HennepinHealthcare Research Institute

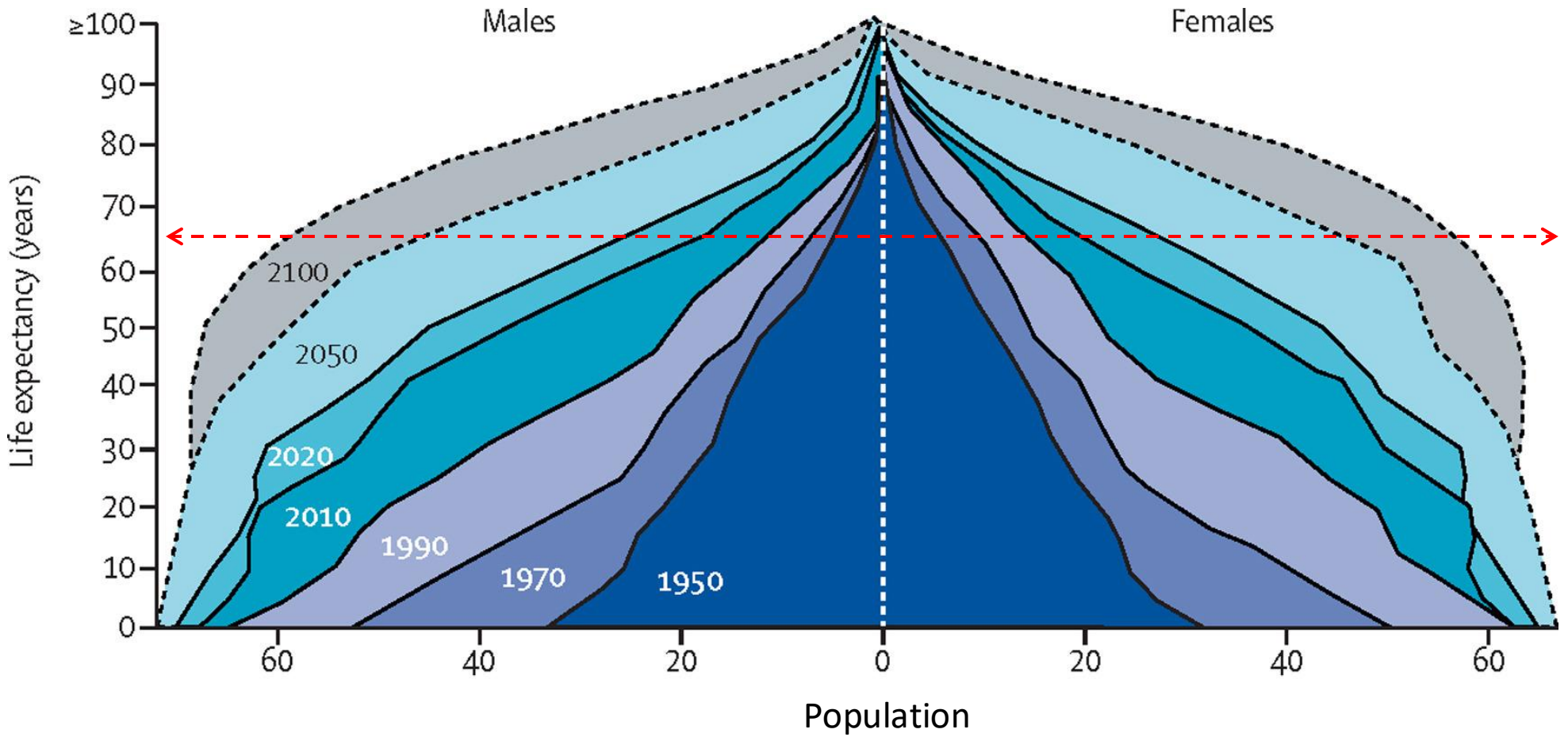
SCHOOL OF PUBLIC HEALTH
UNIVERSITY OF MINNESOTA

Preventive Approach to Advance Brain Health

Behnam Sabayan, MD, PhD, FAHA

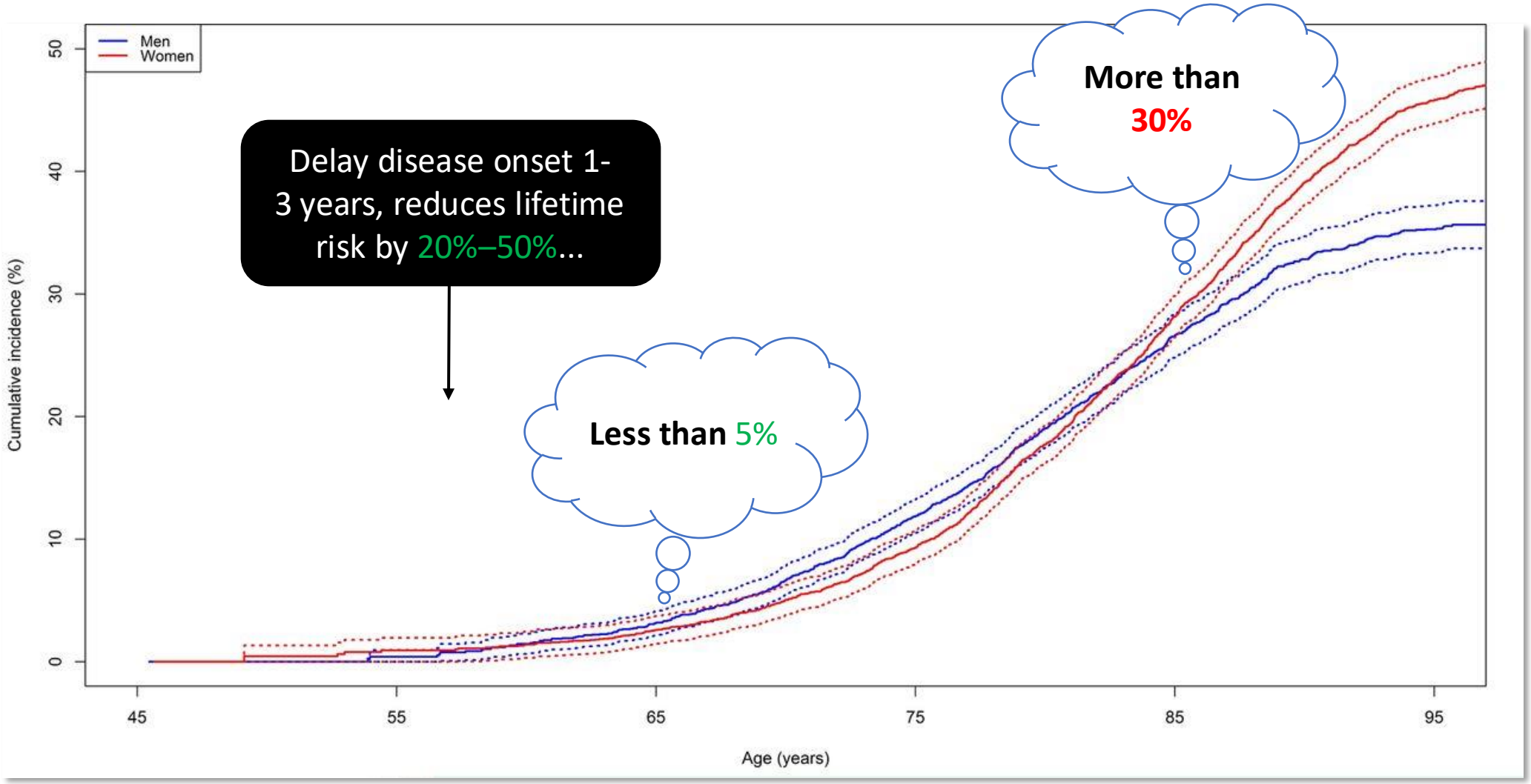
Project ECHO Dementia Didactic, July 2025

A longevity revolution…



Scott. Lancet Healthy Longev 2021; 2: e820–27

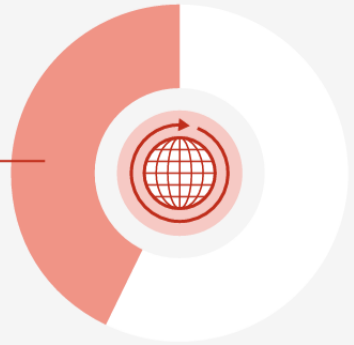
Lifetime risk of a neurological disorder



Licher et al. JNNP. 2019;90(2):148-156.

