

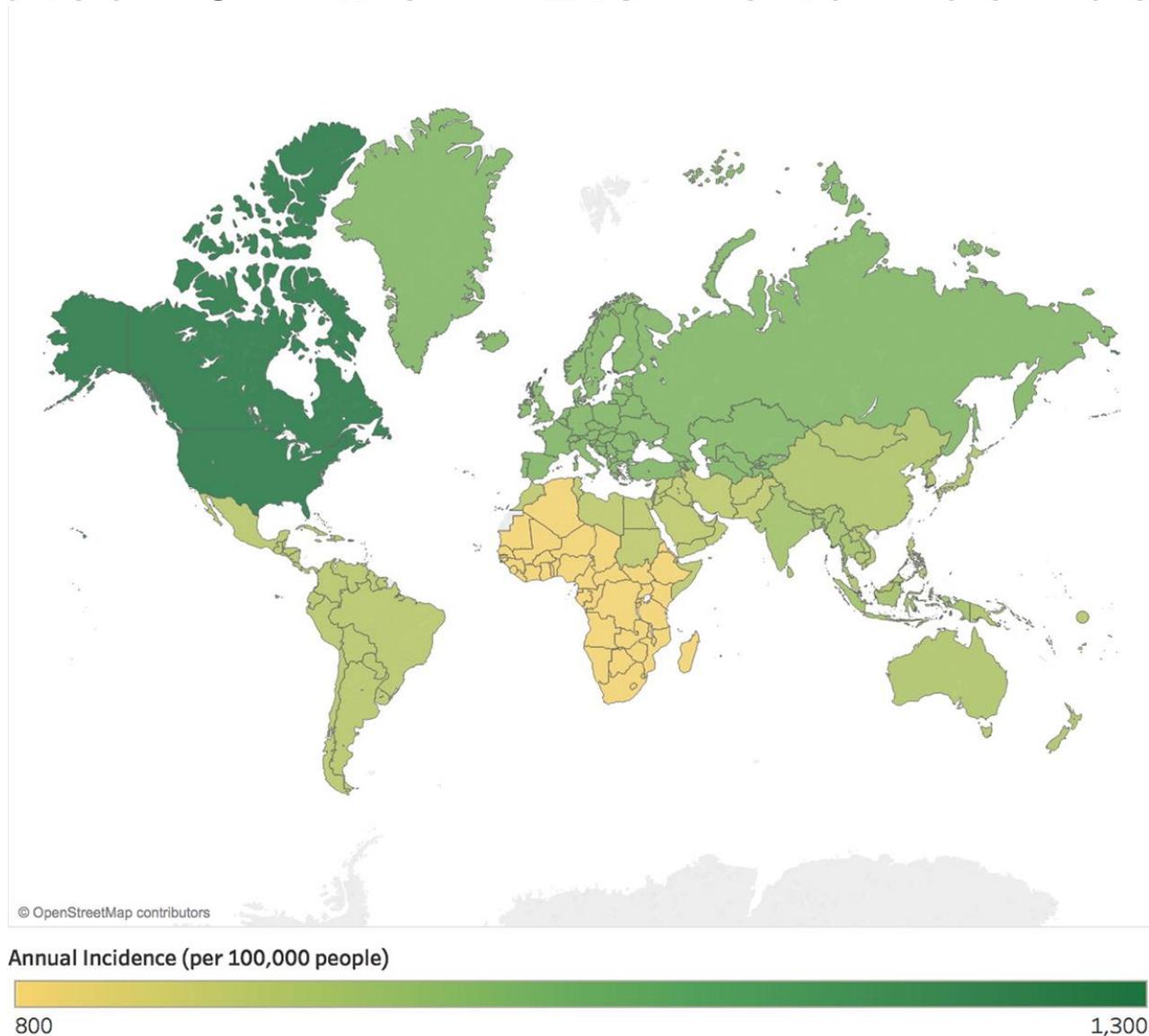
# **TBI and Dementia:**

## **What We Know & What We Don't Know**

### **Kristine Yaffe, MD**

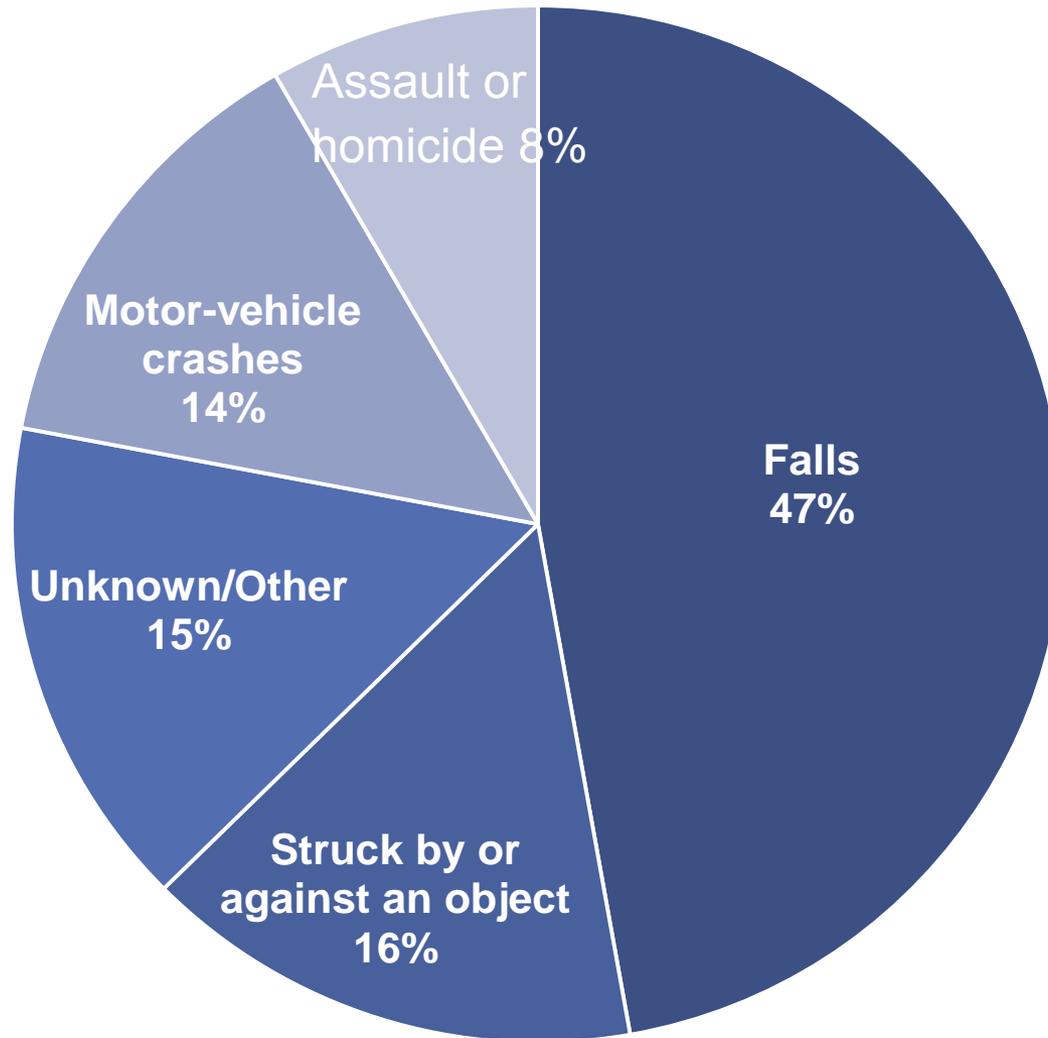
Scola Endowed Chair & Vice Chair  
Professor of Psychiatry, Neurology & Epidemiology  
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# Estimated 70 Million TBIs Worldwide Each Year

