A genetically informed examination of posttraumatic stress disorder and traumatic brain injury's impact on dementia risk in US Veterans

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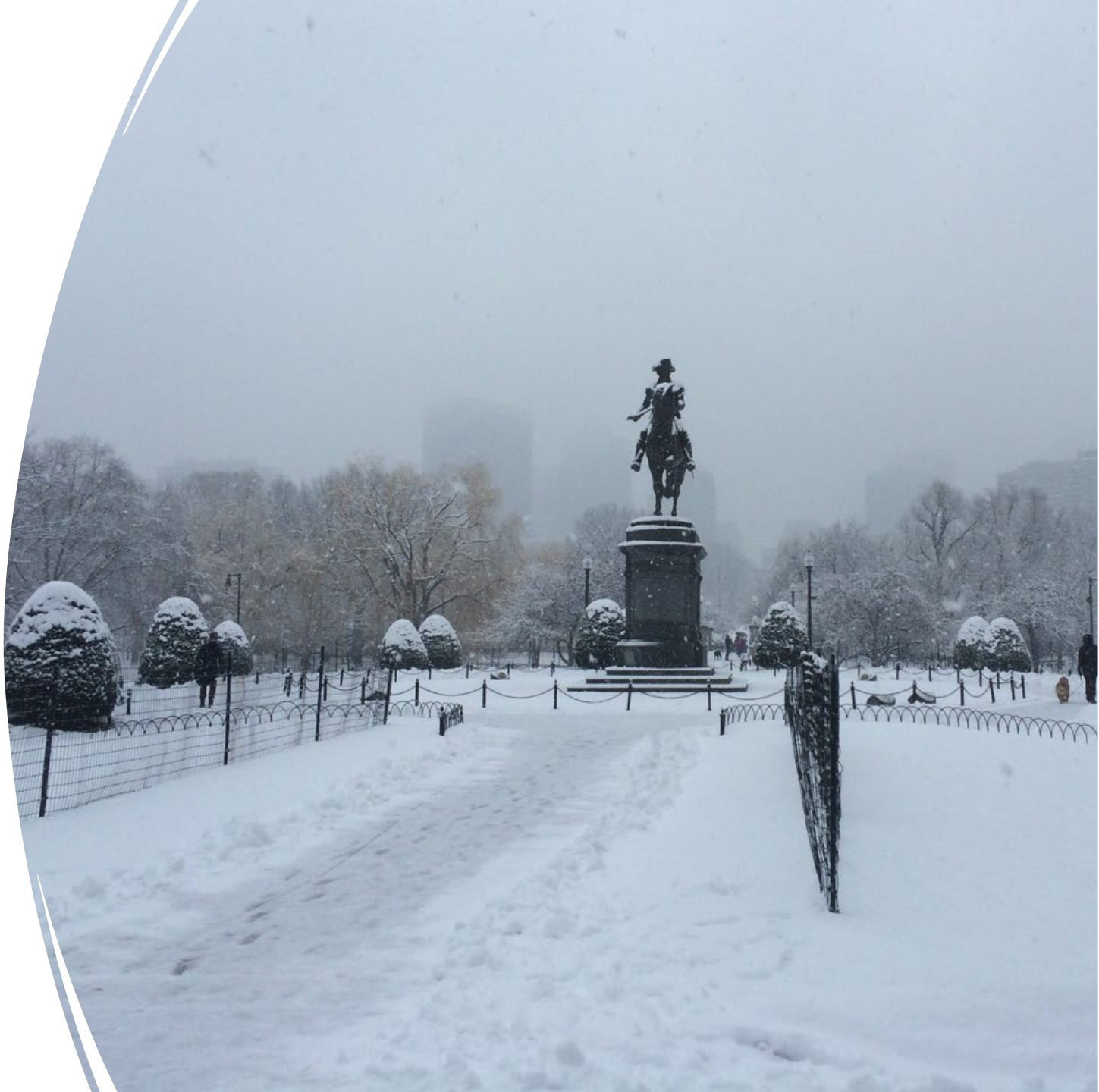

Outline

- Introduction to AD Genetics
- Introduction to MVP
- Identifying Dementia cases in
- Identifying TBI Cases in MVP.
- Analysis Methods
- GxE Results
- Conclusions

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FEATURED ARTICLE

Alzheimer's disease and related dementias among aging veterans: Examining gene-by-environment interactions with post-traumatic stress disorder and traumatic brain injury

Mark W. Logue, Mark W. Miller, Richard Sherva, Rui Zhang, Kelly M. Harrington, Jennifer R. Fonda, Victoria C. Merritt, Matthew S. Panizzon, Richard L. Hauger, Erika J. Wolf, Zoe Neale ... See all authors

First published: 22 December 2022 | https://doi.org/10.1002/alz.12870

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ABSTRACT

Introduction

Post-traumatic stress disorder (PTSD) and traumatic brain injury (TBI) confer risk for Alzheimer's disease and related dementias (ADRD).

Introduction

- AD is the most common form of dementia
  - 60 -80% of dementia cases are AD.
- Women are at higher risk for AD then men.
- Several demographic factors which have been linked to higher rates of AD/Dementia including:
  - Metabolic Syndrome
  - Diabetes
  - Substance abuse
  - Smoking
- In addition, PTSD and traumatic brain injury (TBI) have been lined to a higher risk of dementia.

Alzheimer's Disease Genetics

- Highly penetrant rare dominant mutations in *PSEN1*&2 and *APP* cause early onset Alzheimer's disease (< age 65).
- The more common late-onset form of Alzheimer's disease (AD; onset > age 65) is determined by a mix of genetic and environmental factors.
- The strongest genetic risk factor for AD is the *APOE*:ε4 variant.
  - In White non-Hispanic subjects, each copy confers 3-4x risk.
  - The risk conferred varies by ancestry.
- Genome-wide association studies for AD have identified more than 70 AD-associated loci.
  - Most common AD variants had odds ratios (ORs) in the 0.8 to 1.2 range.

Background

- Military service may place veterans at elevated risk for AD and related dementia due to exposure to traumatic brain injury (TBI) and/or psychologically traumatic events that cause posttraumatic stress disorder (PTSD).

