What Every Athletic Trainer Needs to Know About CTE-Related Symptoms & Behaviors

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Disclosures

- Intellectual Property related to concussion and brain injury assessment
- Intellectual Property related to assessment of dementia after brain injury
- Intellectual Property related to treatment of intracranial hemorrhage

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Abbott Diagnostic Laboratories
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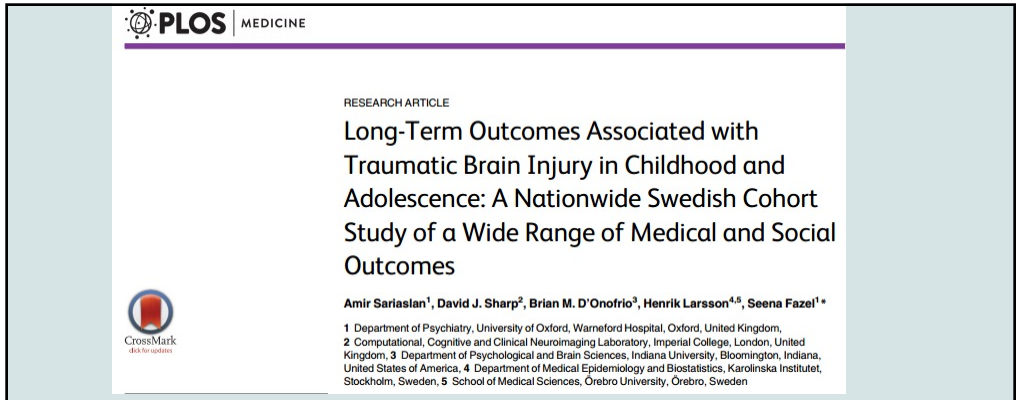
Hennepin County Medical Center
Hennepin Health Foundation
Integra Corporation
Islamic Medical Association of North America
Medtronic Corp
Minnesota Brain Injury Alliance
Minnesota, Texas, Louisiana, Wisconsin, Wyoming High School Coaches Association
National Football League
National Neurotrauma Society
North American Brain Injury Society
Oculogica Inc
OssDsign
Steven and Alexandra Cohen Foundation for Veteran Post Traumatic Stress and Traumatic Brain Injury
United States Veterans Administration and Office of Research and Development
USA Football

2



PLOS | MEDICINE

RESEARCH ARTICLE

Long-Term Outcomes Associated with Traumatic Brain Injury in Childhood and Adolescence: A Nationwide Swedish Cohort Study of a Wide Range of Medical and Social Outcomes

Amir Sariaslan[1], David J. Sharp[2], Brian M. D'Onofrio[3], Henrik Larsson[4,5], Seena Fazel[1]*

1 Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, United Kingdom, 2 Computational, Cognitive and Clinical Neuroimaging Laboratory, Imperial College, London, United Kingdom, 3 Department of Psychological and Brain Sciences, Indiana University, Bloomington, Indiana, United States of America, 4 Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden, 5 School of Medical Sciences, Örebro University, Örebro, Sweden

>109,000 Swedes under age 25 with TBI compared to their siblings
Increased risk: pension disability, psychiatric hospitalization and premature death
Severity and number of injuries correlates with outcome

3

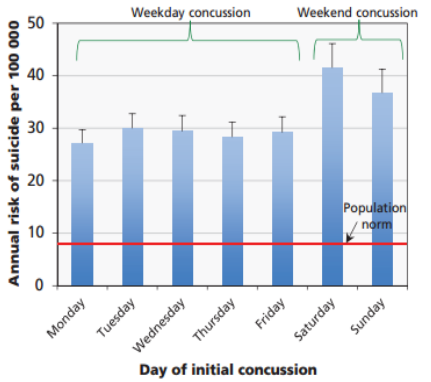
Do sports cause death?

Riding in a car: 25 deaths per million population
Suicide: 25 deaths per million population

Equestrian: 20 deaths per million participants
Biking, snowboarding, skateboarding, skiing: all about 15 deaths per million participants
Playground: about 10 deaths per million participants
Football: fewer than 6 deaths per million participants
Swimming: 140 pediatric deaths per year (confounded denominator)

4

Suicide Risk Is Increased After Concussion 235000 pts followed for 9 years: 31/100,000



Risk of suicide after a concussion

Michael Fralick MD BScH, Deva Thiruchelvam MSc, Homer C. Tien MD MSc, Donald A. Redelmeier MD MS(HSR)

CMAJ Podcasts: author interview at https://soundcloud.com/cmajpodcasts/150790-res

ABSTRACT

Background: Head injuries have been associated with subsequent suicide among military personnel, but outcomes after a concussion in the community are uncertain. We assessed the long-term risk of suicide after concussions occurring on weekends or weekdays in the community.

Methods: We performed a longitudinal cohort analysis of adults with diagnosis of a concussion in Ontario, Canada, from Apr. 1, 1992, to Mar. 31, 2012 (a 20-yr period), excluding severe cases that resulted in hospital admission. The primary outcome was the long-term risk of suicide after a weekend or weekday concussion.

Results: We identified 235 110 patients with a concussion. Their mean age was 41 years, 52% were men, and most (86%) lived in an urban location. A total of 667 subsequent suicides occurred over a median follow-up of 9.3 years, equivalent to 31 deaths per 100 000 patients annually or 3 times the population norm. Weekend concussions were associated with a one-third further increased risk of suicide compared with weekday concussions (relative risk 1.36, 95% confidence interval 1.14–1.64). The increased risk applied regardless of patients' demographic characteristics, was independent of past psychiatric conditions, became accentuated with time and exceeded the risk among military personnel. Half of these patients had visited a physician in the last week of life.

Interpretation: Adults with a diagnosis of concussion had an increased long-term risk of suicide, particularly after concussions on weekends. Greater attention to the long-term care of patients after a concussion in the community might save lives because deaths from suicide can be prevented.

Competing interests: None declared.

This article has been peer reviewed.

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Correspondence to: Donald A. Redelmeier, dar@ices.on.ca

CMAJ 2016. DOI:10.1503/cmaj.150790

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Lehman et al 2016

Suicide Mortality Among Retired National Football League Players Who Played 5 or More Seasons

Everett J. Lehman,*† MS, Misty J. Hein,† PhD, and Christine M. Gersic†
Investigation performed at the National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Cincinnati, Ohio, USA

3439 NFL players from 1959-1988 seasons were studied (minimum of 5 seasons per player)
Followed for 28.9 years after retirement

Players retired-since 1987
6.1/100,000

Players retired- since 2005
12.5/100,000

Average American man- since 2014
20.1/100,000

TABLE 1
Overall Mortality, Selected Causes, National Football League Player Cohort (1960-2013)[a]

Underlying Cause of Death	Observed	Expected	SMR (95% CI)
All deaths	537	901.7	0.60 (0.55-0.65)
All cancers	137	230.8	0.59 (0.50-0.70)
Heart diseases	207	277.1	0.75 (0.65-0.86)
Suicide	12	25.6	0.47 (0.24-0.82)
Assault and homicide	4	27.6	0.14 (0.04-0.37)

[a]SMR, standardized mortality ratio (US referent rates).

Since 2005, NFL players are 48% less likely to commit suicide than the general population

Since 1987, NFL players are 70% less likely to commit suicide than general population!

6

Drugs are assessed by standardized mortality ratio (the increase or decrease in mortality of a study cohort with respect to the general population

If playing in the NFL (for a mimimum of 5 seasons) was treated like taking a drug:

It reduces standardized mortality (measured 30 years later) by half!

Saving 296 lives at the cost of 17 deaths

7

Suicide in the general population and NCAA athletes

Suicide in National Collegiate Athletic Association (NCAA) Athletes: A 9-Year Analysis of the NCAA Resolutions Database

Ashwin L. Rao, MD,*† Irfan M. Asif, MD,‡ Jonathan A. Drezner, MD,† Brett G. Toresdahl, M
and Kimberly G. Harmon, MD†

General Population 12.6 per 100,000

18-22 year old non-college 12 per 100,000

College students 7.5 per 100,000

NCAA *Athlete* 0.93/100,000

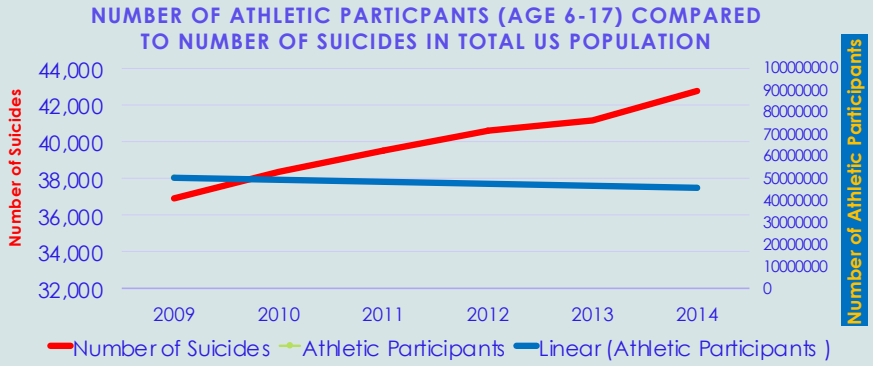
NCAA *Football (male only)* 2.25/100,000

Published Oct 2015

9 year study
3,773,309 participant seasons

8

Decrease in Youth Athletics Compared to Youth Suicide Rate



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Sports Participation as a Protective Factor Against Depression and Suicidal Ideation in Adolescents as Mediated by Self-Esteem and Social Support

Lindsay A. Babiss, MS,* James E. Gangwisch, PhD†

ABSTRACT: *Objective:* Participation in sports has been shown to be protective against depression and suicidal ideation, but little is known about what factors mediate these relationships. No previous studies examined potential mediators between sports participation and suicidal ideation and only one study explored possible mediators between sports participation and depression. Increased sports participation could protect against depression and suicidal ideation by increasing endogenous endorphin levels, boosting self-esteem, improving body image, increasing social support, and affecting substance abuse. *Method:* Multivariate hierarchical logistic regression analyses of Add Health data to explore whether increased participation in sports (none, 1–2, 3–4, or 5 or more times per week) is associated with depression and suicidal ideation and whether exercise, self-esteem, body weight, social support, and substance abuse mediate these relationships. *Results:* As sports participation increases, the odds of suffering from depression decreases by 25% (OR: 0.75; 95% CI: 0.70–0.82) and the odds of having suicidal ideation decreases by 12% (OR: 0.88; 95% CI: 0.83–0.93) after controlling for sex, age, race/ethnicity, public assistance, and physical limitations. Substance abuse, body weight, and exercise did not mediate these associations. Consistent with self-esteem and social support acting as mediators of these relationships, the inclusion of these variables in the multivariate models attenuated the associations for depression (OR: 0.83; 95% CI: 0.75–0.91) and suicidal ideation (OR: 0.93; 95% CI: 0.88–0.99). *Conclusion:* Adolescents should be offered ample opportunity and encouragement to participate in sports, which can protect against depression and suicidal ideation by boosting self-esteem and increasing social support.

