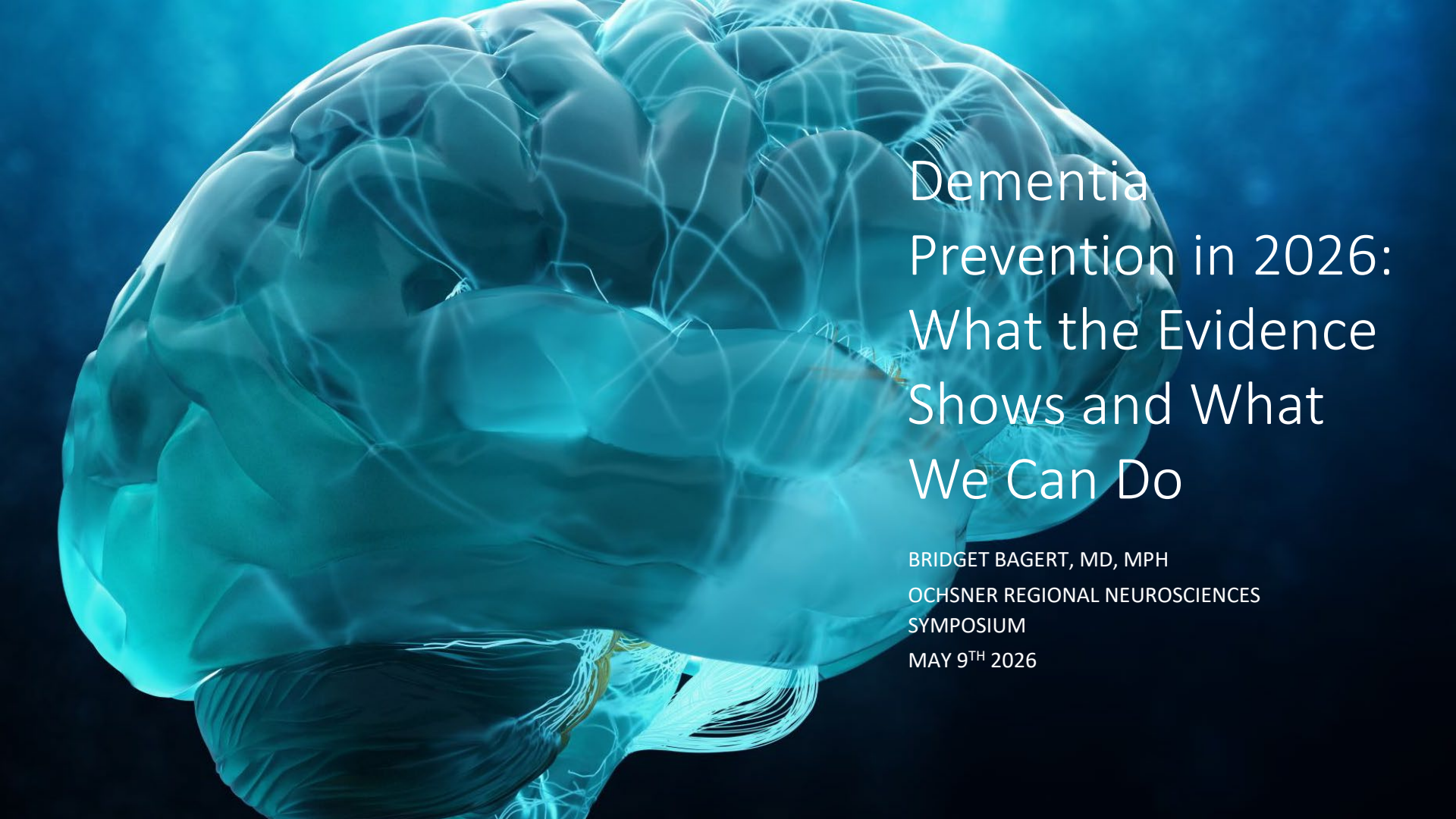


Dementia Prevention in 2026: What the Evidence Shows and What We Can Do

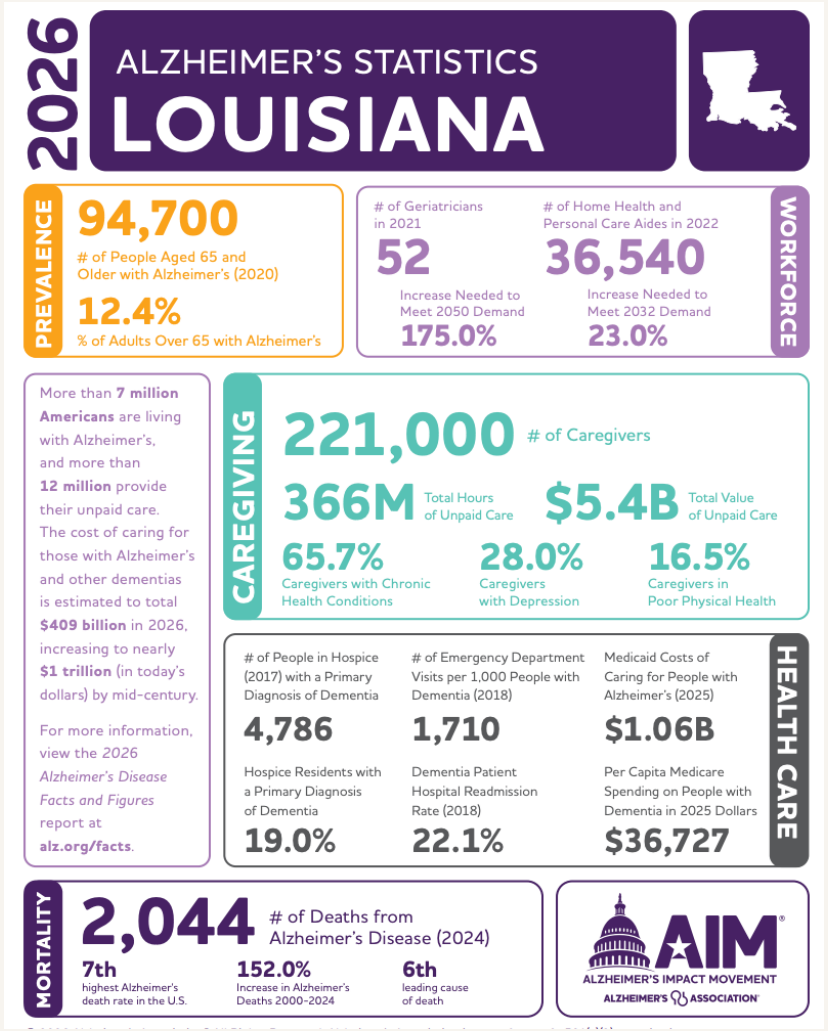
BRIDGET BAGERT, MD, MPH

OCHSNER REGIONAL NEUROSCIENCES SYMPOSIUM

MAY 9TH 2026

DISCLOSURES

- TG Therapeutics: Speaker, Consultant
- Sanofi: Speaker, Consultant
- EMD Serono: Speaker, Consultant
- Genentech: Consultant



- 7th highest Alzheimer's death rate in the US
- 12.4% of adults over 65 years with AD

Conventional Wisdom

- AD not modifiable
- Genetically predetermined
- Biologically relentless – amyloid cascade
- View began to shift in 2015 with the FINGER trial – first RCT that proved multi-lifestyle intervention could protect cognition in at risk older adults
- Then the first Lancet Commission report in 2017 suggested that up to 35% of dementia is potentially preventable

FINGER Trial Overview

Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability · 2015

FINGER was the first large-scale RCT to demonstrate that a multi-domain lifestyle intervention could protect cognitive function in older adults at elevated dementia risk. Conducted across six Finnish centres, it randomised 1,260 adults aged 60–77 — selected for elevated CAIDE dementia risk scores but without dementia or MCI at baseline — to a 2-year structured intervention versus general health advice.

1,260

participants aged 60–77

2 yr

intervention duration

Ngandu T et al. · The Lancet · 2015 | Kivipelto M et al. · Lancet Neurology · 2018

FINGER: Intervention and Outcomes

Four-domain lifestyle intervention vs. general health advice · NTB composite primary outcome

The **intervention covered four domains**: (1) dietary counselling based on Finnish nutrition guidelines; (2) aerobic and strength exercise in supervised group sessions; (3) computer-based cognitive training; and (4) vascular risk monitoring including blood pressure, weight, and metabolic markers.

The **primary outcome was a composite Neuropsychological Test Battery** (NTB) z-score spanning memory, executive function, processing speed, and attention

4

intervention domains
(diet, exercise, cognition, vascular)

NTB

composite cognitive
outcome — 4 domains

Ngandu T et al. · The Lancet · 2015 | Kivipelto M et al. · Lancet Neurology · 2018

FINGER: Results and Key Lessons

Cognitive outcomes, limitations, and legacy

