
Evidence Brief: Traumatic Brain Injury and Dementia

Supplemental Materials

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APPENDIX A. SEARCH STRATEGIES

1. Search for current systematic reviews	
Date Searched: 10/18/18	
Sources:	Strategy:
AHRQ	Search: dementia; Alzheimer's; traumatic brain injury; TBI; Veteran
CADTH	Search: dementia; Alzheimer's; traumatic brain injury; TBI; Veteran
NICE (NHS Evidence)	Search: Veteran AND dementia; Veteran AND Alzheimer's; traumatic brain injury AND dementia; TBI AND dementia; traumatic brain injury AND Alzheimer's; TBI AND Alzheimer's
NLM	Search: Veteran AND dementia; Veteran AND Alzheimer's; traumatic brain injury AND dementia; TBI AND dementia; traumatic brain injury AND Alzheimer's; TBI AND Alzheimer's
ECRI Institute	Search: Veteran AND dementia; Veteran AND Alzheimer's; traumatic brain injury AND dementia; TBI AND dementia; traumatic brain injury AND Alzheimer's; TBI AND Alzheimer's
VA Products: VATAP, PBM, HSR&D publications, VA ART Database	A. http://www.hsrd.research.va.gov/research/default.cfm B. http://www.research.va.gov/research_topics/ C. http://art.puget-sound.med.va.gov/default.cfm Search: dementia; Alzheimer's; traumatic brain injury; TBI
MEDLINE: Systematic Reviews KQ1	Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to October 17, 2018> Search Strategy: ----- 1 exp Veterans/ (14461) 2 veteran\$.ti,ab,kw. (31720) 3 exp Veterans Health/ (1006) 4 (active duty or military or service member\$ or soldier\$ or national guard or reserv\$).ti,ab,kw. (173489) 5 or/1-4 (202846) 6 exp Dementia/ (149164) 7 (dementia or Alzheimer\$).ti,ab,kw. (188667) 8 6 or 7 (225955) 9 5 and 8 (2013) 10 (systematic review.ti. or meta-analysis.pt. or meta-analysis.ti. or systematic literature review.ti. or this systematic review.tw. or pooling project.tw. or (systematic review.ti,ab. and review.pt.) or meta synthesis.ti. or meta-analy*.ti. or integrative review.tw. or integrative research review.tw. or rapid review.tw. or umbrella review.tw. or consensus development conference.pt. or practice guideline.pt. or drug class reviews.ti. or cochrane database syst rev.jn. or acp journal club.jn. or health technol assess.jn. or evid rep technol assess summ.jn. or jbi database system rev implement rep.jn. or (clinical guideline and management).tw. or ((evidence based.ti. or evidence-based medicine/ or best practice*.ti. or evidence synthesis.ti,ab.) and (((review.pt. or diseases category/ or behavior.mp.) and behavior mechanisms/) or therapeutics/ or evaluation studies.pt. or validation studies.pt. or guideline.pt. or pmcbook.mp.)) or (((systematic or systematically).tw. or critical.ti,ab. or study selection.tw. or ((predetermined or inclusion) and criteri*).tw. or exclusion criteri*.tw. or main outcome measures.tw. or standard of care.tw. or standards of care.tw.) and ((survey or surveys).ti,ab. or overview*.tw. or review.ti,ab. or reviews.ti,ab. or search*.tw. or handsearch.tw. or analysis.ti. or critique.ti,ab. or appraisal.tw. or (reduction.tw. and (risk/ or risk.tw.) and (death or recurrence).mp.)) and ((literature or articles or publications or publication or bibliography or bibliographies or published).ti,ab. or pooled data.tw. or unpublished.tw. or citation.tw. or citations.tw. or database.ti,ab. or internet.ti,ab. or textbooks.ti,ab. or references.tw. or scales.tw. or papers.tw. or datasets.tw. or trials.ti,ab. or meta-analy*.tw. or (clinical and studies).ti,ab. or treatment

