STATE OF THE SCIENCE:

PREVENTING ALZHEIMER'S DISEASE AND COGNITIVE DECLINE

Disclosures – Soo Borson MD

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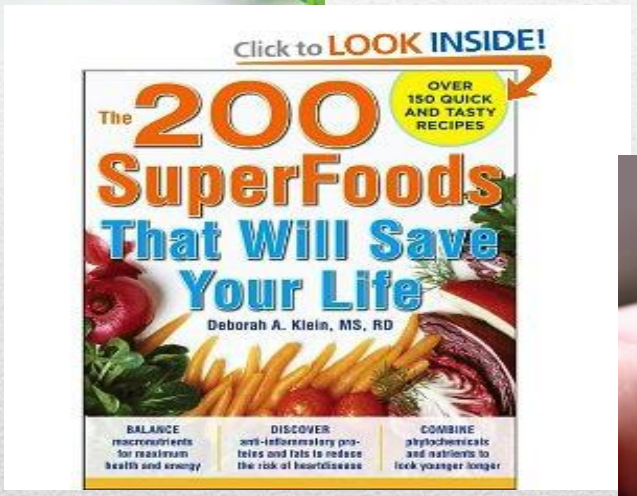
- Ongoing research funding from NHLBI and Veterans Affairs
- No financial conflict of interest

Goals + Learning Objectives

- Summarize conclusions from the 2010 NIH Consensus Conference on Prevention of Alzheimer's and Cognitive Decline
- Review relevant new data
- Discuss ways to implement findings in practice
- Equip you with skills to evaluate ‘headline science’



Ripped from headlines!

“The TRUTH about Alzheimer's treatment and Alzheimer's cure: *And we provide ground-breaking therapeutic kits…and bio-energetic impressions of healthy tissues.”* – Internet ad.

*“***Pharmacist of the Year Makes Memory Discovery of a Lifetime: Is it the Fountain of Youth for Aging Minds?”**

What you’ve been looking for – a real memory pill!

– New York Times, August 25, 2013.

- **"Scientists tell us that we could have a cure in 10 years for Alzheimer's" were it not for "overzealous regulators, excessive taxation and greedy litigators."**
  - *Michelle Bachman, March 2013*
- Targretin Fails: High Hopes Dashed for a New Treatment for Alzheimer's

…and so on…

Everyone's an expert!

The problem

- Equating brain with self
- Fear and ignorance
  - Alzheimer's is about as bad as cancer
    - *MetLife Alzheimer's Survey 2011*
  - It's worse than any other chronic disease
    - *Marist Institute for Public Opinion 2012*
- Complexity
  - Fuzzy boundaries between age-related cognitive decline and early Alzheimer's
  - Complex biology – multiple molecular and cellular processes, brain-body interactions, individual resilience vs vulnerability factors, cumulative effects
- Scientific politics
  - Oversimplication

Daviglus ML, Bell CC, Berrettini W, Bowen PE, Connolly ES, Cox NJ, Dunbar-Jacob JM, Granieri EC, Hunt G, McGarry K, Patel D, Potosky AL, Sanders-Bush E, Silberberg D, Trevisan M. NIH Consens State Sci Statements. 2010 Apr 26–28;27(4):1–30.

National Institutes of Health State-of-the-Science Conference Statement: Preventing Alzheimer's Disease and Cognitive Decline.

What we know

The problem

- ‘In most individuals, cognitive health and performance remain stable over the lifetime, with only a gradual decline in short-term memory and processing speed (that has nuisance impact on life but not its quality). For others, however, the decline in cognitive function progresses to a more serious state of cognitive impairment or into various forms of dementia.’
- Can we prevent these more serious forms of cognitive decline, including Alzheimer’s disease?

Definitions

- Mild cognitive impairment
  - Problems with memory, language, or other essential cognitive functions
  - Severe enough to be noticed by others and reflected on cognitive tests
  - Not severe enough to interfere with daily life
  - Increased likelihood of progression to dementia
- Dementia
  - Progressive global deterioration of cognitive abilities
  - Multiple domains including memory and at least one additional area—learning, orientation, language, comprehension, and judgment
  - Severe enough to interfere with daily life

Two key questions

1. Can we **modify** risk of Alzheimer's disease?

1. Can we **modify** risk of cognitive decline in aging?

What modifiable factors reduce risk of Alzheimer's disease?

