Alzheimer's Disease Prevention (?Risk Reduction)

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Pre-test

Approximately what % of AD is attributed to modifiable risk factors?

A. 20%
B. 40%
C. 60%
D. 80%

Which of the following has demonstrated clear evidence for benefit in AD prevention?

A. Mediterranean diet
B. Vigorous aerobic exercise 30 mins, 3 times a week
C. Cognitive simulation game aimed at improving executive function
D. All of the above
E. None of the above

True or false: There is strong evidence from RCTs for multimodal approach to AD prevention

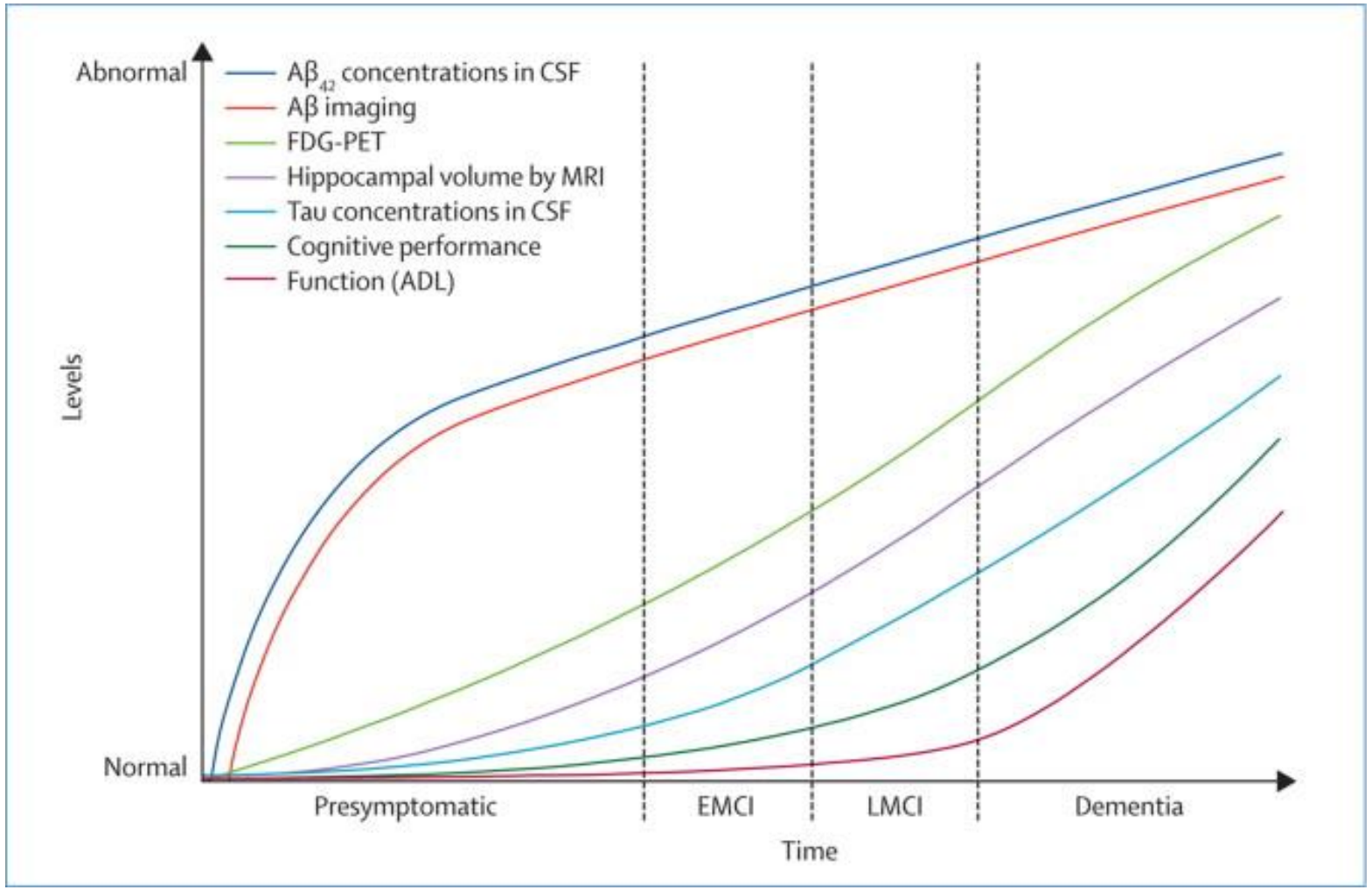
A. True
B. False

True or false: The most effective way to manage AD risk factors is to treat each one independently

A. True
B. False

Some definitions and general concepts…

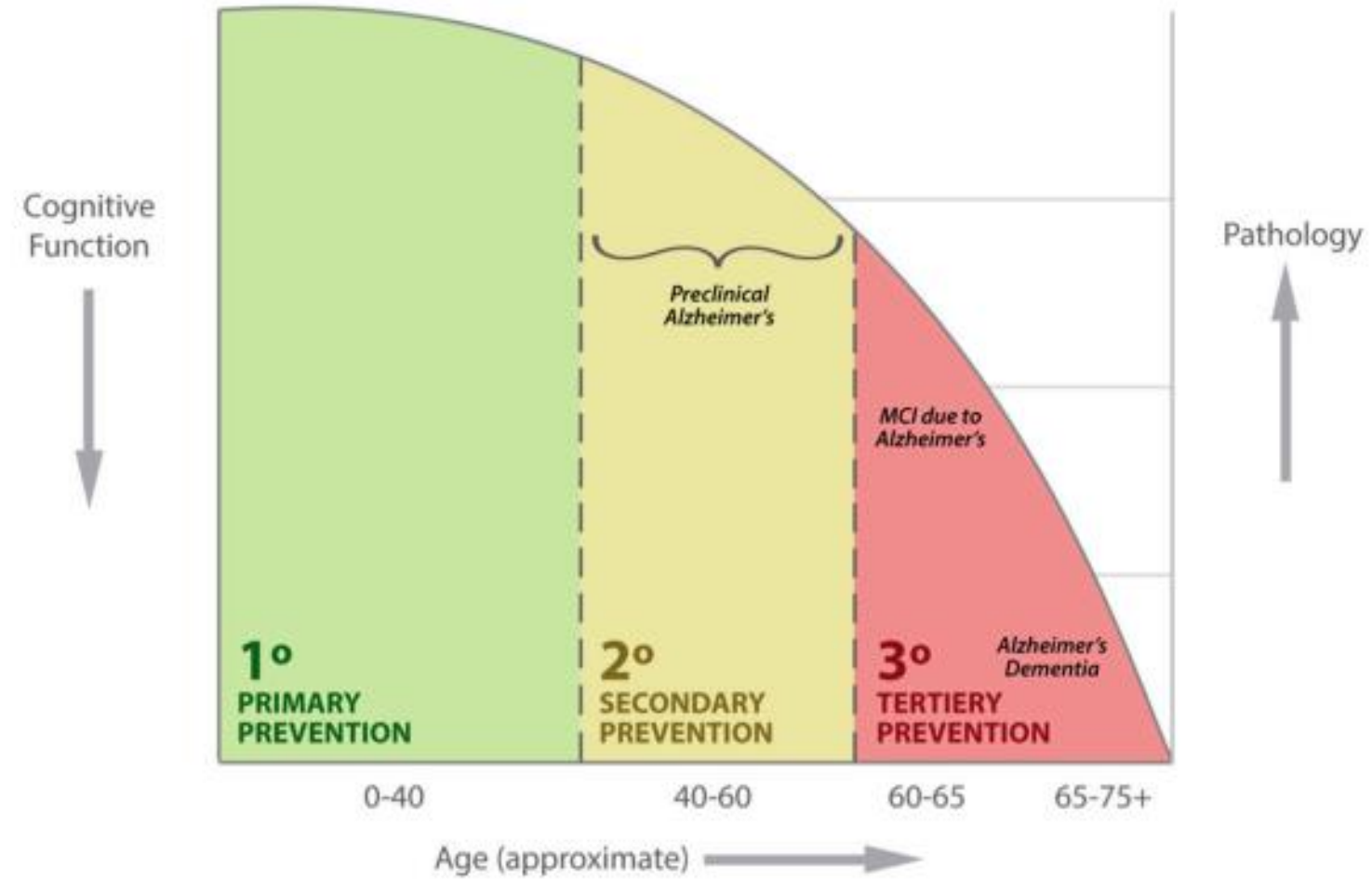
What is Alzheimer's disease?



- Distinction between Alzheimer's disease versus Alzheimer's dementia
- AD has a very long prodromal (asymptomatic phase)
- The earlier intervention, likely the more effective

Peterson et al., Lancet Neurology, 2010

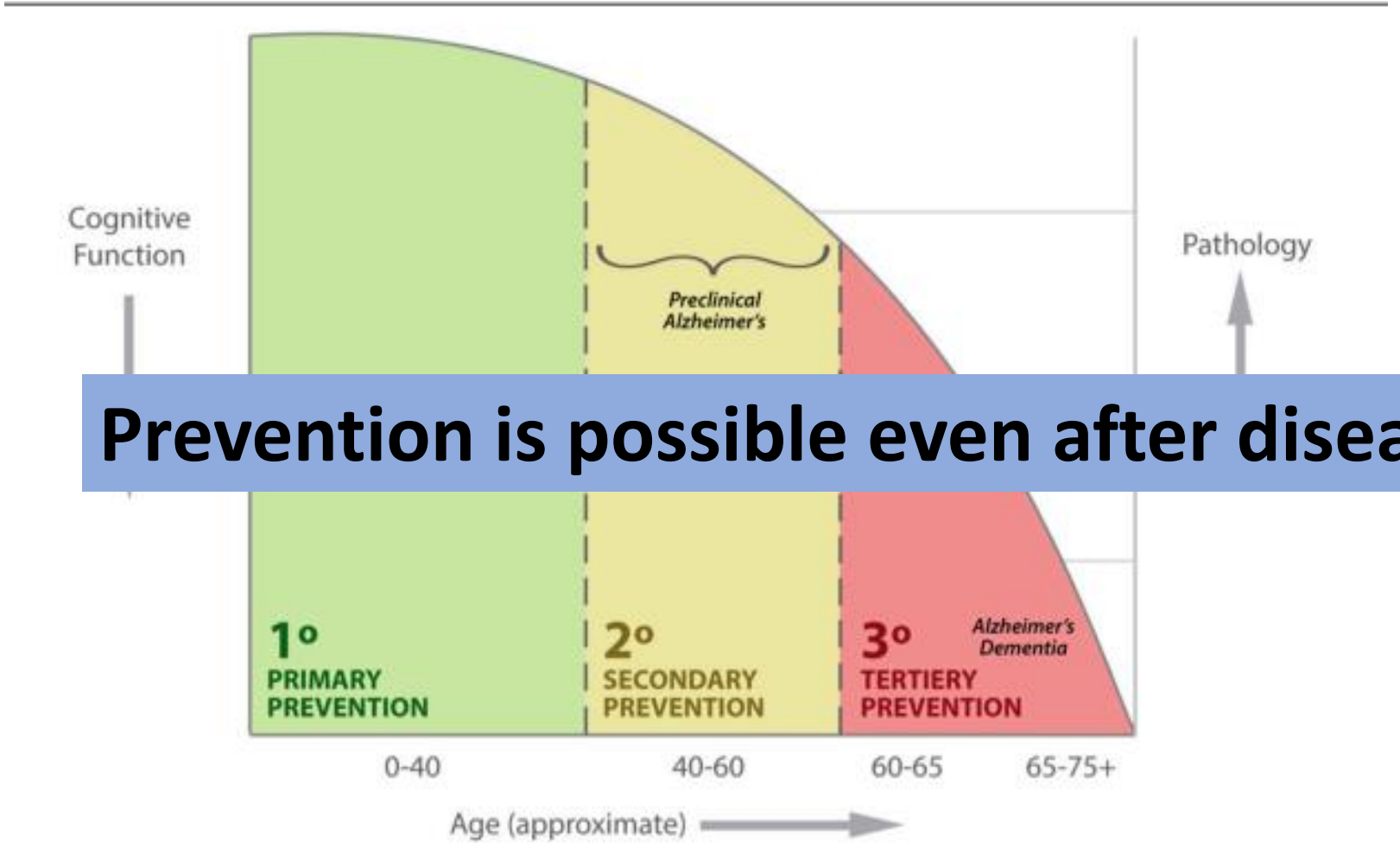
What is AD prevention?