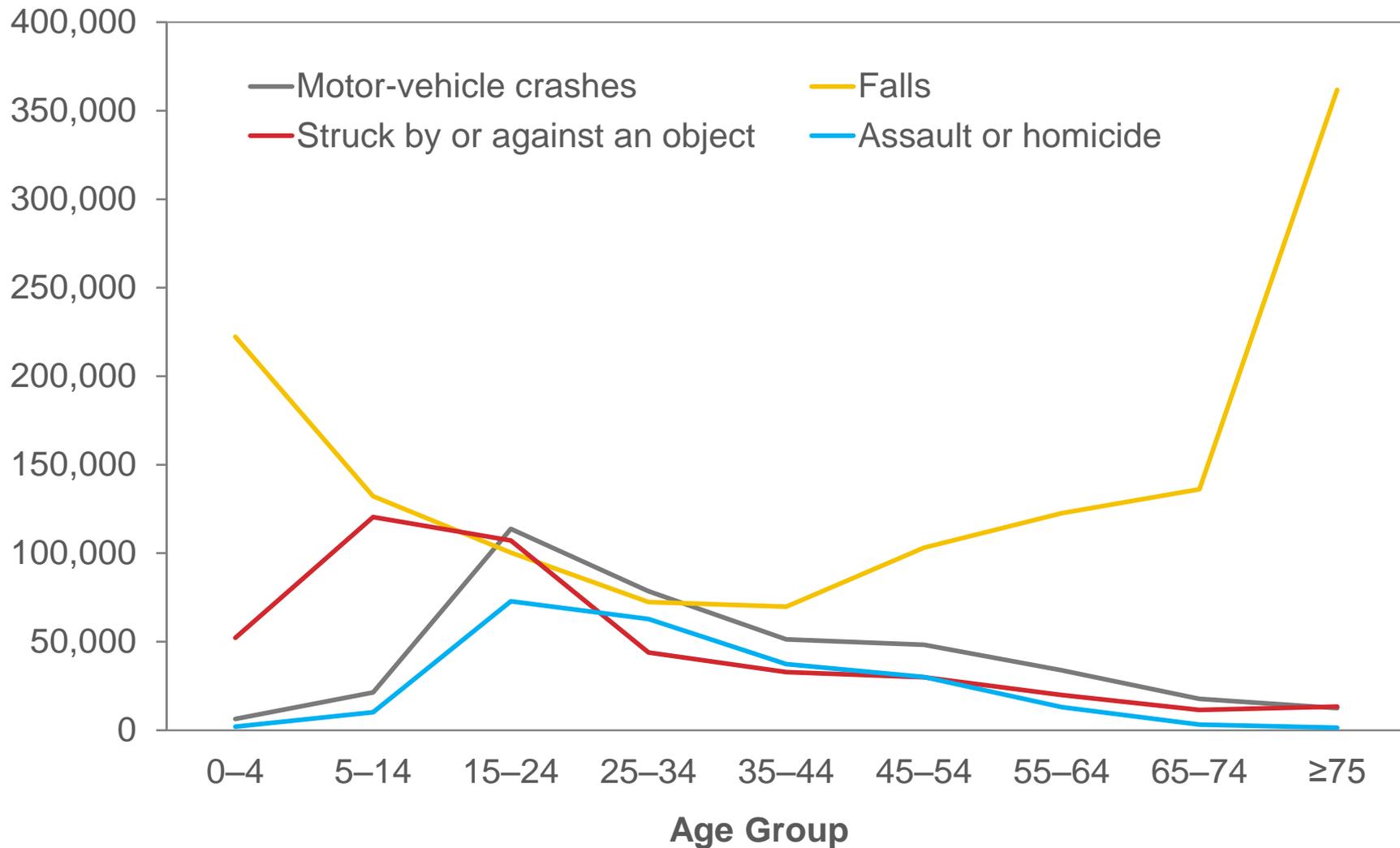


Estimate based on road traffic injuries, systematic review, and meta-analysis of TBI literature. Dewan et al, *J Neurosurg*, 2018.

