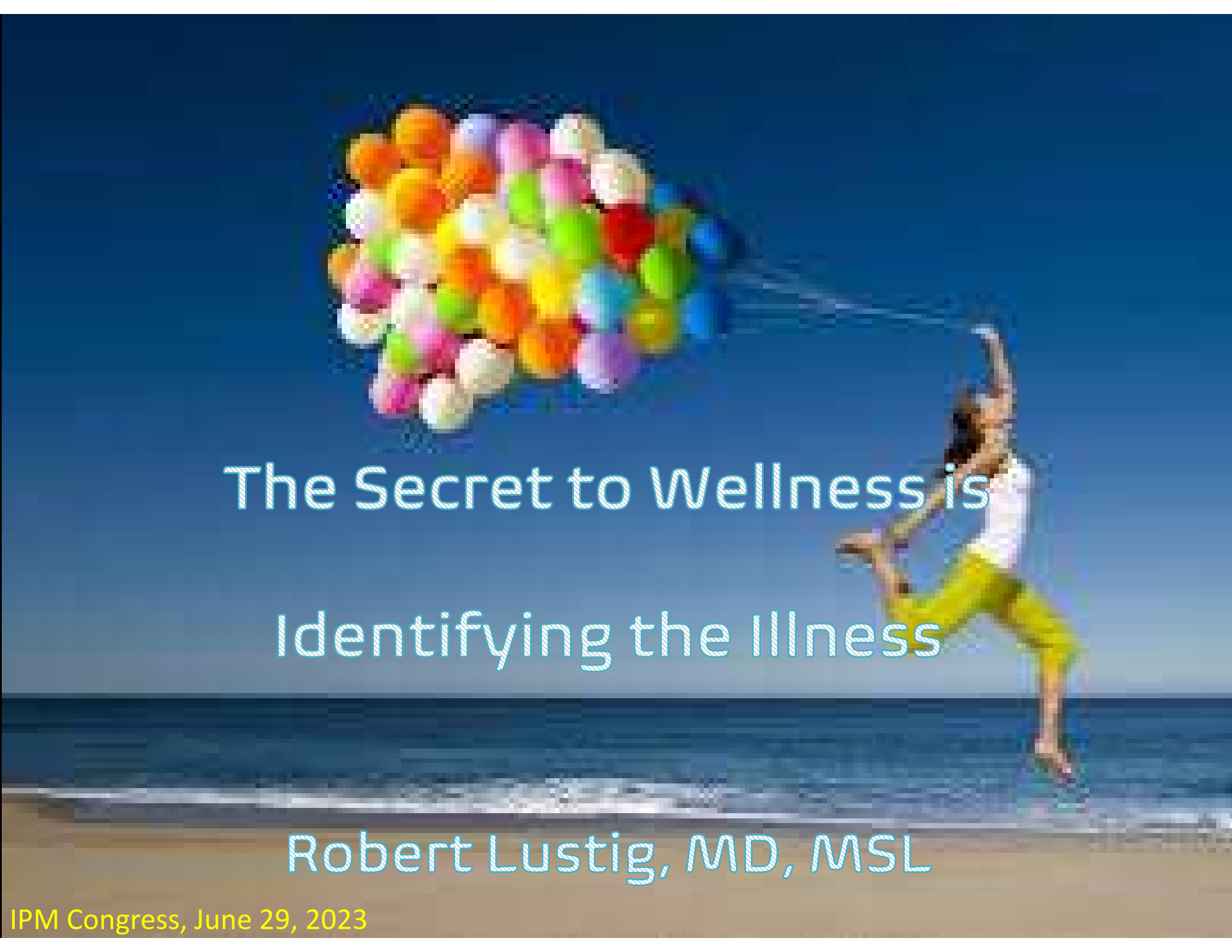
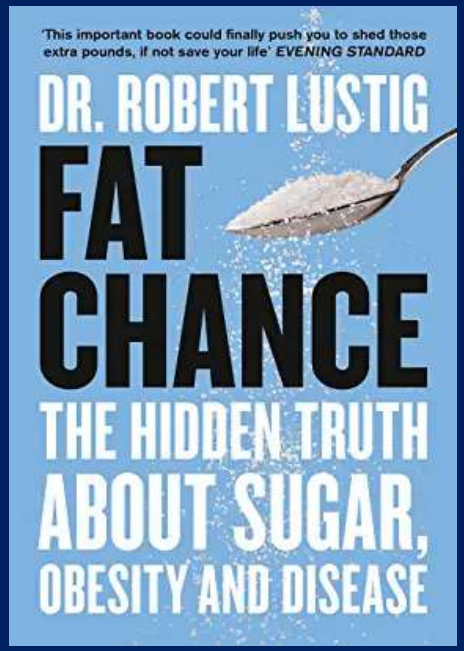
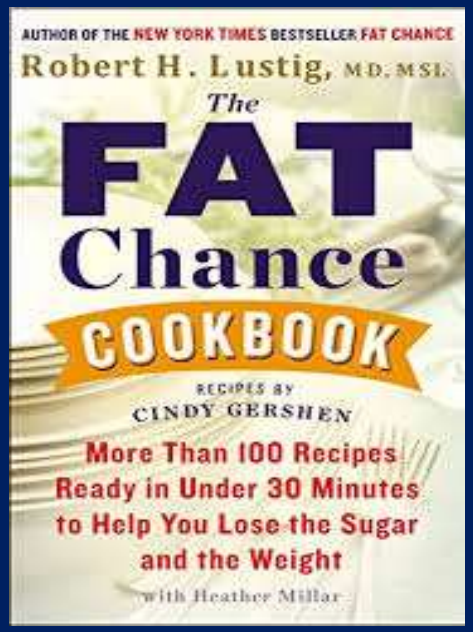
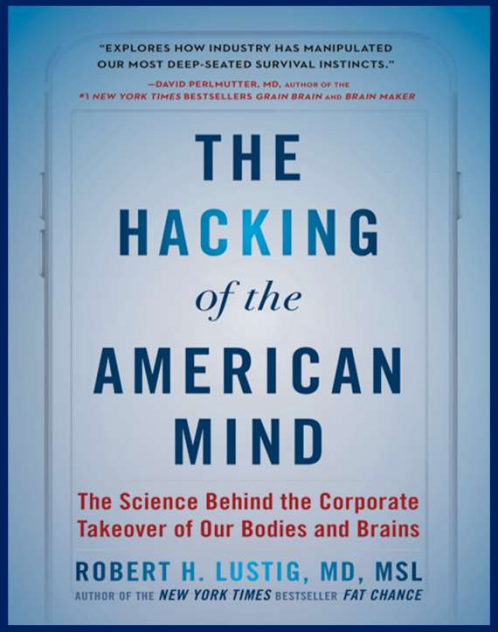
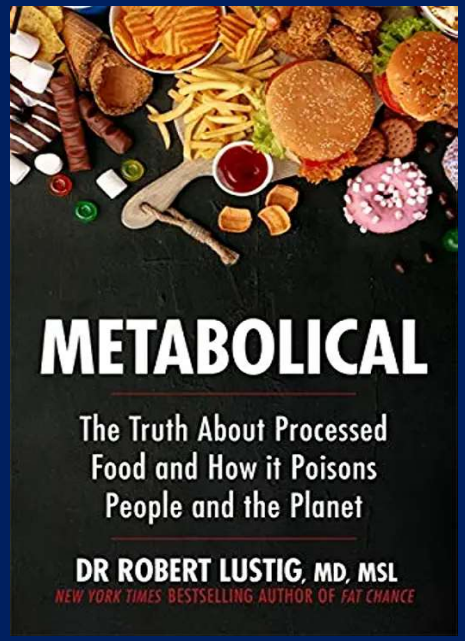

The Secret to Wellness is
Identifying the Illness
Robert Lustig, MD, MSL
IPM Congress, June 29, 2023

# Disclosures




Chief Medical Officer:
BioLumen Technologies
Kalin Health
Foogal
Perfact

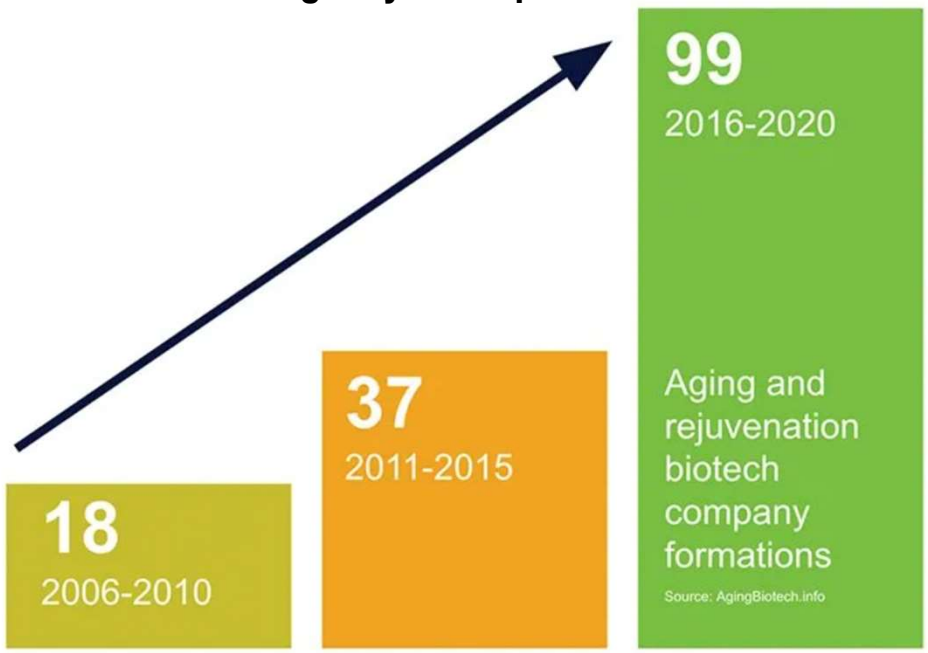
Paid Advisor:
Readout Health
Simplex Health
Myka Bio
Levels Health

I will not be speaking about any of these companies or products

# Wellness (def.):

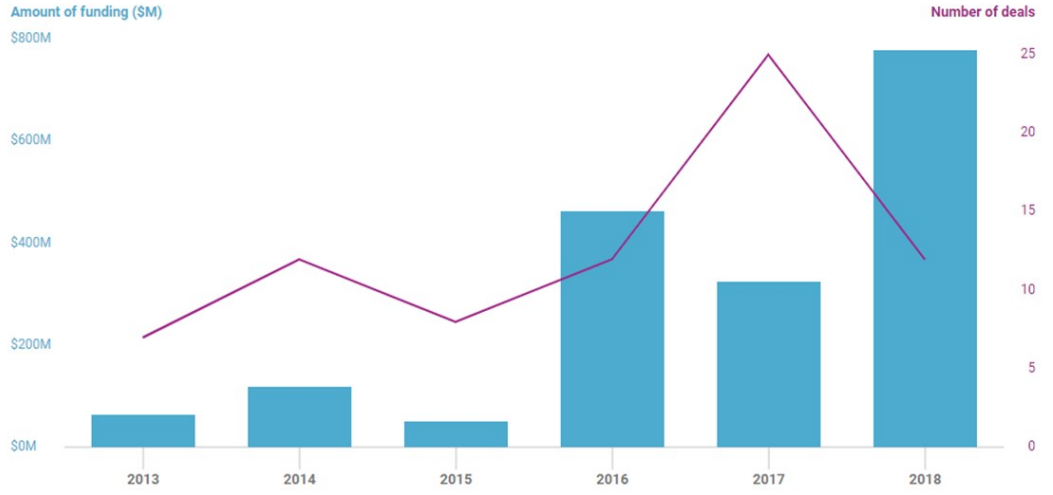
- Metabolic health
- Mental health
- Financial health

## Formation of longevity startups




## Funding to longevity startups

Amount of funding ($M) and number of deals from 2013 – 2018 (as of 9/25/2018)

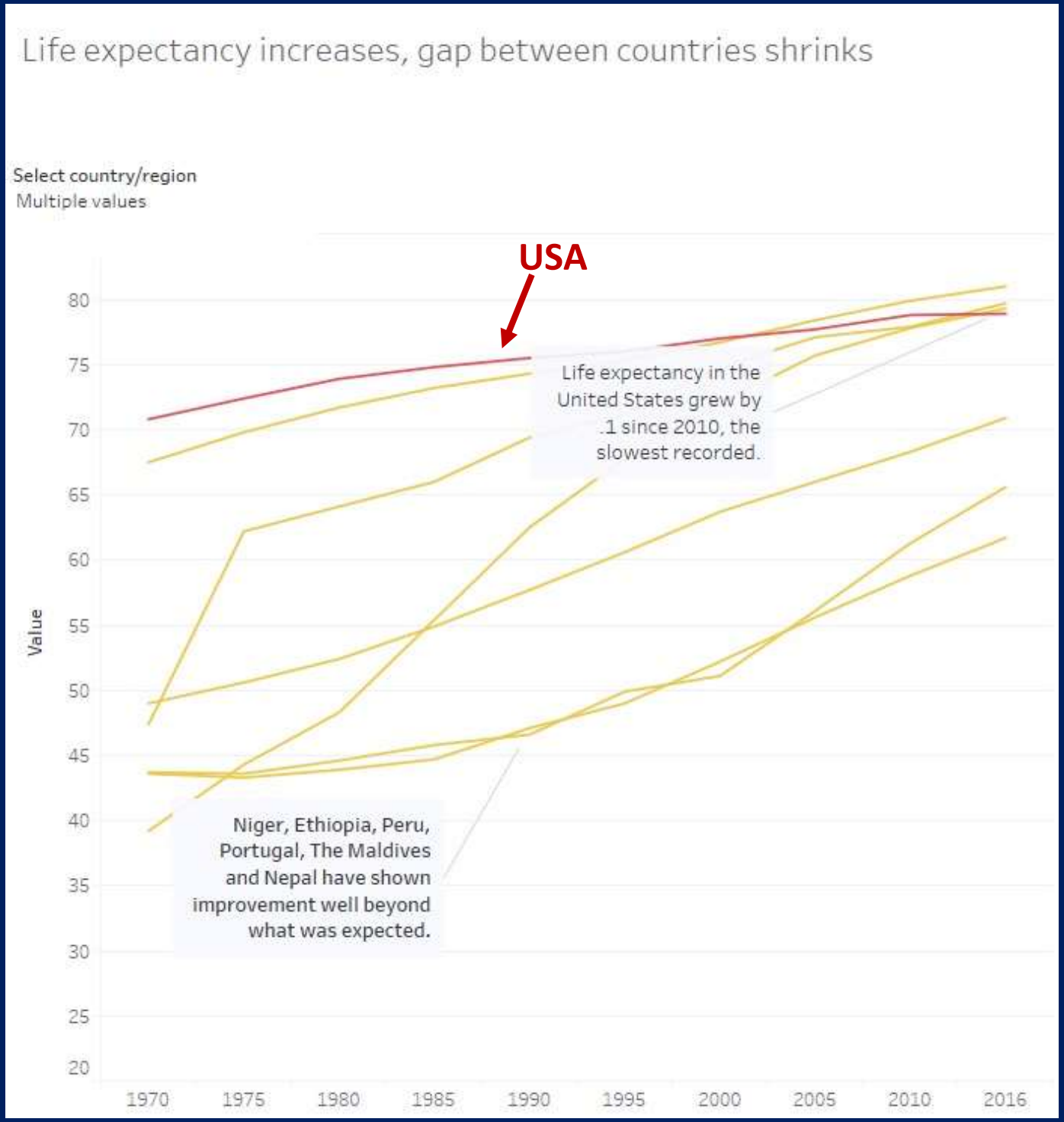



Source: cbinsights.com

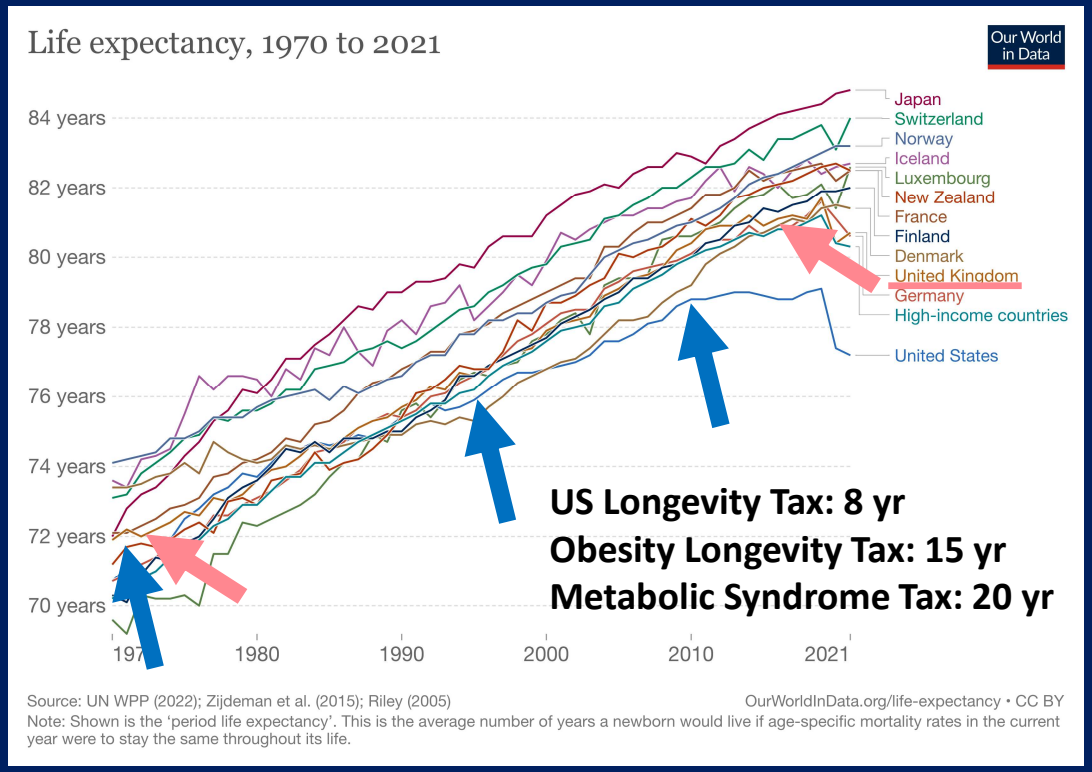
CBINSIGHTS

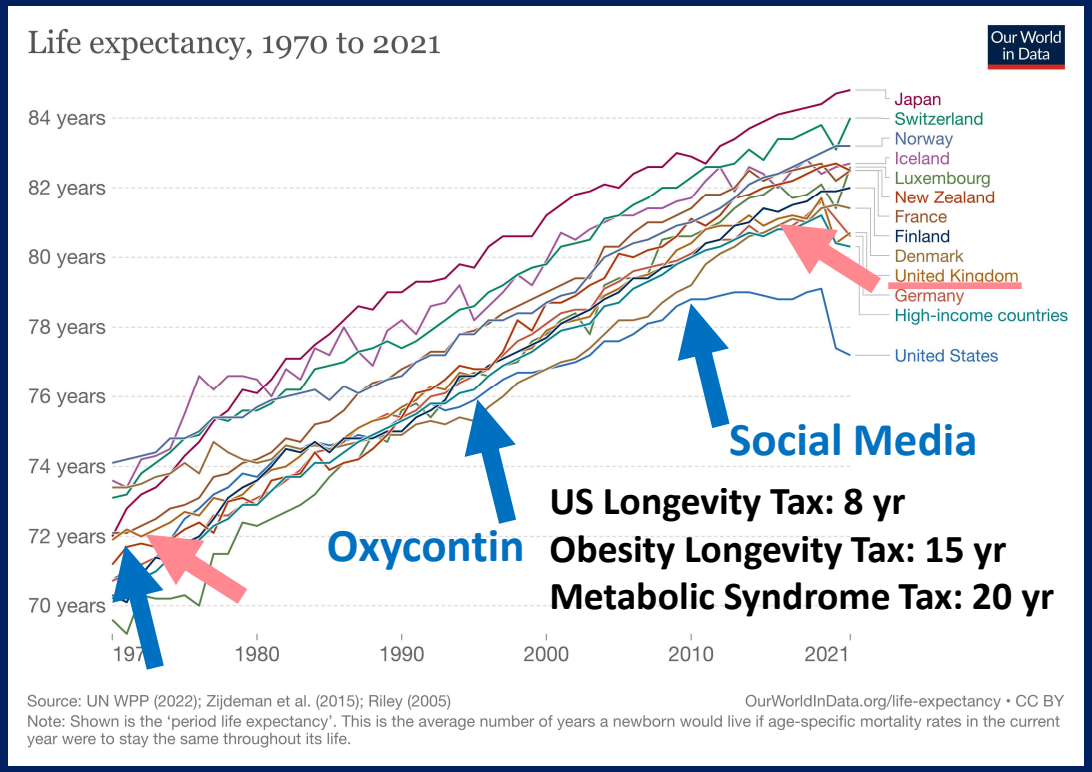
# Axioms:

- There can be no improvement in lifespan unless and until we improve healthspan first
- There can be no improvement in healthspan unless and until we improve both metabolic health AND mental health first
- There can be no improvement in metabolic and mental health without a concomitant improvement in financial health




GBD 2016 Mortality Collaborators , Lancet 390: 1084, 2017


Life expectancy, 1970 to 2021
Our World in Data
84 years
82 years
80 years
78 years
76 years
74 years
72 years
70 years
1980
1990
2000
2010
2021
Japan
Switzerland
Norway
Iceland
Luxembourg
New Zealand
France
Finland
Denmark
United Kingdom
Germany
High-income countries
United States
US Longevity Tax: 8 yr
Obesity Longevity Tax: 15 yr
Metabolic Syndrome Tax: 20 yr
Source: UN WPP (2022); Zijdeman et al. (2015); Riley (2005)
OurWorldInData.org/life-expectancy • CC BY
Note: Shown is the 'period life expectancy'. This is the average number of years a newborn would live if age-specific mortality rates in the current year were to stay the same throughout its life.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Luxembourg
New Zealand
France
Finland
Denmark
United Kingdom
Germany
High-income countries
United States
Social Media
Oxycontin
US Longevity Tax: 8 yr
Obesity Longevity Tax: 15 yr
Metabolic Syndrome Tax: 20 yr
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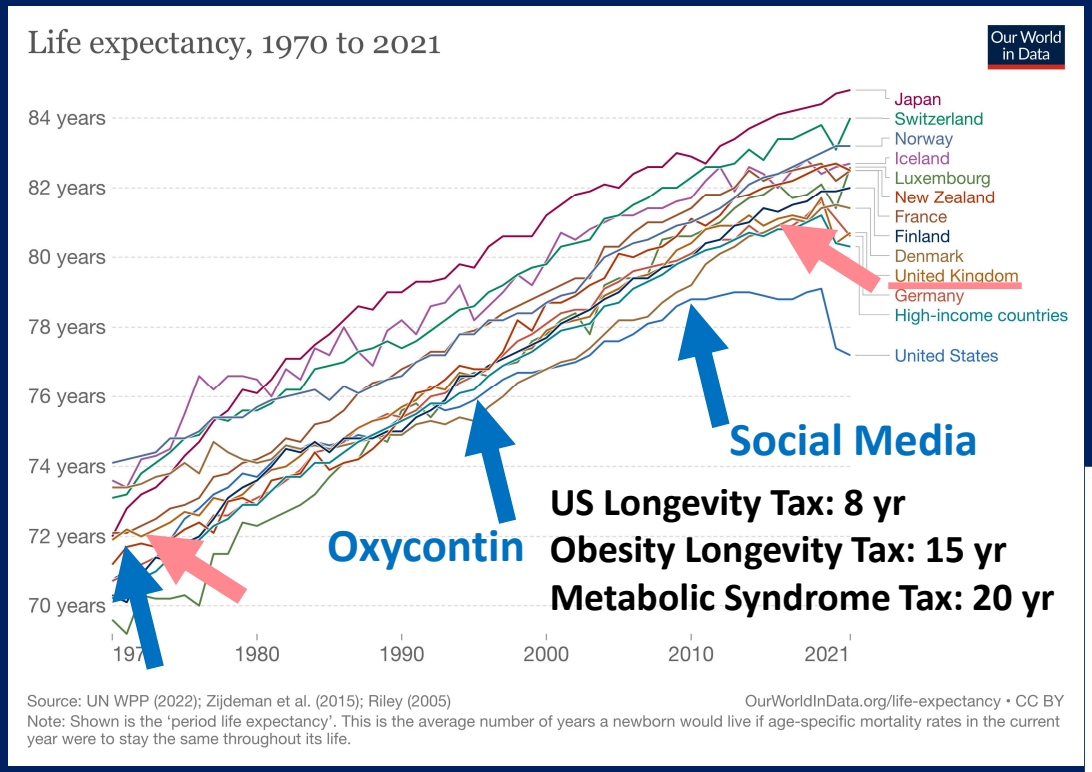
OurWorldInData.org/life-expectancy • CC BY
Note: Shown is the 'period life expectancy'. This is the average number of years a newborn would live if age-specific mortality rates in the current year were to stay the same throughout its life.


Life expectancy, 1970 to 2021
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US Longevity Tax: 8 yr
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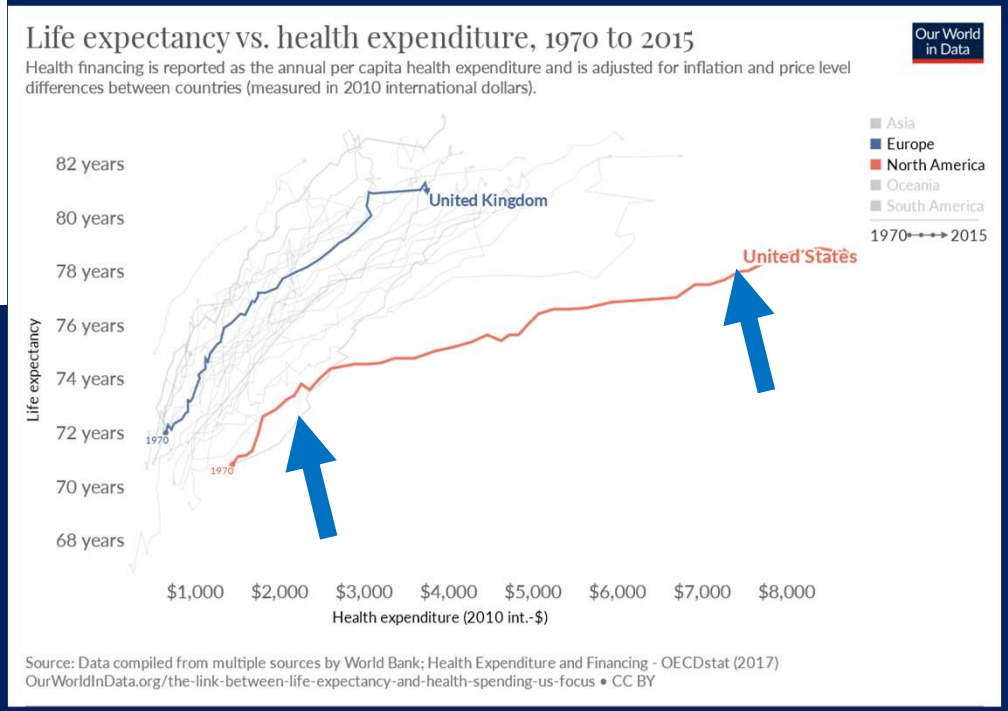
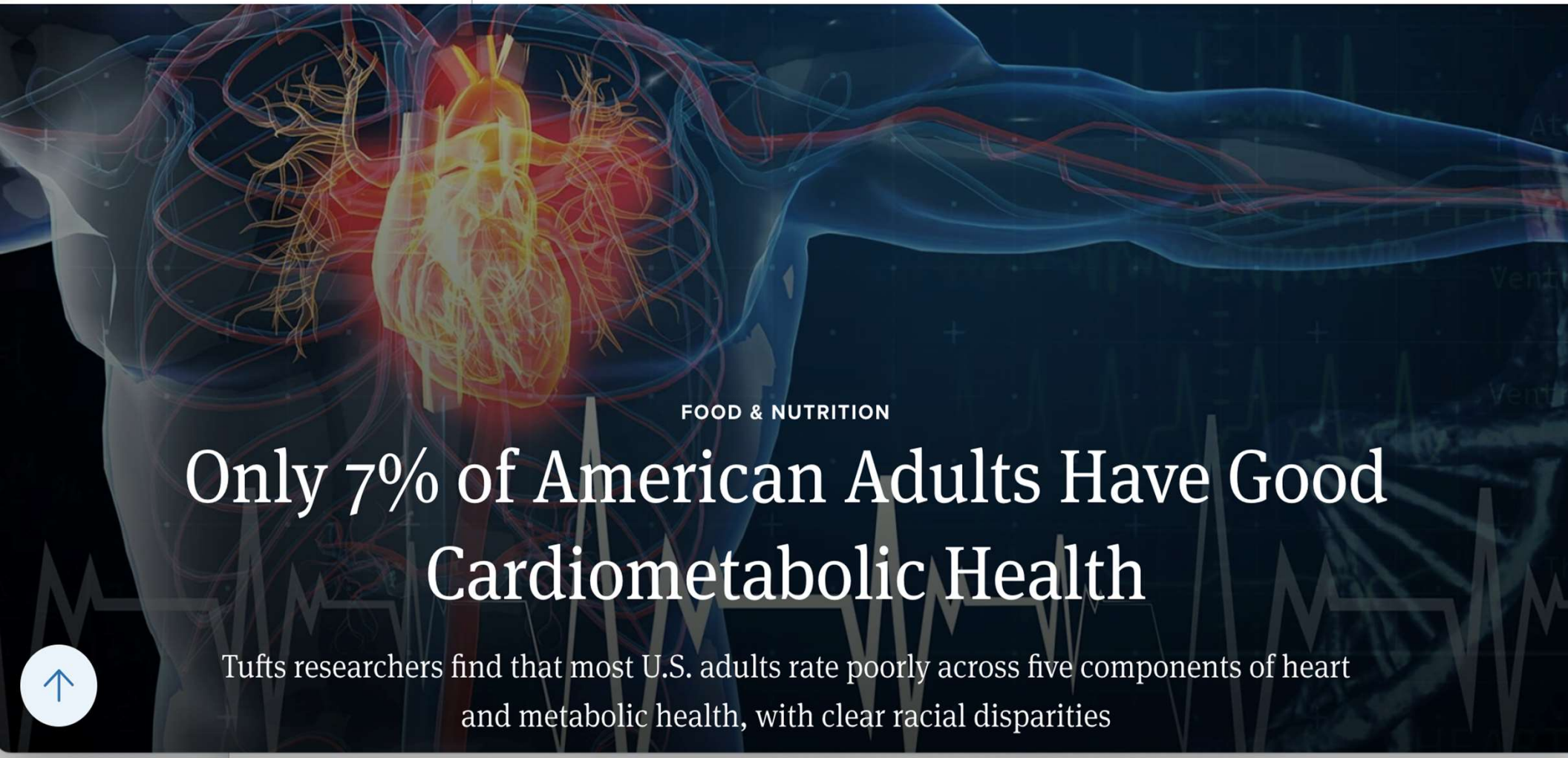
Source: UN WPP (2022); Zijdeman et al. (2015); Riley (2005)
OurWorldInData.org/life-expectancy • CC BY
Note: Shown is the 'period life expectancy'. This is the average number of years a newborn would live if age-specific mortality rates in the current year were to stay the same throughout its life.


Life expectancy vs. health expenditure, 1970 to 2015
Our World in Data
Health financing is reported as the annual per capita health expenditure and is adjusted for inflation and price level differences between countries (measured in 2010 international dollars).
Asia
Europe
North America
Oceania
South America
1970 2015
82 years
80 years
78 years
76 years
74 years
72 years
70 years
68 years
Life expectancy
United Kingdom
United States
1970
1970
$1,000
$2,000
$3,000
$4,000
$5,000
$6,000
$7,000
$8,000
Health expenditure (2010 int.-$)
Source: Data compiled from multiple sources by World Bank; Health Expenditure and Financing - OECDstat (2017)
OurWorldInData.org/the-link-between-life-expectancy-and-health-spending-us-focus • CC BY

# Metabolic Health

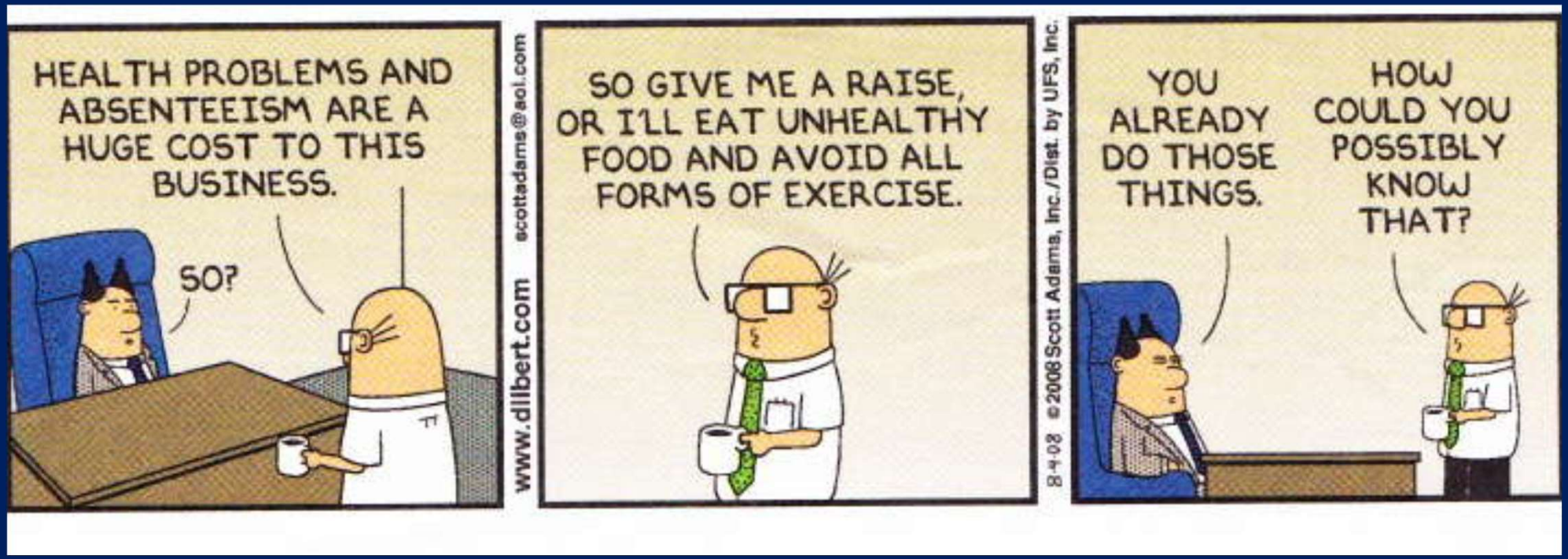




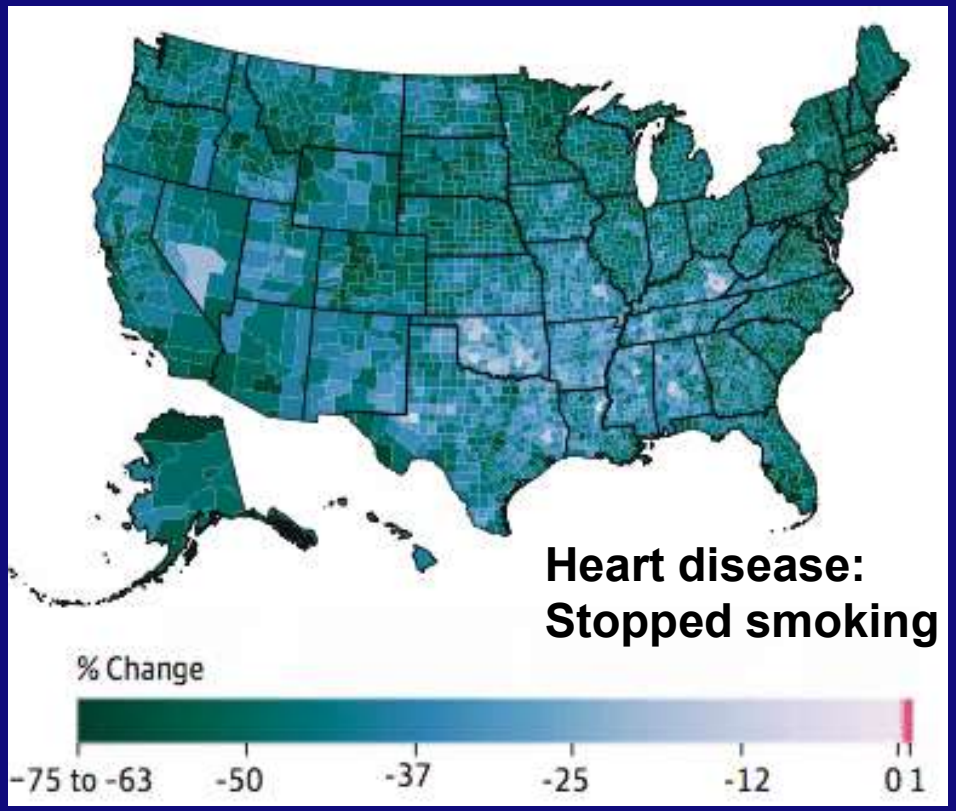
FOOD & NUTRITION

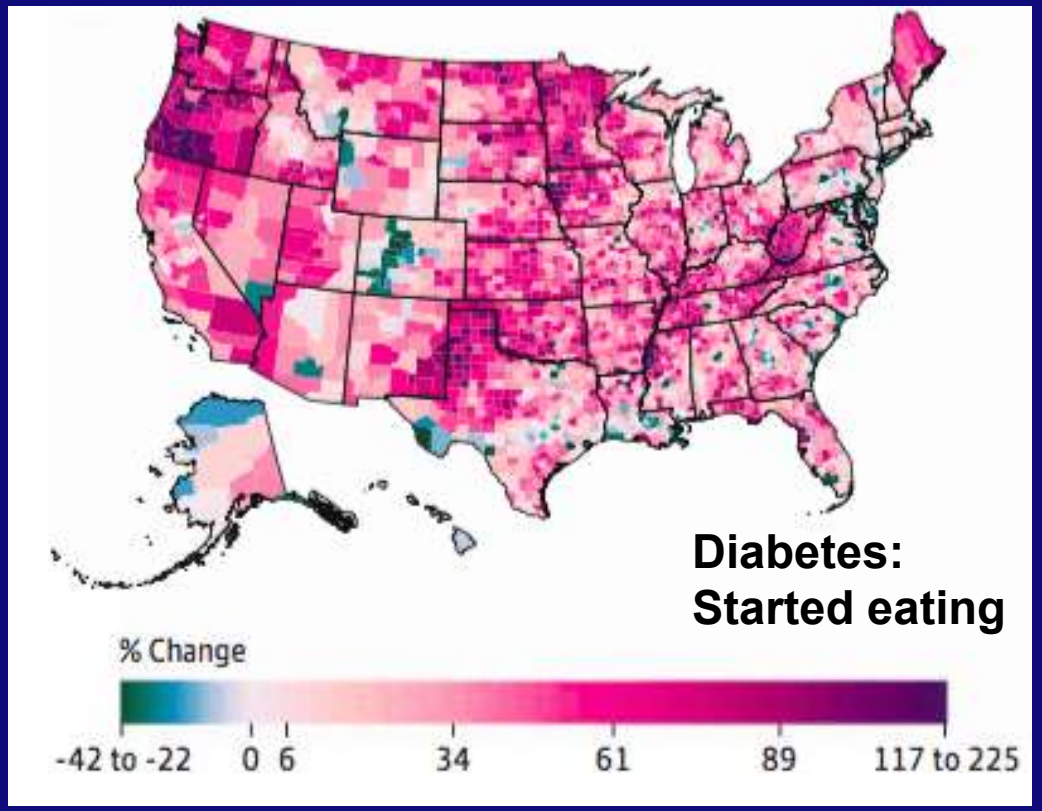
## Only 7% of American Adults Have Good Cardiometabolic Health

Tufts researchers find that most U.S. adults rate poorly across five components of heart and metabolic health, with clear racial disparities


HEALTH PROBLEMS AND ABSENTEEISM ARE A HUGE COST TO THIS BUSINESS.
SO?
www.dilbert.com scottadams@aol.com
SO GIVE ME A RAISE, OR I'LL EAT UNHEALTHY FOOD AND AVOID ALL FORMS OF EXERCISE.
8-4-08 ©2008 Scott Adams, Inc./Dist. by UFS, Inc.
YOU ALREADY DO THOSE THINGS.
HOW COULD YOU POSSIBLY KNOW THAT?