Hodes et al, Frontiers in Neurology 2019

- **Primary prevention:** avoid disease before it occurs, delay onset
- **Secondary prevention:** recognize disease in earliest stage (before obvious symptoms occur) to slow or stop progression
- **Tertiary prevention**: treatment of disease to prevent complications and minimize disability

What is AD prevention?



Prevention is possible even after disease onset

- **Primary prevention:** avoid disease before it occurs, delay onset
- **Secondary prevention:** recognize disease in earliest stage (before ptoms ow or stop progression
- **Tertiary prevention**: treatment of disease to prevent complications and minimize disability

Hodes et al, Frontiers in Neurology 2019

Prevention vs risk reduction

- “Prevention”: laymen use ≠ academic use

- “Risk reduction” (rather than “prevention”)
  - End goal = reduce burden of disease, maintain cognitive health (rather than preventing AD per se)
  - more honest and transparent
  - More realistic, avoid overpromising

- Risk reduction = more suitable in clinical practice

Why AD risk reduction?

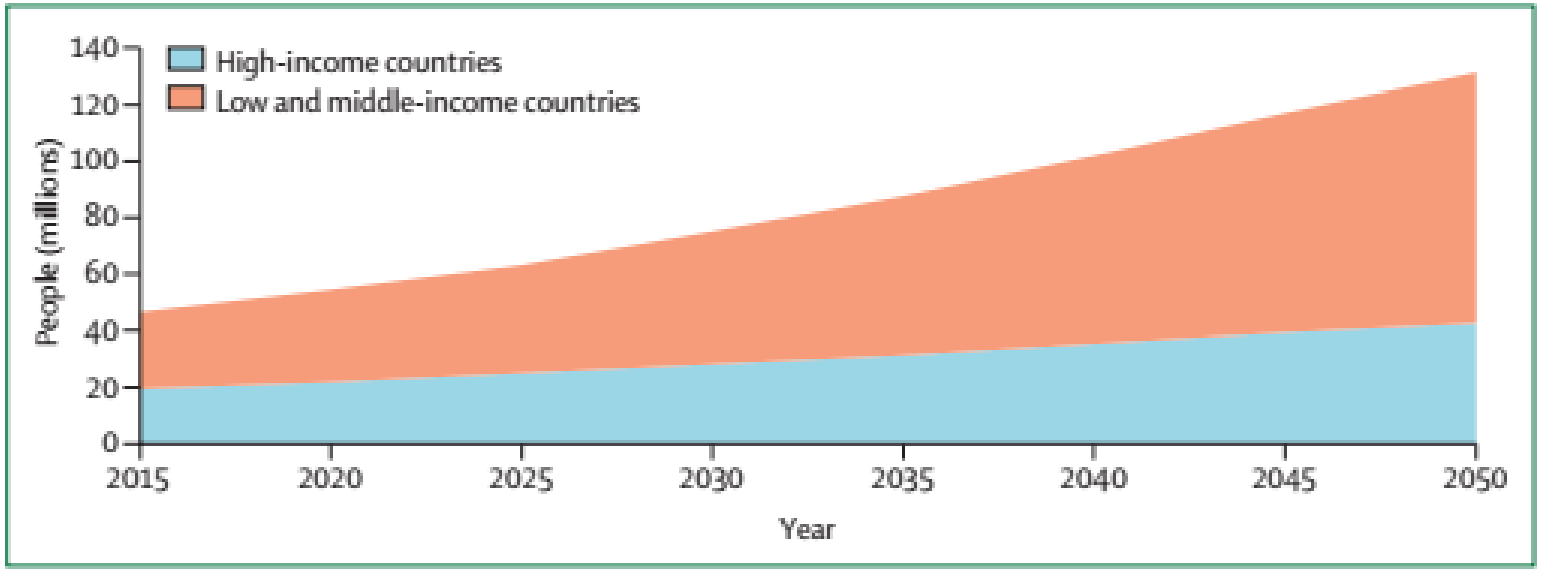
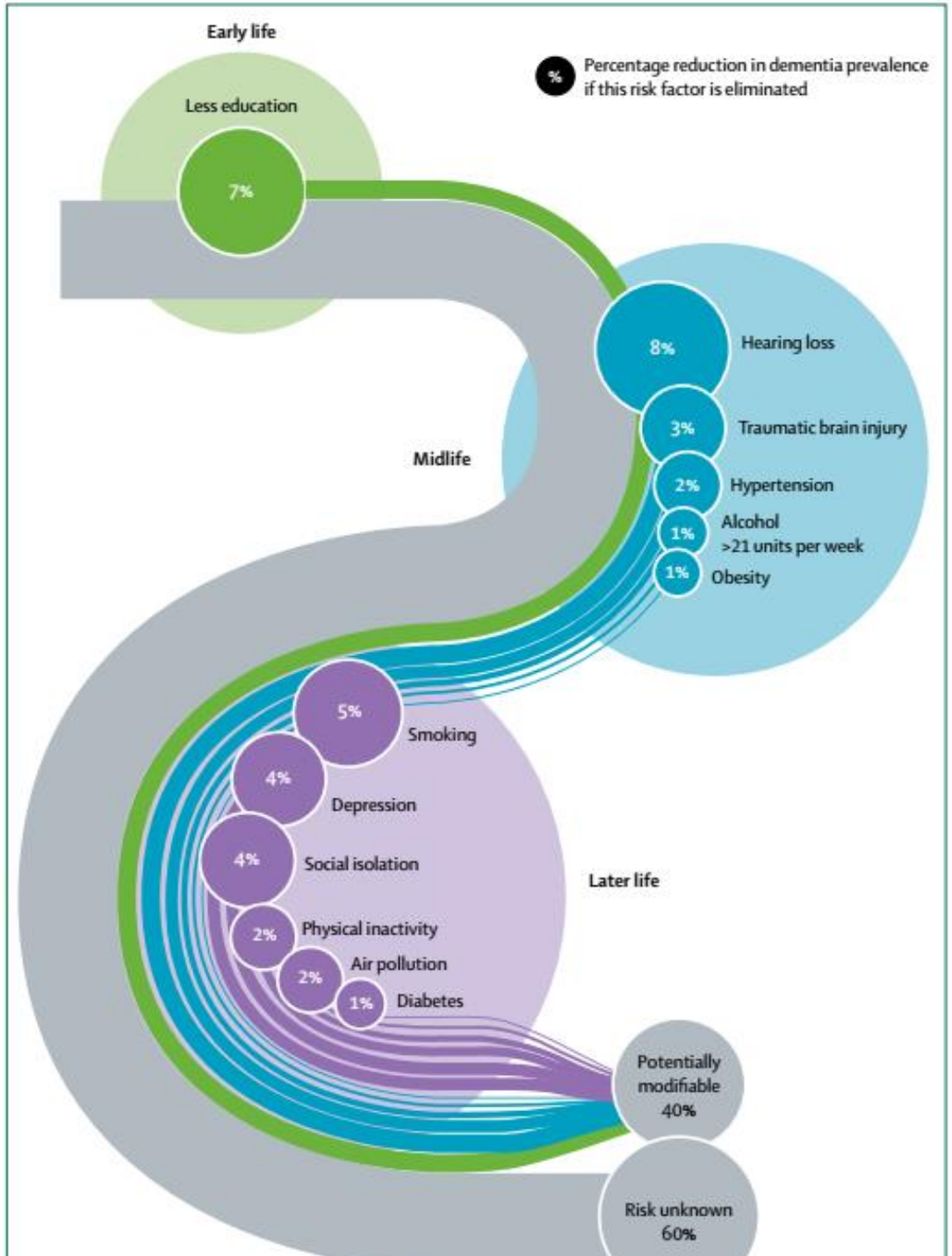


Figure 1: **Growth in numbers of people with dementia in high-income and low and middle-income countries**
Reproduced from Prince and colleagues,[2] by permission of Alzheimer's Disease International.

- AD will be increasingly prevalent

Livingston et al., Lancet 2017

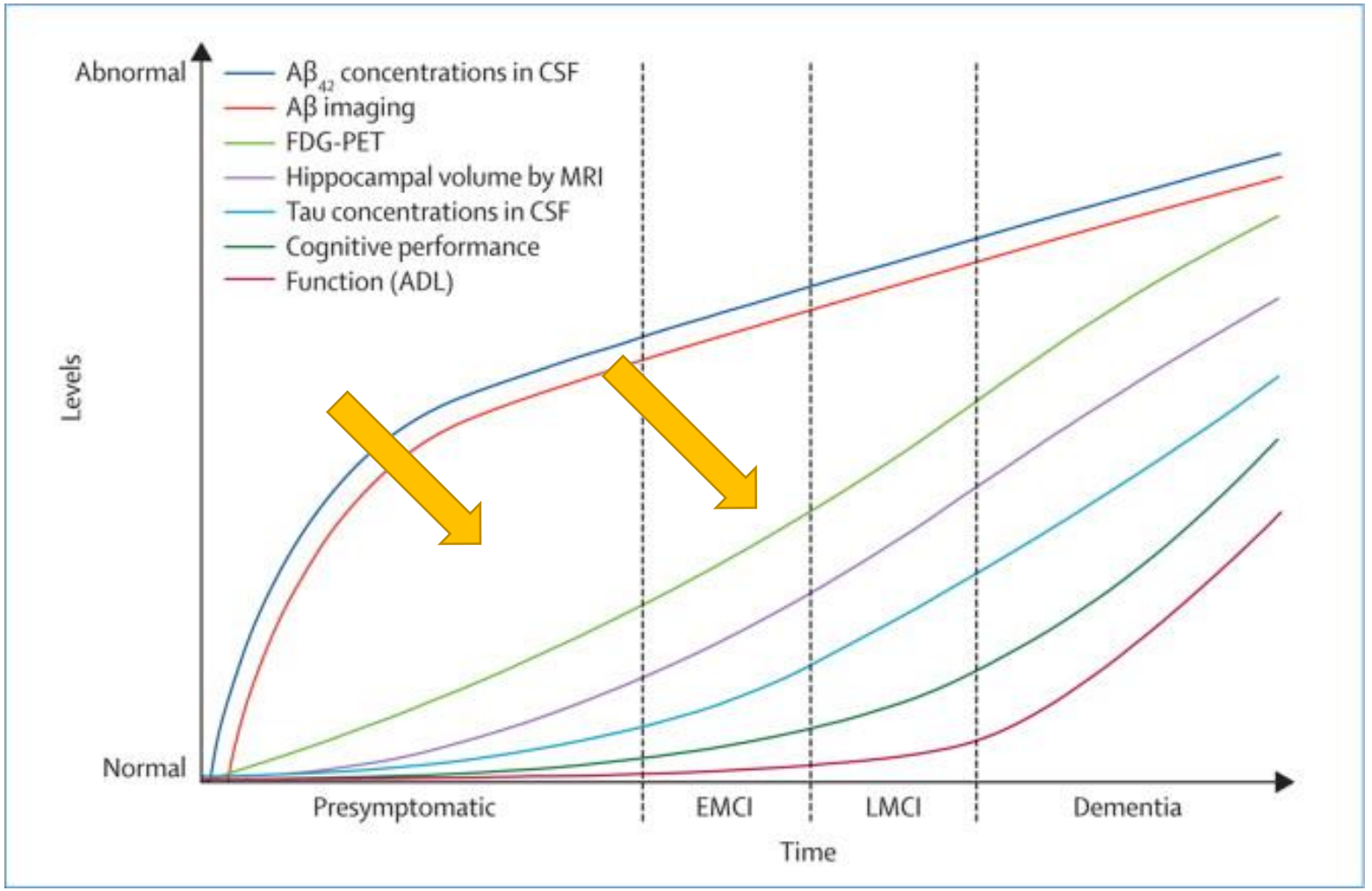


Why AD risk reduction?

