Am J of Geriatric Psychiatry 31:11 (2023) 978–990

Available online at www.sciencedirect.com

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journal homepage: www.ajgponline.org

Regular Research Article

Post-Traumatic Stress Disorder and Risk of Degenerative Synucleinopathies: Systematic Review and Meta-Analysis

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ARTICLE INFO

Article history:
Received March, 30 2023
Accepted April, 25 2023

Key Words:
Stress disorders, post-traumatic
Parkinson disease
Parkinsonian disorders
Lewy body disease

ABSTRACT

Objective: *A systematic review was conducted to answer whether adult-onset post-traumatic stress disorder (PTSD) is associated with increased risk of Parkinson's disease (PD) and related synucleinopathies.* ***Design:*** *A systematic search of Medline (Ovid), Embase (Elsevier), PsycInfo (Ovid), Cochrane Library (Wiley), and Web of Science (Clarivate) was performed using MeSH headings and equivalent terms for PTSD, PD, DLB, and related disorders.* ***Setting:*** *No restrictions.* ***Participants:*** *Eligible articles were published in peer-reviewed journals, sampled adult human populations, and treated PTSD and degenerative synucleinopathies as exposures and outcomes, respectively.* ***Measurements:*** *Extracted data included diagnostic methods, sample characteristics, matching procedures, covariates, and effect estimates. Bias assessment was performed with the Newcastle-Ottawa scale. Hazard ratios were pooled using the random effects model, and the Hartung-Knapp adjustment was applied due to the small number of studies.* ***Results:*** *A total of six articles comprising seven unique samples (total n = 1,747,378) met eligibility criteria. The risk of PD was reported in three retrospective cohort studies and one case-control study. Risk of DLB was reported in one retrospective cohort, one case-control, and one prospective cohort study. No studies addressed potential relationships with multiple system atrophy or pure autonomic failure. Meta-analysis of hazard ratios from four retrospective cohort studies supported the hypothesis that incident PTSD was associated with PD and DLB risk (pooled HR*

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Published by Elsevier Inc. on behalf of American Association for Geriatric Psychiatry.
https://doi.org/10.1016/j.jagp.2023.04.016

1.88, 95% C.I. 1.08−3.24; p = 0.035). ***Conclusions:*** *The sparse literature to-date supports further investigations on the association of mid- to late-life PTSD with Parkinson's and related neurodegenerative disorders.* (Am J Geriatr Psychiatry 2023; 31:978−990)

Highlights

- **What is the primary question addressed by this study?**
  In previous research studies, is there evidence of a link between post-traumatic stress disorder (PTSD) and risk for a subsequent degenerative synucleinopathy, i.e., Parkinson's disease (PD) and related disorders?
- **What is the main finding of this study?**
  Our systematic literature search identified six articles containing seven unique study samples (total n = 1,747,378); five of these articles were registry-based. Meta-analysis of hazard ratios (HR) from four retrospective cohort studies supported the hypothesis that PTSD was associated with incident Parkinson's disease and Lewy body dementia (pooled HR 1.88, 95% C.I. 1.08−3.24; p = 0.035).
- **What is the meaning of the finding?**
  This preliminary evidence for an association between adult-onset PTSD and later development of PD and related degenerative synucleinopathies provides a basis for understanding how presence of certain psychiatric conditions affects risk for neurodegenerative diseases and development of interventions that mitigate that risk.

OBJECTIVE

Degenerative synucleinopathies are characterized by aggregates of misfolded alpha-synuclein in neuronal and/or glial cells of the central and peripheral nervous systems. Of the primary synucleinopathies, namely Parkinson's disease (PD), dementia with Lewy bodies (DLB), multiple system atrophy (MSA), and pure autonomic failure, PD is the most common: nearly 10 million people have PD worldwide, and 90,000 Americans are diagnosed with PD per year.[1] By the year 2030, an estimated 1,238,000 Americans will be living with PD.[2] The combined direct and indirect costs of PD in the United States is $52 billion per year, which includes lost income, social security payments, and treatment.[1]

As current treatments for PD and related disorders are symptomatic, recent research is also focused on strategies to prevent disease onset or slow its progression.[3,4] A critical first step in development of neuro-protective or preventive interventions is identification of at-risk, preclinical individuals, or individuals with early prodromal motor or non-motor features; these individuals would benefit most from these interventions.

It is widely recognized that depressive and anxiety disorders can manifest prior to the onset of PD motor phenomena and the diagnosis of PD. Occurrence of depression was shown to increase risk of a future PD diagnosis in several large epidemiological studies, with odds ratios ranging from 1.2 to 3.2.[5] Anxiety disorders, while relatively less studied, are also implicated as potential risk or prodromal markers.[5] The Movement Disorder Society Research Criteria for Prodromal PD recognizes depressive disturbances, with or without an accompanying anxiety condition, as prodromal markers of PD, albeit with a relatively low positive likelihood ratio of 1.6.[6]

More recently, post-traumatic stress disorder (PTSD) has emerged as a psychiatric syndrome potentially related to PD and neurodegenerative dementias.[7-9] Recent studies linked PTSD to rapid eye movement sleep disorder, one of the strongest prodromal markers of degenerative synucleinopathies.[10,11] Previous systematic reviews reported associations with PTSD and elevated risks of all-cause dementias.[7,12,13] Clarity on

the relationship of PTSD to emergence of specific clinicopathological entities, as opposed to all-cause neurodegenerative disorders, is needed to develop preventive or disease modifying interventions.

