CANADIAN CONCUSSION CENTRE

LIUNA FREE WEBINAR SERIES, MARCH 19, 2024

Title:

Concussion: An Invisible Brain Injury with Consequences

Presenter:

Dr. Carmela Tartaglia

Speaker's Biography

Dr. Tartaglia is an Associate Professor and Clinician-Scientist at the University of Toronto. She received her medical degree from McGill University, completed her residency at the University of Western Ontario and did three years of clinical/research fellowship in cognitive/behavioral neurology at the University of California, San Francisco Memory and Aging Center. She maintains a cognitive/behavioral clinic where she sees people with neurodegenerative disease and post-concussion symptoms within the UHN Memory Clinic. Her clinical and research interests lie in neurodegenerative diseases with a focus on frontotemporal lobar degeneration (FTLD) and possible chronic traumatic encephalopathy.

Concussion: An Invisible Brain Injury with Consequences

CARMELA TARTAGLIA, MD

UNIVERSITY HEALTH NETWORK MEMORY CLINIC

TANZ CENTRE FOR RESEARCH IN NEURODEGENERATIVE DISEASES

CANADIAN CONCUSSION CENTRE
Research | Diagnosis | Solutions

U of T NEUROLOGY

Tanz Centre for Research in Neurodegenerative Diseases
UNIVERSITY OF TORONTO

UHN
Toronto General
Toronto Western
Princess Margaret
Toronto Rehab

DISCLOSURE

- CIHR, NIH
- CLINICAL TRIALS: BIOGEN, ROCHE, ANAVEX, JANSSEN, ELI LILLY, UCB, NOVO NORDISK

TYPES OF BRAIN INJURIES

- **Concussion/mild traumatic brain injury (mTBI)**
  - often used interchangeably
    - mTBI Glascow coma scale 13-15 at 30min post-injury +
      - <30min LOC
      - <24hr post-traumatic amnesia
      - Impaired mental status at time of accident (confusion, disorientation etc)
      - Transient neurological deficit
- Moderate-severe TBI: bruising or contusion, tearing/laceration, bleeding

CONCUSSION

- Acute BRAIN effect of blunt impact or other mechanical energy applied to the head or other body part such as from sudden acceleration, deceleration or rotational forces.
  - trauma does not have to be directly to head, can be from whiplash effect on the brain or trauma elsewhere on the body
  - immediate and temporary alteration of mental functioning due to trauma

MILD TRAUMATIC BRAIN INJURY/ CONCUSSION

- Growing epidemic (sports, military, falls, abuse etc)
- Incidence of mTBI: 200–300/100,000 persons per year for hospitalized patients; 2X as high if non-hospitalized patients included (>700/10000)
- 750,000 concussions/year in NA
- **About 150,000 concussions in Ontario/year**
- Under-reported-most stats from hospitals (most w/ LOC only)

Langlois JA, et al. (2008). *J Head Trauma Rehab*., Hoge CW et al.. *N Engl J Med*. 2008, WHO 2020.

CONCUSSION DIAGNOSIS

- Clinical diagnosis
  - **No diagnostic test**

FDA News Release

FDA authorizes marketing of first blood test to aid in the evaluation of concussion in adults

New quick testing option to help reduce need for CT scans, radiation exposure for patients

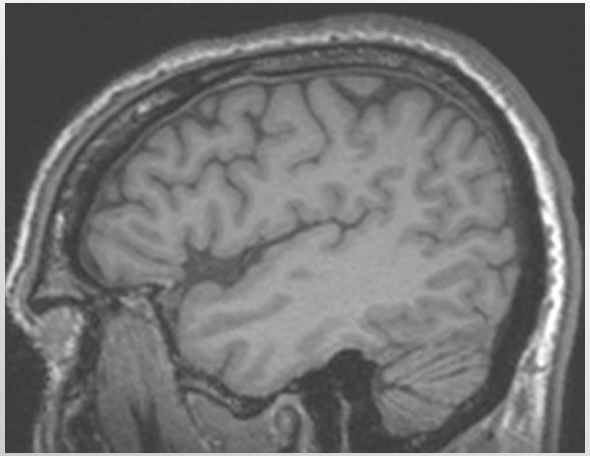
SHARE | TWEET | LINKEDIN | PIN IT | EMAIL | PRINT

