



UW PACC

Psychiatry and Addictions Case Conference

UW Medicine | Psychiatry and Behavioral Sciences

Advances in Dementia Prevention

SUSIE WETSTONE, MD

UNIVERSITY OF WASHINGTON

GERIATRIC PSYCHIATRY FELLOW

JUNE 5, 2025





PREVENT DEMENTIA

ONLY YOU

SPEAKER DISCLOSURES

✓ No conflicts to disclose

PLANNER DISCLOSURES

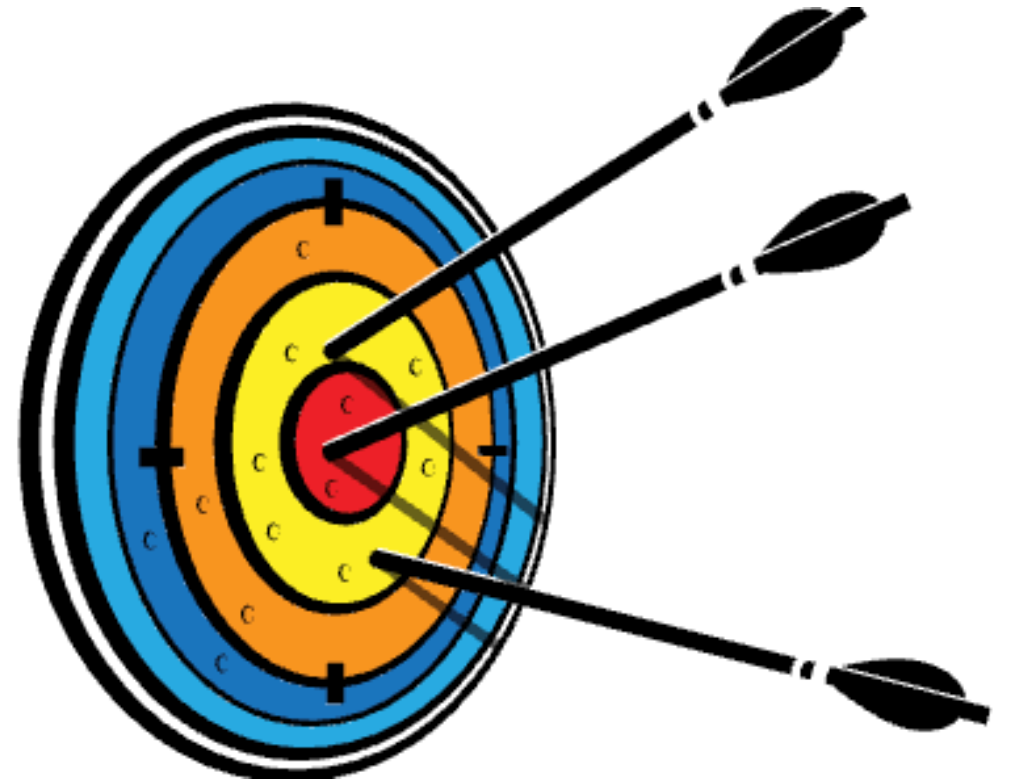
The following series planners have no relevant conflicts of interest to disclose; other disclosures have been mitigated.

Mark Duncan MD
Rick Ries MD
Kari Stephens PhD
Barb McCann PhD

Anna Ratzliff MD PhD
Betsy Payn MA PMP
Esther Solano
Cara Towle MSN RN

OBJECTIVES

1. Learn some dementia pathology
2. Learn some modifiable risk factors
3. Learn some risk reduction strategies
4. Leave hopeful!