Number-one leading cause of disease burden worldwide…

In 2021, around **3·40 billion individuals** had conditions affecting the nervous system, equivalent to…



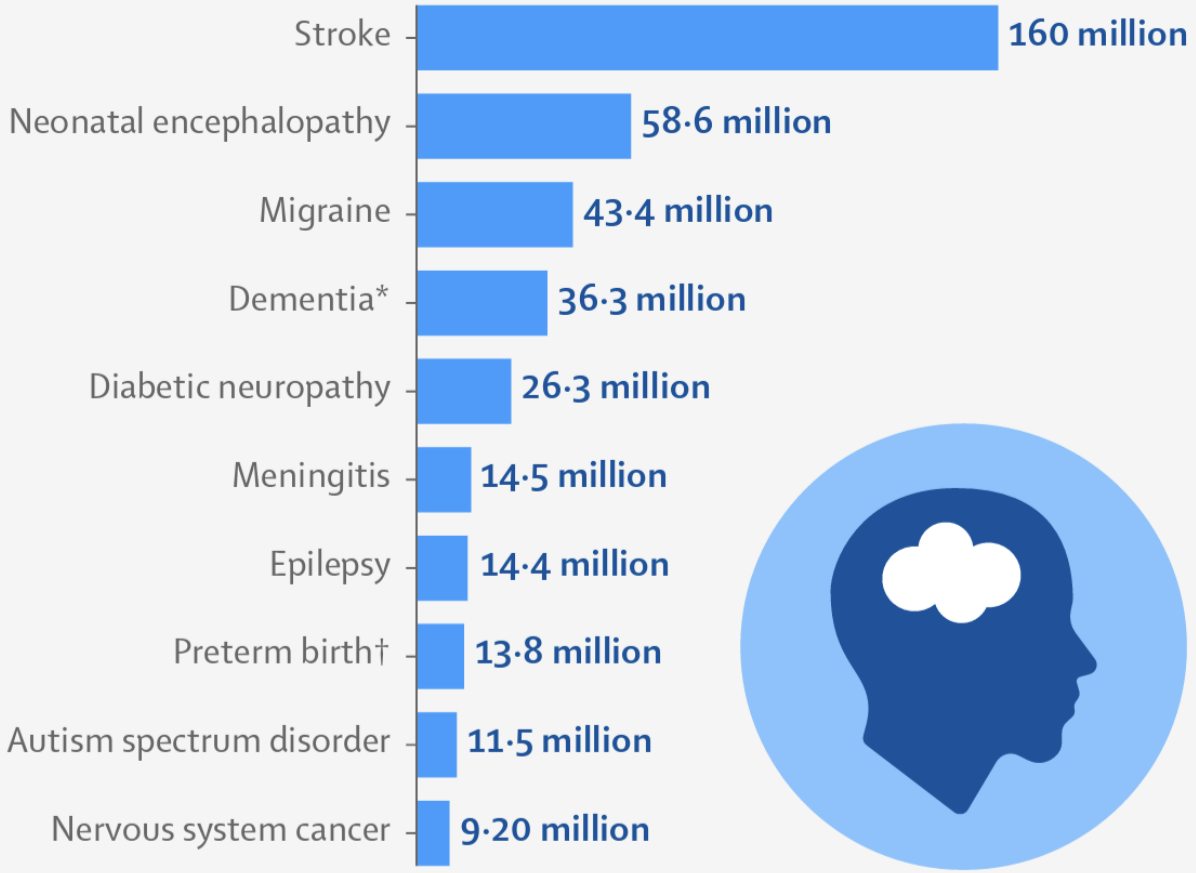
43% of the world population

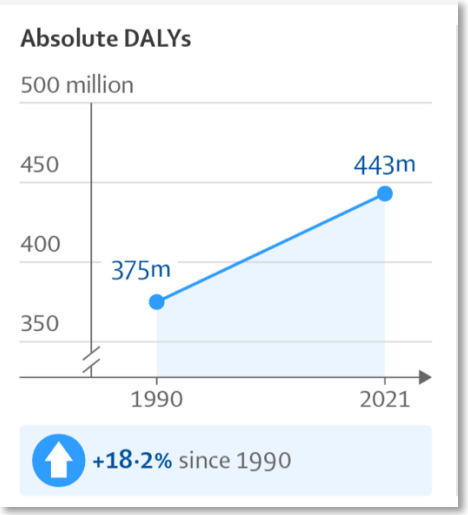
These conditions contributed to…

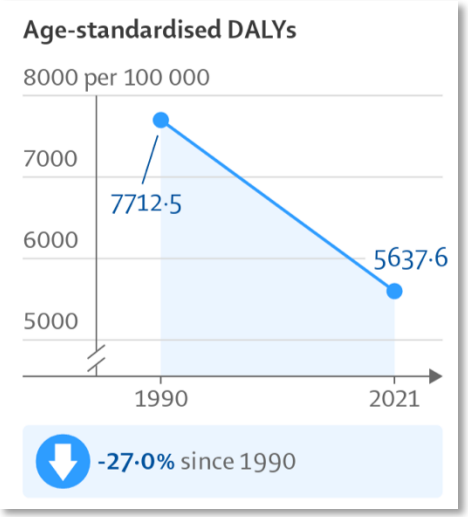
443 million **Disability-adjusted life-years (DALYs)**

… making them the leading cause of disease burden worldwide.

The ten neurological conditions that accounted for the greatest DALYs in 2021 were…







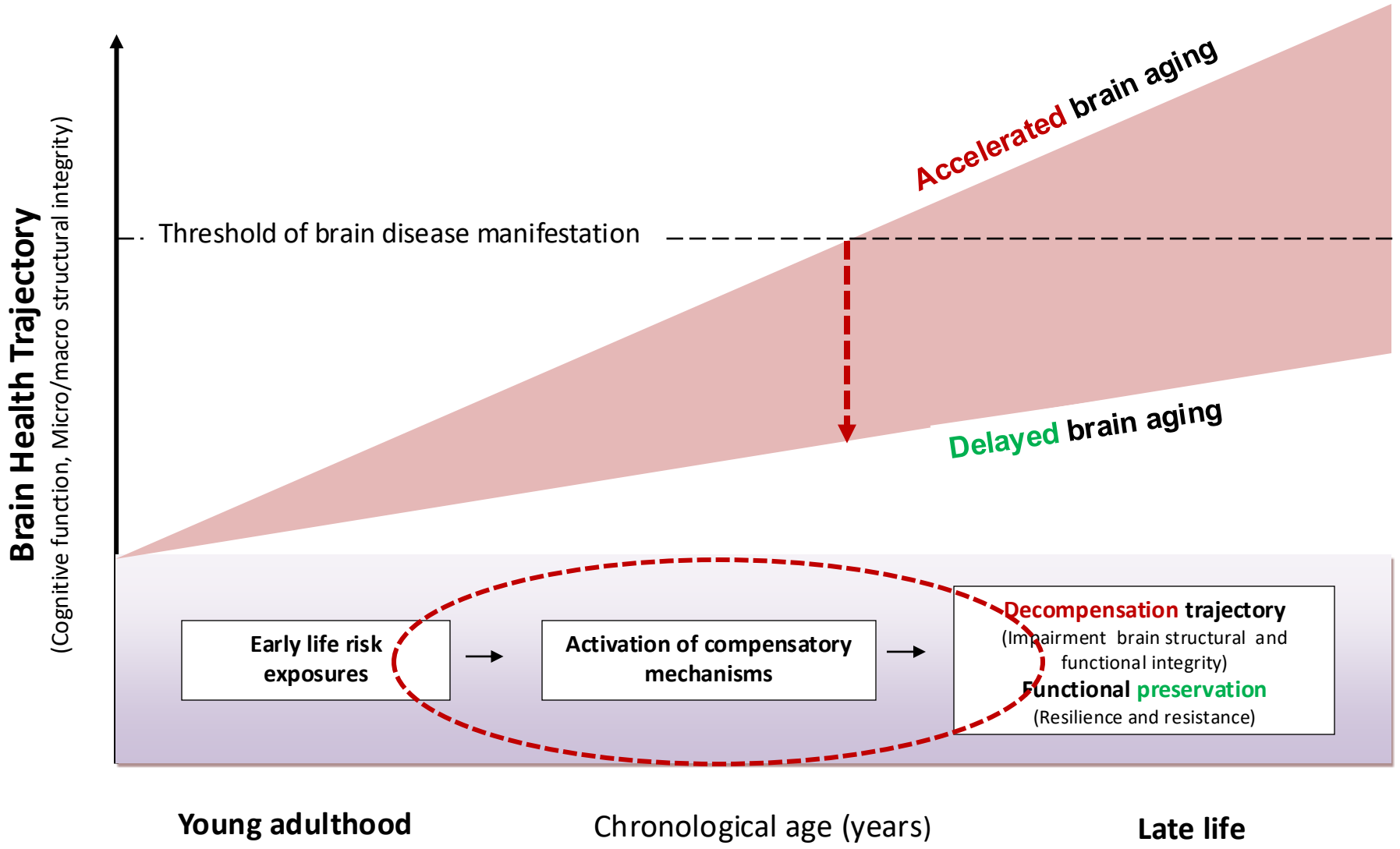
Global Burden of Disease Study 2021. Lancet Neurology 2024; published online March 14. https://doi.org/10.1016/S1474-4422(24)00038-3.

Brain health vs brain disease

- The concept of **"brain health"** has an emphasis on protecting the brain from reaching a **critical point** where overt clinical symptoms are present and disease progression is irreversible.
- Maintenance of brain health is **beyond not having a neurological disease.** Maintenance of brain health leads to preservation of thought processing, planned actions, and sensory, motor, and emotional connections, which all positively influence the quality of lives and well-being of individuals, families, and communities.

Sabayan, et al. Neurology. 2021;97(19):916-919.

