POST-TRAUMATIC STRESS AND RISK OF DEMENTIA

Post-traumatic Stress Disorder as a Risk Factor for Dementia: A Systematic Review and Meta-Analysis

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Abstract

Background: Post-traumatic stress disorder (PTSD) has been identified as a potential risk factor for developing dementia. There are currently however no meta-analyses quantifying this risk.

Aims: To systematically review and quantify the risk of future dementia associated with PTSD across populations.

Method: We searched nine electronic databases up to 25 October 2019 for longitudinal studies assessing PTSD and risk of dementia. We used random and fixed-effects meta-analyses to pool estimates across studies.

Results: PTSD was associated with a significant risk for all-cause dementia, pooled hazard ratio (HR) = 1.61 (95% CI [1.43, 1.81], I^2=85.8%, p<.001; n =1,693,678; 8 studies). Pooled HR was 1.61 (95% CI [1.46, 1.78]; I^2=80.9%, p<.001; n = 905,896; 5 studies) in veterans, and 2.11 (95% CI [1.03, 4.33], I^2=91.2%, p<.001; n = 787,782; 3 studies) in the general population. The association between PTSD and dementia remained significant after excluding studies with high risk of bias (HR 1.55, 95% CI 1.39, 1.73, I^2=83.9%, p<.001; n = 1,684,928; 7 studies). Most studies included were retrospective and there was evidence of high heterogeneity.

Conclusions: This is the first meta-analysis quantifying the association of PTSD and risk of dementia showing that PTSD is a strong and potentially modifiable risk factor for all-cause dementia. Future studies investigating potential causal mechanisms, and the protective value of treating PTSD are needed.

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Declarations of interest

Mia Maria Günak has nothing to disclose.

Jo Billings has nothing to disclose.

Emily Carratu has nothing to disclose.

Natalie Marchant reports grants from Alzheimer's Society, during the conduct of the study.

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Dementia is a major cause of disability for the world's older population, representing the biggest global challenge of the 21st century (1). Around 50 million people live with dementia worldwide, with prevalence rates expected to triple by 2050 (2). Given the lack of disease-modifying treatments, identification and prevention of modifiable risk factors for dementia is an important public health priority (1). Post-traumatic stress disorder (PTSD) has recently been identified as a potential risk factor for developing dementia (3–5). Despite however the increased importance of this association across a range of populations, evidence of the magnitude of this relationship and potential mechanisms remain unknown. PTSD is a stress-related disorder developing after exposure to a traumatic stressor such as (threatened) death, serious injury, or abuse (6), with an increased conditional risk of a PTSD diagnosis around 4% (7). Symptoms of PTSD, such as re-experiencing the traumatic event, avoidance, and hypervigilance often remain untreated for years, resulting in a chronic condition severe enough to impact daily functioning (8,9).

PTSD is understood to arise as a result of strong negative appraisals of the trauma and disturbances in autobiographical memory (10). Recent studies show that PTSD is associated with poor cognitive outcomes in several neurocognitive domains such as processing speed, attention, and working memory (11). Neural structural changes contributing to poor cognitive function have also been observed, although evidence suggests that the association between PTSD and impaired cognition is bidirectional (12). Given the complexity of multiple risk factors contributing to dementia, estimating the risk associated with PTSD is important for informing future preventative strategies (1).

Although a systematic review examining the relationship between PTSD and dementia is now available (5), there are currently no meta-analyses. Given the lack of data on the magnitude of the relationship between PTSD and dementia, and a number of new studies being published, our primary objective in this study was to conduct the first meta-analysis of

the relationship between PTSD and all-cause dementia in the literature. A secondary objective was to review the quality of the evidence.

Method

We followed current guidelines for systematic reviews and meta-analyses (13) and registered the review with PROSPERO (14) (CRD42019130392).

Search strategy

We searched nine databases (MEDLINE, EMBASE, PsycINFO, CINAHL Plus, ProQuest Dissertation and Theses Global, EThOS, OpenGrey, HMIC, and Google Scholar) up to 25 October 2019, using a comprehensive list of search terms (see Supplementary Material). We additionally hand-searched reference lists of relevant reviews in the area. Two reviewers (MMG and EC) independently screened abstracts of the first 50% of all articles identified, resulting in an inter-rater agreement of 99.59% (κ = .83, 95% CI [0.74 to .91], p<.001). The remaining studies were screened by the first reviewer (MMG). All full-text articles were independently reviewed by MMG and EC with any disagreements discussed with the third author (VO).

Selection criteria

We included prospective and retrospective longitudinal studies investigating the association between PTSD and dementia. The population was adults (aged ≥ 18 years), and the comparison group was adults without PTSD. We included studies where a diagnosis of PTSD was based on: a) clinical diagnostic criteria (i.e., International Classification of Diseases; ICD-9 or ICD-10 (15); Diagnostic Statistical Manual III-5; DSM III-5 (6), or comparable), or b) a validated self-report scale. Studies that did not diagnose dementia based on clinical criteria (e.g., NINCDS-ADRDA (16)) were excluded.

Data extraction

Data were extracted independently by two authors (MMG and EC) and included: a) study design; b) participant characteristics; c) outcome measures; and d) risk of bias assessments. Five authors were contacted for missing data, of whom three provided data. Two authors independently assessed risk of bias using a modified version of the Newcastle-Ottawa Scale (NOS) (17,18), addressing: a) selection (i.e., representativeness, sample size, ascertainment of PTSD; dementia not present at baseline), b) comparability and design (study controlling for at ≥ 2 covariates, longitudinal design), and c) outcome (assessment of dementia and follow-up ≥ 5 years; see Table 1; Supplementary Material). Any disagreements were resolved through discussion with a third author. We extracted hazard ratios (HRs) and odds ratios (ORs); and conducted separate meta-analyses as recommended (19).

Statistical analysis

We used the generic inverse variance method with a random-effects model to obtain a pooled risk estimate for studies reporting HRs, and a fixed-effects model for studies reporting ORs (20), using adjusted ratios where possible. We measured heterogeneity by the chi-squared Cochran's *Q* test and the I^2-statistic, and where heterogeneity was detected, we calculated prediction intervals (21). Sources of heterogeneity were explored by performing both subgroup and sensitivity analyses. We additionally examined the impact of each individual study and effect of study quality. We were not able to perform meta-regression as there were less than ten studies that adjusted for the same potential effect modifiers (22) (e.g., only five studies adjusted for traumatic brain injury (TBI); see Table 2). Publication bias was assessed via a funnel plot and the Egger test (23). STATA (Version 15.1.) for Windows and the *metan* commands were used for all meta-analyses.