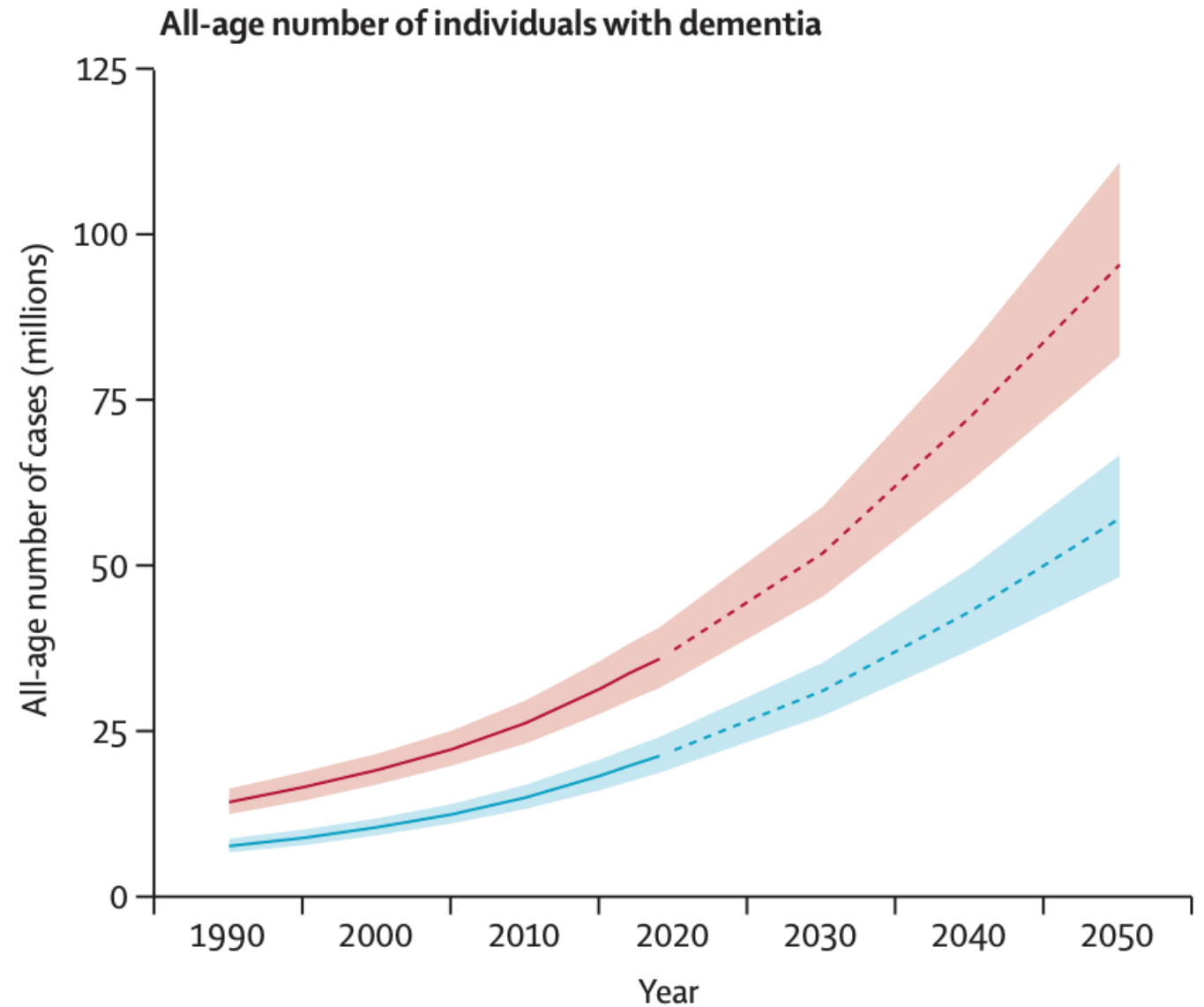


PART 1: WHAT WE KNOW



DEMENTIA FAQ

- 42% expected to get dementia
- Dementia incidence expected to triple by 2050

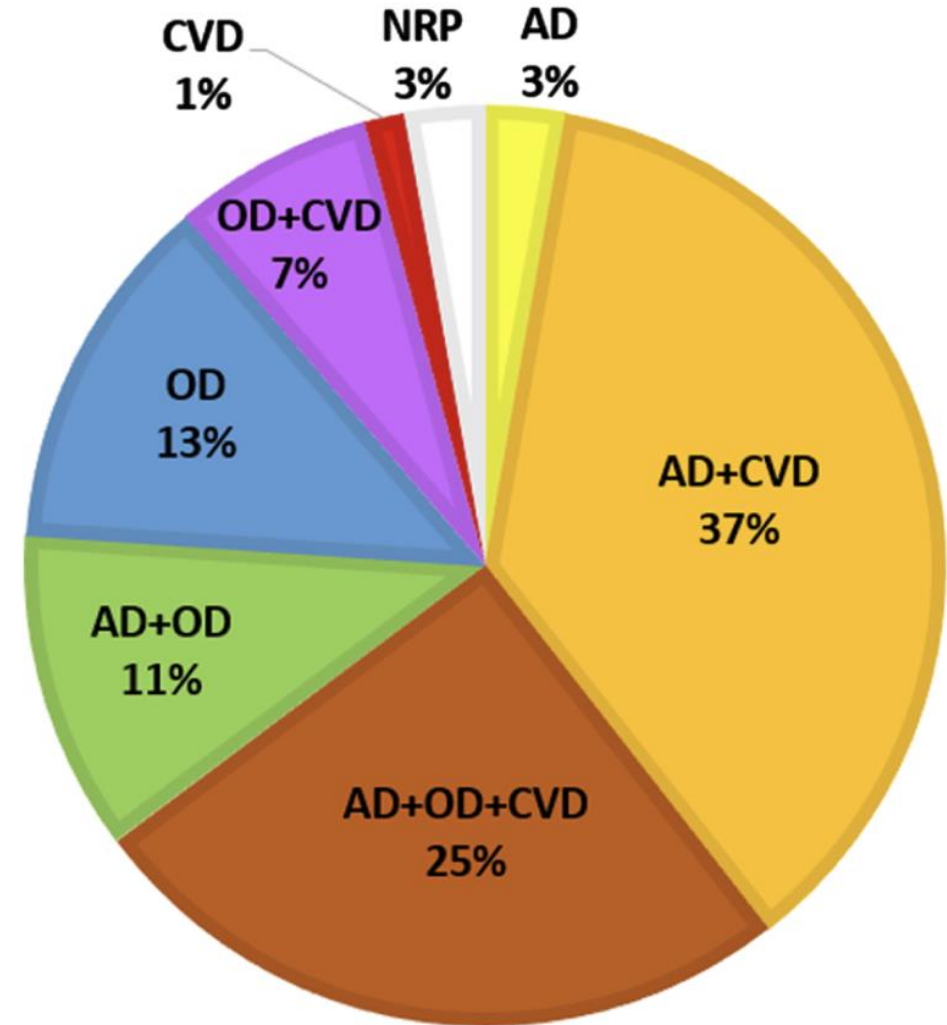


The Lancet, 2022

WHAT IS DEMENTIA?

- • Measurable cognitive impairment + Functional impairment + progressive process
- • Progressive processes:
 - Cerebrovascular disease (CVD)
 - PROTEINOPATHIES: Alzheimer's disease (AD), Dementia with Lewy bodies, PDD, FTD, ALS, CTE, LATE, etc...
- • Most common pathologies:
 - 1st: Mixed 80%
 - 73% have AD pathology
 - 69% have CVD
 - 45% have a non-AD pathology

