

4<sup>th</sup> International  
Alzheimer's Disease  
Conference



مؤتمر ألزهايمر الدولي الرابع ٢٠٢٠

Strategic Supporting Partner



2-4 Jumada II 1441 / 27-29 January 2020  
Conference Hall – KACST HQ  
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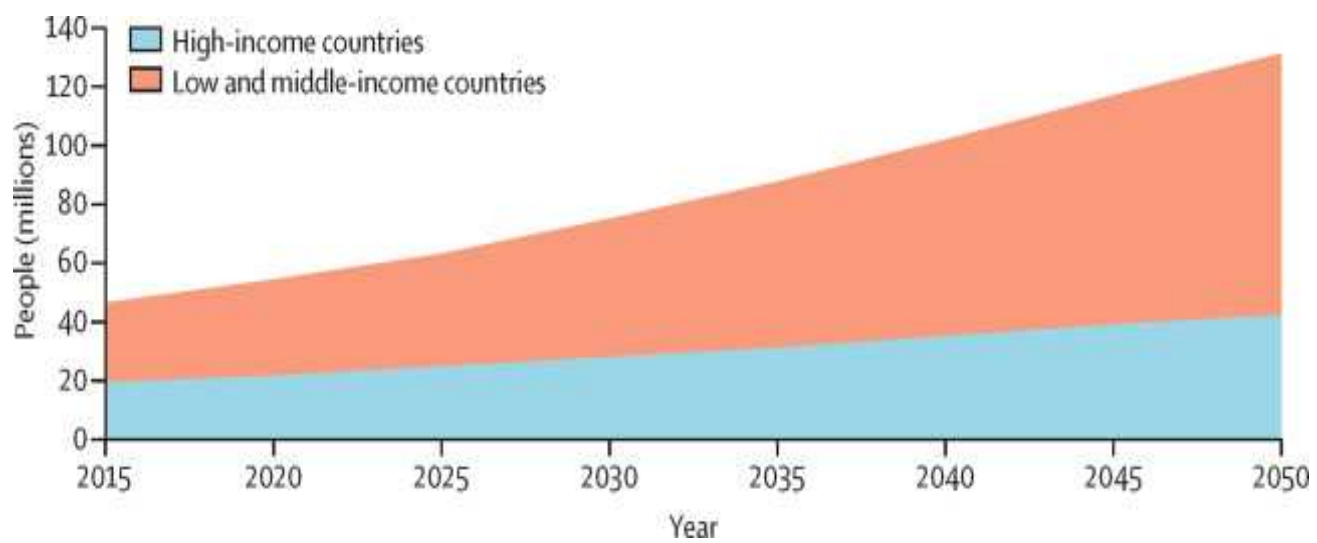
# Preventing Alzheimer's Disease: What Do We Know?

