A 'balanced' review of the CTE literature

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CCBS
Centre for Clinical Brain Sciences

Competing interests

- Given expert independent testimony in Court on a range of neuropsychiatric topics (50% pursuer 50% defender).
- No funding/ fees of >$250 from pharma in last 10 years

Competing interests

- Given exp ony in Court on a range pics (50% pursuer 50
- No funding harma in last 10 yea

Just why is football ignoring all the evidence linking head injuries with CTE and dementia?

- New research suggests a possible link between heading a ball and dementia
- West Brom's Jeff Astle died of a degenerative brain disease in 2002, aged 59
- A coroner said his illness was an 'industrial disease', a reference to his heading

By SAM PETERS FOR MAIL ON SUNDAY
PUBLISHED: 22:29, 18 February 2017 | UPDATED: 00:41, 19 February 2017

Two years ago, FA chairman Greg Dyke apologised to Jeff Astle's family after The Mail on Sunday exposed the football authorities' failure to deliver life-saving research into a possible link between head injuries and dementia.

More than 14 years ago, South Staffordshire coroner Andrew Haigh found that Astle's death in 2002 at the age of 59 had been from 'industrial disease' caused by repeatedly heading footballs.

Three years ago, the former West Bromwich Albion and England striker became the first confirmed case in Britain of an ex-professional footballer dying from chronic traumatic encephalopathy (CTE).

A Stirling University study suggests there is a link between heading in football and dementia

Last week, three months after The Mail on Sunday revealed details of a ground-

THREE of England's World Cup-winning 1966 team are suffering from Alzheimer's - raising fears their brains were damaged by heading heavy footballs

- Nobby Stiles, Martin Peters and Ray Wilson are all battling disease
- Fellow legend Jack Charlton is also suffering severe memory loss
- Fears trio may miss 50th anniversary celebrations later this year
- Neuroscientist said heading footballs may cause 'microdamage' to brain

By VICTORIA FINAN FOR MAILONLINE
PUBLISHED: 09:05, 9 April 2016 | UPDATED: 10:28, 10 April 2016

Three members of the legendary 1966 World Cup winning football team are suffering from Alzheimer's disease, it has been revealed.

Martin Peters, Nobby Stiles and Ray Wilson celebrated their win against West Germany almost 50 years ago, but are now battling the devastating illness - prompting fears their brains were damaged by heading heavy footballs.

There are now concerns the trio may miss the 50th anniversary celebrations planned for later this year.

Sorry, this episode is not currently available on BBC iPlayer Radio

Can heading a football cause dementia?

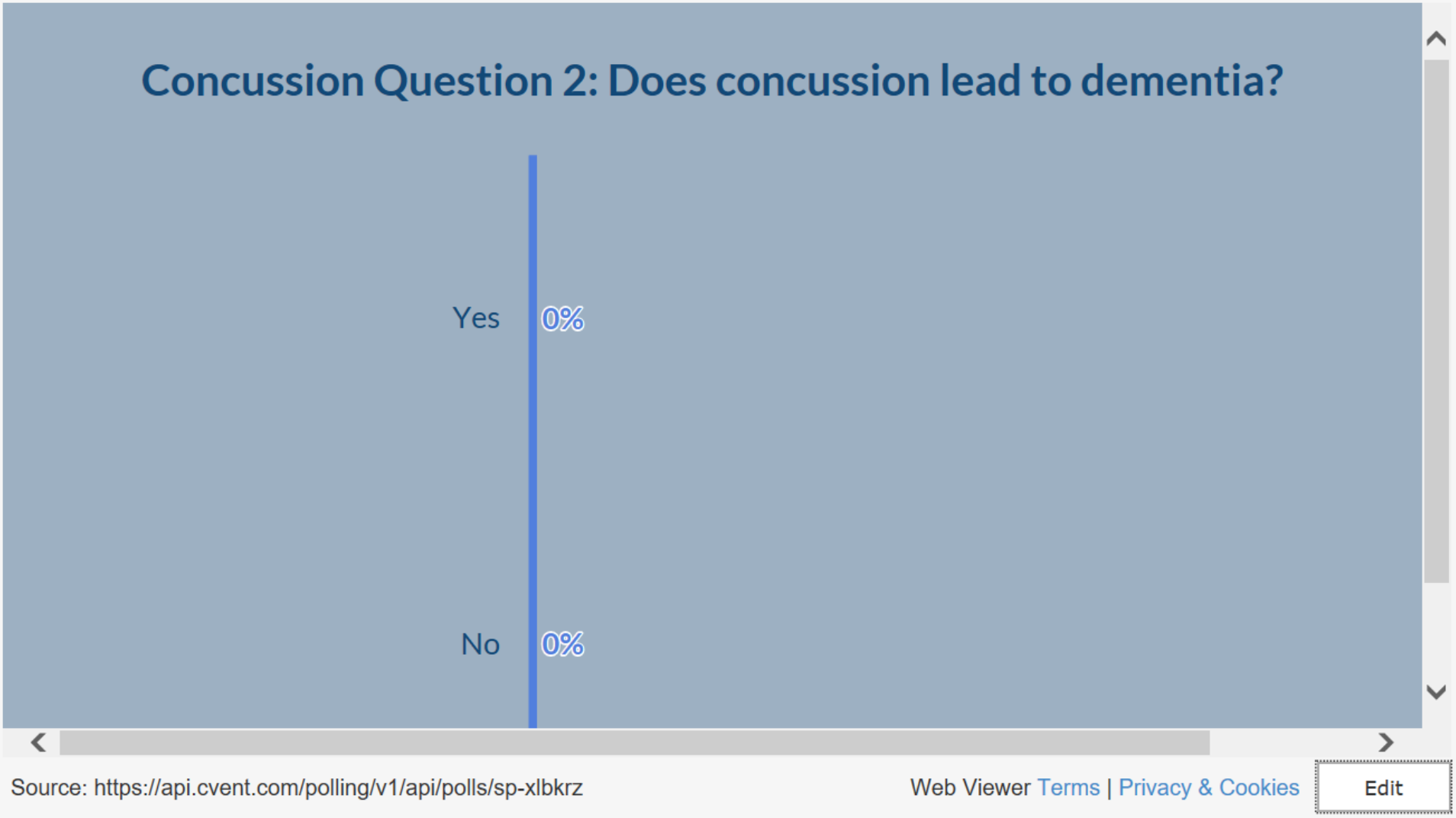
A new study shows that repeatedly heading a football can be linked to developing dementia - w
does this mean for football and other contact sports?

Dawn Astle is the daughter of the former England striker

Concussion Question 1. How dangerous is uncomplicated concussion in its own right?

Source: https://api.cvent.com/polling/v1/api/polls/sp-8rh29j

Edit



Source: https://api.cvent.com/polling/v1/api/polls/sp-xlbkrz

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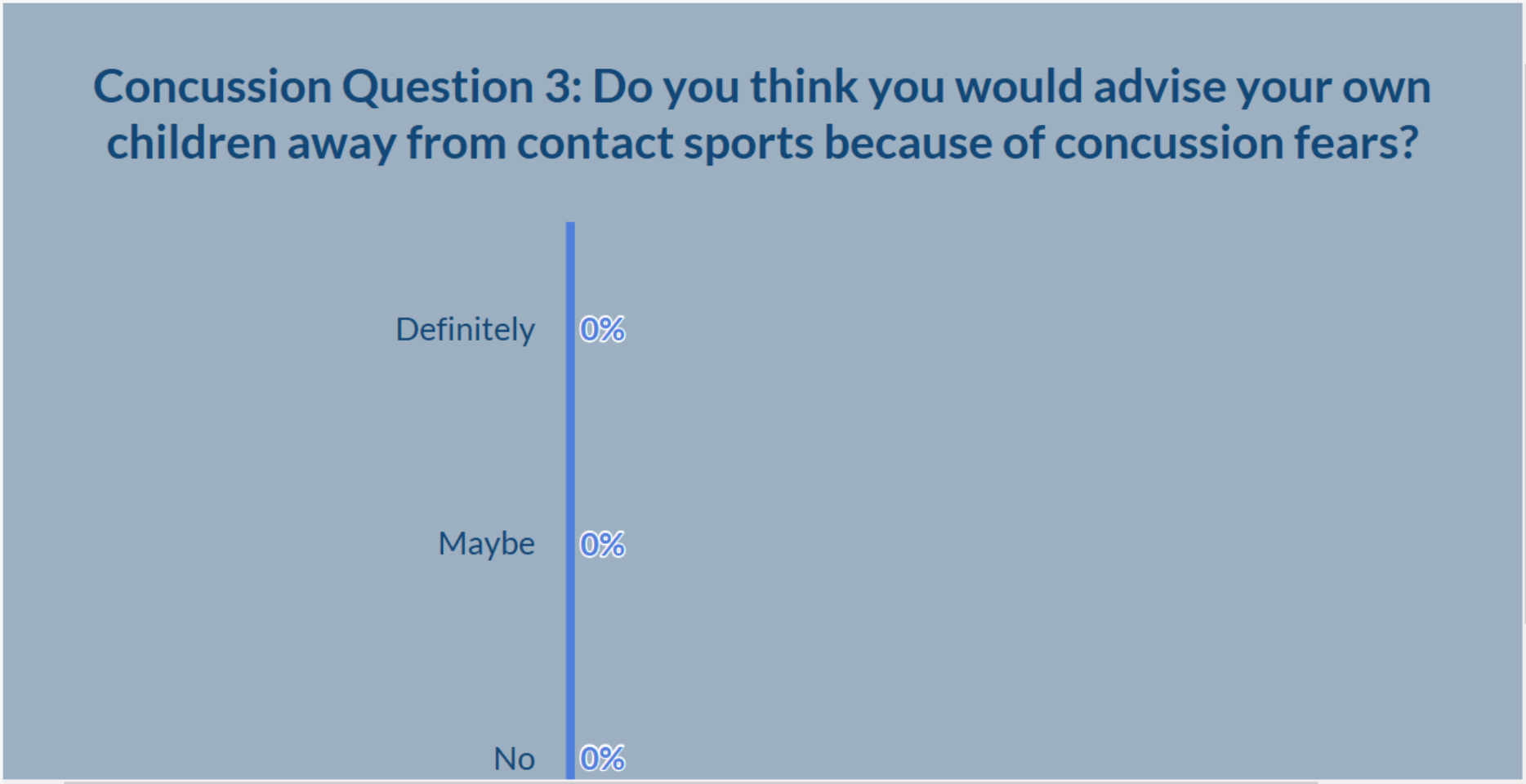
Concussion Question 3: Do you think you would advise your own children away from contact sports because of concussion fears?



Source: https://api.cvent.com/polling/v1/api/polls/sp-o8ciii

Three members of the World Cup 1966 team are now battling Alzheimer's disease - Martin Peters (far left), Ray Wilson (third left) and Nobby Stiles (third right). The team (also including Geoff Hurst, second left, George Cohen, centre, Jack Charlton, second right) often meet up for reunions. Alan Ball (far right) died in 2007.

