 7% of Indonesia's territory), while the whole eastern part of Indonesia (26% of the country's area, consisting of 4 provinces, Maluku, North Maluku, Papua, and West Papua) only composes 3.2% of Indonesia's population (25). That discrepancy, coupled with suboptimal decentralized government policies, causes the lack of support for prehospital transport in rural regions. Studies conducted in Bandung [urban city of West Java province, population density 1,334 people/km (2)] and Belitung (rural city of Bangka Belitung province, population density 90 people/km^2) would best illustrate the difference by having 83.8 and 10.4%, respectively, of their TBI patients admitted to the hospital by ambulance (17, 26, 27).

Shortage of neurosurgical expertise and suboptimal hospital service also contributes significant barriers to the system. Neurosurgeon-to-population ratio is 1:725,000 (371 neurosurgeons), very low compared to the recommended 1:100,000, with the rural community in a greater disadvantage due to its uneven distribution (28). Over 257 (69.2%) neurosurgeons practices in Java, with most hospitals offering CT scan service, whereas Papua only has five CT scan machines and four neurosurgeons (8, 29). North Maluku only has one neurosurgeon and one CT scan machine, of which is located 200 kilometers away from the neurosurgical center. Patients would need to undergo 5 hours of road travel and thirty minutes of sea fare each way, violating the global recommendations for safe neurosurgical evaluation and care (20, 21).

The issues mentioned above should be the topic of discussion between local government and medical professionals involved in

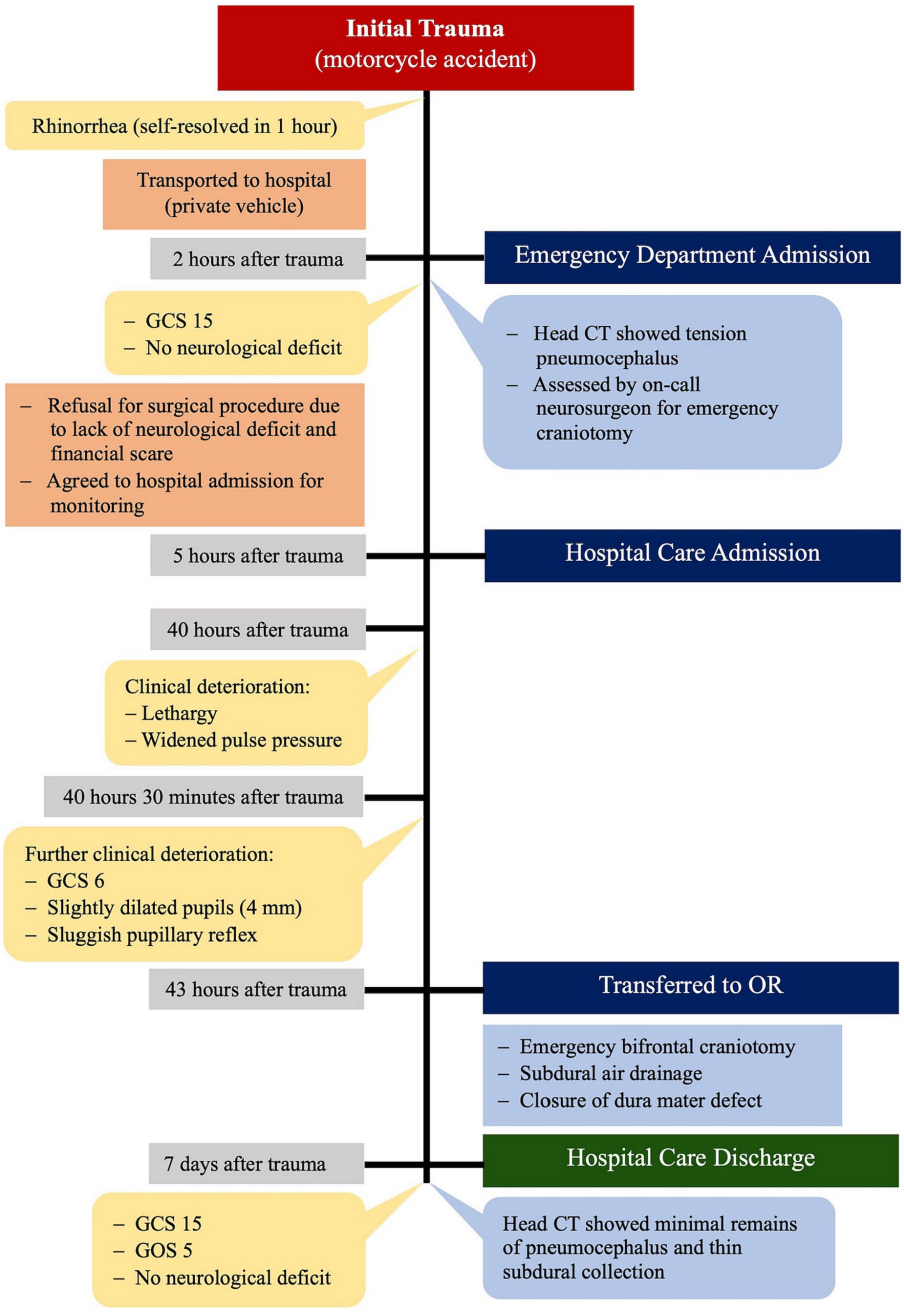

FIGURE 3
Timeline of the case.

Indonesia's neurosurgical care. TBI accounts for 11.9% of trauma cases in Indonesia, making it the third most common cause of traumatic injury for the nation (30). Local 1-year single-centered studies from the national referral hospital and three other secondary-care hospitals in Belitung, Bali, and Papua presented 157, 270, 525, and 393 cases, respectively (26, 31–33). Mortality rate ranges from 7.6 to 29.23%, where the lowest percentage is found in the national referral hospital, and the highest occurred in a secondary-care hospital in Bandung (26, 27, 31, 32, 34–36). Higher patient volume and mortality rate shown in secondary-care hospitals revealed the underperformance of overwhelmed medical service, further proving the need for upgrades in the health care system.

Medical professionals' better insight into difference in Indonesian native's characters and concerns would produce more effective methods in obtaining patients' consent and compliance for comprehensive treatment of their diseases. For the patient in this report, emphasis on major possibility for mortality and perspective concerning possible impoverishing expenditure (e.g.: death of the patient would put his family under a more serious financial loss compared to taking a leave from work and opting for surgery now) should have been the primary focus of doctor-patient discussion, mitigating the delay in administering optimal neurotrauma care.

Universal improvement for the nation's neurotrauma service should start with comprehensive appraisal of all possible issues,

relating to patient, infrastructure, physician, and health resources for every province of Indonesia. The insights acquired from the framework should then be utilized by the stakeholders in creating tangible programs tailored to each region's needs.

Conclusion

Traumatic tension pneumocephalus is a rare presentation of TBI that requires timely diagnosis and treatment. Efforts to reduce delays of TBI management in LMICs should incorporate thorough evaluation for barriers relating to patient, infrastructure, physician, and health resources countrywide.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

AH: Writing – original draft. Writing – review & editing. MN: Writing – review & editing. AN: Writing – original draft. KG: Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Medication utilization in traumatic brain injury patients—insights from a population-based matched cohort study

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Introduction: Traumatic brain injury (TBI) is associated with health problems across multiple domains and TBI patients are reported to have high rates of medication use. However, prior evidence is thin due to methodological limitations. Our aim was thus to examine the use of a wide spectrum of medications prescribed to address pain and somatic conditions in a population-based cohort of TBI patients, and to compare this to a sex- and age-matched cohort. We also examined how patient factors such as sex, age, and TBI severity were associated with medication use.

Methods: We assessed Swedish nationwide registers to include all individuals treated for TBI in hospitals or specialist outpatient care between 2006 and 2012. We examined dispensed prescriptions for eight different non-psychotropic medication classes for the 12 months before, and 12 months after, the TBI. We applied a fixed-effects model to compare TBI patients with the matched population cohort. We also stratified TBI patients by sex, age, TBI severity and carried out comparisons using a generalized linear model.

Results: We identified 239,425 individuals with an incident TBI and 239,425 matched individuals. TBI patients were more likely to use any medication [Odds ratio (OR) = 2.03, 95% Confidence Interval (CI) = 2.00–2.05], to present with polypharmacy (OR = 1.96, 95% CI = 1.90–2.02), and to use each of the eight medication classes before their TBI, as compared to the matched population cohort. Following the TBI, TBI patients were more likely to use any medication (OR = 1.83, 95% CI = 1.80–1.86), to present with polypharmacy (OR = 1.74, 95% CI = 1.67–1.80), and to use all medication classes, although differences were attenuated. However, differences increased for antibiotics/antivirals (OR = 2.02, 95% CI = 1.99–2.05) and NSAIDs/antirheumatics (OR = 1.62, 95% CI = 1.59–1.65) post-TBI. We also found that females and older patients were more likely to use medications after their TBI than males and younger patients, respectively. Patients with more severe TBIs demonstrated increased use of antibiotics/antivirals and NSAIDs/antirheumatics than those with less severe TBIs.

Discussion: Taken together, our results point to poor overall health in TBI patients, suggesting that medical follow-up should be routine, particularly in females with TBI, and include a review of medication use to address potential polypharmacy.

KEYWORDS

traumatic brain injury, medications, pharmacoepidemiology, sex differences, matched cohort study, population-based study

1 Introduction

Traumatic brain injury (TBI) is a leading cause of morbidity and disability across multiple domains (1), including psychiatric health, pain, cognition, and somatic complications involving cardiovascular, respiratory, endocrine, urinary, visual, and gastrointestinal systems (1–8). Consequently, individuals who sustained a TBI are reported to have high rates of medication use, and studies show that 45–85% of TBI patients are prescribed psychotropic and pain medications (9–17). Less is known, however, about the use of non-psychotropic medications in TBI patients since only a small number of studies have examined this. These studies show that diuretics and medications for gastrointestinal and cardiovascular problems are the most commonly prescribed medication classes (9, 12, 14, 17), but prevalence estimates vary widely between studies; e.g., between 5 and 86% for gastrointestinal medications, and 23–40% for cardiovascular medications (9, 12, 14).

TBI patients are also reported to have increased rates of polypharmacy, i.e., the simultaneous use of a large number of medications (9). This can be problematic, as it increases the risk for drug–drug and drug-disease interactions, and could lead to adverse events and worse recovery (9). Still, there is limited knowledge on the extent of polypharmacy in TBI patients due to the inclusion of small and selected clinical samples. There is also limited knowledge on how patient factors such as sex, age, or injury severity are associated with medication use after a TBI. Two studies have pointed to differences in medication use by age and sex (9, 17). However, studies were small which could result in greater differences in comparisons, potentially due to a more biased representation of the population at large (18).

Moreover, studies have not assessed pre-injury medication use, which is a major confound as health problems and healthcare utilization before the TBI are common (19, 20). TBI patients are also a heterogenous group that receive treatment in a variety of settings depending on the nature of their TBI sequelae, but previous studies have mainly included patients with more severe TBIs from specialized settings (e.g., rehabilitation centers) (9, 12, 14, 17). This could result in selection bias and limit the generalizability of findings, since the vast majority (70–90%) of TBIs are mild (1). Furthermore, most studies have lacked a control group of individuals without TBI, limiting the understanding of how medication use patterns may differ from the general population. Another limitation in previous research is the use of retrospective self-reports for assessing medication use, which may be subject to recall bias.

Further research using large representative samples is therefore needed. A thorough examination of medication use in TBI patients, both before and after their injury, is crucial for understanding treatment patterns and potential health implications for patient outcomes. Dispensed medications (i.e., medications collected by the patient at the pharmacy) can be used as a proxy for health conditions, and unlike patient register data in Sweden, which only includes hospitalizations and visits to open specialized care, dispensed medications capture prescriptions initiated within a variety of settings (including private and primary care). Knowledge on pre-and post-TBI medication use can thus inform healthcare providers about broader health concerns in TBI patients. This information is valuable for optimizing medication management strategies, improving long-term care planning, and tailoring interventions to address non-neurological health problems in TBI patients. Furthermore, an assessment of medication use in TBI patients could improve the knowledge-base by identifying frequently prescribed medications that would benefit from TBI patient-specific effectiveness and safety analyses, identify potential polypharmacy, and inform research design by providing knowledge on how important patient factors (such as sex, age, or injury severity) are associated with post-TBI medication use (10). To our knowledge, no study has examined non-psychotropic medications in a nationwide cohort of TBI patients, assessed pre-injury medication use, or included a matched population cohort as a comparison group.

The aim of the current study was to examine the use of a wide spectrum of non-psychotropic medications prescribed to address pain and somatic complications in a population-based cohort of TBI patients during the 12 months before, and 12 months after their TBI, and compare this to a matched population cohort. We also examined how patient factors such as sex, age, and TBI severity were associated with post-TBI medication use in TBI patients.

2 Materials and methods

2.1 Ethics

The project follows the Declaration of Helsinki and was approved by the Swedish Ethical Review Authority (2013/862–31/5), which waived the need for informed consent due to the register-based design.

2.2 Setting and study period

We used Swedish registers with nationwide coverage that were linked through each individual's identification number (21). All data were pseudonymized. The start of study period was July 1, 2005, and the end of the study period was December 31, 2013. The study period was defined according to the data available on medications; we examined medication use 12 months prior to the TBI, and the Swedish Prescribed Drug Register started in July 2005. The data linkage included data until December 2013.

Abbreviations: ATC, Anatomical Therapeutic Chemical; CI, Confidence Interval; GLM, generalized linear model; ICD-10, International Classification of Diseases, 10th revision; NSAID, Non-steroidal anti-inflammatory drug; OR, Odds ratio; RR, risk ratio; TBI, traumatic brain injury.

2.3 Study design and participants

This is a matched population cohort study. TBI patients included all individuals aged 18 and over who were treated for TBI in a hospital or specialized open care between July 1, 2006, and December 31, 2012, to allow for examination of medication use during the 12 months before, and 12 months after, the TBI date. We also included a general population cohort that was matched to each TBI patient on sex and birthyear (1:1 match). Individuals in the matched population cohort were alive and living in Sweden at the date of their matched TBI patient's TBI date and had not been diagnosed with TBI before December 31, 2013.

2.4 Measures

2.4.1 TBI

We used the Centers for Disease Control and Prevention definition of TBI (22) (International Classification of Diseases, 10th revision [ICD-10]: S01.0–S01.9, S02.0, S02.1, S02.3, S02.7–S02.9, S04.0, S06.0–S06.9, S07.0, S07.1, S07.8. S07.9, S09.7–S09.9, T01.0, T02.0, T04.0, T06.0, T90.1, T90.2, T90.4, T90.5, T90.8, T90.9). We included only the incident (i.e., first) TBI diagnosis, thus excluding all individuals who had been diagnosed with TBI before the start of the study period (ICD-9: 800–804, 851–854; ICD-10: as above). Information on ICD-9/10 TBI diagnoses was collected from the Swedish Patient Register (23), which includes all admissions to hospitals and outpatient contacts with specialized open care (including visits to the emergency department). This register has excellent validity on inpatient treatment for ICD-10 TBIs (sensitivity = 95–97%; specificity = 96–98%) (24). However, TBI diagnoses made in specialized outpatient care have not been validated. Missing data in The Swedish Patient Register is around 1% for inpatient treatment, and around 3% for outpatient treatment (23).

2.4.2 Medications

Information was extracted from the Swedish Prescribed Drug Register, which includes information on all prescriptions that have been collected at all pharmacies in Sweden (with less than 0.3% missing information) (25). We classified medications by the Anatomical Therapeutic Chemical (ATC) code that is a globally recognized system for classifying and categorizing pharmaceutical substances based on their therapeutic and chemical properties. We examined a wide spectrum of non-psychotropic medications prescribed to address pain and somatic complications involving cardiovascular, respiratory, endocrine, urinary, visual, and gastrointestinal systems (1–8). Medications included gastrointestinal and diabetes medications (ATC: A01, A02, A07, A10), cardiovascular medications (ATC: C01–C03, C05, C07–C10), genito-urinary medications and sex hormones (ATC: G02–G04), systemic hormonal preparations (ATC: H01–H05), antibiotics and antivirals (ATC: J01, J02, J04, J05), Non-steroidal anti-inflammatory drugs (NSAIDs) and antirheumatics (ATC: M01), respiratory system agents (ATC: R01, R03, R05, R06), and eye medications (ATC: S01). We defined polypharmacy as the presence of five or more different medication classes during 1 year (26).

2.4.3 Demographic measures

Information on sex and age was collected from the Total Population Register (21).

2.4.4 TBI severity

TBI severity was measured in two ways: (1) Receiving inpatient treatment (i.e., being hospitalized for the TBI) vs. receiving outpatient treatment (i.e., treated only in specialized open care) and; (2) Presenting with polytrauma (i.e., having a co-occurring injury to another body part or system on the same day as the TBI; ICD-10: S00-S99, T00-T19, T90-T98, excluding TBI diagnoses) vs. presenting with TBI only.

2.4.5 Diagnosed disorders

Information on diagnosed disorders for the 12 months before (up until the day before the TBI) and the 12 months after the TBI date (starting on the day of the TBI), was collected from the Swedish Patient Register. This included ICD-10 diagnoses recorded during admissions to hospitals and outpatient contacts with specialized open care; psychiatric disorders (F20–F99), substance use disorders (F10–F16, F18–F19), dementia (F00–F03), stroke (I60–I64), epilepsy (G40–G41), sleep disorders (G47), other neurological conditions (A80–A89, G00–G26, G35–G37, G46, G91, I65–I69), cardiovascular disorders (I05–I15, I20–I28, I30–I52, I70–I79), endocrine and metabolic disorders (E00–E07, E10–E16, E20–E35, O24), and gastrointestinal disorders (K25–K31, K50–K51, K70–K77, K80–K85, K90).

2.5 Statistical analyses

We measured the use of any medication (i.e., having collected at least one medication), polypharmacy (i.e., five or more different medication classes), and each of the eight medication classes in TBI patients and the matched population cohort. We divided medication periods into the 12 months before (up until the day before the TBI) and the 12 months after the TBI date (starting on the day of the TBI). When examining prevalence rates, we stratified medication use in the 12 months after the TBI date into two categories: (a) new use (i.e., the first collected prescription during the 24-month study period, was after the TBI date), and (b) prevalent use (i.e., a prescription had also been collected in the 12 months prior to the TBI date). For the matched population cohort, we measured the same time-period as their matched TBI patient.

We estimated the odds ratio (OR) of medication use in TBI patients as compared to the matched population cohort by applying a fixed-effects model using conditional logistic regression (27), where each matched pair was considered a stratum (more details in Supplementary material). This approach allowed us to estimate the OR for medication use in TBI patients relative to the matched population cohort, while controlling for the matched structure (i.e., within-pair variability) of the data. For this analysis, we ran the PROC LOGISTIC procedure in SAS 9.4, using the STRATA statement. In the analyses of post-TBI medication use, the model was adjusted for pre-TBI medication use within the same category (e.g., in the analyses of post-TBI cardiovascular medication use, the model was adjusted for pre-TBI cardiovascular medication use) to account for use that was initiated before the TBI.

To examine how patient- and injury-specific factors were associated with post-TBI medication use, we examined TBI patients only. We performed a generalized linear model (GLM) analysis where the predictor variable was patient sex (female patient vs. male patient) or TBI severity (inpatient vs. outpatient, and polytrauma vs. TBI only), respectively. The response variable was the binary outcome of post-TBI medication use. We ran the PROC GENMOD procedure in SAS 9.4 using a Poisson distribution with a robust variance estimator and log link function. The GLM provides estimates of the risk ratio (RR) on the association between each predictor variable (e.g., sex) and post-TBI medication use (more details in Supplementary material). First, we compared post-TBI medication use (i.e., during the 12 months following the TBI) in female TBI patients as compared to male TBI patients. This model was adjusted for age (as a continuous covariate) and pre-TBI medication use (i.e., use of the medication during the 12 months leading up to the TBI). Second, we investigated if post-TBI medication use varied by TBI severity. We performed two separate GLM analyses for this: (1) We estimated the RR of post-TBI medication use in TBI patients who received inpatient treatment (i.e., were hospitalized) as compared to TBI patients who received outpatient treatment (i.e., specialized open care) and (2) We estimated the RR of post-TBI medication use in TBI patients with polytrauma (i.e., TBI and at least one co-occurring physical injury) as compared to TBI patients without co-occurring physical injuries. Both models were adjusted for sex, age (as a continuous covariate), and pre-TBI medication use.

2.6 Sensitivity analyses

Because age is a strong prognostic factor for negative outcomes after a TBI (28), and older age has been associated with higher medication use after a TBI (9), we carried out sensitivity analyses where we stratified TBI patients by age at injury. We stratified them into four pre-specified age categories; ages 18–30, 31–50, 51–70, and 71 and older, at the time of their TBI. We then examined if post-TBI medication use varied by age by performing a GLM analysis to estimate the RR for medication use in each of the older age categories as compared to TBI patients aged 18–30. The model was adjusted for sex and pre-TBI medication use.

All results are presented with 95% Confidence Intervals (CIs). We followed the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) reporting guidelines for cohort studies.

3 Results

3.1 Characteristics of TBI patients and matched population cohort

We identified 239,425 individuals aged 18 and over who had been treated for an incident TBI in a hospital or specialist outpatient care between July 1, 2006, and December 31, 2012 (Table 1). TBI patients included 41.1% females and 58.8% males, and males were on average younger than females at the date of the TBI (median age for males = 45 years and females =59 years; Supplementary Table S1). Furthermore, 27.0% received inpatient treatment for their TBI and 18.6% presented with polytrauma, i.e., had a co-occurring body injury in addition to the TBI. We matched each TBI patient to an individual in the general population on age and sex (n = 239,425).

TABLE 1 Demographic and health characteristics of individuals with TBI and matched population cohort.

	TBI patients (n = 239,425)	Matched population cohort (n = 239,425)
Age at incident TBI		
18–30	26.8% (64,115)	26.8% (64,115)
31–50	23.2% (55,624)	23.2% (55,624)
51–70	23.2% (55,474)	23.2% (55,474)
71 and older	26.8% (64,212)	26.8% (64,212)
Median age (IQR)	51 (30, 73)	51 (30, 73)
Sex		
Women	41.2% (98,532)	41.2% (98,532)
Men	58.8% (140,986)	58.8% (140,986)
Incident TBI characteristics		
Inpatient treatment	27.0% (64,777)	–
Polytrauma	18.6% (44,509)	–
Diagnoses 12 months before incident TBI		
Psychiatric disorders	5.7% (13,629)	2.0% (4,820)
Substance use disorders	3.3% (7,892)	0.4% (946)
Dementia	1.6% (3,902)	0.3% (723)
Stroke	2.1% (5,076)	0.4% (950)
Epilepsy	1.2% (2,742)	0.2% (562)
Sleep disorders	0.5% (1,084)	0.3% (650)
Other neurological conditions	2.7% (6,480)	0.8% (1,870)
Cardiovascular diseases	11.0% (26,420)	5.5% (13,082)
Endocrine and metabolic disorders	4.7% (11,274)	2.5% (5,971)
Gastrointestinal disorders	2.3% (5,556)	1.2% (2,905)
Diagnoses 12 months after incident TBI		
Psychiatric disorders	6.9% (16,411)	2.1% (4,991)
Substance use disorders	6.2% (14,900)	0.4% (979)
Dementia	3.3% (7,834)	0.4% (898)
Stroke	3.6% (8,589)	0.4% (1,015)
Epilepsy	2.0% (4,688)	0.3% (602)
Sleep disorders	0.6% (1,351)	0.3% (661)
Other neurological conditions	4.7% (11,187)	0.9% (2,172)
Cardiovascular diseases	17.7% (42,272)	6.1% (14,545)
Endocrine and metabolic disorders	6.8% (16,311)	2.7% (6,389)
Gastrointestinal disorders	2.6% (6,272)	1.3% (3,051)

For matched population cohort, 12-month prevalence of diagnoses was calculated from the same TBI date as their corresponding TBI match; Cardiovascular diseases excludes cerebrovascular diseases.

The most common pre-TBI diagnosed disorders were cardiovascular diseases, endocrine and metabolic disorders, and psychiatric disorders (Table 1). During the year after the TBI, rates of all investigated disorders increased in TBI patients. Individuals in the matched population cohort demonstrated lower prevalence rates of all disorders in the 12 months leading up to the TBI date (i.e., the date of their matched TBI patient). In the 12 months after the TBI date, prevalence rates in the matched cohort remained similar for most disorders with the exception of cardiovascular diseases, which increased from 5.5 to 6.1%.

3.2 Medication use during the 12 months before and 12 months after the TBI

In the 12 months leading up to the TBI date, 64.6% of TBI patients had collected a prescription for at least one of the eight medication classes studied, as compared to 51.0% of the population cohort (Figures 1, 2; prevalence rates and details of specific medications within each class in Supplementary Tables S2, S3. Prevalence rates stratified by sex and age categories provided in Supplementary Tables S4, S6, respectively). TBI patients also displayed higher prevalence rates of polypharmacy (i.e., they had collected prescriptions for five or more different medication classes during the 12-month time-period), and of each of the eight medication classes. In the 12 months after the TBI date, prevalence rates of all medications increased slightly in TBI patients, particularly for antibiotics/antivirals (an increase from 25.9% pre-TBI to 30.0% post-TBI). Prevalence rates remained similar in the population cohort in the 12 months after. We also divided post-TBI medication use into two categories; new use (i.e., where the first collected prescription during the 24-month study period was after the TBI date), and prevalent use (i.e., a prescription had also been collected in the 12 months prior to the TBI date). For TBI patients, the largest increases in new use were seen for antibiotics/antivirals, and NSAIDs/antirheumatics, where two-thirds of post-TBI prescriptions were new. The matched cohort presented similar rates in new use.

3.3 Medication use in TBI patients as compared to matched population cohort

We applied a fixed-effects model using conditional logistic regression to compare medication use in TBI patients with that in the matched population cohort (Figure 3; prevalence rates in Supplementary Table S3). In the 12 months before the TBI date, TBI patients were around twice as

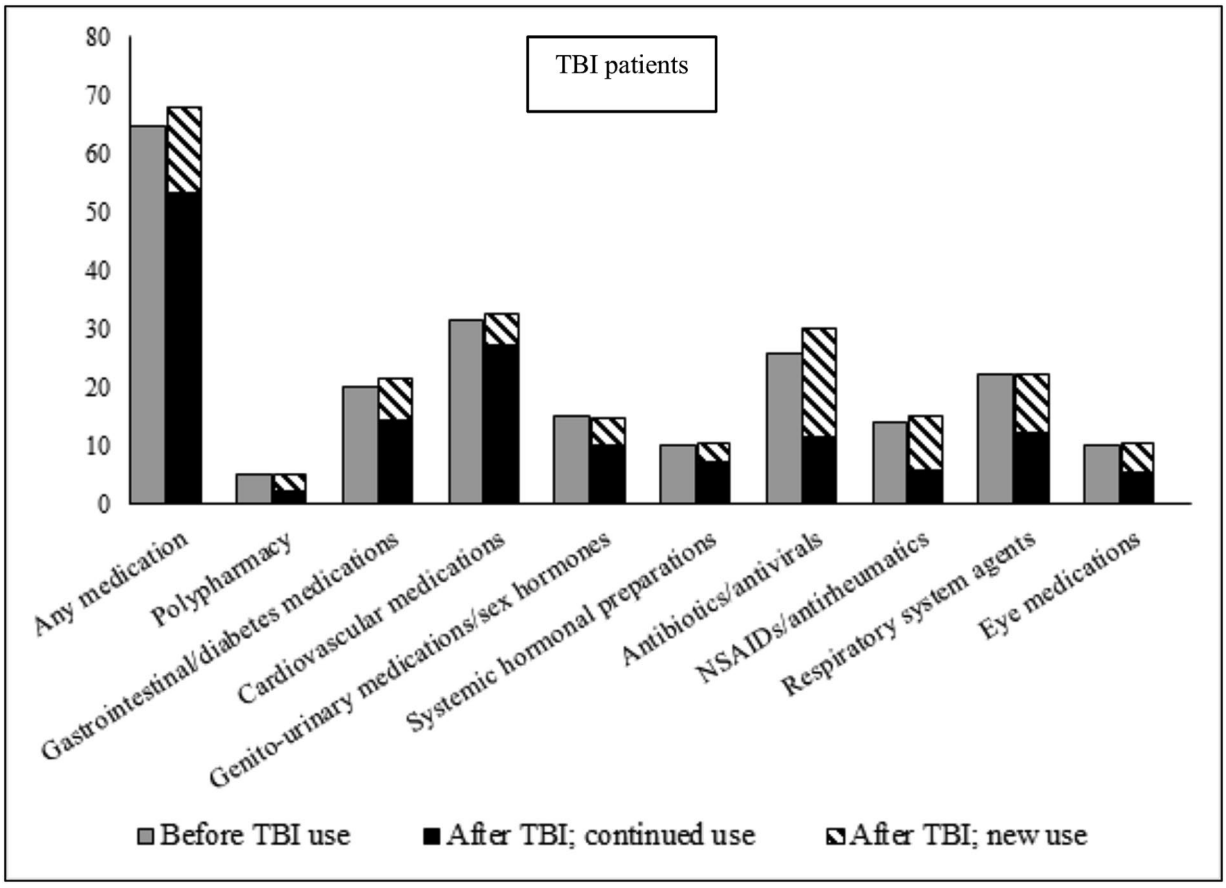

FIGURE 1
Prevalence of medication use during 12 months before, and 12 months after (stratified by continued use and new use), TBI date in TBI patients. Continued use, Used the medication during the 12 months prior to the TBI; New use, Did not use the medication during the 12 months prior to the TBI; NSAIDs, Non-steroidal anti-inflammatory drugs.

