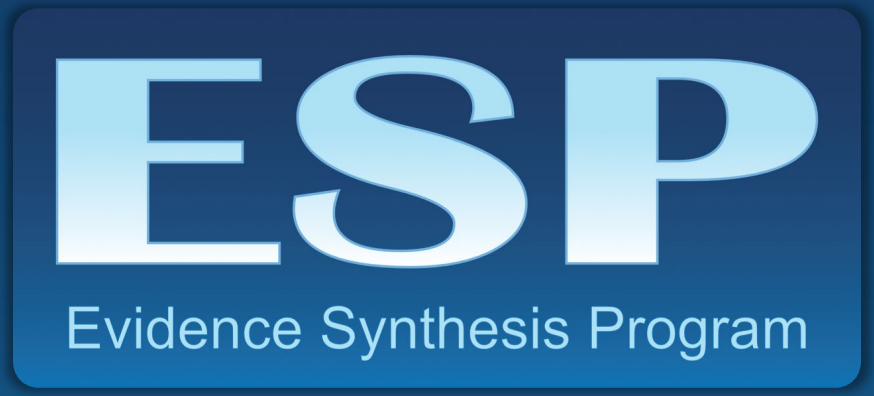

Evidence Brief: Traumatic Brain Injury and Dementia

Kim Peterson, MS
Senior Research Associate

ESP Coordinating Center
Portland VA Medical Center

July 2019

Presentation Outline

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- ESP Background
- Evidence synthesis products overview
- Findings from January 2019 ESP Rapid Review on TBI/Dementia
- Discussion/questions

Acknowledgements

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Operational Partners

Operational partners are system-level stakeholders who have requested the report to inform decision-making. They recommend TEP members; assure VA relevance; help develop and approve final project scope and timeframe for completion; provide feedback on draft report; and provide consultation on strategies for report dissemination.

Ralph DePalma, MD
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Disclosure

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This report is based on research conducted by the Evidence Synthesis Program (ESP) Coordinating Center located at the **Portland VA Medical Center, Portland, OR**, funded by the Department of Veterans Affairs, Veterans Health Administration, Health Services Research and Development. The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. No investigators have any affiliations or financial involvement (*eg*, employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

Poll Question #1

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- What is your primary role in VA?
  - Student, trainee, or fellow
  - Clinician
  - Researcher
  - Administrator, manager or policy-maker
  - Other

Poll Question #2

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- How familiar are you with the ESP?
  - Not at all
  - Somewhat
  - Very familiar
  - Very familiar and I've requested and/or used an ESP report in my work

Poll Question #3

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- How familiar are you with systematic review methodology?
  - Not at all
  - Somewhat
  - Very familiar
  - Very familiar and I've conducted review(s)

Who We Are

ESP
Evidence Synthesis Program

Mission: To make high-quality evidence synthesis available to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans.

"ESP reports are a terrific resource to inform policy decisions. They are methodologically rigorous and available [upon] request."

https://www.hsrd.research.va.gov/publications/esp/

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ESP Center Locations

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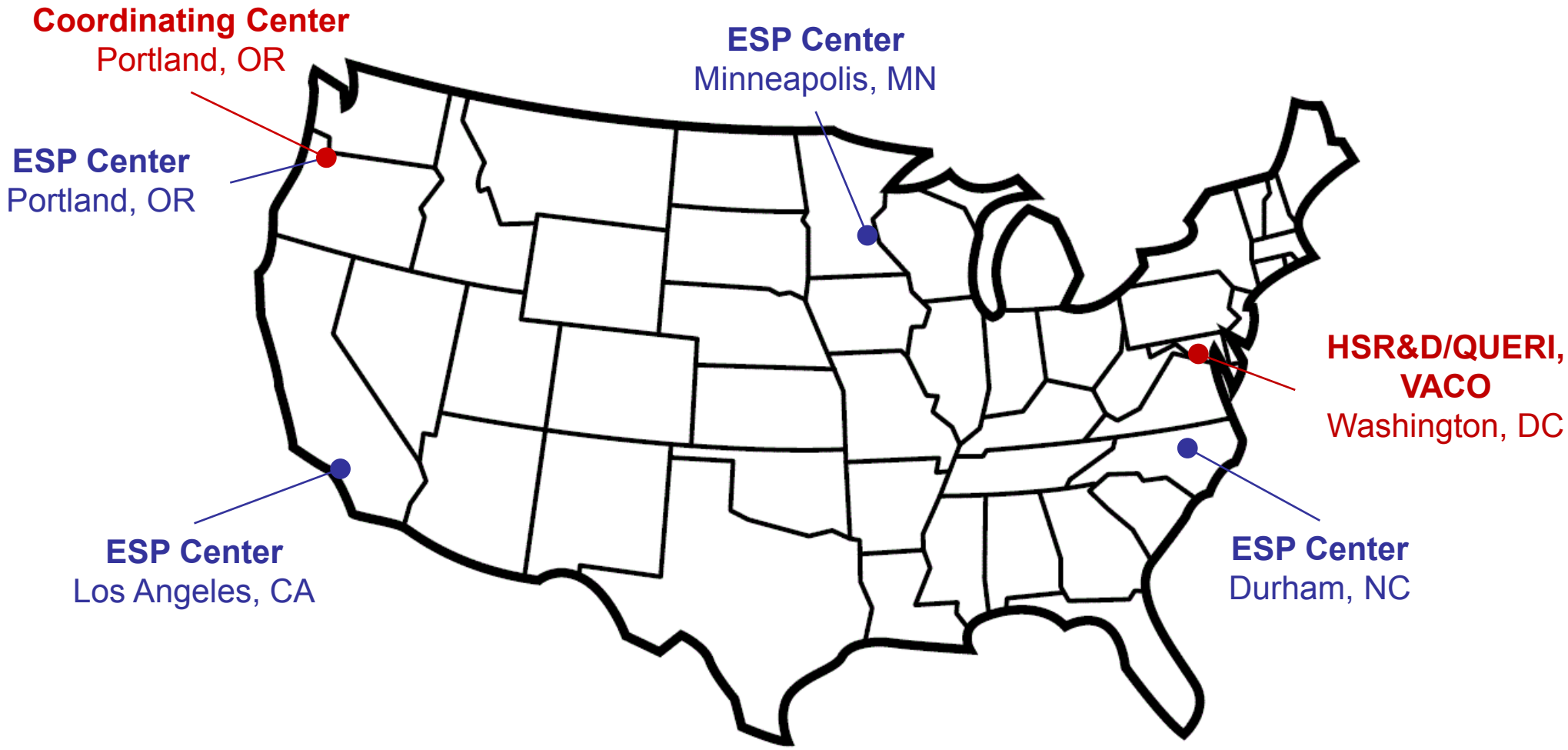