Results

Study selection

We identified a total of 10,462 references (see Figure 1), and after removal of duplicates and irrelevant articles, we retrieved 107 full text records. Of these, 70 were excluded as not relevant, leaving 37 full-text references to be fully assessed for eligibility. Of these, 25 studies were excluded with reasons (see Supplementary Material), leaving a total of 12 studies meeting inclusion criteria, with one study reporting on two independent samples. We pooled data from 10 studies in our meta-analyses.

----------Insert Figure 1 here----------

Study characteristics

All included studies were longitudinal cohort studies, with the majority being retrospective, deriving diagnoses from medical records. Reporting of follow-up varied from 1 to 17 years (*Mdn* = 9 years). All studies except two compared dementia rates in the PTSD group (i.e., PTSD at baseline) with those in a control group (i.e., no PTSD at baseline). Roughead et al. (24) compared two PTSD groups with differing PTSD severity, which authors classified as hospitalised (severe PTSD) versus non-hospitalised (less severe PTSD). We included the severe PTSD group in our meta-analysis, as in this group, PTSD diagnosis was based on clinical criteria.

Sample sizes ranged from 46 to 499,844 (*Mdn* = 15,612), with 1,693,678 participants in total. Age of participants ranged from 51 to 73.6 years, with seven studies on veterans, five studies on the general population, and one study on war refugees. Percentage of females varied from 0.1% to 76.6%, with two studies recruiting either male or female veterans only (24,25). Characteristics of the included studies are presented in Table 1.

Nine studies scored in the higher range of methodological quality (see Supplementary Material). Three studies (26–28) were judged to be of poor quality. Methodological domains

where there was evidence of risk of bias included study design (i.e., retrospective), no comparison control group, and no data as to whether dementia was present at baseline.

----------Insert Table 1 here----------

Primary meta-analysis of PTSD and risk of dementia

Pooled results from eight studies showed that PTSD increased risk of all-cause dementia; pooled HR = 1.61, 95% CI [1.43, 1.81], I^2=85.8%, p<.001; a total of 1,693,678 participants and 89,493 participants with PTSD; median follow-up of 9 years; 95% prediction interval of 1.14 to 2.29 (see Figure 2). Visual inspection of the funnel plot (see Figure 3) suggested no publication bias, which was supported by the Egger test (t=-0.30, p=.771).

----------Insert Figure 2 and Figure 3 here----------

Pooling studies reporting ORs (two studies) showed that PTSD increased dementia risk; OR = 1.99, 95% CI [1.69, 2.35], I^2=65.1%, p=0.090; a total of 15,281 participants and 5,260 participants with PTSD; follow-up ranging from 1 to 9 years. Studies not included in the meta-analysis reported similar findings. In Folnegovič-Šmalc et al. (27), war-refugees with PTSD symptoms had a higher risk of dementia compared to non-war-refugees. Bonanni et al. (28) found that a history of PTSD was more prevalent in people with dementia compared to patients with any other neurological condition (Study 2). In their prospective study, 17.4% (n = 8) of those with PTSD (n = 46) were diagnosed with dementia during a four-year follow-up, 6 of whom developed frontotemporal dementia (Study 1).

Subgroup and sensitivity analyses

Subgroup analyses indicated that risk was higher in the general population compared to veterans; pooled HR = 2.11, 95% CI [1.03, 4.33], I^2=91.2%, p<.001, n = 787,782, versus pooled HR = 1.61; 95% CI [1.46, 1.78], I^2=80.9%, p<.001, n = 905,896, respectively (see Table 2). The effect was slightly higher in studies conducted in countries other than the US versus studies in the US; pooled HR = 2.16, 95% CI [1.09, 4.30], I^2=84.1%, p=.002, n =

303,550, versus pooled HR = 1.55, 95% CI [1.38, 1.73], I^2=88.4%, p<.001, n = 1,390,128. Risk was higher in studies that included ≥ 50% of females; pooled HR = 1.97, 95% CI [1.25, 3.11], I^2=88.0%, p=.001, n = 896,922, versus pooled HR = 1.62; 95% CI [1.43, 1.85], I^2=85.0%, p<.001, n = 613,778, for studies with < 50% female participants. Risk was also higher in studies with a maximum follow-up of < 10 years; pooled HR = 1.70, 95% CI [1.51, 1.91], I^2=87.0%, p<.001, n = 899,034, compared to studies with ≥ 10 years follow-up; 1.38, 95% CI [1.02, 1.86], I^2=58.2%, p=.092, n = 794,644.

Excluding one study of high risk of bias (26) reduced the effect estimate but results remained statistically significant; pooled HR = 1.55; 95% CI [1.39, 1.73], I^2=83.9%, p<.001, n = 1,684,928. The direction and strength of the results remained the same after omitting any single study (see Supplementary Material), with no study substantially affecting between-study heterogeneity (range I^2=80.8%-87.8%; p<.001). Pooling only studies that adjusted for history of TBI slightly increased the overall effect estimate; pooled HR = 1.66; 95% CI [1.42, 1.95], I^2=90.1%, p<.001, n = 1,215,999. Adding both subgroups of the Roughead et al. study (severe and less severe PTSD) slightly decreased risk, however results remained statistically significant; 1.52, 95% CI [1.33, 1.73], I^2=89.5%, p<.001.

----------Insert Table 2 here----------

Discussion

Summary of evidence

To our knowledge, this is the first meta-analysis quantifying the association between PTSD and risk of dementia. We performed a thorough search of almost 8,000 records including studies across a range of populations and countries. Our review found that PTSD is an important and potentially modifiable risk factor for all-cause dementia. Meta-analyses showed that the risk of being diagnosed with dementia in individuals with a diagnosis of PTSD is 1.61 to nearly two times the risk compared to those without a PTSD diagnosis. We

found that after controlling for several confounders the association between PTSD and dementia remained significant.