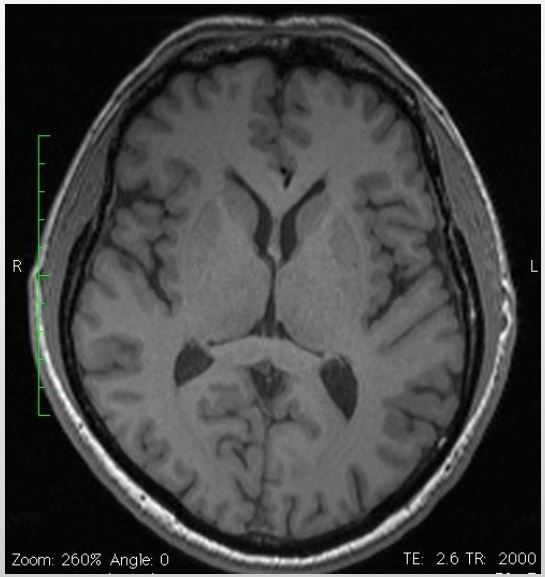
For Immediate Release February 14, 2018

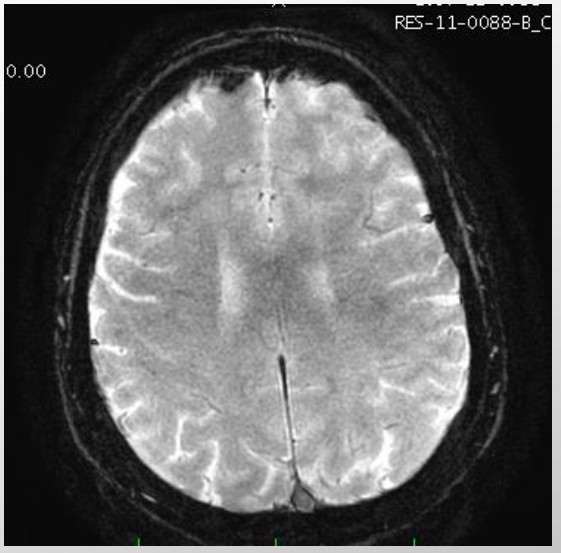
  - Brain trauma indicator test - UCH-l1 and GFAP for more severe injury - cannot diagnose concussion
- Heterogenous population
- No 2 people suffer the same after a head injury

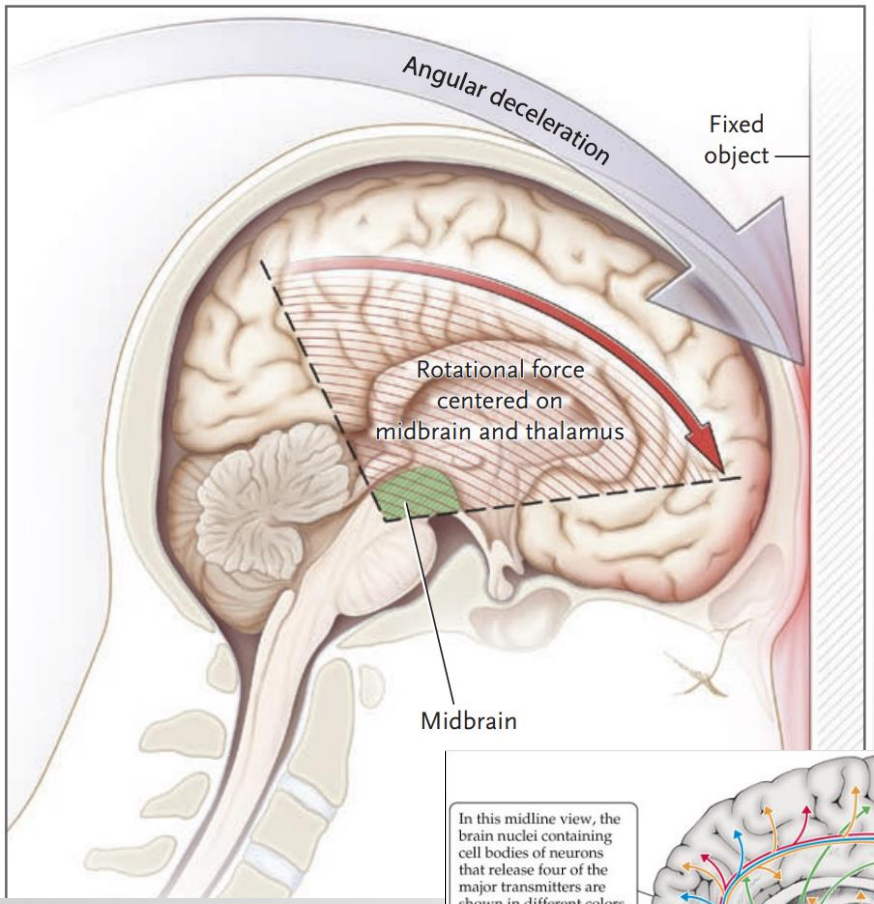
CONCUSSION DIAGNOSIS

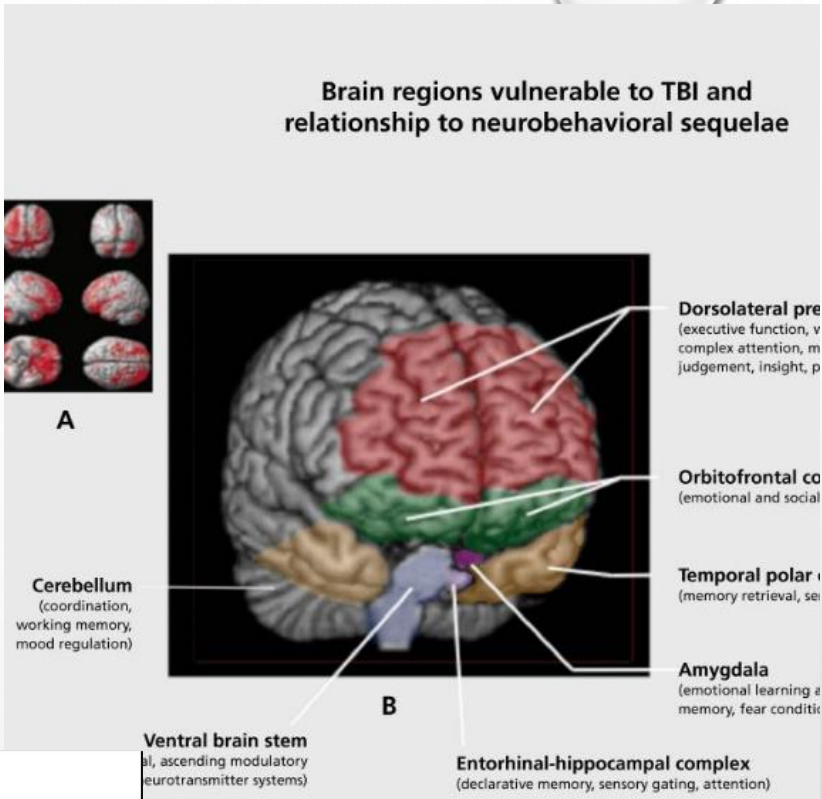
- Usually brain MRI does not show any abnormalities related to concussion but…

