Brain health promotion strategies: Separating evidence-based hope from hopeless pseudo-medicine

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GLOBAL BRAIN HEALTH INSTITUTE
What is “Typical” Cognitive Aging?

Casaletto et al., NIH Toolbox, 2015, JINS
How do we keep our brains looking more like this:

And less like this:
Non-modifiable factors
- Age
- Biological sex
- Family history
- Head trauma

Modifiable factors
- Hypertension
- Hyperlipidemia
- Diabetes
- Depression
- Smoking

Lifestyle factors:
- Cognitive stimulation
- Social isolation/loneliness
- Physical activity
- Healthy sleep
- Nutrition
The projected effect of risk factor reduction on Alzheimer’s disease prevalence

Deborah E Barnes, Kristine Yaffe

At present, about 33.9 million people worldwide have Alzheimer’s disease (AD), and prevalence is expected to triple over the next 40 years. The aim of this Review was to summarise the evidence regarding seven potentially modifiable risk factors for AD: diabetes, midlife hypertension, midlife obesity, smoking, depression, cognitive inactivity or low educational attainment, and physical inactivity. Additionally, we projected the effect of risk factor reduction on AD prevalence by calculating population attributable risks (the percent of cases attributable to a given factor) and the number of AD cases that might be prevented by risk factor reductions of 10% and 25% worldwide and in the USA. Together, up to half of AD cases worldwide (17.2 million) and in the USA (2.9 million) are potentially attributable to these factors. A 10–25% reduction in all seven risk factors could potentially prevent as many as 1.1–3.0 million AD cases worldwide and 184,000–492,000 cases in the USA.
Approximately 30% of cases of dementia may be attributable to key modifiable risk factors:

- uncontrolled vascular disease
- sedentary lifestyle  
  * mental and physical
- depressed mood/stress
- dietary factors and alcohol
What is the relationship between uncontrolled vascular disease, obesity, and dementia?

High triglycerides/cholesterol, Hypertension, diabetes/insulin resistance, smoking, obesity, all increase our risk of cerebrovascular disease and dementia.
Obesity in midlife is associated with 3x risk of Alzheimer disease, and 5x risk of dementia, in late life.

Whitmer RA, et al. BMH. 2005
White matter injury is strongly associated with cognitive impairment
Mechanisms?

Lindbergh et al, under review
Staffaroni et al., in press, Human Brain Mapping
Physical Activity Promotes Better Brain Aging!

Any type is better than being sedentary.

Moderate intensity is the goal, for 150 minutes per week!
High midlife (45 to 65 years old) fitness associated with 88% reduced risk of dementia over 44 years AND, among those who developed dementia, onset was delayed on average 5 years.

Horder, et al. 2018
Walking counts!

33% reduced risk of decline over 6 to 8 years.

Yaffe et al., 2001
Physical Activity Promotes Better Brain Aging

Exercised

Neurogenesis

Sed
Run

![image]

Neurogenesis

Sed Plasma
Run plasma

![image]

Exercised

Blood Factors

![image]

S. Villeda

A. Horowitz

Horowitz et al. under review
Physical Activity Promotes Better Brain Aging

Neurogenesis

Fitbit Study: Healthy Older Adults

Horowitz et al. under review
Never too late!

Increases in Physical Activity over time relate to better brain network synchrony

K. Dorsman et al.
Complexity of Work and Risk of Alzheimer’s Disease: A Population-Based Study of Swedish Twins

Ross Andel,1 Michael Crowe,2 Nancy L. Pedersen,3,7 James Mortimer,4 Eileen Crimmins,5 Boo Johansson,6 and Margaret Gatz3,7

Main finding: those who engaged in more complex work with people had more than 5 times reduced odds of developing Alzheimer disease.
Cognitive activities delay onset of memory decline in persons who develop dementia

ABSTRACT

Background: Persons destined to develop dementia experience an accelerated rate of decline in cognitive ability, particularly in memory. Early life education and participation in cognitively stimulating leisure activities later in life are 2 factors thought to reflect cognitive reserve, which may delay the onset of the memory decline in the preclinical stages of dementia.

