

Healthy Brain Aging and Recent Advances in the Treatment of Alzheimer's Disease

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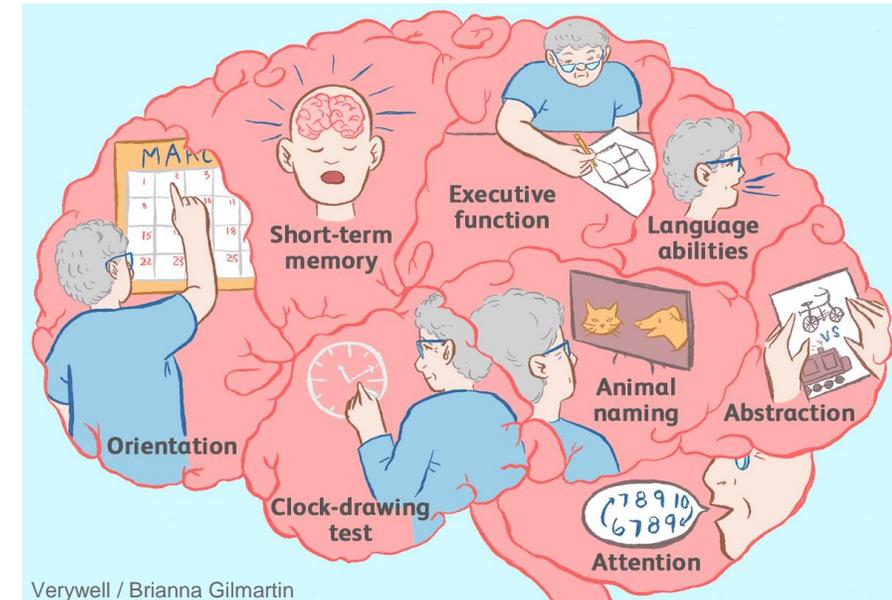


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What is Cognition – more than just memory

- **Cognitive Domains:**

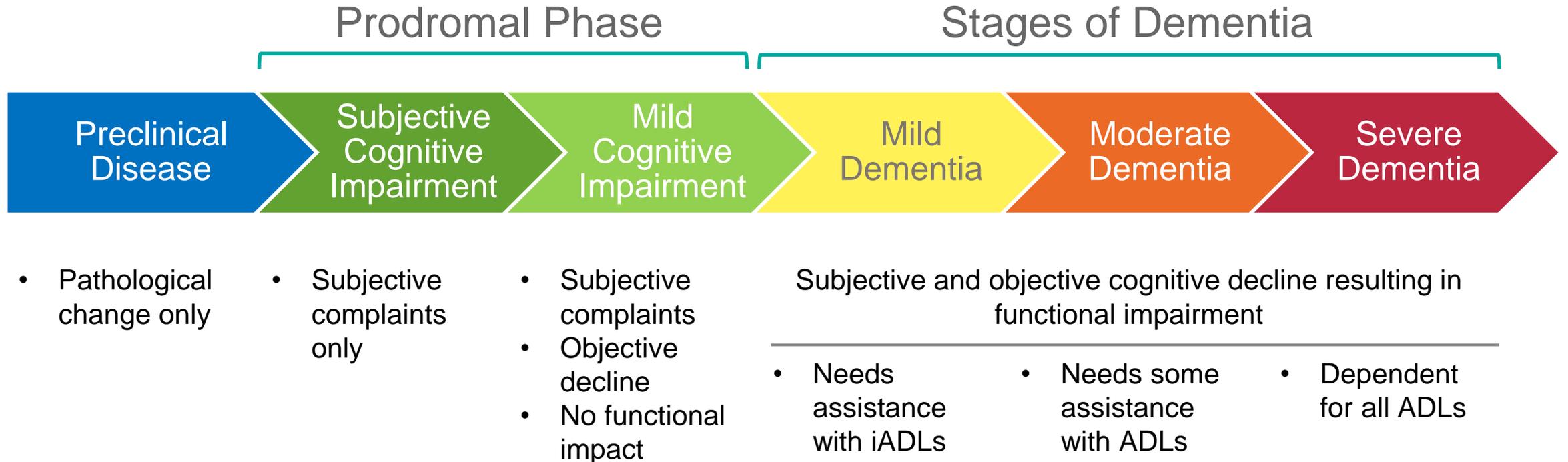
- Memory: learning, short & long-term recall
- Executive: Attention, concentration, multi-tasking, focus
- Visuospatial: navigation, use of tools, recognition of people/faces
- Language: word-finding, fluency, comprehension
- Behavior: depression, anxiety, odd behaviors, changes in personality
- Motor/Sensory



- Different domains localize to different parts of the brain
- Different diseases of the brain impact different domains

Clinical Progression of Cognitive Impairment

iADLs: instrumental activities of daily living (finances, medication, etc)
 ADLs: activities of daily living (bathing, grooming, dressing, eating, etc)



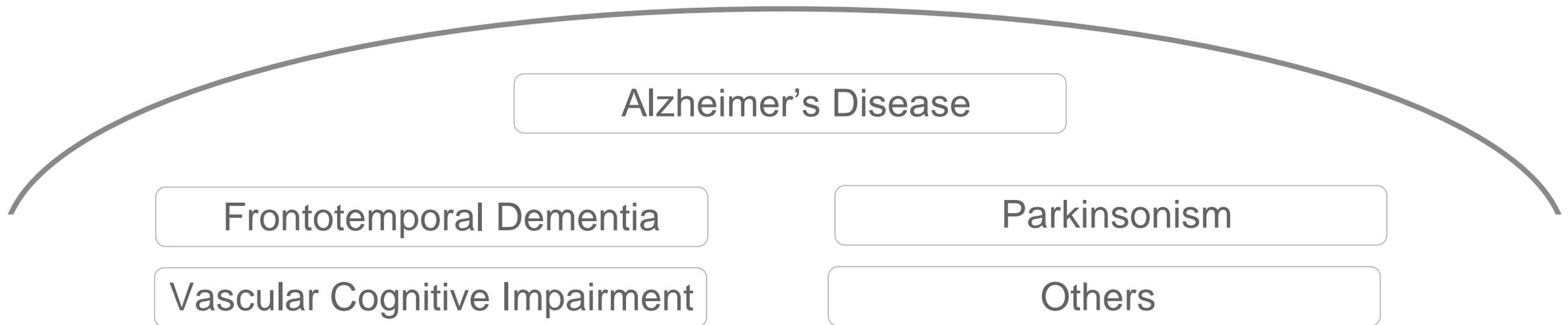
Preclinical disease starts ~10-20 years before any symptoms
 Not all patients progress, particularly in the prodromal phases

