# Protecting Brain Health: Modifiable Risk Factors for Dementia

Nancy B. Isenberg MD, MPH FAAN February 14, 2025



## Disclosure

I have nothing to disclose

## Learning Objectives

- 1.Identify 6 modifiable risk factors for dementia across lifespan
- 2. Apply best practices in Brain Health & Dementia risk reduction
- 3. Develop strategies to emphasize overlapping risks for heart attack, stroke & dementia
- 4.Implement risk reduction strategies in clinic

#### What is brain health and why is it important?

**Yongjun Wang and colleagues** discuss the definition of brain health and the opportunities and challenges of future research

#### A new definition of brain health

Vladimir Hachinski • Abolfazl Avan • Jason Gilliland • Shahram Oveisgharan

Published: May, 2021 • DOI: https://doi.org/10.1016/S1474-4422(21)00102-2

The Brain Health Imperative in the 21st Century—A Call to Action The AAN Brain Health Platform and Position Statement

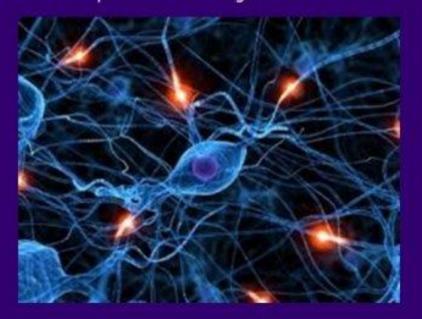
Brain health is defined as the state of brain functioning across cognitive, sensory, social-emotional, behavioral & motor domains allowing a person to realize their full potential over the life course

More importantly, irrespective of the presence or absence of a disease & seen through the interconnected SDOH

WHO (2021)

#### Malleability and Adaptability

Resilience coping is learnable!
Neuroplasticity of the Brain



What we think, do, and pay attention to changes the structure and function on our brains!

UNIVERSITY OF WASHINGTON

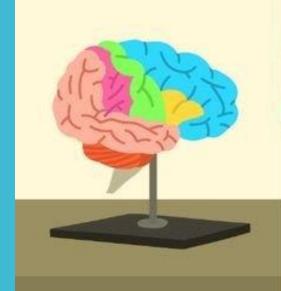
#### The 2 Types of Brain Plasticity

What is Neuroplasticity (aka Brain Plasticity)?

Type 1: Structural Plasticity

Type 2: Functional Plasticity

**Brain Plasticity** 

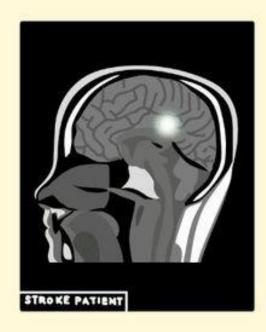


Brain's ability to change and adapt

verywell



Experiences or memories change a brain's physical structure



Brain functions move from damaged area to undamaged area

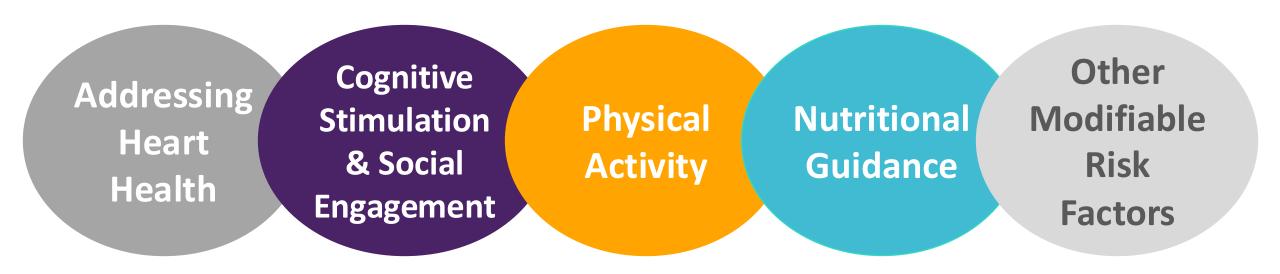
#### Opening Poll

• What do you think is the most important modifiable risk factor to prevent or decrease the disease progression of Dementia?



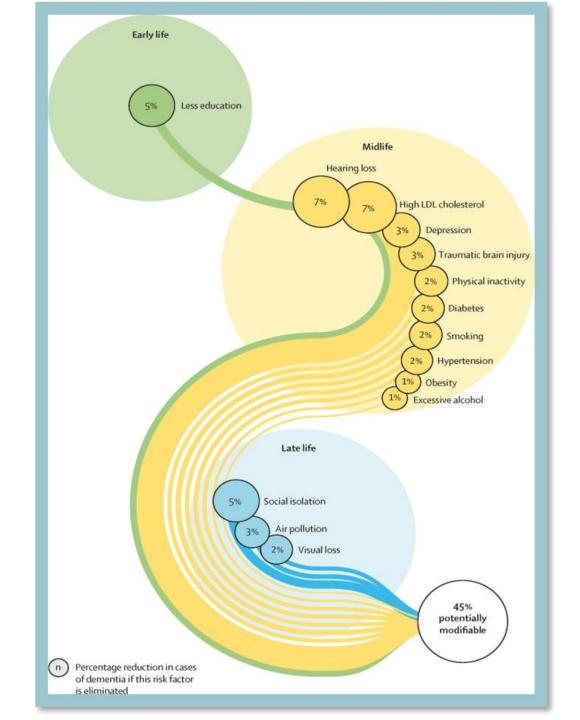
## Multi-Component Approach to Risk Reduction

Synergistic Potential: Multi-Component Approaches to Addressing Dementia Risk Reduction



### Modifiable Risk Factors for Dementia

THE LANCET COMMISSIONS Volume 404, Issue 10452 P572-628 August 10, 2024

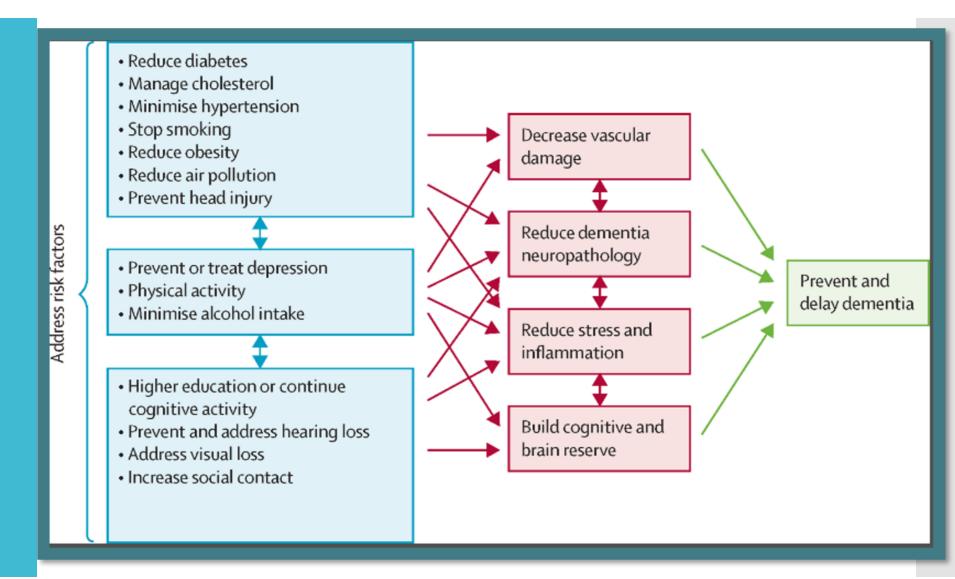


#### **Modifiable Risk Factors for Dementia**

	Cognitive Decline	Dementia
Formal Education (+)	STRONG	STRONG
Traumatic Brain Injury	STRONG	STRONG
Mid and Latelife Hypertension	STRONG	MODERATE
Midlife Obesity	STRONG	MODERATE
Diabetes	STRONG	MODERATE
Physical Activity (+)	STRONG	MODERATE
Smoking	STRONG	MODERATE
Sleep Disorders/Poor Quality	STRONG	MODERATE
Balanced Nutrition (+)	MODERATE	Lower
Cognitive Engagement (+)	MODERATE	Lower

