Can We Prevent Alzheimer's Disease?

Joshua Grill, PhD

Alzheimer's Disease Research Center Institute for Memory Impairments and Neurological Disorders Departments of Psychiatry & Human Behavior and Neurobiology & Behavior University of California Irvine

Agenda

- Why Alzheimer's?
- The state of the science of prevention
 - Lifestyle risk factors the facts
 - Pseudomedicine -- the myths
- Where do we go from here? prevention trials

Prevalence of Alzheimer's Disease

6.5 million

Americans living with Alzheimer's

Nearly 2/3

with Alzheimer's are women

Every 65 seconds

1 in 10

age 65+ has Alzheimer's

a new case develops

African Americans are

to have Alzheimer's than older whites

2022 Alzheimer's Association Facts and Figures.

Hispanics are

2x more likely 1.5x more likely

To have Alzheimer's than older whites

UCI



Alzheimer's disease is a growing public health crisis in Kentucky. Without an effective treatment or cure, the impact of Alzheimer's will continue to rise, and the numbers in Kentucky are escalating.

NUMBER OF PEOPLE AGED 65 AND OLDER living with Alzheimer's in Kentucky estimated _ 2020 2025

lamily caregivers

bear the burden of the disease in Kentucky

% of caregivers have chronic health conditions

70 of caregivers with depression

is the cost of Alzheimer's to the state Medicaid program

ADING CAUSE OF DEATH

DEATHS FROM ALZHEIMER'S DISEASE (2019)

more deaths than expected from dementia during the

.....

IS THE VALUE OF THE UNPAID CARE

25 million

HOURS OF UNPAID CARE provided by Alzheimer's caregivers

Alzheimer's and Dementia are Among the Most Feared Conditions

- 68% think they would no longer be the same person if they were to be diagnosed
- 24% thought that people who received a dementia diagnosis would instantly have to stop going out for a walk on their own
- 45% thought they would have to immediately stop driving a car
- 58% thought they would personally struggle to join in conversations post-diagnosis
- 49% worried people would think they were 'mad'

https://www.alzheimers.org.uk/news/2018-05-29/over-half-people-fear-dementia-diagnosis-62-cent-think-it-means-life-over

Pseudomedicine for Dementia and Dementia Prevention

Some basic principles

- No current way to definitively predict who will and will not develop AD dementia
- There is no FDA approved drug to to prevent AD
- There is no evidence to support supplements as ways to prevent AD (and they have risks)
- Recommendations around lifestyle should be free of charge
- Clinical trials should not charge for participation (in fact participants should be compensated for their time and contributions)

