Mass General Brigham
Spaulding Rehabilitation

Unveiling the Operator's Healthspan: Insights and Implications- Moving from Maladaptation to Adaption

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HOME BASE
VETERAN AND FAMILY CARE
RED SOX FOUNDATION
Massachusetts General Hospital

HOMEBASE BRAIN HEALTH SUMMIT SEPT 11, 2024

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

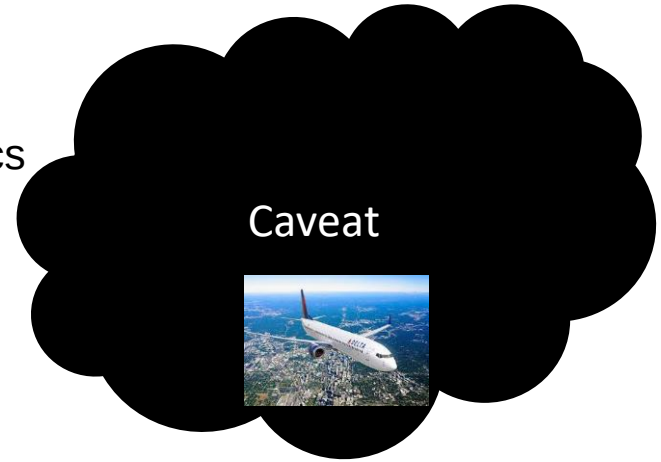
Disclosures

Financial

- Receives royalties from Demos Publishing for serving as co-editor of the textbook *Brain Injury Medicine*
- Evaluates patients in the Massachusetts General Hospital (MGH) Brain and Body Program which is funded by The TRUST and the National Football League Players Association (NFLPA).
- **Receives partial support through federal grants from the National Institute on Disability, Independent Living, and Rehabilitation Research (NIDILRR), National Institutes of Health (NIH), and the U.S. Department of Defense (DoD**).
- **Receives partial support from a grant titled *Football Players Health Study at Harvard University* which is funded by the NFLPA. - PI**

Non-Financial

- Serves as a member of the Scientific Advisory Board (SAB) for Myomo, Inc,NanoDiagnostics
- Serves as a member of the SAB for OneCare.AI Inc.
- Serves as a member of the NFLPA Mackey-White Health and Safety Committee



Objectives

Let's cross worlds-we shall go in and out of the military and sports

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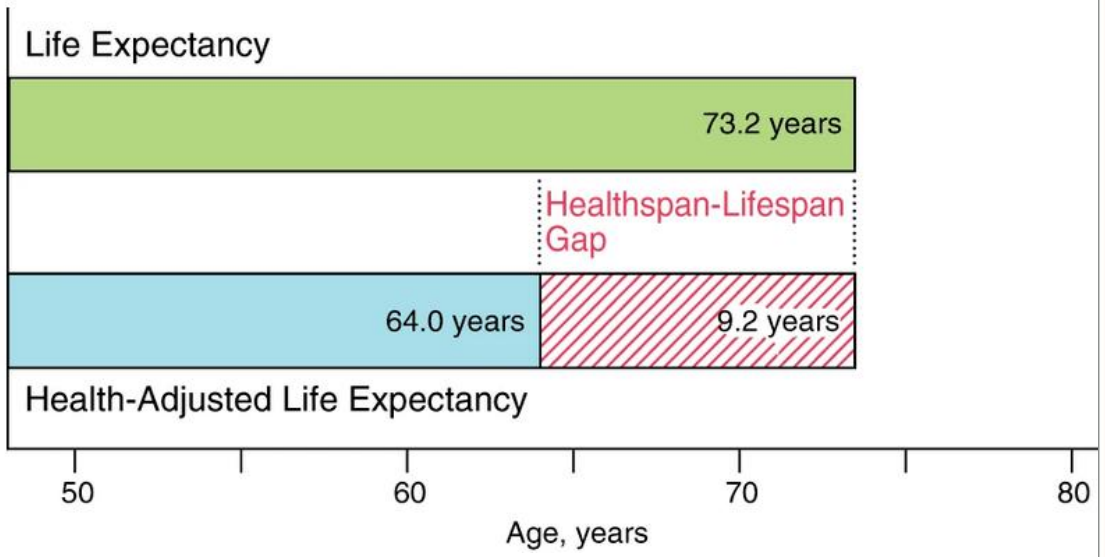
Massachusetts General Hospital

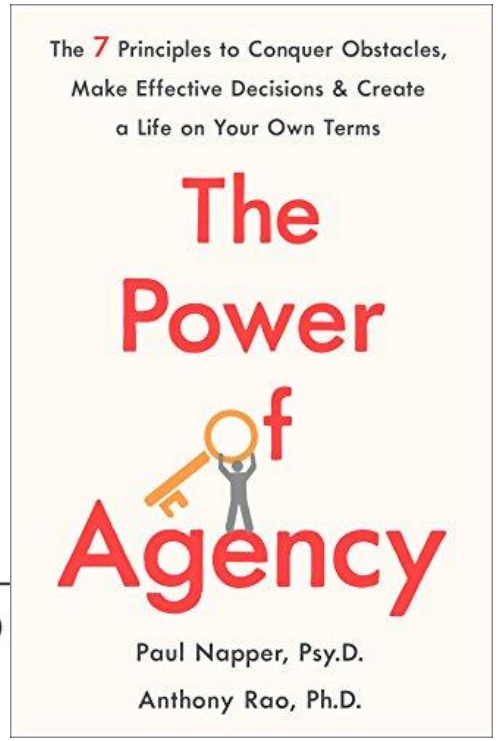
THE FOOTBALL PLAYERS HEALTH STUDY AT HARVARD UNIVERSITY

- Discuss the concepts critical to the whole warrior the whole life
- Identify factors that are critical to understanding the maladaptive phenotype
- Discuss concepts critical to promoting health and adaption
- Caveat: Many of the lessons come different groups

Healthspan versus Lifespan



Garmany et al Nature2021

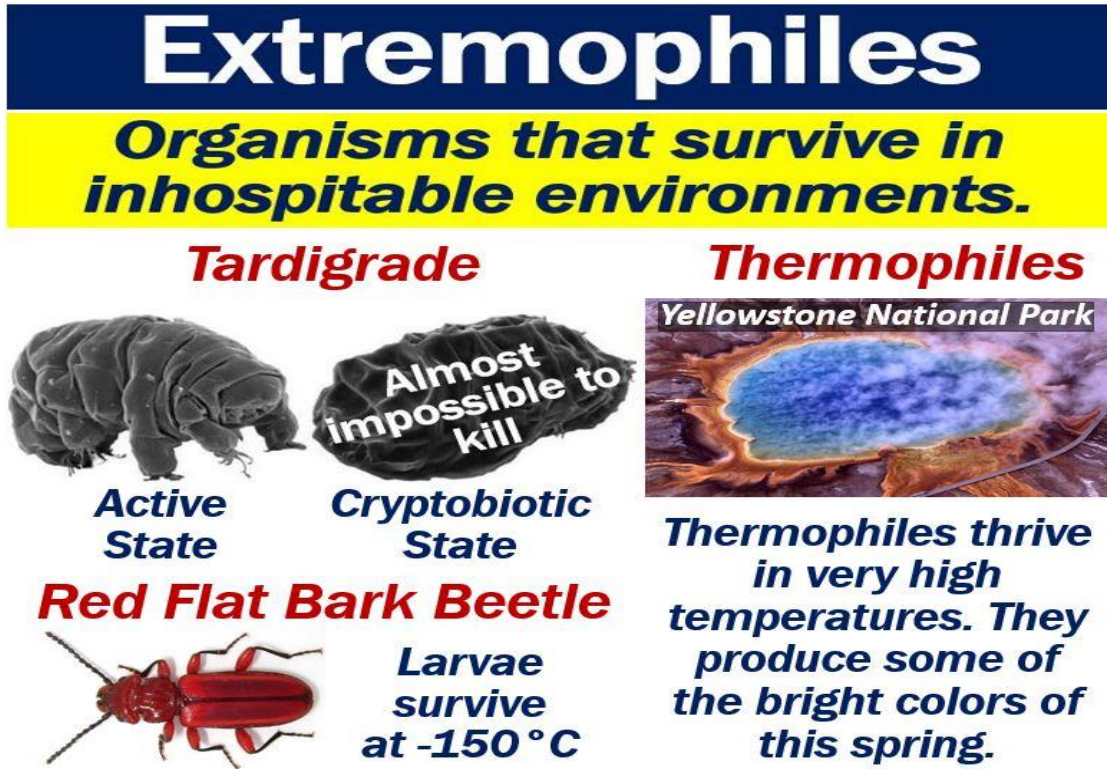


Your *lifespan* is the number of years you live, or quantity. Your *healthspan* is the quality of those years.