Subgroup analyses revealed that the effect in the general population is larger compared to veterans, with an increased risk of 111% and 61%, respectively. That is, in the general population, the risk of being diagnosed with dementia in individuals with PTSD is more than twice the risk compared to those with no PTSD diagnosis. In the veteran population with PTSD however, it is more than one and a half times the risk compared to veterans without PTSD. If the smaller risk observed in veterans is because they are more likely to receive treatment for PTSD compared to the general population, this may indicate that PTSD-related dementia risk could be modified by intervention. For example, in a sample of young to middle-aged individuals, veterans were more likely to have health insurance and receive counselling or psychotherapy compared to non-veterans (29). Access to treatment for PTSD across populations may therefore differentially modify the association between PTSD and dementia.

It is likely that type of trauma, duration of exposure, and pre- and post-trauma environmental factors influence PTSD symptom severity and risk of dementia in different ways, across different populations. TBI, for example, which is independently associated with increased risk of dementia, is more prevalent in some populations (30). In our analysis, when adjusting for history of TBI, counterintuitively the effect estimate increased. This may be explained by a mortality effect whereby individuals with TBI die before they develop dementia (31). While both dementia and PTSD are more prevalent in females, current evidence is mixed in relation to whether sex modifies the association between PTSD and risk of dementia (24–26,32,33). There may be a stronger association among females as the strength of the relationship increased when pooling studies in which $\geq 50\%$ of the sample were women. The increased risk of dementia was highest when pooling studies with a

maximum follow-up < 10 years compared to the pooled risk of studies following participants for ≥ 10 years. This indicates that PTSD might be a prodrome of dementia, and that brain vulnerability remains silent over many years (8).

Only one study reported no significant association between PTSD and dementia (24). Roughead et al. stratified their data by antipsychotic use and found that patients with PTSD who were prescribed antipsychotics had an increased risk of dementia compared to controls without PTSD and being prescribed antipsychotics. Given limited data available, we were not able to examine the effect of antipsychotics as a potential confounder of the association between PTSD and dementia. Comprehensive reporting and harmonisation of potential modifiers across studies will be important for strengthening future meta-analyses.

Mechanisms

The mechanisms of the association between PTSD and dementia remain to a large extent unknown. It has been proposed that certain neurobiological pathways not specific to but potentiated by PTSD may increase risk of developing dementia (11,34). These pathways include altered activity of the hypothalamic-pituitary-adrenal axis (HPA), reduction in the hippocampal volume, and oxidative stress (34) which may in turn contribute to or accelerate dementia neuropathology (12). Constant hypervigilance and recurrent re-experiencing of the trauma may activate threat- and stress-related neurobiological pathways (11,34) increasing vulnerability to dementia. As PTSD symptoms develop, avoidance and withdrawal from daily and social life (6) may result in diminished cognitive stimulation reducing individuals' cognitive reserve, and resilience to neuropathological changes associated with dementia (35,36). PTSD and dementia may also share common underlying genetic vulnerability, with pathways between the two being bidirectional (5,8).

Strengths and limitations

Our meta-analysis extends current knowledge by being the first study to quantify the association of PTSD and all-cause dementia. We used a comprehensive and sensitive strategy to identify studies and included longitudinal studies where PTSD was present before the onset of dementia. We have provided an up to date review of worldwide evidence of the association between PTSD and risk of dementia based on studies with long follow-up periods, reporting on data of almost two million participants. We conducted a series of subgroup and sensitivity analyses to explore heterogeneity, and the prediction interval observed in our meta-analysis is consistent with a significant and important increase in risk of dementia associated with PTSD (21).

Despite these strengths however, our review has several limitations. First, there was substantial statistical heterogeneity between studies, and even though several subgroup and sensitivity analyses were performed, heterogeneity remained high and its sources could not be detected. Our second meta-analysis was based on only two studies and therefore remains limited (22). All included studies were observational cohort studies and most were retrospective. Generally, association does not equate causation and retrospective designs have important flaws. Given that many different healthcare professionals were involved in the diagnoses of PTSD and dementia, measurements may be less consistent and accurate compared to those achieved in the context of a prospective design. Additionally the use of different definitions and classifications of PTSD across studies means that cut-offs will differ influencing diagnosis or 'caseness' (8).

Implications for the future

Future studies are needed to examine the specific contribution of environmental, trauma-related, and neurocognitive mechanisms and how these may interact in increasing vulnerability to cognitive decline (8,34). Further studies are required to address how the use

of different classifications of both PTSD and dementia may influence the estimate of the effect. An important question that arises from our systematic review is whether access to effective and timely treatment for PTSD could potentially reduce the risk of developing dementia. Future studies therefore should examine the preventive potential of treating PTSD and its contribution in preventing or delaying the onset of dementia.

In conclusion, this is the first meta-analysis quantifying the risk of PTSD and dementia providing the latest update of the worldwide literature. Our review provides the first evidence that PTSD is a strong and potentially modifiable risk factor for all-cause dementia. Given the cost of dementia and its consequences for individuals and their families, PTSD prevention strategies should form part of worldwide public health initiatives.

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Data availability

The data that support the findings of this study are available on request from the first and corresponding authors, (MMG and VO); please email v.orgeta@ucl.ac.uk.

Author contribution

Mia Maria Günak: conceptualisation of the review; selection of studies; data extraction; data entry; data analysis; data quality; writing, review and editing of manuscript

Jo Billings: conceptualisation of the review, review and editing of final draft

Emily Carratu: conceptualisation of the review; selection of studies; data extraction; data quality; review and editing of final draft

Natalie Marchant: conceptualisation of the review; review and editing of final draft

Graziella Favarato: conceptualisation of the review; data analysis; review and editing of final draft

Vasiliki Orgeta: conceptualisation of the review; selection of studies; data quality; writing, review and editing of manuscript