Examination of PTSD as an early prodromal feature of degenerative synucleinopathies and its treatment as a potentially modifiable risk factor is of special interest to United States (US) veterans and the veterans affairs (VA) healthcare system. PTSD is highly prevalent among US Veterans: 10.2% of men and 15.5% of women veterans seeking VA care are diagnosed with PTSD.[14] Estimated rates are even higher in Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF veterans, in whom reported prevalence of PTSD is 23%.[15] As those Veterans of recent tours age, there is a parallel increase in their risk of synucleinopathies and indications for preventive interventions.

This systematic review of the available literature examined the evidence for an association between PTSD and subsequent risk of PD and related disorders. Synucleinopathies other than PD (e.g., DLB and MSA) were included in this search to address whether PTSD is associated with alpha-synuclein phenotypes. We hypothesized that PTSD in adult military and civilian samples would be associated with an increased risk of PD and related disorders compared to individuals without PTSD.

METHODS

This systematic review was registered at PROSPERO (CRD42021267547). Methods followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.[16]

Data Sources and Search Strategy

A literature search of Medline (Ovid) was conducted by a professional research librarian on PTSD and PD using MeSH headings ("Trauma and Stressor Related Disorders" and Parkinsonian Disorders) as well as equivalent keywords and phrases and truncated terms (trauma stress related disorders, adjustment disorders, psychological trauma, temporary association, PTSD, PTSD, post-traumatic neurosis, combat neurosis, combat disorder, shell shock, war neurosis, combat stress disorder, delayed onset PTSD, acute and chronic PTSD, intergenerational and transgenerational trauma, historical trauma, moral injuries, and sexual trauma. Parkinson, Parkinson disease, Parkinson disorders, Lewy body, multiple system atrophy, synucleinopathy, alpha synucleinopathy, and idiopathic Parkinson disease).

The exact strategy appears in the Appendix. The search strategy was then translated from Medline (Ovid) to Embase (Elsevier), PsycInfo (Ovid), Cochrane Library (Wiley), and Web of Science (Clarivate).

The initial search was conducted in February 2021. A total of 1,690 citations were identified on the subject matter in all the databases. The citations were combined into an EndNote Library and de-duplicated among themselves. A total of 1,117 unique citations were identified. All studies were included. There were no limits to the search.

The searches were updated on October 20, 2022. The search strategies were the same except for the limit to 2021-present. A total of 368 citations were identified on the subject matter in all the databases. The citations were combined into an EndNote Library and de-duplicated among themselves. A total of 248 unique citations were identified.

The titles and abstracts of these citations were screened by two independent reviewers (MJ, RG, JT, DB, LG, ME, GB, AG) and disagreements resolved by a separate independent reviewer (MJ or LG). If inclusion criteria were not clear from the title or abstract, the article was included for full text review. In addition, the bibliographies of pertinent reviews and included full texts were hand-searched by two independent reviewers (MJ and RG) and added to full text review. Full texts were then screened by two independent reviewers (MJ, JT, RG, DB, LG, ME, GB, AG) and conflicts resolved by a second independent reviewer (MJ, RG, LG, LM).

Study Selection

Studies met the following inclusion criteria: 1) written in English; 2) retrievable as full texts; 3) peer-reviewed, primary research articles (although reviews were searched for pertinent citations); 4) human studies only; 5) adult subjects at time of study entry; 6) prospective cohort, retrospective cohort, case-control, case-series, and clinical trial study designs; 7) assessed for the presence or absence of PTSD via diagnostic interviews, symptom severity scales, established clinical criteria, or medical database codes; 7) assessed for the

presence or absence of degenerative synucleinopathies (PD, DLB, MSA, pure autonomic failure) via established diagnostic criteria (e.g., UK Brain Bank criteria for PD)[17] or medical database code.

Exclusion criteria were the following: 1) animal studies; 2) child populations; 3) not written in English; 4) poster abstracts; 5) not published in peer-reviewed journal; 6) not original research; 7) case reports; 8) did not assess for PTSD exposures, or only assessed emotional traumas or adjustment disorders; 9) lacked degenerative synucleinopathies as an outcome, or identified only as a *formes* fruste degenerative synucleinopathy, for example, rapid eye movement sleep behavior disorder, parkinsonism from other causes, or behavioral manifestations of dementia.

Data Extraction

Data was extracted by two reviewers independently (RG, JT, DB, LG, ME, GB, AG) and conflicts resolved by a third independent reviewer (MJ). Extracted data included 1) study author, year, and country; 2) study design; 3) participant characteristics (e.g., age, medical and psychiatric comorbidities); 4) method of PTSD ascertainment; 5) method of degenerative synucleinopathy ascertainment; 6) duration of study follow up; 7) matching procedures and covariates (when present); and 8) pertinent results.

