Early Stage Investigator Lecture

Powered by Numbers: Leveraging Epidemiology to Foster Prevention of Traumatic Brain Injury-related Sequelae

Presented by:
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NIH National Institutes of Health
Office of Disease Prevention

Penn Medicine

Powered by Numbers: Leveraging Epidemiology to Foster the Prevention of Traumatic Brain Injury-Related Sequelae

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- Associate Editor for Methodology and Statistics at *Neurology*

Outline

- Traumatic Brain Injury (TBI) Epidemiology: Associations with Long-Term Outcomes
- Cognitive Trajectories and Cognitive Outcomes in the Early Post-TBI Time-Period
- Cognitive Trajectories and Dementia Risk in the Late Post-TBI Time-Period
- Biomarkers and Associations of TBI with Dementia Risk: Insights into Disease Mechanism

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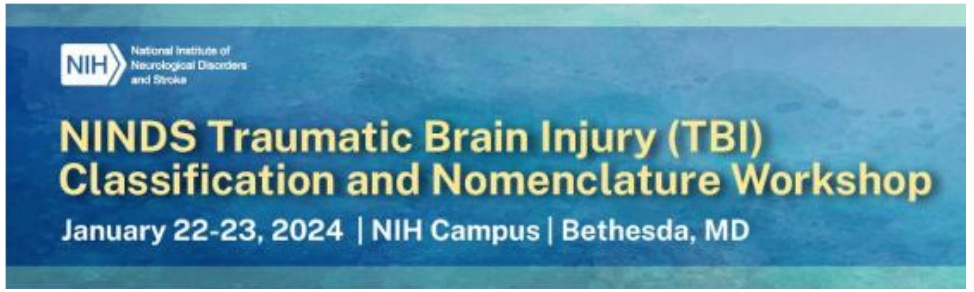
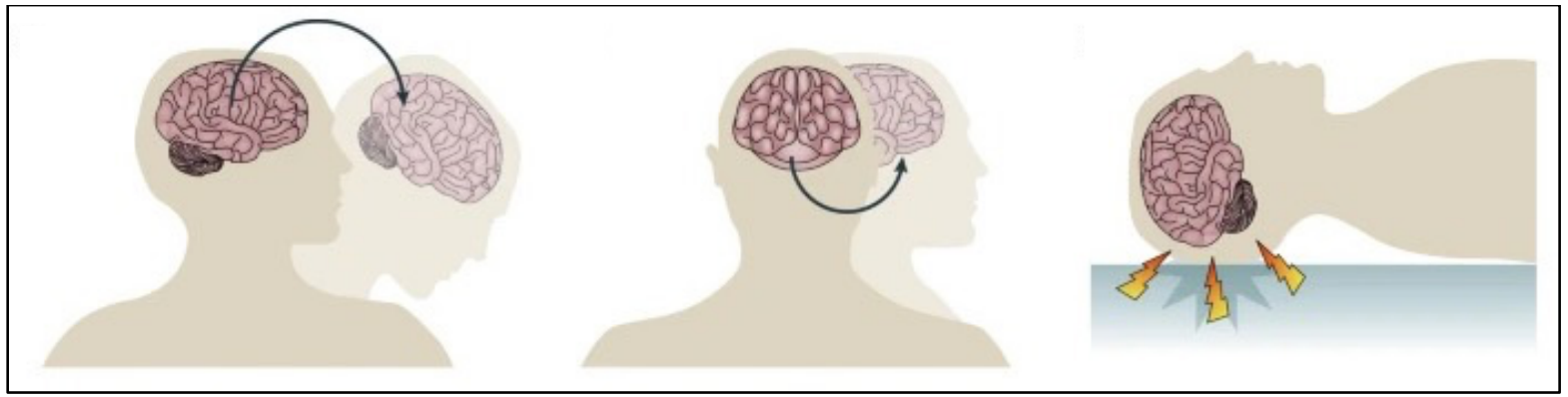
Definition of Traumatic Brain Injury

- **Evolving definition**:
  - Concussion, Mild, Moderate, Severe
  - CBI-M: **C**linical/Symptoms, Blood-based **B**iomarkers, **I**maging, Psychosocial and Environmental **M**odifiers



- **Traumatic brain injury** is an injury caused by a force to the head that results in injury that is apparent on neuroimaging and/or that results in neurologic symptoms, such as loss of consciousness, post-traumatic amnesia, and/or altered mental status.



Global Epidemiology of Traumatic Brain Injury

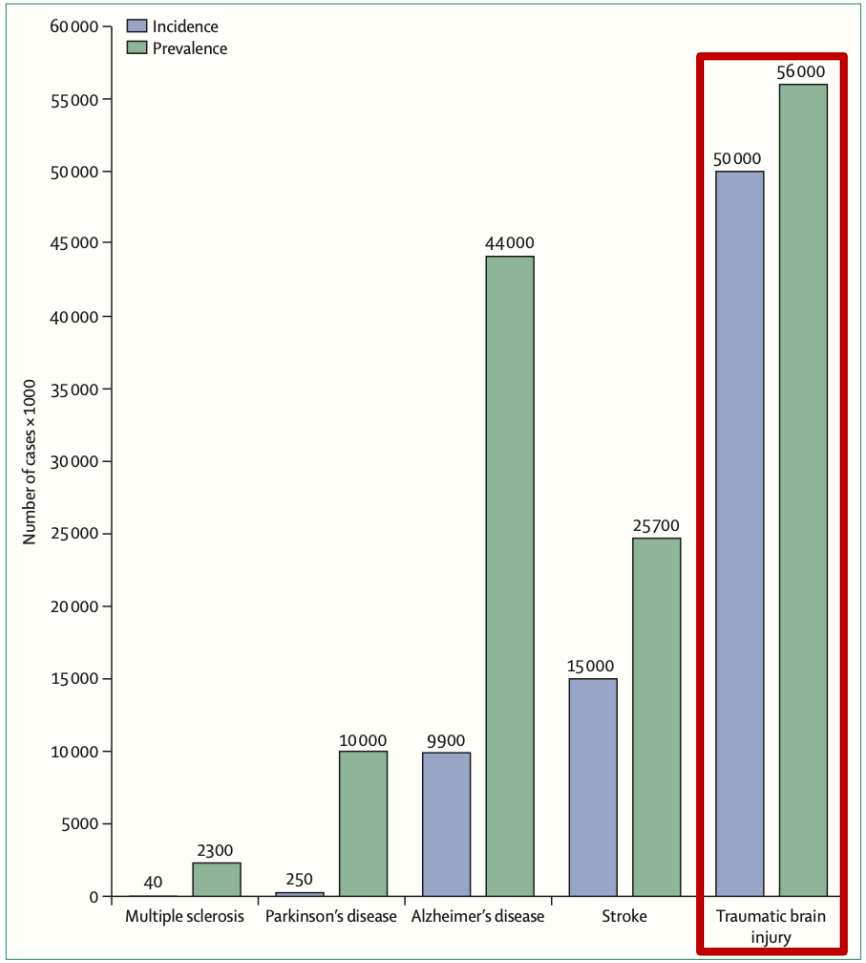
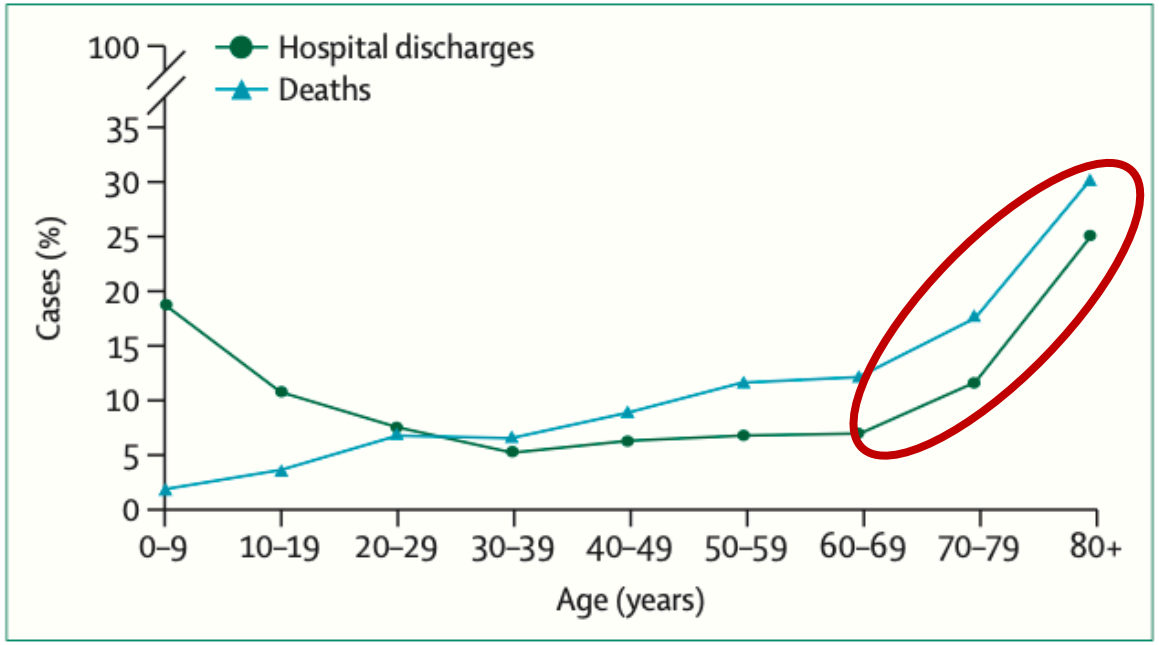
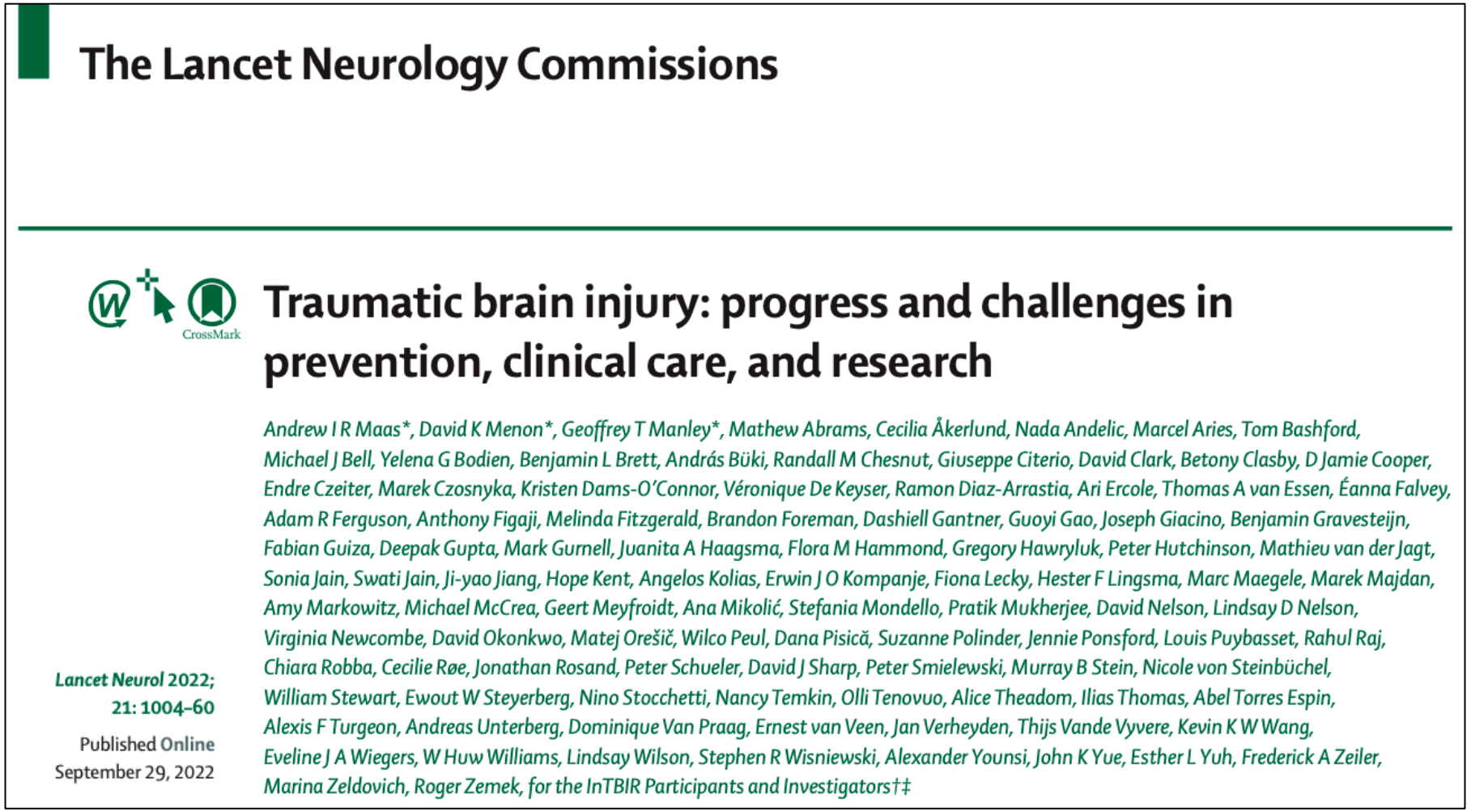


Figure 1: **Global incidence and prevalence of traumatic brain injury compared with other common neurological diseases**



Lancet Neurol 2022;
21: 1004–60

2022 *Lancet Neurology* Commission on Traumatic Brain Injury



The Lancet Neurology Commissions

Traumatic brain injury: progress and challenges in prevention, clinical care, and research

Andrew I R Maas, David K Menon*, Geoffrey T Manley*, Mathew Abrams, Cecilia Åkerlund, Nada Andelic, Marcel Aries, Tom Bashford, Michael J Bell, Yelena G Bodien, Benjamin L Brett, András Büki, Randall M Chesnut, Giuseppe Citerio, David Clark, Betony Clasby, D Jamie Cooper, Endre Czeiter, Marek Czosnyka, Kristen Dams-O'Connor, Véronique De Keyser, Ramon Diaz-Arrastia, Ari Ercole, Thomas A van Essen, Éanna Falvey, Adam R Ferguson, Anthony Figaji, Melinda Fitzgerald, Brandon Foreman, Dashiell Gantner, Guoyi Gao, Joseph Giacino, Benjamin Gravesteijn, Fabian Guiza, Deepak Gupta, Mark Gurnell, Juanita A Haagsma, Flora M Hammond, Gregory Hawryluk, Peter Hutchinson, Mathieu van der Jagt, Sonia Jain, Swati Jain, Ji-yao Jiang, Hope Kent, Angelos Kolias, Erwin J O Kompanje, Fiona Lecky, Hester F Lingsma, Marc Maegele, Marek Majdan, Amy Markowitz, Michael McCrea, Geert Meyfroidt, Ana Mikolić, Stefania Mondello, Pratik Mukherjee, David Nelson, Lindsay D Nelson, Virginia Newcombe, David Okonkwo, Matej Orešič, Wilco Peul, Dana Pisică, Suzanne Polinder, Jennie Ponsford, Louis Puybasset, Rahul Raj, Chiara Robba, Cecilie Røe, Jonathan Rosand, Peter Schueler, David J Sharp, Peter Smielewski, Murray B Stein, Nicole von Steinbüchel, William Stewart, Ewout W Steyerberg, Nino Stocchetti, Nancy Temkin, Olli Tenovuo, Alice Theadom, Ilias Thomas, Abel Torres Espin, Alexis F Turgeon, Andreas Unterberg, Dominique Van Praag, Ernest van Veen, Jan Verheyden, Thijs Vande Vyvere, Kevin K W Wang, Eveline J A Wiegers, W Huw Williams, Lindsay Wilson, Stephen R Wisniewski, Alexander Younsi, John K Yue, Esther L Yuh, Frederick A Zeiler, Marina Zeldovich, Roger Zemek, for the InTBIR Participants and Investigators†‡*

Lancet Neurol 2022; 21: 1004–60

Published Online September 29, 2022

2022 *Lancet Neurology* Commission on Traumatic Brain Injury

Main messages

(1) Worldwide, TBI is a leading cause of injury-related death and disability, with devastating effects on patients and their families.

(2) Wide variations exist in global estimates of TBI incidence and in reported incidence, prevalence, and mortality rates between regions and countries. Variations in approaches to data capture and interpretation probably contribute to these variations, confounding comparisons.

(3) More than 90% of patients presenting to hospital with TBI have mild TBI, but there is little evidence to inform treatment of patients with mild TBI.

(4) In HICs, older patients (≥65 years) who are mostly injured by falls account for 30–40% of hospital admissions for TBI. Frailty and alcohol abuse contribute to falls causing TBI in older people.

(5) People in LMICs are disproportionately affected by TBI, with most injuries caused by road traffic incidents. There are substantial disparities in care, with little infrastructure for emergency pre-hospital care and very little access to post-acute care.

(6) Although there is a strong focus on the risk of sport-related concussion and repetitive head impacts in team sports, most patients seen in hospital with sport-related concussion have sustained the injury during individual sports or recreational activities.