# Over the past 40 years, we've traded one disease for another




Khasan, The Atlantic, Dec. 2016

DIVE BRIEF

# Medicare insolvency still expected by 2026, unchanged by COVID-19, trustees say

Published Sept. 1, 2021

Rebecca Pifer
Senior Reporter

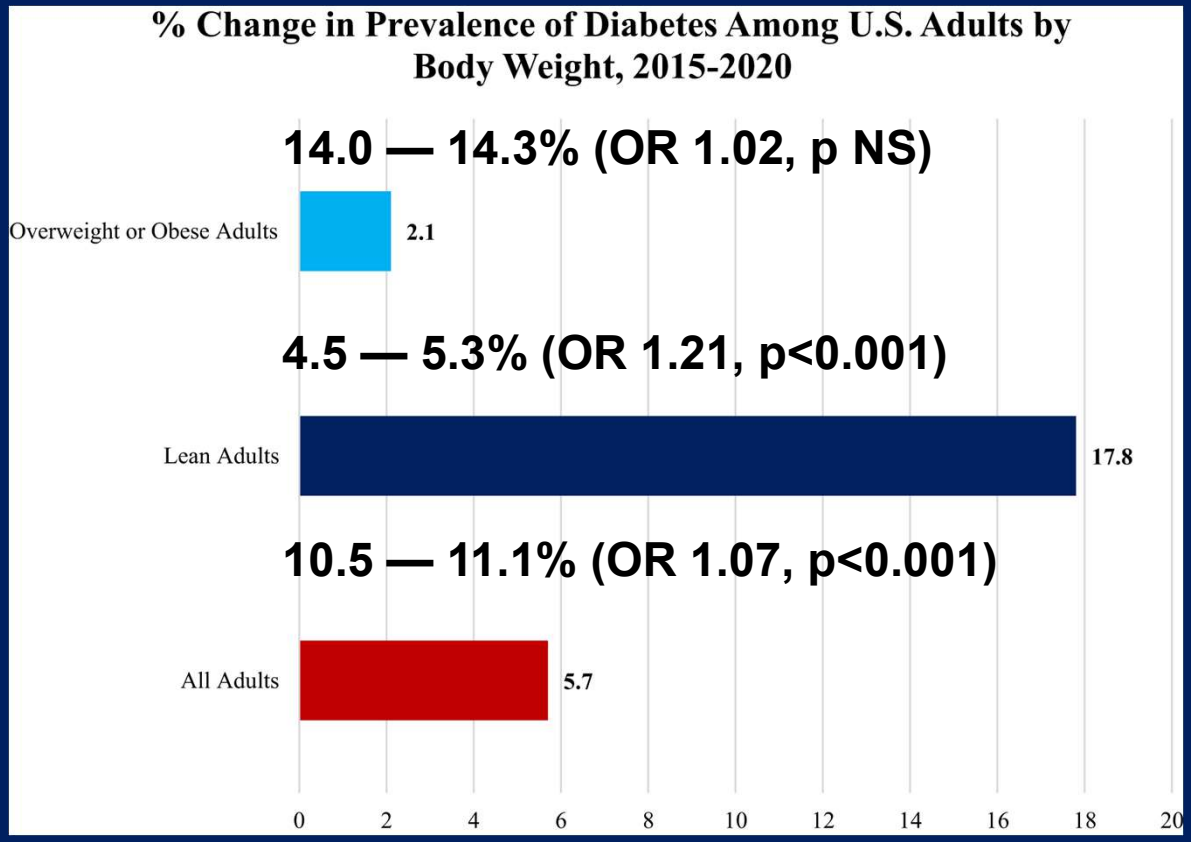
# Costs to the NHS

- Costs for Cardiovascular Disease: 16 billion pounds (PHE 2019)
  - 6.8 million patients
  - **= 2,350 pounds per patient**
- Costs for Cancer: 7.6 billion pounds (Demos/Pfizer 2019)
  - 2.5 million patients
  - **= 3,000 pounds per patient**
- Costs for Diabetes: 17 billion pounds (Zghebi et al. Diab Obes Metab 2017)
  - 4.5 million patients
  - **= 4,000 pounds per patient**
- Costs for Dementia: 25 billion pounds (Alzheimer's Research UK 2022)
  - 944,000 patients
  - **= 26,000 pounds per patient**

**Myth:**

**It's about obesity**

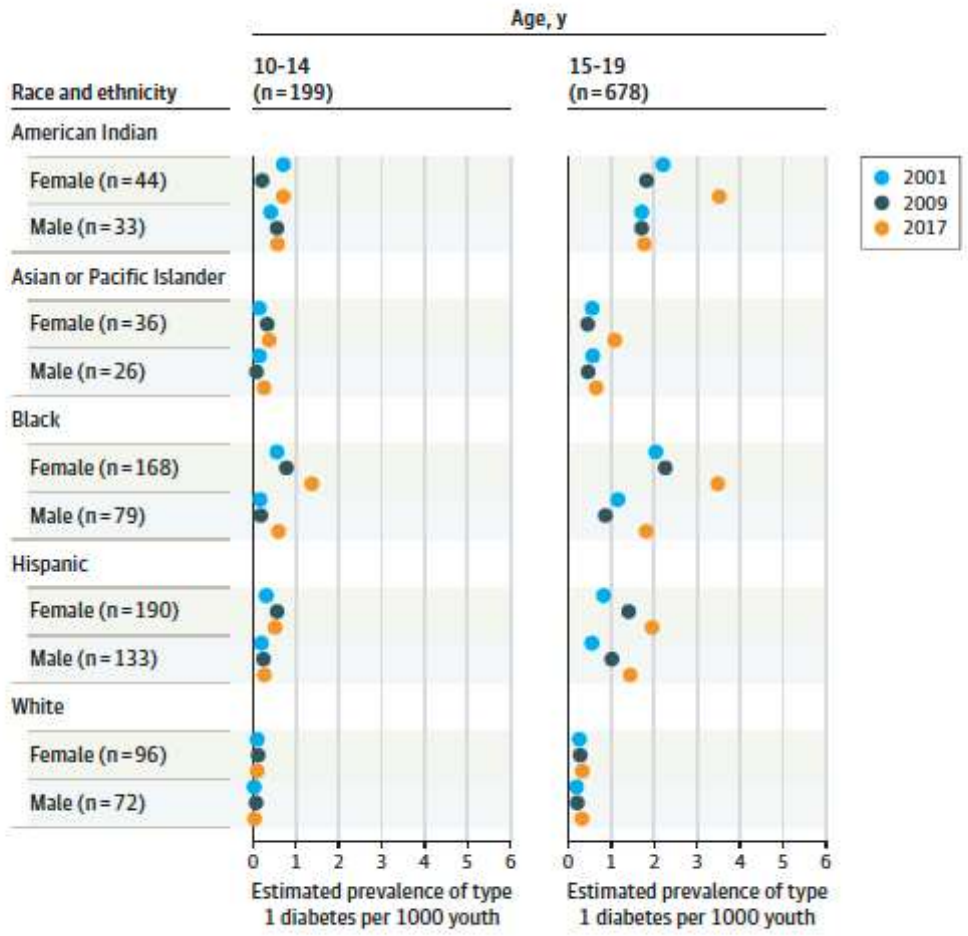
# 1. Trends in the Prevalence of Lean Diabetes Among U.S. Adults, 2015–2020




Adesoba et al. Diab Care 2023;46(4):885, 2023

# 2. Children get T2DM too

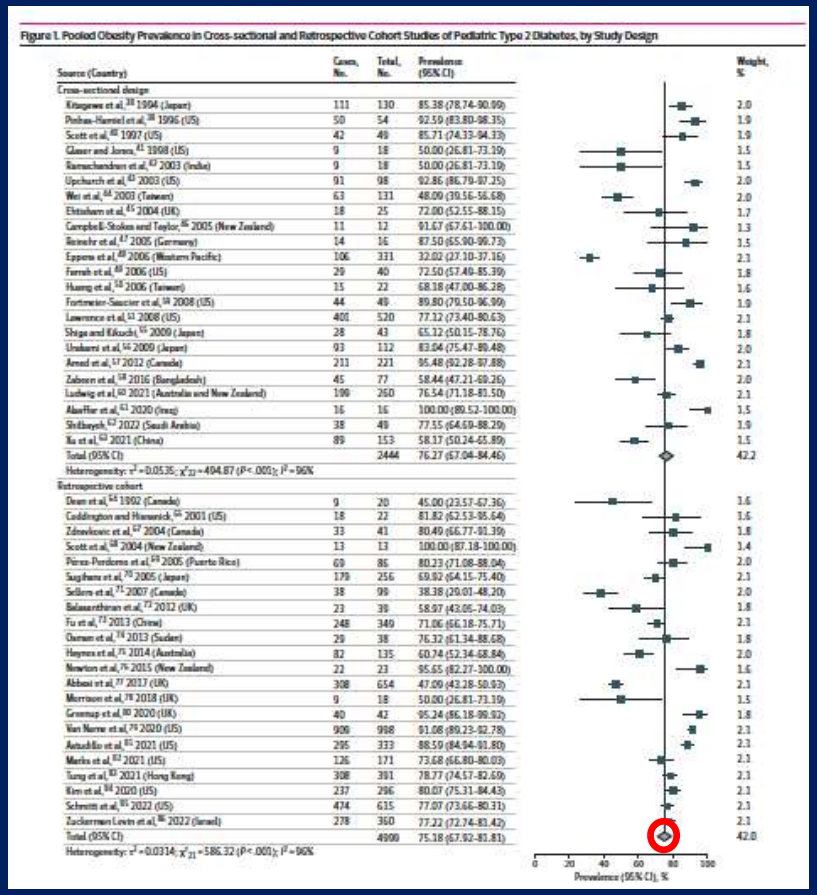
Figure 2. Estimated Prevalence of Type 2 Diabetes by Race and Ethnicity, Age, and Sex for 2001, 2009, and 2017



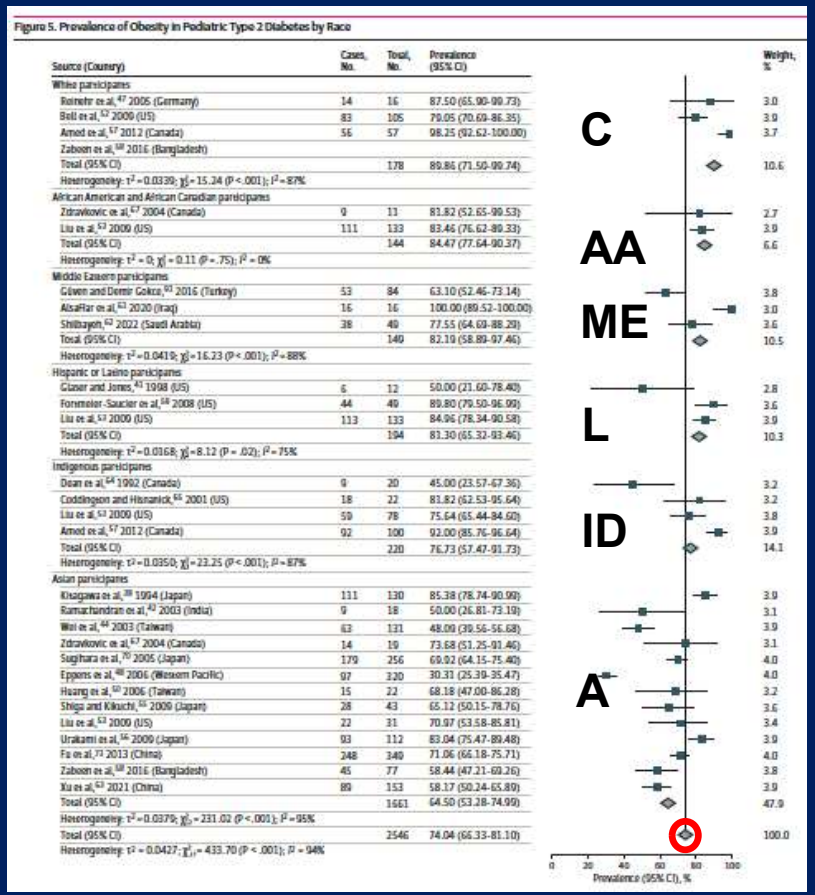

Lawrence et al. JAMA 326:717, 2021

# 2. Meta-analysis: 25% of pediatric T2DM are normal weight

## All studies

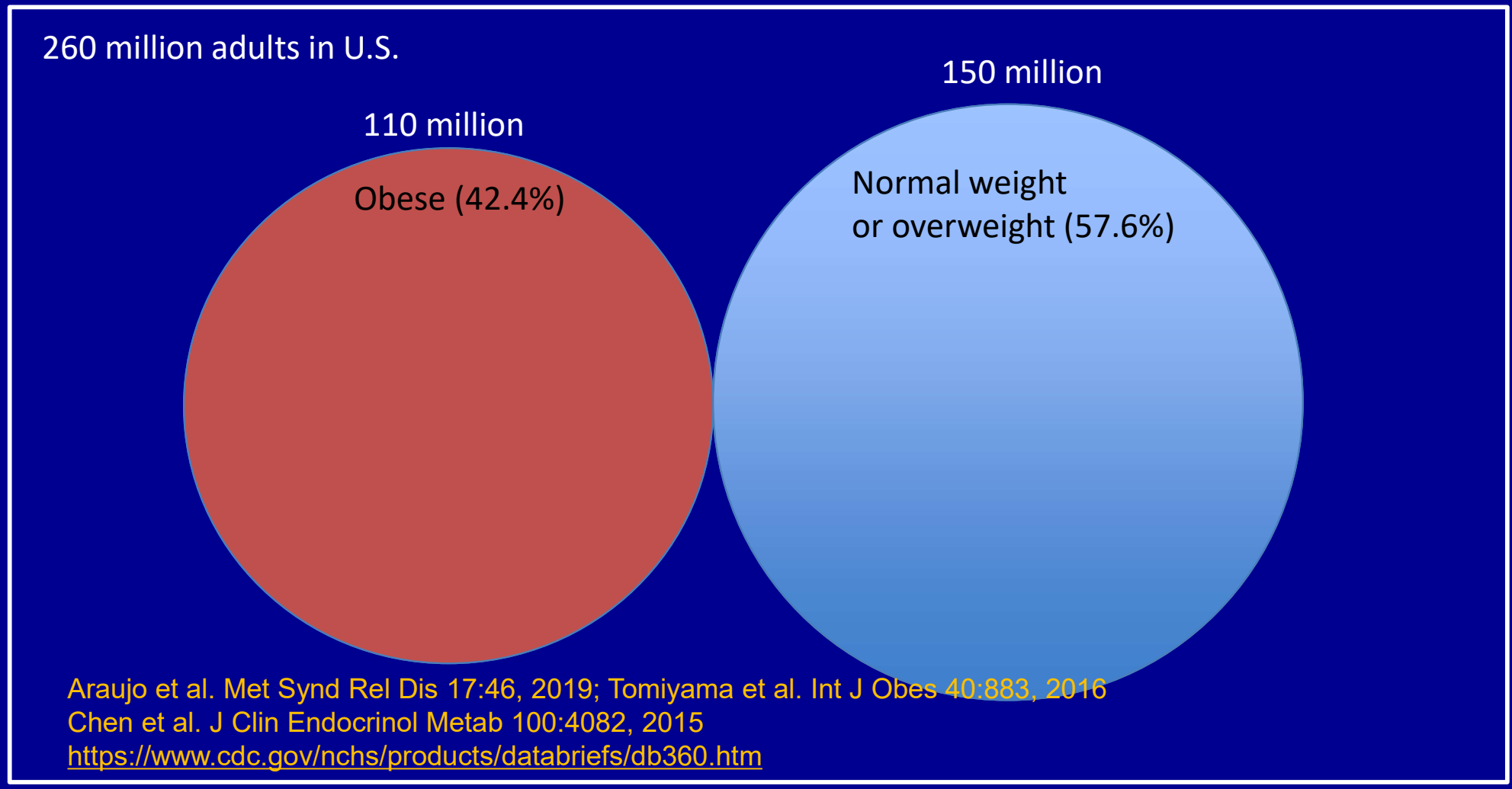



## Stratified by race




Cioana et al. JAMA Network Open 5(12):e2247186, 2022

# "Exclusive" view of obesity and metabolic dysfunction




Araujo et al. Met Synd Rel Dis 17:46, 2019; Tomiyama et al. Int J Obes 40:883, 2016
Chen et al. J Clin Endocrinol Metab 100:4082, 2015
https://www.cdc.gov/nchs/products/databriefs/db360.htm

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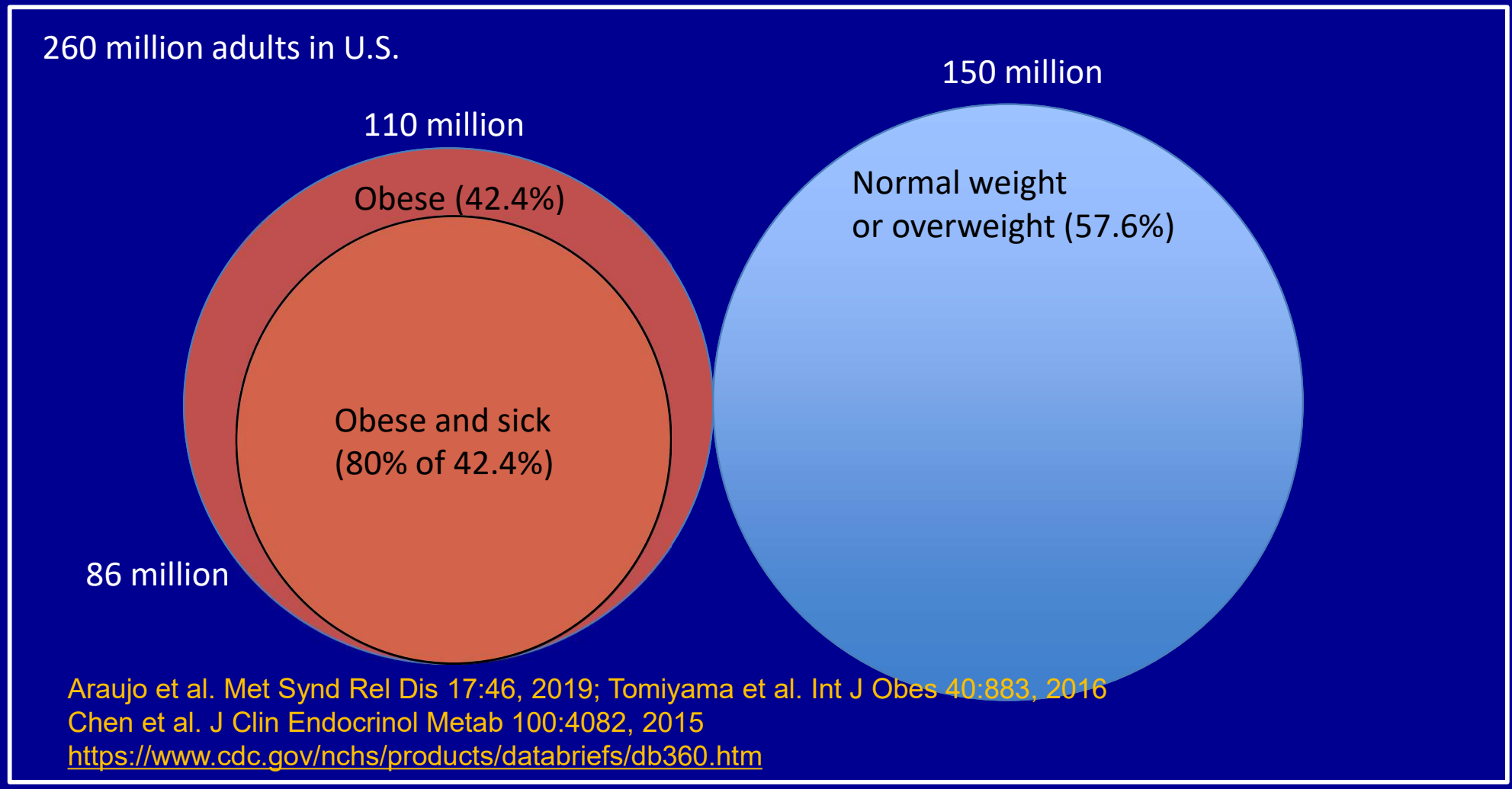


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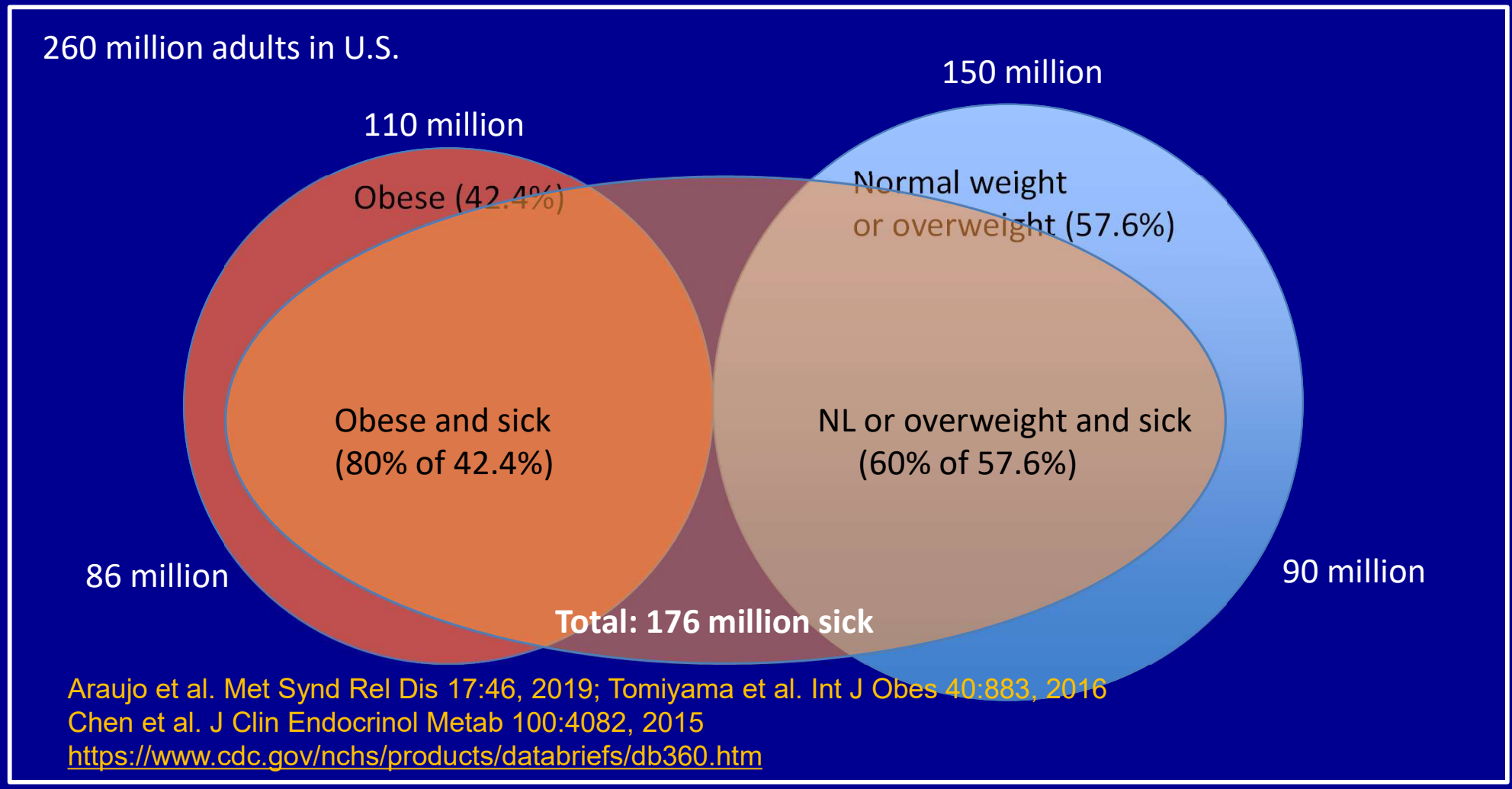
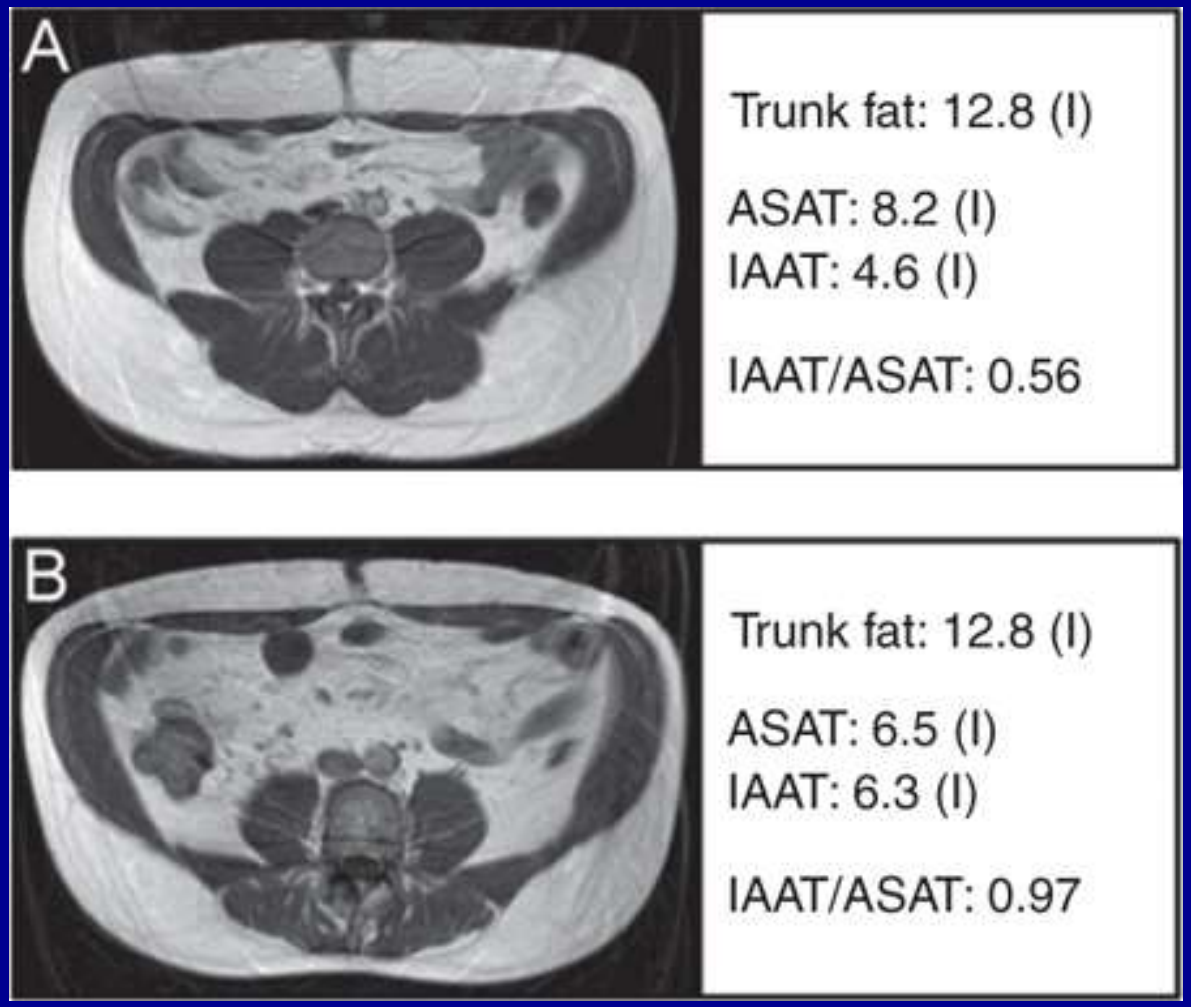



Araujo et al. Met Synd Rel Dis 17:46, 2019; Tomiyama et al. Int J Obes 40:883, 2016
Chen et al. J Clin Endocrinol Metab 100:4082, 2015
https://www.cdc.gov/nchs/products/databriefs/db360.htm

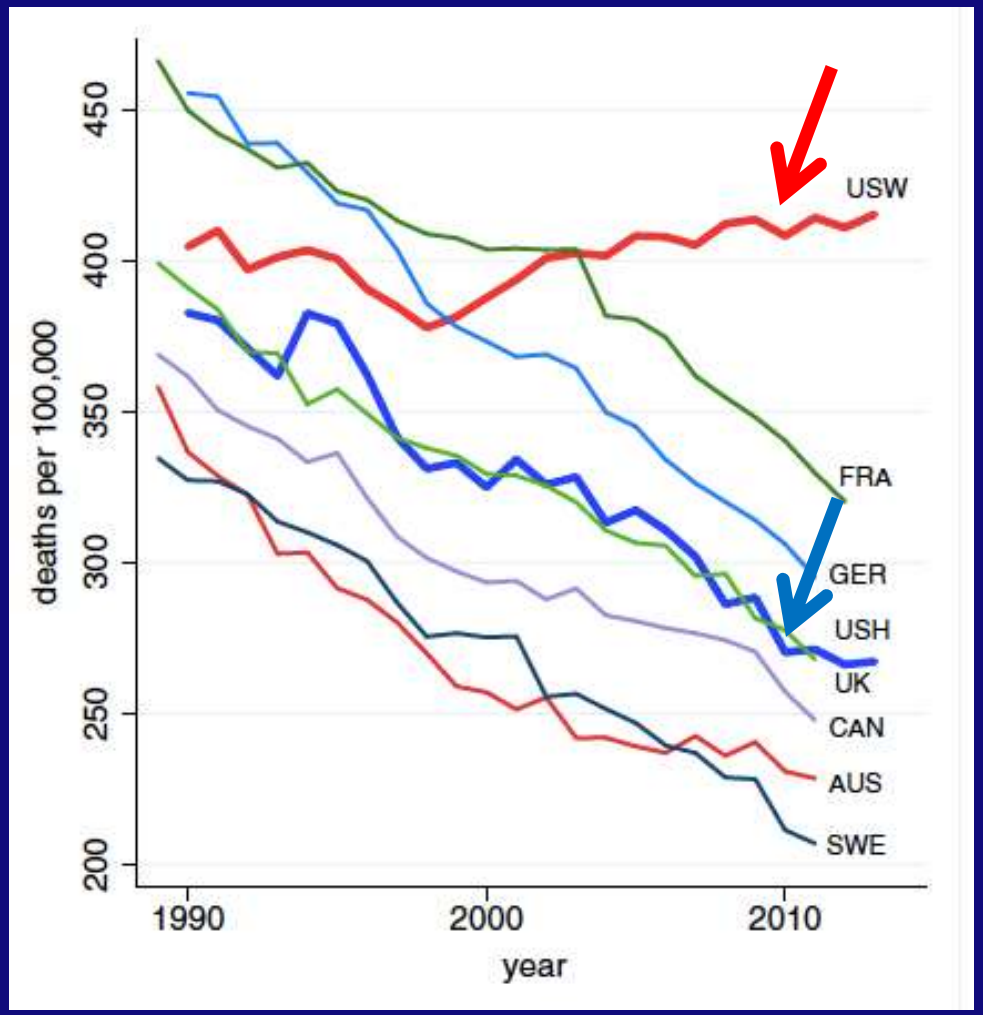
# Relation between visceral and subcutaneous obesity: TOFI (thin on the outside, fat on the inside)