	Cognitive Decline	Dementia
Air Pollution	Lower	Lower
Social Isolation	Lower	Unclear
Depression	Lower	Unclear
Hearing Loss	Lower	Unclear
Moderate Alcohol Use (+)	Lower	Unclear
Hyperlipidemia	Unclear	Unclear
Alcohol Abuse	Unclear	Unclear
Substance Abuse	Unclear	Unclear

### Modifiable Risk Factors for Dementia



#### Lifestyle Medicine for all (DM, CVD, Stroke/VCI)

#### **NUTRITION**

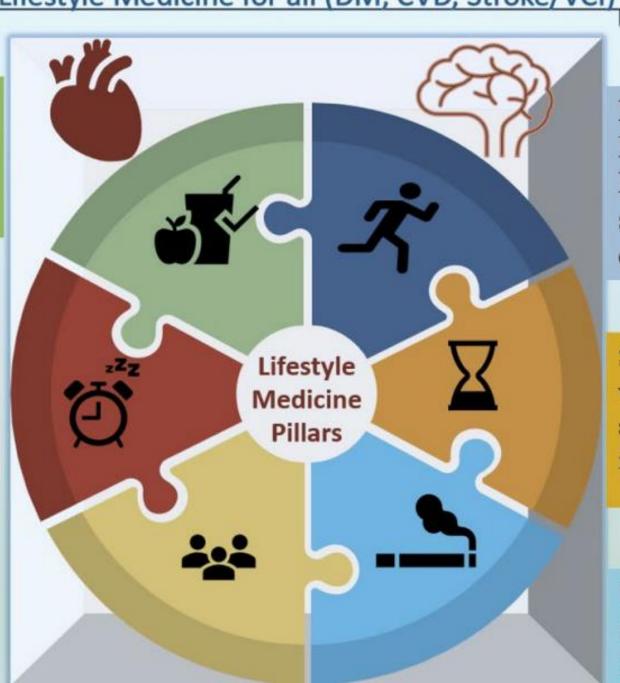
3 common diets associated with cognitive & stroke protection: by 30% DASH, MEDI, MIND

#### **SLEEP HEALTH**

<6h or >9h – higher risk OSA- higher risk by 30% Prolonged naps Prolonged Insomnia Interrupted sleep

#### **SOCIAL CONNECTIONS**

Loneliness & social isolation = increased risk of stroke, recurrence, dementia (~40%)



#### PHYSICAL ACTIVITY

Low PA -20%

Moderate PA ~ 30%

Higher levels of PA-43%

stroke risk reduction,

compared to inactivity

#### STRESS MANAGEMENT

Stress strongly linked with higher risk of HTN, stroke, cognitive impairment, dementia/AD

#### SUBSTANCE USE

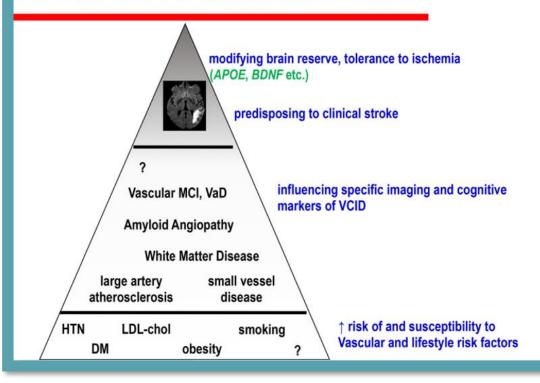
Middle aged smoking = higher risk of cognitive impairment later in life

## Vascular Risk Factors – Dementia & Stroke (& Heart Health)

OPINION

#### Brain health and shared risk factors for dementia and stroke

Hannah Gardener, Clinton B. Wright, Tatjana Rundek and Ralph L. Sacco





HTN - the most significant of all

1 in 3 of middle-aged adults

1 in 2 by 2025

Feigin VL, Lancet Neurol. 2021

Nat Rev Neurol. 2015 Nov





**Blood Pressure** 

ISSN: 0803-7051 (Print) 1651-1999 (Online) Journal homepage: www.tandfonline.com/journals/iblo20

Intensive blood pressure lowering prevents mild cognitive impairment and possible dementia and slows development of white matter lesions in brain: the SPRINT Memory and Cognition IN Decreased Hypertension (SPRINT MIND) study

Sverre E. Kjeldsen, Krzysztof Narkiewicz, Michel Burnier & Suzanne Oparil

- SPRINT MIND
  - Intensive blood pressure lowering prevents MCI
  - Intensive blood pressure lowering slows development of white matter disease
  - o "Intensive" = systolic BP goal <120 mm Hg</p>
    - Additional benefits inc. decreased acute MI, acute coronary syndrome, stroke, acute decompensated heart failure, and cardiovascular death

## 1 Vascular Risk Factors: Hypertension

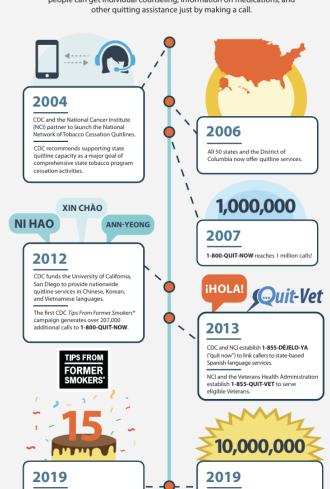
## 1 Vascular Risk Factors: Smoking

- Literature review showed an increased risk of all-cause Dementia
  - Risk increased by 34% for every 20 cigarettes per day
- Former smokers did not show an increased risk for all cause Dementia
- Significantly increased risk of Alzheimer's Disease from current smoking only seen in apolipoprotein Ε ε4 noncarriers
- Current smokers 65-75 years at baseline showed increased risk of all causes Dementia and Alzheimer's disease compared to those aged over 75 years
- Effective Smoking Cessation Interventions
  - 0 1-800-QUIT-NOW
    - CDC Quit Line, operating for 15 years
- Lancet Commission 2024 Recommendations
  - Decrease smoking via public education
  - Price control
  - Prevention of smoking in public spaces
  - Accessibility of smoking cessation advice & support

#### NATIONAL NETWORK OF TOBACCO CESSATION QUITLINES

15th Anniversary

The National Network of Tobacco Cessation Quitlines connects people who want to quit using tobacco to free resources. Regardless of where they live, people can get individual counseling, information on medications, and



1-800-QUIT-NOW reaches 10 million calls!

1-800-QUIT-NOW turns 15 years old!



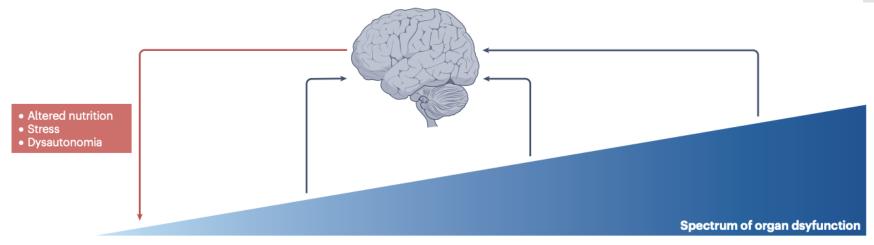
What methods have been effective for smoking cessation in your patients? What resources would you recommend?

#### 2 Comorbidities

## Systemic determinants of brain health in ageing

Eric E. Smith <sup>1</sup> □, Geert Jan Biessels², Virginia Gao³, Rebecca F. Gottesman <sup>4</sup>, Arthur Liesz <sup>5,6</sup>, Neal S. Parikh³ & Costantino Iadecola <sup>3</sup> □

- Increasing evidence links subclinical dysfunction of other organ systems to age-related cognitive decline and dementia
- Pathways that might lead from organ dysfunction to brain dysfunction include systemic endothelial dysfunction, reduced peripheral clearance of wastes (including amyloid-β and tau), systemic inflammation and alterations in the microbiome.