	<p>outcome/ or treatment outcome.tw. or pmcbook.mp.)) not (letter or newspaper article).pt. (326420) 11 9 and 10 (71) 12 limit 11 to english language (69)</p> <p>*****</p>
<p>PsycINFO: Systematic Reviews KQ1</p>	<p>Database: PsycINFO <1806 to October Week 2 2018> Search Strategy: ----- 1 exp Veterans/ (11834) 2 veteran\$.ti,ab,kw. (19086) 3 exp Veterans Health/ (0) 4 (active duty or military or service member\$ or soldier\$ or national guard or reserv\$).ti,ab,kw. (4302981) 5 or/1-4 (4303324) 6 exp Dementia/ (70632) 7 (dementia or Alzheimer\$).ti,ab,kw. (89329) 8 6 or 7 (92597) 9 5 and 8 (91857) 10 (systematic review.ti. or meta-analysis.pt. or meta-analysis.ti. or systematic literature review.ti. or this systematic review.tw. or pooling project.tw. or (systematic review.ti,ab. and review.pt.) or meta synthesis.ti. or meta-analy*.ti. or integrative review.tw. or integrative research review.tw. or rapid review.tw. or umbrella review.tw. or consensus development conference.pt. or practice guideline.pt. or drug class reviews.ti. or cochrane database syst rev.jn. or acp journal club.jn. or health technol assess.jn. or evid rep technol assess summ.jn. or jbi database system rev implement rep.jn. or (clinical guideline and management).tw. or ((evidence based.ti. or evidence-based medicine/ or best practice*.ti. or evidence synthesis.ti,ab.) and (((review.pt. or diseases category/ or behavior.mp.) and behavior mechanisms/ or therapeutics/ or evaluation studies.pt. or validation studies.pt. or guideline.pt. or pmcbook.mp.)) or (((systematic or systematically).tw. or critical.ti,ab. or study selection.tw. or ((predetermined or inclusion) and criteri*).tw. or exclusion criteri*.tw. or main outcome measures.tw. or standard of care.tw. or standards of care.tw.) and ((survey or surveys).ti,ab. or overview*.tw. or review.ti,ab. or reviews.ti,ab. or search*.tw. or handsearch.tw. or analysis.ti. or critique.ti,ab. or appraisal.tw. or (reduction.tw. and (risk/ or risk.tw.) and (death or recurrence).mp.)) and ((literature or articles or publications or publication or bibliography or bibliographies or published).ti,ab. or pooled data.tw. or unpublished.tw. or citation.tw. or citations.tw. or database.ti,ab. or internet.ti,ab. or textbooks.ti,ab. or references.tw. or scales.tw. or papers.tw. or datasets.tw. or trials.ti,ab. or meta-analy*.tw. or (clinical and studies).ti,ab. or treatment outcome/ or treatment outcome.tw. or pmcbook.mp.)) not (letter or newspaper article).pt. (116195) 11 9 and 10 (3125) 12 limit 11 to english language (2927) 13 ((prevalence or frequency or cause\$ or incidence) adj6 (dementia or Alzheimer\$)).ti,ab. (5761) 14 12 and 13 (263)</p> <p>*****</p>
<p>Cochrane Database of Systematic Reviews KQ1</p>	<p>Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to October 17, 2018> Search Strategy: ----- 1 veteran\$.ti,ab,kw. (4) 2 (active duty or military or service member\$ or soldier\$ or national guard or reserv\$).ti,ab,kw. (51)</p>



	<p>3 1 or 2 (54) 4 (dementia or Alzheimer\$).ti,ab,kw. (222) 5 3 and 4 (0)</p> <p>*****</p>
Systematic Reviews (Journal)	Search: dementia; Alzheimer's; traumatic brain injury; TBI; Veteran

2. Systematic reviews currently under development (forthcoming reviews & protocols)	
Date Searched: 10/18/18	
Sources:	Strategy:
PROSPERO (SR registry)	Search: Veteran AND dementia; Veteran AND Alzheimer's; traumatic brain injury AND dementia; TBI AND dementia; traumatic brain injury AND Alzheimer's; TBI AND Alzheimer's
DoPHER (SR Protocols)	Search: dementia; Alzheimer's; traumatic brain injury; TBI; Veteran

3. Current Guidelines	
Date Searched: 10/18/18	
Sources:	Strategy:
VA/DoD Clinical Practice Guidelines	Relevant Results: Management of Concussion-mild Traumatic Brain Injury (mTBI) (2016)