Thomas et al. Obesity doi: 10.1038/oby.2011.142, 2011

# Mental Health

Death rates in US Whites vs. Hispanics, and in other countries




Case and Deaton, PNAS 112:15078, 2015

# Mental Health

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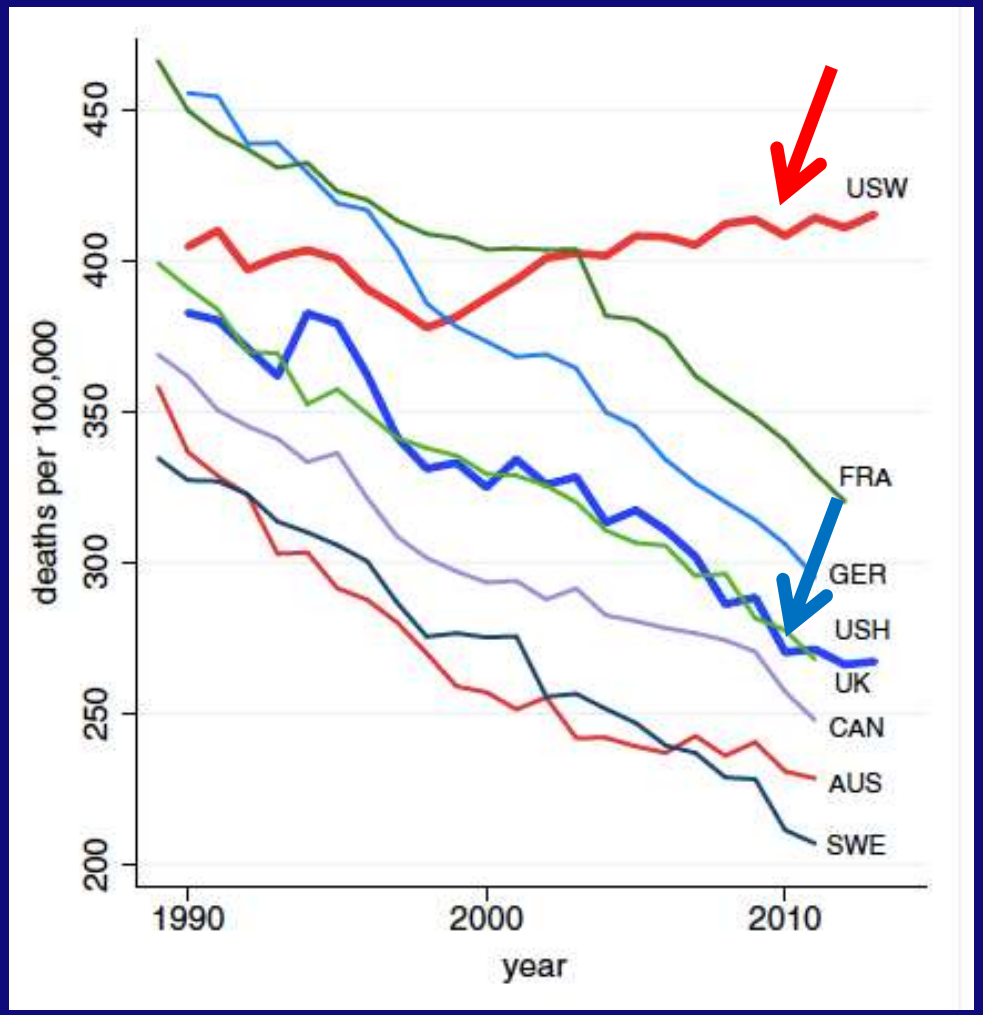
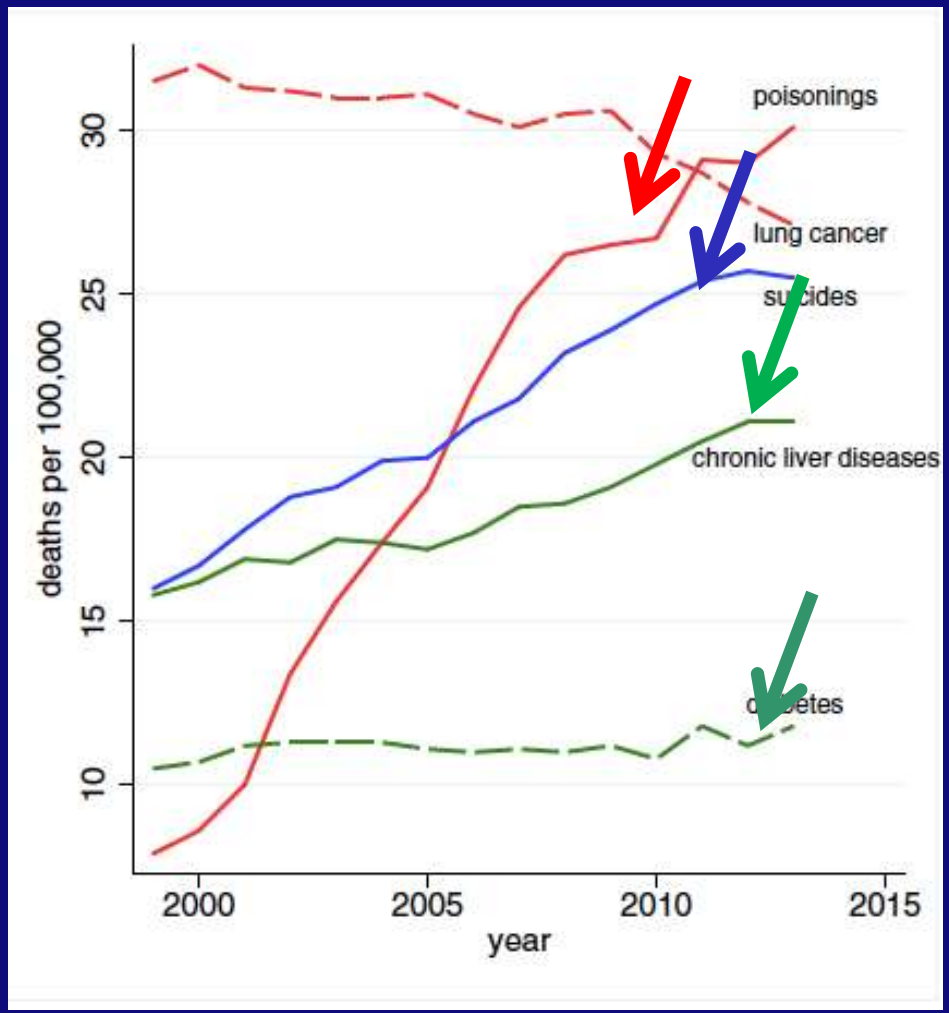


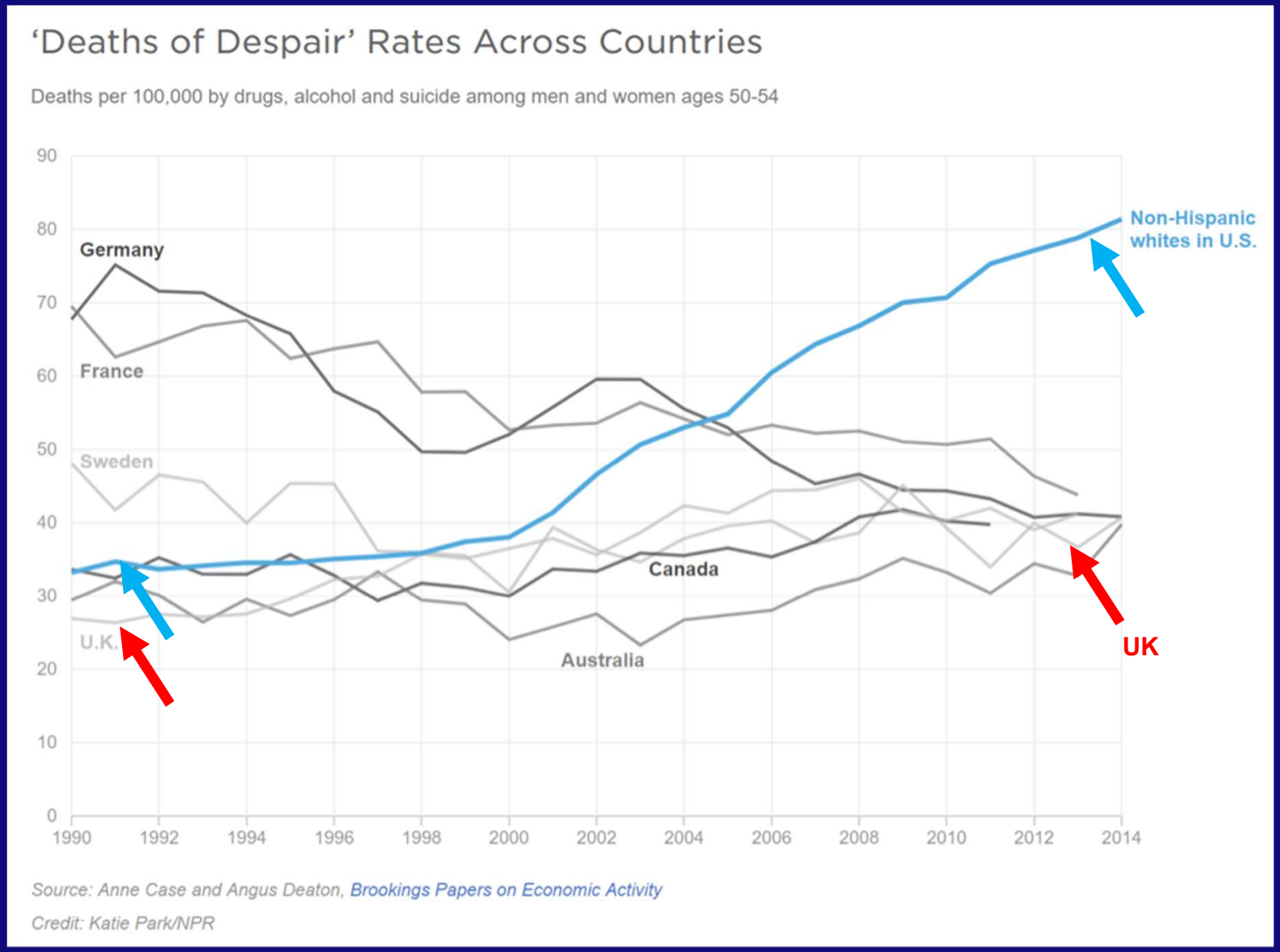

Causes of death in Whites, age 45-54




Case and Deaton, PNAS 112:15078, 2015

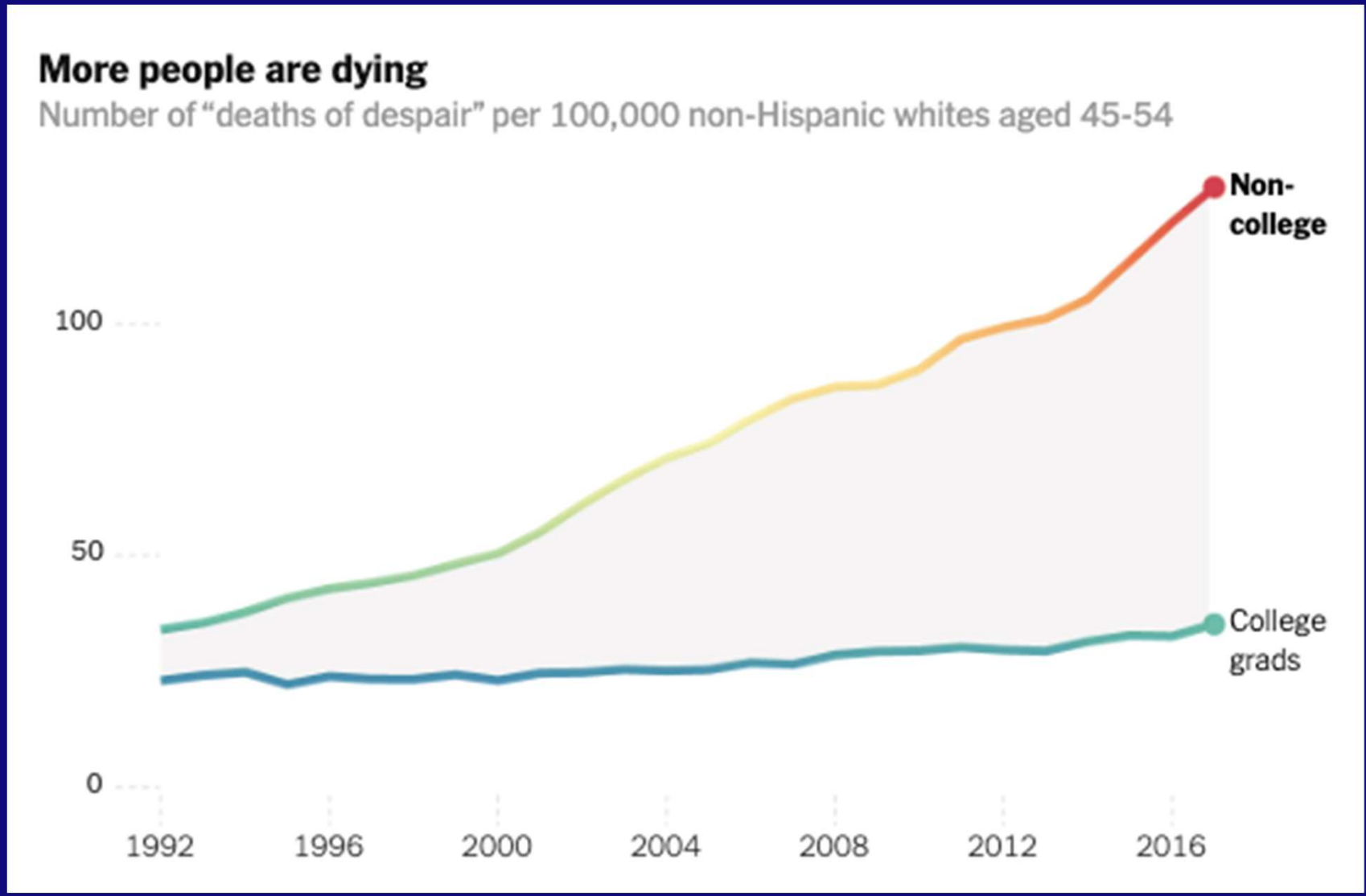
# Mental Health: Deaths of Despair

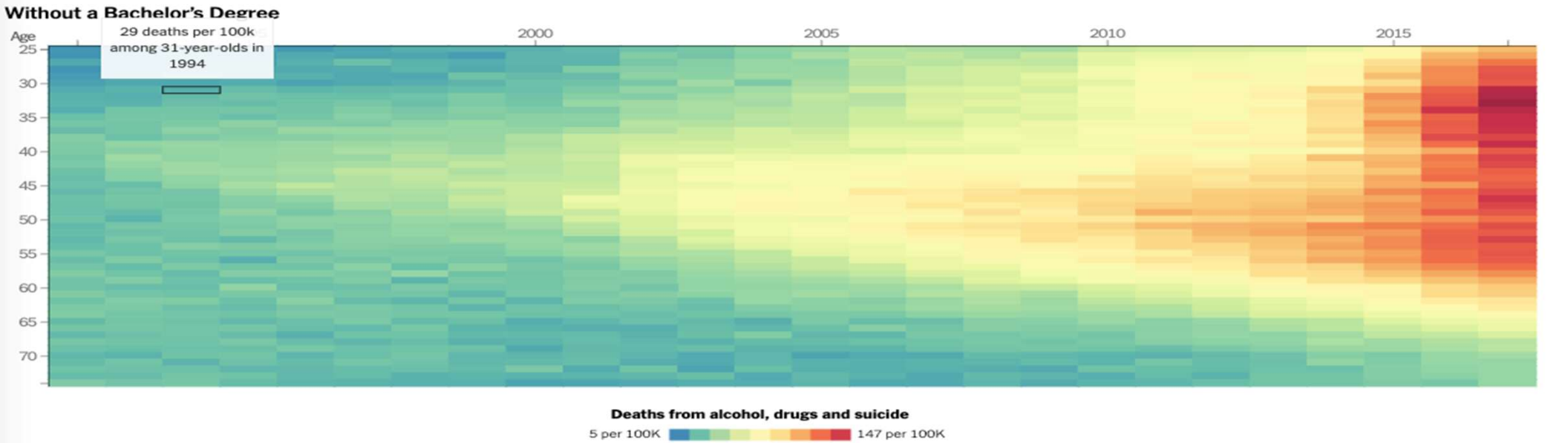
from drugs, alcohol, and suicide

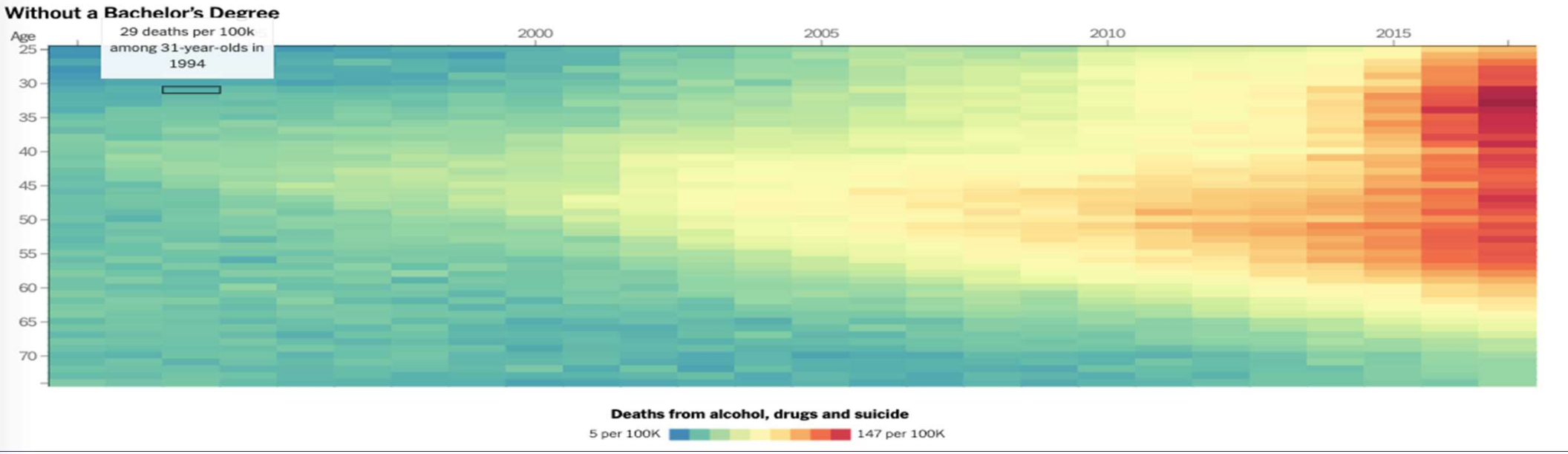



Lindgren-Dwyer et al. JAMA 319:1013, 2018

# Deaths of Despair




Without a Bachelor's Degree
29 deaths per 100k among 31-year-olds in 1994
Age
25
30
35
40
45
50
55
60
65
70
2000
2005
2010
2015
Deaths from alcohol, drugs and suicide
5 per 100K
147 per 100K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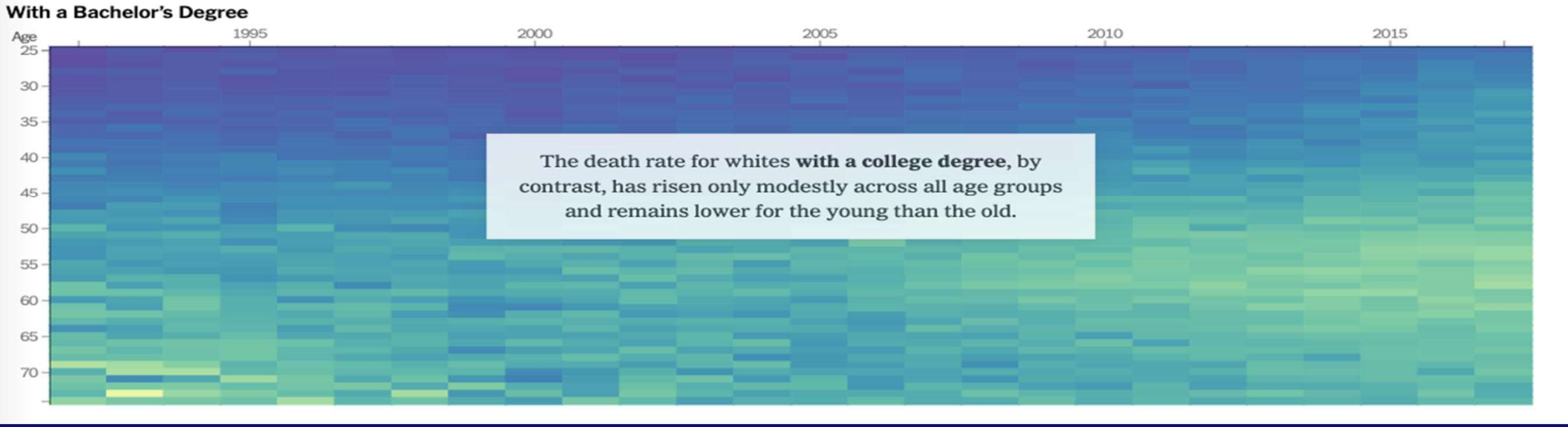
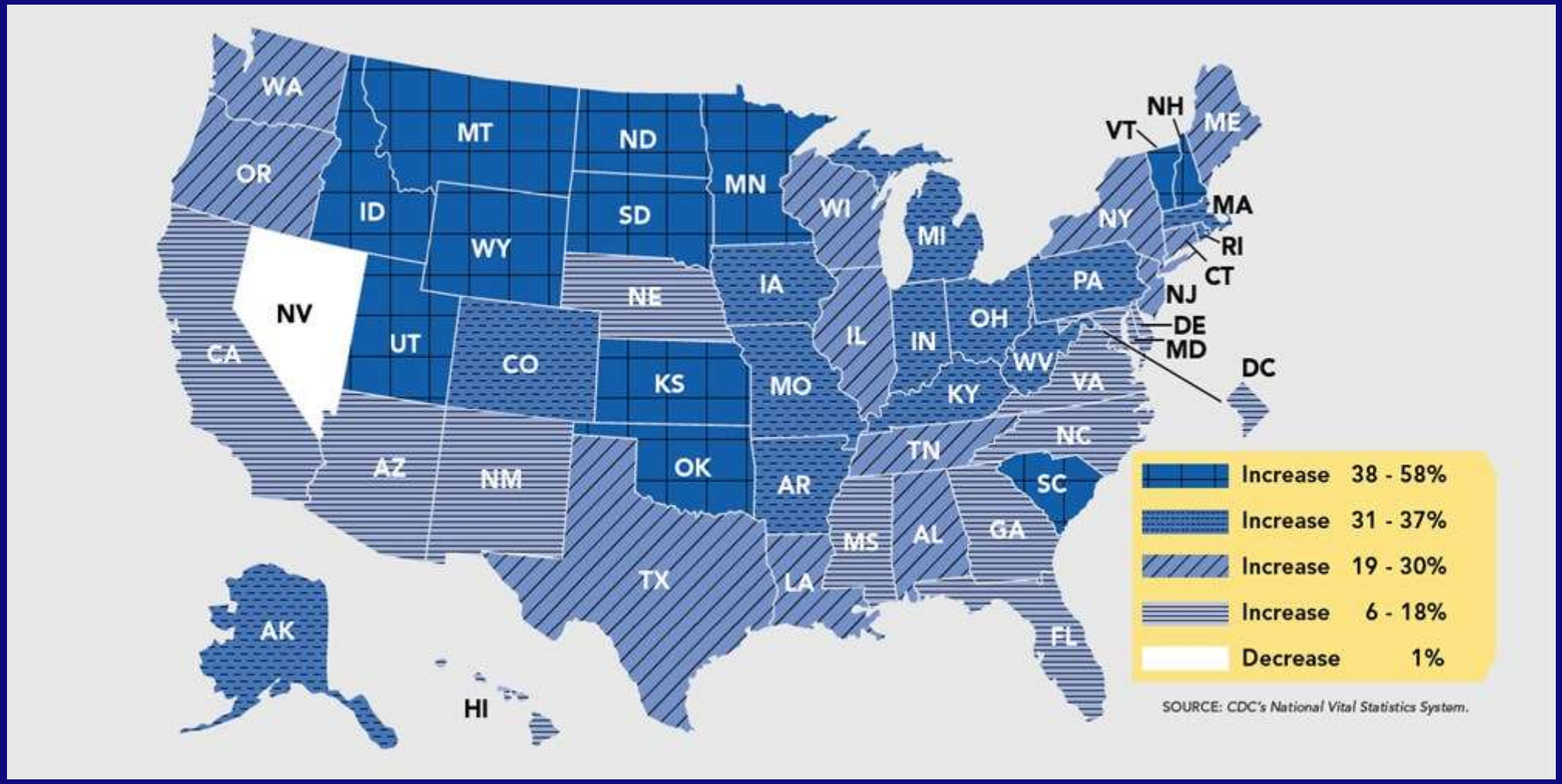

With a Bachelor's Degree
Age
1995
2000
2005
2010
2015
25
30
35
40
45
50
55
60
65
70
The death rate for whites **with a college degree**, by contrast, has risen only modestly across all age groups and remains lower for the young than the old.