We hypothesized that PTSD and TBI will interact with genetic risk for AD such that the dementia risk associated with PTSD and TBI would be greater in carriers of the *APOE* ε4 allele.

Cohort: The Million Veteran Program (MVP)

- MVP is a VA ORD funded program to examine lifestyle and genetic factors in Veteran volunteers (>900K) recruited from VA medical centers.
- MVP volunteers provide a blood sample for genetic analysis, consent to access of their electronic medical record, and complete surveys on a wide range of demographic and health factors.
- Genome-wide genotype data (~650K sites) from a custom Affymetrix chip imputed using African Genome Resources Panel.
- Upcoming genomic data releases will include whole-genome sequence data and DNA methylation data.

Difficulties in AD phenotyping in VA EMR studies:

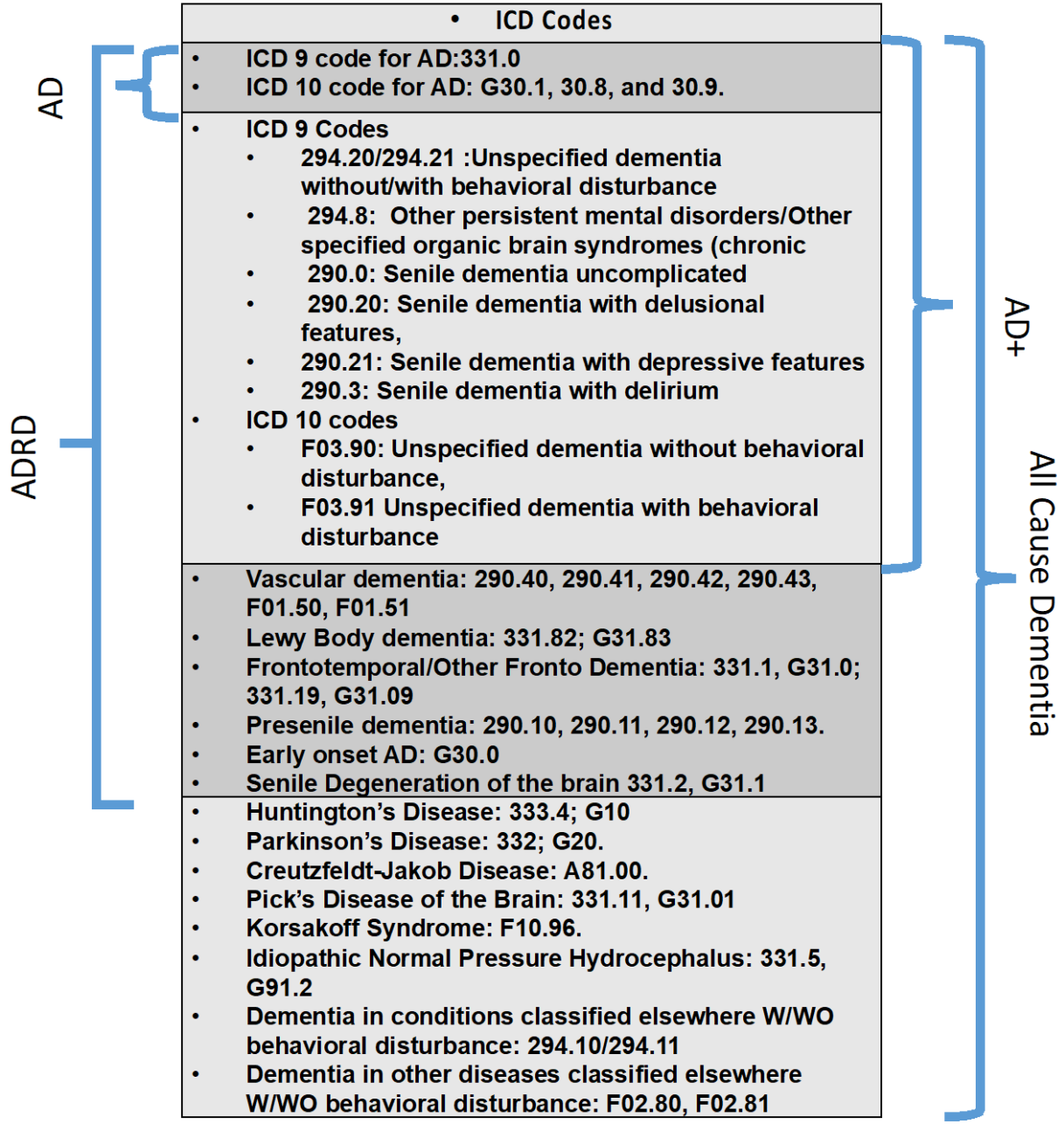
- Only a small handful of AD cases have autopsy or biomarker data.
- The VA EMR includes wide usage of non-specific dementia codes such as I*CD9:294.21 unspecified dementia with behavioral disturbance* in subjects with AD, even in specialty clinics
- AD cases in the VA population have high rates of other dementias (vascular dementia) which can make determining the primary etiology difficult.
- Although prescription data is often easily accessible, several studies have found that including AD medication information can hurt the performance of AD/Dementia classification algorithms.

MVP Cognitive Decline and Dementia During Aging Working Group (AD/MCI WG)

- Chair: Mark Logue
- Co-Chair: Richard Hauger
- Coordinator: Matthew Panizzon
- Founding Member: Victoria Merritt.
- **Representing:**
- MVP015/MVP040: Early Cognitive Impairment as a Function of Alzheimer's Disease Genes and Trauma.
  - PI: Mark Logue.
- MVP022: Clinical Manipulation of Testosterone and Its Impact on Dementia and Health.
  - PI: Richard Hauger.
- MVP026: Examination of Biological Markers Associated with Neurobehavioral and Neuropsychological Outcomes in Military Veterans with a History of Traumatic Brain Injury.
  - PI: Victoria Merritt.

Methods: Phenotypes

- **AD and related dementias (ADRD) cases** had ≥ 2 codes from the list of AD, non-specific dementia, and related dementia ICD codes.
- **Controls** had no dementia codes (ADRD or other dementia) or mild-cognitive impairment (MCI) codes, or prescriptions for AD medication.
- **PTSD** is based on a validated MVP phenotype (Harrington et al. 2019).