System	Asymptomatic alteration in function	Clinically recognized mild-moderate organ dysfunction	Clinical major organ dysfunction
Cardiovascular	Higher BP, enlarged atria	Coronary artery disease, heart failure, atrial fibrillation	Brain ischaemia
Kidney	↓ GFR, ↑ cystatin C, ↑ albumin:creatinine ratio	Mild-moderate kidney disease	Dialysis
Lung	↓ FEV <sub>1</sub> , ↓ FVC	COPD, sleep apnoea	Hypoxia, hypercapnia
Gastrointestinal	Altered microbiota	Inflammatory bowel disease, peptic ulcer disease	Electrolyte abnormalities
Liver	↑ AST:ALT ratio	NAFLD, liver fibrosis	Hepatic encephalopathy
Endocrine	↑ HbA <sub>1c</sub> , impaired fasting glucose	Type 2 diabetes	Hyperglycaemic coma

#### 2 Comorbidities: Chronic Illnesses

CDC's National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP)

#### **CHRONIC DISEASES** IN AMERICA

6 IN 10
Adults in the US

have a chronic disease



4 IN 10
Adults in the US
have two or more

#### THE LEADING CAUSES OF DEATH AND DISABILITY

and Leading Drivers of the Nation's \$3.3 Trillion in Annual Health Care Costs



#### THE KEY LIFESTYLE RISKS FOR CHRONIC DISEASE



TOBACCO



POOR NUTRITION



LACK OF PHYSICAL ACTIVITY

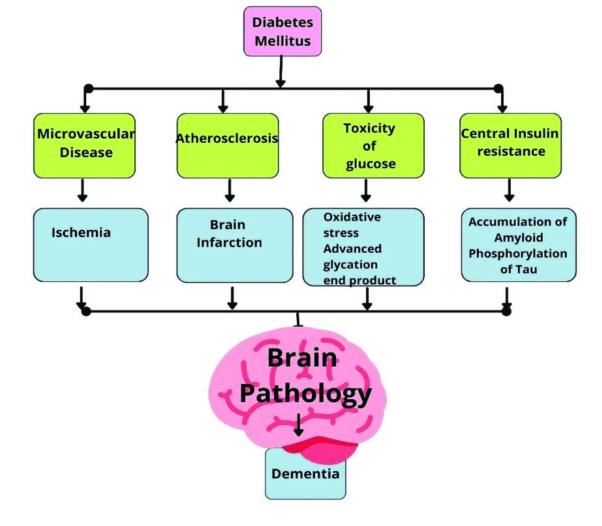


EXCESSIVE ALCOHOL USE

NCCDPHP PREVENTS
CHRONIC DISEASE
AND PROMOTES HEALTH
FOR PEOPLE OF ALL AGES



## Comorbidities: Diabetes



- Diabetes mellitus is associated with 1.5-2.5 fold increase in the risk for Dementia among community dwelling elders
- DM as a risk factor for both Vascular Dementia and Alzheimer's Disease
- <a href="https://www.seattleymca.org/programs-for-health/weight-and-nutrition/diabetes-prevention-program">https://www.seattleymca.org/programs-for-health/weight-and-nutrition/diabetes-prevention-program</a>

#### **Does Obesity Increase the Risk of Dementia: A Literature Review**

<u>Ibrar Anjum</u> <sup>1,⊠</sup>, <u>Muniba Fayyaz</u> <sup>2</sup>, <u>Abdullah Wajid</u> <sup>3</sup>, <u>Wafa Sohail</u> <sup>4</sup>, <u>Asad Ali</u> <sup>5</sup>

Editors: Alexander Muacevic, John R Adler

#### 2: Obesity

- Obesity reduces blood supply to brain and increases neuroinflam, DM2.
- Midlife obesity increase dementia risk
- SAD:High-sugar/high-fat/ Western diet contributes to inflammatory states which increase incidences of both obesity and diabetes.

## comorbidity/ Public Health: Obesity

Review > Am J Geriatr Psychiatry. 2023 Oct;31(10):853-866. doi: 10.1016/j.jagp.2023.06.001. Epub 2023 Jun 11.