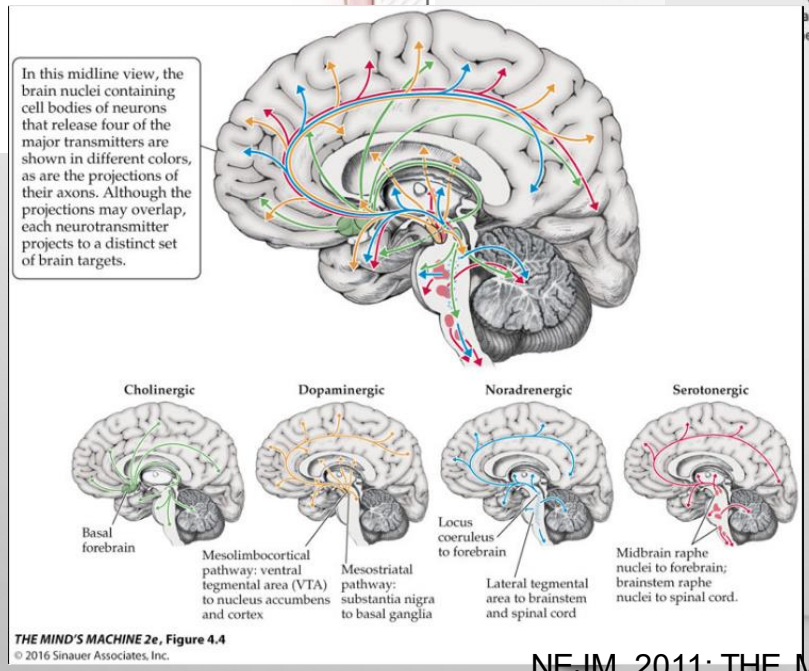












NEJM, 2011; THE MIND'S MACHINE 2004, ARCINIEGAS 2001

CONCUSSION SYMPTOMS VARY AMONG PATIENTS

COGNITIVE SYMPTOMS

Difficulty thinking-confusion

Slowed processing

Difficulty remembering

Unable to concentrate

PERSONALITY/MOOD

Irritable

Depression

Nervous/anxious

More emotional

Sleeping more/less than usual

Insomnia

PHYSICAL

Headache

Tinnitus

Fuzzy or blurry vision

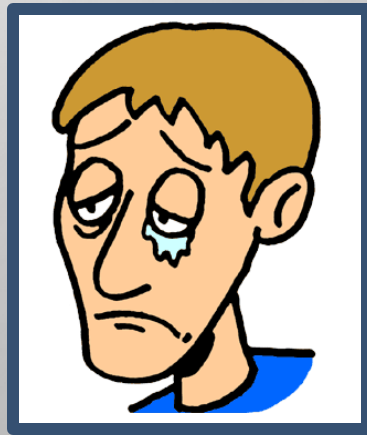
Dizziness/Vertigo

Sensitivity to light or noise

Balance problems

Fatigue

Nausea



CONCUSSION RECOVERY

- Mild injury – complete recovery in about 85-90%
  - Usually 10-14 days in adults; 4 weeks in children
- Neuropsychological function back to normal 5 days
- Diffuse injury - no focal neurological deficits in cranial nerves, motor or sensory exams

PERSISTING/PROLONGED SYMPTOMS OF CONCUSSION

- "...Failure of normal clinical recovery—that is, symptoms that persist beyond expected time frames (ie, >10–14 days in adults and >4 weeks in children)."
- Some guidelines suggest 1 or 3 months
- Doesn't presume an underlying cause
- Focus on symptoms, regardless of cause

McCrory P, et al. Br J Sports Med 2018;51:838–847.