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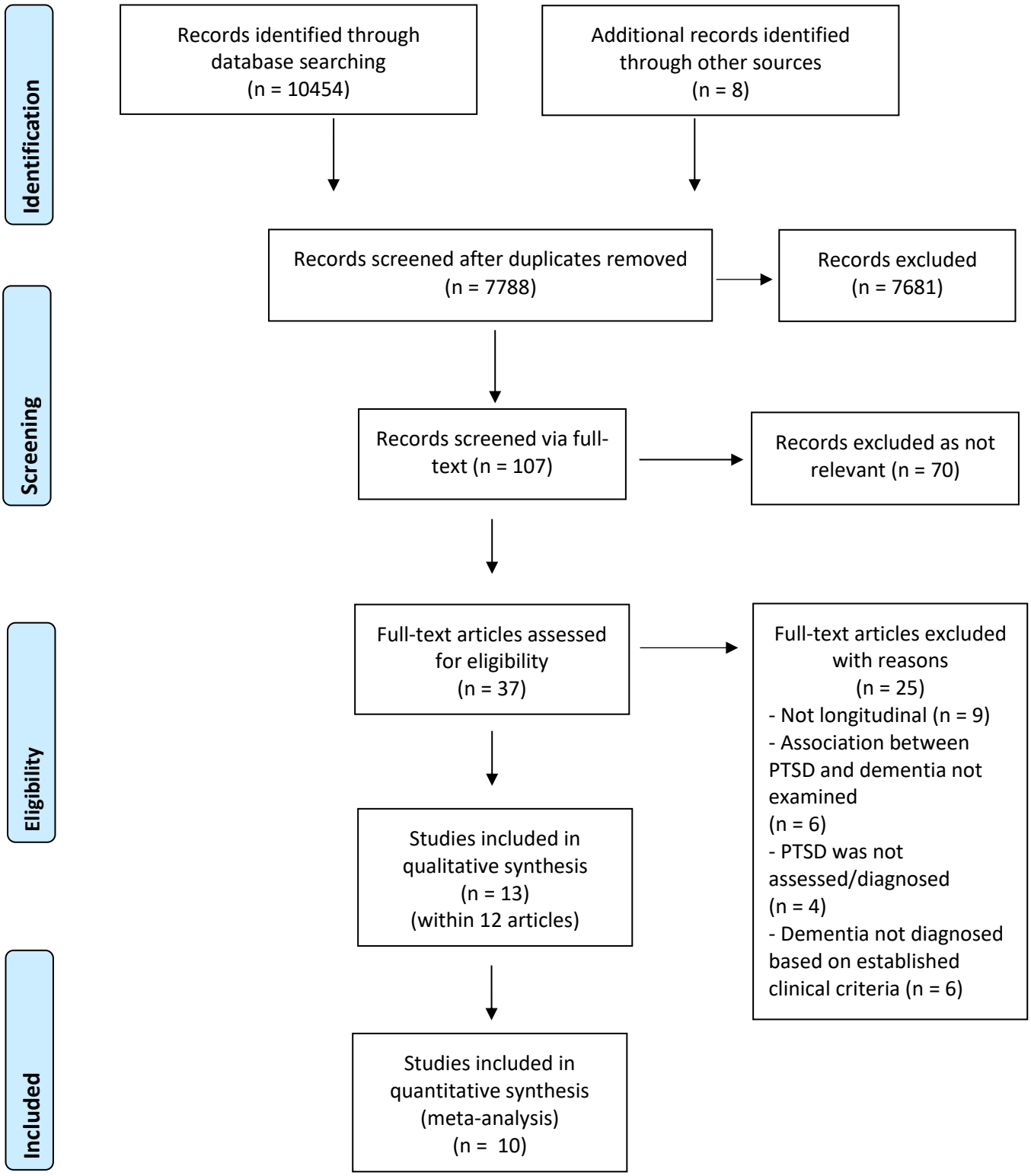

Figure 1. Flowchart of the search and study selection process.

Table 1 Characteristics of Included Studies

Author (year), country	**Study Type**	**Sample at baseline, female (%)**	**Participant recruitment**	**Follow-up (years)**	**Assessment/ Diagnostic criteria**	**Effect estimate after follow-up**[†]	**Variables adjusted**	**Quality rating**
Bhattarai et al. (2018) USA	Retrospective	Veterans *N* = 4800 (50.0) Age: *M* = 64.6	U.S. Department of Veteran Affairs	1 ≤	PTSD – ICD-9 Dementia + cognitive impairment – ICD-9	*OR*: 1.62 95% CI [1.21, 2.16]	- age - marital status - race - sex - depression	Good
Bonanni et al. (2018) Study 1[*] Italy	Prospective	General population *N* = 46 (45.7) Age: *M* = 65.0	Psychiatric/neurology clinic	6 - 10	PTSD – DSM-IV-TR/ CAPS-IV-TR Dementia – NINCDS-ADRDA, DLB and FTD standardised clinical criteria, NINDS-AIREN	Dementia incidence: *n* = 8 out of 46 (17%)		Poor
Study 2[*] Italy	Retrospective	General population *N* = 1136 (53.4) Age: *M* = 73.4	Dementia tertiary/neurology clinic	≤ 10	PTSD – DSM-IV-TR/ CAPS-IV-TR Dementia – NINCDS-ADRDA, DLB and FTD standardised clinical criteria, NINDS-AIREN	PTSD prevalence/ history in patients with dementia: *n* = 38 out of 849 (4.5%) PTSD history/prevalence in patients with any other neurological condition: *n* = 6 out of 287 (2.1%)		Poor Fair

Flatt et al. (2018) USA	Retrospective	General population *N* = 499,844 (54.7) Age: *M* = 71.1	Kaiser Permanente Northern California health system	≤ 13 *M* = 8.0 (*SD* = 4.6)	PTSD – ICD-9 Dementia – ICD-9	*HR*: 1.20 95% CI [1.02, 1.41]	- age - sex - race/ethnicity - vascular factors - TBI - depression	Good
Folnegović-Šmalc et al. (1997) * Croatia	Prospective	Refugees *N* = 1076 (72.5) Aged ≥ 45 years	Refugee camps	2.5	PTSD – Harvard Trauma Questionnaire Dementia – DSM-III-R, NINDCS-ADRDA	Dementia prevalence/ incidence: *n* = 73 out of 538 (13.6%) Dementia in control group: *n* = 15 out of 538 (2.8%)		Poor
Gradus et al. (2018) Denmark	Retrospective	General population *N* = 279188 (59.0) Age: *Mdn* = 51	Danish Psychiatric Central/National Research Patient Registry	≤ 17 *Mdn* = 6.8	PTS – inpatient and outpatient psychiatric diagnoses Dementia – ICD-10	*HR*: 2.0 95% CI [1.3, 3.2]	- age - sex - marital status - depression/anxiety - substance abuse/dependence	Good
Mawanda et al. (2017) USA	Retrospective	Veterans *N* = 417172 (2.1) Age: *M* = 67.7	Veterans Health Administration National databases	≤ 9 *M* = 9.0 (*SD* = 1.1)	PTSD – ICD-9 Dementia – ICD-9	*HR*: 1.55 95% CI [1.45, 1.67]	- age - sex - race/ethnicity/income - vascular factors - TBI - depression - substance abuse/ psychiatric/medical comorbidity	Good
Meziab et al. (2014)	Retrospective	Veterans *N* = 182879 (unknown)	Veterans Health Administration National Care Database	≤ 9	PTSD – ICD-9 Dementia – ICD-9-CM	*HR*: 1.52 95% CI [1.41, 1.64]	- age - sex	Good