JoySpan-T Mayer

YOU DO YOU

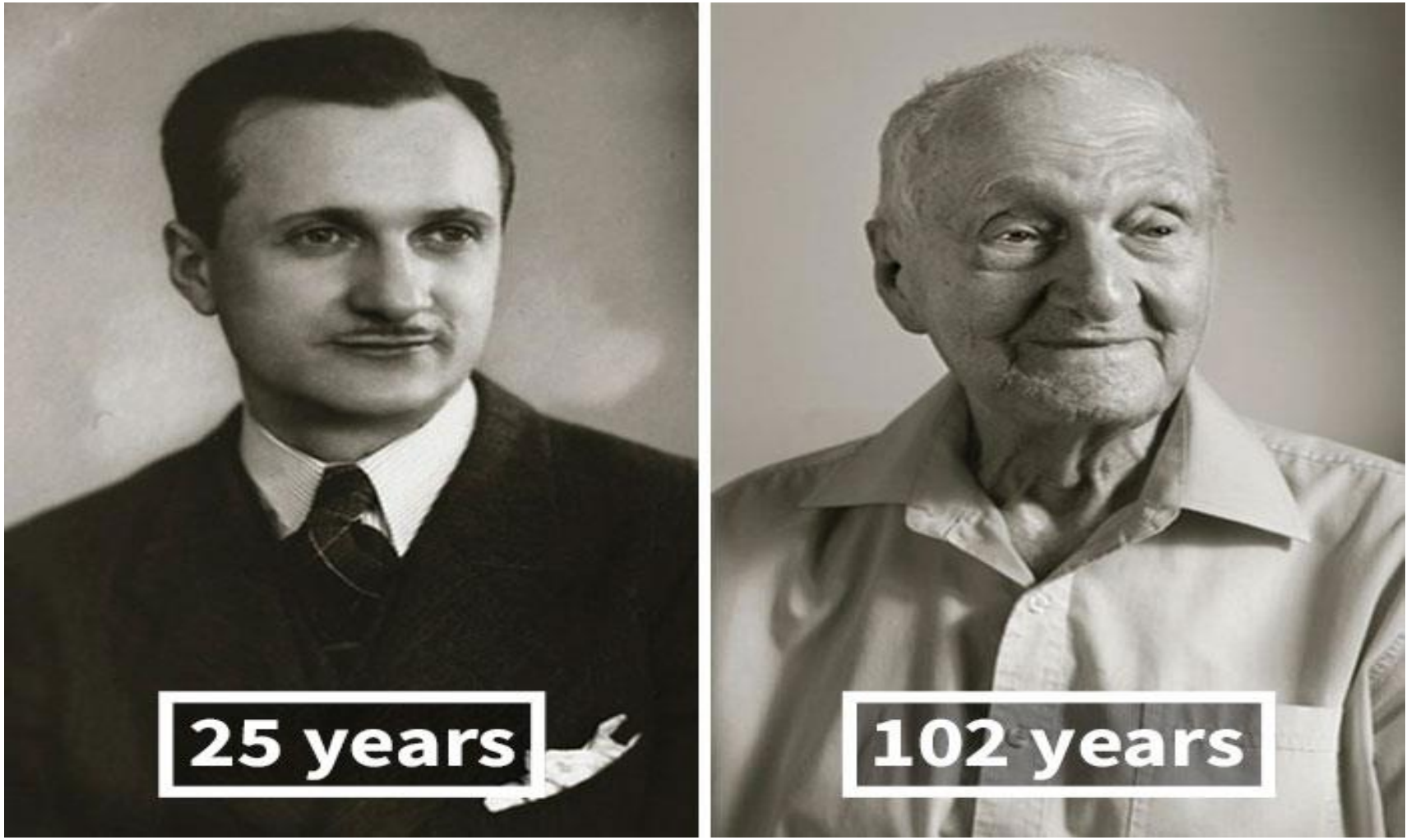
SOF and the Extremes



1 percent of the 1 percent

Extremophiles with extreme exposure

Age matters in almost everything! Less than 55?



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LIMBIC-CENC: Serving America's Heroes

100 Researchers

Largest contributor of data to FITBIR

User Friendly Knowledge Translation Center

11 YEARS OF COLLABORATION

12 COMPLETED STUDIES

300+ PUBLICATIONS

12 ACTIVE STUDIES

23 Research Sites with 3,000+ Participants assessed annually in Prospective Longitudinal Cohort.

2.5 million Unique Participants' Mega-Database analyzed with AI

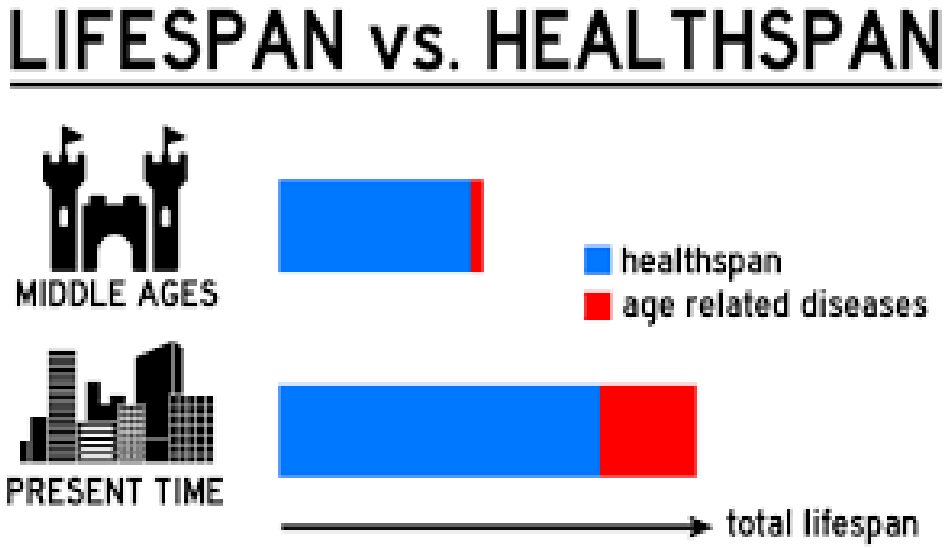
18 ADDITIONAL GRANTS

$127 million

- Largest, ongoing, prospective, longitudinal study of military service and combat exposure
- Big data analyses across DoD to VA to Civilian sources
- Military concussion focus
- Blast and toxic exposure risks
- Dementia risk assessments
- Suicide and mental health factors
- Seizure risks
- Neuroimaging assessments
- Fluid biomarker assessments
- Genomic assessments
- Electrophysiology assessments
- Lifestyle choice and modification assessments
- Health disparity analyses
- Long-COVID impacts

LIMBIC 2013-2023: 100+ researchers; 19 States, 16 Universities, 15 VAMCs and 9 DoD facilities – www.limbic-cenc.org

Creating more health span: when we know better we do better – Targeted therapies and Mitigatory



Targets*

- BP control *
- Sleep
- Belief and social engagement*
- Aerobic activity*
- Diet *
- Pain Control
- Learning new things
- Stress adaption- all humans need a parasympathetic moment

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Lets evaluate the gordian knot of warriors

Links to Chronic Disease in the 1% of the 1%

Military and Civilian

Frame work: Whole Warrior-Whole Life

Early Life

Brain and mental health

Men's health (Testosterone, etc.)

Heart and vascular health

Sleep Quality

Musculoskeletal Health

Cognitive dysfunction and decline

Cardiovascular dysfunction and decline

Chronic Pain & Disability

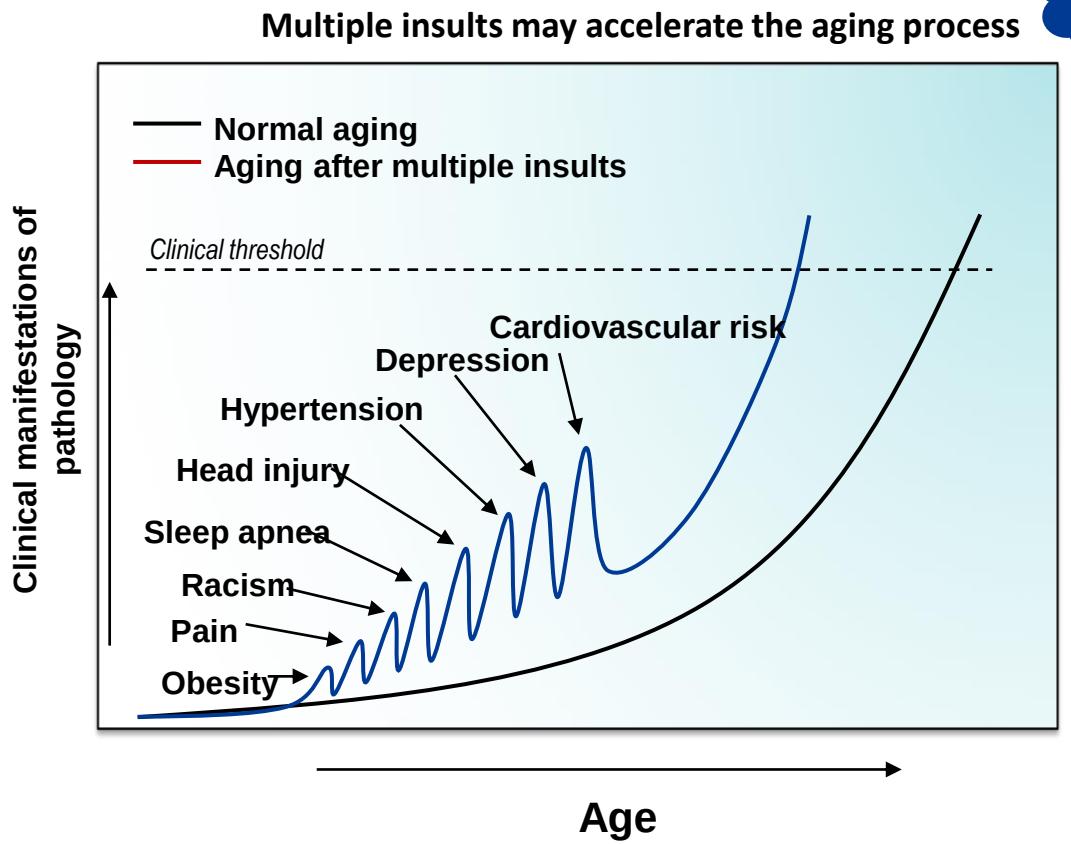
Social determinants of health (*Impactful across the ENTIRE lifespan*)
-Socioeconomic status, experiences with racism, diet, exercise, financial security, smoking and alcohol use, personal network

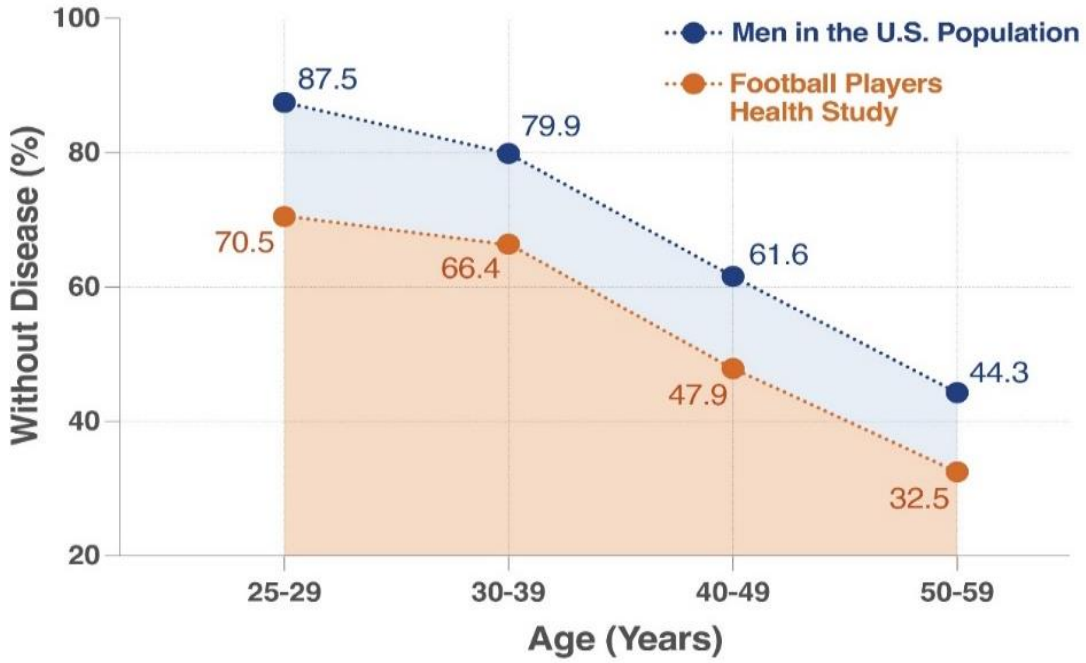
Early cardiovascular, metabolic and musculoskeletal disease

How do we understand the fact that elite athletes with superior fitness in their youth may suffer from conditions associated with advanced age in their 40s, 50s and 60s?