Brain health in aging: (key windows of opportunity)



Sabayan, et al. *Lancet Healthy Longev*. 2023;4(6):e274-e283

Middle Age: Marked by **Accelerated Biological Aging**

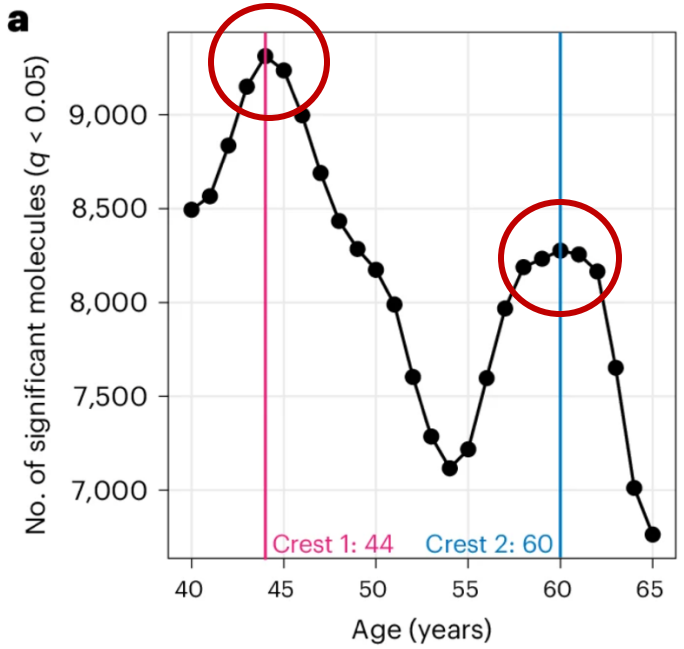
nature aging

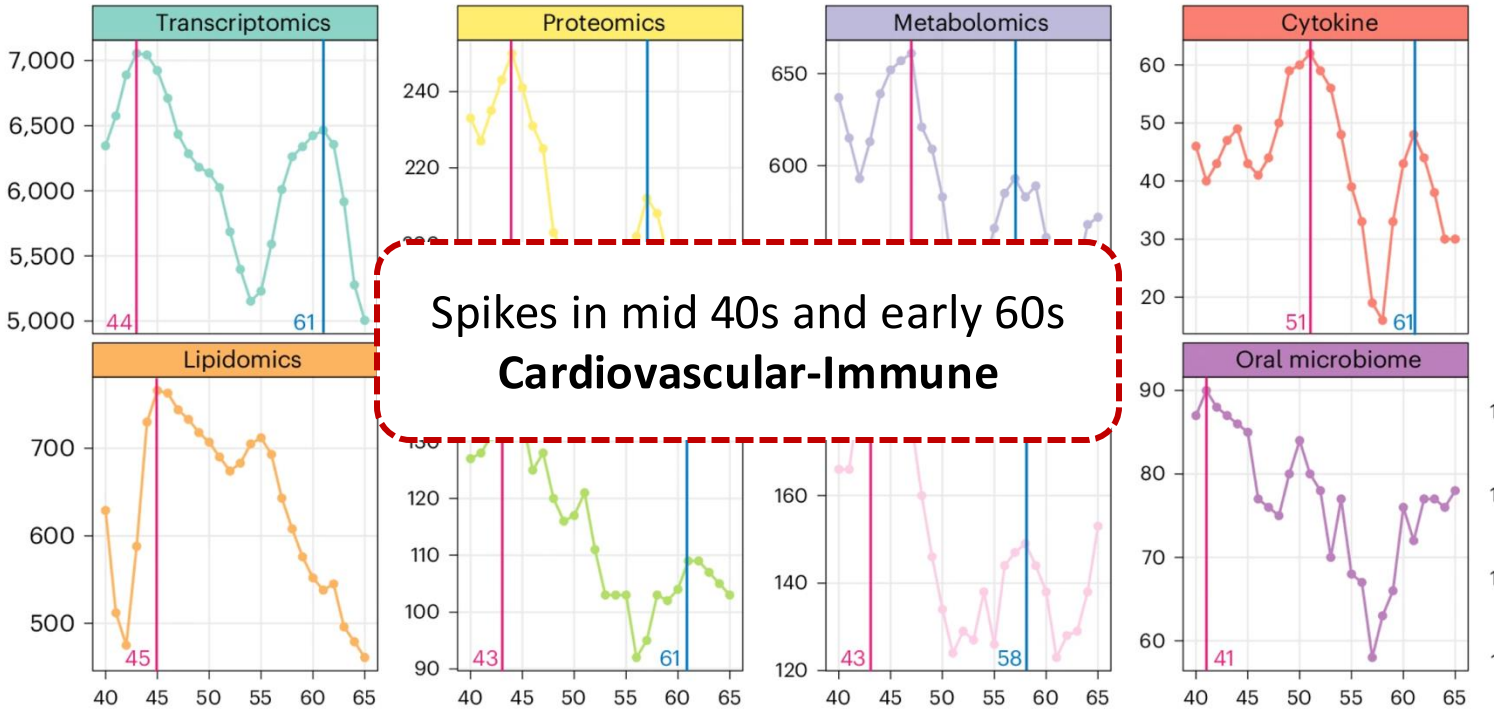
Article

https://doi.org/10.1038/s43587-024-00692-2

Nonlinear dynamics of multi-omics profiles during human aging

The study performed a **comprehensive multi-omics profiling** on a longitudinal human cohort of 108 participants, aged between **25 years and 75 years**.





Shen et al. Nat Aging. 2024;4(11):1619-1634.

PNAS RESEARCH ARTICLE | NEUROSCIENCE OPEN ACCESS

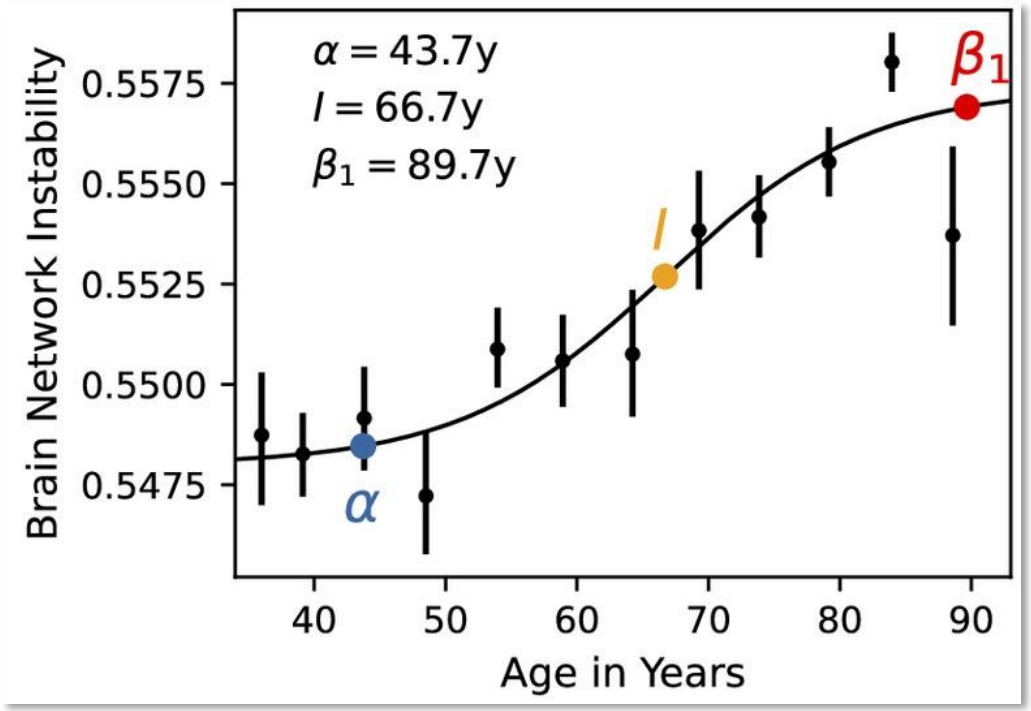
Brain aging shows nonlinear transitions, suggesting a midlife "critical window" for metabolic intervention

Botond B. Antal[a,b,c], Helena van Nieuwenhuizen[b,c,d], Anthony G. Chesebro[a,b,c], Helmut H. Strey[a,b,c], David T. Jones [e], Kieran Clarke[f], Corey Weistuch[g], Eva-Maria Ratai[c], Ken A. Dill [b,1], and Lilianne R. Mujica-Parodi [a,b,c,d,h,1]

Contributed by Ken A. Dill; received August 16, 2024; accepted January 13, 2025; reviewed by Peter Crawford and Mark P. Mattson