Quality of evidence is low and findings are inconsistent

- Chronic diseases and conditions: absence of diabetes, high midlife cholesterol and blood pressure, vascular disease, depression and PTSD
- Nutrition: adequate folic acid intake, low saturated fat consumption, Mediterranean diet, high fruit and vegetable intake, light to moderate alcohol intake, red wine
- Medications: statins, non-steroidal anti-inflammatory agents, antihypertensives, glucose lowering agents, estrogens
- Lifestyle factors: abstinence from smoking, education, cognitive engagement, social support, regular exercise

What modifiable factors reduce risk of cognitive decline?

- Nutrition and diet: 803 published studies + 22 review articles
  - No clear role; maybe fish and Mediterranean type diet
  - Evidence that diet's benefits are limited to low SES seniors
- Medical factors: *absence of* diabetes, high blood pressure, metabolic syndrome
- Medications: no consistent evidence

- Psychological and emotional health: *absence of* depression
- Socioeconomic factors: no consistent evidence (but associated with various ‘risk’ conditions)
- Social and cognitive engagement: high life engagement; avoiding loss of a spouse (high risk of confounding)
- High physical and leisure activity: variable associations (high risk of confounding)

Critiquing the evidence

- Different definitions of “Alzheimer’s disease” and “cognitive decline”.
- Most studies look at how some factor is *statistically – not causally* – associated with cognition.
- “Risk factors” often inter-related, e.g. low SES + diabetes. Which is the risk factor?
- Individual differences are very important but often hard to measure, e.g. “brain reserve”, “neural plasticity”.

Intervention trials we need

- Well enough designed (multidisciplinary teams)
- Large enough (multiple thousands)
- Long enough (years)
- Reproducible enough (methods widely available)
- Well enough funded (very expensive)

Prevention trials: target delayed onset of Alzheimer's disease

- No benefit: ginkgo biloba; vitamin E, estrogen, cholinesterase inhibitors in mild cognitive impairment
- Inadequate evidence: Mediterranean diet
- *But age-adjusted prevalence of AD is already slightly declining in developed economies*

Prevention trials: improve cognition in aging, delay or prevent decline

- No benefit: ginkgo biloba+ vitamin E; statins; soy
- Positive effect of specific antihypertensive meds in limited population: hypertension+vascular disease + stroke, and maybe hypertension+diabetics
- **Positive effect: cognitive training** in older adults with normal cognitive functioning (ACTIVE trial with 5- and 10-year followup)
- **Possible/probable benefit**: **physical activity** (walking; aerobic and resistance training) in cognitively normal or mildly impaired older adults

Facts for thinking critically

- Cognitive decline usually gradual.
- Alzheimer's disease develops over decades. Studies are usually too short.
- When, with whom, and how must we intervene to 'bend the curve' in a positive direction?
- Individual recommendations about preventing cogntive decline and Alzheimer's – not supported by adequate evidence .

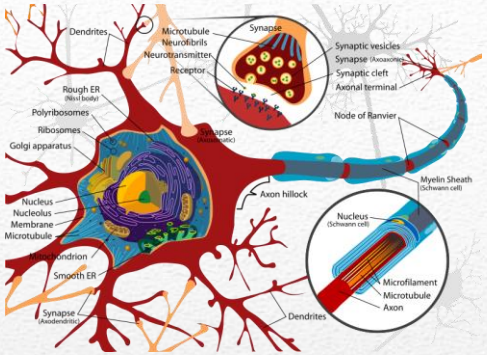
What can we say?

No harm in ‘heart healthy’ guidelines for diet, lifestyle, and activity – but no guarantee of protection from cognitive decline.

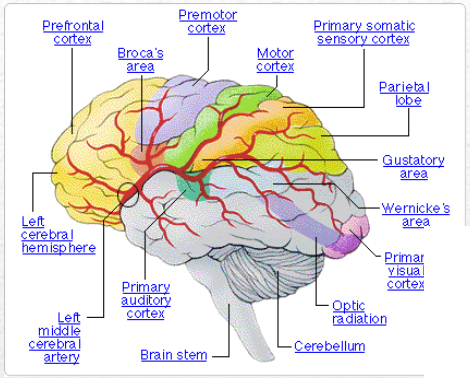
Knowing a bit about the brain helps, e.g.