(7) TBI and criminal offending are closely and bidirectionally related. TBI associated with intimate partner violence affects women more commonly and is associated with worse outcomes compared with other interpersonal violence.

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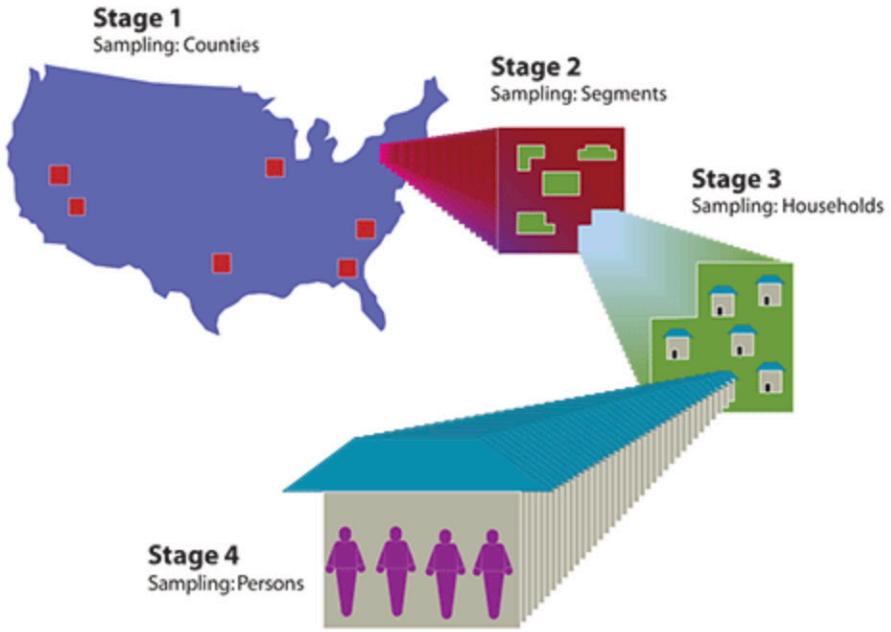
Traumatic Brain Injury Epidemiology: Associations with Long-term Outcomes

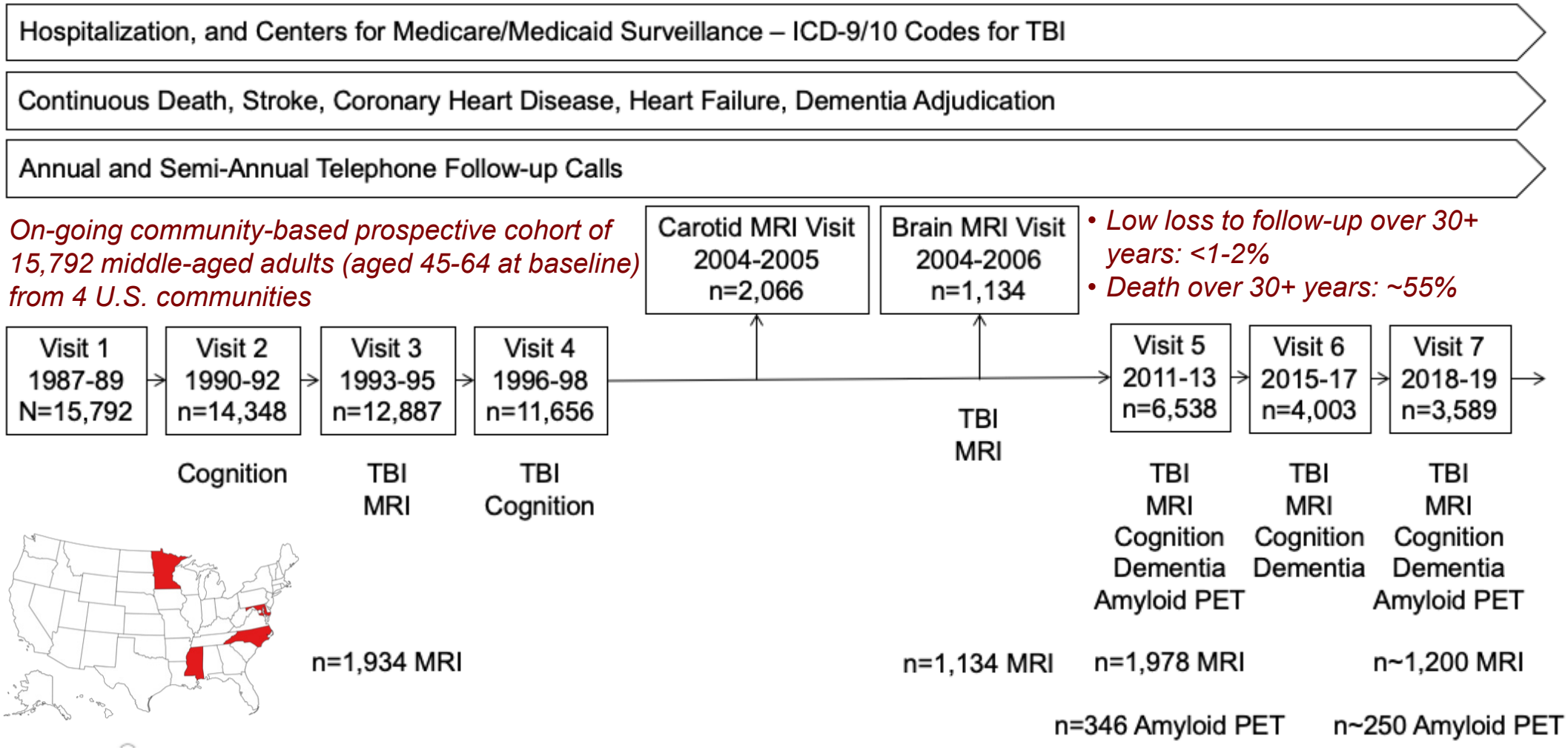
- How do we obtain nationally representative estimates of the burden of traumatic brain injury and its outcomes?
- How can we study long-term outcomes after traumatic brain injury when very few studies designed to study traumatic brain injury starting at the time of injury have long-term follow-up (i.e., 20-30+ years)?
- How can we gain insights into disease mechanism which can be used to inform potential future treatments aimed at preventing traumatic brain injury sequelae?
- **Leverage data from ongoing, deeply phenotyped epidemiologic studies**
  - National Health and Nutrition Examination Survey (NHANES)
  - Atherosclerosis Risk in Communities (ARIC) Study
  - Many other existing epidemiologic studies with opportunities to study traumatic brain injury

National Health and Nutrition Examination Survey (NHANES)

- NHANES is series of cross-sectional surveys conducted yearly (starting in 1999) by the National Center for Health Statistics of the Centers for Disease Control and Prevention
- Participants are selected using a stratified multi-stage probability sampling design of the noninstitutionalized civilian U.S. population
- Survey weights to account for the complex NHANES sampling design make the estimates reported nationally representative of this general U.S. population
- Traumatic brain injury was assessed among individuals aged 40 years or older during the 2011-2012 and 2013-2014 survey cycles using the question, “Have you ever had a loss of consciousness because of a head injury?”



Atherosclerosis Risk in Communities (ARIC) Study



ARIC Study Traumatic Brain Injury Definition

Visit-Based Self-Report Questions

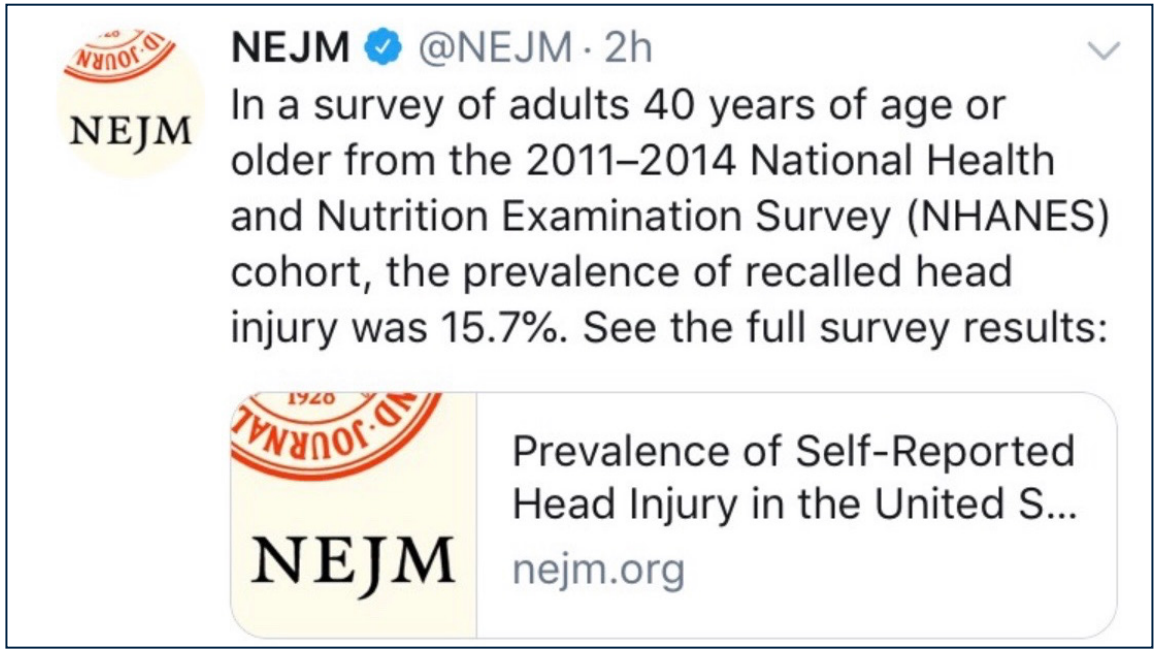
ARIC Visit 3 (1993-1995) 1. Have you ever had a head injury which led you to see a physician or seek hospital care? 2. How many times has this happened? 3. How many of these head injuries resulted in your losing consciousness, no matter how briefly? 4.In what year was your head injury for which you sought medical care?
ARIC Visit 4 (1996-1998) 1. Have you ever had a major head injury? That is, one that resulted in your losing consciousness, no matter how briefly, or that led you to see a physician or seek hospital care? 2. How many times has this happened? 3. How many head injuries resulted in your losing consciousness, no matter how briefly? 4. In what year was your head injury for which you lost consciousness sought medical care?
ARIC Brain MRI Visit (2004-2006)* 1. Have you ever had a head injury that resulted in loss of consciousness (knocked out)? 2. How many times? 3. In what year or how old were you when this first occurred? 4. In what year or how old were you when this last occurred?
ARIC Visit 5 (2011-2013)* 1. Have you ever had a head injury that resulted in loss of consciousness? 2. Have you had a head injury with extended loss of consciousness (>5 minutes)? 3. Have you had a head injury that resulted in long-term problems or dysfunction?
ARIC Visit 6 (2016-2017) 1. Have you ever had a head injury that resulted in loss of consciousness? 2. Have you had a head injury with extended loss of consciousness (>5 minutes)? 3. Have you had a head injury that resulted in long-term problems or dysfunction?
ARIC Visit 7 (2018-2019) 1. Have you ever had a head injury that resulted in loss of consciousness? 2. Have you had a head injury with extended loss of consciousness (>5 minutes)? 3. Have you had a head injury that resulted in long-term problems or dysfunction?

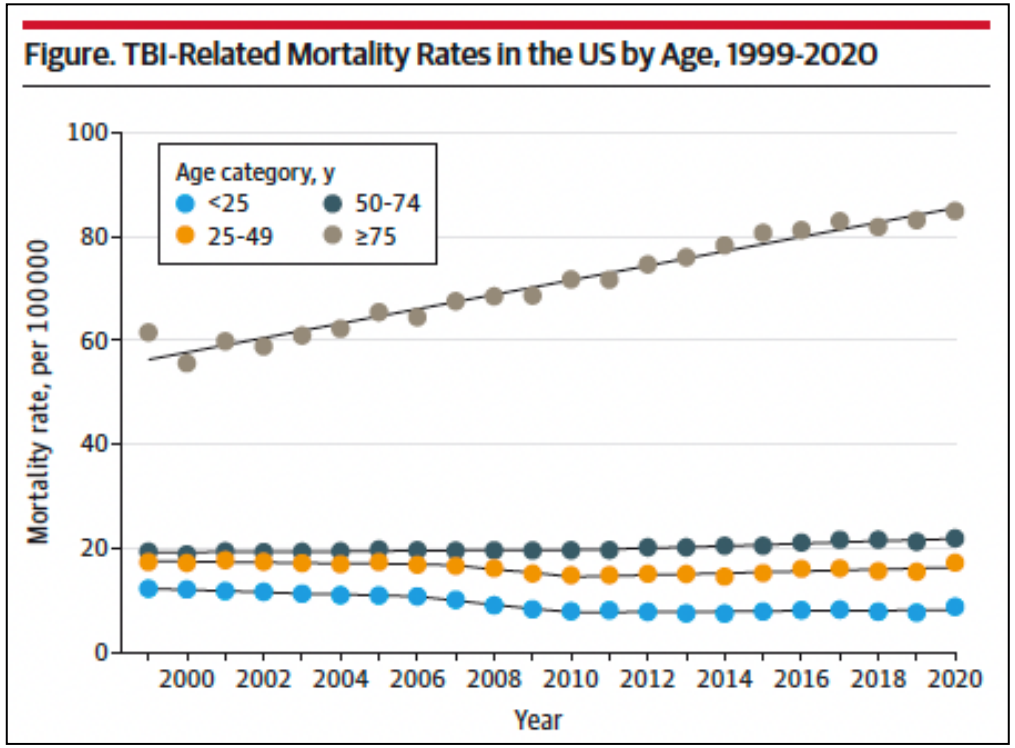
*Questions asked in a subgroup of ARIC participants selected for brain magnetic resonance imaging scans.

Continuously Collected ICD-9/10 Codes

ICD-9 Codes	
800.xx	Fracture of vault of skull
801.xx	Fracture of base of skull
803.xx	Other and unqualified skull fractures
804.xx	Multiple fractures involving skull or face with other bones
850.xx	Concussion
851.xx	Cerebral laceration and contusion
852.xx	Subarachnoid, subdural, and extradural hemorrhage following injury
853.xx	Other and unspecified intracranial hemorrhage following injury
854.xx	Intracranial injury of other and unspecified nature
959.01	Head injury, unspecified
ICD-10 Codes	
S02.0	Fracture of vault of skull
S02.1X	Fracture of base of skull
S02.8	Fractures of other unspecified skull and facial bones
S02.91	Unspecified fracture of skull
S04.02	Injury of optic chiasm
S04.03X	Injury of optic tract and pathways
S04.04X	Injury of visual cortex
S06.X	Intracranial injuries, concussion, traumatic cerebral edema, diffuse and focal traumatic brain injury, traumatic epidural, subdural, and subarachnoid hemorrhage
S07.1	Crushing injury of skull

Epidemiology of Traumatic Brain Injury in the U.S.





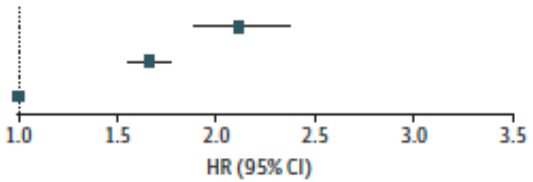
- **Schneider ALC**, Wang D, Ling G, Gottesman RF, Selvin E. Prevalence and Risk Factors for Self-Reported Prior Head Injury in the U.S. *New England Journal of Medicine*. 2018 Sep 20;379(12):1176-1178.
- Shaik NF, Law CA, Elser H, **Schneider ALC**. Trends in Traumatic Brain Injury Mortality in the United States: 1999-2020. *JAMA Neurology*. 2024 Feb 1;81(2):194-195.

