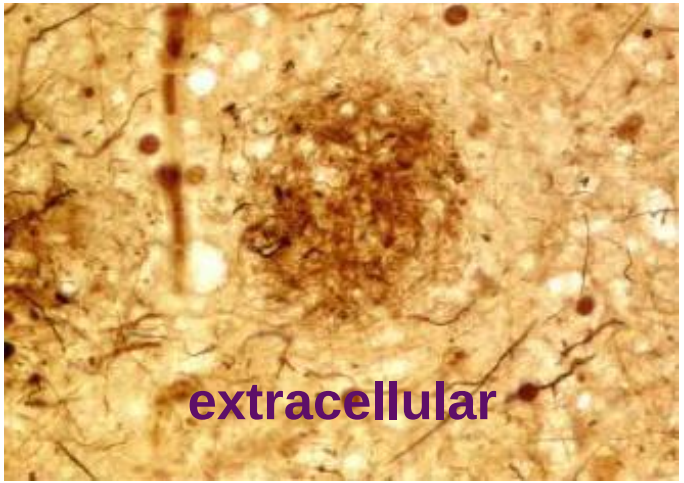
Nieuwe inzichten in preventie en behandeling van dementie

Prof. Dr. J. Tournoy - Gerontologie en Geriatrie - Geheugenkliniek
UZ-KULeuven

Neuropathology of Alzheimer's disease



Macroscopically

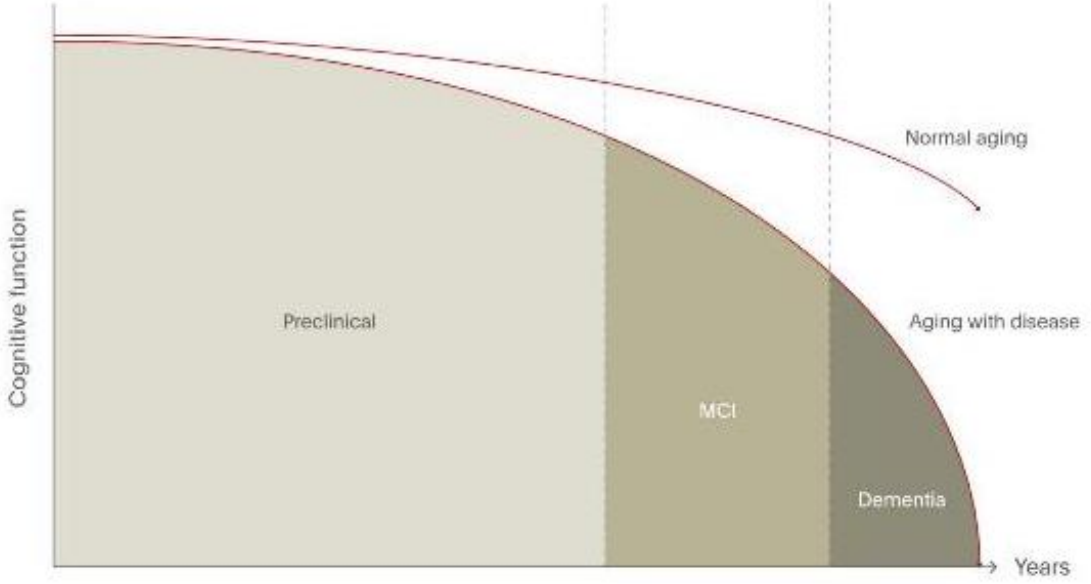
(mediotemporal) cortical atrophy

Microscopically

Presence of amyloid plaques and neurofibrillary tangles



Hypothetical model for the pathological-clinical continuum of Alzheimer's disease

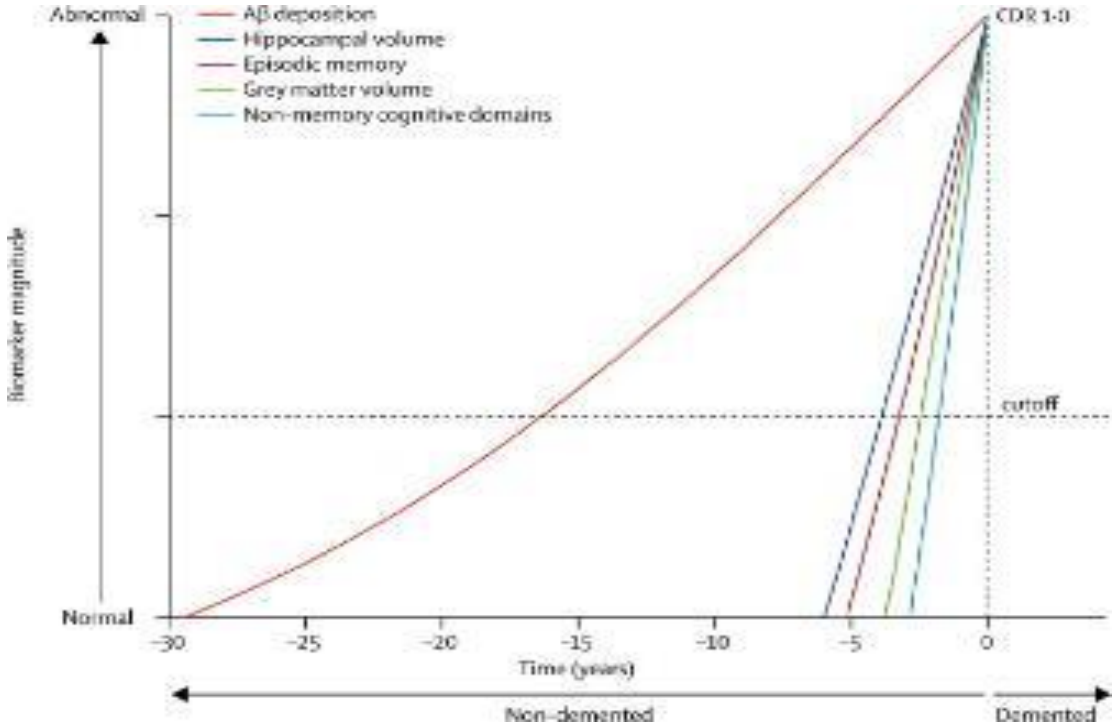


MCI=mild cognitive impairment
Sperling et al. Alzheimers Dement 2011;7(3):280–292