Dementia is not the same as Alzheimer's

Syndrome/Stage of Cognitive Impairment



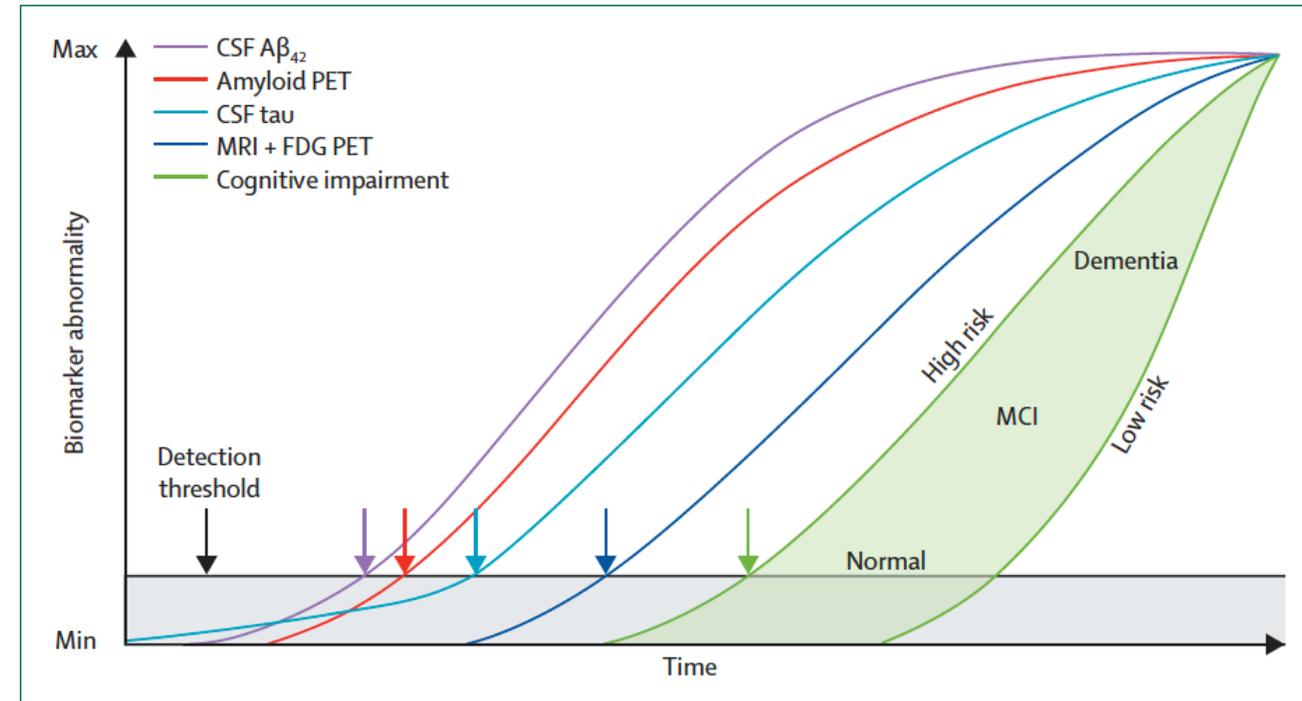
Diagnoses Causing Cognitive Impairment



Example: A patient has a Mild Cognitive Impairment due to Alzheimer's disease

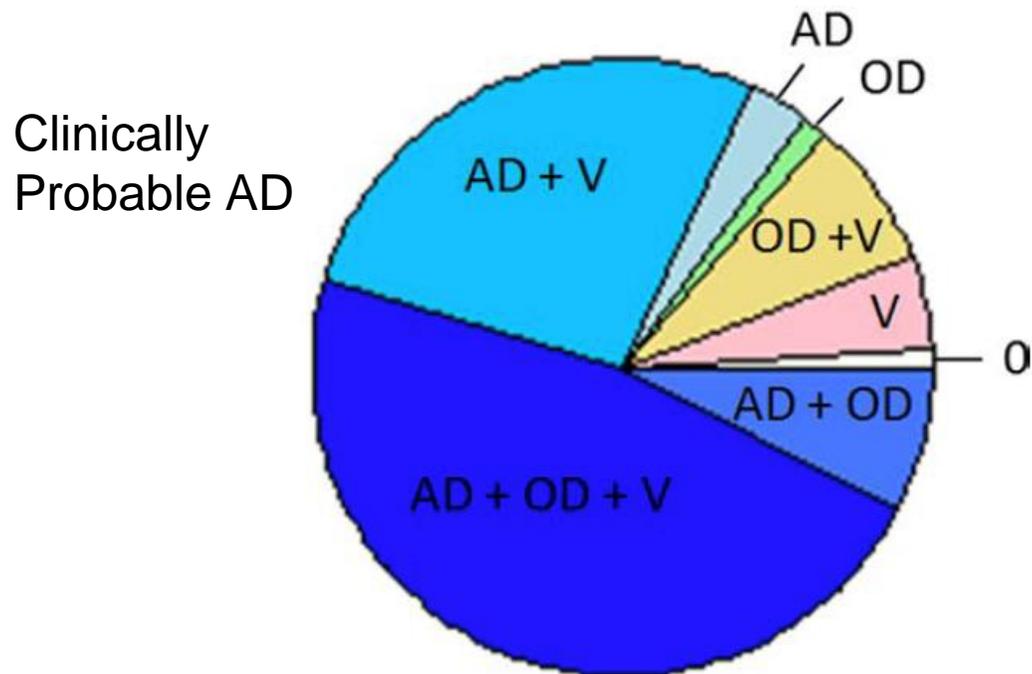
What is Alzheimer's Disease?

- Alzheimer's disease is a pathology. The *accumulation of pathological proteins* (amyloid-beta and tau) in different regions of the brain resulting in neuronal loss and cognitive impairment
- Certain regions of the brain are more vulnerable to the pathology resulting in earlier symptoms
 - ie: hippocampus involved in short-term memory formation is impacted early in Alzheimer's disease

