BRAIN INJURY
RESEARCH SOLUTIONS

The Association Between Concussion and Dementia: An Overview of Reviews

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Abstract

It is estimated that there are nearly three million cases of traumatic brain injury (TBI) in the United States each year, with mild TBI (mTBI)/concussion accounting for approximately 80% of these cases. Dementia is an extremely debilitating condition, and while a number of systematic reviews have established an association between TBI and increased risk of dementia, further clarification regarding the association between dementia and mTBI is needed. We therefore conducted an umbrella review to identify and summarize available systematic reviews on dementia following mTBI to determine and map the current evidence base exploring the association between mTBI and dementia.

We searched the MEDLINE, Embase, Web of Science, Epistimonikos, and the Cochrane Library of Systematic Reviews databases augmented with web-crawler search, vector score search, bibliographic coupling, citation harvesting, and content expert discussion. Our searches ran from database inception until December 2022–February 2023, depending on the database, and identified 4078 citations after deduplication. We used machine learning tools to aid in systematic review identification. After screening, 40 citations were selected for full-text review, with 12 meeting the inclusion criteria. Of the 12 reviews, five pooled studies in a meta-analysis. These pooled estimates ranged from a risk ratio of 1.18 (18% increased risk) to an odds ratio of 1.96 (almost twice as likely), for those with an mTBI history to develop dementia. All five meta-analyses reported statistically significant associations.

While early systematic reviews often reported inconclusive evidence for an association between mTBI and dementia, more recent literature consistently reports an increased risk of dementia in those with a history of mTBI of around twice that of non-TBI populations.

Introduction

It is estimated that there are close to 3 million cases of traumatic brain injury (TBI) in the United States each year.[1] This is a quite common condition, and mild TBI (mTBI), also known as concussion constitutes approximately 80% of these cases.[2] While an Institute of Medicine report previously linked dementia to moderate and severe TBI as early as 2009,[3] the connection to mTBI was more controversial at that time. A number of systematic reviews have been conducted on the association between TBI and dementia. However further clarification regarding the association with mTBI is needed. A preliminary search of MEDLINE, Embase, and Web of Science identified a number of systematic reviews but no overview of reviews (umbrella reviews) mapping the evidence on the association between mTBI and dementia. Umbrella reviews provide a unique and appropriate methodology in cases such as these, where disparate reviews with varied results and clinical scenarios make a clear picture of the evidence underlying a research question challenging.

Our objective was to conduct an umbrella review to identify and summarize the evidence synthesis literature on dementia following mTBI in order to determine and map the evidence base exploring the association between mTBI and dementia.

Methods

Eligibility criteria: We included all systematic reviews regardless of whether they explicitly identified themselves as systematic reviews. We defined *systematic reviews* as studies with a clearly reported research question, a systematic search of at least two databases, and a systematic data synthesis. Population: adult humans with or without pre-existing illness. “Adult” was defined by the primary study authors, but if 80% of the cohort were <18 years of age, we planned to note this. Animal studies, and studies of those <16 years of age were excluded. Exposure: mTBI/concussion. Studies with either self-reported mTBI or using diagnostic criteria for determination were included. Studies of concussions with or without loss of consciousness were included. Comparator: studies using any (or no) comparator were included. Outcome: dementia. Studies of both dementia reported broadly or reported specifically (e.g., Alzheimer’s disease) were included.

No language or date restrictions were used. If we identified studies of interest in languages other than English, we planned to translate them using Google Translate, with essential key details confirmed, when possible, with fluent speakers of that language. No restrictions on peer review or publication status were placed (e.g., posters/abstracts would be included), although we planned to differentiate these evidence sources in the evidence summary.

Based on the above aim and eligibility criteria, we designed, tested, and refined an extensive search of the Pubmed interface of the MEDLINE medical literature database (run December 23, 2022). This search was then translated for the Ovid interface of the

Embase database (run December 23, 2022), the Web of Science (Core Collection) database (run December 23, 2022), Epistimonikos (run February 26, 2023), and The Cochrane Library of Systematic Reviews (run February 26, 2023). Search strategies for all these databases can be found in Appendix A. Other information sources, including for the gray literature, consisted of a web-crawler search (Google Scholar), registry search (PROSPERO), citation harvest, and discussion with content experts. The webcrawler-based search was conducted according to published guidance.[4, 5]

To ensure adequate coverage of the topic, we augmented our search by conducting vector score search and co-citation and bibliographic coupling for all included studies identified. Vector score searching underlies Pubmed's 'Similar Articles Tool' and is based on text weighting across the >30 million MEDLINE citations.[6] We used co-citation and bibliographic coupling to build and visualize a force-directed graph of articles related to included studies. Co-citation and bibliographic coupling were done using the Connected Papers Tool which is based on the Semantic Scholar Paper Corpus (>80 million scientific articles).