Lundbeck Institute
Campus

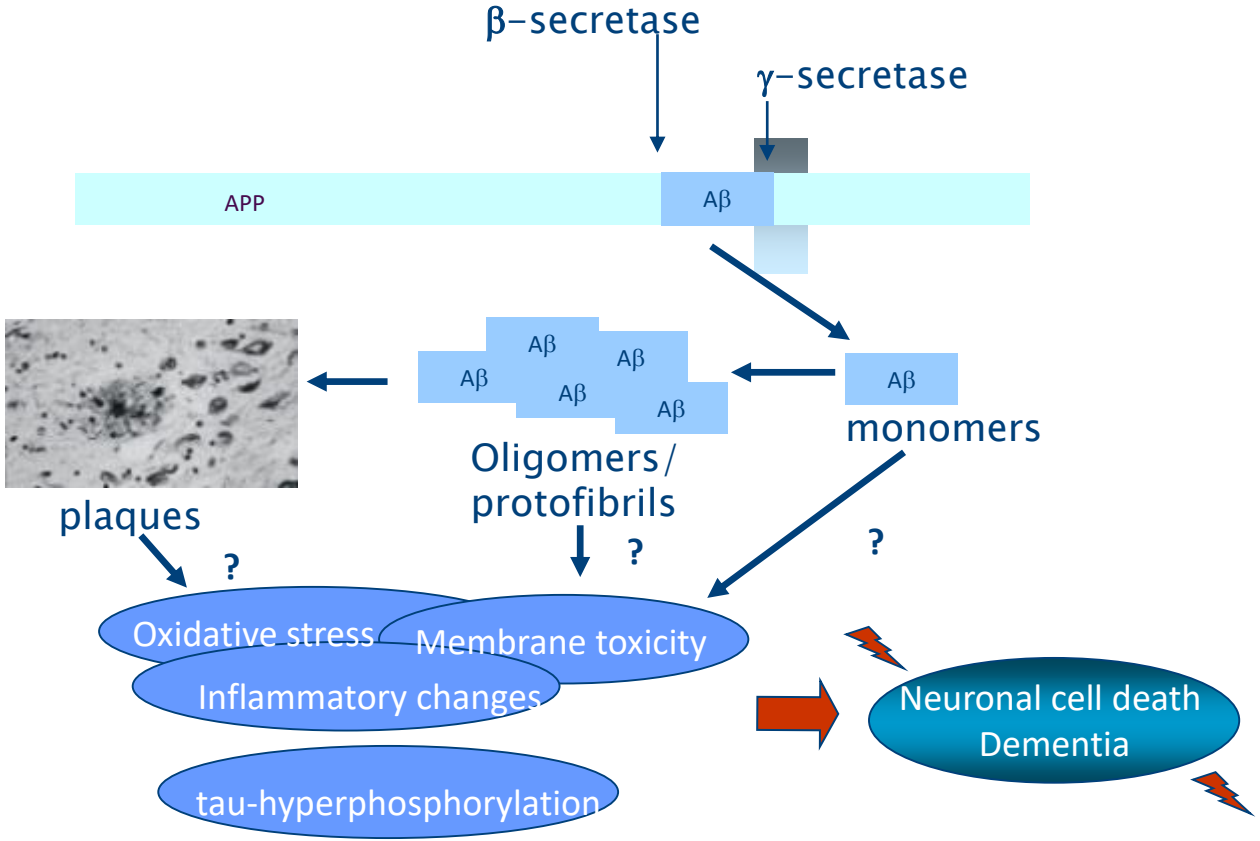
Reisa A Sperling, Paul S Aisen.
Amyloid β deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study
The Lancet Neurology, Volume 12, Issue 4, 2013, 357 - 367