# Leading Causes of TBI, United States 2007-2013



# Leading Causes of TBI by Age

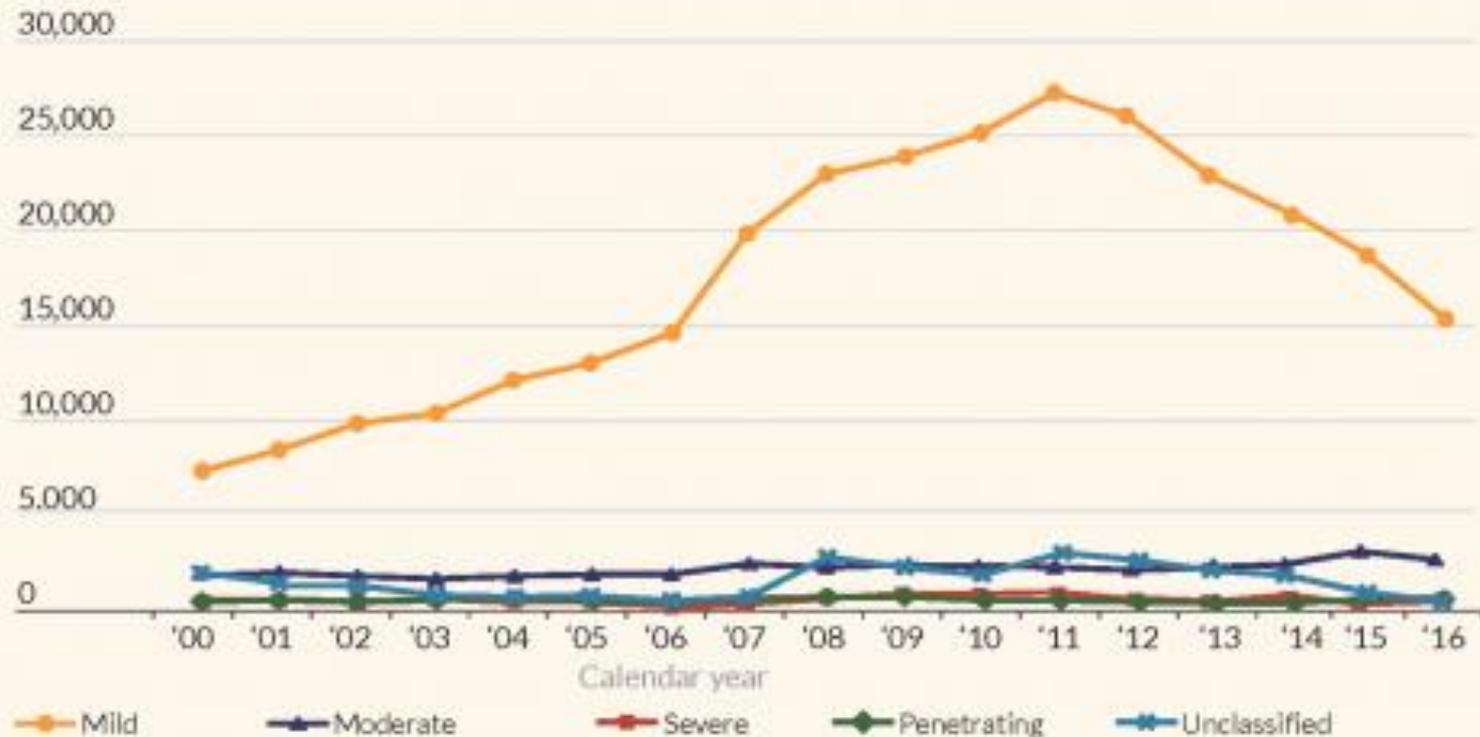


# TBI: Incidence in U.S. Veterans



## DoD Numbers for Traumatic Brain Injury Worldwide - Incidence by Severity

No. of cases



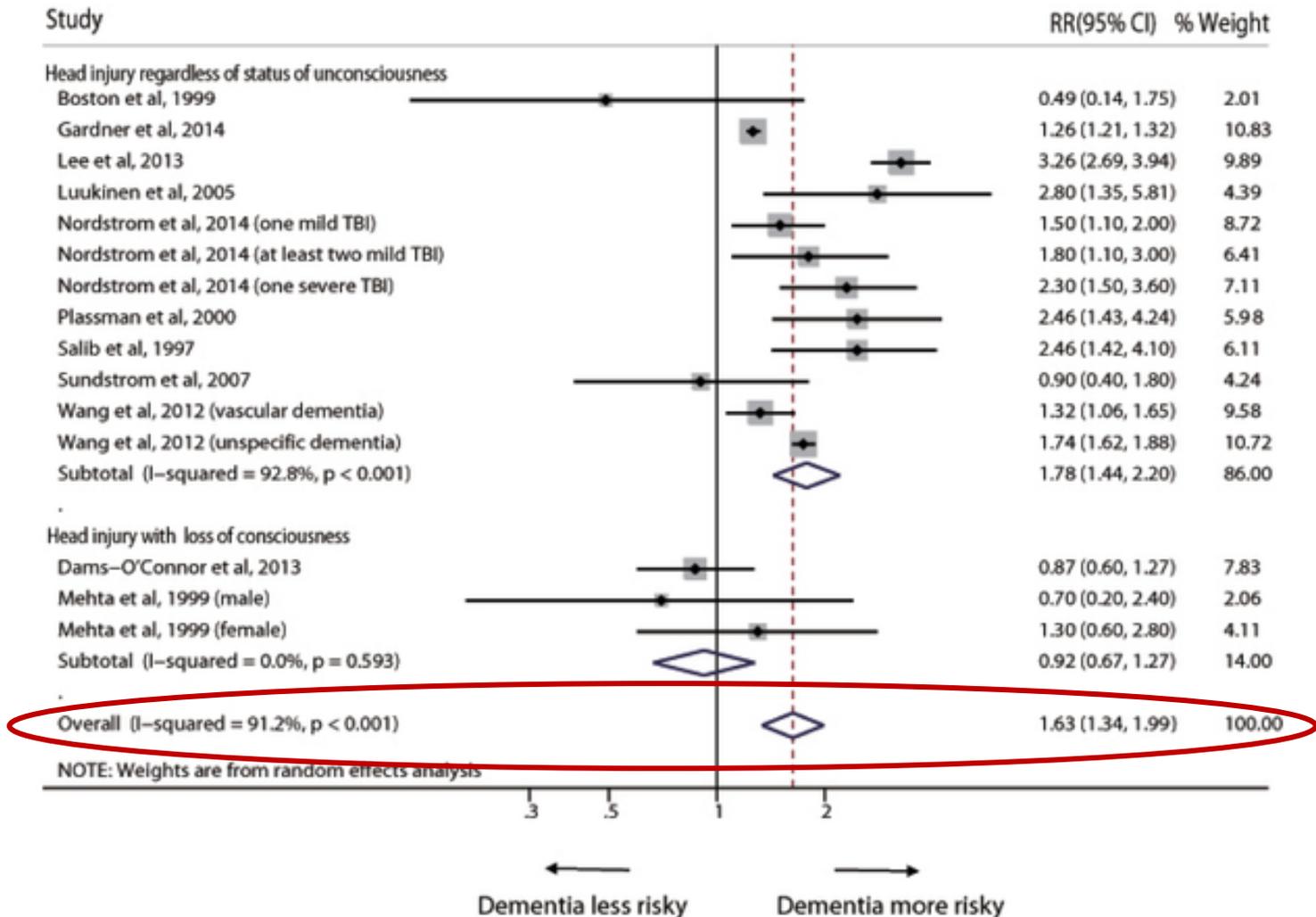
Source: Defense Medical Surveillance System (DMSS), Theater Medical Data Store (TMDS) provided by the Armed Forces Health Surveillance Branch (AFHSB). Prepared by the Defense and Veterans Brain Injury Center (DVBIC)

2000-2016 as of May 10, 2017

# Long-term Effects of TBI & Dementia Risk in U.S. Veterans

- Significant focus on the acute effects of TBI
- While the long-term effects of TBI are unclear
- Large population of older U.S. Veterans at risk for dementia
  - 40% of Veterans are >65 years old
- Dementia associated with increased healthcare utilization and healthcare costs (3x greater)
- Veterans have a unique constellation of military risk factors

# Meta-analysis of Head Injury as a Risk Factor for Dementia in Observational Studies



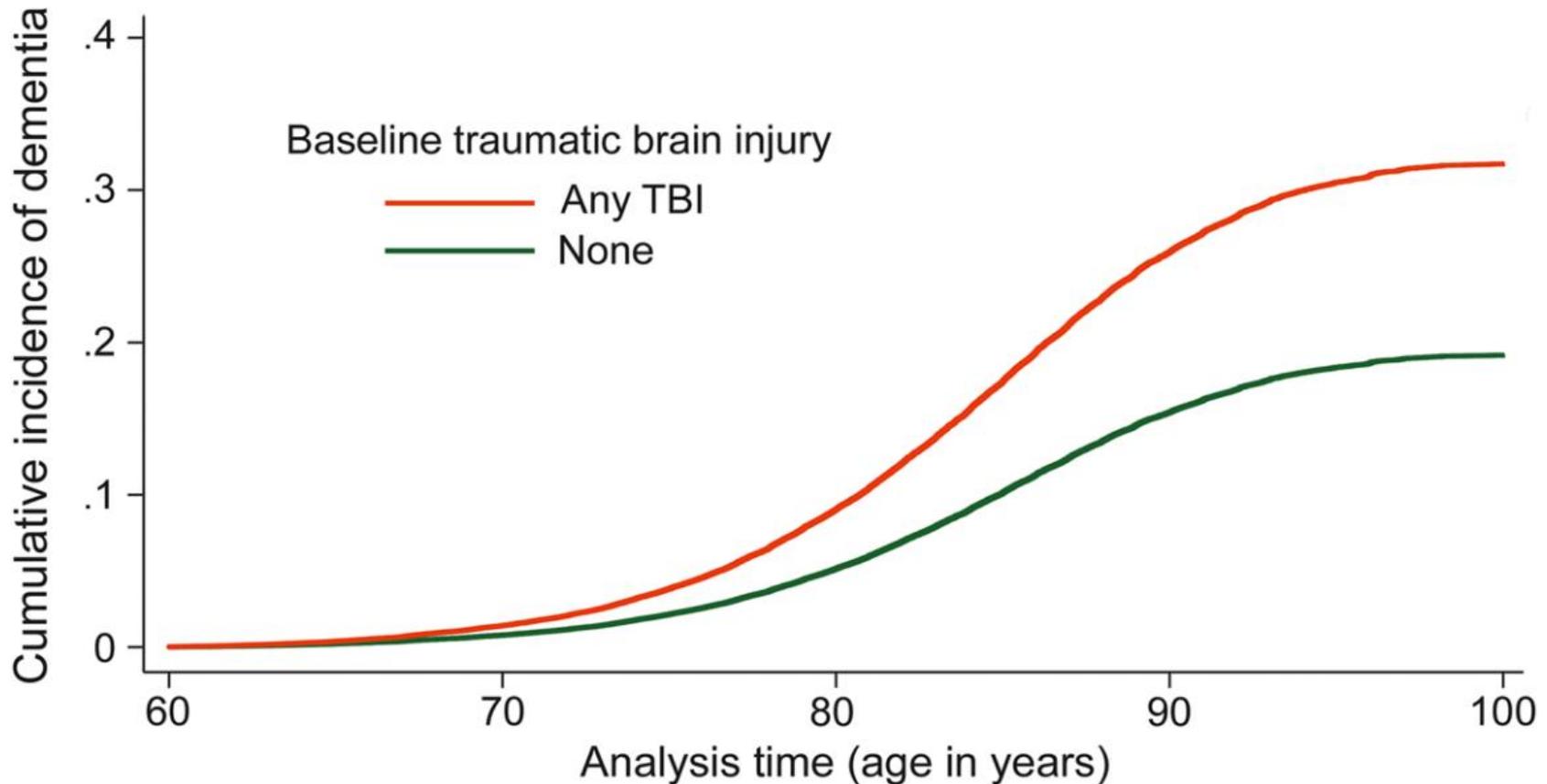
# Plausible Mechanisms Linking TBI to Cognitive Impairment

