McMaster University | Health Forum

Rapid Evidence Profile

Examining the potential causal relationship between post-traumatic stress disorder (PTSD) and Parkinson's disease

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Context

- Post-traumatic stress disorder (PTSD) is a mental health condition that can develop following exposure to extremely traumatic events such as interpersonal violence, combat, life-threatening accidents, or natural disasters.(1)
- Several epidemiological studies have assessed the relationship between PTSD and neurodegenerative disorders, particularly Parkinson's disease.(2-4)
- This rapid evidence profile assesses the potential causal relationship between PTSD and Parkinson's disease by examining whether the existing evidence satisfies six key causal criteria: temporality, strength of association, dose-response relationship, consistency of evidence, specificity, and biological plausibility.

Question

Is there a causal relationship (association) between PTSD and Parkinson's disease, and if so, what is the nature of the relationship?

Box 1: Evidence and other types of information

+ Global evidence drawn upon

Evidence syntheses and single studies selected based on relevance, quality, and recency of search

- No forms of domestic evidence used

- No other types of information used

*** Additional notable features**

Prepared in three business days using an 'all hands on deck' approach

Prepared with input from two subject-matter experts

High-level summary of key findings

- We identified nine evidence documents that explored the potential causal relationship between PTSD and Parkinson's disease, and we deemed eight of these to be highly relevant to the question, including one evidence synthesis and seven single studies.
- Generally, the highly relevant evidence documents report an association between PTSD and Parkinson's disease that meets several of the causal criteria for assessment.
- For the **strength of association**, one high-quality meta-analysis and multiple large-scale epidemiological studies consistently found that individuals with PTSD have a significantly increased risk of developing Parkinson's disease, with hazard and odds ratios ranging from approximately 1.35 to 3.46 across studies.
- For **temporal relationships**, several case-control studies demonstrated that PTSD precedes Parkinson's disease diagnosis by years to decades, with associations persisting even in analyses using extended lag times between diagnoses.
- Few evidence documents addressed **dose-response relationships**; limited evidence suggests higher PTSD symptom severity correlates with greater Parkinson's disease risk, particularly when combined with other trauma-related conditions.

- For **biological plausibility**, several studies proposed mechanisms through which PTSD may contribute to Parkinson's disease, including chronic neuroinflammation, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, shared genetic vulnerabilities, and sleep disturbances (particularly Rapid Eye Movement (REM) sleep behaviour disorder).

Framework to organize what we looked for

- Types of PTSD
  - General PTSD diagnosis (e.g., diagnostic criteria, code)
  - Subtypes of PTSD
    - Acute stress disorder
    - Uncomplicated PTSD
    - Delayed-onset PTSD
    - Dissociative PTSD
    - Comorbid PTSD (including with mood disorders)
    - Secondary traumatic stress
- Parkinson's disease assessment
  - General Parkinson's diagnosis (e.g., diagnostic criteria, code)
  - Disease progression measurements
  - UPDRS (Unified Parkinson's Disease Rating Scale)
  - Non-motor symptom assessments
  - Hoehn and Yahr scale (Stages 1.0–5.0)
    - Stage 1.0: Unilateral involvement only
    - Stage 1.5: Unilateral and axial involvement
    - Stage 2.0: Bilateral involvement without impairment of balance
    - Stage 2.5: Mild bilateral involvement with recovery on retropulsion (pull) test
    - Stage 3.0: Mild to moderate bilateral involvement, some postural instability but physically independent
    - Stage 4.0: Severe disability, still able to walk and to stand unassisted
    - Stage 5.0: Wheelchair bound or bedridden unless aided
- Risk factors of Parkinson's disease
  - Demographic factors (e.g., age, sex, socio-economic status, urbanization level)
  - Genetic factors (e.g., family history, specific gene mutations)
  - Environmental exposures (e.g., pesticides, solvents, metals)
  - Medical/psychiatric comorbidities (e.g., depression, diabetes, epilepsy, migraine, traumatic brain injury)
  - Lifestyle factors (e.g., smoking status, physical activity, diet)
  - Other
- Priority populations
  - Military personnel (active and Veterans)

Box 2: Approach and supporting materials

At the beginning of each rapid evidence profile and throughout its development, we engage one or more subject-matter experts who help us to scope the question and ensure relevant context is taken into account in the summary of the evidence.