Evolutie van de ziekte van Alzheimer

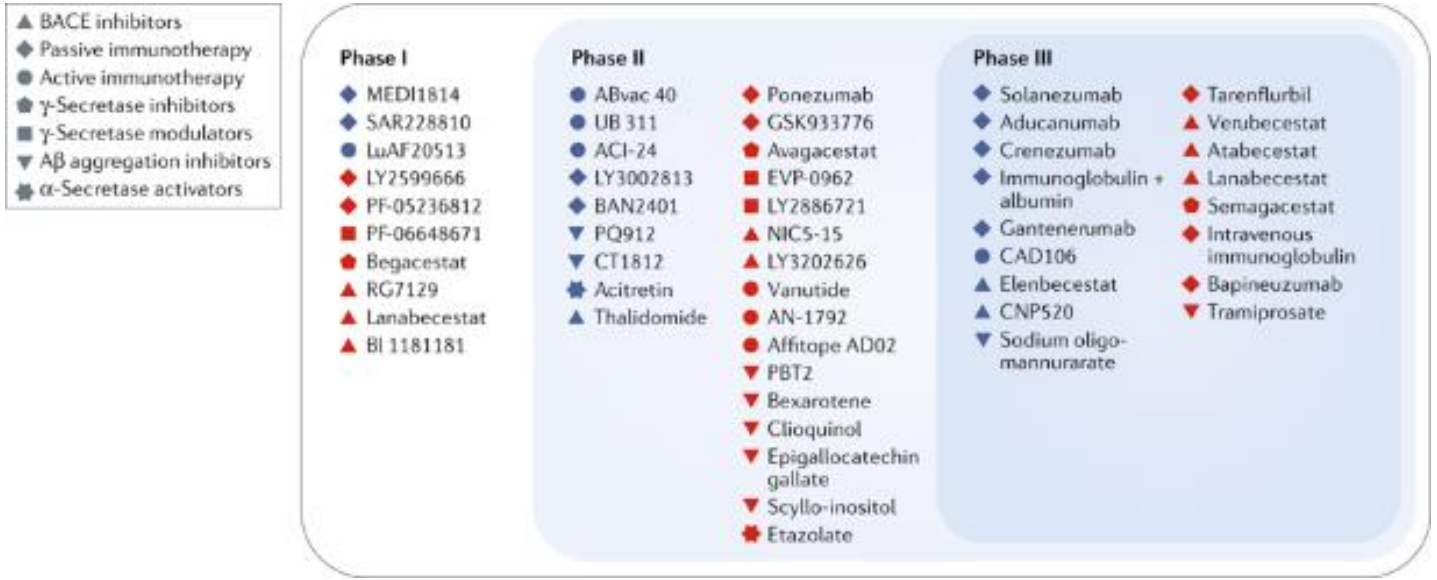


Victor L Villemagne , Samantha Burnham , Pierrick Bourgeat , Belinda Brown , Kathryn A Ellis , Olivier Salvado , C...
Amyloid β deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study
The Lancet Neurology, Volume 12, Issue 4, 2013, 357 - 367

The amyloid cascade hypothesis



A critical appraisal of amyloid-β-targeting therapies for Alzheimer disease



Francesco Panza, Madia Lozupone, Giancarlo Logroscino & Bruno P. Imbimbo
A critical appraisal of amyloid-β-targeting therapies for Alzheimer disease
Nature Reviews Neurology, volume 15, pages73–88 (2019)

A critical appraisal of amyloid-β-targeting therapies for Alzheimer disease

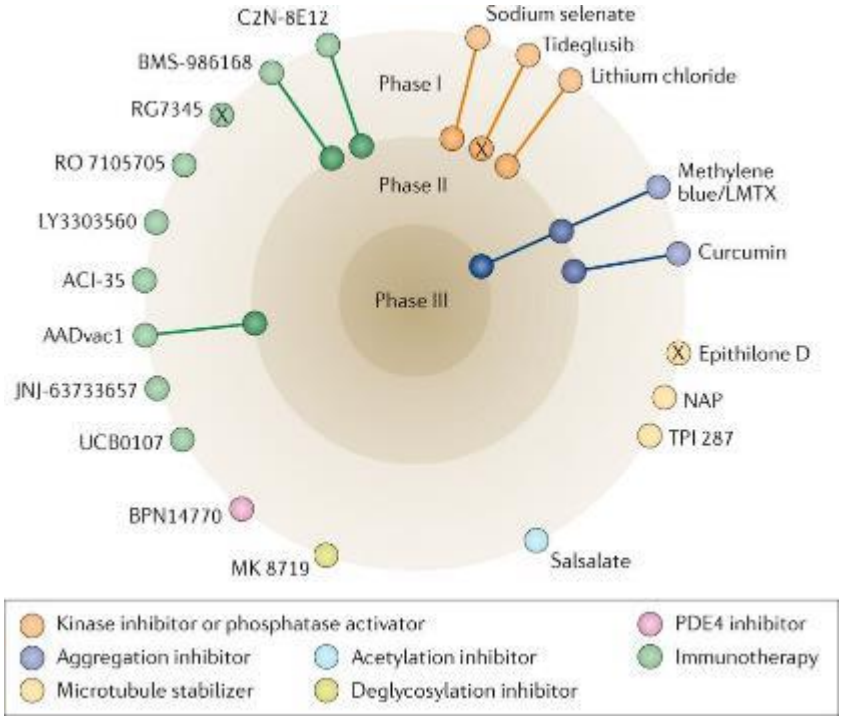
- Inappropriate selection of trial patients,
- Highly variable cognitive and clinical decline,
- Poor target engagement,
- Late intervention,
- Insensitive efficacy measures



Target for new AD treatments

Target Types	Time line	Phase 1	Phase 1/2	Phase 2	Phase 2/3	Phase 3	Phase 4	Approved	Inactive	Discontinued	Not Regulated	Total
Amyloid-Related	View Timeline	4	1	14	5	7	0	0	5	21	0	57
Cholesterol		1	0	0	0	0	1	0	1	0	0	3
Cholinergic System	View Timeline	3	0	0	0	0	0	4	5	18	0	30
Inflammation	View Timeline	3	0	6	3	2	0	0	3	8	0	25
Other	View Timeline	5	0	25	2	4	3	0	6	13	1	59
Other Neurotransmitters	View Timeline	2	0	8	0	4	2	1	1	19	0	37
Tau	View Timeline	5	0	5	0	1	0	0	1	4	0	16
Unknown		1	0	7	0	1	1	0	3	4	0	17

Tau-related compounds in development



Erin E. Congdon & Einar M. Sigurdsson
Tau-targeting therapies for Alzheimer disease
Nature Reviews Neurology, volume 14, pages399–415 (2018)

Future directions



- Can solanezumab prevent or slow the development of symptoms associated with AD
- Getting better insights into aging mechanisms
- Combined targets
- Prevention!