The evaluation of study quality was performed with the Newcastle-Ottawa Scale for cohort and case control studies.[18] This scale assesses risk-of-bias in three domains: 1) methods of group selection (up to 4 stars); 2) comparability of study groups (up to 2 stars); and 3) quality of exposure or outcome ascertainment (up to 3 stars). Possible scores range from 0 to 9 stars, with higher scores indicating less bias. Quality assessment was performed by two independent reviewers (RG, JT, DB, LG, ME, GB, AG), and conflicts resolved by a third independent reviewer (MJ).

Meta-Analysis

A meta-analysis for studies reporting hazard ratio (HR) of PD and related disorders via time-to-event analyses was conducted using the Meta package meta-analysis tool[19] in R software (version 4.1.0).[20] The generic inverse-variance method was used to estimate pooled HR. The random effects model was chosen to account for the high heterogeneity inherent to observational studies.[21] The restricted maximum likelihood estimator was used to calculate the between-study variance τ^2. The Hartung-Knapp adjustment for random effects models was applied due to the small number of studies.[22,23] Between-study heterogeneity was assessed with the Cochrane's Q test and I^2 statistic. A Q test p-value <0.1 or I^2 statistic greater than 50% indicated high heterogeneity between studies. A p value <0.05 was considered statistically significant for all other analyses.

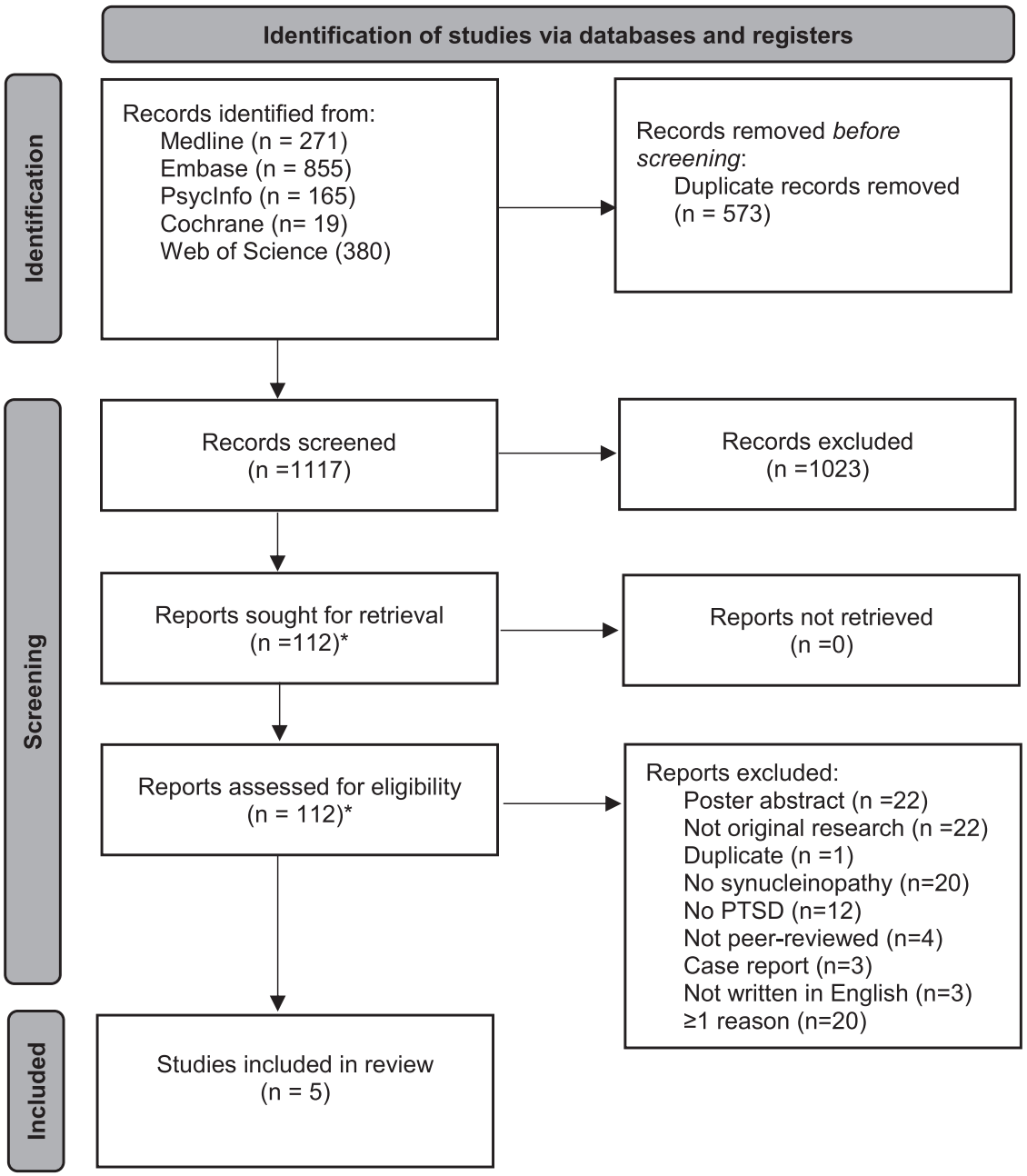
RESULTS

Study Selection

The initial database search identified 1,117 unique abstracts, 94 of which were selected for full text review. An additional 18 citations were identified via hand-searching of full texts and pertinent review articles. These 112 full texts yielded five articles meeting full inclusion and exclusion criteria (see PRISMA diagram in Fig. 1). An updated database search identified 248 new abstracts, 17 of which were selected for full text review. The review of these and two additional full texts identified by hand-searching yielded one additional study (see PRISMA diagram in Fig. 2). In total, six articles comprising seven unique study samples met all inclusion/exclusion criteria.