#### Neuroinflammation: A Modifiable Pathway Linking Obesity, Alzheimer's disease, and Depression

```
Maria Ly <sup>1</sup>, Gary Z Yu <sup>1</sup>, Ali Mian <sup>1</sup>, Austin Cramer <sup>2</sup>, Somayeh Meysami <sup>3</sup>, David A Merrill <sup>3</sup>, Amjad Samara <sup>4</sup>, Sarah A Eisenstein <sup>5</sup>, Tamara Hershey <sup>6</sup>, Ganesh M Babulal <sup>7</sup>, Eric J Lenze <sup>8</sup>, John C Morris <sup>4</sup>, Tammie L S Benzinger <sup>9</sup>, Cyrus A Raji <sup>10</sup>
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- Obesity, depression, and Alzheimer's Disease all have pathophysiology associated with chronic neuroinflammation
- Midlife interventions KEY for dementia prevention
- "Chronic inflammation serves as a key mechanism linking obesity, AD, and depression, encompassing systemic inflammation from metabolic disturbances, immune dysregulation through the gut microbiome, and direct interactions with amyloid pathology and neuroinflammation."





ORIGINAL ARTICLE

f X in ⊠

#### Semaglutide and Cardiovascular Outcomes in **Obesity without Diabetes**

Authors: A. Michael Lincoff, M.D. . , Kirstine Brown-Frandsen, M.D., Helen M. Colhoun, M.D., John Deanfield, M.D., Scott S. Emerson, M.D., Ph.D., Sille Esbierg, M.Sc., Søren Hardt-Lindberg, M.D., Ph.D., +9, for the SELECT Trial Investigators\* Author Info & Affiliations

Published November 11, 2023 | N Engl J Med 2023;389:2221-2232 | DOI: 10.1056/NEJMoa2307563

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ORIGINAL ARTICLE



#### Tirzepatide for the Treatment of Obstructive **Sleep Apnea and Obesity**

Authors: Atul Malhotra, M.D., Ronald R. Grunstein, M.D., Ph.D., Ingo Fietze, M.D., Terri E. Weaver, Ph.D., Susan Redline, M.D., M.P.H., Ali Azarbarzin, Ph.D., Scott A. Sands, Ph.D., +5, for the SURMOUNT-OSA Investigators\* Author Info & Affiliations

Published June 21, 2024 | N Engl J Med 2024;391:1193-1205 | DOI: 10.1056/NEJMoa2404881 VOI 201 NO 12

ORIGINAL ARTICLE

#### **Effects of Semaglutide on Chronic Kidney** Disease in Patients with Type 2 Diabetes

Authors: Vlado Perkovic, M.B., B.S., Ph.D., Katherine R. Tuttle, M.D. 0, Peter Rossing, M.D., D.M.Sc. 0,

Kenneth W. Mahaffey, M.D., Johannes F.E. Mar Thomas Idorn, M.D., Ph.D., Heidrun Bosch-Tra M.D., for the FLOW Trial Committees and Inve

Published May 24, 2024 | N Engl J Med 2024

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ORIGINAL ARTICLE



#### Tirzepatide for Metabolic Dysfunction-**Associated Steatohepatitis with Liver Fibrosis**

Authors: Rohit Loomba, M.D. <sup>10</sup>, Mark L. Hartman, M.D., Eric J. Lawitz, M.D., Raj Vuppalanchi, M.D., Jérôme Boursier, M.D., Ph.D., Elisabetta Bugianesi, M.D., Ph.D., Masato Yoneda, M.D., Ph.D., +9, for the SYNERGY-NASH Investigators\* Author Info & Affiliations

Published June 8, 2024 | N Engl J Med 2024;391:299-310 | DOI: 10.1056/NEJMoa2401943

GLP1 drugs

#### **Original Investigation**

February 12, 2025

## Once-Weekly Semaglutide in Adults With Alcohol Use Disorder

#### A Randomized Clinical Trial

Christian S. Hendershot, PhD<sup>1,2,3</sup>; Michael P. Bremmer, MA<sup>3,4</sup>; Michael B. Paladino, BS<sup>3,4</sup>; et al

#### **GLP-1s in AUD**

- Phase 2, double-blind, parallel arm trial
- Low dose semaglutide reduced the aount of alcohol consumed during a post treatment event
- Semaglutide treatment did not affect the average drinks per calendar day or number of drinking days, but significantly reduced drinks per drinking day and weekly alcohol cravings
- "A significant treatment-by-time interaction indicated that semaglutide treatment predicted greater relative reductions in cigarettes per day in a subsample of individuals with current cigarette use"

## Key takeaways

- GLP-1 drugs effectively promote weight loss and reduce risk of CVD and other diseases.
  - Major challenges: GI side effects, weight regain after cessation, and muscle loss during treatment.

#### Dietary and Lifestyle Synergy

- Combining GLP-1 drugs with dietary changes and physical activity may reduce side effects, enhance efficacy, and optimize metabolic health.
- PREDIMED-Plus trial shows MedDiet + physical activity reduces abdominal fat and preserves muscle mass.
- Powerful effects of combining lifestyle factors and GLP-1 on reducing CVD and mortality in individuals with diabetes in the MVP
- Teaching kitchens can be a useful tool to improve diet quality, support weight maintenance, and preserve muscle mass during and after treatment.

#### Access is Crucial

Financial Barriers: Costly medications and limited nutrition counseling access.

#### Future Directions

- Real-world data on the combined effects of GLP-1 and lifestyle factors on long-term outcomes.
- Trials integrating GLP-1 drugs with lifestyle interventions such as teaching kitchens are urgently needed.

## No evidence of benefit in AD (yet?), however semaglutide study reading out Sept.

▶ J Alzheimers Dis Rep. 2024 May 7;8(1):777–789. doi: <u>10.3233/ADR-230181</u> [2]

## Clinical Evidence for GLP-1 Receptor Agonists in Alzheimer's Disease: A Systematic Review

Yulin Liang a, Vincent Doré b,c, Christopher C Rowe c,d,e, Natasha Krishnadas c,e,\*

▶ Author information ▶ Article notes ▶ Copyright and License information

PMCID: PMC11091751 PMID: <u>38746639</u>

▶ Alzheimers Res Ther. 2025 Jan 8;17:14. doi: 10.1186/s13195-024-01666-7 [2]

evoke and evoke+: design of two large-scale, double-blind, placebocontrolled, phase 3 studies evaluating efficacy, safety, and tolerability of semaglutide in early-stage symptomatic Alzheimer's disease

Jeffrey L Cummings <sup>1,15,∞</sup>, Alireza Atri <sup>2,3,4</sup>, Howard H Feldman <sup>5</sup>, Oskar Hansson <sup>6,7</sup>, Mary Sano <sup>8</sup>, Filip K Knop <sup>9,10,11,12</sup>, Peter Johannsen <sup>12</sup>, Teresa León <sup>12</sup>, Philip Scheltens <sup>13,14</sup>

What methods and interventions have been effective in reducing obesity in your practice?

#### 2 Comorbidities: High LDL Cholesterol

#### Blood cholesterol and risk of dementia in more than 1.8 million people over two decades: a retrospective cohort study



Masao Iwagami, Nawab Qizilbash, John Gregson, Ian Douglas, Michelle Johnson, Neil Pearce, Stephen Evans, Stuart Pocock



- Cohort study with initial results from over 1,000,000 participants over the age of 40 from Jan 1992 to December 2009; with follow up until 2015
- Found a modest positive association between midlife LDL cholesterol and dementia, with an adjusted rate ration (RR) of 1.05 (95% Cl 1.03–1.06) per SD increase in LDL cholesterol (1.01 mmol/L or 39 mg/dL increase).
  - Weaker association between total cholesterol and dementia incidence and no consistent associations for HDL cholesterol and triglycerides
- Associations for LDL cholesterol in people over 65 were weaker compared with people younger than 65 years

## Depression—an underrecognized target for prevention of dementia in Alzheimer's disease

Forugh S. Dafsari<sup>1,2</sup> and Frank Jessen<sup>1,3</sup>

#### 2 Comorbidities: Depression

- Meta-analysis with meta regression of data up to February 28, 2014
- Combined sample size of over 66,000 individuals; with 6,593 cases of Dementia, 2,797 cases of Alzheimer's Disease, and 585 cases of Vascular Dementia
- The increased risk associated with depression did not significantly differ by type of dementia and ranged from 83% to 104% for diagnostic thresholds consistent with major depression.
- Risk associated with **continuous depression symptomatology** measures were consistent with those for clinical thresholds.
- Late-life depression is consistently and similarly associated with a twofold increased risk of dementia.

#### 2 Comorbidities: Depression

#### Slowing Cognitive Decline in Major Depressive Disorder and Mild Cognitive Impairment: A Randomized Clinical Trial

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Tarek K Rajji <sup>1 2 3</sup>, Christopher R Bowie <sup>1 4</sup>, Nathan Herrmann <sup>2 5</sup>, Bruce G Pollock <sup>1 2</sup>, Krista L Lanctôt <sup>2 5</sup>, Sanjeev Kumar <sup>1 2</sup>, Alastair J Flint <sup>2 6</sup>, Linda Mah <sup>2 7</sup>, Corinne E Fischer <sup>2 8</sup>, Meryl A Butters <sup>9</sup>, Marom Bikson <sup>10</sup>, James L Kennedy <sup>1 2</sup>, Daniel M Blumberger <sup>1 2</sup>, Zafiris J Daskalakis <sup>11</sup>, Damien Gallagher <sup>2 5</sup>, Mark J Rapoport <sup>2 5</sup>, Nicolaas P L G Paul Verhoeff <sup>2 7</sup>, Angela C Golas <sup>1 2</sup>, Ariel Graff-Guerrero <sup>1 2</sup>, Erica Vieira <sup>1 2</sup>, Aristotle N Voineskos <sup>1 2</sup>, Heather Brooks <sup>1</sup>, Ashley Melichercik <sup>1</sup>, Kevin E Thorpe <sup>12</sup>, Benoit H Mulsant <sup>1 2 9</sup>; PACt-MD Study Group
```

- JAMA Psychiatry 2025:Over 350 patients in Canada were examined. Use of interventions within this study found that over a median follow up of approx. 4 years, Cognitive Remediation (CR) and Transcranial Direct Current Simulation (tDCS) slowed cognitive decline in older adults with remitted Major Depressive Disorder and Mild Cognitive Impairment; although they did not improve cognition acutely.
- "The effect of CR and tDCS on delaying progression from normal cognition to MCI or MCI to dementia was weak and not significant"
- "The study showed that CR and tDCS, both targeting the prefrontal cortex, is efficacious in slowing cognitive decline in older adults at risk of cognitive decline, particularly those with rMDD (with or without MCI) and in those at low genetic risk for Alzheimer disease."

## Injury Traumatic Brain Injury (TBI)

- Multiple national cohort studies have shown that Traumatic Brain Injury, even mild instances, is a significant independent risk factor for developing Dementia
  - In Taiwanese cohort study, incidence rate of Dementia is 6x higher for people with TBI
  - In Swedish cohort study, risk of Dementia had a dose ± response relationship with regard to TBI severity and number of TBIs

#### Increased Risk of Dementia in Patients with Mild Traumatic Brain Injury: A Nationwide Cohort Study

Yi-Kung Lee<sup>1,2</sup>, Sheng-Wen Hou<sup>3</sup>, Ching-Chih Lee<sup>2,4,5,6</sup>, Chen-Yang Hsu<sup>7</sup>, Yung-Sung Huang<sup>8</sup>, Yung-Cheng Su<sup>1,2</sup>\*

#### RESEARCH ARTICLE

Traumatic brain injury and the risk of dementia diagnosis: A nationwide cohort study

Anna Nordström<sup>1,2</sup>, Peter Nordström<sup>3</sup>\*

## Injury Traumatic Brain Injury (TBI)

## Chronic Traumatic Encephalopathy: A Comparison with Alzheimer's Disease and Frontotemporal Dementia

Orit H. Lesman-Segev, MD<sup>1</sup> Lauren Edwards, BS<sup>1</sup> Gil D. Rabinovici, MD<sup>1,2,3</sup>

- 2020:A thorough examination of Chronic Traumatic Encephalopathy compared Alzheimer's Disease and Frontotemporal Dementia, including epidemiology, existing clinical criteria, imaging, genetics and biomarkers
- Diagnosis requires a detailed clinical history, neurocognitive assessment, physical examination to identify distinguishing clinical features and treatable symptoms.

