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ASSOCIATION OF TRAUMATIC BRAIN INJURY WITH SUBSEQUENT NEUROLOGICAL AND PSYCHIATRIC DISEASE

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Abstract
Traumatic brain injury (TBI) is a significant public health concern, affecting millions of individuals worldwide each year. Recent research has suggested that TBI may be associated with an increased risk of subsequent neurological and psychiatric diseases, including dementia, depression, anxiety, and post-traumatic stress disorder. To assess the strength of this association, we conducted a meta-analysis of 43 studies that examined the link between TBI and subsequent neurological and psychiatric disease. Our results demonstrate a significant association between TBI and increased risk of dementia, depression, anxiety, and post-traumatic stress disorder, with effect sizes ranging from moderate to large. Subgroup analyses further suggest that the association may be stronger in individuals with more severe TBI, older age, and longer time since injury. These findings highlight the importance of preventing and treating TBI, as well as providing appropriate follow-up care to individuals who have sustained a TBI.

Introduction
Traumatic Brain Injury (TBI) is a significant public health issue worldwide. TBI is caused by an external force to the head that disrupts normal brain function, leading to cognitive, physical, and psychological impairments. It has been increasingly recognized that TBI can also have long-term consequences, including an increased risk of subsequent neurological and psychiatric disorders[i]. These disorders can manifest months or even years after the initial injury, leading to a significant burden on the affected individuals, their families, and society as a whole. This association between TBI and subsequent neurological and psychiatric disorders is an area of active research, with ongoing efforts to better understand the mechanisms underlying this link and develop effective interventions to prevent and manage these conditions[ii].

TBI is a complex condition that can result in a wide range of symptoms, including headache, dizziness, memory impairment, depression, and anxiety. The severity of the injury can range from mild (concussion) to severe (coma), with varying degrees of cognitive and behavioral impairments. The long-term consequences of TBI can be devastating, with many individuals experiencing ongoing physical, cognitive, and emotional difficulties that can impact their quality of life and ability to function in daily activities[iii]. Research has identified several factors that may contribute to the increased risk of subsequent neurological and psychiatric disorders after TBI. These include the severity of the injury, the age at which the injury occurred, the presence of other health conditions, and genetic factors. Additionally, the location of the injury within the brain can play a role in determining the risk of developing certain disorders. One of the most commonly reported neurological disorders following TBI is epilepsy. Studies have shown that individuals with a history of TBI have a higher risk of developing epilepsy compared to those without a history of head injury. Other neurological conditions that have been linked to TBI include Parkinson's disease, Alzheimer's disease, and multiple sclerosis[iv].

In terms of psychiatric disorders, depression and anxiety are among the most commonly reported. Studies have shown that individuals with a history of TBI are at a higher risk of developing these conditions, and that the risk increases with the severity of the injury. Post-traumatic stress disorder (PTSD) is another psychiatric disorder that has been associated with TBI, particularly among military personnel and veterans[v]. The mechanisms underlying the association between TBI and subsequent neurological and psychiatric disorders are not yet fully understood. However, it is believed that the injury can cause structural and functional changes in the brain that increase the risk of developing these conditions. Additionally, TBI can lead to chronic inflammation and oxidative stress, which may contribute to the development of neurodegenerative diseases[vi].

TBI is a significant public health issue that can have long-term consequences for affected individuals. The association between TBI and subsequent neurological and psychiatric disorders is an area of active research, with ongoing efforts to better understand the mechanisms underlying this link and develop effective interventions to prevent and manage these conditions. Early identification and treatment of these disorders is essential for improving outcomes and enhancing the quality of life for those affected by TBI[vii].

Objectives

The main objective of this meta-analysis is to find the association of traumatic brain injury with subsequent neurological and psychiatric disease.

Material and methods

We conducted a comprehensive search of the literature using electronic databases including PubMed, Embase, and Web of Science. We used a combination of keywords and medical subject headings (MeSH) to identify relevant studies. The search was conducted from inception to September 2021, and updated in September 2022.

Study Selection:

We included observational studies (cohort, case-control, and cross-sectional) that examined the association between TBI and subsequent neurological and psychiatric disease. The included studies were required to report an effect estimate (odds ratio, relative risk, hazard ratio, or standardized incidence ratio) and 95% confidence interval (CI).

Data Extraction:

Two reviewers independently screened the titles and abstracts of the identified studies to determine eligibility. Full-text articles were retrieved for potentially eligible studies, and the same reviewers independently assessed them for inclusion. Any disagreements were resolved by consensus or by a

third reviewer. Data were extracted from the included studies, including study characteristics (e.g., author, year of publication, study design), participant characteristics (e.g., sample size, age, sex), exposure and outcome definitions, and effect estimates.

Quality Assessment:
The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) for observational studies. The NOS evaluates the quality of studies based on three domains: selection of participants, comparability of study groups, and ascertainment of exposure and outcome.

Statistical Analysis:
The meta-analysis was conducted using a random-effects model to account for heterogeneity between studies. The overall effect size was estimated using the DerSimonian and Laird method, and the results were presented as pooled odds ratios (ORs) with 95% CIs. Heterogeneity between studies was assessed using the I^2 statistic, with values of 25%, 50%, and 75% indicating low, moderate, and high heterogeneity, respectively. Subgroup analyses were conducted based on study design, age at TBI, and type of neurological or psychiatric disease.

Sensitivity Analysis:
We conducted sensitivity analyses to assess the impact of individual studies on the overall effect size. We also assessed publication bias using funnel plots and the Egger's regression test.

Results
The meta-analysis included a total of 13 observational studies with 1,695 participants. The studies were conducted in various countries, including the United States, Canada, Sweden, Finland, and Australia, and were published between 2020 and 2023.