- Total about 40% risk potentially modifiable

Livingston et al., Lancet 2020

Why AD risk reduction?



- Preclinical AD (asymptomatic phase) is very prevalent (46 millions in US alone)… and very long!

- Acting on preclinical or early clinical phase is likely most effective for risk reduction

Peterson et al., Lancet Neurology, 2010

Outline

- Nutrition
- Physical exercise
- Cognitive reserve

- RCTs in AD risk reduction

- Personalized medicine – Individualized AD prevention programs

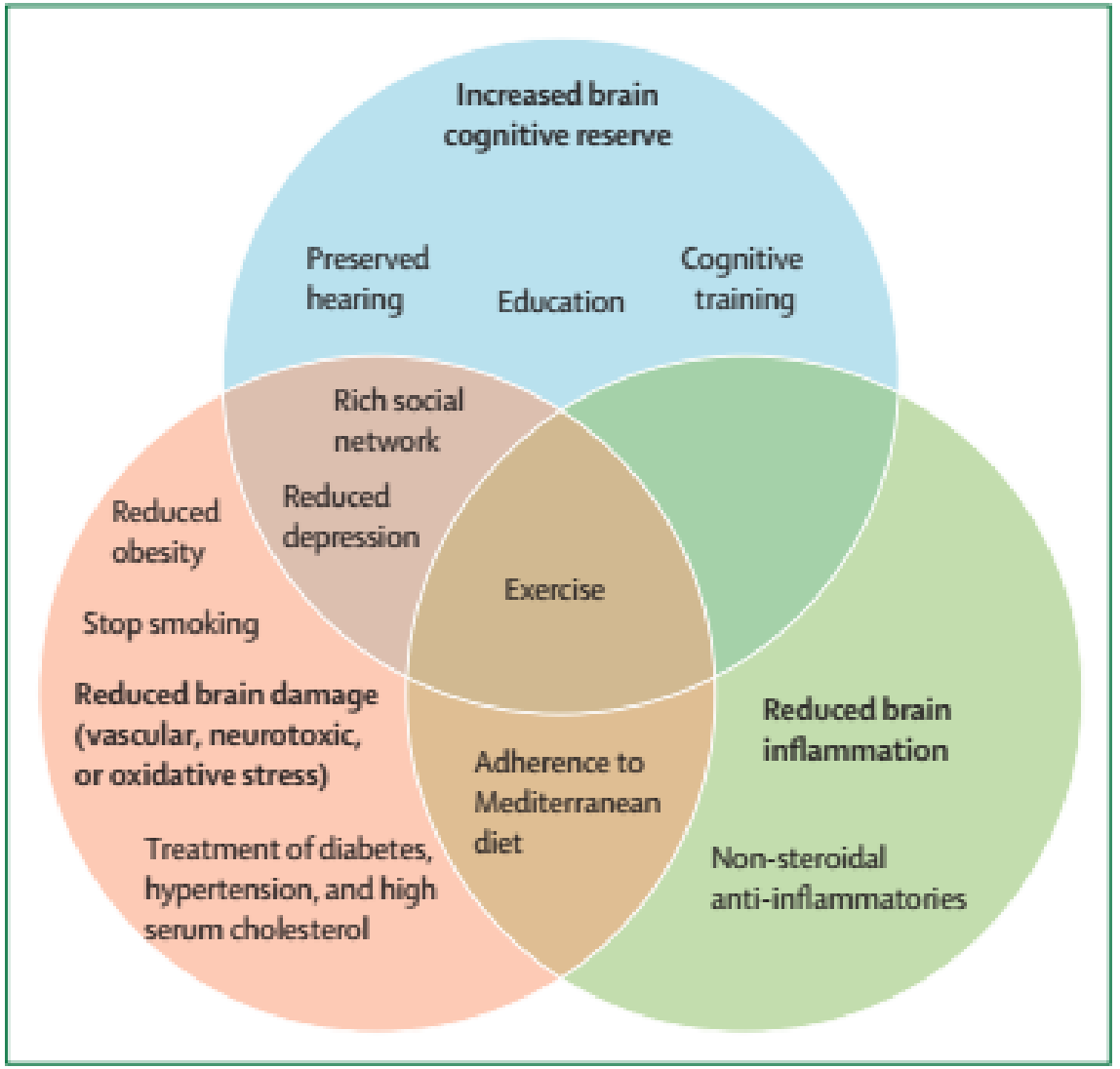


Figure 5: **Potential brain mechanisms for preventive strategies in dementia**

Livingston et al., Lancet 2017

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- **Nutrition**
- Physical exercise
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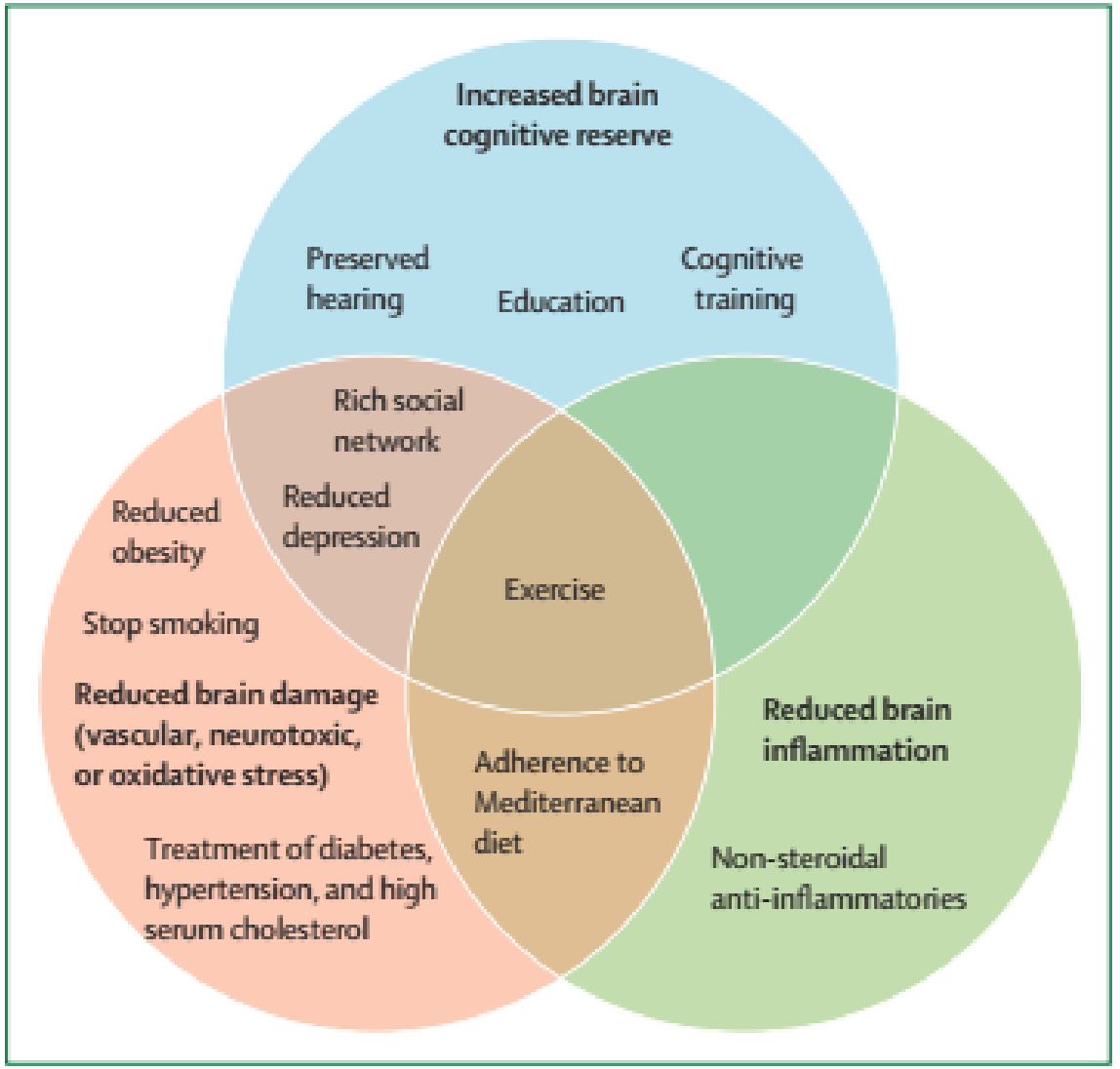


Figure 5: **Potential brain mechanisms for preventive strategies in dementia**

Livingston et al., Lancet 2017

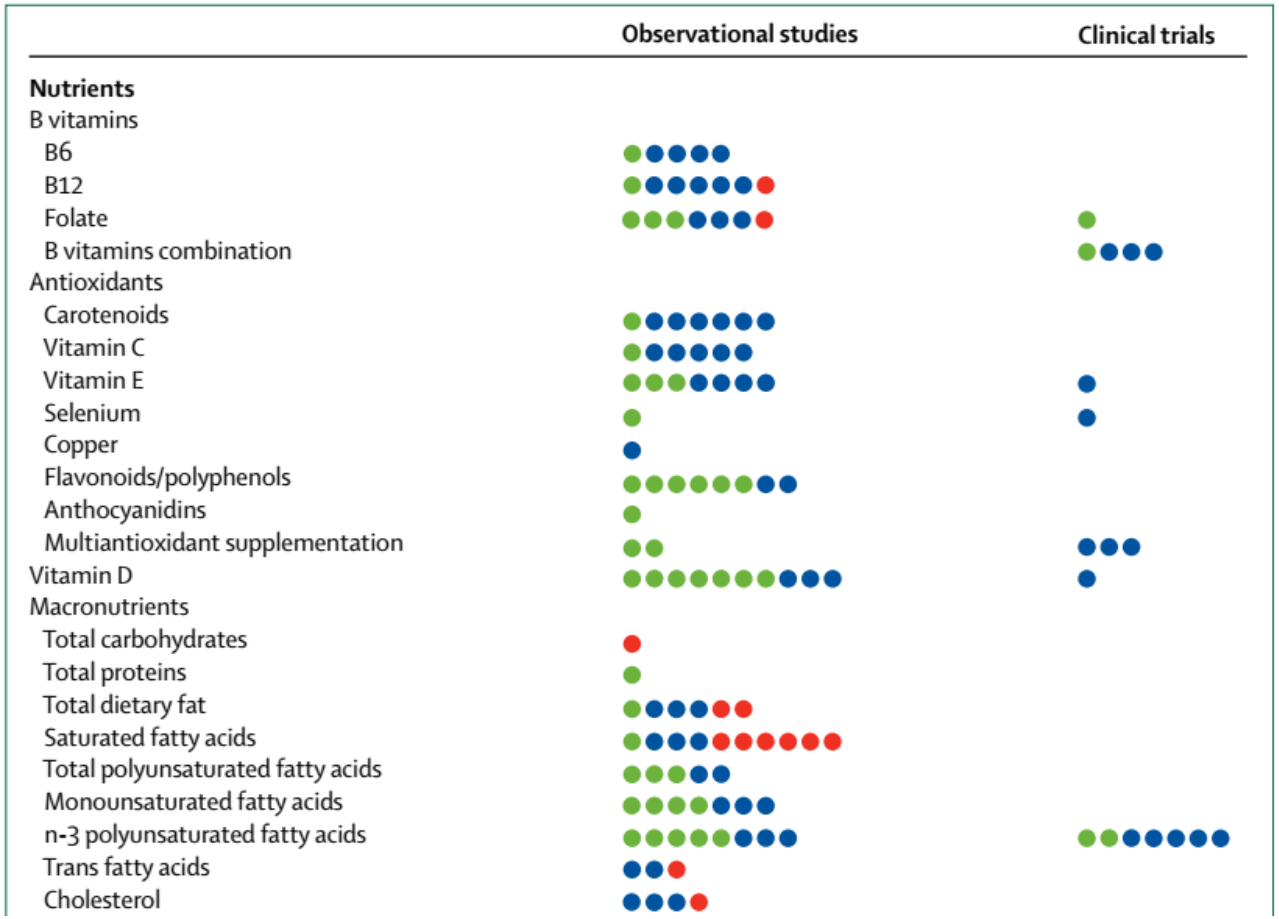
What should we eat (or not eat)?