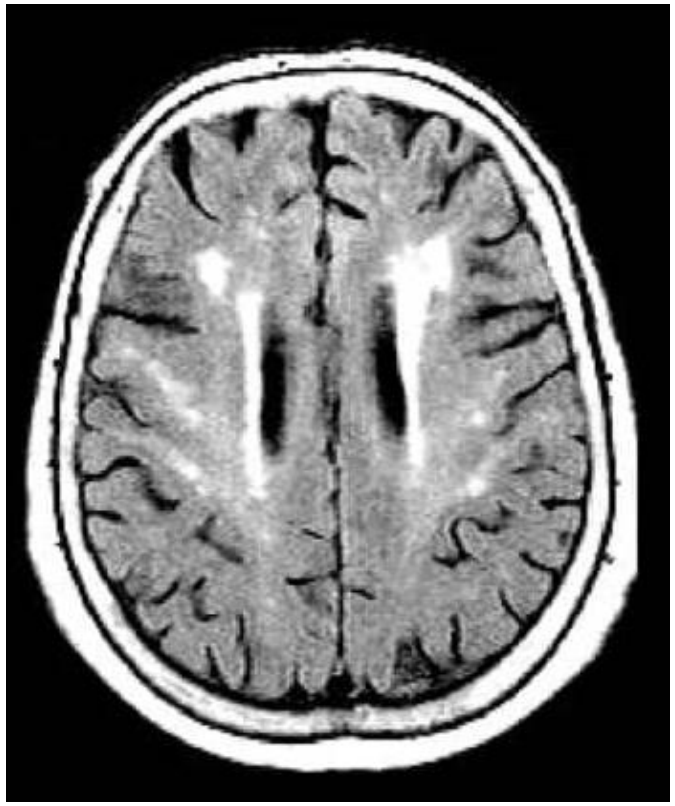
March 3, 2025 | 122 (10) e2416433122 | https://doi.org/10.1073/pnas.2416433122

The landmark alpha was associated most strongly with an increase in HbA1c (t = 4.8, P = 4E-6), while the / landmark was associated most strongly with an increase in systolic blood pressure (t = 5.7, P = 3E-8).



Determinants of brain health: Game of forces!

- Maintenance of brain health is the product of **interacting driving forces**
- Dose, duration and frequency of **risk factor exposure.**
- **Resistance** denotes the ability to avoid adversity and establishment of pathology. **The act of repair and maintenance**.
- **Resilience** denotes the ability to cope in the face of adversity. Inherent individual's **ability to maintain function despite pathology**.

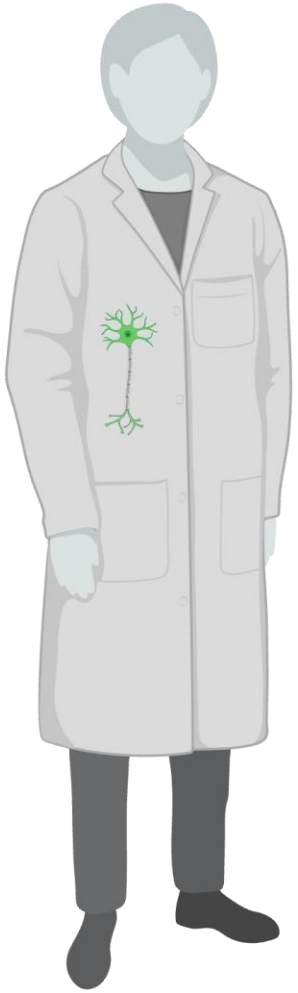


A **64 y/o** Male with history of **HTN, DM, smoking and prior TIAs**. MRI brain showed moderate degrees of **periventricular and subcortical white matter disease** as well as **lacunar infarcts**. He **lives independently**, manages his finances, does not have any focal neurological deficits, **his gait is intact although…** he reports he is slightly slower in his thinking and ambulation as compared to his early 50….

Life course cerebrovascular risk exposure!

Signs of impaired brain structural integrity and vulnerable brain with exhausted resistance…

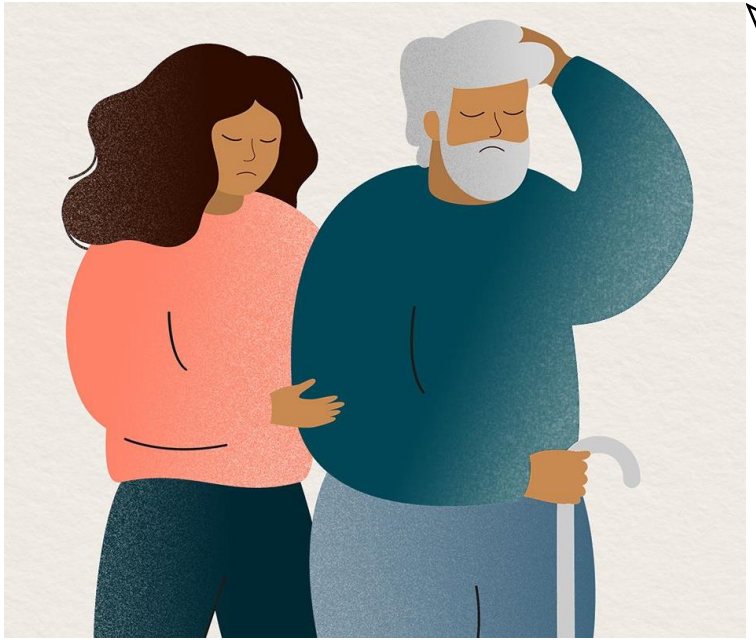
Relatively maintaining brain function with resilience…



Teaching moment!

Pyramid Model of Actions in Preventive Neurology

Sabayan B, et al. Neurology. 2025;105(1):e213785



Jennifer: *I'm 48 years old, and I'm here primarily for my father, but I was wondering if you could also help me with some medical questions…*

You: *Of course. How can I help?*

Jennifer: *Well, as you know, my father was recently diagnosed with dementia—we saw it coming for a while. I also lost my mother 10 years ago after she had a massive stroke. My sister, who is 10 years older than me, had a mini-stroke and is now on blood thinners.*

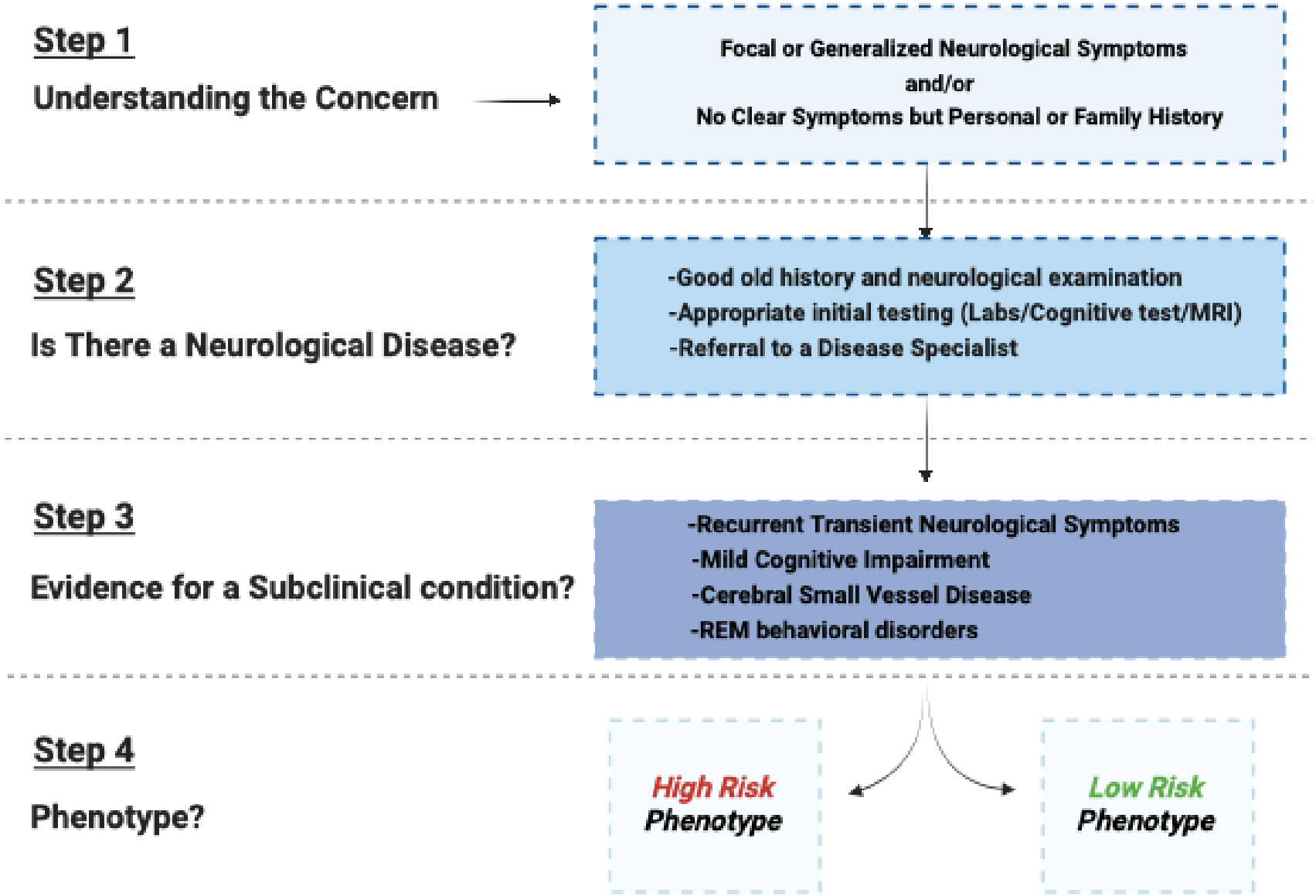
As for me, I'm fairly healthy, but sometimes I forget names, and my cholesterol is mildly elevated. I work as an accountant, so I sit with computer for long hrs. Given my family history, I just want to know—what can I do to lower my risk of stroke and dementia?