# DEATHS OF DESPAIR

## AND THE FUTURE OF CAPITALISM

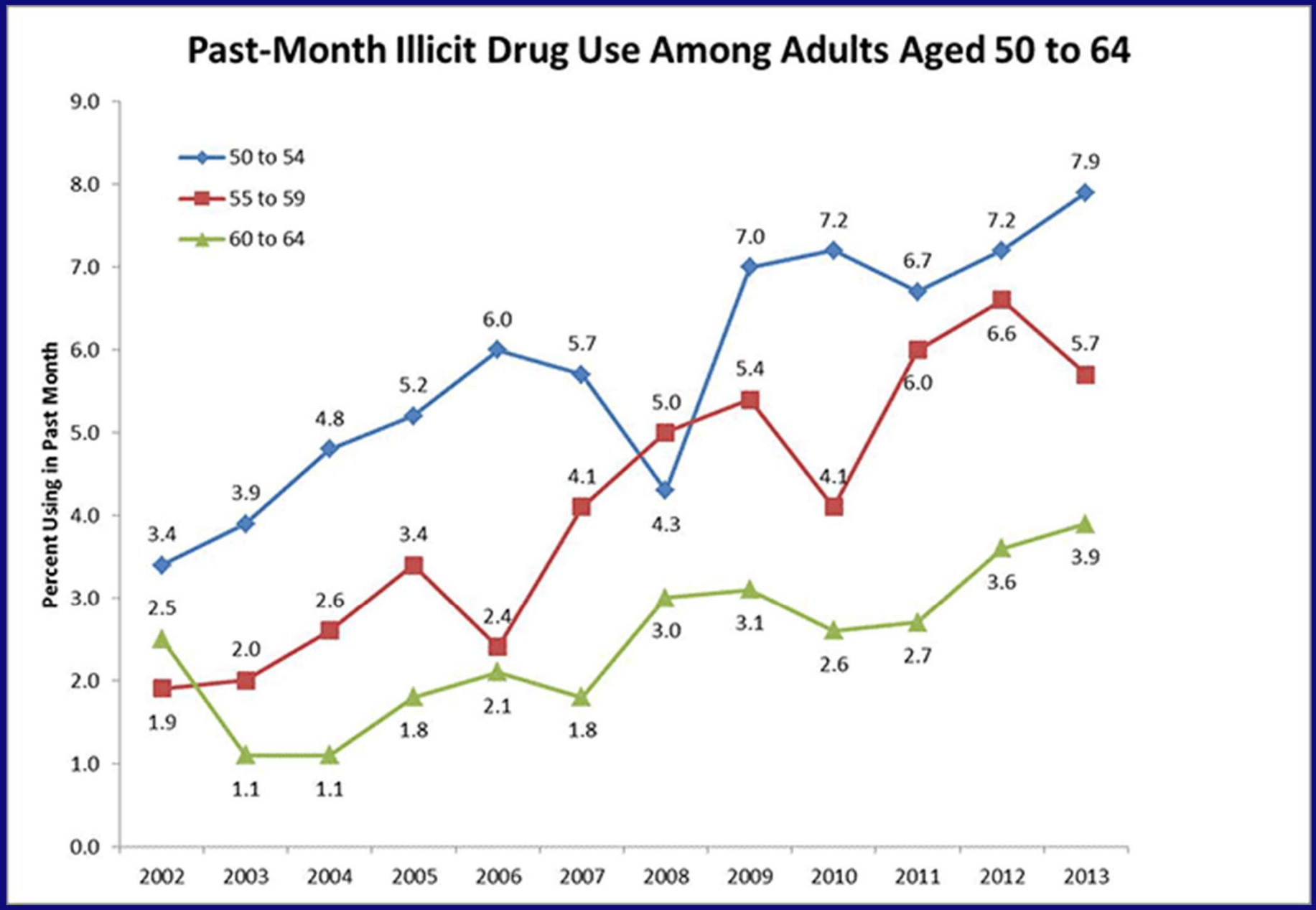
ANNE CASE & ANGUS DEATON

# U.S. Suicide Rates up 30% in 20 years; only half of which had a known mental health problem




CDC, 2018

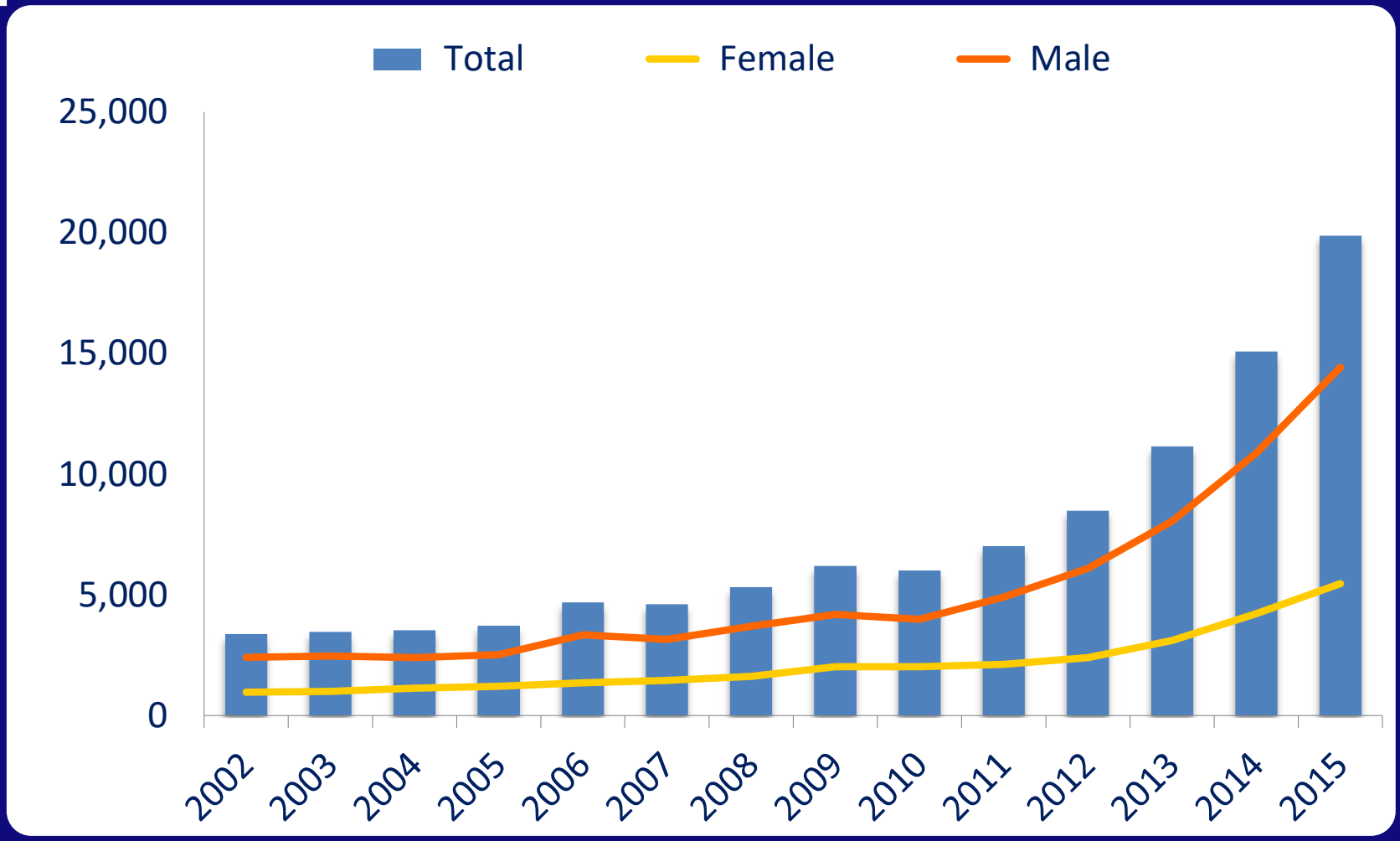
# Illicit drug use in older adults




https://www.drugabuse.gov/publications/drugfacts/nationwide-trends

National Institute on Drug Abuse

# Deaths from Heroin and Non-Methadone Synthetics (e.g. fentanyl)



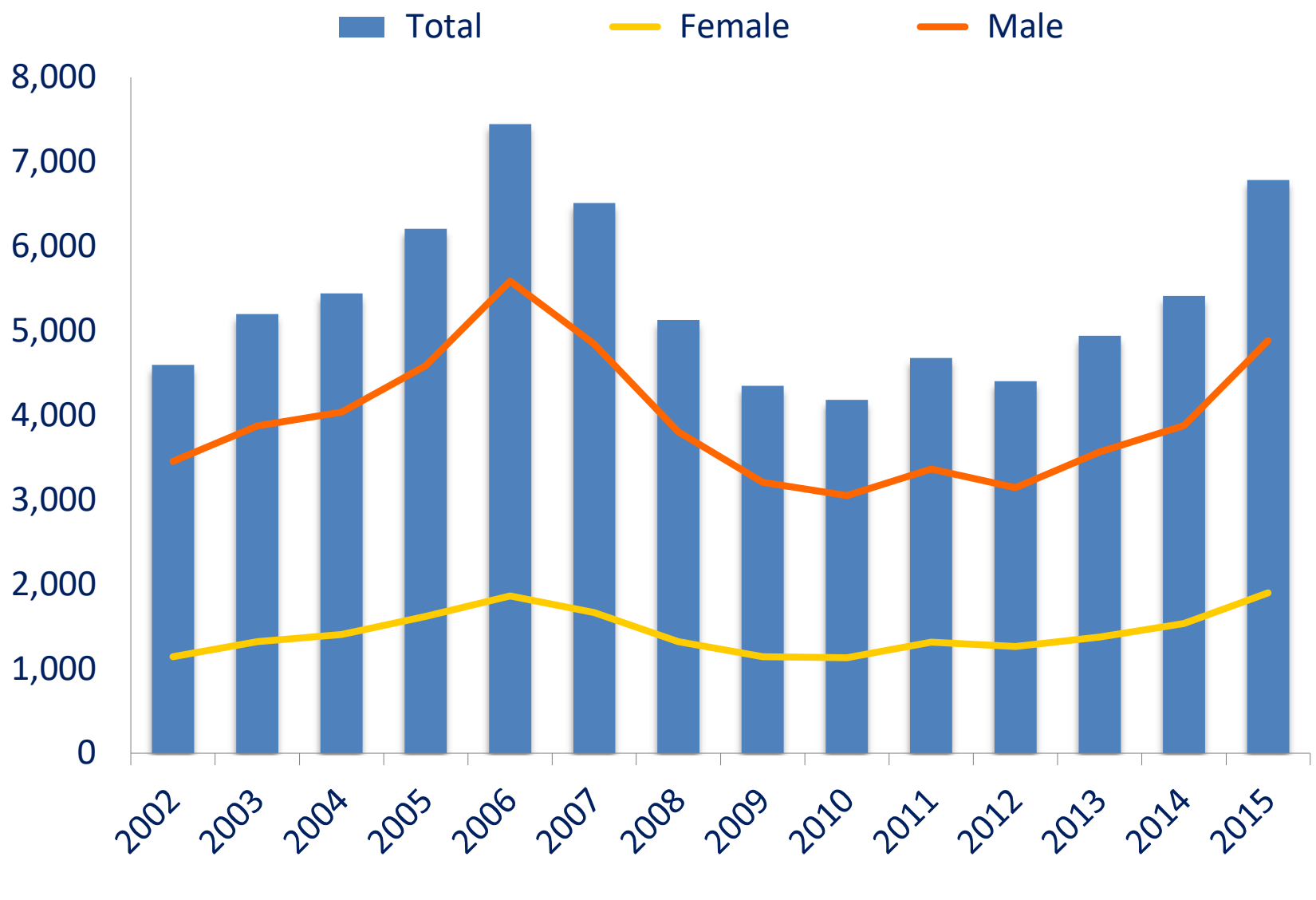

**ICU admissions for opioid overdose up 58% 2009-2015**

Stevens et al. J Am Thoracic Soc Aug 2017

Source: National Center for Health Statistics, CDC Wonder

National Institute on Drug Abuse

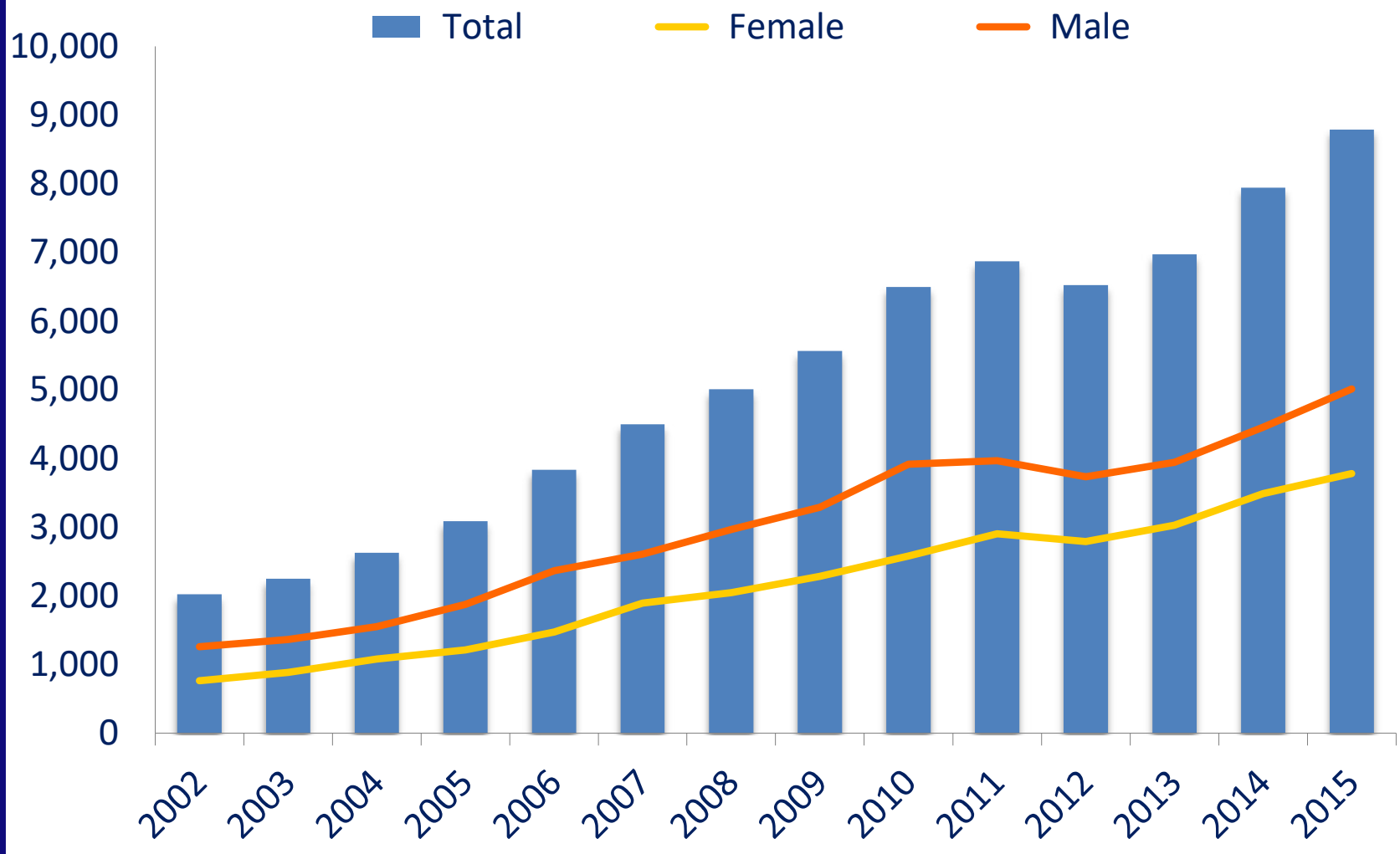
# Deaths from Cocaine




Source: National Center for Health Statistics, CDC Wonder

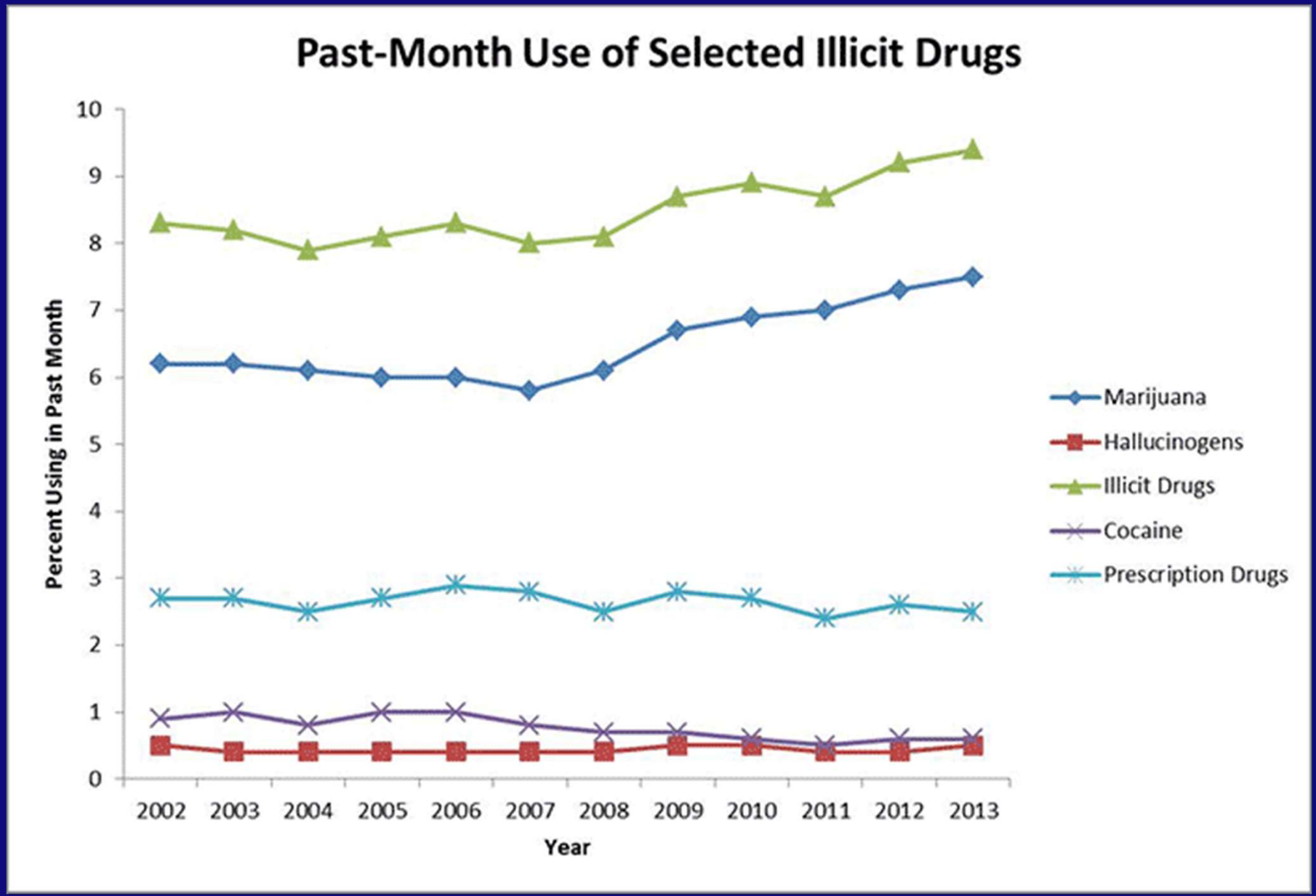
National Institute on Drug Abuse

# Deaths from Benzodiazepines




Source: National Center for Health Statistics, CDC Wonder

# Illicit drug use in U.S.




https://www.drugabuse.gov/publications/drugfacts/nationwide-trends

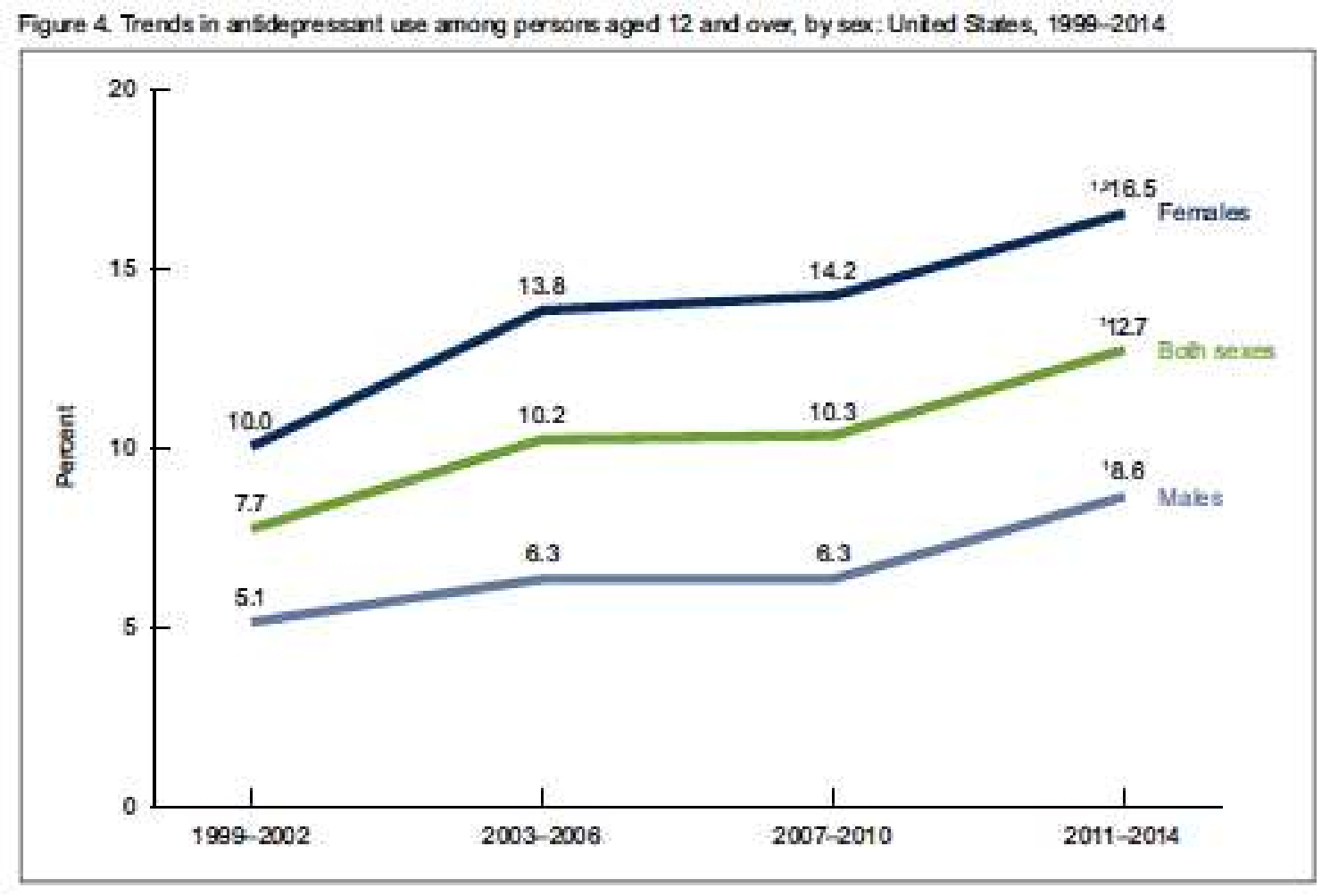
# Alcohol Use Disorder Increasing from 2001 to 2013

Table 3. Prevalence of and Percentage Change in 12-Month *DSM-IV* Alcohol Use Disorder by Sociodemographic Characteristics, 2001-2002 and 2012-2013

| Sociodemographic Characteristic | % (95% CI) NESARC 2001-2002 (n = 43 093) | NESARC-III 2012-2013 (n = 36 309) | % Change |
|---|---|---|---|
| Total | 8.5 (8.0-8.9) | 12.7 (12.1-13.3)[a] | 49.4 |
| Sex | | | |
| Men | 12.4 (11.7-13.1) | 16.7 (15.8-17.6)[a] | 34.7 |
| Women | 4.9 (4.5-5.3) | 9.0 (8.5-9.6)[a] | 83.7 |
| Age, y | | | |
| 18-29 | 16.2 (15.1-17.4) | 23.4 (21.9-24.9)[a] | 44.4 |
| 30-44 | 9.7 (9.0-10.5) | 14.3 (13.3-15.3)[a] | 47.4 |
| 45-64 | 5.4 (4.9-6.0) | 9.8 (9.1-10.5)[a] | 81.5 |
| ≥65 | 1.5 (1.2-1.8) | 3.1 (2.6-3.7)[a] | 106.7 |

Grant et al. JAMA Psychiatry 74:911, 2017

# Antidepressant Use in U.S. 1999-2014




Pratt et al. NCHS Data Brief 283, CDC, Aug 2017

# Substitution of Marijuana for Other Prescription Drugs in Legalized States



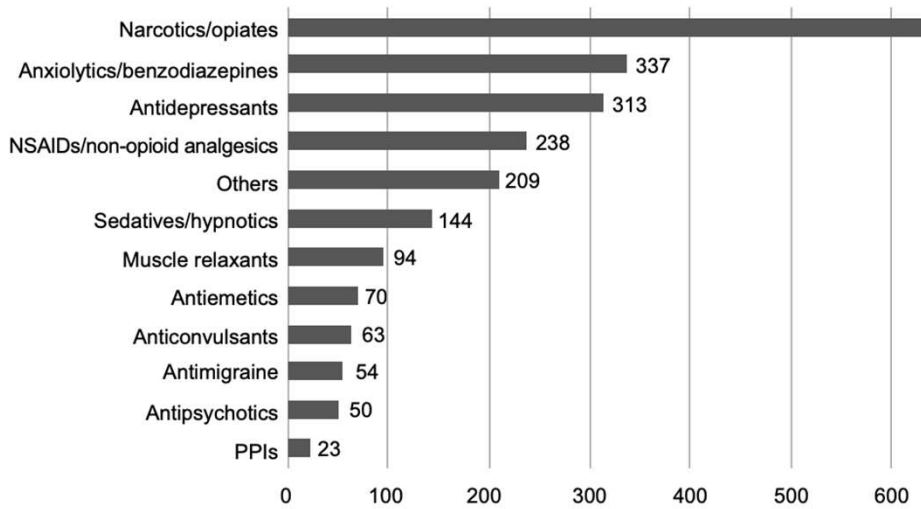



**Figure 1** Number of reported prescription drug substitutions, by drug category, during 2016 (n=2,473).
**Abbreviations:** PPI, proton pump inhibitor; NSAIDs, nonsteroidal anti-inflammatory drugs.

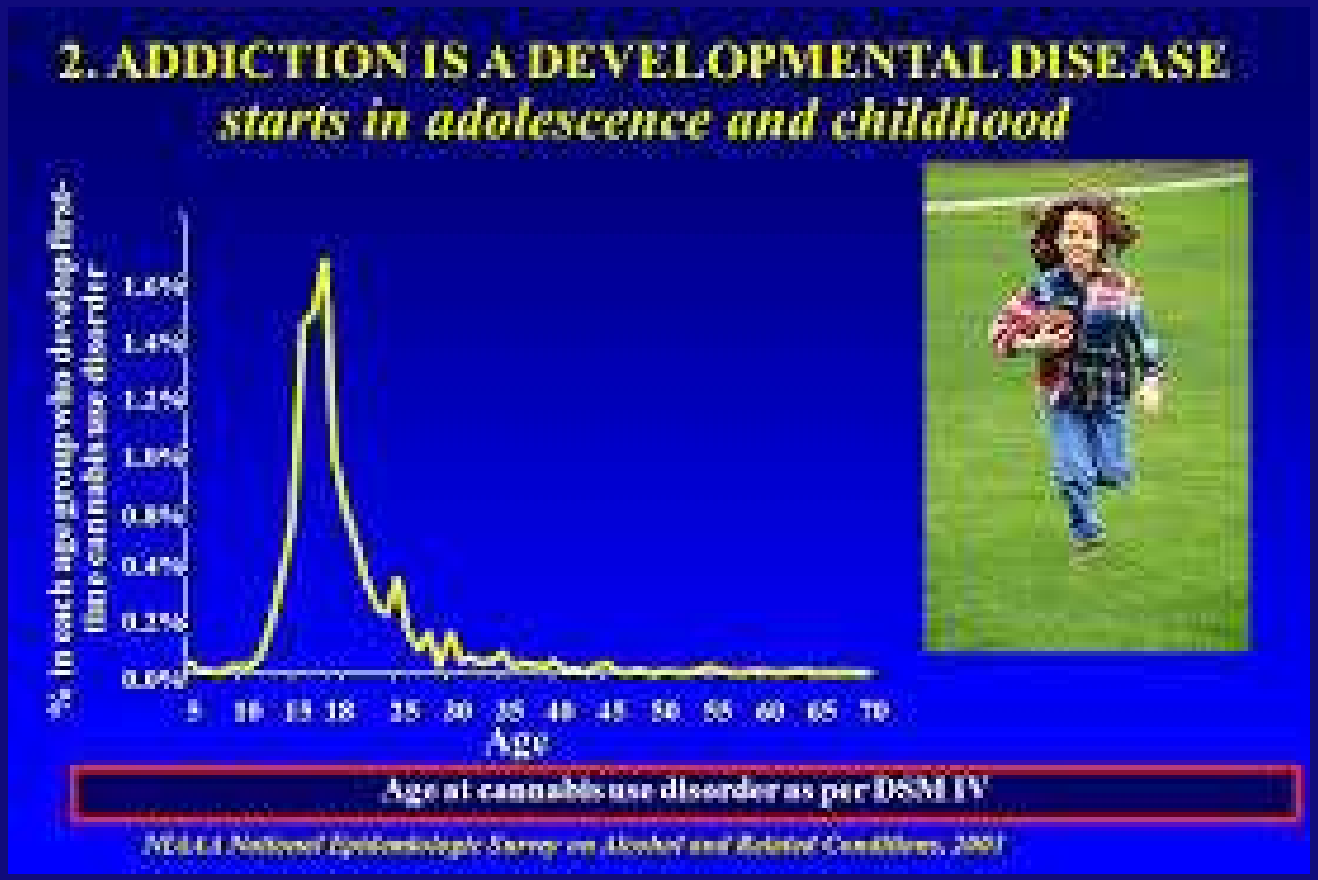
**Table 3** ORs and 95% CIs of reporting ever having used cannabis as a substitute for prescription drugs by user type, stratified by selected sociodemographic characteristics, during 2016 (n=2,740)

| Characteristic | Medical user, OR (95% CI) |
|---|---|
| **Gender** | |
| Female | 6.09 (4.65–7.80) |
| Male | 3.67 (2.91–4.57) |
| **Age (years)** | |
| ≤21 | 4.79 (3.20–7.18) |
| 22–35 | 3.72 (2.92–4.73) |
| 36–50 | 5.32 (3.63–7.78) |
| 51–65 | 16.19 (6.75–38.79) |
| >65 | NA |

**Notes:** Reference, non-medical user. NA, insufficient data in one cell.
**Abbreviations:** OR, odds ratio; CI, confidence interval; NA, not applicable.

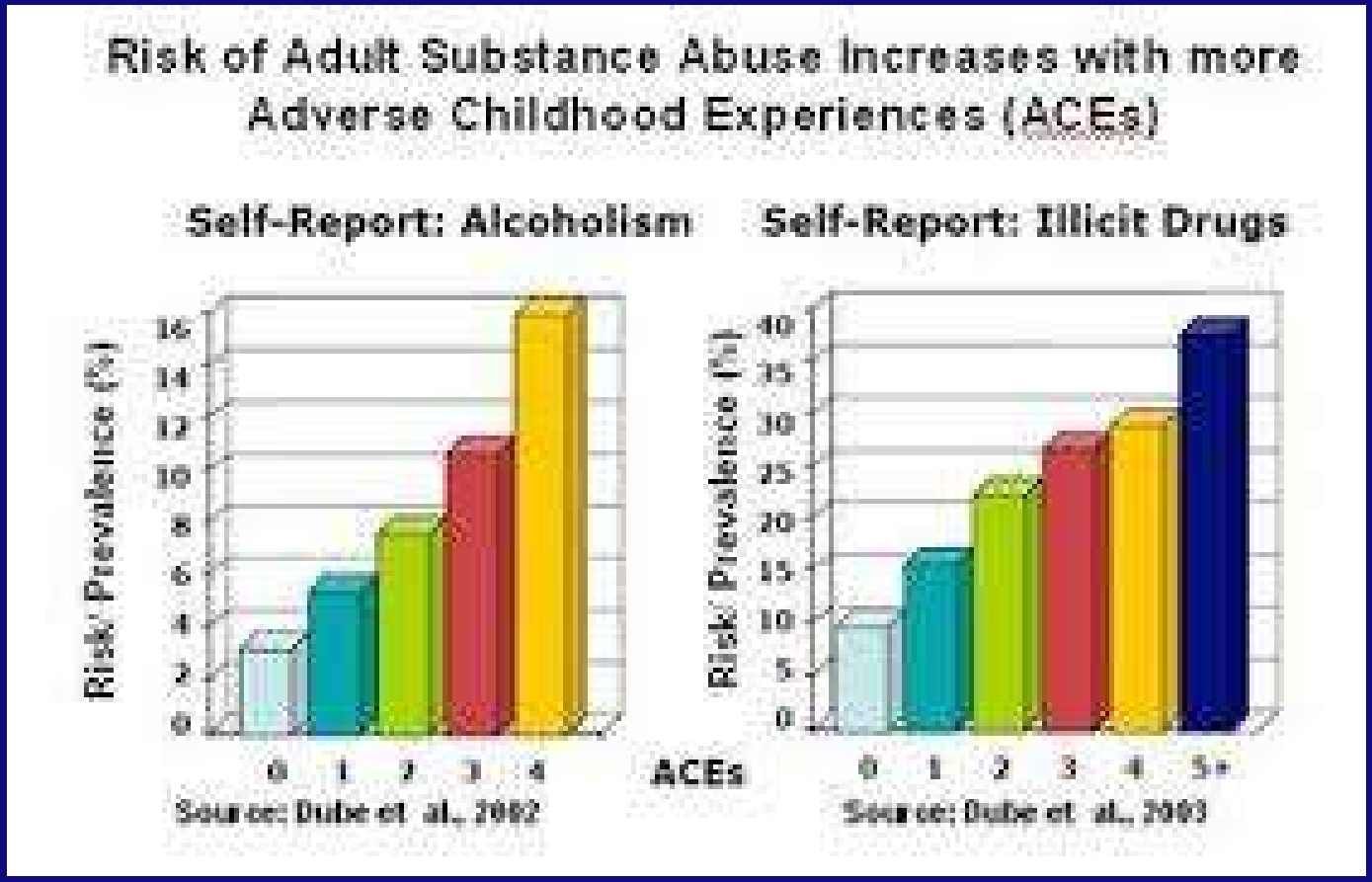
Corroon et al. J Pain Res 10:989, 2017

# Addiction in Children




NIAAA National Epidemiologic Survey of Alcohol and Related Conditions, 2003

# Addiction in Children

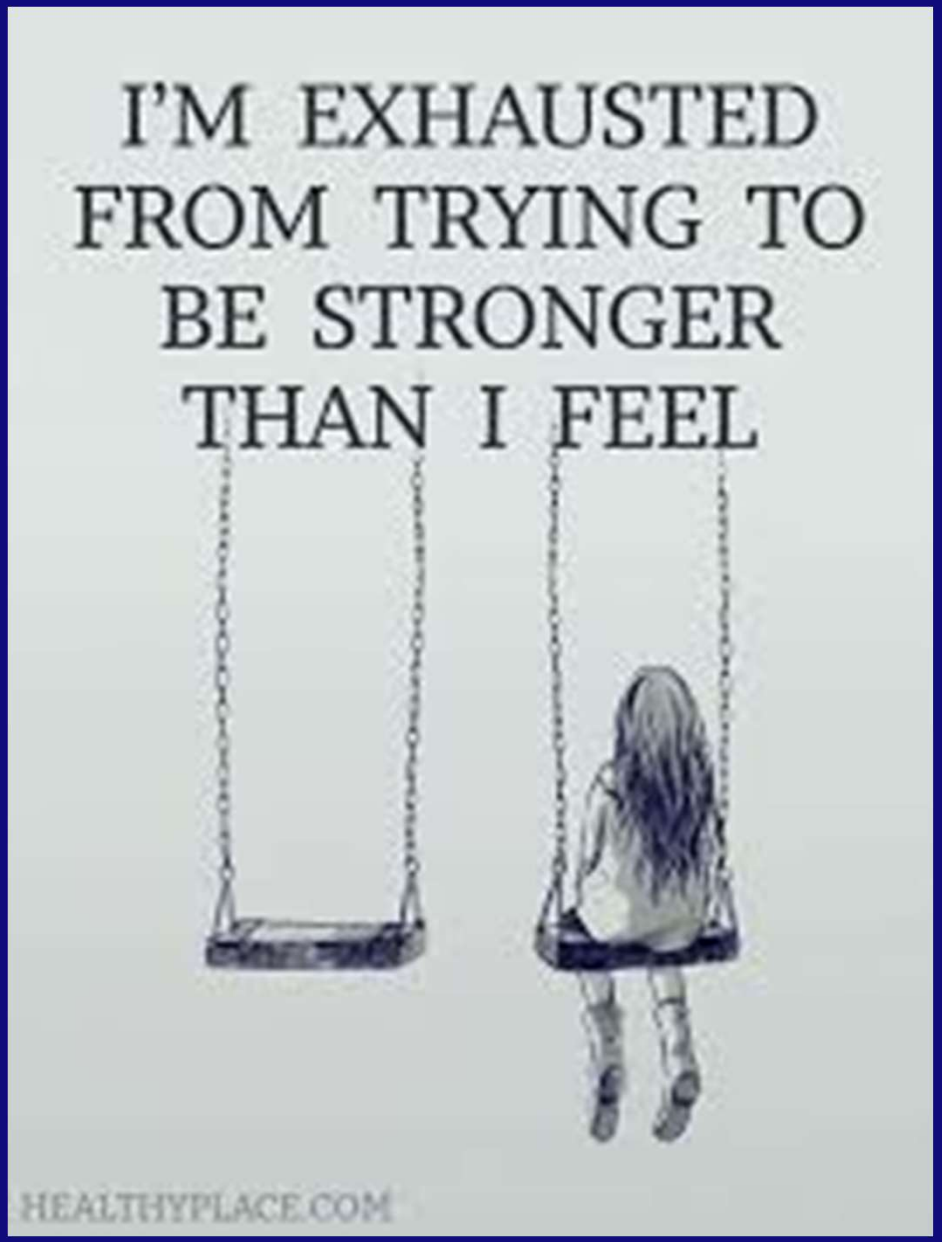


# Depression

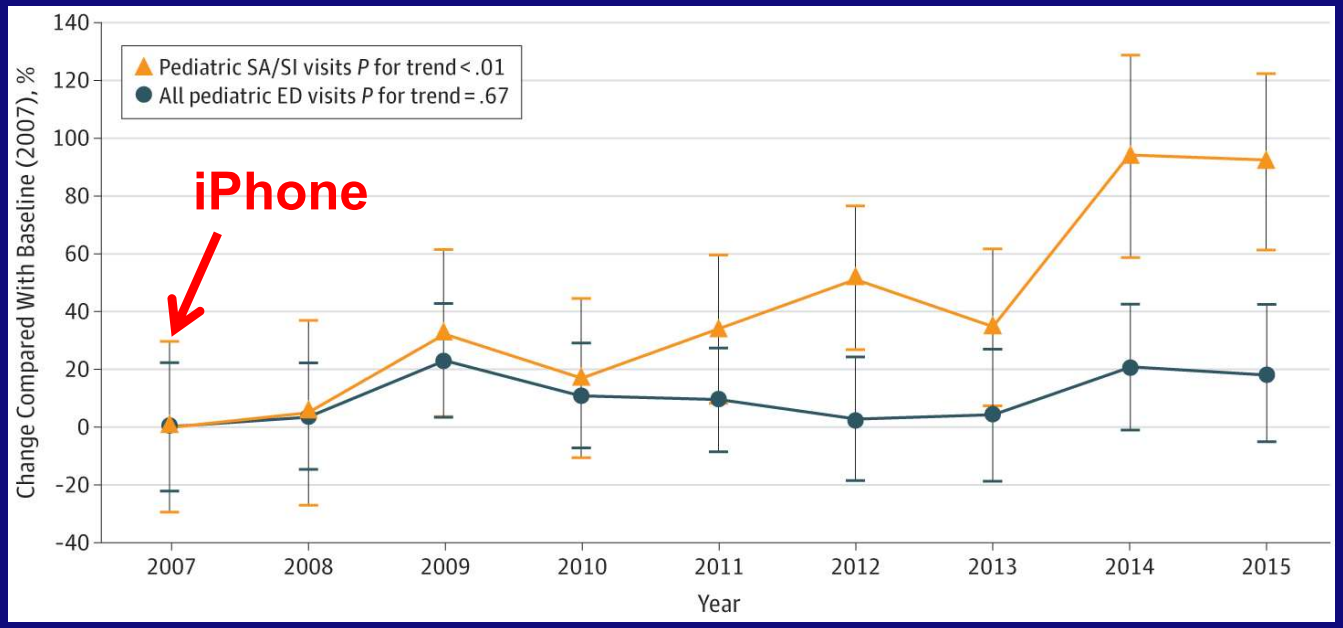
**World Health Organization:**

- **322 million people globally (4.4%)**
- **18.5% increase in prevalence 2005—2015**

# Depression in Children



# ER records of suicidal attempts and ideation amongst children 5-18 yr, 2008—2015




Out-patient encounters with suicidal ideation or self harm:

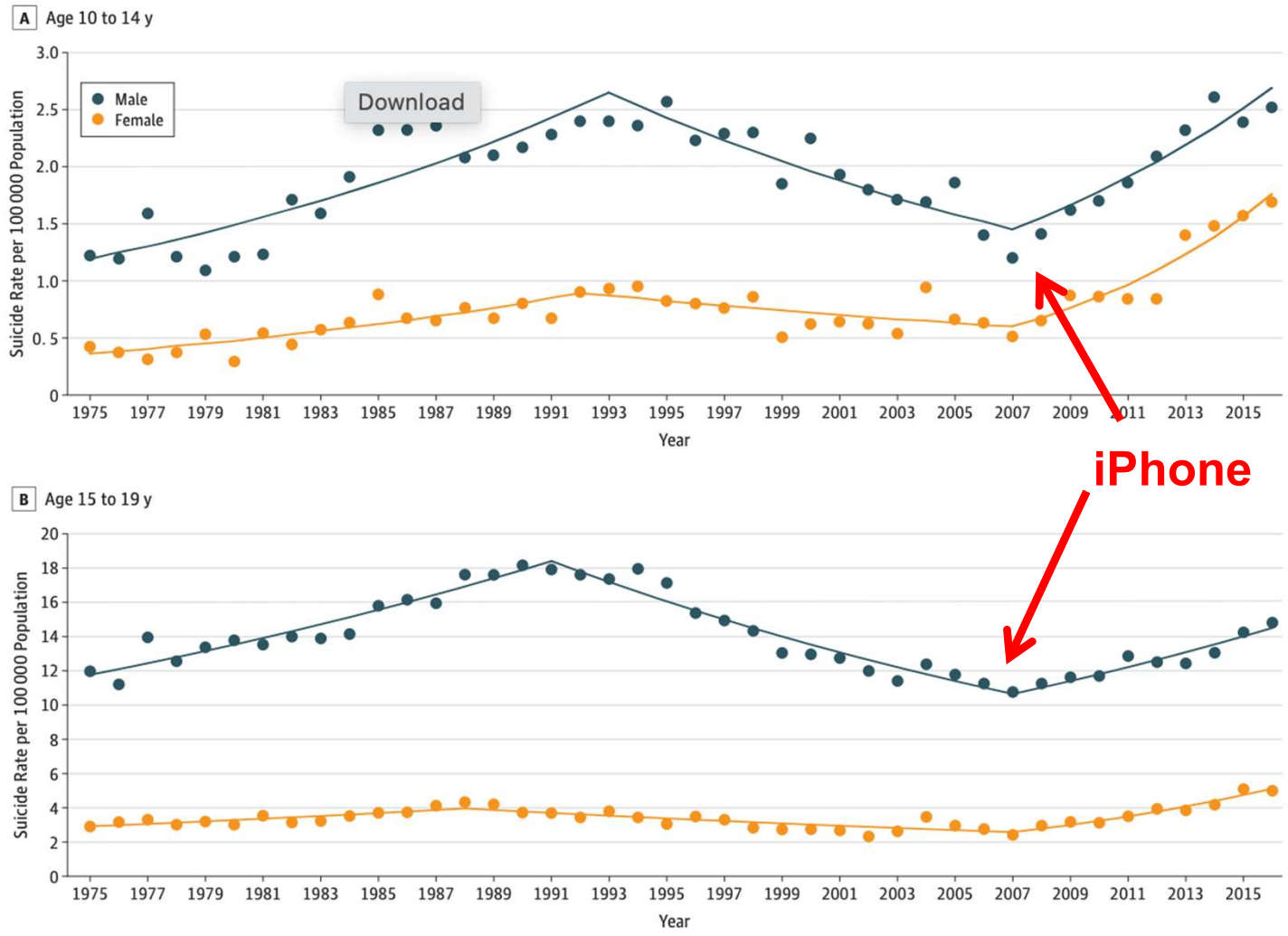
2008 0.67%

2015 1.79%

Burstein et al. JAMA Pediatrics 173:598, 2019

# Suicides in Children ages 10-14 and 15-19

Figure 1. Suicide Trends Among Youth Aged 10 to 19 Years in the United States, 1975 to 2016




Suicide rate trends are displayed as linear segments connected at the joinpoint or year when the slope of each trend changes significantly. Data markers indicate observed rates and solid colored lines indicate model rates.