- Repeated or severe head injury - bad (NFL; Wounded Warriors).
- The skull – less protective than we thought (blast injury).
- The brain – very metabolically active
  - Needs oxygen – blood supply, lungs, and heart must all work well.
  - Needs sugar – insulin resistance is a problem.
- The brain and body talk to each other – for good and ill.
- “Wear and tear” on tissue elements; repair slows down.
- Individual variation is big, and we can’t measure lots of it.

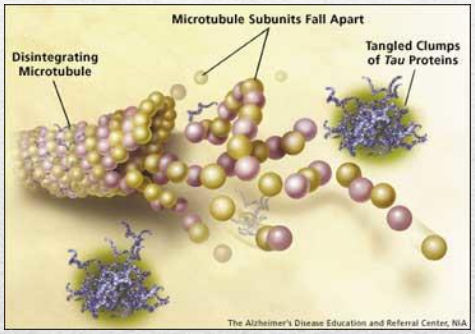
MEMBRANES



micronutrients

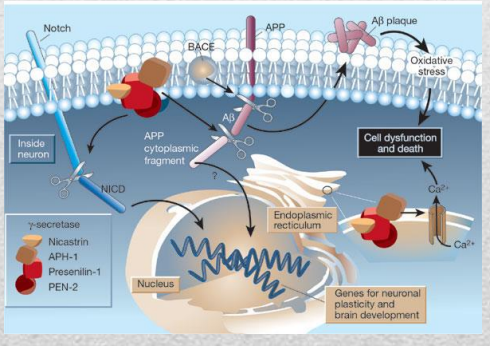


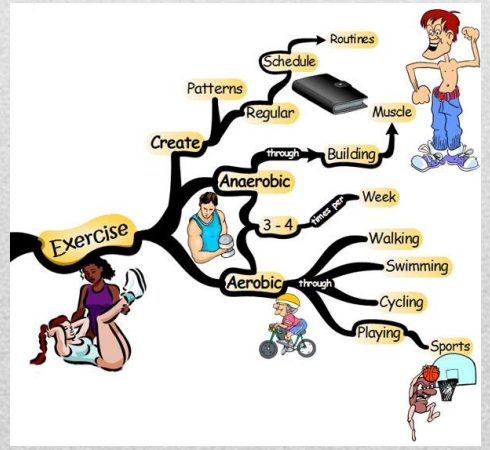
Genes



Amyloid

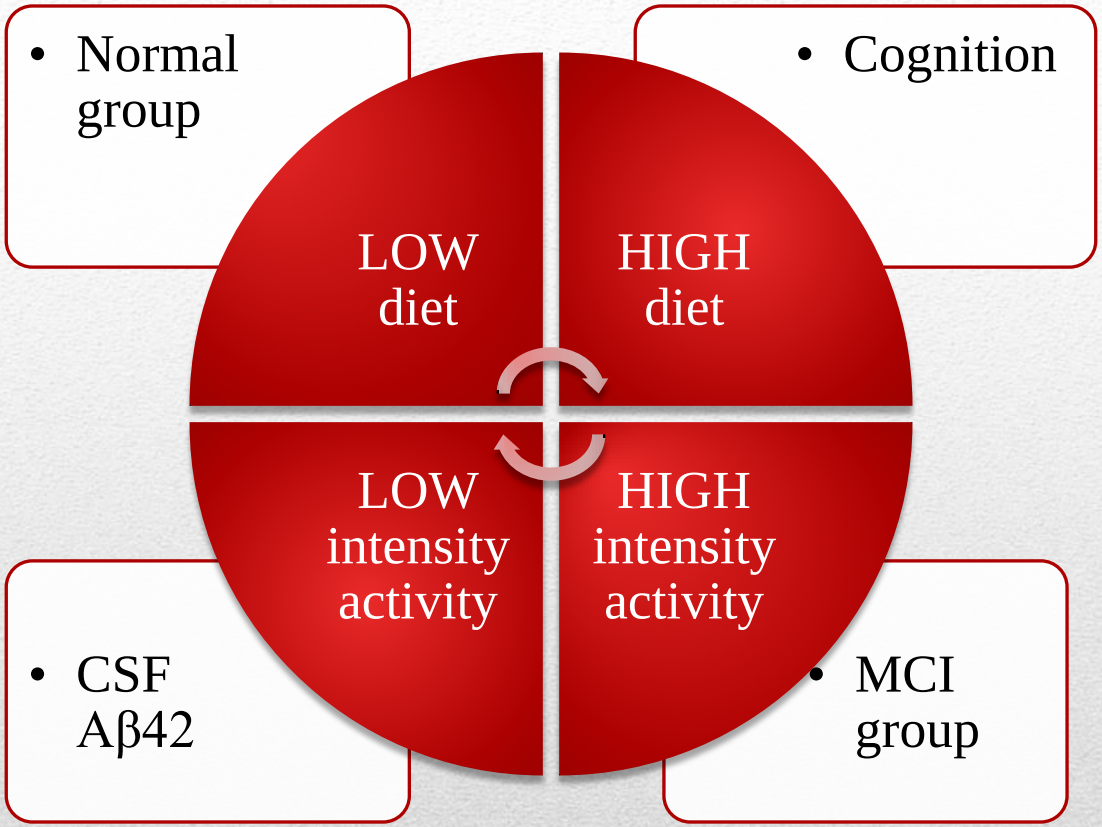
Tau





Aging

Respect complexity



Combining diet + exercise: effect on a key AD biomarker

Baker L et al. J Alz Dis 2012

The logic of this study

Diet dramatically alters levels of Aβ42 in CSF

Low fat/low glycemic index diet, and regular high intensity physical activity - healthier values in both normal and cognitively impaired seniors; reverse for high fat/high glycemic index diet and low intensity physical activity.

Results

- What if we combine diet and exercise?

  Normal seniors: high intensity physical activity reduced negative effects of high-fat, high-glycemic diet

  Mild cognitive impairment: high intensity physical activity increased positive effects of low fat, low-glycemic diet in cognitively impaired seniors
- Limitation: small sample, short duration, only diet randomized; needs larger, longer RCT with diet + exercise randomized

Evaluating the results

- *Is the claim plausible*?
  - YES. Many lines of evidence in humans and mice support synergy of diet and exercise on brain health.
- *Is there a mechanism to explain the effect?*
  - YES. Many basic brain processes are known to be positively influenced by diet and by exercise.

- *How good is the evidence?*
  - FAIR. Exercise was self-reported (not measured objectively); the sample size was small (41 subjects); cognition wasn't consistently affected; Aβ42 isn't equivalent to Alzheimer's disease; study is short-term, can't address long-term outcome.