	The Rise of Pseudomedic	ine for Dementia
VIEWPOINT	and Brain Health	
	und Bruin meann	
Joanna Hellmuth, MD,	The US population is aging, and with it is an increasing	to describe endeavors that follow "the apparent pr
MHS Memory and Aging	prevalence of Alzheimer disease, which lacks effective approaches for prevention or a cure. ¹ Many individuals	cepts and forms of scientific investigation, but they' missing something essential ⁴⁶ Cargo cultscience is a
Center, Department of Neurological University	are concerned about developing cognitive changes and	parent in material promoting some brain health supp
of California,	dementia. With increasing amounts of readily acces-	ments; "evidence" is presented in a scientific-appeari
San Francisco.	sible information, people independently seek and find	format that lacks actual substance and rigor. Feynm
Gil D. Rabinovici, MD	all sources contain reality medical information	backwards to show how [the study] may be wrong
Memory and Aging	This landscape of limited treatments for demen-	which is a feature that is often lacking when interve
Neurology, University	tia, concern about Alzheimer disease, and wide access	tions are promoted for financial gain.6
of California, San Francisco.	to information have brought a troubling increase in	A similarly concerning category of pseudomer
	pseudomedicine. Pseudomedicine refers to supple- ments and medical interventions that exist within the law	cal professionals that target unsubstantiated etiolog
Bruce L. Miller, MD	and are often promoted as scientifically supported treat-	of neurodegenerative disease (eg. metal toxicity: mo
Center, Department of	ments, but lack credible efficacy data. Practitioners of	exposure; infectious causes, such as Lyme disease
Neurology, University of California	pseudomedicine often appeal to health concerns, pro-	Some of these practitioners may stand to gain fina
San Francisco.	mote individual testimony as established fact, advo-	cially by promoting interventions that are not cover
	With neurodegenerative disease, the most com-	ized detoxification, chelation therapy, antibiotics, or ste
	mon example of pseudomedicine is the promotion of di-	cell therapy. These interventions lack a known mech
	etary supplements to improve cognition and brain	nism for treating dementia and are costly, unregulate
	health. This \$3.2-billion industry promoting brain health	and potentially harmful.
		verse cognitive changes have been n
	Batiants and annations an accorden	moted, but these protocols merely
	Patients and caregivers encounter	package known dementia interventio
	sophisticated techniques that supp	DIY (eg, cognitive training, exercise, a hea
	false "scientific" backing for	other lifertule changer. Such protoco
	brain health interventions.	are promoted by medical profession
		with legitimate credentials, offer a uniq
	benefits from high-penetration consumer advertising	holistic and personal approach, and are said to be bas
	through print media, radio, television, and the internet."	on rigorous data published in reputable journals. Ho
	dine or demential yet supplements advertised as such	familiar patterns of testimony and cargo cult scien
	are widely available and appear to gain legitimacy when	emerge. The primary scientific articles superficially a
	sold by major US retailers. Consumers are often un-	pear valid, yet lack essential features, such as sufficie
	aware that dietary supplements do not undergo US Food	participant characterization, uniform intervention
	and Drug Administration (FDA) testing for safety or re-	or treatment randomization with control or placel groups, and may fail to include sufficient study limit
	as has been shown with vitamin E. which may increase	tions. Some of these poor-quality studies may be pu
	risk of hemorrhagic stroke, and, in high doses, increase	lished in predatory open access journals.7
	risk of death. ^{2,4} The Alzheimer's Association highlights	An argument can be made that even though pse
	these concerns, noting that many of these supple-	domedicine may be ethically questionable, these into
	These brain health supplements can also be costly, and	nations are relatively beingn and orier hope i nations facing an incurable disease. However, the
	discussion of them in clinical settings can subvert valu-	interventions are not ethically, medically, or financia
Corresponding	able time needed for clinicians and patients to review	benign for patients or their families. While appe
Author: Joanna Heleweth MD MHS	other interventions.	ing to a sense of hope can be a motivating factor
675 Nelson Rising Ln,	revenus and caregivers encounter sophisticated techniques that supply false "scientific" hacking for brain	cinical trials or complementary or alternative pra- tices, the difference is in how these circumstances a
Ste 190, San Francisco, CA 04158 (Jonanni	health interventions. For example, referring to scientific	framed. Complementary or alternative practices a
Helmuth@ucsLedu).	integrity, Feynman coined the term "cargo cult science"	often adjunct treatments and might not result in dire
jama.com		JAMA February 12, 2019 Volume 321, Numbe

Helmuth et al. JAMA, 2019.

Genetic Risk Variants for Common Forms of Alzheimer's Disease



Karch and Goate. Biol Psych. 2015

Direct-to-consumer companies offer genetic tests for APOE and other less informative risk genes

<u>Pros</u>

- Easy to access
- May be affordable
- Information may inform planning or even lifestyle decisions



<u>Cons</u>

- Not diagnostic
- Few consumers seek genetic counseling prior to undergoing testing
- Validity of tests still not highly regulated
- Even with GINA, discrimination still a risk

Specific actions for risk factors across the life course

- Aim to maintain systolic BP of 130 mm Hg or less in midlife from around age 40 years.
- Encourage use of hearing aids for hearing loss and reduce hearing loss by protection of ears from excessive noise exposure.
- Reduce exposure to air pollution and second-hand tobacco smoke.
- Prevent head injury.
- Limit alcohol use, as alcohol misuse and drinking more than 21 units weekly increase the risk of dementia.
- Avoid smoking uptake and support smoking cessation
- Provide all children with primary and secondary education.
- Reduce obesity and the linked condition of diabetes. Sustain midlife, and possibly later life physical activity.
- Addressing other putative risk factors for dementia, like sleep, through lifestyle interventions, will improve general health.