USA		Age: *M* = 68.4					- socio- economic status/education/income - vascular factors - chronic pulmonary disease/obesity - depression - substance use	
Qureshi et al. (2010) USA	Retrospective	Veterans *N* = 10481 (0.01) Age: *M* = 73.6	Veterans Integrated Service Network Data Warehouse	≤ 9	PTSD – ICD-9 Dementia – ICD-9, use of dementia medication	*OR*: 2.2 95% CI [1.8, 2.6]	- sex - race - vascular factors - TBI - substance abuse - primary care clinic visits	Good
Roughead et al. (2017) Australia	Retrospective	Veterans *N* = 15612 (0) Age: *Mdn* = 57	Australian Department of Veteran's Affairs	≤ 11.5	PTSD – Disability file of DVA records (less severe), ICD-10 (severe) Dementia – ICD-10, any dementia record, use of dementia medication	Less severe PTSD *HR:* 0.81 95% CI [0.62, 1.06] Severe PTSD in those hospitalised *HR*: 1.21 95% CI [0.77, 1.89]	- age - socio-economic status - vascular factors - cancer - depression - substance use - benzodiazepine use	Good
Wang et al. (2016) Taiwan	Retrospective	General population *N* = 8750 (76.6) Age: *M* = 55.4	Taiwan National Health Insurance Research Database	≤ 2	PTSD – ICD-9-CM Dementia – ICD-9	*HR:* 4.37 95% CI [2.53, 7.55]	- sex - depression - alcohol use/substance use disorder - vascular factors - head injury - level of urbanization	Poor

Yaffe et al. (2010) USA	Retrospective	Veterans *N* = 181093 (3.5) Age: *M* = 68.8	Department of Veteran Affairs National Patient Care Database	≤ 7.25 *Mdn* = 7.2 (*IQR* = 0.1 - 7.4)	PTSD – ICD-9-CM Dementia – ICD-9-CM	*HR:* 1.77 95% CI [1.70, 1.85]	- age - sex - race/ethnicity - education/income - vascular factors - cancer - substance use - depression - head injury	Good
Yaffe et al. (2019) USA	Retrospective	Veterans *N* = 109140 (100.0) Age: *M* = 68.5	Veterans Health Administration Medical Center	≤ 7 years *M* = 4.0 (*SD* = 2.3)	PTSD – ICD-9-CM Dementia – ICD-9-CM	*HR:* 1.78 95% CI [1.34, 2.36]	- age - race/ethnicity - education/income - vascular factors - TBI - depression - alcohol/tobacco use	Good

Note. PTSD=Post-traumatic stress disorder; ICD-9=International Classification of Diseases, 9th revision; OR=Odds ratio; HR=Hazard ratio; CI = Confidence Interval; DSM-IV-TR=Diagnostic and Statistical Manual of Mental Disorders, 4th Text Revision; CAPS-IV-TR=Clinician Administered PTSD Scale for DSM-IV-TR; NINCDS-ADRDA=National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders; DLB=Dementia with Lewy bodies; FTD=Frontotemporal dementia; NINDS-AIREN=National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences; M = Mean SD=Standard deviation.

†if not stated otherwise, effect estimate of dementia incidence in PTSD against non-PTSD sample