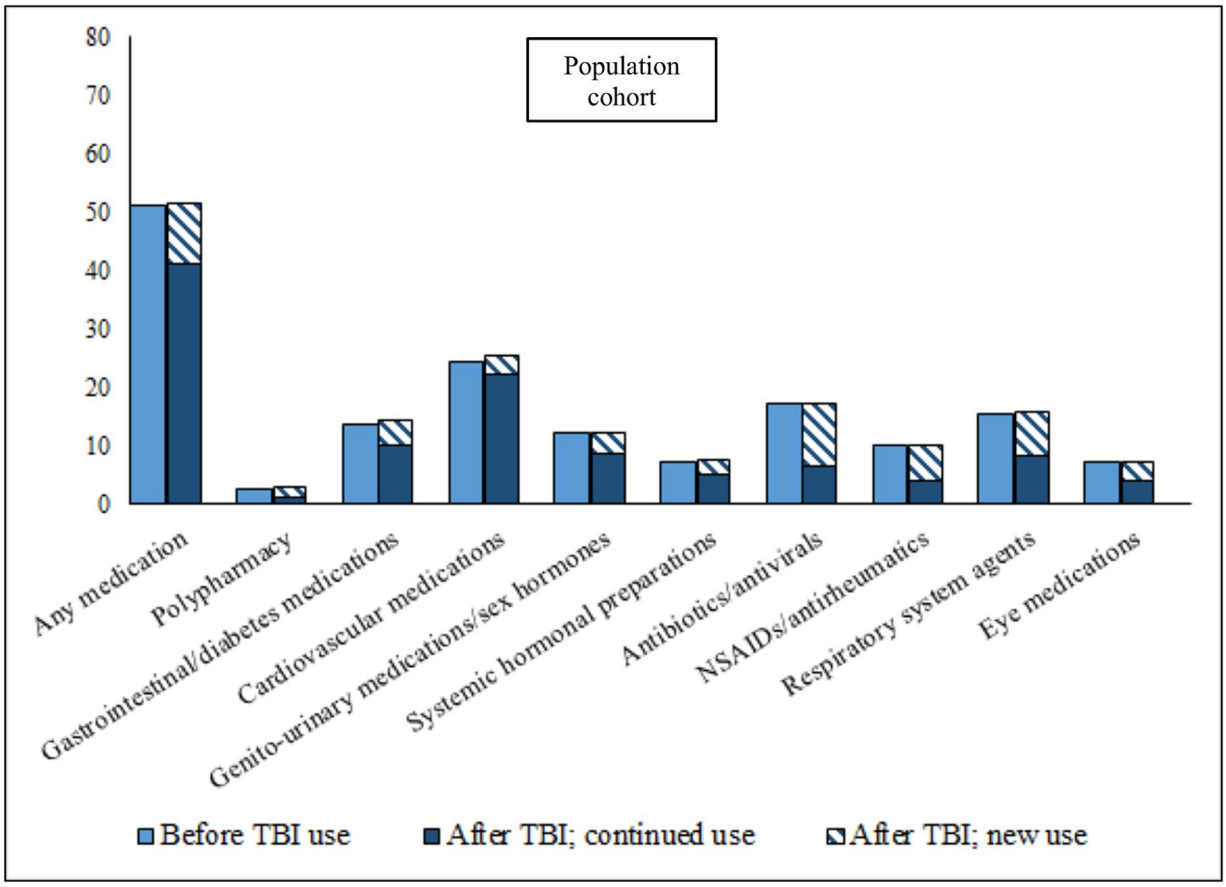

FIGURE 2
Prevalence of medication use during 12 months before, and 12 months after (stratified by continued use and new use), TBI date in matched population cohort. Continued use, Used the medication during the 12 months prior to the TBI; New use, Did not use the medication during the 12 months prior to the TBI; NSAIDs, Non-steroidal anti-inflammatory drugs.

likely to collect any medication (OR = 2.03, 95% CI = 2.00–2.05) and to present with polypharmacy (OR = 1.96, 95% CI = 1.90–2.02) than the matched population cohort. TBI patients demonstrated increased ORs for each of the eight medication classes before the TBI date (ranging between 1.34 for genito-urinary medications/sex hormones and 1.74 for cardiovascular medications). We repeated the same analyses to compare medication use in TBI patients to the matched population cohort in the 12 months after the TBI date, while also adjusting for previous medication use (i.e., in the 12 months leading up to the TBI date). Results showed attenuated ORs for any medication (OR = 1.83, 95% CI = 1.80–1.86), polypharmacy (OR = 1.74, 95% CI = 1.57–1.80), and each of the medication classes (ranging between 1.21 for genito-urinary medications/sex hormones and 1.59 for gastrointestinal/diabetes medications). However, ORs increased after the TBI for antibiotics/antivirals (OR = 2.02, 95% CI = 1.99–2.05), NSAIDs/antirheumatics (OR = 1.62, 95% CI = 1.59–1.65), and eye medications (OR = 1.53, 95% CI = 1.49–1.58).

3.4 Post-TBI medication use in TBI patients by sex

We then examined how patient factors were associated with post-TBI medication use by stratifying TBI patients by sex. We carried out GLM analyses comparing post-TBI medication use in female TBI patients to that male TBI patients, while adjusting for age and previous medication use. During the 12 months after the TBI, female TBI patients presented higher RRs of collecting any medication (RR = 1.15, 95% CI = 1.14–1.16) and of polypharmacy (RR = 1.60, 95% CI = 1.54–1.66) as compared to male TBI patients (Figure 4; prevalence rates in Supplementary Table 4). Female TBI patients also presented increased RRs for all medication classes (ranging between 1.07 and 1.67) except for cardiovascular medications.

3.5 Post-TBI medication use in TBI patients by TBI severity

We also examined how patient factors were associated with post-TBI medication use by stratifying TBI patients by injury severity. We carried out GLM analyses comparing post-TBI medication use in those with more severe injuries to those with less severe injuries (Figure 5; prevalence rates in Supplementary Table S5). First, we compared individuals who had been hospitalized for their TBI to those who received outpatient treatment only. Second, we compared individuals with polytrauma (i.e., TBI plus body injury) to those with only TBI. Models were adjusted for sex, age,

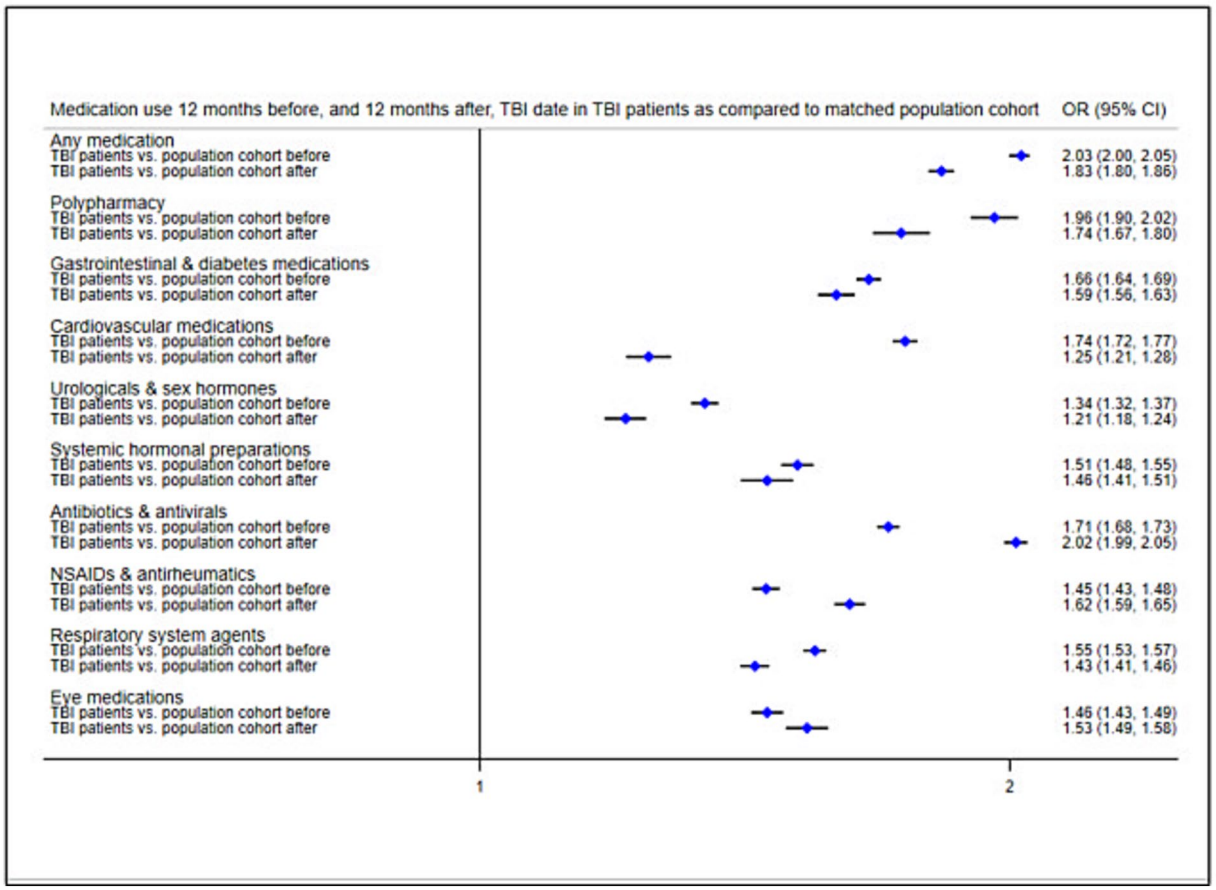

FIGURE 3
Odds ratios of medication use 12 months before, and 21 months after, TBI date in TBI patients as compared to the matched population cohort. Reference group, Matched population cohort; OR, Odds ratio; NSAIDs, Non-steroidal anti-inflammatory drugs.

and previous medication use. Results from both models showed some similarities; during the 12 months after the TBI, individuals with more severe injuries (i.e., hospitalized individuals and individuals with polytrauma) demonstrated increased RRs of collecting gastrointestinal/diabetes medications, antibiotics/antivirals, and NSAIDs/antirheumatics.

3.6 Sensitivity analyses—post-TBI medication use in TBI patients by age category

In sensitivity analyses, we examined how age was associated with post-TBI medication use. We carried out a GLM comparing medication use in TBI patients in different age categories; we compared TBI patients aged 31–50, 51–70, and 71 and older, respectively, to those aged 18–30 (Supplementary Figure S1; prevalence rates in Supplementary Table S6). Analyses were adjusted for sex and previous medication use. Results showed that during the 12 months after the TBI, individuals in the older age categories presented increased RRs of medication use (ranging between 1.14 and 8.36), and the general pattern was that RRs increased with each increasing age category.

4 Discussion

In a nationwide Swedish study, we identified a cohort of 239,425 individuals treated for an incident (i.e., first) TBI and matched them to 239,425 individuals in the general population who had not been treated for TBI. We examined the use of eight different non-psychotropic medication classes for treating pain and somatic complications. We found that TBI patients were twice as likely to use any medication in the 12 months leading up to the TBI date, as compared to the matched population cohort. They were also more likely to use each of the eight medication classes and to present with polypharmacy before their TBI. In the 12 months following the TBI, we found the largest increases in new use (i.e., medication use initiated after the TBI) for antibiotics/antivirals and NSAIDs/antirheumatics, where around two-thirds of prescriptions were new. We also found that TBI patients continued to be more likely to use all medications and to present with polypharmacy as compared to the matched population cohort post-TBI, although differences were attenuated. However, for antibiotics/antivirals, NSAIDs/antirheumatics, and eye medications, differences between TBI patients and the matched cohort increased after the TBI. We also examined how patient factors such as sex, age, and TBI severity were associated with post-TBI medication use in TBI patients. We found that female patients were more likely

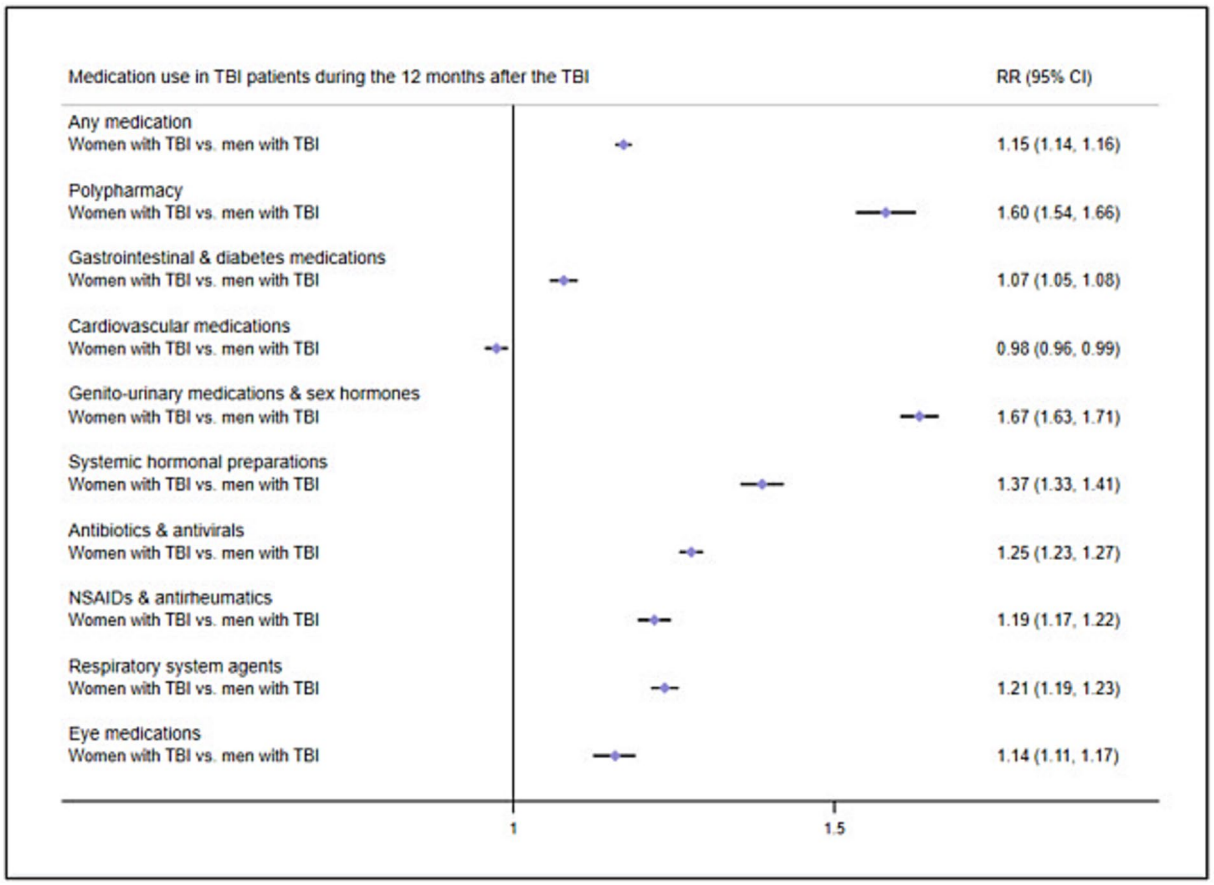

FIGURE 4
Risk ratios of medication use in TBI patients 12 months after the TBI by sex. Reference group, Men with TBI; RR, Risk ratio; NSAIDs, Non-steroidal anti-inflammatory drugs.

than male patients to use medications after their TBI, and that older patients were more likely than younger patients after their TBI. Our results also showed that patients with more severe TBIs demonstrated increased use of certain medications (i.e., gastrointestinal/diabetes medications, antibiotics/antivirals, and NSAIDs/antirheumatics) than those with less severe TBIs.

Our results on pre- and post-TBI medication use are in line with our previous study of the same cohort, where we showed that TBI patients had increased rates of psychotropic and pain medication use, both in the 12 months before and in the 12 months after their TBI (29). In fact, we found only a slight increase in new use (i.e., use initiated after the TBI) for most non-psychotropic medications. The highest rates in new use were shown for antibiotics/antivirals and NSAIDs/antirheumatics, which could be due to penetrating wounds, injury complications, and/or increased pain after the TBI (30–32). These findings add to the growing body of evidence suggesting that health events precede the TBI (19, 20), and could have implications for TBI prevention as well as clinical management after the TBI (33). Prevalence rates in our study were on the lower end of previously reported ranges; for example, we found that 32.5% were prescribed a cardiovascular medication (reported range: 5–86%) and 21.5% were prescribed a gastrointestinal/diabetes medication (reported range: 23–40%) (9, 12, 14). While previous studies mainly included patients in rehabilitation centers with severe injuries, we included a population-based sample where the majority (73%) were not hospitalized for their TBI, which could explain the lower prevalence rates in our study. Differences between studies could also be due to differing sources of prescription information, varying lengths of follow-up, and/or to our study period (2005–2013). Our data cutoff in December 31, 2013 could affect the generalizability of our results to current patient cohorts if prescription practices for the studied medications changed since the study period. However, no fundamental reorganization or new policy has been adapted in Sweden regarding post-TBI care since this period, and no groundbreaking medications have been introduced for TBI patients. Although there have been changes in general prescription patterns for certain drugs used in other medical conditions, such as antibiotic regimes, diabetes, and cardiovascular conditions, our analysis is based on the group and subgroup of drugs classified according to the Anatomical Therapeutic Chemical (ATC) code. Consequently, changes in prescription practices from one medication to another within the same class/group do not affect our estimates. Therefore, the results from our study should remain relevant and generalizable to more recent TBI patients. Furthermore, the most commonly dispensed medication class in our study was cardiovascular medications, in line with previous research (12, 14, 17), and suggesting consistency with newer samples.

We also found higher rates of polypharmacy in TBI patients as compared to the matched population cohort, both before and after the

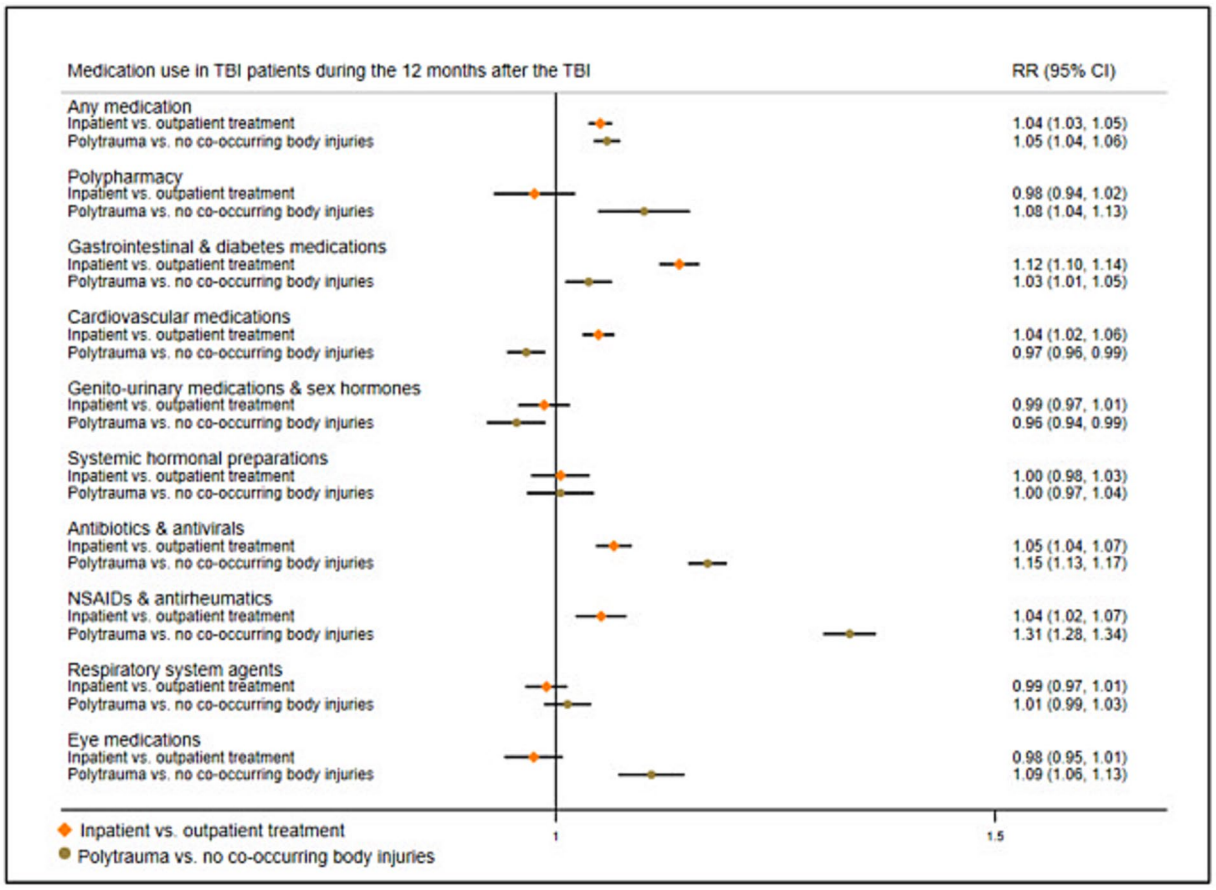

FIGURE 5
Risk ratios of medication use in TBI patients 12 months after the TBI by injury severity. Reference group, TBI patients who received outpatient treatment, and TBI patients with no co-occurring body injuries, respectively; RR, Risk ratio; NSAIDs, Non-steroidal anti-inflammatory drugs.

TBI. Although differences were reduced after the TBI (from OR = 1.96, 95% CI = 1.90–2.02 to OR = 1.74, 95% CI = 1.67–1.80), TBI patients still presented an increased risk of polypharmacy after adjustments for age, sex, and pre-TBI medication use. TBI patients may experience a variety of physical health problems after their injury, including motor impairment, chronic pain, hormonal imbalance, cardiovascular conditions, digestive issues, and sleep disturbances (1–8), that may lead to an overall decline in function. Management of these problems could lead to the unintended use of multiple medications due to separate treatment settings and guidelines (34). However, polypharmacy is of concern as it may affect medication effectiveness and safety, raise the risk of drug–drug interactions, and increase mortality after the TBI (35–37). This suggests that strategies to minimize polypharmacy could be implemented in TBI patients, including central coordination, open communication and collaboration between healthcare professionals, close monitoring of potential adverse effects, and frequent reviews of medication regimens (3).

Female TBI patients in our study were, on average, older than male patients (median age 59 and 45 years, respectively), which may have affected the increased rates of pre-TBI medication use in females. However, female TBI patients also presented increased post-TBI medication use in analyses that were adjusted for age and pre-TBI medication use, which could suggest more morbidity in females after the TBI. Previous studies on sex differences in TBI outcomes have been inconclusive; some studies suggest that females have worse outcomes in a wide range of areas (18), which has been attributed to differences in hormonal and chromosomal factors (38). It has also been suggested that females may report more symptoms after their TBI as it is more socially acceptable for them to admit health problems (38). Our results may thus reflect sex differences in acknowledging health problems and seeking treatment. Nevertheless, female patients are underrepresented in TBI research (38), pointing to a need for more research to examine potential sex differences in TBI outcomes.

TBI patients in our study showed higher rates of diagnosed substance use disorders than the matched population, and rates were almost doubled in the year following the TBI; from 3.3 to 6.2%. Previous studies have reported a high prevalence of pre-injury substance misuse in TBI patients, that in many cases contributed to the TBI (39). It has also been suggested that TBI increases the risk of developing subsequent misuse problems due to neurobiological damage, TBI sequelae (e.g., poor emotional regulation), or maladaptive ways to handle stress or pain stemming from the TBI (40–42). The rise in diagnosed substance use disorders after the TBI in our study may also be influenced by detection bias. This could occur if pre-injury disorders were identified post-injury due to intoxication at the time of the TBI, or increased healthcare contacts post-TBI that affected the likelihood of detection and diagnosis.

Nonetheless, substance use disorders are associated with negative health effects, e.g., cardiovascular or liver diseases (43), which could affect medication rates in the TBI cohort.

5 Strengths and limitations

This study has several strengths; we included all individuals treated for TBI in Sweden during the study period and linked several nationwide registers. Our information on medications was based on individuals collecting their medication from pharmacies, an advance from prescription-only data and self-reports, and data was nearly complete (less than 0.3% missing information) (25). We included medications prescribed in all healthcare settings, i.e., hospitals, rehabilitation centers, open specialized care, and primary care and compared medication use to a population cohort matched on sex and age. Several limitations should be considered; we only examined medications collected at pharmacies, as medications dispensed in hospitals are not available in the Swedish Prescribed Drug Register. For individuals with extended hospital stays, this could lead to an underestimation of medication use. However, the majority of TBI patients (73%) were not admitted overnight, and 99.8% ($n = 238,715$) were discharged within 30 days. Furthermore, we examined collected medications, and had no information on medication adherence. However, collected medications reflect the health problems they were prescribed to address. We could not include patients from the last 10 years due to data availability, which could affect the generalizability of results. Nonetheless, post-TBI treatment strategies in Sweden have remained largely unchanged since the end of our study period in 2013. We also lacked information on anticoagulants, which have been linked to poorer outcomes in TBI patients (44). TBI diagnoses were collected from the Swedish Patient Register, which includes all disorders diagnosed in hospitals and specialized outpatient care, and TBI diagnoses made solely in primary care were not captured. This likely underestimated rates of mild TBIs in the population. We lacked detailed clinical data for the classification of TBI severity (e.g., the Glasgow Coma Scale), but we used other proxies for measuring injury severity, such as hospitalization and polytrauma. Another limitation included the lack of information on the clinical severity of somatic illness, both before and after the TBI. There is a research gap on the severity of somatic illness in TBI patients, and future research should address this gap and its implications in patients with TBI. Moreover, differences between countries in prescription practices or service provision may affect the generalizability of findings. Rates of TBI-related hospital discharges are higher in Sweden as compared to the European average (age-adjusted rate per 100,000 individuals: Sweden 445.8; Europe 287.2) (45), although this could be due to between-country differences in data collection and coding.

6 Conclusion

Our findings showed that individuals who sustained a TBI had a greater likelihood of being prescribed non-psychotropic medications and of polypharmacy, before and after their TBI, than a sex- and age-matched population cohort. These results are in line with previous work on psychotropic and pain medications showing higher medication use in TBI patients both before and after their TBI (29). This suggests that health problems precede the TBI, which could have implications for post-TBI clinical care. Our findings also suggested that female TBI patients were more likely to use medications than their male counterparts. Taken together, these results point to poor overall health in TBI patients, which is a barrier to social participation and negatively influences employment, quality of life, and level of independence (3). This suggests a need for addressing psychiatric and non-neurological symptoms in TBI care, particularly in females with TBI, and to review the use of multiple medications to address potential polypharmacy.

Data availability statement

The datasets presented in this article are not readily available because data may be obtained from a third party and are not publicly available. The Public Access to Information and Secrecy Act in Sweden prohibits us from making individual level data publicly available due to ethical concerns about identification. Researchers who are interested in replicating our work can apply for individual level data from: Statistics Sweden (mikrodata@scb.se) for data from the Total Population Register; the National Board of Health and Welfare (registerservice@socialstyrelsen.se) for data from the Patient Register, the Prescribed Drug Register, and the Cause of Death Register. Requests to access the datasets should be directed to mikrodata@scb.se; registerservice@socialstyrelsen.se.

Ethics statement

The studies involving humans were approved by the Swedish Ethical Review Authority. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because the need for informed consent was waived due to the register-based design.

Author contributions

YM: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. DS: Conceptualization, Writing – review & editing. BD'O: Conceptualization, Funding acquisition, Resources, Writing – review & editing. PL: Conceptualization, Funding acquisition, Resources, Writing – review & editing. HL: Conceptualization, Funding acquisition, Resources, Writing – review & editing. SF: Conceptualization, Writing – review & editing. ER: Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

HL reports grants from Shire Pharmaceuticals, personal fees from and serving as a speaker for Medice, Shire/Takeda Pharmaceuticals and Evolan Pharma AB; and sponsorship for a conference on attention-deficit/hyperactivity disorder from Shire/Takeda Pharmaceuticals and Evolan Pharma AB, all outside the submitted work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1339290/full#supplementary-material

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The effect of antiplatelet and anticoagulant therapies on clinical outcome of patients undergoing decompressive craniectomy: a systematic review

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Objective: This systematic review aims to investigate a potential correlation between the administration of antiplatelets (APs) or anticoagulants (ACs) and perioperative complications, with a particular focus on hemorrhagic events, in patients undergoing decompressive craniectomy (DC). Additionally, the secondary objective is to assess the neurological outcomes in patients undergoing DC while taking APs/ACs, comparing them to patients not on APs/ACs.

Methods: The study utilized PubMed and Science Direct as primary online medical databases for the systematic review. Articles underwent screening based on title, abstract, and full-text review. Four studies meeting the inclusion criteria were selected for comprehensive analysis.

Results: Our findings suggest that the administration of APs/ACs in patients undergoing DC does not significantly impact functional outcomes. Notably, the occurrence of rebleeding within 6 months and other complications, including infections, appears to be less frequent in patients taking APs compared to those not taking APs/ACs.

Conclusion: Literature-derived data on the association between APs/ACs and DC presented considerable heterogeneity and insufficient volume for robust statistical analysis. Consequently, a definitive conclusion regarding the influence of suspending or continuing these therapies on complications and clinical outcomes cannot be confidently reached at present. To address this, a large-scale prospective study is warranted to gather substantial and precise data, facilitating a nuanced understanding of how to balance the risks and benefits associated with antiplatelet and anticoagulant agents in the context of decompressive craniectomy.

KEYWORDS

antiplatelets, anticoagulants, blood thinners, decompressive craniectomy, antithrombotics

1 Introduction

The aging of the global population is an unequivocal phenomenon witnessed in recent decades, with an escalating number of individuals harboring a history of cerebrovascular or cardiovascular diseases. This has paralleled a surge in the demand for antiplatelet (APs) and anticoagulant (ACs) therapies. Concurrently, the population requiring APs/ACs and undergoing noncardiac-related surgeries has witnessed a notable increase (1).

Decompressive craniectomy (DC) is a pivotal life-saving procedure for the release of otherwise unmanageable elevated intracranial pressure (2). While frequently employed in traumatic brain injury and malignant cerebral infarction, DC's utility extends to various pathologies, including subarachnoid hemorrhage, non-traumatic hypertensive and idiopathic cytopenic purpura-related intracranial hemorrhage (3), cerebral venous thrombosis (4, 5), infectious encephalitis (6, 7), subdural empyema (8), among others.

However, this life-saving surgical intervention is accompanied by a considerable incidence of complications (9). The three most recurrent complications encompass hemorrhagic events, infectious/inflammatory manifestations, and disturbances in the cerebrospinal fluid compartment (9). Consequently, neurosurgeons routinely grapple with the management of patients necessitating an emergent decompressive craniectomy while those patients are concurrently prescribed APs/ACs, navigating the complex decision of whether to interrupt or continue these therapies.

The perioperative management of antithrombotic agents poses formidable challenges, given the potential risks of perioperative bleeding and thromboembolic complications (1). Strikingly, to date, no established guidelines on the management of APs/ACs in patients undergoing DC have been formulated (10). The scientific literature on this topic exhibits heterogeneity, with divergent results: some studies indicate no correlation between APs/ACs usage and a heightened rate of complications, while others report an increased incidence of hemorrhagic and/or thrombotic complications in patients on these therapies compared to their counterparts without.

This review seeks to provide a comprehensive synthesis of the current scientific literature, aiming to investigate any potential correlation between APs/ACs and perioperative complications in patients subjected to DC, with a specific focus on hemorrhagic and thrombotic events. A secondary objective involves the evaluation of neurological outcomes in patients undergoing DC, differentiating those taking APs/ACs from those who are not. Ultimately, the review offers valuable insights that aim to guide the intricate perioperative management decisions surrounding the suspension or continuation of APs/ACs in neurosurgical patients undergoing decompression.

2 Methods

2.1 Study design

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (11, 12) (Figure 1).

2.2 Search strategy

PubMed, Ovid MEDLINE, Ovid EMBASE, Scopus, and the Web of Science were selected as online medical databases to conduct the present systematic review. The last search was launched in July 2023.

The review question was formulated according to the PICO criteria, as follows: (P, patients) patients taking anticoagulants or antiplatelet drugs, (I, intervention) undergoing decompressive craniectomy, (C, comparison) if compared to patients not taking these drugs, (O, outcomes) is the outcome worse in terms of disability and complications?

The search terms used were: "decompressive craniectomy AND (aspirin OR antiplatelet OR acetylsalicylic acid OR anticoagulant)."

2.3 Study selection

After removing duplicates, two authors (PZ, CA) independently identified the potentially relevant studies after reading the title, abstract, and full article text. The same authors assessed the full texts of all trials using the eligibility criteria for inclusion. Disagreements were solved through discussion or, if necessary, in consultation with a third reviewer (AS).