Methods: We followed 488 initially cognitively intact community residing individuals with epidemiologic, clinical, and cognitive assessments every 12 to 18 months in the Bronx Aging Study. We assessed the influence of self-reported participation in cognitively stimulating leisure activities on the onset of accelerated memory decline as measured by the Buschke Selective Reminding Test in 101 individuals who developed incident dementia using a change point model.

Main findings: Late life cognitive activities influence "cognitive reserve" independently of level of education. Each additional self-reported day of cognitive activity at baseline delayed the onset of memory decline by 0.18 years.
Take home message:

Late life cognitive activities (e.g., playing games) may promote cognitive stability (beyond baseline education/occupation).

Jonaitis et al., 2013)
ACTIVE Study: **10-year benefits** of processing speed/reasoning training (Rebok et al., 2014)
Active Lifestyles are associated with >60% less cognitive and functional decline in patients with genetic forms of neurodegeneration (FTD)
Genetic FTD Carriers with Active Lifestyles “Outperform” their Brains

Casaletto et al, *under review*
How can I promote "cognitive stimulation"?

Should I buy a "brain training" program?

Novel and challenging.

Many forms...
Stress, age, and inflammation

“Double-hit” Hypothesis

Aging → Inflammation → Perceived Stress → Cognition

Franceschi et al., 2000; Sparkman & Johnson, 2008; Gomez et al., 2005

Ugalde-Muniz et al., 2016
High Perceived Stress Accelerates Immune Activation Aging Trajectories

Casaletto et al., 2018, AJGP
Changes in Inflammation Track with Changes in Cognition

Casaletto et al., 2018, AJGP
Strategies to reduce stress

Deep breathing/Progressive muscle relaxation

Mindfulness-based Stress Reduction (MBSR)

Exercise

Simplifying environment/responsibilities
Mediterranean Diet/Whole Fruits & Vegetables

Higher adherence = Better cognitive outcomes

~30% reduced risk of cognitive decline and dementia

~30% reduced risk of stroke
MIND Diet is associated with Fewer Alzheimer-like Symptoms in Typically Aging Adults

Fox et al., under review
Challenge your brain and support it with nutrients!

NEURAL NETWORKING
Studies currently enrolling!

Fitbit Healthy Brain Aging

How much exercise? Biology associated with exercise?

Activities for Aging Neurogenesis (ActAN) Study

What brain-related pathways change with lifestyle behaviors?

Contact us! Kaitlin.Casaletto@ucsf.edu or Nina.djukic@ucsf.edu
THANK YOU

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How to decode direct-to-consumer interventions for brain health

Joanna Hellmuth, MD, MHS
How to know what to trust?
How does the government regulate supplements?

Dietary Supplement Health and Education Act, 1994, dictates how the Food and Drug Administration (FDA) regulates supplement safety and efficacy.
Dietary Supplement Health & Education Act

Safety of supplements

- Supplements are NOT tested by the FDA for safety
- Supplements are considered “safe” until proven otherwise
- They can only be found “unsafe” after causing harm
- Only gives the FDA permission to stop a company from making a supplement when the agency can prove it poses a significant risk to public health
- Opposite of the FDA process for drug approval
Dietary Supplement Health & Education Act

Safety of supplements

- Supplements may be marketed as "natural" but still may contain hazardous compounds
- Supplements contents may cause side effects or unwanted symptoms
- Supplement compounds may interact with existing medications and medical conditions
Supplement efficacy for brain health

- No dietary supplement has been shown to prevent cognitive decline or dementia
Dietary Supplement Health & Education Act

Efficacy of supplements

- Claims allowed: **statements of structure or function**
  - "Calcium can improve bone strength"
  - “Supplement X can improve memory and concentration”

- FDA does not see or review data supporting these claims
- Companies are supposed to have evidence their claims are true, but FDA is not permitted to examine it
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Dept. Health Human Services 2012 study assessing structure/function claims

- Evaluated 127 supplements to review the extent substantiating data complied with FDA standards

- “Overall, substantiation...for the sampled supplements were inconsistent with FDA guidance on competent and reliable scientific evidence.”

- “These results raise questions about the extent to which structure/function claims are truthful and not misleading.”

