

Preventing dementia through lifestyle: What is the evidence?

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February 10, 2021

Disclosures

- ▶ Board member, Rochester Lifestyle Medicine Institute

Topics

- ▶ What is Lifestyle Medicine?
 - ▶ Course of dementia
 - ▶ Evaluating evidence
 - ▶ Lifestyle studies
 - ▶ NEURO framework
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What is Lifestyle Medicine?

- ▶ “The evidence-based practice of helping individuals and families adopt and sustain healthy behaviors that affect health and quality of life.”



What is Lifestyle Medicine?

- ▶ “The evidence-based practice of helping individuals and families adopt and sustain healthy behaviors that affect health and quality of life.”
- ▶ Identify and address root causes of disease
- ▶ Goal: prevent, treat, and reverse disease
- ▶ 70–80% of chronic disease could be prevented with optimal lifestyle.
- ▶ Foundational



Lifestyle Medicine

Feet



Forks



Fingers

Sleep



Stress



Love



AAMC NEWS

Tuesday, July 24, 2018

Five emerging medical specialties you've never heard of — until now

As medicine evolves, so do the types of doctors most needed. Demand for some of these physicians is already high.



1. Cancer immunologist
2. Nocturnist
3. **Lifestyle medicine physician**
4. Clinical informatics
5. Medical virtualist

Lifestyle Medicine growth

- ▶ ACLM founded 2004
 - ▶ ABLM 2015; first boards 2017
 - ▶ ACLM approved for Specialty and Service Society designation from the AMA 2020
 - ▶ Grew from 565 members in 2014 to 5,600 in 2020
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Impact of dementia in the US

- ▶ Over 5 million Americans are living with Alzheimer's disease
- ▶ 16 million Americans provide unpaid care for people with dementia
- ▶ 1 in 3 older adults dies with Alzheimer's disease or another dementia
- ▶ Older African Americans and Hispanics are more likely, per capita, to have Alzheimer's
- ▶ The cost of care is \$305 billion, and likely to triple by 2050
- ▶ We have not (yet) found good treatments for this condition
- ▶ Delaying the onset of dementia by 5 years would cut the incidence in half.