4. Current primary literature	
Date Searched: 10/18/18	
Sources:	Strategy:
MEDLINE: non SR KQ2	<p>Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to October 17, 2018></p> <p>Search Strategy:</p> <p>-----</p> <p>1 (((traumatic brain injury or TBI) and (onset or early-onset)) adj6 (dementia or Alzheimer\$)).mp. (67) 2 limit 1 to english language (66) 3 limit 2 to humans (46)</p> <p>*****</p>
PsycINFO KQ2	<p>Database: PsycINFO <1806 to October Week 2 2018></p> <p>Search Strategy:</p> <p>-----</p> <p>1 (((traumatic brain injury or TBI) and (onset or early-onset)) adj6 (dementia or Alzheimer\$)).mp. (49) 2 limit 1 to english language (48)</p> <p>*****</p>
CCRCT	<p>Database: EBM Reviews - Cochrane Central Register of Controlled Trials <June 2018></p> <p>Search Strategy:</p> <p>-----</p> <p>1 (((traumatic brain injury or TBI) and (onset or early-onset)) adj6 (dementia or Alzheimer\$)).mp. (5) 2 limit 1 to english language (2)</p> <p>*****</p>
Google Scholar	Search: prevalence of dementia in veterans; prevalence of Alzheimer's in veterans; dementia risk in Veterans; Alzheimer's risk in Veterans; traumatic brain injury AND



	dementia; TBI AND dementia; traumatic brain injury AND Alzheimer's; TBI AND Alzheimer's (limited review to first 500 results)
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5. Supplemental Searching	
Date Searched: 10/18/18	
Sources:	Strategy:
MEDLINE: KQ1	<p>Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to December 06, 2018> Search Strategy:</p> <p>-----</p> <ol style="list-style-type: none"> 1 exp Dementia/ (149916) 2 (dementia or Alzheimer\$).ti,ab,kw. (190779) 3 1 or 2 (228177) 4 prevalence.ti,ab,kw. (551575) 5 exp PREVALENCE/ (260209) 6 4 or 5 (630516) 7 (systematic review.ti. or meta-analysis.pt. or meta-analysis.ti. or systematic literature review.ti. or this systematic review.tw. or pooling project.tw. or (systematic review.ti,ab. and review.pt.) or meta synthesis.ti. or meta-analy*.ti. or integrative review.tw. or integrative research review.tw. or rapid review.tw. or umbrella review.tw. or consensus development conference.pt. or practice guideline.pt. or drug class reviews.ti. or cochrane database syst rev.jn. or acp journal club.jn. or health technol assess.jn. or evid rep technol assess summ.jn. or jbi database system rev implement rep.jn. or (clinical guideline and management).tw. or ((evidence based.ti. or evidence-based medicine/ or best practice*.ti. or evidence synthesis.ti,ab.) and (((review.pt. or diseases category/ or behavior.mp.) and behavior mechanisms/) or therapeutics/ or evaluation studies.pt. or validation studies.pt. or guideline.pt. or pmcbook.mp.)) or (((systematic or systematically).tw. or critical.ti,ab. or study selection.tw. or ((predetermined or inclusion) and criteri*).tw. or exclusion criteri*.tw. or main outcome measures.tw. or standard of care.tw. or standards of care.tw.) and ((survey or surveys).ti,ab. or overview*.tw. or review.ti,ab. or reviews.ti,ab. or search*.tw. or handsearch.tw. or analysis.ti. or critique.ti,ab. or appraisal.tw. or (reduction.tw. and (risk/ or risk.tw.) and (death or recurrence).mp.)) and ((literature or articles or publications or publication or bibliography or bibliographies or published).ti,ab. or pooled data.tw. or unpublished.tw. or citation.tw. or citations.tw. or database.ti,ab. or internet.ti,ab. or textbooks.ti,ab. or references.tw. or scales.tw. or papers.tw. or datasets.tw. or trials.ti,ab. or meta-analy*.tw. or (clinical and studies).ti,ab. or treatment outcome/ or treatment outcome.tw. or pmcbook.mp.))) not (letter or newspaper article).pt. (331841) 8 3 and 6 and 7 (565) 9 limit 8 to english language (541) 10 limit 9 to yr="2016 -Current" (170) <p>*****</p>



APPENDIX B. LIST OF EXCLUDED STUDIES

Exclude reasons: 1 = Ineligible population, 2 = Ineligible intervention, 3 = Ineligible comparator, 4 = Ineligible outcome, 5 = Ineligible setting (eg, inpatient), 6 = Ineligible study design (eg, case report, qualitative methods), 7 = Ineligible publication type (eg, abstract, editorial, letter, narrative review, etc) 8 = Outdated or ineligible systematic review, 9 = Non-English language, 10 = Critique or rebuttal of paper