## Injury Traumatic Brain Injury (TBI)

Review > Nat Rev Neurol. 2024 Nov;20(11):671-684. doi: 10.1038/s41582-024-01024-z. Epub 2024 Oct 3.

#### Fluid biomarkers of chronic traumatic brain injury

```
Susanna Friberg <sup>1</sup> <sup>2</sup>, Caroline Lindblad <sup>1</sup> <sup>3</sup> <sup>4</sup>, Frederick A Zeiler <sup>1</sup> <sup>5</sup> <sup>6</sup> <sup>7</sup> <sup>8</sup>, Henrik Zetterberg <sup>9</sup> <sup>10</sup> <sup>11</sup> <sup>12</sup> <sup>13</sup> <sup>14</sup>, Tobias Granberg <sup>1</sup> <sup>15</sup>, Per Svenningsson <sup>1</sup> <sup>2</sup> <sup>16</sup>, Fredrik Piehl <sup>1</sup> <sup>2</sup>, Eric P Thelin <sup>17</sup> <sup>18</sup>
```

- NFL, Glial Fibrillary protein and tau
  - Current biomarkers of axonal injury, astrogliosis, and amyloid deposition
- No validated objective biomarkers for mTBI or concussion, diagnosis based on clinical symptoms
- No biomarkers for detection of subconcussive trauma
- Limited objective measures to quantify exposure to repetitive head impacts

### 4 Loss of Senses: Hearing Loss

#### Hearing Loss as a Risk Factor for Dementia: A Systematic Review

Rhett S. Thomson, BA; Priscilla Auduong, MD; Alexander T. Miller, BS; Richard K. Gurgel, MD

#### Does hearing loss lead to dementia? A review of the literature

Yosra Nadhimi <sup>a</sup>, Daniel A. Llano <sup>a, b, c, d, \*</sup>

- Systematic literature review of studies with multiple methods found hearing loss associated with Dementia or cognitive decline.
- Literature review shows that hearing loss can lead to pathological hallmarks similar to those seen in Alzheimer's Disease and other Dementias
- Researchers believe an additional "hit" such as aging, APO E genotype, microvascular disease or others may be necessary to trigger an ongoing degenerative process.
  - O Ample evidence that noise and hearing loss cause hippocampal dysfunction
  - Noise induced excitotoxic and oxidative stress cause hippocampal structural changes
- RCT: Hearing intervention versus health education control to reduce cognitive decline in older adults with hearing loss in the USA (ACHIEVE): a multicentre, randomised controlled trial 2023
- (tx beneficial for those at risk for cog decline)

#### 4 Loss of Senses: Untreated Vision Loss

## Untreated Vision Loss as a Modifiable Dementia Risk Factor

Joshua R. Ehrlich, MD, MPH<sup>1,2</sup>

- Longitudinal research conducted over the past 30 years has shown vision impairment as an important risk factor for cognitive decline in Dementia
  - Research beginning ~30 years ago detected strong association between age-related macular degeneration and incident Alzheimer's disease
  - 043 longitudinal studies (as of 2022) reporting on the association between vision impairment and cognitive health
  - Additional studies show population-wide association between vision impairment and dementia in older adults

# 5 Lifestyle Factors: Excessive Alcohol Consumption

- The Lancet commission has identified "excessive alcohol consumption" as >21 UK unites of >12 US units
- An overview of systematic reviews conducted in 2017 found
  - People consuming >14 units/week, a 7 unit increase in alcohol consumption associated with a 17% increase in risk of Dementia
  - Alcohol related hospital admissions were associated with increased Dementia risk
- A meta-analysis of prospective studies found a non-linear association between alcohol consumption and all-cause dementia risk.
  - Alcohol dose associated with lower risk of dementia was limited to at most 12 g/day; with the lowest risk associated with roughly 6 g/day
  - All cause dementia is elevated by ≈10% when the dose surpasses certain levels: 23 drinks/week or 38 g/day. (>3drinks/day)

#### Alcohol consumption and risk of dementia: 23 year follow-up of Whitehall II cohort study

Séverine Sabia, <sup>1,2</sup> Aurore Fayosse, <sup>1</sup> Julien Dumurgier, <sup>3</sup> Aline Dugravot, <sup>1</sup> Tasnime Akbaraly, <sup>2,4,5</sup> Annie Britton, <sup>2</sup> Mika Kivimäki, <sup>2</sup> Archana Singh-Manoux <sup>1,2</sup>

## Alcohol consumption and dementia risk: a dose-response meta-analysis of prospective studies

META-ANALYSIS | Published: 17 January 2017 Volume 32, pages 31–42, (2017) Cite this article

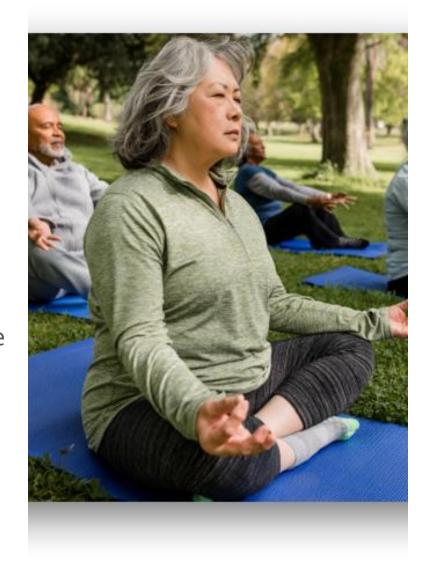
## 5 Lifestyle Factors: Stress Management

- Promoting Physical & Mental Resilience
- Mind body practices
- Meditation slowed the rate of hippocampal volume atrophy in those with mild cognitive impairment when compared to a randomized control group (Wells, et. al, 2013)
- At age 50, brains of meditators were estimated to be 7.5 years younger than those of controls in MRI scans (Luders, et. al, 2016)

doi: 10.1111/jgs.12179.

doi:

10.1016/j.neuroimage.2016.04.007



#### **MIND Diet**

- Emphasis on Plant-Based Foods
  - including vegetables (especially leafy greens), fruits, whole grains, nuts and legumes
  - These foods are rich in vitamins, minerals, antioxidants, and fiber, which are beneficial for gut & brain health
- Adherence to MIND diet reduces risk of AD and slows cognitive decline
- Reduced MCI risk, reduced progression from MCI to AD, decreased risk in all-causes mortality in AD.
- doi:10.2174/156720511796391809



#### **MIND** Diet

- Regular Consumption of Berries
  - Berries are rich in antioxidants known as flavonoids, which have been associated with improved cognitive function
- Daily Servings of Whole Grains
  - Whole grains, such as oats, brown rice, and whole wheat bread
  - Excellent source of fiber and other essential nutrients
- Healthy Fats
  - Healthy fats such as those found in olive oil and nuts are encouraged.
  - These fats provide essential nutrients and may help reduce the risk of cognitive impairment.