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Range of Products for Different Needs

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	Speed (product within 4 months)	Fully follows all SR steps	Critical appraisal of evidence	External peer review
Systematic review		✓	✓	✓
Scoping review	*			*
Evidence map			*	✓
Rapid evidence brief	✓		✓	✓
Evidence assist	✓		✓	
Evidence compendium	✓			
Evidence inventory	✓			

* Possible on a case-by-case basis

ESP Products' Key Characteristics

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Standard Systematic Review (9-12 months)
Comprehensive synthesis using the most methodologically rigorous process. Reviews several broad, overarching key questions.

Scoping Review (4-12 months)
Descriptive overview that identifies gaps and overlap in key concepts and highlights specific and/or unique features of interest.

Evidence Map (9-12 months)
User-friendly visual figure or graph and interpretive summary of a broad research field that provides quick access to questions and answers that previous research has addressed and identifies gaps that are important for VHA.

Rapid Evidence Brief (2-4 months)
Detailed report that generally follows, but streamlines, accepted systematic review methods and PRISMA reporting guidelines.

Evidence Assist™ (1-4 months)
Consultative memorandum with flexible format.

Evidence Compendium (1-2 months)
Brief summary of key features, data abstraction, and bibliography, organized by key features (*eg*, key question, study design, population, *etc*).

Evidence Inventory (1-4 weeks)
Bibliography organized by key features (*eg*, key question, study design, population, *etc*).

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More Information about ESP Rapid Review Program

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Peterson *et al. Systematic Reviews* (2016) 5:132
DOI 10.1186/s13643-016-0306-5

Systematic Reviews

RESEARCH Open Access

User survey finds rapid evidence reviews increased uptake of evidence by Veterans Health Administration leadership to inform fast-paced health-system decision-making

Kim Peterson[1,2*], Nicole Floyd[1], Lauren Ferguson[1,2], Vivian Christensen[1] and Mark Helfand[1,2]

Abstract

Background: To provide evidence synthesis for faster-paced healthcare decision-making, rapid reviews have emerged as a streamlined alternative to standard systematic reviews. In 2012, the Veterans Affairs Evidence-based Synthesis Program (VA ESP) added rapid reviews to support Veterans Health Administration (VHA) operational partners' more urgent decision-making needs. VHA operational partners play a substantial role in dissemination of ESP rapid reviews through a