Four articles initially appeared to meet inclusion criteria but were ultimately excluded. Two retrospective cohort, VA registry-based studies investigated poor sleep quality and traumatic brain injury as risk factors for PD and DLB, respectively.[24,25] However, the primary analyses in these studies adjusted for PTSD, along with several other covariates. Thus, a specific contribution of PTSD to PD and DLB risk could not be extracted from these studies. We considered another registry-based, retrospective cohort study that assessed risk of PD associated with adjustment disorders.[26] However, PTSD diagnosis requires exposure to a traumatic, not necessarily stressful, life event, and manifests with unique symptom clusters (e.g., re-experiencing, hyperarousal) from adjustment disorders. Finally, we excluded one small (n = 16) case control study that assessed an association between PTSD and trauma re-enactment behaviors, but not DLB diagnosis, in Veterans with dementia.[27]

FIGURE 1. PRISMA diagram of original search.

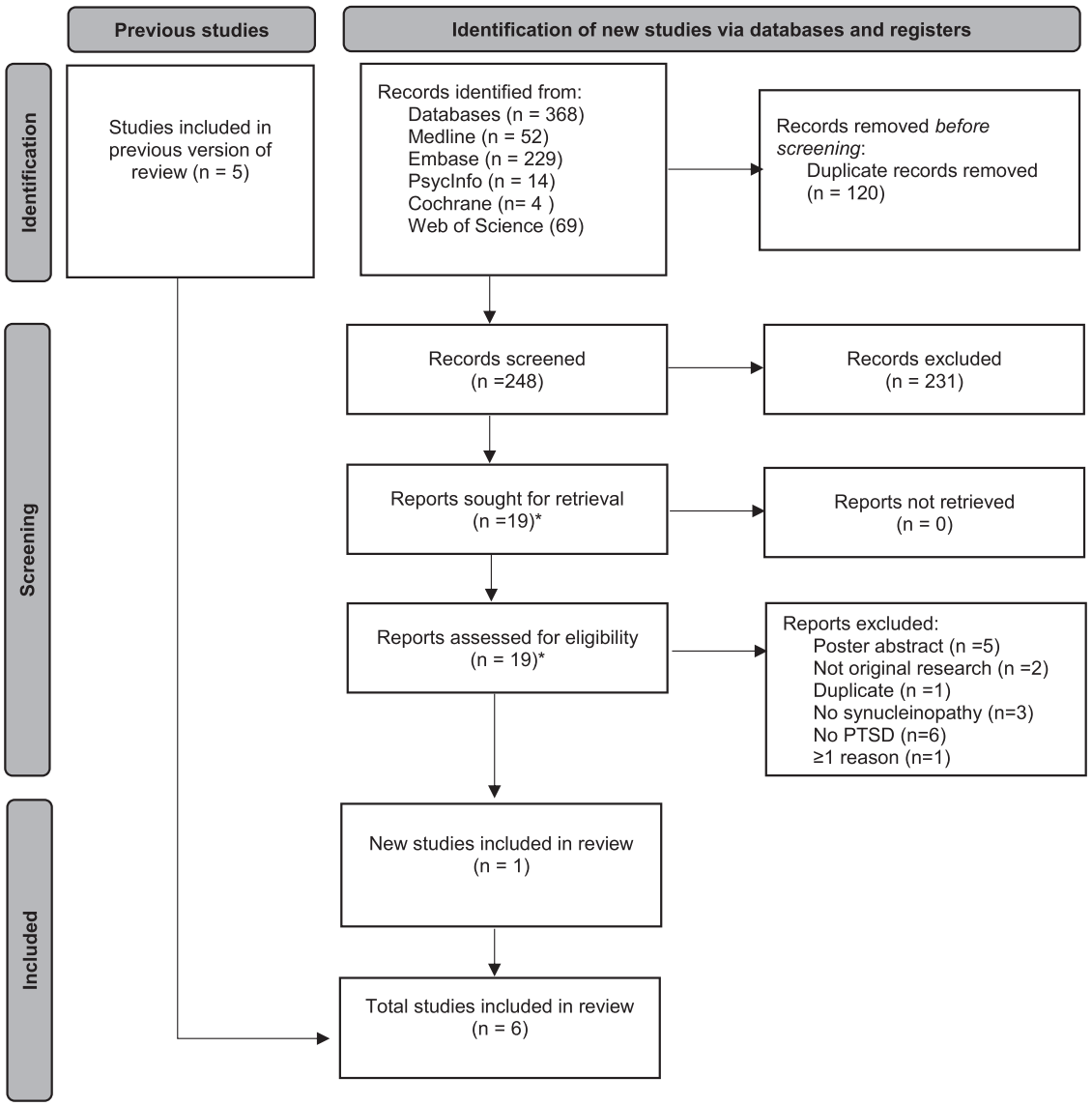


*Total number accounts for 18 additional citations identified from hand-searching of pertinent reviews and included full texts. PTSD: post-traumatic stress disorder.