3 out of 23

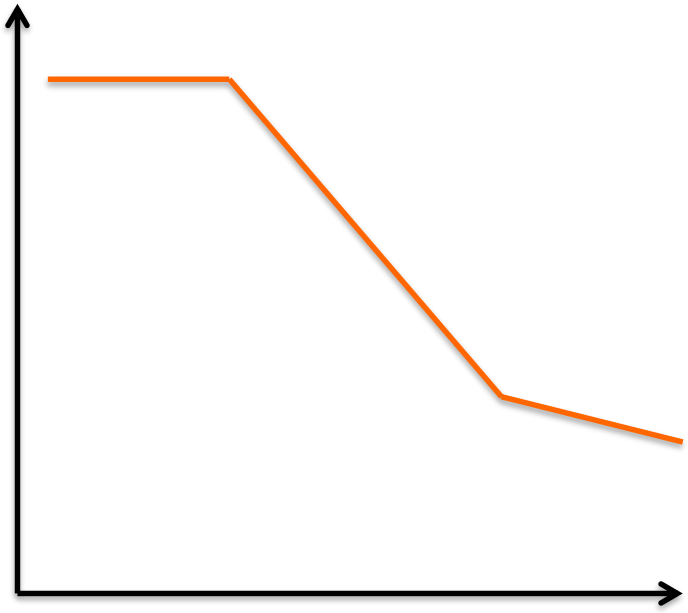
Average age = 77 (p=0.4)

Concussion

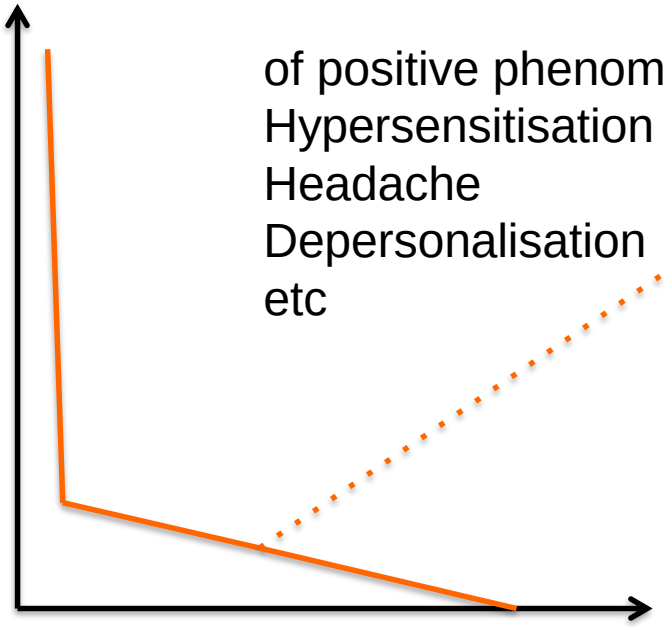
- I mean as a synonym for mild TBI
  - Duration of total LOC <30mins
  - GCS >12
  - PTA < 1 day
- Artificial categorization but vast majority of cases are at mildest end

Clinical course of brain injury

Severe injury



Mild injury



Different phenotype

of positive phenomena
Hypersensitisation
Headache
Depersonalisation
etc

“what has initially been based in physiogenic disturbance readily thereafter becomes prolonged, and nonetheless disabling, by virtue of a complex interplay of psychogenic factors.”

An epidemiological approach

- Epidemiology of CTE
- Epidemiology of mild brain injury
- Epidemiology of alzheimer's risk factors
- Confounding factors

Where does the story start?


52
52
52
52
getty images

What is CTE?

Acta Neuropathol (2016) 131:75–86
DOI 10.1007/s00401-015-1515-z

CONSENSUS PAPER

The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy

Ann C. McKee[1,2,3,4,5] · Nigel J. Cairns[6] · Dennis W. Dickson[7] · Rebecca D. Folkerth[8] · C. Dirk Keene[9] · Irene Litvan[10] · Daniel P. Perl[11] · Thor D. Stein[2,3,4,5] · Jean-Paul Vonsattel[12] · William Stewart[13] · Yorghos Tripodis[3,14] · John F. Crary[15] · Kevin F. Bieniek[7] · Kristen Dams-O'Connor[16] · Victor E. Alvarez[1,2,3,4] · Wayne A. Gordon[16] · the TBI/CTE group

Received: 15 October 2015 / Revised: 29 November 2015 / Accepted: 29 November 2015 / Published online: 14 December 2015

Table 1. Reviewer's evaluation of presumptive CTE cases

Age	Sex	Sport	SDX	COM	Reviewers Responses						
60-65	M	PBX	CTE III		CTE	CTE	CTE	CTE	CTE	CTE	CTE HS
66-70	M	PFB	CTE III		CTE	CTE	CTE	CTE	CTE	CTE HS	CTE PART AGD
66-70	M	PFB	CTE IV		CTE	CTE	CTE	CTE	CTE	CTE PART	CTE ADC HS
76-80	M	PFB	CTE IV	Aß	CTE ADC	CTE ADC	CTE ADC	CTE ADC	CTE AD	CTE AD	CTE AD
60-65	M	PFB	CTE IV	Aß	CTE	CTE	CTE ADC	CTE ADC	CTE ADC	CTE ADC	CTE AD
66-70	M	PFB	CTE IV	Aß	CTE	CTE	CTE ADC	CTE ADC	CTE ADC	CTE AD	CTE AD HS
66-70	M	PFB	CTE IV	Aß	CTE	CTE	CTE	CTE HS	CTE AGD	CTE AD	AGD
80-85	M	PFB	CTE IV	Aß	CTE	CTE ADC	CTE ADC	CTE ADC	CTE AD HS	CTE AD HS	MSA
66-70	M	PFB	CTE IV	Aß	CTE	CTE	CTE	CTE ADC HS	CTE AD HS	HS	GPDC
71-75	M	PFB	CTE IV	Aß, LBD	CTE ADC	CTE ADC	CTE AD HS	CTE AD HS	PSP	PSP	GPDC

Abbreviations: Aß Beta-amyloid plaques, AD Alzheimer's disease, ADC Changes of Alzheimer's disease, AGD Argyrophilic grain disease, COM Co-morbidities; GPDC Guamanian Parkinson's Dementia Complex, HS Hippocampal Sclerosis, LBD Lewy body disease, MSA Multiple System Atrophy, PBX Professional Boxing, PFB Professional Football, SDX Submitted Diagnosis
Red text indicates discrepancies with submission diagnosis of CTE.

AVERAGE AGE 70: %MALE= 100

J Neuropathol Exp Neurol

Vol. 68, No. 7
July 2009
pp. 709–735

REVIEW ARTICLE

Chronic Traumatic Encephalopathy in Athletes: Progressive Tauopathy After Repetitive Head Injury

Ann C. McKee, MD, Robert C. Cantu, MD, Christopher J. Nowinski, AB, E. Tessa Hedley-Whyte, MD, Brandon E. Gavett, PhD, Andrew E. Budson, MD, Veronica E. Santini, MD, Hyo-Soon Lee, MD, Caroline A. Kubilus, and Robert A. Stern, PhD

before retiring at the age of 33 years. In his late 50s, he became forgetful with mood swings and restlessness. He changed from his normally happy easy-going self to become apathetic, socially withdrawn, paranoid, irritable, and sometimes violently agitated. During the next 2 years, he began to confuse close relatives and developed increasing anxiety, aggression, and agitation; on occasion, he was verbally abusive toward his wife and tried to strike her. He required neuroleptics for control of his behavior. The following year, he had episodes of dizziness, which was suspected to be vertigo, and resulted in a hospital admission. Neurological examination found him to be disoriented, inattentive, with very poor immediate and remote memory, and impaired visuospatial skills. Neuropsychological testing showed deficits in all cognitive domains, including executive functioning, attention, language, visuospatial abilities, and profound deficits in learning and memory. Computed tomographic scan and magnetic resonance imaging (MRI) showed generalized cortical atrophy, enlargement of the cerebral ventricles, cavum septum pellucidum, and a right globus pallidus lacuna. An electroencephalogram, an MR angiogram, and a carotid ultrasound were normal. He smoked and drank alcohol occasionally until his early 50s. A first cousin developed dementia in her early 50s, and 3 uncles and 1 aunt (of 11 children) were demented.

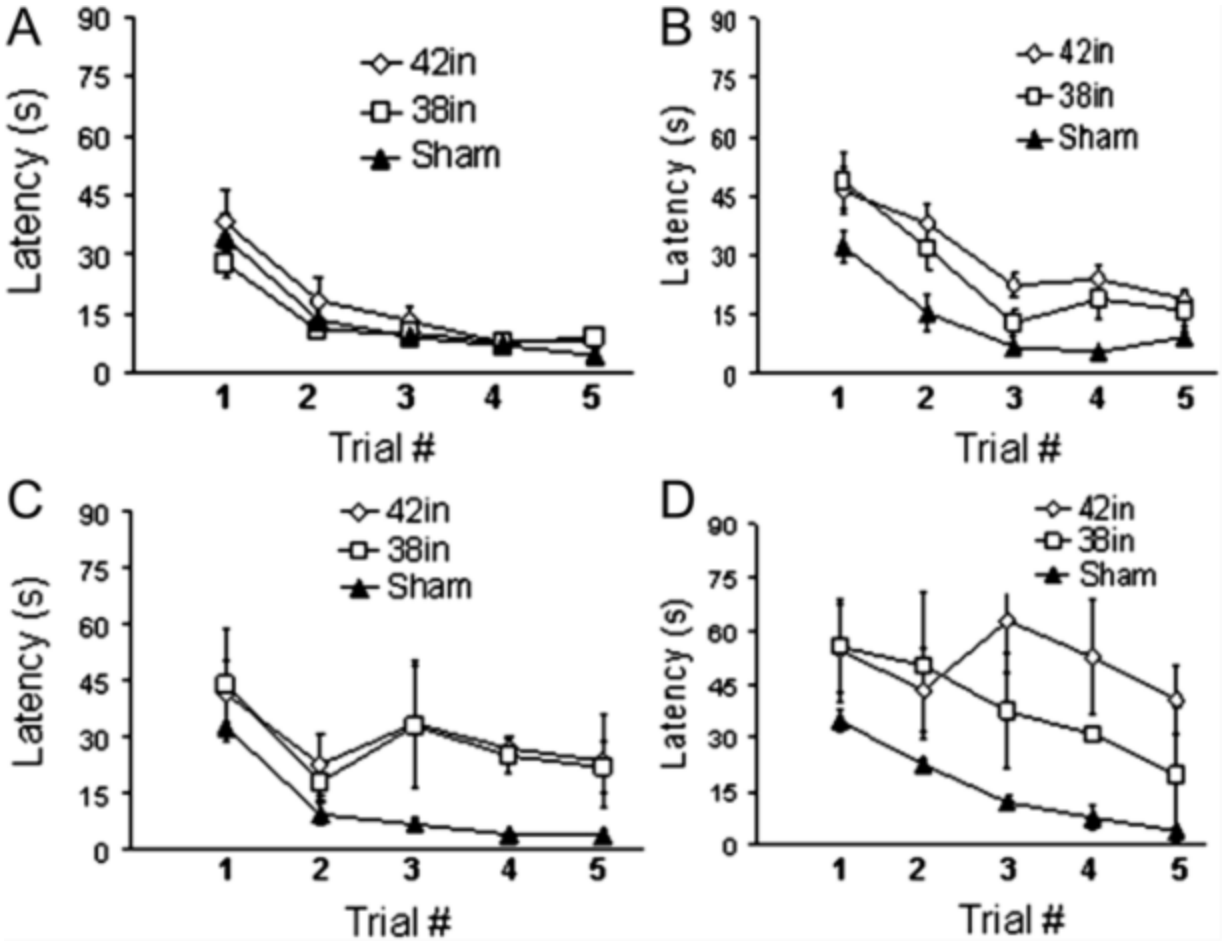
During the following 2 years, he continued to decline in all cognitive domains. He frequently fell and developed a tremor of his left hand. Repeat neuropsychological testing at age 67 years revealed further global deficits, again with prominent impairments in memory. By age 70 years, he had severe swallowing difficulties, diminished upgaze, masked facies, garbled speech, and a slow shuffling gait. Mini-Mental Status Examination several months before death was 7 out of 30. He died at the age of 73 years of complications of pneumonia.