- **Is football wearing these men out early, a "weathering" with consequences that set them on an alternate trajectory of frailty and old age?--- A Path to Health span**

Why?





Grashow et al BJSM 2023

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Factors

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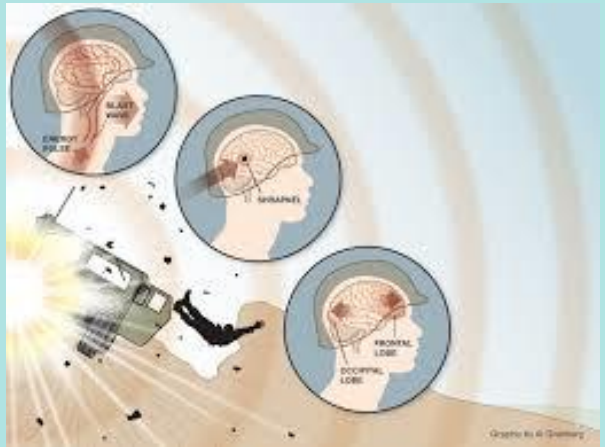
Repeated brain injury is not good

Links to neurodegenerative disease

Football and the military are not the same



The NEW ENGLAND JOURNAL of MEDICINE

Table 3. Mortality with Neurodegenerative Disease Listed as the Primary or a Contributory Cause.

Primary or Contributory Cause of Death	Former Soccer Players (N = 7676)	Matched Controls (N = 23,028)	Hazard Ratio for Death (95% CI)	P Value*
	number (percent)			
Any neurodegenerative disease	222 (2.9)	228 (1.0)	3.53 (2.72–4.57)	<0.001
Neurodegenerative disease subtype				
Dementia not otherwise specified	180 (2.3)	178 (0.8)	3.87 (2.86–5.24)	<0.001
Alzheimer's disease	64 (0.8)	47 (0.2)	5.07 (2.92–8.82)	<0.001
Non-Alzheimer's dementias	121 (1.6)	133 (0.6)	3.48 (2.42–5.00)	<0.001
Motor neuron disease	22 (0.3)	17 (0.1)	4.33 (2.05–9.15)	<0.001
Parkinson's disease	28 (0.4)	44 (0.2)	2.15 (1.17–3.96)	0.01

JAMA Network | Open

Original Investigation | Neurology

Incidence of and Mortality From Amyotrophic Lateral Sclerosis in National Football League Athletes

Daniel H. Daneshvar, MD, PhD; Jesse Mez, MD, MS; Michael L. Alosco, PhD; Zachary H. Baucom, MA; Ian Mahar, PhD; Christine M. Baugh, PhD, MPH; Jhaqueline P. Valle, MPH; Jennifer Weuve, MPH, ScD; Sabrina Paganoni, MD, PhD; Robert C. Cantu, MD; Ross D. Zafonte, DO; Robert A. Stern, PhD; Thor D. Stein, MD, PhD; Yorghos Tripodis, PhD; Christopher J. Nowinski, PhD; Ann C. McKee, MD

Abstract

IMPORTANCE Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease; understanding ALS risk factors is a critical public health issue.

OBJECTIVES To evaluate the incidence of and mortality from ALS in National Football League (NFL)

Key Points

Question What are the incidence and mortality rates of amyotrophic lateral sclerosis (ALS) in athletes who played in the National Football League (NFL)?

Table 2. Amyotrophic Lateral Sclerosis Incidence and Mortality in NFL Athletes

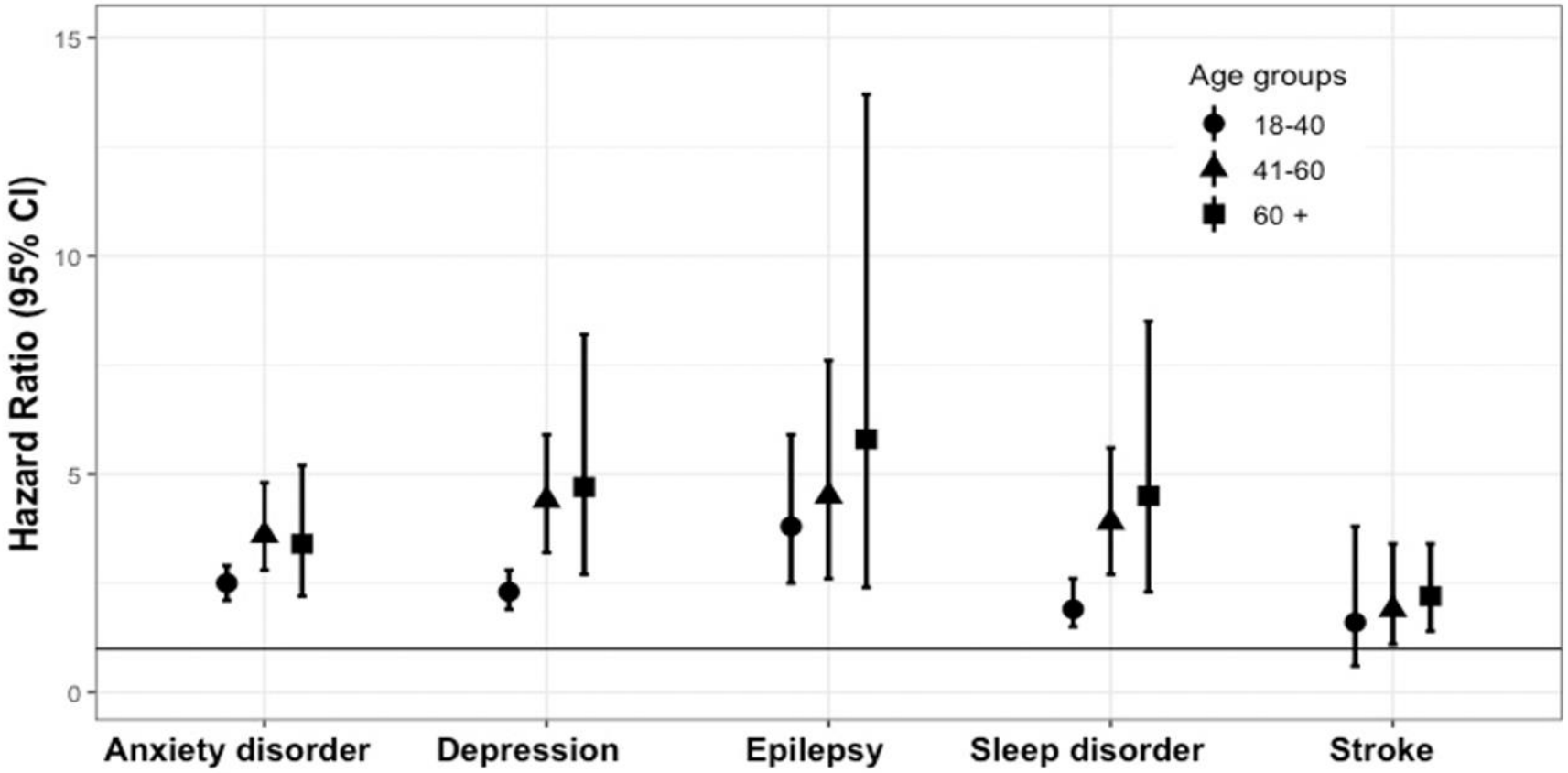
NFL players	Standardized incidence ratio (95% CI)	Standardized mortality ratio (95% CI)
Overall	3.59 (2.58-4.93)	3.94 (2.62-5.69)
Race		
Black	3.63 (1.93-6.21)	4.72 (2.26-8.67)
White	3.50 (2.24-5.21)	3.61 (2.14-5.71)

follow-up, 30.6 [13.7] years). Thirty-eight players received a diagnosis of ALS, and 28 died during the study time frame, representing a significantly higher incidence of ALS diagnosis (standardized incidence ratio, 3.59; 95% CI, 2.58-4.93) and mortality (standardized mortality ratio, 3.94; 95% CI,

Author affiliations and article information are listed at the end of this article.