Ruch et al. JAMA Network Open2(5):e19388, 2019

# Our metabolic health is going down the tubes

**Our metabolic health is going down the tubes**

**Our mental health is going down the tubes**

**Our metabolic health is going down the tubes**

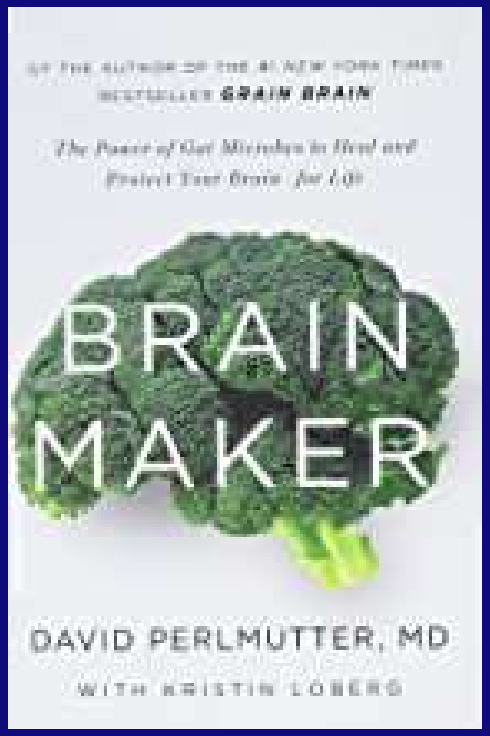
**Our mental health is going down the tubes**

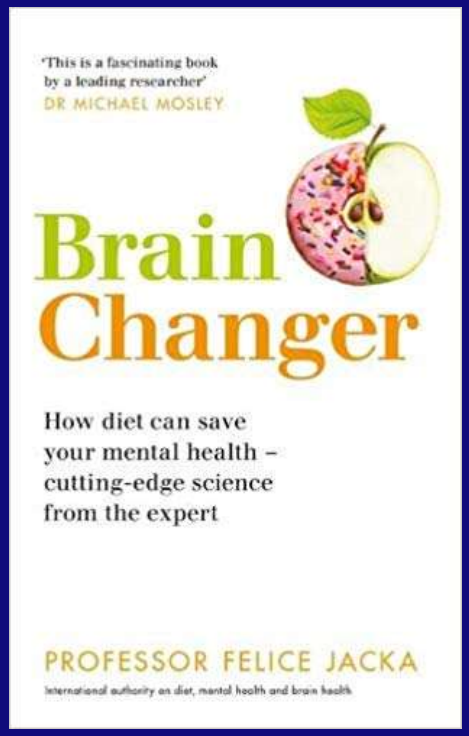
**Our financial health is going down the tubes**

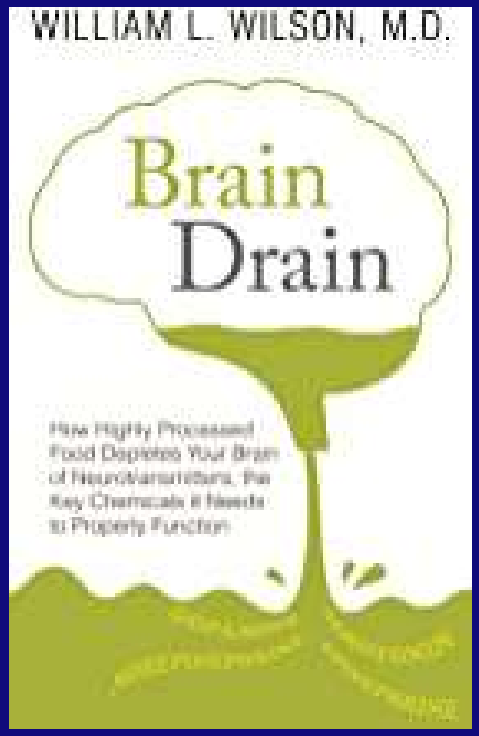
**Coincidence?**

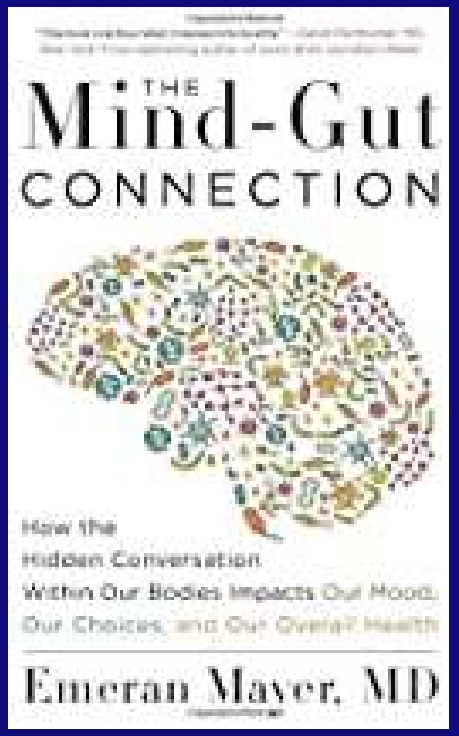
**Or are they related?**

# Many doctors have postulated a relationship between metabolic and mental health




**And there's an annual conference dedicated to exploring this relationship (Nov 2023, virtual)**

**10 Most Obese States**

**> 30% obese**

**10 Most Obese States**

**> 30% obese**

**10 Laziest States**

**< 63% active**

**10 Most Obese States**

**> 30% obese**

**10 Laziest States**

**< 63% active**

**10 Most Unhappy States**

## 10 Most Obese States

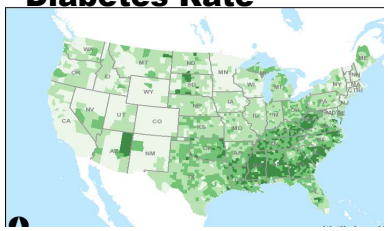
> 30% obese

## 10 Laziest States

< 63% active

## 10 Most Unhappy States

## Diabetes Rate



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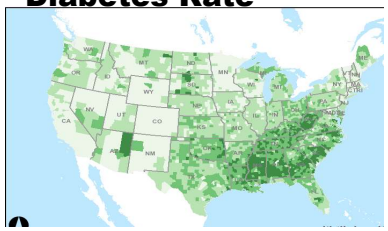
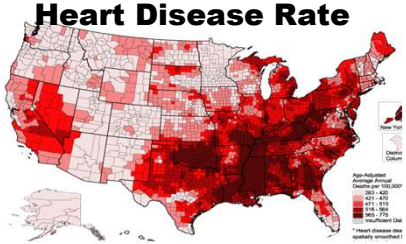


## Heart Disease Rate



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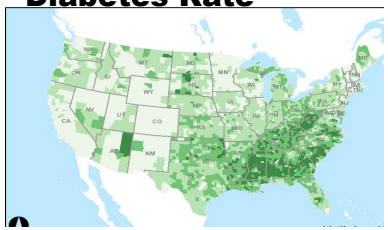
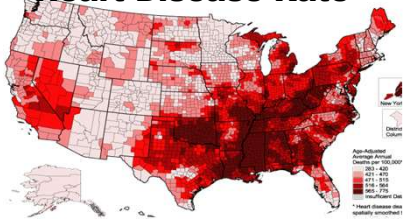
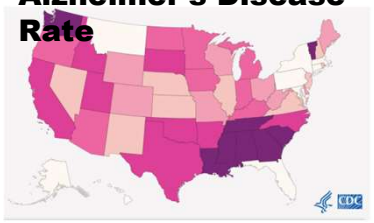


## Heart Disease Rate



## Alzheimer's Disease Rate



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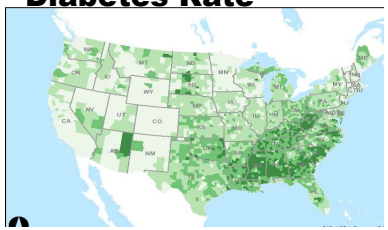

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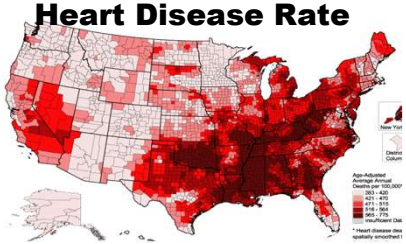
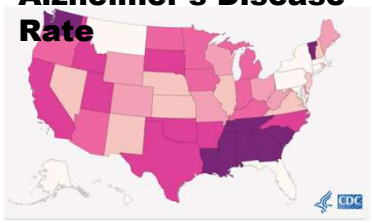
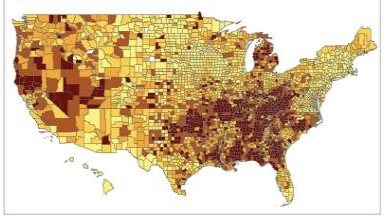


## Alzheimer's Disease Rate



## Opioid Use Rate



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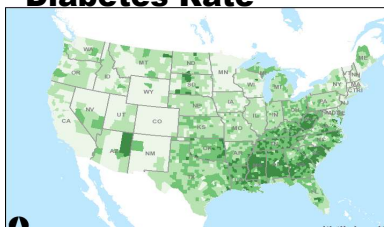

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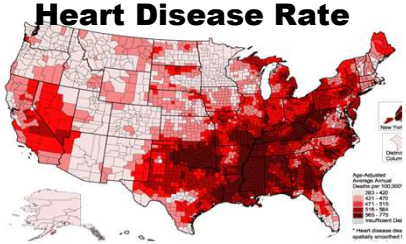

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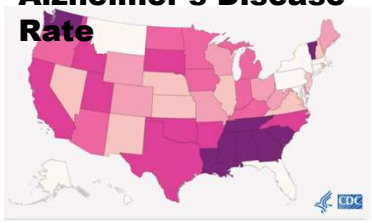

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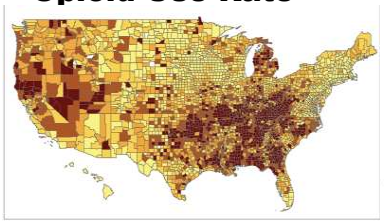
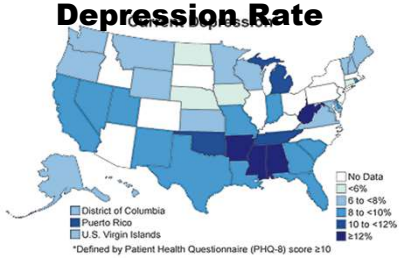


## Depression Rate



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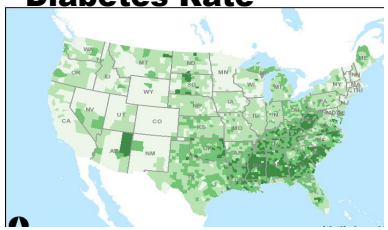

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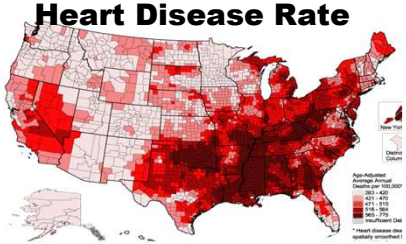

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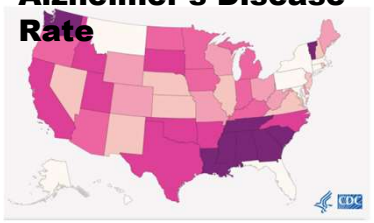

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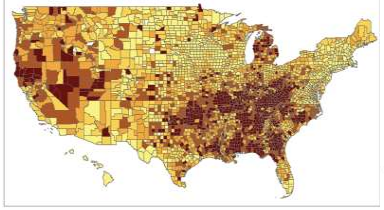
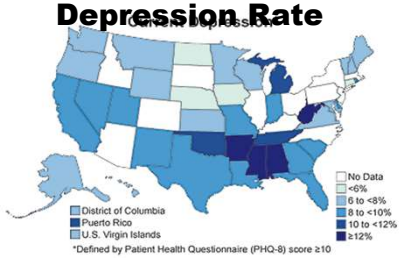
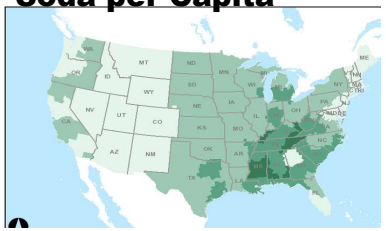


## Depression Rate




## Soda per Capita



# Insulin resistance is a driver of depression

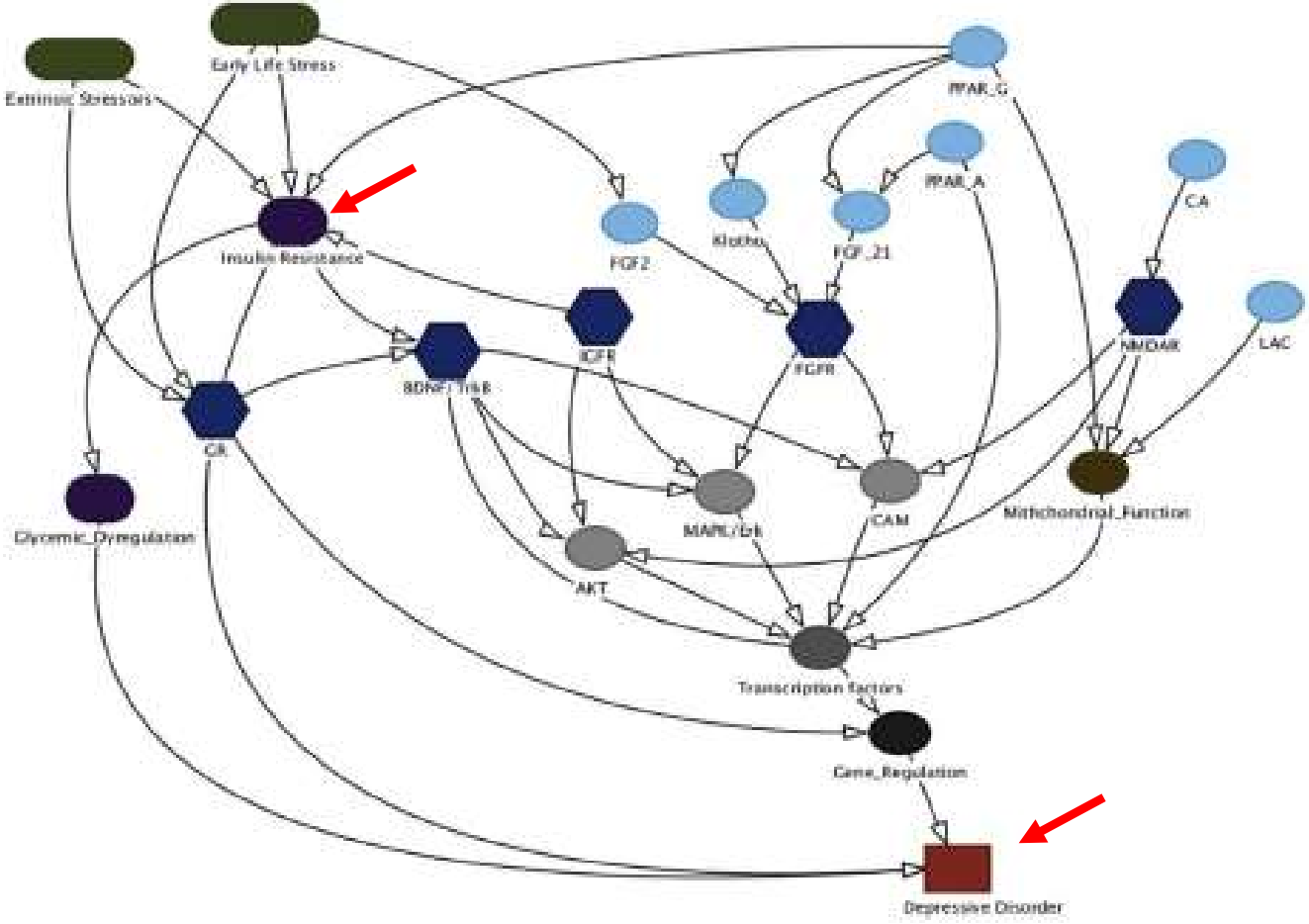
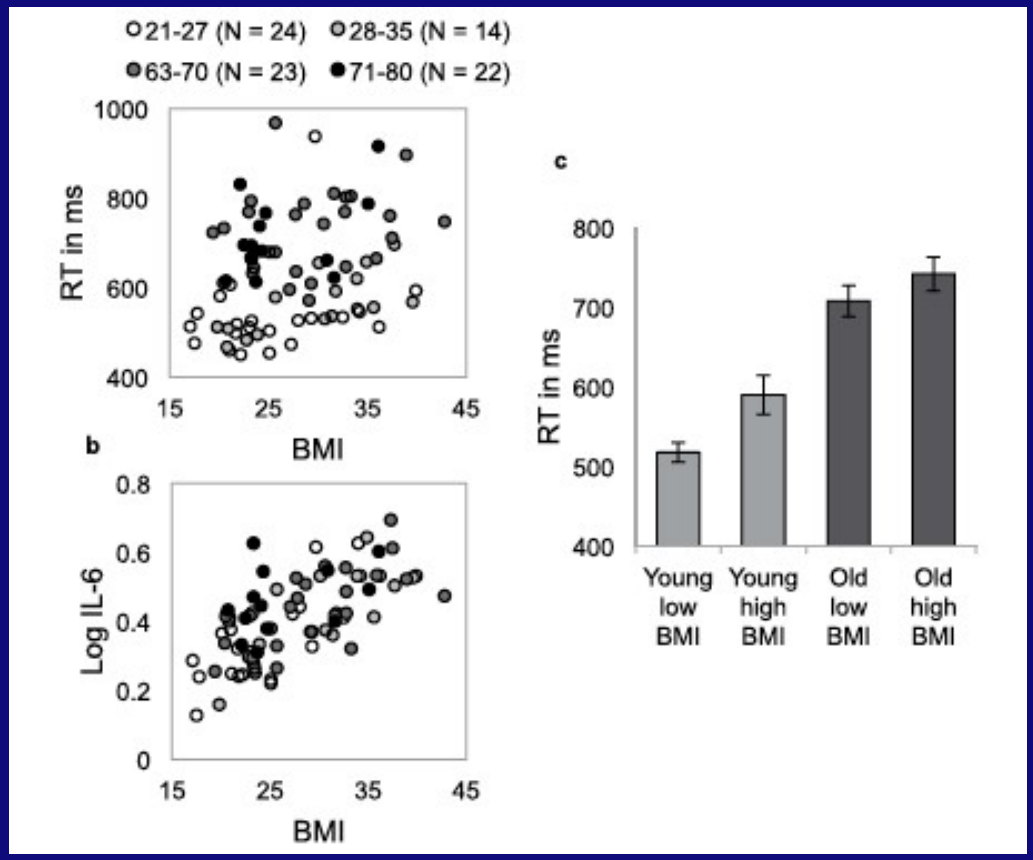
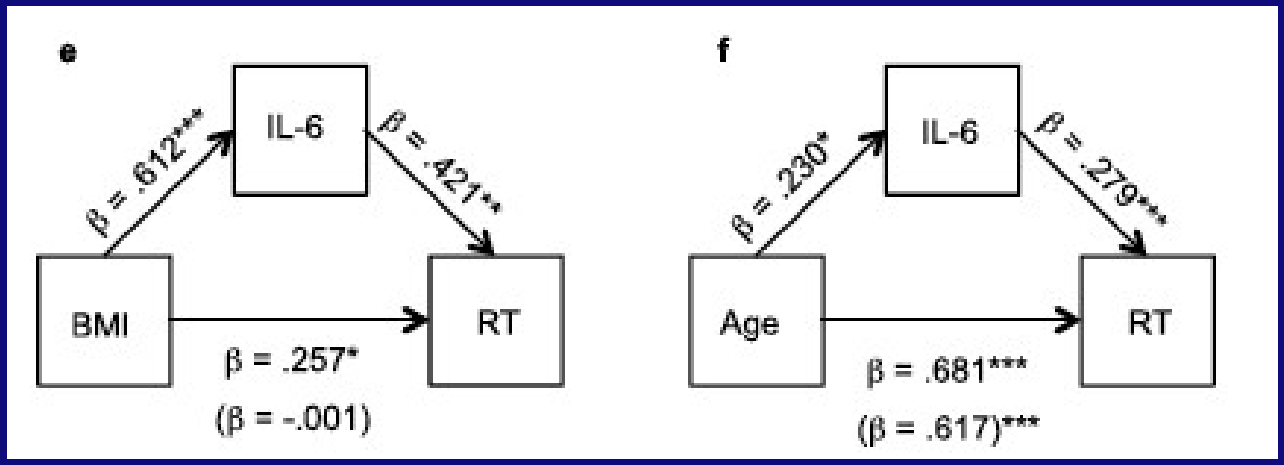



Fig. 1. Moderators and mediators of the insulin resistance-depressive disorders pathway.

Watson et al. Neurophamacology 136:327, 2018

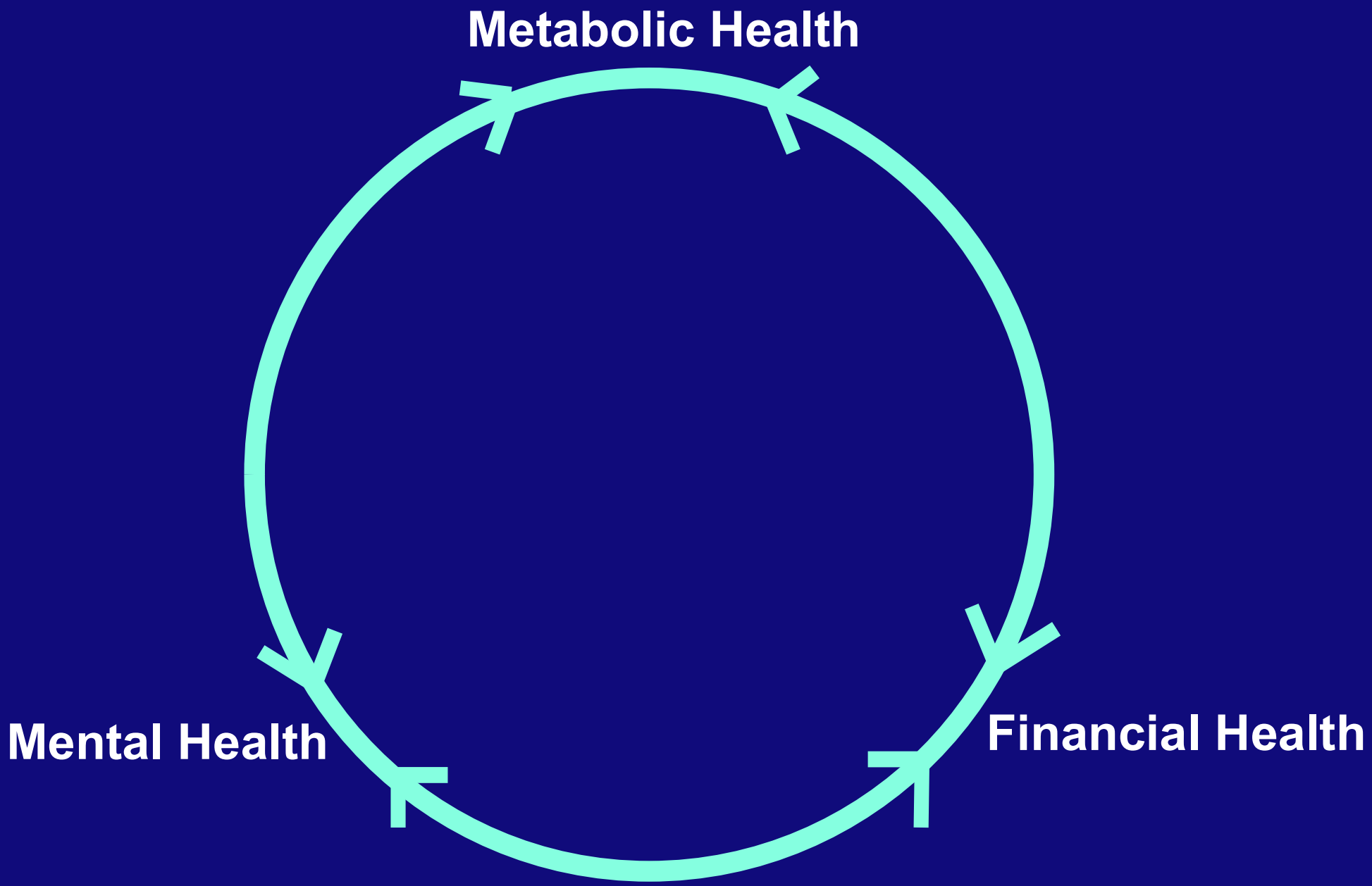
# Reaction time correlates with inflammation, not BMI




Balter et al. Sci Rep 9:15727, 2019

# What's the causality?



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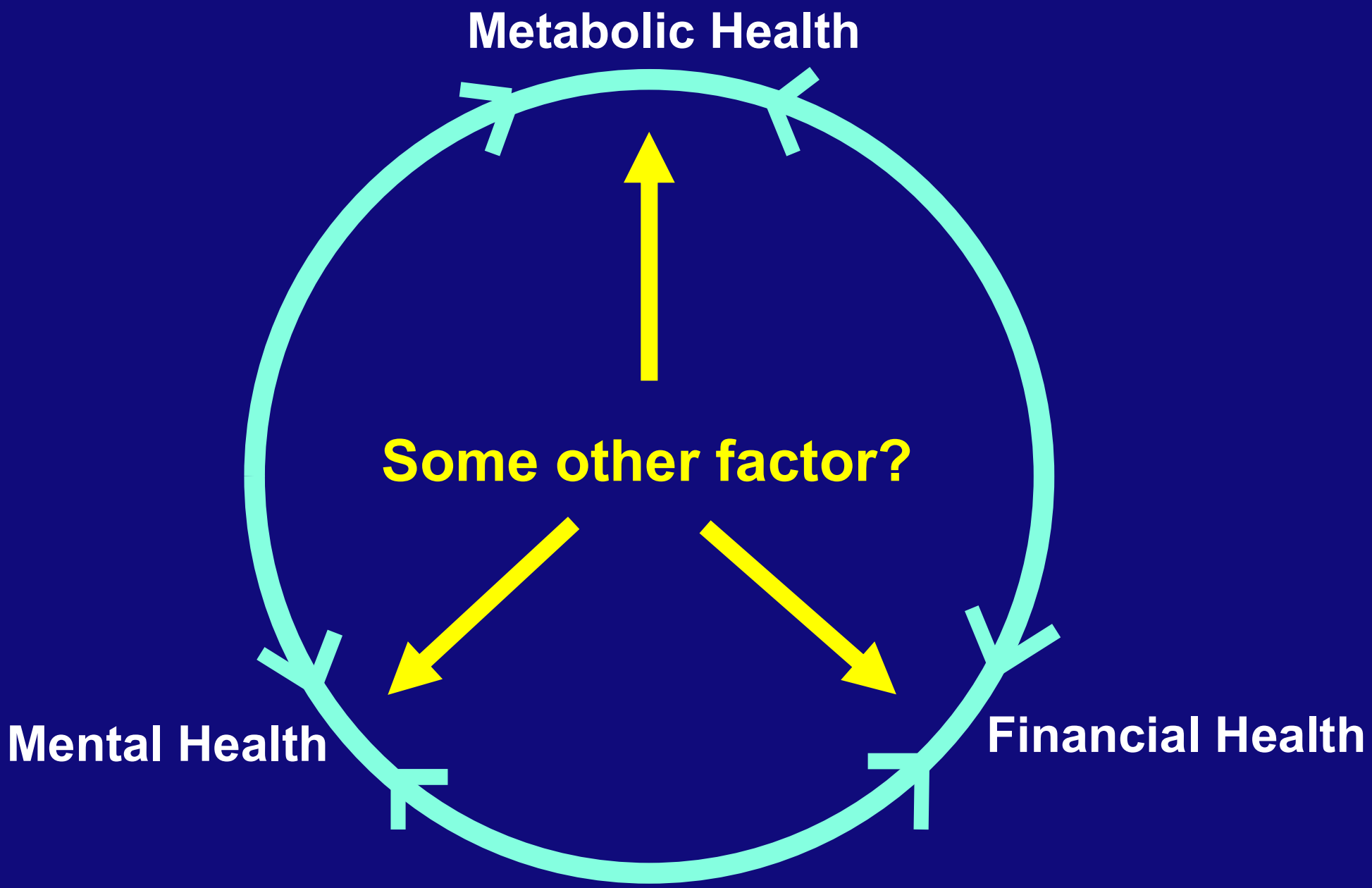

# Does happiness itself directly affect mortality? The prospective UK Million Women Study

*Bette Liu, Sarah Floud, Kirstin Pirie, Jane Green, Richard Peto, Valerie Beral, for the Million Women Study Collaborators*

| | | | |
|---|---|---|---|
| **Serious illness at baseline** | **With illness** | **Without illness** | |
| Cancer | 44481/9579 | 654583/136797 | 0·953 (0·924–0·982) |
| Heart disease | 49035/13329 | 650029/133047 | 0·784 (0·763–0·806) |
| Stroke | 11703/3501 | 687361/142875 | 0·748 (0·710–0·787) |
| Chronic obstructive lung disease | 4924/1902 | 694140/144474 | 0·668 (0·621–0·718) |
| **Current treatment at baseline** | **Treated** | **Not treated** | |
| High blood pressure | 153825/34249 | 545239/112127 | 0·928 (0·911–0·945) |
| Diabetes | 22070/5854 | 676994/140522 | 0·863 (0·829–0·898) |
| Asthma | 49919/13104 | 649145/133272 | 0·848 (0·825–0·871) |
| Arthritis | 79848/22729 | 619216/123647 | 0·763 (0·747–0·780) |
| Depression or anxiety | 29285/25628 | 669779/120748 | 0·224 (0·218–0·229) |
| **Self-rated health at baseline** | **Fair or poor** | **Excellent or good** | |
| Fair or poor | 125393/62859 | 541004/76505 | 0·298 (0·293–0·303) |

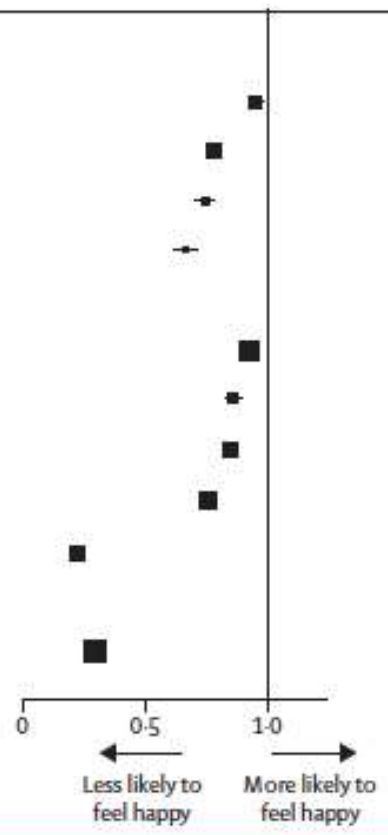


*Figure 2:* **Correlates of being generally happy—relevance of various indices of health at baseline**
Analysis for whole population (N=845 440), including women later excluded for life-threatening health disorders. ORs are adjusted for age, region, area deprivation, body-mass index, qualifications, strenuous exercise, smoking, alcohol, living with a partner, parity, participation in group activities, and sleep duration. OR=odds ratio.

Liu et al. Lancet 387:874, 2016

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| High blood pressure | 153825/34249 | 545239/112127 | 0·928 (0·911–0·945) |

**Findings** Of 719671 women in the main analyses (median age 59 years [IQR 55–63]), 39% (282619) reported being happy most of the time, 44% (315874) usually happy, and 17% (121178) unhappy. During 10 years (SD 2) follow-up, 4% (31531) of participants died. Self-rated poor health at baseline was strongly associated with unhappiness. But after adjustment for self-rated health, treatment for hypertension, diabetes, asthma, arthritis, depression, or anxiety, and several sociodemographic and lifestyle factors (including smoking, deprivation, and body-mass index), unhappiness was not associated with mortality from all causes (adjusted RR for unhappy *vs* happy most of the time 0·98, 95% CI 0·94–1·01), from ischaemic heart disease (0·97, 0·87–1·10), or from cancer (0·98, 0·93–1·02). Findings were similarly null for related measures such as stress or lack of control.

*Figure 2:* **Correlates of being generally happy—relevance of various indices of health at baseline**
Analysis for whole population (N=845440), including women later excluded for life-threatening health disorders. ORs are adjusted for age, region, area deprivation, body-mass index, qualifications, strenuous exercise, smoking, alcohol, living with a partner, parity, participation in group activities, and sleep duration. OR=odds ratio.

Liu et al. Lancet 387:874, 2016

Soc Indic Res (2019) 142:713–732
https://doi.org/10.1007/s11205-018-1923-2

CrossMark

# Role of Life Satisfaction

## Happiness and Longevity: Unhappy People Die Young, Otherwise Happiness Probably Makes No Difference

Bruce Headey[1] · Jongsay Yong[1]

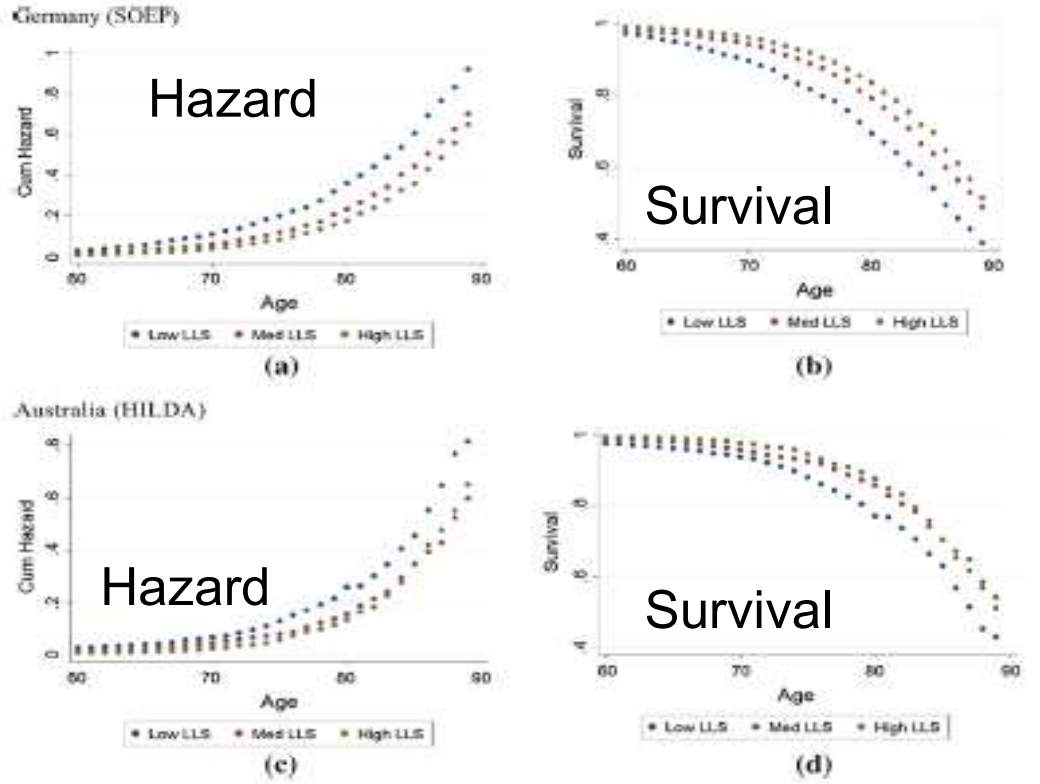



**Fig. 1** Survival and hazard functions: high, medium and low LLS groups. **a** Kaplan–Meier survival function, **b** Nelson–Aalen cumulative hazard, **c** Kaplan–Meier survival function, **d** Nelson–Aalen cumulative hazard

($p<0.001$) and Australia ($p=0.007$). It remains our view, however, that many (perhaps all) of these additional controls could be partly consequences of LS, not just causes. This caveat applies particularly to variables measuring physical exercise, participation in social activities, smoking and perhaps obesity. It also likely that initial health (also included as a control in extended model II) is a consequence as well as a cause of LS.