- Mechanical injury resulting in diffuse axonal injury
- Axonal swelling and degeneration
- Accumulation of proteins including APP, A $\beta$ , and tau
- Breakdown of blood-brain barrier
- Synaptic dysfunction
- Cell death
- Microglial activation and inflammatory responses

# TBI & Dementia Risk in U.S. Veterans

- 188,764 Veterans  $\geq 55$  years old and dementia free
- Measures
  - TBI diagnoses during baseline (ICD-9)
  - Medical/psychiatric comorbidities (ICD-9)
- Dementia diagnoses (ICD-9) over 9 years
- Accounted for competing risk of death

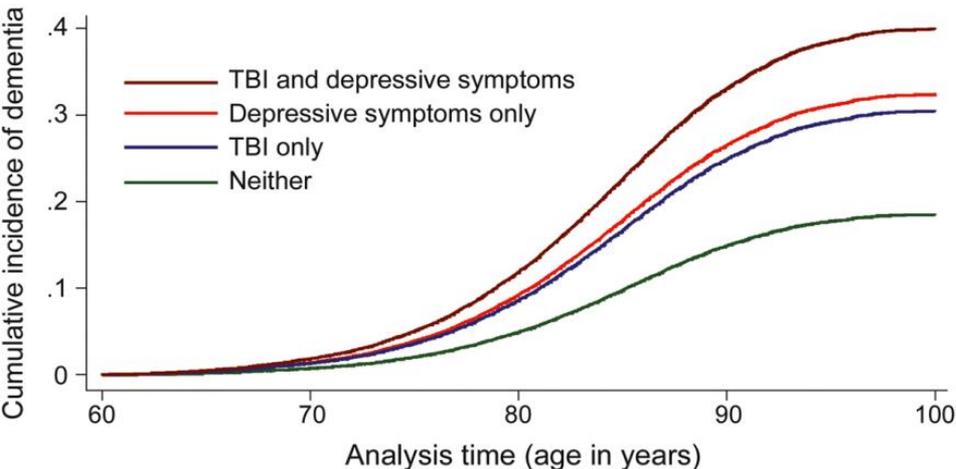
# 60% Increased Risk of Dementia with TBI



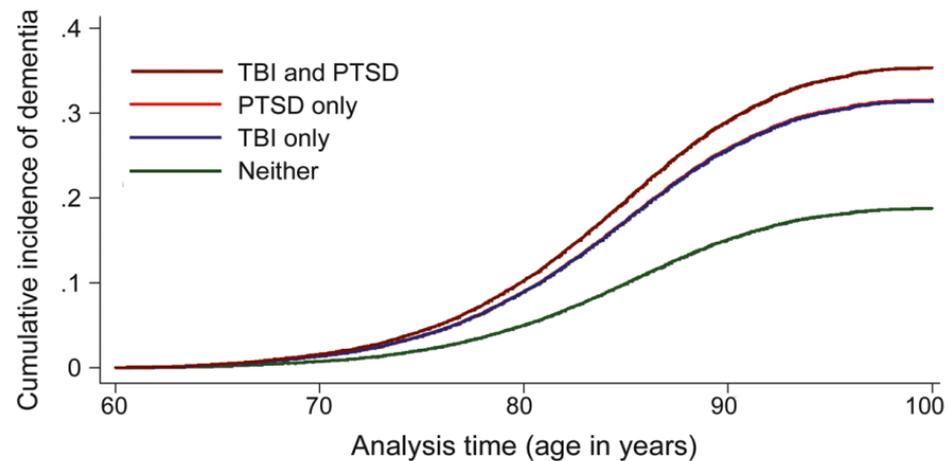
**Adjusted HR:1.57; 95% CI (1.35–1.83)**