We identified evidence addressing the question by searching Medline and PsycINFO. All searches were conducted on 14 April 2025. The search strategies used are included in Appendix 1. In contrast to synthesis methods that provide an in-depth understanding of the evidence, this profile focuses on providing an overview and key insights from relevant documents.

We appraised the methodological quality of any evidence syntheses that were deemed to be highly relevant using the first version of the AMSTAR tool. AMSTAR rates overall quality on a scale of 0 to 11, where 11/11 represents a review of the highest quality, medium-quality evidence syntheses are those with scores between four and seven, and low-quality evidence syntheses are those with scores less than four. The AMSTAR tool was developed to assess reviews focused on clinical interventions, so not all criteria apply to evidence syntheses pertaining to delivery, financial, or governance arrangements within health systems or implementation strategies.

A separate appendix document includes:
1) methodological details (Appendix 1)
2) details about each identified synthesis (Appendix 2)
3) details about each identified single study (Appendix 3)
4) documents that were excluded in the final stages of review (Appendix 4).

This rapid evidence profile was prepared in the equivalent of three days of a 'full-court press' by all involved staff.

    - Law enforcement officers (e.g. RCMP)
    - Other
- Causality assessment
    - Temporal relationship (e.g., PTSD preceding Parkinson's disease onset)
    - Strength of association (e.g., association should meet statistical significance to demonstrate that it was not simply a chance occurrence, study reported data as hazard ratios, relative risks, odds ratios)
    - Dose-response relationship (e.g., PTSD severity correlation with Parkinson's risk)
    - Consistency across evidence (e.g., similar or the same results generated by studies using different methods in different settings)
    - Biological plausibility (neuroinflammatory, HPA axis, and other proposed mechanisms)
    - Specificity (e.g., the exposure is the only cause of the outcome that can be shown)
    - Consideration of confounding variables and mediating factors
- Outcomes
    - Parkinson's disease incidence/onset
        - Age at Parkinson's disease onset
        - Rate of Parkinson's disease progression
        - Response to Parkinson's disease treatment
        - Parkinson's disease related disability

What we found

We identified nine evidence documents that explored the potential causal relationship between PTSD and Parkinson's disease, of which we determined eight to be highly relevant, including:

- one evidence synthesis (systematic review and meta-analysis)
- seven single studies (two retrospective cohort studies, four case-control studies, and one cross-sectional study).

Coverage by and gaps in existing evidence syntheses and domestic evidence

Generally, the highly relevant evidence documents report an association between PTSD and Parkinson's disease. The included documents covered some causality criteria to varying degrees, with the strongest evidence for strength of association and temporal relationship. Few studies addressed dose-response relationships in detail, and while biological mechanisms were proposed, more direct evidence is needed to fully establish biological plausibility.

No Canadian-specific studies were identified among the highly relevant evidence documents, representing a significant gap in understanding how these associations might manifest in the Canadian population specifically. The existing evidence primarily comes from international contexts (United States, Taiwan, Sweden, Israel), and while these findings may have some applicability to the Canadian context, population-specific factors such as differences in health-system features and resources, demographic composition, and patterns of PTSD prevalence and treatment could influence the relationship between PTSD and Parkinson's disease in Canada.

In terms of gaps, the limited number of relevant evidence documents (particularly prospective studies) indicates a need for more empirical research exploring causality between PTSD and Parkinson's disease. While there was variation in study jurisdictions, many studies focused heavily on military Veteran populations, limiting generalizability. Additionally, several studies relied on administrative data and diagnostic codes, which may not fully capture clinical nuances. Future research should focus on producing high-quality prospective evidence that explores the direct impact of PTSD on the onset and progression of Parkinson's disease across diverse populations, including specific Canadian cohorts.

The evidence was also limited in examining how PTSD treatment might modify Parkinson's disease risk, which could be particularly relevant for clinical practice and policy implications in the Canadian healthcare system. Finally, more research is needed to understand how PTSD interacts with other known risk factors for Parkinson's disease in

determining overall disease risk, progression, and outcomes. A summary of this evidence is included following an overview of the causality criteria.