Identifying TBI cases in MVP

Victoria Merritt
San Diego VA
UCSD

Sources of Data

- Self-Report Survey Data
  - MVP Baseline Survey
  - MVP Lifestyle Survey
- ICD 9/10 Codes
- TBI Clinical Reminder Screen/ Comprehensive Traumatic Brain Injury Evaluation (CTBIE)

Section F: Medical History and Health Care Usage

43. **Please tell us if you have been diagnosed with the following conditions. Check the appropriate box and indicate the year of diagnosis and whether you currently take any medication(s) ("TAKE MEDS") for that condition.** *(Mark all that apply)*

Concussion or loss of consciousness	☐	☐☐☐☐	☐
Traumatic brain injury	☐	☐☐☐☐	☐

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Baseline Survey

Million Veteran Program: A Partnership with Veterans

Nervous System Problems

	YES	YEAR DIAGNOSED	TAKE MEDS
Migraine headaches	☐	☐☐☐☐	☐
Other headaches	☐	☐☐☐☐	☐
Memory loss or impairment	☐	☐☐☐☐	☐
Dementia (includes Alzheimer's, vascular, etc.)	☐	☐☐☐☐	☐
Concussion or loss of consciousness	☐	☐☐☐☐	☐
Traumatic brain injury	☐	☐☐☐☐	☐
Spinal cord injury or impairment	☐	☐☐☐☐	☐
Epilepsy / Seizure	☐	☐☐☐☐	☐
Parkinson's disease	☐	☐☐☐☐	☐
Amytrophic lateral sclerosis (Lou Gehring's disease)	☐	☐☐☐☐	☐
Multiple sclerosis	☐	☐☐☐☐	☐
Other nervous system problem	☐	☐☐☐☐	☐

Section E: Military and Environmental Experiences

36. Have you been deployed?

- ☐ Yes
- ☐ No → *(Skip to Q42 on Page 11)*

37. Did you ever serve in a combat or war zone?

- ☐ Yes
- ☐ No → *(Skip to Q42 on Page 11)*

38. Did you have any injury(ies) during your deployment from any of the following? *(Mark all that apply)*

- ☐ Fragment
- ☐ Bullet
- ☐ Vehicular (any type of vehicle, including airplane)
- ☐ Fall
- ☐ Blast (Improvised Explosive Device, RPG, land mine, grenade, etc.)
- ☐ Other
- ☐ None

39. Did any injury received while you were deployed result in any of the following? *(Mark all that apply)*

- ☐ Being dazed, confused or "seeing stars"
- ☐ Not remembering the injury
- ☐ Losing consciousness (knocked out) for less than a minute
- ☐ Losing consciousness for 1-20 minutes
- ☐ Losing consciousness for longer than 20 minutes
- ☐ Having any symptoms of concussion afterward (such as headache, dizziness, irritability, etc.)
- ☐ Head injury
- ☐ None of the above

40. Are you currently experiencing any of the following problems that you think might be related to a possible head injury or concussion? (*Mark all that apply*)

- ☐ Headache
- ☐ Dizziness
- ☐ Memory problems
- ☐ Balance problems
- ☐ Ringing in the ears
- ☐ Irritability
- ☐ Sleep problems
- ☐ Other

MVP Lifestyle Survey Questions from:

3 Question DVBIC TBI Screening Tool

Survey Data: Pros & Cons

- **Baseline Survey**
  - Pros
    - Most MVP participants complete the survey
  - Cons
    - History based on self-report
    - Wording of “Concussion or LOC”
    - Interpretation of “TBI”
    - If not checked, can’t be certain whether that means “no” or if the participant did not answer question

- **Lifestyle Survey**
  - Pros
    - Offers evidence of an injury/event consistent with the definition of TBI
    - Based on a validated instrument
  - Cons
    - History based on self-report.
    - Lower percentage of MVP participants have completed the Lifestyle survey than Baseline.
    - Within question relating to deployments, may not be filled out by others.

ICD 9/10 Codes

ICD-9-CM Diagnosis Codes	310.2, 800.xx, 801.xx, 803.xx, 804.xx, 850.xx, 851.xx, 852.xx, 853.xx, 854.xx, 905.0, 907.0, 950.1, 950.2, 950.3, 959.01, 959.9, V15.52
ICD-10-CM Diagnosis Codes	F07.81, S02.0xxx, S02.1xxx, S02.8xxx, S02.9xxx, S04.02xx, S04.03xx, S04.04xx, S06.0xxx, S06.1xxx, S06.2xxx, S06.3xxx, S06.4xxx, S06.5xxx, S06.6xxx, S06.8xxx, S06.9xxx, S07.1xxx, Z87.820

- Derived from Department of Defense (DoD)/ Armed Forces Health Surveillance Branch (AFHSB)[1].
  - TBI severity classifications determined by DoD/AFHSB criteria.
  - For patients with more than 1 TBI diagnosis recorded during the Fiscal Year, TBI classification is based on the *highest level* of TBI severity that year.

[1]Traumatic Brain Injury: DoD Standard Surveillance Case Definition for TBI Adapted for AFHSB Use. 2016, Armed Forces Health Surveillance Branch: Washington, D.C.

ICD 9/10 Codes: Pros & Cons

- Pros
  - Offers EHR-based record of TBI (though may still ultimately based on self-report data)
  - ICD codes based on consensus review (DoD/AFHSB)
- Cons
  - No clear guidelines regarding “best” approach (no gold standard)
    - Levels of certainty → 1 ICD code vs. 2 ICD codes vs. 1 inpt *or* 2 outpt
    - Time frame → *any* historical diagnosis vs. within a specific period
    - TBI severity
- EHR Data only available starting in 1997, so combat-related TBIs for older veterans may not be represented.

Comprehensive TBI Evaluation (CTBIE)

- Initiated within the VHA in October 2007 to improve the tracking and monitoring of deployment-related TBI (Belanger et al., 2012)
- In order for the CTBIE to be administered, the Veteran must have:
  - (1) Initiated care within the VA
  - (2) Served in the Iraq/Afghanistan conflicts
  - (3) Been *eligible for* and *screened positive* on the 4-item TBI Clinical Reminder Screen
    - Positive screens result in a referral to a TBI specialist who then completes the CTBIE
- Cons
  - CTBIE data only available from FY2008 onward
    - Iraq/Afghanistan-era Veterans only
    - Older Veterans would not be represented.