Dr Loay Basudan

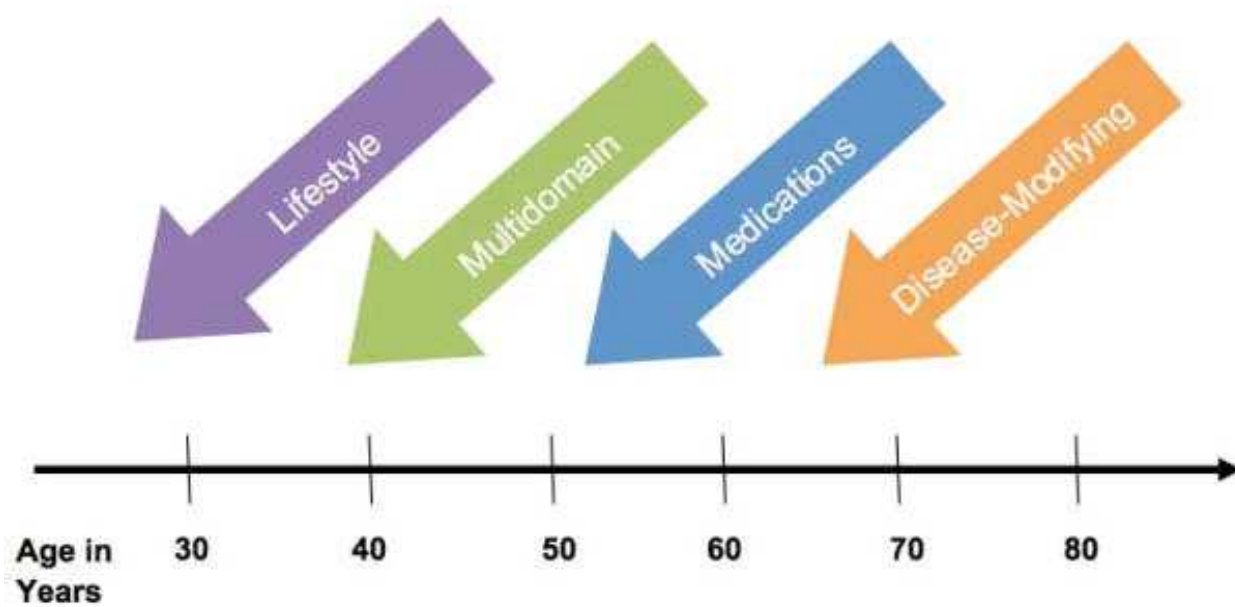


## **Preventing Alzheimer disease is a worthy:**

- Sheer number of those suffering with AD.
- Costliest disease in the world, amounting to \$200 billion annually in the United States alone.
- Preventing or at least delaying the onset of the disease by five years would cut Medicare spending for AD by half.
- Studying potential risk factors for AD and implementing interventions early could lay the tracks for long-term solutions to address this growing chronic problem.
- AD currently does not have a cure or even an effective disease-modifying drug.



[Lancet](#). 2017 Dec 16;390(10113):2673-2734. doi: 10.1016/S0140-6736(17)31363-6. Epub 2017 Jul 20.



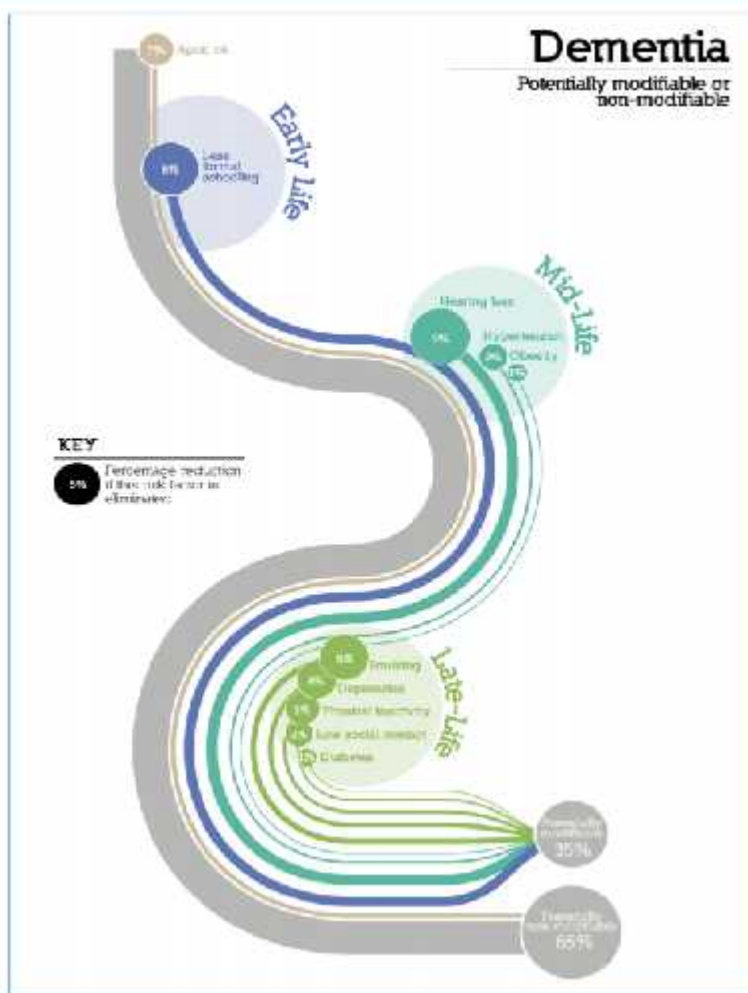


Figure 4. Life course model of contribution of modifiable risk factors to dementia

