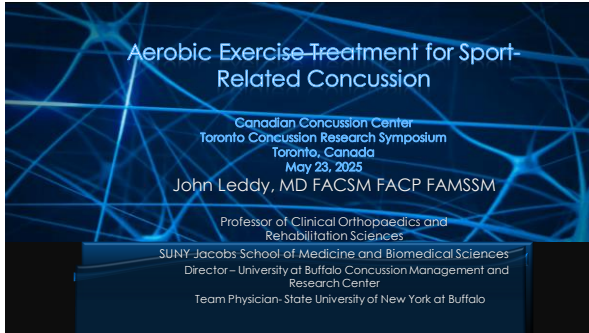




1



Faculty/Presenter Disclosure

- **Faculty:** John Leddy MD
- **Relationships with commercial interests:**
 - **Consulting Fees:** Zeiss
 - **Other:**
 - SAB for NeckCare
 - Minority owner 360 Concussion Care

2



Mitigating Potential Bias

- Content is not about the supporting any organization's products or services.
- Speaker will limit the presentation to a discussion of the evidence and not promote personal opinion.

3

Objectives

Upon completion, the participant will better be able to describe the:

1. Autonomic nervous system physiology of concussion and its relation to post-concussion exercise intolerance.
2. Efficacy, safety, and the effect of adherence, of sub-symptom threshold aerobic exercise early after injury to speed recovery and to prevent delayed recovery in adolescents after sport-related concussion.
3. Role of aerobic exercise treatment in patients with prolonged symptoms and predictors of response to treatment.
4. Taxonomy of concussion.

4

Concussion = Commotio Cerebri or "Shaken Brain"



5

Signs and symptoms of Concussion/mTBI

*Must appear within 72 hours of injury		
Domains	Symptoms	Signs
Cognitive	Confusion Feeling "in a fog" or "Zoned Out" Inability to focus	Anterograde amnesia Retrograde amnesia Loss of Consciousness Disorientation Delayed verbal and motor responses Vacant stare Slurred/Incoherent speech
Somatic	Headache Dizziness Nausea/vomiting Visual disturbances Photophobia, blurry/double vision Phonophobia	Balance disruption Abnormal eye tracking Abnormal Vestibulo-ocular reflex (VOR) Abnormal near point convergence
Affective	Emotional lability Irritability Fatigue Anxiety Sadness	Acts irritable Flat affect
Sleep Disturbances	Trouble Falling asleep Sleeping more than usual Sleeping less than usual	Excessive drowsiness

6

Why consider Exercise to improve Concussion Physiology?

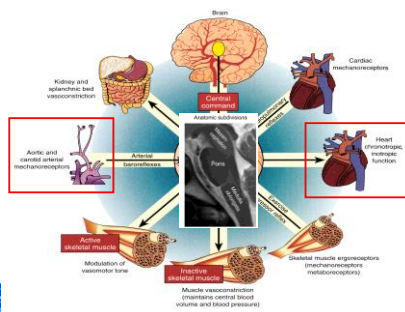
Concussion and deconditioning adverse effects	Exercise beneficial effects
• Autonomic Nervous System • Cerebral Blood Flow • Neuroplasticity • Psychological • Sleep	• Improves ANS balance and CO₂ sensitivity • Improves CBF regulation • Upregulates BDNF genes • Improves Mood • Improves sleep

7

The Physiology of Concussion soon after Injury

The Autonomic Nervous System and Acute SRC

8



9

Injury to the ANS

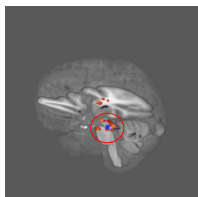
Structure
Autonomic Function
Cerebral Blood Flow Regulation

10

STRUCTURE

DTI Brainstem injury in Concussion

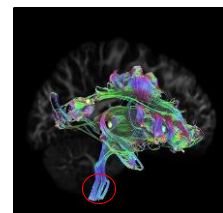
Polak et al J Head Trauma Rehabil 2014



11

Connectivity in the Central Autonomic Network (CAN)

- CAN
 - Midbrain
 - Hypothalamus
 - Amygdala
 - Cingulate gyrus
 - Insula

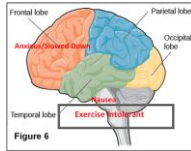


Tractogram reconstruction of key fiber pathways interconnecting regions of the CAN from diffusion MRI.