#### **Asian Diet Pyramid**





#### African Heritage Diet Pyramid





#### Mediterranean Diet Pyramid



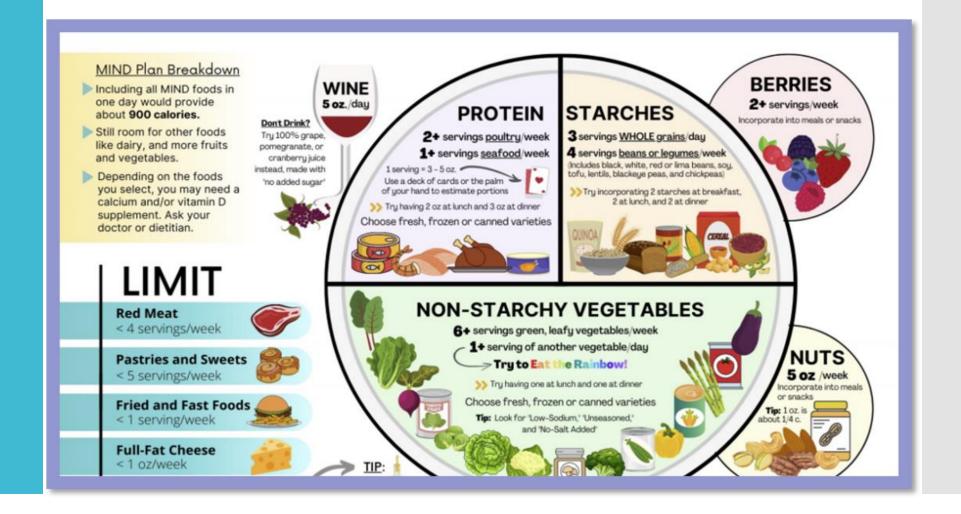


#### Latin American Diet Pyramid La Pirámide de La Dieta Latinoamericana



### 5 Lifestyle Factors: Nutrition

#### **MIND Diet Serving Recommendations**



Letter | Open access | Published: 03 February 2025

# Individual and additive effects of vitamin D, omega-3 and exercise on DNA methylation clocks of biological aging in older adults from the DO-HEALTH trial

Heike A. Bischoff-Ferrari , Stephanie Gängler, Maud Wieczorek, Daniel W. Belsky, Joanne Ryan, Reto W. Kressig, Hannes B. Stähelin, Robert Theiler, Bess Dawson-Hughes, René Rizzoli, Bruno Vellas, Laure Rouch, Sophie Guyonnet, Andreas Egli, E. John Orav, Walter Willett & Steve Horvath

Nature Aging (2025) Cite this article

- Post hoc analysis of 777 trial participants ingesting 2,000 IU vitamin
   D per day & 1 g omega 3 per day
  - Omega 3 slowed DNAm clocks; small protective effect on slowing biological aging over 3 years
  - Vitamin D supplementation, when combined with omega 3 supplementation and/or home exercise showed improvement in 1 biological clock measure

- Algae as a sustainable, affordable protein source
  - High nutritional content, high in protein
    - Omega-3 fatty acids, iron, vitamin K, zinc, magnesium, vitamin B3, vitamin B6, vitamin C, vitamin E
  - Decreased risk of hypertension
  - Decreased risk of diabetes







#### The American Journal of Clinical Nutrition

Available online 18 January 2024
In Press, Corrected Proof (7) What's this?

Original Research Artic

Effect of multivitamin-mineral supplementation versus placebo on cognitive function: results from the clinic subcohort of the COcoa Supplement and Multivitamin Outcomes Study (COSMOS) randomized clinical trial and meta-analysis of 3 cognitive studies within COSMOS

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Chirag M Vyas <sup>1</sup> Q S, JoAnn E Manson <sup>2 3 4</sup>, Howard D Sesso <sup>2 3</sup>, Nancy R Cook <sup>2 3</sup>,

Pamela M Rist <sup>2 3</sup>, Alison Weinberg <sup>2</sup>, M Vinayaga Moorthy <sup>2</sup>, Laura D Baker <sup>5 6</sup>,