	Major dietary sources
B vitamins	
B6[11]	Grains (wholegrain corn or maize, brown rice, sorghum, quinoa, and wheat germ), pulses, nuts and seeds, meat, liver and meat products, and fish
B12[12]	Animal products (dairy products, eggs, meats, fish, and liver), foods that contain yeast or have been exposed to microbial fermentation (eg, beer), and fortified foods (eg, ready-to-eat cereals)
Folate[13]	Dark-green leafy vegetables, legumes, oranges and grapefruit, peanuts and almonds, offal (liver and kidney), and baker's yeast
Antioxidants	
Vitamin C[14]	Fruits (berries, citrus fruits, kiwis, lychees, and papayas), vegetables (Brussels sprouts, cauliflowers, cabbages, sweet peppers, and tomatoes), and herbs and spices (parsley, sorrel, and chives)
Vitamin E[15]	Vegetable oils and fat spreads from vegetable oils, nuts and seeds, some fatty fish (eg, sardines, salmon, herring, swordfish, and trout), egg yolk, and wholegrain cereals
Carotenes[16]	Yellow or orange vegetables (sweet potatoes, carrots, and pumpkins), dark leafy vegetables (spinach, broccoli, and endives), and yellow or orange fruits (apricots, peaches, mangoes, and melons)
Flavonoids[17]	Fruits (mainly citrus fruits, bananas, and berries), vegetables (parsley and onions), tea (black and brewed)
Vitamin D[18]	Fish (especially fatty fish) and fish liver, full-fat dairy products (or fortified low-fat ones), egg yolk, meat and meat products, and offal (particularly liver)
n-3 fatty acids[19]	Fish (for eicosapentaenoic acid and docosahexaenoic acid) and some vegetable oils and nuts (eg, linseeds, rapeseed oil, and walnuts for α-linolenic acid)

Table 1: **Nutrients related to cognitive function**

Scarmeas et al. Lancet 2018

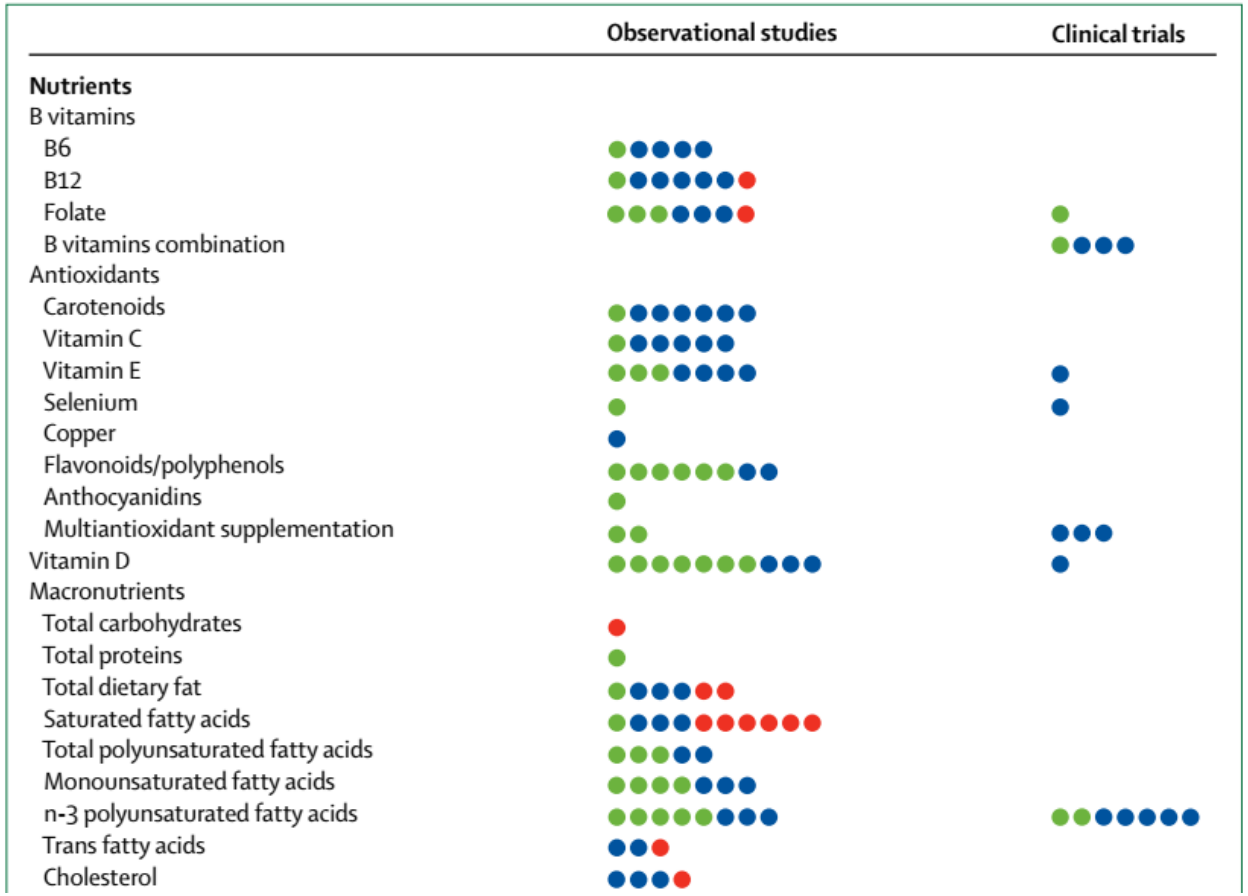
Nutrients and biologically active compounds



- Mostly observational studies
- Most positive studies are observational (many confounds, participants may be more health conscious, more educated, higher socioeconomic status, etc)
- Mixed (including detrimental) results

Scarmeas et al. Lancet 2018

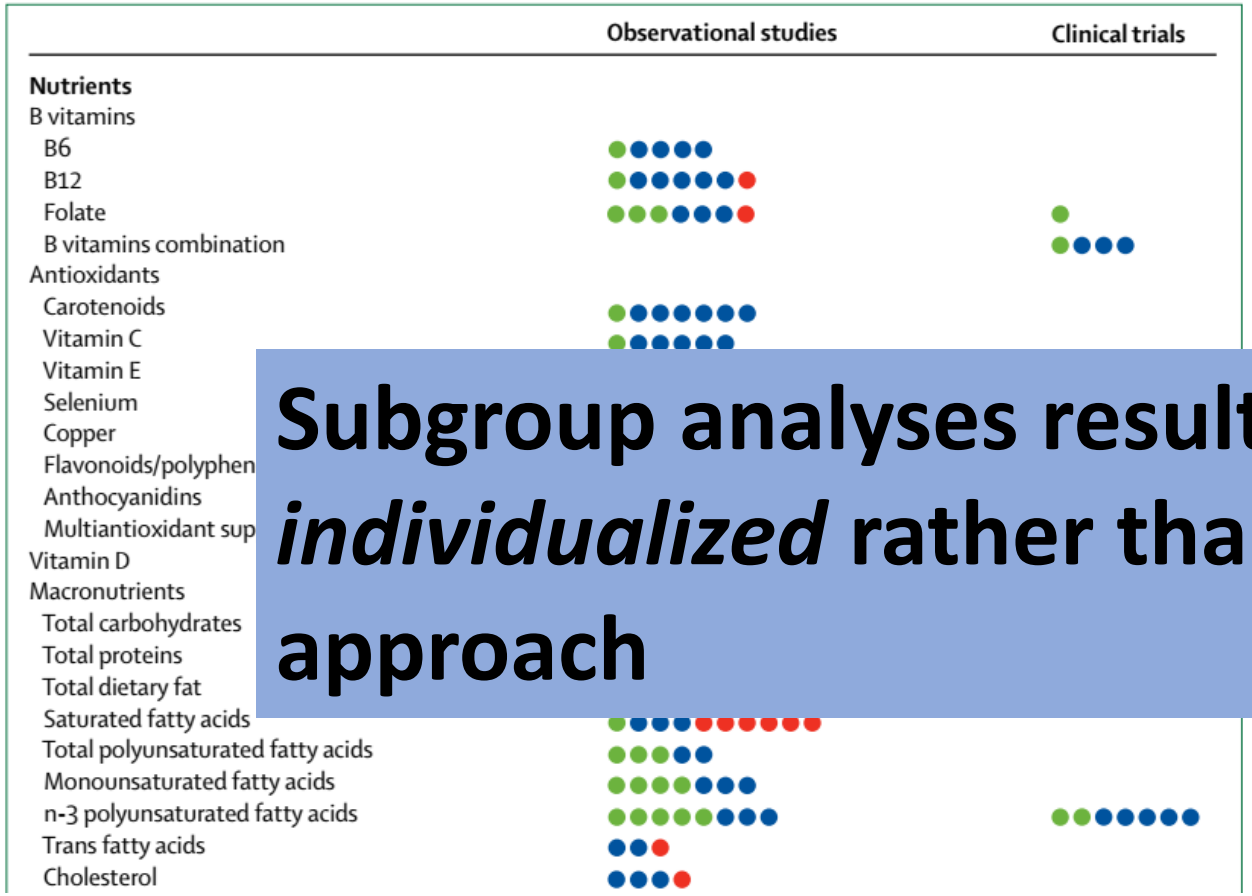
Interesting subgroup analyses



- **Folate**: improves information processing speed in those with high baseline homocysteine and low baseline B12
- Combo of **folate/B6/B12** help preserve semantic memory or temporal orientation in those with prev CAD or ischemic stroke
- **Vit C and E** more protective for current smokers
- **High dietary alpha-linolenic acid** at baseline associated with slower global decline in APOE4 carriers