- *Is it worth doing even if if it doesn't prevent Alzheimer's or cognitive decline?*
  - YOU BE THE JUDGE!

Long-term Effects of Cognitive Training on Everyday Functional Outcomes in Older Adults

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Michael Marsiske, PhD
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Jeffrey Elias, PhD
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Cognitive training: the ACTIVE trial

Willis S et al: JAMA. 2006;296:2805-2814

The logic of this study

- The brain is a learning system; a healthy brain can learn at any age.
- Learning tends to be modality-specific: e.g.to improve memory, train memory.
- Key questions: can cognitive training improve cognitive function in normal elders? Will the effect last over years? Does training transfer to everyday living? Does training slow cognitive decline with age? Are there people for whom it won’t work?

Randomized Training	Cognitive Outcomes	Functional Outcomes
Reasoning →	Reasoning	Everyday problem solving
Memory →	Memory	IADL
Speed →	Attentional speed	Everyday cognitive processing speed
10 sessions + 2 sets of booster training for some participants (1 and 3 years)		***1,2, 5 year effects***

Individual characteristics
Baseline cognitive function
Health conditions
Physical characteristics
Sensory function
Sociodemographics

N = 2802 volunteers
Mean age 74 years
Living independently in 6 cities
265 African American
Control group

Main results

- Training improved cognitive outcomes
  - Modality-specific
  - Immediate
  - Durable over 5 years
- IADL improved early in all groups, then started to decline after year 2; all training groups declined less quickly than controls.
- Reasoning training – best effect on IADL.

Ask yourself…

- Is the claim plausible?
- Is there a mechanism to explain the effect?
- How good is the evidence?
- Is it worth doing even if if it doesn't prevent Alzheimer's or cognitive decline?

Discussion

- Questions?
- Comments?
- How do you evaluate your own risk of cognitive decline?
- Do you engage in prevention activities? If so, what and why? If not, why not?
- How do you advise other about managing aging effects on cognition?