2.4 Data extraction

The extraction and analysis of data were independently performed by two authors (PZ, CA).

The patient demographic and study data extracted included year of publication, age at presentation, sex, and mean follow-up duration. Clinical data included: comorbidities, drugs, preoperative clinical condition, laboratory tests, hematoma characteristics, time of surgery from admission, type of decompressive craniectomy (frontotemporal or bifrontal), intraoperative drugs administration, postoperative conditions up to 72 h after DC, postoperative hemorrhagic complications, thromboembolic complication, and favorable or unfavorable functional outcome at 6 months.

2.5 Eligibility criteria

The selection criteria for this study were grounded in the objective of identifying research articles containing raw data pertaining to patients who underwent decompressive craniectomy. Where feasible, the stratification of data was conducted based on the underlying pathology and the preoperative use of antiplatelet and anticoagulant medications.

The inclusion criteria comprised:

1. Adult patients (aged over 18 years) who underwent DC following brain trauma, cerebral hemorrhage, or ischemic stroke.
2. A subset of the studied population were administered APs or ACs before DC.
3. Accessible data on the group of patients taking APs or ACs and the group not taking APs/ACs.
4. Complete scientific papers written in English.

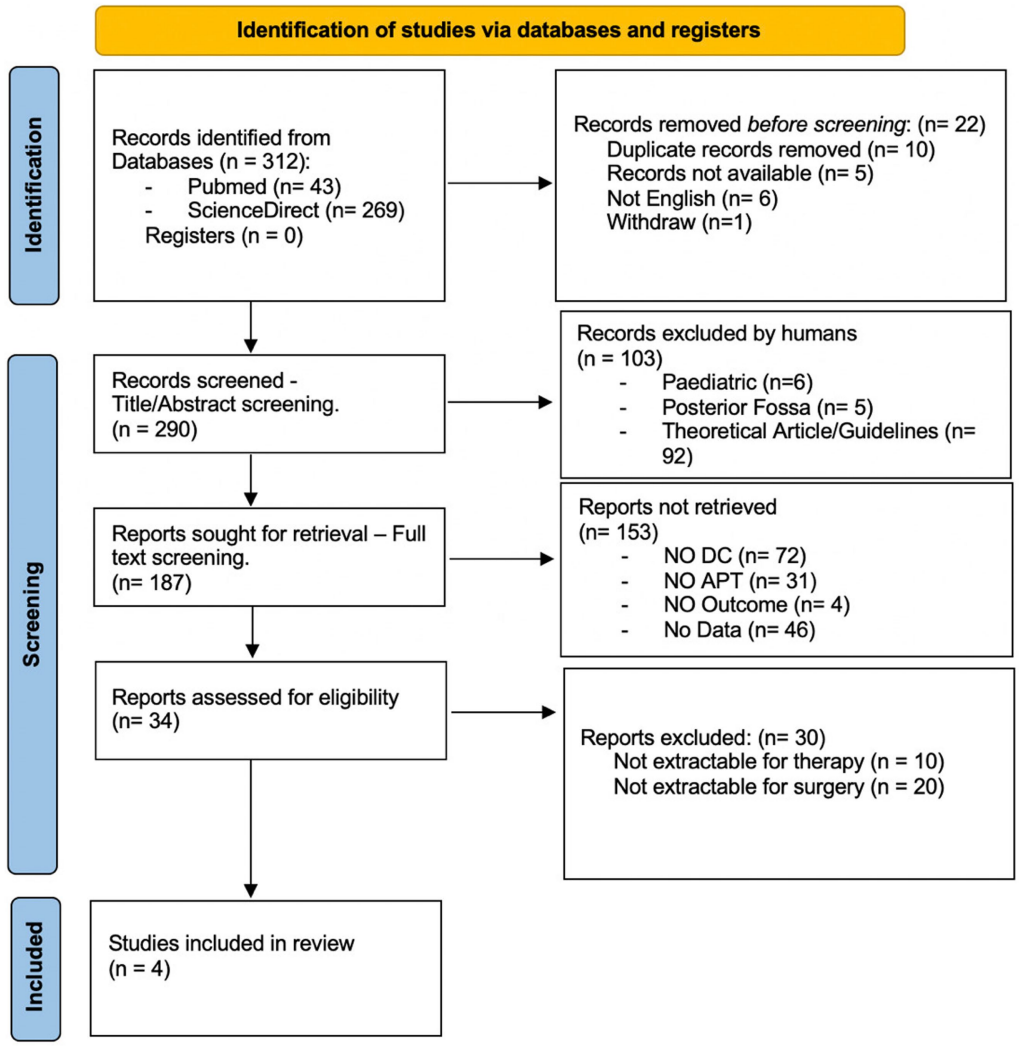

FIGURE 1
Prisma flow chart: flow of information through systematic review. DC, decompressive craniectomy; APT, antiplatelet therapy.

The exclusion criteria entailed:

1. Absence of DC in the study.
2. Absence of APs or ACs use in any subset of the study.
3. Lack of reported outcome scales during the follow-up period.
4. Absence of information regarding the described complications

TABLE 1 Main selected papers.

First author	Year	Type of paper
Schuss P.	2013	Retrospective observational
Han H.	2016	Retrospective observational
Song X.	2016	Retrospective observational
Kinoshita T.	2020	Retrospective cohort

3 Results

The database inquiry using the previously delineated keywords resulted in a total of 312 studies, comprising 43 from PubMed and 269 from ScienceDirect. Prior to screening, 10 duplicated, 5 inaccessible, 6 non-English, and one withdrawn record were eliminated. After the title and abstract were screened, 103 papers were excluded, and after the full article was read, an additional 153 papers were deemed irrelevant to the aims and scopes of the research. Furthermore, 30 articles were excluded due to non-extractable data. Ultimately, four studies were incorporated into this systematic review (Table 1).

The paper selection process is depicted in Figure 1, with the included articles detailed in Table 1.

3.1 Decompressive craniectomy, APs, ACs

Four articles were ultimately selected, each providing data on the percentage of patients taking Aps or ACs, totaling 345 patients who underwent decompressive craniectomy (DC). These patients underwent decompressive craniectomy for various reasons: 86 for acute subdural hemorrhage, 43 for traumatic intracerebral hemorrhage, 101 for

TABLE 2 Type of medications.

Medications	In all patients
APT monotherapy	83
DAPT	12
APT total	95
ACT	9
Combined therapy	0
NO APT/ACT	241
Antithrombotics	104
Total	345

spontaneous intracerebral hemorrhage, 83 for ischemic stroke, and 32 for hemorrhagic stroke. Among the patients, 92 were receiving APs, 9 were receiving ACs, 3 were receiving dual antiplatelet therapy (DAPT), while 241 were not receiving any medication (refer to Table 2).

3.2 Functional outcome (GOS/mRS)

The functional outcome at 6 months was assessed using the Glasgow Outcome Scale (GOS) or modified Rankin Scale (mRS). A favorable outcome corresponds to GOS 4–5 or mRS 0–3, while an unfavorable outcome corresponds to GOS 1–3 or mRS 4–6. Functional outcome data were available for a total of 133 patients undergoing DC (refer to Table 3).

Patients not taking APs or ACs presented a favorable outcome in 47% (34 out of 72) of cases and an unfavorable outcome in 53% of cases (38 out of 72). Patients taking APs/ACs exhibited a favorable outcome in 45% (10 out of 22 patients) and an unfavorable outcome in 55% of cases (12 out of 22 patients). Data regarding functional outcomes were not available for 212 patients.

3.3 Rebleeding

The rebleeding rate before and at 6 months was assessed during follow-up, considering the type of hematoma, localization, chronological distribution of bleeding, and the need for reintervention. Among all patients subjected to DC, including those taking APs or ACs and those not, rebleeding occurred in 108 before 6 months and in an additional 2 at 6 months. Of these 108 patients experiencing rebleeding before 6 months, 35% belonged to the APs/ACs group (38 out of 108), and 48% to the group of patients not taking APs or ACs (52 out of 108). Further details are provided in Table 4.

3.4 Other complications

Regarding non-hemorrhagic complications during convalescence, thromboembolic events (stroke, heart attack, deep vein thrombosis, cardiopulmonary failure), and other complications such as infections were documented. Data on non-hemorrhagic complications were available for 216 patients. Among all patients, the most frequent complication was infection, occurring in 74 patients: 23 in the APs/ACs group (31%) and 51 in the group not taking APs or ACs (69%). Other complications occurred in 37 patients, with 11 in the APs/ACs group (30%) and 26 in the group not taking APs or ACs (70%). Stroke occurred in 11 patients overall, with 3 taking APs/ACs (27%) and 8 not taking them (73%). Further details are reported in Table 5.

Data on the type of pathology and the type of medications are outlined in Table 6.

TABLE 3 Clinical outcome at 6 months.

Outcome—6 months	In all patients	In APT/ ACT	In no APT/ ACT	N/A
Unfavorable outcome: GOS (1–3) mRS (4–6)	85	12	38	35
Favorable outcome: GOS (4–5) mRS (0–3)	48	10	34	4
N/A	212	63	149	-
Total	345	85	221	39

TABLE 4 Bleeding complications.

Bleeding complications	In all patients	In APT/ ACT	In no APT/ ACT	N/A
Rebleeding before 6 months	108	38	52	18
Not rebleeding	237	47	169	21
Total	345	85	221	39

TABLE 5 Other complications.

Other complications (different from bleeding)	In all patients	In APT/ ACT	In no APT/ACT
Stroke	11	3	8
Heart attack	0	0	0
Deep vein thrombosis	0	0	0
Infections	74	23	51
Cardiopulmonary failure	0	0	0
Others	37	11	26
N/A	129	38	91
Total of complications	122	37	85
Total of patients	345	104	241

TABLE 6 Type of pathology.

Type of pathology	In all patients
Trauma aSDH	86
Trauma EDH	0
Trauma SAH	0
Trauma ICH	43
Spontaneous ICH	101
Ischemic stroke	83
Hemorrhagic stroke	32
N/A	0
Total	345

4 Discussion

The data analysis process involved the stratification of available data into distinct subgroups based on factors such as age, underlying pathology, comorbidities, and preoperative clinic. However, the endeavor to establish meaningful subgroups was hindered by the insufficiency and heterogeneity of the available data.

Our observations may indicate that the use of ACs or APs does not alter functional outcomes. Notably, the majority of patients exhibited an unfavorable outcome, irrespective of APs/ACs intake.

Regarding hemorrhagic complications, our data reveal a more consistent occurrence of rebleeding before 6 months in patients not taking APs or ACs (48% vs. 35% in patients taking APs/ACs).

Concerning non-hemorrhagic complications, the infection rate was higher in patients not taking APs or ACs (69% vs. 31% in patients taking APs/ACs), as well as ischemic cerebrovascular insults (73% in patients not taking APs or ACs vs. 27% in patients taking APs/ACs) and other complications (70% in patients not taking APs or ACs vs. 30% in patients taking APs/ACs).

These data imply that patients undergoing DC are vulnerable, exhibiting a higher likelihood of unfavorable outcomes or increased complication rates, irrespective of ACs or APs administration. While these treatments may suggest a higher frailty, such as the presence of cardiovascular diseases, they do not appear to significantly influence the ultimate outcome.

Han et al. (13) conducted a retrospective analysis involving 90 patients with TBI who underwent emergent DC. Nineteen of these patients were using antiplatelet agents before TBI. The incidence of hemorrhagic complications was 52.6% (10 out of 19) in group 1 and 46.5% (33 out of 71) in group 2 ($p = 0.633$). The reoperation rate was 36.8% (7 out of 19) in group 1 and 36.6% (26 out of 71) in group 2 ($p = 0.986$). No statistically significant difference was observed between the two groups.

In a retrospective observational study by Schuss et al. (14) data were collected from 115 patients who underwent decompressive craniectomy due to acute ischemic stroke. They compared patients with and without intravenous thrombolysis (IVT) before DC, assessing functional outcomes at 3 months using the mRS, along with bleeding and other complications. Forty-four patients out of 115 were on antiplatelet therapy before DC (38%). The study concluded that bleeding complications occurred significantly more frequently in patients with antiplatelet use before DC ($p = 0.0003$). In the multivariate analysis, "preoperative use of acetylsalicylic acid" emerged as the only independent predictor associated with bleeding complications ($p = 0.002$). The use of intravenous thrombolysis was suggested to have a more pronounced bleeding effect compared to standard ACs or APs.

Lastly, Kinoshita et al. (15) conducted a retrospective cohort study involving 91 patients with TBI undergoing evacuation of intracranial hemorrhagic lesions. The preoperative use of APs and ACs was also assessed. Regarding outcomes at 6 months and delayed hemorrhage, the study's findings did not indicate a discernible distinction between patients undergoing decompressive craniectomy taking APs/ACs and those not taking these therapies.

Schuss et al. (14) was the only study among the four selected that reported a relapse of antiplatelets on rebleeding complications. In contrast, Han et al. (13) and Song et al. (16) reported that the rate of hemorrhagic complications and reoperation was not affected by APs/ACs.

4.1 Limitations

As previously noted, a primary limitation of this review stems from the paucity of available data in the literature. The inadequacy of data precludes a robust statistical analysis, particularly due to the infrequency with which the association between patients undergoing DC and their potential use of APs or ACs is explored. This current article highlights a significant limitation stemming from the heterogeneous nature of available literature data, presenting challenges in several key aspects. Notable instances of this heterogeneity include the amalgamation of antiplatelet and anticoagulant therapies in numerous studies, despite their distinct pharmacodynamic properties and specific indications. Another crucial aspect is the non-separation of patients undergoing craniotomy and craniectomy surgeries in certain studies, overlooking profound differences in indications, pathology severity, post-surgical complications, and postoperative days in the intensive therapy department. Many investigations on DC outcomes fail to exclusively focus on DC, often encompassing a broader population, leading to data that apply to the entire cohort rather than specifically to those undergoing DC. The incomplete reporting of clinical elements, both pre-and post-operatively, is noted as a significant observation, impeding effective patient stratification. Additionally, some studies either do not report postoperative outcomes or provide data that is challenging to interpret due to unclear definitions and temporal aspects. Lastly, a prevalent practice is the limited presentation of raw data, with many studies synthesizing data without offering access to the raw information, compromising the transparency and interpretability of the findings. Additionally, Kinoshita et al. (15) concentrated on an elderly population, restricting their research to patients aged 60 years or older. Considering this age group within the context of a highly fatal underlying disease introduces a potential bias. Furthermore, none of the studies have investigated strategies for managing APs/ACs or the timing of their interruption, meaning definitive conclusions about the strategy and timing for managing APs/ACs cannot be derived.

4.2 Future perspectives

To address the identified limitations, a comprehensive prospective observational study is imperative, encompassing detailed data on patients undergoing DC and their use of APs/ACs. This study should additionally evaluate the initiation and discontinuation times of these therapies. Such an investigation is essential for informing daily practice and guiding surgeons on the optimal management of antiplatelet and anticoagulant therapies in patients subjected to DC.

5 Conclusion

Although our results tentatively suggest that the use of APs/ACs in patients undergoing DC may not significantly impact the final functional outcome, the occurrence of rebleeding before 6 months and other complications, such as infections, appears to be less frequent. Moreover, the considerable heterogeneity of the data precludes the formulation of definitive guidelines regarding the management of antiplatelet and anticoagulant therapies in patients undergoing DC. A comprehensive prospective

observational study, coupled with an initiative within the scientific community to standardize data reporting methods in neurotrauma articles, is essential. This effort aims to gather sufficient and accurate data, facilitating a nuanced understanding of how to balance the risks and benefits associated with antiplatelet and anticoagulant agents in the context of DC.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

CA: Writing – original draft. PZ: Writing – original draft. GM: Writing – review & editing. MC: Writing – review & editing. PB: Writing – review & editing. AS: Writing – review & editing.

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Conflict of interest

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Association between social determinants of health and pediatric traumatic brain injury outcomes

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Introduction: Social determinants of health (SDH) are factors that may impact outcomes following pediatric traumatic brain injuries (TBI). The purpose of this study was to investigate the relationship between race and functional outcomes in a diverse pediatric population. We further explored how this association may be modified by SDH factors, including insurance status, social vulnerability, and child opportunity.

Methods: A cohort study ($N = 401$) of children aged 0–18 [median = 9.22 years (IQR: 3.56–13.59)] presenting to the Emergency Department at Level I and II Trauma Centers with mild to severe head injuries. Geocoded variables were used to evaluate SDH. The sample was described overall and by racial/ethnic group, which were adjusted for confounders using inverse propensity treatment weights (IPTW). Weighted and unweighted Firth logistic regression models (mortality) and generalized linear regression models (GOS-E scores) were reported without and then with potential effect modifiers.

Results: The sample is majority male (65.84%); race/ethnicity are as follows: White (52.37%), Black/African Americans (35.91%), and Hispanic (11.72%). Black (31.25%) and Hispanic (27.66%) patients had higher rates of severe TBI. 35.89% of White patients were categorized as more socially vulnerable compared to 62.68% Black and 70.21% Hispanic patients. A total 63.64% of White patients were from higher opportunity neighborhoods, compared to 25.87% of Black and 51.06% of Hispanic patients. A total 50.95% of White patients, 25.87% of Black patients, and 17.02% of Hispanic patients were privately insured. There were no differences found between racial and ethnic groups on mortality or GOS-E scores.

Discussion: Patients from minority backgrounds had more severe injuries, many resulting from pedestrian vs. motor vehicle accidents. Additionally, patients from minority backgrounds experience more social vulnerability and lower opportunity. Despite these discrepancies, we did not observe differences on rates of mortality or functional outcomes in either racial or ethnic groups. SDH were not found to impact outcomes. Further research is needed to determine how these complex social and environmental variables impact health outcomes.

KEYWORDS

pediatric, traumatic brain injury, social determinants of health, race, outcomes, mortality

1 Introduction

Traumatic brain injury (TBI) is a leading cause of morbidity and mortality in the United States. The pediatric population is uniquely vulnerable, with over 50,000 annual hospitalized cases (1). Despite an overall decrease in pediatric TBI mortality due to enhanced emergency access and the introduction of evidence-based guidelines (2), the longer-term cognitive, psychological, social, and adaptive morbidities persist among survivors. Pediatric TBI is also heterogeneous, given the wide range of possible mechanisms of injury, severity of injury, and the factors that affect the secondary responses to TBI (3, 4). However, only recently has research examined specific social and environmental factors that may play a role in TBI incidence, management, and outcomes (5).

The influence of social and environmental factors, termed social determinants of health (SDH), on health inequities is substantial, particularly in TBI. Prior studies have shown that TBI disproportionately affects patients from lower socioeconomic backgrounds and minority races (6–10). A recent national study found that racial minorities (Black, Hispanic, and Native Americans), females, older children, and children in lower socioeconomic groups were at increased risk of poor outcomes following TBI, including longer length of stay in the hospital, increased medical complications, higher rates of mortality, and worse functional outcomes (10). Additional contributing factors include decreased use of protective devices (e.g., helmets and restraining seat belts), less access to trauma centers, and underestimated triage scores for minority patients (11–13). Additionally, lower education levels have been shown to contribute to misconceptions around head injuries as well as decreased reporting (12, 14). Caregivers of pediatric patients also report scheduling conflicts and lack of resources as barriers to follow up care with publicly insured and uninsured minority parents reporting lack of resources as the primary barrier (15). It is noteworthy that these results are not uniform, and there are still large gaps in our knowledge.

The term SDH is defined by the World Health Organization as "non-medical factors that influence health outcomes" and are impacted by socioeconomic status and structural mechanisms of society that create inequity (16, 17). These are modifiable and unmodifiable conditions that encompass five key domains: economic, education, social and community context, health and health care, and environment (5, 18). Given the number of variables that fit within SDH, several indices were developed to aggregate factors into holistic measures of life condition to support research within this area. Many of these indices use geocoding, through patient addresses and ZIP codes, which correlates with social, environmental, and demographic information found on public databases such as the U.S. Census.

In order to better understand the impact of neighborhood conditions, researchers developed the Child Opportunity Index (COI). Using data from sources such as the U.S. Census Bureau, Environmental Health Agency, and the Department of Education, the COI measures the quality of resources and conditions (e.g., good early childhood education centers and schools, green spaces, access to healthy food, low poverty) that allow children to develop healthily in the neighborhoods they live in (19). Many studies have found associations with COI and hospital outcomes such that lower-opportunity neighborhoods correlate with increased hospital re-admission or severity of injury (20–22). However, limited studies have utilized the COI within pediatric TBI (22).

Originally developed by the Centers for Disease Control and Prevention (CDC), the social vulnerability index (SVI) was created in order to guide the allocation of resources to communities in need during disasters or disease outbreak (23, 24). This tool organizes 15 census variables into themes of socioeconomic status, including household composition and disability, minority status and language, and housing type and transportation, in order to rank and characterize a community. While this measure has been used to measure areas of vulnerability within a community for health-related applications, it has yet to be applied to the TBI populations.

The aims of this study are to examine the association between patient race and functional outcomes, including mortality and functional outcomes, in pediatric TBIs. We hypothesized that there will be differences between racial groups, including higher rates of mortality and lower GOS-E peds scores, the gold standard in outcome measurements, in patients from minority backgrounds. Further, we expected that the relationship between race and TBI-related outcomes will be moderated by SDH variables (COI, Social Vulnerability Index, and insurance).

2 Materials and methods

2.1 Patient population

The current study is part of a larger prospective investigation examining outcomes in children and adolescents presenting to the Emergency Department at a Level I or a Level II trauma center with a TBI between March 2017 and June 2021 (25). Participants included children <18 years of age who were diagnosed on arrival with a TBI by attending physicians. Additional information on the study protocol can be found here (25). All inclusion and exclusion criteria remain the same except that only patients with the following racial categories were used, based on the primary aims of the study: White, Black, Hispanic. This study was approved by our institutional IRB.

2.2 Study variables

Demographic variables were obtained from caregivers or from electronic medical record in instances where caregivers were not available. Insurance status was obtained from electronic medical records based on status at the time of injury. Glasgow Coma Scale (GCS) was obtained from patient electronic medical records and the lowest reported GCS score, including at the scene and during admission, was used. Patients were categorized into severity groups as follows: mild TBI (GCS 13–15), mild-complicated TBI (GCS 13–15 + skull fractures/intracranial injury), moderate TBI (GCS 9–12), and severe TBI (GCS 3–8). Glasgow Outcome Score-Extended Pediatrics (GOS-E Peds) was obtained through semi-structured interviews on the phone with caregivers of patients only in the moderate/severe TBI groups 6 months (+/− 1 month) post-injury. The GOS-E peds was utilized for this study based on recommendations for its use the NINDS common data elements

(26, 27). Patients were categorized into the following scores: 1 = death, 2 = vegetative state, 3 = lower severe disability, 4 = upper severe disability, 5 = lower moderate disability, 6 = upper moderate disability, 7 = lower good recovery, and 8 = upper good recovery.

2.3 Geocoding

The patient's home address linked to the hospitalization event was used for geocoding across two databases. The Child Opportunity Index (COI) was developed as a summary measure of the quality of neighborhoods in which children live across the US (28). The index quantifies 29 indicators of neighborhood conditions and resources that affect children's healthy development. Each indicator is transformed to a z-score, standardized, and weighted by how strongly it predicts children's long-term health and economic outcomes. Indicators are then combined into overall and domain scores (education, health and environment, and social and economic), and divided into nationally normed quintiles. For the purpose of our study, we used the nationally normed COI overall z-scores. Higher values indicate more opportunity.

The Social Vulnerability Index (SVI) was developed and validated by the CDC/Agency for Toxic Substances and Disease Registry (ATSDR) (23). The index is derived from 15 US census tract variables from the American Community Survey data, and groups them into 4 domains: socioeconomic status, household composition and disability, minority status and language, and housing type and transportation. For each Census tract, there are generated percentile ranks, ranging from 0 (lowest vulnerability) to 1 (highest vulnerability) for all 15 variables combined. In this dataset, the social vulnerability index ranges from 0.0009 to 0.9661 and was dichotomized into patients with more vulnerability or less vulnerability based on whether patients were above or below the average social vulnerability for Georgia (0.4999).

2.4 Statistical analyses

Data were analyzed using SAS v.9.4 (Cary, NC) and CRAN R v.4.3 (Vienna, Austria), and 0.05 was used as the threshold for assessing statistical significance throughout. Analysis took place in several stages. First, descriptive statistics were calculated for the sample overall and compared by racial/ethnic groups. Second, racial/ethnic groups were balanced by potential demographic and clinical confounders (age, sex, severity of injury) using inverse propensity treatment weights (IPTW). Weights were derived from the *twang* v.2.5 package in CRAN R and confounders were considered balanced when standardized mean differences (SMD) <0.25. Average treatment effect (ATE) weights were calculated using 10,000 trees in a gradient boosted model (GBM), and interaction depth specified at 3, and a stop method based on mean effect size. The final weights were trimmed at the 1% and 99% and stabilized to approximately match the original study sample size. Third, clinical outcomes analysis considered the association between race with mortality (binary outcome) and GOS-E Peds (continuous outcome). For each outcome, three factors were considered as potential effect modifiers: social vulnerability index, childhood opportunity index, and insurance status. When mortality was the outcome, Firth's Penalized Likelihood was utilized to estimate odds-ratios and confidence intervals, which adjusts estimates to account for the bias that can occur with rare binary outcomes. For GOS-E Peds, general linear regression models were used, and results presented with least-squares means, 95% CI, and *p*-values. All models present unweighted and weighted results.

3 Results

3.1 Patient demographics

The final sample included 401 patients, with the majority male (65.84%) and sustaining mild TBIs (65.38%). Patients were predominantly school age (median = 9.22 years), with an interquartile range of age between 3.56 to 13.59 years. Of the patient racial distribution, 35.91% were Black, 52.37% were White, and 11.72% were Hispanic. Majority of patients sustained their injury due to a fall, followed by motor vehicle collision and struck by an object. Overall, there were low rates of mortality (3.99%) in the sample and 14.46% of patients required intensive inpatient rehabilitation services (Table 1).

There were no differences in age or sex across racial groups (Table 2). There was a statistically significant association between severity of injury and race ($p < 0.001$). Black and Hispanic patients had higher rates of severe TBI compared to White patients (Table 1), with Blacks experiencing severe TBI at twice the rate of Whites. Similarly, a larger percentage of Black patients sustained moderate TBIs, compared to both Hispanic and White patients. However, nearly half of White patients sustained mild-complicated TBIs, compared to smaller portions of Hispanic and Black patients. Mild TBIs were sustained at similar rates across racial groups. With regard to mechanism of injury, differences across racial groups were also observed ($p < 0.001$; Table 1), such that Black and Hispanic patients were more likely to be injured in motor vehicle collisions, compared to White patients. Additionally, less White patients suffered injuries from pedestrian vs. car accidents, in contrast to Black and Hispanic patients. Black and Hispanic patients had similar percentages of confirmed abuse cases, double that of White patients. However, Black patients had more suspected abuse cases compared to Hispanic and White patients. More White patients were injured by all-terrain vehicles (ATVs) than Black and Hispanic patients.

On average, Black and Hispanic patients stayed in the hospital a day longer than White patients ($p = 0.002$). Although Hispanic patients had the highest mortality rate (6.38%) followed by Black patients (4.86%) and then White patients (2.86%), these differences were not statistically significant. Black and Hispanic patients had higher admission rates to inpatient rehabilitation compared to White patients (Table 1).

3.2 Race/ethnicity and differences in SDH

The SVI groups differed by racial/ethnic group ($p < 0.001$, Table 1), such that lower percentages of White patients were categorized as "more vulnerable" in comparison to higher rates

TABLE 1 Outcomes and social determinants of health effect modifiers by race/ethnicity.

	Overall ($N = 401$)	White ($N = 210$)	Black ($N = 144$)	Hispanic ($N = 47$)	*P*- value
Outcomes					
Died (Yes)	16 (3.99)	6 (2.86)	7 (4.86)	3 (6.38)	0.429
GOSE-peds (continuous, true score)	7 (4–8)	7 (5–8)	5 (2–8)	6 (1–8)	0.722
Positive neuroimaging findings					0.127
No	148 (37.0)	68 (34.35)	57 (42.54)	12 (27.27)	
Yes	252 (63.0)	130 (65.65)	77 (57.46)	32 (72.73)	
Hospital days (Median/IQR)	2 (1–5)	1 (0–4)	2 (1–11.5)	2 (1–6)	**0.002**
Neurosurgery					0.1 03
No	379 (89.18)	193 (91.90)	122 (84.72)	41 (87.23)	
Yes	46 (10.82)	17 (8.10)	22 (15.28)	6 (12.77)	
Mechanism of Injury					**<0.001**
Fall	128 (31.92)	76 (36.19)	37 (25.69)	15 (31.91)	
Motor vehicle crash	108 (26.93)	45 (21.43)	50 (34.72)	13 (27.66)	
Pedestrian vs. motor vehicle	38 (9.48)	14 (6.67)	19 (13.19)	5 (10.64)	
Bike	17 (4.24)	10 (4.76)	4 (2.78)	3 (6.38)	
Struck by/against	39 (9.73)	26 (12.38)	7 (4.86)	6 (12.77)	
Confirmed abuse	7 (1.75)	2 (0.95)	4 (2.78)	1 (2.13)	
Suspected abuse	23 (5.74)	8 (3.81)	13 (9.03)	2 (4.26)	
ATV	31 (7.73)	26 (12.38)	4 (2.78)	1 (2.13)	
Other	10 (2.49)	3 (1.43)	6 (4.17)	1 (2.13)	
Rehab					**0.001**
No	343 (85.54)	192 (91.43)	112 (77.78)	39 (82.98)	
Yes	58 (14.46)	18 (8.57)	32 (22.22)	8 (17.02)	
Effect Modifiers					
Social Vulnerability Index					**<0.001**
Less vulnerable	201 (50.50)	134 (64.11)	53 (37.32)	14 (29.79)	
More vulnerable	197 (49.50)	75 (35.89)	89 (62.68)	33 (70.21)	
Child Opportunity Index					**<0.001**
Less opportunity	205 (51.38)	76 (36.36)	106 (74.13)	23 (48.94)	
More opportunity	194 (48.62)	133 (63.64)	37 (25.87)	24 (51.06)	
Insurance					**<0.001**
None	61 (15.25)	28 (13.33)	27 (18.88)	6 (12.77)	
Private	152 (38.00)	107 (50.95)	37 (25.87)	8 (17.02)	
Public	187 (46.75)	75 (35.71)	79 (55.24)	33 (70.21)	

Statistics shown are Median (IQR); n (%). Bold means statistically significant $p < 0.01$.

of Black and Hispanic patients. Similarly, there were significant differences between racial groups and childhood opportunity ($p < 0.001$). Approximately two-thirds of White patients were in neighborhoods with "more opportunity" followed by Hispanic and then Black patients. With regard to insurance, almost half of our overall sample had public insurance, with significant differences noted between racial groups, including Hispanic patients having the highest rates, followed by Black and White patients, respectively.