# Comorbidities Have an Additive Effect on Dementia Risk

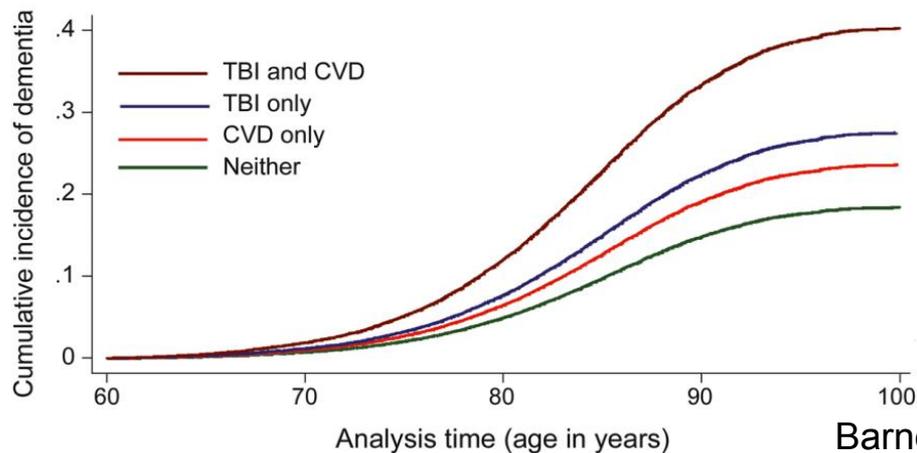
## Depression



## PTSD



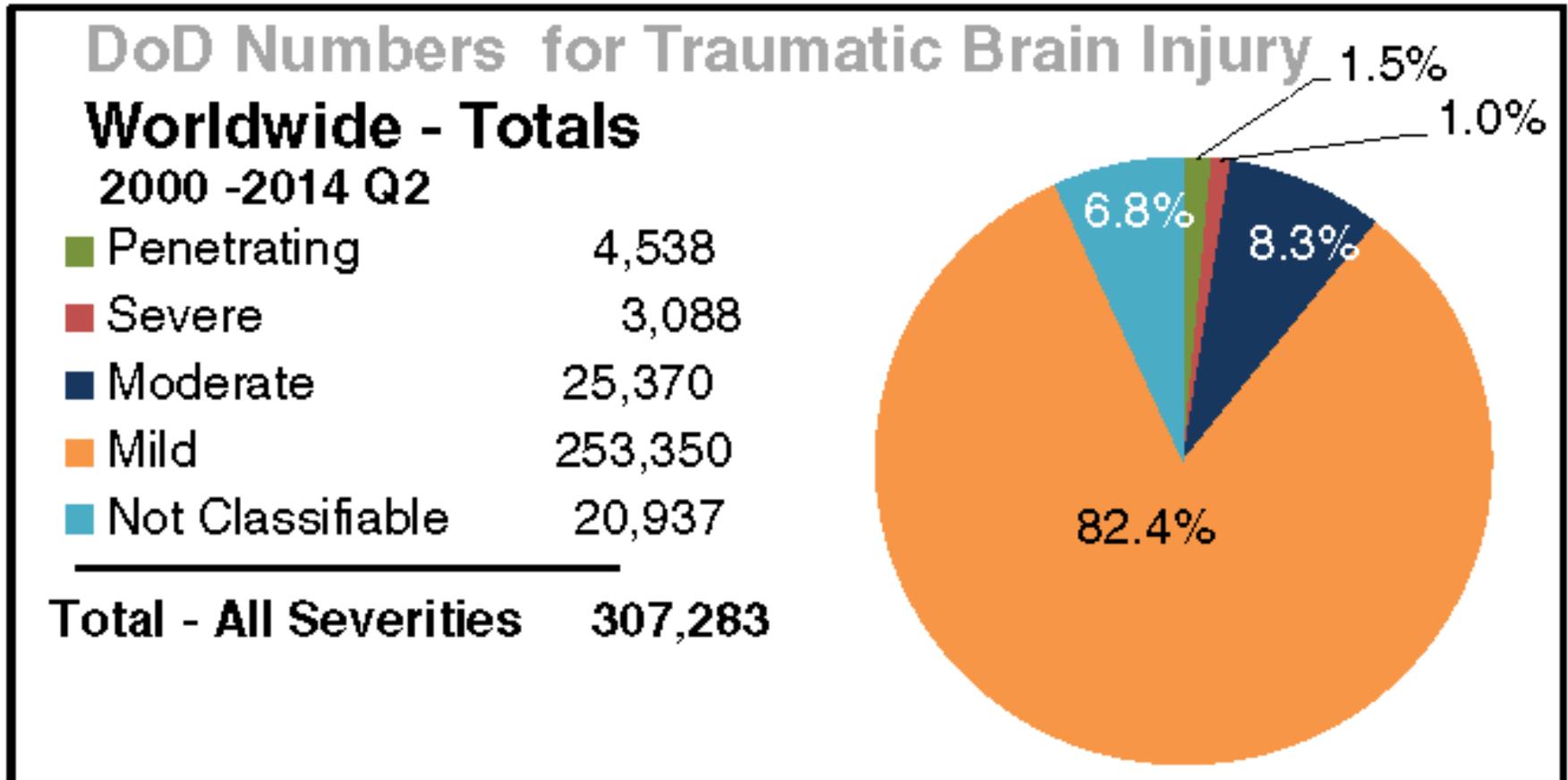
## Cerebrovascular Disease



# Veterans TBI Study: Summary

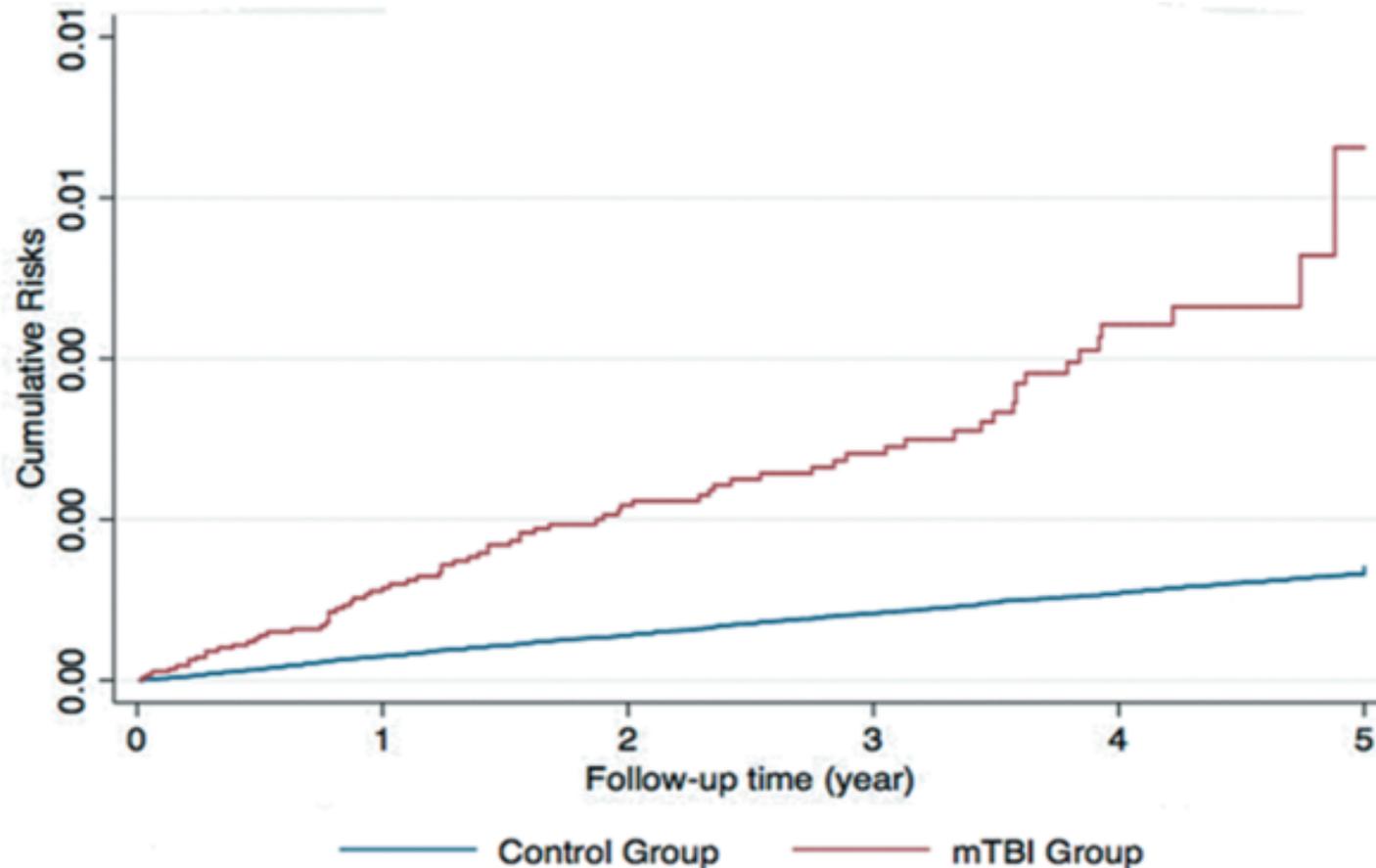
- TBI was associated with almost 60% increase in risk of developing dementia
- Estimate accounted for mortality and adjusted for medical and psychiatric conditions
- Age of dementia onset 2 years earlier in those with TBI compared to those without TBI
- Additive association observed between TBI and other dementia risk factors