Our choice for this study: Baseline Survey responses.

Section F: Medical History and Health Care Usage

43. Please tell us if you have been diagnosed with the following conditions. Check the appropriate box and indicate the year of diagnosis and whether you currently take any medication(s) ("TAKE MEDS") for that condition. *(Mark all that apply)*

Concussion or loss of consciousness	☐	☐☐☐☐	☐
Traumatic brain injury	☐	☐☐☐☐	☐

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Baseline Survey

Million Veteran Program: A Partnership with Veterans

Migraine headaches	☐	☐☐☐☐	☐
Other headaches	☐	☐☐☐☐	☐
Memory loss or impairment	☐	☐☐☐☐	☐
Dementia (includes Alzheimer's, vascular, etc.)	☐	☐☐☐☐	☐
Concussion or loss of consciousness	☐	☐☐☐☐	☐
Traumatic brain injury	☐	☐☐☐☐	☐
Spinal cord injury or impairment	☐	☐☐☐☐	☐
Epilepsy / Seizure	☐	☐☐☐☐	☐
Parkinson's disease	☐	☐☐☐☐	☐
Amytrophic lateral sclerosis (Lou Gehring's disease)	☐	☐☐☐☐	☐
Multiple sclerosis	☐	☐☐☐☐	☐
Other nervous system problem	☐	☐☐☐☐	☐

Methods: Analysis

- We examined both white non-Hispanic (WNH) and African American (AA) MVP participants age 65+.
  - WNH cohort: n=11K cases 170K controls; AA cohort: n= 1.4K cases and 16K controls
- First, we fit a "Simple" logistic model examining ADRD prevalence as a function of TBI and PTSD separately along with *APOE* ε4 and age effects, then a "Full" model was examined which jointly included PTSD, TBI, and potential confounders.
- All models included PCs for ancestry.

Methods: Analysis

- As interpreting interactions from logistic regression models can be ambiguous from a public-health perspective, we calculated the Relative Excess Risk due to Interaction (RERI) which evaluates additive-scale interaction.
- RERI can be computed from logistic regression output (Knol et al. 2007).
  - RERI = 0, indicates exact additivity. RERI > 0 indicates excessive interaction when compared to an additive effect, and RERI < 0 indicates less of an interaction than expected given an additive effect.
  - 95% CIs which do not include 0 are considered significant.

“Simple Model of PTSD (A) and TBI (B) on ADRD risk in White non-Hispanic Participants.

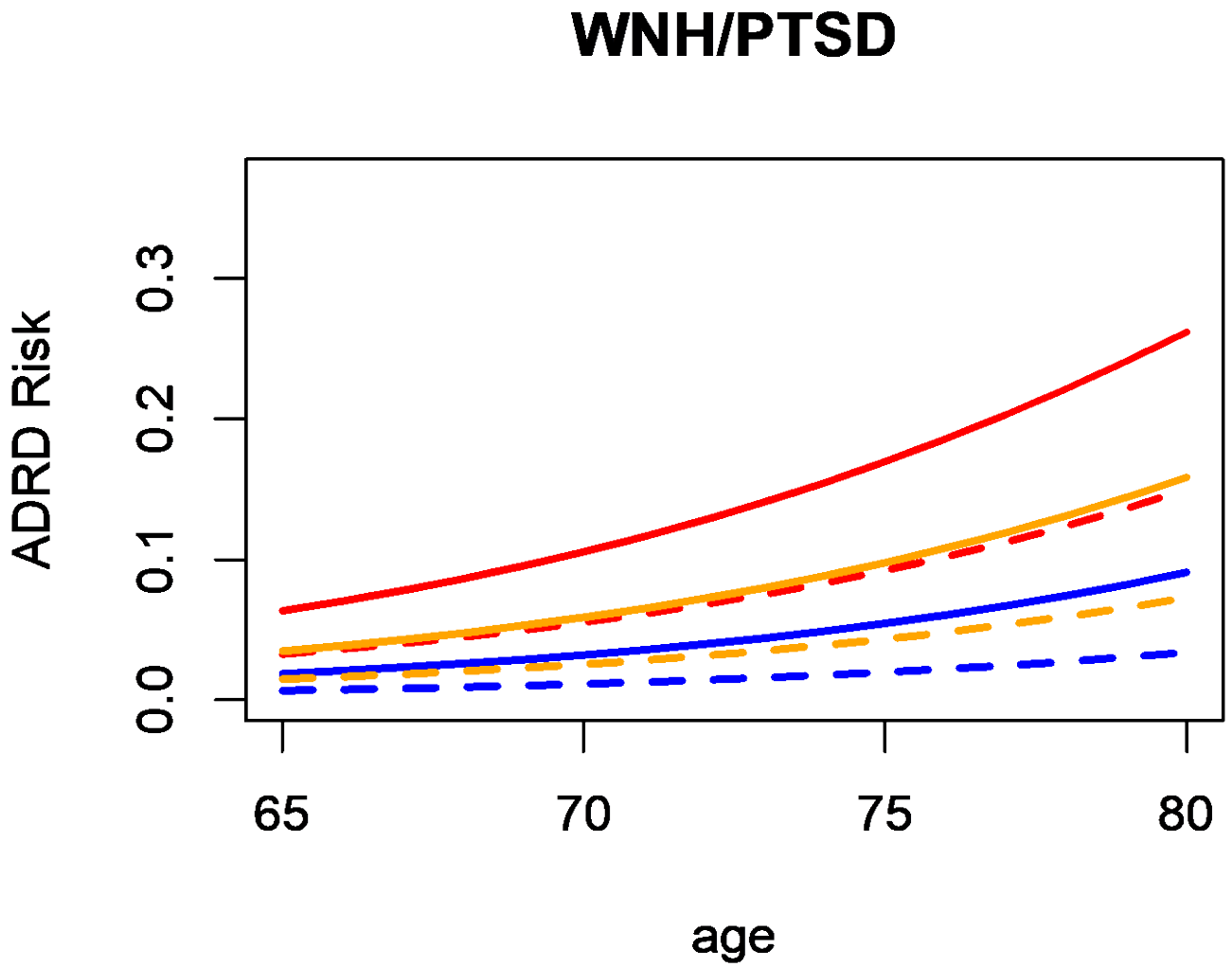
A	Main Effects Model		GxE Model	
	OR	P value	OR	P value
(Intercept)	5.27E-06	0	5.18E-06	0
AGE	1.12	0	1.12	0
PTSD	2.65	1.90E-161	2.85	2.51E-128
APOE:E4	2.18	1.69E-272	2.24	1.05E-248
E4 x PTSD	----	----	0.84	0.0046
B	**Main Effects Model**		**GxE Model**	
	OR	P value	OR	P value
(Intercept)	2.09E-05	0	2.09E-05	0
AGE	1.10	0	1.10	0
TBI	1.96	1.67E-95	2.00	1.85E-68
APOE:E4	2.05	0	2.06	4.61E-294
E4 x TBI	----	----	0.95	0.40