3.3 Mortality by race/ethnicity and SDH

The mortality rate in the overall sample was 3.99%, which differed across racial groups: Hispanic patients (6.38%), Black patients (4.86%), and White patients (2.86%). Table 3 presents models that investigate the association of race/ethnicity and mortality, testing for three possible effect modifiers (COI, SVI, and insurance). Despite differences in overall mortality rates, there were no significant associations detected between racial/ethnic groups

TABLE 2 Balancing racial/ethnic groups to account for potential confounds ($N = 401$).

	White ($N = 210$)	Black ($N = 144$)	Hispanic ($N = 47$)	*P*- value	SMD	IPTW SMD
Confounding variables (to be balanced)						
Child age (Median (IQR))	9.96 (3.61–14.34)	8.06 (3.38–12.47)	10.63 (4.34–13.82)	0.110	0.141	0.056
Sex				0.603	0.109	0.139
Male	136 (64.76)	94 (65.28)	34 (72.34)			
Female	74 (35.24)	50 (34.72)	13 (27.66)			
Severity of Injury				**<0.001**	0.403	0.081
Mild TBI	75 (35.71)	47 (32.64)	13 (27.66)			
Mild-complicated TBI	88 (41.90)	31 (21.53)	15 (31.91)			
Moderate TBI	18 (8.57)	21 (14.58)	6 (12.77)			
Severe TBI	29 (13.81)	45 (31.25)	13 (27.66)			

Racial/Ethnic groups are balanced by age, sex, and severity of injury. SMDs < 0.25 are considered balanced. IPTW SMDs are calculated using stabilized ATE IPTW, truncated at 1% and 99%. Bold means statistically significant $p < 0.01$.

and mortality, and there was no evidence of effect modification for any of the three tested effect modifiers between weighted and unweighted models. For the sake of brevity, regression models will be reported. The following analysis will be descriptive, as small sample sizes in these groups limited the findings.

With regard to social vulnerability, White patients living in less vulnerable neighborhoods had a similar mortality rate to White patients living in more vulnerable neighborhoods (2.99% vs. 2.67%). Conversely, Black and Hispanic patients who lived in less vulnerable neighborhoods had higher mortality rates than those living in more vulnerable neighborhoods (5.66% and 7.14% vs. 4.49% and 6.06%, respectively). Regarding neighborhood opportunity levels, Black and White patients had similar mortality rates whether they came from lower opportunity neighborhoods (4.72% and 2.63%) or higher opportunity neighborhoods (5.41% and 3.01%). Hispanic patients from higher opportunity neighborhoods face twice the mortality rate that Hispanic patients in lower opportunity neighborhoods do (8.33% vs. 4.35%). In low opportunity neighborhoods, Hispanic patients had similar mortality rates to Black patients (4.35% vs. 4.72%). Mortality was highest in publicly insured patients, followed by uninsured patients, and privately insured patients. Across all insurance types, White patients had a consistent mortality rate of about 3%, while Black and Hispanic patients' rates varied greatly. Black patients who were uninsured had twice the mortality rate of Black patients who were publicly insured (11.11% vs. 5.06%).

3.4 Functional outcomes by SDH and race/ethnicity

A quarter of the sample (27.50%) had poor outcomes, as defined by the dichotomized GOS-E Peds score of 1–4. Hispanic patients had the highest average outcome score (95% CI 4.63–7.87), followed by White patients (95% CI 5.51–6.93) and Black patients (95% CI 4.73–6.42). Table 4 presents models that investigate the association of race/ethnicity and mortality and then tests three possible effect modifiers. Findings between weighted and unweighted models did not change interpretations of the results, and for the sake of brevity, will not be reported.

The observed outcome score gap between Black and White patients was larger in less vulnerable areas (5.44; 95% CI 4.16–6.72) vs. (6.23; 95% CI 5.41–7.06) compared to more vulnerable areas (5.67; 95% CI 4.61–6.72) vs. (6.17; 95% CI 4.94–7.40). Outcome scores were comparable between lower opportunity areas compared to higher opportunity areas across racial groups. White (6.38; 95% CI 5.28–7.48) and Hispanic (6.18; 95% CI 1.93–10.43) patients had higher GOS-E peds scores compared to Black patients (5.65; 95% CI 4.69–6.60) in lower opportunity areas. There were less differences across racial groups in the higher opportunity areas (Black: 5.57; 95% CI 3.89–7.25; White: 6.11; 95% CI 5.22–7.00; Hispanic: 6.31; 95% CI 2.40–10.22). Functional outcomes were highest for those with private insurance, with minimal differences across racial groups (Black: 7.41; 95% CI 6.04–8.77; White: 7.04; 95% CI 6.25–7.82; Hispanic: 8.00; 95% CI 2.94–13.06). Within uninsured patients ($N = 7$), Black patients (5.32; 95% CI 3.69–6.94) had higher outcome scores than White patients (2.80; 95% CI 0.18–5.42). Of the publicly insured patients, Black patients (4.68; 95% CI 3.68–5.68) had lower outcome scores than White (5.31; 95% CI 4.28–6.35) and Hispanic patients (5.67; 95% CI 2.74–8.59). Hispanic and Black patients who were privately insured scored 2–3 points higher in their 6-month TBI outcome follow-up than patients of the same race who were publicly insured.

4 Discussion

While racial disparities are well documented in the US health system, there has been less attention within the pediatric TBI literature, particularly how these disparities impact outcomes. The primary objective of this study was to better understand the social-environmental risk factors that contribute to outcomes in pediatric TBI. Our results revealed differences across racial groups with

TABLE 3 Unweighted and weighted regression† models, outcome: mortality $N = 401$.

Characteristic	Alive, $N = 385$ Raw N (row%)	Deceased, $N = 16$ Raw N (row%)	Unweighted OR (95% CI)	P-Value	IPTW OR (95% CI)	P-Value
Race/Ethnicity						
Black	137 (95.14)	7 (4.86)	Reference	-	Reference	-
White	204 (97.14)	6 (2.86)	0.58 (0.20, 1.71)	0.325	1.05 (0.27, 4.07)	0.948
Hispanic	44 (93.62)	3 (6.38)	1.44 (0.38, 5.41)	0.588	2.96 (0.25, 35.69)	0.394
Social Vulnerability (Below Average), Lower Vulnerability $N = 201$						
Race/Ethnicity						
Black	50 (94.34)	3 (5.66)	Reference	-	Reference	-
White	130 (97.01)	4 (2.99)	0.50 (0.12, 2.11)	0.343	0.77 (0.13, 4.41)	0.766
Hispanic	13 (92.86)	1 (7.14)	1.60 (0.20, 12.58)	0.653	3.97 (0.13, 118.26)	0.426
Social Vulnerability (Above Average), Higher Vulnerability $N = 197$						
Race/Ethnicity						
Black	85 (95.51)	4 (4.49)	Reference	-	Reference	-
White	73 (97.33)	2 (2.67)	0.65 (0.13, 3.16)	0.590	1.02 (0.14, 7.67)	0.981
Hispanic	31 (93.94)	2 (6.06)	1.51 (0.30, 7.6)	0.619	3.52 (0.17, 71.48)	0.412
Childhood Opportunity Index (< Average), Lower Opportunity $N = 205$						
Race/Ethnicity						
Black	101 (95.28)	5 (4.72)	Reference	-	Reference	-
White	74 (97.37)	2 (2.63)	0.62 (0.13, 2.87)	0.54	1.02 (0.15, 7.04)	0.982
Hispanic	22 (95.65)	1 (4.35)	1.23 (0.19, 8.19)	0.83	4.17 (0.15, 113.52)	0.397
Childhood Opportunity Index (≥ Average), Higher Opportunity $N = 194$						
Race/Ethnicity						
Black	35 (94.59)	2 (5.41)	Reference	-	Reference	-
White	129 (96.99)	4 (3.01)	0.49 (0.10, 2.46)	0.389	0.66 (0.10, 4.46)	0.674
Hispanic	22 (91.67)	2 (8.33)	1.58 (0.25, 10.16)	0.631	2.40 (0.11, 51.06)	0.576
Insurance (none), $N = 61$						
Race/Ethnicity						
Black	24 (88.89)	3 (11.11)	Reference	-	Reference	-
White	27 (96.43)	1 (3.57)	0.38 (0.05, 2.89)	0.351	0.93 (0.08, 10.26)	0.953
Hispanic	6 (100)	0 (0)	0.54 (0.02, 14.74)	0.714	2.83 (0.03, 286.52)	0.659
Insurance (Private), $N = 152$						
Race/Ethnicity						
Black	37 (100)	0 (0)	0.4 (0.02, 8.19)	0.55	0.88 (0.04, 21.47)	0.938
White	104 (97.20)	3 (2.80)	Reference*	-	Reference	-

(Continued)

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TABLE 3 (Continued)

Characteristic	Alive, $N = 385$ Raw N (row%)	Deceased, $N = 16$ Raw N (row%)	Unweighted OR (95% CI)	P-Value	IPTW OR (95% CI)	P-Value
Hispanic	8 (100)	0 (0)	1.76 (0.07, 43.47)	0.731	7.15 (0.14, 380.02)	0.332
Insurance (Public), $N = 87$						
Race/Ethnicity						
Black	75 (94.94)	4 (5.06)	Reference	-	Reference	-
White	73 (97.33)	2 (2.67)	0.57 (0.12, 2.80)	0.489	1.32 (0.24, 7.31)	0.751
Hispanic	30 (90.91)	3 (9.09)	1.93 (0.44, 8.42)	0.384	4.18 (0.27, 65.11)	0.307

†*Firth's Penalized Likelihood has been applied to these regression models to account for the bias that can occur with rare outcomes.* **Reference group changed to White, as no Black patients were in the deceased group for private insurance.*

regard to TBI injury severity, mechanism of injury, and SDH. Despite these disaprities, we did not find group differences in mortality or functional disability.

Consistent with past literature, our study found differences between racial and ethnic groups on SDH variables, with both Black and Hispanic patients showing higher rates of social vulnerability and lower child opportunity ratings compared to Whites (29, 30). Despite these discrepancies, we were unable to detect differences in race/ethnicity and SDH variables on functional disability and mortality. One possible reason for this finding is that our mortality rates were quite low, leaving the groups within racial categories and SDH quite small, likely under powering our ability to see significant differences. It is also possible that these social and environmental factors may not be as strongly related to 6 months functional disability but are more impactful when examining patient functioning over years following their TBI. Additionally, we had a high attrition rate in our sample, leading to missing data in our functional disability score. When conducting follow up analyses on patients who did not complete the follow up visit, similar rates of missing were found between White and Black patients (∼39%), whereas a higher rate was found among Hispanic patients (∼50%).

Despite the GOS-E peds being considered a gold standard measure of global outcome following TBI, there are several limitations that are worth noting and may have contributed to our null findings. The GOS-E peds is a simple, practical index that rates patients on a crudely defined, ordinal scale, which makes it accessible and easy to use within prospective research studies (27, 31). However, the measure reflects functional deficits and disability from multiple causes, not exclusively brain injury (e.g., polytrauma), which makes it potentially insufficient at measuring the numerous specific sequelae of TBI. Prior studies in adults have found racial disparities on the GOS-E, however, these disparities have not been explored as strongly within pediatrics (32, 33). Given these limitations, it is possible that there are racial and ethnic disparities in sequelae of TBI in children that are not adequately being captured by GOS-E peds.

Geocoding variables are relatively new and have become increasingly popular over the past years to help researchers understand how environmental and neighborhood-level factors contribute to health disparities (34, 35). Since these indices rely on easily accessible databases and simple demographic forms from patients, it can be a useful tool to obtain additional factors that could impact health outcomes. However, there are some notable limitations. Common issues reported with these measures include bias for certain populations, misclassification bias (for racial/ethnic groups) and poor data quality (36). To remedy these factors, it has been recommended that multiple sources are included, using appropriate software tools and exercising caution when finding addresses that may be variable or unknown (28). Despite these challenges, there remains a critical need to examine SDH within this population to not only better understand disparities but to support policy changes that impact the most vulnerable populations. Through this research, we can begin to recognize and integrate social factors that influence health-related behaviors and health status that will ultimately develop more effective treatment plans for children with TBI. Clinically, we can also use this information to both assess and address social needs through appropriate referrals at the onset of the injury when they enter our hospital system to ensure adequate support. Ultimately, clinicians and researchers can work together to build a more equitable healthcare system that enables better health outcomes for all children.

The current study is not without limitations. First, the small sample size did not allow adequate statistical analysis. Categorization by racial and ethnic category and SDH also resulted in small sample sizes, which underpowered our ability to observe results. Due to these small sample sizes, we also chose to focus on the largest sub groups, thus it is not representative of all race and ethnicity categories, including those who identified as 2 or more groups. Similarly with functional outcomes, the patient cohort was smaller due to the high study drop-out rate and due to only following up with patients with moderate to severe brain injury. Additionally, this study only examined outcomes at 6 months post injury. It is possible, and even likely, that these social and environmental factors may not be as strongly related to short term outcomes but are more impactful to long-term functional outcomes. Exploring other functional outcomes, including neurocognitive functioning, behavioral factors, and emotional status, may provide a more comprehensive understanding of outcomes and should be planned

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TABLE 4 Unweighted and weighted general linear regression models, outcome: GOS-E Peds ($N = 80$).

Characteristic	Unweighted LS-Mean GOS-E peds true score (95% CI)	*P*-value	IPTW LS-Mean GOSE true score (95% CI)[a]	*P*-value
Race/Ethnicity				
Black	4.94 (3.95, 5.93)	Ref	5.57 (4.73, 6.42)	Ref
White	6.10 (5.34, 6.85)	0.068	6.22 (5.51, 6.93)	0.250
Hispanic	5.27 (3.49, 7.05)	0.744	6.25 (4.63, 7.87)	0.462
Social Vulnerability (Below Average), Lower Vulnerability $N = 41$				
Race/Ethnicity				
Black	4.92 (3.46, 6.39)	Ref	5.44 (4.16, 6.72)	Ref
White	6.21 (5.22, 7.19)	0.152	6.23 (5.41, 7.06)	0.300
Hispanic	1.00 (−4.29, 6.29)	0.159	1.00 (−8.89, 10.89)	0.379
Social Vulnerability (Above Average), Higher Vulnerability $N = 39$				
Race/Ethnicity				
Black	4.95 (3.73, 6.16)	Ref	5.67 (4.61, 6.72)	Ref
White	5.85 (4.38, 7.31)	0.351	6.17 (4.94, 7.40)	0.537
Hispanic	5.70 (4.03, 7.37)	0.471	6.73 (3.75, 9.71)	0.507
Childhood Opportunity Index (< Average), Lower Opportunity $N = 41$				
Race/Ethnicity				
Black	5.12 (4.04, 6.2)	Ref	5.65 (4.69, 6.6)	Ref
White	6.07 (4.67, 7.46)	0.288	6.38 (5.28, 7.48)	0.321
Hispanic	5.00 (2.59, 7.41)	0.928	6.18 (1.93, 10.43)	0.80
Childhood Opportunity Index (≥ Average), Higher Opportunity $N = 38$				
Race/Ethnicity				
Black	4.5 (2.3, 6.7)	Ref	5.57 (3.89, 7.25)	Ref
White	6.11 (5.07, 7.15)	0.192	6.11 (5.22, 7.00)	0.572
Hispanic	5.50 (3.30, 7.70)	0.525	6.31 (2.40, 10.22)	0.729
Insurance (none), $N = 7$				
Race/Ethnicity				
Black	4.14 (2.31, 5.98)	Ref	5.32 (3.69, 6.94)	Ref
White	2.50 (−0.93, 5.93)	0.403	2.80 (0.18, 5.42)	0.109
Hispanic	NA	NA	NA	NA
Insurance (Private), $N = 36$				
Race/Ethnicity				
Black	7.33 (5.72, 8.95)	Ref	7.41 (6.04, 8.77)	Ref
White	6.70 (5.77, 7.64)	0.504	7.04 (6.25, 7.82)	0.639
Hispanic	8.00 (3.15, 12.85)	0.796	8.00 (2.94, 13.06)	0.823
Insurance (Public), $N = 37$				
Race/Ethnicity				
Black	3.94 (2.72, 5.15)	Ref	4.68 (3.68, 5.68)	Ref
White	5.38 (4.04, 6.73)	0.116	5.31 (4.28, 6.35)	0.385
Hispanic	5.00 (3.47, 6.53)	0.283	5.67 (2.74, 8.59)	0.527

[a] *IPTW weights are calculated using GBM with N = 10,000 trees, stabilized and trimmed at 1% and 99%; Weights adjust for age, sex, and enrollment status as confounding covariates*

in future studies. Additionally, our null findings with regard to race and mortality may be due to the imbalance of racial categories in our sample the fact that mortality was a rare outcome and challenging to model, or other unique aspects of the local context in which this study took place including a larger proportion of younger patients.

Last, we are aware that there may be racial bias in the sample, due to medical mistrust in minority communities and the hesitancy to join research studies leading to less minority participants (37). The majority white sample is not representative of pediatric TBI injuries at our hospital and may over represent those participating families. It is essential to include all racial/ethnic groups within future studies and try to provide comprehensive studies, such as ones with mixed method analysis (30). These methods would help to validate geocoded data while also obtaining greater insight into the long-term outcomes following TBI.

In conclusion, our study found that racial disparities in pediatric TBI do exist as measured by the severity of injury, mechanism of injury and social variables. However, there were no differences in the functional outcomes as measured by mortality and GOS-E scores. Based on these findings, future work should utilize the potential of geocoding to understand the effects of SDH on pediatric TBI outcomes, while also exploring more long-term outcomes and quality of life measures to get a more comprehensive understanding of factors that affect pediatric TBI.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Children's Healthcare of Atlanta Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

KP: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. MM: Conceptualization, Data curation, Writing – original draft, Writing – review & editing, Methodology. GB: Writing – review & editing. SG: Writing – review & editing, Formal analysis. LJ: Formal analysis, Writing – review & editing, Visualization. HM: Writing – review & editing. AR: Writing – review & editing, Conceptualization, Methodology, Project administration. LB: Writing – review & editing, Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Structural neuroimaging markers of normal pressure hydrocephalus versus Alzheimer's dementia and Parkinson's disease, and hydrocephalus versus atrophy in chronic TBI—a narrative review

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Introduction: Normal Pressure Hydrocephalus (NPH) is a prominent type of reversible dementia that may be treated with shunt surgery, and it is crucial to differentiate it from irreversible degeneration caused by its symptomatic mimics like Alzheimer's Dementia (AD) and Parkinson's Disease (PD). Similarly, it is important to distinguish between (normal pressure) hydrocephalus and irreversible atrophy/degeneration which are among the chronic effects of Traumatic Brain Injury (cTBI), as the former may be reversed through shunt placement. The purpose of this review is to elucidate the structural imaging markers which may be foundational to the development of accurate, noninvasive, and accessible solutions to this problem.

Methods: By searching the PubMed database for keywords related to NPH, AD, PD, and cTBI, we reviewed studies that examined the (1) distinct neuroanatomical markers of degeneration in NPH versus AD and PD, and atrophy versus hydrocephalus in cTBI and (2) computational methods for their (semi-) automatic assessment on Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) scans.

Results: Structural markers of NPH and those that can distinguish it from AD have been well studied, but only a few studies have explored its structural distinction between PD. The structural implications of cTBI over time have been studied. But neuroanatomical markers that can predict shunt response in patients with either symptomatic idiopathic NPH or post-traumatic hydrocephalus have not been reliably established. MRI-based markers dominate this field of investigation as compared to CT, which is also reflected in the disproportionate number of MRI-based computational methods for their automatic assessment.

Conclusion: Along with an up-to-date literature review on the structural neurodegeneration due to NPH versus AD/PD, and hydrocephalus versus

atrophy in cTBI, this article sheds light on the potential of structural imaging markers as (differential) diagnostic aids for the timely recognition of patients with reversible (normal pressure) hydrocephalus, and opportunities to develop computational tools for their objective assessment.

KEYWORDS

normal pressure hydrocephalus, Alzheimer's dementia, Parkinson's disease, chronic traumatic brain injury, structural imaging, computational methods

1 Introduction

Normal pressure hydrocephalus (NPH), is a prominent type of dementia that is often reversible via ventricular shunt surgery, with earlier intervention leading to better outcomes (1). A notable discrepancy between the incidence (of patients who had surgical intervention) (2–4) and prevalence rates (5–7) suggests its under-recognition. This is substantiated by an estimate from the Hydrocephalus Association that 80% of patients with NPH remain unrecognized with most frequent misdiagnoses being Alzheimer's Dementia (AD) or Parkinson's Disease (PD) (8), which themselves significantly contribute to the global burden of neurological disorders (9). About half of the cases of NPH are estimated to be idiopathic, and the other half secondary to traumatic brain injury (TBI), tumor, meningitis, or infections (10, 11). Adding complexity to its recognition may be the fact that in the secondary NPH group, while tumors or infection linked to the disease can be detected definitively, a TBI-related origin may not be accurately identified due to incomplete medical history. Therefore, the accurate detection and treatment of NPH may inevitably depend on discerning it from irreversible atrophic pathologies like AD, PD, and post-traumatic degeneration.

In terms of structural neurodegeneration, hydrocephalic ventriculomegaly is the key marker of NPH (12). Idiopathic NPH and NPH secondary to TBI, may differ in their etiology, but remarkable improvement in symptoms of patients with both conditions have been demonstrated after ventricular shunting (1, 13). But because atrophy is a chronic effect of TBI which may cause secondary ventriculomegaly, and has been negatively correlated with shunt outcome, accurately discerning it from hydrocephalic ventriculomegaly on structural imaging (14) is paramount for shunt-surgery decision making. The structural degeneration in AD (15) and PD (16) is also characterized by atrophy. Both atrophy and hydrocephalus can give an appearance of ventricular enlargement, which may set a precedent for misdiagnosis if not examined carefully.

In addition to similar structural neurodegeneration, the cognitive and functional deficits such as dementia and gait impairment caused by these diseases often overlap, rendering misdiagnoses distressingly common. The stretching of the corticospinal tract (CST) in the corona radiata which conducts signal to the legs is thought to produce gait disturbance, a manifestation in most NPH cases, while radial shearing force exerted by enlarging ventricles leads to dementia (17). Loss of structural integrity leads to impairment of cognitive and executive function in AD which may affect gait due to divided attention (18). PD which is thought to arise in the substantia nigra and basal ganglia, is characterized by its motor symptoms including gait impairment (19). Its degenerative impact extends well into the cerebral cortex as atrophy leading to cognitive deficits (20). Chronic TBI (cTBI) also leads to cognitive and gait impairment through its degenerative effects (21, 22).

The neurostructural damage resulting from NPH manifests as distinct imaging markers capturable on Computed Tomography (CT) and Magnetic Resonance Imaging (MRI). CT-based markers have been included as a supporting factor in the diagnostic guidelines for NPH and acute TBI. However, they have not gained prominence relative to neurological, clinical, cerebrospinal fluid (CSF) and blood biomarkers, advanced MRI, and functional imaging, especially in AD, PD, and cTBI. Structural imaging markers may offer a noninvasive solution not only for the accurate detection of NPH, but also for its distinction from irreversible neurodegeneration in AD and PD; and distinguishing between atrophy and hydrocephalus in cTBI. There have been a handful of reviews that have elucidated imaging markers of NPH. Pyrgelis et al. (23) provided a review of functional and structural imaging markers for NPH and highlighted a limited number of them which distinguish it from AD and PD, and Yin et al. (24) presented a mini-review of NPH-specific features. But there have been no focused attempts to highlight the structural imaging markers of NPH along with those that can differentiate it from its mimics AD and PD and shed light on the interplay of atrophy and hydrocephalus in cTBI. This review also comments on the adoption of computational techniques for the objective assessment of these markers and highlights areas where further research is needed.

2 Methodology

We searched PubMed for the keyword "normal pressure hydrocephalus" in combination with the keywords "Alzheimer" and "parkinson." We also searched for "hydrocephalus" and "atrophy," in combination with "traumatic brain injury." Studies that used only structural neuroimaging modalities of (T1/T2/DTI) MRI and CT, and those that studied humans aged 19 years and above were retained. From the resultant set of articles, we present this review of structural imaging markers for NPH. For AD and PD, we provide a brief background of their burden, pathology, structural degenerative markers that differentiate NPH from them. The review of cTBI, and consequent atrophy and hydrocephalus is structured similarly. Articles where (semi) automatic image processing and machine (deep) learning have been applied to assess these features in MRI and CT modalities are also discussed. The key abbreviations and structural imaging marker definitions are in Tables 1, 2 respectively.

TABLE 1 Key abbreviations.

Abbreviation	Description
CSF, WM, GM, ICS, TIV	Cerebrospinal Fluid, White Matter, Gray Matter, Intracranial Space, Total Intracranial Volume
SF, HC, Prtl-C	Sylvian Fissure, High Convexity, Parietal Convexity
ML, SS	Midline, Subarachnoid Space
LV, 3 V, 4 V, TH, FH, *VS*	Lateral Ventricles, Third Ventricle, Fourth Ventricle, Temporal Horn, Frontal Horn, Ventricular Space
AC, PC	Anterior Commissure, Posterior Commissure
DESH	Disproportionately Enlarged Subarachnoid Space Hydrocephalus
PV, CM	Periventricular, Cella Media
CC, CST	Corpus Callosum, Corticospinal tract
lt, bl, mdl, l, r, AP, IS	lateral, bilateral, medial, left, right, anterior–posterior, inferior–superior
CT, HU	Computed Tomography, Hounsfield Unit
MRI (Magnetic Resonance Imaging)	T1/T2 weighted MRI: T1 enhances signal from fatty tissue and suppresses that from water, whereas T2 enhances the signal from water content.
	Fluid attenuated inversion recovery (FLAIR): Used to null out signal from fluid and fat tissues, particularly useful to examine the periventricular space
Diffusion Tensor Imaging (DTI) MRI	Used to capture microstructural integrity based on the underlying physiology of water diffusion in tissues
	Mean Diffusivity (MD): Captures rotationally invariant diffusivity
	Radial Diffusivity (RD): Captures perpendicular diffusivity, more specific to demyelination
	Axial Diffusivity: Captures parallel diffusivity, more specific to axonal degeneration
	Fractional Anisotropy (FA): Measures anisotropy which is affected by WM damage

3 Normal pressure hydrocephalus

Hakim and Adams, first explained the mechanism of NPH using Pascal's law. Presently, at least 700,000 older adults in the US are estimated to be afflicted by the condition (40). Excessive buildup of CSF in the ventricles leads to their enlargement and impingement on the surrounding brain tissue. And due to the compliance of the surrounding brain tissue, intracranial pressure (ICP), remains "normal" (12). Recent studies suggest that the pathogenesis of NPH is complex and is potentially related to CSF dynamics, CSF – interstitial fluid exchange, cortical subarachnoid space (SS) morphology, and venous congestion (41). It is clinically characterized by the Hakim triad which is a combination of gait impairment, urinary incontinence, and cognitive impairment.

The American-European diagnostic guidelines classify NPH into possible and probable subgroups based on clinical evaluation for the Hakim triad, an invasive CSF tap-test with opening CSF pressure of 5–18 mm Hg, medical history, and radiographic assessment of lateral ventricle (LV) enlargement (42). Enlarged temporal horns (TH) and periventricular intensity changes unattributable to ischemia or demyelination are also considered. While they do not endorse a classification of patients with definite NPH based on positive shunt response, the Japanese guidelines take that approach, and include evaluation of sulcal tightness at the high-convexity (HC) of the brain and dilation at the sylvian fissures (SF) (43). Age at onset and presence of other comorbidities are also considered in both guidelines (44). Irrespective of different approaches to classification, a vast majority of patients saw favorable outcomes following shunt surgery (45) and early surgical intervention was found to significantly affect functional outcomes (46). And despite reports of complications (47), advances in surgical procedures guided by computer aided neuronavigation, and infection reduction strategies suggest a promising future for complete reversal of symptoms in NPH (48).

3.1 Structural imaging markers of NPH

Radiological markers are significantly factored in the clinical diagnosis of NPH. Diagnostic standard measures of ventriculomegaly in NPH diagnosis include the callosal angle (CA), Evans-x index (EI-x), and the Disproportionately Enlarged Subarachnoid Space Hydrocephalus (DESH) (42, 43). Several other structural markers describing the effects of NPH on the ventricular and CSF spaces, white matter (WM), and gray matter (GM) structures have been described over the years. The prominent features described in this section are summarized in Table 3.

As CSF spaces are the most distinctly deformed anatomy in NPH, features describing its volume and morphology have been extensively studied and applied in the detection of NPH. A 2007 study of 14 patients with probable NPH (3.5% with shunt response) patients on MRI scans indicated that visually apparent narrowing of CSF spaces at the HC and midline (ML) accurately separated them from age-matched controls (49). Another study of 24 patients with probable NPH who had functional improvement after a CSF-tap test (tap positive), 24 tap negative patients, and 23 age matched controls using on (T2) MRI scans showed that 3 newly proposed metrics – CSF volume at the parietal convexity (Prtl-C), the Evans-z index (EI-z), and upper to lower SS ratio were optimal diagnostic indices of iNPH as they had the highest area under the curve of receiver operating characteristics (AUCROC) in distinguishing between tap-positive and tap-negative patients. Absolute and normalized (by intracranial volume) volumes of the total ventricle and bilateral ventricle spaces, the Evans-y index (EI-y), EI-x, maximum ventricle to brain lengths (in the 3 orthogonal directions), CA, CSF volumes of the SS at the frontal and parietal convexity, SF and basal cistern, and posterior fossa were also among the evaluated features (29).

Changin et al. proposed a simplified CA (simpCA) measure to overcome the need for extensive image processing to obtain the CA and showed that it was significantly lowered in NPH patients as seen on MRI sequences (27). To mitigate nonuniformity and examination of multiple slices required to measure the EI-x, another quantitative measure called the anteroposterior diameter of the lateral ventricle

TABLE 2 Structural imaging markers and definitions.