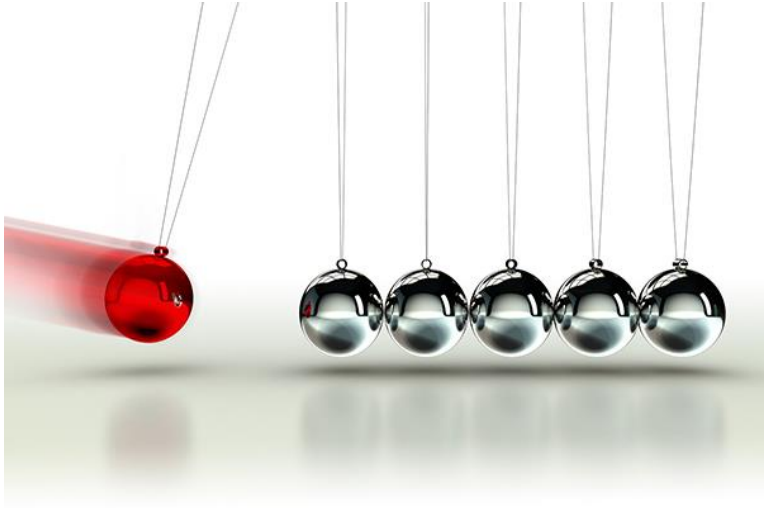
WHO - Draft global action plan on the public health response to dementia. Report by the Director-General

	Global target
Dementia as a public health priority	75% of countries will have developed or updated national policies, strategies, plans, or frameworks for dementia, either stand-alone or integrated into other policies/plans, by 2025
Dementia awareness and friendliness	100% of countries will have at least one functioning public awareness campaign on dementia to foster a dementia-inclusive society by 2025 50% of countries will have at least one dementia-friendly initiative to foster a dementia-inclusive society by 2025
Dementia risk reduction	The relevant global targets defined in, and in keeping with, the global action plan for prevention and control of non-communicable diseases 2013–20 and any future revisions are achieved
Dementia diagnosis, treatment, care, and support	In at least 50% of countries, as a minimum, 50% of the estimated number of people with dementia are diagnosed by 2025
Support for dementia carers	75% of countries provide support and training programmes for carers and families of people with dementia by 2025
Information systems for dementia	50% of countries routinely collect a core set of dementia indicators through their national health and social information systems on which they report every 2 years by 2025
Dementia research and innovation	The output of global research on dementia doubles between 2017 and 2025

Impact of prevention

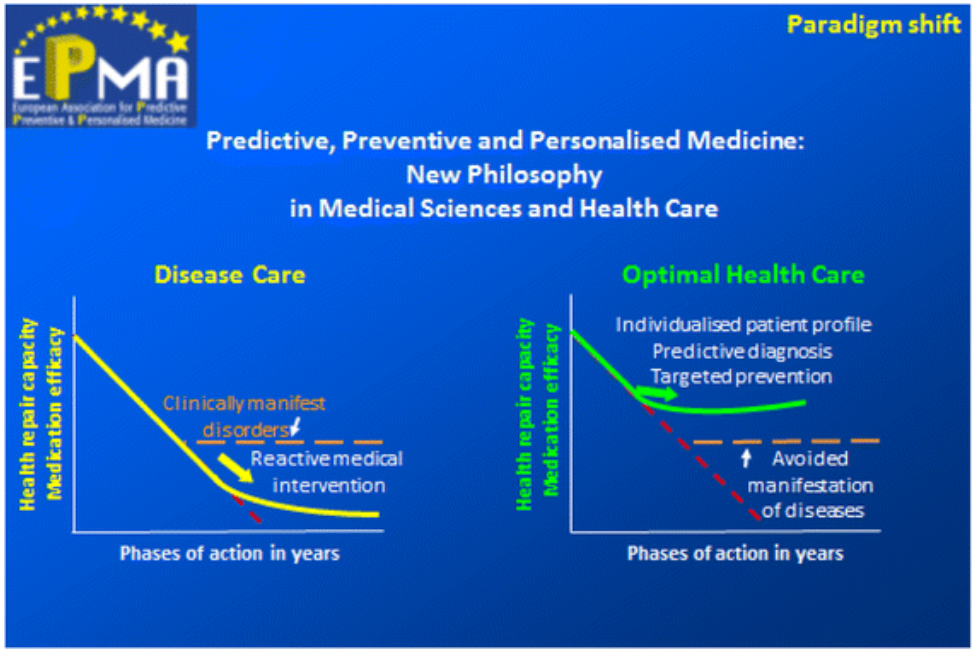
Halve prevalence if delay onset by five years

10% reduction in prevalence of modifiable risk factors, reduce global burden by 1 million



Lancet Neurol. 2014:13(8):788-94

Preventieve vs reactieve geneeskunde



Golubnitschaja O, Baban B, Boniolo G, et al.
Medicine in the early twenty-first century: paradigm and anticipation
EPMA position paper 2016. *EPMA J*. 2016;7(1):23. Published 2016 Oct 25. doi:10.1186/s13167-016-0072-4