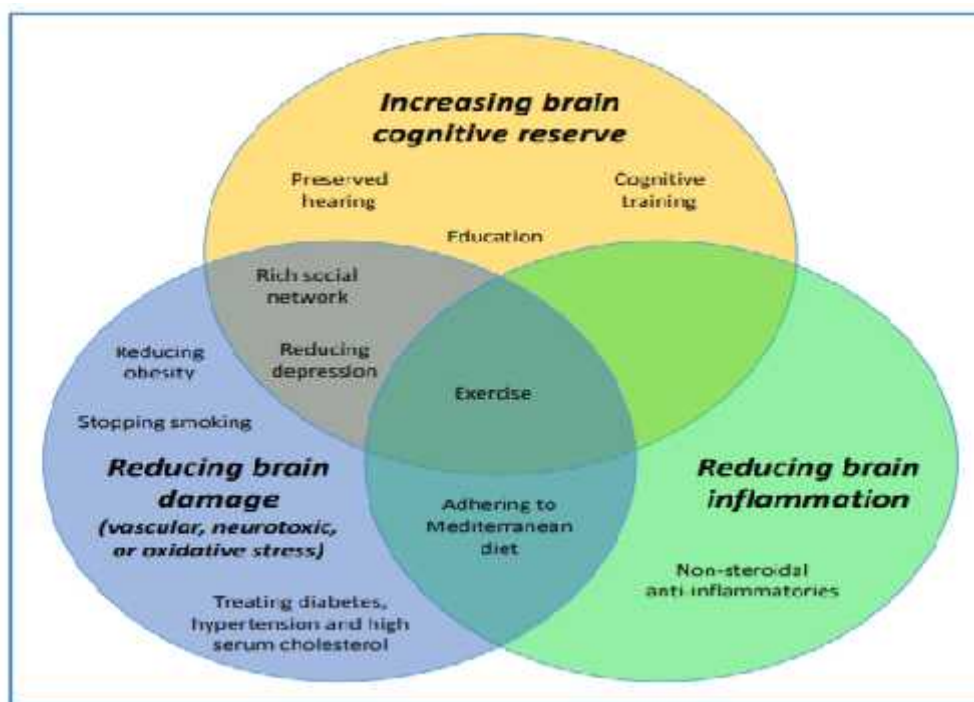


Figure 5. Potential brain mechanisms for preventative strategies in dementia



# Lifestyle and Activity

Intervention	Trial	Study Sample	Duration	N	Outcome Measures	Results
Hypertension	Syst-Eur [26]	Aged 60 and older, not demented	2 years	2,418	MMSE	Positive; dementia was reduced by 50% in active treatment
Hyperlipidemia	HPS [28] PROSPER [29]	Aged 40–80 with coronary artery disease or diabetes, not demented Aged 70–82 with vascular disease or risk factors, not demented	5 years 3.2 years	20,536 5,804	Telephone Interview for Cognitive Status Stroop and MMSE	Negative; statins did not prevent dementia Negative
Diabetes	ACCORD-MIND [30, 31]	Mean age 62, cognitively normal	3.3 years	2,977	Digit Symbol Substitution Test score, total brain volume on MRI	Negative; there was no difference between intensive diabetes therapy vs. standard therapy
Mediterranean Diet (observational only)	Three-City Study [32]	Aged 65 and older, not demented	5 years	1,410	MMSE, Isaacs Set Test, Benton Visual Retention Test, Free and Cued Selective Reminding Test	Positive; the Mediterranean diet was associated with slower cognitive decline on MMSE only
Exercise	FABS [33]	Aged 50 and older, with subjective memory complaints, no dementia	1.5 years	170	ADAS-Cog	Positive; ADAS-Cog improved after physical activity
Cognitive Training	ACTIVE [38–40]	Aged 65–94, cognitively normal	10 years	2,832	Everyday problem-solving, everyday speed, and activities of daily living	Positive; cognitive training, specifically reasoning and speed training, even at 10 years had less decline in ADL
Social (observational only)	Kungsholmen [42]	Aged 75 and older, not demented	3 years	1,203	Incidence of dementia	Positive; a large social network was associated with less dementia

ACCORD-MIND = Action to Control Cardiovascular Risk in Diabetes trial with Memory in Diabetes sub-study; ACTIVE = Advanced Cognitive Training for Independent and Vital Elderly; ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADL = activities of daily living; FABS = Fitness for the Aging Brain Study; HPS = Heart Protection Study; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; PROSPER = Prospective Study of Pravastatin in the Elderly at Risk