*(J Dev Behav Pediatr 30:*376–384, 2009) **Index terms:** sports participation, depression, suicidal ideation, adolescents, epidemiology.

- An increase in sports participation (grades 7-12) leads to a decrease in depression by 25%
- Suicidal ideation decreases by 12% with an increase in sports participation

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What is the Relationship Between Concussion and Dementia?

- 1/3 of Americans have had a concussion in their lifetime,
  2/3 of these concussions are in males
- Dementia occurs about 63.5 per 1000 persons in the US[32]
- **Alzheimer's twice as common in women vs men**
- 5 Million have Alzheimer's – no reliable diagnostic, unknown cause
- Other common types: vascular dementia, frontotemporal dementia, normal pressure hydrocephalus

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What are the risk factors for dementia?

- High blood pressure
- Diabetes
- Sedentary lifestyle
- High fat diet / obesity
- Frequent alcohol use
- Female gender
- Low socioeconomic status (women)
- Sleep apnea
- Hearing loss
- Depression
- Smoking
- Atrial fibrillation
- Genetics
- Decreased level of education (women)
- Mild brain injury if over 65 years of age (men)
- Moderate or severe brain injury if over 55 (men)
- Decreased social contact

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Association of Traumatic Brain Injury With Late-Life Neurodegenerative Conditions and Neuropathologic Findings

Paul K. Crane, MD, MPH; Laura E. Gibbons, PhD; Kristen Dams-O'Connor, PhD; Emily Trittschuh, PhD; James B. Leverenz, MD; C. Dirk Keene, MD, PhD; Joshua Sonnen, MD; Thomas J. Montine, MD, PhD; David A. Bennett, MD; Sue Leurgans, PhD; Julie A. Schneider, MD, MS; Eric B. Larson, MD, MPH

4265 older adults followed for 45190 years

No association between a single brain injury and mild cognitive impairment, Alzheimers or other types of dementia

JAMA Neurology Published online July 11, 2016

Discussion

In 3 prospective cohort studies of older adults free of dementia at baseline and followed up for 45 190 person-years, we did not find associations between TBI with LOC and the risk for incident MCI, AD, or dementia. Of 1537 incident dementia cases across the 3 studies, 1322 were incident AD; we had substantial power for these outcomes. We did not find associations between TBI with LOC and neurofibrillary degeneration or neuritic plaques, although Braak stage V or VI (160 of 525 [30.5%] in ACT and 275 of 1157 [23.8%] in ROS and MAP) and intermediate or frequent neuritic plaques by CERAD criteria (263 of 525 [50.1%] in ACT and 759 of 1157 [65.6%] in ROS and MAP) were common. Including *APOE* genotype had a negligible effect on our results, and we did not find a different risk among *APOE* ε4 carriers. Our total autopsy sample size (1682 autopsies) is nearly 7 times that of a previous evaluation of associations between TBI exposure and Alzheimer pathologic findings[5]; those investigators found associations with neocortical plaques and sex differences that are not confirmed in our study.

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Review > PLoS One. 2017 Jan 9;12(1):e0169650. doi: 10.1371/journal.pone.0169650. eCollection 2017.

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

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

Affiliations + expand

PMID: 28068405 PMCID: PMC5221805 DOI: 10.1371/journal.pone.0169650

True in those who do not have LOC and males only

Results: Data from 32 studies, representing 2,013,197 individuals, 13,866 dementia events and 8,166 AD events, were included in the analysis. Overall, the pooled relative risk (RR) estimates showed that head injury significantly increased the risks of any dementia (RR = 1.63, 95% CI 1.34-1.99) and AD (RR = 1.51, 95% CI 1.26-1.80), with no evidence of publication bias. However, when considering the status of unconsciousness, head injury with loss of consciousness did not show significant association with dementia (RR = 0.92, 95% CI 0.67-1.27) and AD (RR = 1.49, 95% CI 0.91-2.43). Additionally, this positive association did not reach statistical significance in female participants.

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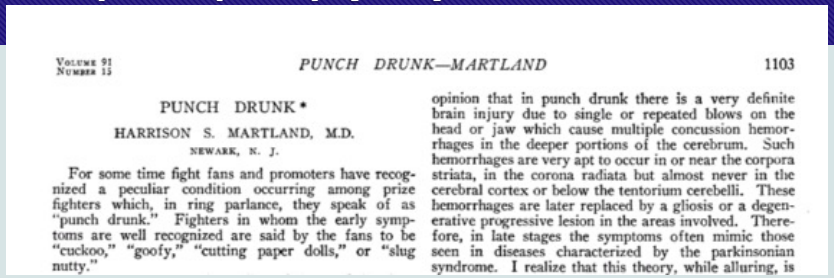
What is Chronic Traumatic Encephalopathy (CTE)



VOLUME 91
NUMBER 13

PUNCH DRUNK—MARTLAND 1103

PUNCH DRUNK *

HARRISON S. MARTLAND, M.D.
NEWARK, N. J.

For some time fight fans and promoters have recognized a peculiar condition occurring among prize fighters which, in ring parlance, they speak of as "punch drunk." Fighters in whom the early symptoms are well recognized are said by the fans to be "cuckoo," "goofy," "cutting paper dolls," or "slug nutty."

opinion that in punch drunk there is a very definite brain injury due to single or repeated blows on the head or jaw which cause multiple concussion hemorrhages in the deeper portions of the cerebrum. Such hemorrhages are very apt to occur in or near the corpora striata, in the corona radiata but almost never in the cerebral cortex or below the tentorium cerebelli. These hemorrhages are later replaced by a gliosis or a degenerative progressive lesion in the areas involved. Therefore, in late stages the symptoms often mimic those seen in diseases characterized by the parkinsonian syndrome. I realize that this theory, while alluring, is

- First discovered in 1928 in NJ boxers published in JAMA
- Found in 17% of living professional boxers in England, named CTE in 1969
- Motor deficits, Dementia
- Pathology described in 1960's and 1970's at Queen's Square, England

15

Omalu et al and McKee et al. presented new definitions for CTE in the 2000s:

Neurosurgery. 2005 Jul;57(1):128-34; discussion 128-34.

Chronic traumatic encephalopathy in a National Football League player.

Omalu BI[1], DeKosky ST, Minster RL, Kamboh MI, Hamilton RL, Wecht CH.

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

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"CTE, as defined in America, is not a neurological entity, but is a culture-specific social phenomenon." Jim Andrikopoulos, British Medical Journal

Editorials

Brain damage in American Football

BMJ 2015 ; 350 doi: http://dx.doi.org/10.1136/bmj.h1381 (Published 24 March 2015)
Cite this as: *BMJ* 2015;350:h1381

frontiers in HUMAN NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 24 May 2013
doi: 10.3389/fnhum.2013.00222

Absence of chronic traumatic encephalopathy in retired football players with multiple concussions and neurological symptomatology

Lili-Naz Hazrati[1,2], Maria C. Tartaglia[2,3], Phedias Diamandis[1], Karen D. Davis[4,5,6,7], Robin E. Green[8], Richard Wennberg[3], Janice C. Wong[1,2], Leo Ezerins[9] and Charles H. Tator[4,7]*

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Current Sports Medicine Reports:
January/February 2014 - Volume 13 - Issue 1 - p 33–37

Is Chronic Traumatic Encephalopathy a Real Disease?

Christopher Randolph, PhD

Abstract
Chronic traumatic encephalopathy (CTE) has received widespread media attention and is treated in the lay press as an established disease, characterized by suicidality and progressive dementia. The extant literature on CTE is reviewed here. There currently are no controlled epidemiological data to suggest that retired athletes are at increased risk for dementia or that they exhibit any type of unique neuropathology. There remain no established clinical or pathological criteria for diagnosing CTE. Despite claims that CTE occurs frequently in retired National Football League (NFL) players, recent studies of NFL retirees report that they have an all-cause mortality rate that is approximately half of the expected rate, and even lower suicide rates. In addition, recent clinical studies of samples of cognitively impaired NFL retirees have failed to identify any unique clinical syndrome. Until further controlled studies are completed, it appears to be premature to consider CTE a verifiable disease.

American football, or other sports involving repetitive head trauma. There have been only a couple of attempts to explore these risks via other methods. In 2005, Guskiewicz *et al.* (6) reported rates of mild cognitive impairment (MCI) and Alzheimer disease (AD) in retired National Football League (NFL) players that seemed to be higher than expected in comparison to population data. These results were based upon the responses to a survey sent to players who are members of the retired players association, and the results may have been subject to ascertainment bias. In addition, there were no controls.

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Does a Unique Neuropsychiatric Profile Currently Exist for Chronic Traumatic Encephalopathy?

Hanlon FM, et al. Curr Sports Med Rep. 2017 Jan/Feb.
Show full citation

Abstract

There is evidence that repetitive mild traumatic brain injury leads to specific patterns of neuropathological findings, labeled chronic traumatic encephalopathy (CTE). However, questions remain about whether these neuropathological changes produce changes in behavior, cognition, and emotional status that are associated with a unique neuropsychiatric profile that can be assessed using currently available clinical tools. Our review of the literature indicates that insufficient evidence currently exists to suggest a distinct neuropsychiatric profile for CTE. Major limitations to the field presently include the relatively nascent nature of the topic, reliance on retrospective next-of-kin reporting, the lack of prospective studies, and similarities in neuropsychiatric symptoms between CTE, other neurodegenerative disorders and forms of psychopathology. Clinicians and researchers alike have a responsibility to adopt a cautious and balanced approach for antemortem assessments to minimize the potential unintended negative consequences of both overdiagnosing and underdiagnosing a clinical entity that has yet to be clearly established.