Evidence Brief: TBI/Dementia

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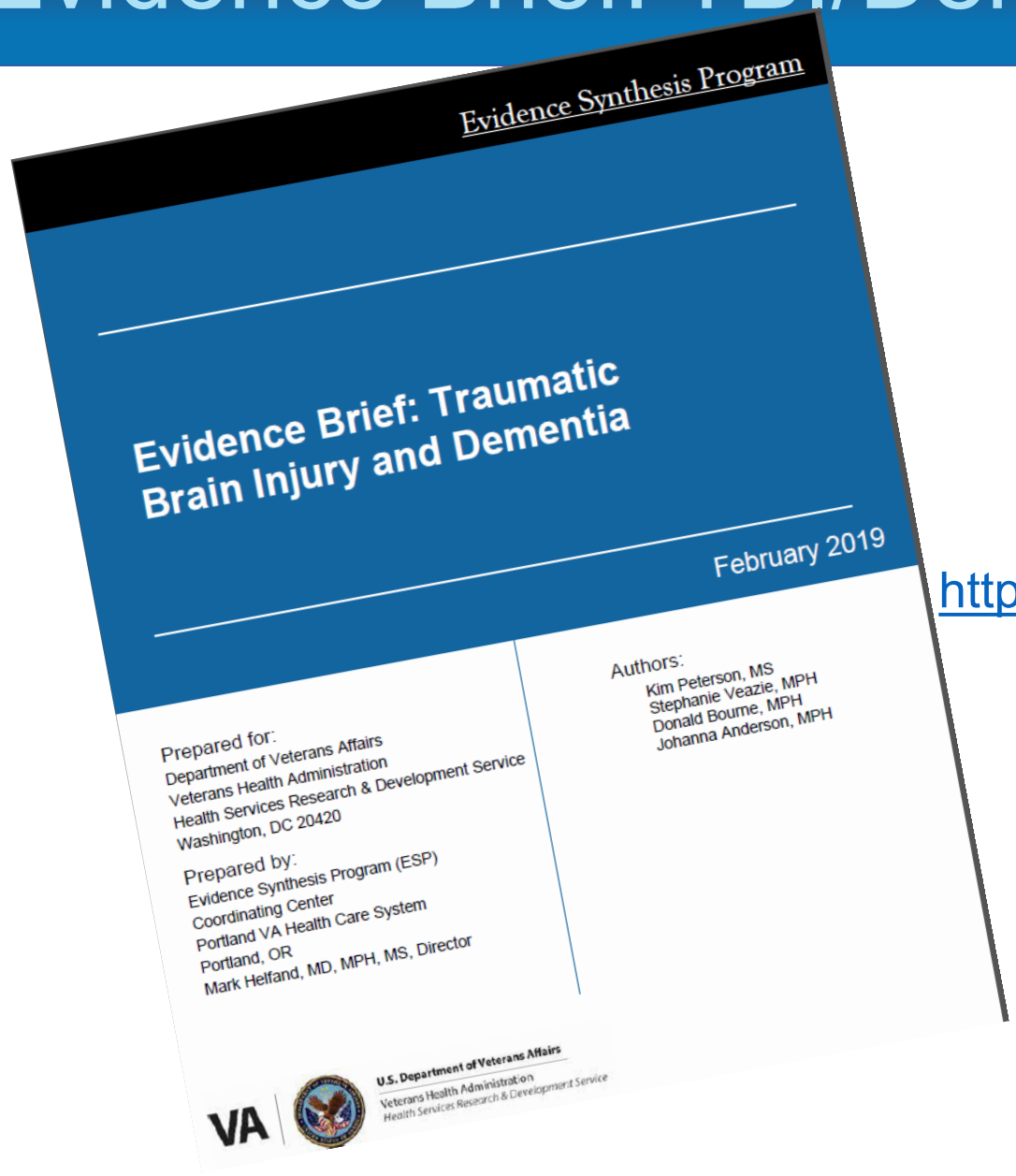

Full-length report available on ESP website:
http://www.hsrd.research.va.gov/publications/esp/reports.cfm

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Poll Question #4

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- Do you do work in these areas:
  - TBI
  - Dementia
  - Both
  - Neither

What Did We Know?

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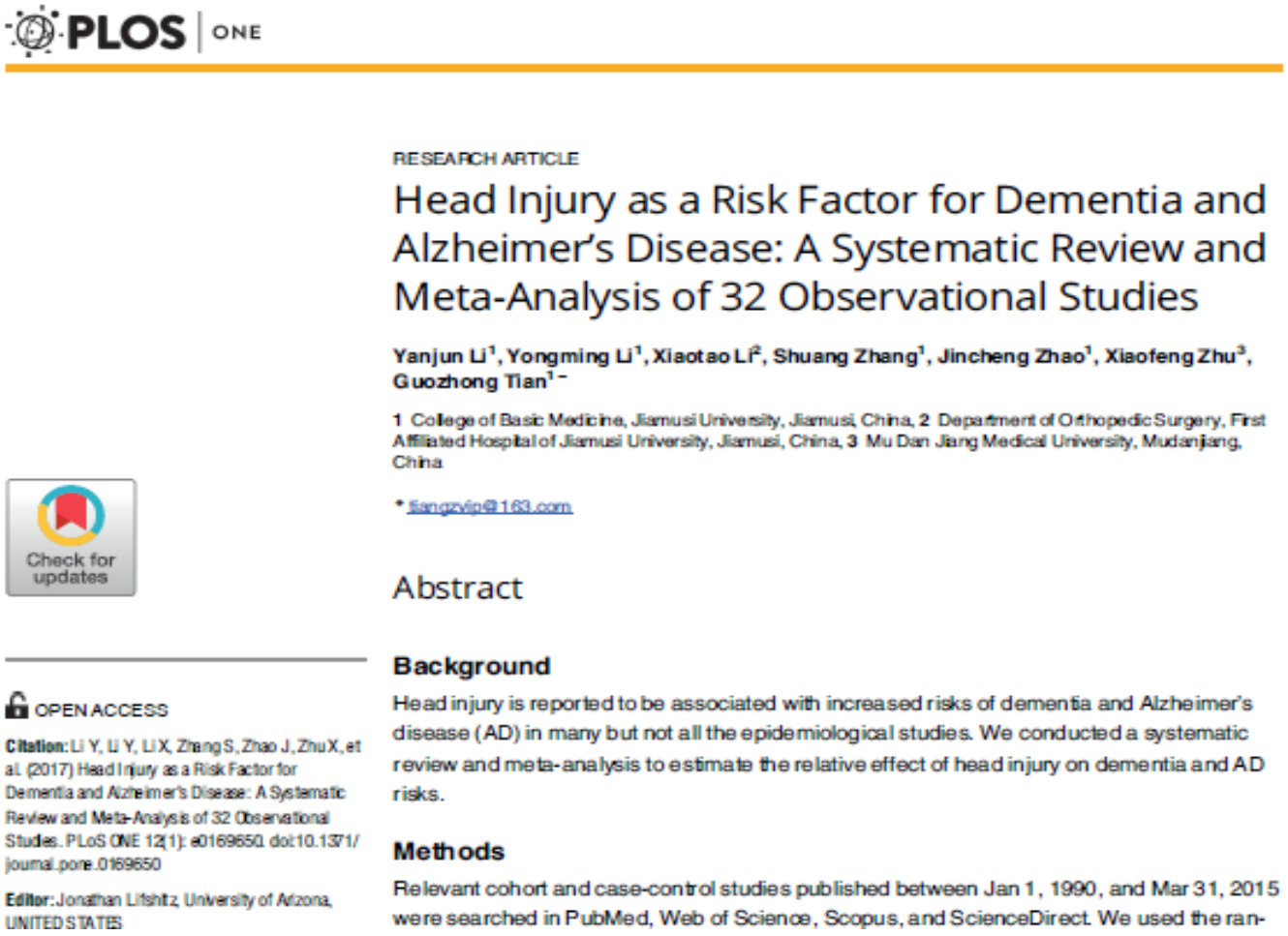