RESEARCH—ANIMAL

Increasing Recovery Time Between Injuries Improves Cognitive Outcome After Repetitive Mild Concussive Brain Injuries in Mice

William P. Meehan III, MD*‡§¶#
Jimmy Zhang, BA§
Rebekah Mannix, MD, MPH‡§¶
Michael J. Whalen, MD§||

BACKGROUND: Although previous evidence suggests that the cognitive effects of concussions are cumulative, the effect of time interval between repeat concussions is largely unknown.
OBJECTIVE: To determine the effect of time interval between repeat concussions on the cognitive function of mice.
METHODS: We used a weight-drop model of concussion to subject anesthetized mice to 1, 3, 5, or 10 concussions, each a day apart. Additional mice were subjected to



From: Increasing Recovery Time Between Injuries Improves Cognitive Outcome After Repetitive Mild Concussive Brain Injuries in Mice

Neurosurgery. 2012;71(4):885-892. doi:10.1227/NEU.0b013e318265a439

So what evidence have we got to support the early clinical phenotype?

UNIVERSITY OF MICHIGAN
ISR 60 INSTITUTE FOR SOCIAL RESEARCH

National Football League
Player Care Foundation

Study of Retired NFL Players

Good stratified sample across US NFL retirees

1625 identified
1025 traceable- 76%
600 extra tracing needed- 47%

Table 5.2 Intermittent Explosive Disorder (IED) screener

	All US Men		NFL retirees	
IED Screener	**30-49**	**50+**	**30-49**	**50+**
Since you left football, have you ever had attacks of anger when all of a sudden you lost control and broke or smashed something worth more than a few dollars?	37.7%	29.0%	21.9%	16.9%
and hit or tried to hurt someone?	21.2%	18.4%	7.1%	9.4%
and threatened to hit or hurt someone?	26.0%	24.4%	20.0%	21.1%
At least one of the above	54.8%	47.2%	30.7%	29.3%

Table 7.1 Depression

	All US Men		NFL retirees	
Lifetime Depression Screener	**30-49**	**50+**	**30-49**	**50+**
Have you ever in your life had a period of time lasting several days or longer when				
most of the day you felt sad, empty or depressed?	44.7%	41.5%	55.9%	47.9%
most of the day you were very discouraged about how things were going in your life?	51.0%	45.5%	61.8%	45.6%
you lost interest in most things you usually enjoy like work, hobbies, and personal relationships?	36.3%	30.5%	47.9%	33.0%
most of the time you were very irritable, grumpy or in a bad mood?	38.9%	22.4%	62.6%	44.2%
All the above	20.7%	15.0%	37.6%	23.0%
At least one of the above	61.2%	58.1%	75.3%	63.3%
Major depression at current time	3.0%	3.9%	3.9%	3.6%
Major depression at some past time but not now			11.5%	10.5%
Reported diagnosis of depression			16.9%	15.6%
Any of the above			25.6%	22.9%

Table 6.5 Arthritis and pain

	All US Men		NFL retirees	
	30-49	50+	30-49	50+
Arthritis and pain				
Arthritis diagnosis	8.7%	32.0%	41.3%	62.4%
Pain lasting most of the day				
Neck	9.4%	13.6%	36.6%	34.1%
Lower back	22.5%	27.6%	55.4%	50.0%
Any joint	20.6%	37.1%	80.0%	77.6%
Migraine / headaches	9.9%	6.8%	27.2%	14.0%
Joint replacement				
Any joint			4.9%	23.2%
Right knee			1.5%	11.3%
Left knee			3.5%	12.7%
Right hip			0.5%	4.6%
Left hip			0.4%	5.0%

What about the neurodegenrative phenotype?

Neurodegenerative causes of death among retired National Football League players

Everett J. Lehman, MS
Misty J. Hein, PhD
Sherry L. Baron, MD
Christine M. Gersic

Correspondence & reprint requests to Mr. Lehman: elehman@cdc.gov

ABSTRACT

Objective: To analyze neurodegenerative causes of death, specifically Alzheimer disease (AD), Parkinson disease, and amyotrophic lateral sclerosis (ALS), among a cohort of professional football players.

Methods: This was a cohort mortality study of 3,439 National Football League players with at least 5 pension-credited playing seasons from 1959 to 1988. Vital status was ascertained through 2007. For analysis purposes, players were placed into 2 strata based on characteristics of position played: nonspeed players (linemen) and speed players (all other positions except punter/kicker). External comparisons with the US population used standardized mortality ratios (SMRs); internal comparisons between speed and nonspeed player positions used standardized rate ratios (SRRs).

Conclusions: The neurodegenerative mortality of this cohort is 3 times higher than that of the general US population; that for 2 of the major neurodegenerative subcategories, AD and ALS, is 4 times higher. These results are consistent with recent studies that suggest an increased risk of neurodegenerative disease among football players. *Neurology*® 2012;79:1970-1974

Table 2 Overall mortality, selected causes, National Football League Players Cohort (1960–2007)

	Underlying[a]		Contributing[b]	
Cause of death	No.	SMR (95% CI)	No.	SMR (95% CI)
All deaths	334	0.53 (0.48-0.59)	782	0.54 (0.51-0.58)
All cancers	85	0.58 (0.46-0.72)	122	0.63 (0.53-0.76)
All cardiovascular diseases	126	0.68 (0.56-0.81)	340	0.71 (0.64-0.79)
All neurodegenerative causes	10	2.83 (1.36-5.21)	17	3.26 (1.90-5.22)
Dementia/Alzheimer disease[c]	2	1.80 (0.22-6.50)	7	3.86 (1.55-7.95)
Amyotrophic lateral sclerosis[d]	6	4.04 (1.48-8.79)	7	4.31 (1.73-8.87)
Parkinson disease[e]	2	2.14 (0.26-7.75)	3	1.69 (0.35-4.94)
All injuries	41	0.63 (0.45-0.86)	57	0.69 (0.52-0.89)
Violence	13	0.27 (0.14-0.46)	13	0.26 (0.14-0.45)
All other causes	59	0.34 (0.26-0.43)	233	0.37 (0.33-0.42)

If football were a drug given to 3349 subjects

- Saves 177 lives
- 27 die of complications

Long-term risk of dementia among people with traumatic brain injury in Denmark: a population-based observational cohort study

Jesse R Fann, Anette Riisgaard Ribe, Henrik Schou Pedersen, Morten Fenger-Grøn, Jakob Christensen, Michael Eriksen Benros, Mogens Vestergaard

Lancet Psychiatry 2018;
5: 424–31
Published Online
April 10, 2018

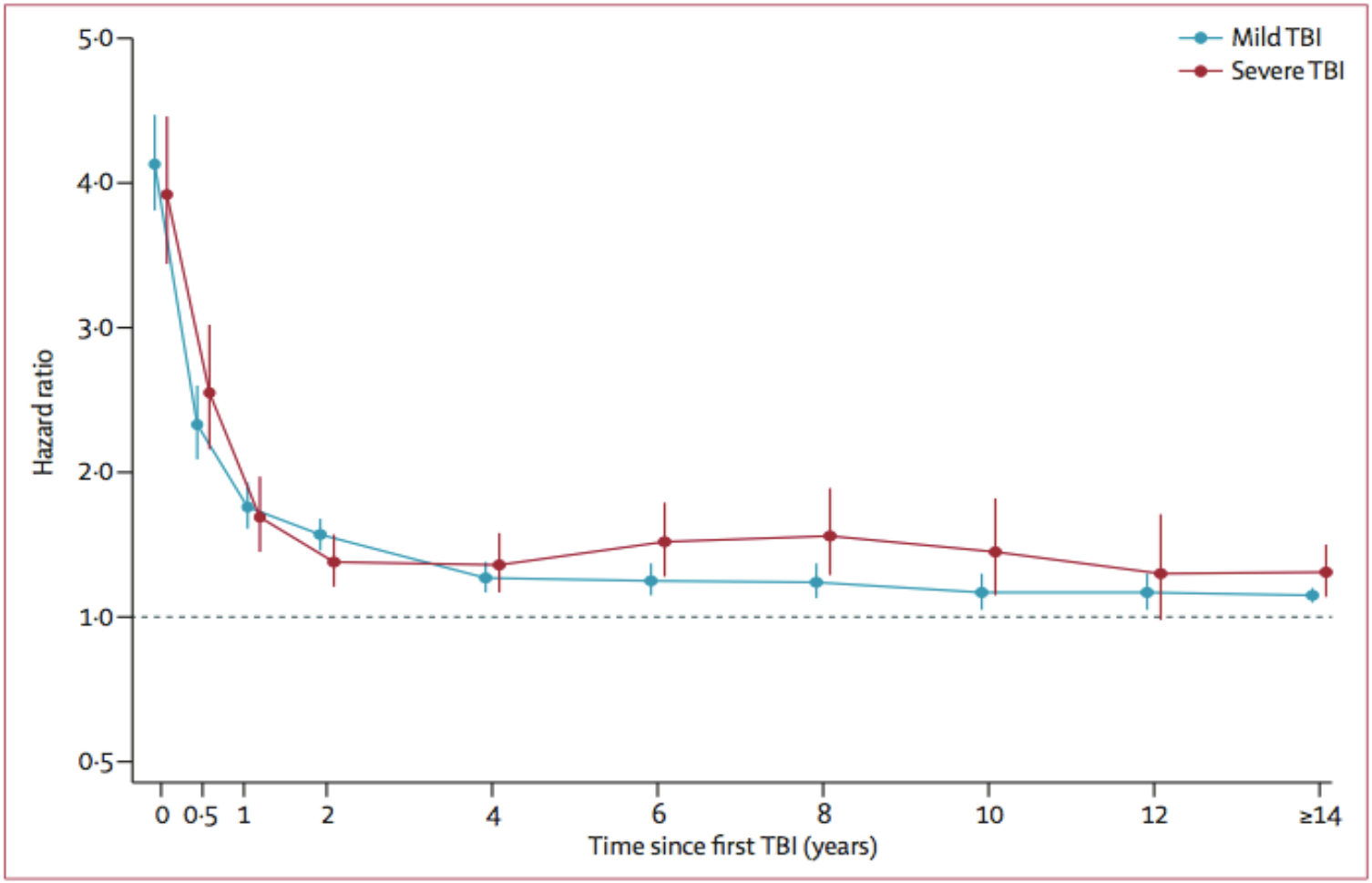


Figure 1: **Risk of dementia according to TBI severity and time since TBI**

What about data from studies of Alzheimer's Disease?