Long-term Risk of Mortality After Traumatic Brain Injury

- TBI was associated with 2 times the risk of mortality over a median of 28 years

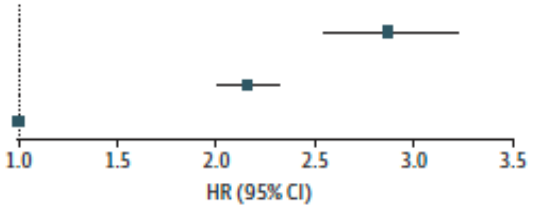
A All-cause mortality risk by head injury vs no head injury

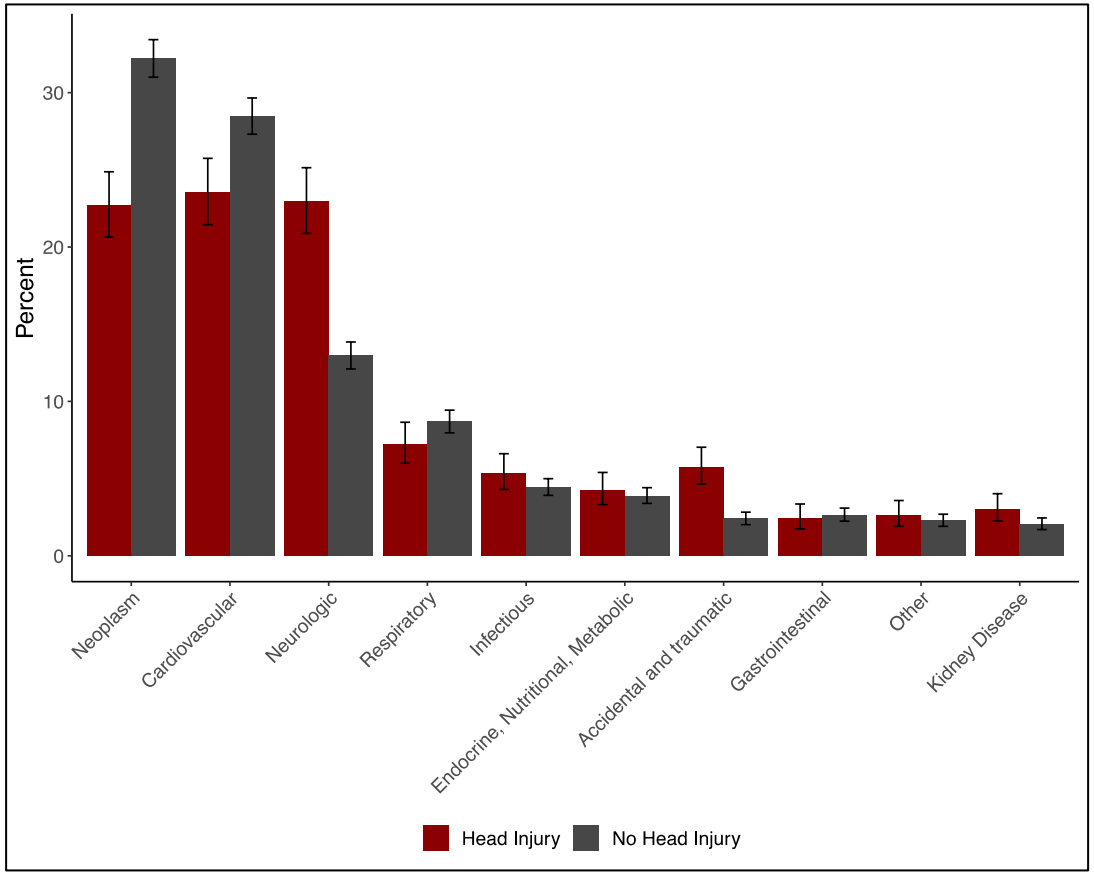
No. of head injuries	No. of participants	Person-years	HR (95% CI)
≥2	330	4003	2.11 (1.89-2.37)
1	1275	29475	1.66 (1.56-1.77)
0	5801	289 204	1 [Reference]



B All-cause mortality by head injury severity vs no head injury

Severity	No. of participants	Person-years	HR (95% CI)
Moderate, severe, or penetrating	299	2847	2.87 (2.55-3.22)
Mild	1031	14881	2.16 (2.01-2.31)
No injury	5801	296 114	1 [Reference]

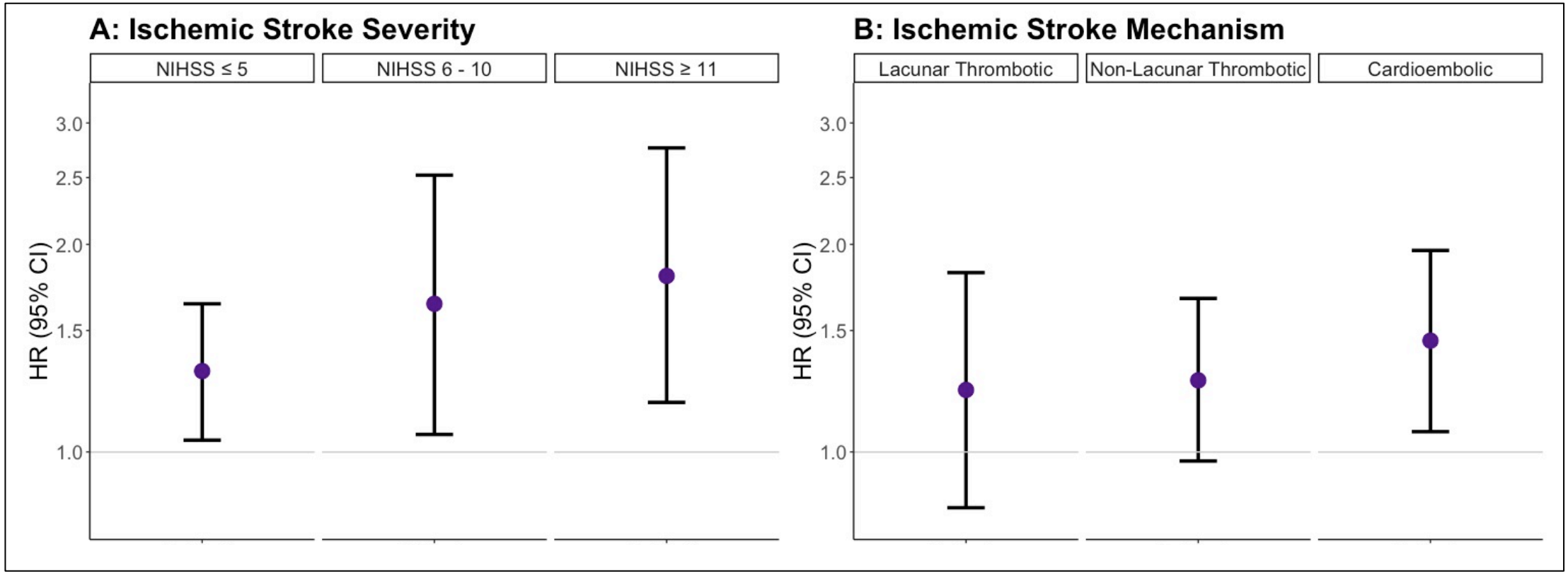




- Elser H, Gottesman RF, Walter A, Coresh J, Diaz-Arrastia R, Mosley T, **Schneider ALC**. Head Injury and Long-term Mortality Risk in Community-Dwelling Adults. *JAMA Neurology*. Mar 1;80(3):260-269.

Traumatic Brain Injury and Stroke Risk

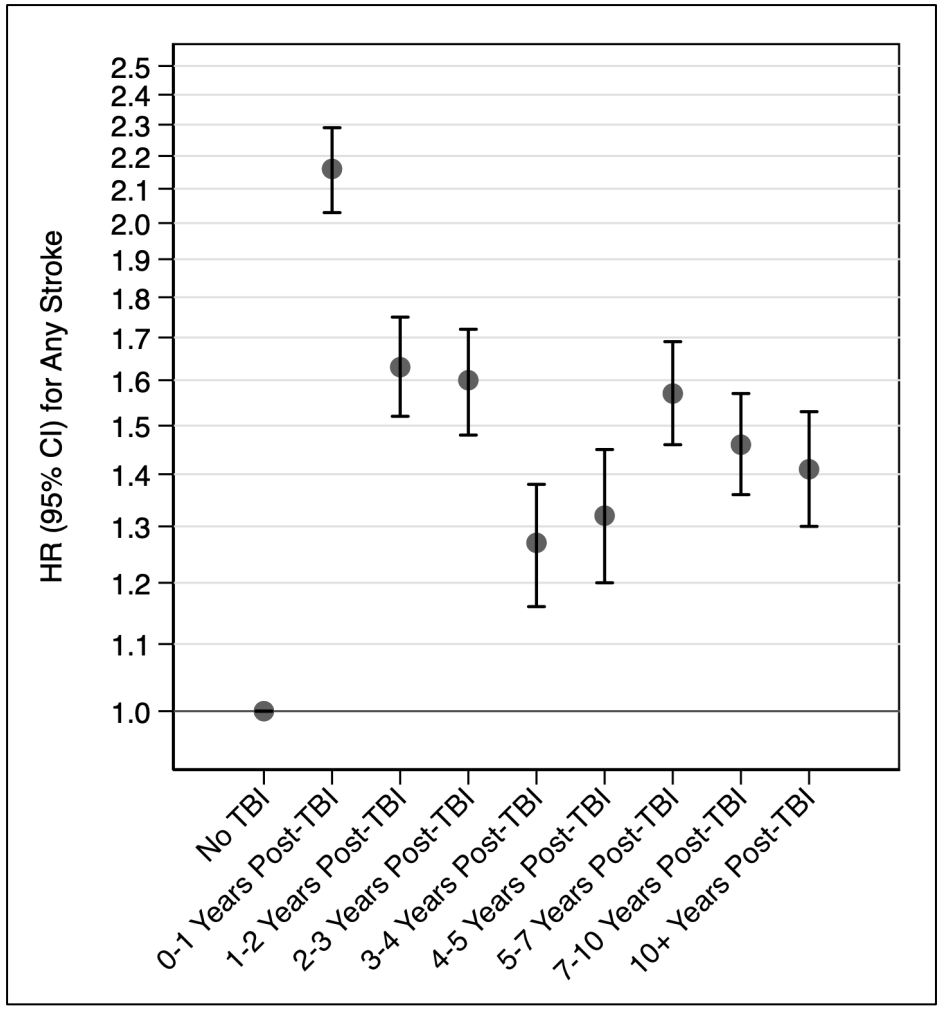
- Traumatic brain injury was associated with 1.3 times the risk of incident ischemic stroke over a median of 27 year of follow-up



- Elser HC, Pappalardo LW, Gottesman RF, Coresh J, Diaz-Arrastia R, Mosley TH, Kasner SE, Koton S, **Schneider ALC**. Head Injury and Risk of Incident Ischemic Stroke in Community-Dwelling Adults. *Stroke*. 2024. In Press.

Traumatic Brain Injury and Stroke Risk

- Among U.S. military veterans aged 18+ years receiving healthcare in the Veterans Health Administration system, traumatic brain injury was associated with 1.7 times the risk of incident stroke
- This risk was highest in the first-year post-injury, but remained elevated for over 10 years post-injury
- The association of traumatic brain injury with hemorrhagic stroke was stronger than the association of traumatic brain injury with ischemic stroke



- **Schneider ALC**, Peltz CB, Li Y, Bahorik A, Gardner RC, Yaffe K. Traumatic Brain Injury and Long-Term Risk of Stroke Among US Military Veterans. *Stroke*. 2023 Aug;54(8):2059-2068.

Traumatic Brain Injury, Physical Functioning, Frailty, and Fall Risk

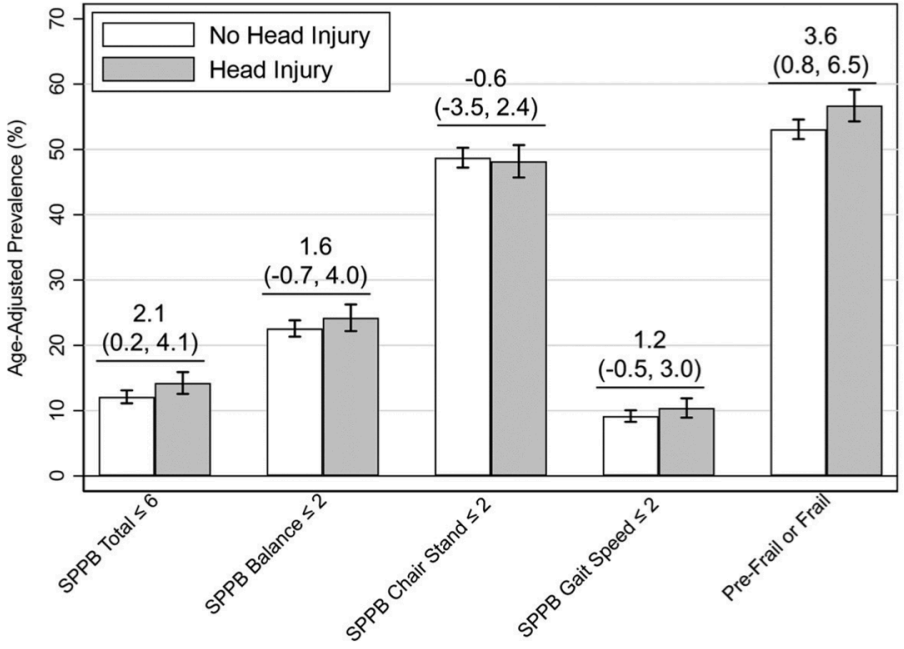
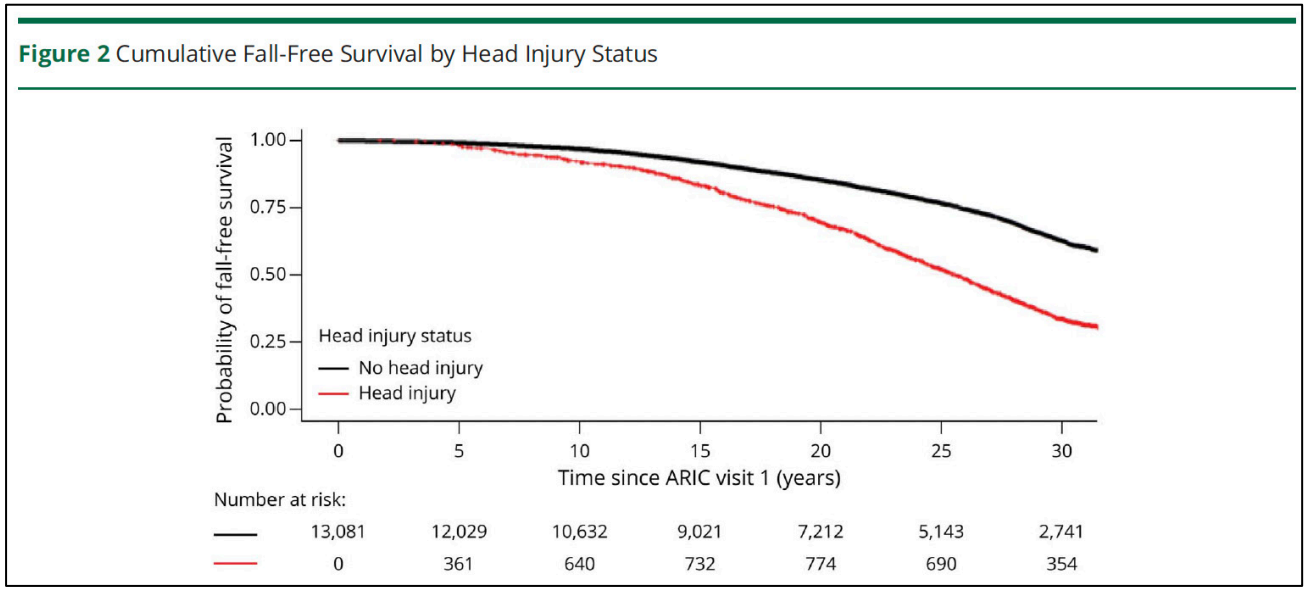


Figure 2. Age-adjusted prevalence (95% confidence interval [CI]) for poor physical functioning on the Short Physical Performance Battery (SPPB < 6) and pre-frailty/frailty. Numbers represent the absolute mean difference in prevalence (95% CI) by head injury status.