The Lancet Commissions: Dementia prevention, intervention, and care

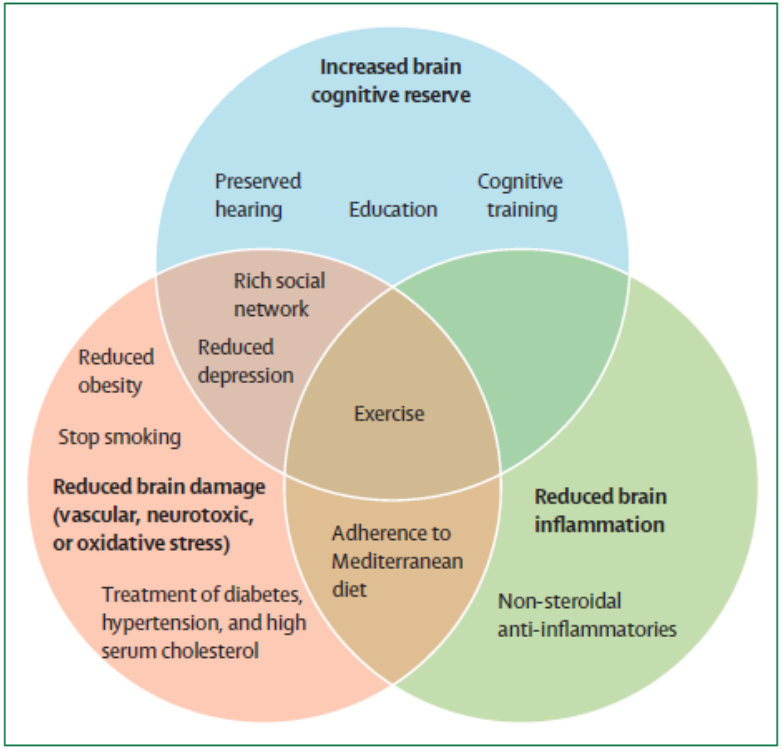


Figure 5: **Potential brain mechanisms for preventive strategies in dementia**

G. Livingston et al
Dementia prevention, intervention, and care
The Lancet - Volume 390, Issue 10113, 16–22 December 2017, Pages 2673-2734

The Lancet Commissions: Dementia prevention, intervention, and care

	Relative risk for dementia (95% CI)	Prevalence	Communality	PAF	Weighted PAF*
Early life (age <18 years)					
Less education (none or primary school only)	1·6 (1·26–2·01)	40·0%	64·6%	19·1%	7·5%
Midlife (age 45–65 years)					
Hypertension	1·6 (1·16–2·24)	8·9%	57·3%	5·1%	2·0%
Obesity	1·6 (1·34–1·92)	3·4%	60·4%	2·0%	0·8%
Hearing loss	1·9 (1·38–2·73)	31·7%	46·1%	23·0%	9·1%
Later life (age >65 years)					
Smoking	1·6 (1·15–2·20)	27·4%	51·1%	13·9%	5·5%
Depression	1·9 (1·55–2·33)	13·2%	58·6%	10·1%	4·0%
Physical inactivity	1·4 (1·16–1·67)	17·7%	26·6%	6·5%	2·6%
Social isolation	1·6 (1·32–1·85)	11·0%	45·9%	5·9%	2·3%
Diabetes	1·5 (1·33–1·79)	6·4%	70·3%	3·2%	1·2%

Data are relative risk (95% CI) or %. Total weighted PAF adjusted for communality=35·0%. PAF=population attributable fraction. *Weighted PAF is the relative contribution of each risk factor to the overall PAF when adjusted for communality.

Table 1: **Potentially modifiable risk factors for dementia**

G. Livingston et al
Dementia prevention, intervention, and care
The Lancet - Volume 390, Issue 10113, 16–22 December 2017, Pages 2673-2734



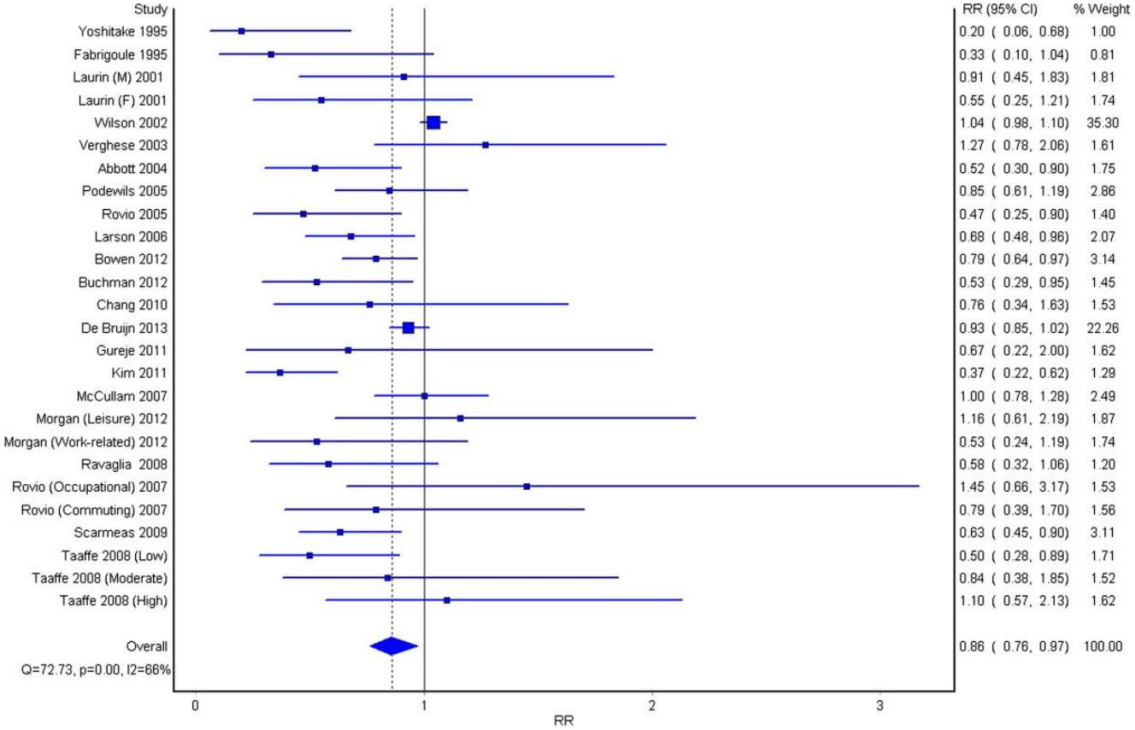
Negatieve studies

- NSAID
- B12/Folic Acid
- Statines
- HRT
- Rosiglitazone
- Ginko



- McGuiness 2016 Cochrane review The ADAPT Research. Alzheimer's & Dementia. 2013:9(6):714-23.
- McCarrey. Hormones and Behavior. 2015:74:167-72.
- DeKosky. Jama. 2008:300(19):2253.
- Walker. American Journal of Clinical Nutrition. 2011:95(1):194-203
- van der Zwaluw. Neurology. 2014:83(23):2158-66.
- Areosa Sastre. Effect of the treatment of Type 2 diabetes mellitus on the development of cognitive impairment and dementia. Cochrane Database Syst Rev. 2017

Exercise - dementia



Blondell SJ, Hammersley-Mather R, Veerman JL.
Does physical activity prevent cognitive decline and dementia?: A systematic review and meta-analysis of longitudinal studies.
BMC Public Health. 2014 May 27;14:510. doi: 10.1186/1471-2458-14-510.