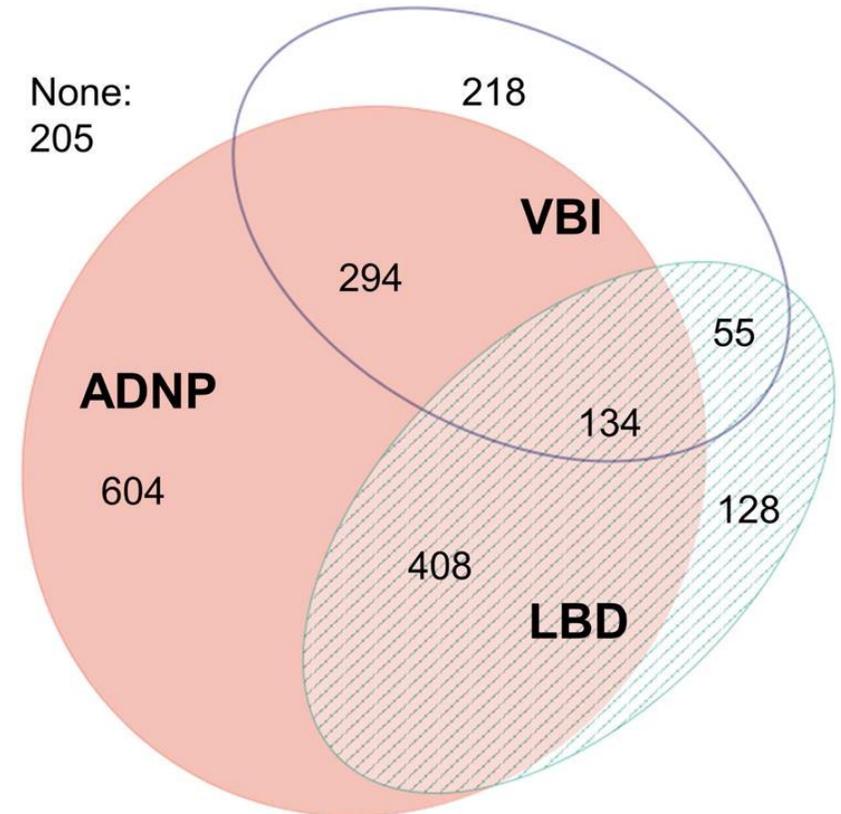


Mixed neuropathology is common

Religious Orders & Rush Memory Aging Project



National Alzheimer's Coordinating Center



Mixed neuropathology ~50-85% of cases at autopsy – particularly in older patients as they accumulate pathology over time

Prevention

- **Goals of Prevention and Why it is Important:**

- Reduce burden of disease on society and patient
- Reduce cost

- **Primary Prevention:**

- Prevent disease before it occurs

- **Secondary Prevention:**

- Early identification disease/ screening
- Reduce impact of disease that has occurred

Primary Prevention Successes

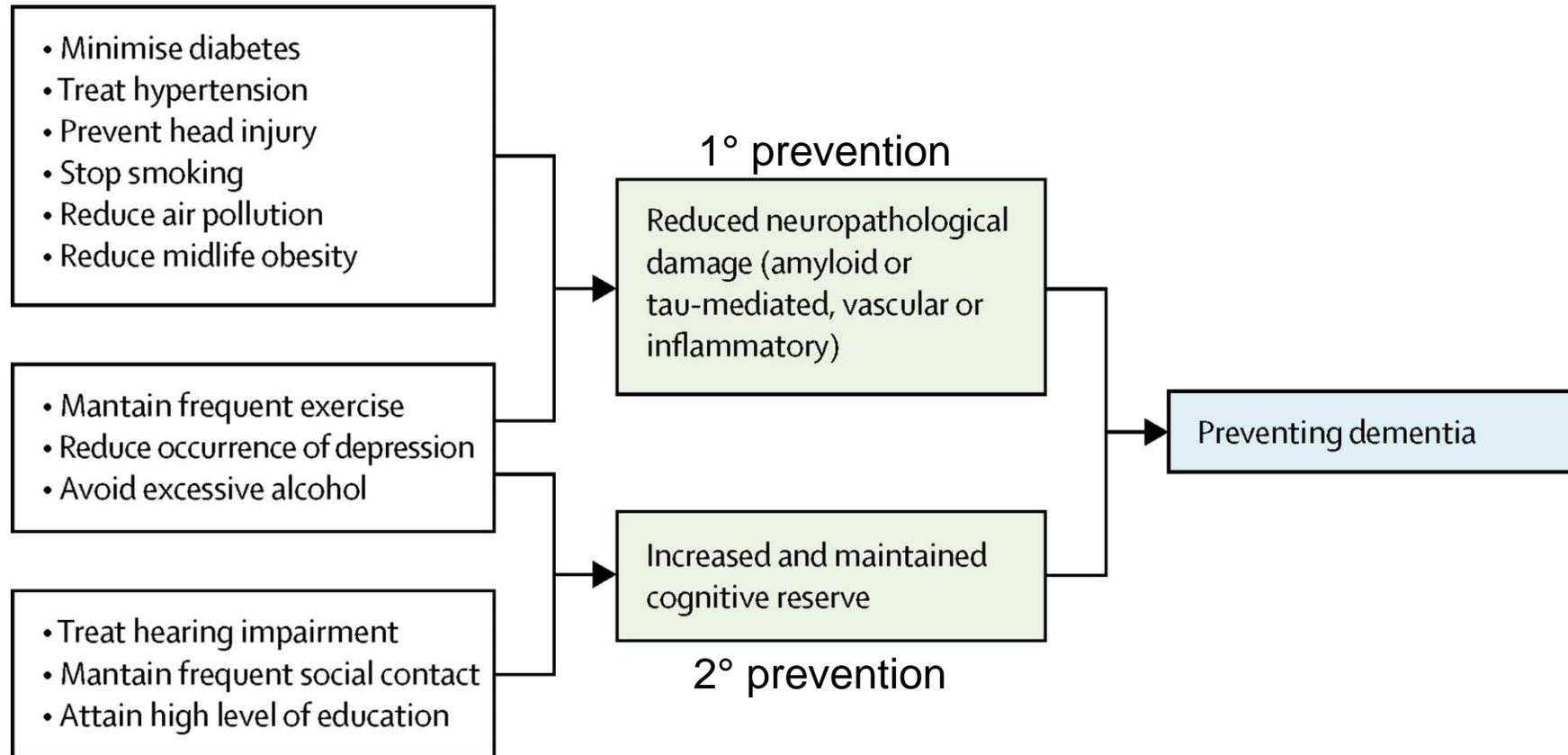
- Vaccinations: flu, polio, smallpox
- Ban on lead paint: reduce plumbism
- Regular exercise: reduce cardiovascular disease