The **intervention group scored 40% better than controls** on the NTB composite (between-group difference 0.04 SD; p=0.03), with the largest benefits in executive function and processing speed.
Both groups improved from baseline, raising questions about practice effects — but the between-group difference held.
Benefit was consistent regardless of APOE-ε4 status.

40%
better NTB score
vs. control (p=0.03)

0.04
SD between-group
difference

APOE
benefit consistent
regardless of ε4 status

Ngandu T et al. · The Lancet · 2015 | Kivipelto M et al. · Lancet Neurology · 2018

Dementia prevention, intervention, and care: 2024 report of the *Lancet* standing Commission

Gill Livingston, Jonathan Huntley, Kathy Y Liu, Sergi G Costafreda, Geir Selbæk, Suvarna Alladi, David Ames, Sube Banerjee, Alistair Burns, Carol Brayne, Nick C Fox, Cleusa P Ferri, Laura N Gitlin, Robert Howard, Helen C Kales, Mika Kivimäki, Eric B Larson, Noeline Nakasujja, Kenneth Rockwood, Quincy Samus, Kokoro Shirai, Archana Singh-Manoux, Lon S Schneider, Sebastian Walsh, Yao Yao, Andrew Sommerlad*, Naaheed Mukadam*

Lancet 2024; 404: 572–628

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See Comment page 501

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Executive summary

The 2024 update of the *Lancet* Commission on dementia provides new hopeful evidence about dementia prevention, intervention, and care. As people live longer, the number of people who live with dementia continues to rise, even as the age-specific incidence decreases in high-income countries, emphasising the need to identify and implement prevention approaches. We have summarised the new research since the 2020 report of the *Lancet* Commission on dementia, prioritising systematic reviews and meta-analyses and triangulating findings from different studies showing how cognitive and physical reserve develop across the life course and how reducing vascular damage (eg, by reducing smoking and treating high blood pressure) is likely to have contributed to a reduction in age-related dementia incidence. Evidence is increasing and is now stronger than before that tackling the many risk factors for dementia that we modelled previously (ie, less education,

majority populations within them, so dementia is more likely to develop at an earlier age.