All citations from all databases and each vector score search and bibliography coupling network were screened. Up to 200 citations from Webcrawler searching were screened per published guidance.[5] Citations in a format that could be uploaded to a citation manager (e.g., .ris, .nbib) were screened using Eppi Reviewer. For expediency, we utilized a machine-learning classifier from the University of York for Systematic Reviews, trained on the DARE systematic review database.[7] All citations scoring <30 using this tool were automatically excluded. All remaining studies were screened by hand. Screening was first conducted on a title/abstract level with studies that were selected, then reviewed, on a full-text level. Included studies were reviewed, summarized, and relevant notes and quotations were extracted.

A narrative synthesis of the included studies was conducted. We reported all systematic reviews that met inclusion criteria regardless of overlap.

Results

Our search identified 4078 citations after deduplication. After screening, 40 citations were selected for full-text review, with 12 meeting the inclusion criteria. Of the 12 reviews, five pooled studies in a meta-analysis (**Table 1**). These pooled estimates ranged from a risk ratio of 1.18 (18% increased risk) to an odds ratio of 1.96 (almost twice as likely). These meta-analyses included results from 22 primary studies (**Table 2**). All five meta-analyses reported statistically significant associations. Additionally, four primary neuroimaging studies were identified in these reviews which reported on a number of neuroradiologic findings associated with mTBI and dementia (**Table 3**).

2020-Present

In 2022, Graham et al published a systematic review with meta-analysis on the association between mTBI and Alzheimer's disease.[8] The researchers identified five studies that met inclusion criteria: three cohort studies [8,10,11] and two case-control studies.[12,13] Risk of bias assessment found three of the five studies to be of high quality and the other two to be of moderate quality. Quantitative synthesis using meta-analysis of all five studies (n=3,149,740) identified a statistically significant 18% increased risk (RR 1.18; 95% CI 1.11 to 1.25). A sensitivity analysis of only the three high-quality studies did not change the risk estimate, improved precision, and lowered heterogeneity (RR 1.18; 95% CI 1.15–1.21; n=3,149,209; I^2 0%).

In 2022, Gu et al also published a systematic review with a meta-analysis on the association between TBI with dementia and Alzheimer's disease.[14] They identified eight studies that reported on mTBI specifically (Stopa 2021,[15] Yang 2019,[16] Barnes 2018,[17] Fann 2018,[9] Cations 2018,[18] Gardner 2014,[19] Nordstrom 2014,[20] and Lee 2013[21]). When meta-analyzed together, these studies suggested a statistically significant increase in dementia in those with mTBI (OR 1.73 95% CI 1.36 to 2.19) compared to those without head injury. This estimate was remarkably similar to their meta-analysis of moderate and severe TBI (OR 1.74 95% CI 1.12 to 2.72) and indeed, a test of interaction between the two (mTBI versus moderate/severe TBI) showed no significant difference (p=0.21).

In 2022, Leung et al published a systematic review with meta-analysis to examine the epidemiological risk of incident all-cause dementia among veterans with TBI.[22] They reported just under a doubling of the risk (hazard) of all-cause dementia for those with an mTBI history (HR 1.91, 95% CI 1.30 to 2.80) with a higher risk when mTBI was recurrent (HR 2.25, 95% CI 1.25 to 4.02). The reporting was sparse and it is unclear which primary studies were included.