Secondary Prevention Successes

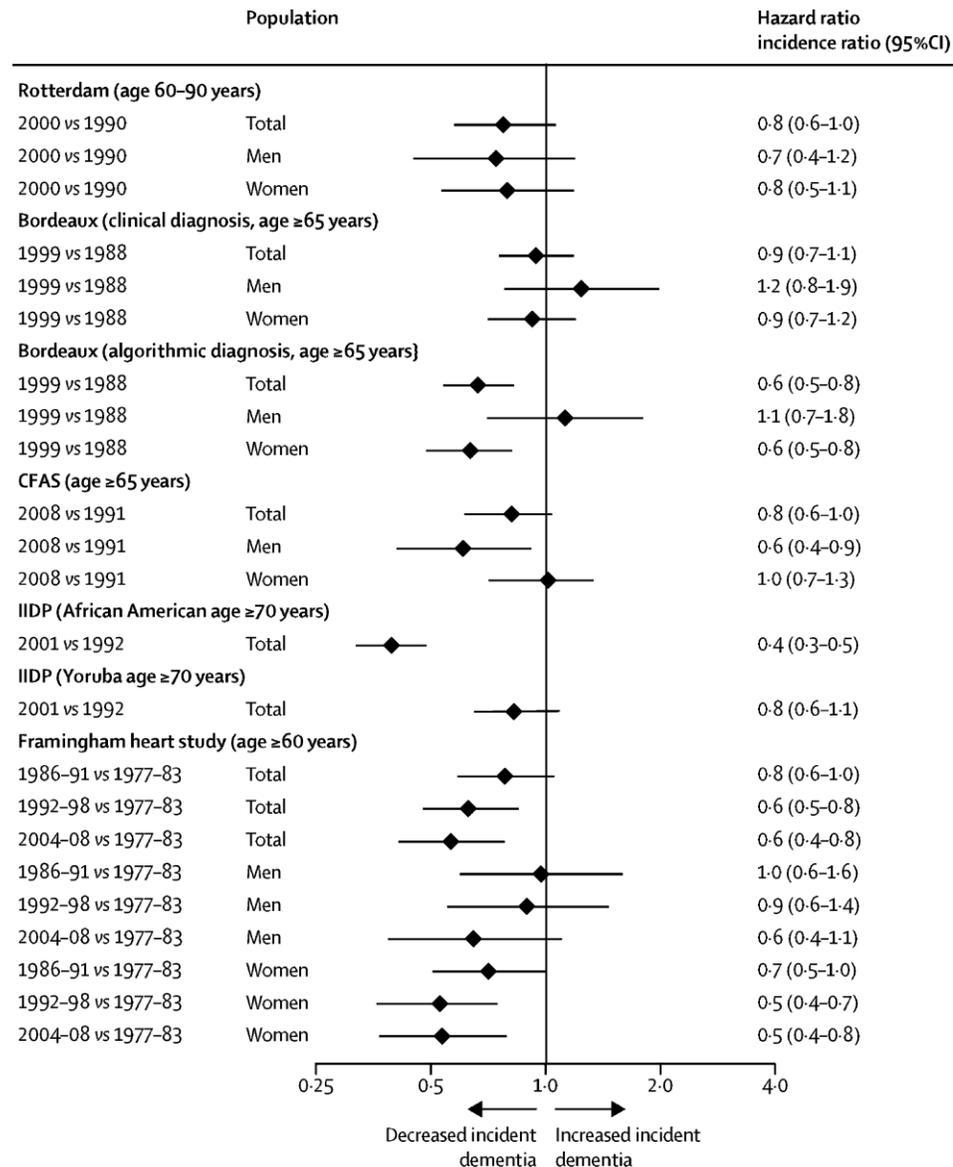
- Aspirin for stroke and heart attack
- Treatment of hypertension
- Mammography for breast cancer
- Colonoscopy for colon cancer

Prevention in Dementia

- Can we delay the accumulation of neuropathologies? (1° prevention)
- Can we increase resilience to neuropathologies in the brain? (2° prevention)



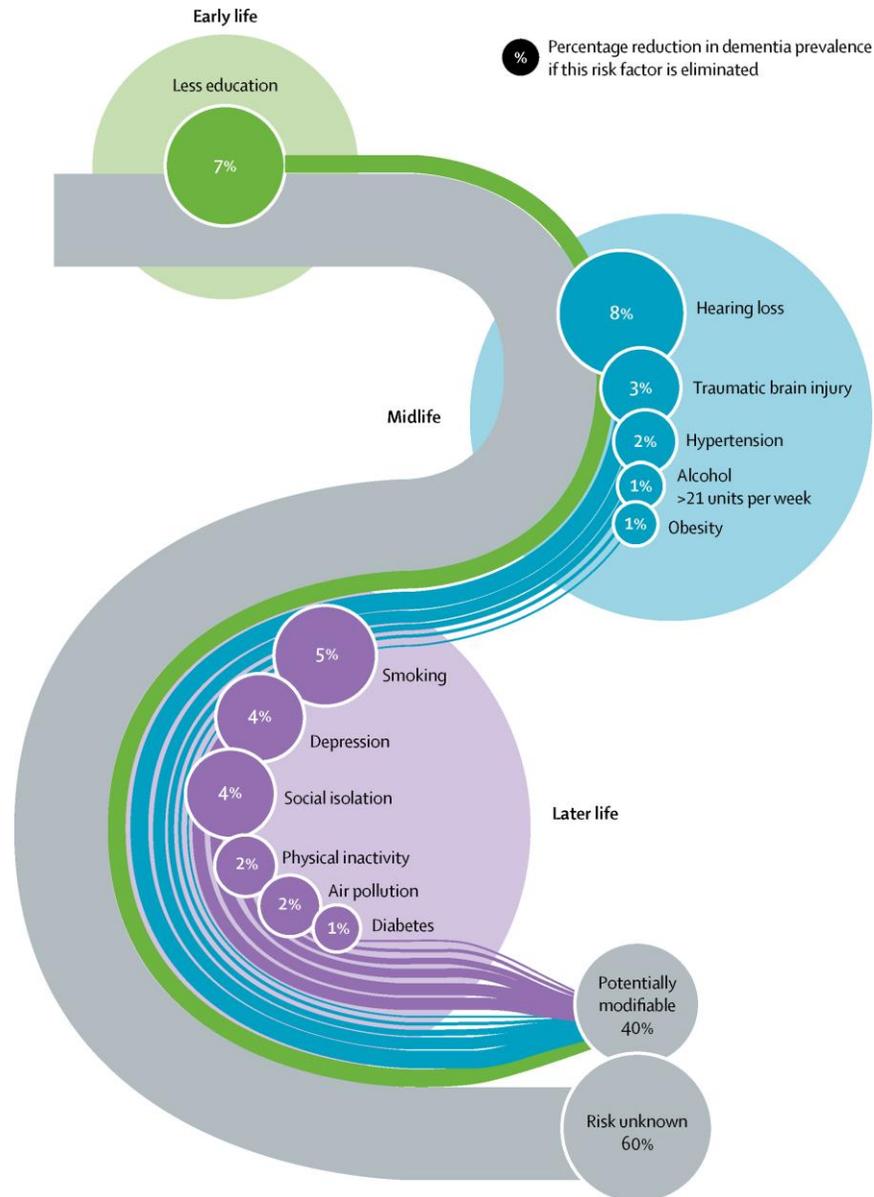
Dementia is modifiable



Age-specific incidence of dementia has fallen particularly in high-income countries, presumably due to:

- Improved education
- Nutrition
- Health care (vascular risk factor management)
- Life-style changes

Risk factor modification throughout life



- Prevention of cognitive impairment occurs throughout the life span, prior to any symptoms of cognitive change
- It is *never too late* to address risk factors for cognitive impairment and dementia
- Earlier is better
- Prevention is possible! → up to 40% of dementia is modifiable

Early Life Education and reduced dementia risk

Table 3. Temporal Trends in the Incidence of Dementia, Stratified by Age, Sex, Educational Level, and Apolipoprotein E ϵ 4 Status.*