*not included in the meta-analyses

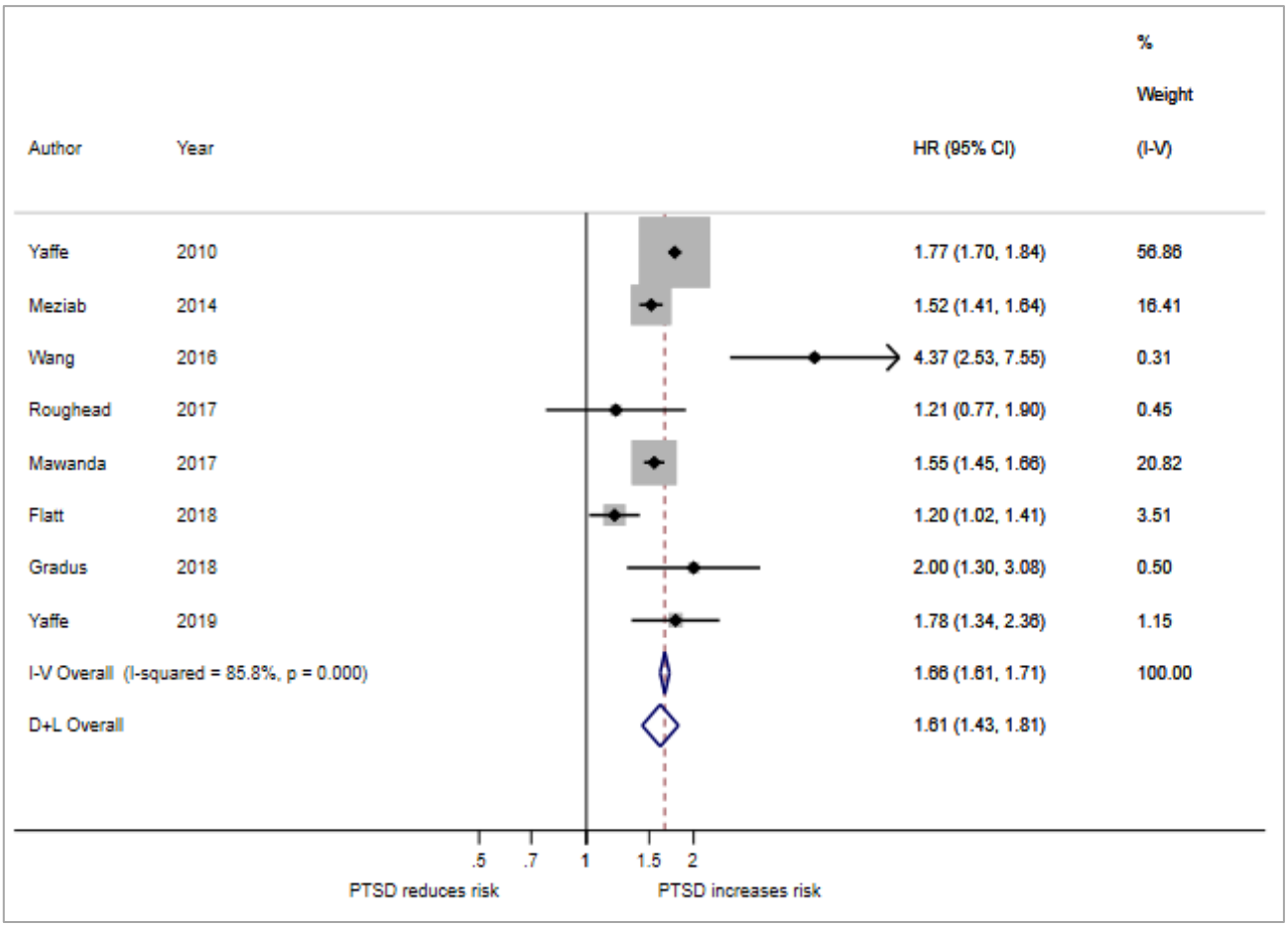

Figure 2. Meta-analysis of hazard ratios of PTSD compared to no PTSD on risk of dementia.

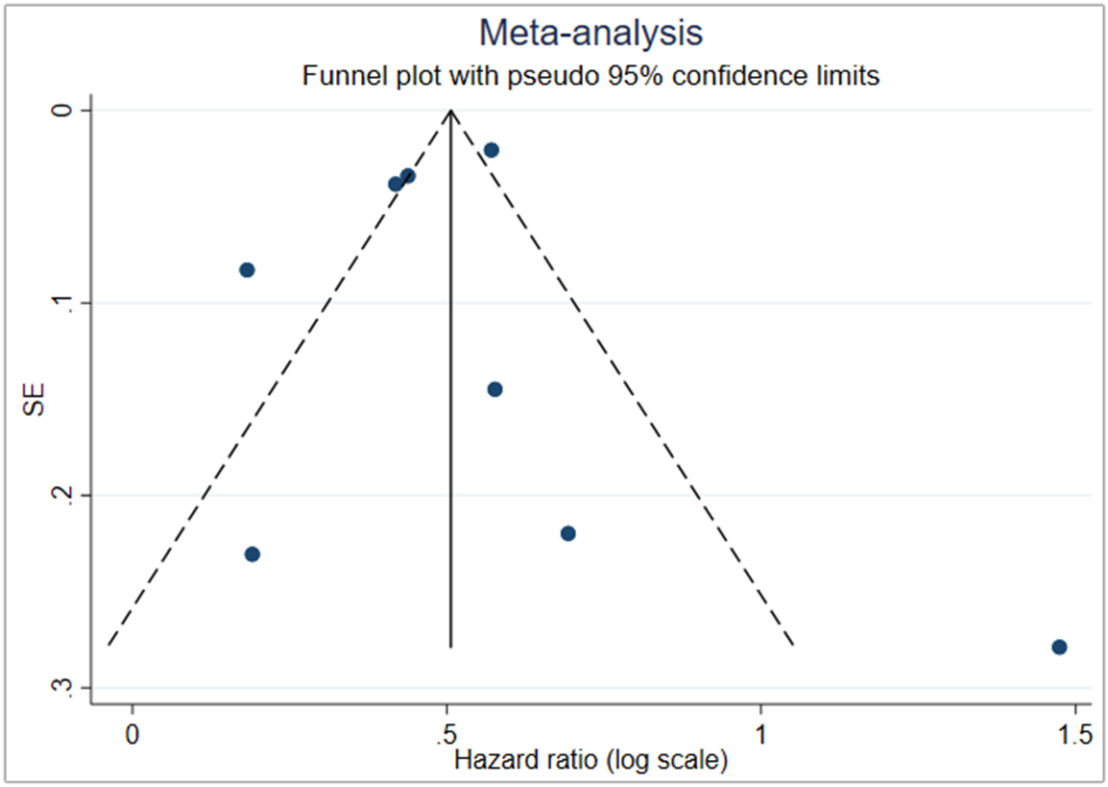

Figure 3. Funnel plot to inspect publication bias.

Table 2 Meta-analysis, subgroup and sensitivity analyses of the association of PTSD and dementia

Analysis[†]	**Number of estimates**	**Heterogeneity *Q*, *p* value and I^2**	**Random effect (95% CI)**
Main analysis	8	49.25 <.001, 85.8%	1.61 [1.43, 1.81]
Population			
Veterans only	5	20.95, <.001, 80.9%	1.61 [1.46, 1.78]
General population only	3	22.75, <.001, 91.2%	2.11 [1.03, 4.33]
Country			
USA only	5	34.57, <.001, 88.4%	1.55 [1.38, 1.73]
Other only[a]	3	12.60, .002, 84.1%	2.16 [1.09, 4.30]
Percentage of females[b]			
< 50% only	3	13.36, .001, 85.0%	1.62 [1.43, 1.85]
≥ 50% only	4	24.96, <.001, 88.0%	1.97 [1.25, 3.11]
Follow-up			
< 10 years	5	30.76, <.001, 87.0%	1.70 [1.51, 1.91]
≥ 10 years	3	4.78, .092, 58.2%	1.38 [1.02, 1.86]
Good quality studies	7	37.16, <.001, 83.9%	1.55 [1.39, 1.73]
Adjusted for covariates and TBI	5	40.29, <.001, 90.1%	1.66 [1.42, 1.95]