BREAKDOWN OF PATHOLOGICAL DIAGNOSES

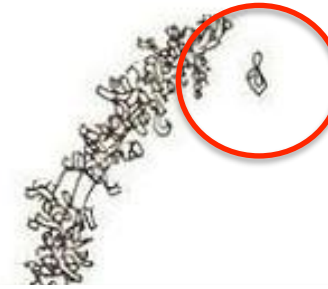


Li, 2023

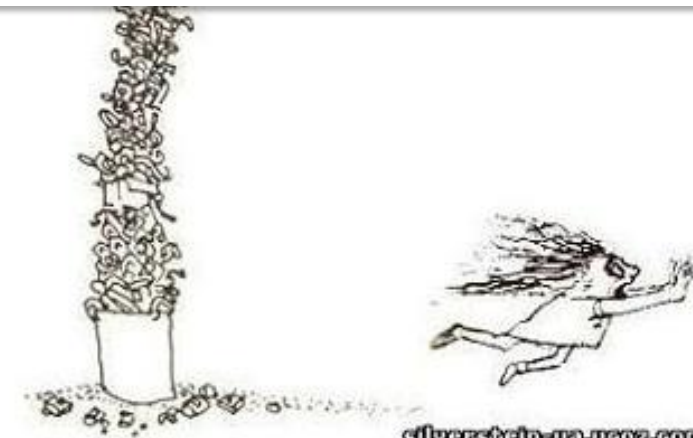
PROTEINOPATHIES

• Protein pathology

Shel Silverstein, 1974



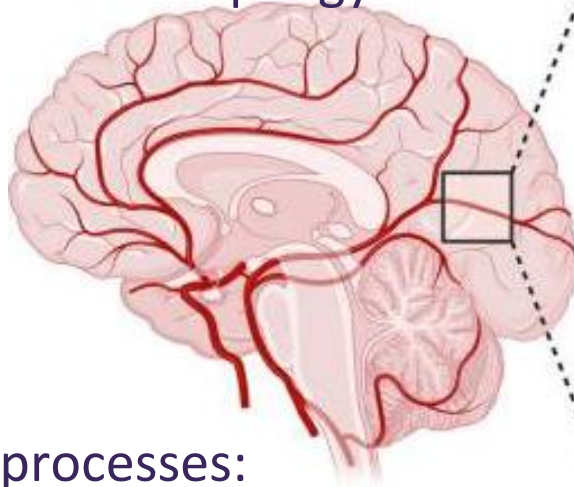
TOO LATE



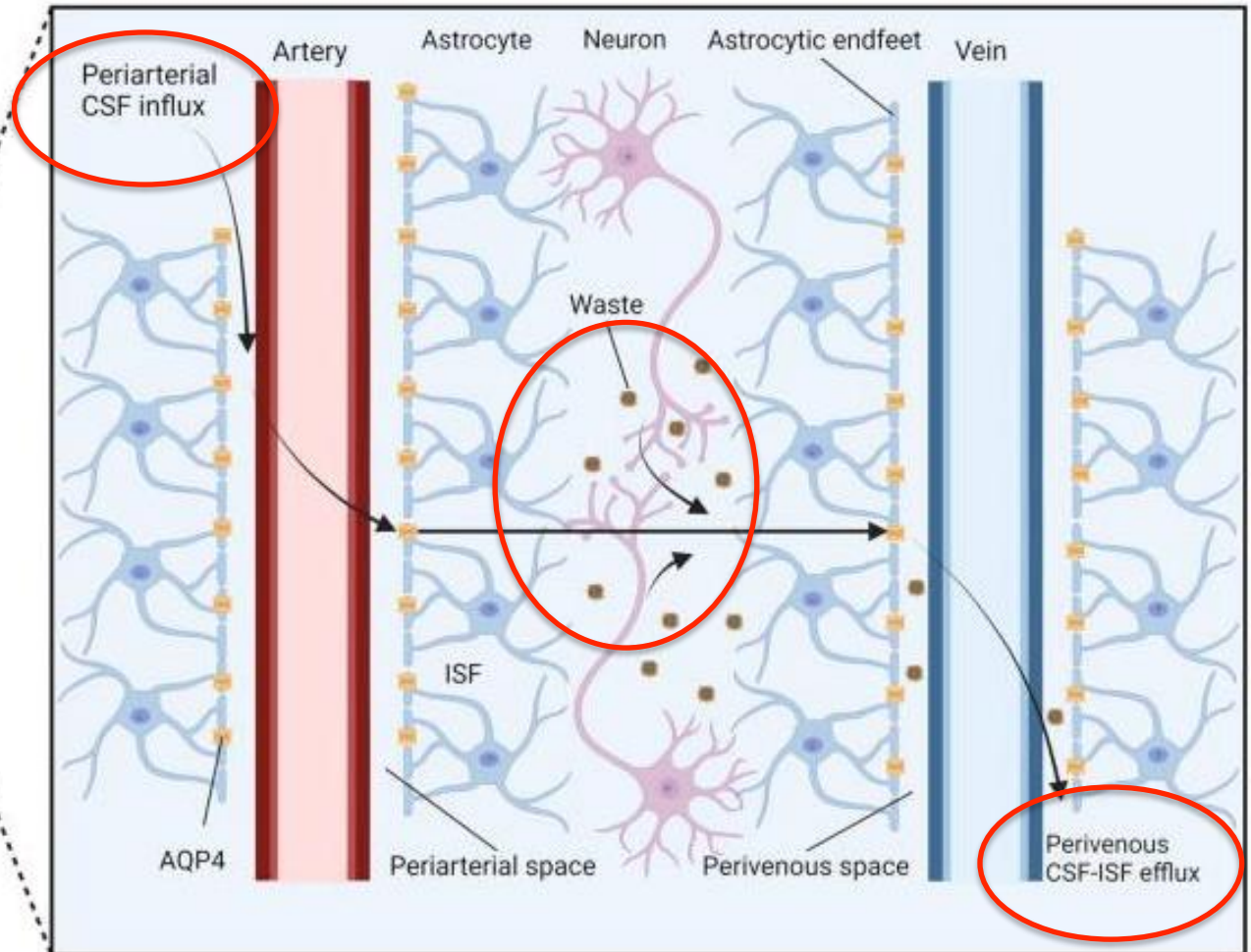
HEALTHY BRAINS WASTE MANAGEMENT SYSTEM

DEEP SLEEP

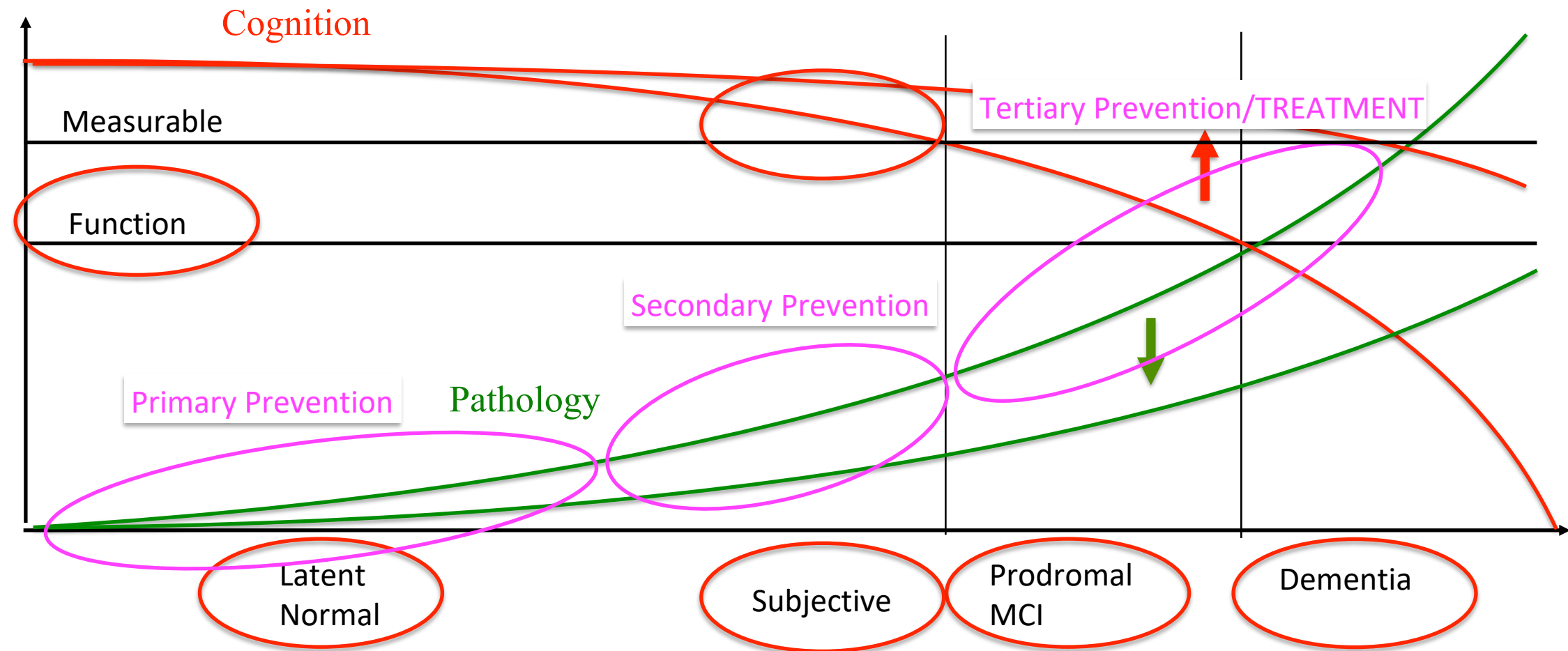
- • Healthy brains have processes to cope:
- • Intracellular processes: proteasomes and autophagy



- • Extracellular processes:
- • Glymphatic system
- • **NEUROINFLAMMATION**



HYPOTHETICAL NEURODEGENERATION TIME LINE



WHY FOCUS ON PREVENTION

- We don't have good treatments
- Keeping the brain healthy can slow progression of protein pathology



Shel Silverstein, 1974

PART 2: RISKY BUSINESS



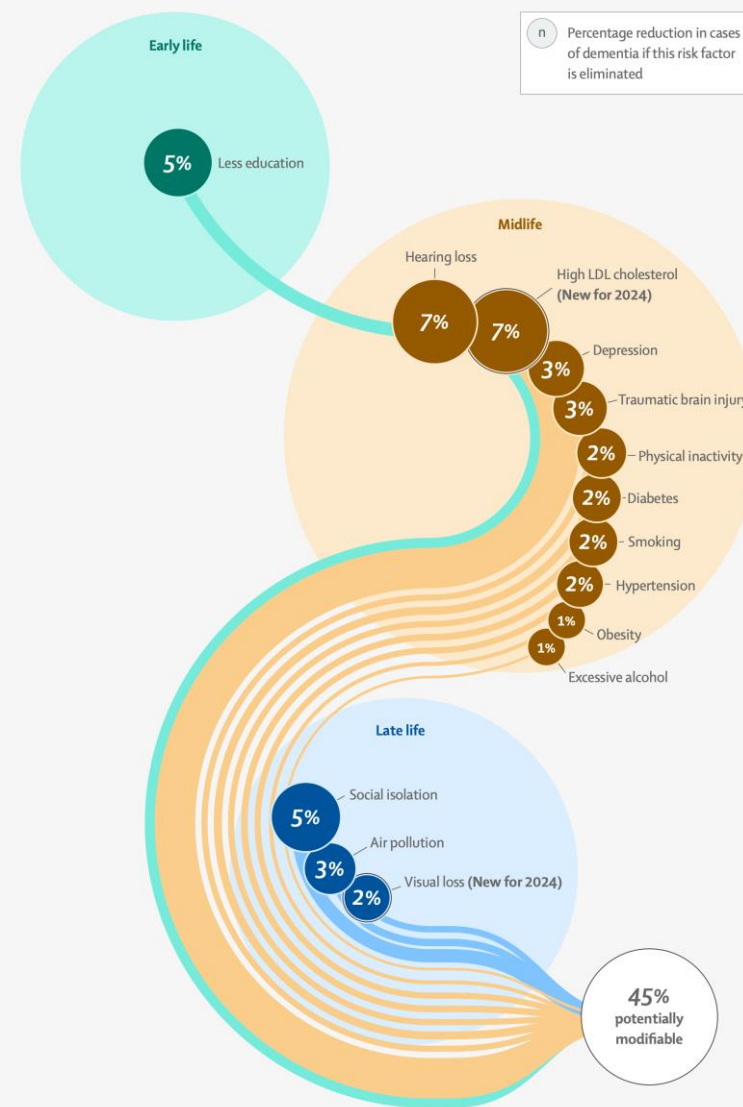
2024 LANCET COMMISSION:

45% OF CASES ARE PREVENTABLE

- 14 modifiable risk factors
 - Early life:
 - Less education 5%
 - Midlife: 18-65
 - Hearing loss 7%
 - High LDL 7%
 - Depression 3%
 - TBI 3%
 - Physical Inactivity 2%
 - Diabetes 2%
 - Smoking 2%
 - Hypertension 2%
 - Obesity 1%
 - Excessive alcohol 1%
 - Late life:
 - Social isolation 5%
 - Air pollution 3%
 - Visual loss 2%

Risk factors for dementia — 2024 update

The 2024 update to the standing Lancet Commission on dementia prevention, intervention, and care adds two new risk factors (high LDL cholesterol and vision loss) and indicates that nearly half of all dementia cases worldwide could be prevented or delayed by addressing 14 modifiable risk factors.



Read the full commission update at [thelancet.com/commissions/dementia-prevention-intervention-care](https://www.thelancet.com/commissions/dementia-prevention-intervention-care)

Livingston G, Huntley J, Liu KY, et al. Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission. *The Lancet* 2024; published online July 31. [https://doi.org/10.1016/S0140-6736\(24\)01296-0](https://doi.org/10.1016/S0140-6736(24)01296-0).