Variable	No. of Cases of Dementia	Total No. of Observation Periods	P Value for Interaction	5-Yr Hazard Ratio (95% CI) [†]				P Value for Trend
				Epoch 2	Epoch 3	Epoch 4	Trend [‡]	
Age at entry (yr)			0.82					
60–69	42	4418		0.43 (0.18–1.00)	0.36 (0.15–0.89)	0.38 (0.15–0.93)	0.65 (0.47–0.89)	0.008
70–79	133	3229		0.91 (0.59–1.42)	0.67 (0.42–1.07)	0.64 (0.36–1.11)	0.83 (0.68–1.00)	0.047
≥80	196	1368		0.86 (0.56–1.33)	0.72 (0.48–1.09)	0.68 (0.44–1.06)	0.86 (0.74–1.01)	0.06
Sex			0.27					
Female	234	5173		0.70 (0.50–1.00)	0.52 (0.36–0.74)	0.53 (0.36–0.78)	0.77 (0.67–0.89)	<0.001
Male	137	3842		0.96 (0.59–1.57)	0.89 (0.55–1.43)	0.64 (0.38–1.08)	0.85 (0.71–1.02)	0.08
Educational level			0.031					
No high school diploma	130	1831		1.46 (0.94–2.26)	0.97 (0.58–1.61)	1.66 (0.87–3.15)	1.11 (0.89–1.39)	0.34
High school diploma	228	6948		0.54 (0.36–0.81)	0.55 (0.38–0.79)	0.46 (0.31–0.67)	0.77 (0.67–0.88)	<0.001

Incidence of dementia from Framingham Heart Study

→ lower relative risk in those that completed high school

Hearing loss and Cognition

Cognitive Assessment ^a	Coefficient (95% CI) ^b		
	All Participants (N = 7385)	Participants With Hearing Aid Nonuse (n = 6551)	Participants With Hearing Aid Use (n = 834)
Memory			
Mild hearing loss	-0.52 (-0.65 to -0.39)	-0.51 (-0.64 to -0.38)	-0.06 (-0.97 to 0.86)
Moderate to severe hearing loss	-1.00 (-1.24 to -0.76)	-1.16 (-1.45 to -0.87)	-0.25 (-1.18 to 0.67)
Use hearing aid	0.01 (-0.21 to 0.23)	NA	NA
Social isolation	-0.61 (-0.74 to -0.48)	-0.55 (-0.69 to -0.42)	-1.07 (-1.47 to -0.67)
Executive function			
Mild hearing loss	-0.38 (-0.65 to -0.11)	-0.41 (-0.69 to -0.13)	0.86 (-1.53 to 3.25)
Moderate to severe hearing loss	-1.56 (-2.07 to -1.06)	-1.60 (-2.23 to -0.97)	-0.35 (-2.77 to 2.08)
Use hearing aid	0.89 (0.45 to 1.34)	NA	NA
Social isolation	-1.06 (-1.32 to -0.80)	-0.98 (-1.25 to -0.70)	-1.65 (-2.38 to -0.92)

- Hearing loss is associated with poorer cognition
- Hearing aid use shows improved cognitive performance
- Social isolation is a mediating factor for the link in untreated hearing loss.

Depression and dementia: a bidirectional relationship

- Depression is a risk factor for later cognitive decline.
- Debated Mechanism
 - Depression creates a vulnerability in the brain for dementia
 - Depression is the earliest manifestation of a degenerative disease/dementia

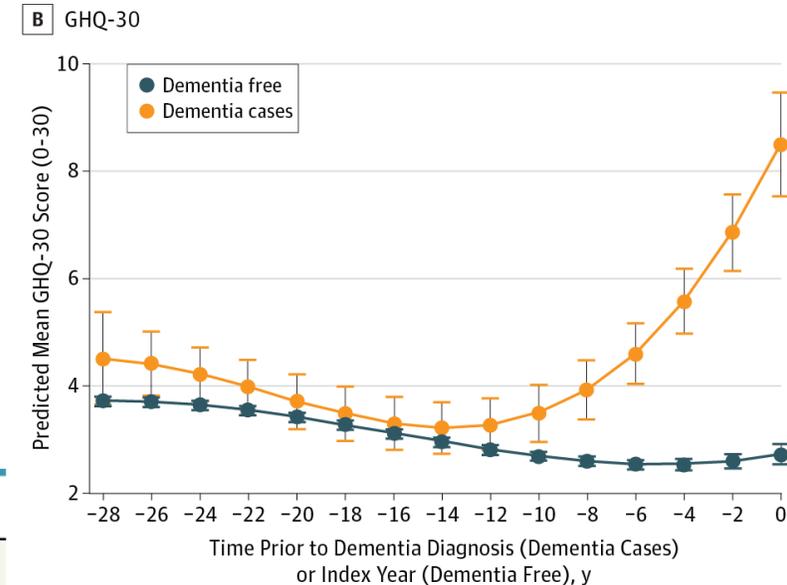


Table 3. Chronic/Recurring GHQ-30 Caseness in Early and Late Study Phase and Incidence of Dementia^a

Variable	Chronic/Recurring GHQ-30 Caseness			
	Early Study Phase (1985, 1989, and 1991)		Late Study Phase (1997, 2001, and 2003)	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Age range, y	35-60	NA	45-74	NA
No. with dementia/total No.	277/9095	NA	198/6948 ^b	NA
Mean follow-up (SD), y	21.7 (3.6)	NA	11.1 (1.8)	NA
Model 1: Analysis Adjusted for Age (Time Scale), Sex, Marital Status, Race/Ethnicity, Education, and Occupation				
Never	1 [Reference]	NA	1 [Reference]	NA
Once	1.21 (0.92-1.58)	.18	1.54 (1.10-2.17)	.01
Twice or more	1.12 (0.81-1.56)	.48	1.89 (1.28-2.78)	.001

Hypertension and Cognitive Impairment

- Persistent midlife hypertension is associated with risk of late-life cognitive impairment (dementia & MCI)
- Midlife HTN associated with reduced brain volume and increased white matter hyperintensities

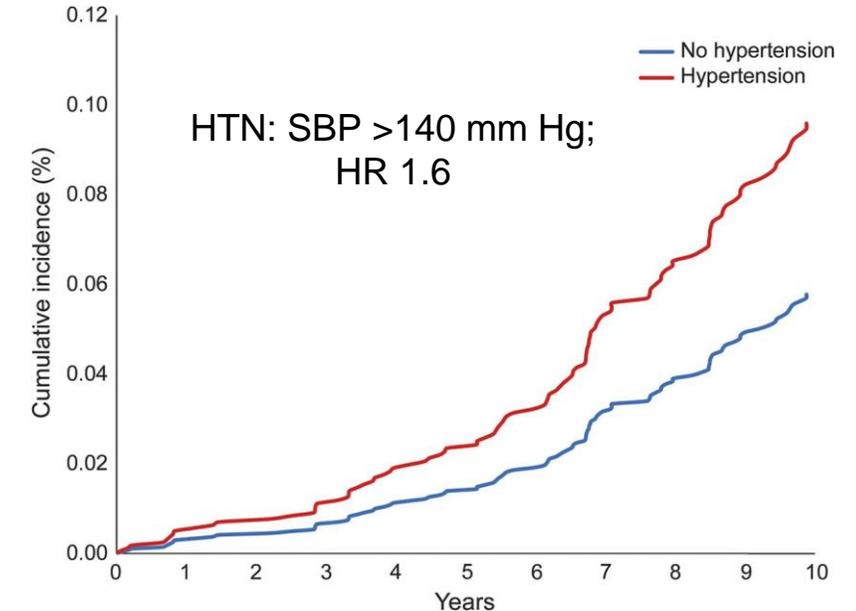


Table 2. Incidence of Probable Dementia and Mild Cognitive Impairment by Treatment Group

