The Cognitive Effects of Mild Traumatic Brain Injury and Resulting Postconcussion Syndrome in High Risk Patients

Terrance Hartmann
Pacific University

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The Cognitive Effects of Mild Traumatic Brain Injury and Resulting Postconcussion Syndrome in High Risk Patients

Abstract

Background: Mild traumatic brain injury with postconcussion syndromes may be correlated with long term cognitive deficits. While 1.7 million traumatic brain injuries are reported each year, this number does not account for the many mild traumatic brain injuries that are not reported each year.

Methods: Exhaustive search of available medical literature using the search engines: OVID, CINAHL, Entrez, and UpToDate. Keywords used were Mild Traumatic Brain Injury, Cognitive Disorders, Psychological Disorders, Neurological Disorders, and Postconcussion Syndrome.

Results: The four articles that remained, presented vastly different conclusions as to the long term cognitive effects of traumatic brain injuries. One widely publicized article by Hoge et al determined that mild traumatic brain injury posed no significant adverse health effects except headache. Another study conducted by De Beaumont et al found that there were cognitive dysfunction 30 years after the last mild traumatic brain injury event had occurred.

Conclusion: Mild traumatic brain injuries do have a direct correlation with cognitive deficits. Post traumatic stress disorder and depression may mask the symptoms of mild traumatic brain injury with postconcussion syndrome and thereby making the diagnoses of this condition difficult. If nationwide and global trends continue, there will be an increase of patients on the very near future. In order to best serve the public it will be necessary to do additional research on how to accurately assess, diagnose, and treat.

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Capstone Project

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Keywords
Mild Traumatic Brain Injury, Postconcussion Syndrome, Cognitive Deficit, Magnetic Resonance Imaging

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The Cognitive Effects of Mild Traumatic Brain Injury and Resulting Postconcussion Syndrome in High Risk Patients

TERRANCE HARTMANN

A Clinical Graduate Project Submitted to the Faculty of the School of Physician Assistant Studies Pacific University Hillsboro, OR

For the Masters of Science Degree, 14 August 2010

Faculty Advisor: Dr. Mark Pedemonte, MD
Clinical Graduate Project Coordinators: Annjanette Sommers MS, PAC & Rob Rosenow PharmD, OD
Biography

[Redacted for privacy]
Abstract

**Background:** Mild traumatic brain injury with postconcussion syndromes may be correlated with long term cognitive deficits. While 1.7 million traumatic brain injuries are reported each year, this number does not account for the many mild traumatic brain injuries that are not reported each year. **Methods:** Exhaustive search of available medical literature using the search engines: OVID, CINAHL, Entrez, and UpToDate. Keywords used were Mild Traumatic Brain Injury, Cognitive Disorders, Psychological Disorders, Neurological Disorders, and Postconcussion Syndrome. **Results:** The four articles that remained, presented vastly different conclusions as to the long term cognitive effects of traumatic brain injuries. One widely publicized article by Hoge et al determined that mild traumatic brain injury posed no significant adverse health effects except headache. Another study conducted by De Beaumont et al found that there were cognitive dysfunction 30 years after the last mild traumatic brain injury event had occurred. **Conclusion:** Mild traumatic brain injuries do have a direct correlation with cognitive deficits. Post traumatic stress disorder and depression may mask the symptoms of mild traumatic brain injury with postconcussion syndrome and thereby making the diagnoses of this condition difficult. If nationwide and global trends continue, there will be an increase of patients on the very near future. In order to best serve the public it will be necessary to do additional research on how to accurately assess, diagnose, and treat. **Keywords:** Mild Traumatic Brain Injury, Postconcussion Syndrome, Cognitive Deficit, Magnetic Resonance Imaging
Acknowledgements