Study Characteristics

Characteristics of included studies are shown in Table 1. There were four registry-based, retrospective cohort studies comparing rates of incident PD[28–30] or DLB[31] in subjects with versus without PTSD. Another registry-based, case-control study by White et al.[9] compared odds of PD in Veterans with or without PTSD.

FIGURE 2. PRISMA diagram of updated search.



*Total includes two citations identified from hand-searching of pertinent reviews and the included full text. PTSD = post-traumatic stress disorder.

The remaining article by Bonanni et al.[32] comprised two study designs: 1) a case-control arm (Arm 1) comparing proportions of PTSD exposures in subjects with dementia, and 2) a prospective cohort arm (Arm 2) reporting incident dementia diagnoses in patients with PTSD. We did not identify any articles that examined the risk of MSA or pure autonomic failure.

In five of six articles (five of seven samples), PTSD diagnosis was ascertained via diagnostic codes from clinical records. In Arms 1 and 2 of Bonanni et al.,[32] on the other hand, PTSD was diagnosed via Diagnostic and Statistical Manual of Mental Disorder, 4th ed. (DSM-IV) criteria[33] and the Clinician Administered PTSD Scale as defined by DSM-IV (CAPS-IV).[34] Of note, CAPS-IV total scores reported in Arm 1 were

TABLE 1. Study Characteristics

Study	Design	Region	Source	Synuclein Type	Age for Inclusion (yrs)	Matching [Ratio]	PTSD Method	Synuclein Method	Primary Outcome
Yaffe[31]	RC	US	VA Database	DLB	≥55	PTSD(-): randomly selected [3:1]	≥2 ICD-9 codes (309.81) for PTSD	ICD-9 code (331.82) for DLB	All-cause dementia
Chan[29]	RC	Taiwan	National Health Insurance Research Database	PD	≥45	PTSD(-): age, sex, time enrolled; [4:1]	ICD-9 code (309.81) for PTSD by board-certified psychiatrist	ICD-9 (332.0) code for paralysis agitans by board-certified neurologist	Incident PD
Song[30]	RC	Sweden	Swedish National Patient Register	PD	≥40 at study end	SRD(-): birth yr and county, sex [10:1]	Swedish Revisions of ICD-9 (309B) and ICD-10 (F43.1) codes for PTSD	Swedish revisions of ICD-9 (332A) and ICD-10 (G20) codes for PD	Incident neurodeg. disease (any)
Barer[28]	RC	Israel	Maccabi Health Care Services Database	PD	>49	PTSD(-): exact birth year, sex [1:1]	ICD-9 code (309.81) for PTSD by MH specialists, hospital DC, or chronic PCP diagnosis	ICD-9 codes (332, 332.0) for PD by neurologist, hospital DC, or chronic PCP diagnosis	Incident PD
White[9]	CC	US	VA Databases	PD	≥30	PD(-): time enrolled, 5-year birth group, gender [4:1]	≥ 1 ICD-9 code (309.81) for PTSD	≥2 ICD-9 codes (332.0) for PD within 3-year period	Associations among PTSD, TBI, and PD
Bonanni[32] Arm 1	CC	Italy	Dementia tertiary clinic	DLB	None	None	Clinician interviews; medical records; DSM-IV; CAPS-IV	Criteria per 2005 Consortium on DLB; imaging; neuropsych; CSF	Proportion of PTSD per dementia subtype
Bonanni[32] Arm 2	PC	Italy	Clinic patients	DLB	None	None	DSM-IV; CAPS-IV (M score 9.3 +/- SD 2.2)	Regularly followed in tertiary dementia clinic	Incident dementia subtypes

Abbreviations (from left to right): Yrs = years; RC = retrospective cohort; US = United States; VA = Veterans Affairs; DLB = dementia with Lewy bodies; PTSD = post-traumatic stress disorder; ICD-9 = International Classification of Diseases, 9th edition, Clinical Modification; PD = Parkinson's disease; SRD = stress-related disorders; ICD-10 = International Classification of Diseases, 10h edition; neurodeg. = neurodegenerative; DC = discharge; PCP = primary care provider; CC = case-control; TBI = traumatic brain injury; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th edition; CAPS-IV = Clinician Administered PTSD Scale for the DSM-IV; CSF = cerebrospinal fluid; PC = prospective cohort; M = mean; SD = standard deviation.

below the recommended threshold for PTSD diagnosis (mean score 9.3, standard deviation 2.2).