12

ANS structure on DTI and exercise intolerance after concussion (unpublished data)

- CA (n=32, 15y, 56% male) 7 days from injury.
- HC = age and sex-matched adolescents with no concussion past year (n=25, 15y, 56% male).
- Pearson correlations analyzed symptoms and regional weighted mean DTI values.
- Concussion symptom limitation on the BCTT significantly associated, after Bonferroni correction, with brainstem FA (p=.01).
- Exercise intolerance linked to brainstem DTI changes, where part of central autonomic control resides.



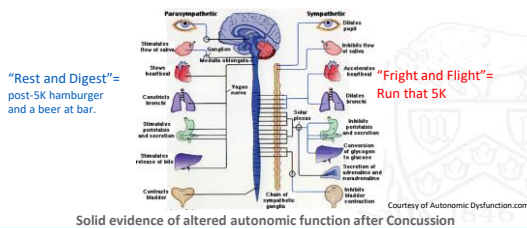
The Physiology of Concussion

ANS Function

13

14

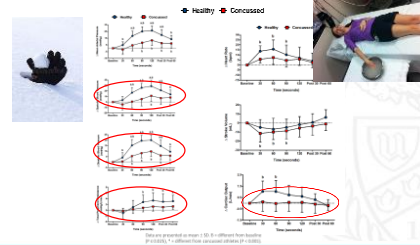
The Autonomic (“automatic”) Nervous System- responsible for exercise performance



Solid evidence of altered autonomic function after Concussion

15

SNS function in College athletes within 1 week of SRC



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The Physiology of Concussion

Cerebral Blood Flow Regulation

CBF by fMRI during a Cognitive Task

(Leddy et al. J Head Trauma Rehabil 2013)



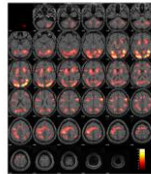
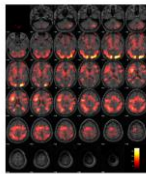
17

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fMRI Cerebral Blood Flow (Laddy et al 2013)

PPCS after stretching - not recovered

Recovered after aerobic exercise = Control



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Assessing the Physiology of Concussion in the Office/Training Room

Orthostatic and Exercise Intolerance

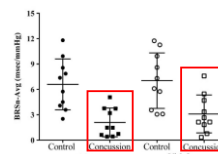
20

Attenuation of Spontaneous Baroreceptor Sensitivity after Concussion LAFONTAINE M et al. Med. Sci. Sports Exerc 2019

- Post-concussion autonomic dysfunction appears to be an anatomical uncoupling or physiological reduction of neurotransmission between central autonomic centers and heart and vasculature.
- Arterial Baroreflex regulates cardiac output and peripheral vascular resistance to maintain cerebral perfusion during orthostatic stress.
- **METHODS**
- 10 collegiate athletes (20 y) after SRC compared with 10 matched controls.
- EKG and beat-to-beat systolic BP measured in seated upright position for 5 min within 48h of concussion and one week later (controls twice a week apart).

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RESULTS AND CONCLUSIONS



- Broad reduction in resting BRS suggests that concussed athletes may have a compromised ability to buffer BP challenges for at least 1 week after injury.
- From a clinical perspective, concussed athletes who possess this dysfunction may report feeling "light-headed" or "dizzy" upon standing or with exercise or weight training.
- This is the definition of **Orthostatic Intolerance (OI)**.

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The Buffalo Concussion Physical Exam (BCPE) and Exercise Testing for helping to establish physiological recovery after SRC



VIDEO OF BCPE available at ubortho.com/services/concussion-management-center Under "Resources for Professionals"



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Assessing the ANS in the Office ORTHOSTATIC VITAL SIGNS to Assess Orthostatic Hypotension and Orthostatic Intolerance

Patient supine 2 min. blood pressure (BP) and heart rate (HR). Have patient stand. Wait 1 min: BP/HR

Orthostatic Hypotension= reduced systolic BP by at least 20 mmHg or reduced diastolic BP by 10 mmHg, if either is associated with ****symptoms**.