Marker	Definition
CA	Callosal Angle. Angle between lateral ventricles as viewed on the coronal plane perpendicular to the AC-PC line at the level of the PC (25)
simpCA	Simplified *CA*. Angle between the LV on the coronal plane perpendicular to the AC-PC line at the level of the midpoint of the CC (26)
ACA	Anterior *CA*. Angle between lateral ventricles as viewed on the coronal plane perpendicular to the AC-PC line at the level of the AC (27)
EI-x	Evans index. Ratio of the maximum width of the frontal horns of the LV (Frontal Horn Diameter (FHD)) and the brain width/inner cranial width as measured on consecutive axial planes parallel to the AC-PC line (25)
mFHI	Ratio of maximal frontal horn width to the bicortical width on the same plane (28)
EI-y	Evans-y index. Ratio of the maximum length of the frontal horns of the LV from the foramen of Monro in the AP direction and the brain length/inner cranial length (29)
EI-z	Evans-z index. Ratio of the maximum height of the frontal horns of the LV from the foramen of Monro in the IS direction and the brain height/inner cranial height (29)
SA	Splenial Angle. Angle subtended by the forceps major of the CC at the midline on the first axial plane with the complete body of the CC visible while moving in the IS direction (30).
CH	Callosal Height. Maximum perpendicular distance between the inferior level of the CC and the line connecting the anterior and posterior extremities of the CC assessed on the midsagittal plane (31)
mCMI	Modified Cella Media Index. Ratio of the maximum cella media width as seen on axial planes normalized by the brain width on the same plane (32).
CMW	Maximum Vertical Width of the Cella Media of the LV. Maximum vertical width of the cella media as seen on the coronal plane at the level of the PC (31)
mTHW	Mean Temporal Horn Width, as seen on axial views (33)
THW	Maximum Vertical Width of the Temporal Horn of the LV, as seen on the coronal plane at the level of the PC (31)
CTR	Ratio of the CMW and TMW (31)
DESH	Disproportionately Enlarged Subarachnoid Space Hydrocephalus. Captures the relationship between high convexity tightness, enlarged sylvian fissure, and ventriculomegaly as a descriptive indicator (34)
SILVER index	The ratio of the SF area to the subarachnoid space area at the vertex measured on a coronal plane (perpendicular to transverse planes parallel to the frontal fossa) at the level of the foramen of Monro (35)
ALVI	Anteroposterior diameter of the lateral ventricle index. Defined as the AP diameter of the LV on the first axial plane with the CM completely visible normalized by the inner brain length along the falx on the same plane (36)
iNPH Radscale	Visual grading, that is a combination of the EI-x, CA, mean width of the TH, narrow HC sulci, dilated SF, focally dilated sulci, and PV hypodensities. Higher values indicate a more severe NPH pathology (37)
BVR	Brain to ventricle ratio. Ratio of the SVW and CMW (31). Ratio of the maximum brain width divided by the maximum LV width assessed on coronal sections at the AC and PC levels (38)
CCD	Callosal-commissural distance. Distance between the inferior level of the CC and the PC assessed on the midsagittal plane, on a line parallel to posterior brain stem margin (31)
CVD	Callosal-ventricular distance. Distance between the inferior level of the CC and the line connecting the roofs of the left and right LVs assessed on the coronal plane at the level of the PC (31)
SVW	Maximum Vertical Width of the Supratentorial Brain. Maximum vertical width of the brain in the supratentorial space assessed on the coronal plane at the level of the PC (31)
BCVI	Bicaudate cerebroventricular index. Ratio of the frontal horns of the LV to the bihemispheric width (39)
Hemispheric CVI	Ratio of each of the frontal horns of the LV to the hemisphere specific width (39)

index (ALVI) on a fixed a standard plane was demonstrated to be better correlated with ventricular volume as compared to the EI-x, and a threshold of 0.5 could detect patients with ventriculomegaly in definite NPH when compared to healthy controls on CT (36). A comprehensive study of interpretable measures of the CSF spaces on MRI evaluated the frontal horn diameter (FHD), DESH, CA, simpCA, maximum vertical width of the supraventricular brain (SVW), cella media width (CMW), temporal horn width (THW), frontal horn vertical diameter (FHVD), callosal ventricular distance (CVD), callosal commissural distance (CCD), callosal height (CH), EI-x, EI-z, cella media to temporal horn ratio (CTR: CMW/THW), and brain to ventricle ratio (BVR: SVW/CMW), showed that all features except the CTR were able capture significant differences between probable NPH and normal controls. However, the capacity of these features in predicting shunt response were not evaluated in the study (31).

Structural imaging markers that predict shunt response in NPH have not been reliably established. A larger study of probable NPH ($n = 229$) patients contrasted with a non-NPH group, manually examined volumes of the LVs, basal cisterns, and SS superior to and at the level of the SF. They also manually evaluated DESH, focally dilated sulci, aqueductal CSF flow void sign, medial temporal lobe atrophy, WM changes, mean temporal horn width (mTHW), EI-x, CA, and the modified cella media index (mCMI) (33). They found that NPH diagnosis was more likely in patients with higher disproportion of the SF-level SS as compared to the supra-SF SS space, and narrower THs (lower mTHW) but concluded that none of the radiological markers could predict shunt response. Given that this study only included patients with EI-x > 0.3, the finding of narrower THs in NPH may be due to patients with atrophic enlargement of the TH being grouped in the non-NPH group.

A quantification of DESH on CT scans was proposed using the SILVER index defined as the ratio of the SF area to the SS area at the

TABLE 3 Structural imaging markers of NPH.

Disease and comparison groups	Structural marker	References	Assessment	Imaging modality
14 probable NPH, 5 definite NPH, 12 NC	CSF volume at the HC, ML: NPH < NC	(49)	Manual	T1 – MRI
24 probable NPH, 24 tap-negative NPH, 23 NC	EI-z: NPH > NC; CSF volume at the Prtl-C, Ratio of CSF volume in upper and lower SS (split by a transverse plane parallel to the AC-PC line, at the level of junction of the straight sinus and vein of Galen): NPH < NC	(29)	Semi-Automatic	T2 – MRI
29 possible NPH (22 probable, 25 definite), 26 NC	SILVER index: NPH > NC	(35)	Manual	CT
75 definite NPH, 55 NC	iNPH Radscale: NPH > NC	(50)	Manual	CT
23 definite NPH, 62 NC	ALVI: NPH > NC	(36)	Manual	CT
140 NPH (33 possible, 53 probable, 54 definite), 52 NC	Ratio of GM (at the thalamus) and WM (anterior bilateral PV space) density (HU): NPH > NC	(51)	Manual	CT
21 definite NPH, 20 NC	CSF volume, GM volume in the precuneus, paracentral lobules (bl), supplementary motor area (bl), left cerebral hemisphere (mdl), cingulate (mdl), paracingulate gyri: NPH > NC; WM volume, GM volume in the temporal lobes (bl), thalamus (bl), hippocampus (bl), insula (bl), amygdala (l), lenticular nucleus (r), putamen (r), and cerebellum: NPH < NC	(52)	Semi-Automatic	T1 and T2 – MRI
35 possible NPH (89% probable), 45 NC	CA, simpCA, BVR: NPH < NC; EI-z, EI-x, DESH, FHD, FHVD, SVW, CVD, CCD, CH, CMW, THW: NPH > NC	(31)	Manual	T1 – MRI
16 possible NPH, 14 NC	Volume of hippocampus, normalized by the intracranial supratentorial volume: NPH < NC	(53)	Manual	Inversion recovery, T1 – MRI
10 possible NPH, 21 headache controls	Posterior part of the cingulate gyrus tighter/narrower than anterior part (Cingulate Sulcus Sign): NPH > headache controls; Concavity of the upper midbrain profile (Upper Midbrain Profile Sign): NPH > headache controls	(54)	Manual	T1, T2, FLAIR MRI
14 NPH, 8 NC	Volumes of the caudate, putamen, thalamus, nucleus accumbens, hippocampus, and pallidum: NPH < NC	(55)	Semi-Automatic	T1 – MRI

NC, Normal Controls.

vertex, which had an AUC of 0.9 in distinguishing NPH from controls, but there was no significant difference between shunt responders and non-responders (35). Another retrospective study that tried to relate various manually evaluated MRI measures including notable ones such as DESH (HC sulcal tightness and SF dilation), the CA, EI-x, maximum 3 V width, maximum width of the TH, maximum anteroposterior diameter of the 4 V, aqueductal flow-void sign, and inter-hemispheric fissure width found no significant differences between shunt responders and non-responders (56). Consolidating several markers of ventriculomegaly and CSF space morphology, Kockum et al. (37) proposed the iNPH Radscale in 2018. They demonstrated that this measure showed consistency when measured on MRI and CT (57), and had a positive correlation with expert radiologist evaluations and classified shunt-responsive NPH patients from healthy controls (50) using CT scans. However, there is also evidence that the Radscale cannot predict shunt response amidst symptomatic individuals and recommended against its sole for shunt-surgery selection (58).

A novel measure called the Splenial Angle (SA), defined on Diffusion Tensor Imaging (DTI) MRI Fractional Anisotropy maps as the angle subtended by the forceps major of the corpus callosum (CC) on axial slices, to capture the effect of ventricular distention on the CC at the ML in probable NPH was shown to have high sensitivity in distinguishing it from controls (30). Left ear extinction in NPH possibly associated with the upward elevation and thinning of the CC was found to be alleviated among patients with NPH post shunting, indicating the range of impairments that may be reversed with surgery (59). Confirming the previous findings of loss of WM integrity in NPH on CT scans, a recent study showed that the ratio of GM density at the thalamus to the WM density at anterior periventricular regions was lower in NPH and could be used to distinguish it from healthy controls. Even though their NPH cohort included definite NPH patients, they were unable to demonstrate the utility of this measure in distinguishing between shunt response in symptomatic patients (51). Hippocampal atrophy was shown to correlate with patients who have higher rates of cognitive impairment in NPH (53). But GM degradation had not been detailed in NPH until recently. Lv et al. (52) compared definite NPH patients with controls using MRI scans and found regional variations in GM volume that were significantly different in the NPH group. GM volume was lowered in specific

temporal areas, thalamus, hippocampus, and the cerebellum. Contrarily, it was increased in medial and parietal regions. Global reduction in WM volumes and increase in CSF volumes were also found (52).

A 2013 study on MRI scans of 16 NPH patients who improved after shunt surgery showed that recovery after surgery was correlated with lower brain deformation before surgery as seen on MRI (60). They captured the ratio of ventricular and SF enlargement to the HC/ML tightness in a single measure of deformity, reflective of DESH, which was shown to improve post-surgery. It is important to note from this study that there may be a threshold to structural damage which may indicate irreparable loss when breached. And as new therapies emerge, it would be critical to accurately identify patients with this type of reversible dementia to optimize care for them. This is where differential diagnosis for NPH including the accurate identification of AD and PD comes to the forefront. The prominent features capturing the difference between NPH and AD/PD are summarized in Table 4.

4 Alzheimer's dementia

Alzheimer's Dementia (AD) is best characterized by the abnormal presence of extracellular amyloid plaques and intracellular neurofibrillary tangles (NFT) of protein tau which leads to a loss of synapses and cell death (78). In the US, AD is prevalent among 6.5 million people (79). Studies have shown that amyloid beta plaques start accumulating in abnormal clumps called oligomers and fibrils in the early stages which is correlated to downstream accumulation of NFT (80). Activated microglia that are unable to keep up with debris clearance cause chronic inflammation and cell death leads to atrophy. In early stages, the medial temporal lobe involving hippocampus, entorhinal cortex, amygdala, and para-hippocampal cortex seem to be most affected along with global atrophy involving the frontal, temporal, and parietal lobes excluding the sensory-motor cortex and occipital regions. Basal ganglia regions like the caudate, putamen, pallidum, and nucleus accumbens also show atrophy (15). Clinical symptoms mainly include loss of memory, decreased executive function, language deficit, loss of vision, and gait instability (78). Diagnosis is based on physical exam, evaluation of patient history, memory, cognitive, and neurological functions along with radiographic imaging. Therapeutic solutions for AD like cholinesterase inhibitors are commonly used to alleviate symptoms. While there is no complete cure for the disease yet, a drug which was shown to remove amyloid plaque deposits in the brain was approved by the FDA and several others are being investigated (79).

4.1 Structural imaging markers for the differentiation between NPH and AD

The medical research community has directed significant efforts to solving the problem of accurately distinguishing between NPH and AD using neuroimaging markers, in the hope that patients with reversible dementia do not get sentenced to a hopeless diagnosis of AD and miss their chance at a better quality of life. Identifying the structural effects of NPH and AD accurately may also find application in predicting patients with poorer shunt outcomes in NPH patients with comorbid AD (81). Expectedly, MRI-based markers and methods have dominated and emerged successfully in this quest. The CSF flow void sign on T2-weighted MR sequences which appears in the cerebral aqueduct was one of the earlier signs of impaired CSF dynamics in NPH, and it was shown to classify it from AD (82). This was also substantiated quantitatively by demonstrating a higher aqueductal CSF flow rate in NPH as opposed to AD, using phase contrast MRI, a few years later (83). However, even though CSF hydrodynamics is impaired in NPH, there is also evidence that it may not provide distinction from AD (84).

Signs of structural integrity loss in specific anatomies affected by the NPH pathology have been promising in segregating AD pathology. Holodny et al. (61) identified the dilation of the peri-hippocampal fissure as a distinctive anatomical marker between NPH and AD, along with the LV and 3 V sizes, as seen on MRI. Potentially indirect effects of ventriculomegaly like the narrowing of the posterior cingulate sulcus as compared to the anterior part and a concave upper midbrain profile, apparent on MRI, was shown to be more likely in NPH as opposed to AD but it was not tested for its sensitivity in classifying NPH from AD (54). While these studies set a promising avenue, extracting features from these specific neuroanatomies on MRI and CT requires significant manual intervention and/or preprocessing in the form of region-of-interest definitions. GM density on T1 and T2 MRI was shown to be significantly higher in the precuneus, frontal and parietal regions (medially and laterally, except around the central sulcus potentially spared due to dilation from aging) when NPH was compared to AD and normal controls. When NPH was compared to normal controls, it was significantly lower in the thalamus, caudate, and perisylvian fissure, but only so in the thalamus when compared to AD. It also revealed the enlargement of the ventricles, SF, and basal cisterns in NPH versus AD and normal controls (62).

WM abnormality has gained importance as a structural marker in differentiating NPH from AD. A 2010 study argued for the use of DTI to detect microstructural integrity of WM in the hippocampus using fractional anisotropy (FA) and mean diffusivity (MD) as more sensitive measures in detecting NPH from AD, as opposed to its whole volume (63). FA and axial diffusivity values measured on DTI MRI at the CST, distention of which is thought to cause gait impairment in NPH, were shown to be highly sensitive in detecting probable NPH from AD, PD with Dementia, and healthy controls (64). In the same year, another study found that higher MD coupled with lower FA in the supratentorial WM of the brain was indicative of NPH versus AD and PD (65). The SA which captures the effect of distention of LVs on the forceps major of the CC (30) was also shown to differentiate between NPH and AD.

In a very insightful finding on DTI, it was demonstrated that the WM structure fornix had reduced volume and cross-sectional area in NPH patients but longer compared to AD and normal controls (66). The FA value in this structure was also lower in NPH as compared to normal controls. Revealing structural damage to the fornix due to LV enlargement, this finding illustrates the power of structural imaging to capture the degenerative effects of NPH on the brain. Kang et al. (67) provided a more anatomically localized insight into WM structural integrity by showing lower FA and higher MD bilaterally in the anterior corona radiata, posterior thalamic radiation, superior longitudinal fasciculus, and external

TABLE 4 Structural imaging markers for differentiation of NPH from AD and PD.

Disease and comparison groups, Reference	Structural marker	Imaging modality
229 probable NPH, 161 non-NPH; All had EI-x > 0.3 (33)	mean width of the TH: NPH < non-NPH; Ratio of CSF volume in SS at the level of and superior to the SF: NPH > non-NPH	CT and MRI
19 probable NPH, 19 NC, 19 AD, 19 PD (30)	SA: NPH < AD, PD, NC	DTI MRI
17 definite NPH, 17 AD (61)	LV volume, 3 V volume: NPH > AD; Perihippocampal fissure volume: NPH < AD	T1 and T2 MRI*
34 probable NPH, 34 AD, 34 NC (62)	GM density in the parietal (lt, mdl), frontal regions (lt, mdl) except in the pre- and post-central gyri, and precuneus, volume of ventricles, sylvian fissure, and basal cisterns: NPH > AD, NC; GM density in thalamus, caudate, and perisylvian fissures: NPH < NC; GM density in thalamus: NPH < AD	MRI – T1 and T2*
13 probable NPH, 15 AD, 15 NC (63)	FA of the hippocampus: AD < NPH < NC; MD of the hippocampus: AD > NPH > NC	DTI MRI*
18 probable NPH, 11 AD, 11 PDD, 19 NC (64)	FA of the CST: NC, PDD, AD < NPH; Axial Diffusivity of the CST: NC, PDD, AD < NPH; Leukoaraiosis in the PV space: NPH > NC, PDD	DTI – MRI*
20 definite NPH, 20 AD, 20 PD (65)	FA of the supratentorial WM: NPH < AD, PD; MD of the supratentorial WM: NPH > AD, PD; Ratio of 3 V, LV volumes and supratentorial ICS: NPH > AD, PD	DTI – MRI*
22 probable NPH (12 definite NPH), 20 AD, 20 NC (66)	Volume, Cross-Sectional Area of the fornix: NPH < AD, NC; Length of the fornix: NPH > AD, NC; FA of the fornix: NPH < NC	DTI – MRI*
28 probable NPH, 28 AD, 20 NC (67)	FA of the anterior coronal radiata (bl), CC, Superior longitudinal fasciculus (bl), Posterior thalamic radiation (bl), External capsule (bl), Middle cerebellar peduncle: NPH < AD, NC; MD at the same locations: NPH > AD, NC	DTI – MRI*
17 probable NPH, 14 AD, 17 NC (68)	FA, MD, RD of cortico-fugal fibers from the frontal and parietal cortex: NPH > NC; FA of the CC (splenium): NPH < NC; RD of the CC (splenium): NPH > NC; FA, MD, RD of the corona radiata in the PV fibers from the frontal and parietal cortex: NPH > AD	DTI – MRI*
34 probable NPH, 34 AD, 34 NC (69)	CA: NPH < AD, NC	T1 – MRI
36 definite NPH, 34 AD, 36 NC (70)	CA: NPH < AD, NC; EI-x: NPH > AD, NC; GM volume: NPH > AD; LV + 3 V volume: NPH > AD, NC; Hippocampus volume: NPH > AD, NC	T1 – MRI*
42 probable NPH, 61 AD, 65 NC (27)	ACA: NPH < AD, NC	T1 – MRI
10 probable/definite NPH, 18 PD, 10 NC (71)	FA of anterior thalamic radiation, forceps minor and major, superior longitudinal fasciculus, CST: NPH < PD, NC; EI-x: NPH > PD, NC	DTI MRI*
5 definite NPH, 5 P, 10 AD, 10 NC (72)	Ventricular Volume, Ratio of Ventricular Volume and ICS volume: NPH > AD, PD, NC; Ventricular Volume/Cortical thickness: NPH > AD, PD, NC	T1 – MRI*
15 definite NPH, 17 AD, 18 NC (73)	Ventricular volume and GM volume: NPH > AD; Ventricular volume: NPH > NC	T1 – MRI*
15 probable NPH, 15 AD, 15 NC (74)	*VS*, SF volume: NPH > AD, NC; HC, ML volume: NPH < AD, NC	T1-MRI*
30 NPH, 10 NPH + AD, 18 AD, 26 NC (38)	Volume of the basal cisterns and SF: NPH, NPH + AD, AD > NC; Volumes of CSF in frontal and parietal convexity SS and upper SS: NPH, NPH + AD < AD; EI-z: NPH, NPH + AD > AD; CA, BVR: NPH, NPH + AD < AD	T2 – weighted MRI*
24 NPH, 22 AD, 40 NC (26)	simpCA: NPH < AD, NC	T1 and T2/FLAIR MR sequences
19 definite NPH, 24 AD, 18 PD, and 14 NC (75)	*VS*, SF volume: NPH > AD, PD, NC; HC, ML volume: NPH < AD, PD, NC; Ratio of *VS*, SF volume and HC, ML volumes: NPH > AD, PD, NC	T1 – MRI*
12 possible NPH (10 probable), 14 AD, and 17 NC (76)	*VS*, SF volume: NPH > AD, NC; HC, ML volume: NPH < AD, NC; Ratio of *VS*, SF volume and HC, ML volumes: NPH > AD, NC	T1 – MRI*
42 probable NPH, 32 AD, 24 NC (77)	CA: NPH < AD, NC; GM volume: NPH > AD; CSF volume: NPH > AD, NC; WM volume: NPH < AD, NC; Ratio of WM to TIV: NPH < AD, NC; Ratio of CSF to TIV: NPH > AD, NC; Ratio of GM to TIV: NPH < NC	T1 – MRI*

"*" indicates that (semi) automatic assessment methods were used. NC, Normal Controls.

capsule of NPH patients as opposed to AD patients, as well as in the CC and the middle cerebral peduncle. They showed the FA was lowered in the splenium of the CC and right external capsule in NPH patients with higher gait disturbance. Another study of WM integrity using DTI parameters like MD, FA, radial diffusivity (RD), and axial diffusivity showed a higher FA, RD, and MD in the corona radiata in periventricular fibers from the frontal and parietal cortices in NPH as compared to AD (68).

When attention is shifted to the structural degenerative markers that are seemingly similar in NPH and AD, ventriculomegaly emerges in the top spot. The CA has long been established as a direct marker that can capture if the ventricular enlargement is due to true hydrocephalus in NPH or a compensated enlargement due to atrophy in AD on MRI (69). This finding has been extensively validated, and even by more recent studies. The simpCA was also shown to be significantly lower in NPH as opposed to AD (26). Using manually annotated CA and EI-x measures on MRI images, an AUC of 0.96 was reported in distinguishing 36 definite NPH patients from 34 AD patients and 36 healthy controls (70). Even though a cut-off of 0.3 is usually recommended for the EI-x, it was found that a cut-off of 0.32 for the EI-x and 100^0 for the CA maximized diagnostic accuracy, and the performance metrics were reported based on this classification. The EI-x cut-off of 0.3 has also been contested with a better proposal of age and sex specific values pointing to higher sensitivity (85). The anterior CA (ACA) was proposed and tested against the conventional CA, and EI-x on MRI scans in distinguishing NPH from AD and healthy controls (27). While it was significantly lower in NPH as compared to AD and healthy controls, it did not outperform the CA in diagnostic accuracy. A subsequent study of its association with gait impairment showed correlation with pre-surgery symptoms and post-operative improvement (86). Overall, we found that numerous distinctive features of NPH versus AD have been studied, but MRI is predominantly used as opposed to CT.

5 Parkinson's disease

Parkinson's disease (PD) is primarily diagnosed in a clinical setting through thorough examination of neurological symptoms that have motor manifestations like tremor, impairment of gait, arm-swing, balance, postural stability, and facial expression, and non-motor manifestations like impairment of behavior and cognition. Definitive diagnostic tests using blood, CSF, or imaging biomarkers do not currently exist (87). The manifestation of dementia in PD (PDD) patients (16) makes some patients more susceptible to misdiagnosis. There are reports that indicate that more than 15% of patients with PD may be misdiagnosed (88), with prominent misdiagnoses including AD (16). NPH may also be misdiagnosed as PD due to parkinsonism (89). Early diagnosis of this disease is challenged by the late manifestation of its defining motor symptoms, heterogeneity in clinical presentations, underlying mechanisms of its subtypes, age at onset, rate of progression, and response to treatment. This is also reflected in the heterogeneity of imaging features which correlate with symptomatic presentation (87).

As a direct consequence of the fact that the source of this synucleinopathy is known to primarily affect the substantia nigra (SN) and basal ganglia, and its microscopic magnitude of origin, imaging markers from structural imaging which rely on the scatter of external radiation like CT and MRI are not recommended for assessment of PD. Rather, functional imaging markers that directly correlate with the function at cellular levels by reflecting the uptake of specific radioactive tracers are the most viable option for detection, especially in early stages. In support of this claim is an article from Dalaker et al. (90) who found that global markers like atrophy and white matter hyperintensities were not significantly distinct in early PD as compared to healthy controls. Recently, Bae et al. (91) reviewed the degenerative markers of the SN on advanced imaging techniques like Nigrosome and Neuromelanin Imaging (NMI) using high field MRI techniques, Quantitative Iron Mapping (QMI), and Single Photon Emission Computed Tomography (SPECT). They highlight studies which have shown highly sensitive classification of PD when iron deposition in the SN driven by dopaminergic cell loss is used as a biomarker. In support of high field and neuromelanin sensitive MRI is a review from 2019 by Prange et al. (92) and from 2016 by Pagano et al. (93) Near normal or diffuse cortical atrophy is associated with PD (94), which raises the possibility of no visible markers of degeneration on CT or MRI. We investigate this further by providing the following review of structural imaging markers in PD and those that can distinguish it from NPH on MRI and CT sequences.

5.1 Structural imaging markers for the differentiation between NPH and PD

The presence of parkinsonian symptoms is not an uncommon occurrence in NPH (95), with case reports that were made as early as 1983 (96) which also recognized that it did not negatively impact shunt outcome. A 1994 report presented insight into the pathophysiological mechanisms of co-occurring hydrocephalus and parkinsonism manifesting as impairment of the nigrostriatal or neural circuits traversing the cortex, striatum, pallidus, and thalamus (97). Their proximity to the enlarged ventricles may introduce mass effects and ischemic changes. According to Akiguchi et al. (89) WM lesions and parkinsonism symptoms (prevalent in 71% of patients) in NPH were reversed after shunt surgery. Given this, differentiating NPH from PD, with which it is so frequently mistaken, is of paramount importance.

DTI has been shown to distinguish between NPH and PD using FA measures at the forceps major and minor, anterior thalamic radiations, CST, and superior longitudinal fasciculus by Marumoto et al. (71). Interestingly, they also found that the EI-x was significantly higher in NPH as compared to PD (100% sensitivity). The anterior thalamic radiation FA measure demonstrated higher specificity as compared to the EI-x in distinguishing NPH from PD. Ventricular dilation and atrophy have been demonstrated in PD (greater at baseline in those with dementia) on MRI (98), so Marumoto et al.'s (71) finding of a higher EI-x in NPH versus PD may suggest that ventricular enlargement in PD may not be as high as NPH. Measures of WM structural deformation and integrity measured through DTI have also been shown to distinguish between NPH and PD. The SA introduced by Chan et al. (30) was significantly higher in NPH versus PD. Kanno et al. (65) found lower FA and higher MD in the supratentorial WM in NPH when compared to PD. Visual evaluation of periventricular WM demonstrated significantly higher leukoaraiosis in NPH when compared to PDD and healthy controls (64). There are a limited number of studies which have examined the structural differentiation between NPH and PD, which may be a general reflection of the fact that structural imaging markers are discouraged in the assessment of PD.

Burton et al. (16) demonstrated GM and overall volume loss in PD as compared to healthy controls localized to the bilateral temporal and occipital lobes, thalami, right putamen, caudate tail, and middle-inferior frontal gyri. A review from 2017 highlights the structural

markers of PD on MRI, with notable volumetric changes seen in the basal ganglia, GM volume loss in the frontal lobe, cingulate, temporal gyri, hippocampus, and loss of cortical thickness in specific frontal and occipital areas as compared to controls (99). Adding to the nuance which can be picked up on structural imaging, a recent study using MRI scans showed a difference in the amount and pattern of GM and cortical atrophy between patients with PD-without-dementia and healthy controls (100). As expected, pronounced structural effects were found in more severe manifestations of the disease. With a comprehensive classification system that factored clinical, demographic, and symptomatic presentations to categorize patients into mild and moderate–severe groups, they found significant differences only between the moderate–severe group and the healthy controls. The CC volume in the mid-anterior and central regions were found to be reduced in PD patients on MRI as compared to healthy controls by Goldman et al. (101). Shape changes and volume loss in the putamen, and shape changes in the caudate were shown to distinguish between PD and healthy controls (102). In a first attempt of its kind, a study from 1985 found that the size of the CSF spaces was increased in patients with PD when compared to normal controls on CT scans (103). Asymmetric ventricular enlargement was reported in PD using MRI scans (104), and later verified on 17 PD patients (105). Longitudinal atrophy and ventricular enlargement measured on MRI has been reported even in PD patients with dementia (106). Amidst the discouragement of structural imaging in the assessment of PD, textural features derived from first and second order grayscale/intensity statistics on T1-MRI scans were shown to be significantly associated with clinical features of PD by a 2021 study (107). In this highly welcome development, they showed that changes in the nigrostriatal pathway in early stages of PD could be captured through structural images, which was supported by correlation with motor symptoms. With these insights into the structural degradation in PD as opposed to normal controls, there is a considerable knowledge pool of structural markers that may be tested for their differentiative capacities from NPH.

6 Computational methods for the detection of NPH and its differentiation from AD and PD

Early adopters of semi-automatic algorithms included an effort to extract volumetric ventricular sizes and cortical thickness for distinction of NPH from AD, PD, and normal controls using MRI, and advocated for the ratio of ventricular size and cortical thickness as a better feature to distinguish between definite NPH ($n = 5$), from the rest, especially as ventricular volumes in NPH and AD may overlap (72). This problem has also been countered by considering the distribution of (normalized) CSF volumes rather than using it as a global measure, as shown by many studies so far. Voxel-based morphometry (VBM) has long been established as a reliable computational tool in MRI studies to assess structural markers of NPH. Yamashita et al. (76) analyzed CSF distribution using VBM on MRI scans and showed significant distinction between NPH ($n = 12$ with 83% probable NPH and 17% definite NPH) when compared to AD and normal controls in terms of LV/SF volumes, and HC/ML volumes. In a measure that reflects DESH, their analysis also showed that the volume of CSF in the LV and SF areas as compared to that in the HC and ML areas was higher in NPH as compared to AD and normal controls. Subsequently, they showed similar trends in those features on a definite NPH cohort, and when it was compared to PD patients (75).

Ishii et al. (74) developed an automatic volumetric CSF segmentation method on T1-MRI, which provided localization into the SF, HC, and ML sulci, as well as the ventricular spaces. They demonstrated the validation of previously known findings that enlarged ventricles and SF, and tight HC sulci were evident in a group of 15 probable NPH patients as opposed to AD and healthy controls. In a more targeted and automatic effort to segment GM, WM, and CSF spaces on T1-MRI, ventricular and GM volume, and gender were found to distinguish shunt-responsive NPH from AD and normal controls (73). Ellingsen et al. (108) developed a segmentation and labeling software to compartmentalize the ventricular system (into lateral, third, and fourth), referred to as RUDOLPH on MRI at a time when limited or no efforts were made for automatic segmentation of highly deformed ventricles. Yamada et al.'s studies on indices characterizing CSF spaces for the optimal distinction of probable NPH from healthy controls (29), AD, and NPH-and-AD cohorts on T2-MRI (38) were also based on semi-quantitative approaches relying on automatic segmentation of brain tissue. In a recent study of CSF distribution, the normalized WM and CSF volumes derived using VBM, along with the CA were shown to provide improved distinction between probable NPH and AD using MRI sequences when compared to the CA alone (77).

Peterson et al. (55) used an automatic segmentation method on T1-MRI to quantify volume in deep subcortical GM structures and showed reduced volume of the caudate, putamen, thalamus, nucleus accumbens, hippocampus, and pallidum in 14 NPH patients as compared to 8 healthy controls. Efforts apart from volumetry have also been made to extract nuanced MRI-based features. Statistical parametric methods using MD histogram analysis from DTI images have also been shown to distinguish between probable NPH and AD/PD/normal controls with minimal manual intervention (109).

Linear and interpretable measures of ventriculomegaly have also been computationally assessed on MRI. Borzage et al. (7) developed an automated methodology to extract CA from MRI from the Open Access Series of Imaging Studies (OASIS) and Alzheimer's Disease Neuroimaging Initiative (ADNI) databases. With a high ICC of 0.9 between the automated measure and expert annotations on 281 images and an innovative approach to coronal pitch correction for image standardization, they showed the utility of data-driven applications in objective evaluation of diagnostic standard features. CT based methods for automatic assessment of interpretable measures have been limited. An automated image-processing methodology to extract the EI-x from CT images reported a correlation coefficient of 0.983 between the automated measure and expert annotations among 44 subjects (12 NPH). However, they applied nonlinear registration for image standardization which would render the brain width as a constant and affect the measurement of the EI-x (110).