JNNP Online First, published on August 20, 2015 as 10.1136/jnnp-2015-310548

RESEARCH PAPER

Meta-analysis of modifiable risk factors for Alzheimer's disease

Wei Xu,[1] Lan Tan,[1,2,3] Hui-Fu Wang,[2] Teng Jiang,[2] Meng-Shan Tan,[1] Lin Tan,[3] Qing-Fei Zhao,[1] Jie-Qiong Li,[1] Jun Wang,[1] Jin-Tai Yu[1,2,3,4]

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/jnnp-2015-310548)

[1]Department of Neurology, Qingdao Municipal Hospital,

ABSTRACT

Background The aetiology of Alzheimer's disease (AD) is believed to involve environmental exposure and genetic susceptibility. The aim of our present systematic review and meta-analysis was to roundly evaluate the association between AD and its modifiable risk factors.

estimated that nearly half of the AD cases globally might be attributable to seven common potentially modifiable risk factors and a marginal (10–25%) reduction of these risk factors could potentially prevent up to 1.1–3.0 million cases worldwide. Recently, two European studies showed that

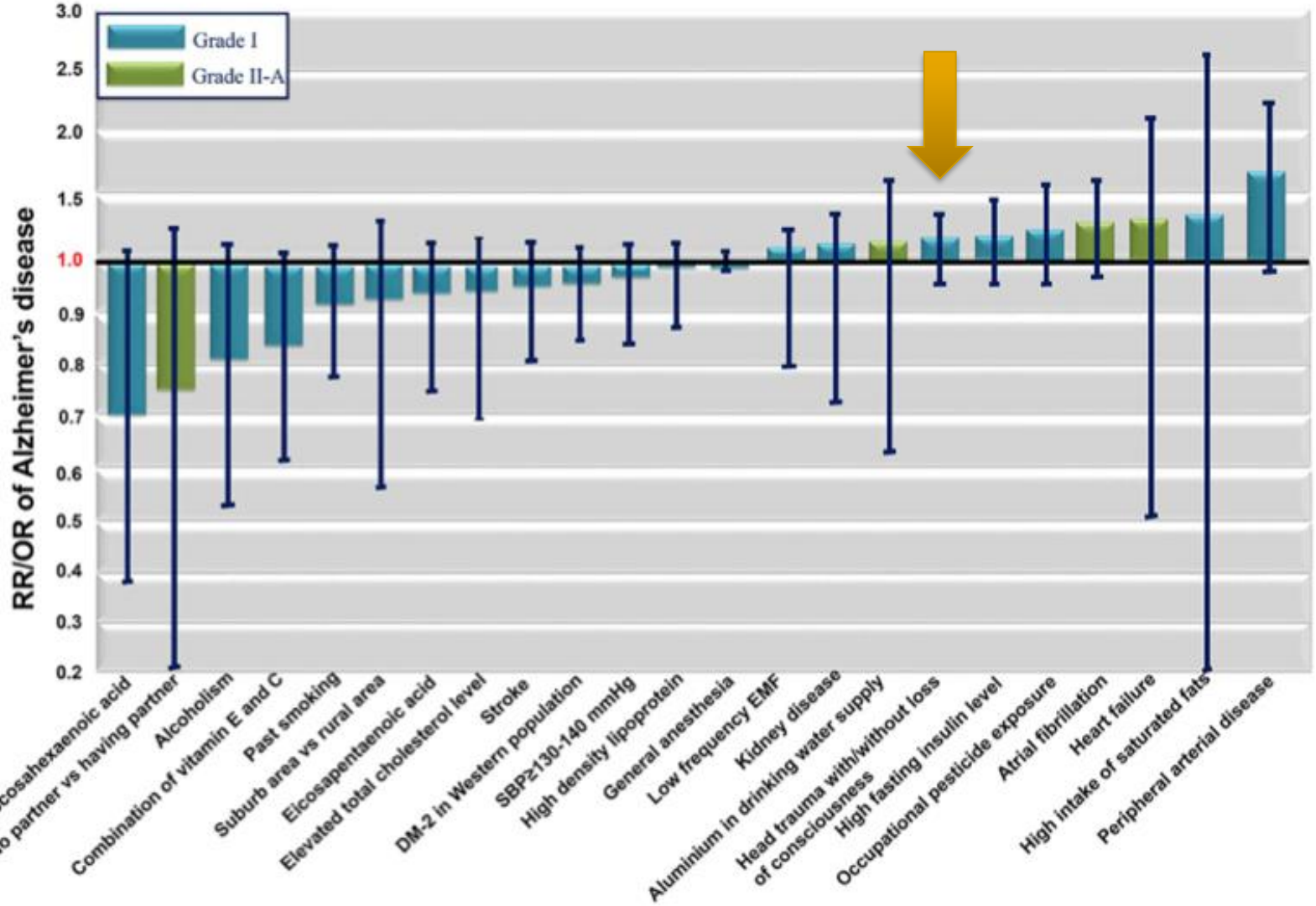


Figure 3 Factors showing no significant association with AD. With a relatively large pooled population (n>5000), a total of 23 (19 with grade I evidence and 4 with grade II-A evidence) factors showed no significant association with AD risk. The height of the strip is representative of the effect size. The length of the longitudinal line is representative of the range of 95% CI (AD, Alzheimer's disease; DM, diabetes mellitus; EMF, electromagnetic field; RR, relative risk; SBP, systolic blood pressure).

mTBI & Alzheimer's pathology?

Table 3. Separate Adjusted Associations Between TBI With LOC and Neuropathologic Findings in ACT and in ROS and MAP[a]

	ACT (N = 525)				ROS and MAP (N = 1064)			
	TBI With LOC ≤1 h (n = 80)		TBI With LOC >1 h (n = 14)		TBI With LOC ≤1 h (n = 96)		TBI With LOC >1 h (n = 23)	
Outcome	RR (95% CI)[a]	*P* Value	RR (95% CI)[b]	*P* Value	RR (95% CI)[b]	*P* Value	RR (95% CI)[b]	*P* Value
Braak stage V or VI	1.22 (0.86-1.73)	.26	1.11 (0.61-2.00)	.74	0.87 (0.55-1.37)	.54	0.85 (0.35-2.06)	.71
CERAD intermediate or frequent	1.01 (0.79-1.29)	.92	0.67 (0.36-1.25)	.21	1.01 (0.78-1.31)	.93	1.16 (0.73-1.85)	.54
Amyloid angiopathy	1.08 (0.73-1.59)	.71	1.02 (0.47-2.20)	.96	1.10 (0.88-1.39)	.41	1.11 (0.72-1.71)	.63
Cystic infarcts	0.83 (0.56-1.24)	.37	1.05 (0.52-2.12)	.88	0.95 (0.68-1.33)	.77	1.24 (0.71-2.15)	.45
Hippocampal sclerosis	0.93 (0.41-2.10)	.86	2.34 (1.02-5.30)	.04	0.84 (0.37-1.93)	.68	0.49 (0.07-3.52)	.48
Cerebral microinfarcts								
Any	0.87 (0.64-1.19)	.39	1.23 (0.73-2.09)	.44	1.03 (0.72-1.46)	.88	1.18 (0.63-2.21)	.61
Any cortical	0.92 (0.65-1.31)	.64	1.12 (0.57-2.18)	.74	0.89 (0.53-1.48)	.66	2.12 (1.12-4.01)	.02
Any deep	0.89 (0.60-1.33)	.58	1.67 (0.95-2.93)	.08	1.16 (0.77-1.76)	.48	1.07 (0.47-2.40)	.88
Lewy bodies								
Any	0.93 (0.55-1.59)	.80	2.64 (1.40-4.99)	.003	1.04 (0.67-1.62)	.85	0.95 (0.39-2.31)	.91
Substantia nigra and/or locus ceruleus	0.96 (0.51-1.80)	.89	3.30 (1.71-6.38)	<.001	1.09 (0.69-1.71)	.82	0.82 (0.31-2.22)	.70
Frontal or temporal cortex	1.49 (0.61-3.64)	.38	5.73 (2.18-15.0)	<.001	1.64 (1.00-2.70)	.051	0.74 (0.18-3.00)	.67
Amygdala and/or limbic[c]	1.30 (0.75-2.24)	.35	1.89 (0.69-5.19)	.22	1.16 (0.73-1.84)	.91	0.91 (0.34-2.44)	.85

What can we learn from mild traumatic brain injury in general?

Archives of Physical Medicine and Rehabilitation 2014;95(3 Suppl 2):S245-56

REVIEW ARTICLE

Systematic Review of the Risk of Dementia and Chronic Cognitive Impairment After Mild Traumatic Brain Injury: Results of the International Collaboration on Mild Traumatic Brain Injury Prognosis

Alison K. Godbolt, MBChB, MD,[a] Carol Cancelliere, DC, MPH,[b,c] Cesar A. Hincapié, DC, MHSc,[b,d] Connie Marras, MD, PhD,[e,f] Eleanor Boyle, PhD,[d,g] Vicki L. Kristman, PhD,[d,h,i,j] Victor G. Coronado, MD, MPH,[k] J. David Cassidy, PhD, DrMedSc[b,c,d,g]

“There are consistent findings that early cognitive deficits in MTBI are largely resolved within a few months post-injury, with most studies suggesting resolution within 3 months. Since this evidence is based on a variety of study designs, in a number of different MTBI populations and through comparisons with both injured and non-injured control groups, we consider it persuasive and consistent evidence.”

“When symptoms were prolonged this often related to background psychological and social issues and that litigation had a significant effect on outcome.”

2014 update

“There is a lack of evidence of an increased risk of dementia after MTBI.”

Why do we all see patients clinically who seem quite disabled after mTBI?

Disability in young people and adults one year after head injury: prospective cohort study

Sharon Thornhill, Graham M Teasdale, Gordon D Murray, James McEwen, Christopher W Roy, Kay I Penny

BMJ VOLUME 320 17 JUNE 2000 bmj.com

Table 3 Outcome related to initial severity of head injury one year later. Values are numbers (percentages) unless stated otherwise

Initial severity	Glasgow coma score	No of patients	Outcome			
			Dead or vegetative	Severe disability	Moderate disability	Good recovery
Mild	13-15	362	29 (8)	71 (20)	100 (28)	162 (45)
Moderate	9-12	97	16 (16)	21 (22)	23 (24)	37 (38)
Severe	3-8	73	28 (38)	21 (29)	14 (19)	10 (14)
Uncertain or not obtained	NA	17	4 (24)	4 (24)	4 (24)	5 (29)

NA=Not applicable.

Reverse causality and attribution bias?

Table 2 Early characteristics of patients selected for follow up and those successfully followed up. Values are numbers (percentages) unless stated otherwise

Characteristics	Selected sample (n=769)	Followed up (n=549)
Median age (years) (range)	38 (14-98)	39 (14-98)
Men	613 (80)	442 (81)
Women	156 (20)	107 (19)
Cause of injury:		
Fall	354 (46)	245 (45)
Assault	219 (28)	156 (28)
Road traffic accident	82 (11)	F63 (12)
Other injury:		
Minor	362 (47)	250 (46)
Moderate to major	167 (22)	130 (24)
Alcohol involved or suspected	529 (69)	368 (67)
Drinking excessive or requiring treatment	301 (39)	227 (41)
Physical limitations	215 (28)	154 (28)
Previous head injury	229 (30)	162 (30)
Previous brain illness*	207 (27)	154 (28)

*Mental problems, stroke, or other condition requiring medical attention.