PLOS ONE

RESEARCH ARTICLE

Head Injury as a Risk Factor for Dementia and Alzheimer's Disease: A Systematic Review and Meta-Analysis of 32 Observational Studies

Yanjun Li[1], Yongming Li[1], Xiaotao Li[2], Shuang Zhang[1], Jincheng Zhao[1], Xiaofeng Zhu[3], Guozhong Tian[1]*

1 College of Basic Medicine, Jiamusi University, Jiamusi, China, 2 Department of Orthopedic Surgery, First Affiliated Hospital of Jiamusi University, Jiamusi, China, 3 Mu Dan Jiang Medical University, Mudanjiang, China

* liangzvip@163.com

Check for updates

OPEN ACCESS

Citation: Li Y, Li Y, Li X, Zhang S, Zhao J, Zhu X, et al. (2017) Head Injury as a Risk Factor for Dementia and Alzheimer's Disease: A Systematic Review and Meta-Analysis of 32 Observational Studies. PLoS ONE 12(1): e0169650. doi:10.1371/journal.pone.0169650

Editor: Jonathan Lifshitz, University of Arizona, UNITED STATES

Abstract

Background

Head injury is reported to be associated with increased risks of dementia and Alzheimer's disease (AD) in many but not all the epidemiological studies. We conducted a systematic review and meta-analysis to estimate the relative effect of head injury on dementia and AD risks.

Methods

Relevant cohort and case-control studies published between Jan 1, 1990, and Mar 31, 2015 were searched in PubMed, Web of Science, Scopus, and ScienceDirect. We used the ran-

Head injury increased dementia risk (RR = 1.63, 95% CI 1.34-1.99) in general population

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. *PLoS One.* 2017;12(1):e0169650.

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Remaining Questions

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- *Risk in Veterans?*
- *Evidence from new studies?*
  - *Barnes 2018 VA study*

ESP Review Objectives

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- KQ1: Describe the comparative prevalence of dementia between Veterans and non-Veterans.
- KQ2: Assess whether previous TBIs affect the risk of dementia among Veterans.

Assess whether prevalence and association between dementia and TBI vary by combat history, era of conflict, or timing of dementia prevalence.

Eligibility Criteria

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Population: US Veterans or military personnel, or Veterans or military personnel from UK, Canada, New Zealand, or Australia

Intervention: N/A

Comparator: Non-Veteran population

Outcomes, Timing, Setting, Study design: Any

Evidence Brief Methods

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- **Search:** MEDLINE®, Cochrane databases and other sources (inception through 10/18) and consulted with experts
- **Study selection:** Based on eligibility criteria
- **Data abstraction:** Study and patient characteristics and results
- **Critical appraisal:** Use of standardized tools
- **Quality control:** Assessments first completed by one reviewer and checked by at least one additional reviewer. Disagreements were resolved by consensus.
- **Peer Review:** 5 experts commented and responses are publicly available

Criteria for Assessing Internal Validity of Individual Studies

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*Adapted tool based on the Joanna Briggs Institute Checklist for Prevalence Studies