Evidence for specific risk factors suggests that all children should be educated, and a long duration of education is beneficial. It is important to be cognitively, physically, and socially active in midlife (ie, aged 18–65 years) and late life (ie, aged >65 years), with novel evidence showing that midlife cognitive activity makes a difference even in people who received little education. The evidence that treating hearing loss decreases the risk of dementia is now stronger than when our previous Commission report was published. Use of hearing aids appears to be particularly effective in people with hearing loss and additional risk factors for dementia. New evidence also suggests that treating depression and smoking cessation might both reduce dementia risk.

We report the new finding that reducing air pollution is linked with improved cognition and a reduction in

Dementia Prevention, Intervention & Care

2024 Lancet Standing Commission Report

Take-away: Up to 45% of all dementia cases may be preventable through modification of 14 known risk factors — across the full human lifespan.

45%
of dementia cases potentially preventable

14
modifiable risk factors identified

2
new factors added vs. 2020 report

Livingston G et al. · The Lancet · 2024

Methods & Study Design

1

Study type

Updated systematic evidence review by the Lancet Standing Commission on Dementia Prevention, Intervention, and Care. This is the third iteration (2017, 2020, 2024).

2

Outcome

Population attributable fraction (PAF) calculated for each modifiable risk factor — the proportion of dementia incidence that would be eliminated if that risk factor were fully removed from the population.

3

Risk factor selection

Factors included if supported by meta-analytic evidence of association with dementia AND biological plausibility. Two new factors added in 2024: uncorrected vision loss (PAF 2%) and elevated LDL cholesterol (PAF 7%).

4

Lifespan model

Risk factors stratified by life stage: early life (<18 yrs) — education; midlife (45–65 yrs) — hypertension, obesity, hearing loss, TBI, alcohol, smoking; late life (>65 yrs) — social isolation, visual loss

5

PAF methodology

Assumes causal relationships — observational evidence, not RCT proof for most factors.

6

Limitations

PAF estimates assume all risk factors are fully modifiable; real-world impact will be lower.

Key Findings

1

Total PAF: 45%

Combined population attributable fraction across all 14 risk factors is 45% — up from 40% in the 2020 report. The remaining 55% of dementia risk is attributed to non-modifiable factors including age and genetics.

2

Largest individual PAFs

Highest PAFs: hearing loss (7%), LDL cholesterol (7%), physical inactivity (4%), depression (3%), social isolation (5%), hypertension (2%),

3

Hypertension — midlife priority

Systolic BP >130 mmHg in midlife significantly increases dementia risk. Treatment to target in the 40–65 age window has the highest modifiable impact per individual patient.

4

Hearing loss underrecognized

Hearing loss carries one of the largest PAFs (7%). Hearing aid use reduces dementia incidence in observational studies.

5

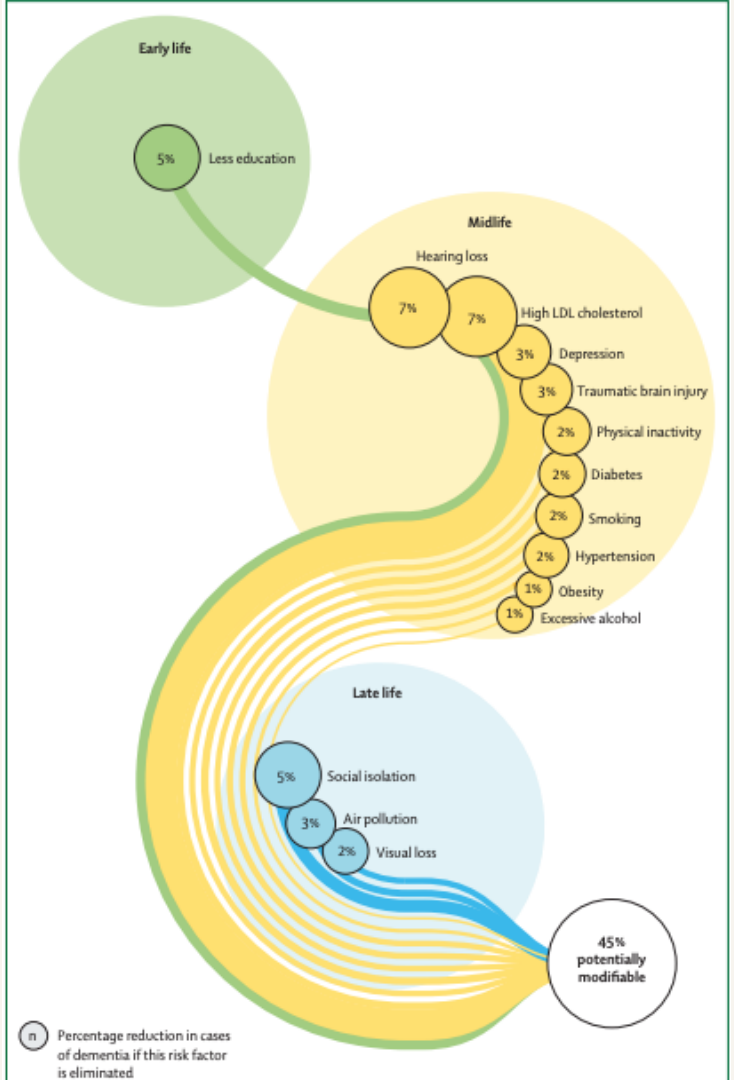
LDL — new in 2024

Elevated LDL (>130 mg/dL) is newly recognized with PAF of 7%.

6

Social isolation — late life

Social isolation carries a PAF of 5% in late life. Loneliness independently associated with 1.5× increased dementia risk in meta-analyses (OR ~1.5, 95% CI 1.3–1.7).