Risk trends of psychiatric and neurological comorbidities following concussion by age

Wow

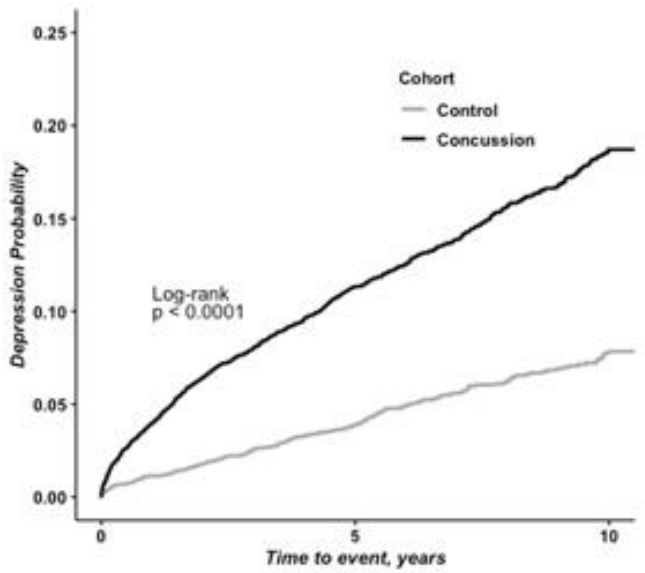


Izzy et al 2021

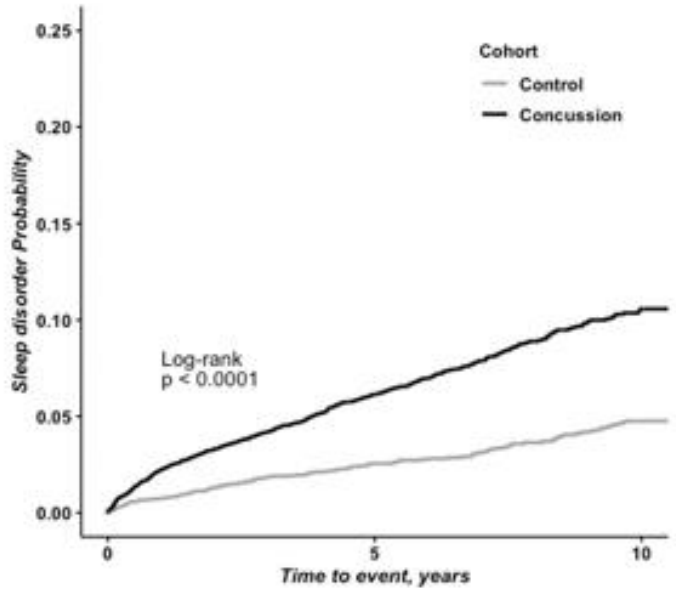
Adjusted for sex and race

Time-to-event for other comorbidities post-concussion

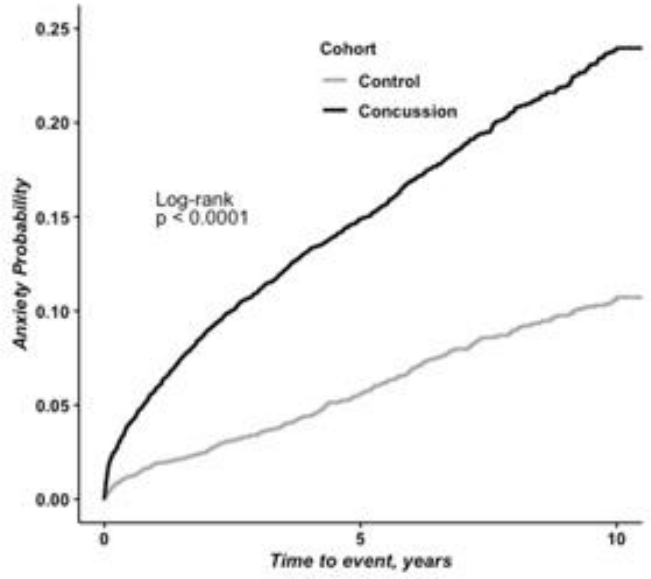
Depression



Sleep disorder



Anxiety disorder



Izzy et al 2021

Adjusted for age, sex and race

JAMA Network Open

Original Investigation | Neurology

Association of Adverse Childhood Experiences Wit and Dementia Among Former Professional US Foo

Andrea L. Roberts, PhD; Ross Zafonte, DO; Lori B. Chibnik, PhD, MPH; Aaron Baggish, MD; Herman Tayl
Alicia J. Whittington, PhD, MPH; Marc G. Weisskopf, ScD, PhD

Abstract

IMPORTANCE Childhood adversities, including neglect, abuse, and other indicators of fam dysfunction, are associated in adulthood with risk factors for poor cognitive and mental hea However, the extent to which these experiences are associated with adulthood cognition-re quality of life and risk for dementia is unknown.

OBJECTIVE To determine the association of 10 adverse childhood experiences (ACEs) with neuropsychiatric outcomes among former National Football League (NFL) players.

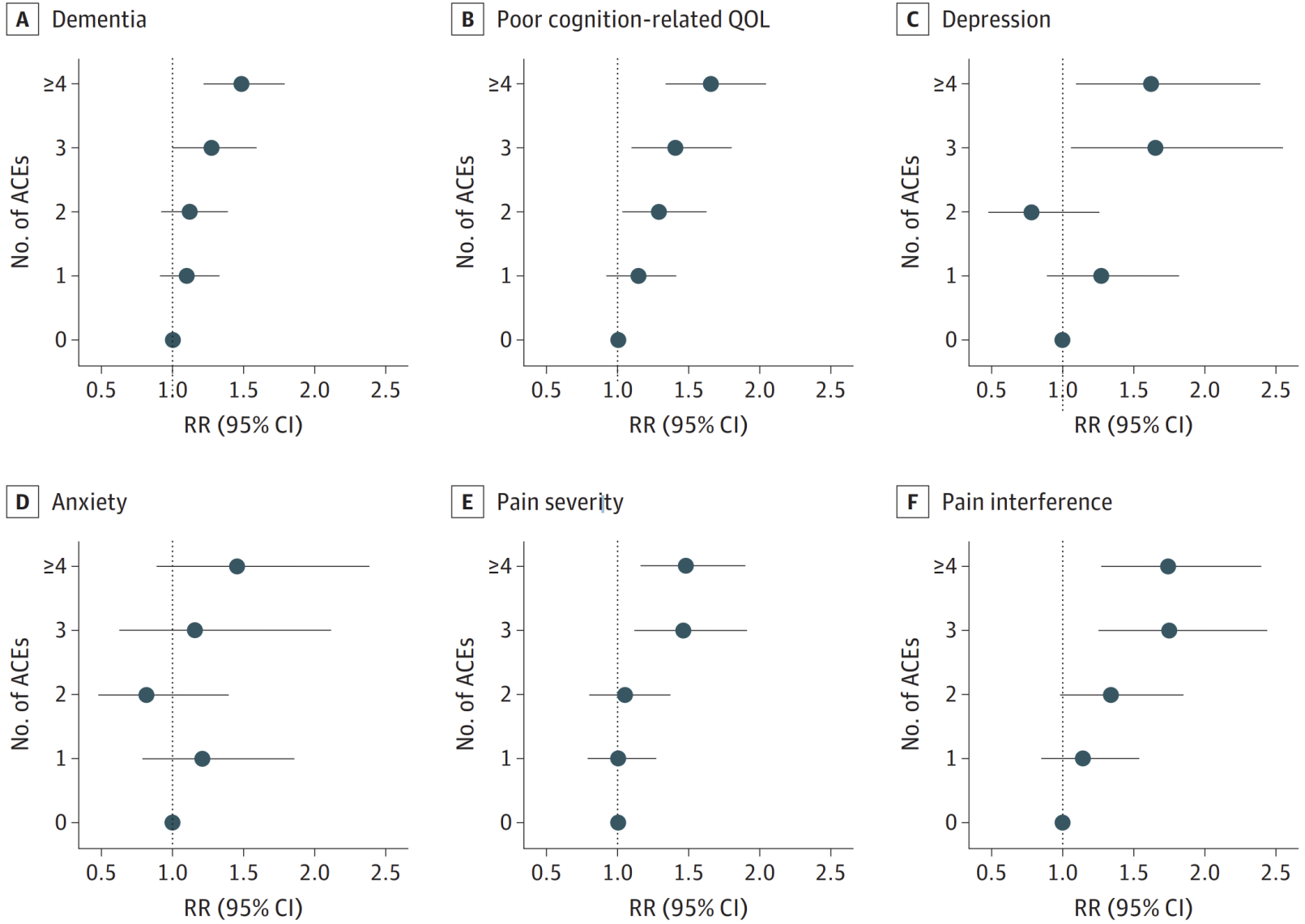
DESIGN, SETTING, AND PARTICIPANTS This cross-sectional analysis used data from the F Player's Health Study at Harvard University, an ongoing longitudinal cohort study from Janu 2015, to November 19, 2021, of former NFL players.

EXPOSURES Ten ACEs were assessed using the Adverse Childhood Experiences Questionn