Criteria for Assessing the Strength of a Body of Evidence

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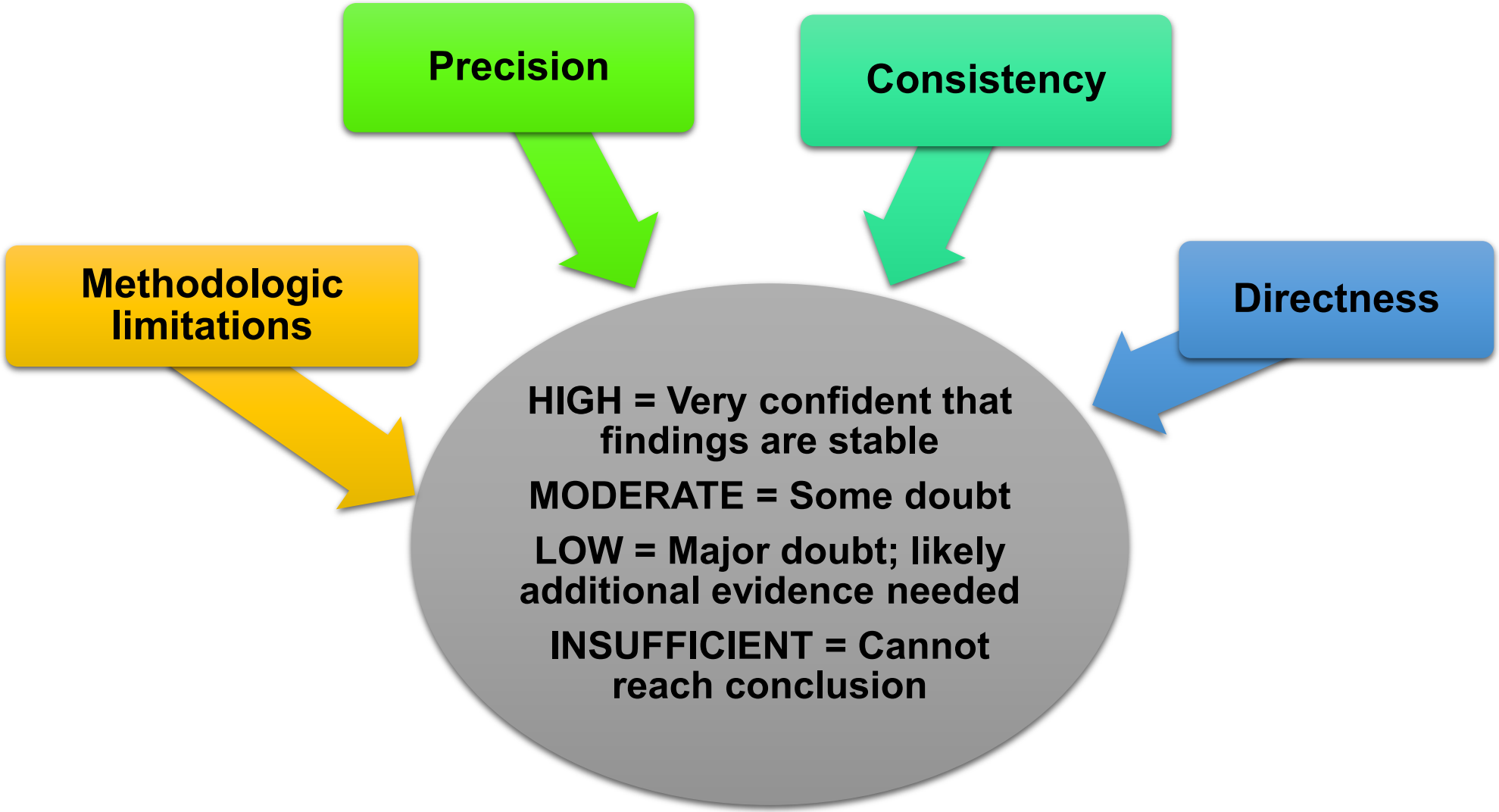

*Based on the AHRQ Methods Guide for Comparative Effectiveness Reviews

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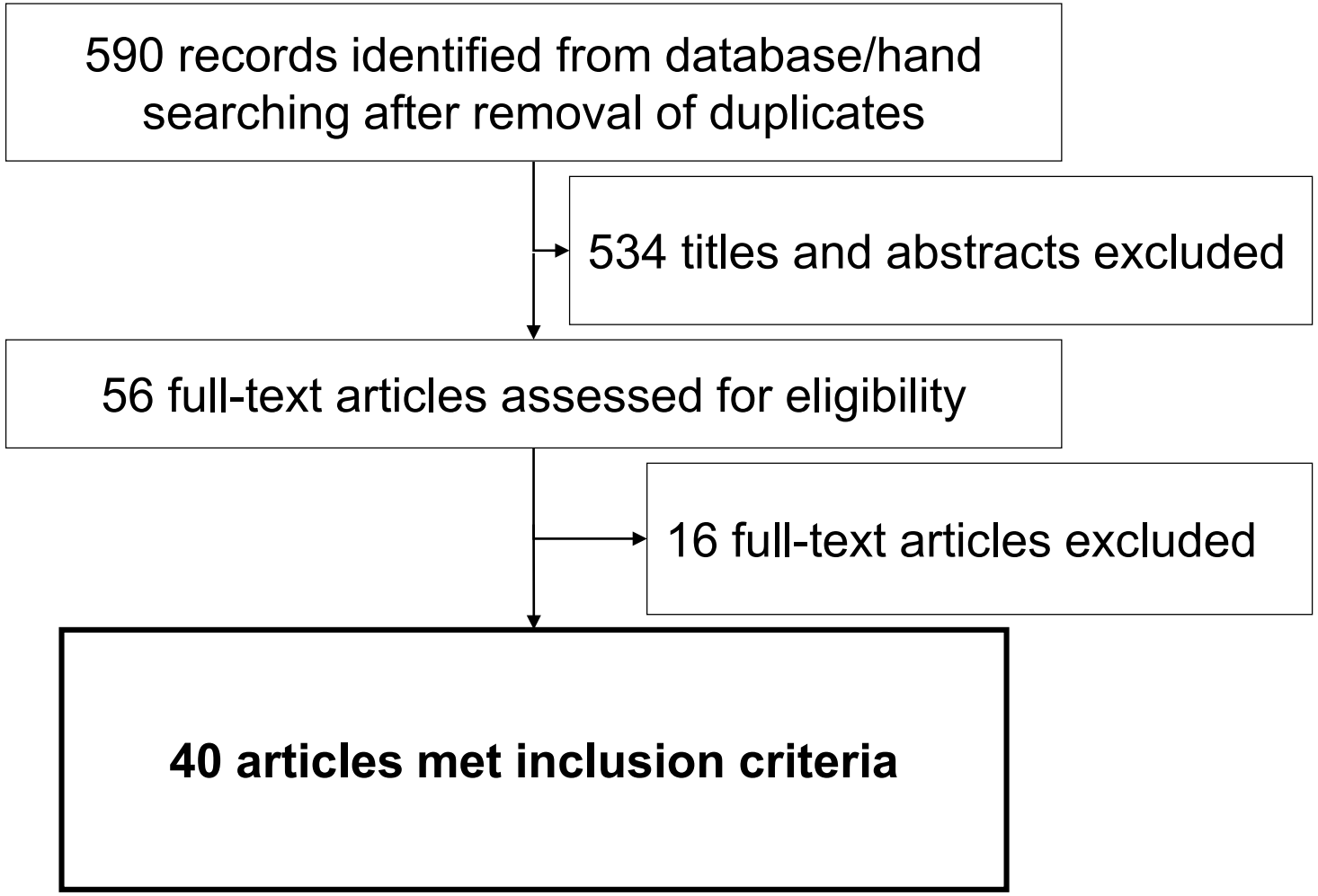
Study Selection