24 Lancet commission: How can we prevent dementia?

Professor Gill Livingston

Professor of Psychiatry of Older People, UCL

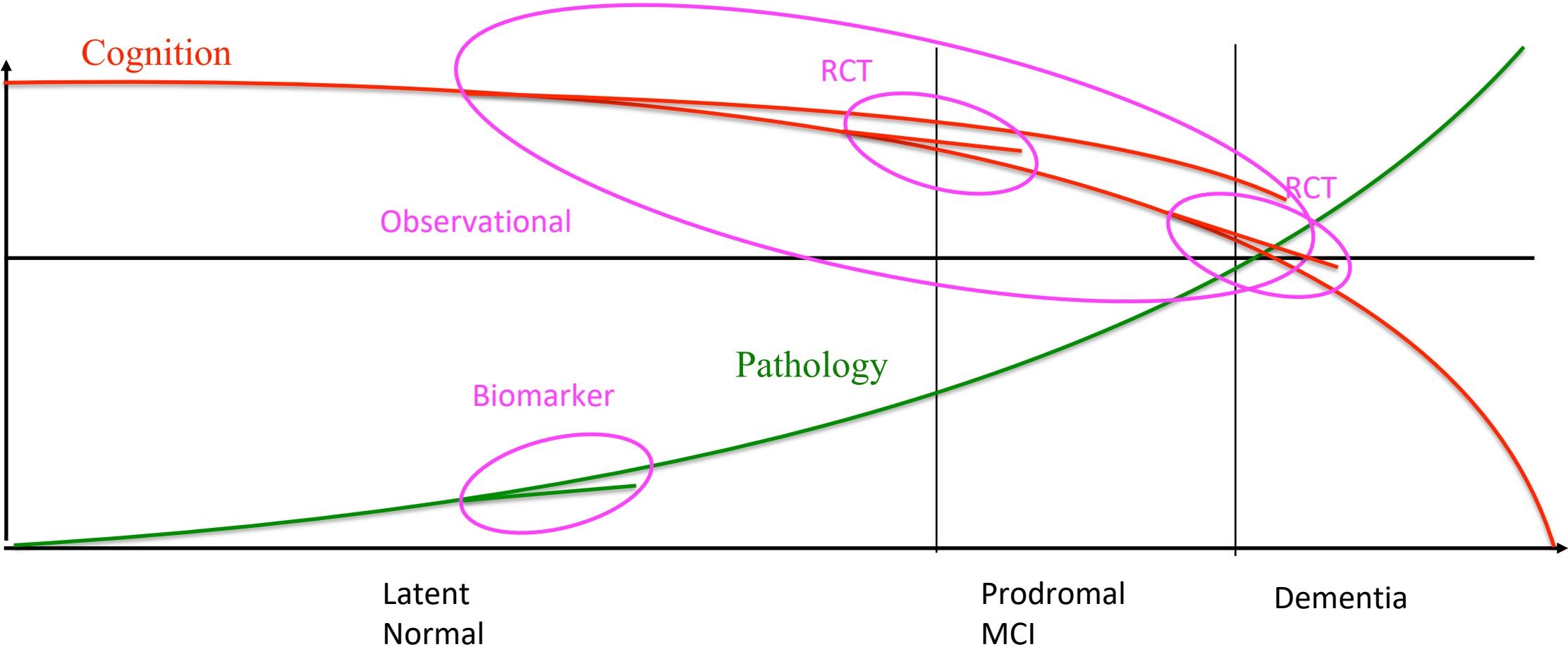
reach^v
BY NIGHTINGALE HAMMERSON



COGNITIVE BREAK

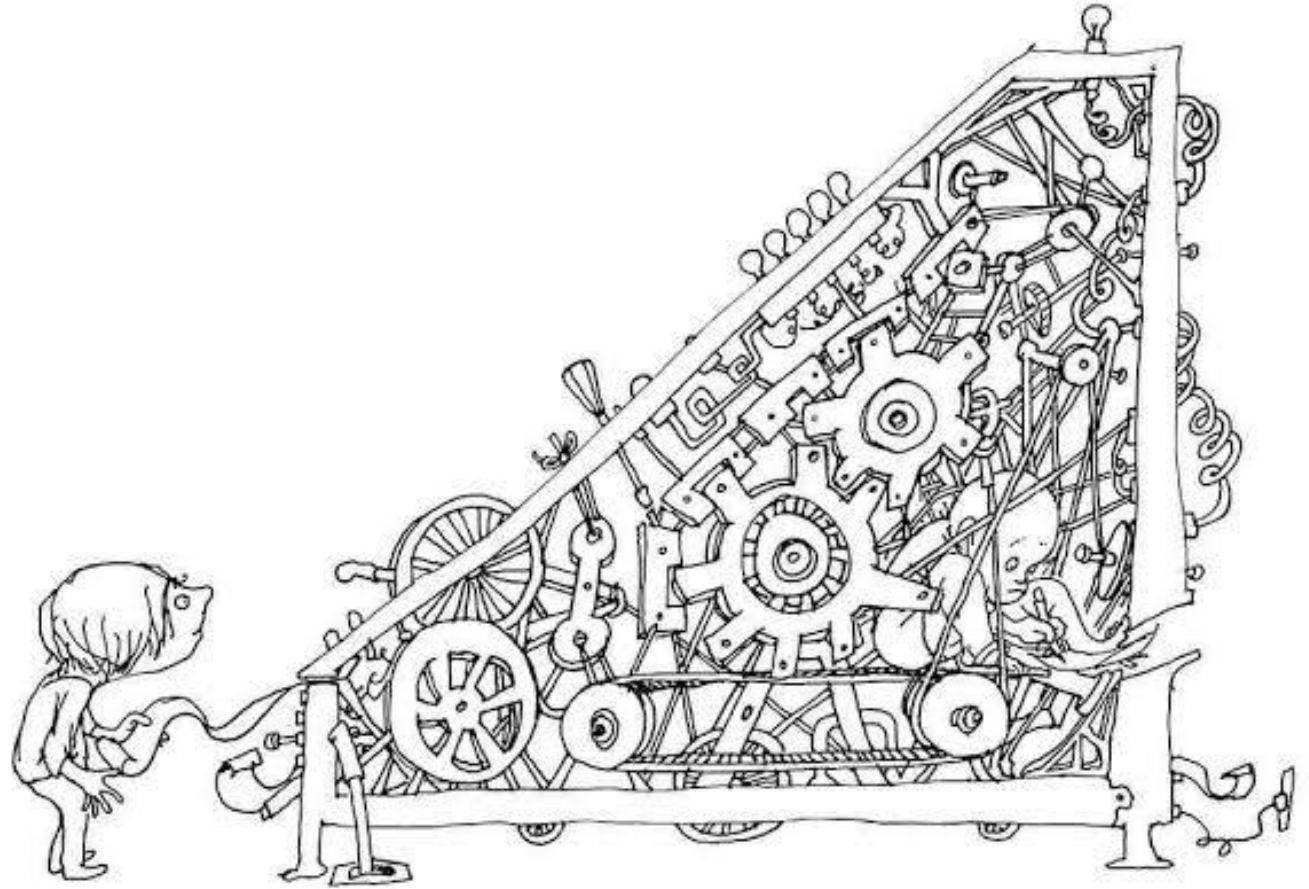


THE TROUBLE WITH STUDIES: OBSERVATIONAL, RCTS, AND BIOMARKERS



OTHER MODIFIABLE RISK FACTORS WITH STRONG SCIENTIFIC SUPPORT

- Menopause
- Chronic systemic inflammation
- OSA
- Elevated homocysteine

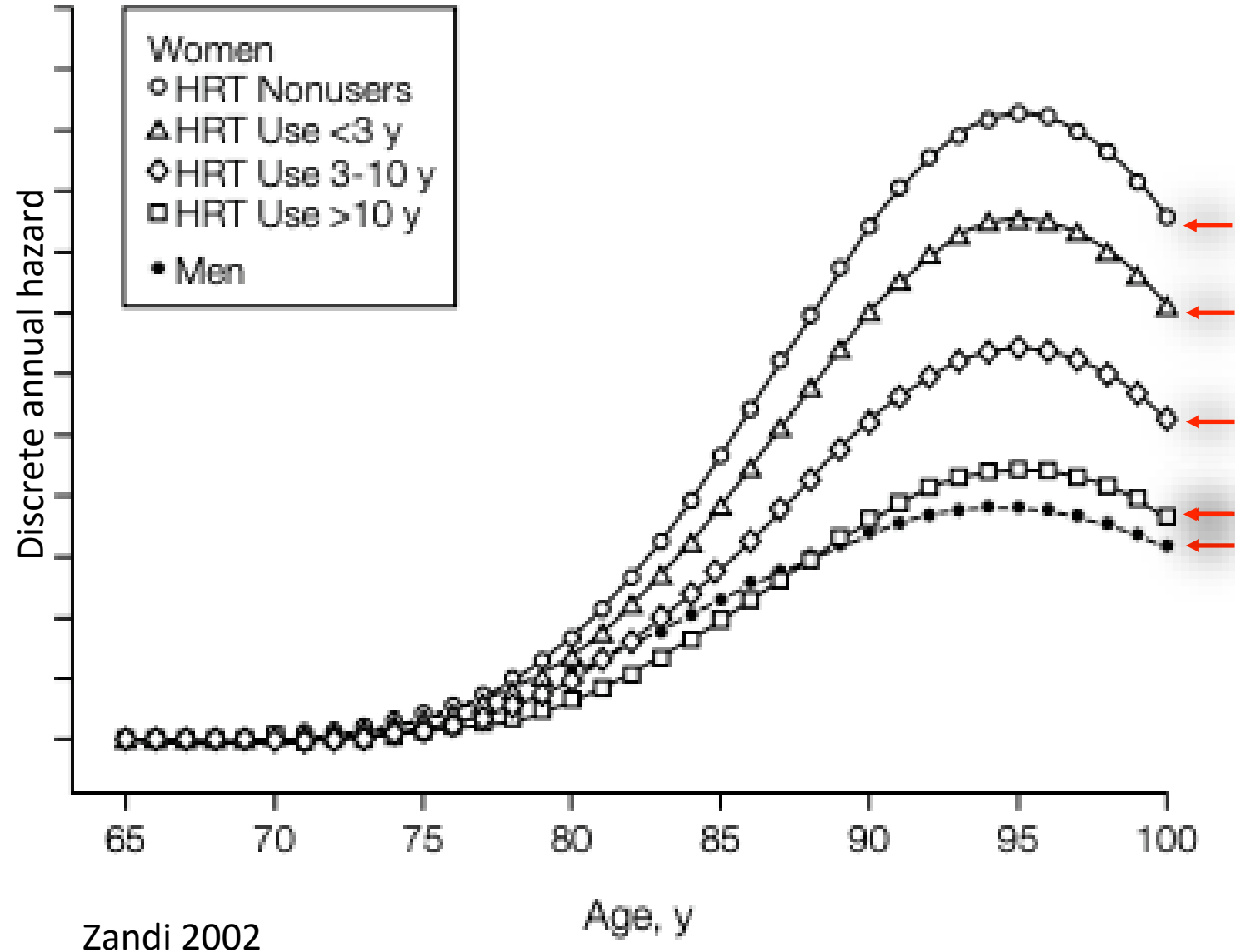


Shel Silverstein, 1981

MENOPAUSE

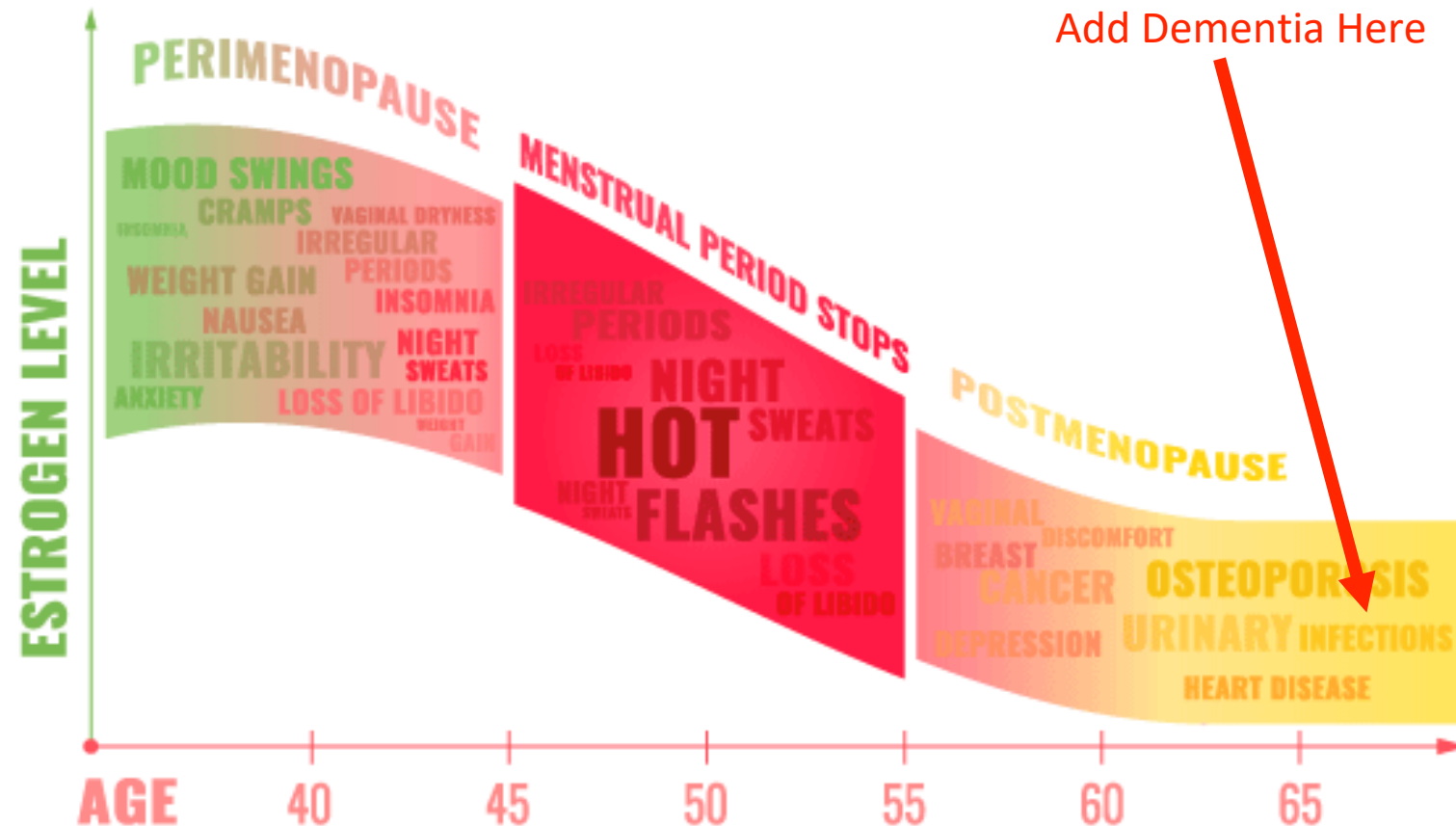
MENOPAUSE/REDUCED ESTROGEN: EVIDENCE

- Sex differences
- The Lancet 2024: MHT increases risk
- Zandi et al 2002: image
- Kim et al 2021: > 50% reduced risk
- Yoo et al 2020: 20% reduced risk with long term hormones
- Nerattini et al 2023: 26% reduced risk if hormones taken > 10y
- Depypere et al 2023: reduced biomarker change



MENOPAUSE/REDUCED ESTROGEN: MECHANISM/TREATMENT

- Proposed mechanism of estrogen:
 - Helps clear protein aggregation
 - Increases brain reserve
 - Anti-inflammatory
- Treatment:
 - MHT
 - Safety
 - Breast cancer
 - Vascular disease
- Would I recommend to my mom?
 - ABSOLUTELY, if she was perimenopausal and symptomatic
 - Soft yes, if she was not symptomatic.
 - MHT for dementia risk reduction?