Orthostatic Intolerance = ****symptoms without OH**.

*Vital signs are obtained in supine and standing position only.

Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology. *Neurology* 1996

24

Symptoms upon postural change and orthostatic hypotension in adolescents with concussion

Haider MN et al. Brain Injury 2021

Question: what is prevalence of Orthostatic Intolerance (OI) in adolescents after sport-related concussion (SRC) vs. healthy controls?

Participants: Adolescents within 10 days of SRC (n = 297, 15 years, 59% male) were compared with age-, BMI- and sex-matched healthy controls (n = 214, 15 years, 58% male).

Methods: BP, heart rate, and complaints of lightheadedness/dizziness were measured after 2-min supine and 1-min standing.

Control Group was assessed once.

Concussion Group was assessed twice.

(1) initial visit (mean 6.0 ± 3 days-since-injury) and

(2) after clinical recovery (mean 46.3 ± 42 days-since-injury).

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Symptoms upon postural change and orthostatic hypotension in adolescents with concussion

Haider MN et al. Brain Injury 2021

• Results

- **Initial visit:** Concussed reported feeling lightheaded/dizzy on postural change more often than the Controls (37% vs 4%, $p < .001$) but did not differ in meeting standard OH criteria (3% vs 5%, $p = .32$).
- Experiencing symptoms did not correlate with meeting OH criteria but correlated with *abnormal VOR*.
- **After clinical recovery:** Concussed *did not differ* in experiencing lightheaded/dizziness on postural change vs. controls (4%, $p = .65$).

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Symptoms upon postural change and orthostatic hypotension in adolescents with concussion

Haider MN et al. Brain Injury 2021

Conclusions

- Adolescents commonly experience lightheaded/dizziness upon postural change after concussion but do not meet the standard criteria for OH.
- These symptoms may be due to altered Baroreflex sensitivity and/or vestibular impairment.
- **Interpretation:** a relatively smaller change in BP with standing causes a clinically important reduction in cerebral perfusion in the concussed brain, which is in a state of impaired cerebral autoregulation.
- Symptoms of OI resolve as the patient recovers.

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Systematic Evaluation of Exercise Tolerance after Concussion

The Buffalo Concussion Treadmill and Bike Tests

28

2016 Berlin CISG Strategy: restoration of "exercise tolerance" before unrestricted return to sport (RTS)

Stage	Aim	Activity	Goal of each step
1	Symptom-limited activity	Daily activities that do not provoke symptoms	Gradual reintroduction of work/school activities
2	Light aerobic exercise	Walking or stationary cycling at slow to medium pace. No resistance training	Increase heart rate
3	Sport-specific exercise	Running or skating drills. No head impact activities	Add movement
4	Non-contact training drills	Harder training drills, eg. passing drills. May start progressive resistance training	Exercise, coordination and increased thinking
5	Full contact practice	Following medical clearance, participate in normal training activities	Restore confidence and assess functional skills by coaching staff
6	Return to sport	Normal game play	

McCrory P et al. Consensus statement on concussion in sport—the 5th international conference on concussion in sport held in Berlin, October 2016. Br J Sports Med. 2017

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The Buffalo Concussion Treadmill Test (BCTT)

- Modified Balke Protocol
- Submaximal symptom-limited threshold = acutely concussed or not recovered.
 - Threshold is represented by the HR at symptom exacerbation.
 - HR used to prescribe sub-threshold exercise.
- Maximum exertion without symptom limit = cardio- and cerebro-vascularly physiologically recovered.
- Introducing the Buffalo Concussion Bike Test (BCBT) (Haider et al Sports Health 2019)



BCTT is safe and reliable in PPCS (Loddy et al. Clin J Sport Med 2010, 2011)



30

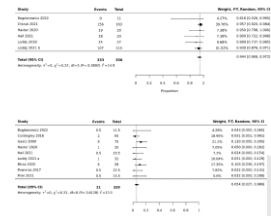
Sensitivity and Specificity of Exercise Intolerance on Graded Exertion Testing for Diagnosing Sport-related Concussion: A Systematic Review and Exploratory Meta-Analysis (Haider et al. J Neurotrauma 2023)