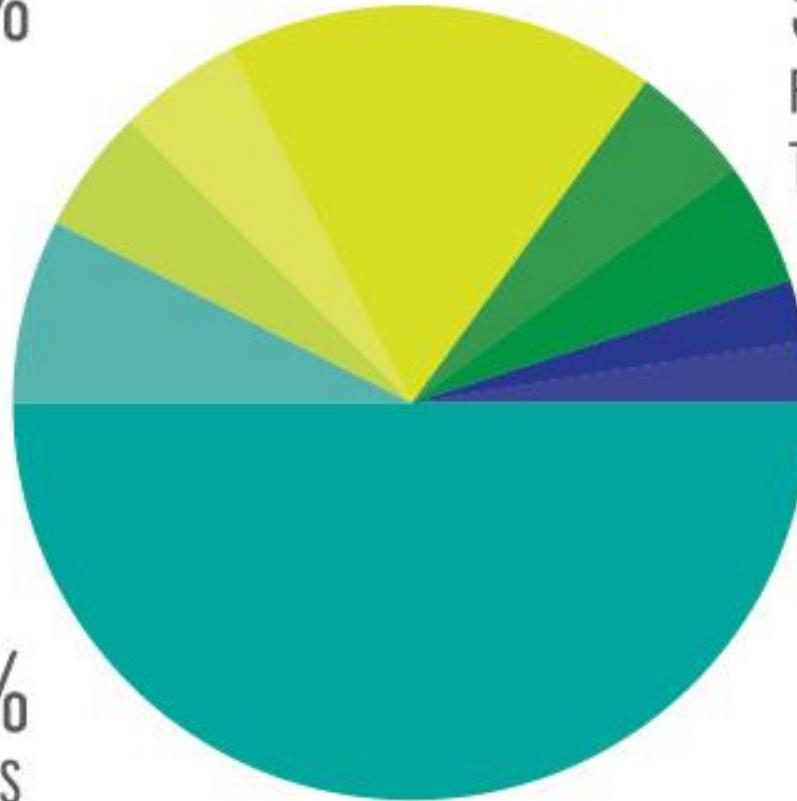
Types of dementia

20-30%
VASCULAR
DEMENTIA

5-10%
FRONTO-
TEMPORAL

<5%
LEWY
BODIES

50-75%
ALZHEIMER'S

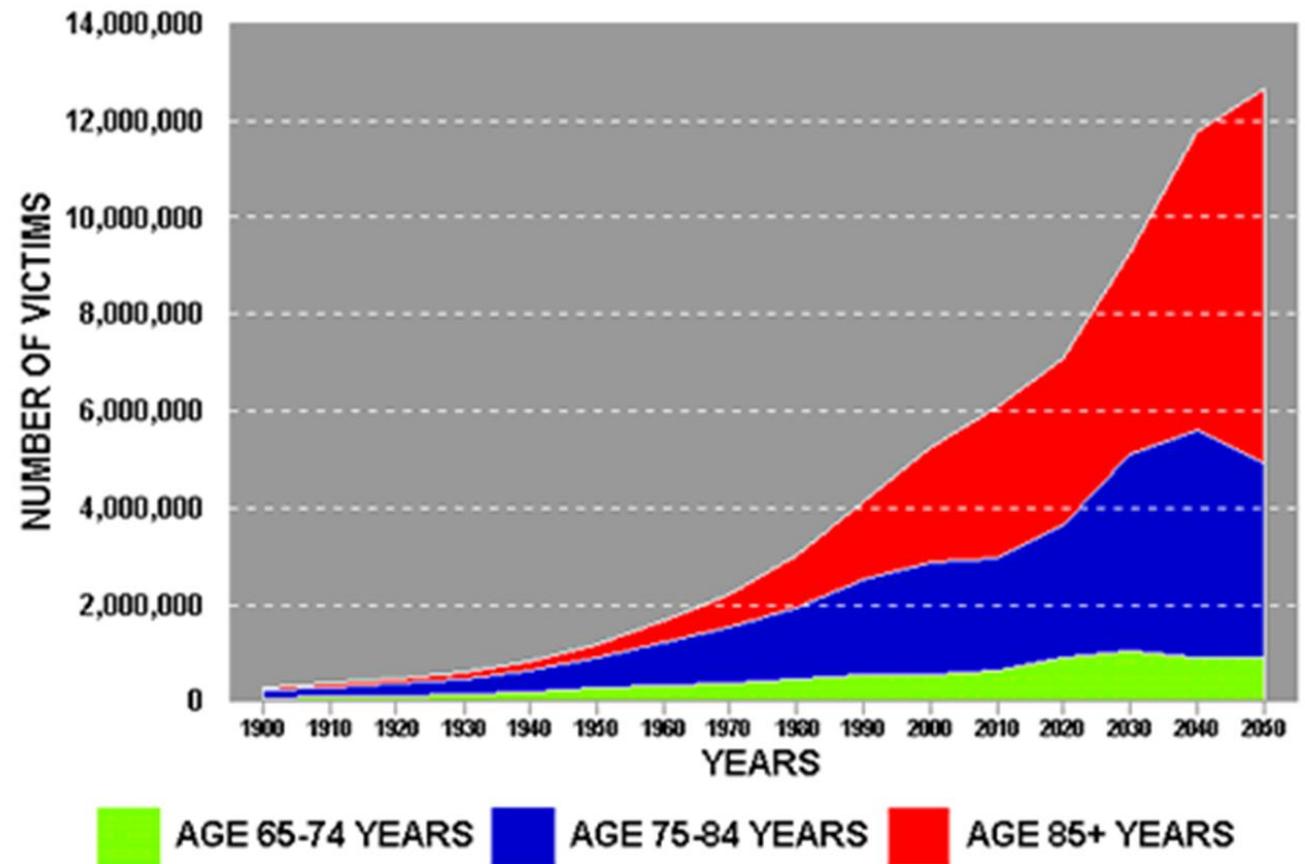


Risk of dementia

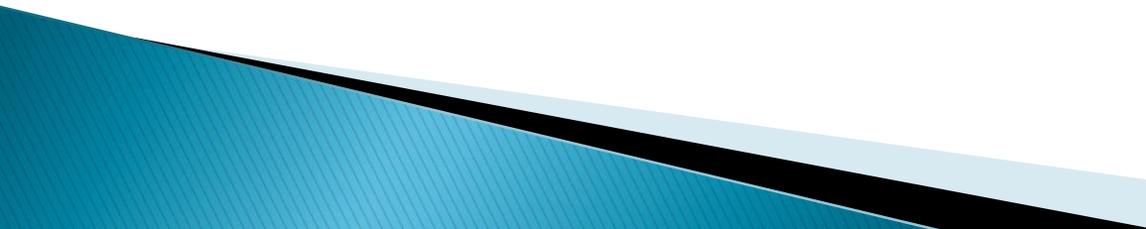
- ▶ Genes
- ▶ Age
- ▶ Lifestyle



Prevalence of Alzheimer's disease in the US



Preventing cognitive decline

- ▶ NIA review 2015
 - ▶ Outcomes:
 - Age-related cognitive decline
 - MCI
 - Alzheimer's disease
 - ▶ AHRQ evidence review
 - ▶ Second opinion – NASEM
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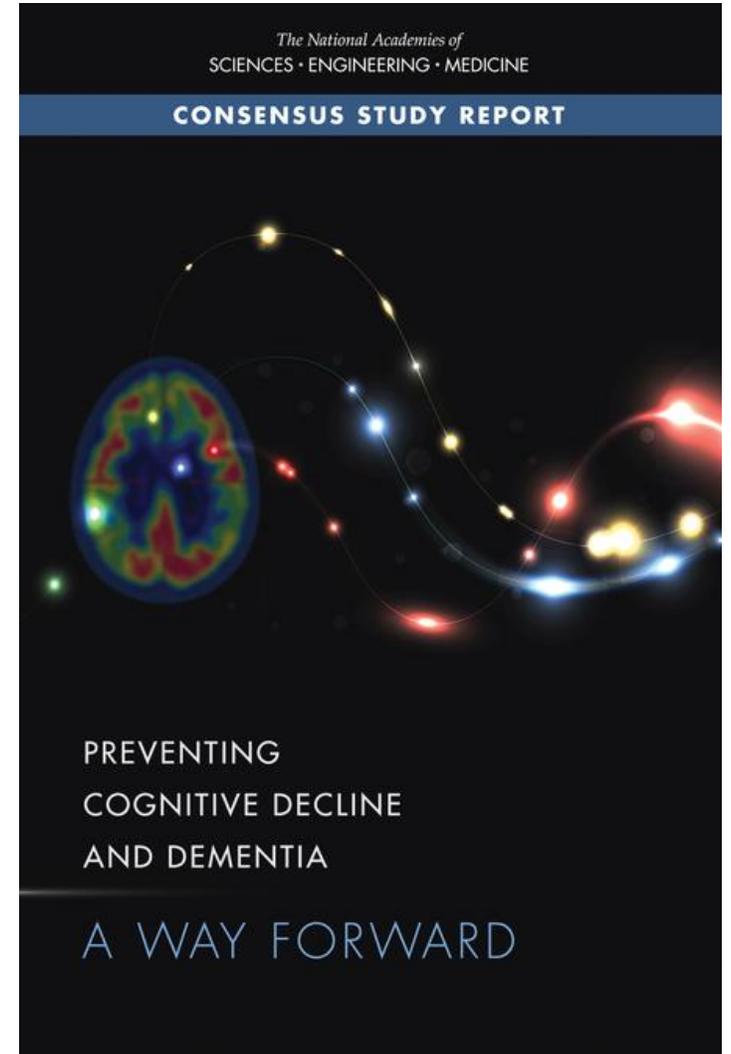
AHRQ review:

Prevention of cognitive decline, MCI, Alzheimer's

- ▶ 693 page document
- ▶ Screened > 9,000 studies
- ▶ 263 studies with 13 interventions
- ▶ No high strength evidence for prevention of 3 outcomes
- ▶ Moderate strength:
 - Cognitive training in adults with normal cognition improves performance in domain trained; little benefit beyond 2 years
- ▶ Physical activity: possible relationship
- ▶ Cognitive training
- ▶ Physical activity
- ▶ Nutraceuticals
- ▶ Diet
- ▶ Multimodal
- ▶ Hormone therapy
- ▶ Vitamins
- ▶ Antihypertensive Rx
- ▶ Lipid lowering Rx
- ▶ NSAIDs
- ▶ Anti-dementia drugs
- ▶ DM treatment
- ▶ Other

NASEM review

- ▶ No definitive evidence of effective prevention
- ▶ “Encouraging but inconclusive”
 - Cognitive training (problem solving, memory, speed of processing)
 - BP management in people with HTN (meds or lifestyle)
 - Physical activity
- ▶ More research needed