PA and dementia

Figure A. High and moderate amounts of physical activity and dementia risk

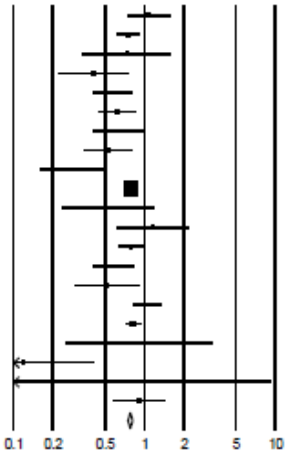
All-cause dementia

High amount of physical activity (>2 hours/week &>3 times/week) vs. Inactivity (<1 hour/week)

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Akbaraly, 2009	1.08	0.74	1.57	0.40	0.69
Browen, 2012	0.75	0.62	0.91	-2.86	0.00
Chang, 2010	0.74	0.34	1.62	-0.76	0.45
Elwood, 2013	0.41	0.22	0.77	-2.79	0.01
Karp, 2006	0.57	0.40	0.81	-3.12	0.00
Larson, 2006	0.62	0.44	0.87	-2.80	0.01
Laurin, 2001	0.63	0.40	0.99	-2.02	0.04
Lee, 2015	0.53	0.34	0.82	-2.83	0.00
Llamas-Velasco, 2015	0.29	0.16	0.52	-4.12	0.00
Luck, 2014	0.79	0.75	0.83	-8.89	0.00
Morgan, 2014(work)	0.53	0.24	1.18	-1.55	0.12
Morgan, 2014(Leisure)	1.16	0.61	2.20	0.46	0.65
Neergaard, 2016	0.79	0.64	0.97	-2.22	0.03
Podewils, 2005	0.58	0.41	0.83	-3.03	0.00
Ravaglia, 2008	0.52	0.29	0.93	-2.20	0.03
Sabia, 2017	1.05	0.82	1.35	0.38	0.71
Soni, 2017	0.82	0.72	0.94	-2.92	0.00
Sumic, 2007(male)	0.91	0.25	3.36	-0.14	0.89
Sumic, 2007(female)	0.12	0.04	0.41	-3.38	0.00
Verdelho, 2012	0.61	0.04	9.30	-0.36	0.72
Verghese, 2003	0.92	0.58	1.45	-0.36	0.72
	0.78	0.74	0.81	-11.63	0.00

Statistics for each study

Odds ratio and 95% CI



Test for heterogeneity: (Q = 49.11, P = 0.00, I^2 = 59.27%)

J Gerontol Nurs. 2018 Oct 1;44(10):22-29.
The Relationship Between Physical Activity and Dementia: A Systematic Review and Meta-Analysis of Prospective Cohort Studies

Hypertension and dementia

Antihypertensive, cognition and dementia

Study or subgroup	log[Hazard ratio]	SE	Weight	Hazard ratio IV, random, 95% CI
Syst-Eur trial 1998 [3]	–0.713	0.364	2.0%	0.49 [0.24, 1.00]
BLSA 2005 [43]	–0.462	0.362	2.0%	0.63 [0.31, 1.28]
Cache County Study 2006 [44]	–0.446	0.227	4.4%	0.64 [0.41, 1.00]
Kungsholmen1999 [40]	–0.357	0.08	13.2%	0.70 [0.60, 0.82]
Rotterdam 2001 [41]	–0.274	0.194	5.5%	0.76 [0.52, 1.11]
US Veteran 2010 § [46]	–0.269	0.051	15.9%	0.76 [0.69, 0.84]
SHEP 1991 [6]	–0.174	0.225	4.4%	0.84 [0.54, 1.31]
Hyvet-Cog 2008 [7]	–0.116	0.13	9.0%	0.89 [0.69, 1.15]
CSHA 2002 [42]	–0.094	0.179	6.1%	0.91 [0.64, 1.29]
US Veteran 2010* [46]	–0.061	0.017	18.1%	0.94 [0.91, 0.97]
CHS 2009 [45]	0.0099	0.076	13.6%	1.01 [0.87, 1.17]
SCOPE 2003 [5]	0.08	0.186	5.8%	1.08 [0.75, 1.56]
Total (95% CI)			100.0%	0.84 [0.75, 0.93]

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 36.43$, df = 11 ($P = 0.0001$); $I^2 = 70\%$
Test for overall effect: $Z = 3.25$ ($P = 0.001$)

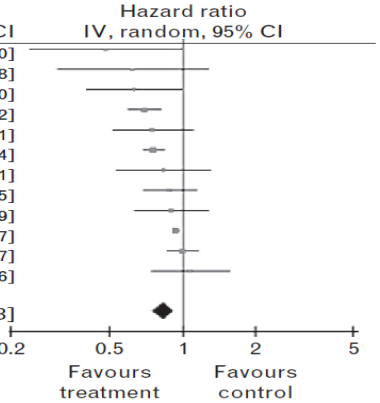




FIGURE 3 Effect of antihypertensive treatment on the incidence of all-cause dementia. Boxes represent the individual study estimates, the size being proportional to the study weight; lines, the 95% confidence interval; and the diamond, the overall effect with a 95% confidence interval. ∗ and § relate to ACEI and ARBs groups, respectively.