Deep learning-based methods have shown promise in the objective and automatic assessment of NPH using structural imaging modalities. Again, MRI dominates this field of investigation. To enable the automatic segmentation and parcellation of the ventricular system in patients with severe ventriculomegaly due to hydrocephalus, Shao et al. (111) developed a deep learning model named VParNet trained on MRI scans of NPH patients and healthy controls, which showed

high agreement with expert annotations and outperformed state-of-the-art. However, they did not test the classification capacity of their model. Irie et al. (112) developed a 3D convolutional-ladder network, and showed that their model can distinguish between probable NPH ($n = 23$), AD, and controls with an accuracy, sensitivity, and specificity of about 90% using MRI scans. By showing regions like the periventricular spaces, hippocampus, and THof the LVs being highlighted in the activation maps sensed by the network on some successfully classified scans, they demonstrated agreement with previous neuroanatomical findings in their findings.

Deep learning methods to assess NPH on CT scans have also emerged recently. Considering an EI-x $\geq$ 0.32 to be an indicator of hydrocephalus, a transfer learning scheme was applied on a large dataset of CT scans to show a classification performance with AUC of 0.93, sensitivity of 93.6%, and specificity of 94.4% in distinguishing hydrocephalus from normal controls (113). Automated segmentation of CSF, subarachnoid, and cerebral spaces on non-contrast CT scans of 27 patients with possible NPH, integrated with indirectly inferred connectome data, was shown to be as effective as the EI-x for prediction with a specificity of 85% and sensitivity of 86% (114). Haber et al. (115) recently developed a convolutional neural network (CNN) which was able to classify patients with definite improvement post-surgery as identified by the 2nd edition of the Japanese guidelines from healthy controls using CT scans setting a promising precedent in the application of deep learning to CT scans in NPH assessment. Further studies are required to study the potential of deep learning in assessing imaging markers that can predict positive and objective shunt response in symptomatic NPH and distinguish it from its mimics.

7 The chronic effects of traumatic brain injury

TBI casts a pervasive shadow, affecting an estimated 27 to 69 million individuals globally each year, with each case carrying significant chronic consequences (116, 117) and pathophysiological connections to various neurodegenerative diseases including NPH, AD, and PD. Its impact can range from concussions and diffuse axonal injury (DAI) which are harder to detect on structural imaging to extra-axial and intracerebral lesions that appear prominently. While acute injury is easily identified on CT and treated surgically, detecting (and differentiating between) its chronic degenerative consequences including atrophy and hydrocephalus which is crucial for optimal management may be challenging.

Subdural hemorrhage (SDH) refers to bleeding that occurs in the subdural space of the brain. And chronic SDHs (cSDH) represent these lesions which may evolve bilaterally in patients with symmetric cranial vaults, but most frequently occur on the side with higher frontal or occipital convexity. They may also be seen at interhemispheric locations in some cases (118). Even though intracranial hypotension and defective coagulation can cause cSDH, mild trauma to the head remains the predominant cause (119). Rupturing bridging veins in the subdural space following trauma may cause hematomas with varying cellular and vascular compositions as they evolve (118). It mostly affects older patients and is diagnosed with CT even though MRI might be more sensitive in isodense cases. Cerebral atrophy has been shown to be a risk factor for cSDH using volumetric analysis of CT scans (120), as well as being a prominent chronic consequence of it (121). Progressive volume loss in cSDH, at rates higher than dementia, have also been reported using volumetric analysis of CT scans (122). While hydrocephalus is also reported to be a risk factor for the development of cSDH following a minor head injury (123), there has been no compelling investigation into its development post cSDH.

Subarachnoid hemorrhage (SAH), which refers to bleeding in the space between the arachnoid and pia mater of the brain, is associated with secondary hydrocephalus (124) and atrophy (125). NPH was shown to develop in 21% of patients within a month following SAH, and improvement was noted in 85% of patients who underwent shunt surgery (126). While SAHs can occur due to nontraumatic causes, it is also estimated to occur in 33–60% of patients with moderate to severe TBI (127). Dilation of the LVs, as assessed with linear measures such as the bicaudate index and dilation rate assessed as change in volume over time on CT (124), atrophy measured indirectly as the modified cella media index (mCMI) and normalized CSF volume on T1-MRI (32), and parenchymal volume loss assessed through volumetric methods (128) are known structural markers of nontraumatic/spontaneous SAH. Hydrocephalus also occurs in traumatic SAH (13, 129, 130) which are usually found in the sulci at the convexities (131). Tian et al. (129) found that it may be correlated with intraventricular bleeding, severity of injury, thickness, and location of the lesion. Overall, we found that there are limited efforts to characterize and differentiate between the structural markers of hydrocephalus and atrophy following traumatic SAH. The prominent features of atrophic and hydrocephalic degradation in cTBI are summarized in Table 5.

7.1 Structural imaging markers of hydrocephalus and atrophy in cTBI

Hydrocephalus is known to be associated with TBI, irrespective of the presence of traumatic lesion (143). Therefore, it is pivotal to differentiate ventriculomegaly resulting from hydrocephalus and atrophy, as the former may be surgically treated. A call for this was made by Marmarou et al. (13) as early as 1996. In their study, 44% of patients with a severe head injury displayed ventriculomegaly (EI-x > 0.3), with 20% of them indicative of hydrocephalus as per CSF dynamics (monitored as intracranial pressure and CSF outflow resistance). Patients with an SAH showed a higher incidence of ventriculomegaly (80%) than those without (30.8%), and hydrocephalus was detected through CSF dynamics in both groups (50 and 9.1%, respectively). They described a methodology which combines the EI-x and CSF dynamics to classify patients as having high pressure hydrocephalus, NPH, or ventriculomegaly secondary to atrophy, and suggested shunting in the high pressure and normal pressure groups. The need for this distinction was reemphasized by Guyot and Michael (14) who also recognized that shunt-response was dependent on the distinction between symptomatic-hydrocephalic and atrophic ventriculomegaly (14), with the former group faring better.

A later study proposed a noninvasive selection criterion for shunt surgery in this group. 45% of patients with a severe TBI were found to have post-traumatic hydrocephalus, and it correlated with decreased perfusion in the temporal lobes, as seen on SPECT imaging 2–4 months after injury was found to improve post shunting (144).

TABLE 5 Structural imaging markers of cTBI.

Disease and comparison groups, Reference	structural marker	Imaging modality
PTH – 29 shunted, 807 not shunted (132)	Higher EI-x, mFHI at discharge correlated with PTH needing shunt	CT
7 without DNL, 8 with DNL (39)	DNL: Acute SDH with contusion Sudden increase in BCVI over 18% after 1 month of injury, Higher hemispheric CVI ipsilateral to injury, Focal hypodensities and prominent sulci ipsilateral to injury WM damage	CT
14 mild or moderate TBI (133)	Rate of decline in volume of brain parenchyma: cTBI > NC	MRI*
21 with mild TBI (134)	High prevalence of brain lesions, correlated with volume loss in whole brain parenchyma after 6 months CSF volume	T2 – MRI, FLAIR, SPECT*
54 with mild TBI, 31 NC (135)	Mean cortical curvature in 25% of (bl) 31 sulcal and 29 gyral regions: cTBI > NC; Deep GM structures most affected	T1 – MRI*
86 with cTBI, 46 NC (136)	Fornix and Hippocampal atrophy: cTBI > NC	MRI*
118 cTBI, 136 NC (137)	CSF volume in the TH and subarachnoid sulci, TH dilation, hippocampal atrophy secondary to WM damage: cTBI > NC	T1 and T2 – MRI*
27 cTBI, 12 NC (138)	Cross Sectional Area – Posterior Cingulate Gyrus, Corpus Callosum, Thalamus: cTBI < NC; Cross Sectional Area – Lateral Ventricle: cTBI > NC; Whole brain volume: cTBI < NC; Lateral ventricle volume, ratio of lateral ventricles to whole brain volume: cTBI > NC	T1, T2-MRI*
24 boxers (repetitive mild trauma), 14 NC (139)	Whole brain volume loss, Degradation of the septum pellucidum, Periventricular and subcortical WM disease, diffusion constant of the brain: cTBI > NC	T1, T2, DTI – MRI*
25 cTBI, 22 NC (140)	Whole brain, WM, Cortical (precuneus, parietal cortex, and paracentral lobule) and subcortical (notably in the CC, amygdala, hippocampus, putamen, and thalamus) volumes: cTBI < NC; CSF and LV volumes: cTBI > NC	T1 – MRI*
28 cTBI, 22 NC (141)	Whole brain, WM structures of the cingulate, GM of the precuneus volumes: cTBI < NC	T1 and T2 – MRI*
50 cTBI, 50 NC (142)	FA in the frontal cortex: cTBI > NC	T1, T2, DTI – MRI*

"*" indicates that (semi) automatic assessment methods were used. NC, Normal Controls; PTH, Post-Traumatic Hydrocephalus; DNL, Delayed Neuronal Loss.

This imaging marker was dependent on functional imaging, but a valuable insight from this study is that even though hydrocephalus may develop within 3 months after injury, ventriculomegaly secondary to atrophy may not be seen until 6 months. This emphasizes the importance of longitudinal imaging to assess the nature of ventriculomegaly in chronic stages. In a recent finding and larger study (n = 836), the incidence of post-traumatic ventriculomegaly was found to be 46% in TBI patients (132). 3.5% of the patients in the study received shunts (post-traumatic hydrocephalus), with an improvement that was seen in 66%. The patients selected for shunting all displayed ventriculomegaly, but clinical decision based on symptoms was a predominant factor in their selection. Those with low pressure hydrocephalus had better outcomes, and the EI-x and modified frontal horn index (mFHI) were found to be higher in the acute phase for those who developed post-traumatic hydrocephalus.

In a study following patients with severe TBI, 88% displayed ventriculomegaly, and in 1–4 months after injury, a distinct atrophy/degradation termed as delayed neuronal loss (DNL) was observed in about 50% of patients through the bicaudate cerebroventricular index (BCVI) on CT scans. This measure progressed rapidly after 1 month of injury, indicating the sudden manifestation of DNL. Interestingly, acute SDH with contusion was the only contrasting finding between patients with DNL and those without it (39). Those patients' CT findings also included the enlargement of the ipsilateral ventricle as measured by the hemispheric cerebroventricular index (CVI), a sudden appearance of a hypodense focal area ipsilateral to injury (confined to areas of the middle and anterior cerebral arteries) and WM damage as opposed to preserved cortical structures.

Whole brain atrophy has been an established marker of degradation in chronic TBI. Using analysis of MRI, it was found to occur post 11 months of injury and was correlated to loss of consciousness (133). In a prospective study of young patients with mild TBI, even though their neurocognitive profiles were normal, it was found that lesions on MRI (T2-weighted) were associated with whole brain atrophy 6 months post injury, emphasizing the essentiality of radiological follow-up in the post-traumatic course after an initial injury is detected (134). Another structural marker which was found to be distinct in mTBI was the mean cortical curvature of various bilateral cortical structures as measured on MRI. This feature is different from the global volumetric ones, in the aspect of quantifying region-specific pattern of atrophy (135).

Evidence of degradation in specific cortical and subcortical structures has also been abundantly described over the years. Another study which conducted MRI analysis of TBI subjects after 2 months of injury found atrophy in the hippocampus and fornix as opposed to controls (136). An MRI-based tissue specific and volumetric analysis of the temporal lobe structures including the SF, hippocampus, THs of the LVs, temporal gyrus and sulcus, and temporal WM stem, showed that CSF volume was increased (in the THs, subarachnoid sulci) which was more related to WM damage than GM in TBI as opposed to controls (137). They also found that the TH dilation was more related to WM damage than hippocampal atrophy.

At a time when it was thought that medial structures were not as affected from TBI as compared to the frontal and temporal regions (which are more susceptible to TBI insult), an MRI based study showed that the cross-sectional area of the posterior cingulate gyrus (PCG), CC, and thalamus was reduced, and that of the LVs was increased in TBI patients as opposed to controls. As WM from the frontal, temporal, and hippocampal areas connect with the PCG, the authors suggested that these localized structural markers may capture trans-neuronal damage in TBI. The total brain volume was decreased, and the LV volume, and the ratio of the latter to the former were increased (138). A diffusion weighted imaging study of boxers showed increased diffusion indicative of microstructural damage, and MRI analysis (T1/T2/DWI/FLAIR) indicated age-inappropriate volume loss, degradation of the septum pellucidum, periventricular and subcortical WM disease as compared to controls (139). About 8 months following a TBI with axonal injury, whole brain atrophy and increased CSF volumes, cortical (precuneus, parietal cortex, and paracentral lobule) and subcortical atrophy (notably in the amygdala, hippocampus, putamen, and thalamus) localized to specific regions were found by analyzing MRI (T1-weighted) scans using a semi-automated morphometric analysis (140). Post 12 months after mild TBI, global brain atrophy, loss in volume of specific WM structures of the cingulate and precuneal GM was detected using T1-MRI (141). Cortical abnormalities may also be detected using diffusion measures such as increased FA in mild TBI (142). While hydrocephalus and (GM, WM) atrophy are well studied structural consequences of cTBI, studies of structural markers that can characterize their interplay in producing an appearance of ventriculomegaly are lacking.

8 Computational methods to assess the chronic effects of TBI

Computational techniques like tensor-based morphometry (TBM) have been used on MRI (T1-weighted) scans to study localized volume loss in cTBI. WM structures including but not limited to the CC, subcortical structures like the caudate (middle and posterior) cingulate, thalamus, frontal and temporal neocortices, and the cerebellum, were shown to be affected after at-least 3 months of moderate–severe TBI as opposed to controls using this technology (145). Ventricular volume was also revealed to be enlarged. This pattern remained irrespective of the presence of macroscopic lesions. SIENA (146), an automated software for brain atrophy quantification on MRI was applied by Trivedi et al. (147), to show significantly higher brain volume decline in mild-to-severe TBI as opposed to normal controls. This software was also used to quantify longitudinal brain atrophy on MRI (T1-weighted) among severe TBI patients and revealed an association between higher rates of brain atrophy and injury severity, and that brain volume change was a better predictor of long-term functional outcome as compared to functional measures at 8 weeks post-injury (148). TBM revealed localized atrophy in the brain stem, thalamus, putamen, and WM structures like the cerebellar peduncles, internal and external capsules, CC, superior and inferior longitudinal fasciculus, and corona radiata as opposed to normal controls. A surface-based morphometry (SBM) study including DTI and high-resolution MRI revealed distinct cortical thinning, GM diffusivity, and loss of integrity in the pericortical WM in TBI patients (149). Developments in the use of computational tools for objective assessment of atrophy after mild TBI have also led to an FDA approved software. It was shown to reliably capture progressive volume loss, and demonstrated degradation in whole brain (parenchyma, CSF, WM), and regional (forebrain, cortical GM, cerebellum, brainstem) structures on T1-MRI as compared to normal controls (150). This tool was subsequently shown to be more sensitive to (progressive) atrophy and asymmetry detection than radiologist interpretations (151, 152). In a very interesting application of this tool to predict previous brain volumes based on current measures, the developers also showed that reliable estimates of brain volumes were obtained on normal subjects. And that TBI patients show rapid progression of cortical atrophy, as opposed to enlargement in the subcortical nuclei and infratentorial spaces, in the few months after injury. As in the case of distinguishing NPH from AD and PD, we found that computational methods to assess atrophy and hydrocephalus cTBI are predominantly MRI based, and deep learning based approaches are lacking.

9 Discussion

There are abundant examinations into features that can classify between NPH and asymptomatic controls, but those that predict shunt response in symptomatic NPH have not been established. Imaging studies have typically focused on predicting probable NPH due to the apparently high clinical value. Therefore, prediction of tap-test/lumbar drain responses using structural neuroimaging markers as a non-invasive alternative for a preliminary assessment of shunt response is a well-studied topic. CSF space morphological features, characterizing the narrowing of the HC/ML sulci and higher SS, enlargement of the SF and lower SS, and vertical expansion of the LVs have been shown to be highly discriminative in predicting tap-test response. The EI-z and DESH capture them in a straightforward and interpretable manner, but the latter would benefit from a computational formulation. Benedetto et al. (35) proposed the SILVER index as a potential solution. However, localized measurements of SS require manual annotation which inevitably introduces observer variability and higher computational cost. Features characterizing GM and WM integrity have also been shown to correlate with tap-test response, but nonuniformity in scanner calibration, noise, and poor soft tissue resolution may impact such density-based measures on CT scans, which is additionally limited by the need for manual annotation on both CT and MRI scans for localized anatomical measurements.

While discriminating the tap-test response is important, the low sensitivity of the tap-test itself toward shunt response (153) suggests that features optimized to predict tap-test response might reflect or exaggerate the low sensitivity. The performance reports of imaging markers as predictors of shunt response in NPH have also been mixed. Features like the iNPH Radscale have shown prognostic value in discriminating shunt responsive from healthy individuals, but there is no compelling evidence that it can predict shunt response in symptomatic individuals. Additionally, response to shunting may depend upon many factors like post-surgery care, presence of comorbidities, physical therapy, shunt complications etc. which need to be considered in future studies. Optimizing the sensitivity of radiographic evaluation to predict NPH related signal whether it is possible, probable, or definite might enable higher screening and lower cases of underdiagnosis.

Addressing the high levels of misdiagnosis in NPH is also crucial to identify and treat patients with this reversible dementia. While features for the distinction of NPH from AD have been well established, we observe that there is a lack of neuroimaging studies to distinguish NPH from PD using structural imaging. Perhaps due to heavy reliance on levodopa response in patients with suspected PD or clinical symptoms. Clinicians and researchers alike must recognize that this is a suboptimal approach which may put true NPH patients at unnecessary risk due to levodopa side effects and delay treatment with shunt-surgery. We have identified features that are discriminative of PD from controls, which may be tested for their application of distinguishing NPH from it. We encourage researchers to explore computational approaches to fully explore the potential of structural imaging in distinguishing between NPH and PD. Shunt surgery is also capable of relieving post-traumatic hydrocephalus. But research is needed to test the potential of structural imaging markers in selecting patients for surgery, as it is riddled with the problem of distinguishing between atrophy and hydrocephalus following TBI. Unfortunately, in more than 20 years post Marmarou et al.'s (13) advocacy for the use of CSF dynamics in patient selection for shunting in post-traumatic hydrocephalus, an alternative solution with noninvasive markers has not been found.

It is also important to distinguish Long Standing Overt Ventriculomegaly in Adults (LOVA), which is a chronic form of hydrocephalus, from NPH. Most cases are thought to arise due to aqueductal stenosis and may have symptomatic overlap with NPH. Patients with LOVA may also see clinical improvement with shunt surgery (154, 155). It is crucial to differentiate it from NPH as it may be extremely sensitive to pressure variations, which needs to be considered while evaluating surgical treatment (endoscopic third ventriculostomy for LOVA versus ventriculoperitoneal shunt for NPH) options. Characteristic neuroimaging finds of LOVA include (third and lateral) ventriculomegaly, decreased prominence of cortical sulci, macrocephaly, and expansion of the sella turcica due to compensatory mechanisms (156). In cases where LOVA occurs with an open aqueduct, where it may be differentiated from Late Onset Idiopathic Aqueductal Stenosis (LIAS), it becomes more crucial to distinguish it from NPH due to their clinical and symptomatic overlap (157). ICP monitoring in LOVA patients was shown to correlate with patient conditions pre- and post-surgery (158), and CSF dynamics was recommended to differentiate them from NPH patients (159). A noninvasive and accurate diagnostic score consisting of clinical features like age, presence/absence of the Hakim triad, headache, nausea/vomit, and neuroradiological features (evaluated on MRI) like the head circumference, EI-x, 3 V width, DESH, sellar bone distortion with the bulging of the 3 V floor was proposed recently by Palandri et al. (157) which was shown to classify probable NPH patients from LOVA and LIAS patients with a high AUC of 0.97, sensitivity of 95.1%, and specificity of 90.6%. Higher values of this diagnostic score correlates with higher EI-x, 3 V width, head circumference, 3 V floor bulging, and lower prominence of DESH which incorporates distinctive neuroradiological findings in LOVA as opposed to NPH. More research is needed to identify imaging markers which can differentiate shunt-responsive NPH from LOVA/LIAS.

Even though the most prominent structural impact of NPH except for WM abnormality can be visualized on CT, most research studies lean toward MRI. We identify some CT based markers which have shown good predictive performance, and further encourage researchers to not only adapt MRI-based features to CT studies, but also develop CT-specific features for this application. CT-imaging biomarkers, as affordable, timely, and accessible diagnostic solutions, with fewer contraindications than MRI may offer a hopeful prospect. Even though MRI is the preferred mode of structural imaging due to its higher soft tissue resolution as opposed to CT, the development of computational tools to extract volumetric, intensity, and texture-based CT-features may reveal the potential in characterizing structural degeneration in NPH and its differential diagnosis from AD and PD. CT is the preferred mode of evaluation for acute TBI, but the distinction between atrophy and hydrocephalus in cTBI is still heavily studied only on MRI. Advances in computational tools, particularly in machine (deep) learning and image processing, may hold the key to discovering novel CT-based markers, and objectively extracting diagnostic standard markers for these conditions.

A popular choice in semi-automatic image processing methods is to integrate domain knowledge through the volumetric characterization of brain regions that are known to be affected. While this has been successful on MRI, obtaining pixel-level ground-truth for segmentation on CT is not only expensive, but difficult to create by visual inspection. Moreover, brain regions are impacted differently in different neuropathologies and developing individual segmentation-based approaches to capture them, and their interactions can be challenging and quickly add complexity. Architectures from CNN models with the inherent capacity to learn feature representations at increasing levels of abstraction, residual networks that utilize skip connections to solve the problem of vanishing gradients in deep architectures, and the U-Net and its variants that optimally integrate local and contextual features have been limited in the assessment of NPH, and mostly on MRI. The potential of such models in solving other problems such as differentiation of (shunt-responsive) NPH from AD/PD, and atrophy/hydrocephalus in cTBI on CT scans should be tested.

Our article has a few limitations. It is a narrative review. Even though the search strategy was methodical, it was not exhaustive in terms of databases as we only included PubMed. We did not conduct a dedicated search for articles pertaining to computational methods which have been reviewed in this paper, but they were isolated from the search described in the "Search Methodology" section.

10 Conclusion

Better recognition of (normal pressure) hydrocephalus is paramount for the timely management of patients with potentially reversible dementia or brain injury. Despite a plethora of knowledge on the discriminative anatomical markers of NPH, only a few like the EI-x, CA, and DESH have notably been included in diagnostic guidelines. While prediction of tap-test/shunt response may offer most assistance to clinicians, discriminating hydrocephalic pathology from irreversible atrophy is necessary to identify patients who may be surgically treated. Anatomical markers that can accurately predict shunt surgical response in symptomatic NPH are yet to be reliably established, which may be complicated by amount of pathological progression prior to surgery, comorbidities, and post-surgical care. Longitudinal evaluation of anatomical markers correlated with symptomatic progression before and after surgery may shed light on expected recovery and planning treatment options. Additionally,

there is a clear under-utilization of CT based markers in distinguishing NPH from AD, and an overall lack of studies assessing its structural differentiation from PD. Investigations into the distinction of the chronic effects of TBI, namely atrophy and (normal pressure) hydrocephalus, using structural imaging markers is also a crucially unaddressed area which may help to identify patients whose symptoms may be alleviated with shunt placement. Computational tools like image processing may help with objective measurement of features that are correlated with NPH pathology on CT; and advances in deep learning may also highlight explainable features with potential for accurate diagnosis. In emergency settings, smaller community care centers, and hospitals that may not have access to advanced imaging and the expertise to assess them, automatic methods for assessing CT scans for the accurate detection of NPH or post-traumatic hydrocephalus may be of immense value in recognizing patients with reversible symptoms. Through this effort, we urge researchers to untangle the web connecting these neurodegenerative conditions, offering hope to millions, and potentially preventing countless more from stumbling down the treacherous path of structural neurodegeneration.

Author contributions

SKS: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. JD: Conceptualization, Methodology, Project administration, Writing – original draft. RG: Conceptualization, Methodology, Writing – review & editing. SC: Investigation, Writing – original draft. RK: Methodology, Project administration, Resources, Supervision, Writing – review & editing. US: Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Intimate partner violence perpetration among veterans: associations with neuropsychiatric symptoms and limbic microstructure

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Background: Intimate partner violence (IPV) perpetration is highly prevalent among veterans. Suggested risk factors of IPV perpetration include combat exposure, post-traumatic stress disorder (PTSD), depression, alcohol use, and mild traumatic brain injury (mTBI). While the underlying brain pathophysiological characteristics associated with IPV perpetration remain largely unknown, previous studies have linked aggression and violence to alterations of the limbic system. Here, we investigate whether IPV perpetration is associated with limbic microstructural abnormalities in military veterans. Further, we test the effect of potential risk factors (i.e., PTSD, depression, substance use disorder, mTBI, and war zone-related stress) on the prevalence of IPV perpetration.

Methods: Structural and diffusion-weighted magnetic resonance imaging (dMRI) data were acquired from 49 male veterans of the Iraq and Afghanistan wars (Operation Enduring Freedom/Operation Iraqi Freedom; OEF/OIF) of the Translational Research Center for TBI and Stress Disorders (TRACTS) study. IPV perpetration was assessed using the psychological aggression and physical

assault sub-scales of the Revised Conflict Tactics Scales (CTS2). Odds ratios were calculated to assess the likelihood of IPV perpetration in veterans with either of the following diagnoses: PTSD, depression, substance use disorder, or mTBI. Fractional anisotropy tissue (FA) measures were calculated for limbic gray matter structures (amygdala-hippocampus complex, cingulate, parahippocampal gyrus, entorhinal cortex). Partial correlations were calculated between IPV perpetration, neuropsychiatric symptoms, and FA.

Results: Veterans with a diagnosis of PTSD, depression, substance use disorder, or mTBI had higher odds of perpetrating IPV. Greater war zone-related stress, and symptom severity of PTSD, depression, and mTBI were significantly associated with IPV perpetration. CTS2 (psychological aggression), a measure of IPV perpetration, was associated with higher FA in the right amygdala-hippocampus complex ($r = 0.400$, $p = 0.005$).

Conclusion: Veterans with psychiatric disorders and/or mTBI exhibit higher odds of engaging in IPV perpetration. Further, the more severe the symptoms of PTSD, depression, or TBI, and the greater the war zone-related stress, the greater the frequency of IPV perpetration. Moreover, we report a significant association between psychological aggression against an intimate partner and microstructural alterations in the right amygdala-hippocampus complex. These findings suggest the possibility of a structural brain correlate underlying IPV perpetration that requires further research.

KEYWORDS

perpetration of violence, diffusion magnetic resonance imaging, veterans, intimate partner violence, perpetration and victimization, traumatic brain injury, limbic system, psychiatric disorders

Introduction

Intimate partner violence (IPV) perpetration is highly prevalent among military veterans, with ~66 to 91% of veterans engaging in psychological aggression, and ~27% reporting physical assaults against their relationship partners (1). Psychological aggression refers to verbal and non-verbal behavior used to dominate, belittle, criticize, isolate, and instill fear in an intimate partner. Physical assault involves the intentional affliction of harm to an intimate partner through physical violence, including shaking, pushing, blows to the head or other parts of the body, and strangulation or other forms of impeded breathing (2). There are several factors that may contribute to the high prevalence of IPV among veterans. War zone-related trauma exposure and stress is tightly bound to the development of psychiatric disorders (3, 4), which, in turn, have been associated with IPV perpetration (5–7). In addition, psychiatric conditions commonly seen in veterans (e.g., posttraumatic stress disorder (PTSD), and depression) are linked to emotion regulation deficits (8–10). Such deficits may further contribute to the risk of perpetrating IPV. Comorbid substance abuse, which is commonly observed in veterans, may further amplify this link to IPV perpetration (11–14).

Moreover, there is a large overlap between psychiatric diagnoses and mTBI among veterans (15–18). Post-concussive symptoms generally subside after a couple of days or weeks following acute head injury (19). However, approximately 15 to 30% of those experiencing mTBI develop long-term impairments (19–21) that may persist even years after the sustained injury. These symptoms may include anger and aggressiveness (19–21) and may also increase the risk of IPV perpetration. While an association between persistent post-concussive symptoms and IPV perpetration has been suggested in a recent study (22), evidence is still limited and requires further investigation. Most importantly, rather than endorsing a direct causal link between mTBI or post-concussive symptoms and IPV perpetration, the individual contribution of post-concussive sub-components (i.e., physical and affective symptoms) needs to be taken into account. Additionally, despite the urgent need for preventive and treatment efforts in this population, even less is known about the underlying patho-mechanism of IPV perpetration among veterans who evince comorbidity of mTBI and psychiatric disorders. Neuroimaging research serves as a tool to unravel brain alterations associated with IPV perpetration, thereby opening the possibility of identifying brain correlates that may serve as treatment targets beyond routine interventions.

IPV perpetration and neuroimaging

War zone-related stress (23), post-deployment psychiatric disorders (24, 25), and mTBI (26) are associated with alterations in brain structure. While brain research in the population of IPV perpetrators is relatively scarce, magnetic resonance imaging (MRI) studies report altered brain function and structure associated with aggressiveness. More specifically, altered functional activity of the brain's limbic system [a brain circuit primarily

responsible for emotion processing (27)] in otherwise healthy individuals with high aggressiveness, and aggressive individuals with borderline and antisocial personality disorder has been reported (28–30). Moreover, decreased volume of the limbic system, particularly the amygdala, has been shown in individuals with aggressive behavior (29, 31, 32). In accordance with these findings, there is initial evidence that IPV perpetration is associated with greater functional activation in limbic areas (33) and smaller amygdala volume (34).

While IPV perpetration may be associated with altered limbic macrostructure, to date, a potential relationship between IPV perpetration and brain *microstructural alterations* has not yet been investigated. Alterations in brain microstructure may provide additional information about underlying abnormal neuronal processes (35, 36), such as tissue composition [e.g., glial changes (37–39), alterations in dendritic arborization (40–42)] or atrophic processes (43).

Diffusion-weighted MRI (dMRI) provides information on even subtle brain microstructural alterations by quantifying the motion of water molecules in tissue (44). Associations between altered limbic gray matter microstructure and war zone-related stress (23), psychiatric disorders (24, 25), and mTBI (26) have previously been reported, while findings on IPV perpetration are lacking.

Given the detrimental outcome of IPV perpetration and the immense overall economic burden of increased healthcare costs and criminal justice persecution (45), improved knowledge and understanding about the associated risk factors and underlying patho-mechanisms of IPV perpetration is needed to establish options for treatment and prevention.

In this study, comprised of a sample of US Iraq/Afghanistan veterans with available dMRI, neuropsychiatric, and IPV assessments, we focus on two core objectives. The first objective is to investigate the association between neuropsychiatric conditions and IPV perpetration. More specifically, we test the likelihood of perpetrating IPV (i.e., psychological aggression and physical assault) in the presence of neuropsychiatric disorders (i.e., PTSD, mood disorder, substance use disorder, or mTBI). Moreover, we test whether greater war zone stress, and neuropsychiatric symptom severity (i.e., PTSD, depressive, and post-concussive symptoms, and alcohol use) are associated with higher IPV perpetration frequency. In the second objective of the study, we employ dMRI to investigate whether IPV perpetration is associated with alterations in limbic gray matter microstructure that may improve our understanding of the neurobiological patho-mechanisms underlying IPV perpetration.