Early life
5%
Less education
Midlife
Hearing loss
7%
7%
High LDL cholesterol
3%
Depression
3%
Traumatic brain injury
2%
Physical inactivity
2%
Diabetes
2%
Smoking
2%
Hypertension
1%
Obesity
1%
Excessive alcohol
Late life
5%
Social isolation
3%
Air pollution
2%
Visual loss
45% potentially modifiable
n
Percentage reduction in cases of dementia if this risk factor is eliminated

US POINTER

Structured vs. Self-Guided Multidomain Lifestyle Intervention

The largest US lifestyle prevention RCT to date — testing whether a structured, coached multidomain program outperforms flexible self-guided lifestyle guidance in protecting cognitive function.

2,091
participants randomized

24 mo
intervention duration

p<0.05
global cognition favoring structured arm

Baker LD, Espeland MA, Whitmer RA et al. · JAMA · 2025

JAMA | Original Investigation

Structured vs Self-Guided Multidomain Lifestyle Interventions for Global Cognitive Function

The US POINTER Randomized Clinical Trial

Laura D. Baker, PhD; Mark A. Espeland, PhD; Rachel A. Whitmer, PhD; Heather M. Snyder, PhD; Xiaoyan Leng, MD, PhD; Laura Lovato, MS; Kathryn V. Papp, PhD; Melissa Yu, MD; Miia Kivipelto, MD, PhD; Ashley S. Alexander, MHSA; Susan Antkowiak, BS; Maryjo Cleveland, MD; Claire Day, BSW; Richard Elbein, MS; Sarah Tomaszewski Farias, PhD; Deborah Felton, BS; Katelyn R. Garcia, MS; Darren R. Gitelman, MD; Sarah Graef, DC; Marjorie Howard, MSPH; Jeffrey Katula, PhD; Katherine Lambert, BA; Olivia Matongo, MPH; Anne Marie McDonald, MEd, MBA; Valory Pavlik, PhD; Rema Raman, PhD; Stephen Salloway, MD, MS; Christy Tangney, PhD; Jennifer Ventrelle, MS; Sharon Wilmoth, BA; Benjamin J. Willliams, MD, PhD; Rena Wing, PhD; Nancy Woolard; Maria C. Carrillo, PhD

IMPORTANCE Identifying new interventions to slow and prevent cognitive decline associated with dementia is critical. Nonpharmacological interventions targeting modifiable risk factors are promising, relatively low-cost, accessible, and safe approaches.

OBJECTIVE To compare the effects of two 2-year lifestyle interventions on cognitive trajectory in older adults at risk of cognitive decline and dementia.

DESIGN, SETTING, AND PARTICIPANTS Single-blind, multicenter randomized clinical trial enrolling 2111 participants from May 2019 to March 2023 (final follow-up, May 14, 2025) at 5 clinical sites in the US. Participant inclusion criteria enriched risk of cognitive decline and included age 60 to 79 years, sedentary lifestyle, and suboptimal diet plus at least 2 additional criteria related to family history of memory impairment, cardiometabolic risk, race and ethnicity, older age, and sex.

INTERVENTIONS Participants were randomly assigned with equal probability to structured (n = 1056) or self-guided (n = 1055) interventions. Both interventions encouraged increased physical and cognitive activity, healthy diet, social engagement, and cardiovascular health monitoring, but differed in structure, intensity, and accountability.

MAIN OUTCOMES AND MEASURES The primary comparison was difference between intervention groups in annual rate of change in global cognitive function, assessed by a composite measure of executive function, episodic memory, and processing speed, over 2 years.

RESULTS Among the 2111 individuals enrolled (mean age, 68.2 [SD, 5.2] years; 1455 [68.9%] female), 89% completed the year 2 assessment. The mean global cognitive composite *z* score increased from baseline over time in both groups, with a mean rate of increase per year of 0.243 SD (95% CI, 0.227-0.258) for the structured intervention and 0.213 SD (95% CI,

Visual Abstract

Editorial page 674

Supplemental conter

Methods & Study Design

1

Design

Multicenter 2-arm RCT. Participants randomized 1:1 to (A) Structured multidomain lifestyle intervention vs. (B) Self-guided flexible intervention.

2

Structured arm (A)

Group-based in-person sessions with trained interventionists. Weekly exercise sessions (aerobic + strength), MIND diet coaching with nutrition counselors, computerized cognitive training (BrainHQ, 3×/week), and quarterly vascular risk monitoring with nurse practitioners.

3

Self-guided arm (B)

Participants received health education materials, goal-setting support, and access to the same 4 lifestyle domains — but without structured group sessions or intensive coaching. Designed to reflect enhanced usual care.

4

Participants

n = 2,091 aged 60–79. Cognitively unimpaired. CAIDE dementia risk score ≥6 (elevated risk). Racially/ethnically diverse: ~30% non-White. Recruited across 5 US sites (Wake Forest, Miami, Wisconsin, San Diego, Minneapolis).

5

Primary outcome

Change in global cognitive function composite score (combining memory, executive function, language, processing speed) from baseline to 24 months.

6

Adherence monitoring

Attendance tracked weekly. Physical activity measured by accelerometry. Dietary adherence assessed by MIND diet score at 6, 12, 24 months. Vascular risk labs drawn quarterly.

Key Findings

1

Primary outcome — global cognition

Structured arm showed significantly greater improvement in global cognitive composite vs. self-guided arm at 24 months ($p < 0.05$). Both arms improved vs. baseline in statistically significant manner

2

Executive function

Largest between-arm differences observed in executive function and processing speed domains. Memory improvement was more modest and not statistically significant between arms.