Step 1: Phenotype the State of Brain Health

Step 2: Identify Areas of Intervention

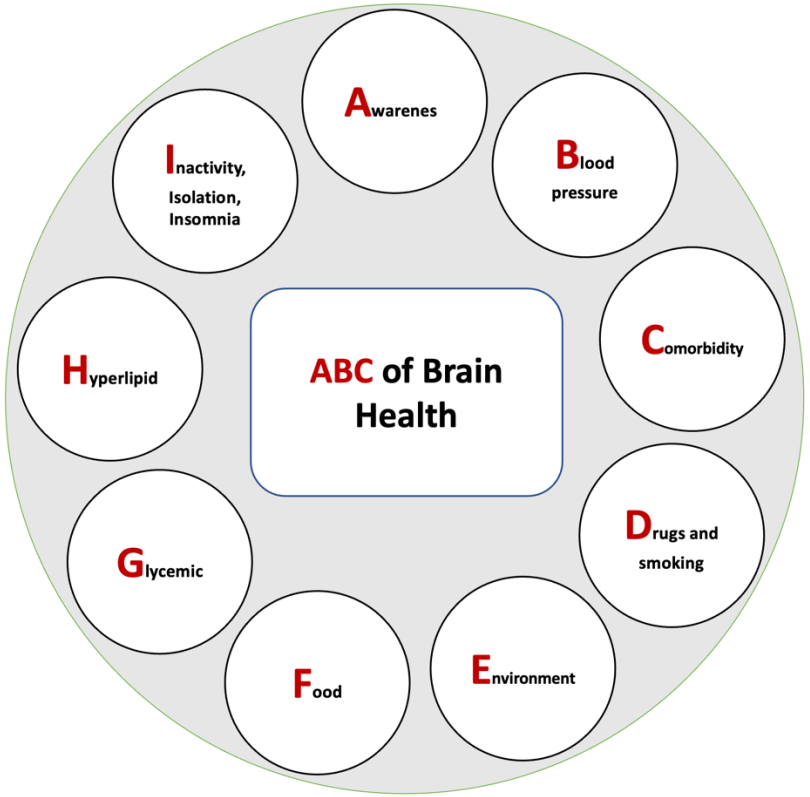
Step 3: Intervention and Team Work

Phenotyping and Assessing Brain Health Status.



Areas of Intervention!

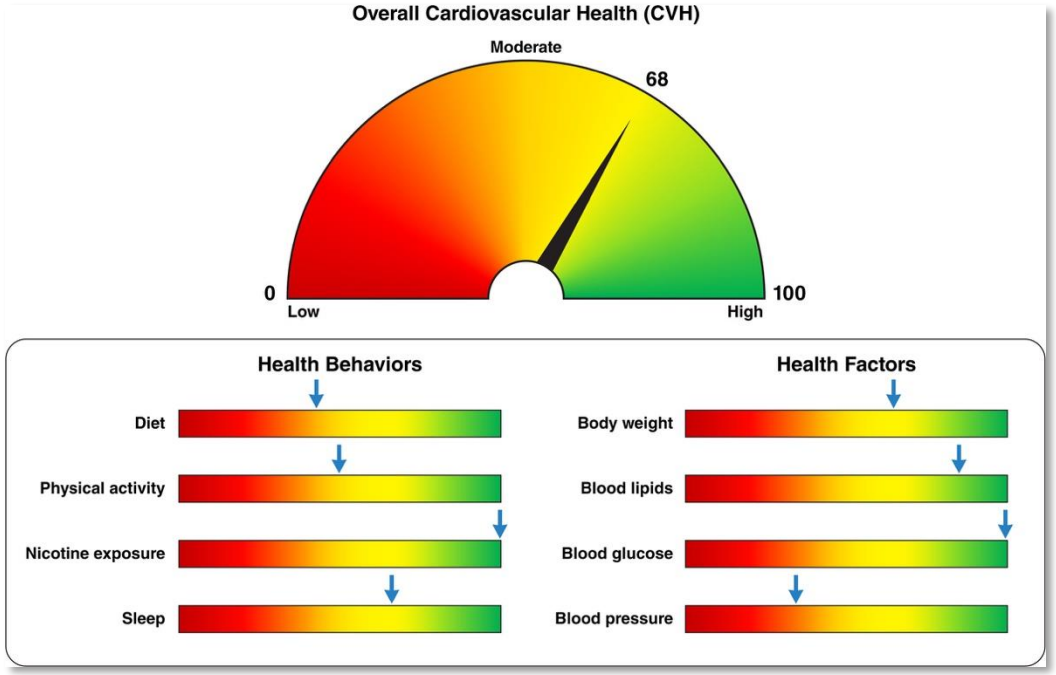
Lloyd-Jones D, et al Circulation. 2022;146(5):e18-e43.



Sabayan B, Semin Neurol. 2022;42(5):571-582.

https://www.massgeneral.org/neurology/mccance-center/about/brain-care-score

Selwa et al Neurology. 2025;104(1):e210226.

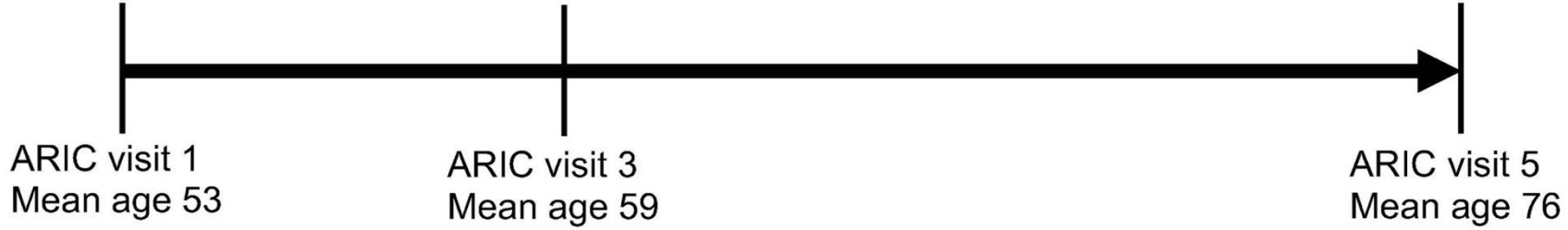


Life's Essential 8™ for kids

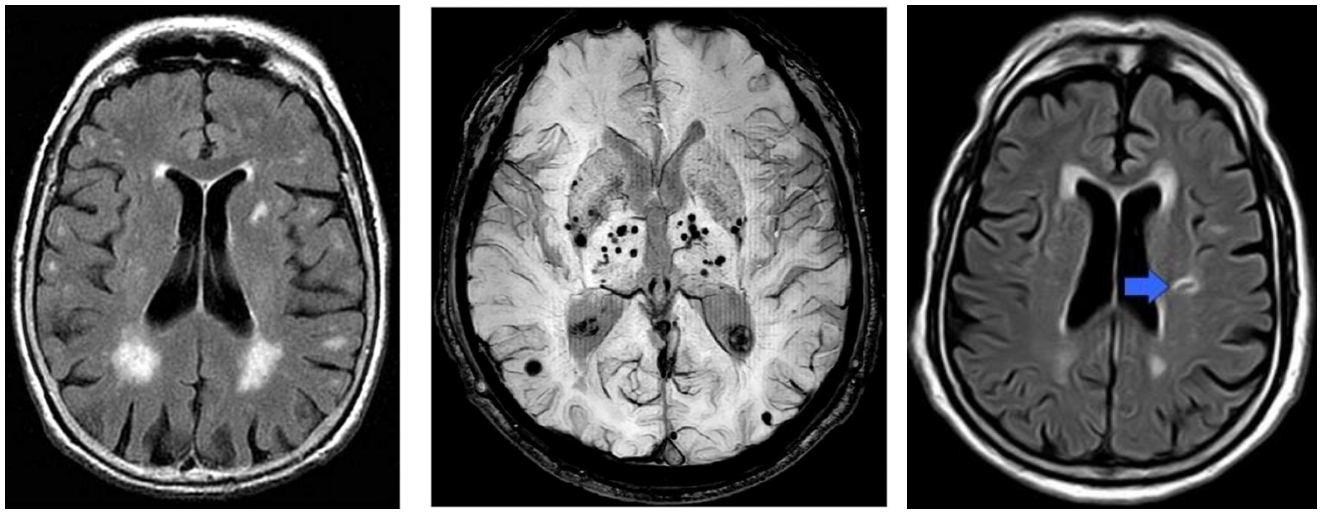
- CV health score from **0 to 100 points**
- Scores below 50 indicate **"poor"**
- 50-79 is considered **"moderate"**
- Scores of 80 and above indicate **"high"**
- Add **TBI and Depression** to the equation

Is there brain-based life-course evidence?

Is improving cardiovascular health linked with lower risk of MRI markers of cerebrovascular disease?