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February 2015:
The feds step in to help define CTE: decide on 4 types
but the condition may be clinically asymptomatic

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

CrossMark

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

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PMC full text: Acta Neuropathol. 2016; 131: 75–86.
Published online 2015 Dec 14. doi: 10.1007/s00401-015-1515-z
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Table 2

Preliminary NINDS criteria for the pathological diagnosis of CTE

Required for diagnosis of CTE
1. The pathognomonic lesion consists of p-tau aggregates in neurons, astrocytes, and cell processes around small vessels in an irregular pattern at the depths of the cortical sulci
Supportive neuropathological features of CTE
p-Tau-related pathologies:
1. Abnormal p-tau immunoreactive pretangles and NFTs preferentially affecting superficial layers (layers II–III), in contrast to layers III and V as in AD
2. In the hippocampus, pretangles, NFTs or extracellular tangles preferentially affecting CA2 and pretangles and prominent proximal dendritic swellings in CA4. These regional p-tau pathologies differ from the preferential involvement of CA1 and subiculum found in AD (Fig. 3)
3. Abnormal p-tau immunoreactive neuronal and astrocytic aggregates in subcortical nuclei, including the mammillary bodies and other hypothalamic nuclei, amygdala, nucleus accumbens, thalamus, midbrain tegmentum, and isodendritic core (nucleus basalis of Meynert, raphe nuclei, substantia nigra and locus coeruleus)
4. p-Tau immunoreactive thorny astrocytes at the glial limitans most commonly found in the subpial and periventricular regions
5. p-Tau immunoreactive large grain-like and dot-like structures (in addition to some threadlike neurites) (Fig. 2h)
Non-p-tau-related pathologies:
1. Macroscopic features: disproportionate dilatation of the third ventricle, septal abnormalities, mammillary body atrophy, and contusions or other signs of previous traumatic injury
2. TDP-43 immunoreactive neuronal cytoplasmic inclusions and dot-like structures in the hippocampus, anteromedial temporal cortex and amygdala (Fig. 4)
Age-related p-tau astrogliopathy that may be present; non-diagnostic and non-supportive [22]
1. Patches of thorn-shaped astrocytes in subcortical white matter
2. Subependymal, periventricular, and perivascular thorn-shaped astrocytes in the mediobasal regions
3. Thorn-shaped astrocytes in amygdala or hippocampus [22]

"the pathognomic lesion consists of p-tau aggregates in neurons, astrocytes and cell processes around small vessels in an irregular pattern at the depths of the cortical sulci"

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ORIGINAL PAPER

Hyperphosphorylated tau in young and middle-aged subjects

Adila Elobeid · Hilkka Soininen · Irina Alafuzoff

Received: 14 September 2011 / Revised: 16 October 2011 / Accepted: 17 October 2011 / Published online: 11 December 2011

Abstract The brain tissue obtained from ninety-five cognitively unimpaired subjects, with ages ranging from 22 to 50 years upon death, were immunohistochemically assessed for neurodegenerative changes, i.e., hyperphosphorylated tau (HPτ) and β-amyloid (Aβ) pathology in predilection neuroanatomical areas. HPτ pathology was observed in the transentorhinal cortex and/or the locus coeruleus (LC) in 33% of the subjects, without any obvious risk factors known to alter the microtubule-associated protein. HPτ pathology was noted in the LC in 25 out of 83 subjects (30%), lacking concomitant cortical Aβ or transentorhinal HPτ pathology. This observation was present even when assessing only one routine section of 7 μm thickness. The recent suggestion of prion-like propagation of neurodegeneration and the finding of neurodegeneration being quite common in middle-aged persons is alarming. It is noteworthy, however, that a substantial number of neurologically unimpaired subjects even at a very old age display only sparse to modest extent of neurodegenerative pathology. Thus, only a subset of subjects with neurodegenerative changes early in life seem to progress to a symptomatic disease with ageing. This observation brings forth the notion that other, yet unknown modifying factors influence the progression of degeneration that leads to a symptomatic disorder. The known association between alterations in the LC and mood disorders, and the finding of the LC being frequently affected with HPτ pathology suggest that clinicopathological studies on young subjects both with or without mood disorders are warranted.

Keywords Locus coeruleus · Hyperphosphorylated tau · Immunohistochemistry · Post-mortem study · Middle-aged · Cognitively unimpaired

"only a subset of subjects with neurodegenerative changes early in life ..progress to a symptomatic disease with ageing…yet unknown modifying factors influence the progression"

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Acta Neuropathol Commun. 2019; 7: 182.
Published online 2019 Nov 14. doi: 10.1186/s40478-019-0822-3
PMCID: PMC6857343
PMID: 31727161

DNA repair deficiency and senescence in concussed professional athletes involved in contact sports

Nicole Schwab,[1,2] Karl Grenier,[1,2] and Lili-Naz Hazrati[1,2]

Different neuropathological changes found in 38 former athletes with a history of TBI

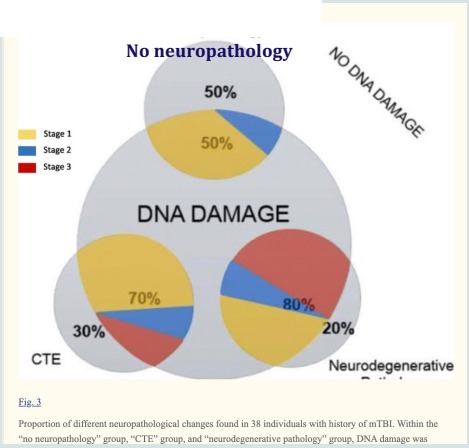

Fig. 3

Proportion of different neuropathological changes found in 38 individuals with history of mTBI. Within the "no neuropathology" group, "CTE" group, and "neurodegenerative pathology" group, DNA damage was

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CTE is equally common in people with and without clinical neurodegenerative symptoms

- CTE prevalence in people with neurodegenerative diseases (11.8%) was the same as in controls (12.8%).
- Patients with CTE died at a mean age of 81 years and that "most positive cases [were] likely to be clinically asymptomatic."
- CTE is found under the microscope in equal proportions of healthy normal asymptomatic people as it is in people with dementia and other diseases.

Acta Neuropathol (2015) 130:891–893
DOI 10.1007/s00401-015-1496-y

CrossMark

CORRESPONDENCE

Histological evidence of chronic traumatic encephalopathy in a large series of neurodegenerative diseases

Helen Ling[1] · Janice L. Holton[1] · Karen Shaw[1] · Karen Davey[1] · Tammaryn Lashley[1] · Tamas Revesz[1]

Table 1 Prevalence of histological evidence of chronic traumatic encephalopathy (CTE) in neurodegenerative disorders and controls

Primary pathological diagnosis	Number of screened cases	Cases with evidence of CTE histology (%)
Progressive supranuclear palsy	50	12 (24)
Parkinson's disease	50	8 (16)
Controls (>age 60 years)	47	6 (12.8)
Alzheimer's disease	20	2 (10)
Corticobasal degeneration	27	2 (7.4)
FTLDs[a]	24	1 (4.2)
Multiple system atrophy	50	1 (2)
	Total number of screened cases: 268	Overall prevalence: 32 (11.9)

FTLD frontotemporal lobar degeneration

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J Neuropathol Exp Neurol
Vol. 80, No. 3, March 2021, pp. 210–219
doi: 10.1093/jnen/nlab001

ORIGINAL ARTICLE

The Second NINDS/NIBIB Consensus Meeting to Define Neuropathological Criteria for the Diagnosis of Chronic Traumatic Encephalopathy

Kevin F. Bieniek, PhD, Nigel J. Cairns, PhD, FRCPath, John F. Crary, MD, PhD, Dennis W. Dickson, MD, Rebecca D. Folkerth, MD, C. Dirk Keene, MD, PhD, Irene Litvan, MD, Daniel P. Perl, MD, Thor D. Stein, MD, PhD, Jean-Paul Vonsattel, MD, William Stewart, PhD, FRCPath, Kristen Dams-O'Connor, PhD, Wayne A. Gordon, PhD, Yorghos Tripodis, PhD, Victor E. Alvarez, MD, Jesse Mez, MD, Michael L. Alosco, PhD, Ann C. McKee, MD, and the TBI/CTE Research Group

November 15, 16 2016

8 neuropathologists
27 cases

"The results of applying the McKee staging system to the cases in this consensus evaluation proved to be inconsistent.."

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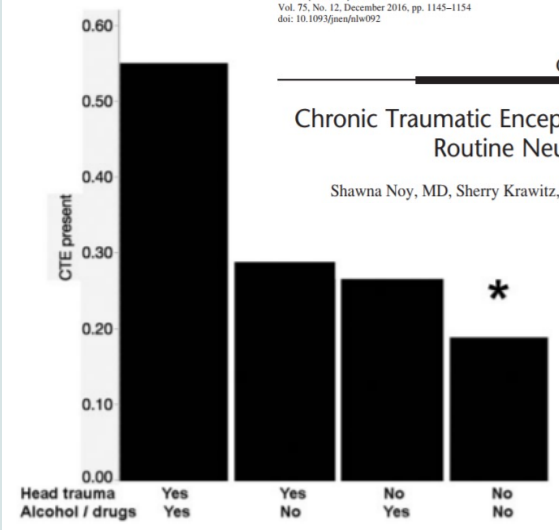

J Neuropathol Exp Neurol
Vol. 75, No. 12, December 2016, pp. 1145–1154
doi: 10.1093/jnen/nlw092

ORIGINAL ARTICLE

Chronic Traumatic Encephalopathy-Like Abnormalities in a Routine Neuropathology Service

Shawna Noy, MD, Sherry Krawitz, MD, PhD, and Marc R. Del Bigio, MD, PhD, FRCPC

"The combined history of head injury and alcohol and/or drug abuse was a significant predictor of any CTE-like changes. Age was also a significant predictor; most with any CTE-like changes were >40 years old. CTE-like changes were not identified at sites of contusion" n=111 subjects

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Contact sport athletes, regardless of injury, are at increased risk for "symptomless" CTE

- CTE pathology in 21/66 former athletes; 3 had prior concussions.
- CTE not seen in 198 non-athletes, of whom 33 had documented head trauma.
- There was no association between clinical symptoms and CTE

Acta Neuropathol (2015) 130:877–889
DOI 10.1007/s00401-015-1502-4

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ORIGINAL PAPER

Chronic traumatic encephalopathy pathology in a neurodegenerative disorders brain bank

Kevin F. Bieniek[1,2] · Owen A. Ross[1] · Kerry A. Cormier[3] · Ronald L. Walton[1] · Alexandra Soto-Ortolaza[1] · Amelia E. Johnston[4] · Pamela DeSaro[4] · Kevin B. Boylan[4] · Neill R. Graff-Radford[4] · Zbigniew K. Wszolek[4] · Rosa Rademakers[1] · Bradley F. Boeve[2] · Ann C. McKee[3,6] · Dennis W. Dickson[1]

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Abstract Chronic traumatic encephalopathy (CTE) is a progressive neurodegenerative disorder linked to repetitive traumatic brain injury (TBI) and characterized by deposition of hyperphosphorylated tau at the depths of sulci. We sought to determine the presence of CTE pathology in a brain bank for neurodegenerative disorders for individuals with and without a history of contact sports participation. Available medical records of 1721 men were reviewed for evidence of past history of injury or participation in contact sports. Subsequently, cerebral cortical samples were processed for tau immunohistochemistry in cases with a documented history of sports exposure as well as age- and disease-matched men and women without such exposure. For cases with available frozen tissue, genetic analysis was performed for variants in *APOE*, *MAPT*, and *TMEM106B*. Immunohistochemistry revealed 21 of 66 former athletes had cortical tau pathology consistent with CTE. CTE pathology was not detected in 198 individuals without exposure to contact sports, including 33 individuals with documented single-incident TBI sustained from falls, motor vehicle accidents, domestic violence, or assaults. Among those exposed to contact sports, those with CTE pathology did not differ from those without CTE pathology with respect to noted clinicopathologic features. There were no significant differences in genetic variants for those with CTE pathology, but we observed a slight increase in *MAPT* H1 haplotype, and there tended to be fewer homozygous carriers of the protective *TMEM106B* rs3173615 minor allele in those with sports exposure and CTE pathology compared to those without CTE pathology. In conclusion, this study has identified a small, yet significant, subset

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Review

A Clinical Approach to the Diagnosis of Traumatic Encephalopathy Syndrome A Review

Nicole Reams, MD; James T. Eckner, MD, MS; Andrea A. Almeida, MD; Andrea L. Aagesen, DO; Bruno Giordani, PhD; Hank Paulson, MD; Matthew T. Lorincz, MD, PhD; Jeffrey S. Kutcher, MD

JAMA Neurology June 2016 Volume 73, Number 6

-CTE is not the problem

-deposition of tau may be a response to injury or opioids that is reparative or normal aging

71% NFL players have abused opioids

The existence of CTE as currently described is not universally accepted in the neuropathology community. Recent research supports the concept that some deposition of tau is associated with normal human aging and does not necessarily indicate a pathologic entity.[13] Some studies also suggest that some tau aggregates may even have a protective role in vivo.[14,15] This supposition raises the question of whether the presence of tau is truly a marker of clinicopathologic features, with some authors suggesting that tau may indeed be a marker of neuronal injury after head trauma but that its association with clinical symptoms may not be causal.[16] Last, postmortem studies of symptomatic, retired professional athletes have described pathologic changes consistent with neurodegenerative diseases other than CTE or mixed pathologic changes with features consistent with CTE and another neurodegenerative disease, making delineation of the clinical and pathologic entities difficult.[17,18] Larger prospective studies that include matched controls are necessary to clarify the relationship between the clinical syndrome of TES and underlying pathologic features.