In 2022, Clark et al conducted a systematic review that synthesized literature published after 2016.[23] Their review identified eight studies (Didehbani 2020,[24] Mendez 2015,[25] Hayes 2017,[26] Rostowsky 2021,[27] Barnes 2018,[17] June 2020,[28] Petersen 2010,[29] and Yang 2015[30]), four of which identified a significant link between mTBI and Alzheimer's disease and related dementias, although not all reported risk estimates. These studies revealed that individuals with a history of mTBI experienced an earlier onset of Alzheimer's disease and related dementias. One of the studies demonstrated that those with mTBI history had a higher polygenic risk score for Alzheimer's disease (p=0.02) compared to those without such a history. Additionally, these individuals displayed reduced cortical thickness and encountered difficulties with episodic memory recall in contrast to participants without mTBI history.[26] Four studies did not provide direct neuropsychological evidence connecting mTBI to Alzheimer's disease. The researchers opine that this discrepancy could be attributed to the limited sensitivity of neuropsychological tests in capturing subtle cognitive changes resulting from mTBI.

In 2020, Gallo et al published a systematic review of 14 studies on concussion and long-term cognitive impairment among elite athletes.[31] They looked at internal (concussed versus non-concussed individuals within a sport), external (athlete versus non-athlete controls), and between-sport comparisons. Of these, only internal comparisons are best positioned to identify the risk of concussion, and the vast majority of studies did not report on dementia per se. In a large cross-sectional study of retired professional American football players, researchers compared self-reported or spouse-reported diagnoses of dementia or cognitive impairment. The study examined both concussed and non-concussed individuals within the sample and compared their prevalence rates with estimates from the general population. The internal comparison revealed that recurrent concussions were associated with a higher likelihood of self-reported doctor-diagnosed cognitive impairment (p=0.002), self-reported memory impairment (p=0.001), and spouse-reported memory impairment (p=0.04).[32]

In 2020, Peterson et al published the results of their systematic review and meta-analysis looking at the comparative prevalence of dementia between Veterans and civilians.[33] They reported on two studies on mTBI and dementia,[17,20] both of which found an increased risk of dementia associated with mTBI (see **Table 2**).

In 2020, Snowden et al conducted a systematic review and meta-analysis of mTBI and dementia.[34] They identified 12 studies (Barnes 2018,[17] Helmes 2011,[35] Lee 2013,[21] Li 2016,[36] Liao 2020,[37] McMillan 2014,[38] Nordstrom 2018,[39] Plassman 2000,[10] Redelmeieret 2019,[40] Sercy 2020,[41] Sundstrom 2007,[42] and Yang 2019[16]), six of which had enough data for pooling in a meta-analysis. The authors found that the overall pooled odds of dementia following an mTBI were close to twice that of those without an mTBI history (OR 1.97 95% CI 1.71 to 2.28).

2010–2019

In a 2017 systematic review, Julien et al[43] identified three studies that reported on mTBI and dementia.[10,21,35] Of the three, only Lee 2013[21] showed a statistically significant increase in dementia with mTBI (OR 3.26; 95% CI 2.69 to 3.94).

The WHO convened an international task force (The World Health Organization Collaborating Centre Task Force on Mild Traumatic Brain Injury and the International Collaboration on Mild Traumatic Brain Injury Prognosis) to explore the sequelae of mTBI. In a 2016 systematic review from the task force, the authors note a single study which reported on dementia after mTBI.[44,45] This was a prospective population-based study in the Netherlands that looked at the incidence of dementia in >6,500 participants aged 55 or older who did not have dementia at baseline. The authors concluded that "mTBI is not a major risk factor for incident dementia."

In 2014, Godbolt et al reported on a systematic review of studies with a minimum of 30 mTBI cases.[46] They found only one "methodologically acceptable study" on mTBI and dementia (Helmes 2011).[35] The authors concluded that the results of this study taken together with previous systematic reviews on the subject suggest that "there is insufficient evidence to draw any conclusion about a potential risk of dementia after mTBI (either single or repetitive injury)."

Earlier than 2010

In 2009, Bazarian et al[47] conducted a systematic review with a narrative summary of studies examining the association between long-term neurological outcomes and TBI. Nine studies met their inclusion criteria, but only two studies reported on concussion and dementia.[10,32] The authors reported that there was evidence for an association between Alzheimer's type dementia and mTBI with loss of consciousness but not without.

In 2004, Carroll et al. published the evidence synthesis of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury.[48] They identified three studies on the association between dementia and mTBI; two cohort studies and one case-control study (Mehta 1999, Graves 1990; Schofield 1997).[11,12,45] The studies were small, and the authors of the WHO report note methodologic issues, namely lack of precision, and that this limited any convincing conclusions. Two of the three studies identified that mTBI is a risk factor for dementia and the third did not.