Scarmeas et al. Lancet 2018

Interesting subgroup analyses

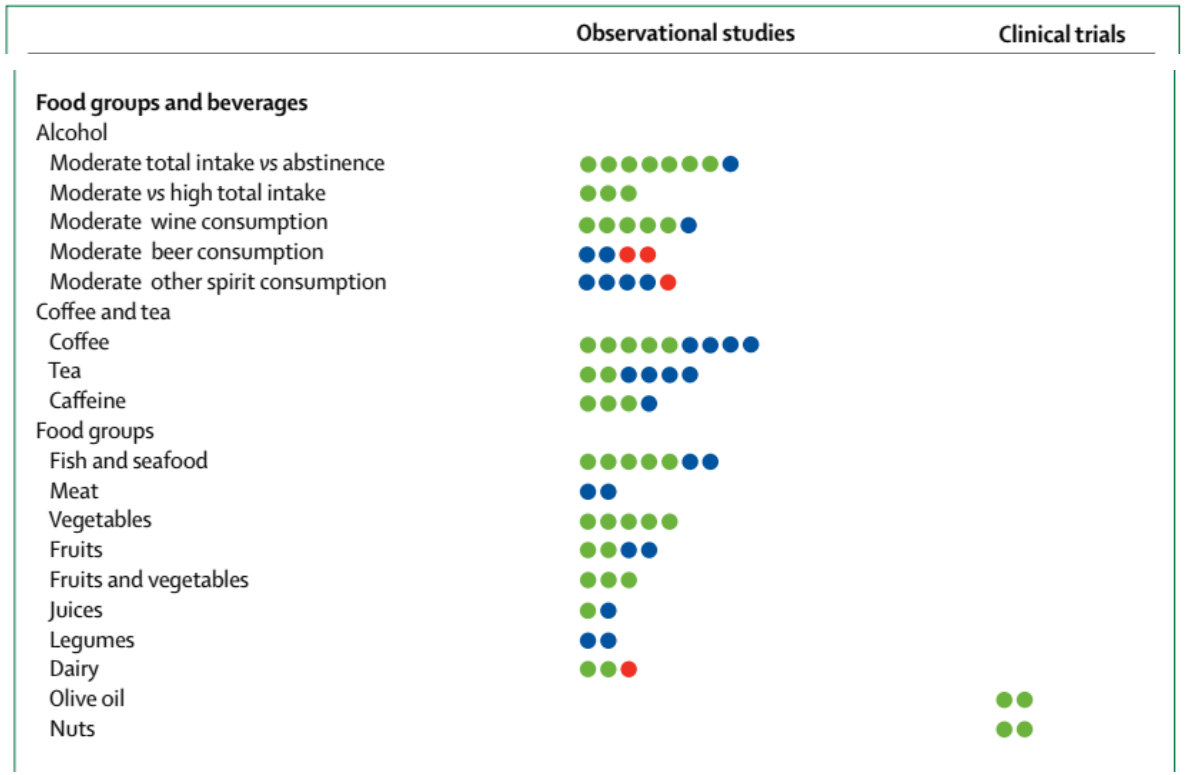


Subgroup analyses results argue for *individualized* rather than one size-fit-all approach

- Folate supplementation: improves information processing speed in those with high baseline homocysteine and low baseline B12
- Combo of folate/B6/B12 help preserve
  D or
  urrent
- High dietary alpha-linolenic acid at baseline associated with slower global decline in APOE4 carriers

Scarmeas et al. Lancet 2018

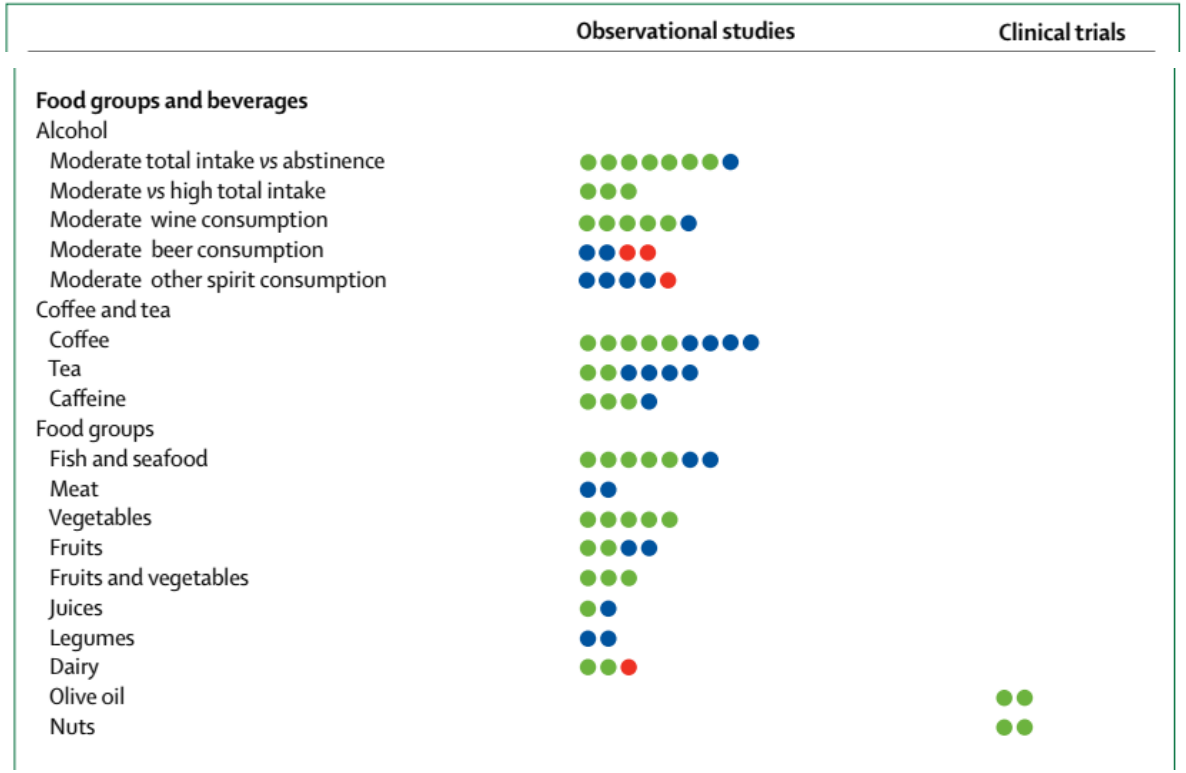
Food groups and beverages



- Again mixed results
- **Alcoholic beverages**:
  - Red wine strongest protective evidence
  - Light to moderate amount (1 glass in women, 1-2 glasses in men)
  - Excessive EtOH disorders very bad
- **Coffee and tea**:
  - Benefit likely from lifelong consumption
  - Not clear which ingredients (caffeine vs other) actually contribute to cognitive protection

Scarmeas et al. Lancet 2018

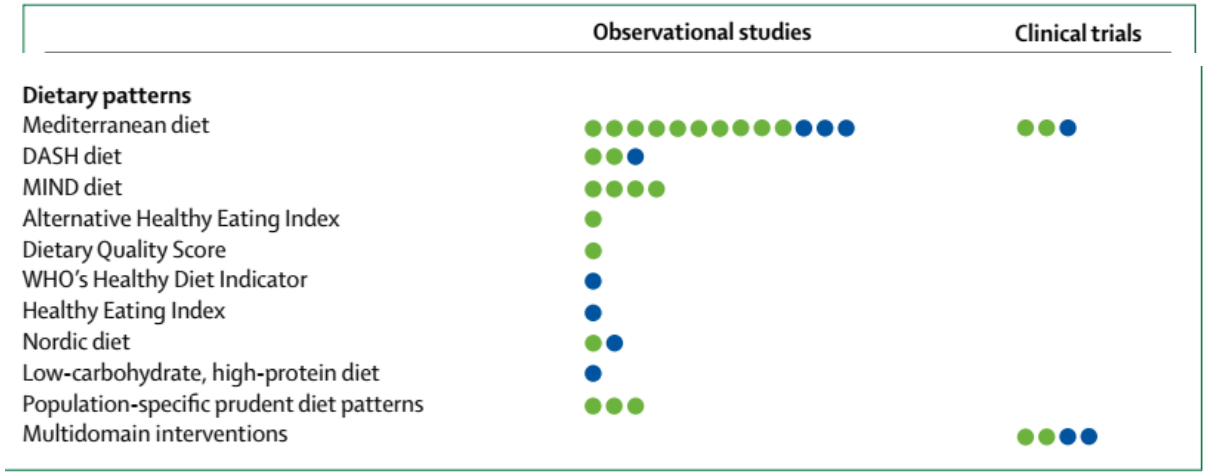
Food groups and beverages



- Overall protective effect of fish consumption stronger for APOE4 carriers… personalized medicine

Scarmeas et al. Lancet 2018

Dietary patterns



- Mediterranean diet
- DASH (Dietary Approaches to Stop Hypertension) diet
- Nordic diet

- More encouraging results for dietary patterns than individual food elements

Scarmeas et al. Lancet 2018

Challenges of risk reduction nutrition studies

- Difficult to accurately assess nutritional status (recall bias)
- Duration of intervention (many studies are short-term)
- Sample selection (participants baseline characteristics)
- Confounding of non-dietary factors (education, physical exercise, socio-economic status)
- Multidimensionality of diet, complex underlying mechanisms, complex relationship with cognitive functions

- Overall studies show more evidence for multidomain interventions including diet

Outline

- Nutrition
- **Physical exercise**
- Cognitive reserve
- RCTs in AD risk reduction
- Personalized medicine – Individualized AD prevention programs

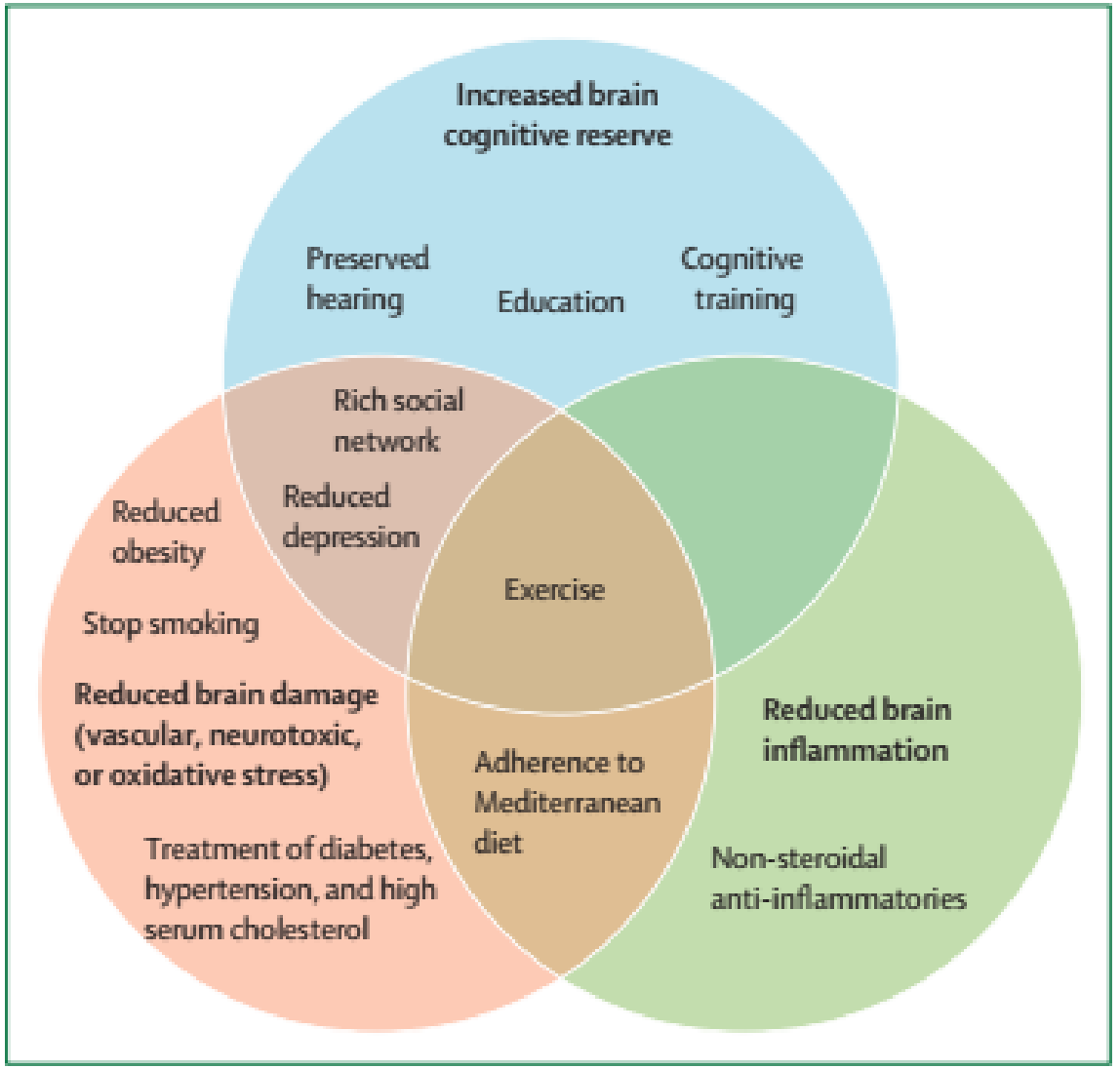


Figure 5: **Potential brain mechanisms for preventive strategies in dementia**

Livingston et al., Lancet 2017

Physical activity and AD risk reduction

- Improvement versus preservation (hypothesis)
  - Preservation: mild-to-moderate intensity, long duration
  - Improvement: high intensity, short duration
  - Relevance for outcome measures (e.g. ADAS-cog measures general function, will be negative in trials aimed at short-term improvement)