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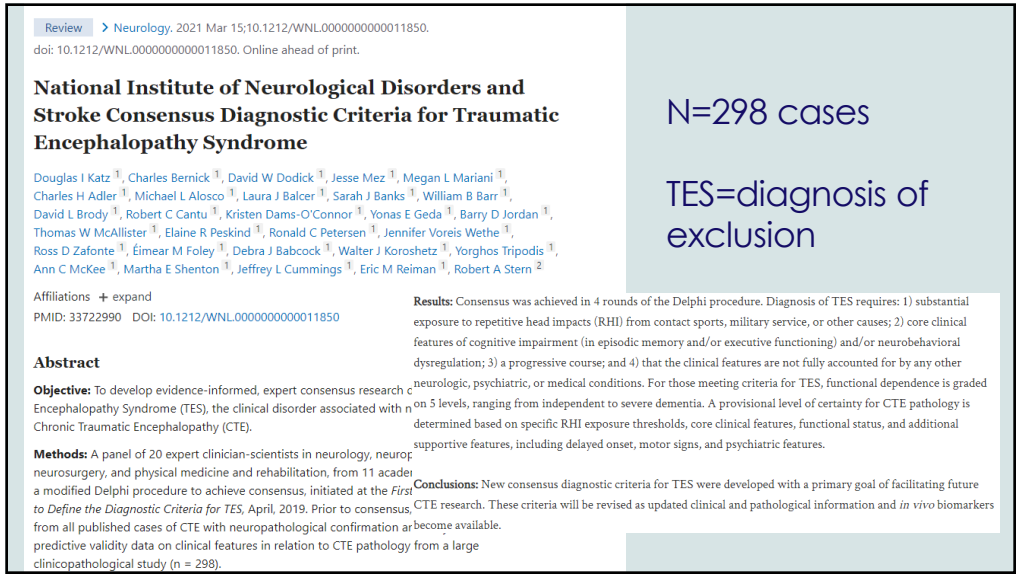

Review > Neurology. 2021 Mar 15;10.1212/WNL.0000000000011850.
doi: 10.1212/WNL.0000000000011850. Online ahead of print.

National Institute of Neurological Disorders and Stroke Consensus Diagnostic Criteria for Traumatic Encephalopathy Syndrome

Douglas I Katz [1], Charles Bernick [1], David W Dodick [1], Jesse Mez [1], Megan L Mariani [1], Charles H Adler [1], Michael L Alosco [1], Laura J Balcer [1], Sarah J Banks [1], William B Barr [1], David L Brody [1], Robert C Cantu [1], Kristen Dams-O'Connor [1], Yonas E Geda [1], Barry D Jordan [1], Thomas W McAllister [1], Elaine R Peskind [1], Ronald C Petersen [1], Jennifer Voreis Wethe [1], Ross D Zafonte [1], Éimear M Foley [1], Debra J Babcock [1], Walter J Koroshetz [1], Yorghos Tripodis [1], Ann C McKee [1], Martha E Shenton [1], Jeffrey L Cummings [1], Eric M Reiman [1], Robert A Stern [2]

Affiliations + expand
PMID: 33722990 DOI: 10.1212/WNL.0000000000011850

Abstract

Objective: To develop evidence-informed, expert consensus research c
Encephalopathy Syndrome (TES), the clinical disorder associated with n
Chronic Traumatic Encephalopathy (CTE).

Methods: A panel of 20 expert clinician-scientists in neurology, neurop
neurosurgery, and physical medicine and rehabilitation, from 11 acade
a modified Delphi procedure to achieve consensus, initiated at the *First to Define the Diagnostic Criteria for TES*, April, 2019. Prior to consensus,
from all published cases of CTE with neuropathological confirmation ar
predictive validity data on clinical features in relation to CTE pathology from a large clinicopathological study (n = 298).

Results: Consensus was achieved in 4 rounds of the Delphi procedure. Diagnosis of TES requires: 1) substantial exposure to repetitive head impacts (RHI) from contact sports, military service, or other causes; 2) core clinical features of cognitive impairment (in episodic memory and/or executive functioning) and/or neurobehavioral dysregulation; 3) a progressive course; and 4) that the clinical features are not fully accounted for by any other neurologic, psychiatric, or medical conditions. For those meeting criteria for TES, functional dependence is graded on 5 levels, ranging from independent to severe dementia. A provisional level of certainty for CTE pathology is determined based on specific RHI exposure thresholds, core clinical features, functional status, and additional supportive features, including delayed onset, motor signs, and psychiatric features.

Conclusions: New consensus diagnostic criteria for TES were developed with a primary goal of facilitating future CTE research. These criteria will be revised as updated clinical and pathological information and *in vivo* biomarkers become available.

N=298 cases

TES=diagnosis of exclusion

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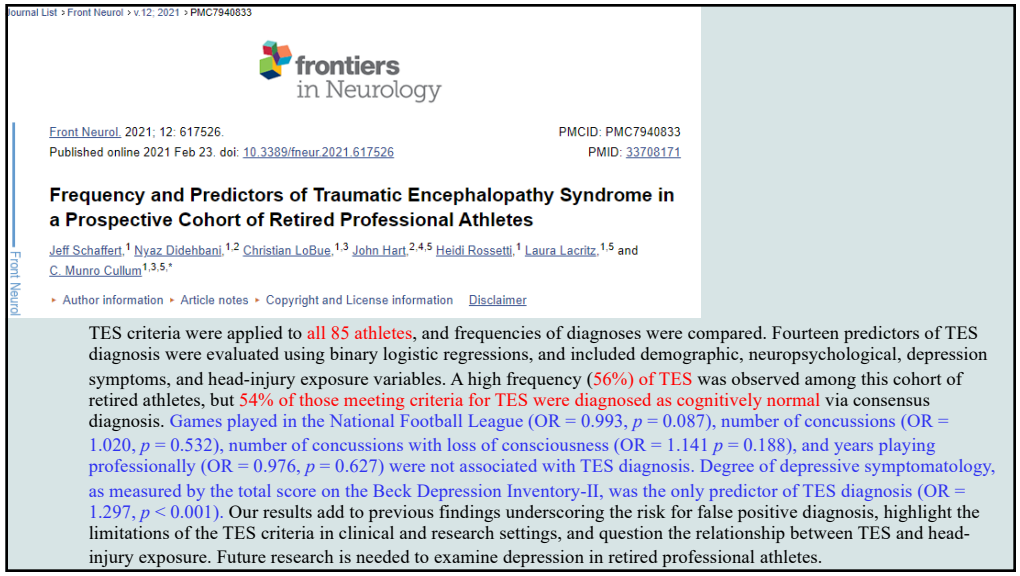

Journal List > Front Neurol > v.12; 2021 > PMC7940833

frontiers in Neurology

Front Neurol. 2021; 12: 617526.
Published online 2021 Feb 23. doi: 10.3389/fneur.2021.617526

PMCID: PMC7940833
PMID: 33708171

Frequency and Predictors of Traumatic Encephalopathy Syndrome in a Prospective Cohort of Retired Professional Athletes

Jeff Schaffert,[1] Nyaz Didehbani,[1,2] Christian LoBue,[1,3] John Hart,[2,4,5] Heidi Rossetti,[1] Laura Lacritz,[1,5] and C. Munro Cullum[1,3,5,*]

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Front Neurol

TES criteria were applied to all 85 athletes, and frequencies of diagnoses were compared. Fourteen predictors of TES diagnosis were evaluated using binary logistic regressions, and included demographic, neuropsychological, depression symptoms, and head-injury exposure variables. A high frequency (56%) of TES was observed among this cohort of retired athletes, but 54% of those meeting criteria for TES were diagnosed as cognitively normal via consensus diagnosis. Games played in the National Football League (OR = 0.993, $p = 0.087$), number of concussions (OR = 1.020, $p = 0.532$), number of concussions with loss of consciousness (OR = 1.141 $p = 0.188$), and years playing professionally (OR = 0.976, $p = 0.627$) were not associated with TES diagnosis. Degree of depressive symptomatology, as measured by the total score on the Beck Depression Inventory-II, was the only predictor of TES diagnosis (OR = 1.297, $p < 0.001$). Our results add to previous findings underscoring the risk for false positive diagnosis, highlight the limitations of the TES criteria in clinical and research settings, and question the relationship between TES and head-injury exposure. Future research is needed to examine depression in retired professional athletes.

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Schwab et al. Acta Neuropathologica Communications (2019) 7:182
https://doi.org/10.1186/s40478-019-0822-3

Acta Neuropathologica Communications

RESEARCH Open Access

DNA repair deficiency and senescence in concussed professional athletes involved in contact sports

Nicole Schwab[1,2], Karl Grenier[1,2] and Lili-Naz Hazrati[1,2*]

Maybe not everyone who plays contact sports is condemned to a neurodegenerative fate?

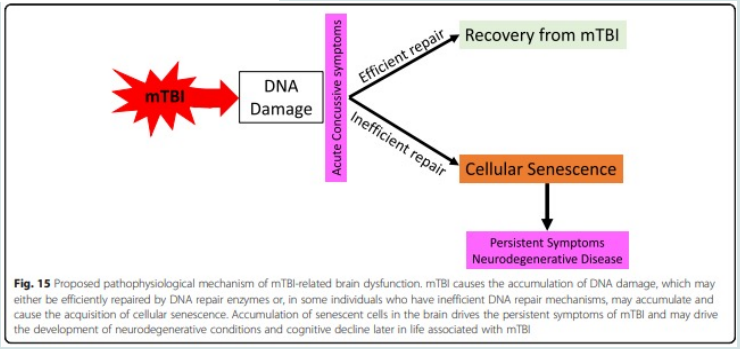

Fig. 15 Proposed pathophysiological mechanism of mTBI-related brain dysfunction. mTBI causes the accumulation of DNA damage, which may either be efficiently repaired by DNA repair enzymes or, in some individuals who have inefficient DNA repair mechanisms, may accumulate and cause the acquisition of cellular senescence. Accumulation of senescent cells in the brain drives the persistent symptoms of mTBI and may drive the development of neurodegenerative conditions and cognitive decline later in life associated with mTBI

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Does football increase risk of dementia?