Prioritized Based on US Veteran-relevance

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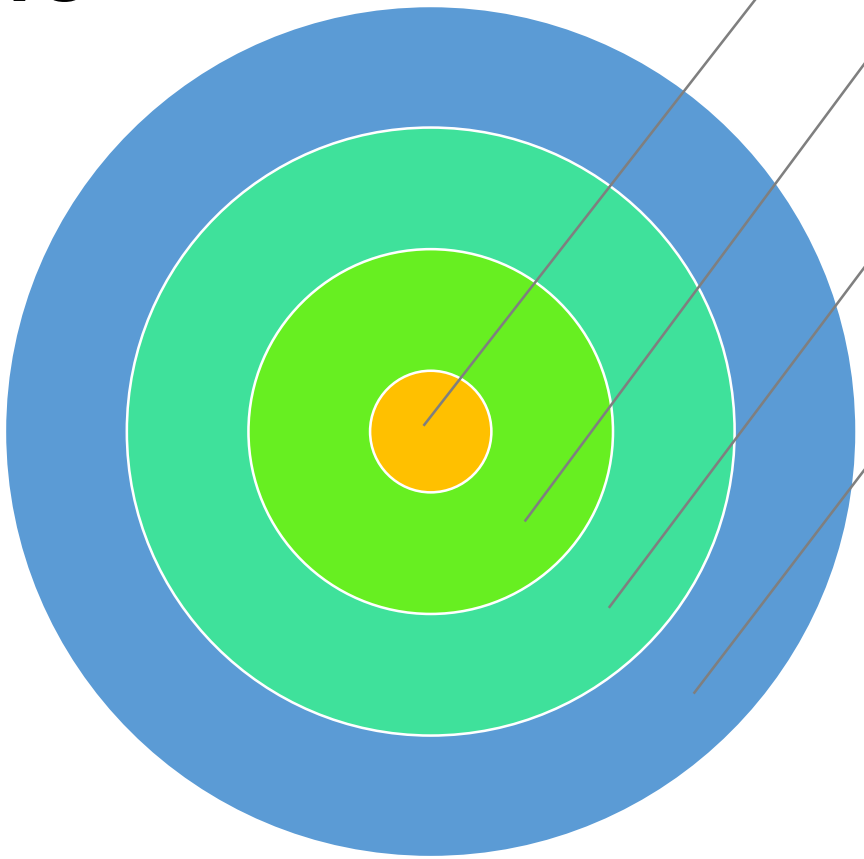
Evidence Tiers



US Veterans (n=4)

Veterans or military personnel from other countries (n=1)

Non-Veterans from US, UK, Canada, New Zealand, Australia (n=10)

Non-Veterans from all other countries (n=25)

Highlighted Best Available Evidence

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- **Dementia prevalence:** 4 studies
- **Association between TBI and dementia overall:** 3 studies
- **Association between TBI and early-onset dementia:** 4 studies

Dementia Prevalence Evidence Overview

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- 1 systematic review in US Veterans (total N=432,461)
- 3 cross-sectional studies in US civilians (total N>21,913)

Dementia Prevalence in Veterans vs Civilians aged ≥ 65 years*

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≈

Veterans: 10.7%

Non-Veterans: 8.8% to 11.6%

*No studies: < 65 years old

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Major Doubts about Finding of Similar Dementia Prevalence in Veterans vs Civilians

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Strengths:

Large, nationally-representative samples

Weaknesses:

Potential confounding from between-population differences in age and sex

General TBI/Dementia Association: Evidence Overview

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- **2 retrospective cohort studies in US Veterans: Barnes 2014, 2018**
  - Total N= 546,322
  - VA National Patient Care and Traumatic Brain Injury Database
  - Veterans with TBI propensity-matched to Veterans without TBI based on patient demographics, medical comorbidities and psychiatric conditions
  - TBI diagnoses by comprehensive TBI evaluation or ICD-9 codes
  - Dementia diagnoses by ICD-9 codes