“Simple Model of PTSD (A) and TBI (B) on ADRD risk in African American Participants.

A	Main Effects Model		GxE Model	
	OR	P value	OR	P value
(Intercept)	3.44E-06	9.99E-178	3.39E-06	3.35E-177
AGE	1.13	5.53E-119	1.13	5.21E-119
PTSD	1.73	3.03E-10	1.80	2.44E-07
APOE:E4	1.69	2.20E-18	1.72	1.25E-14
E4 x PTSD	----	----	0.94	0.62
B	Main Effects Model		GxE Model	
	OR	P value	OR	P value
(Intercept)	1.54E-05	6.00E-233	1.54E-05	7.88E-233
AGE	1.11	7.13E-144	1.11	6.44E-144
TBI	2.69	1.70E-20	2.58	1.46E-11
APOE:E4	1.70	4.70E-27	1.69	2.97E-24
E4 x TBI	----	----	1.08	0.65

MVP 15, GxE analysis of ADRD

Estimated ADRD risk in WNH MVP participants. Solid lines = PTSD cases, dashed= controls. Color represents those with **0 (blue)**, **1 (orange)**, or **2 (red)** copies of *APOE*:E4.



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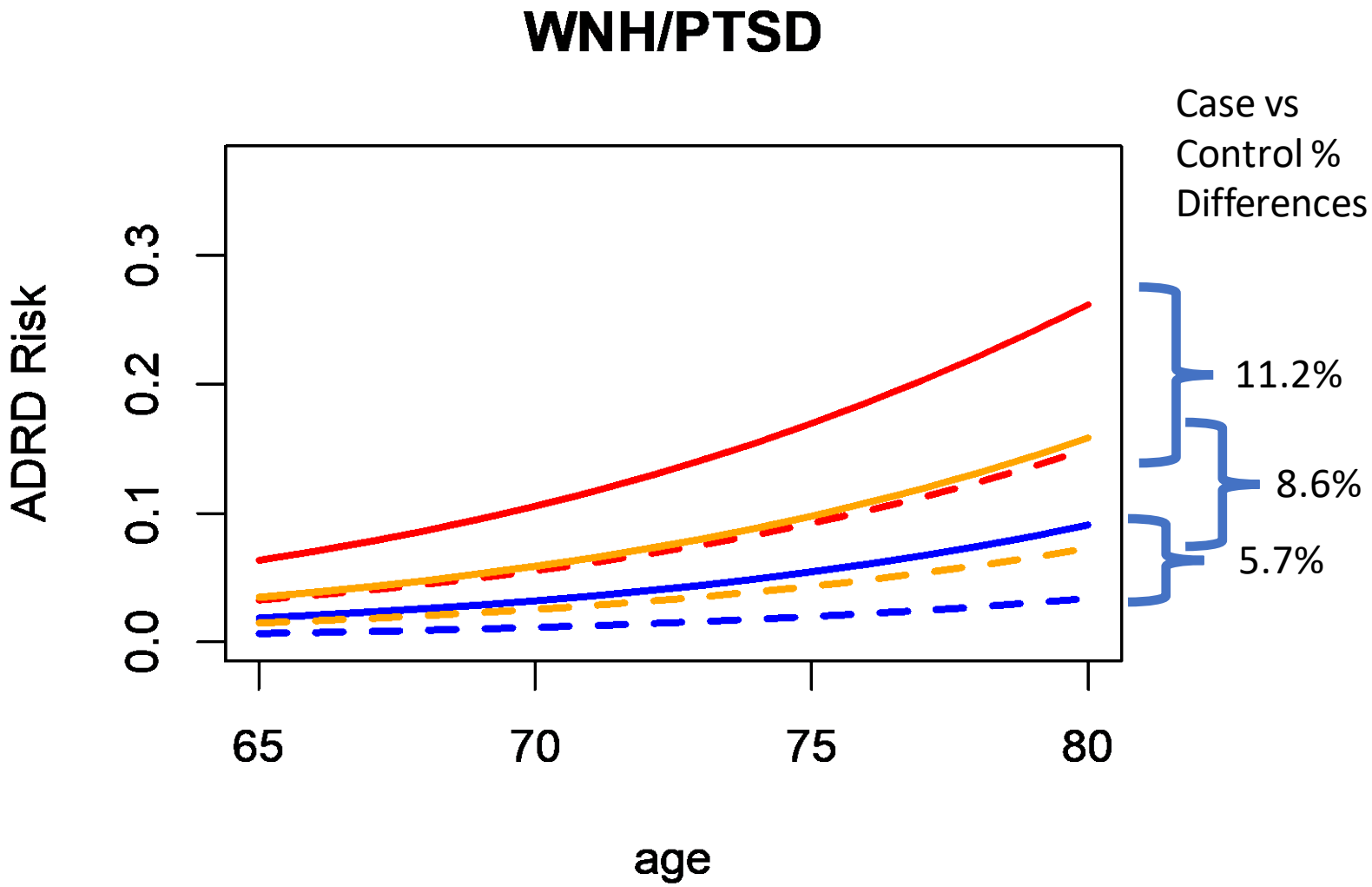