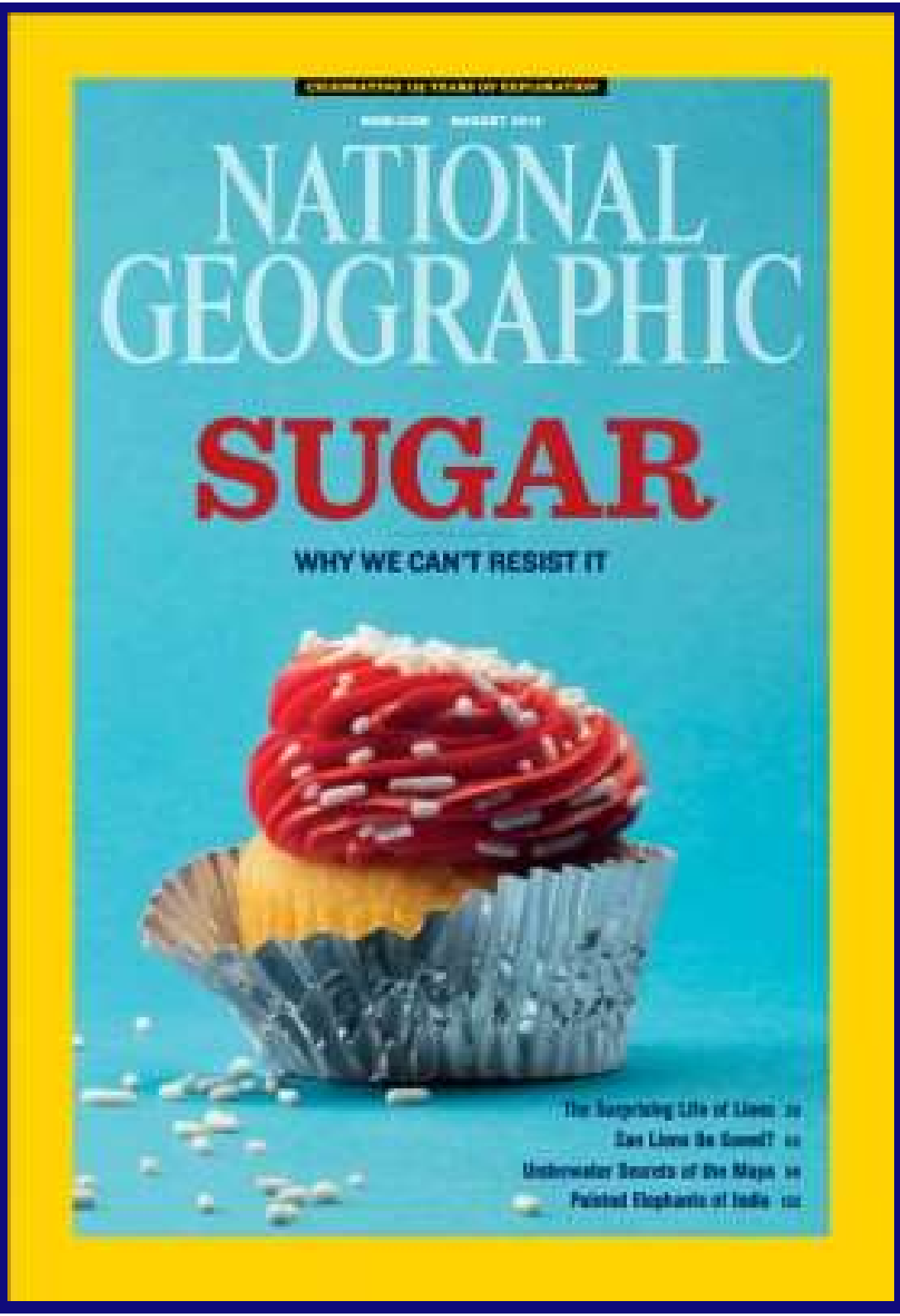
**Unhappiness doesn't kill;**

**it's what we do to "get happy" that does**

Unhappiness doesn't kill;

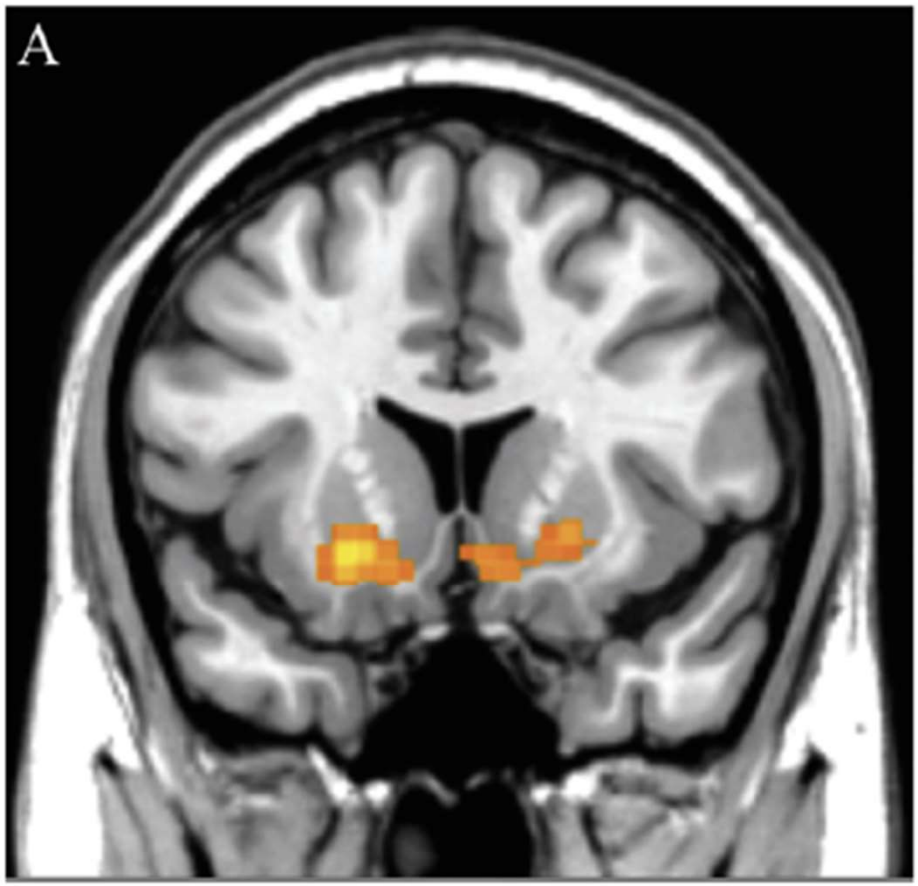
it's what we do to "get happy" that does

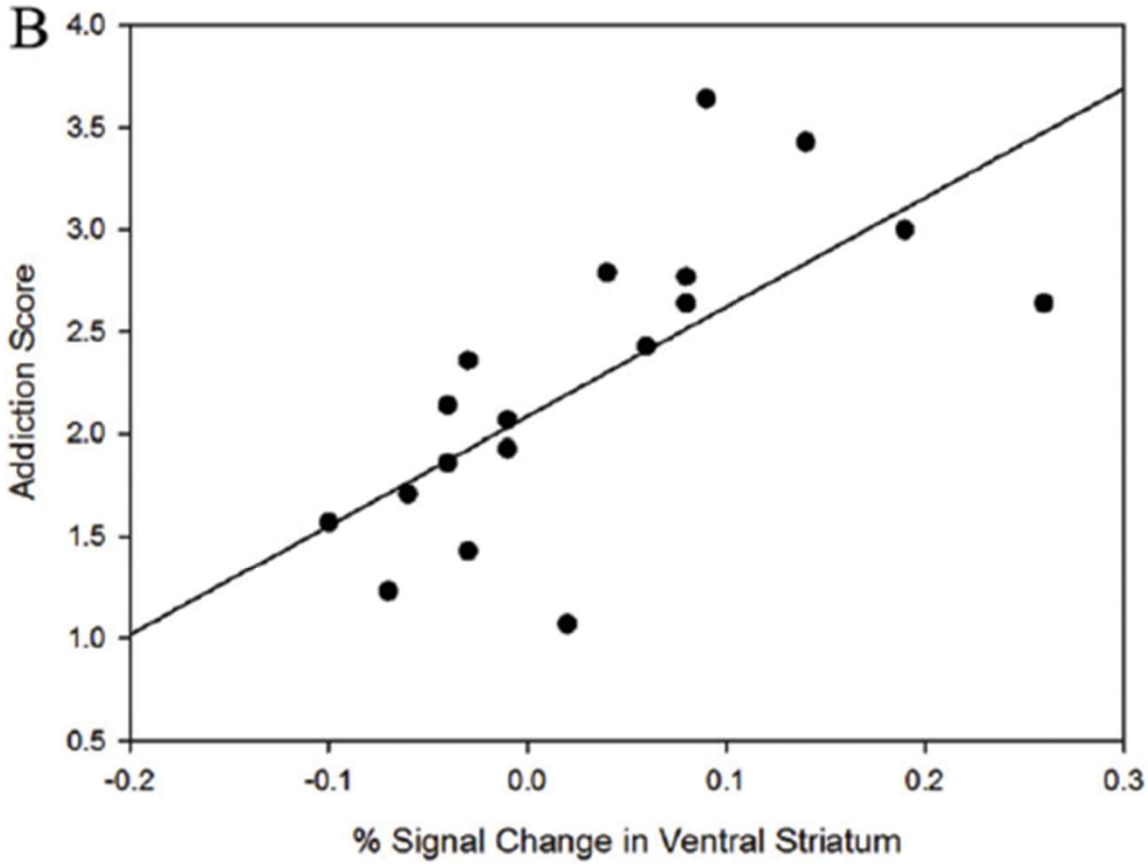
It's the pleasure, stupid


NATIONAL GEOGRAPHIC
SUGAR
WHY WE CAN'T RESIST IT


PUGH
facebook
YOU HAVE
4 NEW
ANXIETIES

# Correlation of fMRI activation of nucleus accumbens (dopamine) with Facebook Addiction Scores




Turel et al. Psych Rep 115:675, 2014

# The driver of technology addiction

# What's the difference between apps we cherish vs. regret?

We partnered with Moment, an app that helps people track their screen time, to ask how much screen time in apps left people feeling happy, and how much time left them in regret.

The rankings below reflect data collected from a pool of 200,000 iPhone users.

## Most Happy

| | % of Users Happy | Daily Usage (Minutes) |
|---|---|---|
| 1. Calm | 99% | 10 |
| 2. Google Calendar | 99% | 3 |
| 3. Headspace | 99% | 4 |
| 4. Insight Timer | 99% | 20 |
| 5. The Weather | 97% | 3 |
| 6. MyFitnessPal | 97% | 8 |
| 7. Audible | 97% | 8 |
| 8. Waze | 96% | 19 |
| 9. Amazon Music | 96% | 7 |
| 10. Podcasts | 96% | 8 |
| 11. Kindle | 96% | 26 |
| 12. Evernote | 96% | 10 |
| 13. Spotify | 95% | 9 |
| 14. Weather | 95% | 2 |
| 15. Canvas | 95% | 5 |

## Most Unhappy

| | % of Users Unhappy | Daily Usage (Minutes) |
|---|---|---|
| 1. Grindr | 77% | 61 |
| 2. Candy Crush Saga | 71% | 46 |
| 3. Facebook | 64% | 59 |
| 4. WeChat | 62% | 97 |
| 5. Candy Crush | 59% | 47 |
| 6. Reddit | 58% | 56 |
| 7. Tweetbot | 58% | 78 |
| 8. Weibo | 57% | 73 |
| 9. Tinder | 56% | 22 |
| 10. Subway Surf | 56% | 32 |
| 11. Two Dots | 53% | 34 |
| 12. Instagram | 51% | 54 |
| 13. Snapchat | 50% | 61 |
| 14. 1010! | 45% | 35 |
| 15. Clash Royale | 42% | 58 |

# The devils you know
# "—*aholic*"

- **Chemical**
  - nicotine
  - alcohol
  - cocaine
  - methamphetamine
  - heroin
  - sugar
- **Behavioral**
  - shopping
  - gambling
  - internet gaming
  - social media
  - pornography

# The hack:

- The systematic confusion and conflation of pleasure with happiness

Pleasure

Happiness

## Pleasure

1. Short lived

## Happiness

1. Long lived

## Pleasure

1. Short lived
2. Visceral

## Happiness

1. Long lived
2. Ethereal

## Pleasure

1. Short lived
2. Visceral
3. Taking

## Happiness

1. Long lived
2. Ethereal
3. Giving

## Pleasure

1. Short lived
2. Visceral
3. Taking
4. Experienced alone

## Happiness

1. Long lived
2. Ethereal
3. Giving
4. Experienced with others

## Pleasure

1. Short lived
2. Visceral
3. Taking
4. Experienced alone
5. Achievable with substances

## Happiness

1. Long lived
2. Ethereal
3. Giving
4. Experienced with others
5. Not achievable with substances

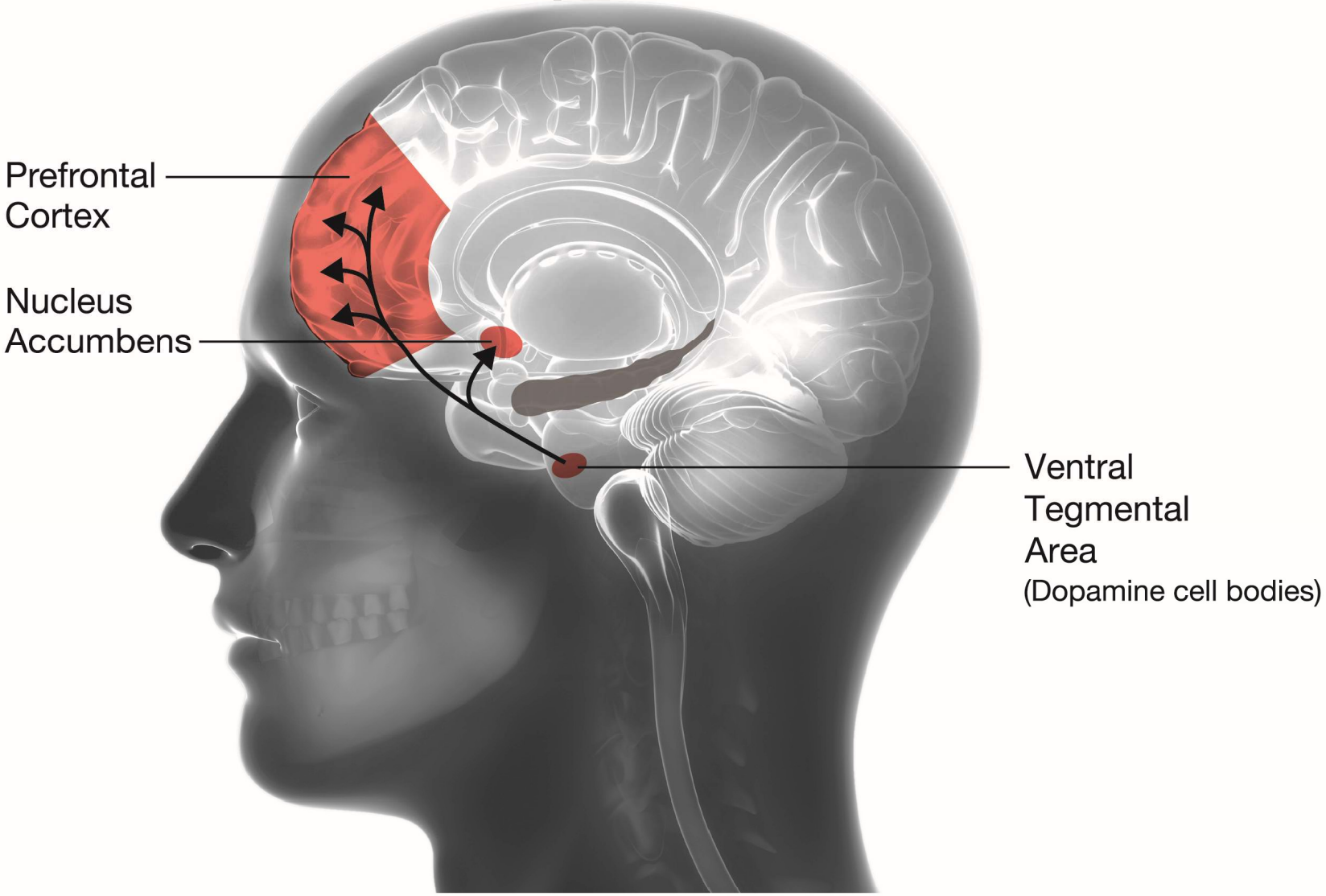
| Pleasure | Happiness |
| --- | --- |
| 1. Short lived | 1. Long lived |
| 2. Visceral | 2. Ethereal |
| 3. Taking | 3. Giving |
| 4. Experienced alone | 4. Experienced with others |
| 5. Achievable with substances | 5. Not achievable with substances |
| 6. Extremes lead to addiction | 6. Can't be addicted to happiness |

| Pleasure | Happiness |
| --- | --- |
| 1. Short lived | 1. Long lived |
| 2. Visceral | 2. Ethereal |
| 3. Taking | 3. Giving |
| 4. Experienced alone | 4. Experienced with others |
| 5. Achievable with substances | 5. Not achievable with substances |
| 6. Extremes lead to addiction | 6. Can't be addicted to happiness |
| 7. Dopamine | 7. Serotonin |

**All of these utilize the same three neural pathways in the "limbic" system of the brain**

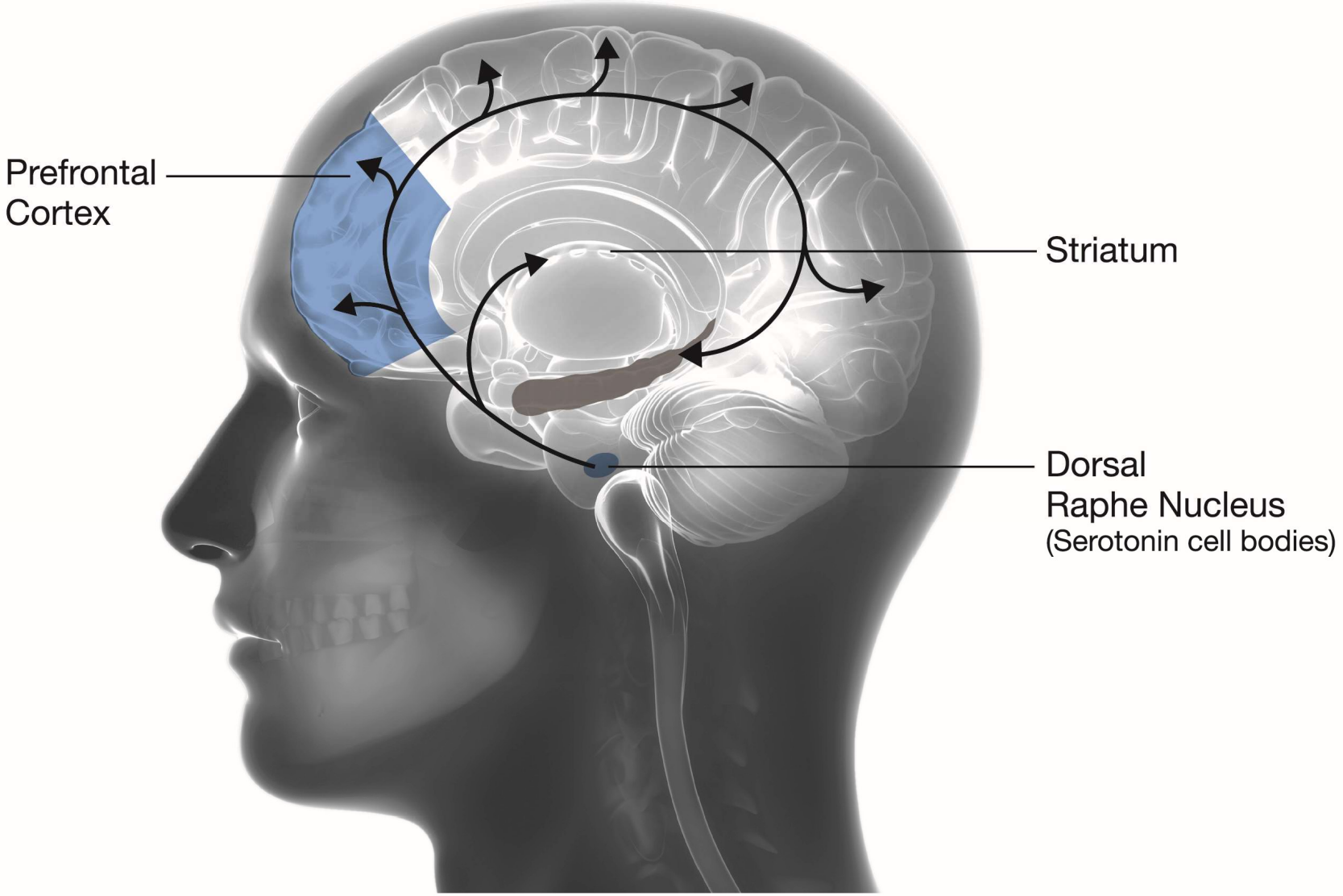
1. The "Reward" Pathway
2. The "Contentment" Pathway
3. The "Stress-Fear-Memory" Pathway

# Reward Pathway
# Dopamine



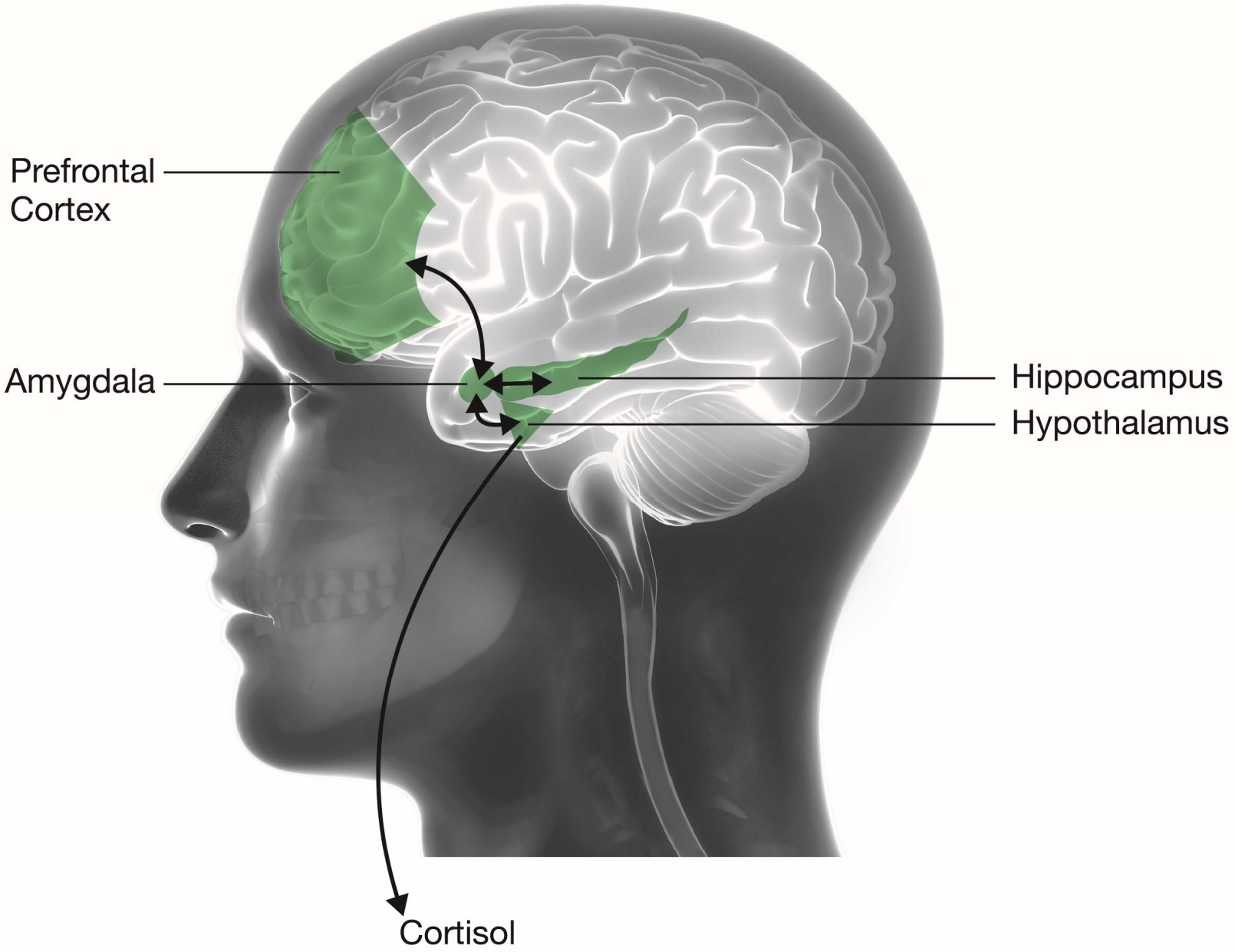

Lustig, Avery Press, 2017

# Contentment Pathway
# Serotonin



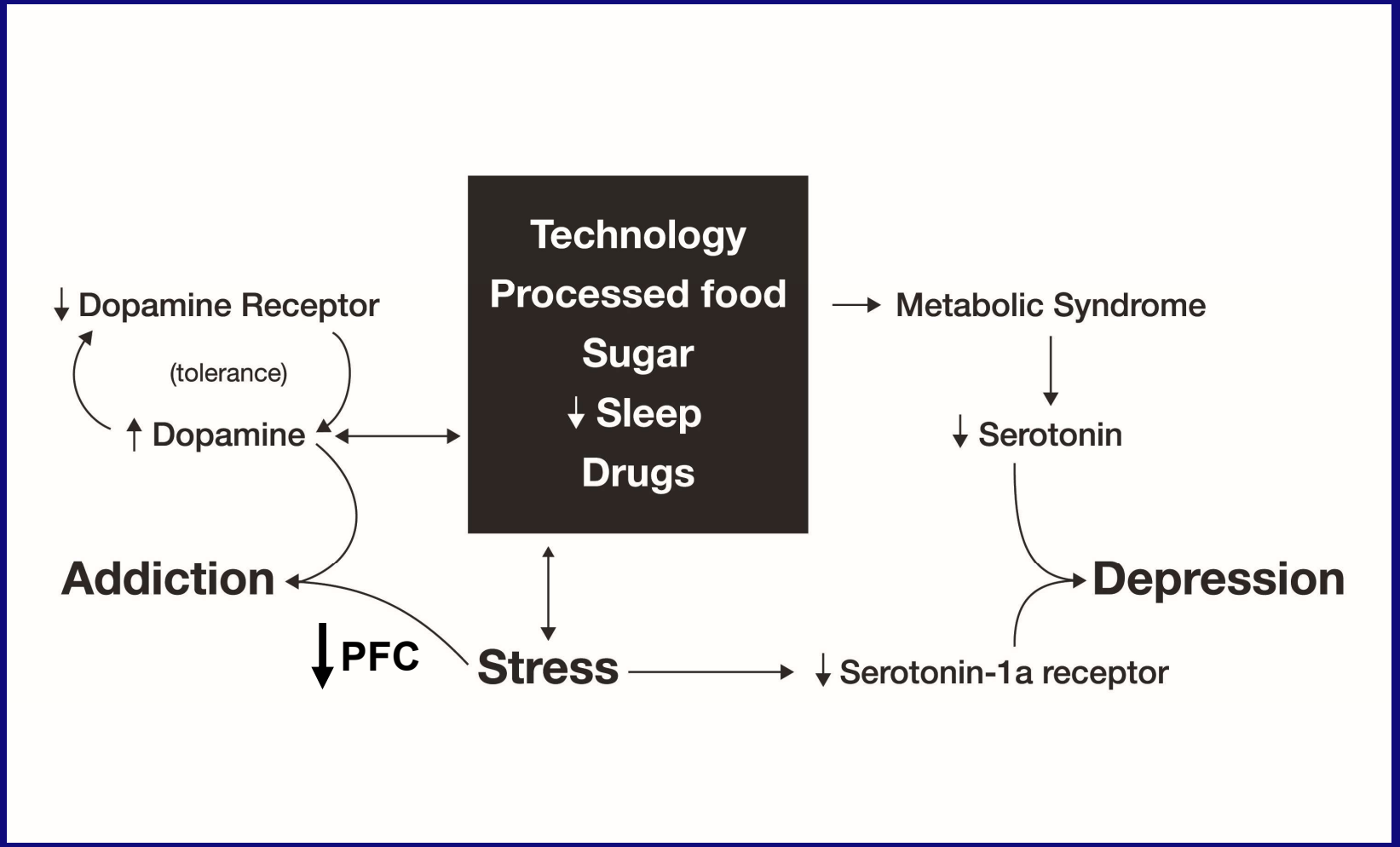

Lustig, Avery Press, 2017

# Stress-Fear-Memory Pathway
# Cortisol




Lustig, Avery Press, 2017

# The dopamine-cortisol-serotonin interaction

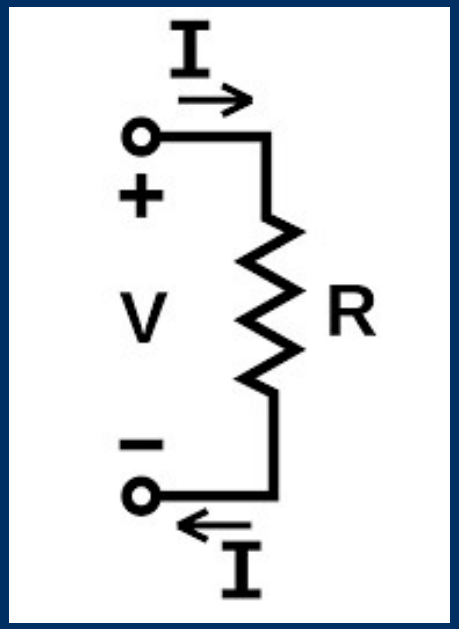



Lustig, Avery Press, 2017

# Excitatory neurotransmitters, down-regulation, and addiction

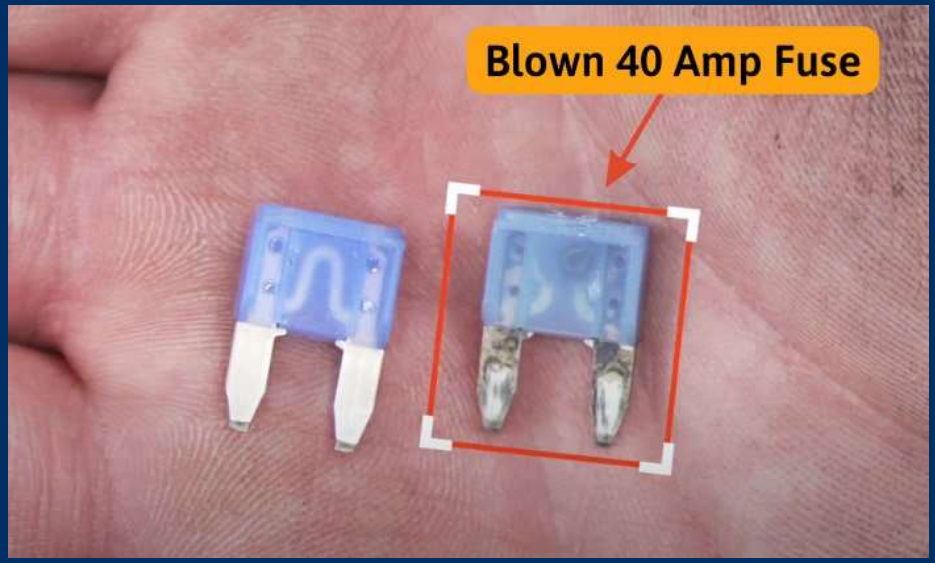
- **Dopamine is excitatory**
- Long-term chronic firing can kill neurons
- To protect themselves, neurons down-regulate the dopamine receptor
- Get a hit, get a rush — receptors go down
- Next time you need a bigger hit to get the same rush (tolerance)
- **When the neurons start to die, that's addiction**

# Ohm's Law and Insulation Resistance




Ohm's Law $I = \frac{V}{R}$

Electric current = Voltage / Resistance

## 1. Not all drugs “fry neurons”:

**Benzodiazepines don’t (GABA – inhibitory)**

**Psychedelics don’t (Serotonin – inhibitory)**

## 2. Only excitatory drugs lead to cell death

**e.g. cocaine, ecstasy, meth, PCP**

## 3. Unmyelinated neurons are more likely to die from chronic excitation, e.g. adolescent PFC’s

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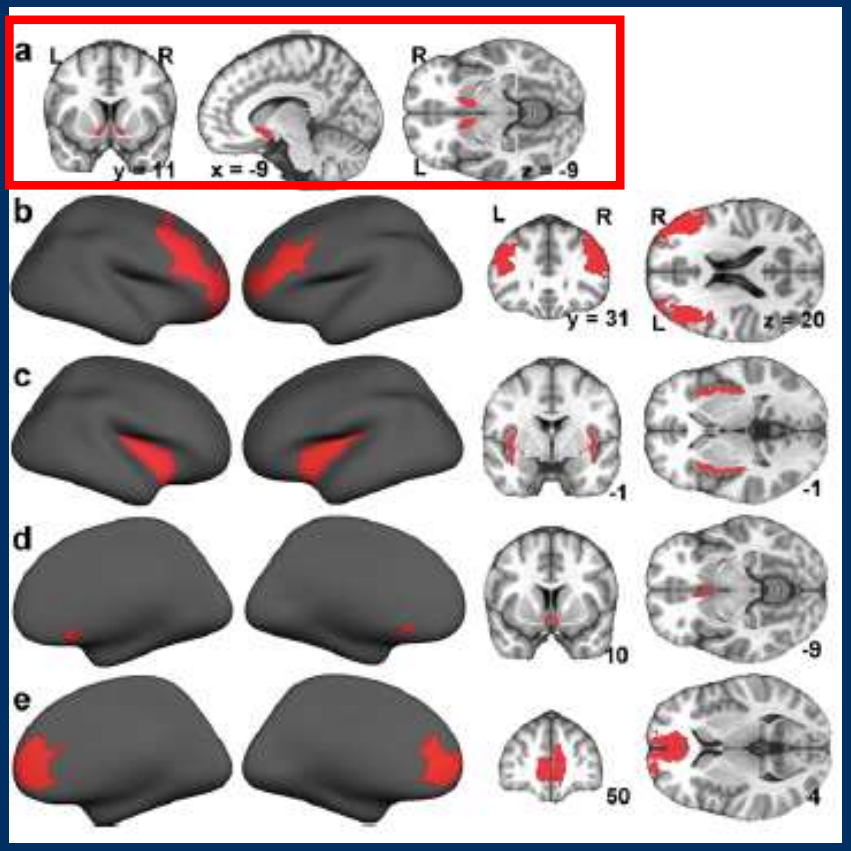
THE MRI SHOWS THAT YOUR BRAIN HAS BEEN HIJACKED BY DOPAMINE PIRATES.
Dilbert.com @ScottAdamsSays
YOU ARE NOW UNDER THE FULL CONTROL OF SOCIAL MEDIA COR— PORATIONS, GAMBLING CASINOS, AND BIG PHARMA.
12-15-17 © 2017 Scott Adams, Inc./Dist. by Andrews McMeel
ARE YOU WRITING ME A PRESCRIP— TION?
NO, I'M BUYING STOCK IN THOSE COMPANIES.