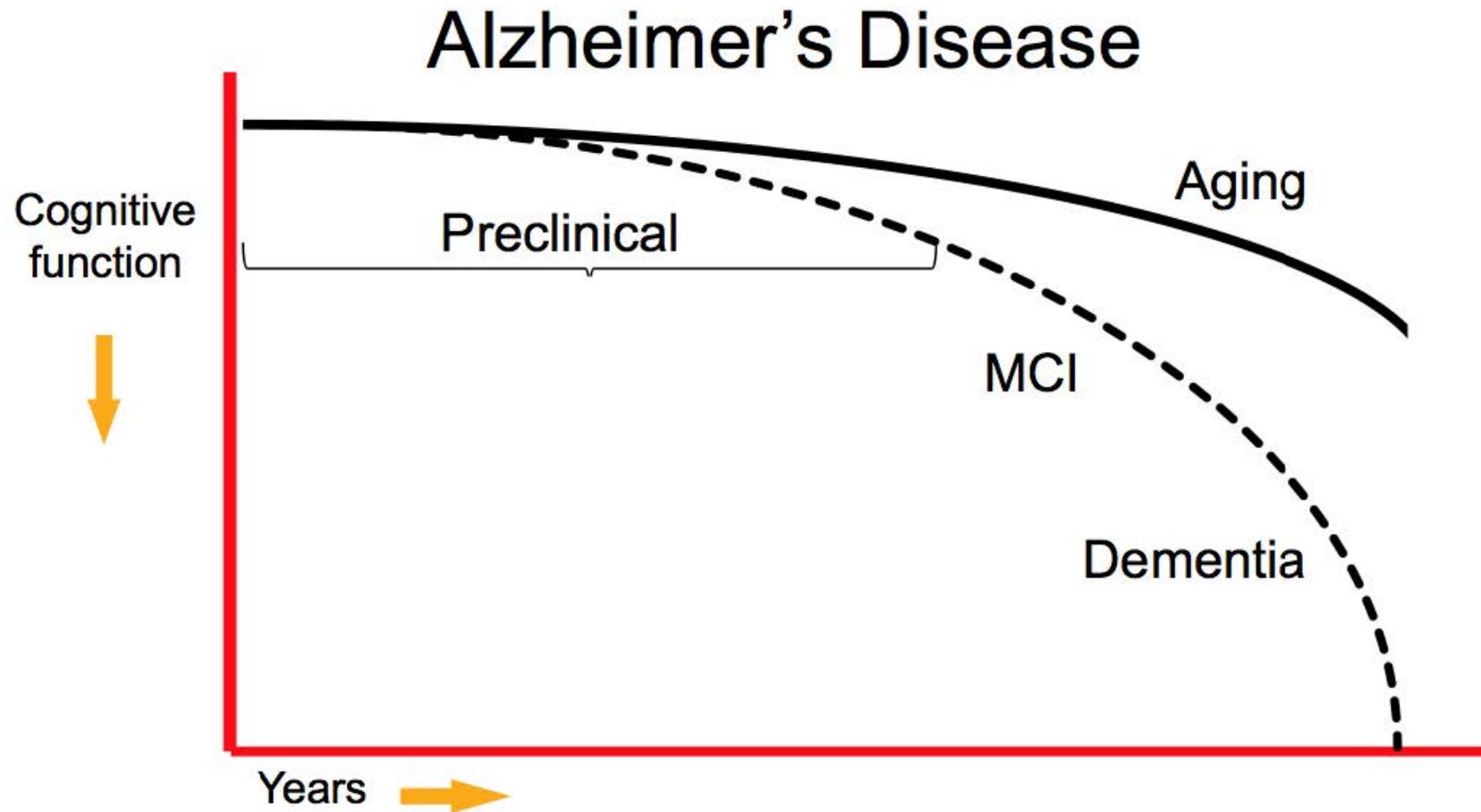


Letter

Dementia (Including Alzheimer's Disease) can be Prevented: Statement Supported by International Experts

- ▶ Estimated that half of Alzheimer's disease attributable to known risk factors
- ▶ Recommended
 - Exercise
 - Eat diets rich in fruits and vegetables
 - Avoid smoking
 - Avoid obesity and diabetes
 - Avoid excess alcohol
 - Treat high blood pressure

Development of Alzheimer's



Since these processes occur for 20 years on average before they become clinically obvious...

...how do we optimally study this?



Challenges with RCTs in Lifestyle Medicine

- ▶ RCTs well suited to study pill or procedure
 - ▶ Long lag time to go from cellular preclinical changes to dementia
 - ▶ Challenges with long-term adherence
 - ▶ Expensive to run
 - ▶ Blinding
 - ▶ Randomization
 - ▶ Generalizability
 - ▶ Observational studies well suited to look at longevity, compression of morbidity and lifetime impact of lifestyle pillars
- ... So what does it mean to be evidence-based?

Hierarchies of evidence applied to lifestyle medicine: HEALM

- ▶ Systematic review: “When RCTs cannot, for whatever reason, serve as the primary evidence source, are there alternative assemblies of evidence that can be used to achieve comparable confidence in a given exposure–outcome relationship?”

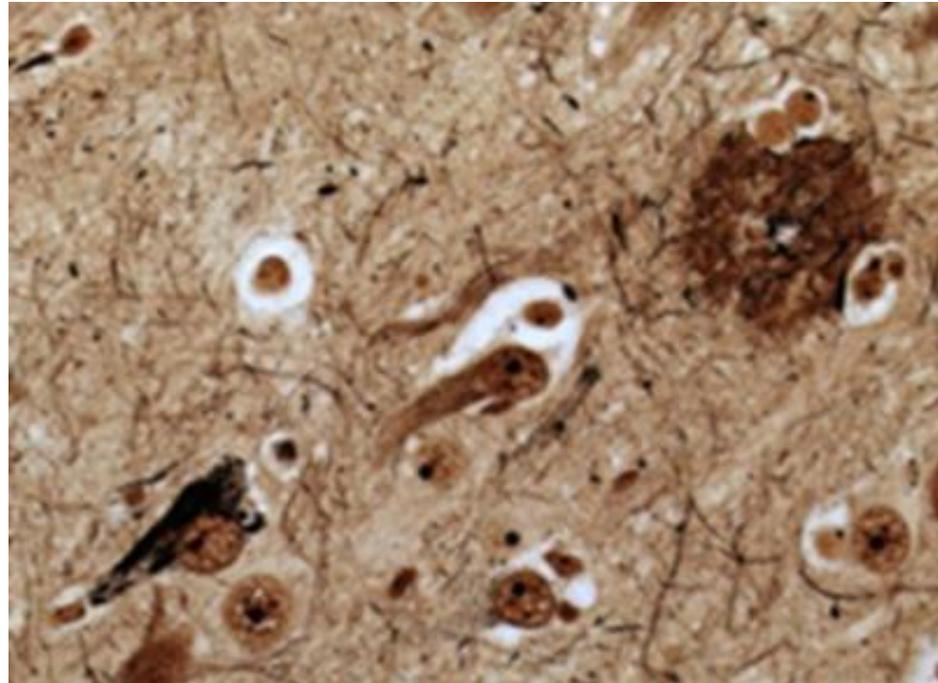
Research Method	Contribution
Basic science	Mechanisms of action
Intervention studies / RCTs	Reliable attribution; control of bias and confounding
Observational epidemiology; large diverse population–based samples	Effects at scale
Observational epidemiology, long time periods	Duration of effects