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List of Abbreviations

DSM-IV.............Diagnostic and Statistical Manual of Mental Health, fourth edition
DSST............................................ Digit Symbol Substitution Test
FLAIR.................................Fluid-Attenuated Inversion Recovery
GCS................................................. Glasgow Coma Scale
IED............................................. Improvised Explosive Device
MMSE............................................. Mini-Mental Status Exam
MRI................................................. Magnetic Resonance Imaging
mTBI ............................................ Mild Traumatic Brain Injury
NCHS .................................. National Center for Health Statistics
NIH................................................. National Institute of Health
NIMHANS .............. National Institute of Mental Health and Neurological Sciences
NINDS ......................... National Institute of Neurological Disorders and Stroke
PCS.................................................. Postconcussion Syndrome
PHQ-15......... Patient Health Questionnaire 15-Item Somatic Symptom Severity Scale
PTSD………………………………………………………….. Post Traumatic Stress Disorder
RCFT…………………………………………………….. Rey-Osterrieth Complex Figure Test
RCS………………………………………………………… Rapid Screen of Concussion
TBI……………………………………………………………… Traumatic Brain Injury

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Appendix A………………………………………………… Patient Health Questionnaire-15
BACKGROUND

The National Center for Health Statistics (NCHS) published a study in 2006 that indicated that from 1995 to 2001 at least 1.4 million traumatic brain injury (TBI) events occurred each year in the United States. Of those, only 50,000 resulted in death and 23,500 were hospitalized. The majority, equaling 1.1 million, were treated in an emergency department and then released. By 2006, the total number had increased to 1.7 million and those treated and released had increased to almost 1.4 million, or roughly a 21.4% and 22.9% increase respectively per year. These numbers do not include the mild traumatic brain injuries (mTBI) that are not seen in an emergency department or that receive no care. While these figures do not exclude pediatric mTBI, the purpose of this review will be limited to the adult population.

TBI occurs when sudden trauma damages the brain by either violently moving the brain inside of the cranium or when a foreign object disrupts the function of brain tissue itself. TBI are classified as either mild, moderate, or severe, depending on the extent of brain damage sustained or severity of symptoms experienced. Mild TBI itself has a loss of consciousness of 30 minutes or less and a Glasgow Coma Scale (GCS) of no less than 13. What makes mTBI increasingly dangerous is the common link it has with Postconcussion Syndrome (PCS). PCS is the cluster of signs and symptoms that appear after a mTBI event, including memory loss, headaches, fatigue, and irritability. The National Institute of Neurological Disorders and Stroke (NINDS), a subdivision of
National Institute of Health (NIH), estimates that at least 40% of patients with mTBI will develop PCS. Patients who experience mTBI events often do not report them immediately or receive little care due to the lack of life threatening capacity of their symptoms. In the wake of recent world combat and national sporting injuries, there has been increased interest in the prognostic outcome in relation to multitude and severity of TBI events and thus it has become one of the most widely studied subjects in recent years. More attention and research is now being applied since there have been increased reports that the cognitive states of these individuals has been altered after they have experienced a mTBI event.

Information about cognitive changes resulting from mTBI events is changing so rapidly that the research conclusions from different studies often directly contradict each other. In January 2008 The New England Journal of Medicine published a study by Col. Charles W. Hoge, MD et al9 concluding that U.S. soldiers returning from Iraq who had suffered a mTBI did not have lingering postconcussive symptoms with the exception of headaches and many of the symptoms they experienced were a direct result of post traumatic stress disorder (PTSD) and depression. However, UpToDate,4 The Mayo Clinic,5 and The Defense and Veterans Brain Injury Center6 have listed symptoms that may present from mTBI to include excessive fatigue, mood changes, loss of concentration, and memory problems in addition to headaches.

METHODS

An exhaustive literature search was conducted using the following search engines: OVID, CINAHL, Entrez, UpToDate. The search was performed using search parameters: Mild Traumatic Brain Injury, Cognitive Disorders, Psychological Disorders,
Neurological Disorders, and Postconcussion Syndrome. Inclusion criteria were adult patients with confirmed cases of TBI that have developed varying signs and symptoms of psychological, neurological, and cognitive disorders. Exclusion criteria were evidence of penetrating head injury, history of previous neurological or psychological diagnosis, hearing or vision impairment, or history of alcohol and substance abuse prior to the TBI event exposure, GCS of less than 13, participants under the age of 18, studies earlier than 2004.