438 Football Players followed for 50 years

Same risk for dementia as members of chorus, glee club or band

MAYO CLINIC

ORIGINAL ARTICLE

High School Football and Risk of Neurodegeneration: A Community-Based Study

Rodolfo Savica, MD, MSc; Joseph E. Parisi, MD; Lester E. Wold, MD; Keith A. Josephs, MD, MST, MSc; and J. Eric Ahlskog, PhD, MD

TABLE 1. Historical Cohort Study of Football Players vs Non–Football Players and Risk of Neurodegenerative Diseases[a]

	Football players (N=438)	Band/glee club/choir members (N=140)	HR	95% CI	*P* value[b]
Follow-up					
Years of follow-up[c]	50.2 (13.7, 57.5)	42.7 (8.8, 55.4)	...	...	.03
Age at follow-up[c]	68.4 (31.5, 75.6)	59.1 (26.7, 73.4)	...	...	.01
Outcome					
Dementia	13	2	1.58	0.36-7.01	.55
Parkinson disease	10	5	0.48	0.17-1.42	.19
Amyotrophic lateral sclerosis	2	1	0.52	0.05-5.68	.59

[a]HR = hazards ratio; CI = confidence interval.
[b]*P* values are for the Wilcoxon rank sum test.
[c]Values are median (25th percentile, 75th percentile).

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Rochester Epidemiology Project

From 1956-70

296 varsity football vs 196 wrestling, swimming, and basketball athletes

Football players more likely to have had a concussion

No difference in likelihood of dementia, Parkinsonism or ALS >50 years after injury

ORIGINAL ARTICLE

MAYO CLINIC

CrossMark

High School Football and Late-Life Risk of Neurodegenerative Syndromes, 1956-1970

Pieter H.H. Janssen; Jay Mandrekar, PhD; Michelle M. Mielke, PhD; J. Eric Ahlskog, PhD, MD; Bradley F. Boeve, MD; Keith Josephs, MD; and Rodolfo Savica, MD, PhD

Abstract

Objective: To assess whether athletes who played American varsity high school football between 1956 and 1970 have an increased risk of neurodegenerative diseases later in life.

Patients and Methods: We identified all male varsity football players between 1956 and 1970 in the public high schools of Rochester, Minnesota, and non–football-playing male varsity swimmers, wrestlers, and basketball players. Using the medical records linkage system of the Rochester Epidemiology Project, we ascertained the incidence of late-life neurodegenerative diseases: dementia, parkinsonism, and amyotrophic lateral sclerosis. We also recorded medical record–documented head trauma during high school years.

Results: We identified 296 varsity football players and 190 athletes engaging in other sports. Football players had an increased risk of medically documented head trauma, especially if they played football for more than 1 year. Compared with nonfootball athletes, football players did not have an increased risk of neurodegenerative disease overall or of the individual conditions of dementia, parkinsonism, and amyotrophic lateral sclerosis.

Conclusion: In this community-based study, varsity high school football players from 1956 to 1970 did not have an increased risk of neurodegenerative diseases compared with athletes engaged in other varsity sports. This was from an era when there was a generally nihilistic view of concussion dangers, less protective equipment, and no prohibition of spearing (head-first tackling). However, the size and strength

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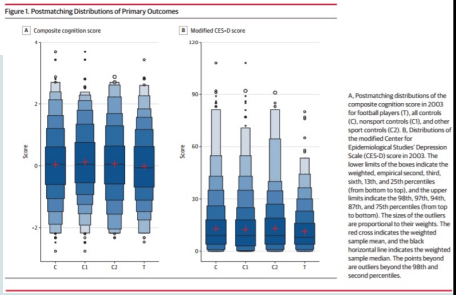
JAMA Neurology | Original Investigation

Association of Playing High School Football With Cognition and Mental Health Later in Life

Sameer K. Deshpande, BS; Raiden B. Hasegawa, BA; Amanda R. Rabinowitz, PhD; John Whyte, MD, PhD; Carol L. Roan, PhD; Andrew Tabatabaei; Michael Baiocchi, PhD; Jason H. Karlawish, MD; Christina L. Master, MD, CAQSM; Dylan S. Small, PhD

men who graduated from a Wisconsin high school in 1957:
834 played football
1858 did not



A, Postmatching distributions of the composite cognition score in 2003 for football players (T), all controls (C), nonsport controls (C1), and other sport controls (C2). B, Distributions of the modified Center for Epidemiological Studies' Depression Scale (CES-D) score in 2003. The lower limits of the boxes indicate the weighted, empirical second, third, sixth, 13th, and 25th percentiles (from bottom to top), and the upper limits indicate the 98th, 97th, 94th, 87th, and 75th percentiles (from top to bottom). The sizes of the outliers are proportional to their weights. The red cross indicates the weighted sample mean, and the black horizontal line indicates the weighted sample median. The points beyond are outliers beyond the 98th and second percentiles.

At ages 54, 65, 72 – no difference in
Cognition
Depression
Behavior/Anger/Anxiety/Alcohol abuse
Kids who did high school football more likely to play sports at age 35

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JNNP Online First, published on October 7, 2016 as 10.1136/jnnp-2016-314279
Neuropsychiatry

RESEARCH PAPER

Long-term health outcomes after exposure to repeated concussion in elite level: rugby union players

T M McMillan,[1] P McSkimming,[2] J Wainman-Lefley,[1] L M Maclean,[1] J Hay,[3] A McConnachie,[2] W Stewart[3,4]

52 players; 29 controls
Averaged 22 years of professional international rugby play
14 concussions on average
Average age of 54 years at assessment

Controls: higher CV disease
No differences in cognitive testing, general or mental health

Results The estimated number of concussions in RIRP averaged 14 (median=7; IQR 5-40). Performance was poorer in RIRP than controls on a test of verbal learning (p=0.022) and of fine co-ordination of the dominant hand (p=0.038) and not significantly different on other cognitive tests (p>0.05). There were no significant associations between number of concussions and performance on cognitive tests. Other than a higher incidence of cardiovascular disease in controls, no group differences were detected in general or mental health or estimates of allostatic load. In RIRP, persisting symptoms attributed to concussion were more common if reporting more than nine concussions (p=0.028), although these symptoms were not perceived to affect social or work functioning.

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So then why does this article about dementia feature a kid in a sports helmet?

IMPERFECT SCIENCE
1.) no controls (normal children change as they develop)
2.) ascertainment bias
3.) outcome measures assess risk of brain injury but not risk/benefit of sports

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$$$$ MOTIVATIONS
Researchers are dependent on positive results and "real life application" for their livelihood!

Lots of people want to profit from "the worried well" and kids playing sports

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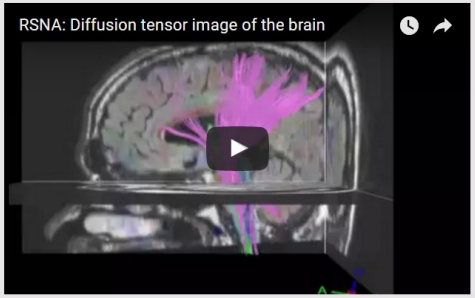
RSNA: Brain Changes Seen in Youth Football Players without Concussion



Researchers have found measurable brain changes in children after a single season of playing youth football, even without a concussion diagnosis, according to a new study published online, October 24, in the journal Radiology.

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25 boys aged 8-13 studied with accelerometers

Change in FA plotted vs risk-weighted cumulative exposure

1. There are no controls in this study

2. One outlier creates "significance"

3. We have no idea what the kids were doing with their accelerometers (?throwing them around)

4. We don't know what the kids were doing outside of football

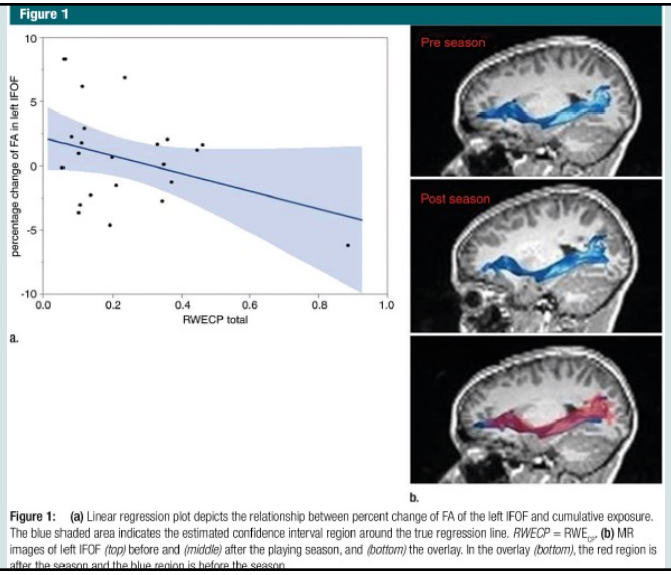

Figure 1: **(a)** Linear regression plot depicts the relationship between percent change of FA of the left IFOF and cumulative exposure. The blue shaded area indicates the estimated confidence interval region around the true regression line. *RWECP* = RWE_{cp}. **(b)** MR images of left IFOF *(top)* before and *(middle)* after the playing season, and *(bottom)* the overlay. In the overlay *(bottom)*, the red region is after the season and the blue region is before the season.

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July 25, 2017

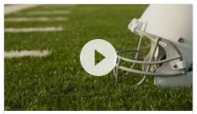
Clinicopathological Evaluation of Chronic Traumatic Encephalopathy in Players of American Football

Jesse Mez, MD, MS[1,2]; Daniel H. Daneshvar, MD, PhD[1,3]; Patrick T. Kiernan, BA[1,2]; et al

Author Affiliations | Article Information

JAMA. 2017;318(4):360-370. doi:10.1001/jama.2017.8334

Top stories



CTE found in 99% of studied brains from deceased NFL players

CNN · 2 hours ago

CTE Discovered in More Than 99 Percent of Deceased NFL Players' Brains in Study

Bleacher Report · 1 day ago

Brain study examined 111 former NFL players. Only one didn't have CTE.

Chicago Tribune · 1 day ago

More for cte study jama

"This study had several limitations. First, **a major limitation is ascertainment bias** associated with participation in this brain donation program. Although the criteria for participation were based on exposure to repetitive head trauma rather than on clinical signs of brain trauma, public awareness of a possible link between repetitive head trauma and CTE may have motivated players and their families with symptoms and signs of brain injury to participate in this research. **Therefore, caution must be used in interpreting the high frequency of CTE in this sample, and estimates of prevalence cannot be concluded or implied from this sample.**

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93 former football players studied --problems: ascertainment bias - no controls

J Neurotrauma. 2016 Mar 30. [Epub ahead of print]

Cumulative Head Impact Exposure Predicts Later-Life Depression, Apathy, Executive Dysfunction, and Cognitive Impairment in Former High School and College Football Players.