#	Citation	Exclude reason
1.	Blakemore A, Kenning C, Mirza N, Daker-White G, Panagioti M, Waheed W. Dementia in UK South Asians: a scoping review of the literature. <i>BMJ Open</i> . 2018;8(4):e020290.	E6
2.	Brayne C. Traumatic brain injury and dementia. <i>The Lancet Psychiatry</i> . 2018;5(5):383-384.	E7
3.	Elder GA. Update on TBI and cognitive impairment in military veterans. <i>Curr Neurol Neurosci Rep</i> . 2015;15(10):68.	E7
4.	Gardner RC, Yaffe K. Traumatic brain injury may increase risk of young onset dementia. <i>Annals of Neurology</i> . 2014;75(3):339-341.	E7
5.	Kenney K, Diaz-Arrastia R. Risk of dementia outcomes associated with traumatic brain injury during military service. <i>JAMA Neurol</i> . 2018.	E7
6.	Kiejna A, Frydecka D, Adamowski T, et al. Epidemiological studies of cognitive impairment and dementia across eastern and middle European countries (epidemiology of dementia in eastern and middle European countries). <i>International Journal of Geriatric Psychiatry</i> . 2011;26(2):111-117.	E7
7.	Kiraly M, Kiraly SJ. Traumatic brain injury and delayed sequelae: a review--traumatic brain injury and mild traumatic brain injury (concussion) are precursors to later-onset brain disorders, including early-onset dementia. <i>TheScientificWorldJournal</i> . 2007;7:1768-1776.	E7
8.	Lang L, Clifford A, Wei L, et al. Prevalence and determinants of undetected dementia in the community: a systematic literature review and a meta-analysis. <i>BMJ Open</i> . 2017;7(2):e011146.	E1
9.	Li Y, Li Y, Li X, et al. Head injury as a risk factor for dementia and Alzheimer's disease: A systematic review and meta-analysis of 32 observational studies. <i>PLoS One</i> . 2017;12(1):e0169650.	E4
10.	LoBue C, Cullum C, Didehbani N, et al. Neurodegenerative dementias after traumatic brain injury. <i>The Journal of Neuropsychiatry and Clinical Neurosciences</i> . 2018;30(1):7-13.	E7
11.	McKee AC, Robinson ME. Military-related traumatic brain injury and neurodegeneration. <i>Alzheimers Dement</i> . 2014;10(3 Suppl):S242-253.	E7
12.	Prince M, Ali GC, Guerchet M, Prina AM, Albanese E, Wu YT. Recent global trends in the prevalence and incidence of dementia, and survival with dementia. <i>Alzheimer's Research & Therapy</i> . 2016;8(1):23.	E4
13.	Sanson J, Duncan C, Grootemaat P, Capell J, Samsa P, Westera A. Younger onset dementia. <i>American Journal of Alzheimer's Disease & Other Dementias</i> . 2016;31(8):693-705.	E4
14.	Stephan BCM, Birdi R, Tang EYH, et al. Secular trends in dementia prevalence and incidence worldwide: a systematic review. <i>Journal of Alzheimer's Disease</i> . 2018;66(2):653-680.	E4
15.	Weiner MW, Harvey D, Hayes J, et al. Effects of traumatic brain injury and	E4

#	Citation	Exclude reason
	posttraumatic stress disorder on development of Alzheimer's disease in Vietnam veterans using the Alzheimer's disease neuroimaging initiative: Preliminary report. <i>Alzheimers Dement (NY)</i> . 2017;3(2):177-188.	
16.	Weiner MW, Veitch DP, Hayes J, et al. Effects of traumatic brain injury and posttraumatic stress disorder on Alzheimer's disease in veterans, using the Alzheimer's disease neuroimaging initiative. <i>Alzheimer's & dementia: the journal of the Alzheimer's Association</i> . 2014;10(3):S226-S235.	E7

APPENDIX C. QUALITY ASSESSMENT OF INCLUDED STUDIES

Quality Assessment of Systematic Reviews

AMSTAR 2 Tool¹

Williamson 2018²

1. Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:	Optional (recommended)	
<input checked="" type="checkbox"/> <u>P</u> opulation	<input checked="" type="checkbox"/> Timeframe for follow-up	<input checked="" type="checkbox"/> Yes
(NA) <input type="checkbox"/> <u>I</u> ntervention		<input type="checkbox"/> No
(NA) <input type="checkbox"/> <u>C</u> omparator group		
<input checked="" type="checkbox"/> <u>O</u> utcome		

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes:

The authors state that they had a written protocol or guide that included ALL the following:

- review question(s)
- a search strategy
- inclusion/exclusion criteria
- a risk of bias assessment

For Yes:

As for partial yes, plus the protocol should be registered and should also have specified:

- a meta-analysis/synthesis plan, if appropriate, *and*
- a plan for investigating causes of heterogeneity
- justification for any deviations from the protocol

- Yes
- Partial Yes
- No

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:

- Explanation for including only RCTs*
- OR Explanation for including only NRSI*
- OR Explanation for including both RCTs and NRSI*

- Yes
- No

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):

- searched at least 2 databases (relevant to research question)
- provided key word and/or search strategy
- justified publication restrictions (e.g. language)

For Yes, should also have (all the following):

- searched the reference lists / bibliographies of included studies
- searched trial/study registries
- included/consulted content experts in the field
- where relevant, searched for grey literature
- conducted search within 24 months of completion of the review

- Yes
- Partial Yes
- No

5. Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:

- at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.

- Yes
- No

6. Did the review authors perform data extraction in duplicate?

For Yes, either ONE of the following:

- | | |
|--|---|
| <input checked="" type="checkbox"/> at least two reviewers achieved consensus on which data to extract from included studies | <input checked="" type="checkbox"/> Yes |
| <input type="checkbox"/> OR two reviewers extracted data from a sample of eligible studies <u>and</u> achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer. | <input type="checkbox"/> No |

7. Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes:

- provided a list of all potentially relevant studies that were read in full-text form but excluded from the review

For Yes, must also have:

- | | |
|---|--|
| <input type="checkbox"/> Justified the exclusion from the review of each potentially relevant study | <input type="checkbox"/> Yes |
| | <input type="checkbox"/> Partial Yes |
| | <input checked="" type="checkbox"/> No |

8. Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following):

- described populations
- (NA) described interventions
- (NA) described comparators
- described outcomes
- described research designs

For Yes, should also have ALL the following:

- | | |
|---|---|
| <input checked="" type="checkbox"/> described population in detail | <input type="checkbox"/> Yes |
| (NA) <input type="checkbox"/> described intervention in detail (including doses where relevant) | <input checked="" type="checkbox"/> Partial Yes |
| (NA) <input type="checkbox"/> described comparator in detail (including doses where relevant) | <input type="checkbox"/> No |
| (NA) <input type="checkbox"/> described study's setting | |
| <input type="checkbox"/> timeframe for follow-up | |

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

RCTs	For Partial Yes, must have assessed RoB from	For Yes, must also have assessed RoB from:	<input type="checkbox"/> Yes <input type="checkbox"/> Partial Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Includes only NRSI
	<input type="checkbox"/> unconcealed allocation, <i>and</i> <input type="checkbox"/> lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)	<input type="checkbox"/> allocation sequence that was not truly random, <i>and</i> <input type="checkbox"/> selection of the reported result from among multiple measurements or analyses of a specified outcome	
NRSI	For Partial Yes, must have assessed RoB:	For Yes, must also have assessed RoB:	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> Partial Yes <input type="checkbox"/> No <input type="checkbox"/> Includes only RCTs
	<input checked="" type="checkbox"/> from confounding, <i>and</i> <input checked="" type="checkbox"/> from selection bias	<input checked="" type="checkbox"/> methods used to ascertain exposures and outcomes, <i>and</i> <input checked="" type="checkbox"/> selection of the reported result from among multiple measurements or analyses of a specified outcome	

10. Did the review authors report on the sources of funding for the studies included in the review?

For Yes	<input type="checkbox"/> Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
---------	---	--



11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs	
For Yes:	
<input type="checkbox"/> The authors justified combining the data in a meta-analysis	<input type="checkbox"/> Yes
<input type="checkbox"/> AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.	<input type="checkbox"/> No
<input type="checkbox"/> AND investigated the causes of any heterogeneity	<input checked="" type="checkbox"/> No meta-analysis conducted
For NRSI	
For Yes:	
<input checked="" type="checkbox"/> The authors justified combining the data in a meta-analysis	<input type="checkbox"/> Yes
<input checked="" type="checkbox"/> AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present	<input checked="" type="checkbox"/> No
<input type="checkbox"/> AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available	<input type="checkbox"/> No meta-analysis conducted
(NA) <input type="checkbox"/> AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review	

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

For Yes:

- | | |
|--|---|
| <input type="checkbox"/> included only low risk of bias RCTs | <input checked="" type="checkbox"/> Yes |
| <input checked="" type="checkbox"/> OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect. | <input type="checkbox"/> No |
| | <input type="checkbox"/> No meta-analysis conducted |

13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?