RESULTS

The comprehensive search criteria used resulted in 4 studies that had broad and conflicting conclusions. Among these conclusions were results that varied from mTBI events resulting in distinct long term effects to it only presenting with headaches (See Table 1).

De Beaumont et al\(^7\) conducted a retrospective cohort study in 2008 of 40 former Canadian University level hockey and football athletes between the ages of 50 and 65. The intention of this study was to quantify the long term effects of mTBI in athletes late in life who had experienced their last injury in early adulthood. Comprised of two experimental groups, the first group consisted of 19 healthy university level athletes with a reported history of sports related mild traumatic brain injury with their last concussion occurring between the ages of 20 and 30. The second group consisted of 21 former healthy university level athletes who reported no prior history of mild traumatic brain injury or neurological insult. Testing consisted of concussion history questionnaire, and Mini-Mental Status Exam (MMSE), general health questionnaire, neuropsychological
assessment using the Rey-Osterrieth Complex Figure Test (RCFT), and diadochokinesia tasks.\textsuperscript{7}

Using the RCFT, a test designed to test a patient’s visual memory and visuospatial ability, De Beaumont et al\textsuperscript{7} were able to demonstrate that athletes who had a prior history of mTBI presented with the decreased cognitive abilities of immediate recall, delayed recall, and recognition. Immediate and delayed recall had decreased to 19.4 from 23.0 and to 18.9 from 22.4 respectively and recognition had decreased from 21.3 to 19.7. De Beaumont et al\textsuperscript{7} also demonstrated results that these athletes have slower electrophysiological responses and diminished diadochokinesia results, even after 20 and 30 years since their last mTBI event.\textsuperscript{7}

In 2004, Sheedy et al\textsuperscript{8} conducted a prospective cohort study of 29 patients who were previously diagnosed with mild traumatic brain injury in the St. Vincent Hospital Emergency Department of Darlinghurst, NSW, Australia. The purpose of this study was to find out if PCS could be predicted by assessing the severity of mTBI in an emergency department setting. Patients were examined and tested one month after diagnosis and compared to 30 patients with mild orthopedic injuries sustained through non-deceleration mechanisms. The orthopedic patients were used as a control group, not only to contrast the neurocognitive differences of the mTBI group, but to help compare the balance deficits experienced by the mTBI group as well.\textsuperscript{8}

Patients were assessed at the bedside inside the emergency department during the acute injury phase of a mTBI event using the Rapid Screen of Concussion (RSC). The RSC is a computer based series of tests used to measure immediate verbal recall, delayed
verbal recall, speed of sentence comprehension, sentence orientation, and the Digit Symbol Substitution Test (DSST).\textsuperscript{8}

It was noted that patients with mTBI performed considerably worse on each of the five RSC tests and continued to get cognitively worse over a period of one month. Patients complained of decreased ability to concentrate and slowed thinking more than they complained of emotional problems such as depression and anxiety. Sheedy et al\textsuperscript{8} were able to predict the onset of PCS with a sensitivity of 91.7\% and specificity of 91.7\%.\textsuperscript{8}

In 2008, Hoge et al\textsuperscript{9} conducted a retrospective cohort study of 2525 U.S. Army infantry soldiers from two U.S. Army combat infantry brigades 3 to 4 months after returning from a year-long deployment in a high combat area and reporting mTBI event. The study participants were selected after being given two questionnaires: a protocol questionnaire to determine suitability for the study and a combat experience study to standardize combat intensity among participants. Soldiers were considered to have experienced a mTBI event if a positive response was given in regards to loss of consciousness, being dazed or confused, or not being able to remember an injury. Physical health was measured based on asking a soldier how they felt overall using the Patient Health Questionnaire-15 (PHQ-15) and the number of primary care appointments they reported attending.\textsuperscript{9}