PROLONGED/PERSISTING SYMPTOMS OF CONCUSSION

- 10% (-58%) of people do not recover from mTBIi within 3 months
- *Heterogeneous concept with different definitions*
- > 15% experience prolonged symptoms (150000)
- ~23,000 Ontarians/year endure prolonged symptoms

Jotwani Curr Sports Med Report, 2010 Jan-Feb;9(1):21-6
Langer J Head Trauma Rehabil 2020

PERSISTENT SYMPTOMS

PHYSICAL

HEADACHE/MIGRAINE
NECK PAIN
DIZZINESS/VERTIGO
NAUSEA
UNSTEADY/OFF-BALANCE
BLURRED/DOUBLE VISION
SENSITIVITY TO SOUND
SENSITIVITY TO LIGHT
TINNITUS
CHANGES IN SLEEP

COGNITIVE

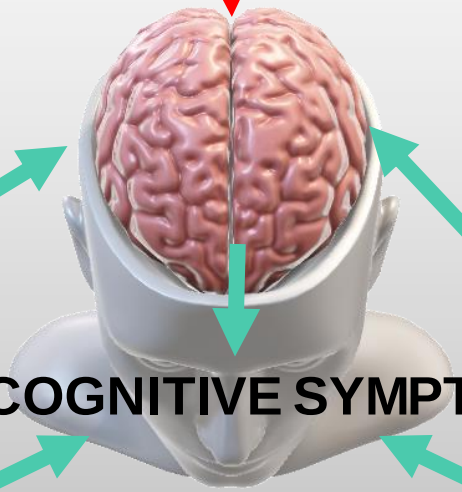
ATTENTION/ CONCENTRATION
MEMORY
PLANNING/ ORGANIZATION
PROBLEM SOLVING
REASONING
SPEECH

PSYCHIATRIC/ BEHAVIORAL

IRRITABILITY
AGITATION
AGGRESSION
DEPRESSION
ANXIETY
PTSD
SUBSTANCE USE/ABUSE
PERSONALITY CHANGE

VICIOUS CYCLE OF CONCUSSION

INJURY



COGNITIVE SYMPTOMS

SOMATIC SYMPTOMS (i.e. sleep, pain, headache, dizziness)

MOOD (i.e. depression, anxiety)

COGNITIVE SYMPTOMS

- Common symptoms: impairment of attention/concentration, speed of information processing, memory, executive
- Patients should get assessed
- Usually cognition improves within 6 months
- Unclear whether persistent cognitive symptoms result from:
    1. Effects of injury
    2. Related to other factors influencing cognition: pain, fatigue, medications, sleep, psychological factors and emotional disturbance (i.e., anxiety and depression)
- Cognitive symptoms usually don't worsen over time- investigate mood, sleep etc

Frenchman, Fox & Mayberry, 2005; Silver, McAllister & Arciniegas, 2009).

POST-TRAUMATIC HEADACHE (PTH)

- Headache within 7 days of the injury or after regaining consciousness
- Most common symptom after concussion: prevalence of 30-90%
  - MANY DON'T REPORT AS UNAWARE IT'S A PCS SYMPTOM
- Mean age 31.7-39.5 yrs
- F>M
- associated with a high degree of disability
- Acute vs chronic
  - Acute PTH:
    - Headache develops within 7 days after head trauma
    - One or other of the following:
      1. Headache resolves within 3 months after head trauma
      2. Headache persists < 3 months since head trauma
  - Chronic headache develops within 7 days & persists for > 3 months after head trauma

POST-TRAUMATIC HEADACHE

Does not refer to one specific headache:

- Tension 6.9-85.7% (33.6)
- Migraine-like 1.9-40.7% (28.6)
- Mixed type
- 60% mild-moderate headache
- Sensitivity to light 1/3
- Sensitivity to sound 1/3
- 71% aggravated by physical activities

- Compounded by medication overuse headache because excessive use of analgesics

RATES OF NEUROPSYCHIATRIC SYMPTOMS FOLLOWING CONCUSSIONS

- Prevalence of psychiatric disorder in PCS extremely high: depression 14-61% & anxiety 18-60%
- More concussions = higher risk
- Can have >1 psychiatric disorder
- Post-traumatic stress disorder symptoms overlap
- Comorbid conditions i.e. substance abuse
- Worsening of pre-morbid psychiatric condition

Vargas 2015; Busch 1998; Fisher 2019; Guskiewicz 2007

RISK FACTORS FOR PERSISTING SYMPTOMS

- Growing literature that pre-injury factors may increase risk for persisting symptoms
- **History of prior concussion**
- **Age**: younger age and slower concussion recovery
- **Sex:** women are higher risk of concussion and persistent symptoms after concussion
- **Mood disorders**: some evidence that previous anxiety and depression can predispose to persistent
- **Previous headache**: some evidence that premorbid migraine sufferer at higher risk of persistent symptoms

Sports Health: A Multidisciplinary Approach 2013;20(10).

MEDICAL FACTORS

(PRE-EXISTING, CONCURRENT OR POST-INJURY SYMPTOMS ASSOCIATED WITH MORE PERSISTENT SYMPTOMS)

- History of previous traumatic brain injury
- History of previous physical limitations
- History of previous neurological or psychiatric problems
- Skull fracture
- Early onset of pain and in particular headache within 24 hours after injury
- Confounding effects of other health-related issues, e.g., pain medications, disabling effects of associated injuries, emotional distress
- Anxiety
- High number of symptoms reported early after injury i.e., high score on the Rivermead or Post Concussion Symptom Questionnaire
  - Vestibular/vestibular-ocular abnormalities
  - Pre-injury sleep disturbance or post-injury changes
  - Reduced balance or dizziness
  - Nausea after injury
  - Memory problems after injury
  - Post-traumatic amnesia (PTA)