Degenerative synucleinopathy ascertainment methods were also dependent on diagnostic codes in five of six articles. Bonanni et al. ascertained dementia subtypes using standardized diagnostic criteria, neuropsychological assessments, neuroimaging, and cerebrospinal fluid markers. Degenerative synucleinopathies were the primary outcomes in three of seven study samples.

The two VA registry-based studies were over 95% male. The studies otherwise differed in terms of age restrictions for inclusion and duration of follow-up, although incident PTSD diagnoses occurred in mid to late life. Types of trauma exposures, when reported, varied among studies and individual samples (Table 1).

Summary of Individual Studies

Table 2 depicts pertinent findings regarding an association between PTSD and degenerative synucleinopathies. Positive associations between PTSD and PD[28,29] and DLB[31] were reported in three of four registry-based, retrospective cohort studies. The additional registry-based, case-control study by White et al.[9] reported a positive association between PTSD and risk of PD. Arms 1 and 2 of Bonanni et al.[32]) reported an association between PTSD and frontotemporal dementia spectrum disorders.

Bias Assessment

Table 3 shows results of the Newcastle-Ottawa scale[18] for cohort and case-control studies. Follow-up durations in three of the four registry-based, retrospective cohort studies were insufficient to detect incident synucleinopathies. Arms 1 and 2 of Bonanni et al.[32] were most at risk of bias due to unclear recruitment methods and inclusion/exclusion criteria. Specifically, Arm 1 did not have a comparator group; no drop-out rates were reported for Arm 2; and analyses of both arms lacked adjustments for confounders.

Meta-Analysis of Retrospective Cohort Studies

To further test the hypothesis that PTSD is associated with increased risk of PD and related disorders, the Meta package tool was used to pool the results of available studies reporting time-to-event data. Four retrospective cohort studies reported HR and were included for meta-analysis.[28-31] A forest plot of individual study estimates and confidence intervals is shown in Figure 3. The individual analysis of the pooled studies yielded a weight of 38.8 %,[31] 14.2%,[29] 11.7%[30], and 35.2%,[28] respectively.

As hypothesized, PTSD was positively correlated with an increased risk of degenerative synucleinopathies (HR 1.88, 95% C.I. 1.08-3.24; p = 0.035). The degree of statistical heterogeneity among studies was high (I^2 = 54%, 95% C.I. 0%−85%; Q = 6.51, df = 3, p = 0.09). Due to the small number of studies and outcomes, additional analyses examining for sources of bias could not be performed. An exploratory assessment for funnel plot asymmetry is presented in the Appendix.[35]

CONCLUSIONS

This systematic review investigated the potential association of PTSD with PD and related synucleinopathies. Our literature search identified seven unique samples from six articles (total n = 1,747,378). The association of PTSD with PD risk was investigated in three retrospective cohort studies and 1 case control study. The association of PTSD with DLB was examined in one retrospective cohort, one case control, and one prospective cohort study; the latter two samples were derived from the same article. Meta-analysis of the four retrospective cohort studies reporting time-to-event data provides initial support for our hypothesis that the relative risk of degenerative synucleinopathies is higher in individuals with versus without PTSD (HR 1.88, 95% C.I. 1.08−3.24; p = 0.035).

Taken together, the limited extant literature indicates a need for further research on mid- to late-life PTSD as a risk factor or prodromal manifestation of degenerative synucleinopathies. This review also exposed gaps in the existing literature that warrant attention in future investigations. For one, PTSD and synucleinopathy diagnostic methods depended primarily on database codes.[28−31] Although PTSD and DLB were diagnosed clinically in the samples derived from Bonanni et al.,[32] methodological issues dampened the conclusiveness of their findings. In addition, longitudinal follow-up of subjects in the four cohort studies available on this topic concluded before all

TABLE 2. Sample Characteristics and Pertinent Findings

Study	Age (yrs) M +/- SD	Follow-up (yrs)	Total (n)	Female (%)	PTSD + (n)	Synuclein + (n)	Covariates	Results (95% C.I.)
Yaffe[31]	PTSD(+): 66.2 +/- 9.0 PTSD(-): 69.9 +/- 8.2	MD 7.2, range 0.1-7.4	181,093	PTSD(+): 2.2 PTSD(-): 4.0	53,155	356	Sex, race/ethnicity, education, income, HTN, DM, MI, cerebVD, cancer, alcohol / substances, tobacco, depression, head injury	aHR = 2.05 (1.59-2.62)
Chan 2017	PTSD(+): 55.69 +/- 8.72 PTSD(-): 55.68 +/- 8.71	≤9	7280	PTSD(+): 76 PTSD(-): 76	1456	60	Age, sex, urbanization, income, depression, HTN, dyslipid, DM, cerebVD, TBI, epilepsy, migraine	aHR = 3.46 (1.72-6.96)
Song[30]	SRD(+): MD 47, IQR 41-56 SRD(-): MD 48, IQR 41-56	MD 4.7 IQR 2.1-9.8	657,083	SRD(+): 60.6 SRD(-): 60.6	3743	75	Education, income, marital status, psych history (any, depression, anxiety, substance use), family history of neurodeg.	aHR = 1.35 (0.61-2.99)
Barer[28]	PTSD(+): 55.8 +/-13.2 PTSD(-): 55.8 +/- 13.2	PTSD(+): M 10.4 +/- SD 4.7 PTSD(-): M 10.2 +/- SD 4.8	16,672	PTSD(+): 48.4 PTSD(-): 48.4	8336	196	age, sex, SES, smoking status, Holocaust or terror attack survivor, HTN, depression, migraine, TBI	aHR = 1.48 (1.10-1.99)
White[9]	75.0 +/- 9.4	Not stated	884,355	1.4	47,898	176,871	Race	cOR = 2.71 (2.66-2.77)
Bonanni[32] Arm 1	DLB: 74.2, SE 0.3 AD: 72.5, SE 0.2 FTD: 60.6, SE 0.5 VaD: 82.4, SE 0.5	≤10 yrs before dementia	849	LBD: 35 AD: 65 FTD: 51 VaD: 49	38	207	None	PTSD% FTD > DLB (χ2=6, p=0.02)
Bonann[32] Arm 2	65 +/- 4.3	M 7.2 +/- SD 1.2	46	46	46	1	None	DLB n=1, AD n=1, svFTD n=6