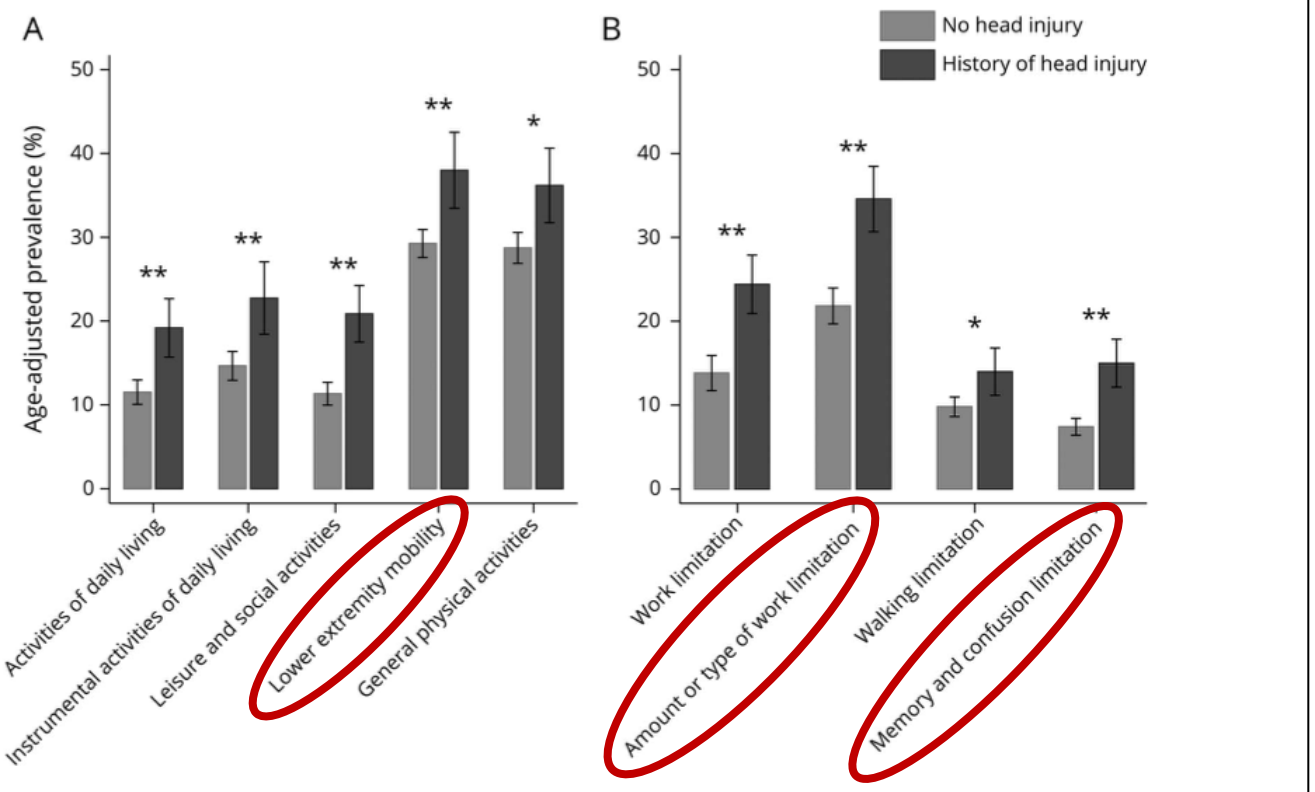
- Traumatic brain injury was associated with 1.7 times the risk of fall over a median of 23 years of follow-up



- Hunzinger K, Walter AE, Rosenthal KA, Windham BG, Palta P, Juraschek SP, Hicks C, Gottesman RF, **Schneider ALC**. Associations Between Prior Head Injury, Physical Functioning, and Frailty in the Atherosclerosis Risk in Communities (ARIC) Study. *Journal of Gerontology: Medical Sciences*. 2024 Apr 1;79(4):glae032. doi: 10.1093/gerona/glae032.
- Hunzinger K, Law CA, Elser H, Walter AE, Windham BG, Palta P, Juraschek SP, Hicks CW, Gottesman RF, **Schneider ALC.** Associations Between Head Injury and Subsequent Risk of Falls: Results from the Atherosclerosis Risk in Communities (ARIC) Study. *Neurology*. Neurology. 2023 Nov 27;101(22):e2234-e2242.

Prevalence of Disability Associated with Traumatic Brain Injury

Figure 2 Age-Adjusted Prevalence (95% confidence interval) of Disability by History of Head Injury With Loss of Consciousness



(A) Physical functioning domains. (B) Functional limitations domains. *$p < 0.01$ comparing no head injury to history of head injury. **$p < 0.001$ comparing no head injury to history of head injury.

- Individuals with prior traumatic brain injury had higher prevalence of disability compared to individuals without traumatic brain injury (47% versus 39%)

Source: **Schneider ALC**, Wang D, Gottesman RF, Selvin E. Prevalence of Disability Associated With Head Injury With Loss of Consciousness in Adults in the United States: A Population-Based Study. *Neurology*. 2021 July 13;97(2):e124-e135.

2020 *Lancet* Commission on Dementia


The Lancet Commissions

Dementia prevention, intervention, and care: 2020 report of the *Lancet* Commission

Gill Livingston, Jonathan Huntley, Andrew Sommerlad, David Ames, Clive Ballard, Sube Banerjee, Carol Brayne, Alistair Burns, Jiska Cohen-Mansfield, Claudia Cooper, Sergi G Costafreda, Amit Dias, Nick Fox, Laura N Gitlin, Robert Howard, Helen C Kales, Mika Kivimäki, Eric B Larson, Adesola Ogunniyi, Vasiliki Orgeta, Karen Ritchie, Kenneth Rockwood, Elizabeth L Sampson, Quincy Samus, Lon S Schneider, Geir Selbæk, Linda Teri, Naaheed Mukadam

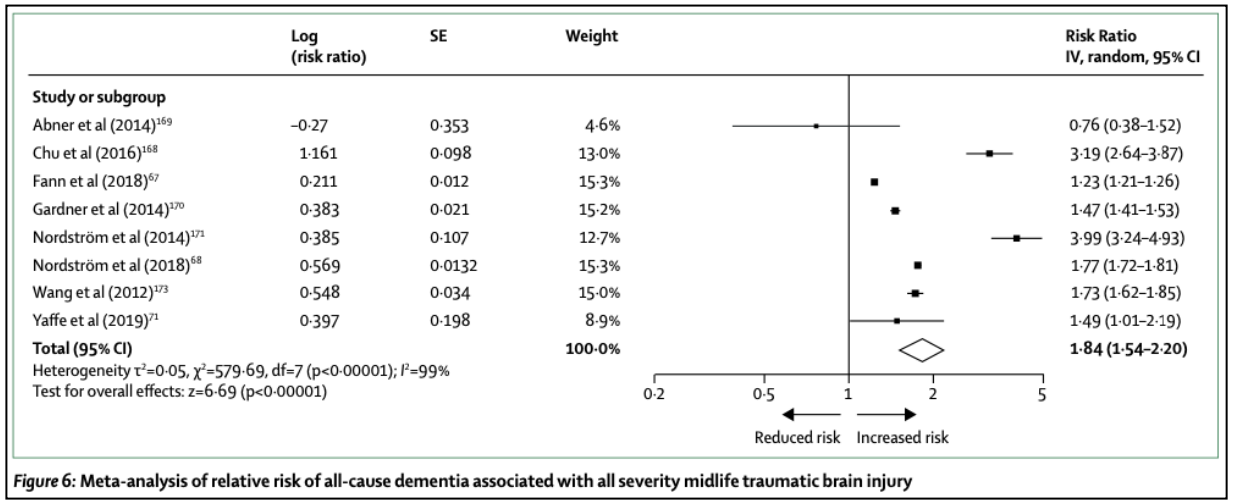


Figure 6: **Meta-analysis of relative risk of all-cause dementia associated with all severity midlife traumatic brain injury**

- Traumatic brain injury was designated as a potentially modifiable risk factor for dementia

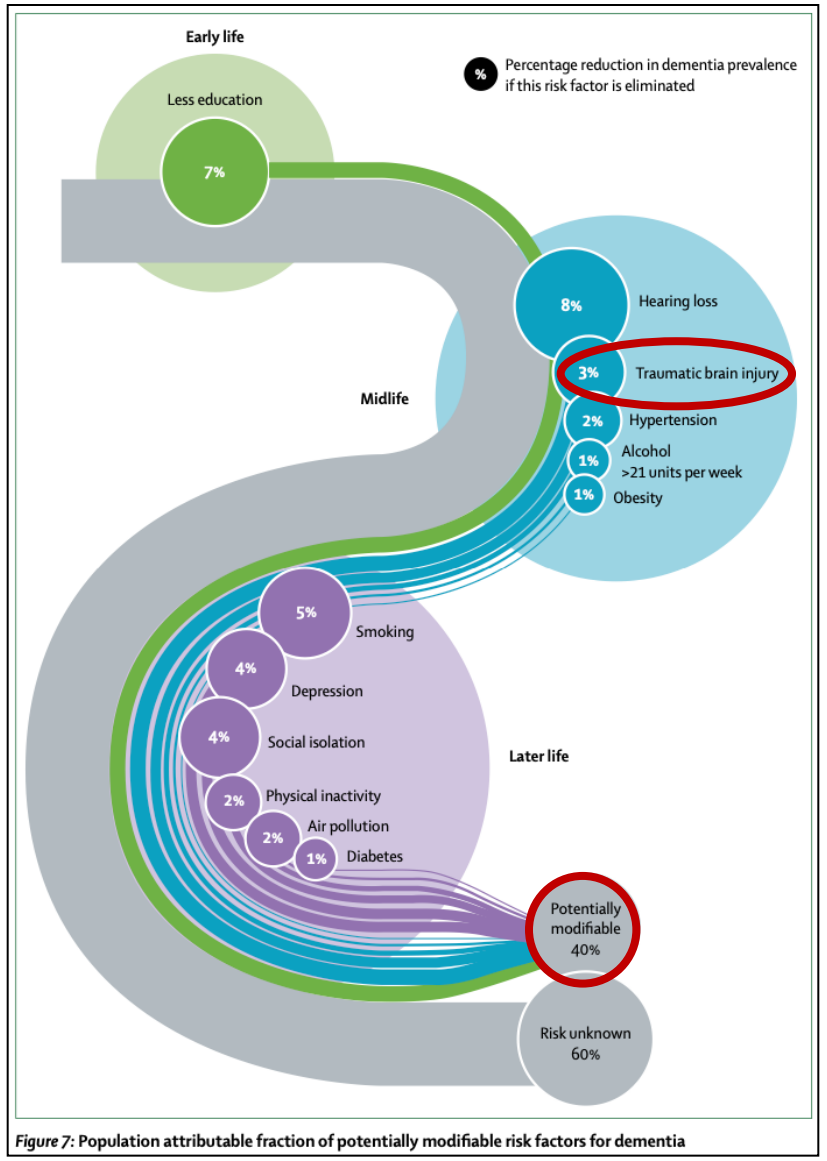
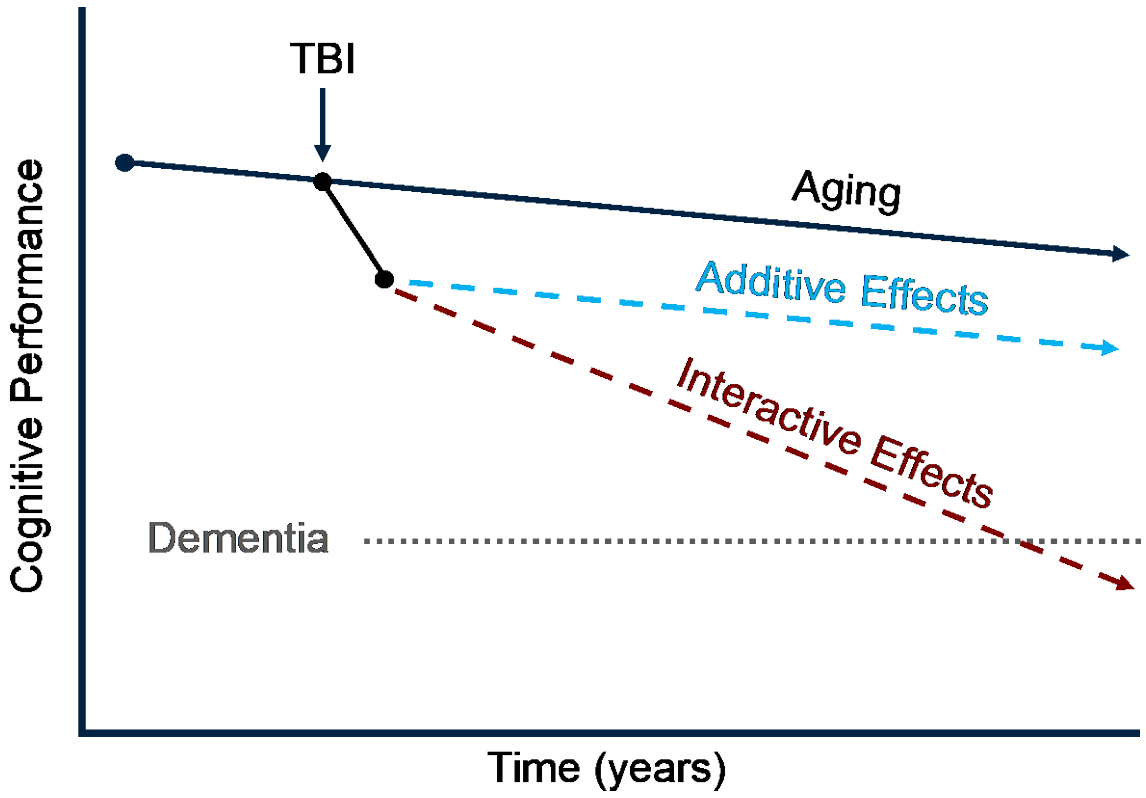


Figure 7: **Population attributable fraction of potentially modifiable risk factors for dementia**

Cognitive Trajectories After Traumatic Brain Injury (1)



- Additive effects trajectory: initial accelerated cognitive decline followed by a parallel rate of subsequent aging over time
- Interactive effects trajectory: initial accelerated cognitive decline followed by a continued accelerated rate of cognitive decline over time

Source: Adapted from: Cole JH, Leech R, Sharp DJ. Prediction of Brain Age Suggests Accelerated Atrophy after Traumatic Brain Injury. *Annals of Neurology.* 2015;77 (4):571-581.

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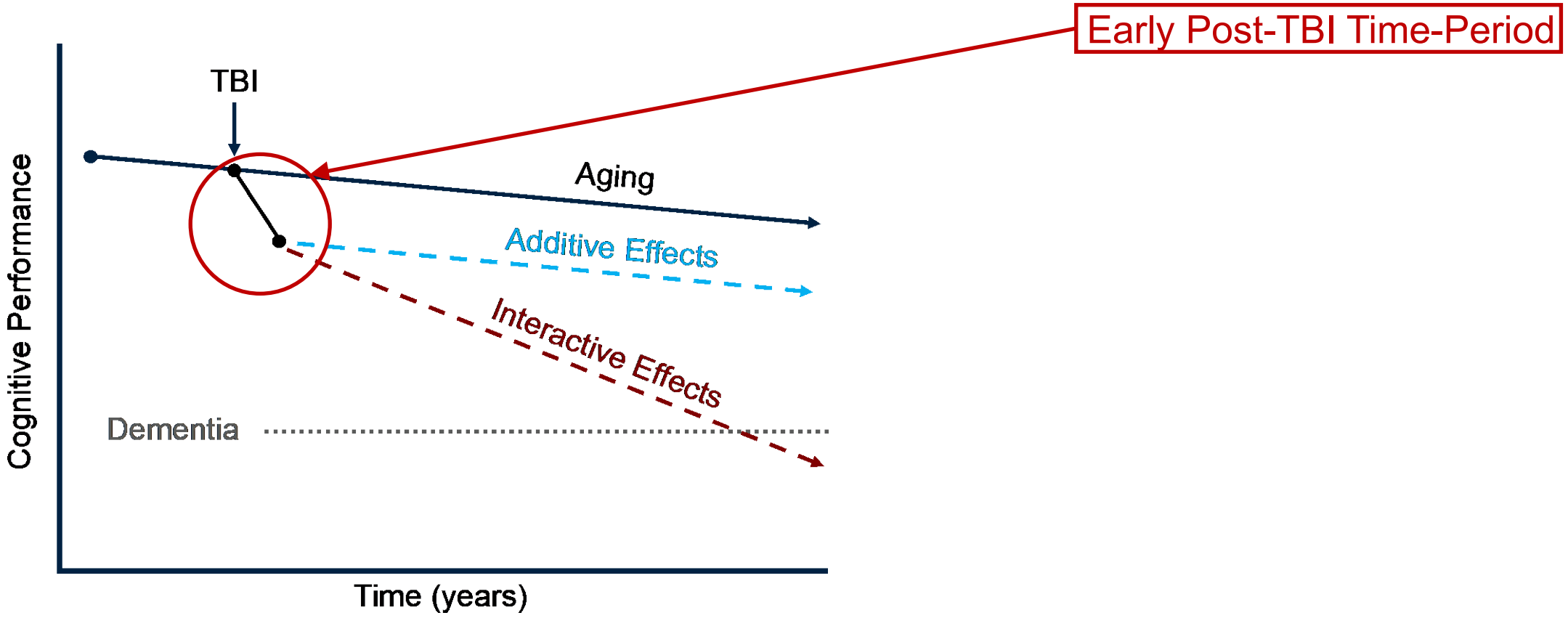
Cognitive Trajectories After Traumatic Brain Injury (2)



Source: Adapted from: Cole JH, Leech R, Sharp DJ. Prediction of Brain Age Suggests Accelerated Atrophy after Traumatic Brain Injury. *Annals of Neurology.* 2015;77 (4):571-581.

Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) Study

On-going cohort of acute traumatic brain injury patients aged 16-100 years (and orthopedic injury and friend controls) recruited from 18 Level 1 trauma centers in the United States

TRACK-TBI Study (2014-2018)

TRACK-TBI LONG Study (2019-present)

TBI Event
Enrollment
(N=2697 TBI and N=599 Controls)

- Head injury
- Vascular risk factor assessment
- Blood specimens

→

2-week Follow-up
In-Person Visit
(N=2006 TBI and N=512 Controls)

- Full cognitive test battery
- Clinical outcomes
- Blood specimens

→

3-month Follow-up
Telephone Visit
(N=1974 TBI and N=497 Controls)

- Telephone cognitive test battery
- Clinical outcomes

→

6-month Follow-up
In-Person Visit
(N=1590 TBI and N=437 Controls)

- Full cognitive test battery
- Clinical outcomes
- Blood specimens

→

12-month Follow-up
In-Person Visit
(N=1322 TBI and N=347 Controls)

- Full cognitive test battery
- Clinical outcomes

→

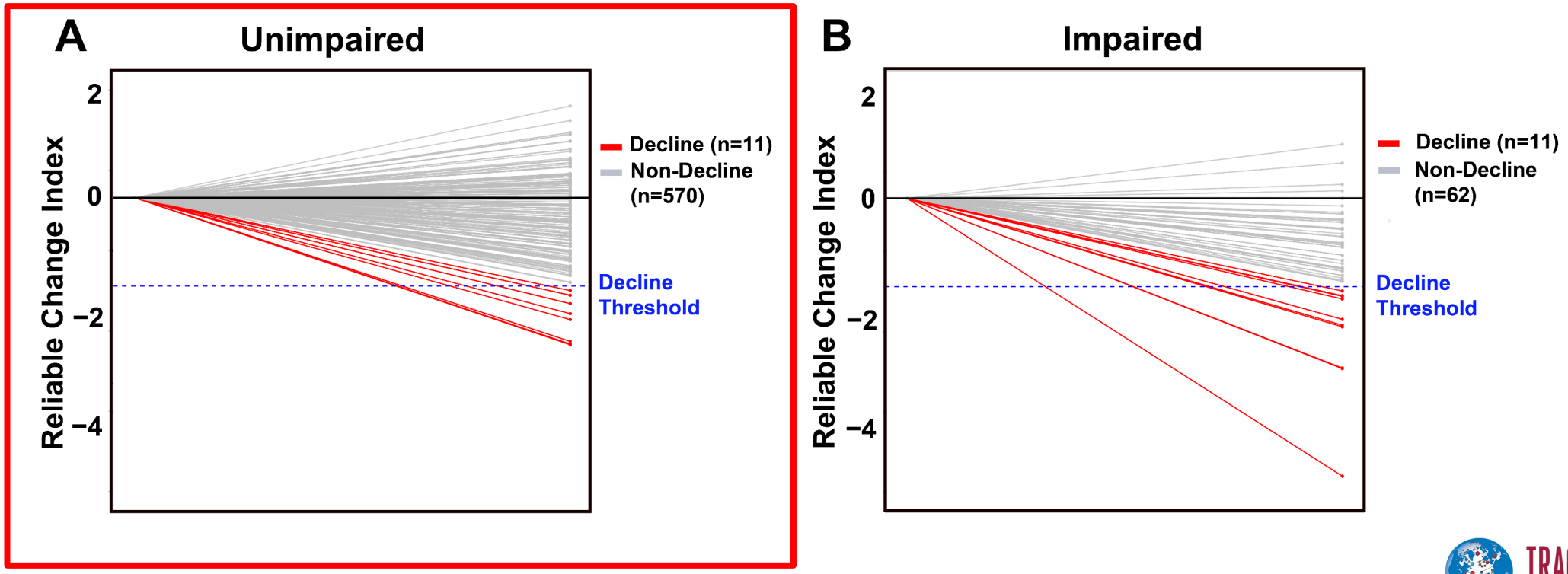
2-5-year Follow-up
Goal up to 4 In-Person and/or Telephone Visits
(Goal n≈1888 TBI and n≈209 Controls)

- Full cognitive test battery and/or telephone cognitive test battery
- Clinical outcomes

TRACK-TBI
Transforming Research and Clinical Knowledge in Traumatic Brain Injury
International Traumatic Brain Injury Research Initiative

Cognitive Outcome One Year After Traumatic Brain Injury

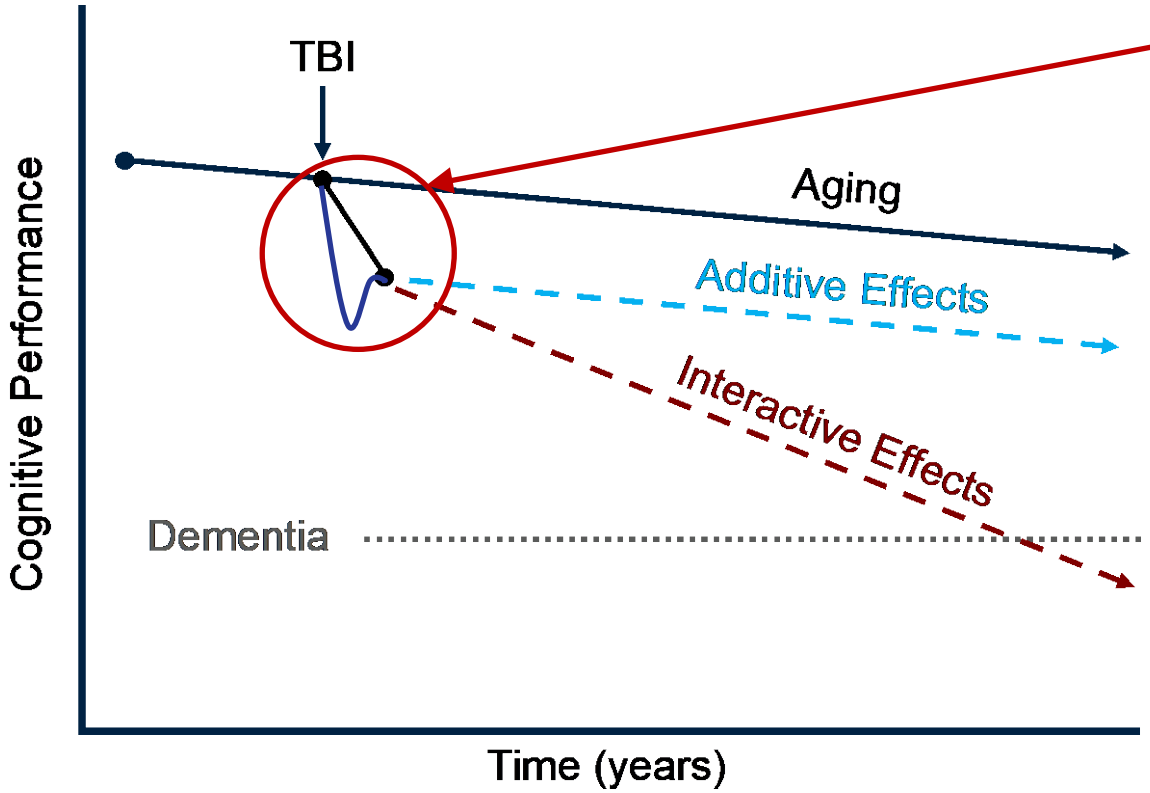
- 13.5% of TBI patients versus 4.5% of controls had a poor 1-year cognitive outcome



TRACK-TBI
Transforming Research and Clinical Knowledge in Traumatic Brain Injury
International Traumatic Brain Injury Research Initiative

Source: **Schneider ALC**, Huie JR, Boscardin WJ, Nelson L, Barber JK, Yaffe K, Diaz-Arrastia R, Ferguson AR, Kramer J, Jain S, Temkin N, Yuh E, Manley GT, Gardner RC. Cognitive Outcome One Year After Mild Traumatic Brain Injury: Results from the TRACK-TBI Study. *Neurology*. 2022 Mar 22;98(12):e1248-e1261.

Cognitive Trajectories After Traumatic Brain Injury (3)



Early Post-TBI Time-Period

- Characterized by heterogeneity with a subset of individuals experiencing a period of post-injury cognitive recovery followed by post-recovery cognitive decline

Source: Adapted from: Cole JH, Leech R, Sharp DJ. Prediction of Brain Age Suggests Accelerated Atrophy after Traumatic Brain Injury. *Annals of Neurology.* 2015;77 (4):571-581.

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- Traumatic Brain Injury (TBI): Associations with Long-Term Outcomes
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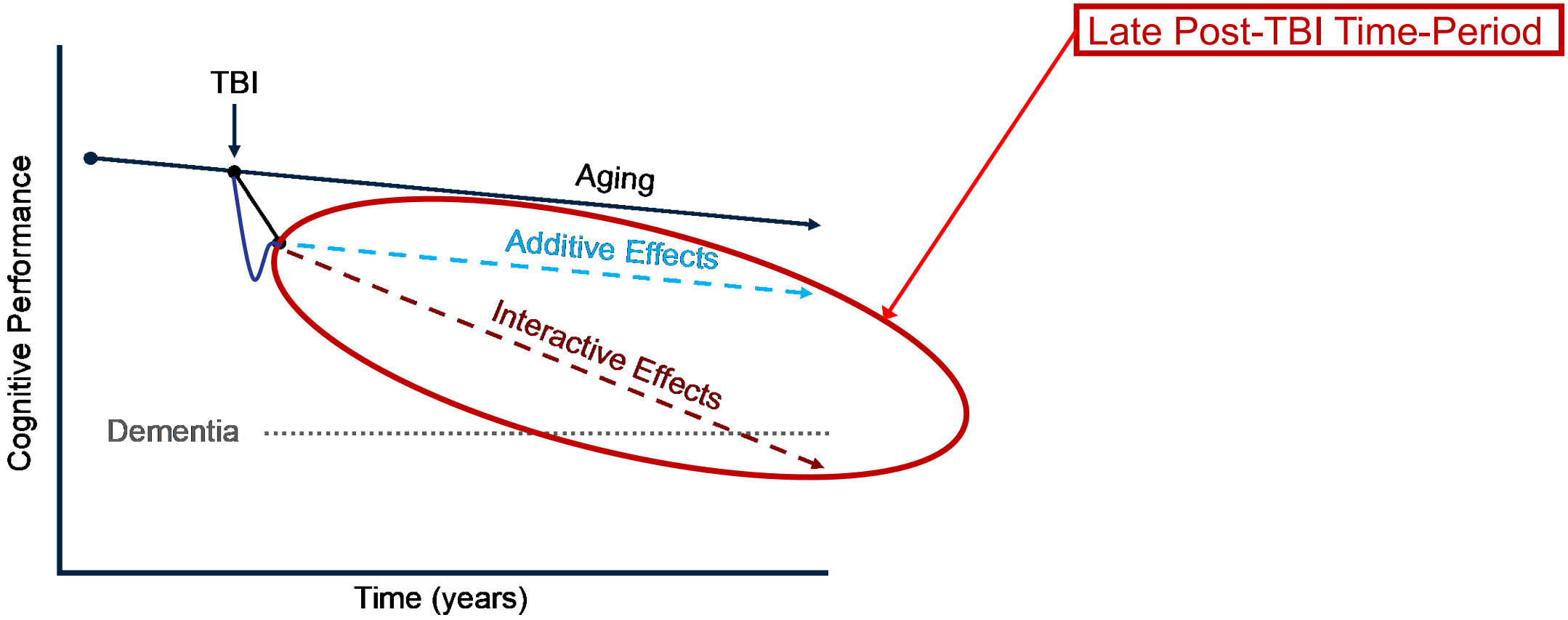
- Cognitive Trajectories and Dementia Risk in the Late Post-TBI Time-Period
- Biomarkers and Associations of TBI with Dementia Risk: Insights into Disease Mechanism

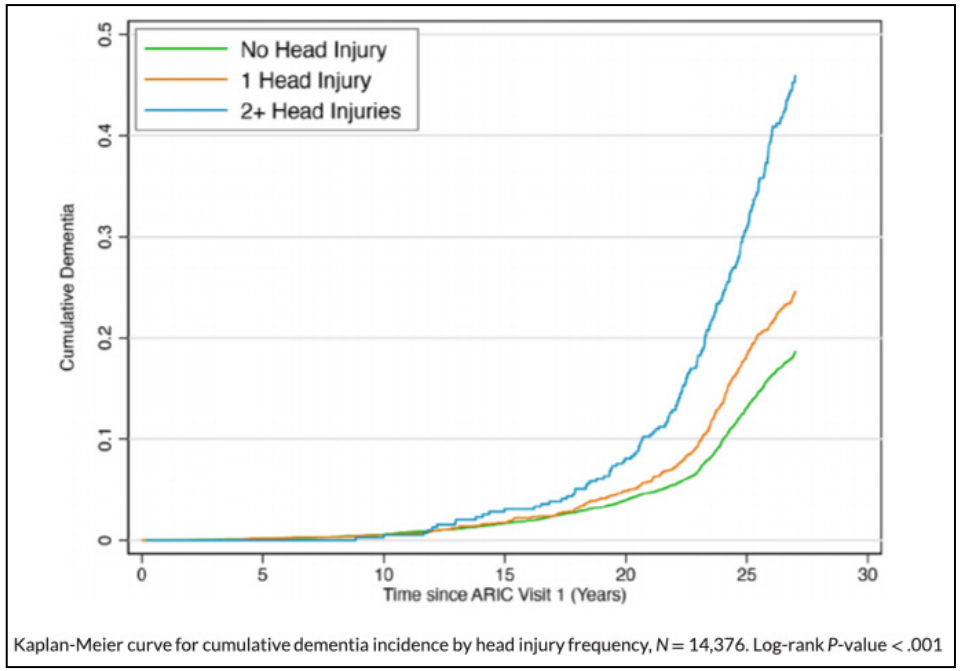
Cognitive Trajectories After Traumatic Brain Injury (4)



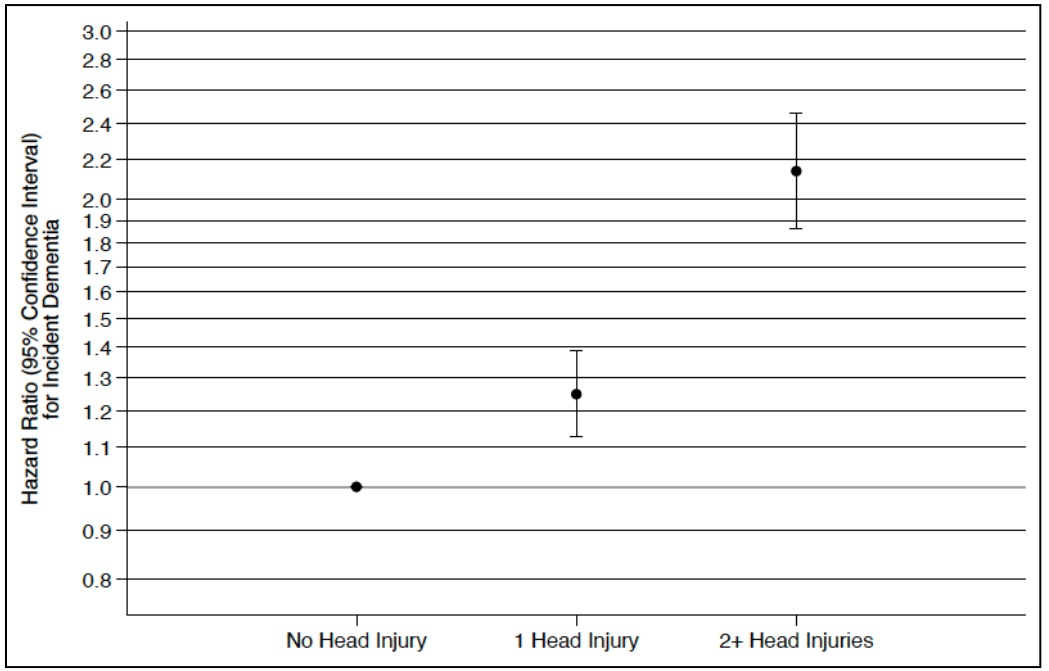
Source: Adapted from: Cole JH, Leech R, Sharp DJ. Prediction of Brain Age Suggests Accelerated Atrophy after Traumatic Brain Injury. *Annals of Neurology.* 2015;77 (4):571-581.