# The Majority of TBIs are Mild



But fewer studies have considered the range of TBI severity and dementia risk

# Mild TBI and Risk of Dementia: A Nationwide Cohort in Taiwan



aHR = 3.26 (95% CI, 2.69–3.94)

Adjusting for gender, urbanization level, socioeconomic status, and comorbidities

# Mild TBI Increases Risk of Early Onset Dementia

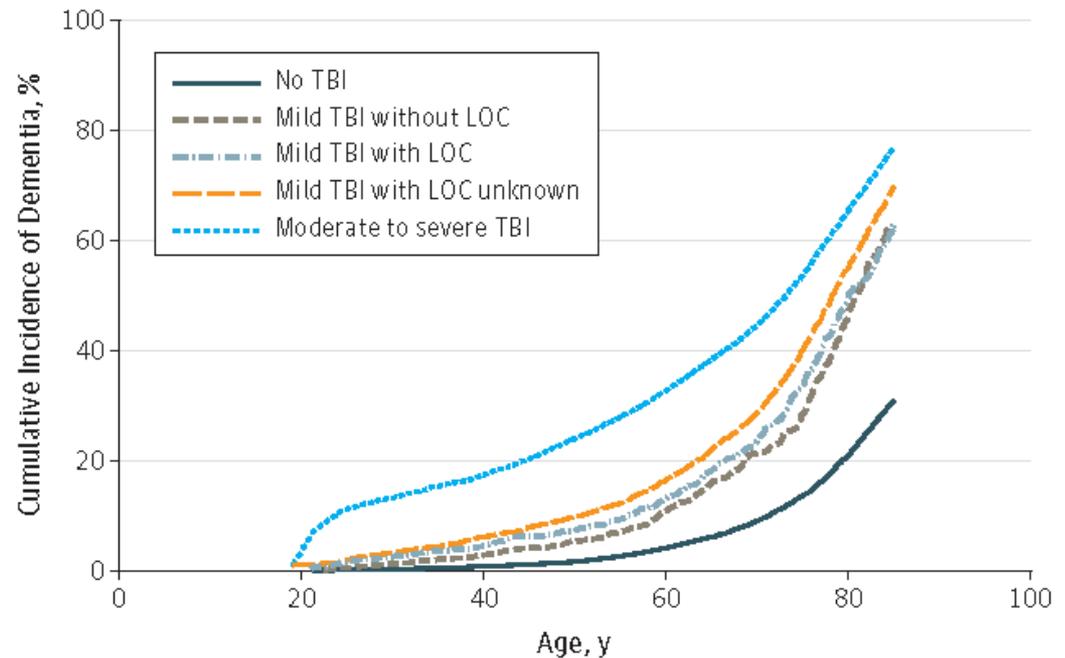
- Cohort of 811,622 Swedish young men
- Data from national registry
- Median follow-up: 33 years
- TBI diagnosis by ICD codes
- Outcome: Dementia before 65 years of age
- Adjusted for sociodemographic factors, family history, comorbidities, and lifestyle factors

TBI Type	Dementia Cases (n)	HR (95%CI)
1 mild TBI	59	1.5 (1.1-2.0)
>1 mild TBI	18	1.8 (1.1-3.0)
1 severe TBI	25	2.3 (1.5-3.6)

# Mild TBI & Dementia Risk in U.S. Veterans

- 357,558 Veterans  $\geq 55$  years old and dementia free
- 178,779 Veterans with TBI and propensity-matched comparison sample of 178,779 Veterans without TBI
- Measures
  - TBI diagnosis from Comprehensive Traumatic Brain Injury database or ICD-9 codes using Defense and Veterans Brain Injury Center 2012 Criteria
  - Severity classified as none, mild, moderate, or severe
  - mTBI categorized as without LOC, with LOC, or LOC status unknown
- Dementia diagnosis by ICD-9 codes

# Risk of Dementia Diagnosis Increases with TBI Severity



TBI Severity	Adjusted Hazard Ratios of Dementia (95% CI)
No TBI	Ref
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)

Adjusted for demographic, medical conditions, and psychiatric disorders

# Summary of Recent Epidemiological Studies

- Strong epidemiological evidence for TBI as a risk factor for dementia
- Emerging data for the role of mild TBI and neurodegenerative outcomes
- Inclusion of objective TBI measures
- Large studies with long follow up to address issues of power and reverse causation
- Age and medical and psychiatric comorbidities are critical factors

# From Punch Drunk to Chronic Traumatic Encephalopathy

- Punch Drunk
  - First report in JAMA in 1928
- Dementia Pugilistica
- “CTE is a progressive neurodegeneration clinically associated with memory disturbances, behavioral and personality changes, parkinsonism, and speech and gait abnormalities... There is overwhelming evidence that the condition is the result of repeated sublethal brain trauma...” (McKee et al., 2009)
- Mostly seen in boxers and football players



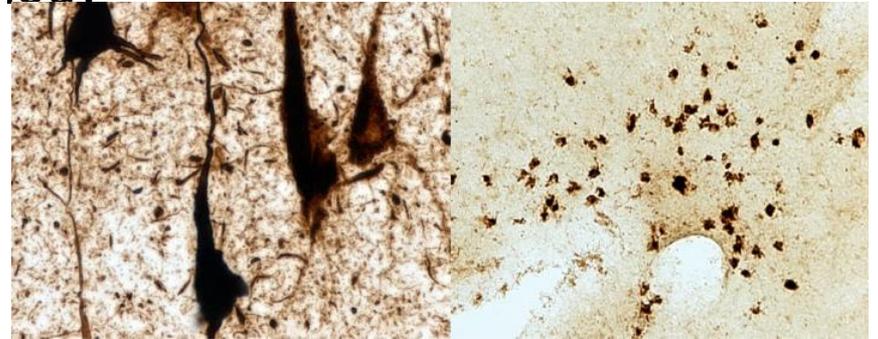
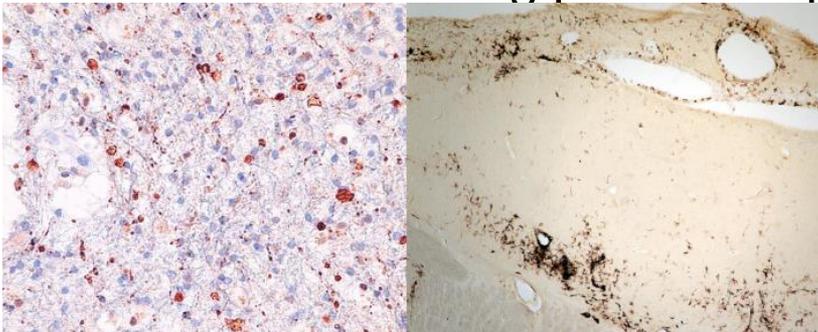
# Chronic Traumatic Encephalopathy: Pathology