Conclusion

In conclusion, we conducted an extensive search of the medical and gray literature and identified and screened over 4000 citations, Twelve of which met inclusion criteria. Of the 12 reviews, five pooled studies in a meta-analysis with estimates for the association between dementia and mTBI ranging from a risk ratio of 1.18 (18% increased risk) to an odds ratio of 1.96 (almost twice as likely). All five meta-analyses reported statistically significant associations. Additionally, four primary neuroimaging studies were identified which reported on a number of neuroradiologic findings associated with mTBI and dementia. While early systematic reviews often reported inconclusive evidence for an association between mTBI and dementia, more recently there has been a significant increase in primary studies with the resultant pooled estimates more convincing and consistently reporting risks of dementia in those with an mTBI of around twice that of a non-TBI population.

Table 1 Meta-analysis of mTBI and Dementia with Pooled Results

Meta-Analysis	Pooled Effect Size for mTBI
Graham 2022	RR 1.18 (95% CI 1.11 to 1.25)
Gu 2022	OR 1.73 (95% CI 1.36 to 2.19)
Leung 2022	HR 1.91 (95% CI 1.30 to 2.80)
Leung 2022 recurrent mTBI	HR 2.25 (95% CI 1.25 to 4.02)
Snowden 2020	OR 1.96 (95% CI 1.70 to 2.26)

RR=risk ratio/rate ratio; OR=odds ratio; HR=hazard ratio; CI=confidence interval

Table 2 Primary Studies Cited in Included Systematic Reviews

Primary Study with Risk Estimates	Effect Size and 95% CI
Barnes 2018 w/o LoC	RR 2.36 (95% CI 2.10 to 2.66)
Barnes 2018 w/ LOC	RR 2.51 (95% CI, 2.29 to 2.76)
Cations 2018	Conditional OR 0.65 (95% CI 0.31 to 1.38)
Didehbani 2020	**
Fann 2018	HR 1.13 (95% CI 1.13 to 1.20)
Gardner 2014 aged 55-64	HR 1.11 (0.80 to 1.53)
Gardner 2014 aged 65-74	HR 1.25 (1.04 to 1.51)
Gardner 2014 aged 75-84	HR 1.21 (1.08 to 1.36)
Gardner 2014 aged 85+	HR 1.25 (1.09 to 1.44)
Graves 1990	RR 4.85 (95% CI 1.72 to 13.66)
Helmes 2011	OR 0.85 (95% CI 0.29 to 2.25)
Lee 2013	OR 3.26 (95% CI 2.69 to 3.94)
McMillan 2014	**
Mehta 1999	Dementia RR 1.0 (95% CI 0.5 to 2.0)

	Alzheimer's disease RR 0.8 (95% CI 0.4 to 1.9)
Mendez 2015	**
Nordstrom 2014 1 mTBI & Alzheimer's	HR 1.0 (95% CI 0.5–2.0)
Nordstrom 2014 2+ mTBI & Alzheimer's	HR 2.5 (95% CI 0.8–8.1)
Nordstrom 2014 1 mTBI & Other dementia	HR 3.8 (95% CI 2.8–5.2)
Nordstrom 2014 2+ mTBI & Other dementia	HR 5 10.4 (95% CI 5 6.3 to 17.2)
Nordstrom 2018	OR 1.63 (95% CI 1.57 to 1.68)
Nordstrom 1 mTBI	RR 1.5 (95% CI 1.1 to 2.0)
Norstrom >1 mTBI	RR 1.8 (95% CI, 1.1 to 3.0)
Peterson 2010	**
Plassman 2000	OR 1.23 (95% CI 0.28–5.31)
Redelmeier 2019	OR 2.17 (95% CI 2.09 to 2.25)
Schneider 2021*	HR 1.38 (95% CI 1.24 to 1.55)
Schofield 1997	RR 1.70 (95% CI 0.39 to 7.50)
Sundstrom 2007 with APOE e4	OR 5.2 (95% CI 2.0 to 14.0)
Sundstrom 2007 without APOE e4	OR 0.9 (95% CI 0.4 to 1.8)
Stopa 2021	OR 2.3 (95% CI 2.0 to 2.6)
Tolppanen 2017	RR 1.18 (95% CI 1.15 to 1.22)
Yang 2019	OR 1.79 (95% CI 1.71 to 1.88)

RR=risk ratio/rate ratio; OR=odds ratio; HR=hazard ratio; CI=confidence interval; LoC=loss of consciousness

*Identified in independent search. Not in a systematic review.