- No single gold standard test to diagnose SRC.
- Concussion-related *exercise intolerance* a frequent finding in athletes early after SRC.
- Eligible studies
 - Graded exercise tolerance tests in symptomatic concussed (> 90% of sample SRC *within 14 days of injury*) for **Sensitivity**
 - At clinical recovery from SRC, in healthy athletes, or both for **Specificity**

31

Sensitivity and Specificity of Exercise Intolerance on Graded Exertion Testing for Diagnosing Sport-related Concussion: A Systematic Review and Exploratory Meta-Analysis (Haider et al. J Neurotrauma 2023)

- Exercise intolerance in those with SRC: pooled estimated **Sensitivity= 94.4%** (95% CI 90.8, 97.2).
 - To help **rule in** SRC.
- Exercise intolerance in those without SRC: pooled estimated **Specificity= 94.6%** (95% CI 91.1, 97.3).
 - To help **rule out** SRC or to **establish recovery** from SRC.



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RISK FACTORS FOR DELAYED RECOVERY-BEYOND 30 DAYS FROM DATE OF INJURY CISG AMSTERDAM STATEMENT (PATRICIOS J ET AL BJSM 2023)

- High burden (number, severity) of initial visit concussion symptoms.
- Initial visit >1 week from date of injury.
- Continuing to play with symptoms of concussion.
- More than one prior concussion and/or a prolonged recovery from a concussion.
- Pre-existing mental health, migraine headache, sleep, learning or vestibular disorder.
- Cervical spine injury.
- Significant autonomic dysfunction (orthostatic and/or **exercise intolerance**).

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Early Exercise Tolerance Testing and Early Physical Examination Findings are Useful for Prognosis after SRC.

UB RCT (Leddy et al. CSM 2018)

Degree of early exercise tolerance was strongest predictor of recovery: lower tolerance = longer recovery (p=0.0032)

When combined with a brief physical examination of the cervical, vestibular and oculomotor systems, good ability to predict who will recover within 2 weeks of injury.



Every 1 beat per minute increase in heart rate threshold resulted in a .82 day shorter recovery.

34

WE CAN TREAT ACUTE CONCUSSION AND PPCS

The Best Way To Improve Control of
ANS: **Aerobic Exercise training**

35

WITH EXERTION TESTING (Leddy et al. Exercise is Medicine for Concussion. CSMR 2018)

- Establish the diagnosis by systemic evaluation of exercise tolerance
 - Sub max symptom-limited threshold on the treadmill or bike
- Sub-threshold exercise prescription ("Exercise is Medicine")
 - **90%** of HRT on BCTT = training target HR.
 - **HR monitor is KEY to prevent athlete from under or over-exertion.**
 - 20 min/day minimum at target HR, not including warmup/cool down.
 - *Stop at **symptom exacerbation** (>2 point increase from pre-exercise resting value on a 0-10 point scale). So, can exceed 20 min.
 - Bike first, then running. 6-7 d/wk.
 - **Increase target HR 5-10 bpm every 3 to 7 days (or re-test).**
 - **≥ 80% age-predicted max HR x 20 min without symptoms for 2 days= "Cardiovascular and Cerebrovascular Physiological Recovery"**

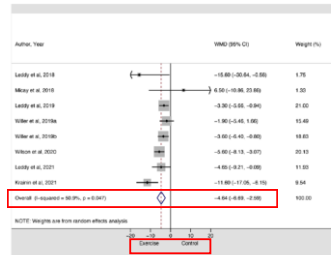
36

Rest and exercise early after sport-related concussion: a systematic review and meta-analysis

John J Leddy,¹ Joel S Burma,² Clodagh M Toomey,³ Alix Hayden,⁴ Gavin A Davis,⁵ Franz E Babi,⁶ Isabelle Gagnon,^{7,8} Christopher C Giza,^{9,10} Brad G Kurowski,¹¹ Noah D Silverberg,¹² Barry Willet,¹³ Paul E Ronsley,¹⁴ Kathryn J Schneider,¹⁵

To cite: Leddy JJ, Burma JS, Toomey CM, et al. *Br J Sports Med* 2023;57:762–770.