- Memory (cognitive) improvements after exercise trials are highly variable, need to understand source of this variability

Mechanisms of physical activity mediated risk reduction

- Indirect effects via influence on other modifiable risk factors of Alzheimer's disease;
  - via reducing vascular RFs (obesity, cardiovascular disease, diabetes)
  - exercise has antidepressant effect

- Muscles may release factors beneficial for brain during exercise

- Understanding mechanisms above may help develop pharmacological interventions that mimic exercise (e.g. BDNF, IGF, VEGF, etc)

Most physical activity studies are negative

Outcome	Conclusion	Strength of Evidence (Justification)
Multicomponent physical activity vs. attention control (*k* = 4; *n* = 1885)		
Dementia	Unable to draw conclusion	Insufficient (medium study limitations, imprecise, unknown consistency)
MCI	Unable to draw conclusion	Insufficient (medium study limitations, imprecise, unknown consistency)
Brief cognitive test performance	No benefit (*n* = 155; 6 mo–1 y)	Insufficient (medium study limitations, indirect, imprecise, inconsistent)
Multidomain neuropsychological performance	No benefit (*n* = 1635; 2 y)	Low (medium study limitations, indirect, unknown consistency)
Executive function/attention/processing speed	No benefit (*n* = 1885; 6 mo–1 y)	Low (medium study limitations, indirect, imprecise)
Memory	No benefit (*n* = 1836; 6 mo–1 y)	Low (medium study limitations, indirect, imprecise)
Aerobic training vs. attention control (*k* = 6; *n* = 531)		
Dementia	Limited data	Insufficient (limited data)
MCI	No data	Insufficient (no data)
Brief cognitive test performance	No benefit (*n* = 162; 6 mo–1 y)	Insufficient (medium study limitations, indirect, imprecise)
Multidomain neuropsychological performance	Limited data	Insufficient (limited data)
Executive function/attention/processing speed	Unable to draw conclusion	Insufficient (medium study limitations, indirect, imprecise, inconsistent)
Memory	Unable to draw conclusion	Insufficient (medium study limitations, indirect, imprecise, inconsistent)
Resistance training vs. attention control (*k* = 3; *n* = 315)		
Dementia	No data	Insufficient (no data)
MCI	No data	Insufficient (no data)
Brief cognitive test performance	No data	Insufficient (no data)
Multidomain neuropsychological performance	No data	Insufficient (no data)
Executive function/attention/processing speed	No benefit (*n* = 120; 6 mo)	Insufficient (medium study limitations, indirect, imprecise, inconsistent)
Memory	No benefit (*n* = 172; 6 mo)	Insufficient (medium study limitations, indirect, imprecise, inconsistent)
Tai chi vs. attention control (*k* = 1; *n* = 93)		
Dementia	No data	Insufficient (no data)
MCI	No data	Insufficient (no data)
Brief cognitive test performance	No data	Insufficient (no data)
Multidomain neuropsychological performance	No data	Insufficient (no data)
Executive function/attention/processing speed	Limited data	Insufficient (limited data)
Memory	No data	Insufficient (no data)

- Many positive associations from cohort studies, but controlled trials data mostly insufficient

- Cognitive benefit appear limited to aerobic exercise (because mediated through improvement of vascular diseases?)

Brasure et al. Annals of Internal Medicine, 2017

Slightly more encouraging multimodal studies

Physical activity plus diet vs. attention control (*k* = 2; *n* = 79)		
Dementia	No data	Insufficient (no data)
MCI	No data	Insufficient (no data)
Brief cognitive test performance	Limited data	Insufficient (limited data)
Multidomain neuropsychological performance	No data	Insufficient (no data)
Executive function/attention/processing speed	Unable to draw conclusion	Insufficient (medium study limitations, indirect, imprecise, inconsistent)
Memory	Limited data	Insufficient (limited data)
Physical activity plus protein supplementation vs. attention control (*k* = 1; *n* = 58)		
Dementia	No data	Insufficient (no data)
MCI	No data	Insufficient (no data)
Brief cognitive test performance	No data	Insufficient (no data)
Multidomain neuropsychological performance	No data	Insufficient (no data)
Executive function/attention/processing speed	Limited data	Insufficient (limited data)
Memory	Limited data	Insufficient (limited data)
Physical activity and cognitive training (*k* = 1; *n* = 134)		
Dementia	No data	Insufficient (no data)
MCI	No data	Insufficient (no data)
Brief cognitive test performance	Limited data	Insufficient (limited data)
Multidomain neuropsychological performance	Limited data	Insufficient (limited data)
Executive function/attention/processing speed	No data	Insufficient (no data)
Memory	No data	Insufficient (no data)

Continued on following page

- Multimodal approach is most likely to be effective
- Physical activity combined with diet combined with cognitive stimulations

Brasure et al. Annals of Internal Medicine, 2017

How to increase yield of physical activity studies

- Regular physical activity may need to begin earlier in life
- Needs longer-duration studies (beyond 6-24 months), Follow-up in most RCTs are not long enough to reveal benefit
- Needs to take into account compliance (often not mentioned)
- Need to identify intervention characteristics (type, duration, intensity)

- Identify population traits that trend toward significance (age when physical activity began, intervention duration, baseline activity level) → Individualized approach
- It is **never too late to start physical activity!**

Outline

- Nutrition
- Physical exercise
- **Cognitive reserve**
- RCTs in AD risk reduction
- Personalized medicine – Individualized AD prevention programs

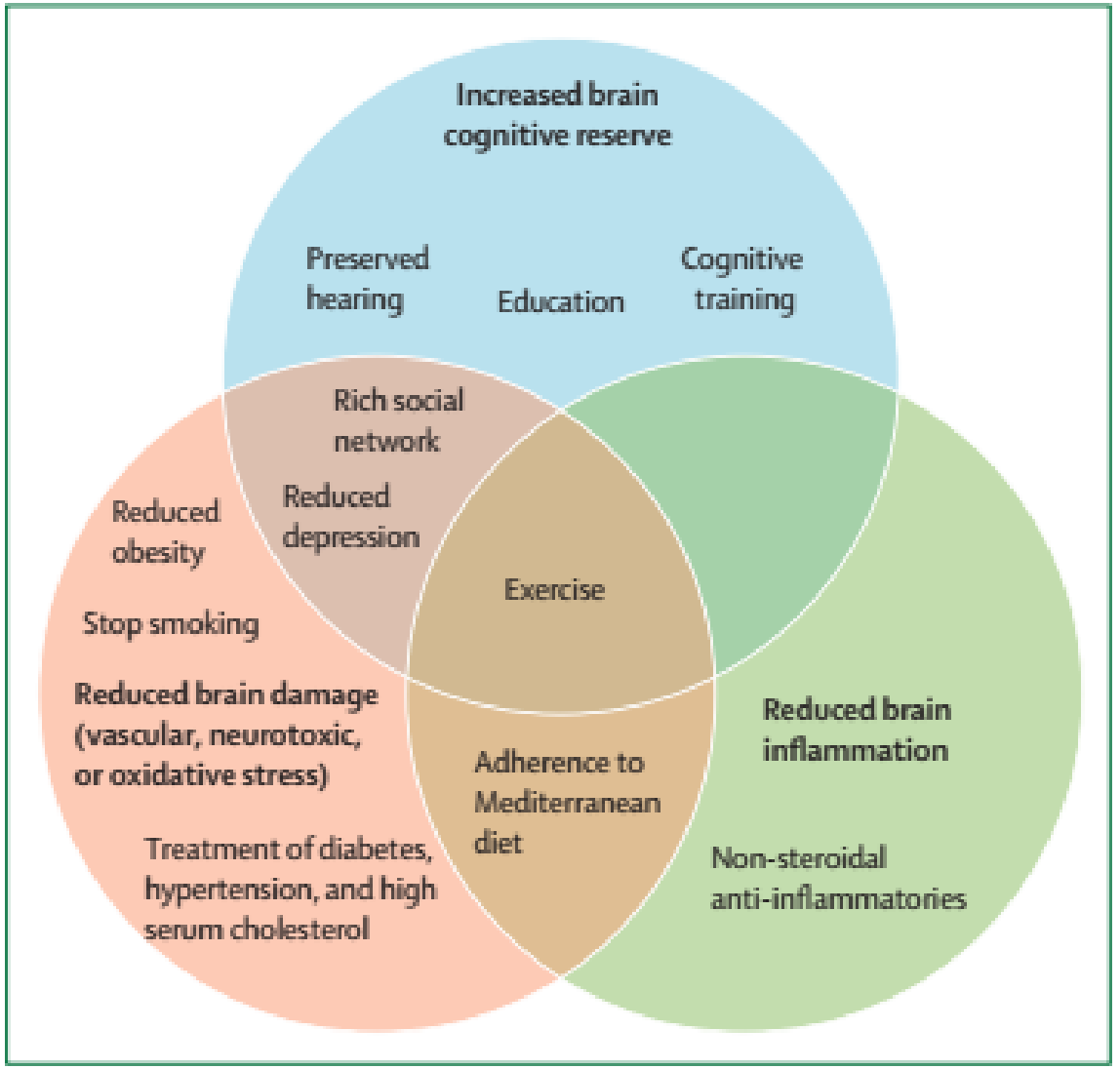


Figure 5: **Potential brain mechanisms for preventive strategies in dementia**

Livingston et al., Lancet 2017

What is cognitive reserve?