# Decreased myelinization in nucleus accumbens in depression



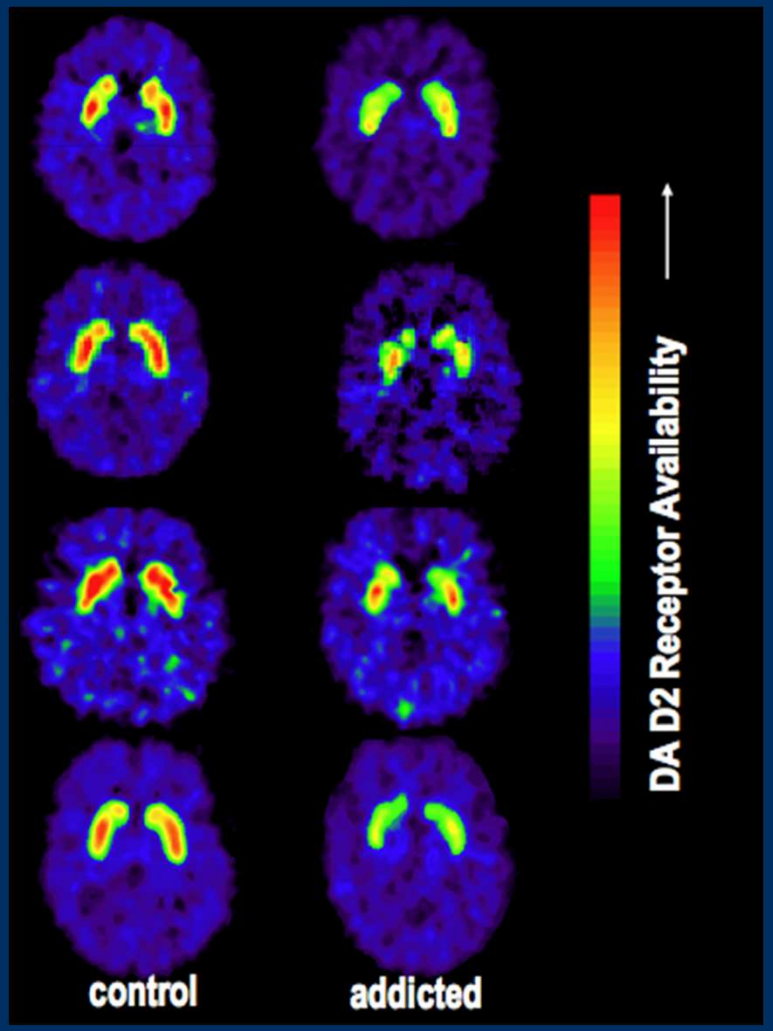

| ROI | MDD | | CTL | | F | p-value | Partial $\eta^2$ |
|---|---|---|---|---|---|---|---|
| | *M/EMM* | *SE* | *M/EMM* | *SE* | | | |
| Without whole-brain R1 covariate | | | | | | | |
| NAcc | 0.635 | 0.004 | 0.650 | 0.004 | 7.33 | 0.008 | 0.09 |
| LPFC | 0.734 | 0.004 | 0.745 | 0.004 | 4.40 | 0.039 | 0.05 |
| Insula | 0.628 | 0.002 | 0.634 | 0.002 | 3.62 | 0.061 | 0.05 |
| sgACC | 0.610 | 0.004 | 0.625 | 0.004 | 5.69 | 0.019 | 0.07 |
| mPFC | 0.726 | 0.004 | 0.734 | 0.004 | 1.57 | 0.214 | 0.02 |
| Lateral striate[a] | 0.665 | 0.009 | 0.675 | 0.009 | 0.65 | 0.421 | 0.01 |
| Lateral extrastriate[a] | 0.718 | 0.005 | 0.726 | 0.005 | 1.38 | 0.244 | 0.02 |
| Medial striate[a] | 0.740 | 0.005 | 0.749 | 0.005 | 2.02 | 0.160 | 0.03 |
| Medial inferior extrastriate[a] | 0.641 | 0.005 | 0.647 | 0.005 | 0.80 | 0.374 | 0.01 |
| Medial superior extrastriate[a] | 0.681 | 0.005 | 0.695 | 0.005 | 4.22 | 0.043 | 0.05 |
| Whole-brain R1 covariate | | | | | | | |
| NAcc | 0.636 | 0.004 | 0.649 | 0.004 | 5.89 | 0.018[b] | 0.07 |
| LPFC | 0.738 | 0.003 | 0.741 | 0.003 | 0.59 | 0.445 | 0.01 |
| Insula | 0.630 | 0.002 | 0.632 | 0.002 | 0.86 | 0.358 | 0.01 |
| sgACC | 0.614 | 0.004 | 0.622 | 0.004 | 2.15 | 0.147 | 0.03 |
| mPFC | 0.731 | 0.003 | 0.729 | 0.003 | 0.35 | 0.555 | 0.01 |
| Lateral striate[a] | 0.672 | 0.008 | 0.668 | 0.008 | 0.10 | 0.758 | 0.00 |
| Lateral extrastriate[a] | 0.723 | 0.004 | 0.721 | 0.004 | 0.04 | 0.848 | 0.00 |
| Medial striate[a] | 0.745 | 0.003 | 0.744 | 0.003 | 0.01 | 0.920 | 0.00 |
| Medial inferior extrastriate[a] | 0.644 | 0.004 | 0.644 | 0.004 | 0.00 | 0.949 | 0.00 |
| Medial superior extrastriate[a] | 0.686 | 0.004 | 0.690 | 0.004 | 0.65 | 0.421 | 0.01 |

Sacchet and Gotlib, Sci Rep 7:2200, 2017

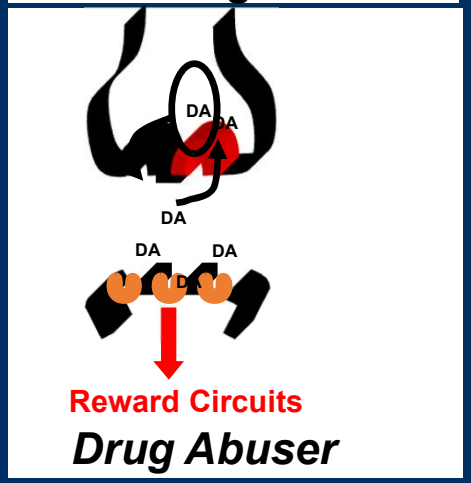
# Dopamine receptors are lower in addiction









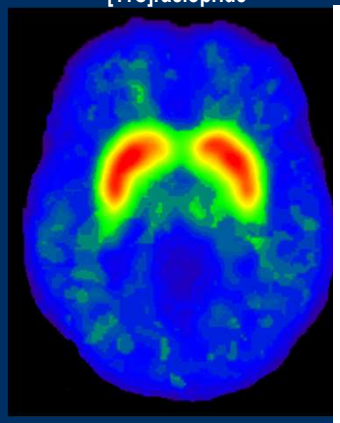




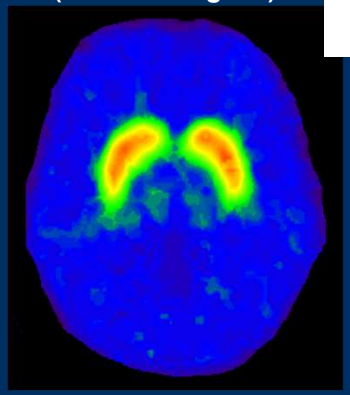

Volkow et al., 2002

# Lower dopamine receptors in obesity as well

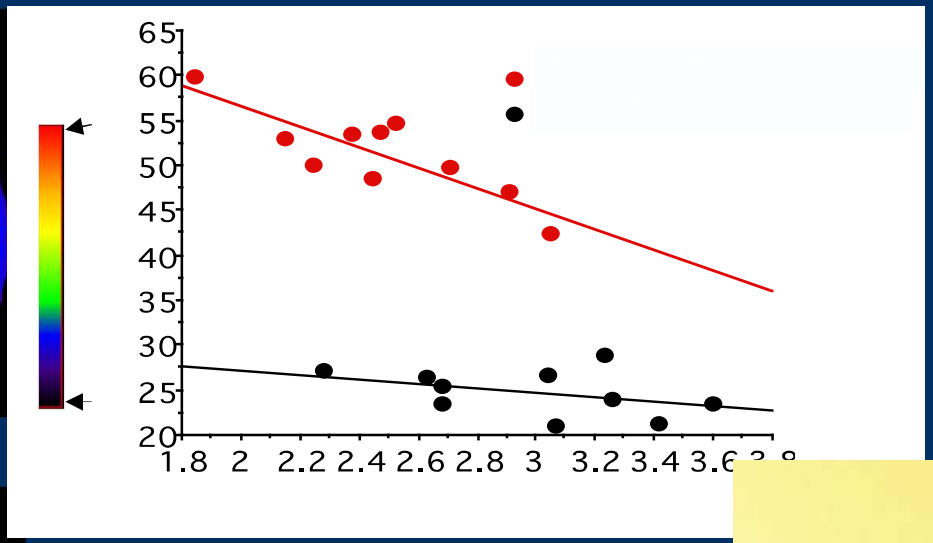
[11C]raclopride



10 Control Subjects
(BMI: 25±3 kg/m2)

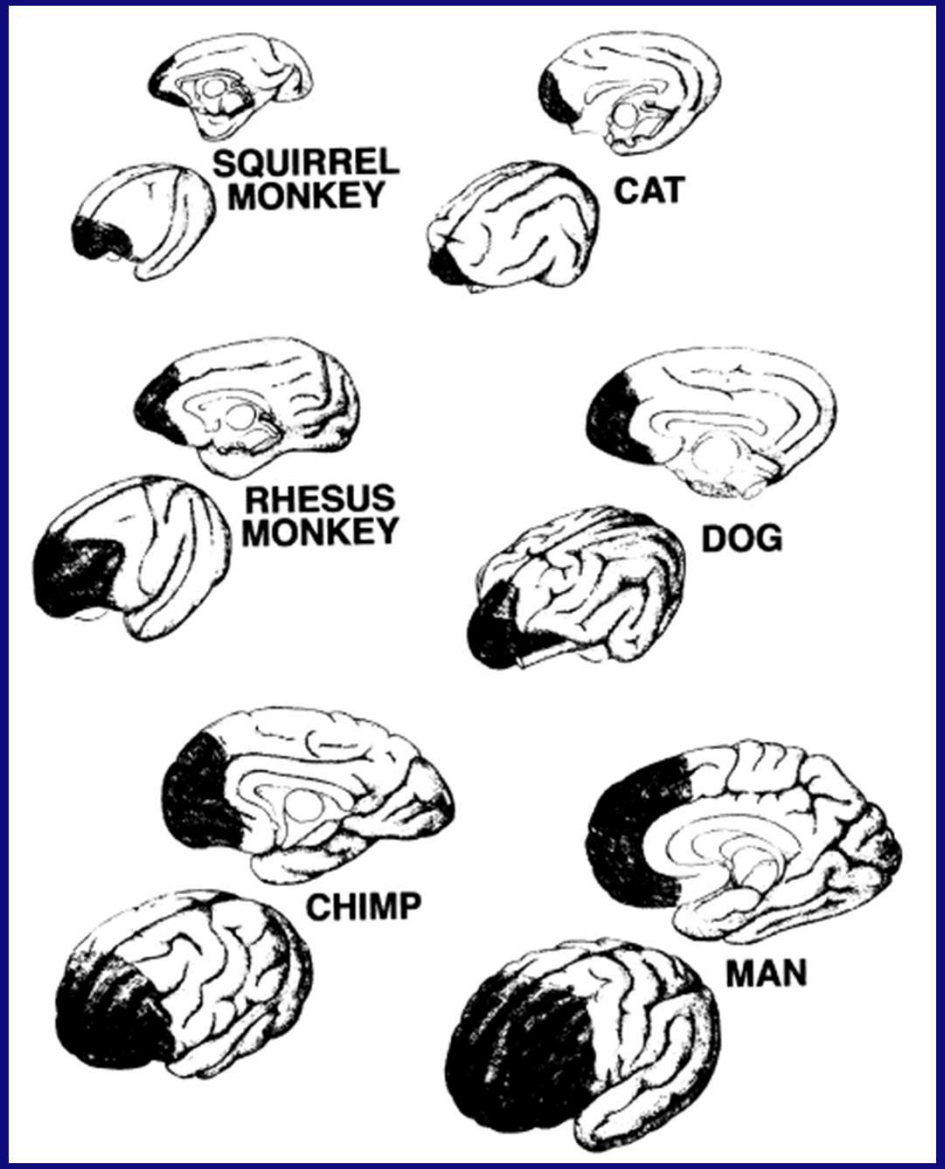


10 Obese Subjects
(BMI: 51±5 kg/m2)



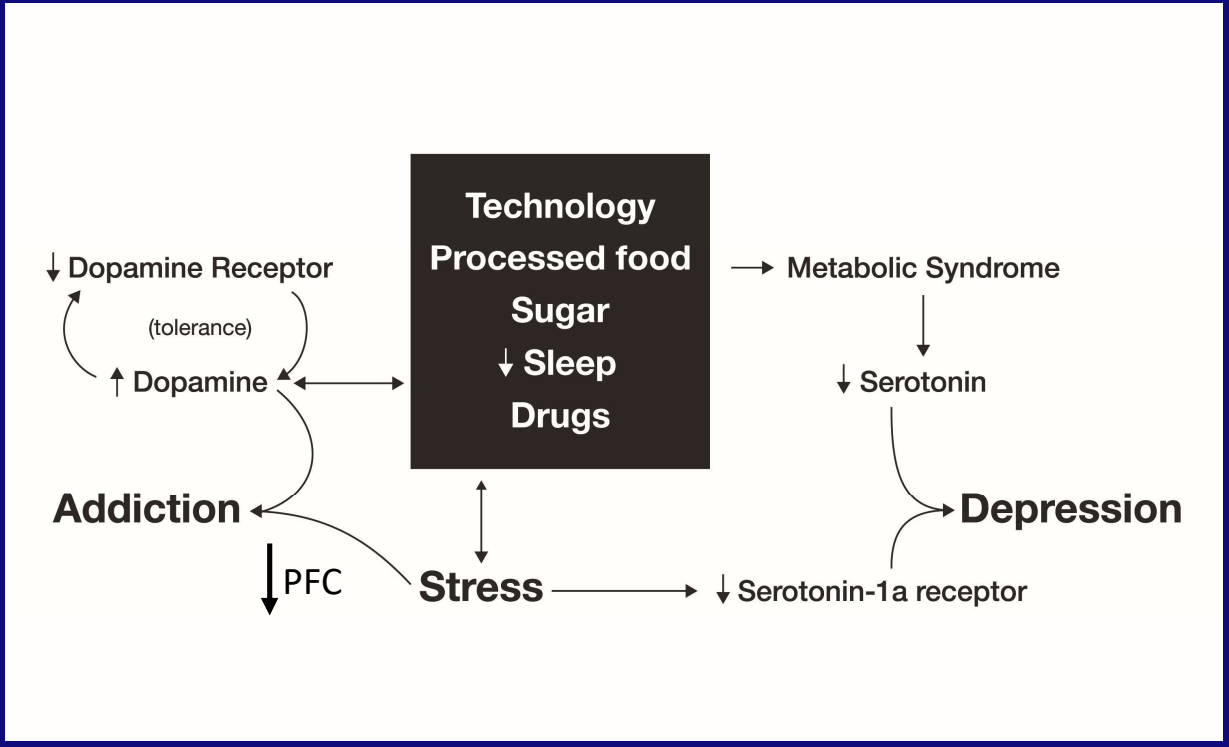

Wang et al, Lancet 2001

# The prefrontal cortex (PFC)
# The "executive function center"
# The "Jiminy Cricket" of your brain



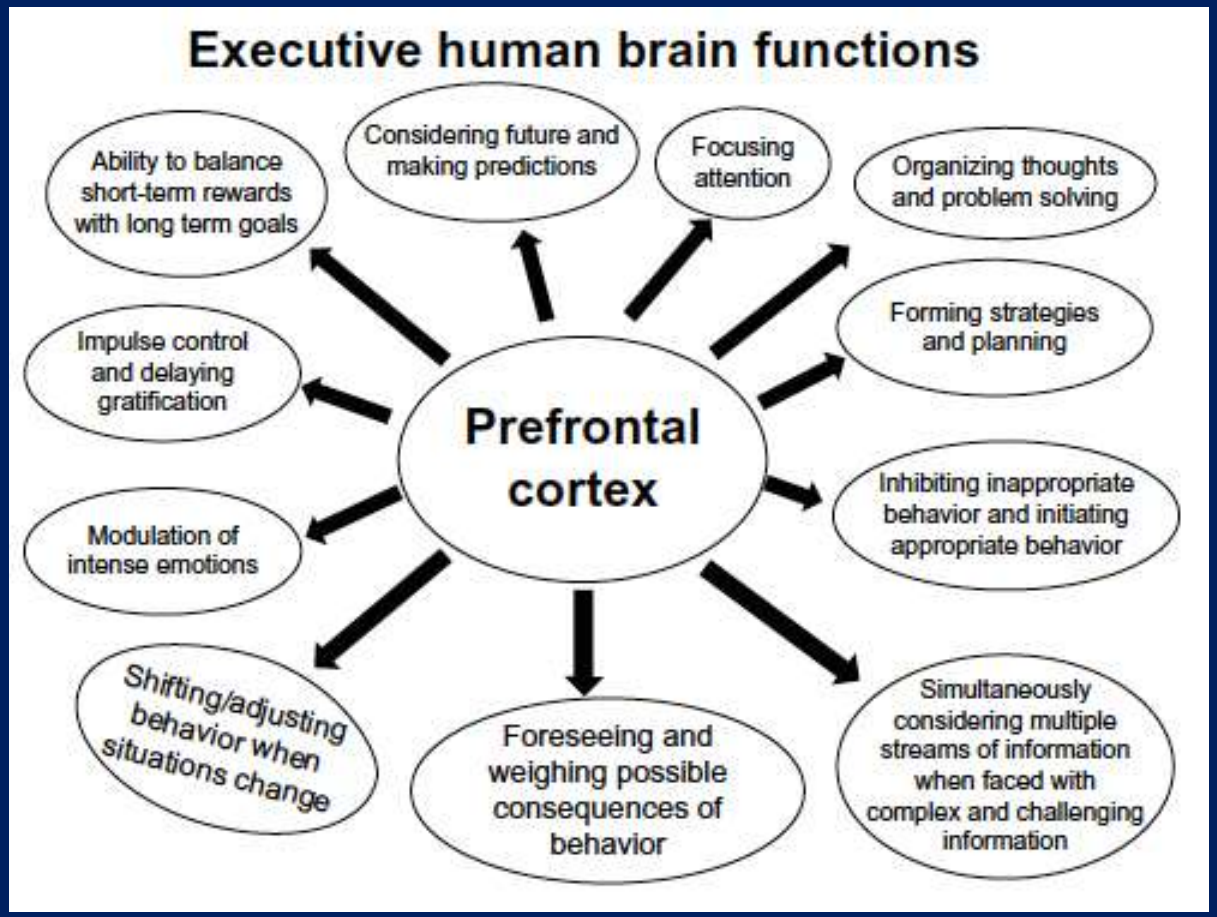

Fuster, J Neurocytol 31:373, 2002

# The dopamine-cortisol-serotonin interaction



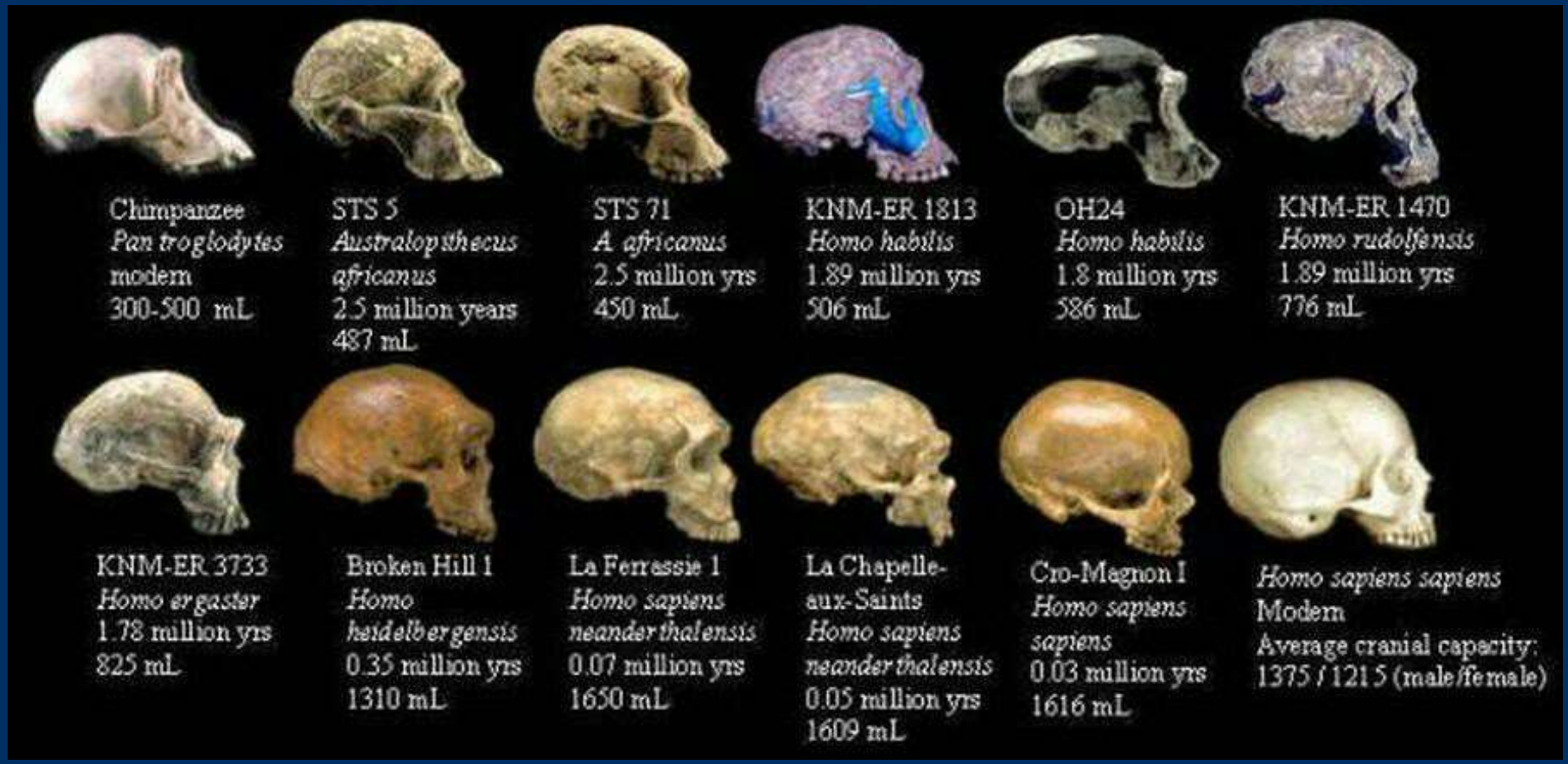

Lustig, Avery Press, 2017

# Functions of the adult PFC

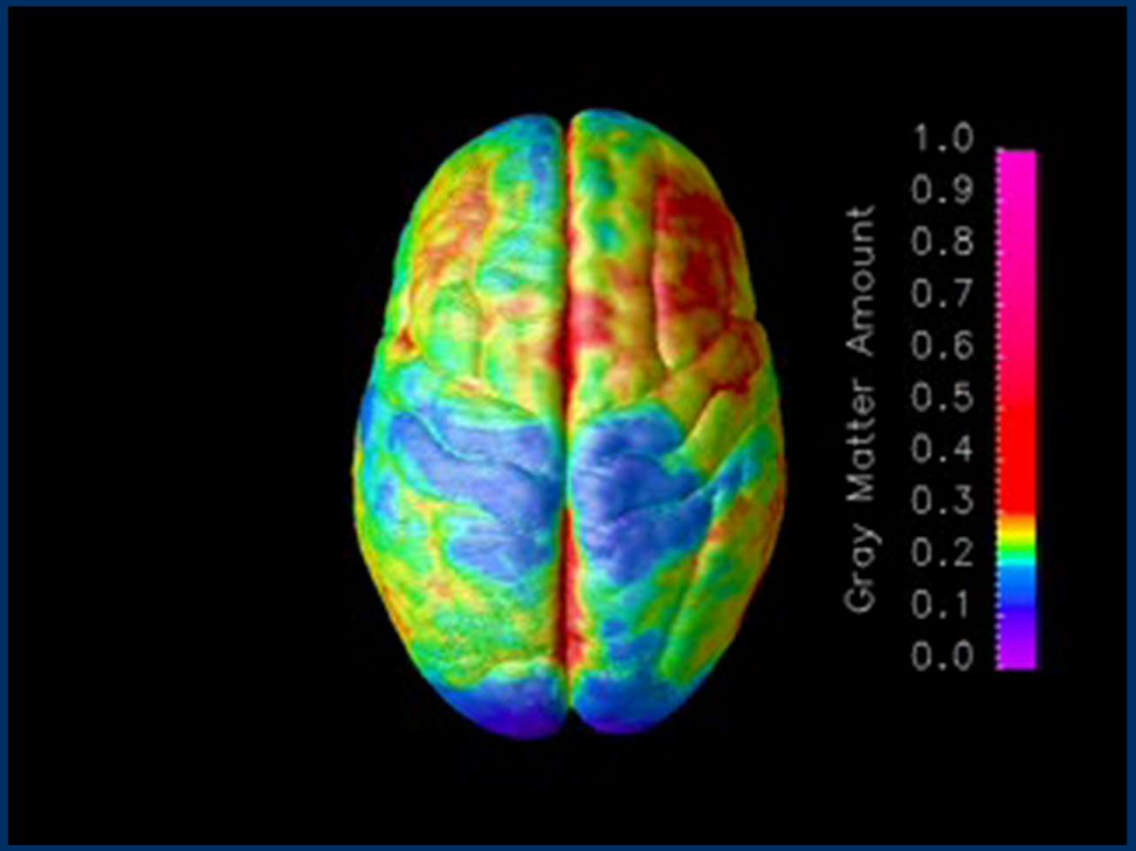



Arain et al. Neuropsych Dis Treat 9:449, 2013

# Evolution of the skull in hominids

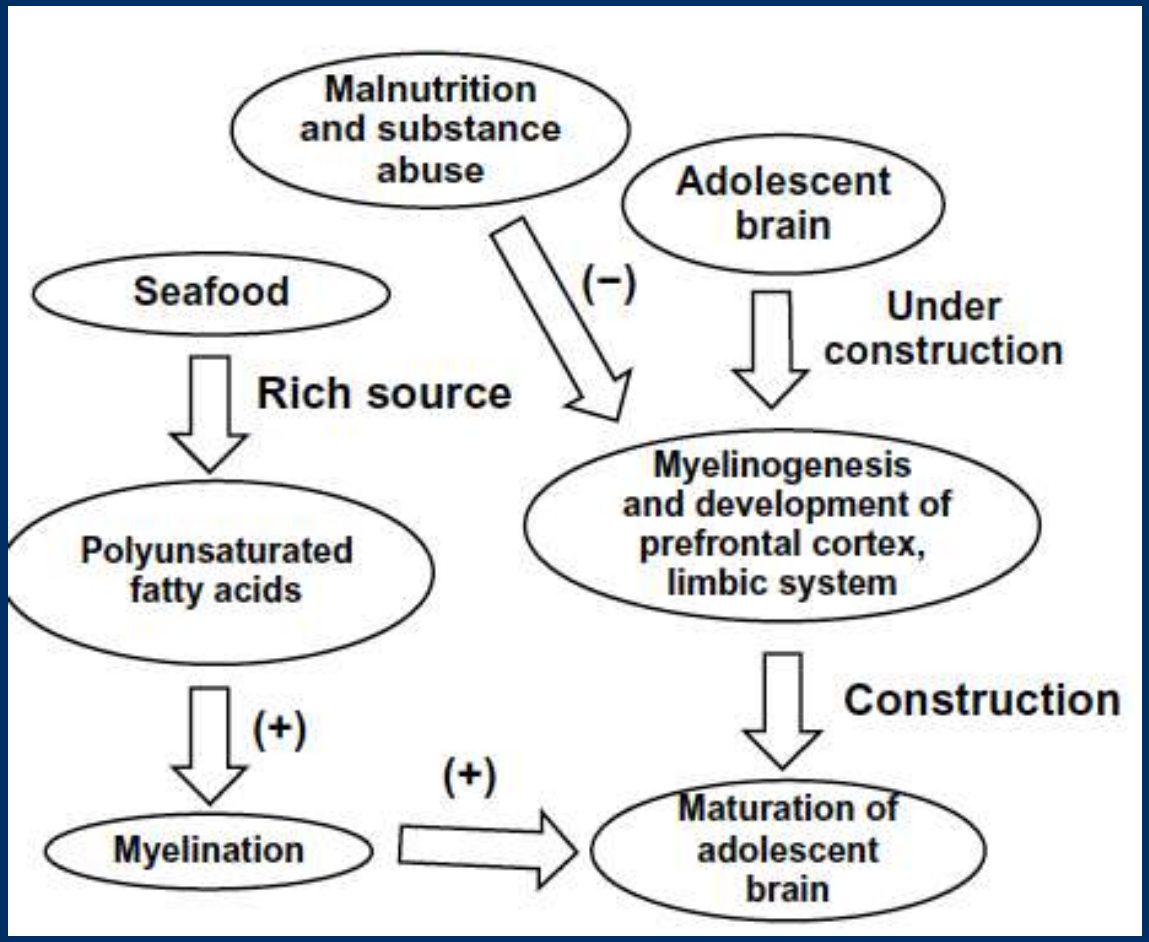


## Ontogeny recapitulates phylogeny:
## The PFC is the last area to develop, and the last to myelinate



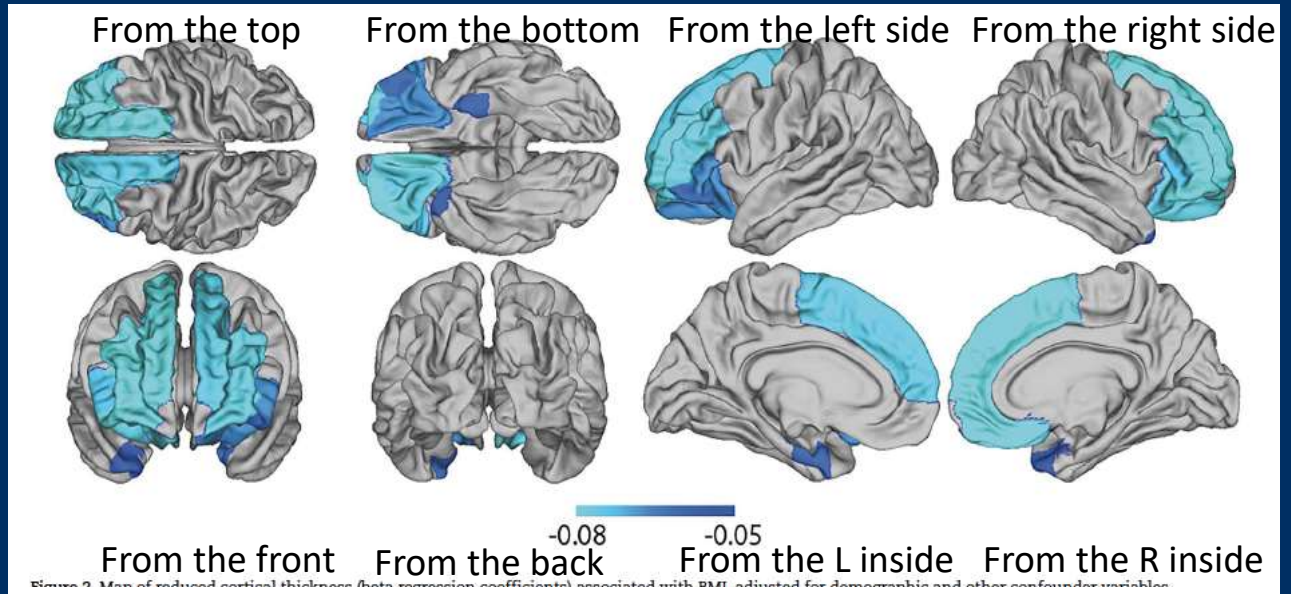

Gogtay et al, Proc Natl Acad Sci 101:8174, 2004

# Drug abuse inhibits organization and functioning of the PFC in adolescents




Arain et al. Neuropsych Dis Treat 9:449, 2013

Cortical thickness and BMI




Cortical thickness and executive function

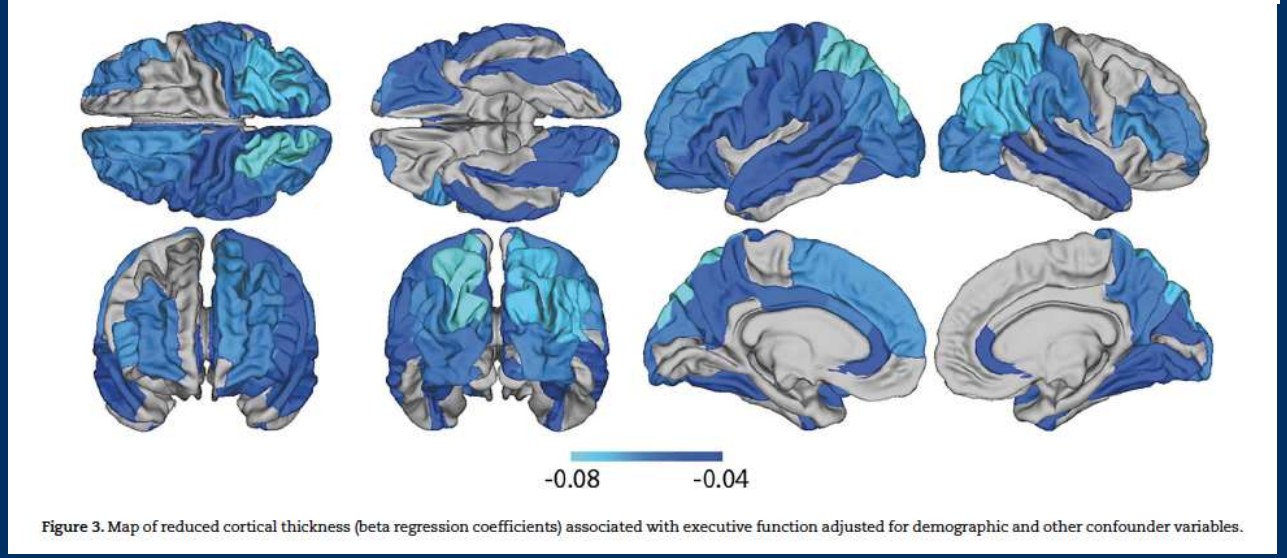



Figure 3. Map of reduced cortical thickness (beta regression coefficients) associated with executive function adjusted for demographic and other confounder variables.

Ronan et al. Cerebral Cortex, 30:2519, 2020

# Reduced hippocampus but more CSF in adolescents with metabolic syndrome

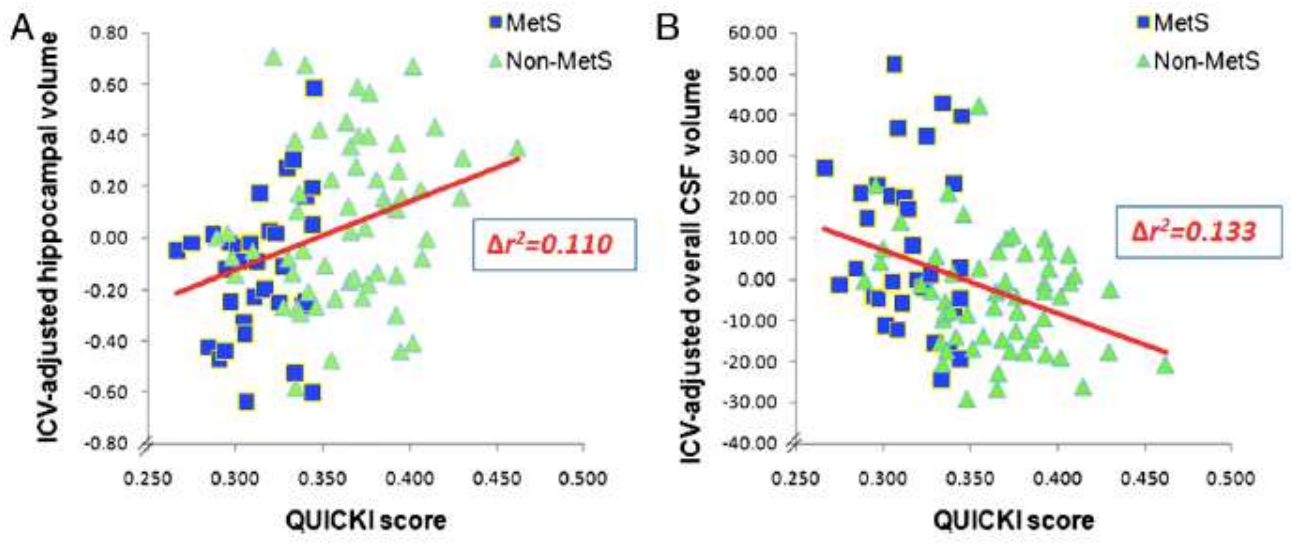



FIGURE 3
Lower QUICKI scores (more IR) were associated with smaller ICV-adjusted hippocampal volumes ($n = 91$) (A) and larger ICV-adjusted overall CSF volumes ($n = 92$) (B).

Yau et al. Pediatrics 130:e856, 2012

# Reduced prefrontal cortical function in adolescents with metabolic syndrome

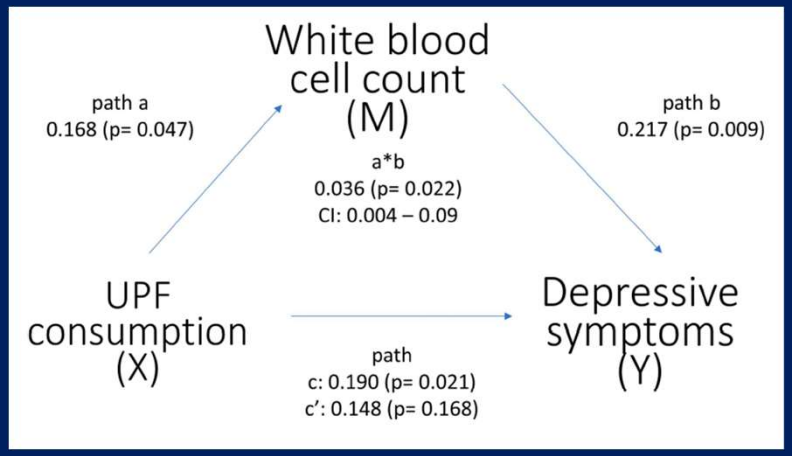
**Table 2.** Domain scores by MetS classification group.