Key findings from included evidence documents

Strength of association

One high-quality evidence synthesis and seven single studies provide substantial findings on the strength of association between PTSD and Parkinson's disease. Jones et al. conducted a systematic review and meta-analysis examining the risk of degenerative synucleinopathies, including Parkinson's disease, among adults with PTSD. Their meta-analysis of four retrospective cohort studies found that incident PTSD was associated with increased risk of Parkinson's disease and dementia with Lewy bodies (pooled HR 1.88, 95% CI 1.08–3.24; p=0.035).(5)

White et al. conducted a population-based matched case-control study among Veterans using Veterans Affairs (VA) healthcare facilities from 1999 to 2013. Among 176,871 Parkinson's disease cases and 707,484 matched controls, PTSD was associated with a 2.71-fold increased odds of Parkinson's disease (95% CI 2.66–2.77), even after adjusting for race and other confounders.(6)

In a nationwide retrospective longitudinal study using Taiwan's National Health Insurance Research Database, Chan et al. identified 1,456 patients aged ≥45 years with PTSD and matched them with 5,824 individuals without PTSD. After comprehensive adjustment for demographic factors and comorbidities, they found patients with PTSD had a 3.46-fold (95% CI 1.72–6.96) increased risk of developing Parkinson's disease.(3)

Similarly, Barer et al. conducted a population-based retrospective cohort study in Israel with 8,336 patients with PTSD matched to 8,336 controls. Their findings showed patients with PTSD had a 1.48-fold (95% CI 1.10–1.99) increased risk for Parkinson's disease compared to matched controls.(2)

Using a cohort of 158,122 U.S. Veterans with healthcare utilization between 1999 and 2021, Weaver et al. employed a nested case-control design with rigorous Parkinson's disease case validation through medical record review. They found that a PTSD diagnosis was significantly associated with Parkinson's disease (OR=1.35; 95% CI 1.15–1.58) after adjusting for potential confounders. This association strengthened when restricted to cases where PTSD diagnosis preceded Parkinson's disease diagnosis (OR=1.53; 95% CI 1.30–1.81).(7)

Scott et al. conducted a large-scale case-control study examining 71,933 Parkinson's disease cases and 287,732 matched controls from VA healthcare data. They demonstrated that PTSD increased the odds of subsequent Parkinson's disease at all preceding 5-year intervals going back 60 years, with odds ratios ranging from 1.5 (95% CI 1.4–1.7) to 1.9 (95% CI 1.9–2.0).(8)

In a focused case-control study using the National Alzheimer's Coordinating Centre Uniform Data Set, Pietrzykowski et al. compared older adults (65+ years) with and without a history of PTSD (n=472; 236 pairs). They found significantly higher prevalence of Parkinson's disease among individuals with a history of PTSD (2.1% vs. 0.4%), alongside other conditions including depression, anxiety, and traumatic brain injury (TBI).(9)

Finally, Neilson et al. conducted a cross-sectional study of 216 U.S. Veterans with chronic pain and 30 controls to examine the "polytrauma clinical triad" (PTSD, TBI, and chronic pain) and its relationship to prodromal Parkinson's disease. They found that 27% of those with the triad met criteria for prodromal Parkinson's disease, compared to 18% of those with chronic pain alone and 8.3% of controls. The severity of polytrauma symptoms was significantly correlated with prodromal Parkinson's disease probability (r=0.28; p=0.03).(10)

Temporal relationship

Multiple studies established temporal relationships between PTSD and subsequent Parkinson's disease development. Scott et al. anchored PTSD onset to the midpoint of military active duty (typically in Veterans' late 20s), decades before the onset of Parkinson's disease, and found that PTSD was associated with significantly increased odds of later Parkinson's disease at each five-year interval across the entire 60-year period (OR range 1.5; 95% CI 1.4–1.7 to. 1.9; 95% CI 1.9–2.0). This extended observation period convincingly establishes that PTSD precedes Parkinson's disease by decades rather than representing a prodromal symptom.(8)