Mark A Espeland <sup>5 7</sup>, Lok-Kin Yeung <sup>8</sup>, Adam M Brickman <sup>8 9 10</sup>, Olivia I Okereke <sup>1 3 4</sup> Q S
```

- Factorial trial of 573 participants
  - Daily multivitamin mineral supplementation found to have favorable 2 year change in episodic memory
  - Meta-analysis indicates multivitamin mineral supplementation benefits global cognition and episodic memory
  - Support the benefits of this therapy in preventing cognitive decline among older adults

# EAT FOOD. NOT TOO MUCH. MOSTLY PLANTS. (& mostly homecooked)

- Assess needs/preferences/willingness of others
- Especially the grocery shopper
- Referral to dietician/nutritionist/ vSMAs Food for Thought
- Consider incremental changes
- Harm reduction model
- Pre-packaged meals
- Personal & Planetary Health/sustainability
- Consider different textures, spices, plate to food contrast
- Importance of routines, traditions, time to slow down, chew, taste & eat
- Consider involving company or family
- https://youtu.be/wmmoSZgNg-4?si=IFNBorTM11xoDkgm
- HOMEMADE

# Food for Thought





What resources in your community and practice have helped improve nutrition or nutrition access?

# 5 Lifestyle Factors: Sleep

#### Sleep Disorders: Signs and Symptoms

- Obstructive sleep apnea
  - Loud or frequent snoring
  - Choking, gasping, or witnessed pauses in breathing during sleep
  - Daytime sleepiness
- Restless legs syndrome
  - Overwhelming urge to move the legs, worse in the evening or night
  - Burning, creepy-crawling sensation, or itching in the legs
- REM behavior disorder
  - Acting out dreams
- Insomnia
  - Difficulty falling asleep or staying asleep, accompanied by daytime sleepiness and fatigue
  - Prevalence is about 50% in older adults
  - Cognitive behavioral therapy for Insomnia (CBT-I) is first-line treatment



Neurobiology of Disease Volume 145, November 2020, 105054



n ...

Obstructive Sleep Apnea and Its Treatment in Aging: Effects on Alzheimer's disease Biomarkers, Cognition, Brain Structure and Neurophysiology

Anna E. Mullins <sup>a</sup>, Korey Kam <sup>a</sup>, Ankit Parekh <sup>a</sup>, Omonigho M. Bubu <sup>b</sup>, Ricardo S. Osorio <sup>b, 1</sup>, Andrew W. Varga <sup>a</sup> A <sup>1</sup> ⊠

# 5 Lifestyle Factors: Sleep

- Sleep deprivation increases plaque build-up in the brain
- Restorative sleep allows our brains to clear toxins and waste that can interfere with neuronal function
- Sleep helps us consolidate memories
- In people affected by dementia, lack of sleep can cause agitation, and other sequalae such as falls

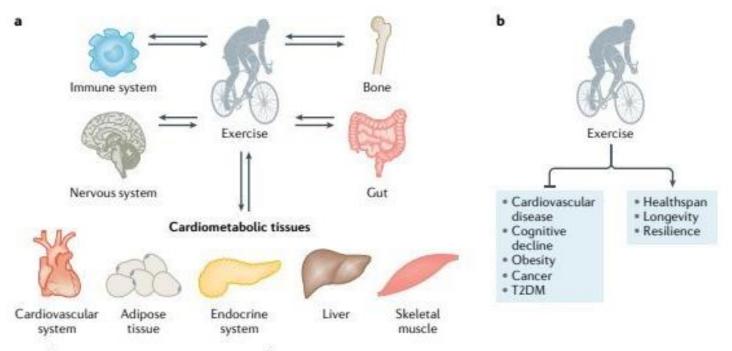


Fig. 1 | The systemic effects of exercise. a | Organs and tissues that can serve as source of exerkines and that are directly affected by exercise. b | Exercise results in profound health benefits, including reductions in the presence or severity of certain diseases, as well as increases in healthspan, longevity and resilience. T2DM, type 2 diabetes mellitus.

• Exerkines are exercise-stimulated biochemicals that play key roles in improving neurological, cardiovascular, immune, and metabolic health.

# YOUR BRAIN LOVES THE GYM

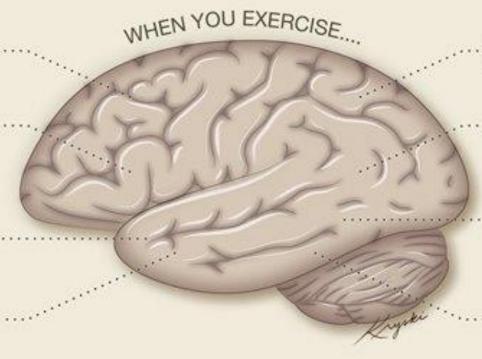
(OR SIDEWALK, BIKE TRAIL, POOL,...)

Norepinephrine is released, improving attention, perception and motivation.

Brain-derived neurotrophic factor (BDNF) is released, protecting and repairing neurons from injury and degeneration.

> Hormones combine with BDNF to grow brain cells, regulate mood and provide mental clarity.

The hippocampus, a part of the brain concerned with learning and memory, grows in size with regular exercise over time.



Endorphins are released, dulling the sensation of pain.

Serotonin is released, enhancing mood.

Blood flow to the brain increases, delivering more oxygen and nutrients and improving waste removal.

Dopamine is released, improving motivation, focus and learning.

- Exercise is associated with prolonged survival for people living with Alzheimer's Disease
- Physical fitness assessed with treadmill exercise testing (peak Vo2)
  was associated with better preservation of gray matter volumes
  among both cognitively normal seniors and those with early AD
  (Burns, et. al, 2008)
- Population based study with 357 participants studied prospectively , When incident AD cases who were physically inactive were compared to those with physical activity, those with more physical activity had a lower mortality risk (Scarmeas, et. al, 2011)
- Recent meta-analysis reinforces the association between physical activity and reduced risk of dementia. A comprehensive study involving over 250,000 participants found that regular physical activity significantly decreased the incidence of all-cause dementia and Alzheimer's disease (Iso-Markku, et. al, 2022.

- Over 90 meta-analyses in the last 5 years
- Highest quality/most consistent evidence
- Likely multiple mechanisms of action (Wilckens et al., 2021, Hippocampus)
- Likely beneficial in multiple domains
  - Cognition (processing speed, EF>memory) (Wang et al., 2020, Aging)
  - Physical function/mobility/falls (Lai et al., 2019, AM J Phys Med Rehabil)
  - Sleep (O'Caoimh et al., 2019)
  - Neuropsychiatric symptoms (Watt, et al, 2021, BMJ)
- Pooled effects highest for delaying onset>MCI>dementia
  - Group > individual
  - Across settings, including home-based (de Almeida, 2020, Gerontologist)

- At least 150 mins of moderate aerobic physical activity per week
  - o30 mins for 5 days/week
- At least 75 mins of vigorous aerobic physical activity per week
  - Cannot sing or talk during this type of activity
- Strength/Resistance Training At least 2x per week, best combined with aerobic activity
- Balance Training Practice 3x per week (e.g., Tai Chi, Qigong, yoga, heel to toe walks)







# 6 Public Health: Air Pollution

#### Air Pollution and Incidence of Dementia

A Systematic Review and Meta-analysis

Ehsan Abolhasani, MD, MSc (D), Vladimir Hachinski, MD, DSc (D), Nargess Ghazaleh, MD, MSc, Mahmoud Reza Azarpazhooh, MD, Naghmeh Mokhber, MD, FRCPC, and Janet Martin, PharmD, MSc (HTA) (D) AUTHORS INFO & AFFILIATIONS

- A systematic review and meta-analysis conducted on research available through August of 2021 found multiple articles covering a total population of over 91 million individuals, with 6% diagnosed with Dementia.
- The risk of dementia increased by 3% per 1 μg/m3 increment in PM2·5
- "The association between dementia per 10 µg/m3 increment in NOx was less clear, although a significant association could not be ruled out, and there was high heterogeneity across studies.
- ""Existing evidence suggests a significant association between exposure to PM2·5 and incidence of dementia and nonsignificant association between dementia and NOx, NO2, and O3 exposure. However, results should be interpreted in light of the small number of studies and high heterogeneity of effects across studies."

#### Circulation

#### **ORIGINAL RESEARCH ARTICLE**

#### Impact of Healthy Lifestyle Factors on Life **Expectancies in the US Population**

Physical activity (≥3.5h/week)



Body-mass index (18.5-24.9 kg/m<sup>2</sup>)



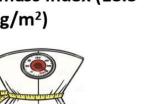


Adherence to five low-risk lifestylerelated factors was associated with 70% lower mortality and could extend life expectancy at age 50 by 10 years (free of chronic diseases) in US adults, compared to individuals who adopted zero low-risk lifestyle factor.









Light/Moderate alcohol Drinking