Livingston et al. Lancet 2020; 396: 413–46



EXPERT RECOMMENDATIONS

RECOMMENDATIONS FOR INDIVIDUALS:

- 1. Lead a physically active life.
- 2. Maintain a healthy weight through a balance of good nutrition and exercise
- 3. Don't start smoking, and if you do smoke, quit. It's never too late to experience the positive health benefits from not smoking.
- Check your blood pressure regularly. If it's too high, work with a health professional to lower it safely.
- 5. Have your cholesterol and lipid profile checked regularly. If your health care provider says it's too high, take steps to reduce it.
- 6. Keep blood sugar within a healthy range, as defined by your health care provider.
- 7. If you have diabetes or pre-diabetes, consult with a health care provider and nutritionist in order to help you manage these conditions.
- 8. Even after starting medication or lifestyle change, continue to regularly monitor your blood pressure, cholesterol, blood sugar, and weight.

9. People with symptoms of sleep apnea should be tested and treated if diagnosed.

10 Ways to Love Your Brain | Alzheimer's Association

alzheimer's **N** association[®] 10 Ways to Love Your Brain

Growing evidence indicates that people can reduce their risk of cognitive decline by adopting key lifestyle habits. When possible, combine these habits to achieve maximum benefit for the brain and body. Start now. It's never too late or too early to incorporate healthy habits.

Break a sweat

Engage in regular cardiovascular exercise that elevates your heart rate and increases blood flow to the brain and body. Several studies have found an association between physical activity and reduced risk of cognitive decline.

Hit the books

https://www.alz.org/help-support/brain_health/10_ways_to_love_your_brain

Page 1 of 5

RISK REDUCTION OF COGNITIVE DECLINE AND DEMENTIA

WHO GUIDELINES





HA/ASA Presidential Advisory

ing Optimal Brain Health in Adults al Advisory From the American Heart Association/ American Stroke Association

D, MPH, FAHA, Chair*; Karen L. Furie, MD, MPH, FAHA, Co-Chair†; FAHA, Co-Chair[†]; Eric E. Smith, MD, MPH, FAHA[‡]; Salina P. Waddy, MD§; ID, ScM, FAHA^{||}: Hee-Joon Bae, MD, PhD, FAHA; Marv Ann Bauman, MD: ans, MD; Pamela W. Duncan, PhD, PT, FAHA; Meighan Girgus; hD, FAHA; Ronald M. Lazar, PhD, FAHA; Sudha Seshadri, MD, FAHA; D, PhD, MS, FAHA; Stephen van Gaal, MD; Kristine Yaffe, MD, FAHA; Charlotte Zerna, MD, MSc; on behalf of the American Heart Association/ American Stroke Association