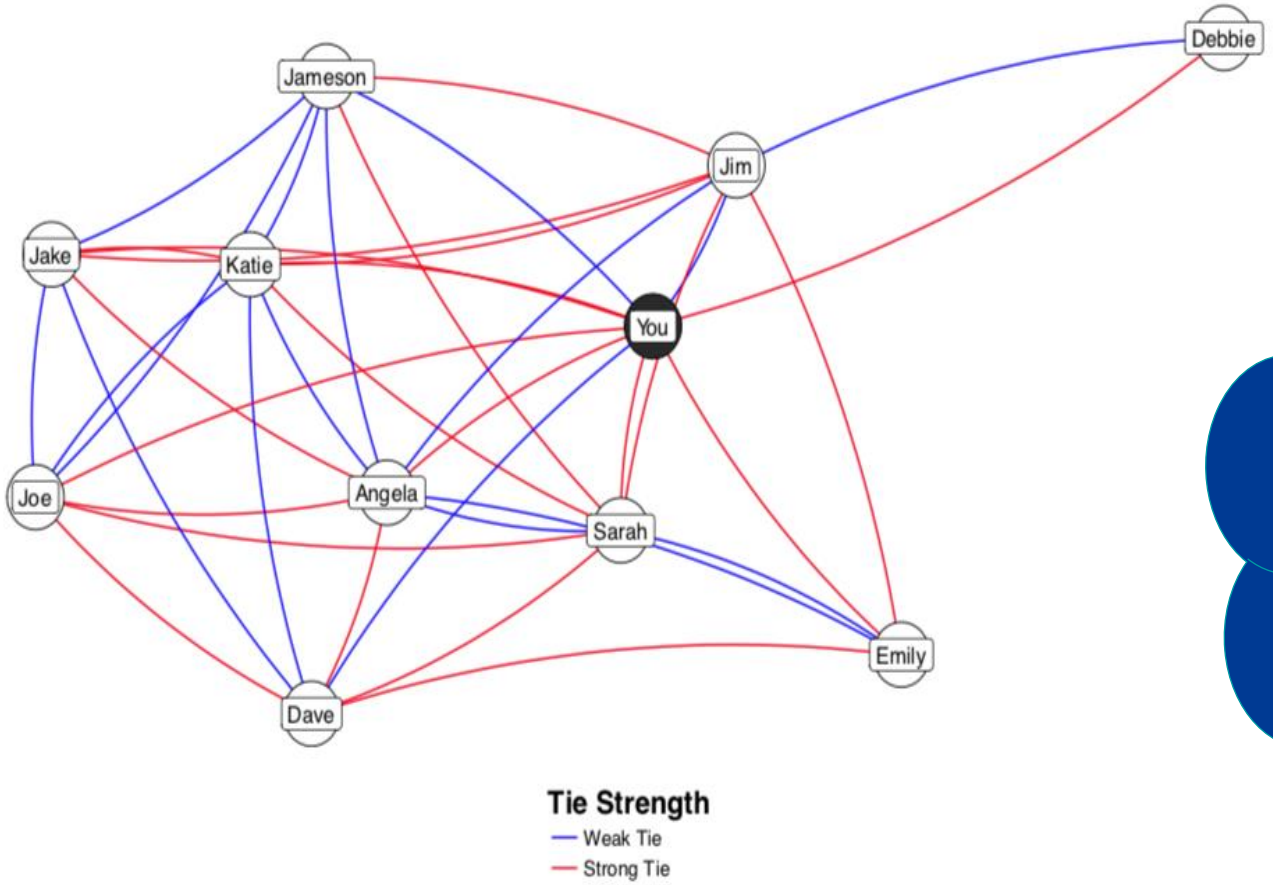
MAIN OUTCOMES AND MEASURES Dementia symptoms were assessed using the AD8: T Washington University Dementia Screening Test; cognition-related quality of life was assess the short form of the Quality of Life in Neurological Disorders; depression was assessed wit Patient Health Questionnaire-9; anxiety was assessed with the Generalized Anxiety Disorde pain intensity and pain interference in daily life were assessed with the Brief Pain Inventory ratios (RRs) assessing the association between ACEs and neuropsychiatric outcomes were e using generalized estimating equations, adjusted for age, race, and childhood socioeconomi and further adjusted for playing position, concussions incurred during football play, and nu seasons played in the NFL.

RESULTS A total of 1755 men (mean [SD] age, 57.2 [13.5] years) who were former professio football players were included in the analysis. Five hundred twenty players (29.6%) identifie Black, 1160 (66.1%) identified as White, and 75 (4.3%) identified as other race or ethnicity. Players

Figure. Adverse Childhood Experiences and 6 Neuropsychiatric Health Outcomes



The Personal Network Study



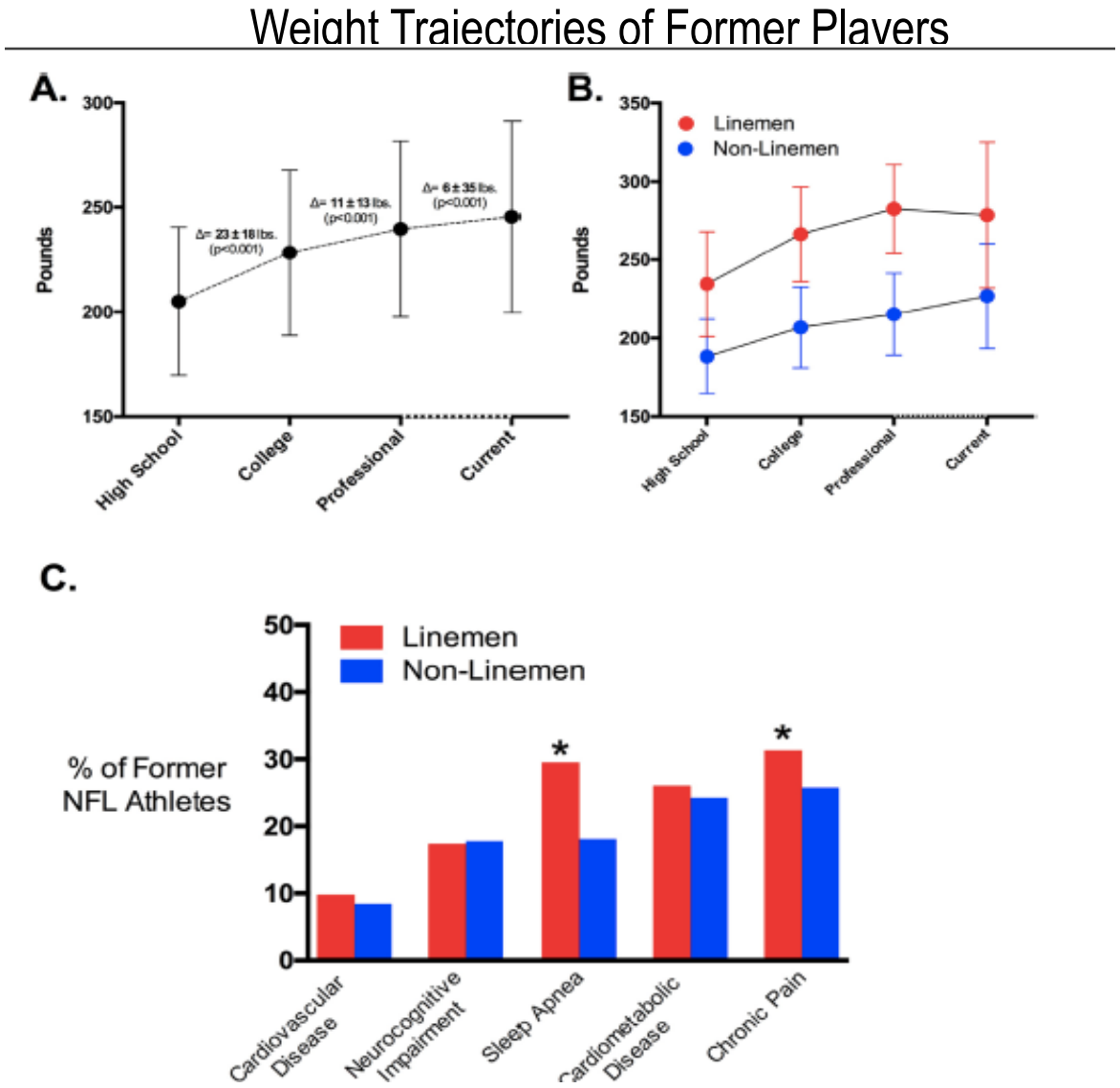
How can this help
Isolation not so good

Dhand A et al. Sci Reports 2021

Weight Gain *(Churchill et. al. Am J Med, 2018)*

Average weight gain from high school to time of survey was 40 pounds

- Significantly elevated odds of cardiometabolic disease, sleep apnea and chronic pain: HS to College
- Significantly elevated odds of cardiovascular disease, cardiometabolic disease, sleep apnea and neurocognitive impairment: College to Pro



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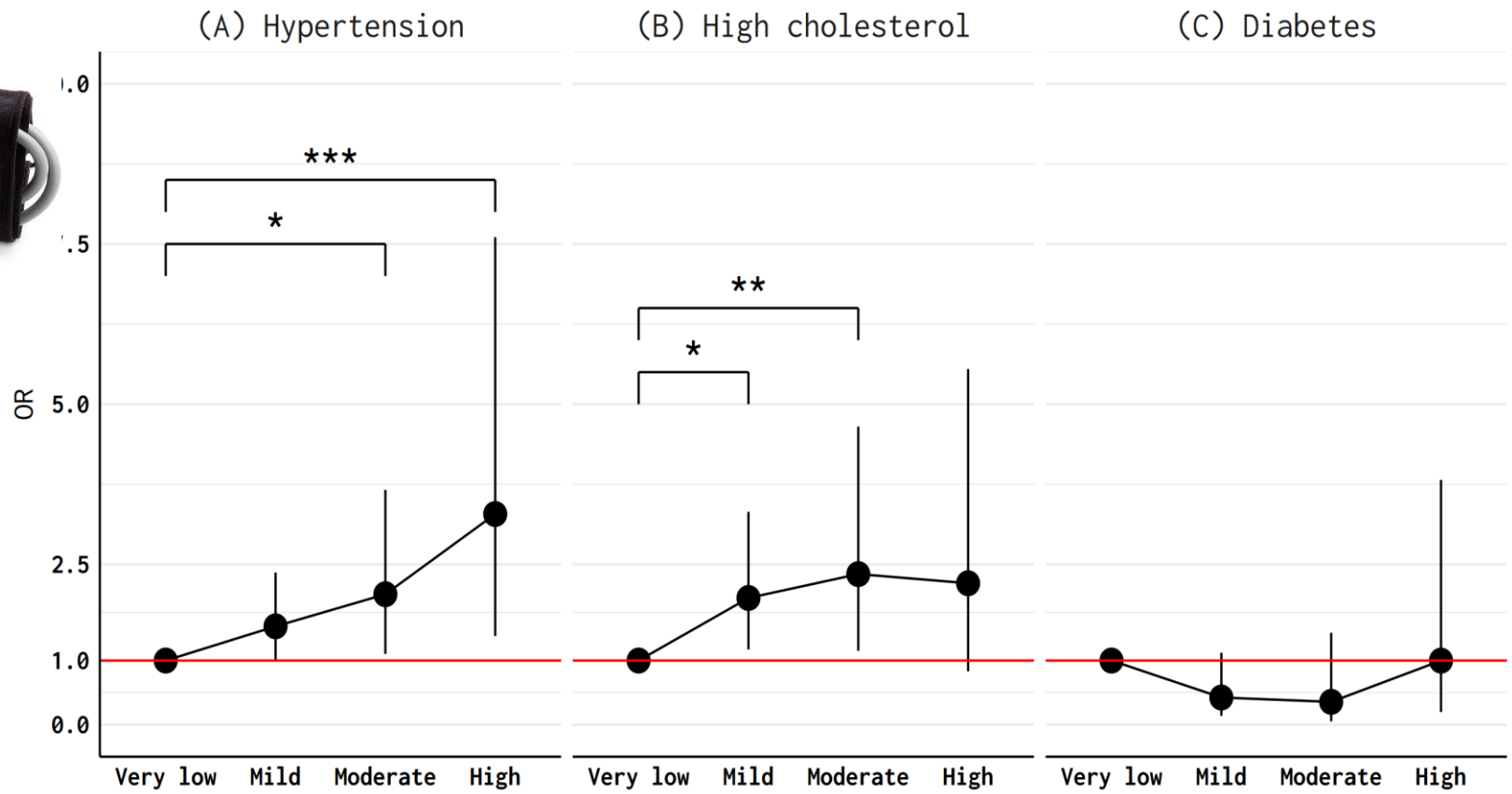
Interventions for the now