Hierarchies of evidence applied to lifestyle medicine: HEALM

- ▶ “Evidence is strongest when the unique contributions of these diverse methods are synthesized.”
- ▶ Recommend
 - If RCT feasible and available – GRADE
 - If RCT feasible and not available – OCEBM
 - If RCT not feasible – HEALM
- ▶ HEALM score
 - Range 0–9, with 7 or more as highest level
 - Synthesizes multiple sources

3 hypotheses of Alzheimer's

- ▶ Increase in amyloid plaques
 - Increased production in younger, genetically high-risk
 - Reduced metabolism and removal among older individuals

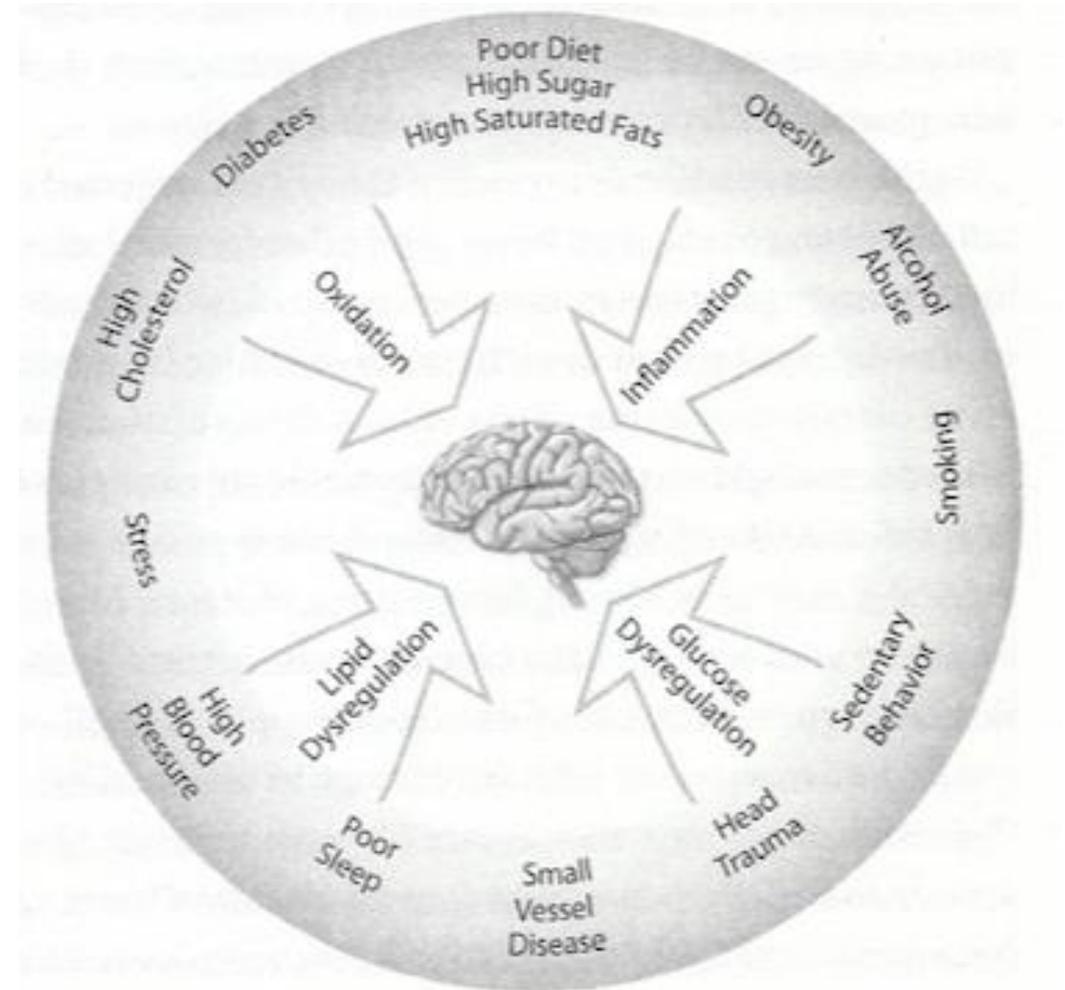


3 hypotheses of Alzheimer's

- ▶ Increase in amyloid plaques
 - Increased production in younger, genetically high-risk
 - Reduced metabolism and removal among older individuals
- ▶ Vascular disease predicts
 - Vascular dementia
 - Increased amyloid deposition
 - Neurodegeneration
- ▶ Dementia is due primarily to aging and neurodegeneration, independent of amyloid and vascular disease

4 common processes leading to dementia

- ▶ Inflammation
- ▶ Oxidation
- ▶ Glucose dysregulation
- ▶ Lipid dysregulation



Sherzai and Sherzai. *The Alzheimer's Solution*, 2017
Keene, *Up To Date*, 2018.

BLUE ZONES

LONGEVITY HOTSPOTS

LOMA LINDA
CALIFORNIA

NICOYA
COSTA RICA

SARDINIA
ITALY

ICARIA
GREECE

OKINAWA
JAPAN

BLUE ZONE LIFE LESSONS



MOVE NATURALLY



RIGHT TRIBE



RIGHT OUTLOOK



EAT WISELY

The Nun Study

- ▶ High linguistic ability
- ▶ Folate status
- ▶ Consistent exercise
- ▶ Normal body weight
- ▶ Adaptive coping style