For Yes:

- | | |
|--|---|
| <input type="checkbox"/> included only low risk of bias RCTs | <input checked="" type="checkbox"/> Yes |
| <input checked="" type="checkbox"/> OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results | <input type="checkbox"/> No |

14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?

For Yes:

- | | |
|---|---|
| <input type="checkbox"/> There was no significant heterogeneity in the results | <input checked="" type="checkbox"/> Yes |
| <input checked="" type="checkbox"/> OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review | <input type="checkbox"/> No |

15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?

For Yes:

- performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias

- Yes
- No
- No meta-analysis conducted

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

For Yes:

- The authors reported no competing interests OR
- The authors described their funding sources and how they managed potential conflicts of interest

- Yes
- No

Quality Assessment of Observational Studies

Author Year	Selection bias	Detection bias	Confounding bias	Appropriateness of data analysis	Overall Rating
	1. Was the sample frame appropriate to address the target population? 2. Were study participants sampled in an appropriate way? 3. Was the sample size adequate (nationally representative or geographically diverse)? 4. Were the study subjects and the setting described in detail?	5. Were valid methods used for the identification of the condition (dementia)? 6. Was the condition (dementia) measured in a standard, reliable way for all participants?	7. Is confounding of the effect of intervention unlikely in this study? 8. Are groups balanced in terms of factors that might bias the exposure and outcome association? 9. Are the appropriate confounding factors reported and adjusted for in study design or analysis? 10. Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study?	11. Was the data analysis conducted with sufficient coverage of the identified sample? 12. Was there appropriate statistical analysis? 13. Was the response rate adequate, and if not, was the low response rate managed appropriately?	
KQ1					
Hudomiet, 2018 ³	Yes Nationally representative sample.	Unclear Telephone Interview for Cognitive Status (TICS) a 27-point cognitive scale that included an immediate and delayed 10-noun free recall test, a serial seven subtraction test, and a backwards count from 20 test.	NA	Yes	Fair
Langa, 2017 ⁴	Yes Nationally representative sample.	Unclear Telephone Interview for Cognitive Status (TICS) a 27-point cognitive scale that included an immediate and delayed 10-noun free recall test, a serial seven subtraction test, and a backwards count from 20 test.	NA	Yes	Fair



Author Year	Selection bias	Detection bias	Confounding bias	Appropriateness of data analysis	Overall Rating
	1. Was the sample frame appropriate to address the target population? 2. Were study participants sampled in an appropriate way? 3. Was the sample size adequate (nationally representative or geographically diverse)? 4. Were the study subjects and the setting described in detail?	5. Were valid methods used for the identification of the condition (dementia)? 6. Was the condition (dementia) measured in a standard, reliable way for all participants?	7. Is confounding of the effect of intervention unlikely in this study? 8. Are groups balanced in terms of factors that might bias the exposure and outcome association? 9. Are the appropriate confounding factors reported and adjusted for in study design or analysis? 10. Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study?	11. Was the data analysis conducted with sufficient coverage of the identified sample? 12. Was there appropriate statistical analysis? 13. Was the response rate adequate, and if not, was the low response rate managed appropriately?	
Plassman, 2007 ⁵	Yes Nationally representative sample.	Yes A 3-4 hour in-home neuropsychological and clinical assessment as well as expert clinician adjudication	NA	Yes	Fair
KQ2					
Barnes, 2014 ⁶	Yes National VHA database, random sample of 200,000 Veterans aged 55 and older, no dementia at baseline.	Yes ICD-9 codes.	Yes Adjusted for demographics, medical comorbidities, and psychiatric conditions.	Yes	Fair
Barnes, 2018 ⁷	Yes All VHA pts from 1 TBI and 1 general patient database.	Yes ICD-9 codes.	Yes Adjusted for demographics, medical comorbidities, and psychiatric conditions.	Yes	Fair