TBI and Dementia Risk

- TBI was associated with 1.4 times the risk of dementia over a median of 25 years of follow-up among 14,376 ARIC study participants (24% with TBI)



Kaplan-Meier curve for cumulative dementia incidence by head injury frequency, $N = 14,376$. Log-rank P-value < .001

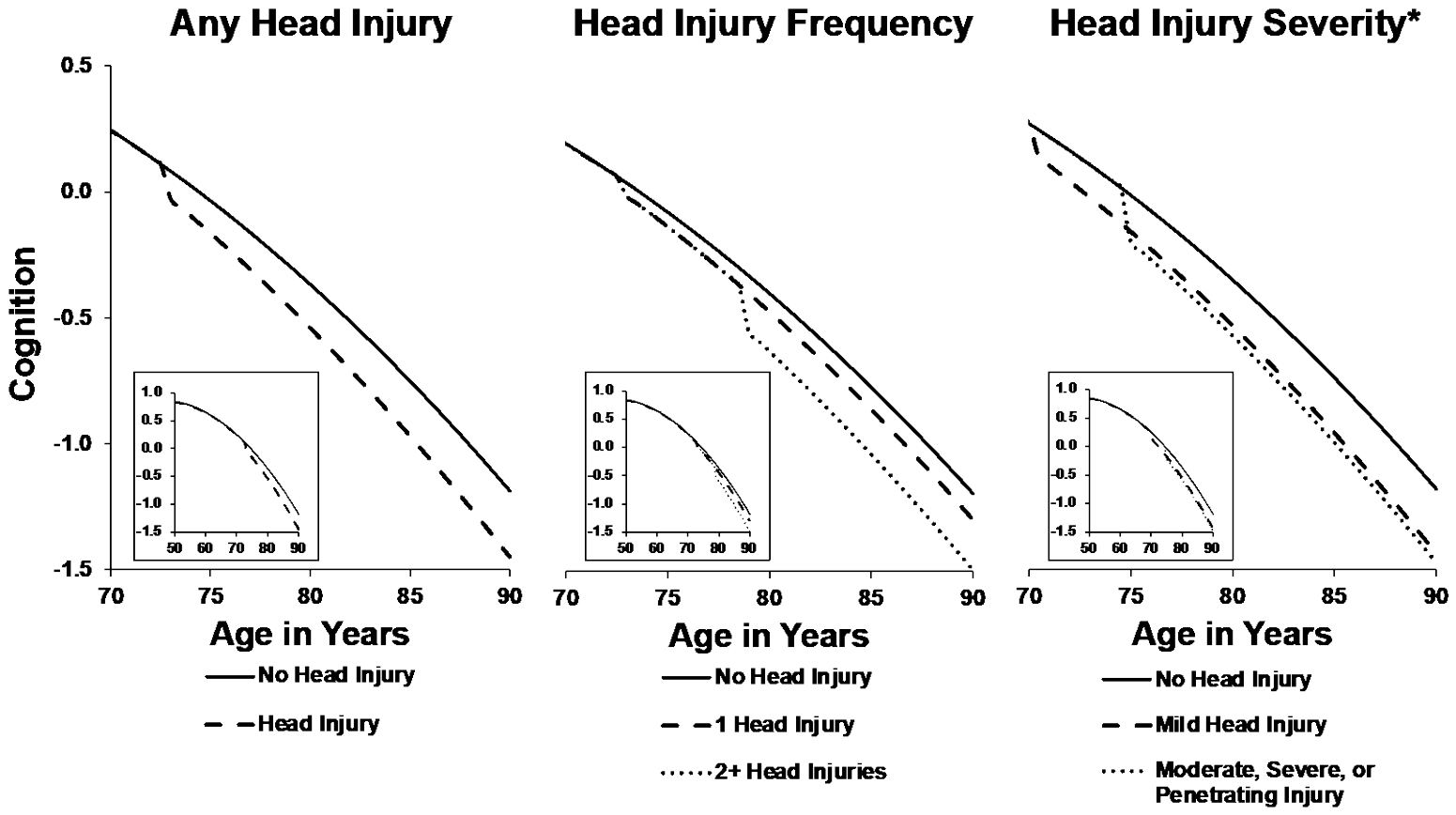


ARIC

Source: **Schneider ALC**, Selvin E, Latour L, Turtzo LC, Coresh J, Mosley T, Ling G, Gottesman RF. Head Injury and 25-Year Risk of Dementia. *Alzheimer's and Dementia.* 2021 Sep;17(9):1432-1441.

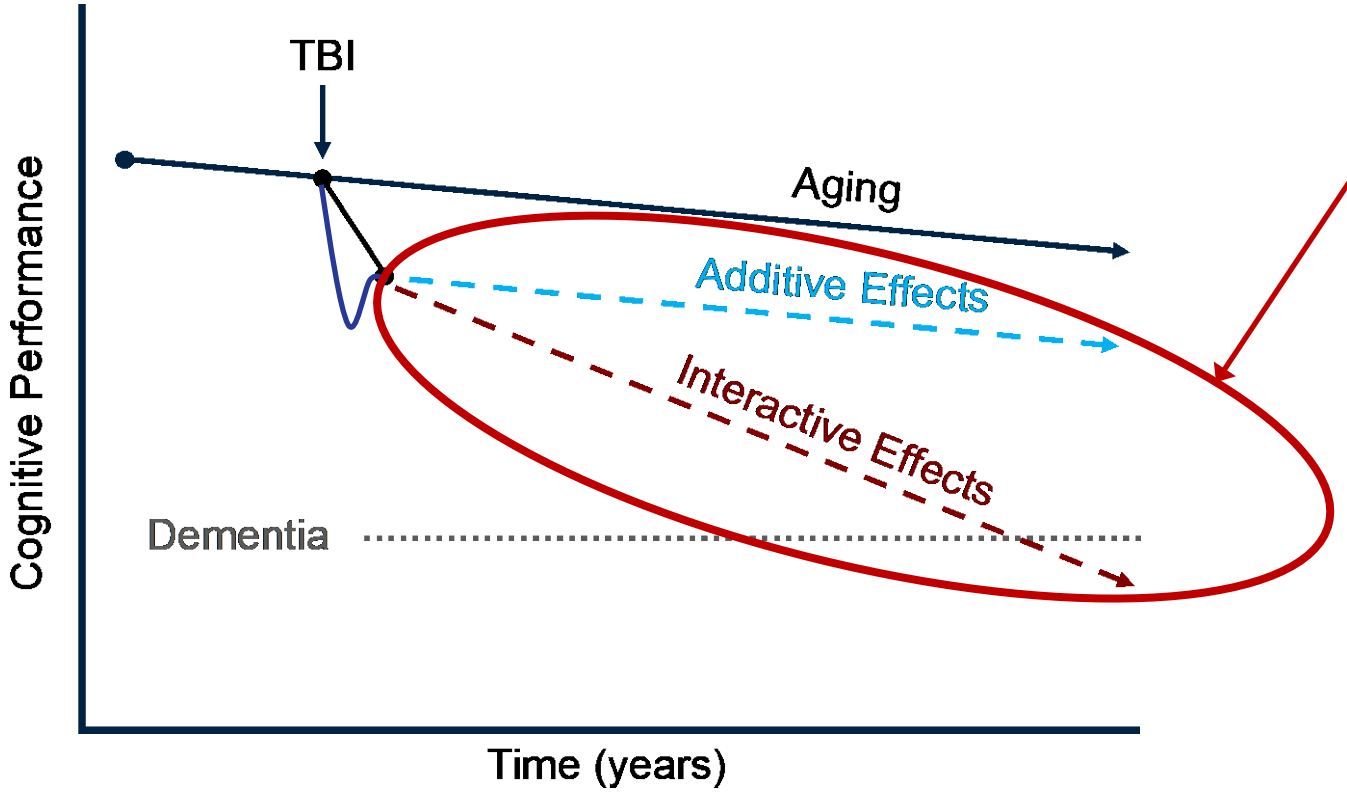
Traumatic Brain Injury and 30-Year Cognitive Decline

- Over 30-years, the difference in cognitive decline between individuals with versus without TBI is equivalent to individuals with TBI being 7.4 years older at baseline



Source: **Schneider ALC** et al. Manuscript Under Review.

Cognitive Trajectories After Traumatic Brain Injury (5)



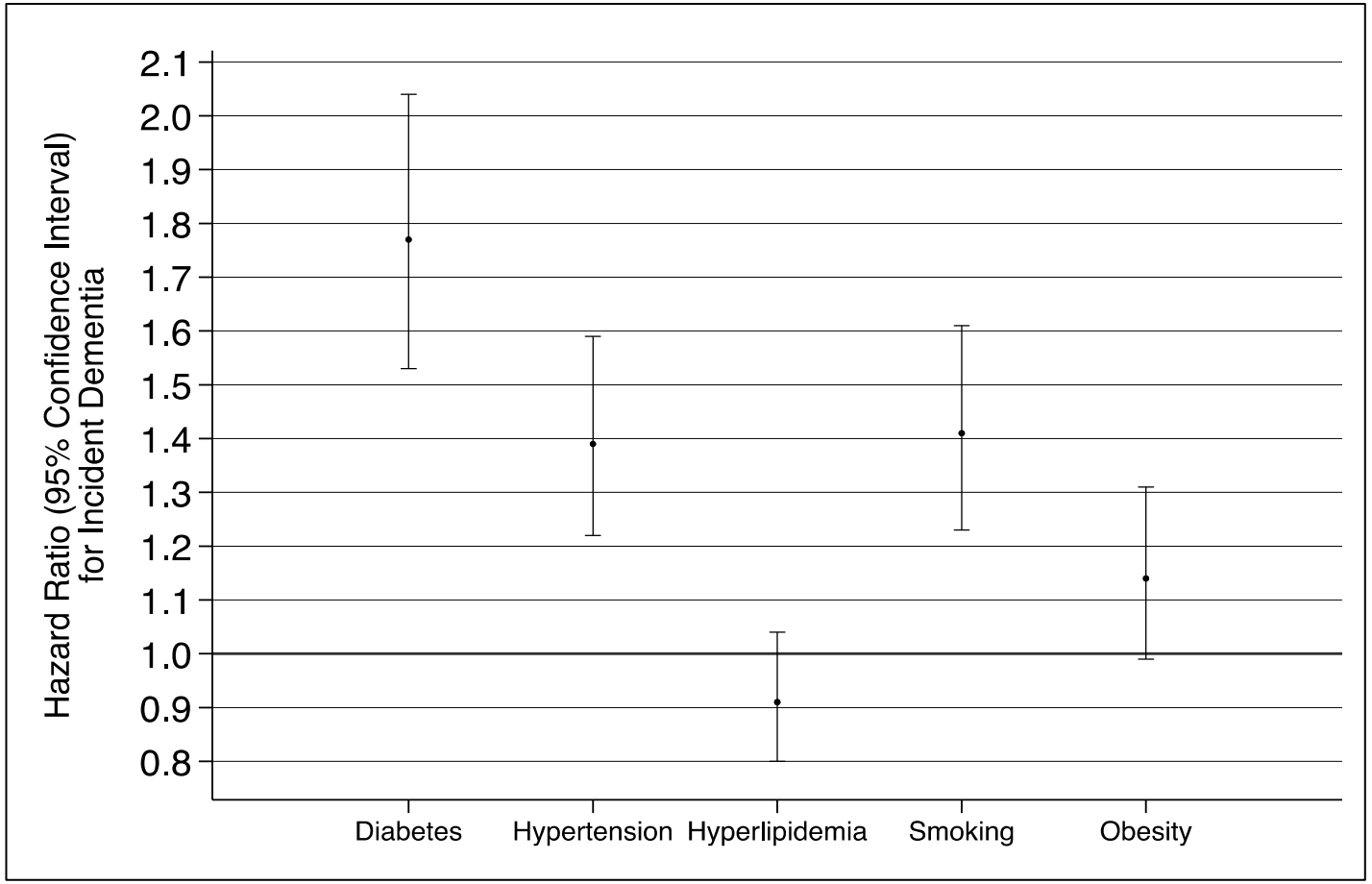
Late Post-TBI Time-Period

- Characterized by an accelerated rate of cognitive decline over time

Source: Adapted from: Cole JH, Leech R, Sharp DJ. Prediction of Brain Age Suggests Accelerated Atrophy after Traumatic Brain Injury. *Annals of Neurology.* 2015;77 (4):571-581.

Vascular Risk Factors and Dementia Risk

- Among 15,744 participants aged 45-64 years at baseline (55% female, 27% black), diabetes, hypertension, and smoking were significantly associated with increased dementia risk over a median 25-years of follow-up.



- Adapted from: Gottesman RF, Albert MS, Alonso A, Coker LH, Coresh J, Davis SM, Deal JA, McKhann GM, Mosley TH, Sharrett AR, **Schneider ALC**, Windham BG, Wruck LM, Knopman DS. Associations Between Midlife Vascular Risk Factors and 25-Year Incident Dementia in the Atherosclerosis Risk in Communities (ARIC) Cohort. *JAMA Neurology*. 2017 Oct 1;74(10):1246-1254.

Traumatic Brain Injury, Vascular Risk Factor Comorbidities, and Dementia Risk

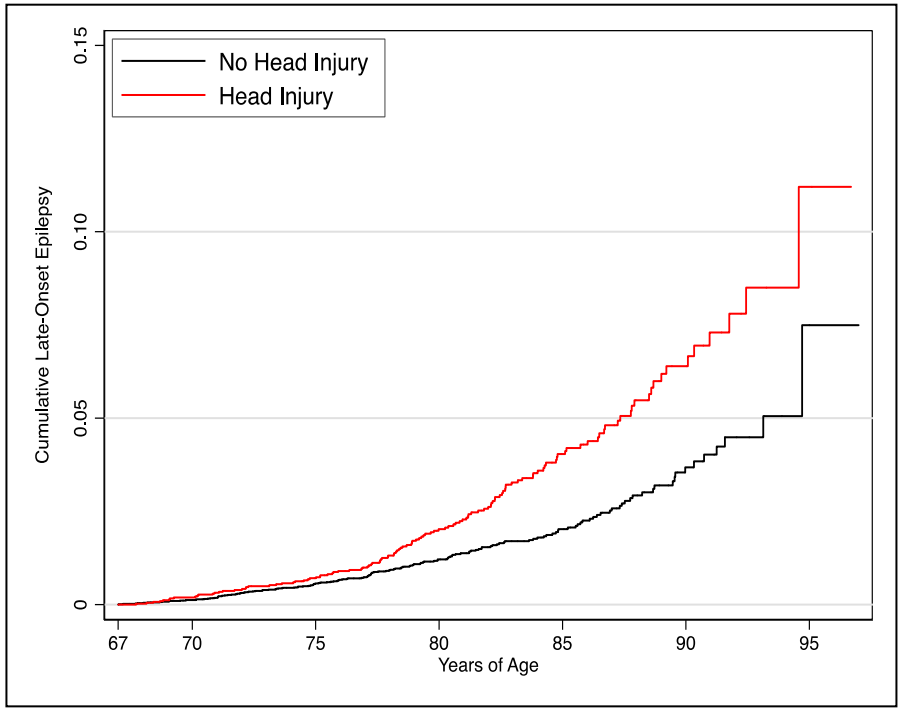
- Among 14,376 white and black ARIC study participants followed or a median of 25-years, head injury in the presence of at least 1 vascular risk factor was associated with significantly higher risk of dementia compared to no head injury and compared to head injury in the absence of any vascular risk factor comorbidities.

	Hazard Ratio (95% Confidence Interval)
No head injury	1 (Reference)
Head injury and no vascular risk factors*	1.20 (1.03-1.41)
Head injury and 1+ vascular risk factors*	1.62 (1.47-1.79)

*Vascular risk factors: diabetes, hypertension, smoking

Post-traumatic Epilepsy

- Among 8,878 participants (aged 67+ years, 30% with prior TBI), TBI was associated with 1.9 times the risk of epilepsy over a median of 11 years



	Hazard Ratio (95% Confidence Interval)
Any TBI	1.9 (1.4-2.4)
Number of TBIs	
0 TBIs	1 (Reference)
1 TBI	1.4 (1.0-1.9)
2+ TBIs	3.6 (2.5-5.0)
TBI Severity	
No TBIs	1 (Reference)
Mild TBI	1.6 (1.2-2.2)
Moderate/severe TBI	3.4 (2.2-5.3)

ARIC

Source: **Schneider ALC**, Gottesman RF, Krauss GL, Gugger J, Diaz-Arrastia R, Kucharska-Newton A, Huang J, Johnson EL. Association of Head Injury with Late-Onset Epilepsy: Results from the Atherosclerosis Risk in Communities (ARIC) Cohort. *Neurology*. 2022 Feb 22;98(8):e808-e817.