Candidates and Targets

Long-term risk of cardiovascular disease after traumatic brain injury: screening and prevention

Saef Izzy, Rachel Grashow, Farid Radmanesh, Patrick Chen, Herman Taylor, Rita Formisano, Fiona Wilson, Meagan Wasfy, Aaron Baggish, Ross Zafonte

PRESS



Lancet Neurol 2023; 22: 959–70

See **Comment** page 878

Hypertension

DEMENTIA

The Association of Age at Diagnosis of Hypertension With Brain Structure and Incident Dementia in the UK Biobank

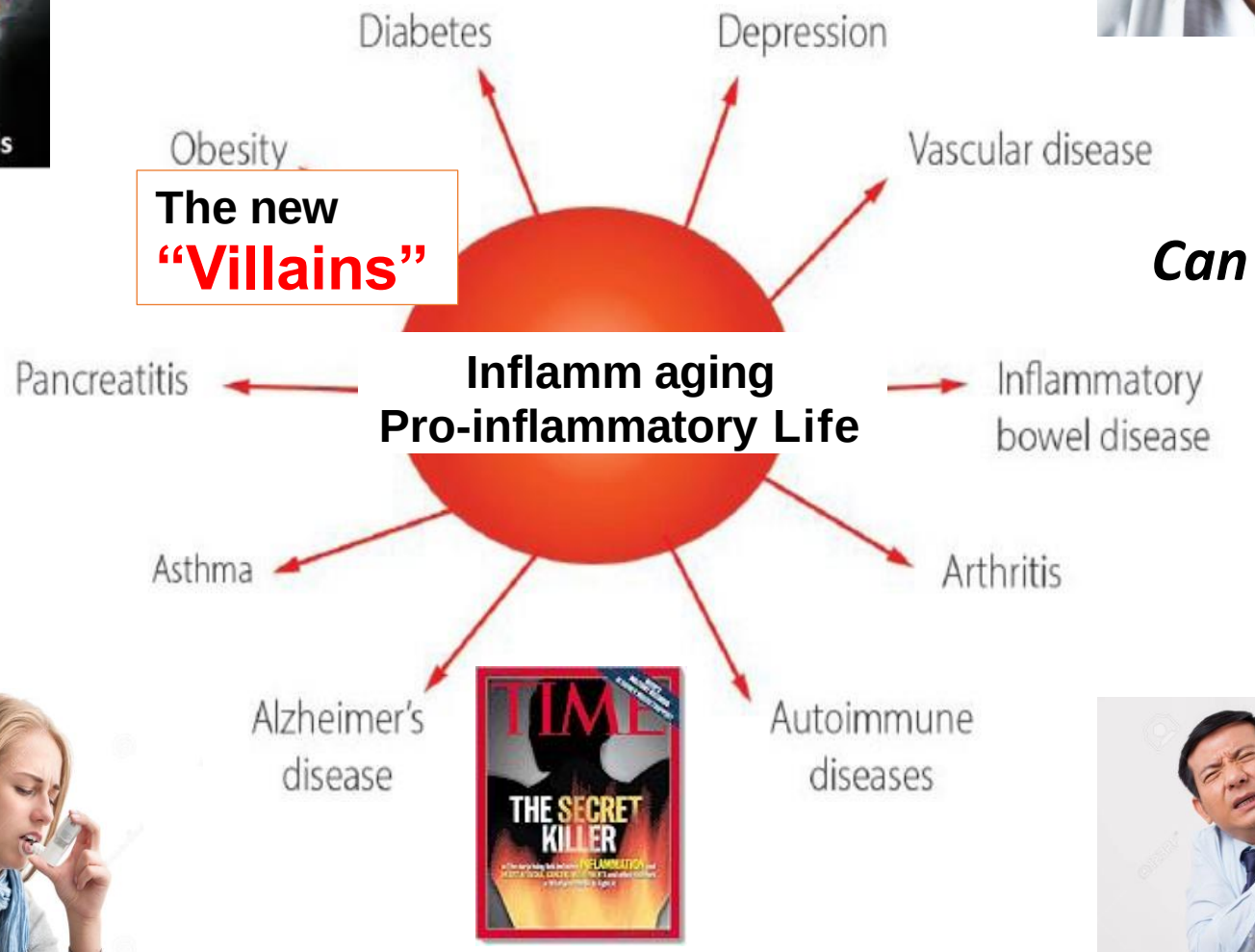
Xianwen Shang, Edward Hill, Zhuoting Zhu, Jiahao Liu, B. Zongyuan Ge, Wei Wang, Mingguang He

Tan et al

diabetes

Common Theme
Excessive Inflammation

The new "Villains"



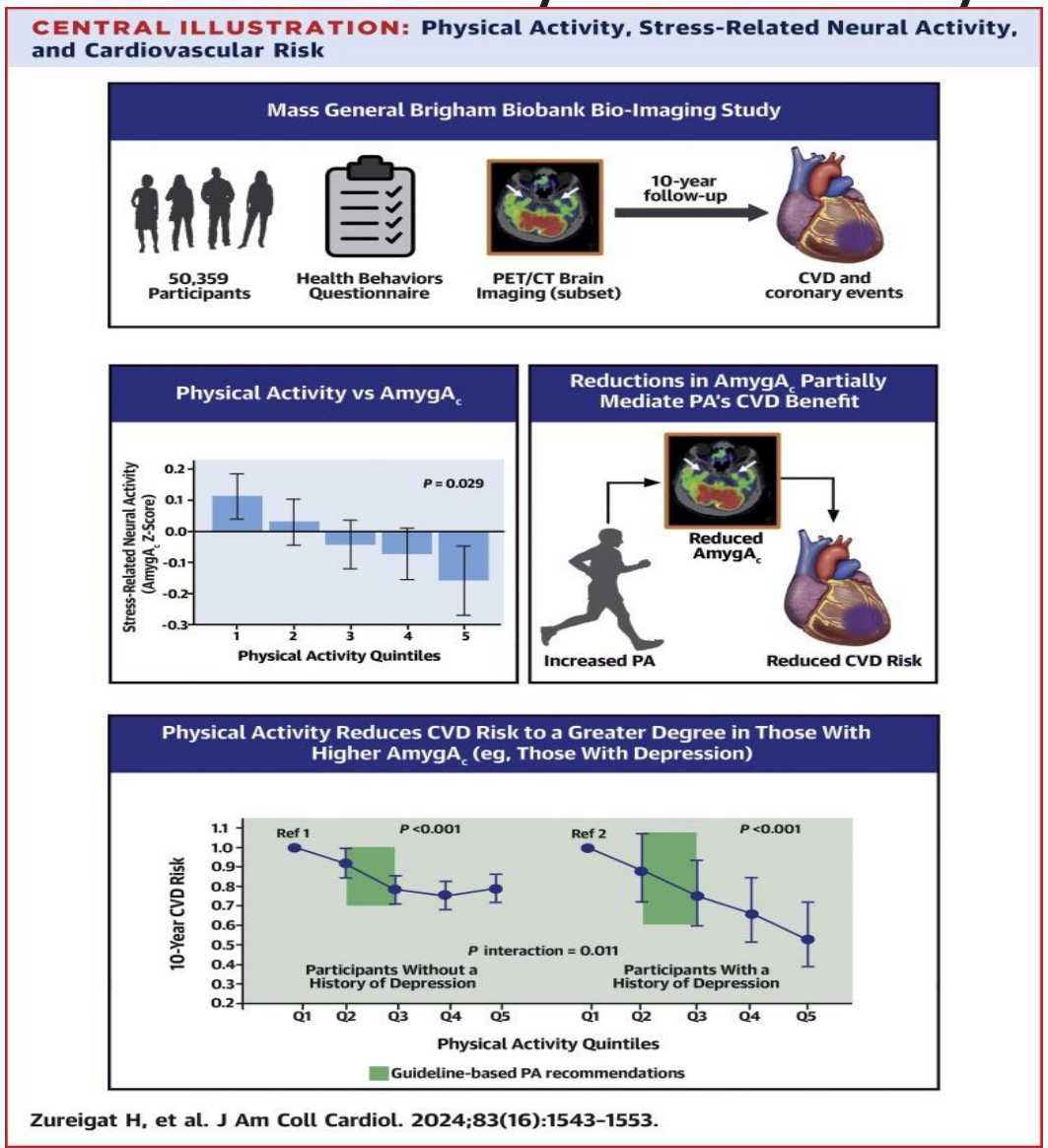
Epigenetic clock and multiomics

Can we help?

Passive and Active

Chronic Stress : Lifestyle

Effect of Stress-Related Neural Pathways on the Cardiovascular Benefit of Physical Activity



Zureigat H, et al. J Am Coll Cardiol. 2024;83(16):1543–1553.

People with depression had larger reductions in cardiovascular disease risk from physical activity than those without depression

Even greater reductions if they exercised for more than the recommended 150 weekly minutes.

Exercise acts via the stress brain mechanism!