Abbreviations (from left to right): M = mean; SD = standard deviation; yrs = years; PTSD = post-traumatic stress disorder; HTN = hypertension; DM = diabetes; MI = myocardial infarction; cerebVD = cerebrovascular disease; aHR = adjusted hazard ratio; C.I. = confidence interval; dyslipid = dyslipidemia; TBI = traumatic brain injury; SRD = stress-related disorders; MD = median; IQR = interquartile range; neurodeg. = neurodegenerative disease; SES = socioeconomic status; cOR = conditional odds ratio; DLB = dementia with Lewy Bodies; AD = Alzheimer's dementia; FTD = frontotemporal dementia; VaD = vascular dementia.

TABLE 3. The Newcastle-Ottawa Scale for Assessing the Quality of Selected Studies

Cohort Studies	Representativeness (0–1)	Selection (0–1)	Ascertainment (0–1)	Outcome not present (0–1)	Comparability (0–2)	Assessment of outcome (0–1)	Follow-up length (0–1)	Adequacy follow-up (0-1)	Total
Barer[28]	1	1	1	1	2	1	1	1	9
Song[30]	1	0	1	1	2	1	0	1	7
Bonanni[32] (Arm 2)	0	0	1	1	0	1	1	1	5
Chan 2017	1	1	1	1	2	1	0	0	7
Yaffe[31]	1	1	1	1	2	1	0	1	8
Case Control Studies	**Case definition (0–1)**	**Representativeness of cases (0–1)**	**Selection of controls (0–1)**	**Definition of controls (0–1)**	**Comparability (0–2)**	**Ascertainment of exposure (0-1)**	**Ascertainment same for cases/controls (0–1)**	**Non-response rate (0-1)**	**Total**
White[9]	0	1	1	1	2	0	1	1	7
Bonanni[32] (Arm 1)	1	0	0	0	2	1	1	0	5

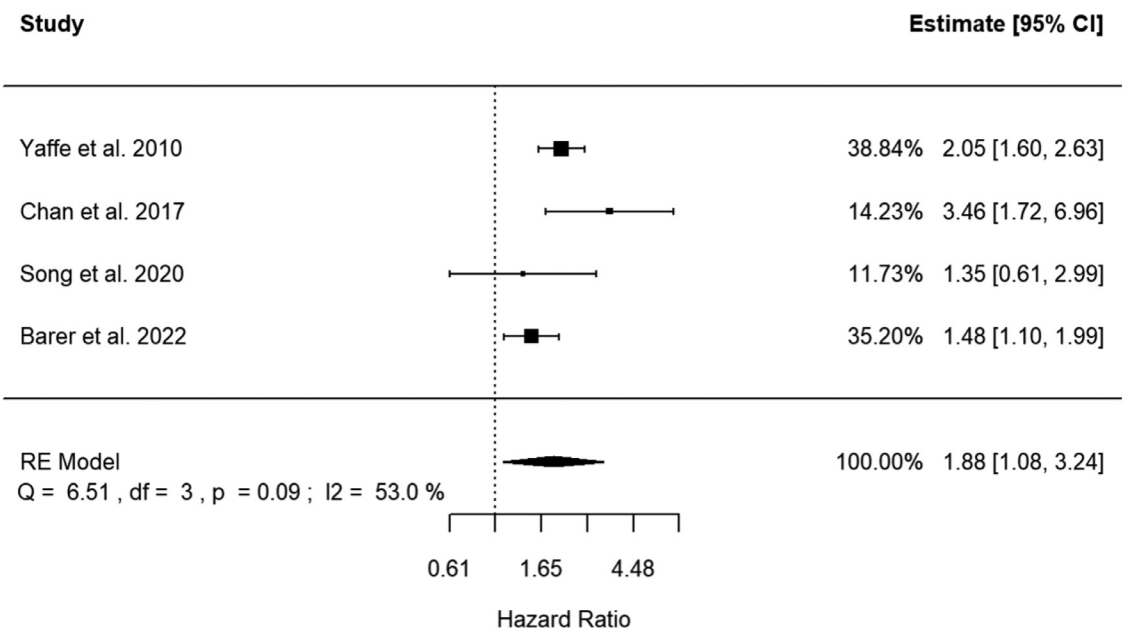
participants were above the age of 65 years, and only two of those studies included degenerative synucleinopathies as a primary outcome. Thus, the aggregate number of degenerative synucleinopathy outcomes (n = 687) was comparatively less than the total number of subjects recruited (n = 862,128) in the meta-analyzed studies. Furthermore, the identified investigations of PTSD did not include less prevalent synucleinopathies (e.g., MSA and pure autonomic failure). Ideally, future cohort studies will include standardized assessments for PTSD and prodromal or manifest alpha-synucleinopathies.