Note: TBI=Traumatic brain injury; [†]All subgroup and sensitivity analyses include studies of hazard ratios only; [a]one study each conducted in Taiwan, Denmark, Australia; [b]one study excluded due to missing values

Search Strategy of the Review for Medline

1. flashback*.mp.
2. disaster*.mp.
3. victim*.mp.
4. “stress disorder*".mp.
5. "acute stress*".mp.
6. (PTSD or post?traumatic* or "vicarious trauma*" or "complex trauma*").mp.
7. exp combat disorders/ or exp psychological trauma/ or exp stress disorders, post-traumatic/ or exp stress disorders, traumatic, acute/ or exp Battered Child Syndrome/ or exp natural disasters/ or exp child abuse, sexual/ or exp human trafficking/ or exp rape/ or exp violence/ or exp adverse childhood experiences/ or exp domestic violence/ or exp gender-based violence/ or exp gun violence/ or exp intimate partner violence/ or exp physical abuse/ or exp terrorism/ or exp torture/ or exp workplace violence/ or exp war crimes/ or exp genocide/ or exp "adult survivors of child adverse events"/ or exp "adult survivors of child abuse"/ or exp Dissociative Disorders/
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. Dement*.mp.
10. "alzheimer* disease".mp.
11. (AD or FTD or VAD or DLB).mp.
12. ("mild cognitive impairment" or MCI).mp.
13. exp dementia/ or exp alzheimer disease/ or exp dementia, vascular/ or exp Frontotemporal Dementia/
14. 9 or 10 or 11 or 12 or 13
15. 8 and 14

Table 1 Modified Newcastle-Ottawa Scoring scale assessing study quality

	Selection
1)	Representativeness of the exposed cohort
	a) Truly representative (1 point)
	b) Somewhat representative (1 point)
	c) Selected group of users (0 points)
	d) No description of the derivation of the cohort (0 points)
2)	Selection of the non-exposed cohort
	a) Drawn from the same community as the exposed cohort (1 point)
	b) Drawn from a different source (0 points)
	c) No description of the derivation of the non-exposed cohort (0 points)
3)	Ascertainment of exposure
	a) Secure record (e.g., medical records) (1 point)
	b) Structured interview (1 point)
	c) Written self-report (0 points)
	d) No description (0 points)
	e) Other (0 points)
4)	Demonstration that outcome of interest was not present before follow-up
	a) Yes (1 point)
	b) No (0 points)
	Comparability and Design[†]
1)	Comparability of cohorts on the basis of the design or analysis
	a) Study controls for two or more covariates (1 point)
	b) Study controls for less than two covariates (0 points)
2)	Longitudinal study design
	a) Prospective longitudinal/cohort study (1 point)
	b) Retrospective longitudinal/cohort study (0 points)
	Outcome
1)	Assessment of outcome
	a) Independent blind assessment (1 point)
	b) Record linkage (1 point)
	c) Self-report (0 points)
	d) No description (0 points)
	e) Other (0 points)
2)	Was follow-up long enough for outcome to occur (at least 5 years)
	a) Yes (1 point)
	b) No (0 points)
3)	Adequacy of follow-up of cohorts
	a) Complete follow-up – all subjects accounted for (1 point)
	b) Subjects lost to follow-up unlikely to introduce bias – number lost less than or equal to 20%, or description provided for those lost (1 point)
	c) Follow-up rate less than 80% and no description of those lost (0 points)
	d) No statement (0 points)

Note: Good: 3 or 4 points in selection domain AND 1 or 2 points in comparability domain AND 2 or 3 points in outcome domain; fair: 2 points in selection domain AND 1 or 2 points in comparability domain AND 2 or 3 points in outcome domain; poor: 0 or 1 point in selection domain OR 0 points in comparability domain OR 0 or 1 points in outcome domain; [†]Modified for the systematic review

Table 2 Excluded studies with reasons

Study	Reasons of exclusion
Chao (2017)	Cross-sectional study on memory impairment in veterans of Gulf War; dementia not diagnosed based on established clinical criteria.
Charles et al. (2006)	Retrospective study on life traumatisms preceding dementia; PTSD symptoms not assessed or diagnosed.
Cho et al. (2016)	Retrospective study on protective and risk factors for mortality in old veterans; association between dementia and PTSD not examined.
Clouston et al. (2016)	Prospective cohort study on the association between PTSD and cognitive impairment in world trade center responders; dementia not diagnosed based on established clinical criteria.
Clouston et al. (2017)	Prospective cohort study on world trade center-related exposures, PTSD and cognitive function; dementia not diagnosed based on established clinical criteria.
Clouston et al. (2018)	Prospective cohort study on PTSD and increased risk of MCI in world trade center responders; MCI not diagnosed based on clinical criteria; duplicate with above.
Cortina et al. (2011)	Cross-sectional study on prevalence of PTSD and depression among veterans; dementia not diagnosed based on established clinical criteria.
Elias et al. (2017)	Cross-sectional study assessing amyloid beta and tau deposition in Vietnam war veterans living with PTSD; dementia not diagnosed based on established clinical criteria.
Eren-Koçak et al. (2008)	Cross-sectional study on memory and prefrontal function in survivors of the 1999 earthquakes in Turkey; dementia not diagnosed based on established clinical criteria.
Hart et al. (2008)	Cross-sectional study on cognitive function in former World War II prisoners of war; dementia not diagnosed based on established clinical criteria.
Hikichi et al. (2016)	Prospective cohort study on exposure to the 2011 Great East Japan Earthquake and Tsunami disasters and risk of cognitive decline; association between PTSD and dementia not examined.
Ishiki et al. (2015)	Prospective cohort study on cognition and activities of daily living in older people affected by the 2011 Great East Japan earthquake; PTSD and dementia not assessed or diagnosed based on established clinical criteria.
Kodesh et al. (2019)	Retrospective cohort study on past Holocaust exposure and risk of dementia; association between PTSD and dementia not examined.