Dietary Supplement Health & Education Act

Efficacy of supplements

- Claims that are illegal: **statements of prevention, treatment, or cure of a disease process**
  - “Calcium can improve osteoporosis”
  - “Supplement X can improve Alzheimer’s symptoms”
How are these statements perceived?

“Clinically proven to improve memory”

“Clinically proven to improve Alzheimer’s symptoms”
How would you interpret this label now?
How would you interpret this label now?
The Rise of Pseudomedicine for Dementia and Brain Health

The US population is aging, and with it is an increasing prevalence of Alzheimer disease, which lacks effective approaches for prevention or a cure. Many individuals are concerned about developing cognitive changes and dementia. With increasing amounts of readily accessible information, people independently seek and find material about brain health interventions, although not all sources contain quality medical information.

This landscape of limited treatments for dementia, concern about Alzheimer disease, and wide access to information have brought a troubling increase in "pseudomedicine." Pseudomedicine refers to supplements and medical interventions that exist within the law and are often promoted as scientifically supported treatments, but lack credible efficacy data. Practitioners of pseudomedicine often appeal to health concerns, promote individual testimony as established fact, advocate for unproven therapies, and achieve financial gains.

With neurodegenerative disease, the most common example of pseudomedicine is the promotion of dietary supplements to improve cognition and brain health. This $3.2-billion industry promoting brain health to describe endeavors that follow "...the apparent precepts and forms of scientific investigation, but they're missing something essential..." Cargo cult science is apparent in material promoting some brain health supplements; "evidence" is presented in a scientific-appearing format that lacks actual substance and rigor. Feynman suggested a feature of scientific integrity is "bending over backwards to show how [the study] may be wrong...," which is a feature that is often lacking when interventions are promoted for financial gain.

A similarly concerning category of pseudomedicine involves interventions promoted by licensed medical professionals that target unsubstantiated etiologies of neurodegenerative disease (eg, metal toxicity; mold exposure; infectious causes, such as Lyme disease). Some of these practitioners may stand to gain financially by promoting interventions that are not covered by insurance, such as intravenous nutrition, personalized detoxification, chelation therapy, antibiotics, or stem cell therapy. These interventions lack a known mechanism for treating dementia and are costly, unregulated, and potentially harmful.
Shortly after...

The New York Times

Supplement Makers Touting Cures for Alzheimer’s and Other Diseases Get F.D.A. Warning

The F.D.A. also suggested that Congress strengthen its authority over the $40 billion industry, which sells as many as 80,000 kinds of powders and pills with little federal scrutiny.  Robert K. Chin/Alamy
What was in the FDA action?

- Warning letters to 17 supplement manufacturers
- Strong consumer warning
  “fly in the face of true science”
  “offered by…scam artists”
  “These products are a waste of money”
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WARNING & ONLINE ADVISORY LETTERS:
Products making illegal, unproven claims about Alzheimer’s treatment

FDA
Supplements like these are still legally sold without review of safety or efficacy
Limitations of the FDA

- FDA ultimately has limited enforcement due to the Dietary Supplement Health and Education Act of 1994
- Limited resources to act on even on the illegal claims
- Doesn’t impact the supplements we are most often asked about (perfectly legal but misleading structure/function claims)

What can do you?
What can do you?

- Understand that supplements may or may not be safe for you.
- Know that supplement manufacturers can make broad claims about improving brain function and do not provide evidence to the FDA supporting these claims.
- Empower your friends and family to accurately interpret the labels on supplements.
- Consider focusing your resources on interventions with evidence supporting brain health.
Brain Booster in a Bottle? Don’t Bother
To support brain health as you age, start with the same foods that can help to keep your heart healthy.

UCSF Researchers Call Out Brain Health Supplements as ‘Pseudomedicine’
Dietary supplements that purport to improve brain health are "pseudomedicine," according to a recent paper published in JAMA by a team of UCSF researchers. They say that although there is no known nutritional supplement

Do Nutritional Supplements Fight Dementia?

Science Versus Pseudo-Science: What Really Works to Prevent Cognitive Decline?
UCSF Memory and Aging Center

Thank you!