Zureigat et al J American College of Cardiology 2024

Ornish et al. Alzheimer's Research & Therapy (2024) 16:122
https://doi.org/10.1186/s13195-024-01482-z

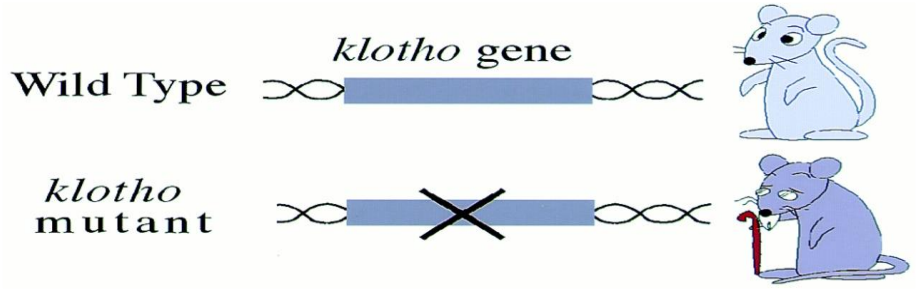
Alzheimer's Research & Therapy

RESEARCH Open Access

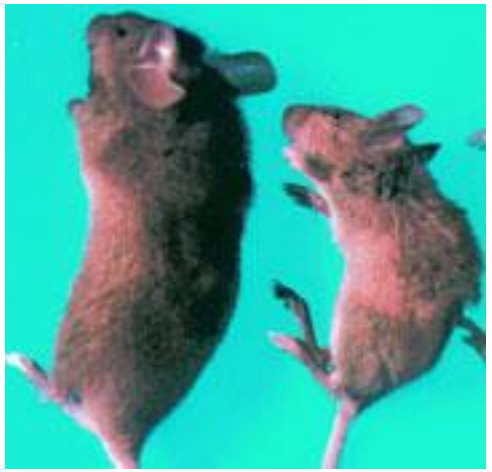
Effects of intensive lifestyle changes on the progression of mild cognitive impairment or early dementia due to Alzheimer's disease: a randomized, controlled clinical trial

Dean Ornish[1,2*], Catherine Madison[1,3], Miia Kivipelto[4,5,6,7], Colleen Kemp[8], Charles E. McCulloch[9], Douglas Galasko[10], Jon Artz[11,12], Dorene Rentz[13,14,15], Jue Lin[16], Kim Norman[17], Anne Ornish[1], Sarah Tranter[8], Nancy DeLamarter[1], Noel Wingers[1], Carra Richling[1], Rima Kaddurah-Daouk[18], Rob Knight[19], Daniel McDonald[20], Lucas Patel[21], Eric Verdin[22,23], Rudolph E. Tanzi[13,24,25,26] and Steven E. Arnold[13,27]

Klotho as a candidate biomarker



Muscle Brain Axis



Wild type Klotho mutant

Kuro-O et al, *Nature* 1997

Exercise Increases Klotho and Changes TREM2

nature reviews nephrology

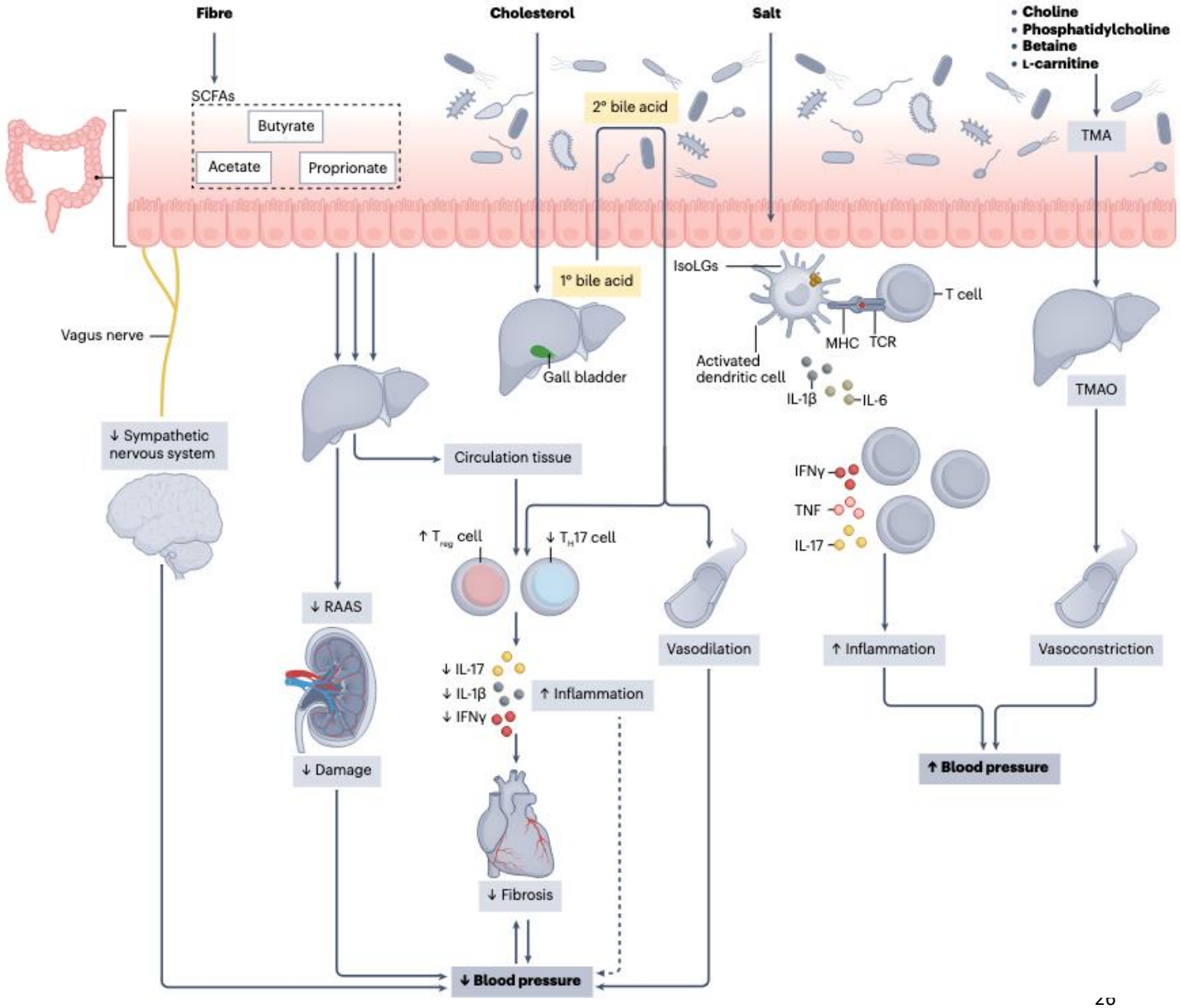
Review article

The gut microbiome and hypertension

Joanne A. O'Donnell[1,4], Tenghao Zheng[1,4], Guillaume Meric[2] & Francine Z. Marques[1,3]

Microbiota interactions with multiple factors can affect cardiovascular disease

- Stress (vagal nerve)
- Diet (fiber, cholesterol, salt, TMA)
- Inflammation (IL-17, INFg, TNFa)



Microbiota-Gut Brain and Behavior Interactions

Low Omega-3-
Walter Reed data

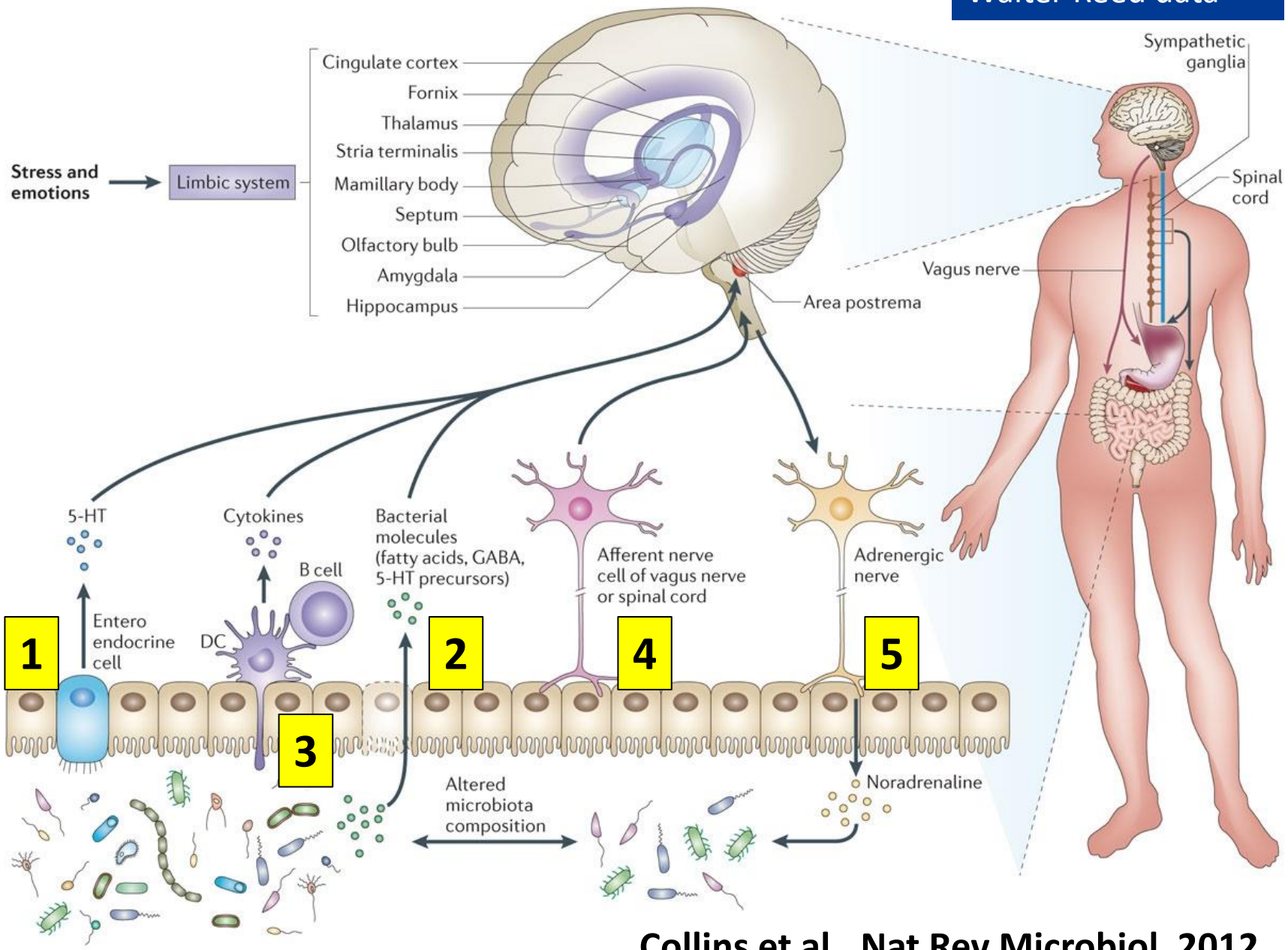
1. Bacteria can induce our gut cells to make neurotransmitters