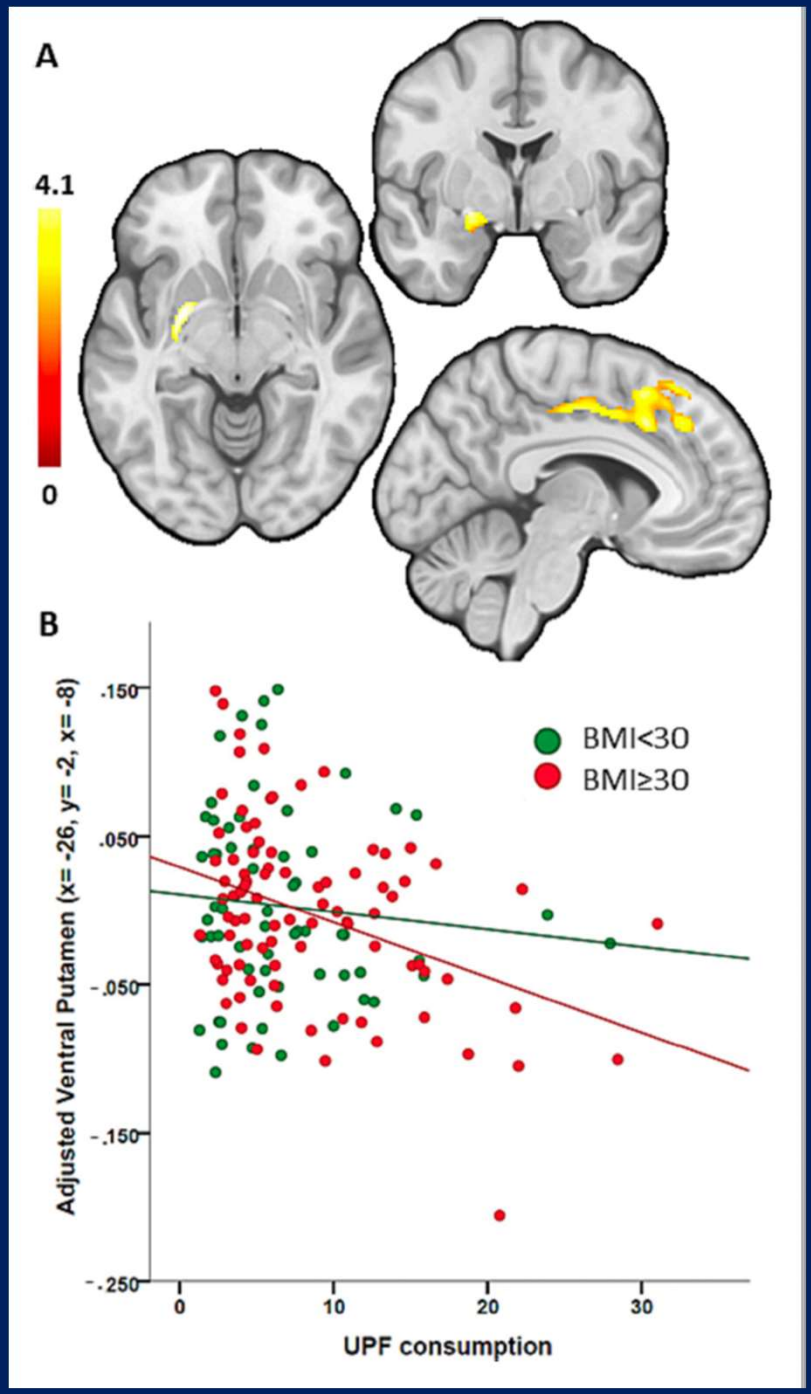
| | No MetS ($n = 204$) | MetS ($n = 84$) | $p$ | Effect Size ($r$) |
|---|---|---|---|---|
| Memory | 100.88 (13.86) | 97.94 (15.55) | 0.195 | 0.08 |
| Processing Speed | 100.57 (13.46) | 100.64 (13.14) | 0.774 | 0.03 |
| Executive Function | 101.47 (14.34) | 96.97 (15.43) | 0.020 | 0.15 |
| Reaction Time | 100.39 (13.69) | 101.03 (12.81) | 0.790 | 0.02 |
| Complex Attention | 103.93 (10.17) | 101.32 (11.25) | 0.109 | 0.11 |
| Cognitive Flexibility | 101.61 (14.20) | 96.53 (16.00) | 0.020 | 0.15 |
| Verbal Memory | 100.68 (14.07) | 98.18 (15.19) | 0.225 | 0.07 |
| Visual Memory | 100.18 (14.92) | 99.21 (14.41) | 0.674 | 0.03 |

Yau et al. Pediatrics 130:e856, 2012

# Consumption of ultra-processed foods is associated with depression, mesocorticolimbic volume, and inflammation

| Brain regions | x | y | z | *t* | CS | *p*-Value |
|---|---|---|---|---|---|---|
| All participants | | | | | | |
| Ventral posterior cingulate | −2 | −53 | 23 | 3.63 | 121 | <0.001 |
| Middle cingulate gyrus | −9 | 6 | 42 | 3.35 | – | *0.056* |
| L amygdala | −20 | −2 | −14 | 2.95 | – | 0.030 |
| Participants with obesity | | | | | | |
| L ventral putamen[a] | −26 | −2 | −8 | 4.07 | 143 | <0.001 |
| L amygdala[b] | −20 | −2 | −14 | 2.84 | – | 0.039 |
| Dorsomedial frontal cortex[b] | −6 | 18 | 53 | 3.37 | – | 0.044 |



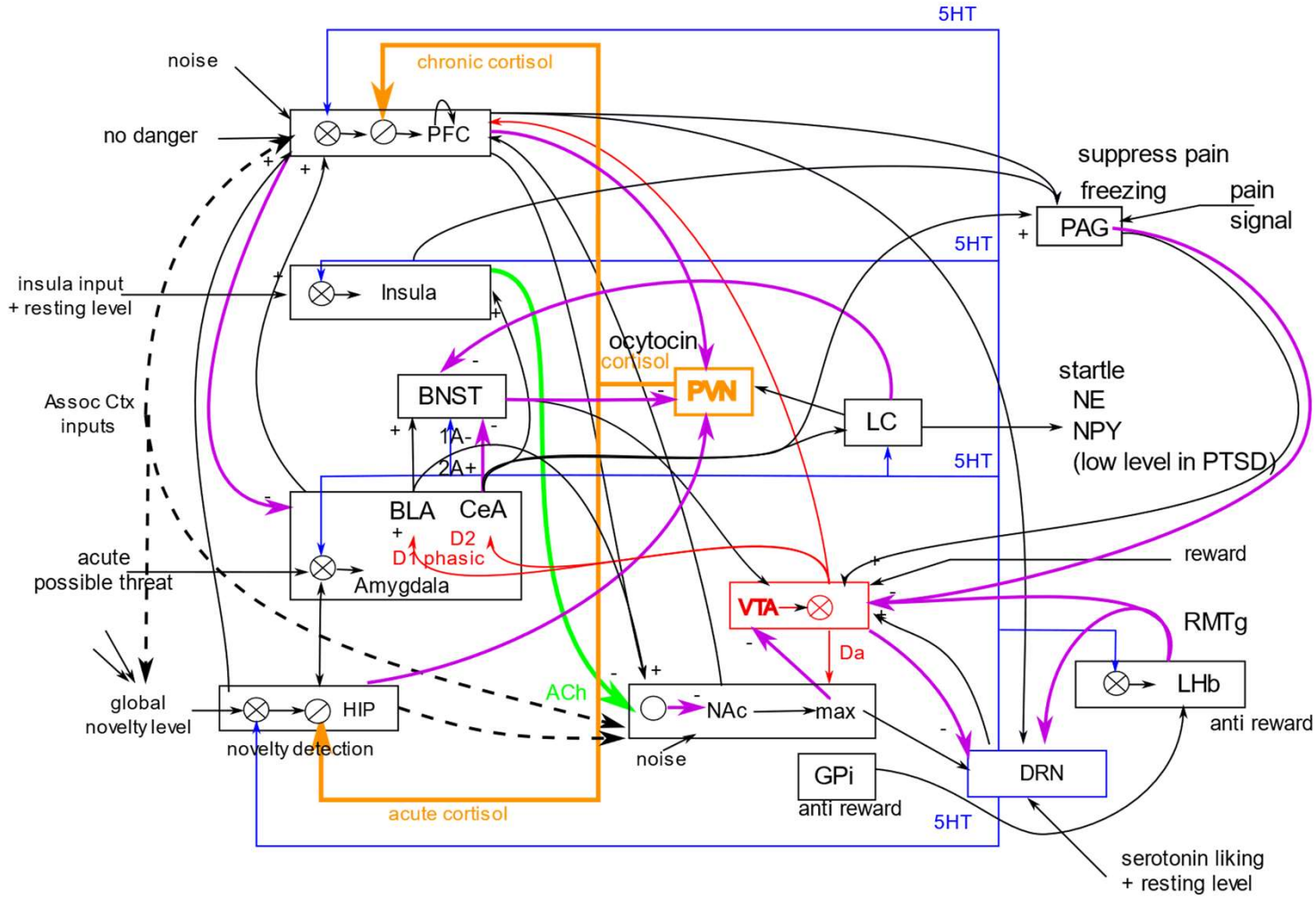

Contreras-Rodriguez et al. J Affective Dis 335:340, 2023

# Mental Health Problems Increasing in Prevalence and Severity

## All inhibited by the Prefrontal Cortex:

- Nucleus Accumbens — Addiction
- Dorsal Raphe Nucleus — Depression
- Amygdala — Anxiety / Pain
- Associative Cortex — Inattention
- Insula — Hate

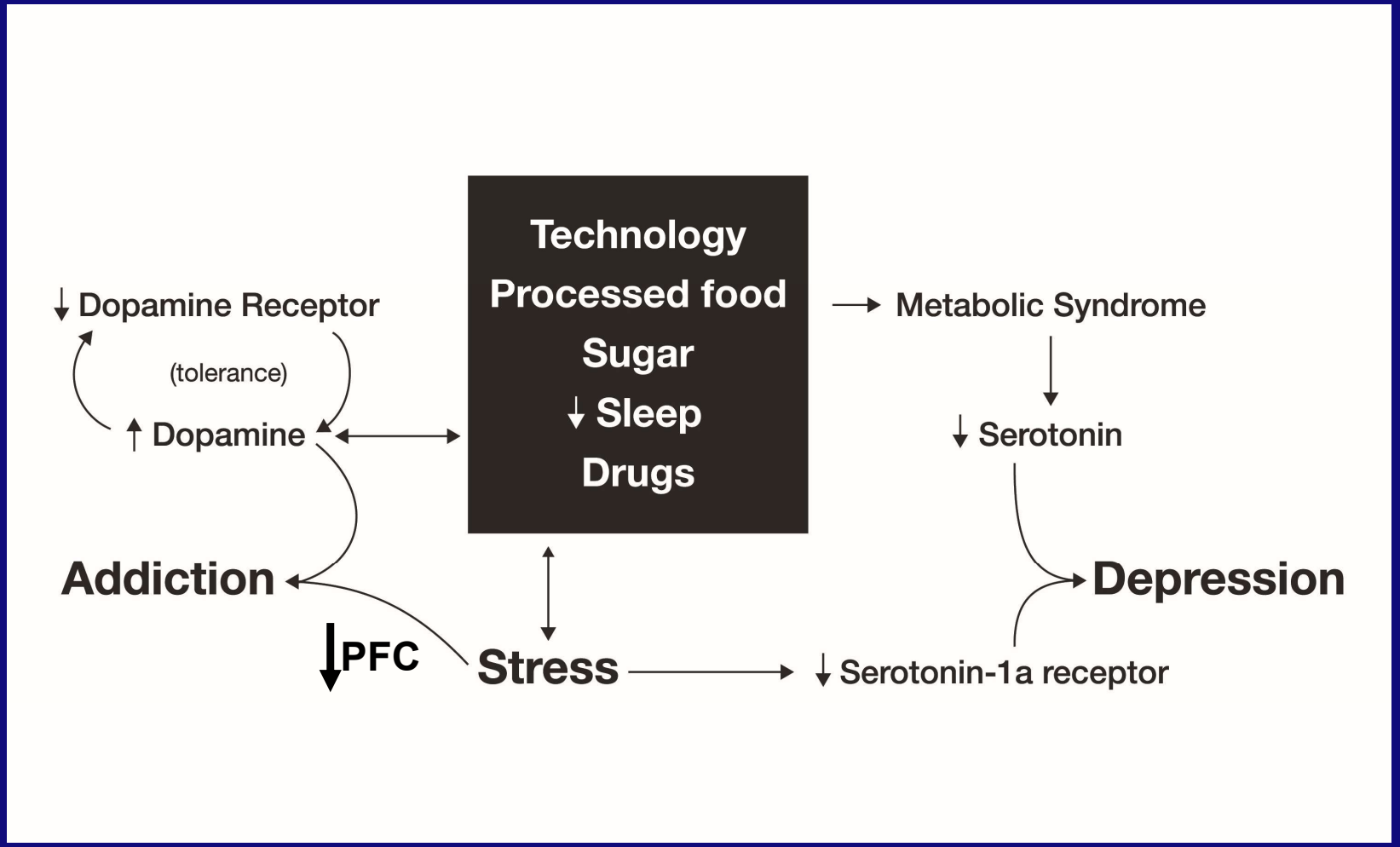
# Computational Model of the Limbic System




Gaussier/Lustig

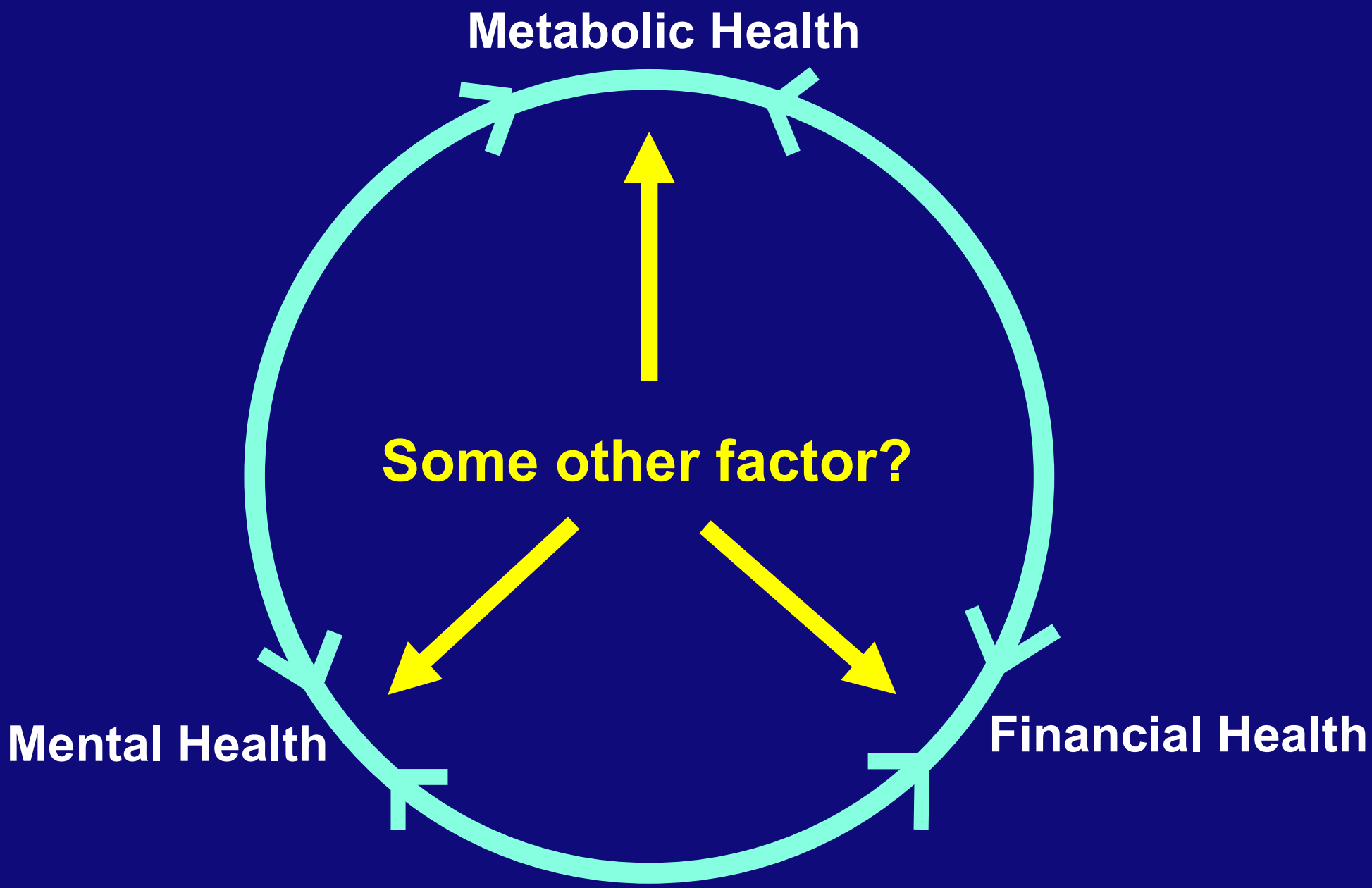
lateral habenula (LHb) periaqueducal grey (PAG) rostromedial mesopontinetegmental nucleus (RMTg)

# The dopamine-cortisol-serotonin interaction

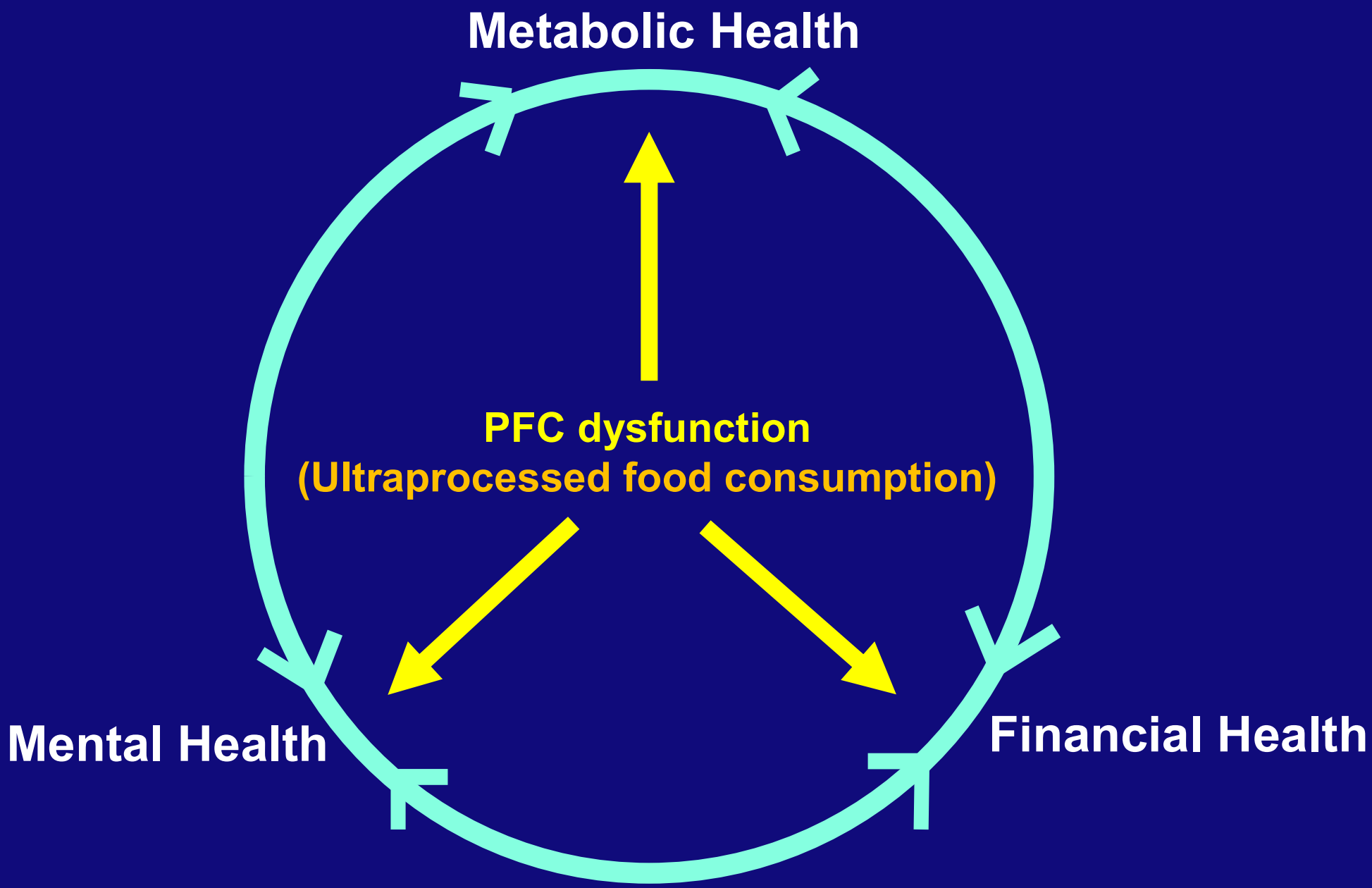



Lustig, Avery Press, 2017

# What's the causality?



# What's the causality?



# What can we do personally?

**The Four C's: all evidence-based and clinically proven to:**

**up your serotonin;**
**tamp down your dopamine;**
**lower your cortisol —**

**or your money back!**

# Reclaiming Conversation

## The Power of Talk in a Digital Age

CONNECT

Sherry Turkle

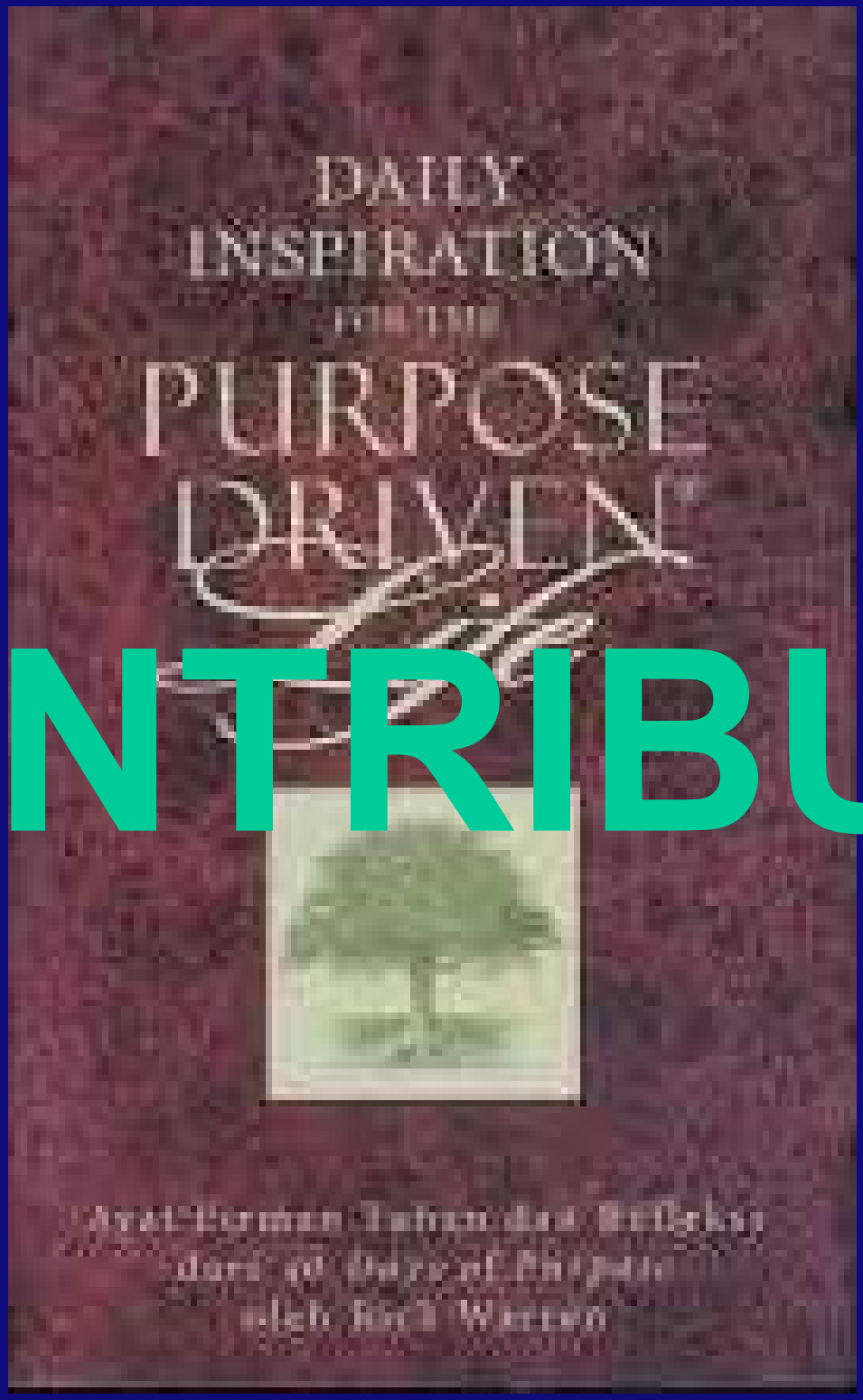
AUTHOR OF *ALONE TOGETHER*

# Connect (1)

- Religion's ability to increase happiness is not through belief, but through social interaction
- Interpersonal (face-to-face) connection activates "mirror neurons" responsible for empathy
- Empathy is required for serotonin generation

# Connect (2)

- Yet social media generates dopamine
- Studies show that Facebook use leads to social isolation and depression
- Sherry Turkle, MIT —Social media means we're "alone together"




CONTRIBUTE

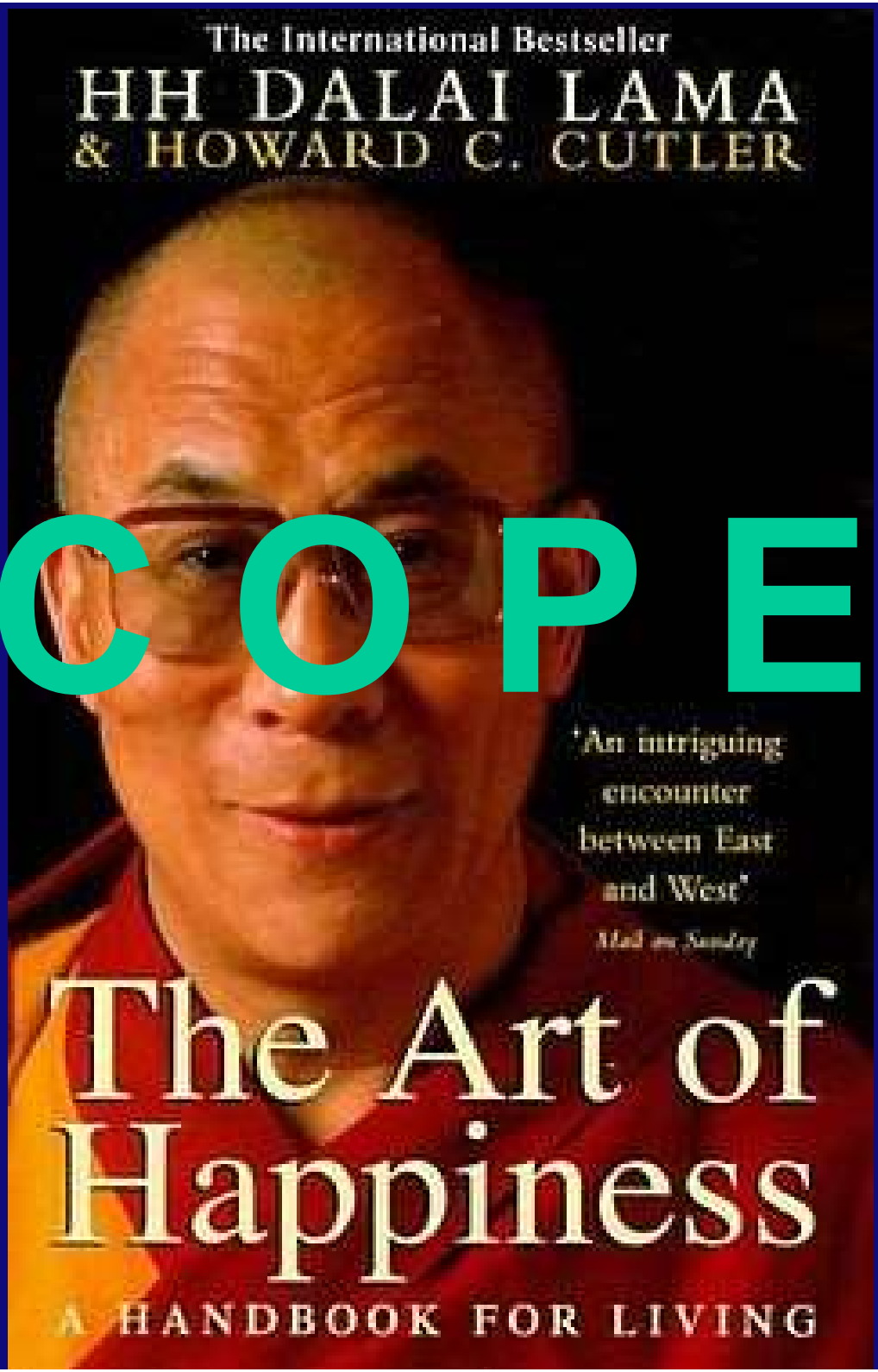
# Contribute (1)

- Padding your bank account is not contributing; lottery winners are not happy
- Those who value financial success derive less contentment; however, saving rather than spending increases happiness
- Spending money on yourself increases pleasure and makes you a consumer; spending money on others makes you an individual and increases happiness

# Contribute (2)

- Can you derive happiness from your work?
  Only if:
    — you can see your work helping others; and
    — your boss can see it too

- Altruism, volunteerism, philanthropy —
  anything that contributes to “the greater good” —
  all generate serotonin and emotional well-being


The International Bestseller
HH DALAI LAMA
& HOWARD C. CUTLER
'An intriguing encounter between East and West'
Mail on Sunday
The Art of Happiness
A HANDBOOK FOR LIVING

COPE

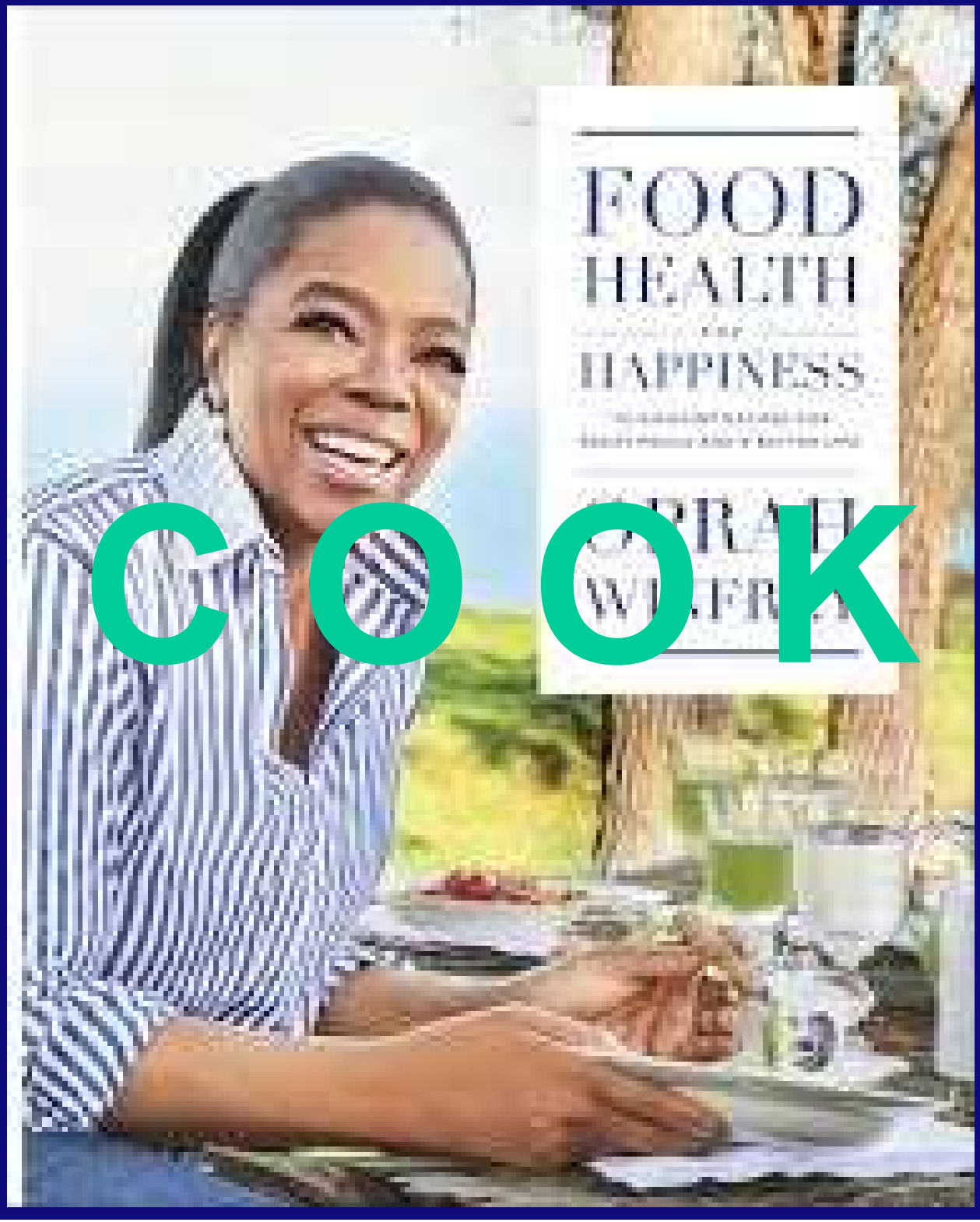
# Cope (1)

- Sleep deprivation increases amygdala (fear) and cortisol output, and inhibits prefrontal cortex function
  - 35% of adults get less than 7 hours of sleep
  - 23% suffer from clinical insomnia
  - Some of those have obstructive sleep apnea
  - Caffeine reduces sleep; increases your dopamine

- Multitasking is “smoke and mirrors” — only 2.5% of the population can do it; drives up cortisol in the rest

# Cope (2)

- Screens are the antithesis of sleep
  - Stress, blue light activating the midbrain
  - Kids who charge their cellphone in their room get 28 minutes less sleep per night
  - Smartphone apps for wellness do not yet show benefit
- Mindfulness activates the prefrontal cortex, and increases connectivity in “empathy” brain regions
  - Improves metabolic health, alleviates depression
- Exercise as good as SSRI’s in alleviating depression
  - additive with mindfulness


FOOD
HEALTH
HAPPINESS
COOK

# Cook (1)

- Reward-eating drive can be blocked by opiate antagonists

- Processed food is:
  - Low tryptophan (precursor to serotonin)
  - Low omega-3 fatty acids (anti-inflammatory, stabilize neuronal membranes, increases contentment)
  - High sugar (addiction, metabolic syndrome)
  - Low fiber (prevents metabolic syndrome)

- One-third of Americans do not know how to cook
  - Hostage to the processed food industry for life

# Cook (2)

- The REAL FOOD movement is in high gear
- Companies who don't change will be left in the dust (unless they buy up and kill the start-ups)
- Nestle, Unilever, Mars, and Danone have signed a public letter committing to change
- Cooking is *connecting; contributing; and coping*

# Saturday July 1, 2023, 9:10AM

# QEII Centre

## The True Purpose of Nutrition

## (spoiler alert: it's METABOLIC HEALTH)