Study	Reasons of exclusion
Krasnov et al. (2015)	Prospective cohort study on early ageing in Chernobyl clean-up workers; association between PTSD and dementia not examined.
Loganovsky et al. (2018)	Cross-sectional study on neuropsychiatric characteristics of antiterrorist operation combatants in Ukraine; dementia not diagnosed based on established clinical criteria.
Mohamed et al. (2018)	Cross-sectional study on the association of TBI and/or PTSD and increase in amyloid beta accumulation in Vietnam War veterans; dementia not diagnosed based on established clinical criteria.
Mohamed et al. (2019)	Cross-sectional study on the association between TBI and/or PTSD increase tau deposition in the brain of Vietnam War veterans; dementia not diagnosed based on established clinical criteria.
Raad (2017)	Retrospective cohort study on chronic health conditions among homeless veterans with physical disabilities; aassociation between PTSD and dementia not examined.
Ravona-Springer et al. (2011)	Retrospective cohort study on exposure to Holocaust and World War II concentration camps and risk of dementia; PTSD symptoms not assessed or diagnosed.
Ritchie et al. (2011)	Cross-sectional and longitudinal study on the association between adverse childhood environment and cognitive function in community dwelling older people; PTSD symptoms not assessed or diagnosed.
Sperling et al. (2011)	Brief report on risk of dementia in Holocaust survivors with PTSD; unclear whether this is a longitudinal study; contact with author not possible.
Tsolaki et al. (2010)	Retrospective cohort study on the association between stressful life events and cognitive impairment in older people with dementia; PTSD symptoms not assessed or diagnosed.
Weiner et al. (2017)	Preliminary findings of a prospective cohort study assessing risk of TBI and/or PTSD and developing Alzheimer's disease in Vietnam Veterans using biomarkers and measures of cognitive function; dementia not diagnosed based on established clinical criteria.
Yehuda et al. (2005)	Cross-sectional study investigating learning and memory in ageing combat veterans of the World War II, the Korean War, and the Vietnam War with PTSD; dementia not diagnosed based on established clinical criteria.
Yehuda et al. (2006)	Prospective cohort study assessing cognitive function in Holocaust survivors with and without PTSD compared to a non-exposed cohort; dementia not diagnosed based on established clinical criteria.

Note. PTSD: Posttraumatic stress disorder; MCI: Mild cognitive impairment; TBI: Traumatic brain injury.

Table 3 Methodological quality of included studies

	Selection				Comparability		Outcome		Overall Quality
	Represen-tativeness	Control group	Ascertainment of Exposure	Outcome not at baseline	Adjusted Covariates	Study type	Assessment of outcome	Follow-up†	
Bhattarai et al. (2018)	1	1	1	1	1	0	1	1	Good
Bonanni et al. (2018)									
Prospective cohort	0	0	1	0	0	1	1	1	Poor
Retrospective cohort	1	0	1	0	1	0	1	2	Fair
Flatt et al. (2018)	1	1	1	1	1	0	1	1	Good
Folnegović-Šmalc et al. (1997)	1	0	0	0	0	1	1	1	Poor
Gradus et al. (2018)	1	1	1	1	1	0	1	1	Good
Mawanda et al. (2017)	1	1	1	1	1	0	1	1	Good
Meziab et al. (2014)	1	1	1	1	1	0	1	1	Good
Qureshi et al. (2010)	1	1	1	0	1	0	1	1	Good
Roughead et al. (2017)	1	1	0	1	1	0	1	1	Good
Wang et al. (2016)	1	1	1	1	1	0	1	0	Poor
Yaffe et al. (2010)	1	1	1	1	1	0	1	1	Good
Yaffe et al. (2019)	1	1	1	1	1	0	1	1	Good

Note. †Up to 2 points for follow-up

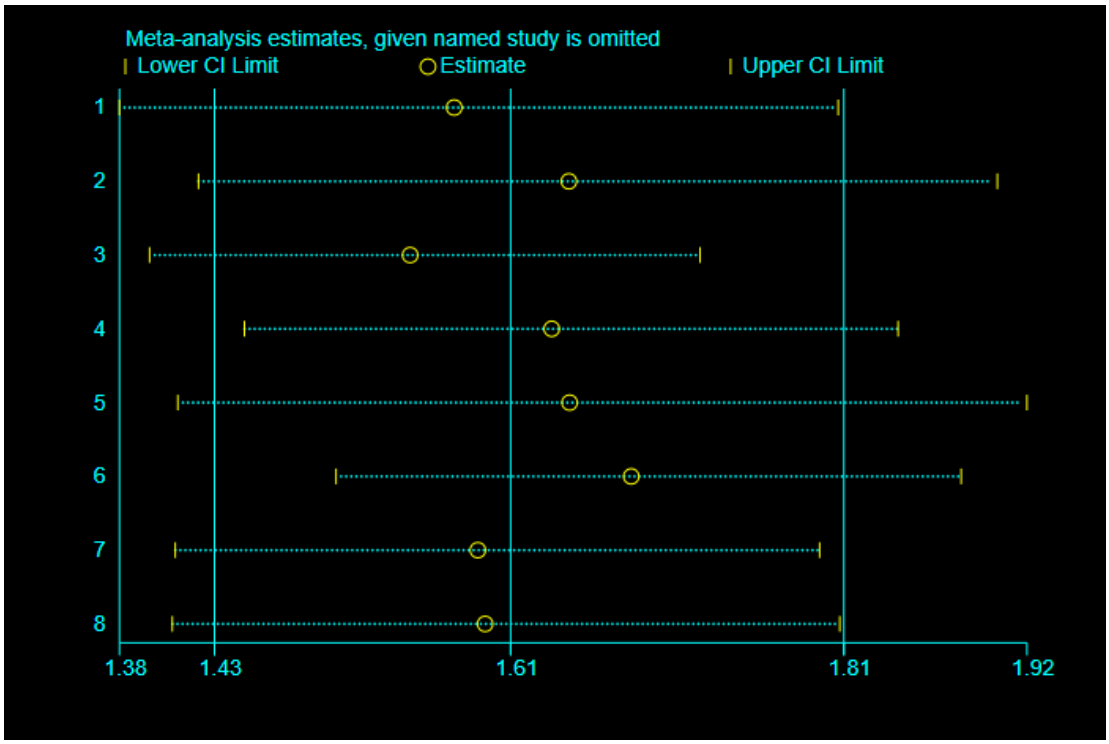

Figure 1. Sensitivity analyses to explore the impact of each individual study on the association between PTSD dementia.