Montenigro PH[1], Alosco ML[2], Martin B[3], Daneshvar DH[4], Mez J[5], Chaisson C[6,7], Nowinski CJ[8], Au R[9], McKee AC[10], Cantu RC[11,12], McClean MD[13], Stern RA[14], Tripodis Y[15,16].

Author information

Abstract

Repetitive head impacts (RHI) refer to the cumulative exposure to concussive and subconcussive events. Although RHI is believed to increase risk for later-life neurological consequences (including chronic traumatic encephalopathy), quantitative analysis of this relationship has not yet been examined due to the lack of validated tools to quantify lifetime RHI exposure. The objectives of this study were: 1) to develop a metric to quantify cumulative RHI exposure from football, that we term the cumulative head impact index (CHII); 2) to use the CHII to examine the association between RHI exposure and long-term clinical outcomes; and (3) to evaluate its predictive properties relative to other exposure metrics (i.e., duration of play, age of first exposure, concussion history). Participants included 93 former high school and collegiate football players that completed objective cognitive and self-reported behavioral/mood tests as part of a larger ongoing longitudinal study. Using established cut-off scores, we transformed continuous outcomes into dichotomous variables (normal versus impaired). The CHII was computed for each participant and derived from a combination of self-reported athletic history (i.e., number of seasons, position(s), levels played), and impact frequencies reported in helmet accelerometer studies. A bivariate probit, instrumental variable model revealed a threshold dose-response relationship between the CHII and risk for later-life cognitive impairment ($p<0.0019$), self-reported executive dysfunction ($p<0.0003$), depression ($p<0.0009$), apathy ($p<0.0040$), and behavioral dysregulation ($p<.0001$). Ultimately, the CHII demonstrated greater predictive validity relative to other individual exposure metrics.

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Interrelationships Among Neuroimaging Biomarkers, Neuropsychological Test Data, and Symptom Reporting in a Cohort of Retired National Football League Players

Andrew W. Kuhn, BS; Scott L. Zuckerman, MD; Gary Solomon, PhD; Ira Casson

INTRODUCTION: Repetitive brain trauma (RBT) in American football has become a topic of recent interest. The objective of this study was to assess the interrelationships among neuroimaging findings with neurocognitive test performance and symptom endorsement in a cohort of retired professional (National Football League [NFL]) football players.

METHODS: Magnetic resonance imaging (MRI) scans were performed in 45 retired NFL players. Three neuroimaging parameters were recorded by blinded, board-certified neuroradiologists: (1) the absence or presence of small or large cavum septum pellucidum; (2) a global mean score of fractional anisotropy (FA); and (3) the presence or absence of microhemorrhages (microbleeds). The subjects underwent a battery of 9 paper-and-pencil neuropsychological tests (yielding 12 separate scores), a computerized neurocognitive test, and multiple (4) symptom and depression scales. The associations among the 3 independent neuroimaging results with these outcome measures were assessed using Pearson, Spearman Rank, and Point-Biserial Correlations.

RESULTS: Data from 45 retired NFL players (average age: 46.7 years) were analyzed. The retirees reported an average of 6.9 (±6.2) concussions and 13.0 (±7.9) sport-related "dings" in the NFL. Assessment of cavum septum pellucidum yielded a negative finding in 10 subjects (22%), while 32 (71%) had a small, and 3 (7%) had a large one. Four (9%) of the subjects had microhemorrhages present and average FA mean was 0.459 (±0.035). Number of sport-related "dings" was correlated with an increased risk of microhemorrhages ($r = 0.305$, $P = .042$). The majority (50.8%) of the correlations obtained among the 3 neuroimaging parameters and the neurocognitive/symptom scores were below the threshold of a "small" effect size ($r < 0.10$). The remaining (49.2%) correlations fell somewhere between "small" and "medium" effect sizes ($0.1 < r < 0.3$). However, all correlations were statistically nonsignificant.

CONCLUSION: The current results demonstrate minimal and statistically nonsignificant correlations among neuroimaging, neurocognitive, and symptom scores in a cohort of NFL retirees. The results indicate that, in this cohort, neuroimaging findings do not relate directly to neurocognitive test performance and clinical symptom burden. Although an often-accepted paradigm, associating the severity of structural brain changes with neurocognitive performance and symptom presentation after chronic RBT is complex, may involve other moderating variables, and requires further study.

45 former NFL players studied - Ascertainment bias can be used to demonstrate either side!

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Age of first exposure to football and later-life cognitive impairment in former NFL players

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ABSTRACT

Objective: To determine the relationship between exposure to repeated head impacts through tackle football prior to age 12, during a key period of brain development, and later-life executive function, memory, and estimated verbal IQ.

Methods: Forty-two former National Football League (NFL) players ages 40–69 from the Diagnosing and Evaluating Traumatic Encephalopathy using Clinical Tests (DETECT) study were matched by age and divided into 2 groups based on their age of first exposure (AFE) to tackle football: AFE <12 and AFE ≥12. Participants completed the Wisconsin Card Sort Test (WCST), Neuropsychological Assessment Battery List Learning test (NAB-LL), and Wide Range Achievement Test, 4th edition (WRAT-4) Reading subtest as part of a larger neuropsychological testing battery.

Results: Former NFL players in the AFE <12 group performed significantly worse than the AFE ≥12 group on all measures of the WCST, NAB-LL, and WRAT-4 Reading tests after controlling for total number of years of football played and age at the time of evaluation, indicating executive dysfunction, memory impairment, and lower estimated verbal IQ.

Conclusions: There is an association between participation in tackle football prior to age 12 and greater later-life cognitive impairment measured using objective neuropsychological tests. These findings suggest that incurring repeated head impacts during a critical neurodevelopmental period may increase the risk of later-life cognitive impairment. If replicated with larger samples and longitudinal designs, these findings may have implications for safety recommendations for youth sports. *Neurology*® 2015;84:1114–1120

Study of 42 former NFL players:

No controls
Ascertainment bias

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Age at first exposure to tackling does not result in increased risk of neurocognitive deficits

American Journal of Sports Medicine February 2016

Participation in Pre–High School Football and Neurological, Neuroradiological, and Neuropsychological Findings in Later Life

A Study of 45 Retired National Football League Players

Gary S. Solomon,*† PhD, Andrew W. Kuhn,‡ BA, Scott L. Zuckerman,† MD, Ira R. Casson,§ MD, David C. Viano,‖¶ DrMed, PhD, Mark R. Lovell,# PhD, and Allen K. Sills,* MD
Investigation performed at Vanderbilt University School of Medicine, Nashville, Tennessee, USA

Background: A recent study found that an earlier age of first exposure (AFE) to tackle football was associated with long-term neurocognitive impairment in retired National Football League (NFL) players.

Purpose: To assess the association between years of exposure to pre–high school football (PreYOE) and neuroradiological, neurological, and neuropsychological outcome measures in a different sample of retired NFL players.

Study Design: Cross-sectional study; Level of evidence, 3.

Methods: Forty-five former NFL players were included in this study. All participants prospectively completed extensive history taking, a neurological examination, brain magnetic resonance imaging, and a comprehensive battery of neuropsychological tests. To measure the associations between PreYOE and these outcome measures, multiple regression models were utilized while controlling for several covariates.

Results: After applying a Bonferroni correction for multiple comparisons, none of the neurological, neuroradiological, or neuropsychological outcome measures yielded a significant relationship with PreYOE. A second Bonferroni-corrected analysis of a subset of these athletes with self-reported learning disability yielded no significant relationships on paper-and-pencil neurocognitive tests but did result in a significant association between learning disability and computerized indices of visual motor speed and reaction time.

Conclusion: The current study failed to replicate the results of a prior study, which concluded that an earlier AFE to tackle football might result in long-term neurocognitive deficits. In 45 retired NFL athletes, there were no associations between PreYOE and neuroradiological, neurological, and neuropsychological outcome measures.

Keywords: concussion; football; National Football League; exposure; youth

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frontiers in Neurology

REVIEW
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Age of First Exposure to Contact and Collision Sports and Later in Life Brain Health: A Narrative Review

Grant L. Iverson[1,2,3,4*], *Flonn Büttner*[5] *and Jaclyn B. Caccese*[6,7]

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The best available evidence to date suggests that earlier AFE to contact or collision sports is not associated with worse cognitive functioning or mental health in (i) current high school athletes, (ii) current collegiate athletes (84, 87, 88, 90, 111, 123, 124), or (iii) middle-aged men who played high school football (85, 86).

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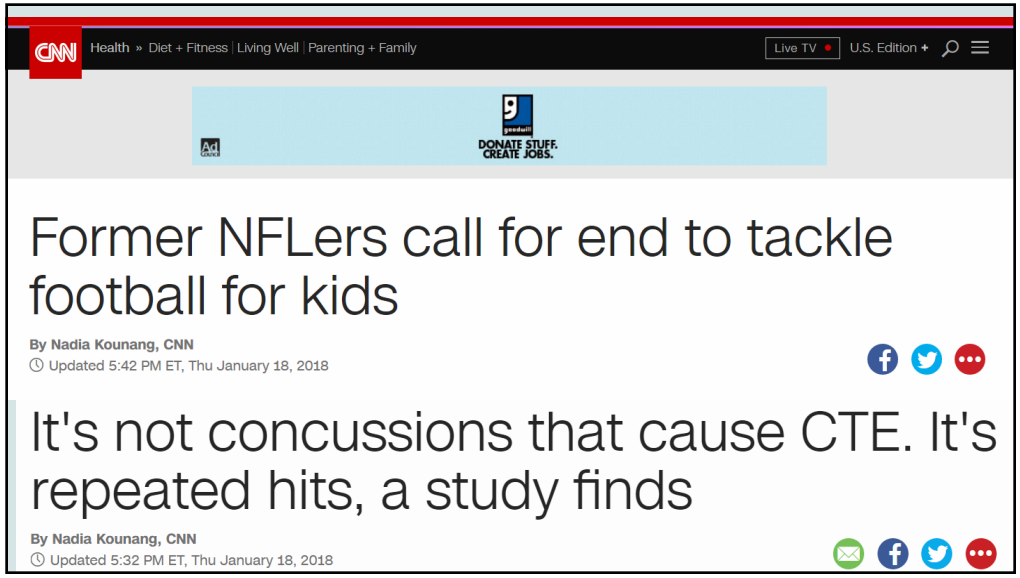

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DON'T START BANNING STUFF WHEN YOU DON'T UNDERSTAND IT!

Neurologic decline is complex, with multiple causes (not just brain injury) and pathophysiologies and treatment of a "single pathology" especially one with dubious connection to symptoms is unlikely to be successful.

When you can't accurately measure and classify a problem, don't count on being able to treat it!