3

Vascular risk factor control

Structured arm achieved significantly better BP control (mean SBP reduction ~4 mmHg greater vs. self-guided, $p < 0.05$) and better LDL reduction. Fasting glucose did not differ significantly between arms.

4

Physical fitness gains

Structured arm showed significantly greater improvement in 400-meter walk time (a validated functional fitness measure) and grip strength vs. self-guided. Effect size: Cohen's $d \approx 0.25$ at 24 months.

5

MIND diet adherence

Structured arm achieved significantly higher MIND diet score at 24 months. MIND diet adherence was independently associated with cognitive composite improvement in both arms.

6

Subgroup: high-risk participants

Pre-specified subgroup analysis: participants with CAIDE score ≥9 (highest tertile of risk) showed the largest cognitive benefit from structured intervention — suggesting greatest gain where risk is highest.

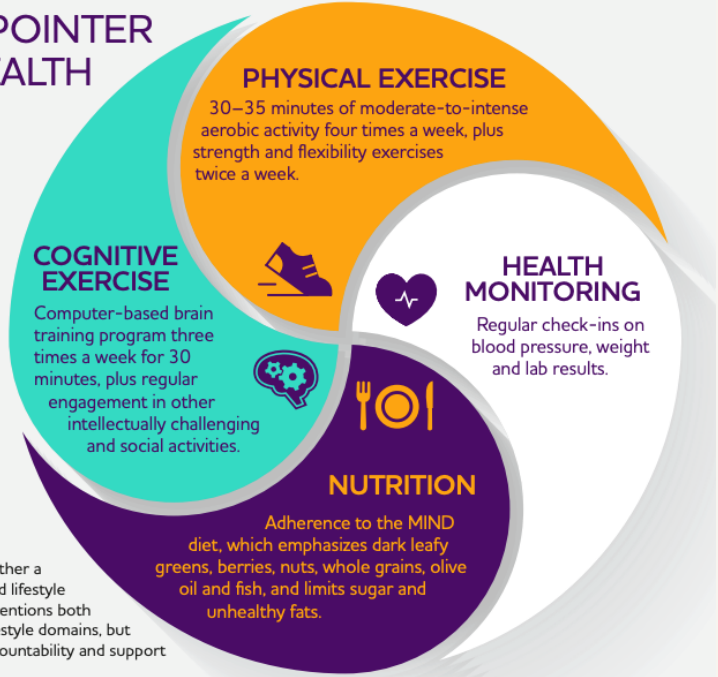
U.S.POINTER
ALZHEIMER'S ASSOCIATION

U.S. POINTER Results Show That Healthy Behaviors Have a Powerful Impact on Brain Health

This two-year clinical trial found that simultaneously targeting risk factors for cognitive decline – including regular physical activity, a brain-healthy diet, cognitive and social engagement and health monitoring – can improve brain function in older adults. While the cognitive health of all participants in U.S. POINTER improved, the group* that followed a more structured program improved even more, helping to protect thinking and memory from the normal decline that often comes with aging over the two-year period of the study. These results provide powerful, actionable guidance for promoting brain health in aging populations.

Learn more at **alz.org/uspointer**

THE U.S. POINTER BRAIN HEALTH RECIPE*



*Participants followed either a self-guided or structured lifestyle program. The two interventions both focused on the same lifestyle domains, but differed in structure, accountability and support provided.

Online Multidomain Lifestyle Intervention

Brodaty et al. · Nature Medicine · February 2025

The largest lifestyle prevention RCT ever conducted — 6,104 participants, fully online, 3-year follow-up, and a statistically significant improvement in global cognition.

6,104
participants —
largest lifestyle RCT to date

p<0.001
primary outcome
(global cognition)

Methods & Study Design

1

Design

Single-blind RCT. 1:1 randomization. Intervention: personalized online coaching in 2–4 lifestyle modules. Control: online access to module-matched health information only — no coaching. Fully remote; no clinic visits.

2

Intervention modules

Four evidence-based modules: (1) Physical activity — tailored aerobic and resistance programs; (2) Nutrition — Mediterranean diet coaching; (3) Cognitive training — online brain training program; (4) Depression/anxiety treatment — guided CBT. Each participant assigned 2–4 modules based on their individual risk profile.

3

Personalization algorithm

Baseline risk factor assessment determined module assignment. Intensity adjusted at 6-month intervals.

4

Participants

n = 6,104. Age 55–77. Community-dwelling Australians. Dementia-free at baseline. Required ≥1 modifiable dementia risk factor. 64% female. Excluded: existing dementia diagnosis, MCI

5

Primary outcome

Change in global cognitive composite z-score (combining processing speed, memory, executive function, and learning) from baseline to 36 months.

6

Adherence and retention

79% of participants completed the 3-year assessment.

Key Findings

1

Primary outcome — met

Global cognitive composite z-score: intervention group +0.28 (95% CI 0.25–0.32) vs. control +0.10 (95% CI 0.07–0.13). Between-group difference: 0.18 SD (95% CI 0.13–0.23, $p < 0.001$). Statistically significant and pre-specified.

2

Physical activity

Intervention group increased moderate-to-vigorous physical activity by a mean of +42 min/week vs. +18 min/week in control at 36 months ($p = 0.003$).

3

Dietary Quality

Mediterranean diet adherence score increased significantly in the intervention arm (+3.1 points vs. +0.9 points, $p < 0.001$). Effect was sustained through 36 months.