- "[…]hypothetical construct that moderates the effects of age-related decline and pathological damage. […] structural and dynamic capacities of the brain that ***buffer against atrophies and lesions***." (Cheng, *Curr Psych Rep*, 2016)

- "difference between an individual's expected and actual cognitive performance, given their underlying brain structure and level of vulnerability to neuropathological changes; a condition in which an ***individual has observed cognitive performance better than expected given their brain's structure***" (Salinas et al. *JAMA network*, 2021)

Cognitive reserve in action

- Proxy measures of cognitive reserve:
  - Premorbid intelligence (IQ)
  - Education attainment
  - Occupational complexity
  - Linguistic ability (bilingualism)

- Tolerate atrophies and insults, and delay symptom onset
  - One additional year of education → 13-18% reduction in likelihood of receiving a diagnosis of AD within 1 year of death (*controlling for neuropathology at death*)
  - High level of cognitive activity → 50% reduction in risk of developing dementia in next 4-5 years (*after controlling for confounders*)

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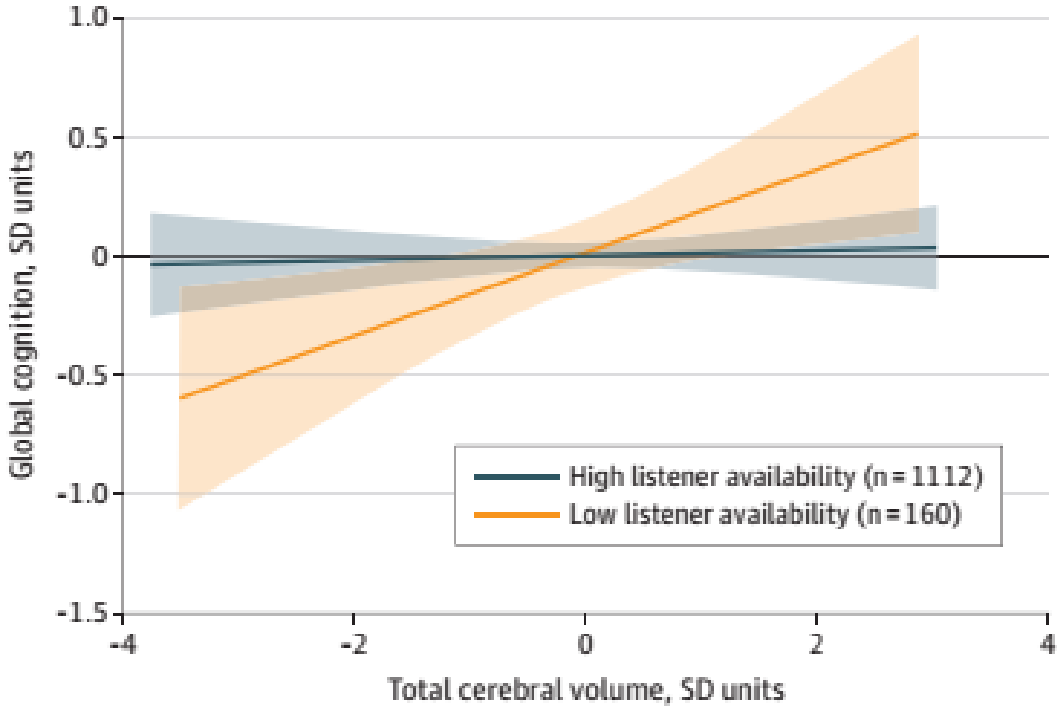
Caveat: those with higher cognitive reserve experience a more rapid course of decline afterwards…

  - High level of cognitive activity → 50% reduction in risk of developing dementia in next 4-5 years (*after controlling for confounders*)

Social network – a more nuanced look

- Framingham cohort, 2171 adults
- Examined 5 different forms of social network
  1. listening
  2. Advice
  3. love-affection
  4. emotional support
  5. sufficient contact

- brain pathology measured with MRI
- cognitive ability measured with neuropsychological tests



Only high listener availability for those < 65 yo → greater cognitive reserve

Salinas et al. JAMA network, 2021

Cognitive stimulation

- Usually tailor-made to stimulate specific functions of abilities (attention, memory, speed of processing, executive)
- Cognitive healthy older adults can benefit (behave like young adults without training), but benefit much weaker in those with cognitive impairment
- Lack of transfer to untrained task, more importantly lack of transfer to daily life, therefore lack ecological value
- Many initially targeted episodic memory, whereas targeting working memory or executive function (that targeting prefrontal networks) may allow them to compensate better when overloaded

Cognitive reserve studies so far mixed or inconclusive results

- Current evidence → mixed and inconclusive for impact of cognitive activity on brain structure and physiology
- Difficult to account for the large variety of cognitive activities
- Difficulty to tease out social stimulation (group activities) and physical activity effect of some activities
- No established ways to rate or define intensity cognitive activity

Examples of cognitive reserve activities

Reading
using computer
board/card games
Mahjong
participating in forums or discussions
Writing
calligraphy and painting
Handicraft
playing musical instruments
Singing
going to museum
Investment in stock market
Gambling
Etc, etc

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- Nutrition
- Physical exercise
- Cognitive reserve

- **RCTs in AD risk reduction**

- Personalized medicine – Individualized AD prevention programs

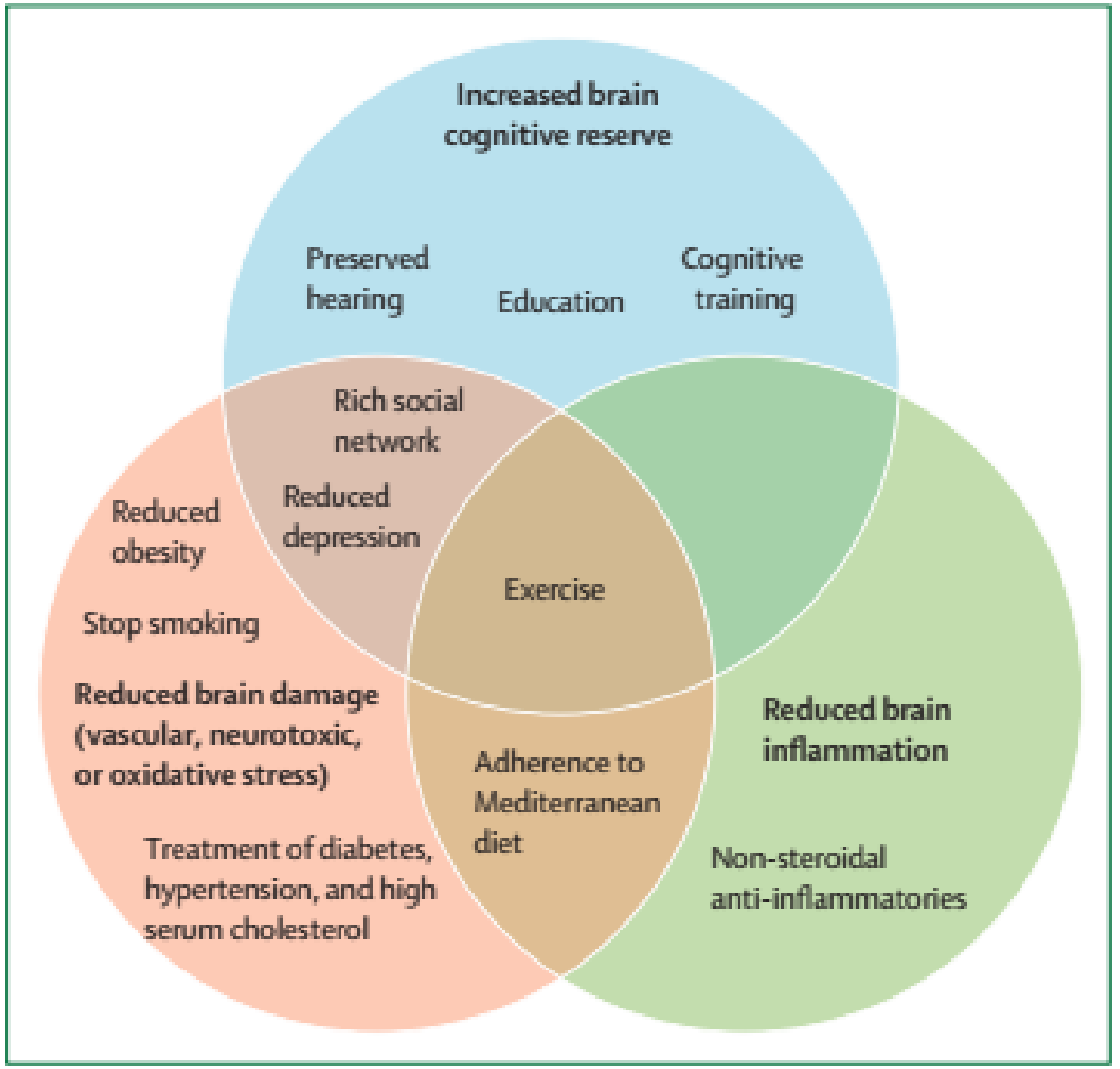

Figure 5: **Potential brain mechanisms for preventive strategies in dementia**

Livingston et al., Lancet 2017

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

Tiia Ngandu, Jenni Lehtisalo, Alina Solomon, Esko Levälahti, Satu Ahtiluoto, Riitta Antikainen, Lars Bäckman, Tuomo Hänninen, Antti Jula, Tiina Laatikainen, Jaana Lindström, Francesca Mangialasche, Teemu Paajanen, Satu Pajala, Markku Peltonen, Rainer Rauramaa, Anna Stigsdotter-Neely, Timo Strandberg, Jaakko Tuomilehto, Hilkka Soininen, Miia Kivipelto

Lancet 2016

Effectiveness of a 6-year multidomain vascular care intervention to prevent dementia (preDIVA): a cluster-randomised controlled trial

Eric P Moll van Charante, Edo Richard*, Lisa S Eurelings, Jan-Willem van Dalen, Suzanne A Ligthart, Emma F van Bussel, Marieke P Hoevenaar-Blom, Marinus Vermeulen, Willem A van Gool*

Lancet 2016

Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial

*Sandrine Andrieu, Sophie Guyonnet, Nicola Coley, Christelle Cantet, Marc Bonnefoy, Serge Bordes, Lawrence Bories, Marie-Noëlle Cufi, Thierry Dantoine, Jean-François Dartigues, Françoise Desclaux, Audrey Gabelle, Yannick Gasnier, Alain Pesce, Kristel Sudres, Jacques Touchon, Philippe Robert, Olivier Rouaud, Philippe Legrand, Pierre Payoux, Jean-Paul Caubere, Michael Weiner, Isabelle Carrié, Pierre-Jean Ousset, Bruno Vellas, for the MAPT Study Group**

Lancet 2017

	Participants	Intervention	Measures	Outcome
FINGER 2-year Finland	N = 2654 60-77 yo CAIDE score at least 6 cognition =/< expected	Combined program: brain-healthy diet, exercise, cognitive training, stimulating social activity, careful monitoring of vascular risk	Improve or maintain cognitive fxn (*z*-score of combined neuropsy tests)	beneficial regardless of baseline characteristics

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PreDIVA 6 year Netherlands	N = 3625 70-78 yo	multidomain cardiovascular intervention: individually tailored lifestyle advice for vascular RFs Drug treatment for HTN, DLP, DM, +/- antithrombotic treatment	1o outcome: cumulative incidence of dementia and disability score 2o outcomes: incident cardiovascular disease and mortality	No effect on incidence of dementia, or cardiovascular disease, or mortality

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MAPT 3 year France & Monaco	N = 1680 memory complaint, but non-demented, 1 IADL affected or slow gait speed	Randomized to 4 groups: 1. Placebo 2. omega-3 PUFA 3. multidomain intervention (exercise, cognitive activities, nutrition) 4. omega-3 + multidomain	combined cognitive score (recall of the Free and Cued Selective Reminding test, MMSE orientation items, Digit Symbol Substitution Test, Category Naming Test)	no between group difference

Negative results, but…

- **PreDIVA:** Effect signal in subgroup of patients with HTN but not on medication or patients with no baseline cardiovascular disease (i.e. not treated)

- **MAPT:** Those with high CAIDE dementia risk score (mostly vascular) and baseline positive amyloid scan showed signal of improvement in combined group