THE WALL STREET JOURNAL

Pfizer abandons costly hunt for new Alzheimer's, Parkinson's drugs

Published: Jan 7, 2018 5:24 p.m. ET

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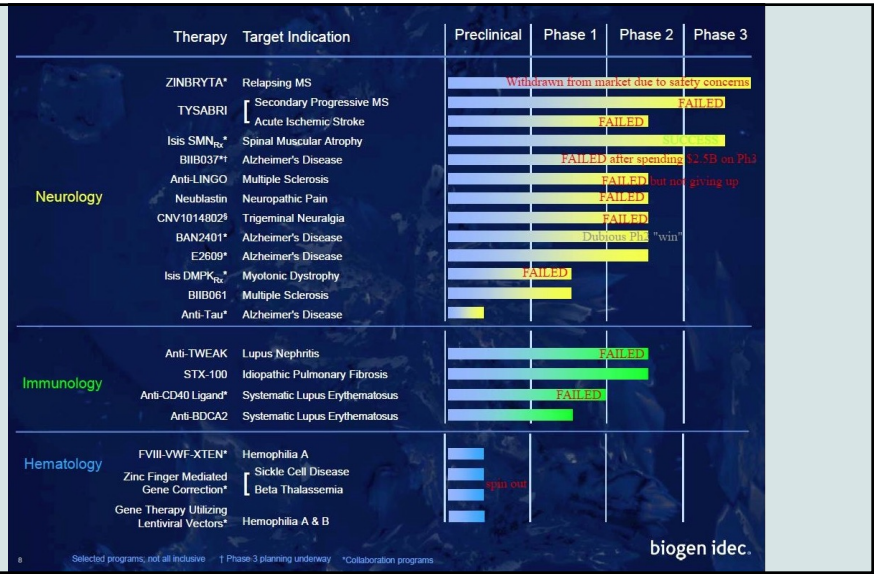
Twitter:

$BIIB



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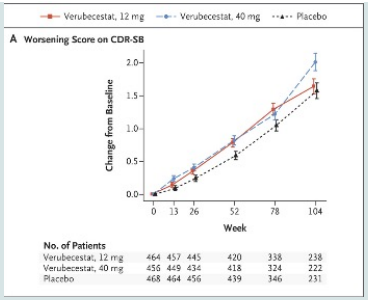
The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE

Randomized Trial of Verubecestat for Prodromal Alzheimer's Disease

Michael F. Egan, M.D., James Kost, Ph.D., Tiffini Voss, M.D., Yuki Mukai, M.D., Paul S. Aisen, M.D., Jeffrey L. Cummings, M.D., Sc.D., Pierre N. Tariot, M.D., Bruno Vellas, M.D., Ph.D., Christopher H. van Dyck, M.D., Merce Boada, M.D., Ying Zhang, Ph.D., Wen Li, Ph.D., et al.

CONCLUSIONS

Verubecestat did not improve clinical ratings of dementia among patients with prodromal Alzheimer's disease, and some measures suggested that cognition and daily function were worse among patients who received verubecestat than among those who received placebo. (Funded by Merck Sharp & Dohme; ClinicalTrials.gov number, NCT01953601.)



"…scores on the CDR-SB were also higher (signifying more impairment of cognition and daily functioning) in the 40-mg group than in the placebo group at 13, 26, and 52 weeks, with the lower limit of unadjusted confidence intervals greater than 0, suggesting but not confirming the possibility of worse performance at these earlier time points in

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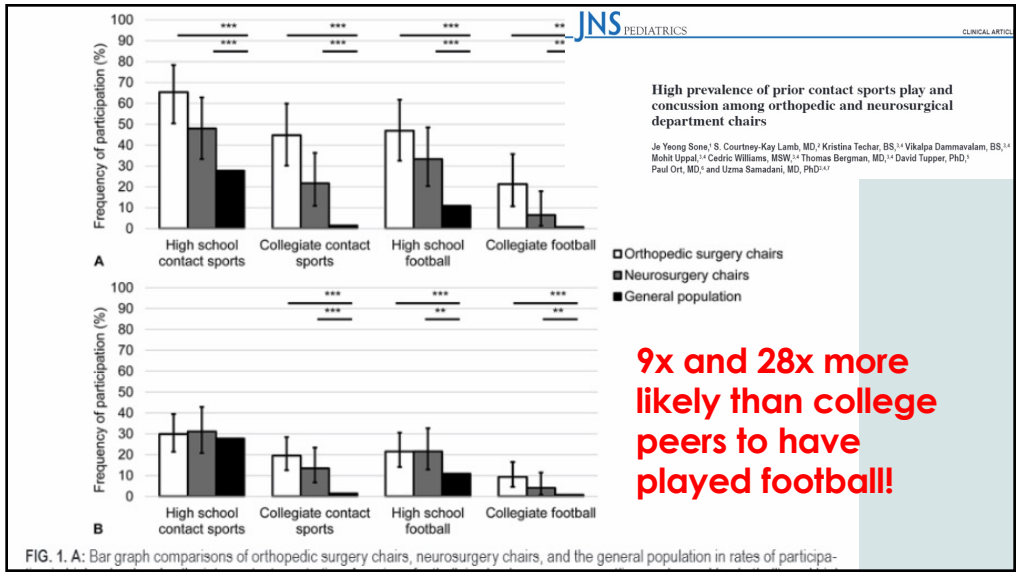
JNS PEDIATRICS
High prevalence of prior contact sports play and concussion among orthopedic and neurosurgical department chairs
Frequency of participation (%)
High school contact sports
Collegiate contact sports
High school football
Collegiate football
A
B
Orthopedic surgery chairs
Neurosurgery chairs
General population
9x and 28x more likely than college peers to have played football!
FIG. 1. A: Bar graph comparisons of orthopedic surgery chairs, neurosurgery chairs, and the general population in rates of participa-

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76% orthopedic chairs
86% neurosurgery chairs
90% TBI experts
allowed their own children to play contact sports

suggesting that the more one understands brain injury the more likely they are to allow children to play contact sports

>70% pediatricians surveyed want to ban tackle football

Only 5.4% feel comfortable treating a child with PCS

			Does the subject have any child or children who have played contact sports?		
			None	Yes	Total
js2: Which sample group?	Orthopedic Surgery Chairs	Count	7	22	29
		% within js2: Which sample group?	24.1%	75.9%	100.0%
		% within Does the subject have any child or children who have played contact sports?	46.7%	31.0%	33.7%
	Neurosurgery Chairs	Count	6	32	38
		% within js2: Which sample group?	15.8%	84.2%	100.0%
		% within Does the subject have any child or children who have played contact sports?	40.0%	45.1%	44.2%
	Other TBI Experts (non-chair neurosurgeons, scientists, and chairs of other departments)	Count	2	17	19
		% within js2: Which sample group?	10.5%	89.5%	100.0%
		% within Does the subject have any child or children who have played contact sports?	13.3%	23.9%	22.1%
Total		Count	15	71	86
		% within js2: Which sample group?	17.4%	82.6%	100.0%
		% within Does the subject have any child or children who have played contact sports?	100.0%	100.0%	100.0%

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What Do These Men Have In Common?


Franklin D. Roosevelt


Dwight D. Eisenhower


John F. Kennedy


Richard Nixon


Gerald Ford


Jimmy Carter

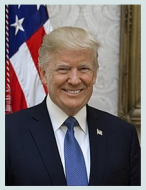

Ronald Reagan


George H. W. Bush


Bill Clinton


George W. Bush


Barack Obama


Donald Trump

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We think we understand the risk of contact sports….

But do we really???

And what about the benefits?

……

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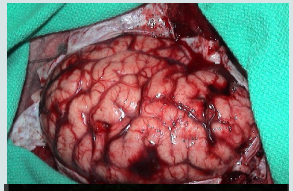

BENEFIT	RISK
None	High blood pressure Vascular disease Cancer Lung disease
None	Seizures Headaches Motor Disorders Depression Executive Dysfunction Cognitive Delay
Reduces Obesity and Diabetes Reduces Depression/SI Reduces High Blood Pressure Reduces Heart Disease Reduces Stroke Reduces Dementia Reduces 13 Types of Cancer Risk Complex Psychosocial Benefit ???	Brain or Other Injury

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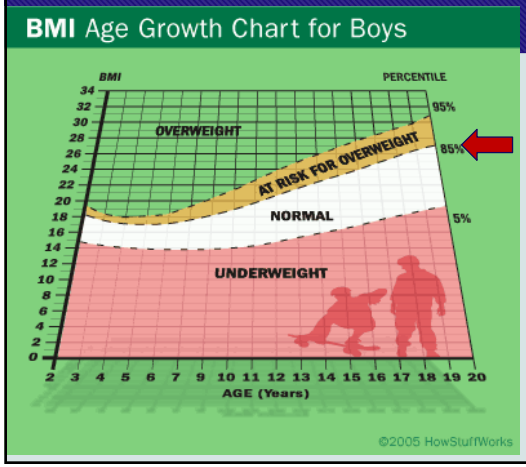
The children who choose to play football have an average BMI of 26.3 and thus are at highest risk for complications of obesity



>1,000,000 American children play high school football (track 2nd, b-ball 3rd)
An additional >1,000,000 play Pop Warner or other league football
#1 participation sport in American high schools

If even half of those children became sedentary (rejected soccer, cross country and other fall sport options) the resultant increase in sedentary lifestyle/obesity risks would be enormous **(hypertension, diabetes, cardiovascular disease, 13 cancers, osteoporosis)**

BMI of 17-25 is considered healthy

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The obese child sees a greater cardiovascular risk reduction than the lean child with aerobic interval training

Impaired Cardiac Function Among Obese Adolescents

Effect of Aerobic Interval Training

Charlotte Bjork Ingul, MD, PhD; Arnt Erik Tjonna, PhD; Tomas Ottemo Stolen, PhD; Asbjorn Stoylen, MD, PhD; Ulrik Wisloff, PhD

Objectives: To measure cardiac function before and after 3 months of aerobic interval training in obese adolescents and to compare the findings with those in lean counterparts.

Design: Exercise intervention study. Cardiac function was assessed by echocardiography and maximal oxygen uptake by ergospirometry.

Setting: The obese adolescents were referred from general practice to the St Olav University Hospital, Trondheim, Norway, and the control group was recruited from 2 schools.

Participants: Ten obese adolescents (mean [SD] age, 14.8 [1.2] years; mean [SD] body mass index [BMI; calculated as weight in kilograms divided by height in meters squared], 33.5 [4.3]) and 10 lean counterparts (mean [SD] age, 14.9 [1.3] years; mean [SD] BMI, 20.4 [3.0]) participated.

Intervention: Aerobic interval training (4 × 4 minutes at 90% of maximal heart rate, 40 minutes of training in total) was performed twice per week for 13 weeks among the obese adolescents, whereas the lean counterparts only performed the tests.

Main Outcome Measures: Left ventricular end-diastolic volume, stroke volume, and maximal oxygen uptake.