2. Bacteria can produce neurotransmitters

3. Microbiota modulate immune cells which migrate to the brain

4. Microbiota signal through the vagus nerve to affect pain responses and anxiety

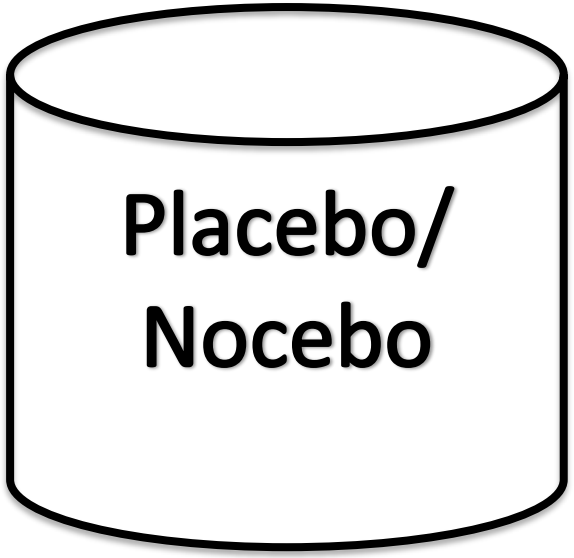
5. Brain → microbes via the adrenergic nerve

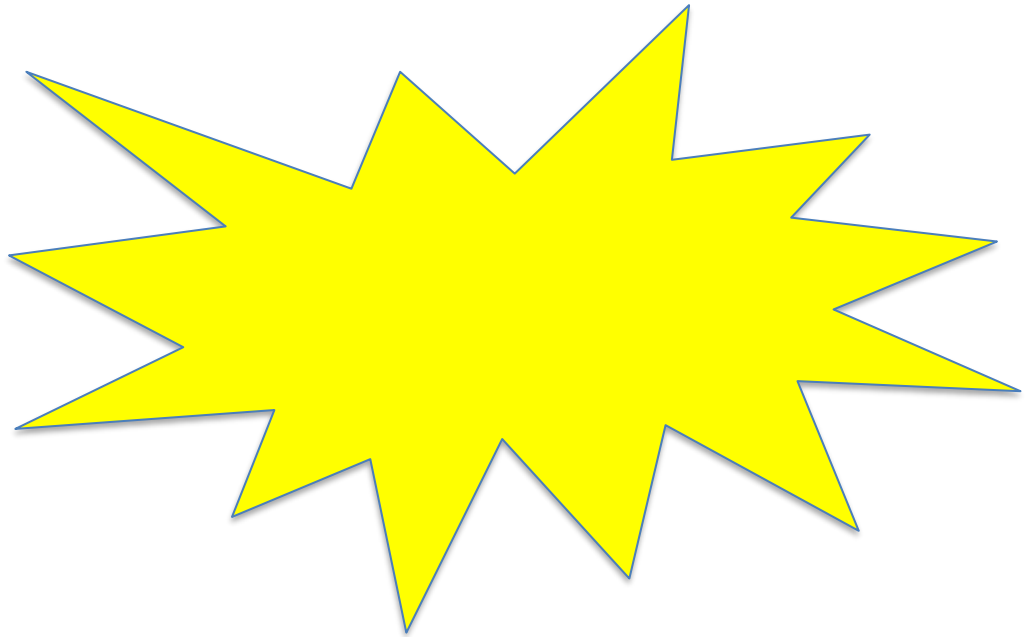


Collins et al., Nat Rev Microbiol, 2012

Placebo/ Nocebo is not equivalent to nothing: More than anoying!

Have we been biased?



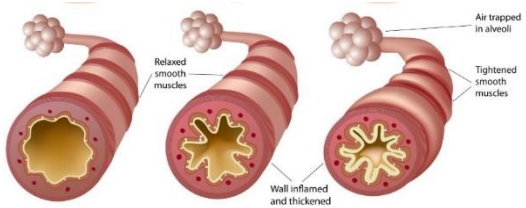


What we perceive is not what the world really is

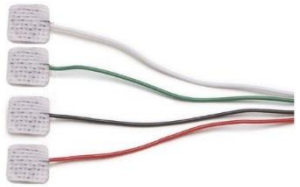
-Ongaro and Kaptchuck2018

Expectations: nocebos in the lab

SPAULDING REHABILITATION NETWORK
MASSACHUSETTS GENERAL HOSPITAL
BRIGHAM AND WOMEN'S HOSPITAL
HARVARD MEDICAL SCHOOL TEACHING HOSPITAL



Nocebo nebs in asthmatics cause asthma attacks (Luparello 1968).



Induce HA pain in college students (Schweiger 1981).

Nocebo injections cause food allergy sx (Jewett 1990).

Induced non-specific symptoms through suggestion or demonstration (Papoiu 2011; Lorber 2007; Mazzoni 2010)

Adverse effects to placebo occur in ~20-25% of subject (Barsky 2002).

Increased rates with warning (Barsky 2002; Mondaini 2007).

Symptoms mimic the adverse effect profile of active drugs (Rief 2009; Amanzio 2009).

Tackling Personal Health

A conversation checklist with your healthcare provider

☑	ASK ABOUT YOUR...	TO SEE IF YOU HAVE...	PREVENTION/ TREATMENT OPTIONS
☐	Blood Pressure	High blood pressure (Hypertension)	
☐	Blood sugar (HbA1c)	High blood sugar (Diabetes or prediabetes)	
☐	Cholesterol (LDL, HDL, total cholesterol)	High cholesterol (Hyperlipidemia)	
☐	Testosterone and urinary symptoms	Low testosterone, prostate issues	
☐	Sleep habits	Insomnia, sleep apnea, REM sleep behavior disorder, etc.	
☐	Pain	Chronic pain condition or neuropathy	
☐	Memory, thinking, concentration	Cognitive dysfunction	
☐	Feelings of sadness, worry, irritability, moodiness	Depression, anxiety	
☐	Weight	Weight issues or obesity	

Did you know? Thinking or memory issues can result from high blood pressure, diabetes, sleep apnea, chronic pain, anxiety, and depression.

If you need a healthcare provider, visit:

www.health.gov/myhealthfinder/doctor-visits/regular-checkups/choosing-doctor-quick-tips

www.playerstrust.com *(Check website for eligibility)*

KEY:

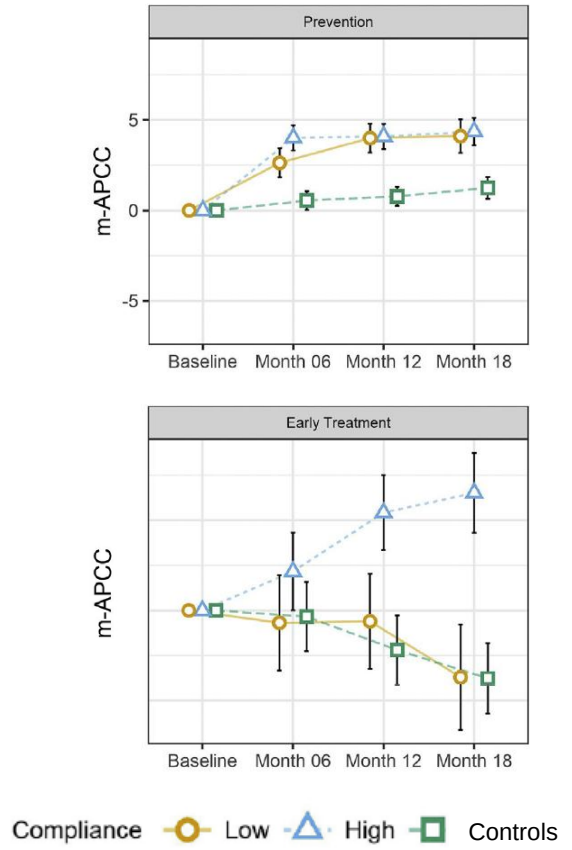
Tips:

1. Bring a friend or family member
2. Share your medical and family history
3. Be honest
4. Ask questions
5. Take notes

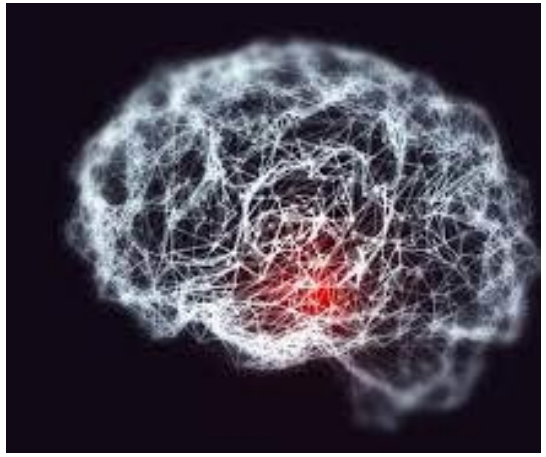
Effect of interventions on Alzheimers patients

Isaacson et al. (2019) recruited clinical and pre-clinical Alzheimers patients

- Preclinical patients received “prevention” treatment
- Clinical patients received “early treatment”
- Interventions included medication, vitamins, exercise, nutrition, sleep, cognitive training, stress reduction
- Followed every 6 months



Conclusions



- Brain injury may increase risk of medical and behavioral health problems as well as ND/ CTE pathology disease
- A complicated maladaptive phenotype may exist in some persons- we can attack now!!!
- The directionality may go multiple ways and maladaptive early aging may be occurring

Healthspan counts! Treat Now and Target For Later

Medicine is the most human of the sciences and the most scientific of the humanities –H. Taylor, MD, MPH

What is needed?