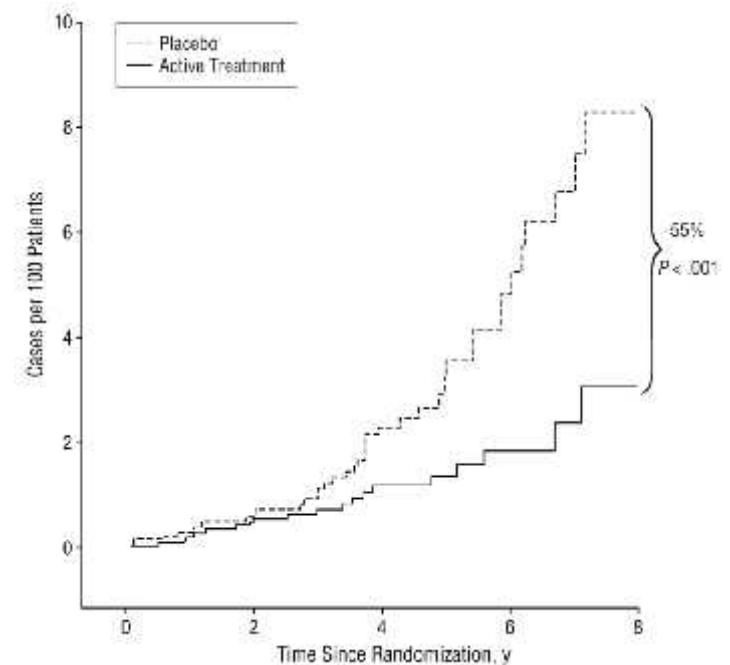


# Antihypertensive Therapy

- ❑ Hypertension appears to be associated with an increased risk of both vascular dementia and AD.
- ❑ The effect of antihypertensive treatment on reducing risk is uncertain and may be most important in midlife.
- ❑ lowering the prevalence of hypertension by 25 percent could reduce the incidence of AD by nearly 100,000 cases.
- ❑ More prevention with diuretics and/or calcium channel blockers.

[Lancet Neurol.](#) 2011 Sep;10(9):819-28. doi: 10.1016/S1474-4422(11)70072-2. Epub 2011 Jul 19.

[Lancet.](#) 1998 Oct 24;352(9137):1347-51.







## Mediterranean diet

- ❑ Diet high in:
  - Fruits, Vegetables, Whole grains, beans, nuts, and seeds.
  - Olive oil as an important source of fat.
  - There are typically low amounts of fish, poultry, and dairy products, and there is little red meat.
- ❑ Lower incidence of MCI,AD and slower rates of cognitive decline.
- ❑ Large randomized trial (PREDIMED) have suggested that adherence to a Mediterranean diet improves cardiovascular outcomes, including stroke, and these effects may directly or indirectly promote lower dementia risk

[N Engl J Med.](#) 2013 Apr 4;368(14):1279-90. doi: 10.1056/NEJMoa1200303. Epub 2013 Feb 25

[BMJ.](#) 2019 Feb 7;364:l341. doi: 10.1136/bmj.l341



# Physical exercise

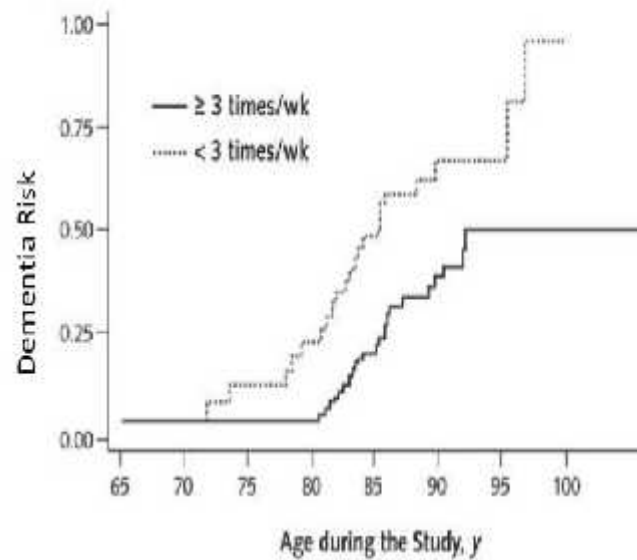
## **Benefits of Physical Activity:**

- Prevents cardiovascular disease.
- Increases independence.
- Reduces body weight.
- Alleviation of depression.



# Physical exercise

Those exercising more than three times a week, are more likely to be dementia free as they age