4

Depression and anxiety

PHQ-9 score improved significantly in intervention vs. control (mean difference −1.2 points, $p < 0.01$). Anxiety scores (GAD-7) also improved (mean difference −0.9, $p = 0.02$). Depression module completion predicted the largest individual cognitive gains.

JAMA Internal Medicine | Original Investigation

Effect of Personalized Risk-Reduction Strategies on Cognition and Dementia Risk Profile Among Older Adults
The SMARRT Randomized Clinical Trial

Kristine Yaffe, MD; Eric Vittinghoff, PhD; Sascha Dublin, MD, PhD; Carrie B. Peltz, PhD; Lynn E. Fleckenstein, MA; Dori E. Rosenberg, PhD, MPH; Deborah E. Barnes, PhD, MPH; Benjamin H. Balderson, PhD; Eric B. Larson, MD, MPH

IMPORTANCE Modifiable risk factors are hypothesized to account for 30% to 40% of dementia; yet, few trials have demonstrated that risk-reduction interventions, especially multidomain, are efficacious.

OBJECTIVE To determine if a personalized, multidomain risk reduction intervention improves cognition and dementia risk profile among older adults.

DESIGN, SETTING, AND PARTICIPANTS The Systematic Multi-Domain Alzheimer Risk Reduction Trial was a randomized clinical trial with a 2-year personalized, risk-reduction intervention. A total of 172 adults at elevated risk for dementia (age 70-89 years and with ≥2 of 8 targeted risk factors) were recruited from primary care clinics associated with Kaiser Permanente Washington. Data were collected from August 2018 to August 2022 and analyzed from October 2022 to September 2023.

INTERVENTION Participants were randomly assigned to the intervention (personalized risk-reduction goals with health coaching and nurse visits) or to a health education control.

MAIN OUTCOMES AND MEASURES The primary outcome was change in a composite modified Neuropsychological Test Battery; preplanned secondary outcomes were change in risk factors and quality of life (QOL). Outcomes were assessed at baseline and 6, 12, 18, and 24 months. Linear mixed models were used to compare, by intention to treat, average treatment effects (ATEs) from baseline over follow-up. The intervention and outcomes were initially in person but then, due to onset of the COVID-19 pandemic, were remote.

RESULTS The 172 total participants had a mean (SD) age of 75.7 (4.8) years, and 108 (62.8%) were women. After 2 years, compared with the 90 participants in the control group, the 82 participants assigned to intervention demonstrated larger improvements in the composite cognitive score (ATE of SD, 0.14; 95% CI, 0.03-0.25; $P = .02$; a 74% improvement compared with the change in the control group), better composite risk factor score (ATE of SD, 0.11; 95% CI, 0.01-0.20; $P = .03$), and improved QOL (ATE, 0.81 points; 95% CI, −0.21 to 1.84; $P = .12$). There were no between-group differences in serious adverse events (24 in the

Visual Abstract

Supplemental content

SMARRT Trial

Systematic Multi-Domain Alzheimer's Risk Reduction Trial

A precision-medicine approach to dementia prevention: interventionists built and updated individualized risk-reduction plans for each participant, targeting their specific top modifiable risk factors.

172

participants randomized

p=0.04

cognitive composite favoring intervention

–0.84

point improvement in dementia risk score

Yaffe K, Vittinghoff E, Dublin S et al. · JAMA Internal Medicine · January 2024

Methods & Study Design

1

Design

Pilot RCT. 1:1 randomization. Intervention: individualized, adaptive risk-reduction program delivered by interventionists. Control: health education (mailed materials quarterly).

2

Risk factor assessment

Participants assessed at baseline across 12 modifiable risk domains

3

Individualized intervention protocol

Each participant's top 2–3 risk factors were targeted first. Action plans updated every 3 months based on progress. No standardized protocol

4

High-risk medications

Deprescribing of anticholinergic and sedative/hypnotic medications (benzodiazepines, Z-drugs) was an explicit intervention target

5

Participants

n = 172 (86 intervention, 86 control). Age ≥70. Cognitively unimpaired. CAIDE score ≥6. Enrolled from Kaiser Permanente Northern California. Mean age 74.1 years; 57% female; 40% non-White.

6

Outcomes

Primary: composite cognitive score (modified Neuropsychological Test Battery) at 24 months. Secondary: CAIDE dementia risk score change,

Key Findings

1

Primary cognitive outcome

Composite cognitive score: intervention arm showed significant improvement vs. control at 24 months (standardized mean difference +0.23, 95% CI 0.01–0.44, p = 0.04). Effect driven primarily by executive function domain.

2

Dementia risk score

CAIDE dementia risk score decreased by −0.84 points in the intervention arm vs. +0.12 points in control (p = 0.02).

3

Physical activity

IPAQ physical activity score increased significantly more in intervention vs. control (p = 0.01).

4

Sleep quality

PSQI score improved (lower = better sleep) in intervention arm: mean change −1.4 vs. −0.3 in control (p = 0.03).

5

Medication deprescribing

Anticholinergic Cognitive Burden score decreased significantly more in intervention vs. control (mean difference −0.6 points, p = 0.04).

6

Adherence and individualization

Mean number of action plan updates: 7.2 over 24 months. Most frequently targeted domains: physical activity (76%), sleep (61%), BP control (52%), depression (44%), and medications (35%). High-frequency targeting correlated with larger CAIDE improvement.