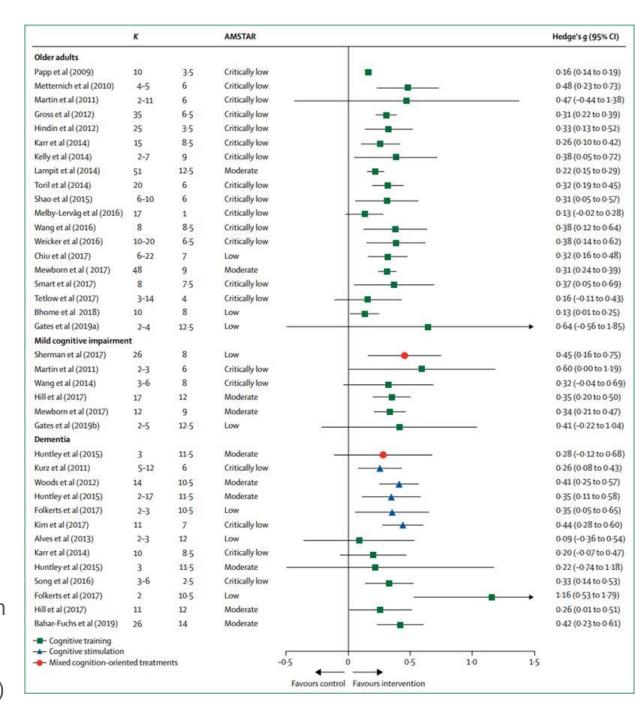


# 6 Public Health: Decreased Education

- Years of formal education has some of the most consistent and strongest evidence as a protective factor against dementia
- Builds Cognitive reserve
- Fewer years of formal education is associated with lower socioeconomic status; lower education levels are also associated with less physical activity, more diabetes, more hypertension
- Lifelong learning is also neuroprotective

# 6 Public Health: Lifelong Learning

- Addressing this modifiable risk factor through lifelong learning
- In a meta-analysis of 15 RCTs, there was consistent evidence that cognitive stimulation benefits people with mild to moderate dementia (Woods, et. al, 2012).
- Study at a nursing home in Italy where 40 sessions (8 weeks) of cognitive stimulation compared to placebo showed significant improvement in cognitive and behavioral symptoms in patients with mild to moderate dementia (Mapelli & Nocita, 2013)



# 6 Public Health: Social Isolation

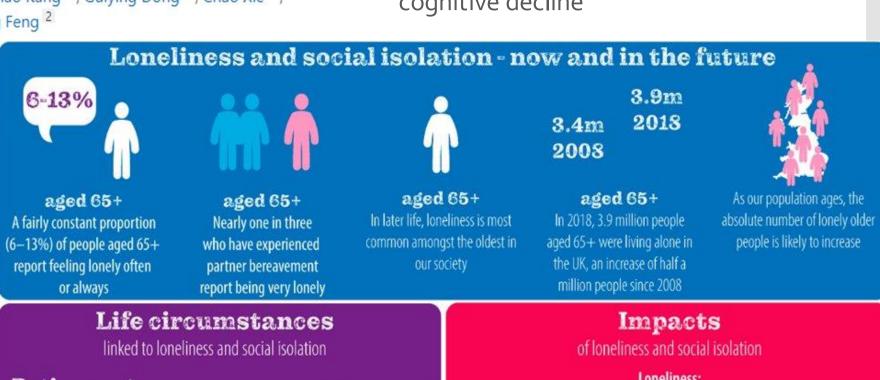
- Alzheimer's & Dementia
- RESEARCH ARTICLE
- Open Access
- Late-life social activity and subsequent risk of dementia and mild cognitive impairment
- · Yi Chen, Francine Grodstein, Ana W. Capuano, Tianhao Wang, David A. Bennett, Bryan D. James
- First published: 27 December 2024
- Rush MAP: 1923 elders followed for 6.7 years: higher social activity resulted in 5 year delay in dementia onset
- https://doi.org/10.1002/alz.14316

#### Associations of Social Isolation and Loneliness With Later Dementia

Chun Shen <sup>1</sup>, Edmund T Rolls <sup>1</sup>, Wei Cheng <sup>1</sup>, Jujiao Kang <sup>1</sup>, Guiying Dong <sup>1</sup>, Chao Xie <sup>1</sup>, Xing-Ming Zhao <sup>1</sup>, Barbara J Sahakian <sup>1</sup>, Jianfeng Feng <sup>2</sup>

 Increased social interaction has been shown to be of benefit by minimizing the sense of loneliness, isolation, stress and vascular factors that contribute to cognitive decline

## 6 Public Health: Social Isolation



Retirement

Poor physical and mental health

Bereavement

Poverty

Living alone

Caring for somebody

#### Loneliness:

- key risk factor for depression in older age
- linked with a 40% increased risk of dementia

#### Social isolation:

- strongly linked to cardiovascular disease

Loneliness, social isolation, and living alone are all associated with an increased risk of early death.

# 6 Public Health: Social Isolation

Review > Ageing Res Rev. 2020 Mar;58:101002. doi: 10.1016/j.arr.2019.101002. Epub 2019 Dec 30.

### A Third of Community-Dwelling Elderly With Intermediate and High Level of Alzheimer's Neuropathologic Changes Are Not Demented: A Meta-Analysis

Mahmoud Reza Azarpazhooh <sup>1</sup>, Abolfazl Avan <sup>2</sup>, Lauren E Cipriano <sup>3</sup>, David G Munoz <sup>4</sup>, Mahdiyeh Erfanian <sup>5</sup>, Amin Amiri <sup>6</sup>, Saverio Stranges <sup>7</sup>, Vladimir Hachinski <sup>8</sup>

Healthy Lifestyle and Cognition in Older Adults With

# Common Neuropathologies of Dementia Klodian Dhana <sup>1 2</sup>, Puja Agarwal <sup>2 3</sup>, Bryan D James <sup>2 3</sup>, Sue E Leurgans <sup>3 4</sup>, Kumar B Rajan <sup>1 2</sup>, Neelum T Aggarwal <sup>3 4</sup>, Lisa L Barnes <sup>3 4</sup>, David A Bennett <sup>3 4</sup>, Julie A Schneider <sup>3 4 5</sup>

# Intersection of Modifiable Risk Factors

- Exercise
- Low Alcohol
- Nutrition

- 586 brain autopsies of people who had a mean age of 90.9 years at the time of death, Lifestyle habits linked to dementia risk more than amyloid plaques or abnormal blood flow in their brains.
- Participants in this study had registered with RUSH University's Memory and Aging Project. Individuals self-reported their lifestyle habits.
- Smoking
- At least 150 min physical activity/wk
- Limited alcohol
- MIND diet score
- Cognitive Activities
- The researchers estimated that **just 12%** of cognition-related measurements were affected by amyloid plaques.

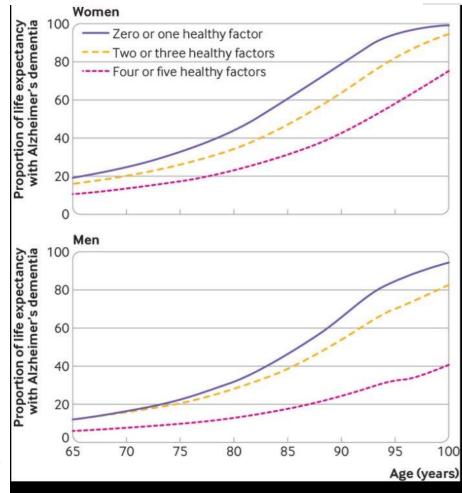
# Intersection of Modifiable Risk Factors

- Nonsmoking
- Exercise
- Nutrition
- Community

# Healthy lifestyle and life expectancy with and without Alzheimer's dementia: population based cohort study

*BMJ* 2022; 377 doi: https://doi.org/10.1136/bmj-2021-068390 (Published 13 April 2022) Cite this as: *BMJ* 2022;377:e068390

- -Nonsmoking
- -≥150 min/wk moderate/vigorousintensity physical activity
- -light to moderate alcohol consumption
- -high-quality Mediterranean-DASH
   Diet Intervention for
   Neurodegenerative Delay diet (upper 40%)
- -Engagement in late-life cognitive activities (upper 40%)
- 4-5 healthy factors ~60% lower risk of AD
- 2449 MEN AND WOMEN AGE 65 AND OLDER



See this image and copyright information in PMC

**Fig 2** Proportion of life expectancy spent with Alzheimer's dementia according to categories of lifestyle score in women and men. Proportion is computed by dividing life expectancy lived with Alzheimer's dementia by total life expectancy at a given age (supplementary tables 2 and 3). A behavior was classified as low risk or healthy if it met several criteria: Mediterranean-DASH Diet

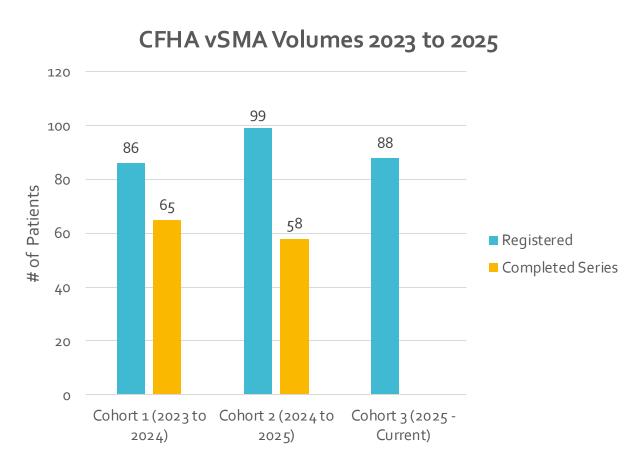
# Women & Brain Health: Sex Effect & Decreased Benefits of Lecanemab in Females

#### The higher benefit of lecanemab in males compared to females in CLARITY AD is probably due to a real sex effect

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Daniel Andrews 1 2, Simon Ducharme 3 4, Howard Chertkow 4 5 6 7 8 9,
Maria Pia Sormani 10 11, D Louis Collins 1 2 4; Alzheimer's Disease Neuroimaging Initiative
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- Phase 3 trial found Lecanemab slowed cognitive decline by 27%, however subgroup analyses indicated a 31% sex difference in the effect and suggested limited to no effectiveness in females
- Further examination by Andrews et al showed statistically nonsignificant difference in cognitive decline that would not explain the difference in effectiveness
- "Lecanemab is likely less effective in females than males, but we cannot conclude the drug is ineffective in females"

# Virtual Shared Medical Appointment (vSMA) Series: Paving the Path to Better Brain Health



#### **Patient Feedback:**

"I am learning a lot from these sessions. I'm so glad I rolled in it...I appreciate the time and the effort that [Dr. Dotson] & staff and everyone else involved in making these programs available to me."

"[W]e appreciate being included in the Healthy Aging program. We feel fortunate to have access to such important information and are grateful for the time and energy that is put into presenting each module."

"For me as the caregiver it had good information. I enjoyed getting to know Dr. Isenberg and the staff a bit. I especially liked the class on nutrition. I made each recipe and liked each one. The banana bread was so simple and tasty. I had not used tofu for a long time, and now we are back at it."

I was extremely impressed with Dr Nancy Isenberg's handling of the subject, and the impressive booklet that accompanied the series. Excellent production with easy reading that steered students into (probably) unchartered waters! I would also like to express my best wishes to everyone in the team."



# Comments, Ouestions & Answers





In examining modifiable risk factors, what are your thoughts?

What risk factors have you had successful interventions for?

What resources exist in your practices and communities?

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