L Marpillat, I Macquin-Mavier, AI Tropeano, AC Bachoud-Levi and P Maison.
Antihypertensive classes, cognitive decline and incidence of dementia: a network meta-analysis.
J Hypertens. 2013:31(6):1073-82.

Hypertension and dementia

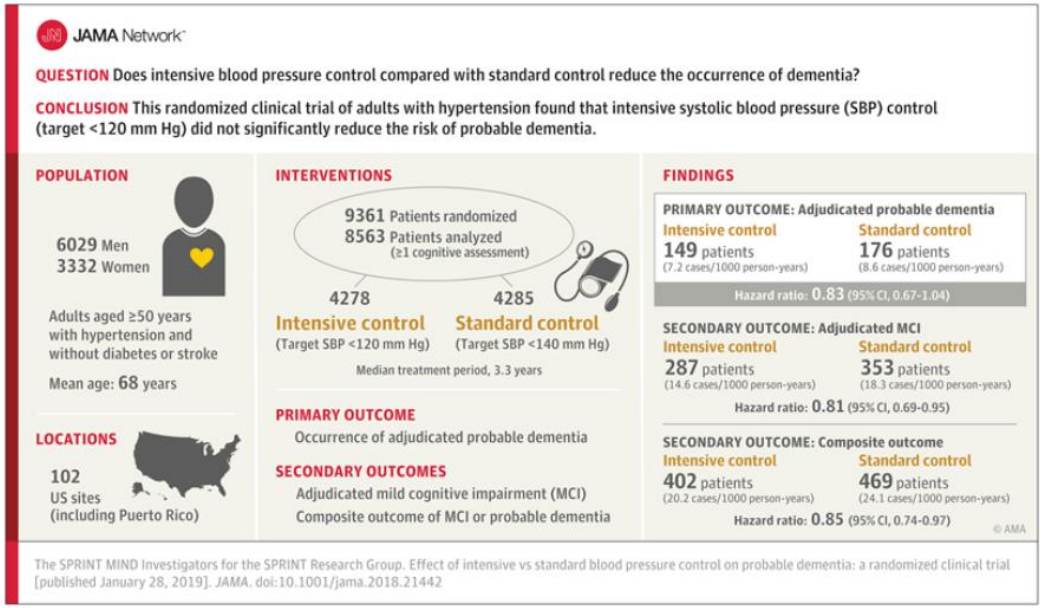


Figure Legend:

Intensive vs Standard Blood Pressure Control and Probable Dementia

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 Intern Med, 321(6):553-561 (2019) doi:10.1001/jama.2018.21442

JAMA Network
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Hypertension and dementia

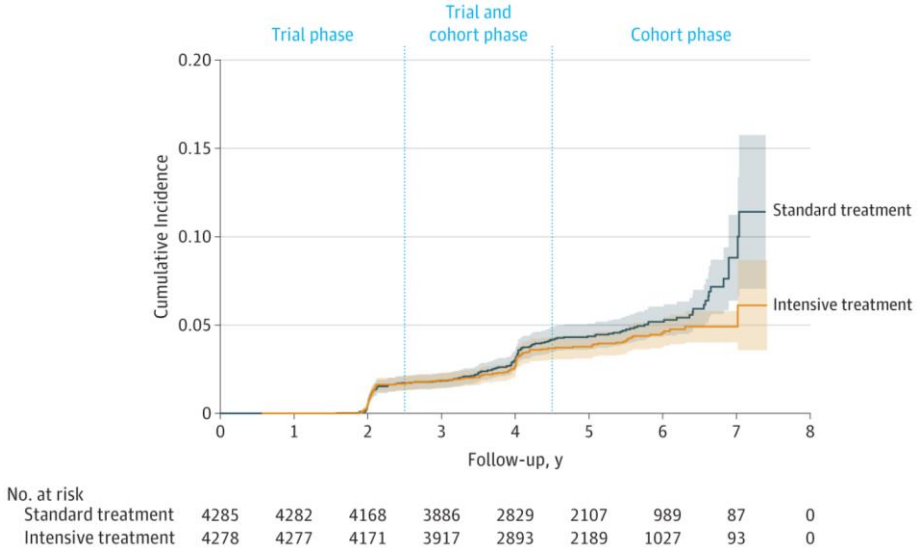

Figure Legend:

Probable Dementia by Treatment GroupShaded regions indicate 95% confidence intervals. Median follow-up time was 5.14 years (interquartile range, 3.91-6.00) for the intensive treatment group and 5.07 years (interquartile range, 3.87-5.98) for the standard treatment group. For group comparison of incidence, hazard ratio, 0.83; 95% CI, 0.67-1.04; P=.10.

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 Intern Med, 321(6):553-561 (2019) doi:10.1001/jama.2018.21442