Forest Plot of early PA and Prescribed Aerobic Exercise Treatment on Recovery



Meta-analysis

- Sub-symptom threshold aerobic exercise treatment (based on formal exercise testing) should be prescribed to adolescents as soon as 2 days after SRC, which facilitates recovery by a mean of -4.64 days (95% CI -6.69, -2.59).
- Grading of Recommendations, Assessment, Development and Evaluations (GRADE) recommendation is high.

37

38

JAMA Pediatrics | Original Investigation

Early Subthreshold Aerobic Exercise for Sport-Related Concussion A Randomized Clinical Trial

John J. Leddy, MD, Mohammad N. Haider, MD, Michael J. Ellis, MD, Rebekah Morris, MD, Scott R. Darling, MD, Michael S. Freitas, MD, Heidi N. Suffoletto, MD, Jeff Leuter, PhD, Dean M. Cordingley, MSc, Barry Willet, PhD

JAMA. 2023;329(10):e20230101. doi:10.1001/jama.2023.0101

Published online February 1, 2023.

Sub-threshold exercise for the Rx of Acute Sport-related Concussion

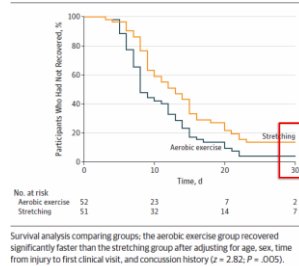
Leddy et al. JAMA Pediatrics 2019

	Aerobic Exercise (n = 52)	Stretching (n = 51)	p-value
Age (years)	15.3 ± 1.6	15.4 ± 1.7	0.753
Sex	46% female	47% female	0.927
Previous concussions	0.71 ± 0.8	0.67 ± 0.9	0.773
Time since injury (days)	4.9 ± 2.2	4.8 ± 2.4	0.883
Initial Visit symptom score on PCSS	30.8 ± 16.5	33.3 ± 19.7	0.479
Initial Visit resting HR	74.5 ± 12.7	75.2 ± 12.3	0.796
Initial Visit HR at symptom exacerbation	136.9 ± 26	136.6 ± 21	0.952
Duration of Initial Visit (BCTT (minutes))	8.65 ± 4.88	8.64 ± 4.32	0.717

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Figure 2. Kaplan-Meier Estimates of Time to Recovery



Aerobic Exercise group recovered in mean of 13 days [IQR]10, 18.5], $p = .009$ vs. 17 days [IQR 13, 23] for Stretching Exercise group.

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42

JAMA Pediatrics | Original Investigation

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John J. Leddy, MD, Mohammad N. Haider, MD, Michael J. Ellis, MD, Rebekah Morris, MD, Scott R. Darling, MD, Michael S. Freitas, MD, Heidi N. Suffoletto, MD, Jeff Leuter, PhD, Dean M. Cordingley, MSc, Barry Willet, PhD

JAMA. 2023;329(10):e20230101. doi:10.1001/jama.2023.0101

Published online February 1, 2023.

Rest after concussion in adolescents (Grool et al 2016):

~35% at one month

Placebo Stretching Group: 15% PPCS

Aerobic Exercise Group: 5% PPCS

But... not statistically significant.

Concussion Guidelines Step 2: Evidence for *Subtype* Classification

Lumba-Brown et al Neurosurgery 2019

- Multidisciplinary expert workgroup defined most common concussion subtypes and their associated conditions.
- Meta-analysis of literature from 1990 to 2017 and classified "subtypes" within 3 days of concussion (any MOI).
- 5 Subtypes and 2 associated conditions (*symptom reports only*)
 - Cognitive
 - Ocular-Motor
 - Headache/migraine
 - Vestibular
 - Anxiety/Mood
 - Associated conditions: sleep disturbance and cervical strain.