Methods

Participants

Veterans of the Iraq and Afghanistan wars (Operation Enduring Freedom/Operation Iraqi Freedom; OEF/OIF) were recruited as part of the Translational Research Center for TBI and Stress Disorders (TRACTS) study (46). Out of the first 384 consecutively recruited veterans, a small subset of 49 male veterans had assessments available on IPV perpetration, and structural and dMRI data. All 49 veterans consented to sharing their data with investigators outside of TRACTS and provided written informed consent. Study protocols were approved by the Institutional Review Board of the VA Boston Healthcare System.

Diagnostic and clinical assessment

Assessment of intimate partner violence

Perpetration of violence against a relationship partner in the past year was assessed using the *psychological aggression* and *physical assault* scales of the Revised Conflict Tactics Scales (CTS2) (47), a 78-item questionnaire referring to IPV. The frequency of psychological aggression (8 items: e.g., "I called my partner fat or ugly," "I shouted or yelled at my partner") and physical assault (12 items: e.g., "I beat my partner up," "I choked my partner," "I threw something at my partner that could hurt") were assessed on a 6-point scale (0 = *never* to 6 = *more than 20 times*). A summed score was computed from all of the items from each sub-scale (CTS2 psychological aggression and CTS2 physical assault).

Assessment of war zone-related stress

War zone-related stress was assessed with the combat experiences and post-battle experiences sub-scales of the Deployment Risk & Resilience Inventory (DRRI) (48). The DRRI sub-scales (DRRI-Combat and DRRI-Other) consist of 16 questions concerning combat or war zone-related events (e.g., DRRI-Combat: "I personally witnessed someone from my unit or an ally being seriously wounded or killed," DRRI-Other: "I saw civilians after they had been severely wounded or disfigured"). The DRRI-Combat uses a 5-point scale (0 = *never* to 4 = *daily or almost daily*), while the DRRI-Other scale uses a binary response format (0 = *no* and 1 = *yes*). Summed scores were computed from all items of each sub-scale.

Assessment of PTSD

Current diagnosis of PTSD and PTSD symptom severity were assessed using the 30-item Clinician-Administered PTSD Scale for DSM-IV (CAPS-IV) (49) which captures reexperiencing, avoidance and numbing, and hyperarousal symptoms of the traumatic event. Sub-scores for each sub-scale and a total PTSD symptom severity score were calculated by summing frequency and intensity scores rated from 0 = *absent* to 4 = *extreme/incapacitating*.

Assessment of depression

Mood disorder was diagnosed with the non-patient research version of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/NP) (50). Depression severity was assessed with the Depression, Anxiety and Stress Scale 21-items (DASS-21) (51). The depression sub-scale comprises seven items (e.g., "I felt down-hearted and blue," "I felt I wasn't worth much as a person") that are scored from 0 = *did not apply to me at all* to 3 = *applied to me very much or most of the time*. Scores of the seven items were summed into a total score.

Assessment of substance use and drinking history

Substance use disorder was diagnosed with the non-patient research version of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/NP) (50). Lifetime burden of alcohol consumption was estimated using a retrospective, interview-based procedure measuring total lifetime exposure to alcohol by assessing

the number of standard drinks consumed (lifetime drinking history total).

Assessment of mild traumatic brain injury and post-concussive symptoms

History of mTBI was assessed using the Boston Assessment of TBI-Lifetime (BAT-L) (52). The BAT-L classifies a TBI as mild if loss of consciousness equals 30 min or less, and posttraumatic amnesia or an altered mental status does not exceed 24 h. Mild TBI is further classified into grade 1–3, where a higher grade refers to greater mTBI severity. A total mTBI frequency and severity score was computed from the number and severity of all mTBIs prior to, during, and post-military deployment.

Post-concussive symptoms during the last two weeks were assessed using the Neurobehavioral Symptom Inventory (NSI), a 22-item self-report questionnaire (53). Severity of vestibular, somatosensory, cognitive, and affective persistent post-concussive neurobehavioral symptoms (e.g., "feeling dizzy," "headaches," "difficulty making decisions," "feeling anxious") were rated on a 5-point scale (0 = *none* to 4 = *very severe*). Sub-scores for each sub-scale, as well as a summed total score, were calculated.

Magnetic resonance imaging

Image acquisition

MRI data were acquired on a 3-Tesla Siemens TIM Trio scanner (Siemens Healthcare, Erlangen, Germany) at the VA Medical Center in Boston, MA, United States. T1-weighted structural MPRAGE scans (256 slices, T1 = 1,000 ms, TR = 2,530 ms, TW = 3.32 ms, voxel size = 1 mm^3, flip angle = 7°, FOV = 256 × 256 mm^2) and dMRI scans using a single-shot echo-planar sequence with a twice-refocused spin-echo pulse (64 axial slices with no inter-slice gap, 60 gradient directions with a *b*-value of 700 s/mm^2 and 10 additional scans with *b* = 0 gradients, TR = 10.000 ms, TE = 103 ms, voxel size = 2 mm^3, FOV = 256 mm^2) were obtained.

Image processing

Pre-processing of the structural T1-weighted and dMRI data was performed using our in-house image processing pipeline. First, the images were axis-aligned, centered, and motion-corrected. DMRI data was corrected for eddy current effects using the FMRIB Software Library (version 5.1) (54, 55). Image quality of T1-weighted and dMRI data was checked for artifacts using the 3D Slicer program (version 4.5) (56). T1-weighted and diffusion masks covering the entire brain were automatically created and manually corrected in 3D Slicer where necessary. Automated segmentation of brain regions from T1-weighted data was performed using FreeSurfer (version 5.1.0) (57).

Using in-house software (58), free-water (FW) imaging was also implemented to obtain voxel-wise free-water corrected fractional anisotropy (FA) measures for each participant. By separating the MRI signal into two compartments (58), FW imaging is able to eliminate partial volume with extracellular FW [e.g., caused by cerebrospinal fluid (CSF) contamination, edema, or atrophy] in each voxel. Given the correction for FW, FA serves as a more accurate marker for tissue than the conventional FA measure (59). FreeSurfer parcellation label maps were non-linearly registered from the individual T1-weighted space to the respective diffusion MRI space to obtain diffusion metrics for selected limbic regions (amygdala-hippocampus complex, cingulate, entorhinal, and parahippocampal cortex). Amygdala and hippocampus were combined into one region of interest to ensure higher parcellation accuracy (60). Average diffusion measures (FA) were calculated for limbic gray matter structures.

Statistical analysis

Descriptive statistics for demographic and clinical variables were performed using IBM SPSS Statistics 27 (61). A false discovery rate (FDR)-corrected (62) *p*-value of 0.05 was chosen to indicate statistical significance.

IPV perpetration and neuropsychiatric conditions

Percentages were calculated to display the proportion of veterans who engaged in IPV perpetration (i.e., psychological aggression; physical assault). Odds ratios were calculated to portray the odds of IPV perpetration in veterans with PTSD, mood disorder, substance use disorder, or mTBI. To assess the associations between neuropsychiatric symptom severity and IPV perpetration frequency, we calculated partial correlations between frequency of IPV perpetration (CTS2 psychological aggression and CTS2 physical assault) and (1) war zone-related stress (combat and post-battle experiences), (2) psychiatric symptoms (PTSD symptoms, depressive symptoms, lifetime drinking), and (3) mTBI (mTBI frequency and severity, post-concussive symptoms). Age was included as a covariate.

Associations between limbic microstructure and IPV perpetration

To assess whether IPV perpetration was linked to brain structural alterations, we calculated partial correlations between frequency of IPV perpetration (CTS2 psychological aggression and CTS2 physical assault) and limbic microstructure (left/right amygdala-hippocampus complex, cingulate, parahippocampal gyrus, entorhinal cortex FA). Age was included as a covariate. In an additional step, clinical risk factors that showed significant correlations with IPV perpetration were included as covariates.

CTS2 physical assault perpetration deviated from normality according to the Kolmogorov–Smirnov test ($D = 0.405(49)$, $p < 0.001$). We, thus, performed non-parametric partial correlations between frequency of CTS2 physical assault and war zone-related stress, psychiatric and mTBI symptoms and limbic microstructure.

Results

IPV perpetration and neuropsychiatric conditions

Sample characteristics are displayed in Table 1. In the total sample ($N = 49$), the following neuropsychiatric conditions were present: PTSD ($n = 28$, 57.143%), mood ($n = 12$, 24.490%), substance disorder ($n = 9$, 18.367%), and mTBI ($n = 32$, 65.306%). Notably, there was substantial overlap of the neuropsychiatric diagnoses (Figure 1), meaning that the majority of individuals had more than one diagnosis.

TABLE 1 Sample characteristics ($N = 49$).

		Mean ± SD	Range
Age (years)		32.939 ± 8.368	21–55
Number of OEF/OIF deployments		1.265 ± 0.491	1–3
Number of other stressful deployments		0.388 ± 0.786	0–3
Total duration of OEF/OIF deployments (months)		12.714 ± 6.745	3–29
Total duration of other deployments (months)		2.939 ± 8.063	0–49
CTS2 psychological aggression perpetration		10.531 ± 8.282	0–32
CTS2 physical assault perpetration		0.633 ± 1.270	0–6
Race		*n*	%
	American Indian or Alaska Native	0	0.000
	Asian	0	0.000
	Black	5	10.204
	Hispanic or Latino	3	6.122
	Native Hawaiian or Pacific Islander	0	0.000
	White	41	83.673
Service branch			
	Army	8	16.327
	Army National Guard	18	36.735
	Air Force	6	12.245
	Air Force National Guard	6	12.245
	Coast Guard	0	0.000
	Navy	3	6.122
	Marines	8	16.327
	Reserves	2	4.041
Neuropsychiatric diagnoses			
Psychiatric diagnoses	PTSD	28	57.143
	Mood disorder	12	24.490
	Substance use disorder	9	18.367
mTBI	Lifetime mTBI	32	65.306

SD, Standard deviation; OEF, Operation Enduring Freedom; OIF, Operation Iraqi Freedom; PTSD, Post-traumatic stress disorder; mTBI, Mild traumatic brain injury. Psychiatric diagnoses are indicated as lifetime diagnoses. % of total N. participants may fall into multiple categories.

The frequency of psychological aggression and physical assault in the context of neuropsychiatric diagnoses is shown in Figure 2.

Forty-three veterans (87.755%) engaged in psychological aggression against their intimate partners, and 14 (28.571%) exerted physical assault at least once or twice during the past year. Frequency of IPV perpetration (none to severe) is displayed in Figure 3. Veterans with PTSD, mood disorder, substance use disorder, and mTBI had higher odds of engaging in IPV perpetration compared to those with none of these afflictions (Figure 4).

This figure displays the frequency of IPV perpetration (i.e., psychological aggression and physical assault).

This figure displays the odds of IPV perpetration (i.e., psychological aggression and physical assault) in veterans with PTSD, mood disorder, substance use disorder, and mTBI. Please note that there is a large overlap of neuropsychiatric diagnosis and mTBI among veterans (15–18). Of the total sample ($N = 49$), 12 participants were diagnosed with one single neuropsychiatric diagnosis (24.49%). Most individuals were diagnosed with more than one disorder ($n = 28$, 70% of the individuals with a neuropsychiatric diagnosis; please refer to Figure 1).

Partial correlations showed significant associations between higher scores on CTS2 psychological aggression and greater war zone-related stress, PTSD, depressive, and post-concussive symptoms (Table 2). Moreover, CTS2 psychological aggression was significantly associated with all PTSD sub-scales (reexperiencing; avoidance and numbing; and hyperarousal symptoms) and with all post-concussive sub-scales (vestibular; somatosensory; cognitive; and affective symptoms). In contrast, higher scores on the CTS2 physical assault measures were significantly associated with greater post-concussive symptoms, and with PTSD, and depressive symptoms, although only correlations between avoidance and numbing symptoms of PTSD, and vestibular, somatosensory, and cognitive sub-symptoms of post-concussive symptoms were significant (Table 2). Associations between CTS2 psychological aggression and physical assault with lifetime drinking failed to reach significance.

Associations between IPV perpetration and limbic microstructure

Higher scores on CTS2 psychological aggression were significantly associated with higher FA in the right amygdala-hippocampus complex ($r = 0.400$, $p = 0.005$, Table 2, Figure 5). This association remained significant when additionally controlling for war zone-related stress, PTSD, depressive, and post-concussive symptoms ($r = 0.389$, $p = 0.011$). There was no significant association between CTS2 physical assault and limbic microstructure.

Discussion

In the present study, OEF/OIF veterans diagnosed with PTSD, mood disorder, substance use disorder, or mTBI had increased odds of perpetrating IPV (i.e., psychological aggression and physical assault). Moreover, greater war zone-related stress, PTSD, depressive, and post-concussive symptoms were significantly associated with increased IPV perpetration frequency, while lifetime drinking failed to reach significance. The diffusion imaging analysis of limbic microstructure showed a significant association between greater IPV psychological aggression and higher FA in the right amygdala-hippocampus complex, suggesting the possibility of a structural brain correlate underlying IPV perpetration that requires further investigation.

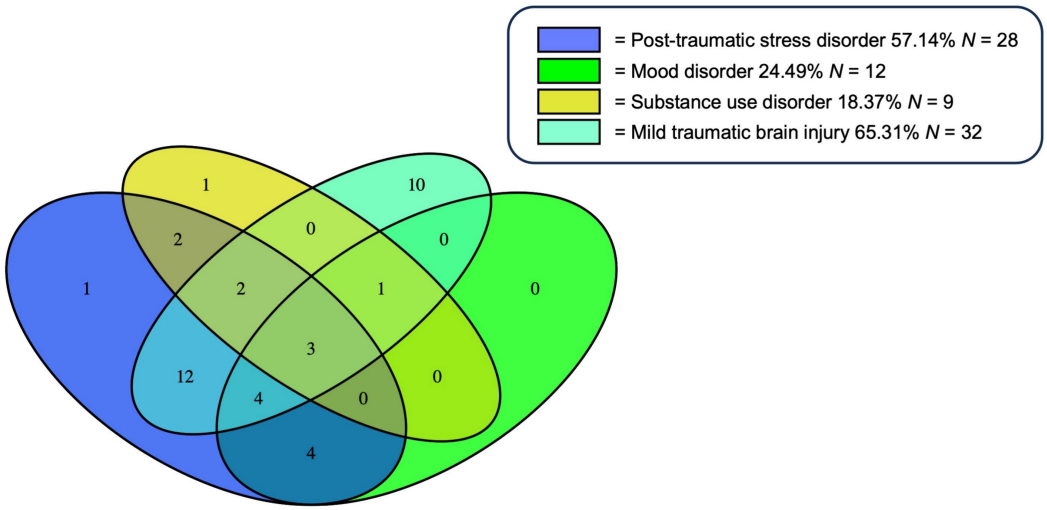

FIGURE 1
Overlap of Neuropsychiatric Diagnoses. % of total *N* (=49). Of the total sample (*N* = 49), 40 participants had at least one but often times multiple neuropsychiatric diagnoses. This Venn diagram illustrates the overlap of the neuropsychiatric diagnoses: Posttraumatic stress disorder (PTSD), mild traumatic brain injury (mTBI), substance use, and mood disorder. Percentages given for each diagnosis in the legend represent the proportion in relation to the total sample (*N* = 49). Of note, the sum of all percentages does not equal 100% due to comorbidity of multiple diagnoses in some participants.

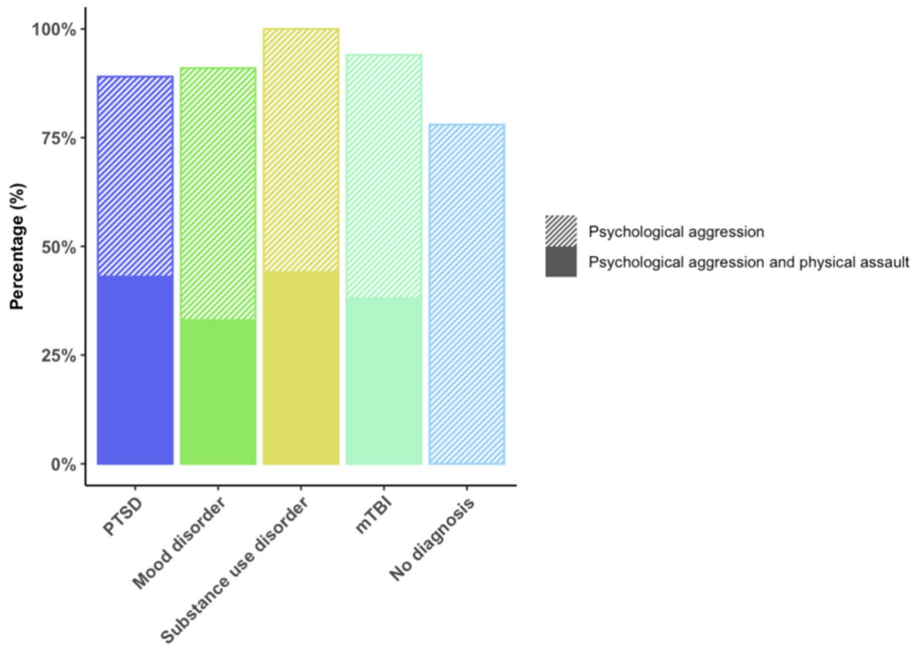

FIGURE 2
Frequency of psychological aggression and physical assault in the context of neuropsychiatric diagnoses. % of psychological aggression or combined psychological aggression and physical assault among veterans with the respective neuropsychiatric diagnosis.

IPV perpetration and neuropsychiatric conditions

Consistent with previous findings (1), we found that approximately 90% of veterans in this study perpetrated psychological aggression and approximately 30% physically assaulted their relationship partner at least once or twice during the past year. We also observed higher odds of IPV perpetration in veterans with psychiatric disorders (i.e., PTSD, mood, substance use disorder) and mTBI. Most remarkably, veterans with PTSD had six times higher odds of physically assaulting their relationship partners than those without PTSD. While several psychiatric disorders have been associated with an increased likelihood of IPV perpetration (14, 63), a particularly strong relationship between PTSD and IPV perpetration has repeatedly been

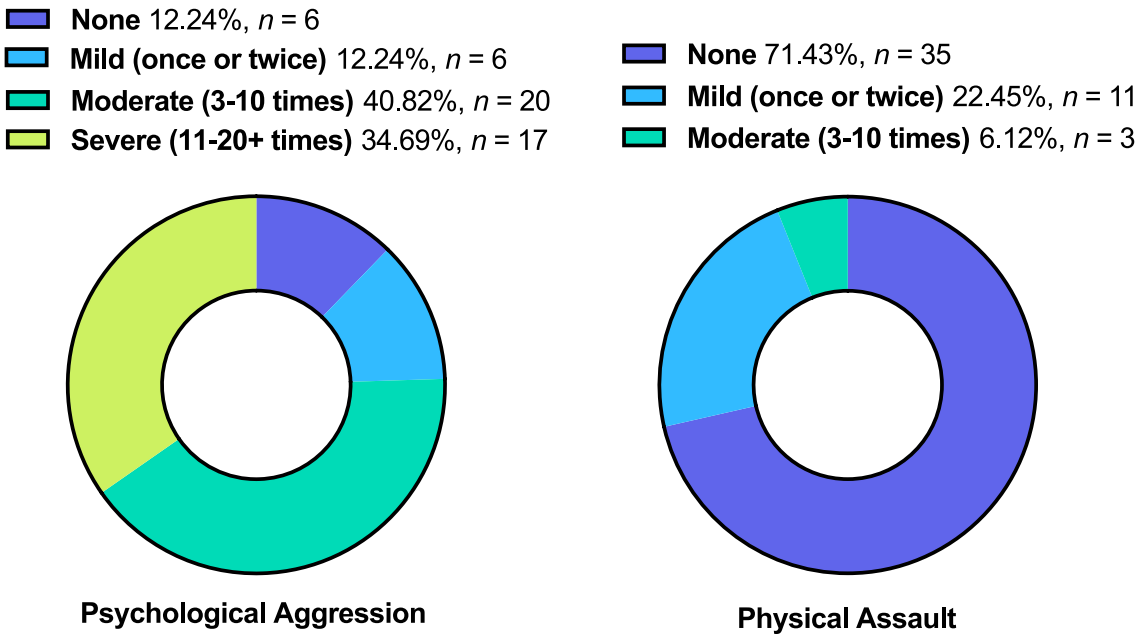

FIGURE 3
Frequency of IPV Perpetration. % of total (*N* =49). This figure displays the frequency of IPV perpetration (i.e., psychological aggression and physical assault).

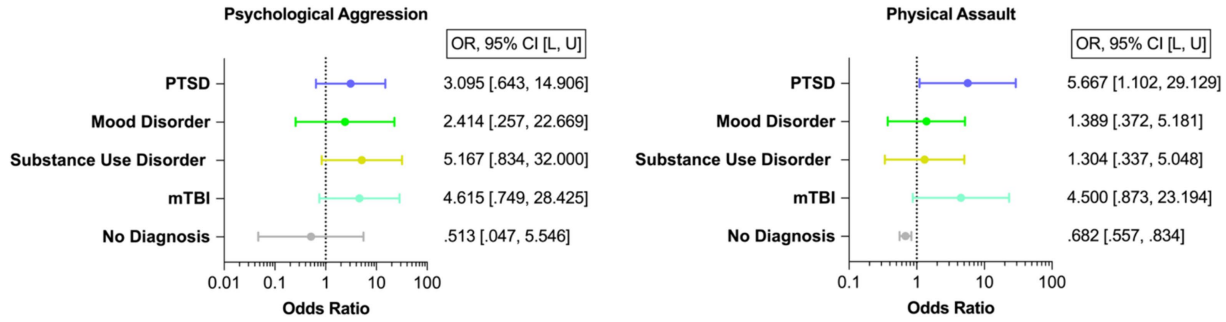

FIGURE 4
Odds of IPV Perpetration. PTSD, Post-traumatic stress disorder; mTBI, Mild traumatic brain injury. This figure displays the odds of IPV perpetration (i.e., psychological aggression and physical assault) in veterans with PTSD, mood disorder, substance use disorder, and mTBI. Please note that there is a large overlap of neuropsychiatric diagnosis and mTBI among veterans. Of the total sample (*N* = 49), 12 participants were diagnosed with one single neuropsychiatric diagnosis (24.49%). Most individuals were diagnosed with more than one disorder (*n* = 28, 70% of the individuals with a neuropsychiatric diagnosis; please refer to Figure 1).

observed (64). However, it is important to note the preliminary nature of the current study due to the limited sample size.

Anger and aggressiveness are common features of PTSD (65), and the hyperarousal symptoms of PTSD have been especially associated with an increased likelihood of perpetrating IPV (66–69). Individuals with PTSD experience a hyper aroused "survival mode" state (70), constantly scanning their environment for potentially threatening triggers to be prepared for fight or flight (71). It has been suggested that there is a hypersensitivity to even mildly threatening affective provocations that the perpetrator may be unable to control and deal with appropriately (72).

Interestingly, while reexperiencing, avoidance and numbing and hyperarousal symptoms of PTSD were all associated with psychological aggression perpetration, it was only avoidance and numbing symptoms that were significantly associated with physical assault perpetration. Thus, while associations between reexperiencing, hyperarousal, and physical assault may have failed to reach significance due to the limited overall sample size and limited variance in the physical assault measure, there, nonetheless, appears to be a particularly strong connection between avoidance and numbing and emotion regulation deficits.

Individuals with PTSD who perpetrate IPV often exhibit information processing and emotion regulation deficits, therefore misinterpreting their partners intentions. This may lead to excessive rage that translates into violence (8, 73, 74). Further, avoidance of unpleasant memories or thoughts is a maladaptive emotion regulation strategy that disrupts the process of integrating traumatic memories (75) and may, therefore, reinforce a volatile internal environment that

TABLE 2 Associations between IPV perpetration, war zone-related stress, Psychiatric symptoms, mTBI, and limbic microstructure.

			Psychological aggression			Physical assault		
	N	mean ± SD	*r*	*p*	*p**	*r*	*p*	*p**
War zone-related stress								
Combat experiences	48	13.686 ± 11.591	0.401	**0.005**	**0.005**	−0.105	0.489	0.883
Post-battle experiences	48	6.729 ± 5.069	0.494	**<0.001**	**<0.001**	0.022	0.883	0.883
Psychiatric symptoms								
PTSD	49	44.265 ± 29.492	0.537	**<0.001**	**<0.001**	0.303	**0.036**	0.072
Reexperiencing	49	12.000 ± 9.478	0.411	**0.004**	**0.006**	0.265	0.068	0.102
Avoidance and numbing	49	16.388 ± 12.369	0.513	**<0.001**	**<0.001**	0.350	**0.015**	0.072
Hyperarousal	49	15.878 ± 10.262	0.540	**<0.001**	**<0.001**	0.248	0.089	0.107
Depression	49	6.898 ± 8.347	0.362	**0.011**	**0.013**	0.309	**0.033**	0.072
Lifetime drinking	48	1814.337 ± 2294.930	0.242	0.104	0.104	−0.106	0.478	0.478
Mild traumatic brain injury								
mTBI frequency and severity	49	1.816 ± 2.555	0.199	0.176	0.352	0.170	0.249	0.249
Post-concussive symptoms	49	18.408 ± 16.647	0.447	**0.001**	**0.002**	0.367	**0.010**	**0.020**
Vestibular	49	1.000 ± 1.607	0.474	**0.001**	**0.004**	0.424	**0.003**	**0.012**
Somatosensory	49	3.939 ± 4.105	0.342	**0.017**	**0.017**	0.326	**0.024**	**0.032**
Cognitive	49	4.408 ± 4.518	0.350	**0.015**	**0.017**	0.371	**0.010**	**0.020**
Affective	49	7.551 ± 6.810	0.421	**0.003**	**0.006**	0.248	0.089	0.089
Gray matter fractional anisotropy								
Left amygdala-hippocampus complex	49	0.350 ± 0.017	0.199	0.175	0.467	0.206	0.161	0.641
Left cingulate	49	0.247 ± 0.013	0.141	0.340	0.605	0.141	0.339	0.641
Left entorhinal cortex	49	0.315 ± 0.030	−0.210	0.153	0.467	0.042	0.776	0.858
Left parahippocampal gyrus	49	0.293 ± 0.028	0.055	0.711	0.813	0.128	0.387	0.641
Right amygdala-hippocampus complex	49	0.353 ± 0.016	0.400	**0.005**	**0.040**	0.219	0.135	0.641
Right cingulate	49	0.284 ± 0.019	0.111	0.454	0.605	0.104	0.481	0.641
Right entorhinal cortex	49	0.317 ± 0.034	0.031	0.834	0.834	−0.026	0.858	0.858
Right parahippocampal gyrus	49	0.283 ± 0.023	0.116	0.431	0.605	0.117	0.429	0.641

SD, Standard deviation; IPV, Intimate partner violence, PTSD, Post-traumatic stress disorder, mTBI, Mild traumatic brain injury. FA, Fractional anisotropy tissue. Psychological aggression and Physical assault, Sub-categories of the Revised Conflict Tactics Scales (CTS2). All analyses were controlled for age. *p** False Discovery Rate (FDR) corrected *p*-value.

may contribute to impulsive or aggressive behavior as a means of releasing or managing overwhelming emotions.

Deficiencies in emotion processing and regulation have similarly been observed in individuals suffering from a mood disorder (9, 76), which may explain the link between depression and IPV perpetration (14, 77, 78). The depressed perpetrator interprets their intimate partner's behavior as negative or intentional and is, therefore, more inclined to engage in psychological and physical violence (78).

In addition, our findings confirm previous reports of greater odds of IPV perpetration in veterans with substance use disorder (79, 80). Intoxication impairs rational cognitive functioning and diminishes behavioral inhibition, lowering an individual's threshold to engage in violence (81). Moreover, substance abuse reinforces PTSD and depressive symptoms, further exacerbating the risk of IPV perpetration (82). Previous studies have shown that alcohol use may moderate the relationship between other risk factors (i.e., PTSD, depression) and IPV perpetration (83–85). While we report higher odds of IPV perpetration in veterans with a clinician-diagnosed substance use disorder, alcohol use frequency, in and of itself, in the absence of a diagnosis of substance abuse, was not significantly associated with IPV perpetration. Thus, despite the well-established link between alcohol use and IPV perpetration (11–14, 86), our study did not reveal a significant association between lifetime drinking history and IPV perpetration. This discrepancy may be attributed to the nuanced nature of the relationship between alcohol and IPV perpetration, where diagnosable alcohol use disorder could be a more

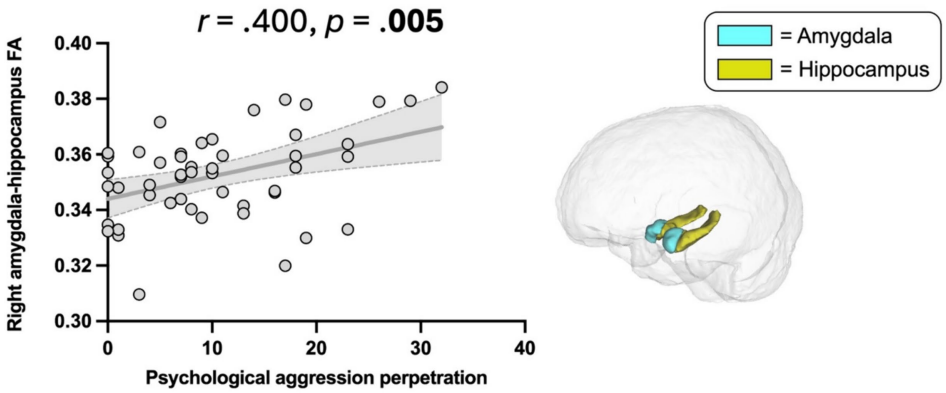

FIGURE 5
Association between Psychological aggression perpetration and amygdala-hippocampus complex FA. Psychological aggression, revised conflict tactics scales (CTS2) (47); FA, Fractional anisotropy. Scatter plot illustrating the significant correlation between psychological aggression perpetration and higher FA in the right amygdala-hippocampus complex ($p = 0.005$).

critical factor than mere frequency of alcohol consumption. Notably, in our study only $n = 9$ veterans qualified for a diagnosable substance use disorder. It is, thus, possible that the limited variance in the data and the small sample size of those with a diagnosable substance use disorder may have impacted our ability to detect an effect. Moreover, of the $n = 9$ veterans with substance use disorder, $n = 8$ were also diagnosed with PTSD, mTBI, or a mood disorder.

Our study's unique contribution lies in shedding light on the complex interplay of neuropsychiatric symptoms and IPV perpetration among veterans. It is crucial to recognize that while alcohol use is a relevant factor, its relationship with neuropsychiatric conditions, such as PTSD, mTBI and depression, may have a more direct impact on the risk of IPV perpetration. Future research, employing larger samples and multivariate statistical modeling, can probe these intricate relationships, offering a more nuanced understanding of the factors influencing IPV within the veteran population.