The concept of shared risk factors

Epilepsy

RESEARCH PAPER

Predictors of new-onset seizures: a 10-year follow-up of head trauma subjects with and without traumatic brain injury

Kalle Vaaramo,[1] Jussi Puljula,[1] Sami Tetri,[2] Seppo Juvela,[3] Matti Hillbom[1]

[1]Department of Neurology,

ABSTRACT

seizures following TBI,[6] while another has reported

Editorial commentary

Mild traumatic brain injury and epilepsy: alcohol misuse may underpin the association

Killian A Welch,[1] Christopher Derry[2]

Mild traumatic brain injury (mTBI) is (although this difference fell short of

shown to be effective in reducing alcohol consumption. Indeed, a recent multicentre trial found that even simple feedback about the hazardous nature of a patient's drinking combined with a patient information leaflet outlining the deleterious effects of alcohol on health was associated with a significant reduction in hazardous drinking.[9] Based on this, and Vaaramo *et al*'s study, further evaluation of alcohol interventions following head injury

Could there be specific risk factors other than mTBI in athletes?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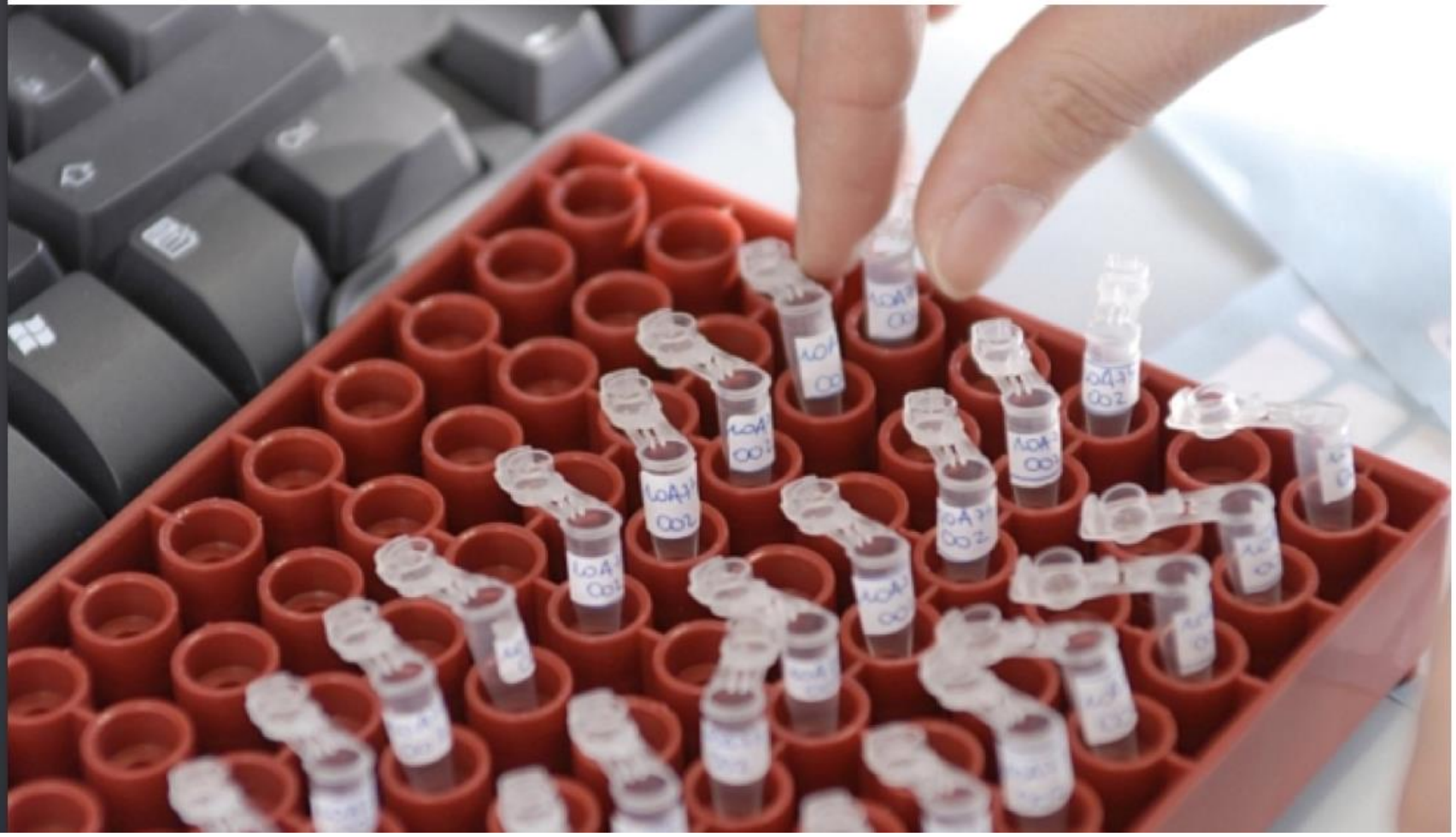
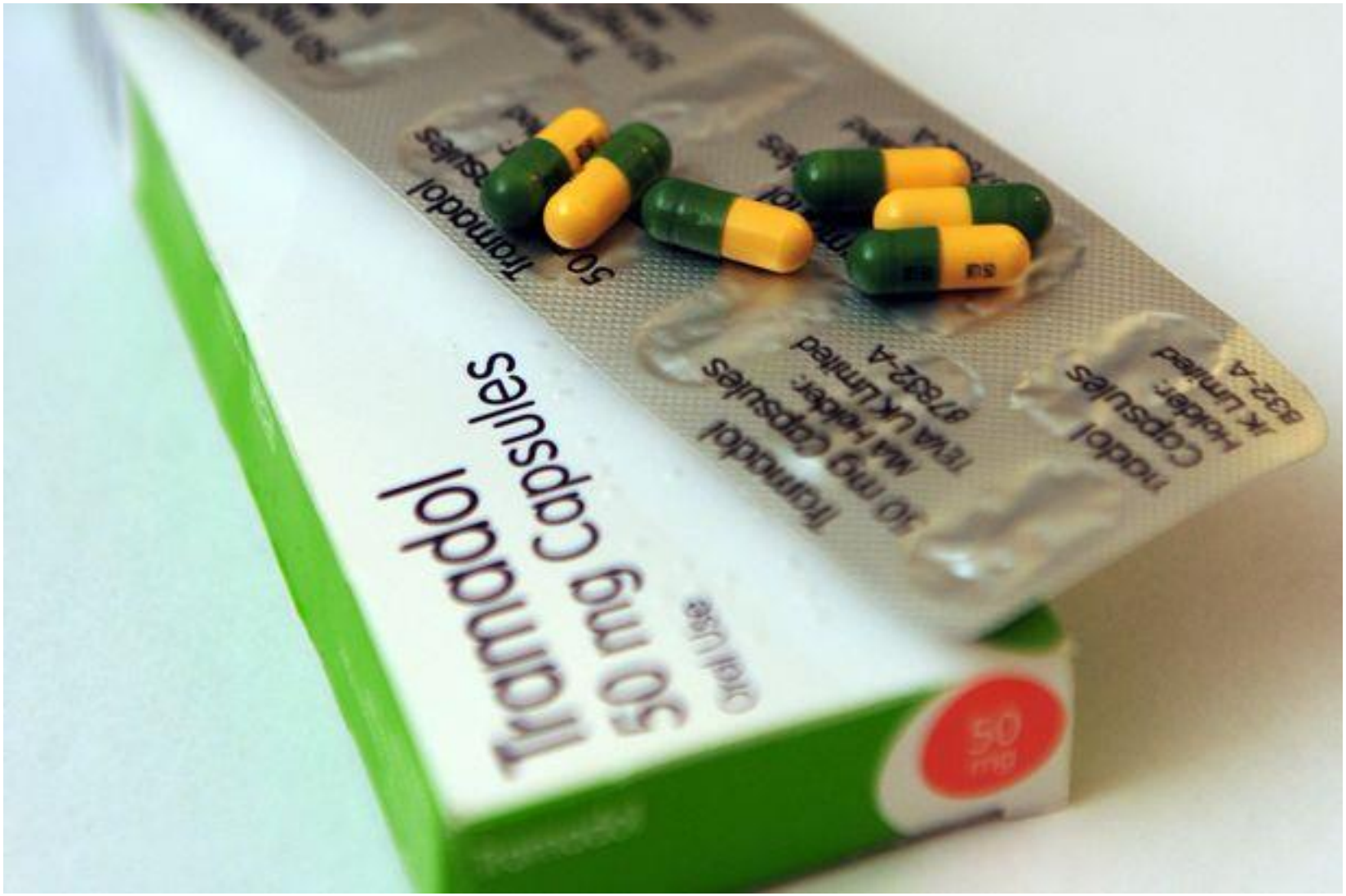
Rugby uncovered: Union is the dirtiest sport in Britain, and its doping problem is growing

Rugby uncovered is a series which puts rugby under the microscope before the World Cup. Part three focuses on rugby's dangerous supplement culture



Other factors


Tramadol
50 mg capsules
Oral use
50 mg

PNAS PLUS

Tau protein is essential for stress-induced brain pathology

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Edited by Bruce S. McEwen, The Rockefeller University, New York, NY, and approved May 2, 2016 (received for review January 28, 2016)

Exposure to chronic stress is frequently accompanied by cognitive and affective disorders in association with neurostructural adaptations. Chronic stress was previously shown to trigger Alzheimer's-like neuropathology, which is characterized by Tau hyperphosphorylation and missorting into dendritic spines followed by memory deficits. Here, we demonstrate that stress-driven hippocampal deficits in wild-type mice are accompanied by synaptic missorting of Tau and enhanced Fyn/GluN2B-driven synaptic signaling. In contrast, mice lacking Tau [Tau knockout (Tau-KO) mice] do not exhibit stress-induced pathological behaviors and atrophy of hippocampal dendrites or deficits of hippocampal connectivity. These findings implicate Tau as an essential mediator of the adverse effects of stress on brain structure and function.

Tau | stress | hippocampus | depression | memory deficits

The cytoskeletal protein Tau is implicated in the establishment of Alzheimer's disease (AD) (1) as well as excitotoxicity (1)

Two-way ANOVA analysis of the Y-maze data revealed CUS × Genotype interactions for both, distance traveled [$F_{(1, 65)} = 4.024$, $P = 0.04$], and time spent [$F_{(1, 65)} = 4.614$, $P = 0.03$] in the novel arm of the apparatus. Exposure to CUS resulted in deficits in spatial memory in WT ($p_{dist} = 0.02$; $p_{time} = 0.02$), but not Tau-KO ($p_{dist} = 0.98$; $p_{time} = 0.95$), mice; no differences were found between WT and Tau-KO control (nonstressed) animals ($p_{dist} = 0.84$; $p_{time} = 0.77$) (Fig. 1*A* and *SI Appendix*, Fig. S1). Total distance traveled in the three arms of the maze did not differ between any of the groups (Fig. 1*B*). Results from the MWM test confirmed that CUS induces impairments in spatial learning/memory in WT, but not Tau-KO, mice [significant CUS × Genotype interaction in distance swum to reach the escape platform [$F_{(1, 35)} = 7.467$, $P = 0.01$]; CUS increased the distance swum in WT mice only ($P \leq 0.05$) (Fig. 1*C*). The NOR test showed that recognition memory was also disrupted by CUS in WT, but not Tau-KO, mice. Specifically, we found a CUS × Genotype interaction [$F_{(1, 37)} = 4.387$, $P = 0.04$] on the discrimination index.

Significance

Exposure to stressful events is a well-known inducer of neuronal atrophy implicated in the development of neuropsychiatric and neurological pathologies (e.g., depression and Alzheimer's disease), although the underlying molecular mechanisms remain elusive. The current study demonstrates that absence of the cytoskeletal protein Tau blocks stress-evoked hippocampal synaptic signaling and morphofunctional damages related to both neuronal structure and connectivity as well as subsequent behavioral deficits. These findings suggest, for the first time to our knowledge, that Tau protein is a key regulator of neuronal malfunction found in stress-driven hippocampal pathology.