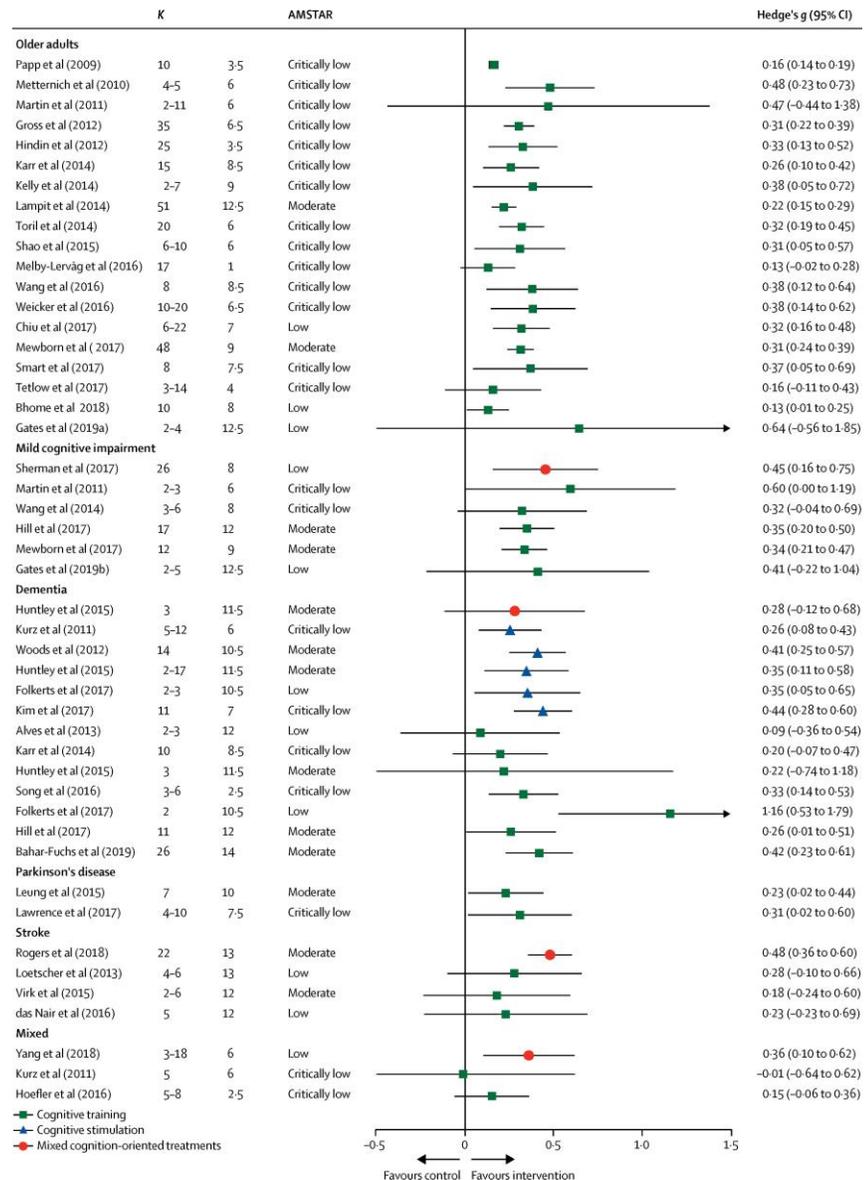
Outcomes	Intensive: SBP <120 mmHg; Standard: SBP <140 mmHg		Treatment Group		Hazard Ratio (95% CI) ^a	P Value
			Intensive	Standard		
	No. With Outcome/Person-Years	Cases per 1000 Person-Years	No. With Outcome/Person-Years	Cases per 1000 Person-Years		
Probable dementia	149/20 569	7.2	176/20 378	8.6	0.83 (0.67-1.04)	.10
Mild cognitive impairment ^b	287/19 690	14.6	353/19 281	18.3	0.81 (0.69-0.95)	.007
Composite of mild cognitive impairment or probable dementia	402/19 873	20.2	469/19 488	24.1	0.85 (0.74-0.97)	.01

McGrath ER et al. Blood pressure from mid- to late life and risk of incident dementia. *Neurology*. 2017; 89(24)

The SPRINT MIND Investigators for the SPRINT Research Group. Effect of Intensive vs Standard Blood Pressure Control on Probable Dementia: A Randomized Clinical Trial. *JAMA*. 2019;321(6):553-561.

Lane CA et al. Associations between blood pressure across adulthood and late-life brain structure and pathology in the neuroscience substudy of the 1946 British birth cohort (Insight 46): an epidemiological study. *Lancet Neurol*. 2019; 18: 942-952

Cognitive-oriented treatments improved cognition



Lots of poor-quality/small studies, however all studies trend toward improvement,

variety of conditions

- Cognitively normal
- Mild cognitive impairment
- Dementia
- Parkinson's disease

STAY COGNITIVELY ACTIVE!!

No specific cognitive program or intervention is recommended

→ do something you enjoy!!



Diet, dietary supplements and Cognition

Table 4. Baseline Cognitive Function Measured With Composites and Changes by Intervention Group

Variable	Mean (95% CI)			P Value
	Mediterranean Diet Plus Extravirgin Olive Oil	Mediterranean Diet Plus Nuts	Control Diet	
Memory^a				
Unadjusted model ^b				
Baseline	-0.06 (-0.02 to 0.08)	0.04 (-0.12 to 0.20)	0.04 (-0.14 to -0.23)	.56
Change	0.04 (-0.10 to 0.17)	0.08 (-0.06 to 0.22)	-0.14 (-0.29 to 0.004)	.08
Fully adjusted model ^c				
Baseline	0.02 (-0.11 to 0.15)	0.013 (-0.13 to 0.16)	-0.04 (-0.20 to -0.11)	.82
Change	0.04 (-0.09 to 0.18)	0.09 (-0.05 to 0.23) ^d	-0.17 (-0.32 to -0.01)	.04
Frontal Cognition^e				
Unadjusted model ^b				
Baseline	0.06 (-0.10 to 0.23)	0.02 (-0.16 to 0.21)	-0.10 (-0.33 to 0.12)	.41
Change	0.23 (0.07 to 0.38) ^d	-0.02 (-0.27 to 0.22)	-0.28 (-0.53 to -0.03)	.002
Fully adjusted model ^c				
Baseline	-0.06 (-0.25 to 0.13)	0.04 (-0.20 to 0.27)	0.12 (-0.11 to -0.34)	.50
Change	0.23 (0.03 to 0.43) ^d	0.03 (-0.25 to 0.31)	-0.33 (-0.57 to -0.09)	.003
Global Cognition^e				
Unadjusted model ^b				
Baseline	0.06 (-0.06 to 0.18)	0.21 (0.06 to 0.36)	0.22 (0.06 to 0.39)	.17
Change	0.05 (-0.08 to 0.18) ^d	-0.06 (-0.24 to 0.11)	-0.36 (-0.56 to -0.15)	.001
Fully adjusted model ^c				
Baseline	-0.07 (-0.17 to 0.04)	-0.05 (-0.16 to 0.06)	-0.07 (-0.19 to 0.05)	.97
Change	0.05 (-0.11 to 0.21) ^d	-0.05 (-0.27 to 0.18)	-0.38 (-0.57 to -0.18)	.005