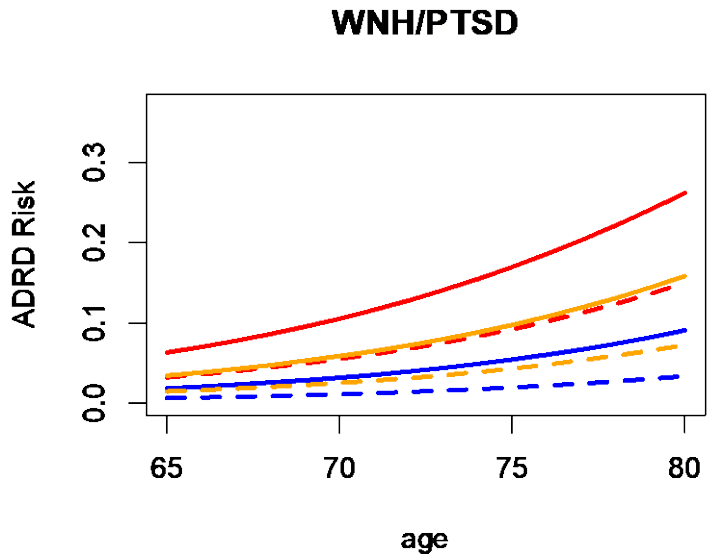
RERI estimates and 95% CIs for the PTSD and TBI x *APOE* interactions

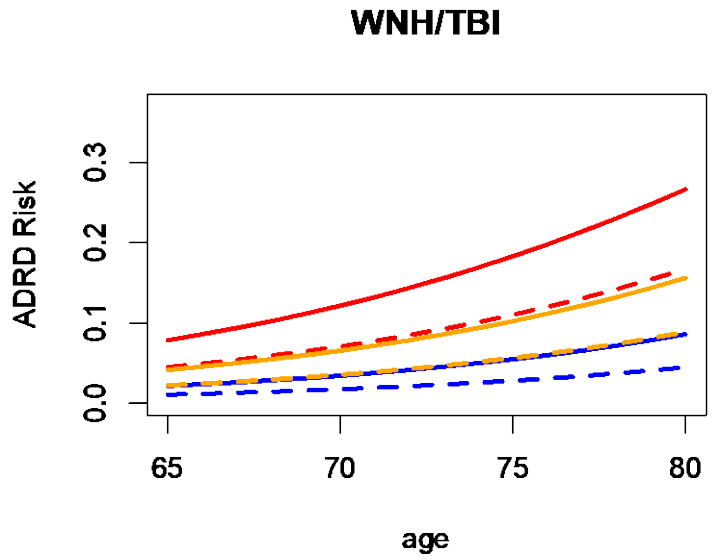
		EUR			AA	
	estimate	lower	upper	Estimate	Lower	Upper
PTSD	1.28	0.75	1.81	0.37	-0.21	0.95
TBI	0.86	0.48	1.24	1.45	0.15	2.75

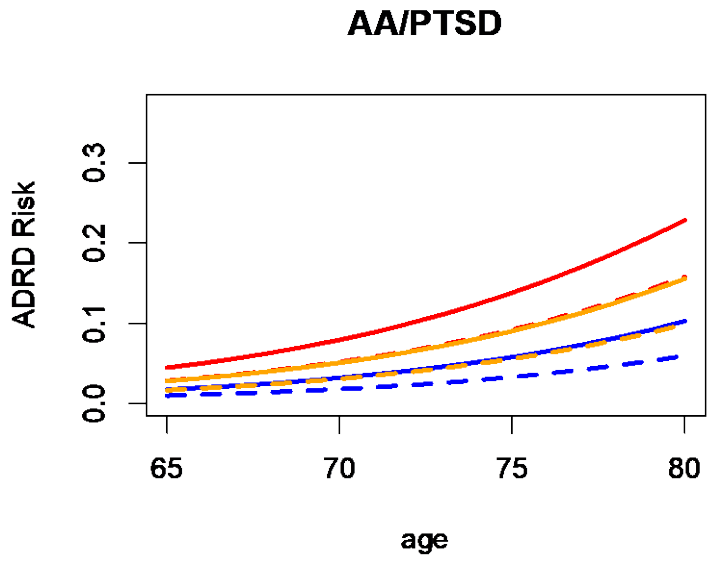
- RERI estimates are significantly different from 0 for PTSD and TBI in WNH particpants, and TBI in AA participants.
- The highest estimate is for TBI in AA participants.

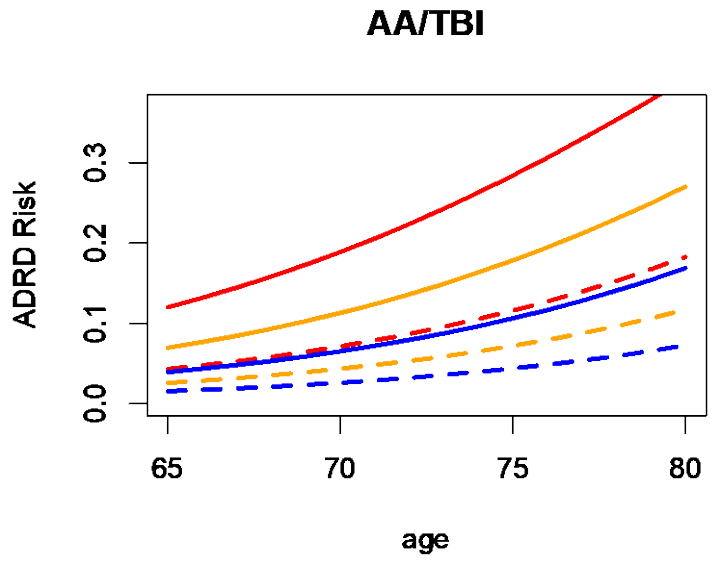
MVP 15, GxE analysis of ADRD

Estimated ADRD risk in WNH and AA MVP participants. Solid lines = PTSD or TBI cases, dashed= controls. Color represents those with **0 (blue)**, **1 (orange)**, or **2 (red)** copies of *APOE*:E4.