J Neurol Neurosurg Psychia

RESEARCH PAPER

Multicentre, cross-cultural, population-based, case–control study of physical activity as risk factor for amyotrophic lateral sclerosis

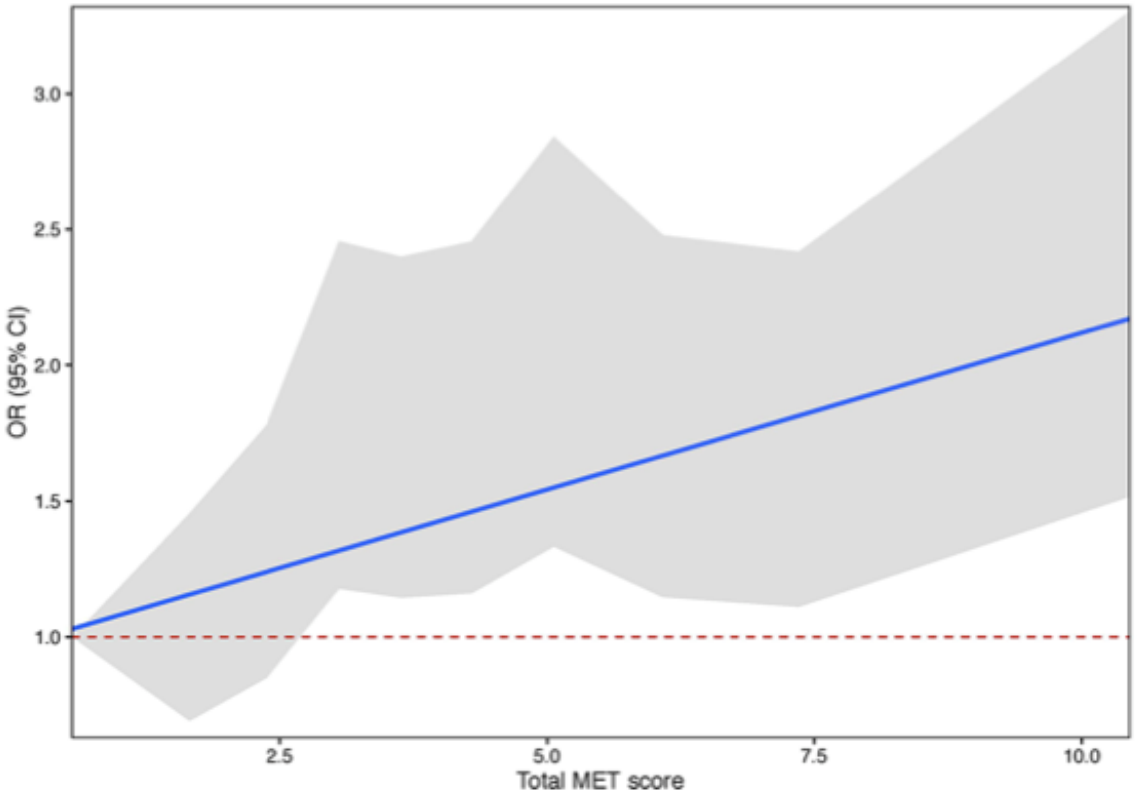


Figure 2 The risk of amyotrophic lateral sclerosis (OR) associated with a certain lifetime MET score of all activities combined (in the complete case dataset) using a lifetime MET score of zero as the reference. MET, metabolic equivalent of task.

If not mTBI- any other known risk factors?

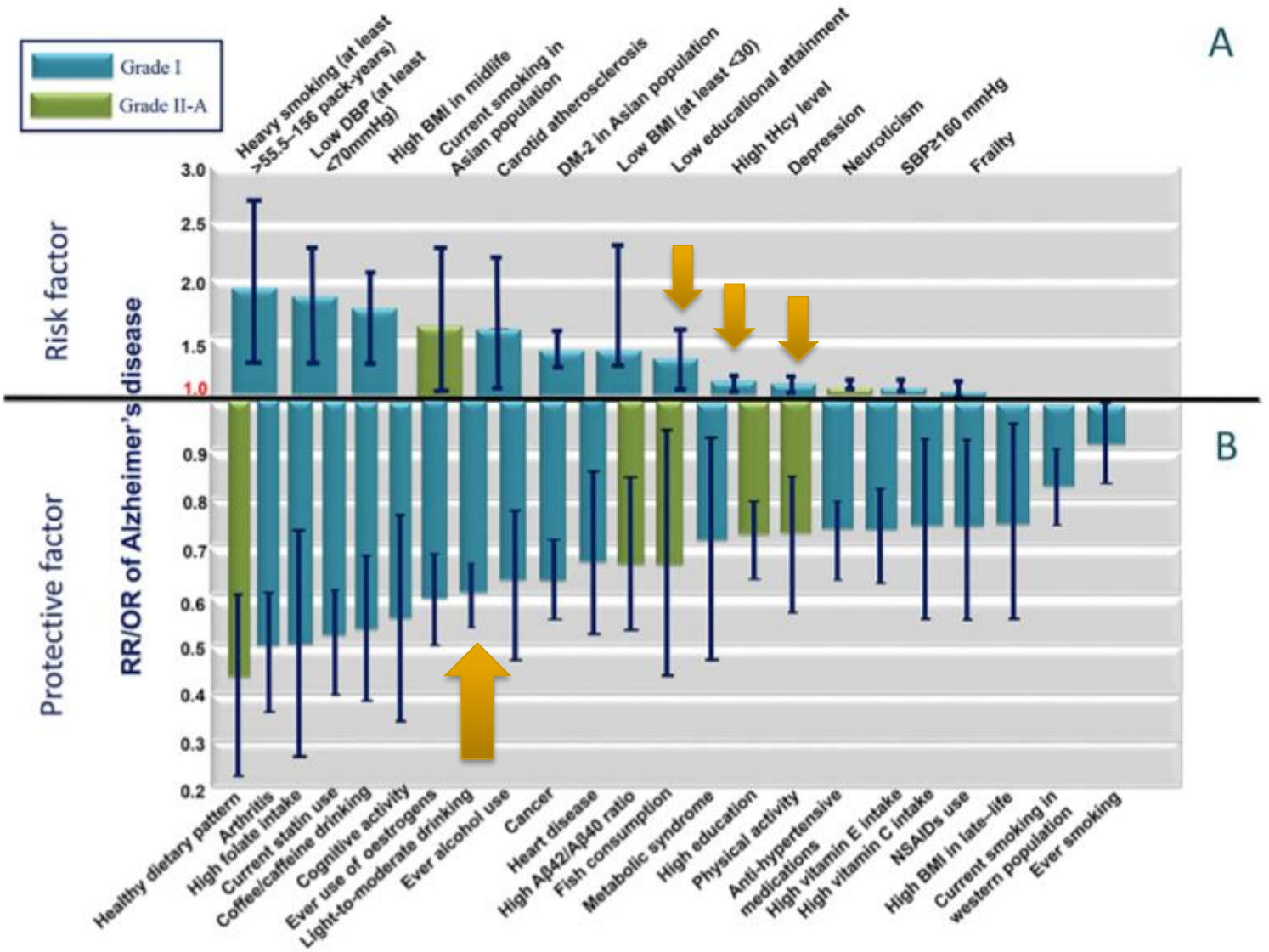
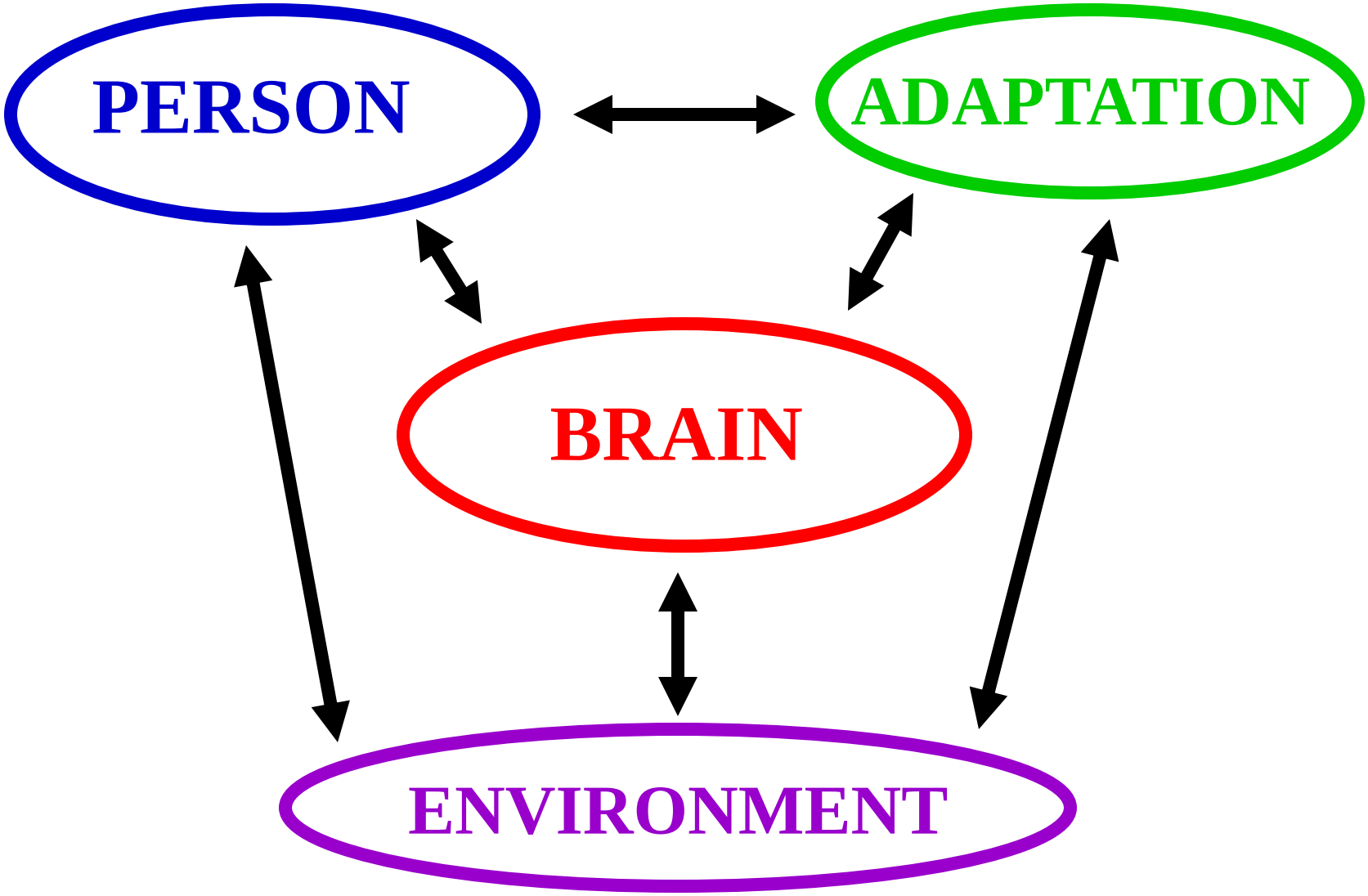
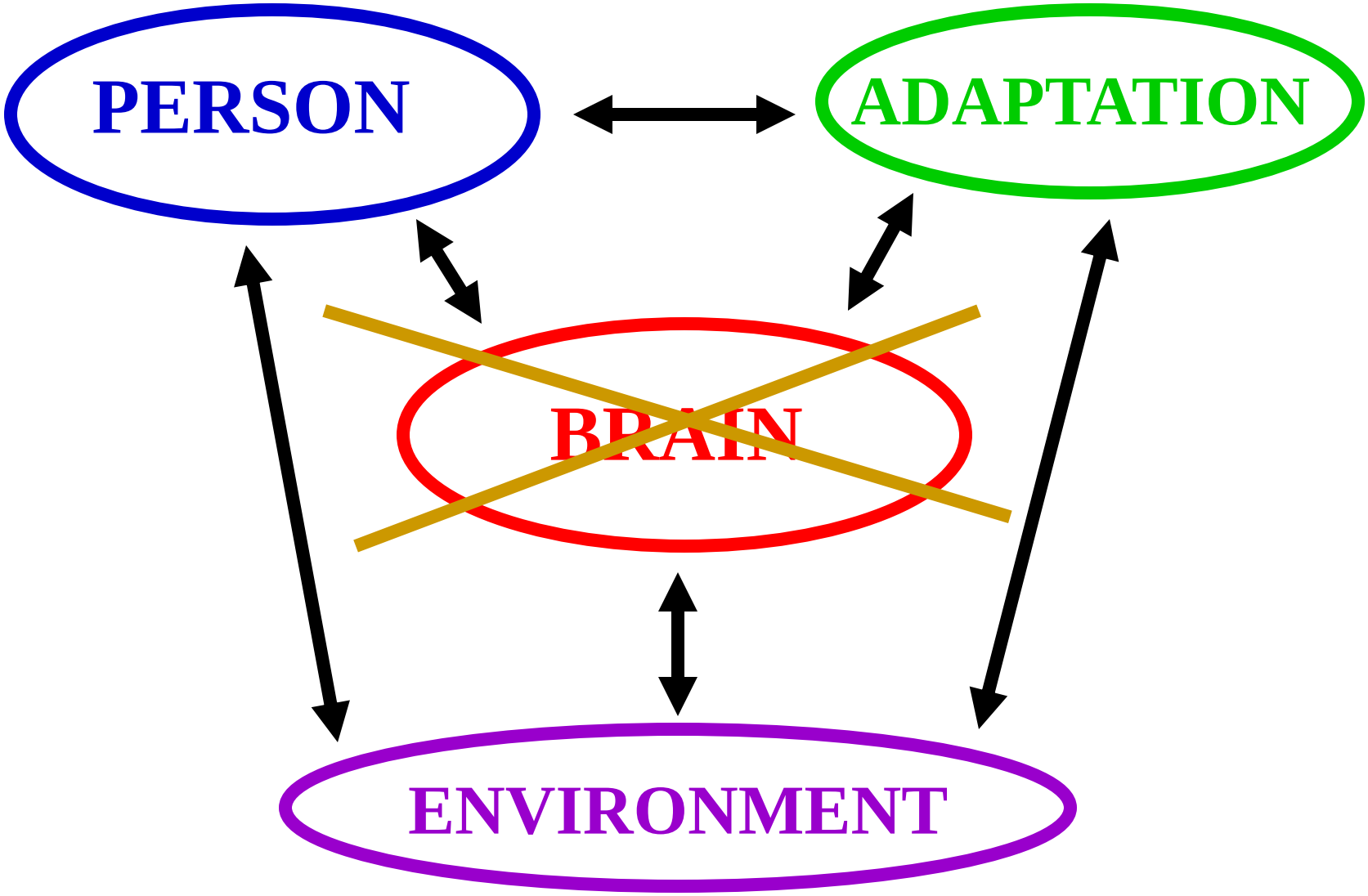