Change in cardiovascular health (Life's Simple 7) within midlife (visit 1 to visit 3) and from midlife to late-life



White matter hyperintensity volume

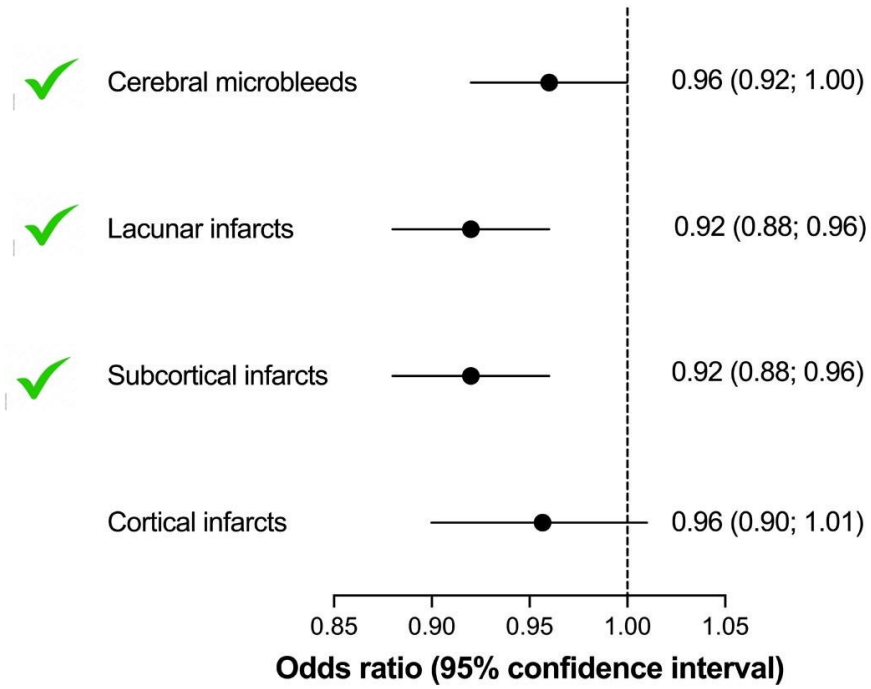
Brain microbleeds

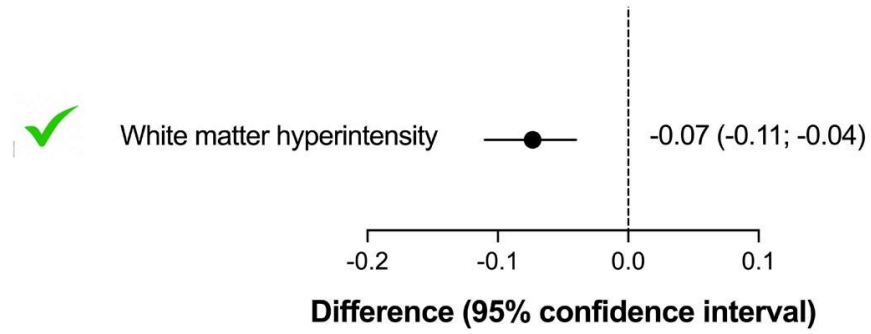
Lacunar, subcortical, and cortical infarcts

Sedaghat et al. Stroke. 2023;54:1280–1288

Change in Cardiovascular Health within Midlife

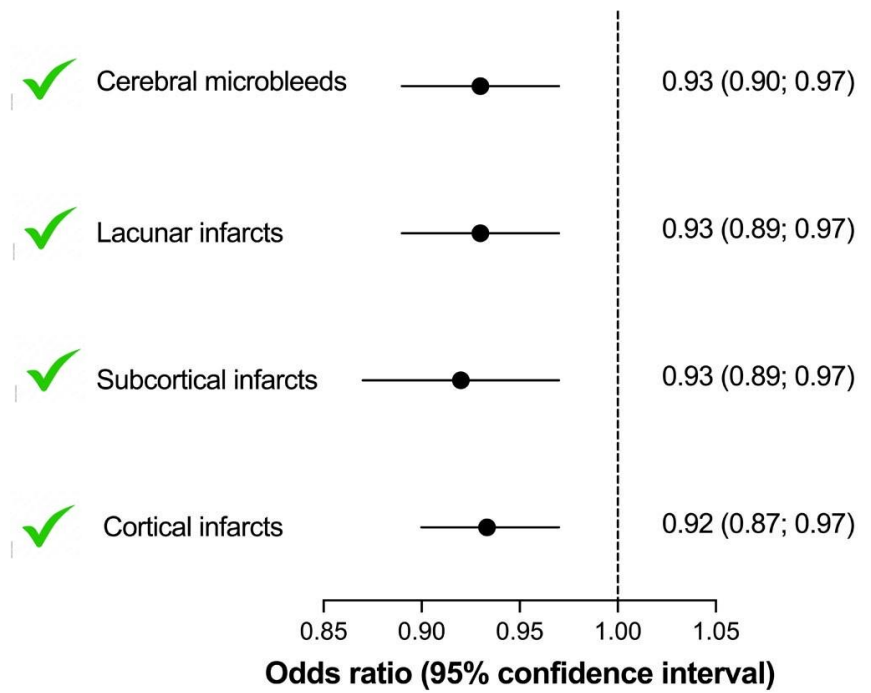
Per-point increase in the difference in 14-point cardiovascular health score

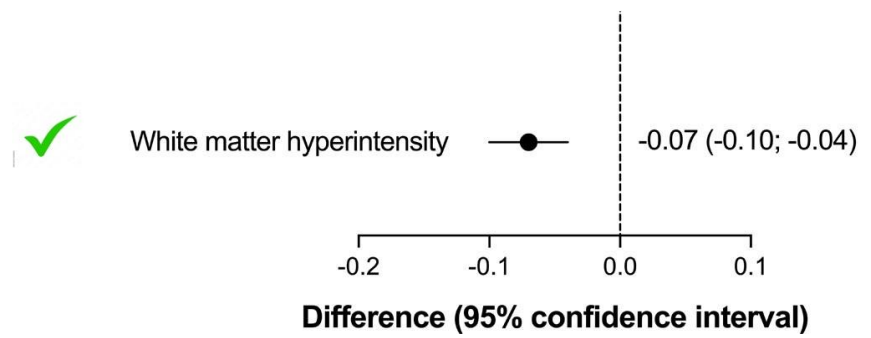




Change in Cardiovascular Health between Midlife and Late-life

Per-point increase in the difference in 14-point cardiovascular health score





ALZHEIMER'S ASSOCIATION | Alzheimer's & Dementia®
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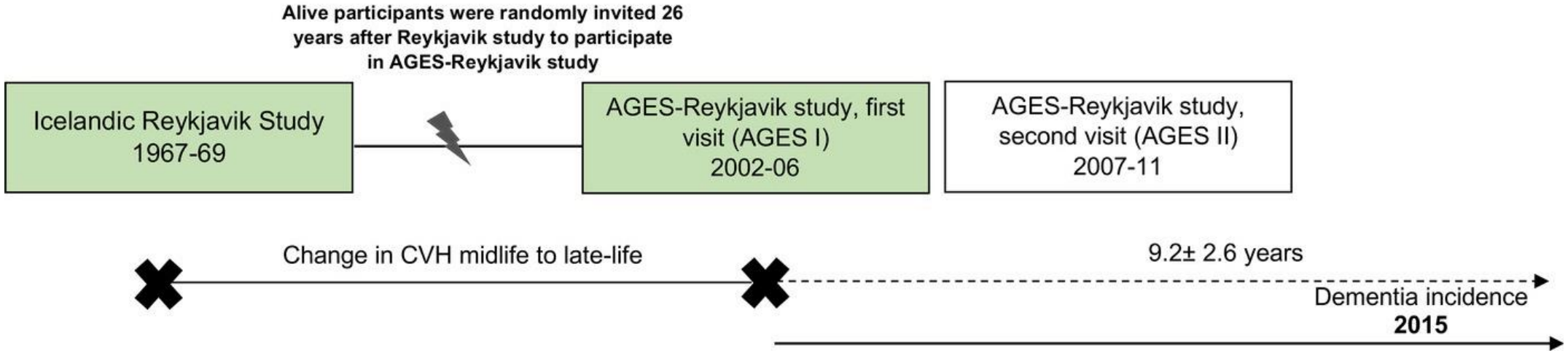
RESEARCH ARTICLE | Open Access

Association of change in cardiovascular risk factors with incident dementia

Sanaz Sedaghat, Pamela L. Lutsey, Yuekai Ji, Jean-Philippe Empana, Farzaneh Sorond, Timothy M. Hughes, Thomas H. Mosley, Rebecca F. Gottesman, David S. Knopman, Keenan A. Walker, Vilmundur Gudnason, Lenore J. Launer, Thomas T. van Sloten ... See fewer authors

Cardiovascular risk modification in midlife is key for dementia prevention.