Source: Larson *et al* 2006



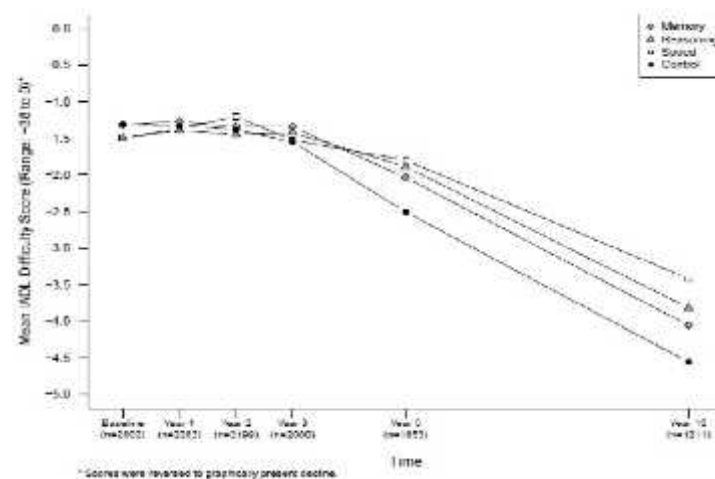
**More Exercise = Less Dementia Risk**



# Cognitive training

## The ACTIVE trial:

- ❑ Randomly assigned 2832 older adults to one of three cognitive interventions or a control group.
- ❑ Found that a 10-week training program in inductive reasoning (but not in verbal memory or speed of processing) resulted in improved performance on the IADLs that was sustained at five years.
- ❑ The rate of incident dementia at five years was unaffected.





## Role of education and cognitive reserve

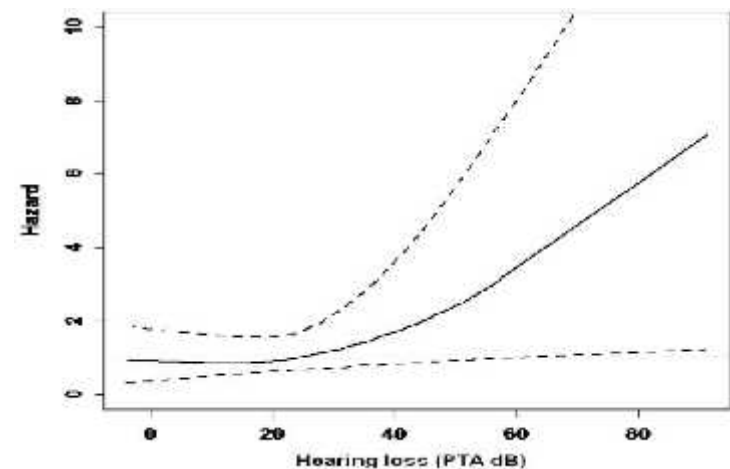
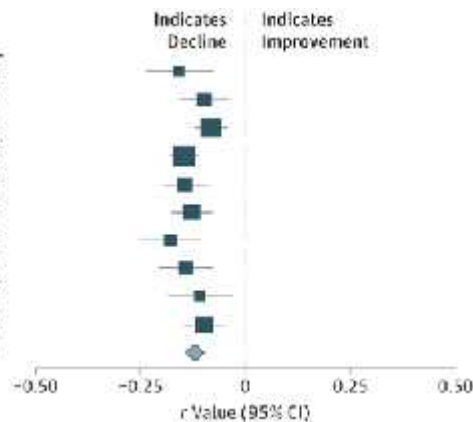
- ❑ Higher levels of education have been associated with a reduced risk of dementia, or at least a later onset of symptoms relative to neuropathologic disease burden.
- ❑ Advanced education is believed to represent a higher cognitive reserve that decreases the impact of degenerative pathology on cognitive function, rather than providing a protective effect against the accumulation of amyloid or other pathologic changes.



# Hearing Loss and Incident Dementia

- ❑ Mild hearing loss is associated with two-fold greater risk for dementia.
- ❑ Severe hearing loss is associated with 5 times greater risk over 10 years .
- ❑ Rate of cognitive decline is accelerated in dementia patients with hearing loss .
- ❑ Participants with hearing loss experienced rates of cognitive decline that were 30-50% faster than those with normal hearing.

Outcome	No. of Participants/Events	r Value (95% CI)
Attention	5159/11	-0.16 (-0.24 to -0.07)
Delayed recall	3808/7	-0.10 (-0.15 to -0.04)
Fluency	4629/9	-0.08 (-0.12 to -0.04)
Global cognition	7702/15	-0.15 (-0.18 to -0.11)
Immediate recall	6747/15	-0.14 (-0.20 to -0.09)
Processing speed	10560/20	-0.13 (-0.18 to -0.08)
Reasoning	3128/12	-0.18 (-0.25 to -0.10)
Semantic memory	2906/10	-0.14 (-0.20 to -0.08)
Visuospatial ability	669/5	-0.11 (-0.19 to -0.03)
Working memory	4855/9	-0.10 (-0.15 to -0.05)
Summary	15 620/113	-0.12 (-0.14 to -0.10)



[Arch Neurol. 2011 Feb; 68\(2\): 214–220.](#)