COGNITIVE BREAK



CHRONIC SYSTEMIC INFLAMMATION

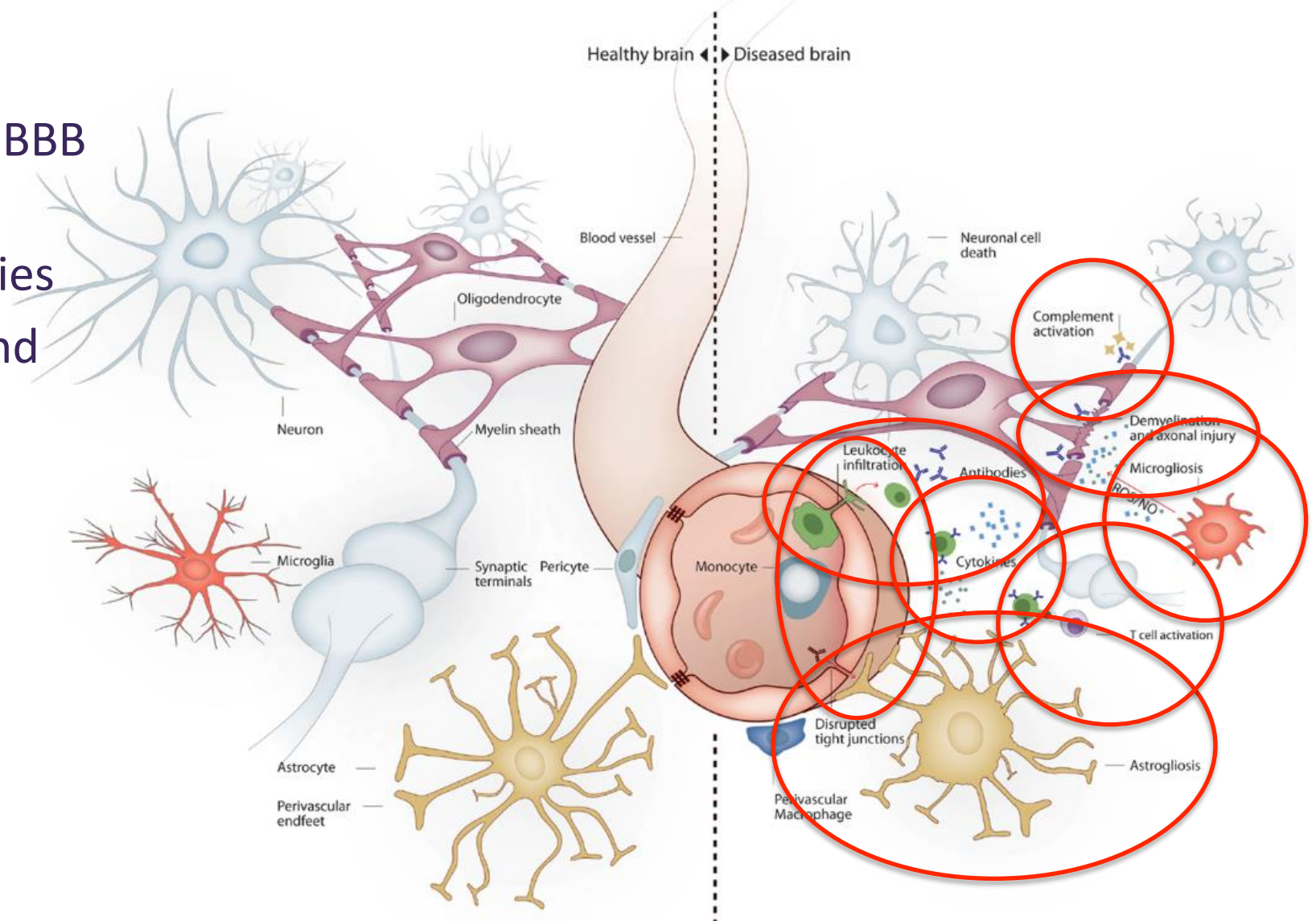
CHRONIC SYSTEMIC INFLAMMATION: EVIDEN

- • Cooper et al 2023:
 - IBD -> 1.9 x prevalence and RA -> 1.6 x prevalence
- • Chang et al 2016:
 - In RA, NSAID use over 6 years normalized risk
- • Mekli et al 2023:
 - inflammatory markers => 35% increased risk
- • Tejera et al 2024:
 - race, inflammation, and dementia

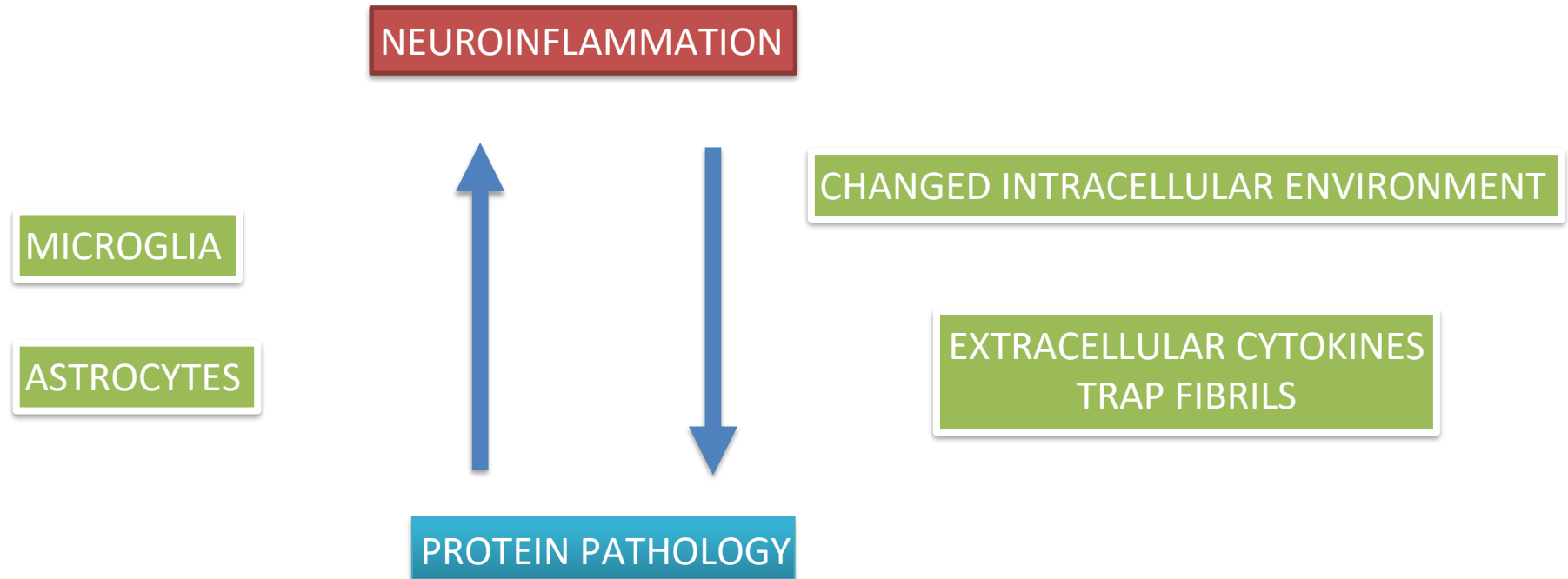


SYSTEMIC INFLAMMATION TRIGGERS NEUROINFLAMMATION

- Increased permeability of BBB
- infiltration of peripheral immune cells and antibodies
- Activation of astrocytes and microglia
- Activation of T cells and complement
- Release of cytokines
- Demyelination and axonal injury