A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial

Tiia Ngandu, PhD • Jenni Lehtisalo, MSc • Alina Solomon, PhD • Esko Levälahti, MSc • Satu Ahtiluoto, MD • Prof Riitta Antikainen, PhD • et al. Show all authors

- **CAIDE** Risk Score, involving information on age, educational level, hypertension, hypercholesterolemia, obesity, and physical inactivity.
- **Multidomain** intervention (diet, exercise, cognitive training, vascular risk monitoring)

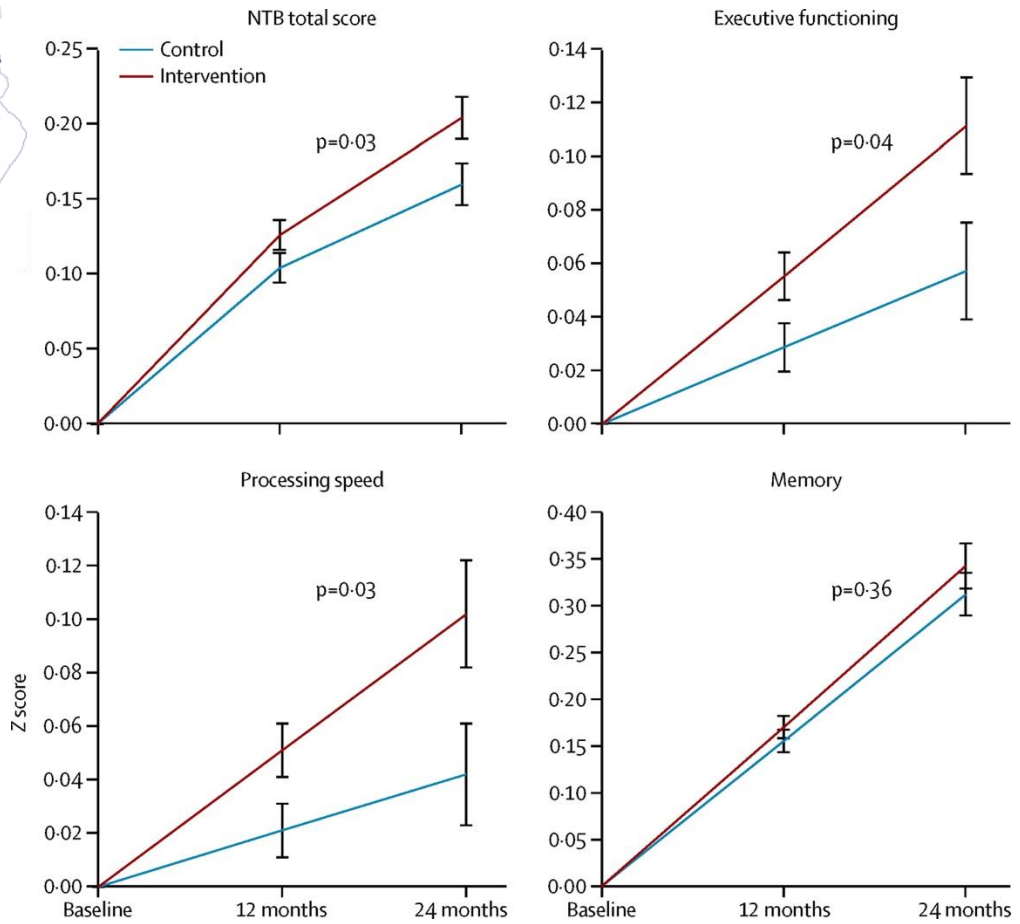
Intervention group compared to control group

Overall cognition
25%
greater improvement

Executive function ✓
83%
greater improvement

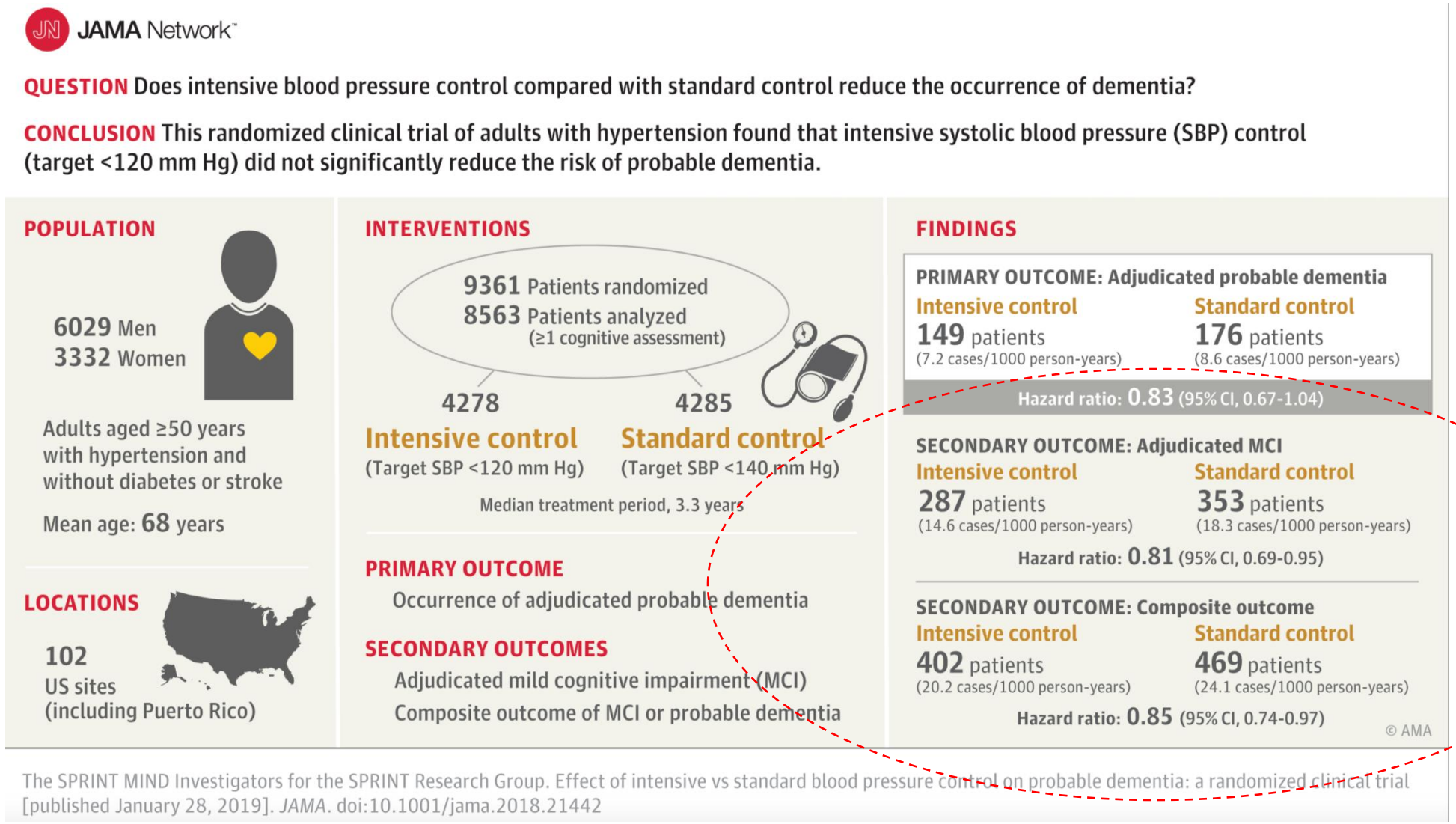
Complex memory tasks
40%
greater improvement

Processing speed ✓
150%
greater improvement



Lancet. 2015;385(9984):2255-63.

Intensive Blood Pressure Control and Cognitive Impairment



The SPRINT MIND Investigators for the SPRINT Research Group. Effect of intensive vs standard blood pressure control on probable dementia: a randomized clinical trial [published January 28, 2019]. *JAMA*. doi:10.1001/jama.2018.21442

Original Investigation

ONLINE FIRST

November 27, 2023

Effect of Personalized Risk-Reduction Strategies on Cognition and Dementia Risk Profile Among Older Adults

The SMARRT Randomized Clinical Trial

Kristine Yaffe, MD[1,2,3,4]; Eric Vittinghoff, PhD[2]; Sascha Dublin, MD, PhD[5]; et al

Aged 70 to 89 years with at least 2 dementia risk factors. 62.8% female.