# Multidomain Interventions

## Multidomain Interventions The European Dementia Prevention Initiatives

<b>Trial</b>	<b>Intervention</b>	<b>Study Sample</b>	<b>Duration</b>	<b>N</b>	<b>Outcome Measures</b>	<b>Results</b>
PreDIVA [44]	Nurse led intensive management of cardiovascular risk factors	Aged 70–78, MMSE > 23, absence of dementia	6 years	3,700	Incidence of dementia	Trial ongoing; results pending
FINGER [45]	Nutrition, exercise, cognitive training, social activity, management of cardiovascular risk factors	Aged 60–75, average or low-average cognitive scores with high CAIDE risk score	2 years	1,200	Modified Neuropsychological Battery, Stroop Test, Trailmaking Test A and B	Preliminary results positive
MAPT [17]	Nutritional, physical, cognitive, as well as omega-3	Aged 70 and older, frail elderly, MMSE > 24	3 years	1,200	Change in cognitive function by Grober and Buschke Test	Trial ongoing; results pending

FINGER = Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability; MAPT = Multidomain Alzheimer Preventive Trial, MMSE = Mini-Mental State Examination, PreDIVA = Prevention of Dementia by Intensive Vascular Care



# Medication Interventions

## Medication Interventions

Intervention	Trial	Study Sample	Duration	N	Outcome Measures	Results
Anti-Inflammatory	ADAPT [49]	70 and older, cognitively normal	7 years	2,528	Incidence of MCI and AD dementia	Negative; there were concerns of adverse cardiovascular effects, and there was no evidence that NSAIDs prevented AD or slowed cognitive decline
Estrogen and Progesterone	WHIMS [55]	65 and older women, without probable dementia	4 years	4,532	Incidence of dementia, 3MSE	Negative; estrogen alone and both hormones together increased the risk for probable dementia

3MSE = Modified Mini Mental State Examination, ADAPT = AD Anti-inflammatory Prevention Trial, NSAIDs = non-steroidal anti-inflammatory drugs, WHIMS = Women's Health Initiative Memory Study





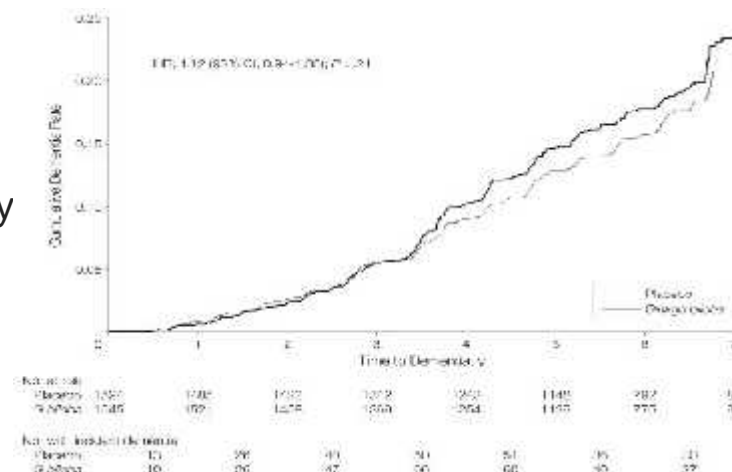
# Medication Interventions

## Cholinesterase inhibitors:

- ❑ Low quality evidence suggests that cholinesterase inhibitors, do not delay the development of dementia in patients with mild cognitive impairment.
- ❑ These drugs are not recommended for this purpose.

## Ginkgo biloba for prevention of dementia:

- ❑ A multi-center, randomized, double-blind placebo-controlled study
- ❑ 3069 older adults (75 years or older).
- ❑ Six years of follow-up.
- ❑ Treatment was not effective in reducing the incidence of AD.





## Supplemental Interventions

**Omega-3 fatty acids:** Mixed Finding

**Beneficial effects of docosahexaenoic acid on cognition in age-related cognitive decline (MIDAS):**

Randomized, double-blind, placebo-controlled, clinical study was conducted at 19 U.S. clinical sites.

**CONCLUSIONS:** 24 week supplementation with 900 mg/d DHA improved learning and memory function in ARCD and is a beneficial supplement that supports cognitive health with aging.

**Effect of Omega-3 Fatty Acids, Lutein/Zeaxanthin, or Other Nutrient Supplementation on Cognitive Function (AREDS2):**

Double-masked randomized clinical trial, retinal specialists in 82 US academic and community medical centers.

Long-chain polyunsaturated fatty acids (LCPUFAs) (1 g) and/or lutein (10 mg)/zeaxanthin (2 mg) vs placebo.

**CONCLUSIONS:** Among older persons with AMD, oral supplementation with LCPUFAs or lutein/zeaxanthin had no statistically significant effect on cognitive function.