IPV perpetration and post-concussive symptoms

Remarkably, there is also a high overlap between psychiatric and persistent post-concussive symptoms, and both have been shown to be associated with IPV perpetration. Particularly interesting, we observed significant associations between post-concussive symptoms and IPV perpetration, while there was no significant relationship between the number of sustained mTBIs and IPV perpetration. A recent veteran study revealed similar findings, reporting that only persistent post-concussive symptoms but not TBI diagnosis itself predicted IPV perpetration at a one-year follow-up (22). Indeed, there are some indications that it may not be those who experience mTBI, but rather a minority of individuals who develop persistent post-concussive symptoms, who are at risk for engaging in IPV (22, 87).

Post-concussive symptoms greatly overlap with psychiatric symptoms and especially comorbidity with PTSD is common in the veteran population (10, 17). However, the analysis of the sub-components of persistent post-concussive neurobehavioral symptoms in our study revealed that not only the cognitive and affective post-concussive symptoms but also vestibular and somatosensory symptoms were associated with IPV perpetration.

Vestibular symptoms may encompass dizziness, vertigo, and general problems with balance and spatial orientation, while somatosensory symptoms include headaches, sensitivity to light and noise or vision problems. It has previously been shown that physical health conditions lead to higher odds of perpetrating IPV (88), as physical health conditions are often associated with discomfort or even pain that has been shown to increase aggressive behavior (89). It has been argued that increased stress due to physical health complaints depletes stress regulation resources, thus enabling aggressive behaviors. Moreover, Individuals with physical health issues may experience a sense of diminished control over their own bodies which they may compensate by attempting to exert control over their partners (88). It is also conceivable that physical health complaints lead to significant emotional distress that further reinforces a relationship with IPV perpetration. Moreover, affective symptoms including anxiety, depression, and irritability as well as cognitive complaints such as poor concentration, forgetfulness and difficulty making decisions are common long-term symptoms following mTBI. Cognitive and affective complaints may lead to poor frustration tolerance. Indeed, post-concussive symptoms have been found to significantly interfere with emotion regulation and psychosocial functioning (10), potentially explaining the link with IPV perpetration (90). Interestingly, it has even been suggested that deficits in emotion regulation can discern between those who do or do not perpetrate violence (91). Thus, addressing emotion regulation deficits emerges as a critical factor in facilitating the recovery of both psychiatric and post-concussive symptoms (92). In doing so, interventions have the potential to mitigate the impact of these symptoms and to proactively prevent acts of violence.

Associations between limbic microstructure and IPV perpetration

We showed a significant association between psychological aggression perpetration and higher FA of the right

amygdala-hippocampus complex. Higher gray matter FA may reflect greater tissue density, and an enhanced tissue organization through strengthened axonal and dendritic connections (35, 36, 40–42). To date, findings on gray matter diffusion in psychiatric samples are limited. We previously showed an association between higher FA of the amygdala-hippocampus complex and greater war zone-related stress (23) and PTSD symptoms (24), suggesting that stress-related experiences alter limbic microstructural integrity. Similarly, increased diffusion in several regions (including the amygdala and hippocampus) was shown in individuals with persistent post-concussive symptoms following mTBI compared to controls (26). In accordance with these findings, our study revealed an association between higher amygdala-hippocampus FA and greater psychological aggression perpetration frequency. We speculate that our findings may constitute a brain structural reflection of the previously observed greater amygdala and hippocampus activity that coincides with IPV perpetration (33, 72).

Hyperresponsivity of the amygdala and related limbic structures is not only a core feature of violence perpetration (33, 72, 93, 94), but also of PTSD symptomatology (95–100) and the associated emotion regulation deficits (101). Similarly, individuals with post-concussive symptoms exhibit functional and structural alterations of the amygdala that have been linked to emotion dysregulation (102, 103). The amygdala and hippocampus are vulnerable to extensive stress hormone exposure (104, 105) and the adverse effects of head impacts (106–108), contributing to the emergence and maintenance of both post-concussive symptoms and PTSD symptoms (109–111). Moreover, since the amygdala is immediately activated in threatening situations (112) and the hippocampus is crucial for memory retrieval and consolidation (113), it has been suggested that even in response to only mildly threatening situations, the IPV perpetrator may remember previous encounters of threat and social conflict that elicit inappropriate hyperarousal and consequent psychological abuse or physical assault (72). Indeed, it has been suggested that IPV perpetrators have lower perspective-taking abilities in the face of greater personal distress (114), show deficits in information processing, and misinterpret their partners intentions (73). In turn, constant hyperarousal states prohibit the adequate judgment of social cues, and increase the likelihood of misinterpreting them for malicious intentions which may further translate into violence perpetration (70, 73).

Notably, our findings persisted even when accounting for PTSD, depressive, and post-concussive symptoms, suggesting that amygdala microstructure is associated with psychological aggression above and beyond other clinical risk factors for IPV perpetration. A potential explanation may be the link between emotion dysregulation and IPV perpetration (115). Indeed, it has previously been shown that emotion dysregulation fully accounts for the association between PTSD and IPV perpetration (74).

Interestingly, we demonstrated an association between psychological aggression perpetration and enhanced amygdala-hippocampus microstructure only in the right hemisphere. The right amygdala has been suggested to be particularly involved in affective information retrieval (116) and unconscious information processing (117). Unconscious threat perception elicits inappropriate hyper-aroused reactions that may translate into violence (72). The right hemisphere, and particularly the right amygdala may, thus, contribute to violent outbursts through emotion dysregulation and information processing deficits. To date, one study linked right amygdala volume to IPV perpetration (34). Others, however, have associated violence perpetration with the left amygdala, showing an increased connectivity between limbic and paralimbic structures in the left hemisphere of violent offenders (94). Future research needs to address whether IPV perpetration is associated with lateralization of limbic structural alterations.

While we report a significant association between higher FA in the amygdala-hippocampus complex, we did not detect significant associations between the cingulate, parahippocampal gyrus, entorhinal cortex, and IPV perpetration. The amygdala-hippocampus complex has well-established roles in emotional processing and memory, both relevant to IPV perpetration. It is possible that the surrounding limbic structures – while part of a larger operating network responsible for emotional processing – are not the primary loci for the specific behavior under consideration. Moreover, the multifaceted nature of IPV, with psychological and physical components explored in this study, could mean that different brain regions contribute to distinct aspects of the behavior. The limited overall sample size in our sample poses challenges, as the variability might not have been sufficient to establish a robust relationship with structural alterations in these particular brain regions. It is possible that our sample of 49 veterans was not sufficiently powered to detect a significant relationship between IPV perpetration and microstructural alterations. Moreover, while a large proportion of veterans in our sample engaged in moderate or even severe psychological aggression perpetration (~90% $N = 43$), only a minority third reported physical assaults (~30% $N = 14$). Consequently, there may not have been enough variance in the physical assault measure to capture a relationship with brain alterations. Further research with more robust samples is warranted to deepen our understanding of the nuanced neural underpinnings of IPV perpetration.

Limitations and future directions

We acknowledge several study limitations. First, our findings are based on a relatively small sample of male military veterans. Consequently, the results of the current study represent preliminary results that require validation in larger and more diverse samples for robustness and generalizability. A replication of our study using a larger sample size and including female perpetrators is required. It is worth noting that according to the Centers for Disease Control and Prevention (CDC), approximately 1 in 2 women and 2 in 5 men have reported experiencing contact sexual violence, physical violence, and/or stalking victimization by an intimate partner at some point in their lifetime (118). While studies have shown that men are more likely to perpetrate physical violence against intimate partners (119, 120), it is important to acknowledge that women can also be engage in IPV, and their perpetration may manifest in different forms. Moreover, underreporting of IPV is common due to various factors such as stigma, fear, and cultural norms. Additionally, research on IPV perpetration by females is still evolving, and further studies are needed to better understand the prevalence and dynamics of female-perpetrated IPV. Second, our findings result from a cross-sectional study design, meaning that we cannot infer causality between the studied variables. While we assume that deployment-related mental health issues fuel IPV perpetration, it is similarly possible that IPV perpetration reinforces the emergence and maintenance of neuropsychiatric symptoms. Third, we captured psychological aggression and physical assault perpetration, but not sexual abuse, which may require special preventive and treatment efforts. In general, therapeutic options for IPV perpetration may particularly focus on PTSD alleviation, as successful PTSD treatment reduces anger and aggressiveness among veterans (121, 122). In turn, specific anger and

aggression management programs for veterans may lower PTSD and related symptoms and improve anger expression. For example, STEP-Home is a transdiagnostic civilian reintegration 12-week workshop for 9/11 veterans, specifically designed to improve emotional regulation and impulse control, thereby decreasing anger and aggressiveness (123). In addition, novel treatment options, such as neurofeedback, may assist with regulating amygdala activity and, thus, control overreactive emotional states that lead to violence (124–126). Fourth, early life stress and childhood trauma history was not directly assessed in this study, despite their previously reported association with brain structure and function (127). Future studies should consider incorporating direct assessment measures such as the Childhood Trauma Questionnaire (CTQ) (128). Last, the analysis of gray matter diffusivity comes with resolution constraints, limiting the characterization of microstructural features. The complexity of gray matter organization poses challenges in accurately discerning diffusion orientations and partial volume effects arising from the proximity of gray matter to cerebrospinal fluid and white matter, impacting measurement precision. Despite our attempts to limit these issues using free-water modeling, the FA measure remains unspecific and is only an approximation of underlying microstructural characteristics.

Conclusion

Veterans with psychiatric disorders and/or mTBI exhibit higher odds of engaging in IPV perpetration. Further, the more severe the symptoms of PTSD, depression or mTBI, and the greater the experienced war zone-related stress, the greater the frequency of IPV perpetration. Emotion regulation and information processing deficits may underlie the link between neuropsychiatric symptoms and IPV perpetration. Moreover, we report a significant association between psychological aggression against an intimate partner and microstructural alterations in the right amygdala-hippocampus complex. The findings suggest the possibility of a structural brain correlate underlying IPV perpetration which may constitute a brain structural reflection of previously reported limbic hyperresponsivity during aggressive states.

Author's note

SH's contribution to this body of work represents his own expertise and opinions and should not be viewed as the opinion of the Uniformed Services University, Defense Health Agency, Department of Defense, or the Federal government.

Data availability statement

The data are not publicly available because the dataset contains information that could compromise the privacy of research participants. The data that support the findings of this study are available upon reasonable request.

Ethics statement

The studies involving humans were approved by Institutional Review Board VA Boston Healthcare System. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

PR: Conceptualization, Data curation, Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. CH: Conceptualization, Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. JS-H: Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing. EK: Data curation, Methodology, Writing – original draft, Writing – review & editing, Validation. VS: Data curation, Methodology, Writing – original draft, Writing – review & editing. LB: Visualization, Writing – original draft, Writing – review & editing. LP: Visualization, Writing – original draft, Writing – review & editing. YR: Methodology, Software, Writing – original draft, Writing – review & editing. SB: Methodology, Software, Writing – original draft, Writing – review & editing. OP: Methodology, Software, Writing – original draft, Writing – review & editing. DS: Writing – original draft, Writing – review & editing. SH: Writing – original draft, Writing – review & editing. CE: Conceptualization, Validation, Writing – original draft, Writing – review & editing. CF: Resources, Validation, Writing – original draft, Writing – review & editing, Conceptualization, Investigation. WM: Conceptualization, Investigation, Resources, Validation, Writing – original draft, Writing – review & editing. MS: Conceptualization, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. IK: Conceptualization, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing.

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Conflict of interest

IK is a professor at Ludwig-Maximilians-University Munich (paid position). She serves as European Editor at Journal of Neurotrauma (unpaid position) and as Vice President of the European Neurotrauma Organization (unpaid position). She receives research grant funding from the National Institutes of Health, the European Research Council, the German Ministry for Research and Education. She receives funding for a research study on sport-related concussion from Abbott Inc. The Ludwig-Maximilians-University hospital received donations for her research from the Schatt Foundation and from Mary Ann Liebert Inc. She receives royalties for book chapters published by Thieme Publishers. Her spouse is employee at Siemens and she thus holds stock options at Siemens and Siemens Healthineers. IK's in-kind contributions: PhD students working under her supervision receive scholarships from the Villigst Foundation, the Konrad Adenauer Foundation, the Studienstiftung des deutschen Volkes, the China Scholarship Council collaboration with Ludwig-Maximilians-University Munich, the Harvard Munich Club, and Fulbright. MS is Professor of Psychiatry and Radiology at Harvard Medical School and is employed by Brigham and Women's Hospital. She has grant funding from the National Institute of Mental Health and formerly from VA Merit Awards and from the National Institute of Neurological Diseases and Stroke. She serves on the editorial board of several professional journals (unpaid), on NIH study sections (Honoria minimum), and she receives royalties for book chapters and books published by Thieme Publishers, Elsevier, and Cambridge University Press (minimal). She receives funding also for legal cases as a consultant and an expert witness related to mild traumatic brain injury and the use of diffusion tensor imaging in the courtroom. MS's in-kind contributions include PhD, MD, MD-PhD trainees and junior faculty working under her mentorship, many of whom have received K awards and grant support for their research. EK received speaker honoraria and financial compensation for travel expenses from Medtronic, UCB, Livanova, and Eisai and has participated in clinical trials for Medtronic, UCB and Precisis, all unrelated to the submitted work. Her research is supported by the Medical Clinical Scientist Program (MCSP). SH is a retired United States Army Medical Corps Officer. He is a consultant for the National Football League Players Association, Major League Soccer Players Association, SCS Consulting LLC. He is an advisory board member for the Project Enlist (Veterans Advisory Board of the Concussion Legacy Foundation), NanoDX, Prevent Biometrics, Owl Therapeutics Inc., University of Michigan Concussion Center, and Collaborative Neuropathology Network Characterizing Outcomes of TBI (CONNECT-TBI). He is a co-PI for the Long-term Impact of Military-relevant, Brain Injury Consortium – Chronic Effects of Neurotrauma Consortium (LIMBIC-CENC).

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Publisher's note

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Gender and race in neurotrauma: part 1-identifying inequalities in leadership, academics, and clinical trial management

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Gender and racial equality, or the lack thereof, is a constantly recurring theme in neurosurgery and under-reported in neurotrauma literature. This perspective piece addresses the underrepresentation and challenges faced by women and racial minorities in neurosurgery, and within the workforce of neurotrauma, specifically. The literature demonstrates that there is still a scarcity of females and racial minorities in neurosurgery leadership positions and that females are less likely to receive invited papers. The persistent challenges in navigating gender and racial dynamics in neurosurgery/neurotrauma underscore the need for progress in advancing intersectionality within the field, emphasizing the importance of addressing inequalities. Several strategies to improve gender and racial diversity in neurotrauma workforce, leadership and academics are presented.

KEYWORDS

clinical trial, gender, diversity, leadership, academics

Introduction

In 2008, the Board of the Directors of the American Association of Neurological Surgeons (AANS) collaborated with Women in Neurosurgery (WINS) to compose a white paper to promote the recruitment and retention of women in neurosurgery, given their historical status of being deemed "less than a minority" (1, 2). Women entering neurosurgical residency programs faced significant and disproportionate obstacles in their path to becoming surgical experts (2). Beyond neurosurgery, the surgical field was previously known to be dominated by Caucasian males, which is beginning to shift as women now make up most of medical school class graduates (3–8). Recent data suggests a stark increase in the number of women neurosurgical residents. For a while, such disparity was attributed to numerous factors including the perceived department culture, lack of concordant mentors and the "pipeline effect," where poor female representation in the upper levels of academic surgery was explained by the small candidate pool (3, 4, 9, 10). However, persistence of the gap despite females beginning to occupy a higher proportion of the surgical workforce, indicates other contributors to this ongoing issue (3, 6, 8, 9). Lack of diversity in the workforce and among those involved in other academic leadership and research endeavors have both direct and indirect impacts on the quality of patient care. It may lead to the direct oversight of the unique needs and challenges faced by certain subsets of the population and indirectly, the narrow range of perspectives discussed may hinder innovation and development of inclusive policies. As the field of neurosurgery makes efforts to increase the numbers of female surgeons, there is an evident need to concurrently adapt the surrounding culture to the new wave of trainees while attending to the inherent biases ingrained into the fabric of the field (2). In this paper,

we present an overview of the current state and progression of gender and racial diversity in neurosurgery, with a specific focus on the neurotrauma workforce. Additionally, we offer a compilation of recommendations aimed to both inspire interested individuals to pursue their passion in the evolving environment.

Neurosurgery leadership underrepresentation

The underrepresentation of women and racial minorities in neurosurgical leadership is a global concern that demands attention. Notably, there is a lack of studies specifically addressing gender or racial diversity within neurotrauma leadership, highlighting a significant gap in research. Female neurosurgeons face challenges in obtaining leadership positions within organizational neurosurgery globally, both within surgical societies and among institutional academic ranks. Several studies have investigated the underrepresentation of these groups and placed an emphasis on the importance of acknowledging and addressing this disparity, encouraging neurosurgical societies worldwide to take proactive steps to mitigate these problems. A cross-sectional study examining the representation of women on neurosurgical editorial boards revealed that only approximately 9% of positions are held by women, a percentage comparable to the number of practicing female academic neurosurgeons (11). This finding suggests that biases in the selection of editorial board members may not be readily identifiable, but efforts to recruit and retain women in neurosurgery are crucial to rectify existing discrepancies.

It has also been well documented that there is a scarcity of women in leadership positions within academic neurosurgery. Notably, in 2011 Dr. Karin Muraszko, was the first and only female chair of a neurosurgical department (3) and over a decade later, there are currently only three female department chairs of a neurosurgery, Drs. Ellen Air (Detroit), Aviva Abosch (Nebraska) and Linda Liau (UCLA). Furthermore, Dr. Shelley Timmons (Illinois) is the only former female chair who has also been a neurotrauma specialist. The data reinforces that women constitute a minority in neurosurgical leadership, accounting for less than 15% of total opportunity spots at major neurosurgical conferences over a 5-year period (12). Additionally, there had never been a female president for any major neurosurgical society until 2019. The American Association of Neurological Surgery was notably male dominated, highlighting persistent gender disparities in leadership roles. Additionally, female neurosurgeons make up just 6.3% (1,024/16294) of the American Association of Neurological Surgeons (AANS) members (13). However, global efforts by committees such as the Women in Neurosurgery Committee of the World Federation of Neurosurgical Societies and the Task Force on Diversity established by the European Association of Neurosurgical Societies are actively working toward addressing gender diversity in neurosurgery (14, 15).

Discordance in neurosurgery authorship

The underrepresentation of women and minority authors in neurosurgery publications remains a persistent challenge, even as the overall number of underrepresented neurosurgeons have increased. While studies have investigated various aspects of gender diversity within neurosurgery such as authorship patterns and research productivity, there is a notable gap in research focusing on the racial backgrounds of neurosurgeon authors. The literature lacks comprehensive data specifically analyzing racial/ethnic minority authorship rates in neurosurgery and neurotrauma publications as most studies focus solely on gender disparities in authorship. Several studies have reported a significant increase in female authorship in high-impact neurosurgical research publications, particularly in the United States and Canada (16). Despite this progress, disparities persist as female authorship rates remain low at 13.4% ($n = 570$) for first authors and 6.8% ($n = 240$) for last authors, suggesting potential biases in collaboration patterns (17). Interestingly, no significant difference is found between single-blind and double-blind peer review processes (17). There is also evidence that female first authors tend to collaborate with female senior authors (18). Data from 2015 to 2019 indicates a modest rise in the number of female neurosurgeons. However, the representation of women as authors in neurosurgical and spine journals remains strikingly low, with only 8.3 and 5.8% serving as first and last authors, respectively (13). In spine specific research, the representation and longevity of female physician-investigators in spine-related research journals from 1978 to 2016 was investigated and showed doubling of female representation, especially as first authors (19). However, this growth plateaus after the year 2000, and female physician-investigators are less likely to continue participating in spine-related research, publishing fewer articles compared to their male counterparts.

Discussion

This compilation of studies serves as a pivotal contribution to the neurotrauma research landscape, directing its focus to diversity. The significance of this endeavor lies in its targeted effort to fill a substantial knowledge gap that has persisted within the field. By concentrating specifically on women and minorities, these studies illuminate aspects of neurotrauma that have historically received inadequate attention, thereby enriching the overall discourse on diversity in neurotrauma. The application of a gender and a racial lens is particularly noteworthy, as it goes beyond mere recognition of differences and actively seeks to comprehend the influence of social structures on a spectrum of outcomes. Crucially, these articles bring to the forefront the challenges associated with grappling with the intricacies of gender and racial dynamics within the broader domain of neurotrauma research. In essence, these studies represent the need for a crucial step forward in advancing intersectionality in this field.

The critical relationship between leadership diversity and patient access to various opportunities, including clinical trial participation, cannot be overlooked. Unrepresentative leadership has known adverse consequences, including compromised scientific integrity where results cannot be generalized beyond the stated study population, negatively implicating patients who will not benefit from such research investments (20). However, a positive relationship between enhanced leadership diversity and trial enrollment was demonstrated by Chhaya et al. (21). In this study, trials with female first and senior authors had a significantly higher proportion of female clinical trial participants, suggesting a promising trend toward increased female trial enrollment over time as support for female and minority scientists to take on these roles grows (21).

With respect to diversity in research, it is important to analyze representation among researchers. Although women have begun to occupy more academic surgical leadership positions, they remain a minority. Only 19% of academic surgery faculty are female (5) and women were reported to make up only 8% of professors, 13% of associate professors and 26% of assistant professors of surgery (5, 22). Unfortunately, the many factors considered when determining academic promotion including research productivity and occupation of academic leadership positions, are known to be influenced by gender (5, 22). Prior studies have identified women to hold fewer positions on journal editorial boards, to have fewer publications, and to advance in academic rank slower when compared to their male counterparts (3, 5, 6, 23). This is further impacted by a prior concern for a self-perpetuating bias where grant funding is preferentially awarded to experienced surgeons, many of whom are male (24). In a study by Krebs et al. (5), women were found to hold 26.4% of the National Institute of Health (NIH) R01 grants, both a minority and an overrepresentation of the proportion of women in academic surgery. Interestingly, female primary investigators were twice as likely to be first-time recipients and to have obtained the grant in the last 5 years, suggesting a more recent shift toward improved female representation in R01 funding (5). Furthermore, these individuals were more likely to come from departments with a high proportion of female chairs and faculty, potentially pointing to a supportive environment where success in leadership and research co-exist (5).

Roadmap to closing the gender and racial gap in neurotrauma workforce

Despite women's increased participation in traditionally male-dominated fields, the term "glass ceiling" remains a pervasive metaphor for the persistent underrepresentation of women in leadership roles in the absence of clear obstacles preventing their advancement (25, 26). The term "sticky floor" was further applied secondary to the realization that women were given fewer resources at the beginning of their career to support their ascent up the institutional ladder (25, 26). The presence of a glass ceiling and sticky floor in surgical specialties extends in part from the historical roles men and women have previously occupied in society, with little acknowledgement of the intellect and skill such individuals currently have to offer (26). To compound the inherent difficulty posed by traditional gender roles, women often face additional obstacles due to societal expectations of their role in managing household responsibilities (25, 26). Such competing pressures and the clinical and training demands associated with surgical specialties disproportionately affect women and as a result, females are more likely to change the focus of their practice to accommodate familial responsibilities and are twice as likely to leave academia (27–30). Furthermore, the pipeline effect, characterized by the ongoing attrition of women and minorities at each career stage, has been proposed as an additional factor contributing to the diversity challenges in the field, with minority females being particularly affected (31). Among general surgery residents, increased incidences of racial discrimination have been linked to feelings of burnout and eventual attrition from the field, with Black residents, particularly Black females, facing the highest prevalence of discrimination (32–34). While such data is currently unavailable in the field of Neurosurgery, female neurosurgical residents are known to leave the specialty at a greater rate than their male counterparts (34, 35). It is therefore critical to acknowledge that efforts to address racial or gender biases in isolation may not be sufficient to attend to the unique barriers faced at the intersection of the two.

Mentors play a crucial role in guiding individuals toward personal and professional growth, and this role is not limited to the fields of academic surgery or medicine. Previous research has identified both the beneficial role demographically-concordant mentors play in career development and navigation of the health care system, and the role lack of mentorship plays as a deterrent to entering certain surgical fields (36–43). In agreement with the previous finding surrounding NIH funding, most female students in a study by Neumayer et al. demonstrated that those who pursued a surgical career graduated from medical schools with a higher proportion of female surgical faculty, suggesting the beneficial role of visible female role models and mentors (44). Therefore, the development and implementation of mentorship programs aimed at providing accessible and compatible opportunities are important to encourage female and minority students to both pursue their surgical interests and aspire for academic positions if so desired (4, 27, 37, 45, 46). Although a mentor who is demographically concordant can provide strategic advice for areas outside of medicine, including strategies for maintaining a healthy work-life balance, it is important to recognize the greater importance of a mentor's desire to teach over similar demographics (5, 36). Therefore, further teaching on how to seek a mentor and how to be an effective mentor may improve both the quantity and quality of these relationships (36).

Although improvements to recruitment are critical to advancing the diversity of future generations of surgeons, integrating supports that promote surgeon retention and career-satisfaction are equally as important in maintaining a diverse workforce (46, 47). Sexism in the workplace has multiple manifestations from outright acts of harassment to more covert measures including omission of females in certain interactions, referral biases, and the inclination to question a women's commitment to their career based on their dedication to their family (26, 47). Additionally, it is crucial to acknowledge the evident but often unspoken impact of structural racism, whereby policies, practices, and institutional norms perpetuate racial disparities, irrespective of individual actions (48, 49). Efforts to address acts of gender and racial discrimination cannot be carried out in silos as such acts are significantly impacted by the institutional environment, culture, and other social forces (39). However, simultaneously addressing the lack of parity in surgical leadership and mentorship accessibility may serve as a start to bring greater awareness to such issues (39). Providing and normalizing the use of protected personal time for familial responsibilities in addition to workshops that sensitize staff to common gender and racially-derived issues can help reduce implicit bias and foster a more inclusive environment that attracts and retains female and minority surgeons (26, 29, 46). Furthermore, establishing a diverse leadership group that encourages the reporting of offensive or discriminatory behavior may reduce the role of discrimination in hindering female progression in the field of academic surgery (26, 29).

Although a lot of work is required to approach parity in representation among faculty, within leadership and within research,

TABLE 1 Recommendations on how to improve diversity in neurotrauma workforce.

Workforce diversity	
Recommendations	Supporting evidence
Integrate leadership training into medical education	- Integrating leadership training into core medical education would serve to empower females with the skills and confidence required to pursue academic leadership positions, ultimately leading to a greater proportion of strong, female leaders. - Prior research suggests that enhanced female departmental leadership may contribute to a supportive environment conducive to applying for and receiving substantial research grants (5).
Improve demographically concordant mentorship opportunities	- The evident lack of female neurosurgeons may foster feelings of loneliness and isolation in younger surgical trainees who do not have a demographically concordant role model to see themselves in or debrief unique experiences with (3). - However, effective mentoring relationships do exist without demographic concordance, therefore, investing in robust mentorship programs that outline and address specific barriers the mentee may face as they enter the neurosurgical field would also be beneficial.
Adapt to the unique needs of female and minority surgeons	- Establishing a flexible environment that supports the various roles and responsibilities of the residents and staff to both improve neurosurgeon recruitment and retention (2, 22) for individuals otherwise swayed by such factors.
Adjusting expectations of neurosurgical trainees and staff	- Adjusting expectations and adapting to the growing priority on work-life balance may help attract young, competent and passionate trainees to a field historically perceived to inherently oppose such beliefs. - With ongoing medical and technological advances, flexibility in educational and practice approaches may allow for better support for the improved work/life balance desired by some within the generations of neurosurgeons to come (3).
Identify and address biases inherent to the environment	- Identify and attend to discriminatory practices within the multiple levels of neurosurgical recruitment, any of which may deter females and minorities from pursuing their desires to enter the field. - Addressing such factors may aid in fostering a safer and more equitable review process that mitigates the strength of the well-ingrained biases and stereotypes associated with the field (22, 47, 50).

it is important to acknowledge the steps that have been taken. Worldwide, surgical societies have implemented strategies to enhance organizational culture and consequentially improve both the recruitment and retention of female surgeons (22). Furthermore, organizations such as the Gender Equity Initiative in Global Surgery hope to address gender disparities in surgical specialties in low- and middle-income countries by 2030, with approaches from a variety of avenues (22). To build upon existing steps, Table 1 outlines our recommendations toward improving diversity among neurosurgeons, which have downstream effects on the associated culture, academic achievements, and patient care.

The surgical field has been predominantly composed of Caucasian males, with Neurosurgery being no exception (3). Improved diversity in the workforce has parallelled both the changing demographic of medical school class graduates and implementation of targeted efforts. Which is critical given the direct and indirect impacts lack of diversity has on patient care (2–8). As highlighted in this paper, female neurosurgeons hold fewer organizational leadership positions and compose a minority of first and last authorship positions in comparison to their male counterparts (11, 19). The articles discussed in this review explored how institutional structures and embedded norms influence gender and racial dynamics within neurotrauma and emphasize the significant gaps that remain despite an insurgence of aligned research. Although we are beginning to see a rise in the proportions of female neurosurgeons who occupy leadership or lead/senior author roles, several obstacles including societal expectations, the embedded culture, and lack of demographically concordant mentors, still exist. Efforts to address gender and racial discrimination are growing, however, solitary efforts may not be sufficient to address the unique barriers faced by individuals at the intersection of gender and racial minority status. To effectively enhance diversity in the neurotrauma workforce, individuals are encouraged to employ various strategies and guidelines (Table 1) to foster inclusivity and equitable representation.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

IC: Writing – review & editing, Writing – original draft, Visualization, Conceptualization. TS: Writing – review & editing, Writing – original draft, Visualization, Conceptualization. AP: Validation, Resources, Writing – review & editing. ET: Methodology, Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Conceptualization.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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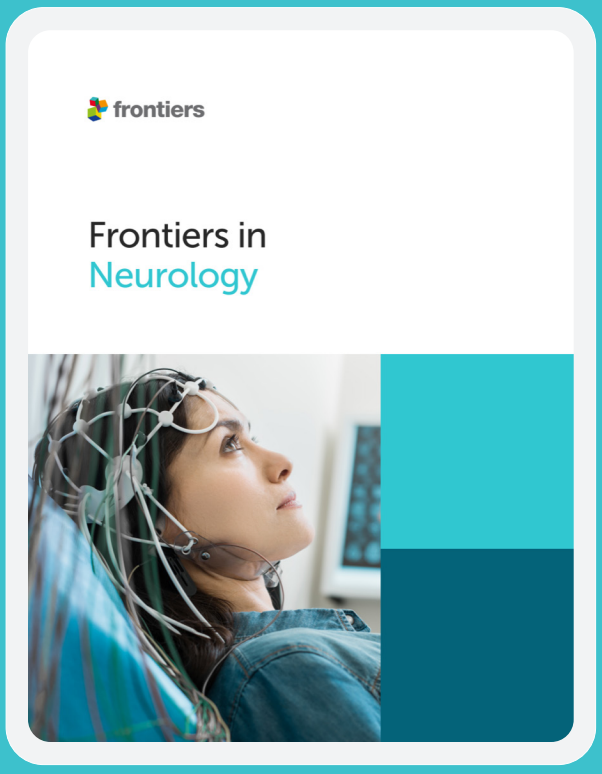

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