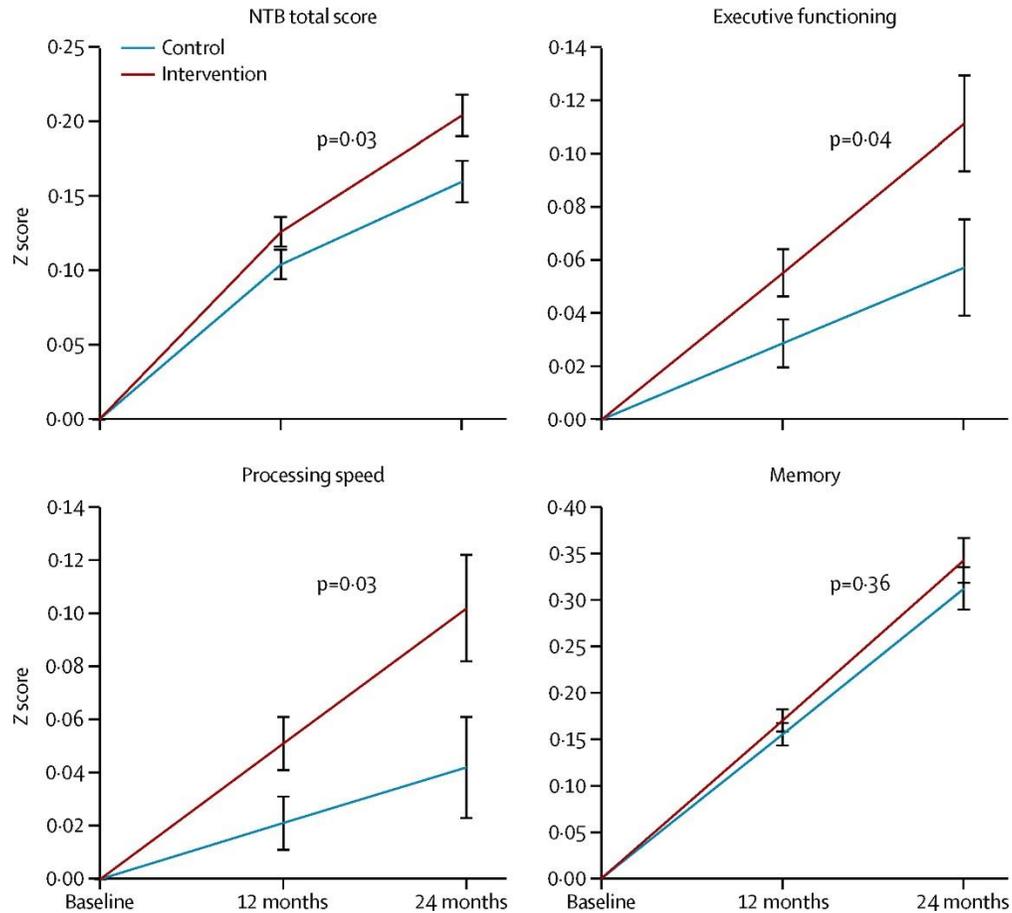


Wang et al. J Alzheimer's Dis 2012;28(3):637-645
Iacono et al. Neurology 2009; 73(9): 665-673.

FINGER trial

- ▶ Randomized trial to prevent cognitive decline
- ▶ 1200 at-risk subjects
- ▶ 2 year program
- ▶ Multicomponent intervention
 - Nutrition
 - Exercise
 - Cognitive training
 - Encouragement of social connectedness
 - Management of vascular risk factors

FINGER trial outcomes

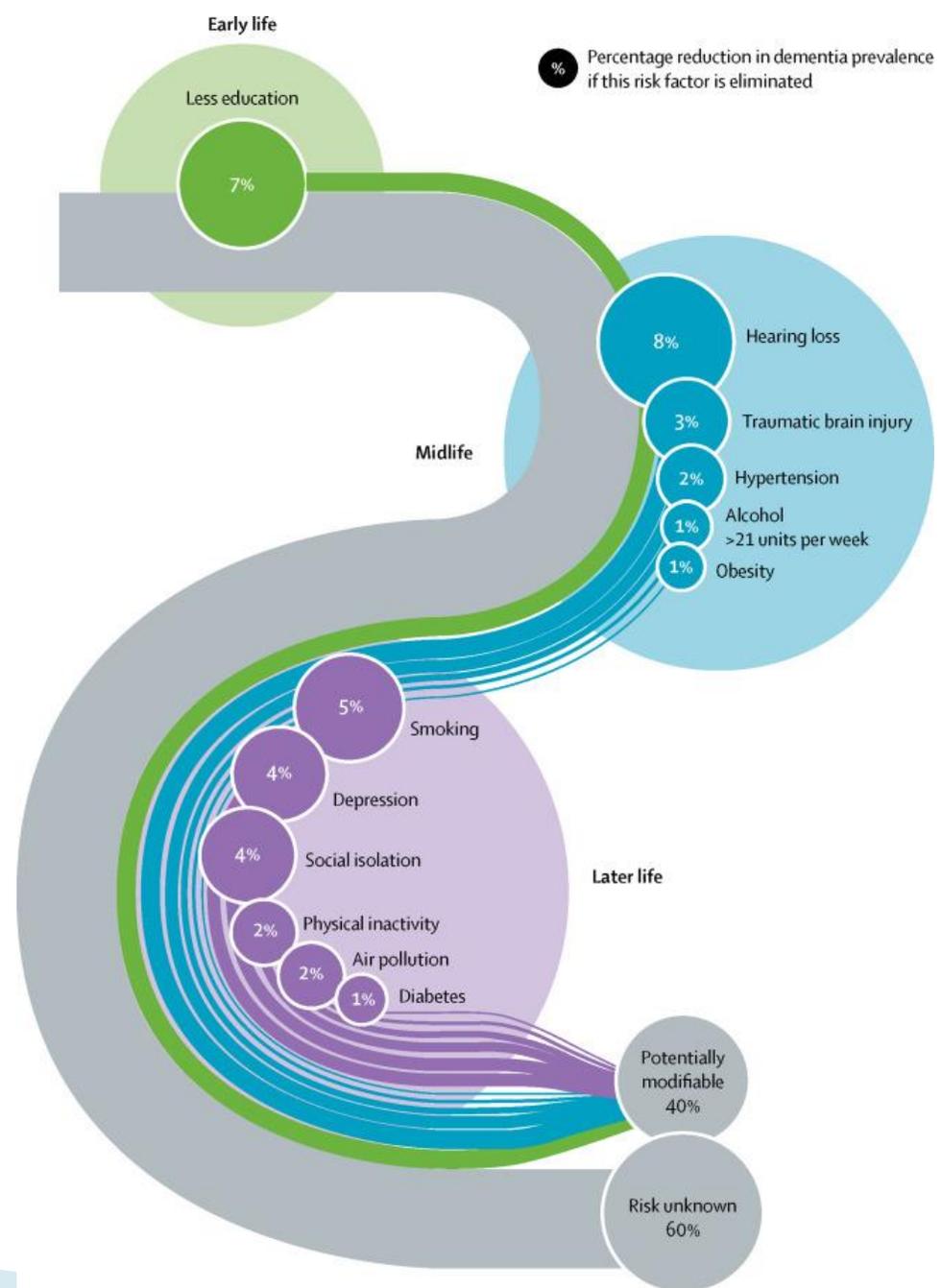


Risk of cognitive decline

Realm	OR	P-value
Overall	1.31	0.04
Memory	1.23	0.12
Executive function	1.29	0.04
Processing speed	1.35	0.01