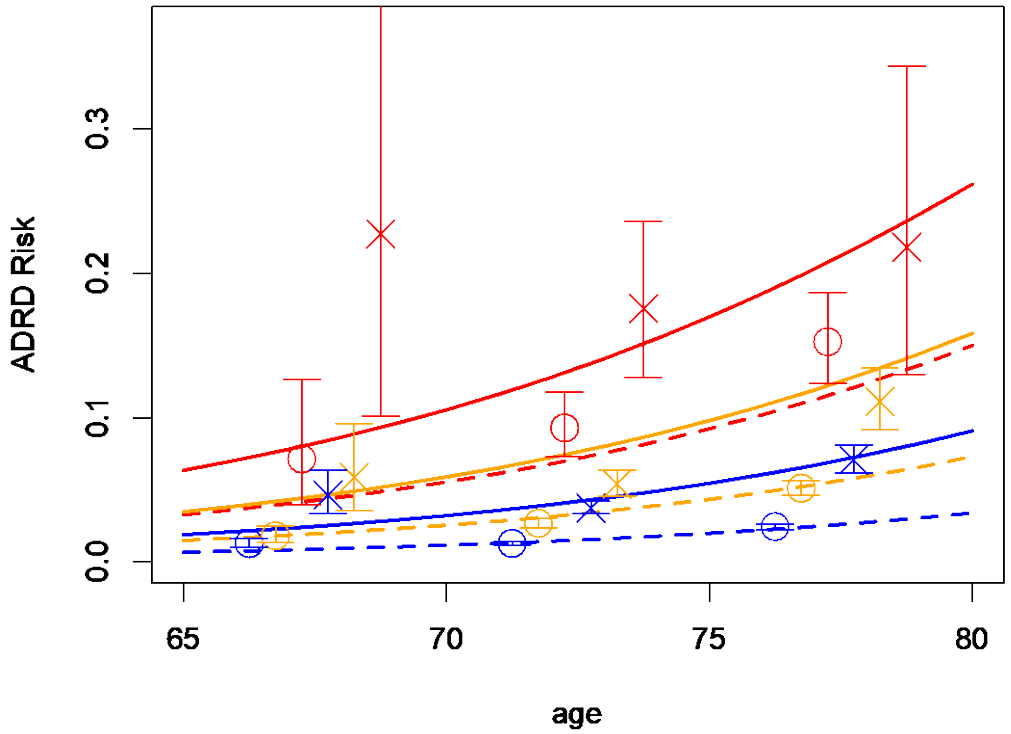




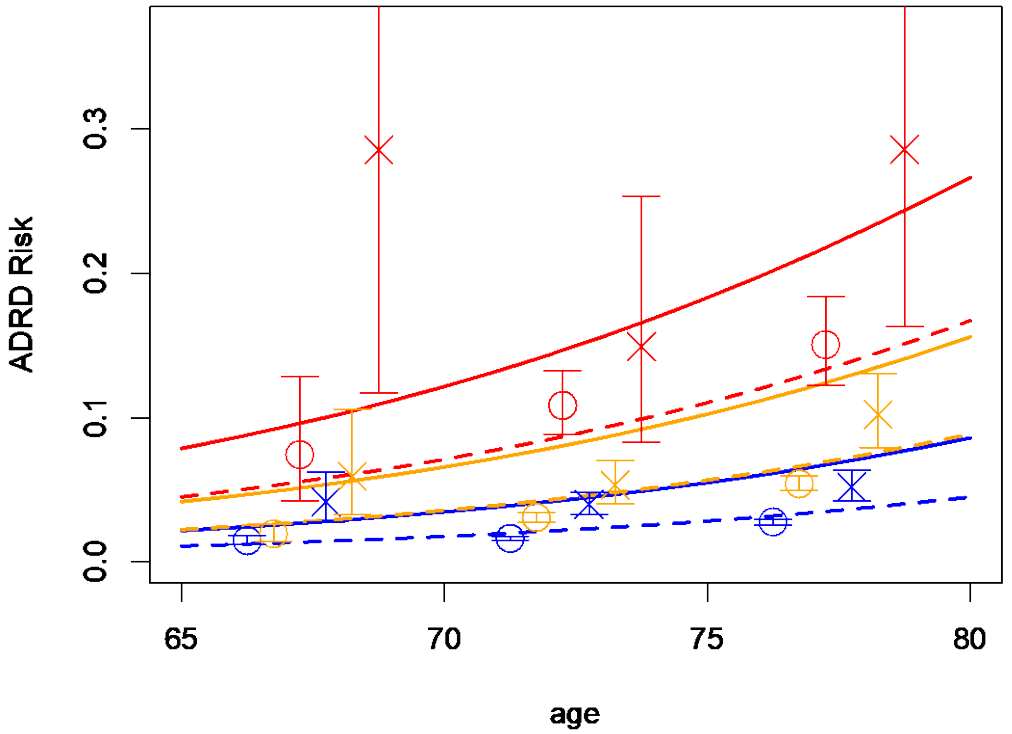
WNH Simple Models vs. Observed percentages in 5 year age bins.

Xs and solid lines indicate cases, Os and dashed lines represent controls.
Bars represent 95% CIs.

PTSD



TBI



“Full” ADRD Model and Follow-up Model Results

- PTSD and TBI have independent effects, as the estimates and significance was very similar when both were included in the model together.
- These models also indicated that associations were not due to confounding with alcohol use, smoking, or education.
- No higher order interactions were significant.
- Follow up models examining an AD PRS based on Kunkle et al. 2019 AD GWAS excluding the *APOE* region in the WNH MVP cohort indicated association with ADRD, but did not display interactions with PTSD and TBI.

Conclusions

- *APOE* ε4, PTSD, and TBI are all major ADRD risk factors in US Veterans.
- The ADRD prevalence difference between PTSD cases and controls (WNH) and TBI cases and controls (WNH & AA) increases as a function of *APOE* ε4.
- This study's findings suggest that PTSD and TBI history can be an important component of genetic dementia risk assessment in Veterans.

Limitations

- TBI classification based only on self-report without a measure of TBI severity.
- We focused on MVP participants with onset >65.
  - There is evidence that PTSD and TBI may be associated with earlier AD onset.
  - However, there are also studies that indicate that ICD-code based dementia classifications are less reliable in subjects with onset < 65.
  - Therefore, our study may underrepresent the total contribution of PTSD and TBI to dementia prevalence in the VA.