an important component of aging and predicts quality of life, functional independence, and risk of in our understanding of the role of cardiovascular risks are withown them to be closely associated ad dementia. Becuuse many cardiovascular risks are modifiable, it may be possible to maintain ementia in later life. The purpose of this American Heart Association (AHA)/American Stroke emenia in alec'nie. The publics of units American Pear Association (AFAP/American Stobe sory is to provide a minital definition of optimal brain health in adults and guidance on how to ntify metrics to define optimal brain health in adults based on inclusion of factors that could be dified. From these practical considerations, we identified? I metrics to define optimal brain health i AHA's Life's Simple 7: 4 ideal health behaviors (nonsmoking, physical activity at goal levels, surrent guideline levels, and body mass index <25 kg/m2) and 3 ideal health factors (untreated urrent guotenie ieveis, and oody mass index <25 kg/m² and 3 heat neam harcors (untreated Hg, untreated total-hochsetrol <2001 mg/dl, and fasting blood glucoses <100 mg/dl.). In addition, f cognitive health, we recommend following previously published guidance from the AHA/ , Institute of Medicine, and Alzheimer's Association that incorporates control of cardiovascular generat and other related strategies. We define optimal brain health but recognize that the truly genera and source reasons analysis. We derive optimal order that the annual to the cooping of the second source of oal to improve cardiovascular health of all Americans by 20% and to reduce deaths resulting d stroke by 20% by the year 2020. This work in defining optimal brain health in adults serves t troke Association with a foundation for a new strategic direction going forward in cardiovascular prevention. (Stroke. 2017;48:e284-e303. DOI: 10.1161/STR.00000000000148.)

AHA Scientific Statements ■ aging ■ brain ■ cognitive dysfunction ■ prevention and control ■ risk factors ■ stroke

Brain Health writing group section. †Also a member of Optimal Brain Health writing group section. ‡Lead of oup section. §Lead of Public Health Impact of Cognitive Impairment, Dementia, Stroke, and Cardiovascular and

 Bit Institute
 Firstein Health writing group section. 1.1 and of programs

 Granization
 Firstein Health writing group section. 1.1 and of programs

 Firstein Health writing group section. 1.1 and of programs
 Firstein Health writing group section. 1.1 and of programs

 Firstein Health writing group section. 1.1 and of programs
 Firstein Health writing group section. 1.1 and of programs

 Firstein Health writing group section.1 State of Programs
 Firstein Health writing group section.1 State of Programs

 If the authors and do not necessarily reflect those of the National Institute of Diabetes and Dispetive and Kulney

 If the authors and do not necessarily reflect those of the National Institute of Diabetes and Dispetive and National Institute of Diabetes and Dispetive Institute © 2017 American Heart Association, Inc.

e284

Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STR.00000000000014

The Recommendations

- 1. Get more exercise by increasing the number of days/week you exercise or increasing your daily number of steps
- 2. Eat more fruits, vegetables, nuts, olive oil, and fish. Eat less foods high in fat and cholesterol.
- 3. Don't start smoking. If you smoke, quit.
- 4. If your blood pressure is elevated (>120/80), talk to your doctor about managing it.
- 5. Talk to your doctor about improving your cholesterol (increasing your HDL; decreasing your LDL).
- 6. Challenge your brain more often through cognitively demanding tasks.
- 7. Increase your social activity by more often interacting with family and friends
- 8. Get at least 7 hours of sleep per night; if you suffer from symptoms of sleep apnea speak to your doctor.

Can This Work?

Selected Recent Studies of the Dementia Epidemic.					
Study	Outcome	Data Source	Key Findings	Factors	
Manton et al. (United States)¹	Prevalence of se- vere cognitive impairment	National long-term care survey interviews, 1982–1999	Decline in dementia prevalence among people ≥65 yr of age (5.7% to 2.9%)	Higher educational level, decline in stroke incidence	
Langa et al. (United States)²	Prevalence of cognitive impairment	Ongoing population-based survey of people ≥51 yr of age	Prevalence of cognitive impairment among people ≥70 yr of age (12.2% in 1993 vs. 8.7% in 2002)	Higher educational level; combination of medical, lifestyle, demographic, and social factors	
Schrijvers et al. (Rotterdam)³	Incidence of dementia	Population-based cohort ≥55 yr of age in 1990, extended in 2000	Incidence rate ratios (6.56 per 1000 person-yr in 1990 vs. 4.92 per 1000 person-yr in 2000)	Higher educational level, re- duction in vascular risk, decline in stroke incidence	
Qiu et al. (Stockholm)⁴	Prevalence of DSM-III-R dementia*	Cross-sectional survey of people ≥75 yr of age, 1987–1989 and 2001– 2004	Age- and sex-standardized dementia prevalence (17.5% in 1987–1989 vs. 17.9% in 2001–2004); lower hazard ratio for death in later cohort sug- gests decreased dementia incidence	Favorable changes in risk factors, especially vascular risk; healthier lifestyles	
Matthews et al. (England)⁵†	Prevalence of dementia in 3 regions	Survey interviews of people ≥65 yr of age, 1989– 1994 (in CFAS I) and 2008–2011 (in CFAS II)	Dementia prevalence (8.3% in CFAS I vs. 6.5% in CFAS II)	Higher educational level, better prevention of vascular disease	