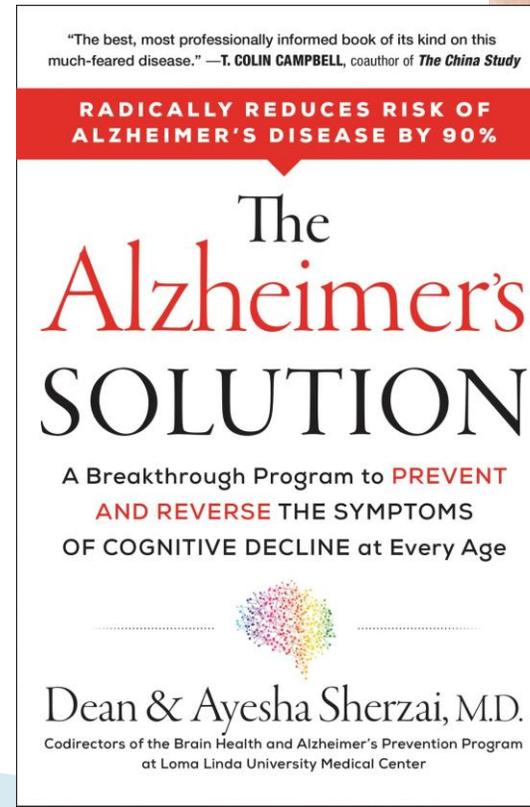
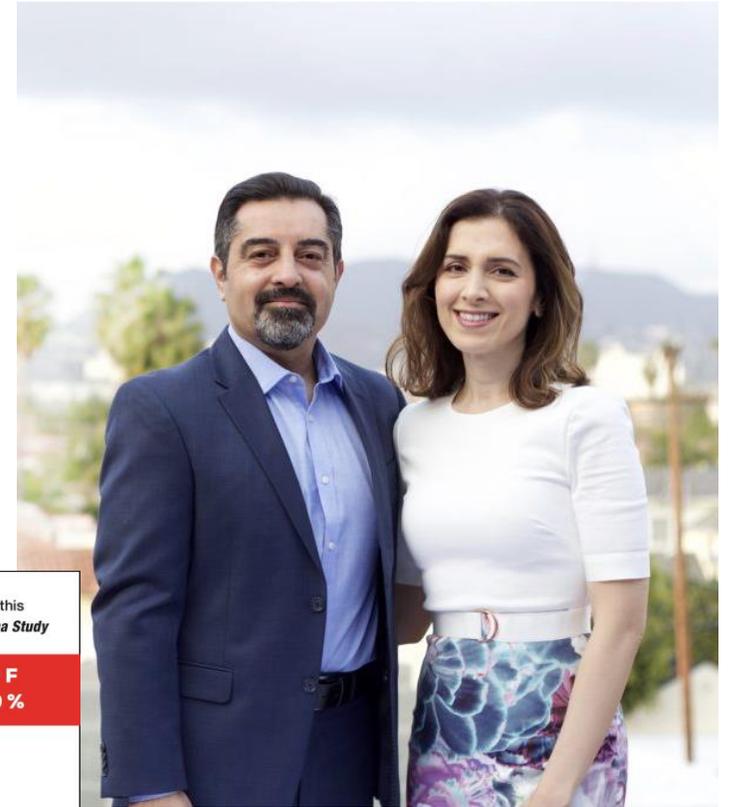
Lancet commission on dementia

- ▶ 12 potentially modifiable risk factors
- ▶ Account for around 40% of worldwide dementias
- ▶ Potential for prevention may be highest in low- and middle-income countries
- ▶ “Never too early and never too late” for prevention
- ▶ Culture, poverty and inequality are the key drivers of the need for change
- ▶ Low education
- ▶ Hypertension
- ▶ Hearing impairment
- ▶ Smoking
- ▶ Obesity
- ▶ Depression
- ▶ Physical inactivity
- ▶ Diabetes
- ▶ Low social contact
- ▶ Excessive alcohol
- ▶ TBI
- ▶ Air pollution



NEURO

- ▶ Nutrition
- ▶ Exercise
- ▶ Unwind
- ▶ Rest
- ▶ Optimize





Nutrition



Mediterranean diet

- ▶ Systematic review of longitudinal studies
- ▶ 5 studies with at least 1 year follow up
- ▶ Highest vs lowest MeDi tertile
 - MCI incidence (3600 participants) HR 0.73
 - AD incidence (3900 participants) HR 0.64
 - Any cognitive impairment (MCI or AD) HR 0.67
- ▶ Middle vs lowest MeDi tertile
 - MCI incidence HR 0.82 (trend)
 - AD incidence HR 0.87 (NS)

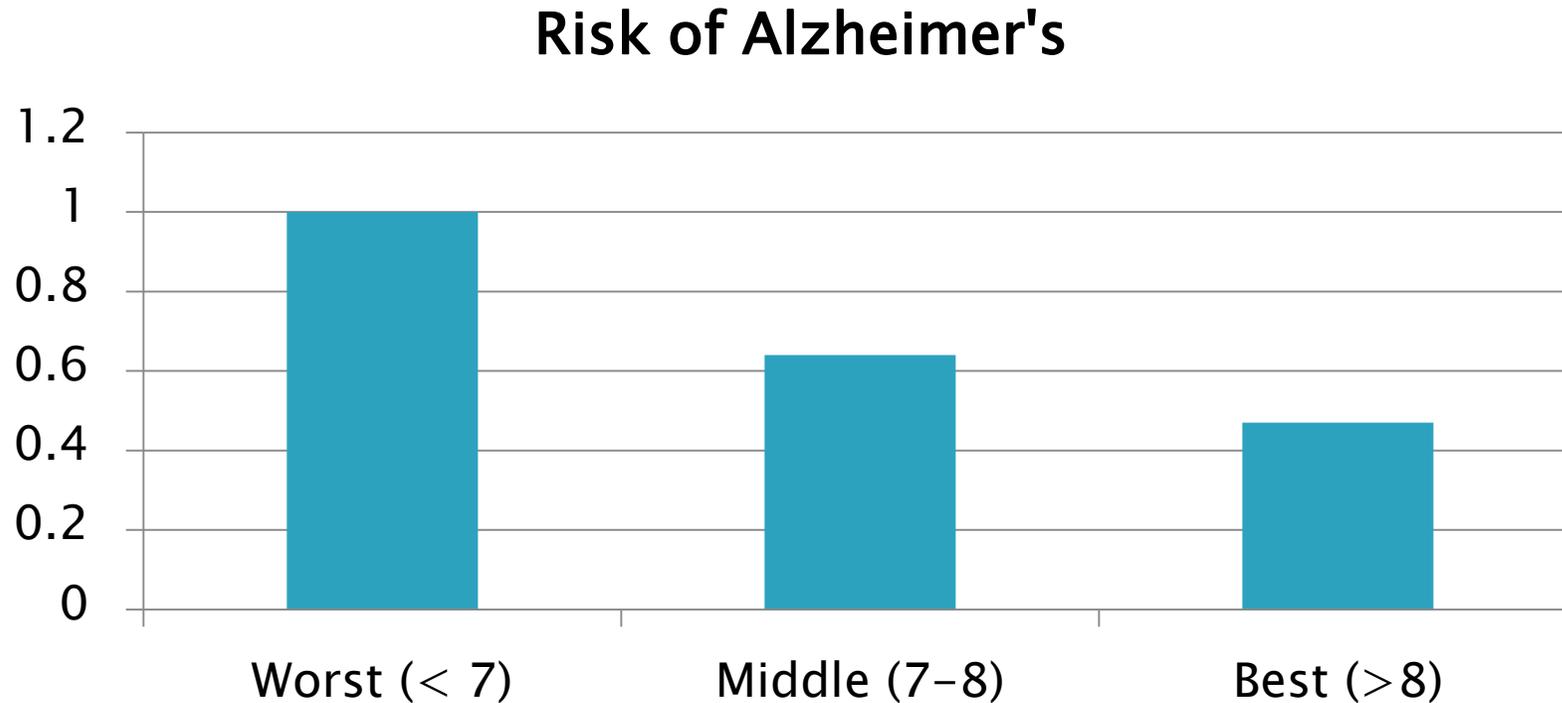
Nutrition and cognition: MIND diet

- ▶ Hybrid of the Mediterranean and DASH diets
 - Specifies berries
 - Specifies green leafy vegetables
 - Less emphasis on fish (vs. M)
 - Less dairy (vs. D)
 - More beans and nuts (vs. D)

Morris et al, Alzheimer's and Dementia, 2015;1-8.