Post-traumatic Epilepsy and Dementia Risk

- Over a median of 25-years of follow-up of 12,558 individuals, post-traumatic epilepsy was associated with greater dementia risk than TBI or epilepsy alone

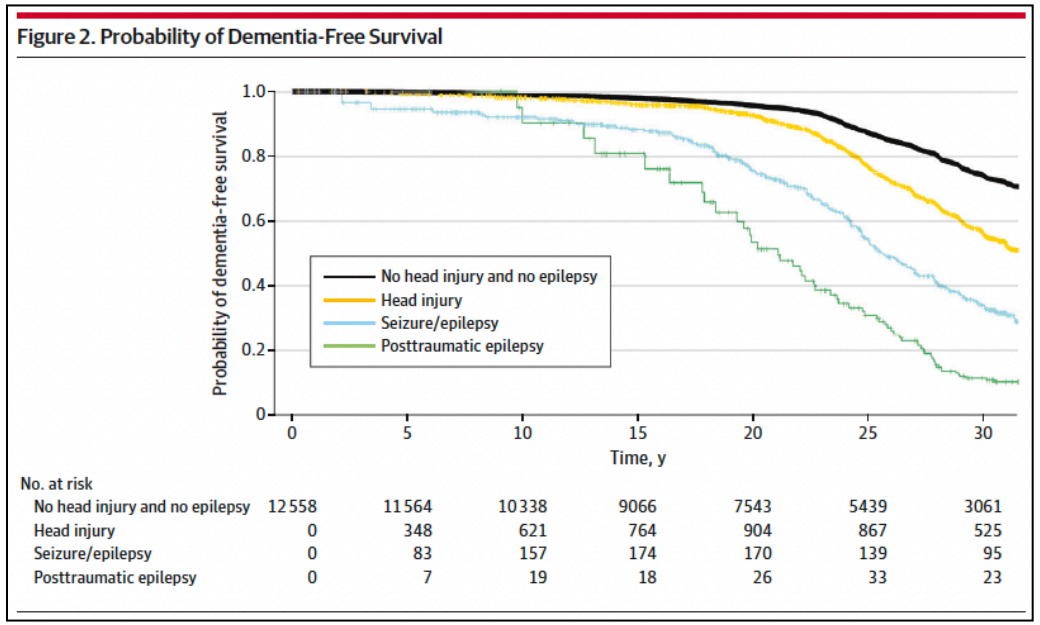


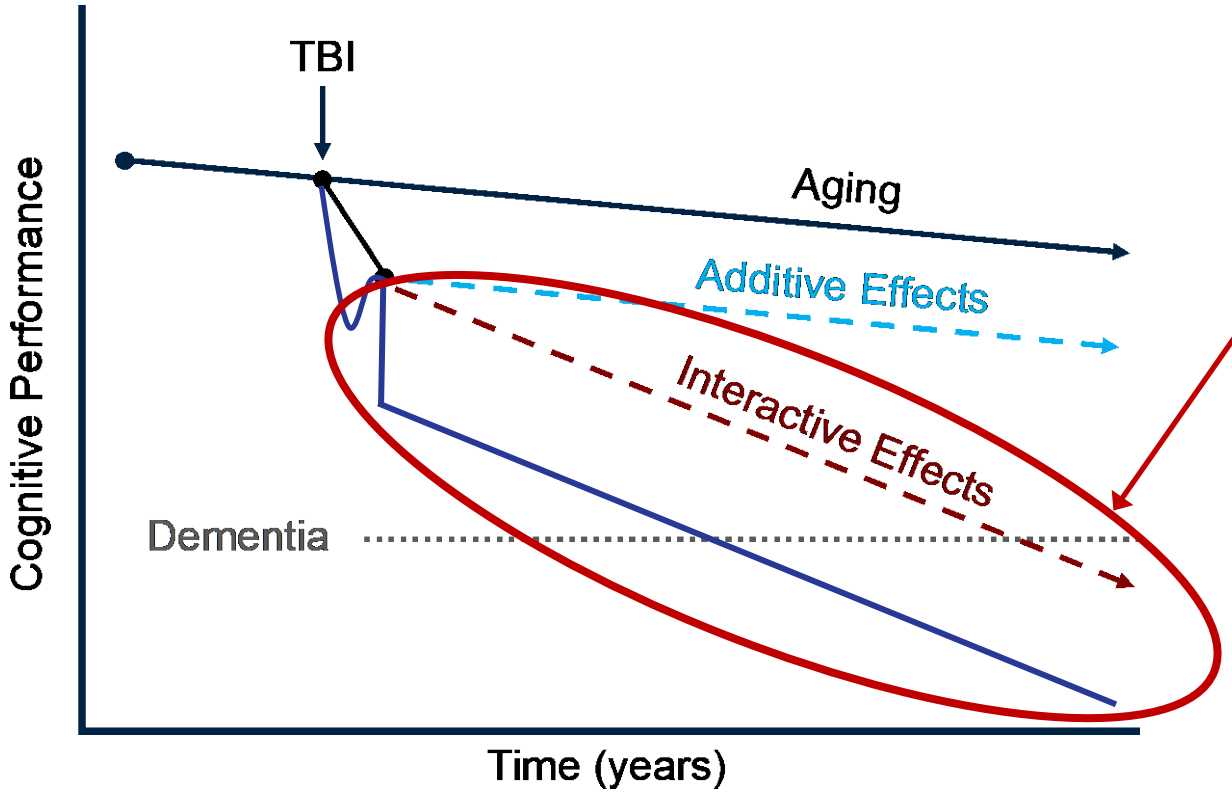
Table 2. Associations of Head Injury, Seizure/Epilepsy, and Posttraumatic Epilepsy With Dementia Risk

Characteristic	No head injury and no epilepsy	Head injury	Seizure/epilepsy	Posttraumatic epilepsy
No. of dementia cases/PYs	1796/226 858	489/19 024	156/3942	57/548
Unadjusted IR per 1000 PYs (95% CI)	7.92 (7.55-8.29)	25.70 (23.48-28.09)	39.58 (33.61-46.30)	103.93 (78.72-134.66)
Cox proportional hazards models, HR (95% CI)				
Model 1[a]	1 [Reference]	1.64 (1.48-1.82)	2.81 (2.39-3.31)	4.85 (3.72 6.33)[b,c]
Model 2[d]	1 [Reference]	1.63 (1.47-1.80)	2.77 (2.35-3.26)	4.78 (3.66-6.25)[b,c]
Model 3[e]	1 [Reference]	1.63 (1.47-1.80)	2.61 (2.21-3.07)	4.56 (3.49-5.95)[b,c]
Fine-Gray proportional hazards models accounting for competing risk of death, HR (95% CI)				
Model 1[a]	1 [Reference]	1.70 (1.55-1.86)	1.62 (1.40-1.88)	3.04 (2.42-3.81)[b,c]
Model 2[d]	1 [Reference]	1.69 (1.54-1.85)	1.66 (1.43-1.93)	3.04 (2.42-3.83)[b,c]
Model 3[e]	1 [Reference]	1.71 (1.56-1.87)	1.61 (1.38-1.87)	3.00 (2.38-3.76)[b,c]

ARIC

Source: **Schneider ALC**, Law CA, Gottesman RF, Krauss G, Huang J, Kucharska-Newton A, Jensen FE, Gugger JJ, Diaz-Arrastia R, Johnson EL. Post-traumatic Epilepsy and Dementia Risk. *JAMA Neurology*. 2024 Feb 26;81(4):346-53.

Cognitive Trajectories After Traumatic Brain Injury (6)



Late Post-TBI Time-Period

- Characterized by an accelerated rate of cognitive decline over time that is influenced in an additive manner by comorbidities

Source: Adapted from: Cole JH, Leech R, Sharp DJ. Prediction of Brain Age Suggests Accelerated Atrophy after Traumatic Brain Injury. *Annals of Neurology.* 2015;77 (4):571-581.

Outline

- Traumatic Brain Injury (TBI): Associations with Long-Term Outcomes
- Cognitive Trajectories and Cognitive Outcomes in the Early Post-TBI Time-Period
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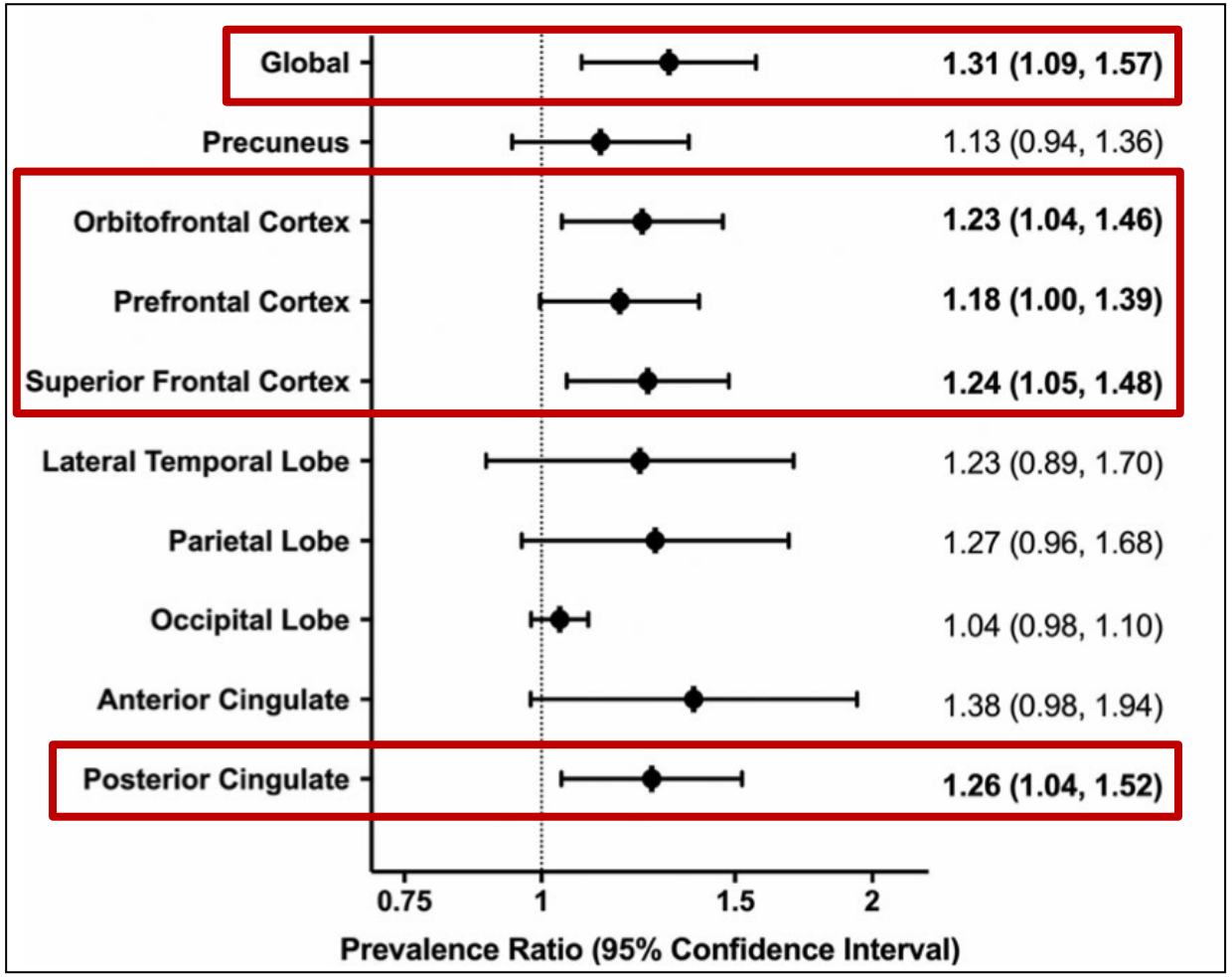
Traumatic Brain Injury and Brain Amyloid Deposition

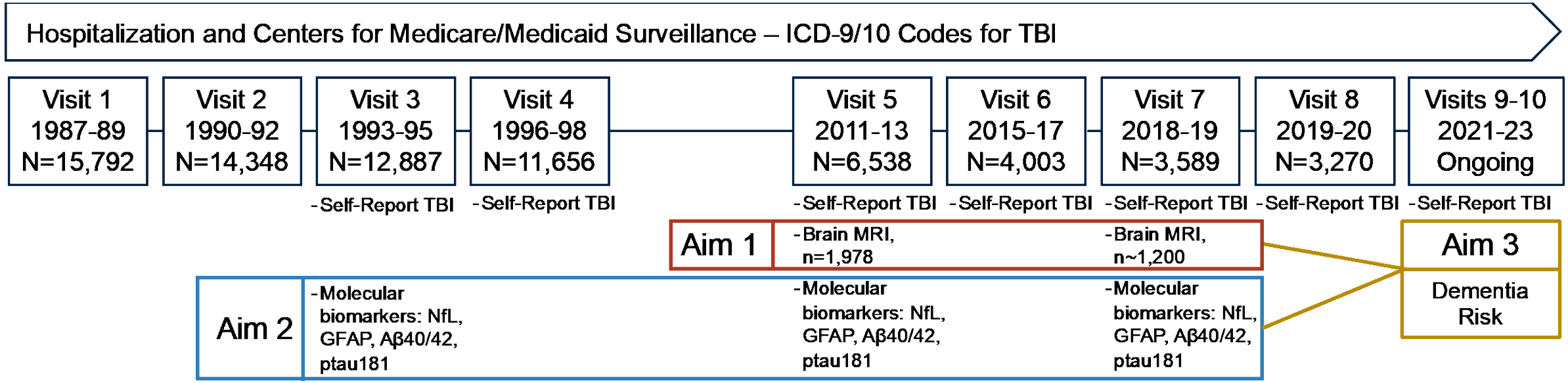


- Cross-sectional analysis of 329 individuals without dementia (24.6% with prior TBI)
- Brain amyloid deposition assessed using Florbetapir (18^{F}) PET imaging
- Number of TBIs was associated with elevated brain amyloid deposition in a dose-dependent manner globally, and in the orbitofrontal, prefrontal, and superior frontal cortices

ARIC

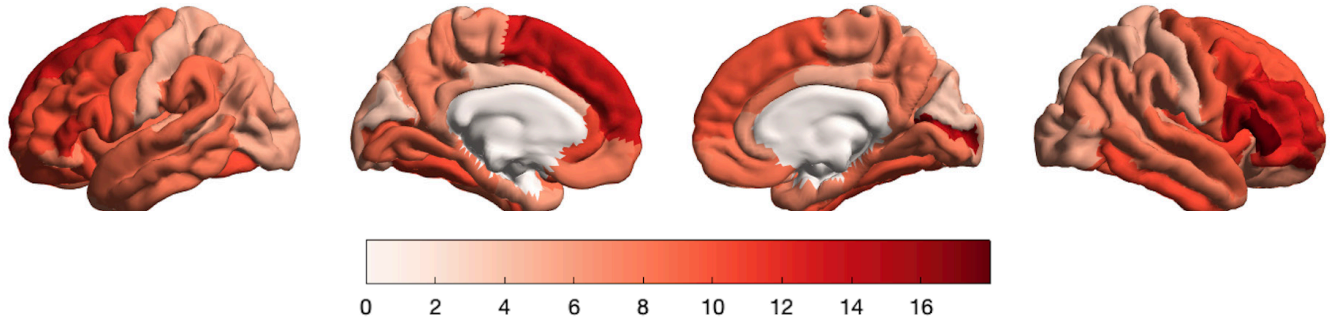
Source: **Schneider ALC**, Selvin E, Liang M, Latour L, Turtzo LC, Koton S, Coresh J, Mosley T, Whitlow CT, Zhou Z, Wong DF, Ling G, Gottesman RF. Association of Head Injury with Brain Amyloid Deposition: The ARIC-PET Study. *J Neurotrauma*. 2019 Sep1;36(17):2549-2557.

Traumatic Brain Injury, Changes in MRI and Blood-Based Biomarkers Over Time, and Dementia



Traumatic Brain Injury and MRI Biomarkers

- Cross-sectional study of 1,642 participants attending ARIC Visit 5 in 2011-2013 (26% with TBI, MRI occurring a median of 38 years after first TBI)



Proportion of participants with TBI with cortical thickness region of interest z-score <-1.5

Source: Walter A … **Schneider ALC**. Manuscript in Preparation.

Traumatic Brain Injury and MRI Biomarkers

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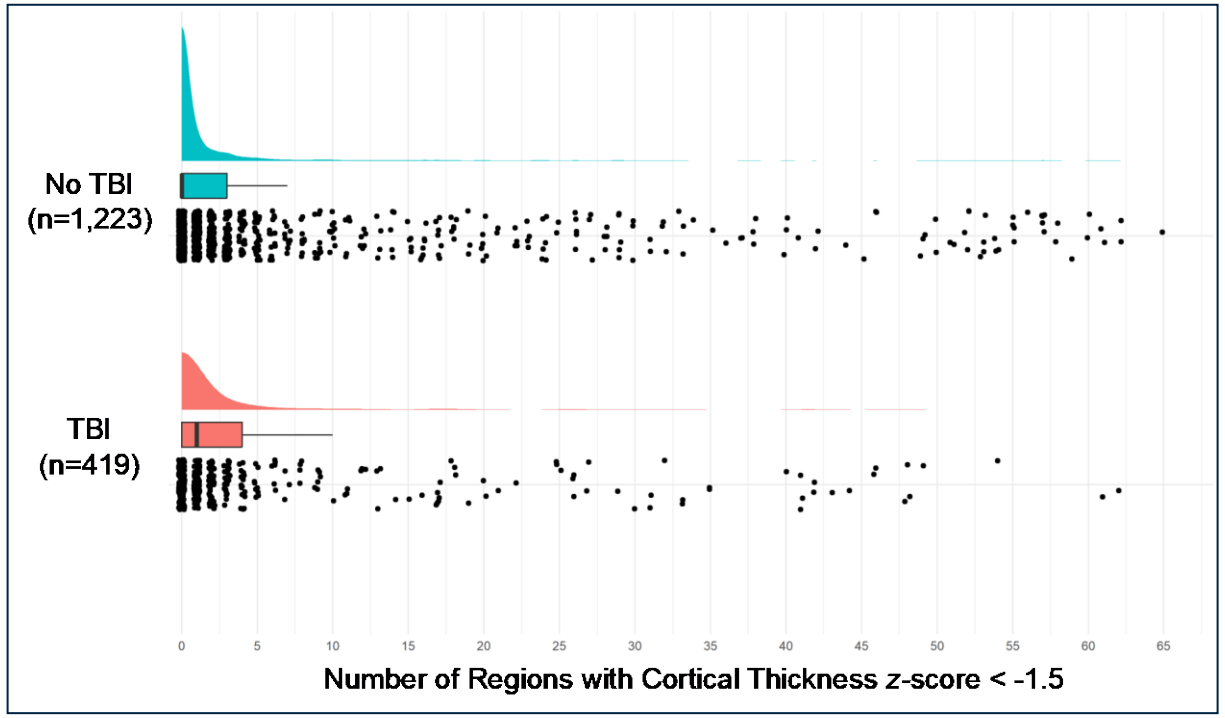
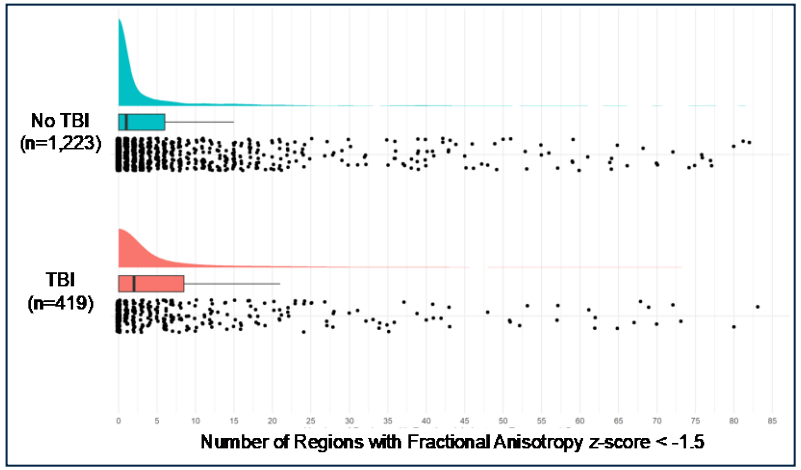
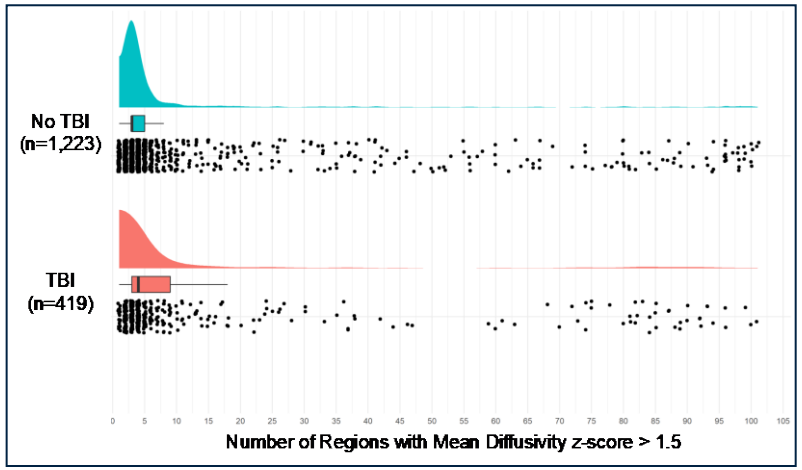