Of the 2525 soldiers included 4.9\% and 10.3\% reported loss of consciousness and altered mental status with no loss of consciousness respectively. There were 17.2\% who reported an injury but did not experience any loss of consciousness or altered mental status. The remaining 1706 soldiers, or 67.6\% of the participants, reported neither injury
nor any adverse effects. Both the groups that reported no adverse effects were used as reference groups for comparison (See Table 2).\textsuperscript{9}

Hoge et al,\textsuperscript{9},although coming to the conclusion that 43.9\% of the 124 soldiers reporting loss of consciousness met the Diagnostic and Statistical Manual of Mental Health, fourth edition (DSM-IV) criteria for PTSD indicating a strong link between the two, it was reported that mTBI was not significantly associated with adverse physical health outcomes or symptoms, minus headaches.\textsuperscript{9}

Datta et al\textsuperscript{10}, in 2009, conducted a prospective, observational, cohort study of 20 patients at a tertiary hospital in Bangalore, India using patients with mTBI and PCS lasting three or more months in duration. The purpose of the study was to determine if there was a correlation between neuropsychological deficits and lesions presenting on Magnetic Resonance Imaging (MRI). All patients underwent a neuropsychological evaluation using the National Institute of Mental Health and Neurological Sciences (NIMHANS) Neuropsychological Battery for head injuries. All neuropsychological testing included digit symbol substitution, digit vigilance test, finger tapping test, complex figure test, auditory verbal learning test, Wisconsin card sorting test, animal name test, Stroop color test, Token test, and Tower of London Test and were administered by the same two assessors. All MRI images were obtained using spell T1, T2, and fluid-attenuated inversion recovery (FLAIR) sequences and were analyzed by a single radiologist who was blinded to all patient data.\textsuperscript{10}

All patients in the study by Datta et al\textsuperscript{10} had various significant deficits in verbal learning and memory, sustaining attention, impaired planning, and response inhibition (See Table 3).\textsuperscript{10} Eleven of these patients displayed MRI lesions in multiple areas,
including frontal, temporal, and occipital lobes, and the deep corpus collosum area. MRI results, however, only had a sensitivity of 55% in patients with frontal lobe lesions and sensitivity and specificity of 29% and 33% respectively. 10

**DISCUSSION**

In recent years, with ongoing global events involving combat and significant injuries to professional athletes of contact sports, there has been an increased focus on the long-term effects of traumatic brain injuries. The focus of this review was to demonstrate a correlation, if any, between patients diagnosed with mTBI and PCS and long-term cognitive deficits. As the reviewed studies indicate, there is some disagreement as to the exact long-term cognitive effects that mTBI and PCS has on patients. This is a highly evolving subject that is difficult to study due to several factors including lack of patients reporting symptoms at time of the incident and the similar symptoms that this condition shares with other neuropsychological diagnosis such as PTSD and depression. Many of the patients who are at high risk for mTBI, such as members of the military or professional athletes, feel that they stand to lose a lot in the way of their careers and financial stability by immediately admitting to any mTBI symptoms. Thus they are reluctant to report any events, despite the severity and presence of any subsequent symptoms.

Sheedy et al8 and De Beaumont et al7 both found on their respective studies significant cognitive deficits repeat for patients who had experienced a mTBI event. Sheedy et al8 followed patients from 12 hours to one month after the mTBI event and found a significant increase in fatigue, memory problems, concentration difficulty, slower thinking, headache, and irritability. Examining a longer time period, De Beaumont et al7
found that even athletes who had experienced a mTBI event 30 years prior demonstrated significant deficits. Datta et al\textsuperscript{10} were able to demonstrate that not only were there cognitive deficits and all the patients involved in the study but were able to find anatomical brain defects on many of them using MRI. Admittedly one of the limitations to this study was that all the patients were diagnosed with PCS as well as mTBI.