Association Between Dementia and TBI in Veterans

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With TBI

6% to 16%

>

Without TBI

3% to 10%

Dementia Risk Increased with TBI Severity*

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Severity of TBI	Adjusted Hazard Ratio for Dementia (95% CI)
Mild TBI, without LOC	2.36 (2.10, 2.66)
Mild TBI, with LOC	2.51 (2.29, 2.76)
Mild TBI, LOC unknown	3.19 (3.05, 3.33)
Moderate/Severe TBI	3.77 (3.63, 3.91)

*Barnes DE, Byers AL, Gardner RC, Seal KH, Boscardin WJ, Yaffe K. Association of mild traumatic brain injury with and without loss of consciousness with dementia in US military veterans. *JAMA Neurol.* 2018;75(9):1055-1061.

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Some Doubts about Finding of Increased Risk of Dementia Following TBI

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Strengths:

Nationally-representative, valid ascertainment methods, controlled for some important confounding

Weaknesses:

Potential residual confounding from unmeasured genetic and lifestyle factors

Related Cyberseminar

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Mild TBI Diagnosis and Management Strategies

TBI and Dementia: What We Know and What We Don't Know

by Kristine Yaffe, MD
Seminar date: 7/31/2018

Description: Description: This seminar will summarize research findings on the association between traumatic brain injury and increased risk of dementia. In addition to reviewing the most up-to-date literature, the presentation will also highlight results from studies of veterans and discuss implications and future directions. Intended Audience: Clinicians and researchers interested in TBI outcomes and veterans' health including those in neurology, psychiatry, and geriatrics.

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TBI/Dementia Association by *Timing* of Dementia Onset: Evidence Overview

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- 4 retrospective cohort studies among:
  - Swedish men conscripted for military service, N=811,622 (Nordstrom 2014*)
  - US Veterans, N=948 (McMurtray 2006)
  - US civilians, total N=13,705 (Mendez 2015, Schaffert 2018)

*Nordstrom P, Michaelsson K, Gustafson Y, Nordstrom A. Traumatic brain injury and young onset dementia: a nationwide cohort study. *Ann Neurol.* 2014;75(3):374-381.

Characteristics of Swedish Study of Young-Onset Dementia (Nordstrom 2014)

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- Mean age = 18 years
- National patient register
- Men with TBI propensity-matched to controls based on patient demographics, medical comorbidities and psychiatric conditions
- ICD-8, 9, and 10 codes for dementia and TBI diagnoses
- Median of 33 years of follow-up

Possible Relationship Between TBI and Early-onset Dementia in Nordstrom 2014*

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Number/Severity of TBI	Hazard Ratio for Dementia (95% CI)
1 mild	1.5 (1.1 to 2.0)
> 1 mild	1.8 (1.1 to 3.0)
1 severe	2.3 (1.5 to 3.6)

*In model adjusted for all confounders

Some Doubts about Finding of Increased Risk of *Early-onset* Dementia Following TBI

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Strengths:

Nationally-representative, very long follow-up

Weaknesses:

Potential residual confounding from unmeasured genetic and lifestyle factors

Evidence Gaps: Future Research

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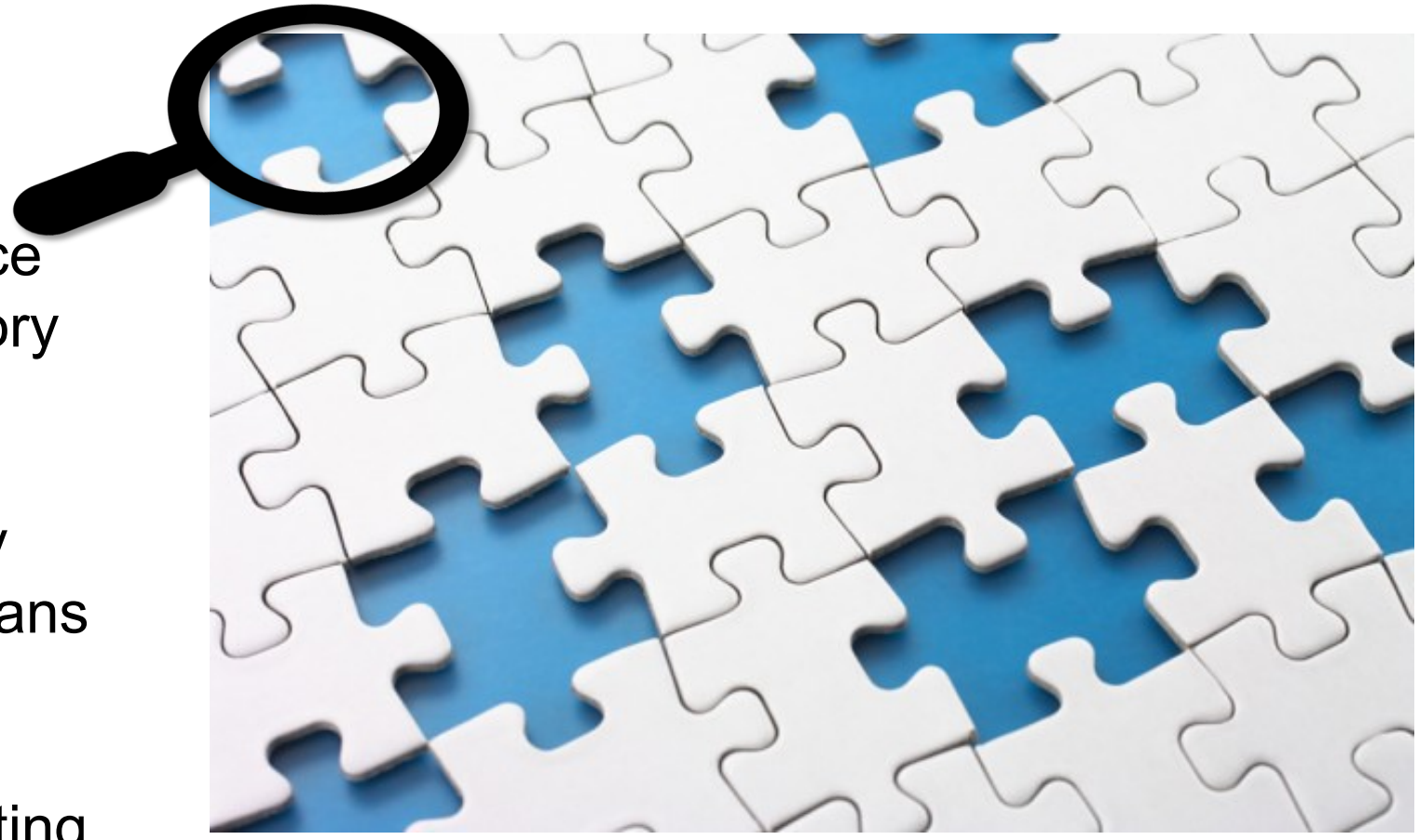
- Direct comparison of dementia prevalence in Veterans and non-Veterans
- Veteran dementia prevalence by combat deployment history or era of conflict
- Association of TBI and early onset dementia in US Veterans
- Role of brain injury severity, mode, multiple TBI, and setting on dementia prevalence or onset