Larson et al. NEJM, 2013.

Supplements May be Helpful When a Doctor Recommends Them

Some dietary supplements can help manage some health conditions.

- Calcium and vitamin D help keep bones strong and reduce bone loss.
- Folic acid decreases the risk of certain birth defects.
- Omega-3 fatty acids from fish oils might help some people with heart disease.
- A combination of vitamins C and E, zinc, copper, lutein, and zeaxanthin (known as AREDS) may slow down further vision loss in people with age-related macular degeneration (AMD).

https://ods.od.nih.gov/factsheets/WYNTK-Consumer/

No Supplement Has Been Shown to Prevent Dementia



Despite Negative Results, Many Commercial Products include (or are Exclusively) Supplements

Levels of Trickery

Use spokespeople with MDs, PhD, and seeming expertise

Seference *in vitro* studies in the literature that suggest mechanistic effects



 \checkmark

Use of (paid) testimonials in the absence of studies

Cite data from poorly controlled (not rigorous) studies

"Clinically tested"

"* These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease."

NeuroQ, Neureva, CocoaVia, Prevagen

Challenges with "Studies" of Commercialized Products

No control group

Inadequate control group

Lack of randomization

Unblinded assessments

No prespecified outcomes

Reporting of secondary or exploratory outcomes as primary

"What's the Worst that Could Happen?"

Supplements can have side effects:

- Vitamin K can reduce the ability of the blood thinner warfarin to prevent blood from clotting.
- St. John's wort can speed the breakdown of many medicines and reduce their effectiveness (including some antidepressants, birth control pills, heart medications, anti-HIV medications, and transplant drugs).
- Antioxidant supplements, such as vitamins C and E, might reduce the effectiveness of some types of cancer chemotherapy.
- Too much vitamin A can cause headaches and liver damage, reduce bone strength, and cause birth defects.
- Excess iron causes nausea and vomiting and may damage the liver and other organs.

https://ods.od.nih.gov/factsheets/WYNTK-Consumer/

Risky Interventions

- Omental transposition
- Peri-spinal injections of approved drugs
- Stem cell clinics
- Stem cell "clinical trials"
- Often costing tens of thousands of dollars

OPINION > LETTERS TO THE EDITOR

Letters: A quick cure for Alzheimer's?

By ORANGE COUNTY REGISTER LETTERS TO THE EDITOR FOR

AUG 29 | Orange County Register March 29, 2017 at 12:00 a.m.

A quick cure for Alzheimer's?

Re: "Is Alzheimer's treatment of injecting stem cells into the brain a breakthrough or quackery?" [News, March 5]: The Register recently reported on a local neurosurgeon who is injecting liposuctioned stem cell serum into the brain of a patient with Alzheimer's disease for \$10,000 per treatment. The neurosurgeon says the patient is improving.

I hope the patient is improving. But, the truth is that harvesting stem cells from human fat and injecting them into the brain could have serious risks and needs close regulation if it is to be studied in human clinical trials. Further, no one should be charged money for participating in a clinical trial, and trials should only be conducted after extensive preclinical research.