Chan et al. established temporality through a longitudinal design, identifying individuals diagnosed with PTSD between 2002 and 2009 and following them until 2011 to observe Parkinson's disease development. Patients with PTSD not only had a higher incidence rate of Parkinson's disease (2.0% vs. 0.5%) but also developed it earlier (3.18 ± 2.07 years after PTSD diagnosis compared to 4.51 ± 2.58 years in controls). Importantly, sensitivity analyses excluding cases diagnosed during the first year and first three years of observation confirmed this relationship, strengthening evidence that PTSD preceded Parkinson's disease.(3)

White et al. mitigated concerns about reverse causation by requiring a minimum one-year lag time between PTSD and Parkinson's disease diagnoses. In their dataset, PTSD prevalence was significantly higher in Parkinson's disease cases than in matched controls (10.3% vs. 4.2%). Their sensitivity analysis using a three-year lag time continued to show significant associations (adjusted HR 3.44 (95% CI 3.36–3.53) with three-year lag versus 2.71 (95% CI 2.66–2.77) with one-year lag), further supporting PTSD as a risk factor rather than a consequence of early, undiagnosed Parkinson's disease.(6)

Barer et al.'s study followed individuals diagnosed with PTSD between 2000 and 2019 for an average of 10.4 years, finding Parkinson's disease developed in 1.4% of patients with PTSD versus 0.9% of patients without PTSD. Although sensitivity analyses excluding Parkinson's disease cases diagnosed in the first year after PTSD showed slightly attenuated associations (HR 1.36; 95% CI 0.96–1.83 vs. HR 1.33; 95% CI 0.96–1.83), the temporal relationship remained positive, supporting PTSD as preceding Parkinson's disease. This study also highlighted a notably stronger association in men over 72 years old (HR 1.95; 95% CI 1.16–3.28), suggesting potential age-dependent effects.(2)

Dose-response relationship

Relatively few studies have specifically examined how different levels of PTSD severity (mild, moderate, severe) or duration influence subsequent Parkinson's disease risk, which would constitute a true dose-response analysis. However, a few evidence documents suggest that PTSD symptom intensity may correlate with Parkinson's disease risk, providing preliminary support for a dose-response relationship.

Scott et al. found that Veterans with more severe trauma-related symptoms showed higher probabilities of developing Parkinson's disease. They also identified significant synergism between TBI and PTSD in influencing Parkinson's disease risk, with synergy index (SI) values consistently exceeding additive expectations across most time periods (mean SI=1.19, range: 1.11–1.28). Furthermore, they discovered that chronic pain and migraine demonstrated the strongest synergistic effects when combined with PTSD and TBI in increasing Parkinson's disease risk.(8)

Similarly, Neilson et al. found a direct correlation between polytrauma symptom severity and prodromal Parkinson's disease probability, suggesting that the cumulative burden of trauma symptoms is associated with increased neurodegeneration risk. Their research on the "polytrauma clinical triad" (PTSD, TBI, and chronic pain) revealed that individuals with all three conditions showed the highest proportion of prodromal Parkinson's disease features compared to those with fewer conditions.(10)

Biological plausibility

While these studies primarily establish epidemiological associations between PTSD and Parkinson's disease, several proposed biological mechanisms could explain this relationship. The temporal sequence observed in multiple studies (where PTSD diagnosis precedes Parkinson's disease diagnosis) strengthens the case for potential causality beyond mere correlation. Three studies discussed how PTSD-associated chronic inflammation might contribute to neurodegeneration through microglial activation and increased pro-inflammatory cytokines.(3; 5; 8)

Additionally, four studies examined or discussed sleep disturbances, particularly Rapid Eye Movement (REM) sleep behaviour disorder and insomnia, as potential mechanisms linking PTSD and Parkinson's disease. REM sleep behaviour disorder is both a well-established prodromal marker for synucleinopathies and significantly more prevalent in individuals with PTSD, suggesting a shared neurobiological vulnerability.(2; 5; 8; 10)