Figure 2 Factors showing significant positive (A) and negative (B) association with AD. With a relatively large pooled population (n>5000), (A) a total of 13 (11 with grade I evidence and 2 with grade II-A evidence) factors showed a trend of increasing risk of AD while (B) a total of 23 (18 with grade I evidence and 5 with grade II-A evidence) factors showed a trend of decreasing risk of AD. The height of the strip is representative of the effect size. The length of the longitudinal line is representative of the range of 95% CI (AD, Alzheimer's disease; BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; NSAIDs, non-steroidal anti-inflammatory drugs; RR, relative risk; SBP, systolic blood pressure; tHcy, total homocysteine).

So where might this go clinically?


PERSON
ADAPTATION
BRAIN
ENVIRONMENT

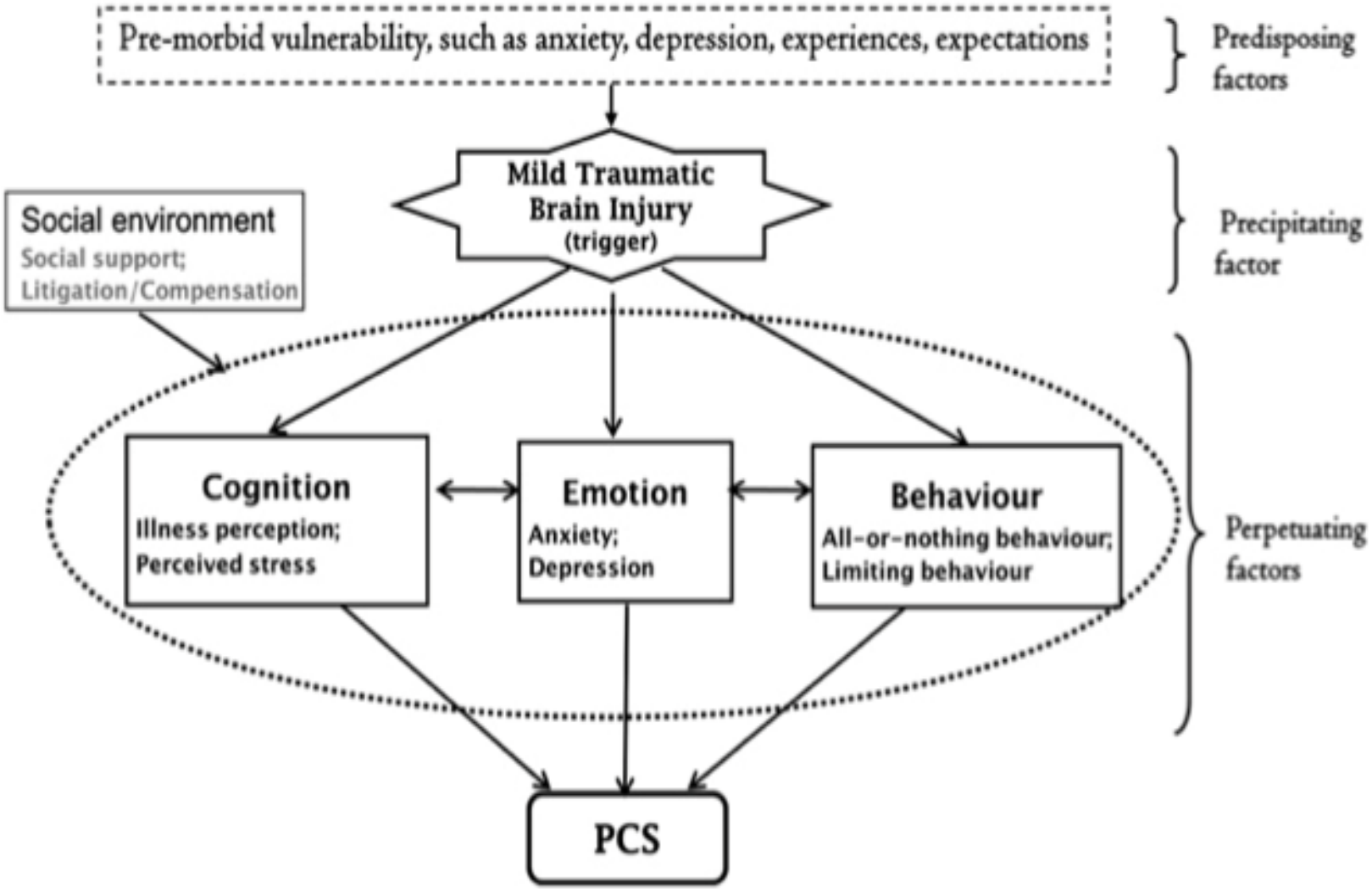

PERSON
ADAPTATION
BRAIN
ENVIRONMENT

Neurosurgery

RESEARCH PAPER

When a minor head injury results in enduring symptoms: a prospective investigation of risk factors for postconcussional syndrome after mild traumatic brain injury

Ruihua Hou,[1] Rona Moss-Morris,[2] Robert Peveler,[1] Karin Mogg,[3] Brendan P Bradley,[3] Antonio Belli[1]


Pre-morbid vulnerability, such as anxiety, depression, experiences, expectations
Predisposing factors
Mild Traumatic Brain Injury (trigger)
Precipitating factor
Social environment
Social support;
Litigation/Compensation
Cognition
Illness perception;
Perceived stress
Emotion
Anxiety;
Depression
Behaviour
All-or-nothing behaviour;
Limiting behaviour
Perpetuating factors
PCS

Research paper

EDITOR'S CHOICE

Psychological approaches to treatment of postconcussion syndrome: a systematic review

Amal Al Sayegh,[1] David Sandford,[2] Alan J Carson[3]

► Additional material is published online only. To view these files please visit the journal online (http://jnnp.bmj.com).

ABSTRACT

Background and aim Postconcussion syndrome (PCS) is a term used to describe the complex, and controversial, constellation of physical, cognitive and emotional

helpfully conducted a high-quality systematic review of the epidemiological evidence and suggested that there are no MTBI attributable, objectively measured cognitive deficits beyond 1–3 months postinjury in

So we what do we know?

We can be sure that…

- …..the major public health crisis in developed world is obesity and lack of activity not concussion
- ……participating in contact sport reduces overall mortality substantially
- …….that mTBI is complex and head injuries do not occur at random. The risk factors for injury occurring may influence post injury presentations
- ……association is not proof of causality

We can be pretty sure that

- …..on going symptoms 3 months after mTBI are generally not explained by neural pathology
- Multiple mTBIs over a short period may be different and there may be genetic risks
  - Supports Scottish concussion guidelines
- …..that if mTBIs do increase risk of dementias that increase in risk is low (if it exists at all).
- …..that there are multiple confounders to these data sets
- ….a functional disorder model of persistent symptoms after mTBI is well supported by epidemiological data