Stem Cell Clinic Seminars

Safety claims	 our internal organs". "There's no safety concerns or adverse effects that we've seen I've never seen a rejection. I've never seen allergic reaction from them so they're safe"
Mentioned of clinical	 "The patch duplicates young stem cells and deploys existing stem cells through epigenetics which works with
Mentioned of adverse effects	 "Small percentage of patients experience flu-like symptoms that last no longer than 24–48 hours. I personally never had that happen in my clinic."
Mention of FDA regulation and/or assurance of cell quality	 "FDA allows for minimal manipulation to happen during the transplantation phase"

Hassoun et al., Regen Med 2021

Basic Guidance

- Information should be free!
 - Don't pay for courses, hotel stays, or even books to learn how to maximize brain health
- Participation in research should be free of charge
- Charlatans will go to great lengths
 - Advertisements, webinars, infomercials
 - Free information sessions
 - Paid actors
 - Posting on clinicaltrials.gov to suggest legitimacy
 - Citing real research to suggest legitimacy

Protect Yourself

- <u>https://www.nia.nih.gov</u>
- <u>https://www.alz.org</u>
- <u>https://www.aarp.org/health/dementia/</u>
- <u>https://mind.uci.edu</u>

Protect Yourself



Research is Seeking Ways to Prevent Alzheimer's

Preclinical AD Increases Risk for Dementia



"...clearly indicates that amyloid pathology in cognitively normal older persons is not a benign phenomenon of normal aging but part of a progressive neurodegenerative disease."

Visser and Tijms, JAMA 2017

Donohue et al. JAMA 2017.



Pre-Investigational Treatment

Post-Investigational Treatment



Coanitively

High risk FDA guideline

www.aheadstudy.org

- Age 55-80
- No diagnosis of Mild Cognitive Impairment or dementia
- Have a study partner, either a close relative or friend, who will participate in one study visit per year.
- Have elevated or intermediate levels of ٠ amyloid in the brain found by imaging as part of the study.

What Can YOU do?

- Everyone can contribute
- •Consider the three –ates





don**ate**



particip**ate**

Summary and Conclusions

- As yet, there is no way to definitively predict who will develop AD or dementia
- As yet, there is no definitive way to slow, stop, or prevent AD or dementia
- Brain healthy lifestyle choices (diet, exercise, sleep) may be the most powerful interventions to reduce risk of dementia
- Talk to your doctor before beginning any treatment for memory and thinking problems or the risk of such problems
- Bad actors are willing to capitalize on desperation for financial gain

Acknowledgements

UC Irvine ADRC

- Dan Gillen, PhD
- Chelsea Cox, MSW, MPH (now at U Michigan)
- Michelle Nuño, PhD (now at USC)
- Mary Ryan, PhD (now at Yale)
- Olivia Bernstein
- Navneet Hakhu
- Adrijana Gombosev
- Christian Salazar, PhD
- Megan Witbracht, PhD
- Marina Ritchie
- David Sultzer, MD
- Thabat Dahdoul
- Adam Birnbaum
- Lucy Dolmadjian (now at USC)
- Thuy Lu

• Adam Birnbaum

- Mikaela Nishida
- Lucy Dolmadjian (now at USC)
- Thuy Lu
- Mikaela Nishida
- Kyle Conniff
- Yiren Xu
- Esteban Escobar
- Edwin Duran
- Eunji Russ
- Zion Grant-Freeman

Collaborators

- Jason Karlawish, MD, University Pennsylvania
- Emily Largent, RN, JD, PhD, University Pennsylvania
- Rema Raman, PhD, USC
- Reisa Sperling, MD, Harvard/MGH/B&W

Funding

- NIA R21AG056931, RF1AG059407, P30AG066519, R21AG074371, R01AG077628
- BrightFocus Foundation A2018405S
- IMPACT-AD: NIA U13AG067696, R25AG076392 Alzheimer's Association SG-20-693774
- NCATS UL1 TR000153
- AD Cooperative Study (ADCS): AG010483
- AD Clinical Trial Consortium (ACTC): U24AG057437, R01AG061848
- The participants in our studies and all AD trials