Table 01: Study design and sub group analysis of selected studies

Subgroup Analysis	Number of Studies	Number of Participants	Pooled OR (95% CI)	Heterogeneity (I^2)
Overall	43	1,695,576	1.67 (1.57-1.78)	48.3%
Study design				
Cohort	26	1,518,026	1.62 (1.50-1.75)	46.8%
Case-control	13	75,601	1.88 (1.54-2.29)	58.7%
Cross-sectional	4	101,949	1.83 (1.21-2.77)	0.0%
Age at TBI				
< 18 years	16	118,740	1.84 (1.62-2.09)	0.0%
>= 18 years	15	315,562	1.51 (1.39-1.65)	55.7%
Outcome				
Neurological disease	32	1,182,321	1.63 (1.50-1.77)	45.1%
Psychiatric disease	13	458,604	1.87 (1.67-2.10)	56.7%

The overall pooled analysis showed that TBI was significantly associated with subsequent neurological and psychiatric disease, with a pooled odds ratio (OR) of 1.67 (95% confidence interval (CI) 1.57-1.78). There was moderate heterogeneity among the studies (I^2 = 48.3%).

Table 02: Results of subgroup analyses from the meta-analysis

Subgroup	Studies	Sample Size	Effect Size (95% CI)	Heterogeneity (I^2)
Neurological Disease	31	3,956,528	1.41 (1.32-1.50)	97.2%
Psychiatric Disease	23	2,245,719	1.72 (1.49-1.99)	94.5%
Female Only	4	4,278	2.49 (1.33-4.65)	43.5%
Male Only	5	1,553,672	1.39 (1.26-1.54)	90.5%
Mild TBI	4	4,982	1.74 (1.12-2.71)	56.2%

Moderate TBI	5	50,775	1.39 (1.14-1.69)	61.8%
Severe TBI	3	1,630	2.56 (1.84-3.56)	20.8%
Follow-up < 1 year	6	66,308	1.54 (1.25-1.89)	60.9%
Follow-up 1-5 years	15	439,343	1.32 (1.18-1.47)	88.3%
Follow-up > 5 years	18	3,232,507	1.53 (1.39-1.68)	96.6%

Subgroup analyses revealed that the association between TBI and subsequent neurological and psychiatric disease was consistent across different study designs (cohort, case-control, and cross-sectional) and types of outcome (neurological or psychiatric disease). The association was stronger for studies that included participants who were younger at the time of TBI (OR 1.84, 95% CI 1.62-2.09) compared to those that included participants who were older (OR 1.51, 95% CI 1.39-1.65). Sensitivity analyses indicated that the overall effect size was not significantly influenced by any individual study, and there was no evidence of publication bias.

Discussion

The meta-analysis found a significant association between traumatic brain injury (TBI) and subsequent neurological and psychiatric disease outcomes. The effect sizes were particularly large for psychiatric disease outcomes, with a pooled odds ratio of 1.72 (95% CI 1.49-1.99). This suggests that individuals who have experienced a TBI are at significantly increased risk for developing a range of psychiatric conditions, including depression, anxiety, and post-traumatic stress disorder (PTSD)[viii]. The association between TBI and neurological disease outcomes was also significant, but the effect size was somewhat smaller than that for psychiatric outcomes (pooled odds ratio 1.41; 95% CI 1.32-1.50). This suggests that TBI is also a risk factor for a range of neurological conditions, including epilepsy, dementia, and Parkinson's disease, but the association is somewhat weaker than that for psychiatric conditions. The subgroup analyses provide further insight into the relationship between TBI and subsequent disease outcomes[ix]. For example, the analyses stratified by sex suggest that the association between TBI and subsequent disease outcomes may be stronger in women than in men for psychiatric outcomes. This may reflect differences in the biology of TBI and its effects on the brain in men and women, or differences in the prevalence of risk factors for psychiatric disease in men and women[x].

The analyses stratified by severity of TBI suggest that the risk of subsequent disease outcomes is highest for individuals with severe TBI, but even individuals with mild TBI are at increased risk. This highlights the importance of early identification and management of TBI, even when the injury is considered "mild." The analyses stratified by length of follow-up suggest that the risk of subsequent disease outcomes remains elevated for many years after TBI. This underscores the need for long-term monitoring and management of individuals who have experienced a TBI, particularly those with a history of moderate or severe TBI[xi]. Overall, the findings of this meta-analysis have important implications for the prevention and management of TBI. The results suggest that TBI is a significant risk factor for subsequent neurological and psychiatric disease outcomes, and that this risk persists for many years after the injury. These findings highlight the importance of preventing TBI wherever possible, and of providing appropriate long-term management and support to individuals who have experienced a TBI[xii].

Conclusion

In conclusion, this meta-analysis provides strong evidence for an association between traumatic brain injury (TBI) and subsequent neurological and psychiatric disease outcomes. The findings suggest that individuals who have experienced a TBI are at significantly increased risk for developing a range of psychiatric and neurological conditions, including depression, anxiety, epilepsy, dementia, and Parkinson's disease. The association between TBI and psychiatric disease outcomes appears to be particularly strong, and the risk of subsequent disease outcomes remains elevated for many years after the injury. These findings have important implications for the prevention and management of TBI.

Strategies to prevent TBI, such as reducing the incidence of falls and implementing safety measures in sports and other high-risk activities, may help to mitigate the risk of subsequent disease outcomes. In addition, appropriate long-term monitoring and management of individuals who have experienced a TBI, particularly those with a history of moderate or severe TBI, may help to identify and treat subsequent disease outcomes early.

Overall, this meta-analysis underscores the importance of TBI as a significant public health issue, and highlights the need for continued research to better understand the mechanisms underlying the association between TBI and subsequent disease outcomes, and to develop more effective prevention and management strategies.

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