NEUROINFLAMMATION TRIGGERS PROTEIN PATHOLOGY



CHRONIC SYSTEMIC INFLAMMATION: PREVENTION

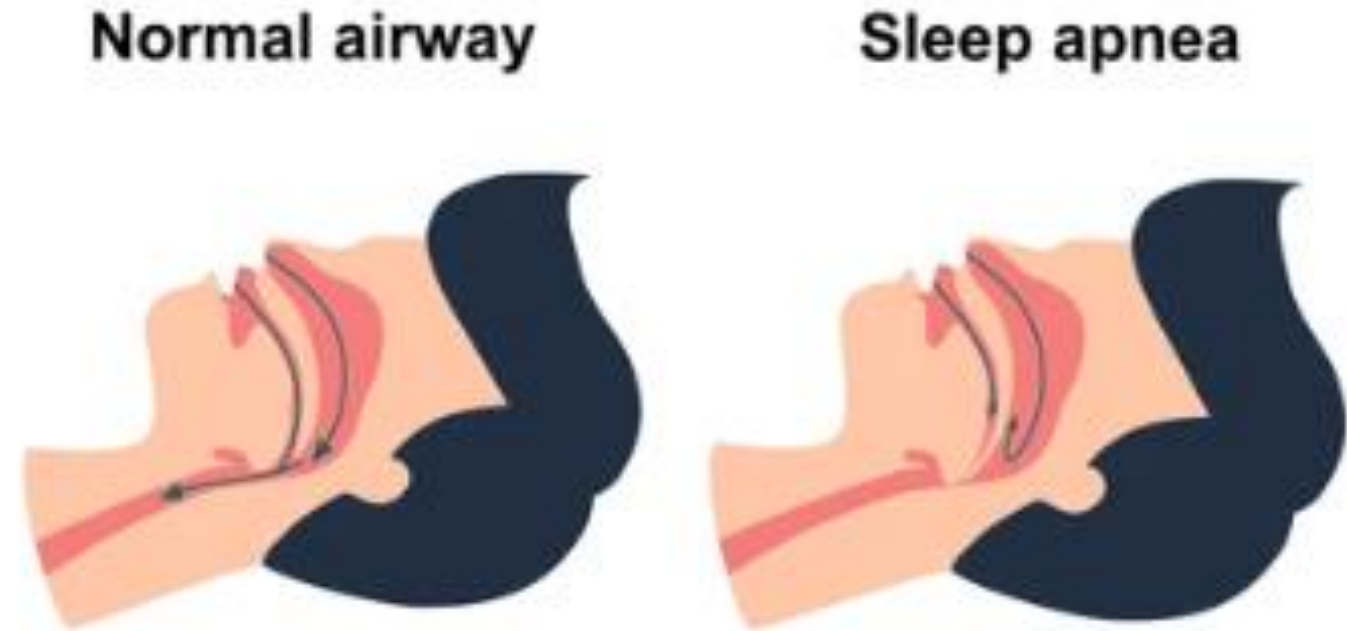
- Vaccines:

- The Lancet: cohort studies of rabies, tetanus, diphtheria, pertussis, herpes zoster, influenza, hepatitis A, typhoid, hepatitis B decrease dementia risk
- Eytting et al 2025: Cohort study without group difference! 20% RR reduction for vaccination

SLEEP APNEA

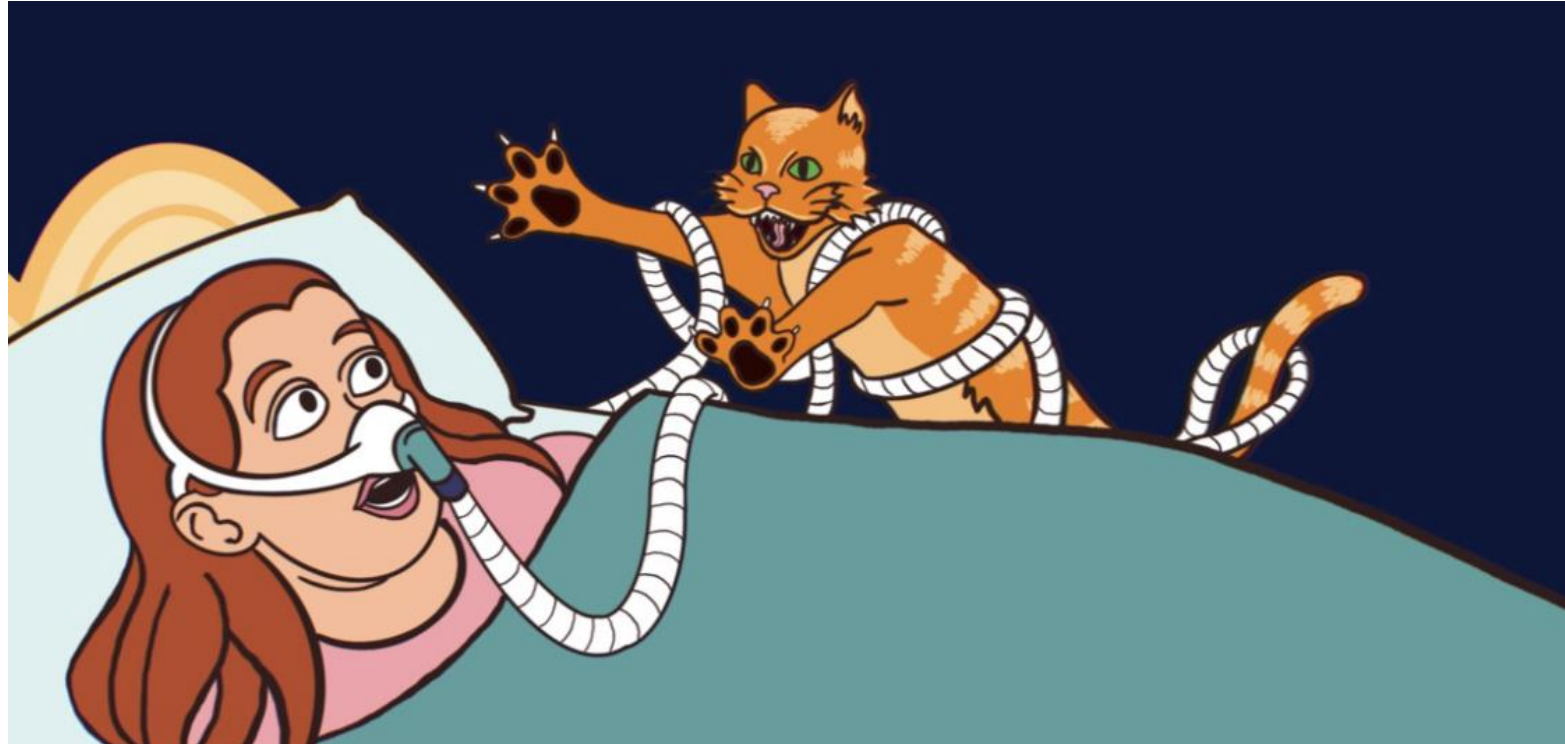
OSA: EVIDENCE

- • Guay-Gagnon et al 2022:
 - 1.3M, 15y followup.
 - OSA -> HR of 1.4
- • Shieu et al 2022:
 - 60k people. PAP is protective
- • Motamedi et al 2018:
 - mod-severe OSA -> elevated tau and IL-6
 - Worse OSA -> higher tau
- • Proposed mechanism:
 - Cerebrovascular disease
 - Chronic intermittent hypoxia
 - Decreased glymphatic function
 - Inflammation

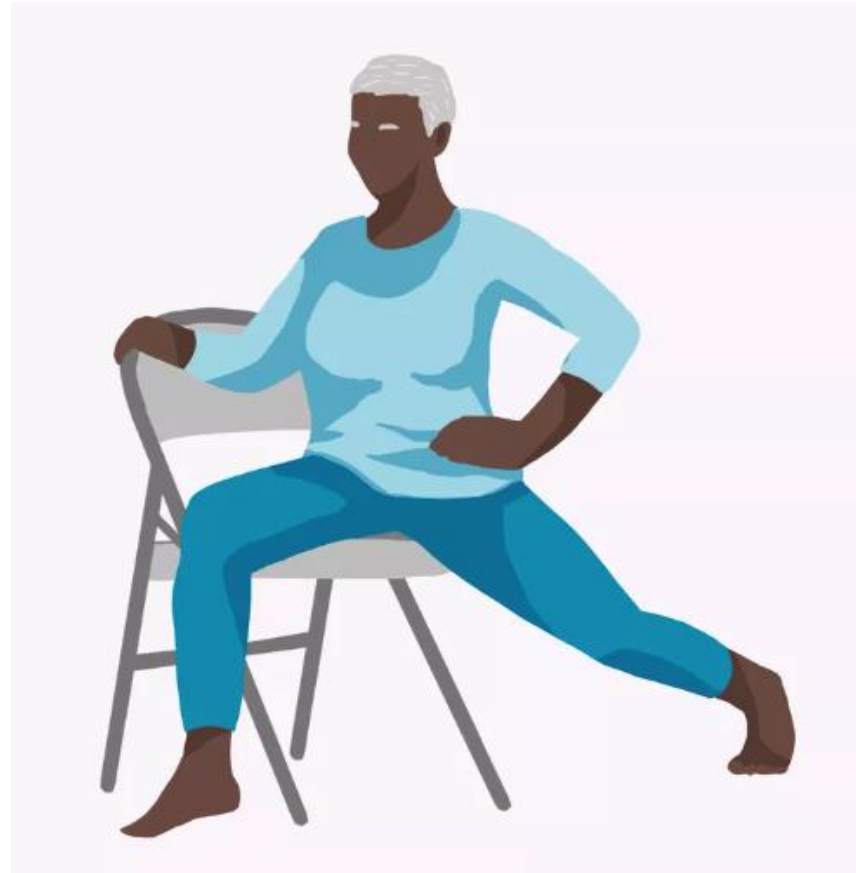


OSA: TREATMENT

- • Treatment/Treatment Risks:
 - For moderate - severe: PAP therapy
 - For mild: treat symptomatically, lots of options
- • Would I recommend to my mom?
 - 100%
 - Educate!
 - Screen for PTSD!