ONF guidelines, 2018

CONTEXTUAL FACTORS

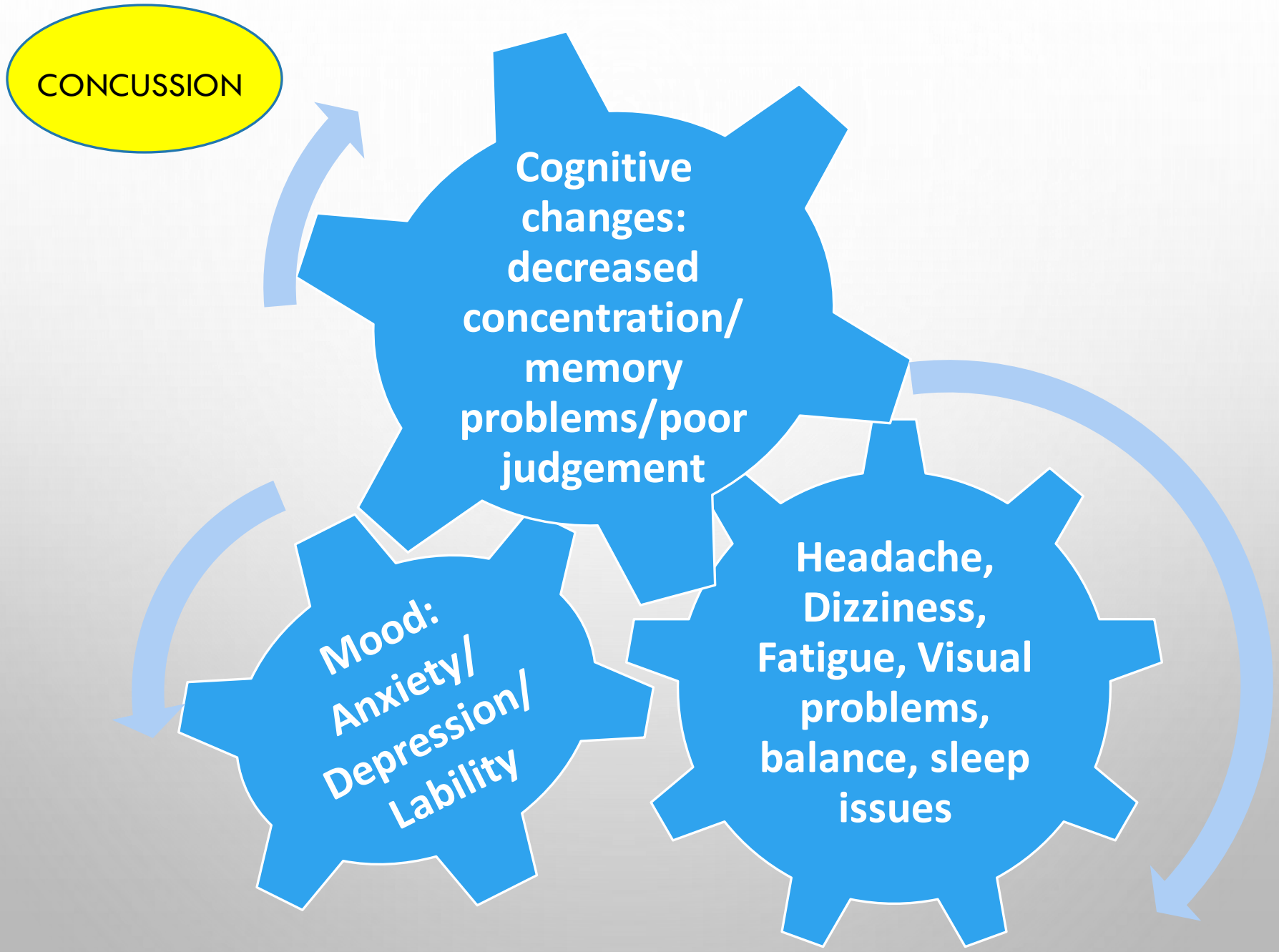
(PERSONAL, PSYCHOSOCIAL, ENVIRONMENTAL ASSOCIATED WITH MORE PERSISTENT SYMPTOMS)

- Injury sustained in a motor vehicle accident
- Potential influence of secondary gain issues related to litigation and compensation
- Not returning to work or significant delays in returning to work following the injury
- Being a student
- Presence of life stressors at the time of the injury
- Higher levels of symptom reporting is associated with mood symptoms and heightened self-awareness of deficits
- Older age
- Lack of social supports
- Lower education/low social economic status
- Female gender
- Lower Resiliance
- Returning to a contact/ risk of contact sport activity

ONF guidelines, 2018

Why care?

- Prolonged symptoms are often non-specific
- Factors other than concussion can lead to ‘concussion- like’ symptoms
- Such factors may be related to the initial concussive event, but may also pre-date or follow it
- Diagnostic challenges
- Symptoms secondary to concussion may include:
  - (i) psychological sequelae of traumatic experience (e.g., Depression, anxiety, PTSD)
  - (ii) pain sequelae, including headache, caused by orthopedic injury or whiplash
  - Injuries
- Medication side effects


CONCUSSION
Cognitive changes: decreased concentration/ memory problems/poor judgement
Headache, Dizziness, Fatigue, Visual problems, balance, sleep issues
Mood: Anxiety/ Depression/ Lability

TREATMENT OF PERSISTENT SYMPTOMS OF CONCUSSION

Treat the symptoms:

1. Anti-depressants for mood (depression, anxiety); CBT/GMT for mood
2. Headache prophylaxis: amitriptyline, gabapentin, candesartan etc
3. Sleep apnea - CPAP; melatonin for difficulty getting to sleep
4. Vestibular physiotherapy for balance
5. Low-impact exercise
6. Modified return to work/school/play

DELAYED EFFECTS OF CONCUSSION/MTBI

- TBI (all severities) associated with increased risk of dementia
- Lancet Report: TBI is a modifiable risk factor for dementia
  - Single mTBI increased risk of dementia (OR 1.6, 95% CI 1.6–1.7)
  - Multiple TBIs increased the risk of dementia OR 2.8, 2.5–3.2
  - Study of 178779 veterans with TBI with propensity matched veterans without TBI found dementia risk was associated with TBI severity (**HR 2.4, 95% CI 2.1–2.7 for mild TBI without loss of consciousness; 2.5, 2.3–2.8 for mild TBI with loss of consciousness;** and 3.8, 3.6–3.9 for moderate to severe TBI)
  - A cohort study of 28815 older adults with concussion, found the risk of dementia doubled, with 1 in 6 developing dementia over a mean follow-up of 3.9 years

Tolppanen, 2017 Alz Dem; Barnes JAMA 2019 Neurology; Yaffe 2019 Neurology; Redelmeier 2019 JAMA Neurology; Livingston 2020 Lancet

DELAYED EFFECTS OF TBI

CHRONIC TRAUMATIC ENCEPHALOPATHY (CTE)

- **Progressive**, neurodegenerative process
- Triggered by repetitive mild traumatic brain injury (mTBI) - including concussive & subconcussive blows
- Evolves **slowly** over decades
- Symptoms usually appear **years after injury**

CHRONIC TRAUMATIC ENCEPHALOPATHY

- First described in boxers but now observed in hockey, football and other sports as well as military, motor vehicle accidents, abuse.

CTE OUTSIDE OF ATHLETES: 0 - 2.2%

- ADAMS ET AL: 1 OF 164 BRAIN DONORS FHS STUDY (0.6%)
- FORREST ET AL: 0 OF 310 VIENNA TRANS-DANUBE AGEING STUDY
- POSTNUPTA ET AL: 3 OF 532 DONORS IN SEATTLE ACT STUDY (0.6%)
- SUTER ET AL, 2022: 4 OF 180 DONORS ROYAL PRINCE ALFRED HOSPITAL
- IN SYDNEY, AUSTRALIA (2.2%)
- MCCANN ET AL, 2022: 5 OF 636 SYDNEY BRAIN BANK (0.8%)

MTBI/CONCUSSION & DEMENTIA

- Increasing evidence that mTBI can increase risk of Dementia
  - retrospective population-based case-controlled 25 yr retrospective study using province-wide (Man) medical health data collected 1 Apr-31 Mar 1990–1991 to 2014–2015
  - 28021M (mean age ±sd, 25±18yrs) & 19462W (30±21 years) in concussion group; 81871M (25±18 years) & 57159W (30±21yrs) in the matched control group
  - Outcomes: Dementia, ADHD, PD, Mood disorder

Table 4 Hazard ratios for risk of dementia diagnosis

Age of diagnosis			
	Mean±SD		
Control	73.8±19.3	Corrected for SEF and CMI	
Concussion	71.0±19.6		
Model 1a		**Model 1b**	
HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
1.75 (1.63 to 1.87)	<0.001	1.72 (1.61 to 1.84)	<0.001
Model 2a Sex interaction		**Model 2b**	
0.95 (0.83 to 1.09)	0.49	0.93 (0.82 to 1.07)	0.33
Model 3a Multiple concussion		**Model 3b**	
1.70 (1.59 to 1.82)	<.001*	1.67 (1.56 to 1.79)	<.001*
1.63 (1.26 to 2.11)	<0.001†	1.62 (1.25 to 2.10)	<0.001†
1.19 (0.62 to 2.28)	0.60‡	1.20 (0.63 to 2.30)	0.60‡
Model 4a Controlling for other conditions of interest		**Model 4b**	
1.55 (1.45 to 1.67)	<0.001	1.54 (1.43 to 1.65)	<0.001
Model 5a Proportionality model		**Model 5b**	
0.97 (0.97 to 0.98)	<0.001	0.97 (0.97 to 0.98)	<0.001

Morissette MP, et al. Fam Med Com Health 2020;**8**:e000390.

MTBI/CONCUSSION & PARKINSON'S DISEASE

Table 5 Hazard ratios for risk of Parkinson's disease diagnosis

Age of diagnosis			
	Mean±SD		
Control	62.0±17.5		
Concussion	59.6±17.3	Corrected for SEF and CMI	
Model 1a		**Model 1b**	
HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
1.61 (1.45 to 1.80)	<0.001	1.57 (1.41 to 1.75)	<0.001
Model 2a Sex interaction		**Model 2b**	
0.94 (0.76 to 1.16)	0.56	0.94 (0.76 to 1.16)	0.55
Model 3a Multiple concussion		**Model 3b**	
1.58 (1.42 to 1.76)	<.001*	1.54 (1.38 to 1.72)	<.001*
1.11 (0.70 to 1.76)	0.67†	1.11 (0.70 to 1.76)	0.67†
2.91 (1.28 to 6.65)	0.01‡	2.96 (1.29 to 6.77)	0.01‡
Model 4a Controlling for other conditions of interest		**Model 4b**	
1.31 (1.17 to1.46)	<0.001	1.28 (1.15 to 1.44)	<0.001
Model 5a Proportionality model		**Model 5b**	
0.98 (0.98 to 1.02)	0.81	0.98 (0.98 to 1.02)	0.88