Moreover, Chan et al. and Jones et al. both discussed HPA axis dysregulation as a potential mechanism linking PTSD to Parkinson's disease, with Chan et al. highlighting altered cortisol and corticotropin-releasing hormone (CRH) dynamics leading to neuroinflammation and dopaminergic neuron damage, while Jones et al. referenced neuroendocrine alterations more broadly within the context of stress-related neurodegeneration.(3; 5)

Finally, Jones et al. also discussed the possibility of shared genetic vulnerability between PTSD and Parkinson's disease, referencing evidence from genome-wide association studies. These shared genetic factors involve dopamine neurotransmission (Dopamine Receptor D2 (DRD2), Solute Carrier Family 6 Member 3(SLC6A)), mitophagy and programmed cell death (PARK2), and protein aggregation (FKBP506 binding protein genes) – suggesting common biological pathways that might predispose individuals to both conditions.(5)

Next steps based on the identified evidence

- While the association between PTSD and Parkinson's disease meets several causal criteria including temporality relationship and strength of association, future research should focus on better establishing dose-response relationships by examining how PTSD severity, duration, and treatment affect subsequent Parkinson's disease.
- Studies exploring detailed biological mechanisms linking PTSD and Parkinson's disease are needed, including longitudinal research measuring inflammatory markers, HPA axis function, sleep architecture changes, and neuroimaging to track potential pathways from PTSD to neurodegeneration.
- Canadian-specific research is particularly needed to understand how these associations manifest within Canada's healthcare system and population, including potential differences in risk factors, healthcare access, and treatment approaches.
- Direct resources toward specialized neurological care and community-based support programs within healthcare systems serving populations with high PTSD prevalence.

References

1. Yehuda R, Hoge CW, McFarlane AC, et al. Post-traumatic stress disorder. *Nature Reviews Disease Primers* 2015; 1(1): 1-22.
2. Barer Y, Chodick G, Glaser Chodick N, Gurevich T. Risk of Parkinson disease among adults with vs without posttraumatic stress disorder. *JAMA Netw Open* 2022; 5(8): e2225445.

3. Chan YE, Bai YM, Hsu JW, et al. Post-traumatic Stress Disorder and Risk of Parkinson Disease: A Nationwide Longitudinal Study. *Am J Geriatr Psychiatry* 2017; 25(8): 917-923.
4. Song H, Sieurin J, Wirdefeldt K, et al. Association of stress-related disorders with subsequent neurodegenerative diseases. *JAMA Neurol* 2020; 77(6): 700-709.
5. Jones MB, Gates R, Gibson L, et al. Post-traumatic stress disorder and risk of degenerative synucleinopathies: Systematic review and meta-analysis. *Am J Geriatr Psychiatry* 2023;31(11): 978-990.
6. White DL, Kunik ME, Yu H, et al. Post-traumatic stress disorder is associated with further increased Parkinson's disease risk in veterans with traumatic brain injury. *Ann Neurol* 2020;88(1): 33-41.
7. Weaver FM, Cao L, Stroupe KT, et al. Post-traumatic stress disorder and risk of Parkinson's disease in a veteran cohort. *J Parkinsons Dis* 2024;14(6): 1265-1269.
8. Scott GD, Neilson LE, Woltjer R, Quinn JF, Lim MM. Lifelong Association of disorders related to military trauma with subsequent Parkinson's disease. *Mov Disord* 2023; 38(8): 1483-1492.
9. Pietrzykowski MO, Jackson CE, Gaudet CE. Co-occurring mental and physical health conditions among older adults with and without post-traumatic stress disorder: A Case control study. *J Geriatr Psychiatry Neurol* 2025; 38(3): 191-200.
10. Neilson LE, Balba NM, Elliott JE, et al. The potential role of chronic pain and the polytrauma clinical triad in predicting prodromal PD: A cross-sectional study of U.S. Veterans. *Clin Park Relat Disord* 2024; 10: 100253.

Wu N, Wang Q, Bain T, DeMaio P, Whitelaw H, Ciurea P, Ali A, Bhuiya AR, Sivanesanathan T, Wilson MG. Rapid evidence profile report #94: Examining the potential causal relationship between post-traumatic stress disorder (PTSD) and Parkinson's disease. Hamilton: McMaster Health Forum, 30 April 2025.

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