- Frontal and temporal atrophy

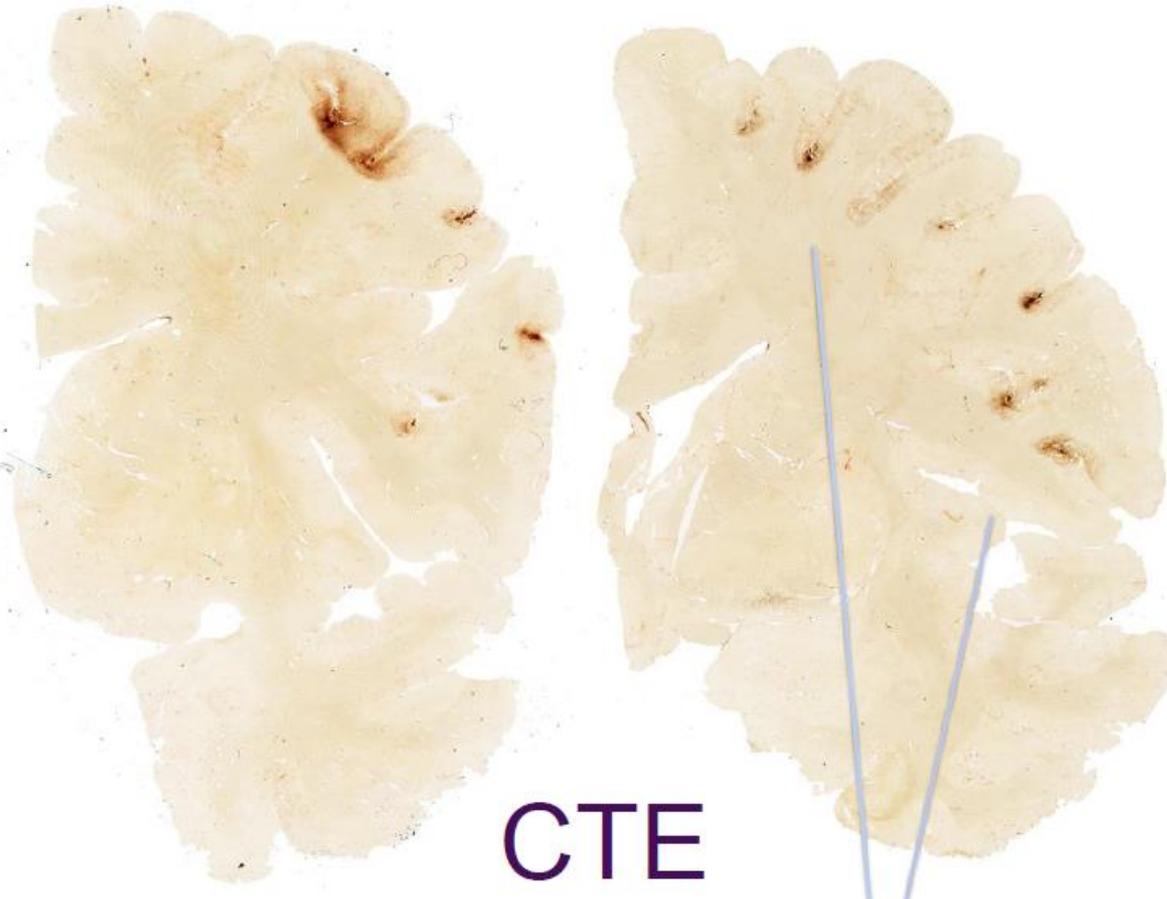


1. Severe dilation of lateral ventricle
2. Severe dilation of third ventricle
3. Cavum septum pellucidum
4. Marked trophy of the medial temporal lobe
5. Shrinkage of mammillary bodies

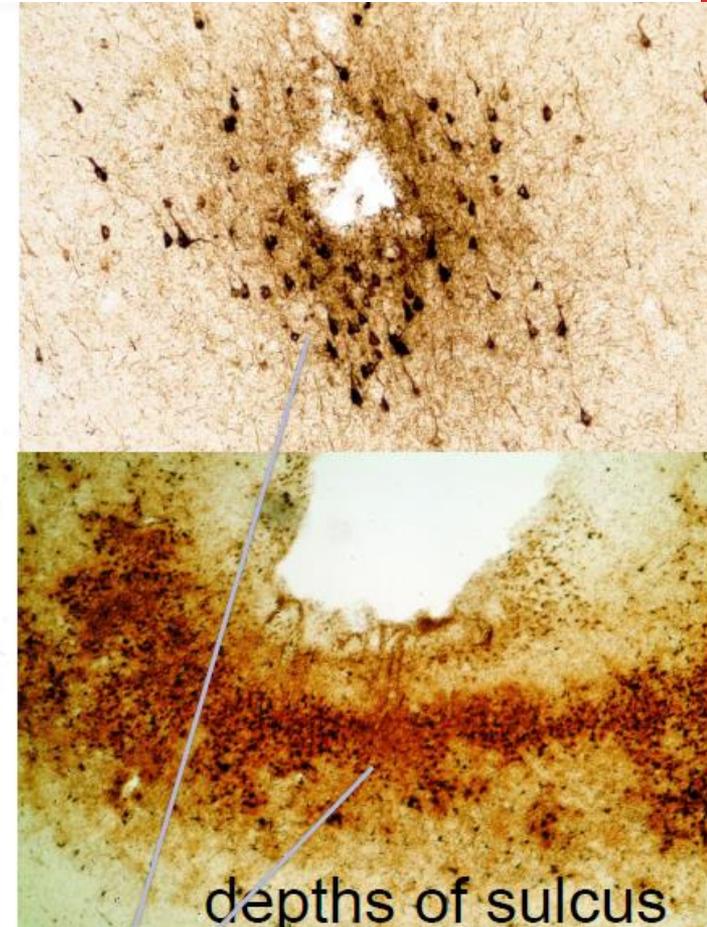
- Axonal degeneration
- Hyperphosphorylated tau
- TAR DNA-binding protein 43 pathology