Figure 2. Prevalence and Combination of Risk Factors for the 172 Participants in the Systematic Multi-Domain Alzheimer Risk Reduction Trial

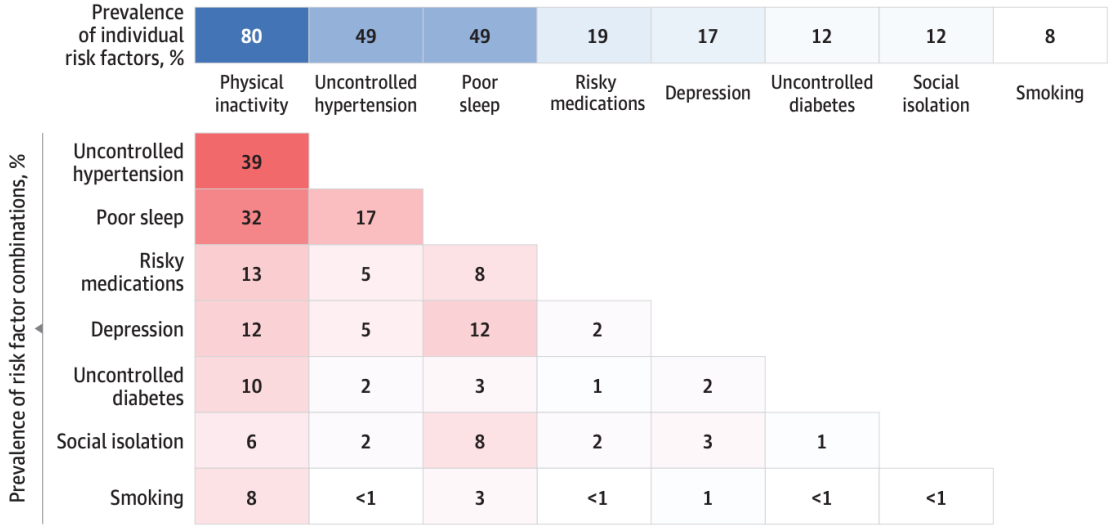
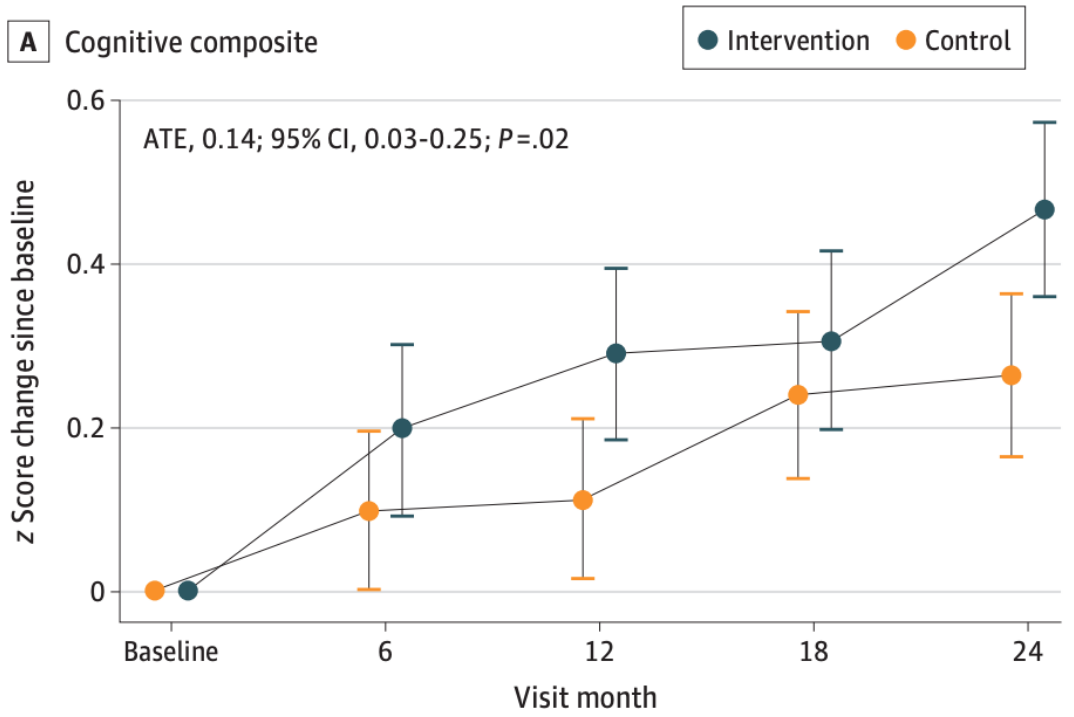


Figure 3. Primary and Secondary Outcomes



JAMA Intern Med. 2024;184(1):54-62.

Increasing evidence from clinical trials,…

nature medicine

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Article | Published: 28 January 2025

An online multidomain lifestyle intervention to prevent cognitive decline in at-risk older adults: a randomized controlled trial

Design: Single-blind RCT
Population: Community-dwelling 55-70 yrs adults
Sample Size: *n* = 6,104, 64% F
Risk Profile: At increased risk

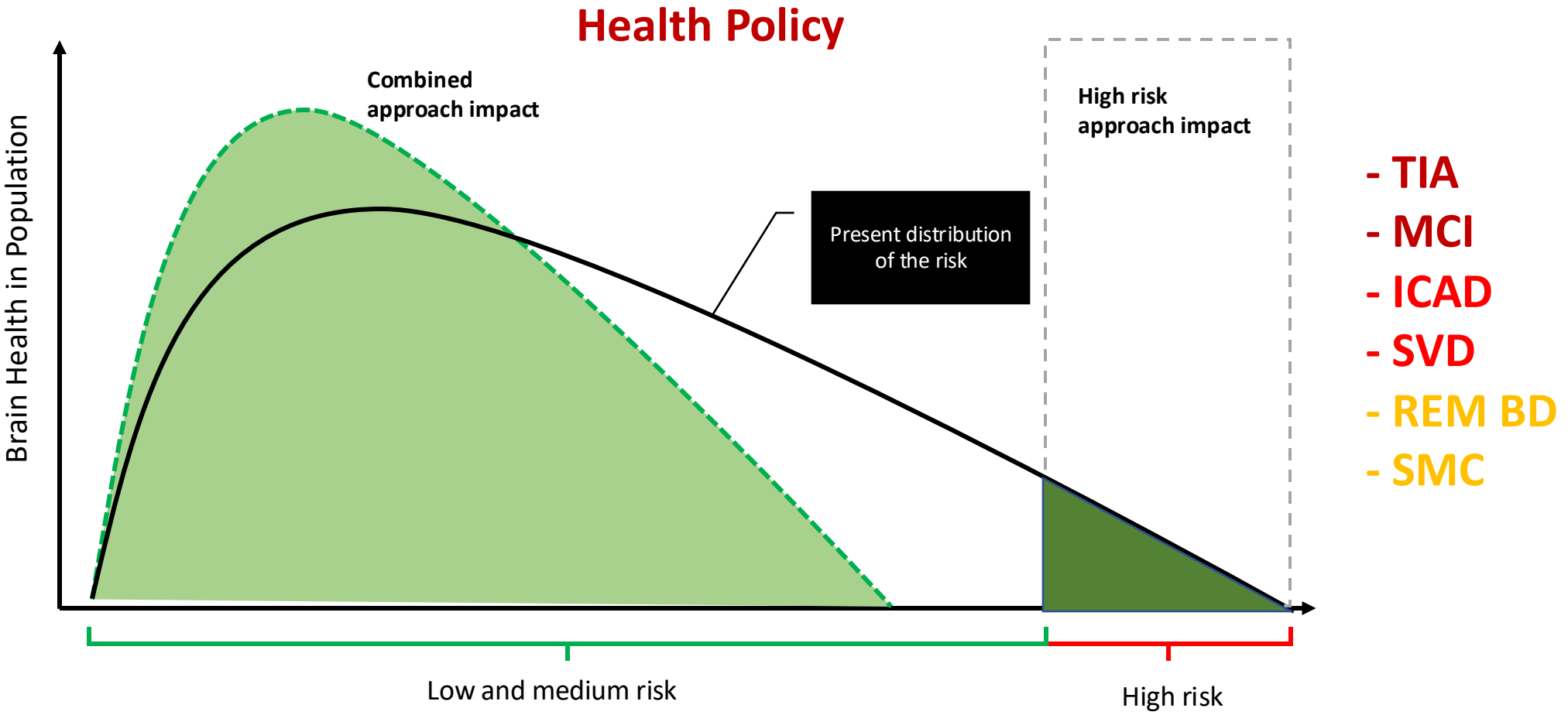
Personalized digital intervention targeting diet, exercise, and mental well-being can slow cognitive decline and reduce dementia risk in at-risk middle aged and older adults.

Successful trials tend to:
- Focus on AT RISK (CV) but cognitively intact
- Focus on MULTI-DOMAIN intervention

Less discussed observations:
- Adherence can be challenging, at least about a third of participants.

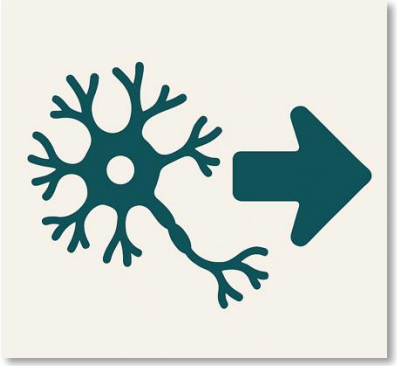
Where should we go from here?

Population vs **High Risk** Approach in Prevention



Sabayan et al. Clin Geriatr Med. 2023;39(1):1-14.

Future Direction



- **Biomarkers** of “Pre-Clinical” high risk brain health phenotypes**.**
- AI will change the landscape for early detection and monitoring (**AI-biofeedback**).
- **Power of** patients’ data and **EMR.**
- **Preventive Neurology**: An evolving field.

Wrap up…

- **Brain health is maleable**—Family history/current risks are not the destiny.
- **Midlife** is the sweet spot for prevention**.**
- **We** can practice preventive neurology at **every level**—clinical, community, and policy.
- **Start with** brain health **phenotyping** to guide **personalized** care.
- **Think prevention:** from high-risk to the general population.
- **Preventive neurology** is a developing field—training and expertise are growing

Appreciate all colleagues and collaborators!

National Institute on Aging

University of Minnesota

HennepinHealthcare Research Institute

Brain health: The art of brain preservation!