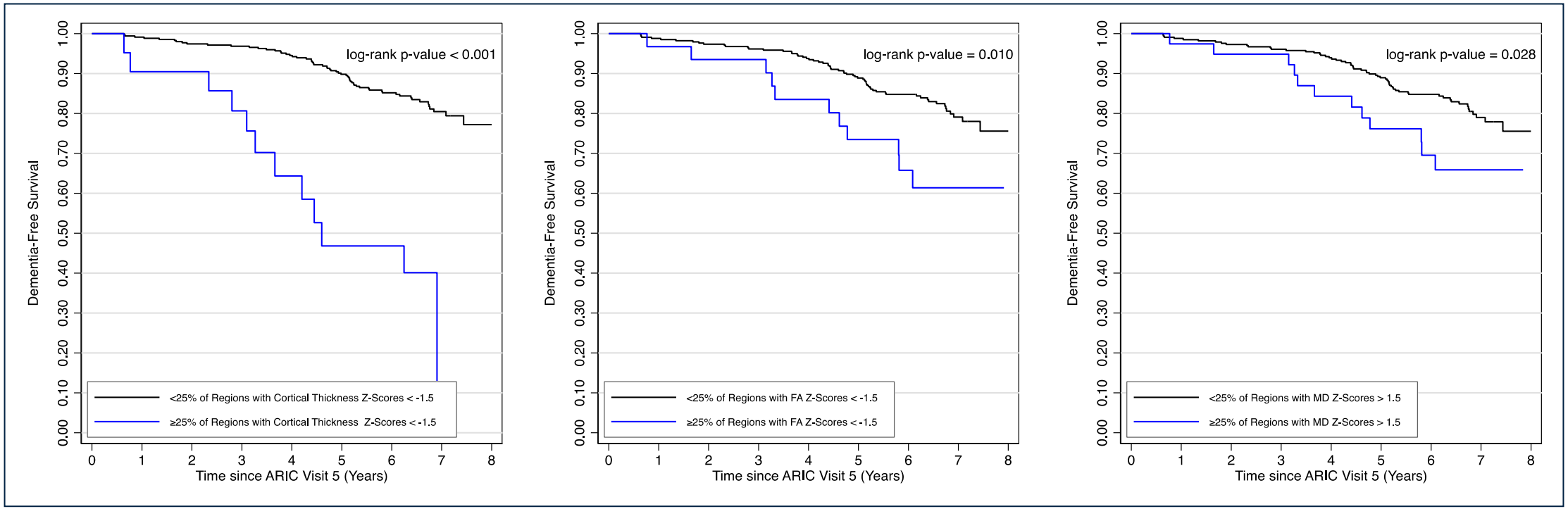




Source: Walter A ... **Schneider ALC**. Manuscript in Preparation.

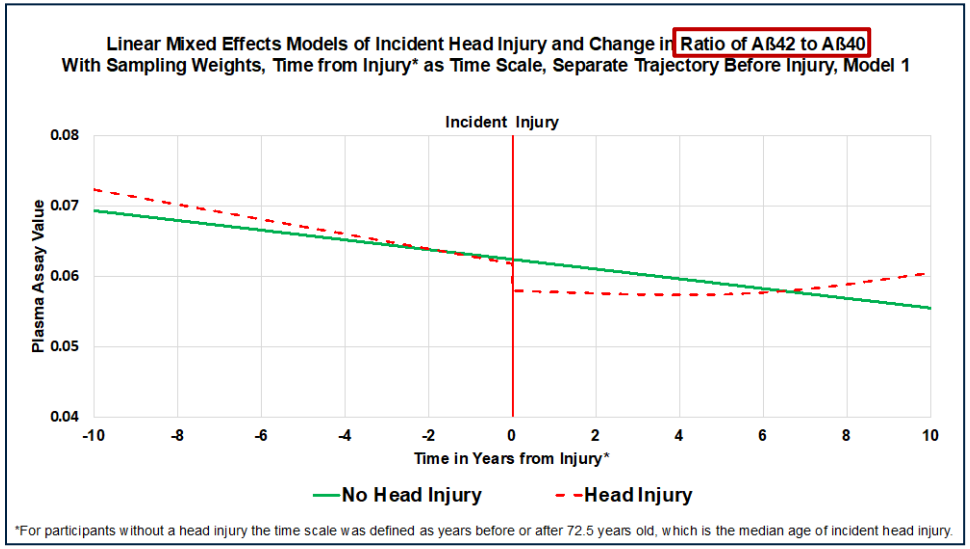
Traumatic Brain Injury, MRI Biomarkers, and Dementia

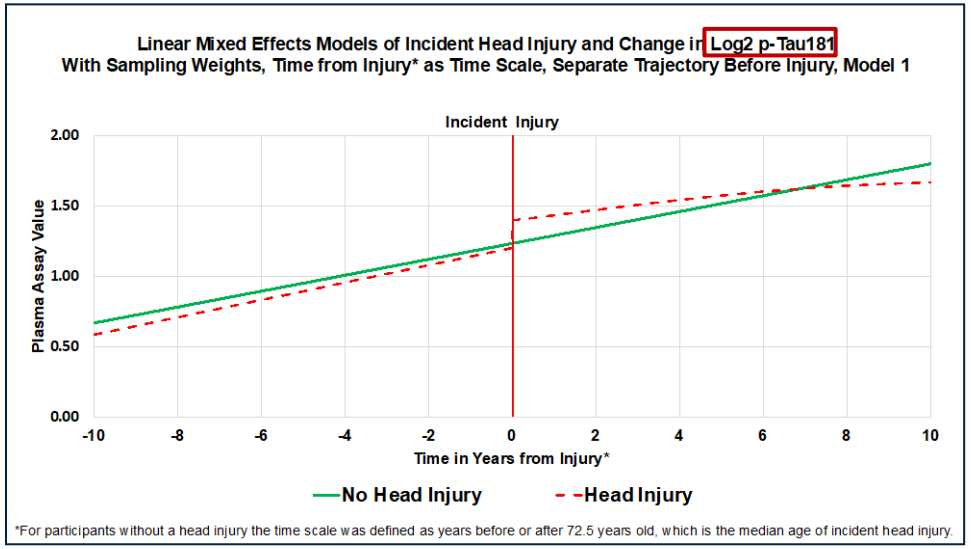
- Prospective study of participants with prior TBI who attended ARIC Visit 5 in 2011-2013 and underwent a brain MRI with follow-up of a median of 8 years

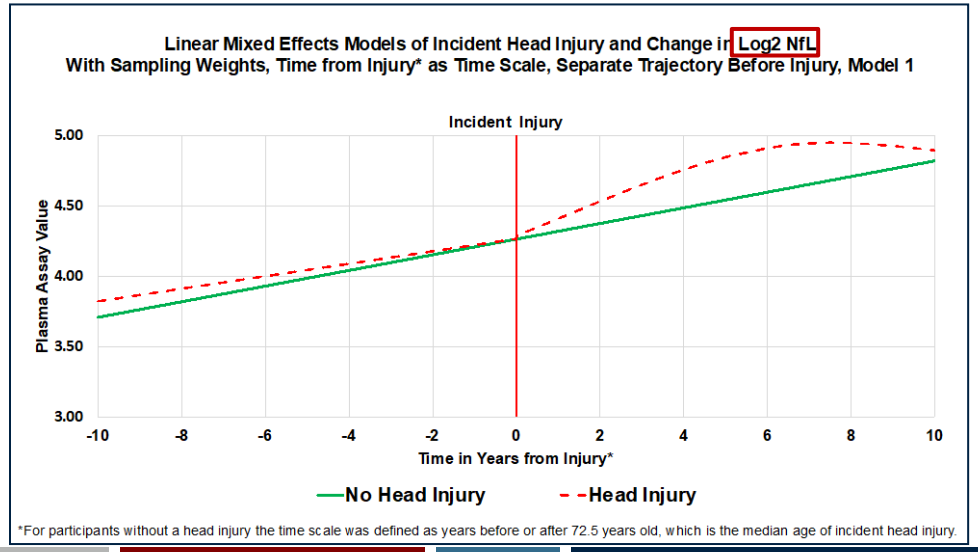


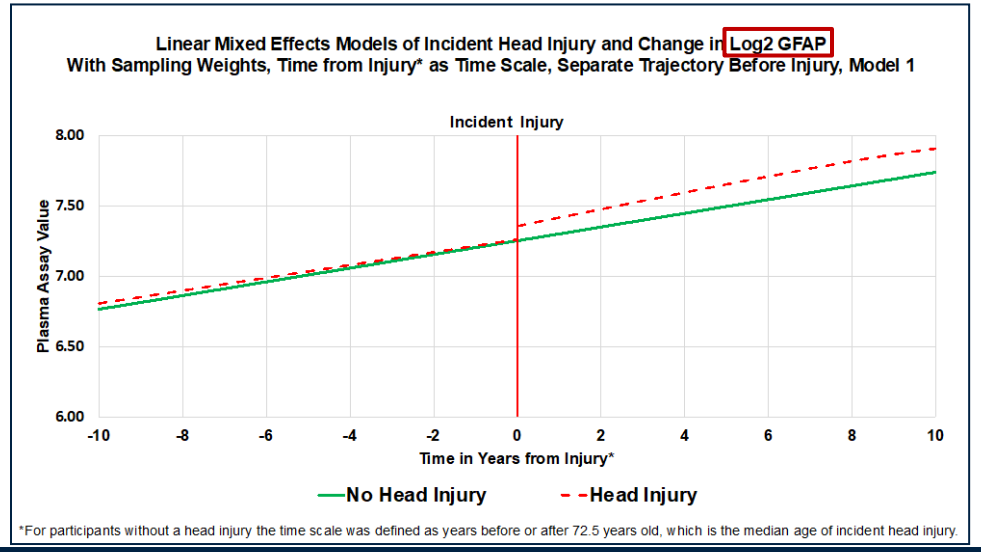
Source: Walter A ... **Schneider ALC**. Manuscript in Preparation.

Traumatic Brain Injury and Blood-Based Biomarkers





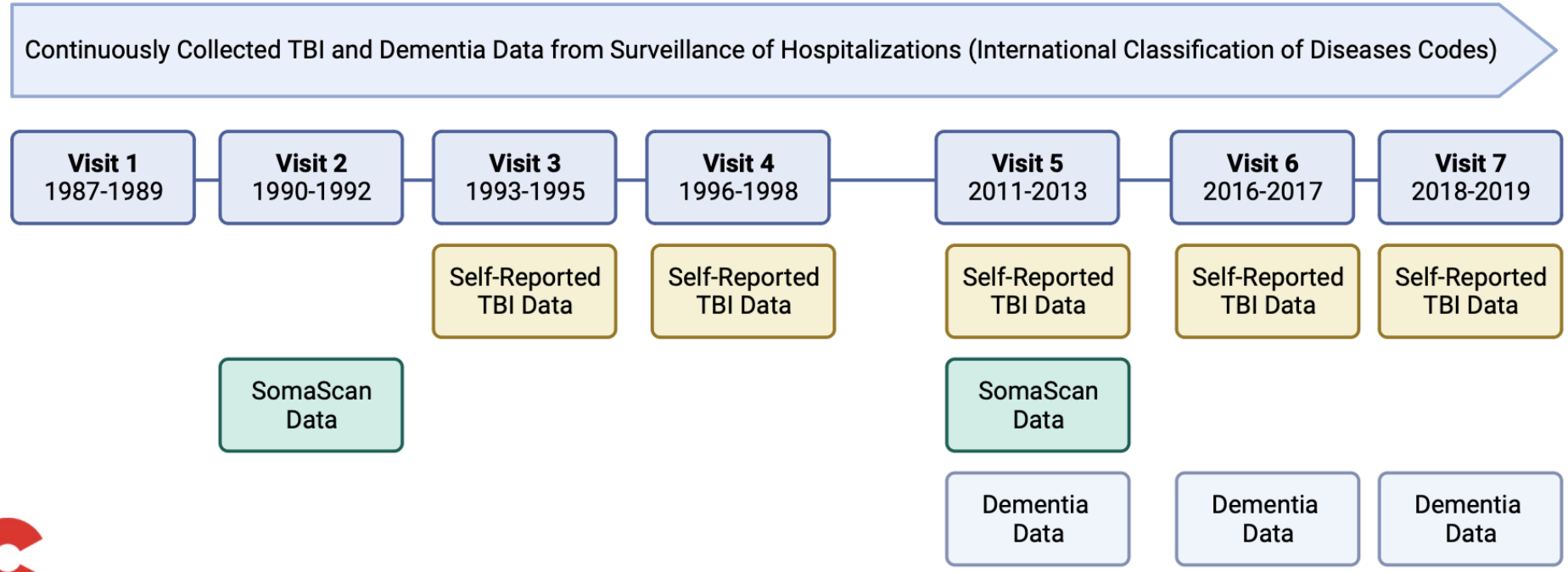




Source: Walter A ... **Schneider ALC**. Manuscript in Preparation.

Large-Scale Proteomics for Dementia Risk after TBI

- Aim: To determine if the plasma proteomic changes that occur prior to the onset of dementia are similar or different among individuals with versus without a history of TBI.
- These analyses will provide insight into if TBI accelerates ongoing neurodegenerative processes, if TBI represents a distinct neurodegenerative process, or a combination thereof.



ARIC

Conclusions

- Leveraging data from ongoing deeply phenotyped epidemiologic studies provides unique opportunities to provide nationally representative estimates of TBI burden, to study long-term outcomes of TBI, and to gain insights into disease mechanism
- TBI is common and is associated with significant mortality and morbidity, including cognitive impairment and dementia
- Cognitive trajectories after TBI are characterized by a period of post-injury improvement followed by post-recovery decline with continued accelerated long-term decline that is influenced in an additive manner by comorbidities
- However, patterns of post-TBI cognitive trajectories are heterogenous, and future work dedicated to the early prediction of patients with poor cognitive outcomes will be important for future studies focused on disease mechanism, prevention, and treatment

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• Collaborators

- Rebecca Gottesman, MD, PhD - NIH/NINDS
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- Alexa Walter, PhD - University of Pennsylvania
- Holly Elser, MD, PhD - University of Pennsylvania
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- Nancy Temkin, PhD - University of Washington
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- **ARIC Study:** NHLBI Contracts 75N92022D00001, 75N92022D00002, 75N92022D00003, 75N92022D00004, 75N92022D00005

- **ARIC Neurocognitive Study:** NHLBI, NINDS, NIA, NIDCD U01HL096812, U01HL096814, U01HL096899, U01HL096902, and U01HL096917

- **TRACK-TBI Study:** NINDS RC2NS069409, U01NS086090, DoD W81XWH-14-0176

Thank You!

- Please reach out to me if you have any questions or are interested in collaboration!
- Email: Andrea.Schneider@pennmedicine.upenn.edu