Author Year	Selection bias	Detection bias	Confounding bias	Appropriateness of data analysis	Overall Rating
	1. Was the sample frame appropriate to address the target population? 2. Were study participants sampled in an appropriate way? 3. Was the sample size adequate (nationally representative or geographically diverse)? 4. Were the study subjects and the setting described in detail?	5. Were valid methods used for the identification of the condition (dementia)? 6. Was the condition (dementia) measured in a standard, reliable way for all participants?	7. Is confounding of the effect of intervention unlikely in this study? 8. Are groups balanced in terms of factors that might bias the exposure and outcome association? 9. Are the appropriate confounding factors reported and adjusted for in study design or analysis? 10. Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study?	11. Was the data analysis conducted with sufficient coverage of the identified sample? 12. Was there appropriate statistical analysis? 13. Was the response rate adequate, and if not, was the low response rate managed appropriately?	
McMurtray, 2006 ⁸	No Sampling appropriate (all patients in 4-year period at memory clinic). Study was only conducted in 1 VA. Not a lot of descriptive data of patient comorbidities etc.	Yes Patients had impairment in 2 or more areas of cognition that caused social/occupational functioning.	No Almost no data on comorbidities, no adjustment for confounders in data analyses.	Yes	Fair
Mendez, 2015 ⁹	Yes National Alzheimer's database (populated from NIA-funded Alzheimer's Disease Centers).	Yes "Clinically probable AD dementia" diagnosed at an Alzheimer's center seems appropriate.	No Matched controls on gender and years of education (within three years), but no data on comorbidities.	No They didn't statistically compare EOD vs LOD on baseline characteristics or control for confounders. Hard to say what's driving the difference in TBI between those groups.	Fair
Nordstrom, 2014 ¹⁰	Unclear Large sample, but not enough information to determine if it's nationally representative.	Yes ICD 8, 9, 10 codes for vascular dementia, alcohol dementia, and dementia of unspecified type but not Lewy bodies, etc.	Yes Adjusted for demographics, medical comorbidities, psychiatric conditions, and family history.	Yes	Fair

Author Year	Selection bias	Detection bias	Confounding bias	Appropriateness of data analysis	Overall Rating
	1. Was the sample frame appropriate to address the target population? 2. Were study participants sampled in an appropriate way? 3. Was the sample size adequate (nationally representative or geographically diverse)? 4. Were the study subjects and the setting described in detail?	5. Were valid methods used for the identification of the condition (dementia)? 6. Was the condition (dementia) measured in a standard, reliable way for all participants?	7. Is confounding of the effect of intervention unlikely in this study? 8. Are groups balanced in terms of factors that might bias the exposure and outcome association? 9. Are the appropriate confounding factors reported and adjusted for in study design or analysis? 10. Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study?	11. Was the data analysis conducted with sufficient coverage of the identified sample? 12. Was there appropriate statistical analysis? 13. Was the response rate adequate, and if not, was the low response rate managed appropriately?	
Schaffert, 2018 ¹¹	Yes National Alzheimer's database (populated from NIA-funded Alzheimer's Disease Centers).	Yes Diagnoses made by team of physicians and autopsy-confirmed	No Adjusted for sex, education, and race, but not comorbidities.	Yes	Fair

Abbreviations: TBI = traumatic brain injury; EOD = early-onset Alzheimer's; LOD = late-onset Alzheimer's; ICD = International Classification of Disease; VA = Veterans Affairs; Veterans Health Administration; NIA = National Institute on Aging



APPENDIX D. ONGOING STUDIES/EXISTING REGISTRIES

PI or Researcher Institution	Study Title Identifier	Population	Comparator	Outcomes of Interest	Estimated completion
William Walker ^{12,13} Virginia Commonwealth University; McGuire VA Medical Center	Chronic Effects of Neurotrauma Consortium (CENC) Multi-Centre Observational Study	US Veterans who served in recent military conflicts	TBI vs no TBI	Chronic and late-life effects of mild traumatic brain injury (mTBI), including those that may stem from neurodegeneration such as dementia or CTE.	NA: objective is to create a comprehensive database for researchers.
Rudy Rull ¹⁴ Naval Health Research Center	Millennium Cohort Study	US military service members	TBI vs no TBI	Collected information on TBIs, but not on dementia. However, dementia outcomes could be added.	Enrollment ended in 2014 and participants will be followed for 21 years.
David Weir ¹⁵ University of Michigan	Health and Retirement Study (HRS) and the Aging, Demographics, and Memory Study (ADAMS)	US civilians	NA	Prevalence of dementia.	NA: objective is to create a comprehensive database for researchers.
Raymond Rosen ¹⁶ VA Boston Healthcare System; New England Research Institutes; Department of Defense	Project VALOR (Veterans' After-discharge Longitudinal Registry)	US Veterans from Operation Iraqi Freedom/ Operation Enduring Freedom	TBI vs no TBI	Collected information on TBIs, but not on dementia. However, dementia outcomes could be added.	NA: objective is to create a comprehensive database for researchers.
Mohammed Ahmed ¹⁷ University of California, San Diego	National Alzheimer's Coordinating Center (NACC) Database	US civilians	TBI vs no TBI	Collected information on the progression and diagnosis of dementia.	NA: objective is to create a comprehensive database for researchers.
Victoria Davey ¹⁸ Veteran Affairs Office of Patient Care Services	Vietnam Era Health Retrospective Observational Study (VE-HEROeS) NCT02825602	US Veterans who served during the Vietnam era	TBI vs no TBI	Dementia	TBD: Study is active, not recruiting.