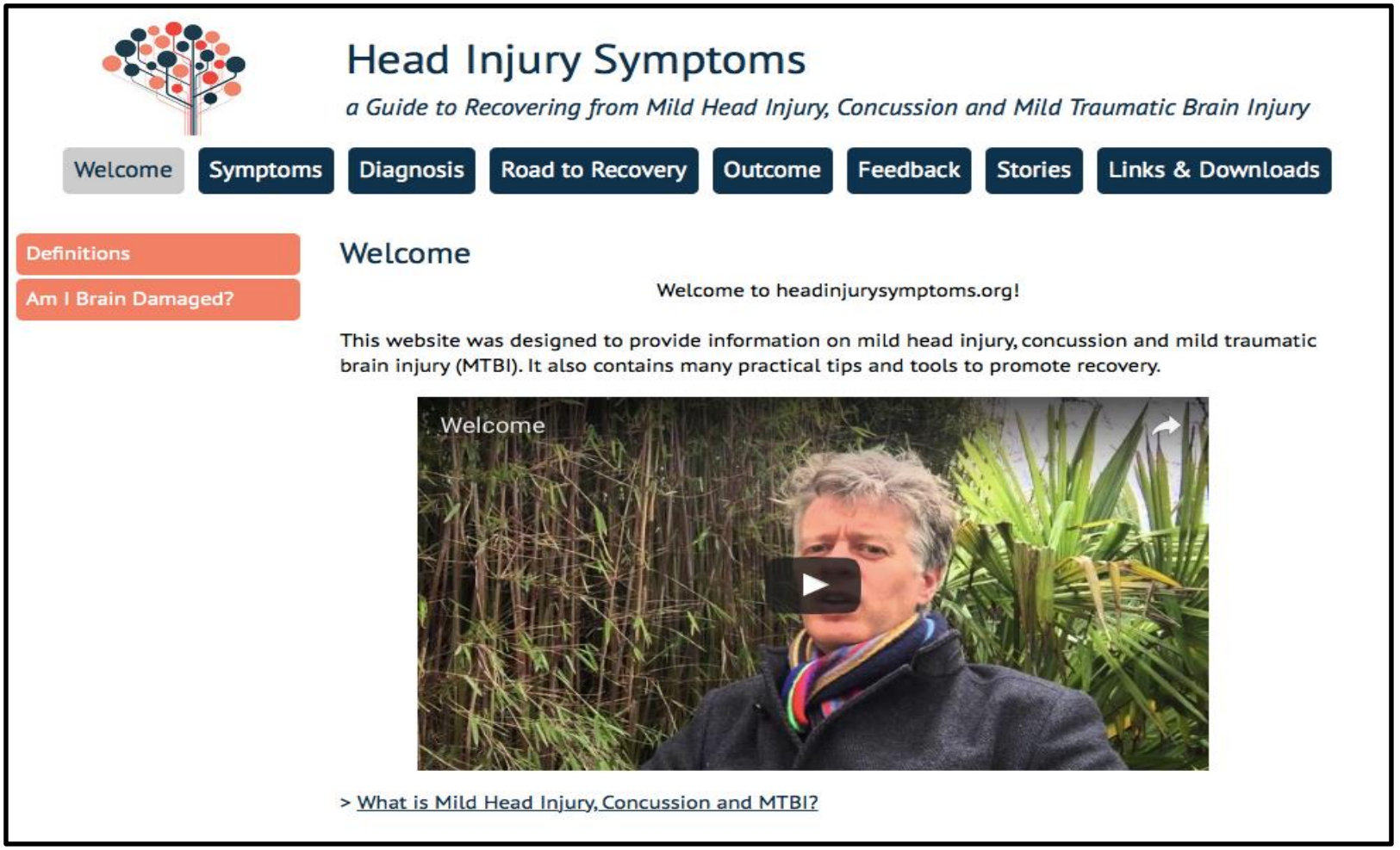
We should be more questioning about

- ….extrapolations from small highly selected cohorts and small imaging studies- don't know what the results mean and there are major issues with reproducibility
- ….neuropathology- it is always described as gold standard- but next time you read a paper pretend it is any other investigation and ask if this was MRI study would I accept these methods (and is the data even in the paper- it is usually not!)

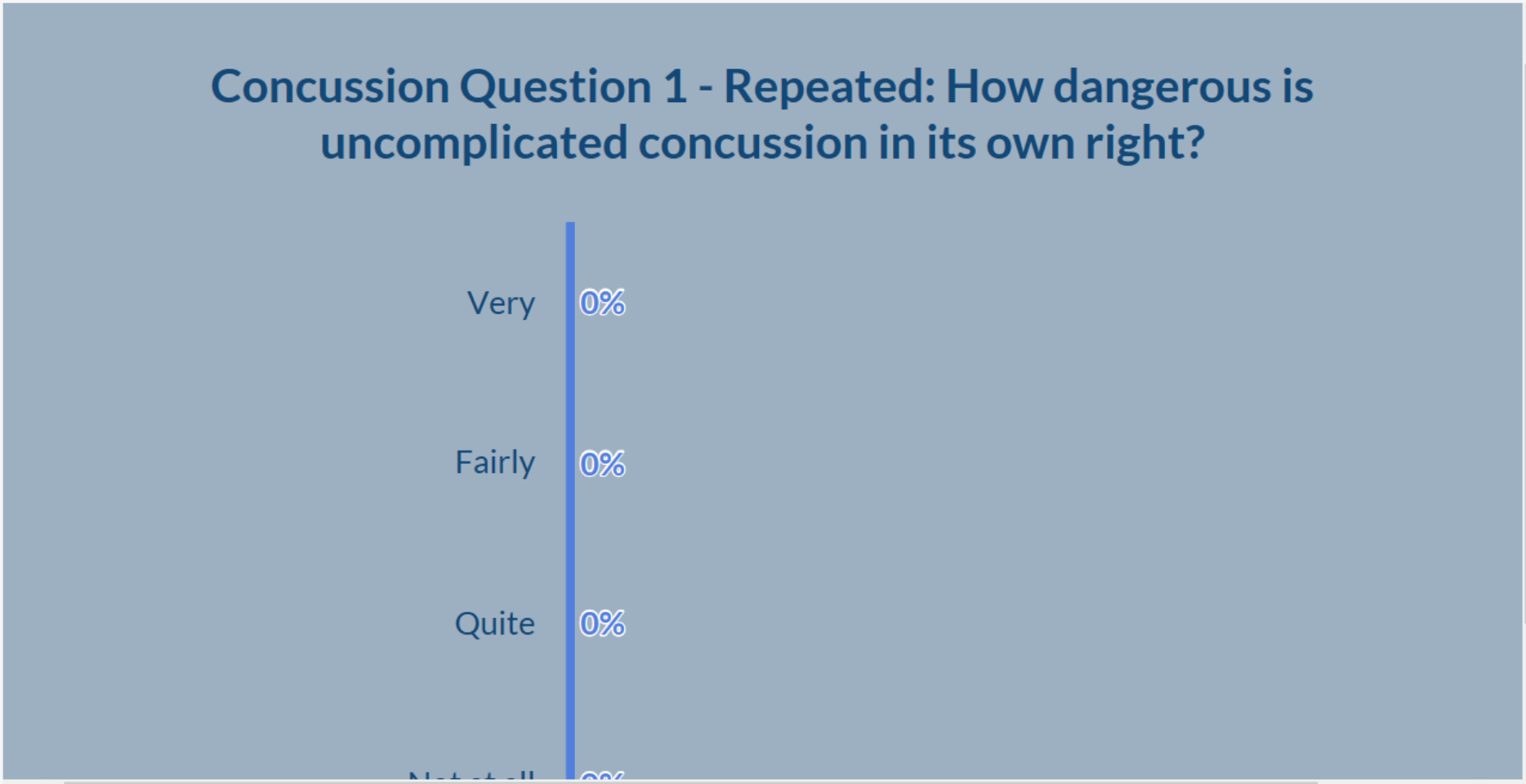
We should be more questioning about

- ….the nature of CTE and is it really an distinct disorder, and if so is head trauma a risk (or the only risk)
- ….talking about ‘dementia’ as a *unitary* concept
- …assuming that because we find evidence of ‘change’ on a biological measure that that ‘explains’ the disorder.
- ….the extent that commercial interests are swaying this field- concussion has become an industry

www.headinjurysymptoms.org



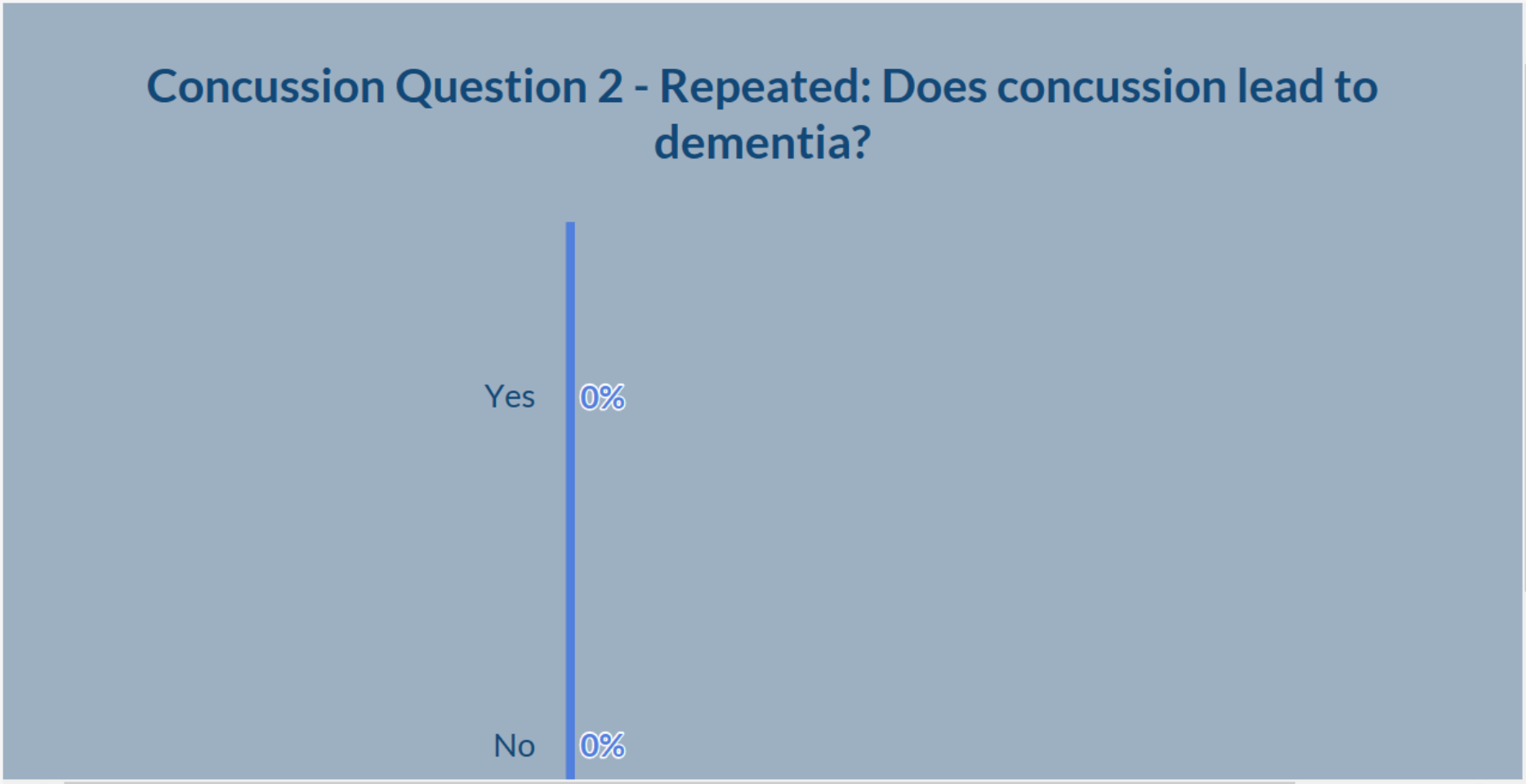
a.carson@ed.ac.uk @alancarson15



Source: https://api.cvent.com/polling/v1/api/polls/spermvk5

Edit

Concussion Question 2 - Repeated: Does concussion lead to dementia?



Source: https://api.cvent.com/polling/v1/api/polls/spcuadjc

Edit

Concussion Question 3 - Repeated: Do you think you would advise your own children away from contact sports because of concussion fears?

Source: https://api.cvent.com/polling/v1/api/polls/sp-a9g7wx