The study conducted by Hoge et al\textsuperscript{9}, however, found that mTBI events were not associated with physical health outcomes, except for headache, and that many of the symptoms that the soldiers were experiencing were due to PTSD and depression. However there are significant limitations to this study. The study was performed by conducting two anonymous questionnaires only and no physical exam. And while 43.9% of all soldiers who reported a loss of consciousness met the criteria for PTSD, many of these soldiers experienced their mTBI event under more gruesome circumstances such a detonation of an Improvised Explosive Device (IED). As this is often the case with combat scenarios, this would also put them at significant risk for PTSD and thereby possibly masking any cognitive deficits.

**CONCLUSION**

Protective equipment and medical advancements have developed to the point where more patients are surviving high impact injuries. While patients are surviving, there is an increased likeliness that they will experience a TBI event. Due to lack of readily apparent life threatening symptoms, many patients never report having experienced a mTBI or any subsequent symptoms. It is extremely difficult to get an accurate number of these events happening each year in the United States because of this. This is especially true for the high-risk patients of the military and professional athletes.
who see this as a possible detrimental effect on their career. However, when patients do not feel that their livelihood is at stake, they appear to be more willing to be honest about the symptoms they have experienced. When patients are assessed immediately after an event and subsequently followed, there seems to be an obvious connection between mTBI events and cognitive deficits. This is even more evident if the patient develops PCS as a result of the mTBI. More studies should be performed following high risk patients at more regular intervals and for a longer duration as they continue throughout careers that continue to expose them to possible TBI events. To ensure complete and accurate data, special care must be taken to ensure patient anonymity and prevent a possible co-diagnosis of neuropsychological disorders such as PTSD and depression. As imaging technologies become more advanced and screening techniques become more thorough, we may be able to accurately predict, diagnose, and treat mTBI events earlier and thereby possibly preventing lasting cognitive impairment.
REFERENCES


**TABLES**

**Table 1: Summary of Reviewed Articles**

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<thead>
<tr>
<th>Study</th>
<th>Yr. published</th>
<th>Patients/Population</th>
<th>Comparison</th>
<th>Outcome(s)</th>
<th>Study type</th>
<th>Comments</th>
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<tr>
<td>De Beaumont et al⁷</td>
<td>2008</td>
<td>40 Previous university level athletes</td>
<td>Previous mTBI event exposure to non-exposure</td>
<td>Exposed group displayed cognitive deficits</td>
<td>Case-Control Study</td>
<td>Last event occurred 20-30 years prior</td>
</tr>
<tr>
<td>Sheedy et al⁸</td>
<td>2004</td>
<td>29 mTBI patients with current exposure 30 Orthopedic Patients</td>
<td>Mild TBI exposure to non-exposure with PCS prediction</td>
<td>Exposed group developed cognitive deficits</td>
<td>Prospective Cohort Study</td>
<td>Orthopedic patients were used to assess balance deficits</td>
</tr>
<tr>
<td>Hoge et al⁹</td>
<td>2008</td>
<td>2525 Infantry soldiers with previous mTBI exposure</td>
<td>Symptoms compared to PTSD and depression diagnosis</td>
<td>When adjusted for PTSD and depression; no cognitive correlation</td>
<td>Case-Control Study</td>
<td></td>
</tr>
<tr>
<td>Datta et al,¹⁰</td>
<td>2009</td>
<td>20 patients with current mTBI exposure</td>
<td>Brain lesions on MRI with current mTBI exposure</td>
<td>Inconclusive connection between brain lesions and mTBI exposure</td>
<td>Prospective Observational Cohort Study</td>
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Table 2: Number of patients with impaired neuropsychological test results.\textsuperscript{10}
Table 3: Physical Health Status After Deployment According to Type of Injury During Deployment. 9