# PHF-tau Neuronal & Glial Pathology

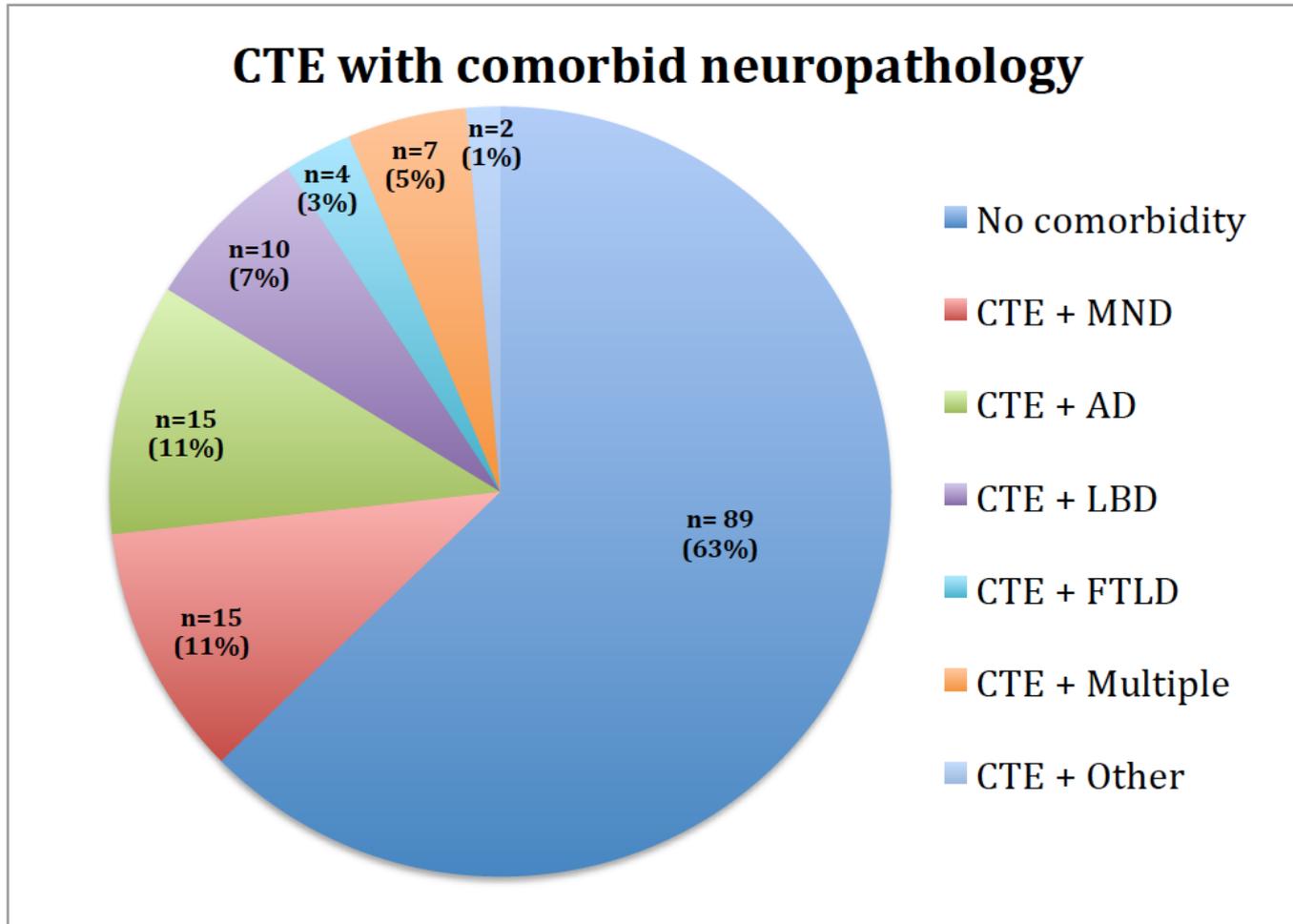


Focal epicenters of depth of sulci



Perivascular

# CTE Neuropathology



# Chronic Traumatic Encephalopathy: Clinical Symptoms?

- Based on retrospective data collection
- Possible selection bias
- Symptoms occur many years after repeated concussive or subconcussive blows to the head

## **Cognitive**

- Memory
- Executive dysfunction
- Impaired attention

## **Mood changes**

- Depression, suicidality
- Hopelessness

## **Behavioral changes**

- Physical and/or verbal violence
- Explosivity
- Loss of Control
- Short Fuse

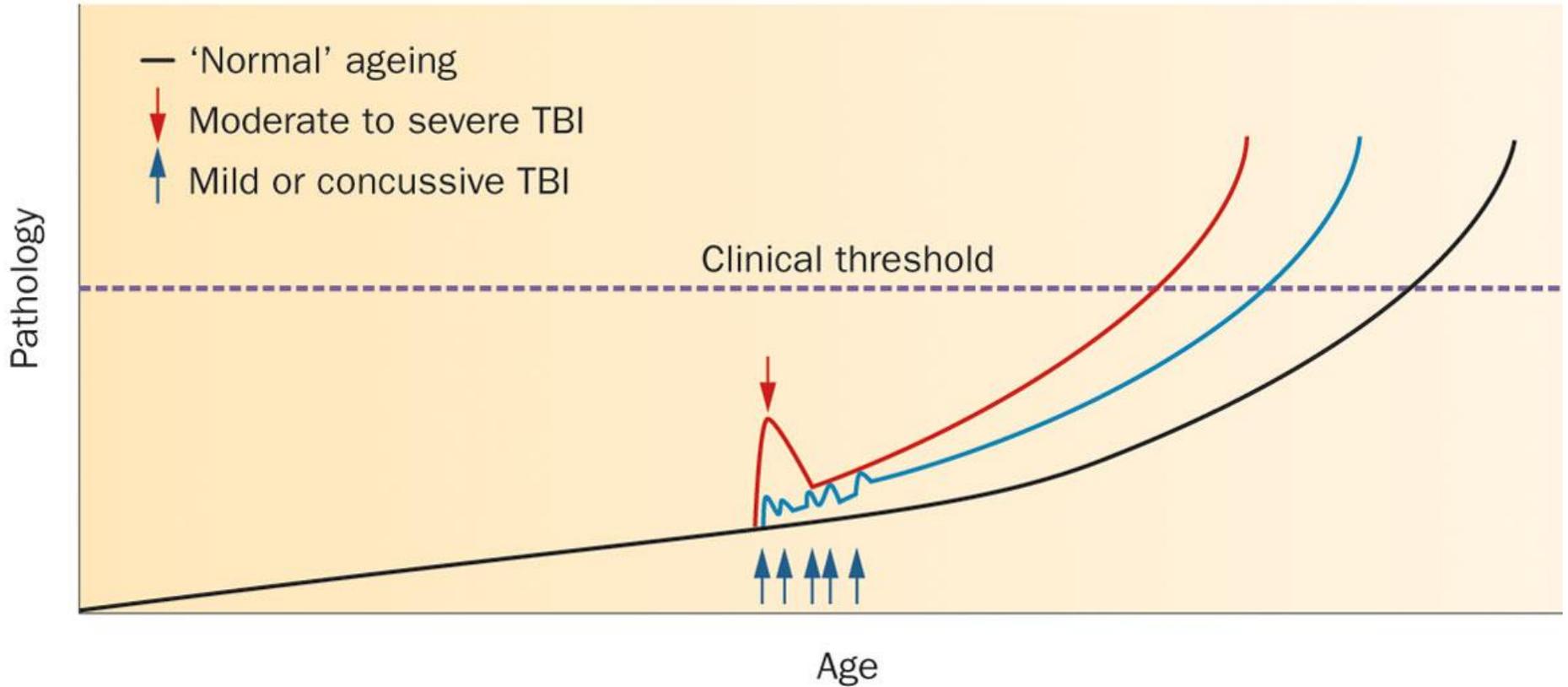
## **Motor impairment**

- Parkinsonism

# What is Chronic Traumatic Encephalopathy?

- Current evidence based mostly on postmortem neuropathology
- No consensus on clinical criteria, thus prevalence is not known
- Possibly biased due to reliance on retrospective interviews with family and friends
- Distinct cohort, mostly of athletes, which as a group may have other unidentified risk factors and possible differences between groups of athletes, ie football vs boxing
- Prolonged period between exposure and symptoms
- Other pathologies may be involved

# Hypothetical Model of TBI & Dementia



# Summary: TBI & Dementia

- TBI associated with increased risk of dementia, even after many decades
- More and more evidence suggests that even mild TBI increases risk
- Critical interaction of TBI with other dementia risk factors including PTSD
- Many questions still remain regarding chronic traumatic encephalopathy

# Clinical Implications

- Clinicians need to be aware of the long-term effects of TBI including mild TBI on brain health and dementia risk
- Veterans with a history of TBI need to be screened for neurodegenerative diseases particularly as they age

# Strategies to Improve Brain Health in Veterans with TBI

- Treatment and screening of comorbidities
  - Cardiovascular conditions
  - Depression/PTSD
  - Sleep
- Increase/maintain healthy lifestyle behaviors
  - Smoking cessation
  - Physical activity
- Advances in dementia research point towards multi-domain prevention/intervention strategies
- Long-term effects of cognitive rehabilitation/training remain unclear

# Next Steps

- Need more rigorous prospective studies of TBI to understand long-term outcomes as well as progression of chronic traumatic encephalopathy
- Continued exploration of mechanisms for the association of TBI with dementia through blood biomarkers, neuroimaging, and neuropathology
- More research on treatment/rehabilitation to potentially reduce dementia risk and other neurodegenerative outcomes
- Develop prevention trials targeting veterans at risk for neurodegenerative disease

**Thank You!**