Morissette MP, et al. Fam Med Com Health 2020;**8**:e000390

MTBI/CONCUSSION

Regardless of age, sex, socioeconomic status and residence, having suffered a single concussion in one's lifetime increased the likelihood of later being diagnosed with:

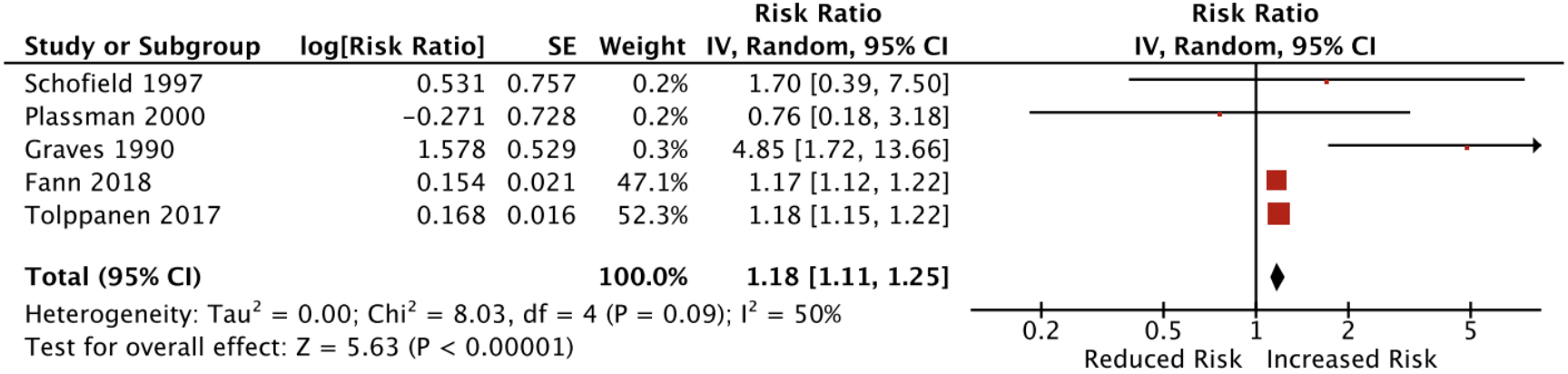
Parkinson's disease by 57%
Dementia by 72%
ADHD (Attention-Deficit Hyperactivity Disorder) by 39%
Mood and Anxiety Disorders (MADs) by 72%
Sustaining multiple concussions further increased the risk for developing both PD and dementia.

Morissette MP, et al. Fam Med Com Health 2020;8:e000390.

Mild Traumatic Brain Injuries and Future Risk of Developing Alzheimer's Disease: Systematic Review and Meta-Analysis

Table 1
Study characteristics, baseline demographics, factors adjusted for, follow up duration and relative risks

Author + Region	Study Design	Sample Size	Head Injury Measure	AD Measure	Follow-up (y)	Age (y), Mean (SD)*	Female *n* (%)	RR (95% CI)**	Adjustment
Graves et al. (1990) USA [36]	Case-control	260	Structured Interview	DSM-III-R, NINCDS-ADRDA	10–30	64.9 (NR)	60 (46)	4.85 (1.72, 13.66)	Age, family history of AD
Schofield et al. (1997) USA [35]	Cohort	271	Structured Interview	NINCDS-ADRDA	>30	75.3 (7.3)	197 (73)	1.70 (0.39, 7.50)	Age, sex, education
Plassman et al. (2000) USA [34]	Cohort	1776	Medical Records	DSM-III-R, NINCDS-ADRDA	51–53	72.9 (NR)	0	0.76 (0.18, 3.18)	Education, age, *APOE* ε4
Tolppanen et al. (2017) Finland [37]	Case-control	352,581	National Register	NINCDS-ADRDA, DSM-IV	>5	80.1 (7.1)	230,580 (65)	1.18 (1.15, 1.22)	Socioeconomic position, physical health, drug use
Fann et al. (2018) Denmark [33]	Cohort	2,794,852	National Register	ICD-9	4–18	80.7 (8.7)	NR	1.17 (1.12, 1.22)	Sociodemographic, substan abuse, stroke, cardiovascular diseases, diabetes, hip fracture, asthma or chronic obstructive pulmonary diseases, use of antipsychotics, antidepressants, antiepileptics, benzodiazepines and related drugs



Graham, Journal of Alzheimer's Disease 87 (2022) 969–979

TBI & LEWY BODY DISEASE PATHOLOGY

- In prospective cohort studies (Religious Orders Study and the Memory and Aging Project (ROS and MAP) + Adult Changes in Thought (ACT)
  - 7130 partcipants; 1,589 autopsy. Exposure—self reported TBI (free of dementia)
  - TBI with LOC < or > 1hr
  - 865 participants reported TBI with LOC
  - In >45,000 person-years of follow-up,: 1,537 dementia and 117 incident PD
    - No association between TBI with LOC and incident dementia or Alzheimer's disease
    - There were associations between TBI with LOC and incident Parkinson's disease and progression of parkinsonian signs
    - Association between TBI with LOC and Lewy bodies