EXERT Trial Overview

Exercise in Adults with Mild Memory Problems · Phase 3 RCT · Baker et al. 2025

EXERT was the longest-ever Phase 3 RCT of exercise in older adults with amnestic mild cognitive impairment (aMCI). Sedentary adults aged 65+ were randomised to 18 months of supervised moderate-high intensity aerobic training (AX) versus low-intensity stretching, balance, and range-of-motion exercise (SBR). Exercise was supervised for the first 12 months, then participants continued independently for a further 6 months.

296
participants randomised

18
months total (12 supervised)

aMCI

EXERT: Cognitive Outcomes

EXERT Trial · Primary outcome: ADAS-Cog-Exec global cognitive composite

There was no between-group difference in cognitive trajectory — aerobic and stretching exercise performed equally on the ADAS-Cog-Exec composite. Crucially, both groups showed no cognitive decline over 12 months of supervised exercise.

=

no difference between
aerobic vs. stretching

Stable

cognition in both arms
over 12 months

Baker LD et al. · Alzheimer's & Dementia · 2025

EXERT: Key Lessons

EXERT Trial · Interpretation and clinical implications

The surprising finding that low-intensity stretching matched aerobic exercise challenges the assumption that vigorous exercise is necessary for cognitive benefit — structured, supported movement of any intensity may be what matters.

Any

intensity may protect — aerobic ≠ stretching

150

min/week target for sedentary MCI patients

Baker LD et al. · Alzheimer's & Dementia · 2025

LIGHT Trial Overview

Lifestyle Intervention in memory clinics of General and academic Hospitals Trial · Ongoing

LIGHT is a 1-year multicentre RCT based at Maastricht UMC+ and Amsterdam UMC, targeting older adults already referred to Dutch memory clinics with subjective cognitive decline (SCD) or mild cognitive impairment (MCI).

300

participants
(≥50 yrs, SCD or MCI)

≥2

modifiable risk factors
required for inclusion

2025

recruitment start —
results expected ~2027

Janssen N et al. · Alzheimer's Research & Therapy · 2026 · NCT06832761

LIGHT: Intervention & Outcomes

Three-component intervention vs. general health advice

The intervention combines: (1) three individual sessions with a certified lifestyle coach to set personalised goals; (2) vouchers for local brain-healthy services (exercise, social activities, diet); and (3) access to breinzorg.nl, an online dementia risk self-management platform. The primary outcome is the LIBRA2 score — a validated composite of 15 modifiable risk and protective factors — at 12 months.

Blood is also banked for future APOE genotyping and AD biomarkers (amyloid, p-tau) — though these are not active trial outcomes.

LIBRA2

primary outcome —
15-factor dementia risk score

3

intervention components
(coach, vouchers, digital)

Banked

amyloid & p-tau samples
for future analysis only

Janssen N et al. · Alzheimer's Research & Therapy · 2026 · NCT06832761

Irisin

- Produced in muscle when it contracts
- Travels to brain and produces BDNF

Protective effect of irisin against Alzheimer's disease

Kang Chen[1,2], Kun Wang[2]* and Tianhui Wang[1,2]*

[1]Tianjin Key Lab of Exercise Physiology and Sports Medicine, Tianjin University of Sport, Tianjin, China, [2]Institute of Environmental and Operational Medicine, Academy of Military Medicine Sciences, Academy of Military Sciences, Tianjin, China

Despite being one of the greatest global challenges for health and social care in the 21st century, Alzheimer's disease (AD) lacks specific medicine. Irisin, an exercise-generated muscle factor, emerges as a potential hormone for AD prevention and treatment because of its role in promoting the browning of white adipose tissue, accelerating energy expenditure, regulating energy metabolism, and improving insulin resistance. The study reviews classic hallmarks of AD and irisin's physiology before discussing the possible mechanism by which irisin protects against AD in terms of its effects related to molecular biology and cellular biology. Results reveal that irisin sharpens learning memory by inducing the production of brain-derived neurotrophic factor (BDNF), lowers the production of inflammatory factors, protects neurology through astrocytes, and ameliorates AD symptoms by improving insulin resistance. The review aims to facilitate future experimental studies and clinical applications of irisin in preventing and treating AD.

KEYWORDS

irisin, Alzheimer's disease, BDNF, neuroprotection, neuroinflammation

Midlife cardiovascular fitness and dementia

A 44-year longitudinal population study in women

Helena Hörder, PhD, Lena Johansson, PhD, XinXin Guo, MD, PhD, Gunnar Grimby, MD, Silke Kern, MD, PhD, Svante Östling, MD, and Ingmar Skoog, MD

Neurology® 2018;90:e1298-e1305. doi:10.1212/WNL.0000000000005290

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Abstract

Objective

To investigate whether greater cardiovascular fitness in midlife is associated with decreased dementia risk in women followed up for 44 years.

Methods

A population-based sample of 1,462 women 38 to 60 years of age was examined in 1968. Of these, a systematic subsample comprising 191 women completed a stepwise-increased maximal ergometer cycling test to evaluate cardiovascular fitness. Subsequent examinations of dementia incidence were done in 1974, 1980, 1992, 2000, 2005, and 2009. Dementia was diagnosed according to DSM-III-R criteria on the basis of information from neuropsychiatric examinations, informant interviews, hospital records, and registry data up to 2012. Cox regressions were performed with adjustment for socioeconomic, lifestyle, and medical confounders.

Results

Compared with medium fitness, the adjusted hazard ratio for all-cause dementia during the 44-year follow-up was 0.12 (95% confidence interval [CI] 0.03–0.54) among those with high fitness and 1.41 (95% CI 0.72–2.79) among those with low fitness. High fitness delayed age at dementia onset by 9.5 years and time to dementia onset by 5 years compared to medium fitness.