- Argument for individualized treatment → Personalized (precision) medicine

Outline

- Nutrition
- Physical exercise
- Cognitive reserve

- RCTs in AD risk reduction

- **Personalized medicine – Individualized AD prevention program**

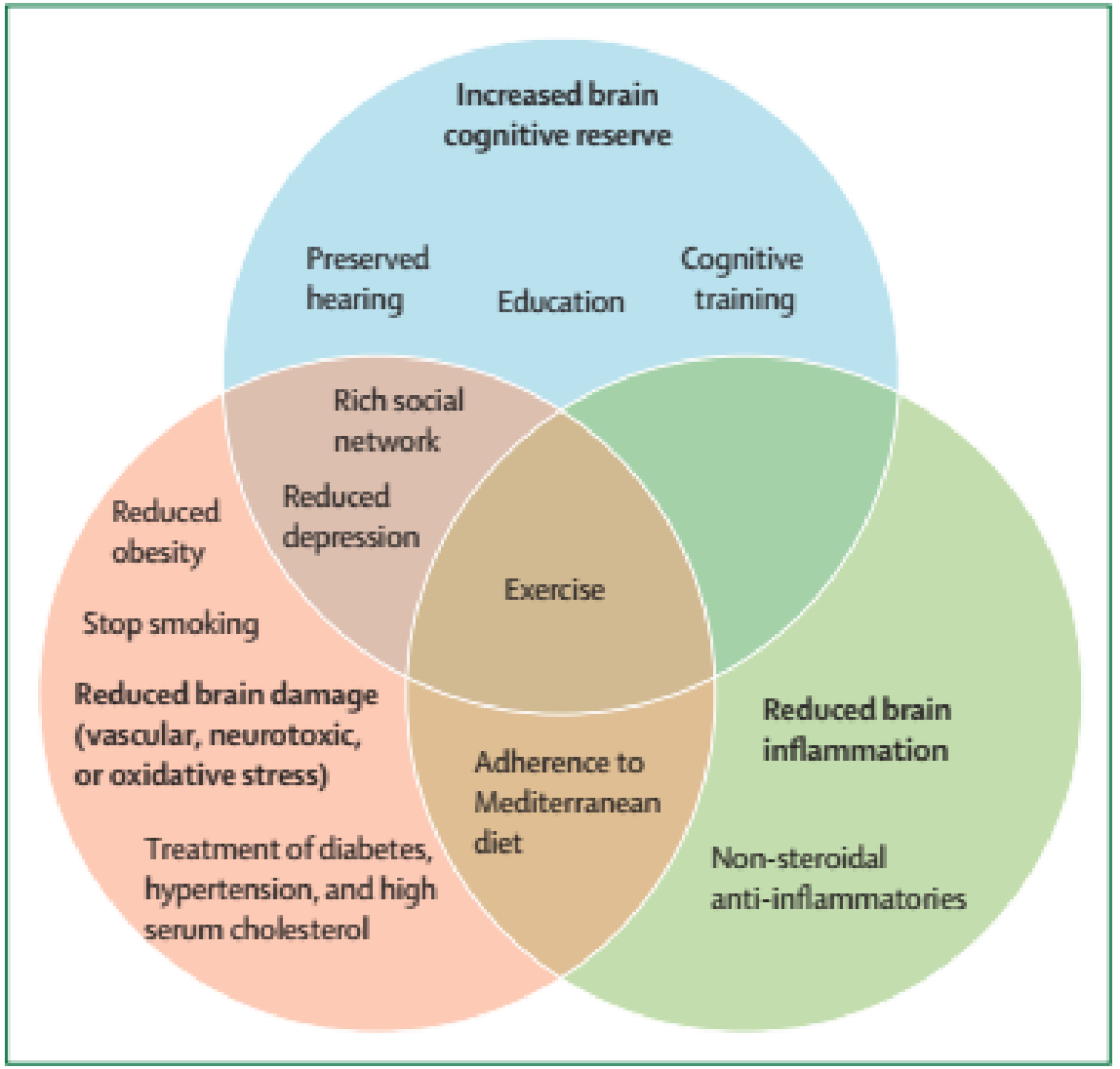

Figure 5: Potential brain mechanisms for preventive strategies in dementia

Livingston et al., Lancet 2017

Why precision medicine approach?

- **Precision medicine:** an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person

- **Alzheimer's Prevention Clinic** (APC) at Cornell/New York was founded in 2013, led by Dr. Richard Isaacson
  - Evaluating AD risk
  - Comprehensive plan toward risk assessment
  - Longitudinal q6months follow-up, evaluation of N=1 effectiveness
  - Deliver personalized risk management

Deep phenotyping

ABCs of dementia prevention

A) Anthropometrics (e.g., % body fat, lean muscle mass, waist-to-hip ratio)

B) Blood biomarkers (e.g., genetic analysis; lipid profile; inflammatory, metabolic, and nutritional biomarkers)

C) Cognition (via computer-based and traditional neuropsychological testing)

Clinical history

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Prevention strategies

targeted cardiovascular risk factor management

physical exercise

nutrition (dietary patterns and/or single nutrients or multinutrients)

oral hygiene

sleep

cognitive engagement and enhancement

social interaction

stress management

sense of purpose

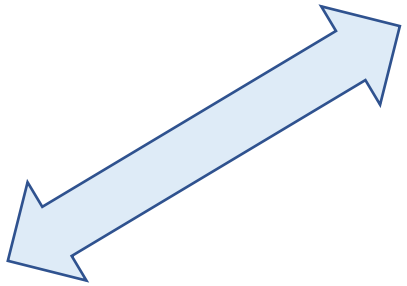
Clinical trials

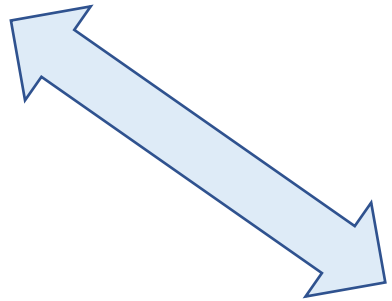
ongoing care with a primary care physician

Etc.

Triangulation between ABCs of AD prevention

B) Blood biomarkers (e.g., genetic analysis; lipid profile; inflammatory, metabolic, and nutritional biomarkers);





Example: when AD biomarkers are borderline and cognitive function lower than expected → more aggressively treat borderline high lipid values (instead of solely relying on traditional reference ranges)

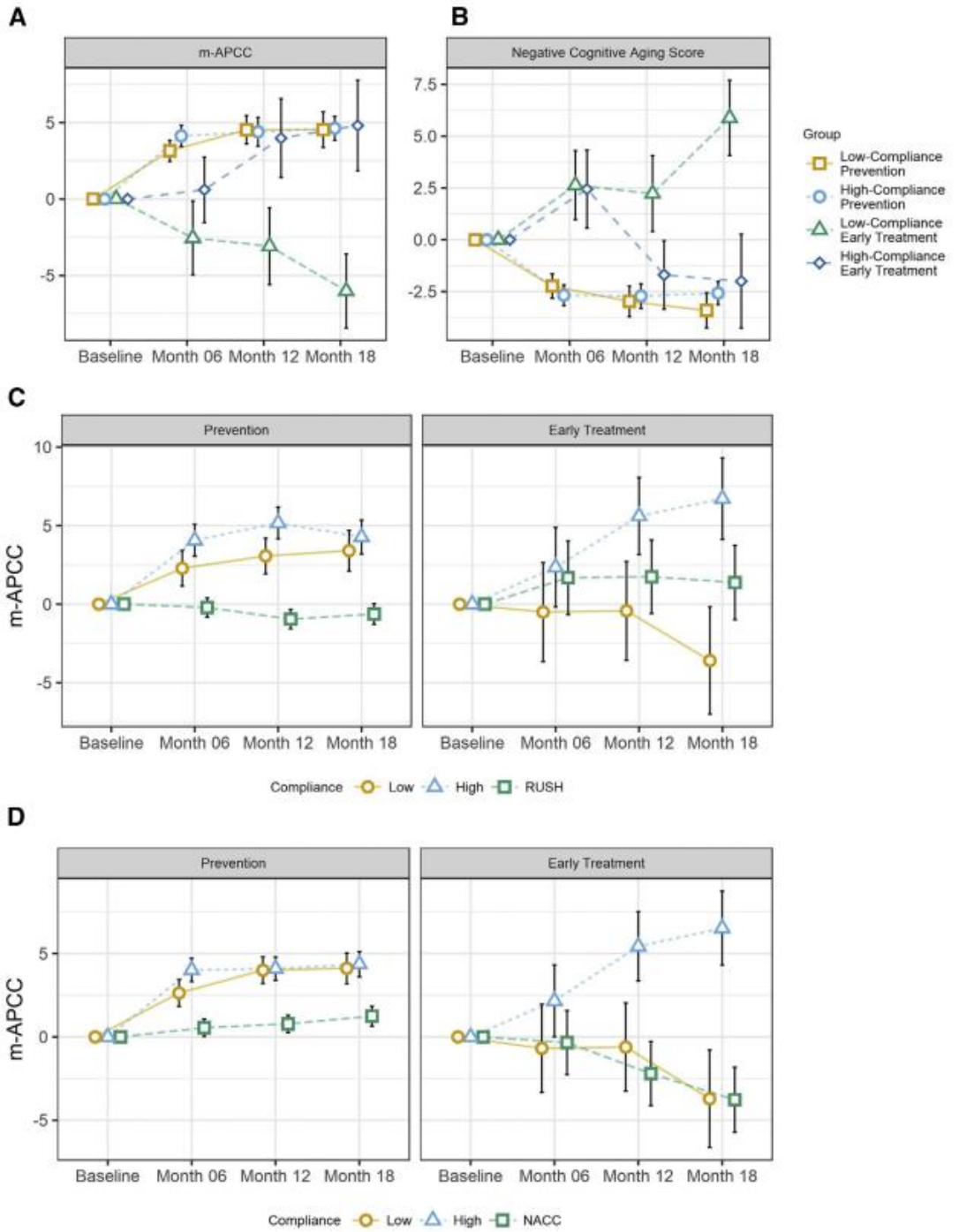
A) Anthropometrics (e.g., % body fat, lean muscle mass, waist-to-hip ratio)

C) Cognition (via computer-based and traditional neuropsychological testing).

Does this model work?

- 174 patients followed over 18 months, divided into normal cognition (“prevention”) and MCI (“early treatment”) groups, low compliance and high compliance groups

- compared to historical controls and their own baseline, high compliance group did better (even the MCI’s improved)



Post-test

Approximately what % of AD is attributed to modifiable risk factors?

A. 20%
B. 40%
C. 60%
D. 80%

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Which of the following has demonstrated clear evidence for benefit in AD prevention?

A. Mediterranean diet
B. Vigorous aerobic exercise 30 mins, 3 times a week
C. Cognitive simulation game aimed at improving executive function
D. All of the above
E. None of the above

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True or false: There is strong evidence from RCTs for multimodal approach to AD prevention

A. True
B. False

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A. True

B. False

True or false: The most effective way to manage AD risk factors is to treat each one independently

A. True
B. False

True or false: The most effective way to manage AD risk factors is to treat each one independently

A. True

B. False

Summary

- More than a third of AD risk factors are modifiable, therefore large window of opportunity for intervention
- There are many potential areas of intervention (physical exercise, nutrition, cognitive reserve, etc)
- Multimodal will likely be more effective than unimodal intervention, and earlier the better; but no clearly convincing evidence yet re: specifics of when/how/how much/whom
- Targeted individualized prevention strategy likely more effective than one-size-fit-all approach, but more data is needed

Things not addressed in this talk but likely equally (or more) important

- Vascular risk factors (hypertension, dyslipidemia, diabetes, metabolic syndrome, tobacco smoking)
- Mood disorders, other psychosocial factors (relationship, profession)
- Sleep
- Social determinants of health
- Etc, etc

Questions?