## Supplemental Interventions

### **Antioxidant vitamins:**

- ❑ vitamin E, vitamin C, beta-carotene, and selenium.
- ❑ Preclinical and autopsy studies suggest that oxidative stress may be important in the pathogenesis of Alzheimer disease (AD) and other forms of dementia.
- ❑ some observational studies have found an association between higher dietary intake of antioxidants and lower risk of AD, independent of measured confounders.
- ❑ In multiple large randomized clinical trials in older individuals with normal cognition or mild cognitive impairment, supplementation with a variety of antioxidant vitamins, has shown no impact on cognitive change or incident dementia over follow-up times that have ranged from 7 to 10 years.

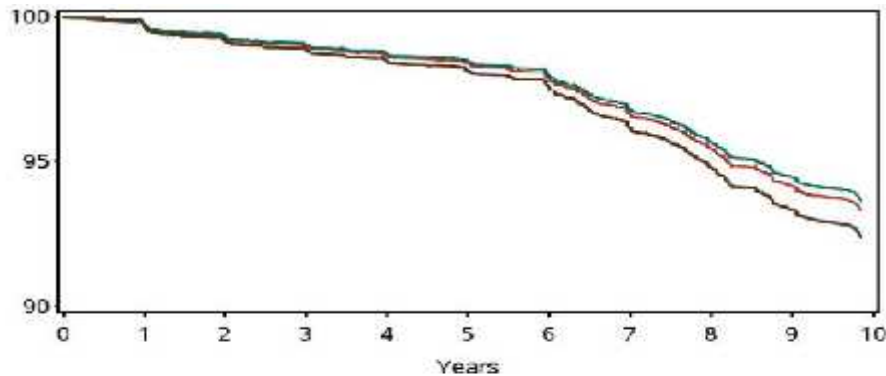
[Neurology](#). 2004 Nov 9;63(9):1705-7.



# Supplemental Interventions

Association of Antioxidant Supplement Use and Dementia in the Prevention of Alzheimer’s Disease by Vitamin E and Selenium Trial (PREADViSE).

- ❑ A double-blind, randomized controlled trial in 2002 which transformed into a cohort study from 2009–2015.
- ❑ 7,540 men, of whom 3,786 continued into the cohort study. Participants were at least 60 years old at study entry and were enrolled at one of 130 SELECT sites.



No. at risk	0	1	2	3	4	5	6	7	8	9	10
S	1881	1873	1744	1614	1469	1332	1105	755	573	384	202
E	1799	1787	1685	1533	1382	1253	999	689	480	350	163
C	1888	1822	1692	1552	1418	1274	1071	746	532	384	176
P	1830	1817	1703	1569	1423	1271	1057	737	547	389	186

Adjusted hazard ratios (HR\*) by study arm for both the mITT analysis and the weighted analysis

Treatment	ITT		Weighted**	
	HR (95% CI)	P value	HR (95% CI)	P value
Vitamin E	0.88 (0.64–1.20)	0.41	0.64 (0.61–1.15)	0.27
Selenium	0.83 (0.61–1.13)	0.23	0.60 (0.59–1.09)	0.16
Combined	1.00 (0.74–1.35)	0.98	0.99 (0.74–1.32)	0.93

[JAMA Neurol. 2017 May 1; 74\(5\): 567–573.](https://doi.org/10.1001/jama.neuro.2017.0000)



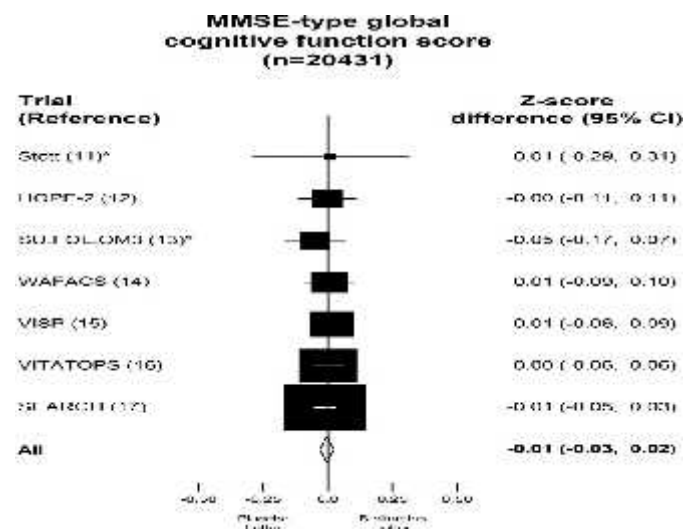
## Supplemental Interventions

### Vitamins B6, B12, and folate:

- ❑ Elevated serum homocysteine and/or low serum levels of folate, vitamin B6, and Vitamin B12 may be associated with impaired cognition and risk of dementia.
- ❑ There is no convincing evidence from clinical trials that vitamin supplementation prevents dementia.