Component	Point
Whole grain $\geq 3/d$	1
Green leafy $\geq 6/wk$	1
Other veg $\geq 1/day$	1
Berries $\geq 2/wk$	1
Red meat $< 4/wk$	1
Fish $\geq 1/wk$	1
Poultry $\geq 2/wk$	1
Beans $> 3/wk$	1
Nuts $\geq 5/wk$	1
Fast/fried food $< 1/wk$	1
Olive oil as primary oil	1
Butter, margarine $< 1 T/d$	1
Pastries $< 5/wk$	1
Cheese $< 1/wk$	1
Alcohol 1/d	1

MIND diet – Alzheimer's incidence in 4–5 years



- ▶ When the top 1 / 3 of MIND scores was compared to the bottom 1 / 3, the difference was the equivalence of 7.5 years of aging.

Morris et al, Alzheimer's and Dementia, 2015;1-8.



E

xercise

Exercise and the brain

- ▶ Exercise leads to
 - Less brain atrophy
 - Improved plasticity
 - Increased cerebral blood flow
 - Increased cerebral blood volume
 - Reduced inflammation
 - Decreased cortical amyloid
 - ? Nerve growth
 - ? Blood vessel growth
 - ? Resistance to brain insults

Impact of exercise

- ▶ Systematic review and meta-analysis
- ▶ RCTs, exercise interventions, community-dwelling adults > 50
- ▶ 36 studies
- ▶ Physical exercise improved cognitive function
 - Moderate impact overall (SMD 0.29)
 - Aerobic, resistance, multicomponent and tai chi all effective
 - Duration of 45–60 minutes per session
 - At least moderate intensity
 - Independent of baseline cognitive status



Unwind = Reduce stress

- ▶ Stress can:
 - Increase anxiety and depression
 - Impair immune function
 - Impair attention
 - Increase inflammation
 - Increase oxidative by-products
 - Lead to brain atrophy
 - Increase beta amyloid
 - Change gene expression
 - Lead to weight gain
 - Disrupt other healthy lifestyle behaviors

Stress reduction and cognitive function

- ▶ Chronic and perceived stress associated with
 - Lower cognitive performance
 - Faster cognitive decline
- ▶ Regular meditation can improve cognitive function in healthy individuals
- ▶ Long-term meditation may delay age-related decline in cognitive function
- ▶ MBSR RCT in patients with MCI showed improved cognitive performance
- ▶ Need larger studies

Socialization

- ▶ Systematic review of 812K people
 - Higher lifelong risk of dementia among
 - Lifelong single (RR 1.4)
 - Widowed (RR 1.2)
- ▶ Systematic review of 102K people; 51 longitudinal studies
 - Higher social contact => better late-life cognitive function
- ▶ Meta-analysis 8800 people with follow up > 10 years
 - Good social engagement moderately protective against dementia (RR 0.9)
- ▶ Mechanisms
 - Enhances cognitive reserve
 - Encourages beneficial behaviors
 - ?reverse causality

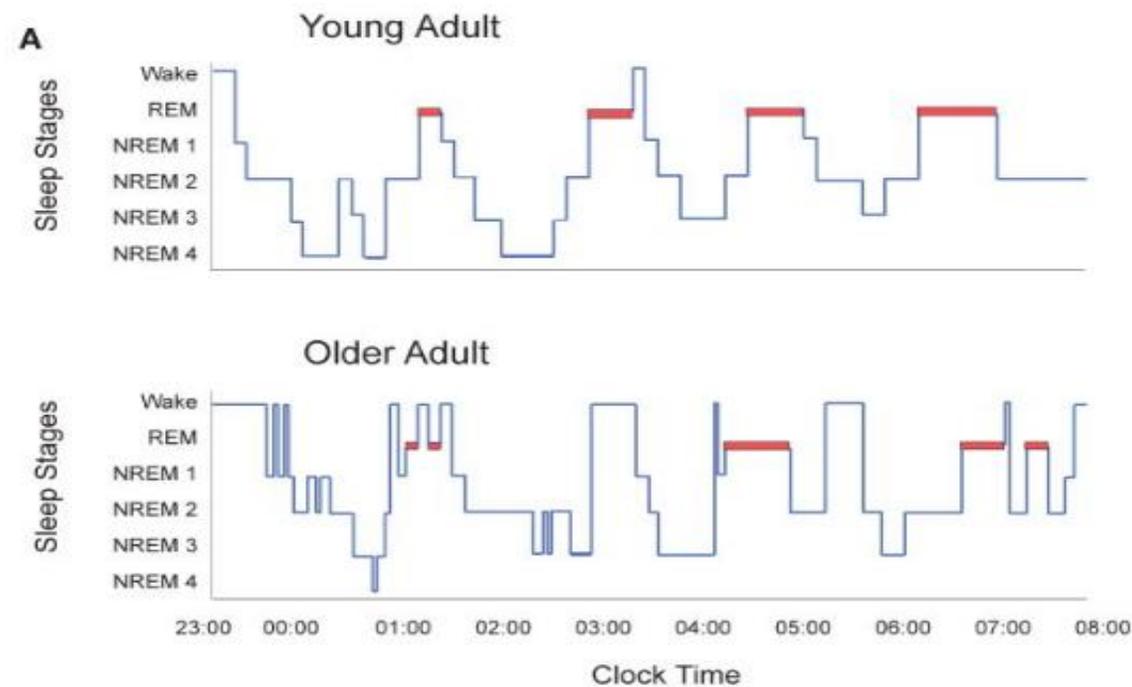


Rest



Rest

- ▶ Most people in the US don't get enough sleep
- ▶ Recommendation is 7–8 hours per night
- ▶ Sleep architecture changes with age