APPENDIX E. PEER REVIEW COMMENT TABLE

Comment #	Reviewer #	Comment	Author Response
<i>Are the objectives, scope, and methods for this review clearly described?</i>			
1	1	Yes	None
2	2	Yes	None
3	3	Yes	None
4	4	Yes	None
5	5	Yes	None
<i>Is there any indication of bias in our synthesis of the evidence?</i>			
6	1	No	None
7	2	No	None
8	3	No	None
9	4	No	None
10	5	No	None
<i>Are there any <u>published</u> or <u>unpublished</u> studies that we may have overlooked?</i>			
11	1	Yes - Most recent K Yaffe on sex differences might be considered	<p>Thank you. We have added the following reference to the background section where we had already identified sex as a potential confounder of the relationship between TBI and dementia.</p> <p>Snyder HM, Asthana S, Bain L, et al. Sex biology contributions to vulnerability to Alzheimer's disease: A think tank convened by the Women's Alzheimer's Research Initiative. <i>Alzheimer's & dementia: the journal of the Alzheimer's Association</i>. 2016;12(11):1186-1196.</p>
12	2	No	None
13	3	No	None
14	4	Yes - They are embedded in my comments	See comments in "additional suggestions or comments" section.
15	5	No	None
<i>Additional suggestions or comments can be provided below. If applicable, please indicate the page and line numbers from the draft report.</i>			
16	1	Accept as is	None
17	2	None, this report includes all of the relevant references and presents the material in the appropriate scientific manner. Highly readable format and clear conclusions.	None

18	3	Page 1 line 46 How about the rate of EOD	<i>We added the sentence “No studies were identified on the comparative prevalence of dementia among younger (<65 years) Veteran and civilian populations” to both the Executive Summary and Findings sections.</i>
19	3	Page 2 line 19 and the Prospective Chronic Effects (instead of “and the Chronic Effects of Neurotrauma Consortium (CENC))	<i>We clarified that research from VE-HEROeS is retrospective and research from CENC is prospective.</i>
20	3	Page 2 line 46 6 to 16%	<i>Corrected so this says “6 to 16%.”</i>
21	3	Page 5 line 13 delete "such as PTSD"	<i>PTSD is one example of a mental health condition whose symptoms overlap with TBI. However, we deleted the specific mention of it here as the important point is that TBI and dementia have overlapping symptoms.</i>
22	3	Page 5 line 25 along with academic and private entities	<i>Changed “partners” to “entities.”</i>
23	3	Page 5 lines 43-45 Incorrect, CTE goes back to the 1920's	<i>Deleted “relatively newly identified.”</i>
24	3	Page 17 lines 27-28 Amyloid is not associated with TBI dementia or the loosely described condition of CTE. This study has many problems and probably should be avoided.	<i>We deleted this sentence and instead reference the Barnes 2018 study, which describes other potential causal pathways.</i>
25	3	Page 17 57-60 (the two mentions of “dementia”) Should read Alzheimer's Disease, not dementia	<i>Changed to “Alzheimer’s Disease.”</i>
26	3	Page 18 line 5 CENC0001	<i>Changed to “CENC0001”</i>
27	4	Given the study limitations, the report could include MCI and other clinical neurodegenerative syndromes in relation to TBI.	<i>To the “Clinical and Future Research Implications” section of the Discussion, we added a sentence suggesting the need for an updated systematic review in the future that has a broader scope of neurodegenerative syndromes, including MCI.</i>
28	4	It would also be informative for the authors to extract the confounding variables of most concern.	<i>We reported information on which confounders were controlled for in each study in “Appendix C: Quality Assessment of Included Studies” which appears in the Supplementary Materials. In cases where authors did not adequately control for confounders, we noted which of these confounders were of most concern.</i>
29	5	excellent report	<i>None</i>

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