### Effects of homocysteine lowering with B vitamins on cognitive aging: meta-analysis of 11 trials with cognitive data on 22,000 individuals.

CONCLUSION: Homocysteine lowering by using B vitamins had no significant effect on individual cognitive domains or global cognitive function or on cognitive aging.





# Supplemental Interventions

## Vitamin D:

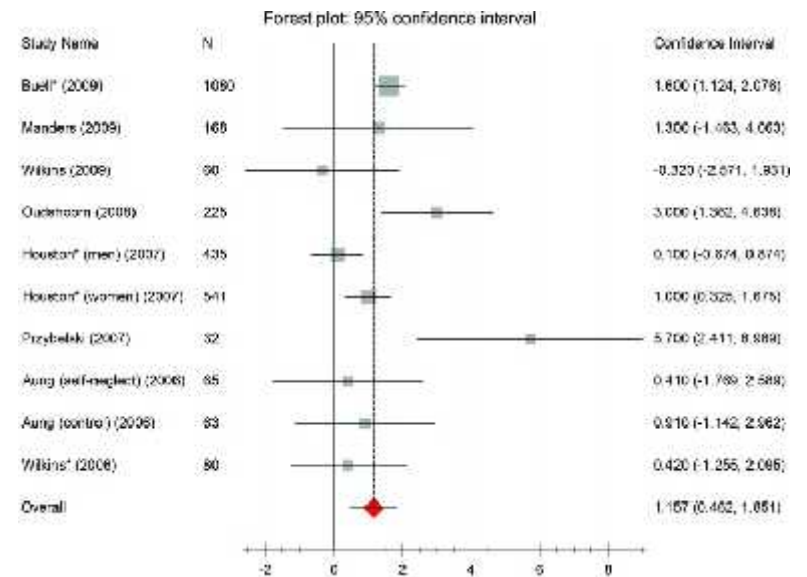
There is some evidence that vitamin D deficiency is associated with cognitive impairment in older adults.

## Vitamin D, cognition, and dementia: a systematic review and meta-analysis.

CONCLUSION: Lower vitamin D concentrations are associated with poorer cognitive function and a higher risk of AD. Further studies are required to determine the significance and potential public health benefit of this association.

- ❑ Whether vitamin D supplementation in healthy adults or those with vitamin D deficiency reduces risk of cognitive decline or dementia is not clear.
- ❑ There is low quality evidence that it is not beneficial for these Outcomes.

[Neurology](#). 2012 Sep 25;79(13):1397-405





# Secondary Prevention Trials

hope to treat underlying pathophysiology so as to prevent cognitive symptoms from ever developing

## Disease-Modifying Interventions

Trial	Location	Intervention	Study Sample	Duration	N	Outcome	Start
API-ADAD [65]	Colombia	Crenezumab	Aged 30–60, presenilin-1	5 years	600	API-Composite [83]	2013
API-APOE4 [69]	North America and Europe	Anti-amyloid vaccine CAD106 or BACE inhibitor	APOE4 homozygotes	5 years	1,300	API-Composite [84]	2015
DIAN-TU [72]	U.S. and Canada	Gantenerumab Solanezumab	Cognitively normal, MCI, or mild AD dementia; ADAD mutations	2 years	210	Cogstate, CSF Abeta and PET amyloid deposition	2013
A4 [19]	60 centers in U.S., Canada, and Australia	Solanezumab	Aged 65–85, cognitively normal with elevated amyloid burden on amyloid PET	3.25 years	1,000	ADCS-PACC, C3	2014
TOMMORROW [80]	50 centers around the world	Pioglitazone	Cognitively normal; genetic risk of TOMM40 and APOE4	5 years	6,000	Incidence of MCI due to AD	2014

A4 = Anti-Amyloid Treatment for Asymptomatic AD; ADCS-PACC = Alzheimer's Disease Cooperative Study-Preclinical Alzheimer's Cognitive Composite; API = Alzheimer's Prevention Initiative; BACE = Beta-site amyloid precursor protein cleaving enzyme; C3 = Computerized Cognitive Composite; DIAN = Dominantly Inherited Alzheimer's Network





# DEMENTIA

9 WAYS TO REDUCE YOUR RISK

**1** IN **3**

cases of dementia  
could be prevented  
by addressing these  
lifestyle factors



Source: Lancet Commission on Dementia Prevention and Care  
Credit: Keck Medicine of USC