JAMA Neurol. 2016 September 01; 73(9): 1062–1069

HOW ABOUT HEAD TRAUMA & MND/ALS

COMMENTARY

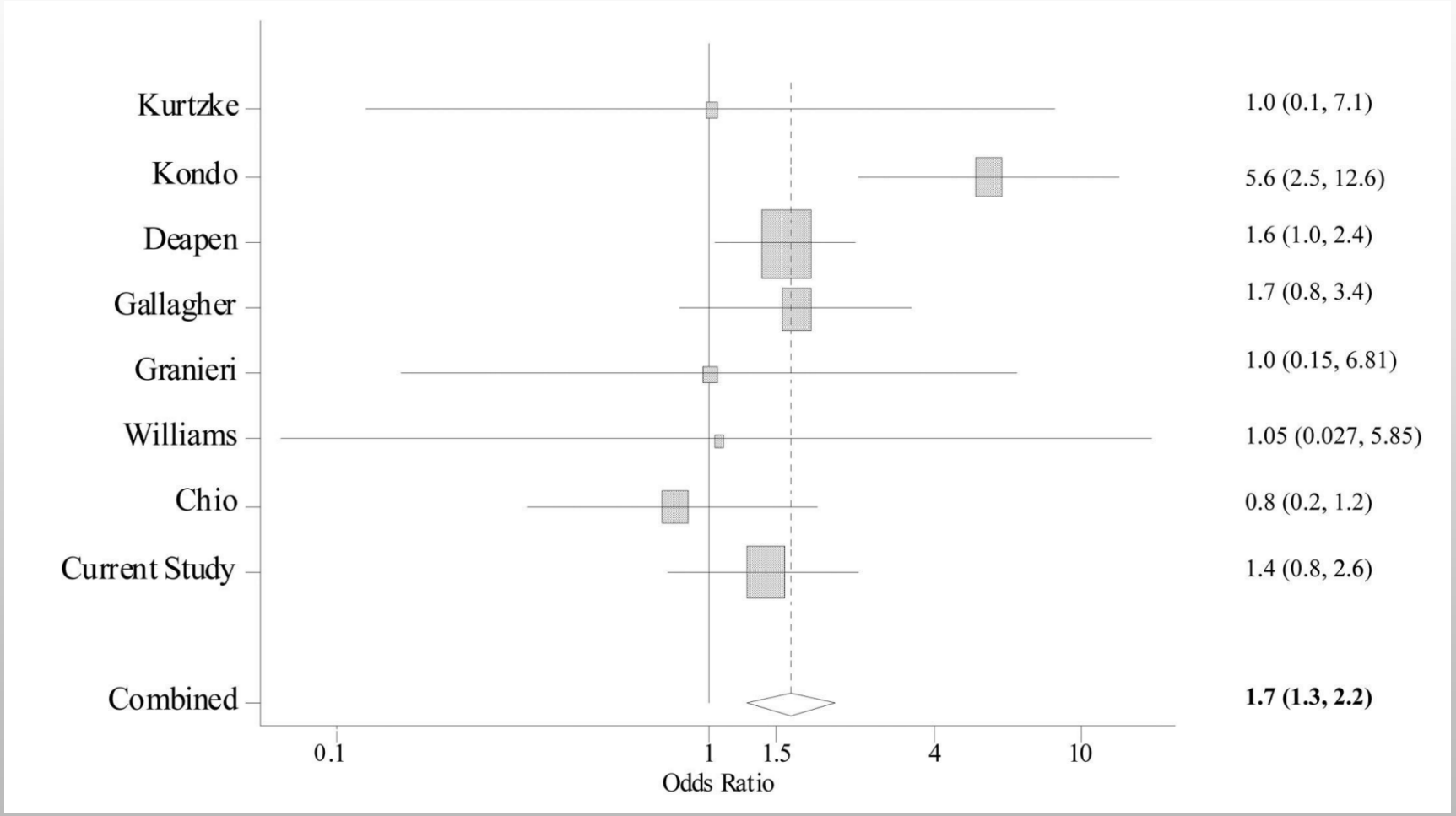
Soccer, neurotrauma and amyotrophic lateral sclerosis: is there a connection?

Ornella Piazza[1,2], Anna-Leena Sirén[1] and Hannelore Ehrenreich[1]

CURRENT MEDICAL RESEARCH AND OPINION VOL. 20, NO. 4, 2004, 505–508

CONCUSSION/MTBI & MOTOR NEURON DISEASE/ALS

Risk of ALS 1.7 times (95 % CI: 1.3, 2.2, $p < 0.001$) higher among individuals with head injuries



Am J Epidemiol. 2007 Oct 1; 166(7): 810–816.

DELAYED EFFECTS OF TBI

SUMMARY

- Concussion are the result of brain trauma
- Symptoms varied and include memory problems, headache, dizziness, sleep issues, psychiatric
- Persisting symptoms can occur
- Concussions/mTBI are implicated in delayed neurodegenerative disease including AD, PD, FTD/ALS
- Repeated concussions are the only known risk factor for CTE but very rare in non-professional contact sports
- Mitigating risk by focusing on the other modifiable risk factors

THANK YOU

Carmela.tartaglia@uhn.ca