Results: Maximal oxygen uptake was 41.4% lower among the obese adolescents compared with the lean counterparts, but the maximal oxygen uptake increased by 8.6% ($P = .008$) after intervention. Obese adolescents initially had 7.8% and 14.5% lower left ventricular end-diastolic and stroke volumes, 21.3% reduced global strain rate and 16.3% global strain, reduced mitral annulus excursion and systolic/diastolic tissue velocity, longer isovolumic relaxation time, and longer deceleration time compared with the lean counterparts. No group difference was observed after the intervention. Aerobic interval training increased the ejection fraction but was lower compared with the lean counterparts. Aerobic interval training reduced fat content by 2.0% ($P = .005$) among the obese adolescents.

Conclusions: Aerobic interval training almost restored an impaired systolic and diastolic cardiac function among obese adolescents when compared with lean counterparts. These results may have implications for future treatment programs for obese adolescents.

Trial Registration: clinicaltrials.gov Identifier: NCT00184236

Arch Pediatr Adolesc Med. 2010;164(9):852-859

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The kids who are most likely to experience medical benefit from playing football are those who may not have predilection for other sports

Exercise Dose and Diabetes Risk in Overweight and Obese Children

A Randomized Controlled Trial

Catherine L. Davis, PhD
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Jennifer L. Waller, PhD
Jerry D. Allison, PhD
B. Adam Dennis, MD
Reda Bassali, MD
Agustín Meléndez, PhD
Colleen A. Boyle, PhD
Barbara A. Gower, PhD

Context Pediatric studies have shown that aerobic exercise reduces metabolic risk, but dose-response information is not available.

Objectives To test the effect of different doses of aerobic training on insulin resistance, fatness, visceral fat, and fitness in overweight, sedentary children and to test moderation by sex and race.

Design, Setting, and Participants Randomized controlled efficacy trial conducted from 2003 through 2007 in which 222 overweight or obese sedentary children (mean age, 9.4 years; 42% male; 58% black) were recruited from 15 public schools in the Augusta, Georgia, area.

Intervention Children were randomly assigned to low-dose (20 min/d; n=71) or high-dose (40 min/d; n=73) aerobic training (5 d/wk; mean duration, 13 [SD, 1.6] weeks) or a control condition (usual physical activity; n=78).

Main Outcome Measures The prespecified primary outcomes were postintervention type 2 diabetes risk assessed by insulin area under the curve (AUC) from an oral glucose tolerance test, aerobic fitness (peak oxygen consumption [$\dot{V}O_2$]), percent body fat via dual-energy x-ray absorptiometry, and visceral fat via magnetic resonance, analyzed by intention to treat.

Results The study had 94% retention (n=209). Most children (85%) were obese. At baseline, mean body mass index was 26 (SD, 4.4). Reductions in insulin AUC were larger in the high-dose group (adjusted mean difference, −3.56 [95% CI, −6.26 to −0.85] × 10^3 μU/mL; $P = .01$) and the low-dose group (adjusted mean difference, −2.96 [95% CI, −5.69 to −0.22] × 10^3 μU/mL; $P = .03$) than the control group. Dose-response trends were also observed for body fat (adjusted mean difference, −1.4% [95% CI, −2.2% to −0.7%]; $P < .001$ and −0.8% [95% CI, −1.6% to −0.07%]; $P = .03$) and visceral fat (adjusted mean difference, −3.9 cm^3 [95% CI, −6.0 to −1.7 cm^3]; $P < .001$ and −2.8 cm^3 [95% CI, −4.9 to −0.6 cm^3]; $P = .01$) in the high- and low-dose vs control groups, respectively. Effects in the high- and low-dose groups vs control were similar for fitness (adjusted mean difference in peak $\dot{V}O_2$, 2.4 [95% CI, 0.4-4.5] mL/kg/min; $P = .02$ and 2.4 [95% CI, 0.3-4.5] mL/kg/min; $P = .03$, respectively). High- vs low-dose group effects were similar for these outcomes. There was no moderation by sex or race.

Conclusion In this trial, after 13 weeks, 20 or 40 min/d of aerobic training improved fitness and demonstrated dose-response benefits for insulin resistance and general and visceral adiposity in sedentary overweight or obese children, regardless of sex or race.

Trial Registration clinicaltrials.gov Identifier: NCT00108901

JAMA. 2012;308(11):1103-1112

CHILD OBESITY AND OVERweight are epidemic in US children.[1] A third of elementary school–aged children are overweight or obese.[2] Childhood obesity is associated with a number of adverse conditions formerly thought to occur only in adults, including type 2 diabetes and atherosclerosis.[3-5] Overweight, minority race/ethnicity, and family history of diabetes are risk factors for type 2 diabetes in youth.[6]

The Diabetes Prevention Program demonstrated reduction in diabetes risk among adults with prediabetes through diet and exercise.[7] Some dose-response relationships between exercise and metabolic risk have been demonstrated in adults.[10] Previous studies in children have shown reduction in metabolic risk factors through exercise,[11-13] but dose-response information needed to formulate evidence-based public health recommendations

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	Units	Predicted	Pre Actual	Pre % Pred.	Post Actual	Post % Pred.
FVC	L	4.27	3.71	87 %	3.75	88 %
FEV1	L	3.64	2.57	71 %	2.55	70 %
FEV1/FVC	%	85 %	69 %	81 %	68 %	80 %
FEF25-75%	L/S	3.86	1.72	45 %	1.66	43 %
PEF	L/S	7.48	6.06	81 %	5.98	80 %
Exp. Time	Sec.		6.08		5.63	
Best FVC	L	4.27	3.71	87 %	3.75	88 %
Best FEV1	L	3.64	2.57	71 %	2.55	70 %

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Perhaps the children could play tennis… or maybe golf?

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I didn't make it Past the 3 Sponsors!!!!!

Membership Information

WCC offers three levels of membership - Golf Membership, Sporting Membership and Social Membership; with each category offering a different level of access to our facilities. Each prospective Member must be sponsored by at least three current Wayzata Country Club Members.

Wayzata Country Club is a private, member-owned country club.
Membership is extended by invitation only.

For more information or to inquire about our memberships by invitation, please contact:
Marget Seehof, Membership Director | 952-475-9741 | membership@wayzatacc.com

MEMBERSHIP CATEGORIES	SPONSOR REQUIREMENTS
GOLF MEMBERSHIP Several golf Membership categories are available depending on age and residency. Privileges include all golf facilities and services, Pool and Tennis facilities, Trap & Skeet facility, Archery Park, Massage Therapy Center, Winter Wonderland, private and corporate event spaces*, as well as all social and dining privileges. An initiation fee, monthly dues and an annual food purchase minimum are required of these Membership categories. The terms and conditions and period of time for payment of the initiation fee is based on the age of the new golf Member; the age of the younger spouse in the case of married nominees, at the time the nomination documents are received.	**Must have the following sponsors:** Any combination of: • Full Privilege Golf • Full Privilege Junior Golf • Senior Golf • Restricted Non-Resident

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Sports are not one size fits all - We need to get kids active however we can!
Focus needs to be on manipulating the risk/benefit threshold to optimize benefit!

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Reduce Risk by Following American Academy of Pediatrics Recommendations

- Follow the rules
- Reduce contact drills/practices
- Neck strengthening
- Tackle technique improvement

- WHEN AN INJURY OCCURS A KID SHOULD HAVE PROPER CARE

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Manipulate the Risk/Benefit Threshold
Contract with the Child Not to Push Through the Injury! – this requires culture change

The Coach-KID-AT-parent-team relationship is critical

Parents/coaches/AT need to listen and care but not PUSH

WHEN AN INJURY OCCURS A KID SHOULD HAVE PROPER CARE!!

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Keep the Endgame In Mind!!
Goal of Long Healthy Life (99.9%) or Playing in the Pros

- The child needs to understand that they will play their best game if they are healthy
- Therefore they should be incentivized to report injuries
- WHEN AN INJURY OCCURS A KID SHOULD HAVE PROPER CARE

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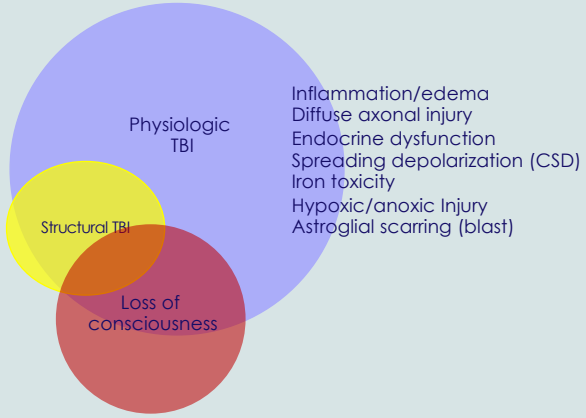
In addition to making sports safer, we also need to focus on better diagnosis and treatment of brain injury



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Mechanisms for Assessing the Central Nervous System

Physical and psych examination – physiology	fxl heterogeneity, skilled examiner, time, bias
Plain films (xray) – what it looks like	radiation, not much information
EEG – electrical activity	technician, interpreter, time,
Angiography – what it looks like	radiation, not full information, $
EMG/NCS/SSEPS – assesses integrity	painful, technician, time,
CT scan – what it looks like	radiation, technician, time, $
TCDs, orbital, transcutaneous flow – blood flow.	technician, arbitrary #
MRI scan - what it looks like, some fx	time, technician, claustrophobia/instability, $$
ICP /licox monitoring – pressure, brain O_2	risk of devastating hemorrhage, arbitrary #, $$
Serum markers – molecular biology	time dependent; requires blood, lab
Uncalibrated eye movement tracking	patient needs to be able to open eyes
Pupillometry	less conscious patient

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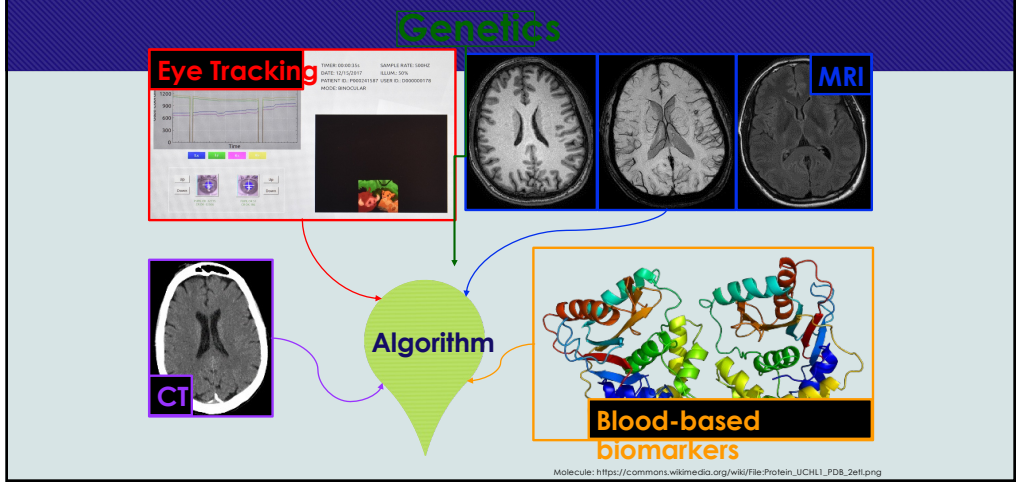
Hierarchical Approach to Classification of Problem



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Thank You!!

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