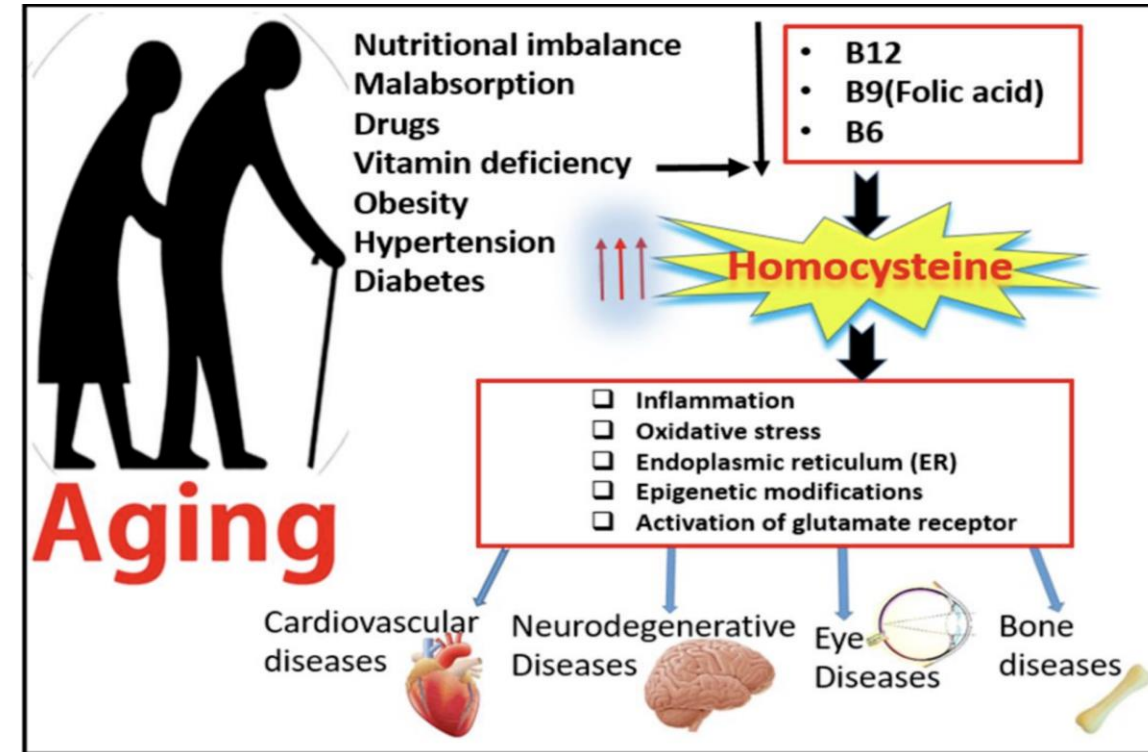
COGNITIVE BREAK



HOMOCYSTEINE

ELEVATED HOMOCYSTEINE: EVIDENCE

- Causes: B6, B9, B12 deficiency (restricted diets)
 - Also: MTHFR gene mutations, some medications, smoking, alcohol, aging, males, diabetes, RA, low thyroid, PPIs, obesity
 - Prevalence 10-50%
- B6, B9, and B12 supplementation (+ Omega 3)
- The Lancet: not a MODIFIABLE risk factor.
- Secondary/tertiary prevention vs primary prevention, again.



Tawfik et al, 2021

ELEVATED HOMOCYSTEINE: MECHANISM/TREATMENT

- Mechanism:
 - Mostly vascular: vascular calcification, cerebral microangiopathy, endothelial dysfunction, impaired NO activity, increased oxidative stress
- Treatment:
 - B6, B9, B12 supplementation + Omega 3
- Would I recommend to my mom?
 - 100%
 - GOOD BET
- Should we check homocysteine levels in midlife?

YES



HOW MUCH CERTAINTY DO WE NEED?

- • Pros and cons of the Lancet
 - • Good bets vs quackery
 - • For the sake of trying to reduce tremendous suffering, can we tolerate less certainty?
-
- Cognitive concerns? Want to know more? Ask me!
 - Susie Wetstone, MD
 - wetstone@uw.edu



Shel Silverstein, 1974

REFERENCES (SELECTED)

- Chang, K et al. Prolong Exposure of NSAID in patients with RA will decrease the risk of dementia: A nationwide population-based cohort study. *Medicine*. 2016;95(10)
- Cooper, J et al. A meta-analysis investigating the relationship between inflammation in autoimmune disease, elevated CRP, and the risk of dementia.
- Depypere, H et al. Dementia prevention, intervention, and care: Comments on the 2024 report of the Lancet standing Commission. *Maturitas*. 2025
- Depypere, H et al. Menopause hormone therapy significantly alters pathophysiological biomarkers of Alzheimer's disease. *Alzheimer's & Dementia*. 2023;19:1320-1330
- Eytting, M et al. A natural experiment on the effect of herpes zoster vaccination on dementia. *Nature* 2025.
- Guay-Gagnon, M et al. Sleep apnea and the risk of dementia: A systematic review and meta-analysis. *J Sleep Res*. 2022 Oct;31(5)
- Kim, Y et al. Association between menopausal hormone therapy and risk of neurodegenerative disease: Implications for precision hormone therapy. *Alzheimers Dement (N.Y.)* 2021 May 13;7(1)
- Livingston, G et al. Dementia Prevention, intervention, and care: 2024 report of the Lancet standing Commission. *The Lancet*. 2024;404:572-628
- Livingston, G. 24 Lancet commission: How can we prevent dementia? Youtube video.
- Mekli, K et al. Association between an inflammatory biomarker score and future dementia diagnosis in the population-based UK Biobank cohort of 500k people. *PlosOne*. 2023
- Motamedi, V et al. Elevated tau and IL6 concentrations in adults with OSA. *Sleep Medicine*. 43 (2018) 71-76
- Nerattini, M et al. Systematic review and meta-analysis of the effects of menopause hormone therapy on risk of Alzheimer's disease and dementia. *Front Aging Neuroscience*. 2023 October 23;15:1260427
- Pomirchy, M. Herpes Zoster Vaccination and Dementia Occurrence. *JAMA* 2025
- Sankowski, R et al. Systemic inflammation and the brain: novel roles of genetic, molecular, and environmental cues as drivers of neurodegeneration.
- Shieu, M et al. Positive Airway Pressure and Cognitive Disorders in Adults with OSA. *Neurology*. 2022;99(4):e334-e346
- Silverstein, Shel Sarah Cynthia Sylvia Stout Would Not Take the Garbage Out. *Where the Sidewalk Ends*. 1974
- Stafford, J et al. Psychiatric disorders and risk of subsequent dementia: systematic review and meta-analysis of longitudinal studies. *International J of Geriatr Psych*. 2022. 37(5)
- Stevenson-Hoare J et al. Severe psychiatric disorders are associated with increased risk of dementia. *BMJ Mental Health*. 2024; 27:1-7
- Szlufik, S et al. Glymphatic System Pathology and Neuroinflammation as Two Risk Factors of Neurodegeneration. *Cells*. 2024 Feb 5;13(3):286
- Tejera, C et al. The mediating role of systemic inflammation and moderating role of radicalization in disparities in incident dementia. *Communications Medicine* 4,142 (2024)
- The Lancet. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019
- Wang, J et al. Mechanisms of glutamate metabolic function and dysfunction in vascular dementia. *Neuroprotection*. 2024; 2:33-48.
- Weiner, M et al. TBI and PTSD are not associated with AD pathology measured with biomarkers. *Alzheimers Dement* 2023; 19(3):884-895
- Yoo, JE et al. Female Reproductive factors and the risk of dementia: a nationwide cohort study. *European Journal of Neurology*. 2020. 27(8):1448-1458
- Zandi P et al. Hormone Replacement Therapy and Incidence of Alzheimer's Disease in Older Women. The Cache County Study. *JAMA*. 2002; 288(17):2123-2129
- Zhang, L et al. Associations of PTSD symptoms with amyloid burden in cognitively normal older adults. *Frontiers in Aging Neuroscience*. 2024.