Notable Ongoing Research

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- VE-HEROeS (Vietnam Era Health Retrospective Observational Study)
  - Examining lifetime TBI and dementia diagnoses by deployment status

- CENC (Chronic Effects of Neurotrauma Consortium):
  - Examining late neurologic effects of mTBI in OEF/OIF/OND combat, including CTE (CENC0001C)

Conclusions

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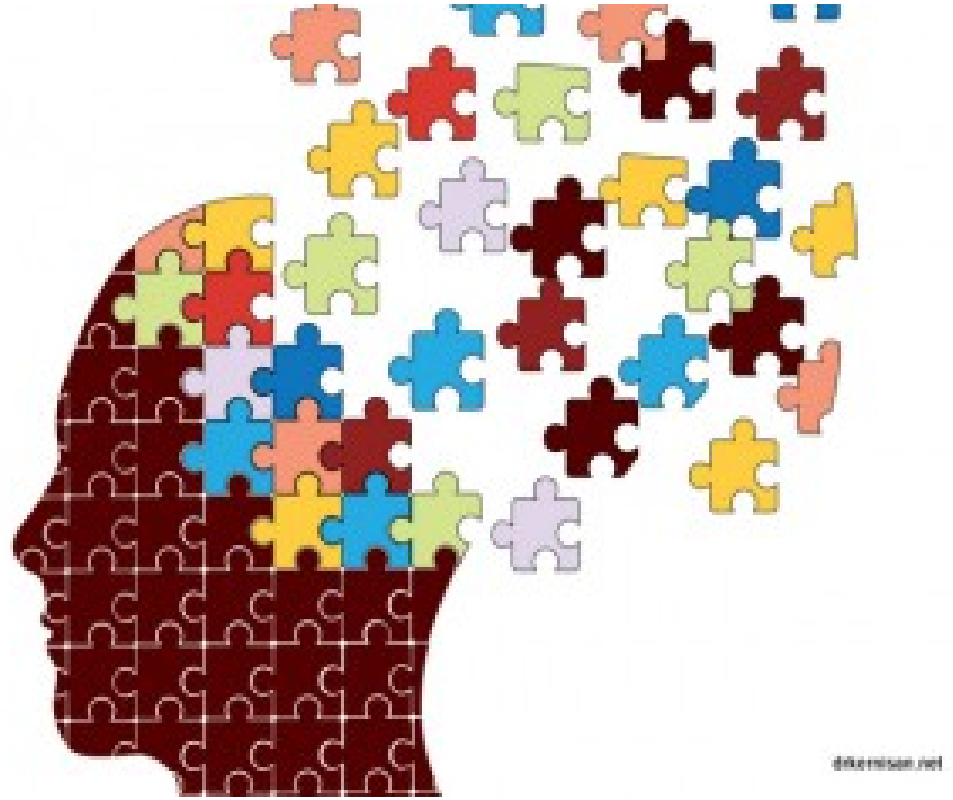
- Dementia prevalence appears similar in Veteran and non-Veteran populations.
- TBI appears associated with an increased risk of dementia in Veterans.
- Key areas for future research: Timing of dementia onset, and mechanisms of the association between TBI and dementia



Questions?

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If you have further questions, please feel free to contact:

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Full-length report and cyberseminar available on ESP website:

http://www.hsrd.research.va.gov/publications/esp/