<table>
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<tr>
<th>Physical Health during the Past Month</th>
<th>Injury with Loss of Consciousness (N = 124)</th>
<th>Injury with Altered Mental Status (N = 260)</th>
<th>Other Injury (N = 435)</th>
<th>No Injury (N = 1706)</th>
<th>P Value for Loss of Consciousness vs. Other Injury</th>
<th>P Value for Altered Mental Status vs. Other Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor overall health</td>
<td>15/119 (12.6)</td>
<td>17/237 (6.6)</td>
<td>29/422 (6.9)</td>
<td>38/1665 (2.3)</td>
<td>0.04</td>
<td>0.90</td>
</tr>
<tr>
<td>≥2 Missed workdays due to illness</td>
<td>28/120 (23.3)</td>
<td>40/256 (15.6)</td>
<td>61/419 (14.6)</td>
<td>122/1671 (7.3)</td>
<td>0.02</td>
<td>0.71</td>
</tr>
<tr>
<td>≥2 medical visits for physical condition</td>
<td>51/120 (42.5)</td>
<td>84/256 (32.8)</td>
<td>123/426 (28.9)</td>
<td>331/1678 (19.7)</td>
<td>0.005</td>
<td>0.28</td>
</tr>
<tr>
<td>PHQ-15 score of ≥15†</td>
<td>30/121 (24.8)</td>
<td>41/254 (16.1)</td>
<td>48/426 (11.3)</td>
<td>85/1683 (5.1)</td>
<td>&lt;0.001</td>
<td>0.07</td>
</tr>
<tr>
<td>Physical symptoms included in PHQ-15‡</td>
<td></td>
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<td></td>
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<tr>
<td>Stomach pain</td>
<td>14/120 (11.7)</td>
<td>20/249 (8.0)</td>
<td>37/421 (8.8)</td>
<td>71/1674 (4.2)</td>
<td>0.34</td>
<td>0.73</td>
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<tr>
<td>Back pain</td>
<td>40/121 (33.1)</td>
<td>78/253 (30.8)</td>
<td>122/424 (28.8)</td>
<td>311/1678 (18.5)</td>
<td>0.36</td>
<td>0.57</td>
</tr>
<tr>
<td>Arm, leg, or joint pain</td>
<td>45/121 (37.2)</td>
<td>105/252 (41.7)</td>
<td>168/423 (39.7)</td>
<td>387/1673 (23.1)</td>
<td>0.62</td>
<td>0.62</td>
</tr>
<tr>
<td>Headache</td>
<td>39/121 (32.2)</td>
<td>45/254 (17.7)</td>
<td>51/421 (12.1)</td>
<td>141/1674 (8.4)</td>
<td>&lt;0.001</td>
<td>0.04</td>
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<tr>
<td>Chest pain</td>
<td>17/121 (14.0)</td>
<td>7/253 (2.8)</td>
<td>20/425 (4.7)</td>
<td>40/1675 (2.4)</td>
<td>&lt;0.001</td>
<td>0.21</td>
</tr>
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<td>Dizziness</td>
<td>10/120 (8.3)</td>
<td>15/254 (5.9)</td>
<td>13/425 (3.1)</td>
<td>31/1680 (1.8)</td>
<td>0.01</td>
<td>0.07</td>
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<td>Fainting spells</td>
<td>5/120 (4.2)</td>
<td>2/253 (0.8)</td>
<td>8/423 (1.9)</td>
<td>7/1678 (0.4)</td>
<td>0.17</td>
<td>0.34</td>
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<tr>
<td>Heart pounding or racing</td>
<td>23/120 (19.2)</td>
<td>25/253 (9.9)</td>
<td>21/425 (4.9)</td>
<td>62/1679 (3.7)</td>
<td>&lt;0.001</td>
<td>0.01</td>
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<tr>
<td>Shortness of breath</td>
<td>17/120 (14.2)</td>
<td>19/254 (7.5)</td>
<td>30/421 (7.1)</td>
<td>54/1675 (3.2)</td>
<td>0.02</td>
<td>0.86</td>
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<td>Constipation, loose bowels, or diarrhea</td>
<td>26/120 (21.7)</td>
<td>31/253 (12.3)</td>
<td>50/424 (11.8)</td>
<td>115/1681 (6.8)</td>
<td>0.006</td>
<td>0.86</td>
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<td>Nausea, gas, or indigestion</td>
<td>22/120 (18.3)</td>
<td>34/253 (13.4)</td>
<td>65/423 (15.4)</td>
<td>132/1677 (7.9)</td>
<td>0.43</td>
<td>0.49</td>
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<td>Pain or problems during sexual intercourse</td>
<td>10/120 (8.3)</td>
<td>8/253 (3.2)</td>
<td>16/425 (3.8)</td>
<td>16/1673 (1.0)</td>
<td>0.04</td>
<td>0.68</td>
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<tr>
<td>Fatigue</td>
<td>59/111 (53.2)</td>
<td>92/232 (39.7)</td>
<td>136/393 (34.6)</td>
<td>388/1542 (25.2)</td>
<td>&lt;0.001</td>
<td>0.21</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>61/117 (53.8)</td>
<td>111/247 (44.9)</td>
<td>157/422 (37.2)</td>
<td>402/1666 (24.1)</td>
<td>0.001</td>
<td>0.05</td>
</tr>
<tr>
<td>Other postconcussive symptoms§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memory problems</td>
<td>29/118 (24.6)</td>
<td>41/233 (16.2)</td>
<td>58/422 (13.7)</td>
<td>124/1680 (7.4)</td>
<td>0.005</td>
<td>0.38</td>
</tr>
<tr>
<td>Balance problems</td>
<td>10/120 (8.3)</td>
<td>17/254 (6.7)</td>
<td>12/424 (2.8)</td>
<td>26/1677 (1.6)</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>Ringing in the ears</td>
<td>28/110 (25.5)</td>
<td>45/251 (17.9)</td>
<td>59/422 (14.0)</td>
<td>99/1675 (5.9)</td>
<td>0.01</td>
<td>0.17</td>
</tr>
<tr>
<td>Concentration problems</td>
<td>37/118 (31.4)</td>
<td>65/250 (26.0)</td>
<td>76/420 (18.1)</td>
<td>170/1667 (10.2)</td>
<td>0.002</td>
<td>0.02</td>
</tr>
<tr>
<td>Irritability</td>
<td>67/118 (58.1)</td>
<td>118/248 (47.6)</td>
<td>154/419 (36.8)</td>
<td>499/1659 (24.7)</td>
<td>&lt;0.001</td>
<td>0.006</td>
</tr>
</tbody>
</table>