- Mediterranean or Nordic diet:
 - High intake of vegetables, fruits, legumes, whole grains.
 - Lower intake of saturated lipids and meats
- No evidence that vitamins, oils, or dietary supplements preserve cognitive function or prevent dementia
- WHO guidelines: Mediterranean diet, no supplements/vitamins

MIND Diet: Mediterranean-DASH Intervention for Neurodegenerative Delay diet

The Bristol
ASSISTED LIVING

MIND DIET: WHAT TO EAT + WHAT TO LIMIT

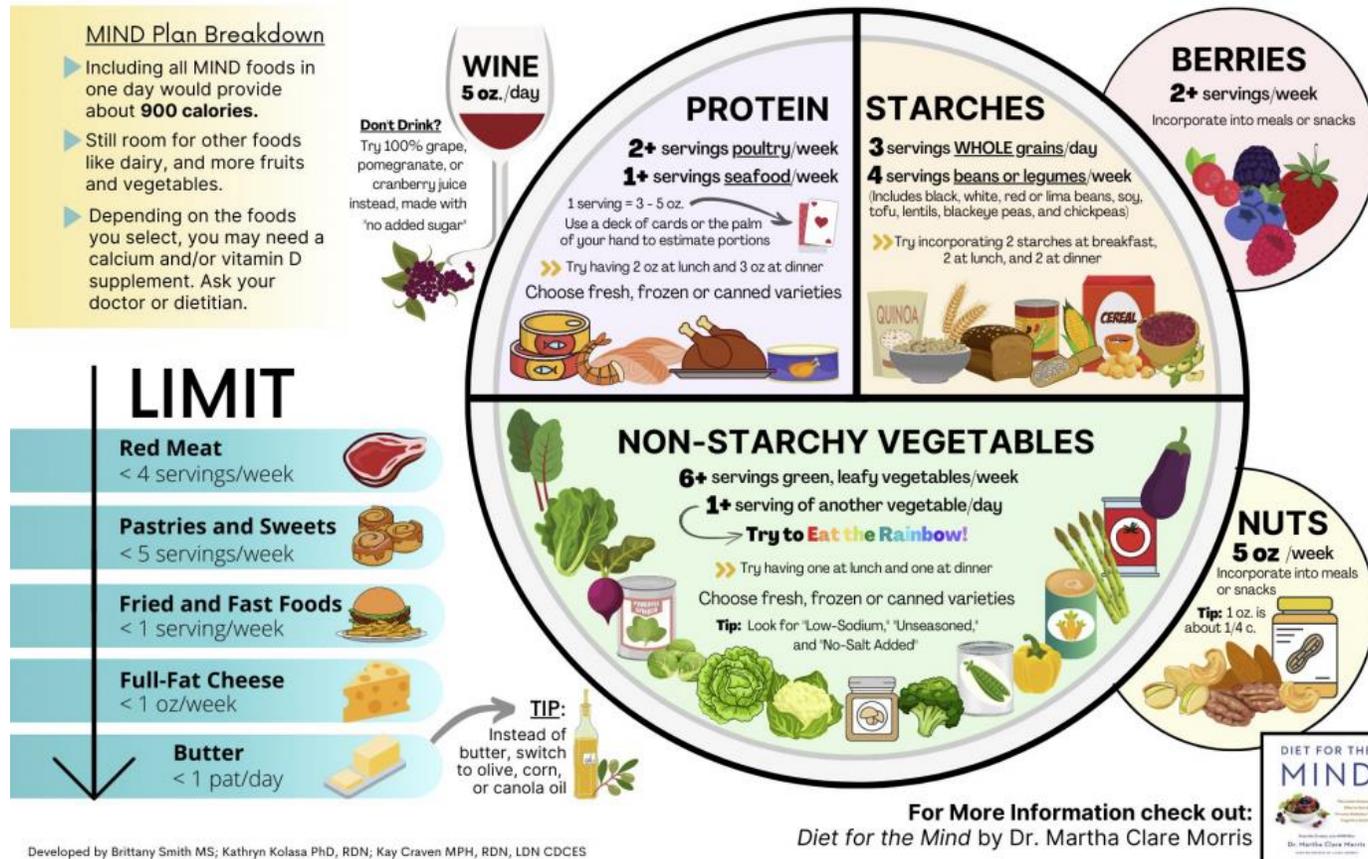
EAT	Greens	Veggies	Berries	Nuts	Olive oil
					
LIMIT	Whole grains	Fish	Beans	Poultry	Red wine
					
LIMIT	Butter	Cheese	Red meat	Fried foods	Sweets
					

MIND Diet: Mediterranean-DASH Intervention for Neurodegenerative Delay diet

MIND Plan

Mediterranean-DASH Intervention for Neurodegenerative Delay

- An eating approach emphasizing foods found effective in reducing dementia risk and slowing cognitive decline.
- The more you follow the MIND plan, the more you reduce your risk for Alzheimer's Disease



Developed by Brittany Smith MS; Kathryn Kolasa PhD, RDN; Kay Craven MPH, RDN, LDN CDCES
Department of Family Medicine, East Carolina University; November, 2020

Morris MC, et al. MIND diet slows cognitive decline with aging. *Alzheimer's & Dementia*. 2015;11:1015.

Morris MC, et al. MIND diet associated with reduced incidence of Alzheimer's disease. *Alzheimer's & Dementia*. 2015;11:1007.