Conclusions

Among Swedish women, a high cardiovascular fitness in midlife was associated with a decreased risk of subsequent dementia. Promotion of a high cardiovascular fitness may be included in strategies to mitigate or prevent dementia. Findings are not causal, and future research needs to focus on whether improved fitness could have positive effects on dementia risk and when during the life course a high cardiovascular fitness is most important.

RELATED ARTICLE

Editorial
Fitness and dementia risk: Further evidence of the heart-brain connection
Page 675

Gerontology

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Kicking Back Cognitive Ageing: Leg Power Predicts Cognitive Ageing after Ten Years in Older Female Twins

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Key Words
Cognition · Age-related changes · Physical performance · Physical activity · Postmenopausal women · Healthy ageing · Structural MRI · Functional MRI · Twin studies · Leg power

Abstract

Background: Many observational studies have shown a protective effect of physical activity on cognitive ageing, but interventional studies have been less convincing. This may be due to short time scales of interventions, suboptimal interventional regimes or lack of lasting effect. Confounding through common genetic and developmental causes is also possible. ***Objectives:*** We aimed to test whether muscle fitness (measured by leg power) could predict cognitive change baseline leg power, physical activity and subsequent cognitive change, adjusting comprehensively for baseline covariates (including heart disease, diabetes, blood pressure, fasting blood glucose, lipids, diet, body habitus, smoking and alcohol habits, reading IQ, socioeconomic status and birthweight). A discordant twin approach was used to adjust for factors shared by twins. A subset of monozygotic pairs then underwent magnetic resonance imaging. The relationship between muscle fitness and brain structure and function was assessed using linear regression modelling and paired t tests. ***Results:*** A striking protective relationship was found between muscle fitness (leg power) and both 10-year cognitive change [fully adjusted model standardised β-coefficient (Stdβ) = 0.174, p = 0.002] and subsequent total grey matter (Stdβ = 0.362, p = 0.005). These effects were robust in discor-

Cardio or Strength Training?

BOTH!

10 HEALTHY HABITS FOR YOUR BRAIN

TAKE CHARGE OF YOUR BRAIN HEALTH. THESE HEALTHY HABITS CAN LOWER THE RISK OF DEVELOPING COGNITIVE DECLINE AND POSSIBLY DEMENTIA. THIS IS TRUE EVEN FOR PEOPLE WITH A HISTORY OF DEMENTIA IN THEIR FAMILIES.

Follow as many of these tips as possible to achieve the most benefits for your brain and body. It's never too late or too early. Start now!

Protect your head

Help prevent an injury to your head. Wear a helmet for activities like biking, and wear a seatbelt. Protect yourself while playing sports. Do what you can to prevent falls, especially for older adults.

Be smoke-free

Quitting smoking can lower the risk of cognitive decline back to levels similar to those who have not smoked. It's never too late to stop.

Get moving

Engage in regular exercise. This includes activities that raise your heart rate and increase blood flow to the brain and body. Find ways to build more movement into your day — walking, dancing, gardening — whatever works for you!

Challenge your mind

Be curious. Put your brain to work and do something that is new or hard for you. Learn a new skill. Try something artistic. Challenging your mind may have short- and long-term benefits for your brain.

Control your blood pressure

Medications can help lower high blood pressure. And healthy habits like eating right and physical activity can help too. Work with a health care provider to control your blood pressure.

Manage diabetes

Type 2 diabetes can be prevented or controlled by healthier eating, increasing physical activity and medication, if necessary.

Sleep well

Good quality sleep is important for brain health. Stay off screens before bed and make your sleep space as comfortable as possible. Do all you can to minimize disruptions. If you have any sleep-related problems, such as sleep apnea, talk to a health care provider.

Stay in school

Education reduces your risk of cognitive decline and dementia. Encourage youth to stay in school and pursue the highest level of training possible. Continue your own education by taking a class at a local library, college or online.

Eat right

Eating healthier foods can help reduce your risk of cognitive decline. This includes more vegetables and leaner meats/proteins, along with foods that are less processed and lower in fat. Choose healthier meals and snacks that you enjoy and are available to you.

Maintain a healthy weight

Talk to your health care provider about the weight that is healthy for you. Other healthy habits on this list — eating right, physical activity and sleep — can help with maintaining a healthy weight.

Learn more at alz.org/healthyhabits.

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Dementia Prevention

Key clinical lessons from these studies

1

Prevention spans the entire lifespan

Risk accumulates from early life through late life. Addressing modifiable factors at any stage confers benefit — it is never too early or too late.

2

Nearly half of dementia cases may be preventable

Fourteen modifiable risk factors — including education, hearing loss, hypertension, high LDL, and vision loss — account for ~45% of global dementia burden.

3

Multi-domain, personalised interventions outperform single targets

Simultaneously addressing physical activity, diet, cognitive engagement, and vascular risk produces greater benefit than any individual intervention.

4

Anticholinergic polypharmacy is a modifiable risk

Cumulative anticholinergic burden is associated with cognitive impairment. Medication review and deprescribing should be part of prevention.

5

Effect sizes are modest and control groups also improve

Both arms typically improve in multi-domain trials. Between-group differences, while significant, are small.

6

Benefit is consistent but risk burden falls unequally

Effects hold across sex, and ethnicity. Modifiable risk burden is highest in low-income and minoritised populations, who stand to gain most.

The Future

1. **Future trials will incorporate blood biomarkers, p-tau217**

2. **Digital screening to identify at risk patients**
   Online cognitive tests, wearables, and algorithms to identify risk factor patterns

3. **Precision prevention**