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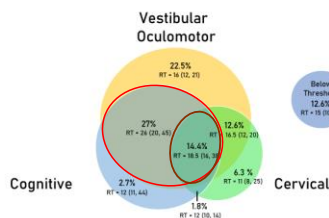
Concussion Guidelines Step 2: Evidence for Subtype Classification

Lumba-Brown et al Neurosurgery 2019

- Concussion subtypes in pediatrics and adults
 - Headache/migraine and cognitive were the most prevalent.
 - In pediatrics, prevalence of the vestibular subtype was also high.
 - Insufficient information for analysis of cervical strain.
- Concluded that comprehensive acute concussion assessment should incorporate evaluations of all 5 subtypes and associated conditions.
- N= 25 studies with **3743 total subjects**.

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VENN DIAGRAM OF **EARLY** (10 DAYS) PHENO(SUB)TYPES AFTER SRC BASED ON **SYMPTOMS AND SIGNS** IN ADOLESCENTS (LEDY ET AL 2021).

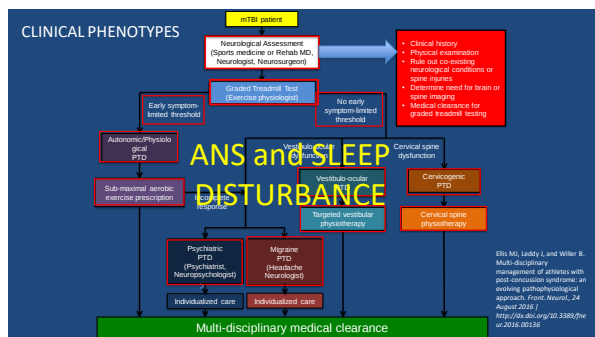


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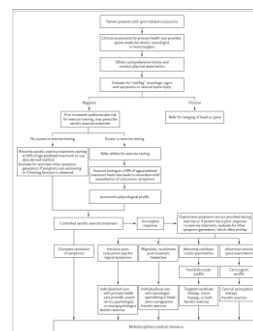
What is not in this diagram?

- All the following are **pervasive** (not specific to one pheno(sub)type)
 - ANS dysfunction (underlying mechanism)
 - Treatment is aerobic exercise.
 - Headache (very common to all pheno(sub)types)
 - most common symptom with a wide differential diagnosis and Rx approach.
 - Sleep disturbance (very common to all pheno(sub)types)
 - sleep hygiene and other more intensive approaches if needed.
- Note: mood disorder subtypes are typically seen *later* in recovery.
- Note: sex was not a significant modifier for the subtypes except that most of the purely cervical injuries were in females.

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Ledy JJ. NEJM 2025;392:483-93

54

Final word on Concussion “Phenotyping”

- “Phenotype” probably *not* best term. Subtype? Clinical Profile?
- Need **a lot of data** to appropriately pheno(sub)type.
 - Ideally: symptoms, signs, imaging, cognitive, exertional, genetic, biomarkers...
 - Can't phenotype-based on one approach because of **Overlap**.
 - *Timing of phenotyping* is important as it will likely change from the initial visit to one-two weeks later.
 - WHEN you intervene with a potential therapy is as important as WHETHER you intervene.
- Need a **huge sample size** to appropriately pheno(sub)type.
 - 2017 Lumba-Brown meta-analysis: total n= ~4000.
 - UB data suggest that n >2000 needed in a prospective study for statistically significant phenotyping based solely on physical exam signs!



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Somatic	Headache Dizziness Orthostatic Intolerance Voice/vibrations Phonophobia, blurry/double vision Photophobia	Balance disruption Abnormal eye-tracking Exercise Intolerance Autism near-point convergence
Affective	Emotional lability Irritability Fatigue Anxiety Sadness	Acts irritable Flat affect
Sleep Disturbances	Trouble Falling asleep Sleeping more than usual Sleeping less than usual	Excessive drowsiness

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DR. EMMET DENSMORE (1837-1911)

American businessman, physician and natural hygiene advocate who promoted an early version of the Paleolithic diet. **NYU grad 1885**. He promoted a fruit and meat diet, which he believed was the natural food of primal man. He said “bread is the staff of death”

“Medicine is not a science: it is empiricism founded on a network of blunders”



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“To get back to my youth I would do anything in the world, except exercise, get up early, or be respectable.”

Oscar Wilde

QUESTIONS?

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