The inclusion criteria in this study focused on PTSD and degenerative synucleinopathies in order to guide subsequent research on potential mechanisms linking these disorders. For example, shared risk may co-locate to genes that encode for proteins involved in dopamine neurotransmission (e.g., DRD2 and SLC6A), mitophagy and programmed cell death (PARK2), and protein aggregation (FKB506 binding proteins genes).[36–44] Cell-to-cell propagation of alpha-synuclein may be stimulated by pro-inflammatory cytokines that are elevated in individuals with PTSD.[45–49] Investigations of the relationship between PTSD and degenerative synucleinopathies would also inform mechanisms linking PTSD, as a neuropsychiatric syndrome, to rapid eye movement sleep disorder.[10,50]

Several questions regarding PTSD and its association with degenerative synucleinopathies remain unanswered by this review and the scant amount of literature. Future studies are needed to confirm our findings and investigate whether certain comorbidities, such as exposures to traumatic brain injury (TBI)[9] or insomnia,[25] confound the association between PTSD and degenerative synucleinopathies. Future work will need to clarify whether PTSD and risk of degenerative synucleinopathies is distinct from that impact of other emotional disorders[30] and associations with other age-related dementias.[7,13,31] Finally, examination is needed on the impact of sample characteristics (e.g., veterans),[7] age of PTSD onset, and PTSD symptom clusters on relative risk.

The limitations of this review provide additional context for interpretation of the findings. The predominance of observational and database studies prevents assumptions about causation and diagnostic accuracy, respectively. As is typical for meta-analyses of observational studies,[7,21,51] heterogeneity in our

FIGURE 3. Forest plot of effect sizes and confidence intervals of pooled studies reporting time-to-event data.



CI: confidence interval, RE: random effects, HR: hazard ratio, Q: Cochrane's Q, df: degrees freedom.

meta-analysis was significant. Different population risks for PD and DLB may contribute, in part, to this heterogeneity.[52] However, the small number of studies precluded additional statistical analyses and highlights a need for future studies on this topic.

In conclusion, the small number of studies-to-date provide preliminary evidence of an association between mid- to late-life onset PTSD and subsequent development of PD and related neurodegenerative synucleinopathies. Prospective cohort studies that incorporate standardized neuropsychiatric assessments, examinations for prodromal and manifest synucleinopathies, and sufficient follow-up durations are needed to confirm these initial findings.

AUTHOR CONTRIBUTIONS

MJ contributed to the study conception and design, data collection, data analysis, and writing of the manuscript; LG, RG, and LM contributed to study conception and design, data collection, and writing of the manuscript; DB, GB, AG, JT, and ME, contributed to data collection and writing of the manuscript; BV contributed to data collection and writing of the manuscript; RJ and RL contributed to data analysis and writing of the manuscript.

DATA STATEMENT

The data has not been previously presented orally or by poster at scientific meetings.

The contents do not represent the views of the U.S. Department of Veterans Affairs or the United States Government.

DISCLOSURES

Melissa B. Jones, Ricardo E. Jorge, and Ruosha Li, are pending study drug support for a VA CSR&D investigator-initiated trial (VA Career Development Award # IK2CX002363-01A1) from Acadia Pharmaceuticals. Ricardo E. Jorge and Ruosha Li receive study drug support for an investigator-initiated trial (DoD Award # W81XWH-21-1-0450) from Pfizer Pharmaceuticals. Ricardo E. Jorge receives study drug support for a VA Cooperative Studies Program trial (CSP 2018) from Pfizer Pharmaceuticals. Laura Marsh,

receives study drug support for a VA Cooperative Studies Program trial (CSP 2015) from Acadia Pharmaceuticals. The other authors have no conflicts of interest to disclose.

This work was supported by the Center for Alzheimer's and Neurodegenerative Diseases at Baylor College of Medicine; Career Development Award # IK2CX002363-01A1 from the U.S. Department of Veterans Affairs Clinical Science Research and Development (CSR&D) Service; the Translational Research Center for TBI and Stress Disorders (TRACTS) (B9268-X) from the U.S. Department of Veterans Affairs Rehabilitation Research and Development (RR&D) service, and the Mental Health Care Line at the Michael E. DeBakey Veterans Affairs Medical Center.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jagp.2023.04.016.

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