**While review authors include this study in a systematic review of mTBI and dementia, we do not believe the study actually meets these strict criteria (e.g., mild cognitive impairment vs dementia, unclear mTBI population)

Table 3. Neuroimaging Findings

Study	Findings Summary
Hayes 2017	● mTBI and high genetic risk showed reduced cortical thickness in Alzheimer's disease-vulnerable regions. ● Males with mTBI and high genetic risk for Alzheimer's disease were associated with cortical thinning as a function of time since injury. ● A moderated mediation analysis showed that mTBI and high genetic risk indirectly influenced episodic memory performance through cortical thickness, suggesting that cortical thinning in Alzheimer's disease-vulnerable brain regions is a mechanism for reduced memory performance.
June 2020	● Greater brain atrophy in temporal lobe white matter and hippocampus in concussion patients. ● Differences in white matter microstructure using DTI, including increased radial and axial diffusivity in the fornix/stria terminalis, anterior corona radiata, and superior longitudinal fasciculus. ● In ^{15}O-water PET, higher resting cerebral blood flow was seen at first imaging visit in orbitofrontal and lateral temporal regions, and both increases and decreases were seen in prefrontal, cingulate, insular, hippocampal, and ventral temporal regions with longitudinal follow-up.
Rostowsky 2021	● The spatial pattern of cerebral white matter degradation observed in Alzheimer's disease is broadly similar to the pattern of diffuse axonal injury observed in TBI. ● Using machine learning, we find that the severity of AD-like brain changes observed during the chronic stage of mTBI can be accurately prognosticated based on acute assessments of post-traumatic mild cognitive impairment. ● These findings suggest that acute post-traumatic cognitive impairment predicts the magnitude of AD-like brain atrophy, which is itself associated with AD risk.
Yang 2015	● Amyloid-PET study showed an increase of amyloid accumulation and allele frequency of APOE4 in the mTBI patients with cognitive impairment.

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Appendix A. Search Strategies Across Databases

MEDLINE (Pubmed)

(“brain concussion”[MeSH Terms] OR (“brain”[All Fields] AND “concussion”[All Fields]) OR “brain concussion”[All Fields] OR “concussion”[All Fields] OR “concussions”[All Fields] OR “concussed”[All Fields] OR “concussive”[All Fields] OR “mTBI”[All Fields] OR “mild TBI”[All Fields] OR “brain injuries, traumatic”[MeSH Terms]) AND (“Dementia”[MeSH Terms] OR “Dementia”[All Fields])

Embase (Ovid)

1. brain concussion/
2. traumatic brain injury/
3. concussion.mp.
4. dementia/ or dementia.mp.
5. 1 or 2 or 3
6. 4 and 5
7. Limit 5 to (human and “remove medline records”)

Web of Science (Core Collection)

(ALL=(dementia) AND (ALL=(concussion) OR (TS=traumatic brain injury))) AND (AB=(“metaanalysis”) OR AB=(“meta analysis”) OR AB=(“meta-analysis”) OR AB=(“systematic review”) OR TI=(“meta analysis”) OR TI=(“metaanalysis”) OR TI=(“meta-analysis”) OR TI=(“systematic review”))

Epistimonikos

(title:((title:(dementia AND (concussion OR traumatic brain injury OR mtbi)) OR abstract:(dementia AND (concussion OR traumatic brain injury OR mtbi)))) OR abstract:((title:(dementia AND (concussion OR traumatic brain injury OR mtbi)) OR abstract:(dementia AND (concussion OR traumatic brain injury OR mtbi)))))

Cochrane Library of Systematic Reviews

([mh “brain concussion”] OR (brain AND concussion) OR “brain concussion” OR concussion OR concussions OR concussed OR concussive OR mTBI OR “mild TBI” OR [mh “brain injuries, traumatic”]) AND ([mh Dementia] OR Dementia)