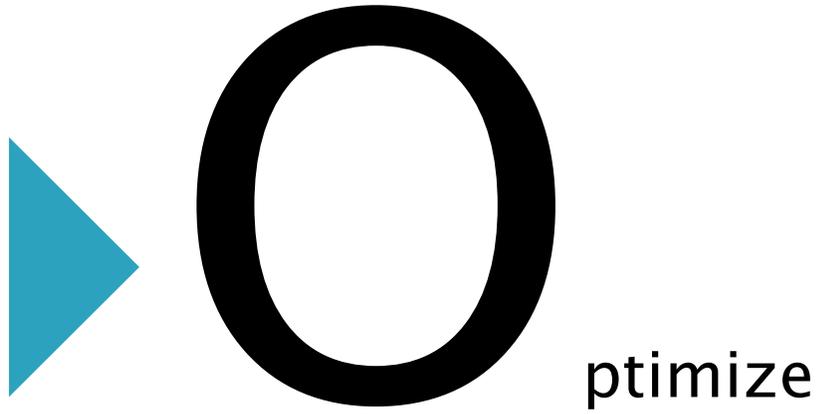


Sleep

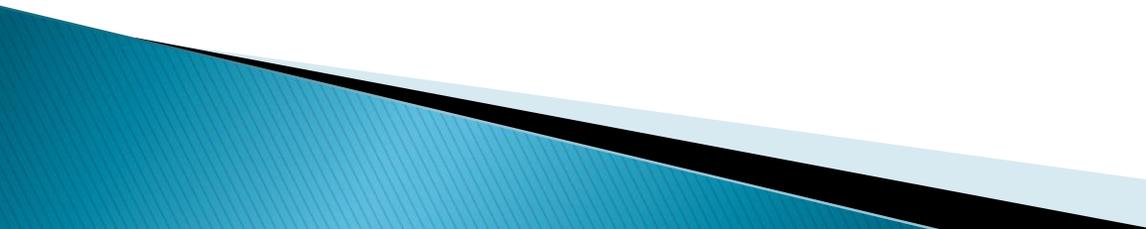
- ▶ U-shaped association between sleep duration and risk of MCI/dementia
- ▶ Proposed mechanisms
 - Beta amyloid deposition
 - Reduced glymphatic clearance
 - Low-grade inflammation
 - Increased tau protein
 - Hypoxia

People who don't get enough sleep

- ▶ Have a 40% lower ability to make new memories
- ▶ Meta-analysis looking at sleep disturbance and onset of dementia
 - 18 longitudinal studies with 246K subjects and average of 9.5 yrs follow up
 - People with sleep disturbance had increased incidence of dementia (RR 1.2), Alzheimer's disease (RR 1.5), and vascular dementia
 - Not all excluded those with cognitive impairment at baseline



Optimize = complex tasks that engage multiple regions of the brain

- ▶ Attention and concentration
 - ▶ Emotions and emotional processing
 - ▶ Executive function
 - ▶ Language processing
 - ▶ Motor speed and coordination
 - ▶ Verbal learning and memory
 - ▶ Visual learning and memory
 - ▶ Visuospatial processing
- 

Examples of complex tasks

- ▶ Learn a new language
 - ▶ Learn / play a musical instrument
 - ▶ Program a computer
 - ▶ Write a book
 - ▶ Karaoke and singing
 - ▶ Perform stand-up comedy
 - ▶ Dance
 - ▶ Play chess, bridge or other card games
 - ▶ Mentor
 - ▶ Volunteer to tutor children
 - ▶ Make jewelry, crafts
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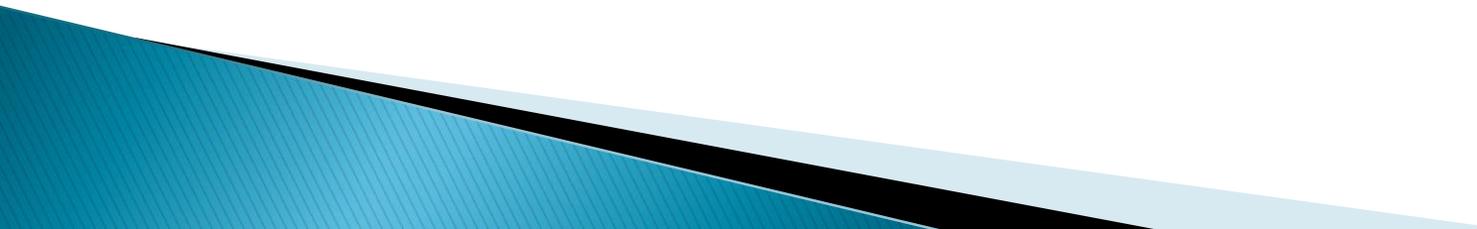
Cognitive training

- ▶ 3 recent meta-analyses
- ▶ Computer-based trials
- ▶ Mixed conclusions 2 / 3 found effect; 1 / 3 evidence insufficient
- ▶ No long-term, high-quality evidence
- ▶ Moderate effect for individuals with MCI on
 - General cognition
 - ADLs

Continued learning

- ▶ Longitudinal observational study of 15K community-dwelling Chinese adults aged 65+
- ▶ Free of dementia at baseline
- ▶ Excluded those who developed dementia within 3 years
- ▶ Adjusted for health and other behaviors
- ▶ Risk of incident dementia was 0.71 for those with intellectual activities at baseline

Beyond NEURO: Other things to think about

- ▶ Sensory input
 - ▶ Medications
 - ▶ Obesity
 - ▶ Smoking
 - ▶ Dental health
- 

Hearing and vision

- ▶ People with mild hearing loss have twice the risk of developing dementia. People with moderate hearing loss have 3 times the risk.
 - More brain atrophy, esp temporal lobe / hippocampus
 - Social isolation
 - Less input
 - Cognitive load
- ▶ Treating hearing loss can improve cognition.
- ▶ Vision impairment increases dementia risk.
- ▶ Having both puts people at especially high risk.

Medications

- ▶ Benzodiazepines
- ▶ Anticholinergics
 - Tricyclic antidepressants
 - First generation antihistamines
 - Bladder antimuscarinics
- ▶ PPIs

Obesity

- ▶ Systematic review of 19 longitudinal studies
- ▶ 589K people aged 35–65
- ▶ BMI ≥ 30 associated with 1.3X risk of dementia in late life

Smoking

- ▶ Smokers are at higher risk of dementia than non-smokers
- ▶ Faster decline in memory, cognitive flexibility, executive function, global cognition
- ▶ Especially in men
- ▶ Among 50K men > 60 yo, stopping smoking for > 4 years reduced risk of dementia in subsequent 8 years (HR 0.9)
- ▶ Mechanisms not completely clear, but likely multiple
 - Risk factor for vascular disease
 - Brain atrophy
 - Lung function

Dental health

- ▶ Gum disease and tooth decay lead to chronic inflammation
 - ▶ Tooth loss is correlated with small strokes
 - ▶ ? Bacterial role in dementia
- 

Summary

- ▶ It takes many years (~20) to develop dementia
 - ▶ It is likely that many cases of dementia can be prevented through lifestyle
 - We have mechanistic, observational, and interventional evidence to support this
 - ▶ Estimates are 40–50% of cases are preventable
 - ▶ Delaying the onset of dementia by 5 years could reduce prevalence by 50%
- 