† PHQ-15 somatic symptom scale
‡ The numbers and percentages of persons reporting “bothered a lot” (for all symptoms except fatigue or sleep disturbance) or “more than half the days” (for fatigue and sleep disturbance) are shown. One symptom from the PHQ-15 pertaining to menstrual cramps was not included, since there were so few women in the study.
§ The numbers and percentages of persons reporting “bothered a lot” (for memory problems, balance problems, and ringing in the ears) or “more than half the days” (for concentration problems and irritability).
FIGURES

Figure 1: Rey-Osterrieth Complex Figure.\textsuperscript{11}
APPENDICES

Appendix A: Patient Health Questionnaire 15-Item Somatic Symptom Severity Scale (PHQ-15)\textsuperscript{12}

The PHQ-15 comprises 15 somatic symptoms from the PHQ, each symptom scored from 0 (“not bothered at all”) to 2 (“bothered a lot”). Patients are asked to rate the severity of each symptom as:
- 0 (“not bothered at all”),
- 1 (“bothered a little”), or
- 2 (“bothered a lot”).

The PHQ-15 is intended to function as a continuous measure of somatic symptom severity. The PHQ-15 score is divided into several categories to illustrate more clearly the relationship between graded increases in somatic symptom severity and various health outcomes.

<table>
<thead>
<tr>
<th>Levels of Somatic Symptom Severity</th>
<th>PHQ-15 score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal</td>
<td>0–4</td>
</tr>
<tr>
<td>Low</td>
<td>5–9</td>
</tr>
<tr>
<td>Medium</td>
<td>10–14</td>
</tr>
<tr>
<td>High</td>
<td>15–30</td>
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