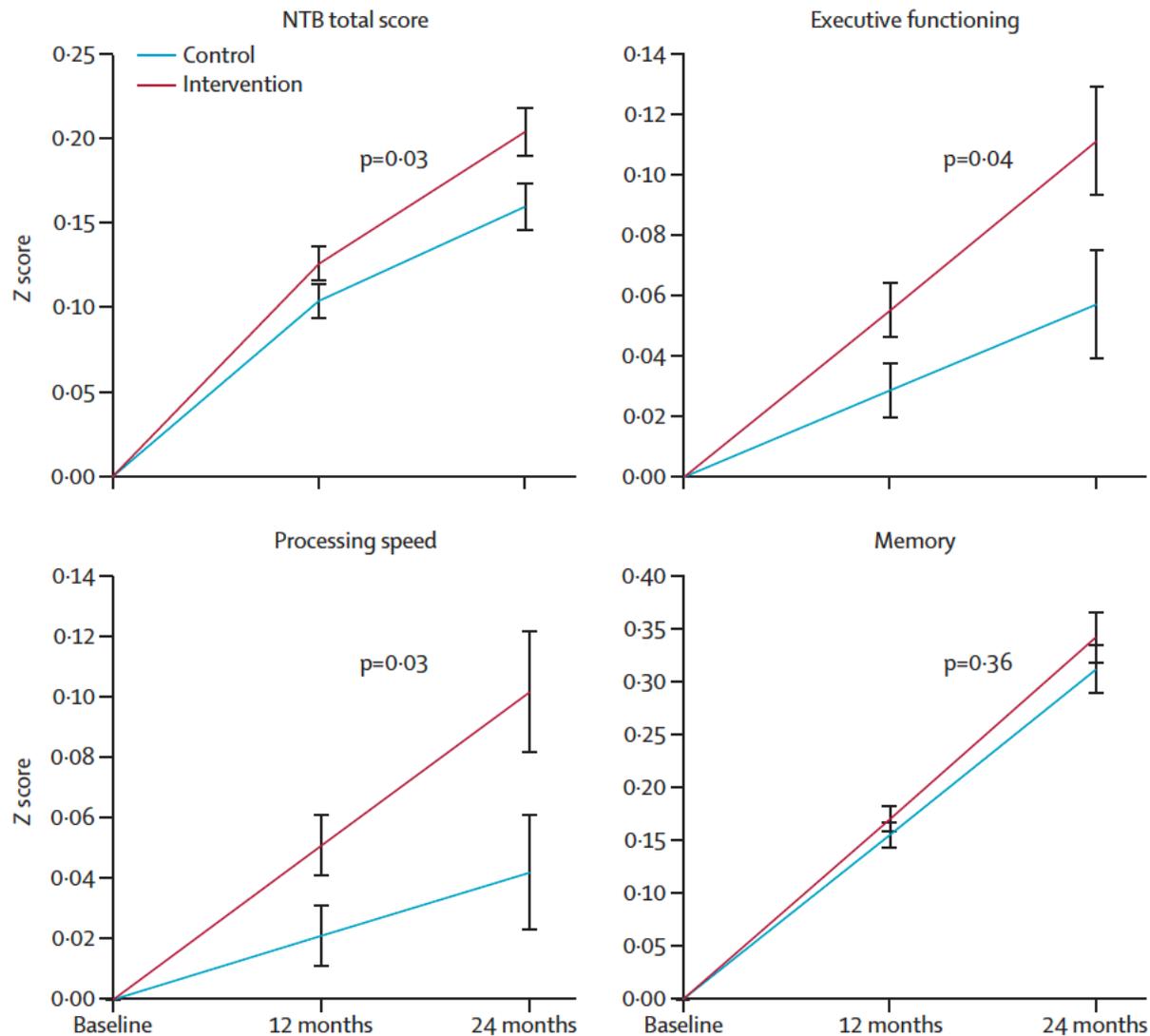
Healthy life-style/cardiovascular risk and Cognition

Additive effects of cardiovascular risk factors on development of dementia

“standard” drink
~14 g

Lifestyle factor	Low-risk category	High-risk category		
MIND diet	Upper 2/5ths (highest 40%) of the score distribution	Bottom 3/5ths (lower 60%) of the score distribution		
Physical activity	≥150 min/wk in moderated or vigorous activities	<150 min/wk or sedentary		
Cognitive activity	Upper 2/5ths (highest 40%) of the distribution	Bottom 3/5ths (lower 60%) of the distribution		
Smoking	Never or former smoker	Current		
Alcohol intake	Women ≥1–<15 g/d, men ≥1–<30 g/d	Nondrinkers or women ≥15 and men ≥30 g/d		
		No. of healthy lifestyle factors		
	Overall population	0-1	2-3	4-5
CHAP				
Incidence rate per 100 person-y (95% CI)	2.61 (2.46–2.76)	5.22 (4.65–5.79)	2.59 (2.39–2.78)	1.22 (1.02–1.43)
Absolute rate difference (95% CI)		1 (Reference)	–2.63 (–3.24 to –2.03)	–4.00 (–4.46 to –3.39)
MAP				
Incidence rate per 100 person-y (95% CI)	3.82 (3.32–4.31)	6.47 (4.44–8.49)	4.08 (3.39–4.77)	2.66 (1.96–3.35)
Absolute rate difference (95% CI)		1 (Reference)	–2.39 (–4.53 to –0.25)	–3.81 (–5.96 to –1.66)

Multi-domain interventional trials



- FINGER Trial: double-blind randomized, 1260 60-77-year-old with normal cognition
- 1:1 ratio to a 2-year multidomain intervention (diet, exercise, cognitive training, vascular risk monitoring), or a control group (general health advice).
- Interventions can improve/maintain cognitive function
- Larger, multi-site and multi-national interventional trials are on-going (World-wide FINGERS, US-POINTER)

Strategies for Dementia Risk Reduction

Targeted on individuals

- Treat hypertension and aim for systolic blood pressure <130 mm Hg in midlife
- Use hearing aids for hearing loss; we need to help people wear hearing aids as many find them unacceptable, too difficult to use, or ineffective
- Avoid or discourage drinking 21 or more units of alcohol per week
- Prevent head trauma where an individual is at high risk
- Stopping smoking is beneficial regardless of age
- Reduce obesity and the linked condition of diabetes by healthy food availability and an environment to increase movement
- Sustain midlife, and possibly late-life physical activity

Strategies for Dementia Risk Reduction

Population-wide

- Prioritise childhood education for all, worldwide
- Implement social public health policies that reduce hypertension risk in the entire population
- Develop policies that encourage social, cognitive, and physical activity across the life course for all (with no evidence for any specific activities being more protective)
- Scrutinise the risks for hearing loss throughout the life course, to reduce the risk of exposure to this risk factor
- Reduce the risk of serious brain trauma in relevant settings, including occupational and transport
- National and international policies to reduce population exposure to air pollution
- Continue to strengthen national and international efforts to reduce exposure to smoking, both for children and adults, and to reduce uptake and encourage cessation

Treatment of Dementia

Non-pharmacological behavioral & safety interventions

Medications for Cognitive Symptoms

- Cholinesterase inhibitors
 - Throughout the disease
- Memantine
 - Moderate and severe stages

Medications for Neuropsychiatric symptoms

- Mood changes
 - Irritability, agitation
- Sleep changes
 - Sleep/wake cycle changes

Treatment of Dementia – New developments

- June 7th – the FDA approved a new medication, aducanumab, for the treatment of Alzheimer's disease
- Aducanumab clears amyloid plaques from the brain
- Monthly infusion of monoclonal antibody
- Studied in:
 - Mild cognitive impairment (mild cognitive changes, no functional changes)
 - With confirmed amyloid pathology/Alzheimer's disease
- Mixed results from clinical trials regarding slowing of cognitive decline
 - 1 Clinical trial with a slowing of cognitive decline by 22% at 78 weeks
 - Another clinical trial with no effect of the medication

Treatment of Dementia – New developments

- Points to Remember about Aducanumab
 1. It's an exciting step forward for the potential management of individuals with Alzheimer's disease
 2. The medication may be appropriate for a specific group of patient with early cognitive changes before any functional decline
 3. Most importantly, this medication incentivizes early diagnosis and detection of cognitive impairment. Early diagnosis enhances quality of life for patients and families



Thank you!
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Questions?