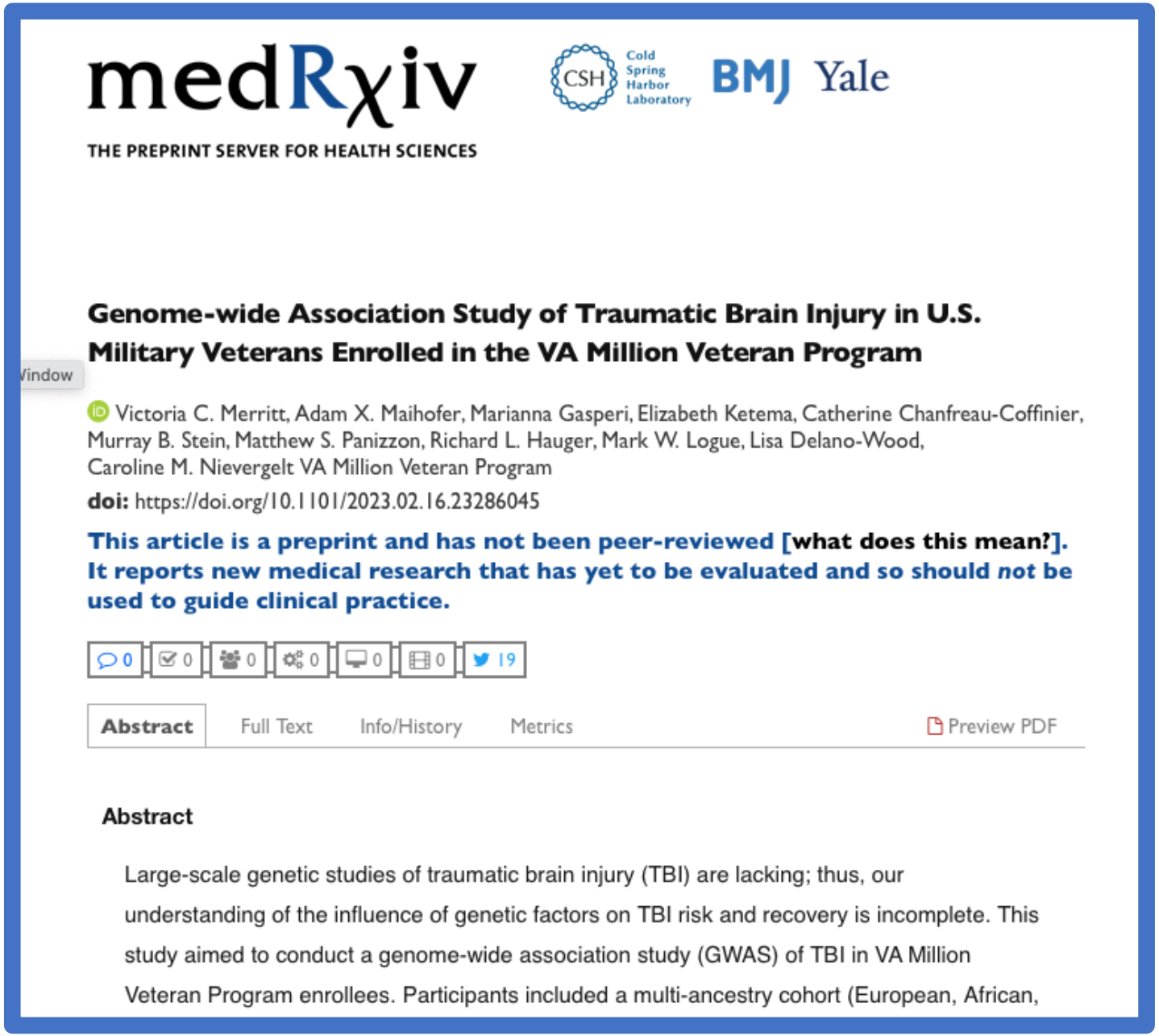
Future Work

- We are looking at validating our ICD-code diagnoses in “earlier” onset dementia cases.
- Our analysis is cross-sectional. We are currently preparing a retrospective cohort analysis (Cox regression) which may remove some potential for bias.

MVP040

- **Aim 1**: Continue to generate ADRD GWASs and use them to investigate multi-ethnic dementia risk scores.
- **Aim 2:** Explore multivariate GxE analyses of dementia phenotypes using methods that simultaneously estimate the effect of multiple risk factors.
- **Aim 3:** Refine our current dementia phenotypes and use machine learning to identify additional dementia cases in the VA EMR.

PREPRINT GWAS of TBI in MVP is currently available!



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Genome-wide Association Study of Traumatic Brain Injury in U.S. Military Veterans Enrolled in the VA Million Veteran Program

Victoria C. Merritt, Adam X. Maihofer, Marianna Gasperi, Elizabeth Ketema, Catherine Chanfreau-Coffinier, Murray B. Stein, Matthew S. Panizzon, Richard L. Hauger, Mark W. Logue, Lisa Delano-Wood, Caroline M. Nievergelt VA Million Veteran Program

doi: https://doi.org/10.1101/2023.02.16.23286045

This article is a preprint and has not been peer-reviewed [what does this mean?]. It reports new medical research that has yet to be evaluated and so should *not* be used to guide clinical practice.

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Abstract

Large-scale genetic studies of traumatic brain injury (TBI) are lacking; thus, our understanding of the influence of genetic factors on TBI risk and recovery is incomplete. This study aimed to conduct a genome-wide association study (GWAS) of TBI in VA Million Veteran Program enrollees. Participants included a multi-ancestry cohort (European, African,

Thanks to:

- Co-authors: Mark W. Logue, Mark W. Miller, Richard Sherva, Rui Zhang, Kelly M. Harrington, Jennifer R. Fonda, Victoria Merritt, Matthew S. Panizzon, Richard L. Hauger, Erika J. Wolf, Zoe Neale, J. Michael Gaziano.

- MVP "Cognitive Decline and Dementia During Aging" Working Group
- MVP Leadership and MVP Data Cores

MVP Participants

- **Funding:** This research is based on data from the Million Veteran Program, Office of Research and Development, Veterans Health Administration, and was supported by VA BLR&D grant 1 I01 BX004192 (MVP015, ML PI).