JAMA Network
Date of download: 4/15/2019
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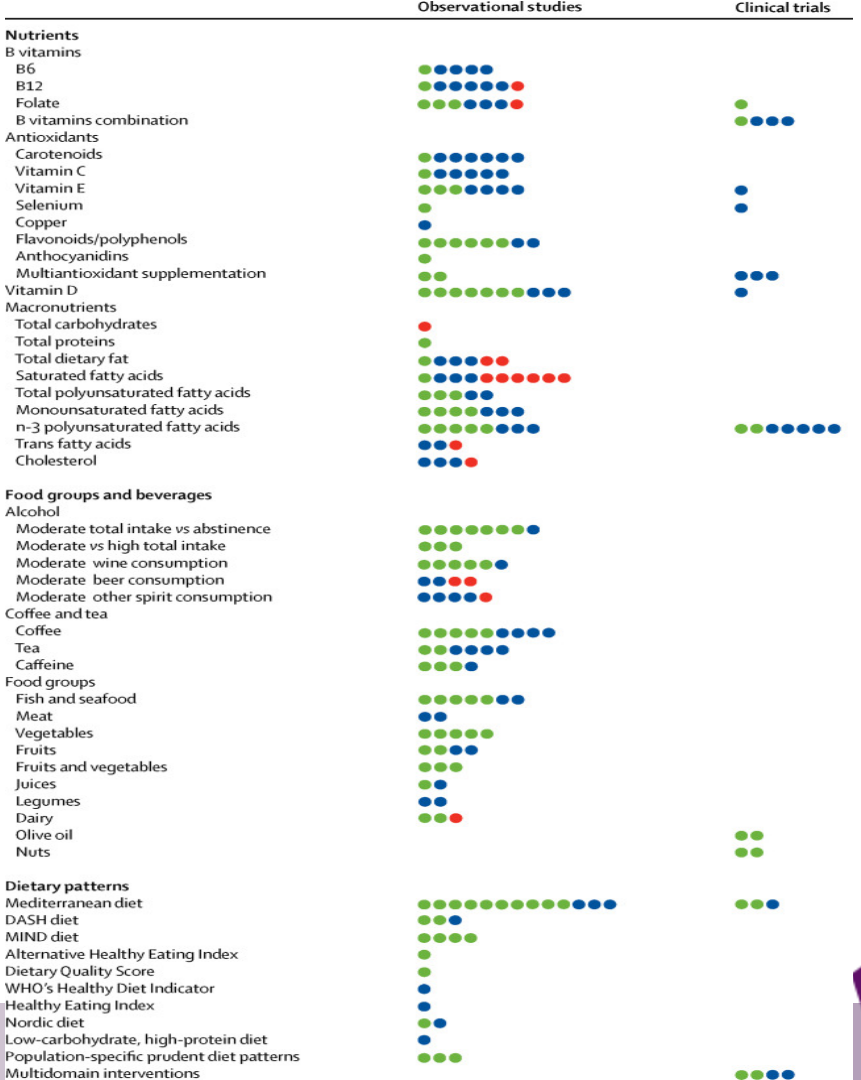
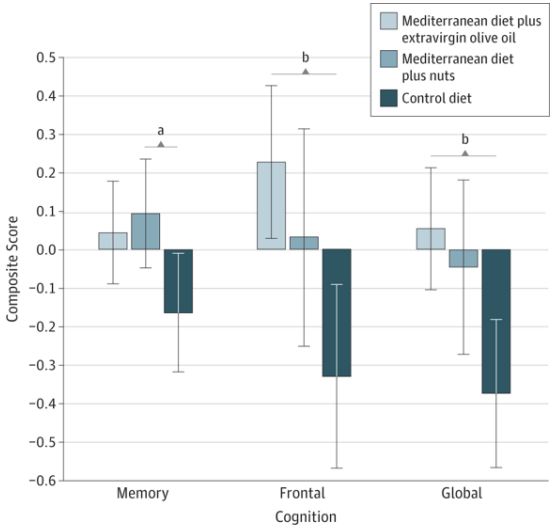
Nutrition and prevention of cognitive impairment



Scarmeas, The Lancet Neurology 2018

Evidence of interventions preventing dementia

Mediterranean diet and age-related cognitive decline





C Valls-Pedret, A Sala-Vila, M Serra-Mir, D Corella, R de la Torre, MA Martinez-Gonzalez, EH Martinez-Lapiscina, M Fito, A Perez-Heras, J Salas-salvado, R Estruch, E Ros
JAMA Intern Med, 175(7):1094-1103 (2015) doi:10.100**Mediterreanean diet and age-related cognitive decline: A randomized clinical trial**
1/jamainternmed.2015.1668

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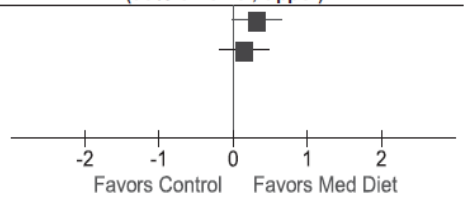
Mediterranean diet and age-related cognitive decline

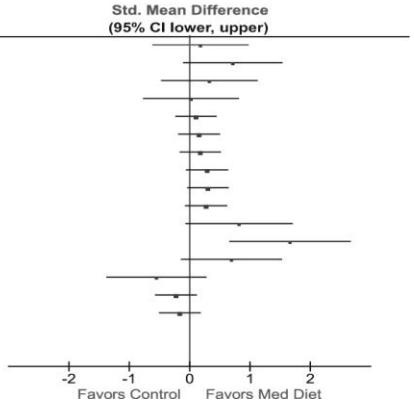
(A) Global cognition	Med Diet			Control				Std. Mean Difference
Study or Subgroup	Mean	SD	n	Mean	SD	n	Weight	(95% CI lower, upper)
Valls-Pedret 2015 (57) (MMSE) Med EVOO	0.16	1.29	127	-0.26	1.29	48	50.7%	0.32 [-0.01, 0.66]
Valls-Pedret 2015 (57) (MMSE) Med Nuts	-0.07	1.29	112	-0.26	1.29	48	49.3%	0.15 [-0.19, 0.49]
Total (95% CI)			239			96	100.0%	0.24 [-0.00, 0.47]

Heterogeneity: Tau² = 0.00; Chi² = 0.54, df = 1 (P = 0.46); I² = 0%



(B) Verbal and visual memory	Med Diet			Control				Std. Mean Difference
Study or Subgroup	Mean	SD	n	Mean	SD	n	Weight	(95% CI lower, upper)
McMillan 2011 (41) (Immediate word recall)	1.25	2.05	12	0.87	2.05	13	3.4%	0.18 [-0.61, 0.97]
McMillan 2011 (41) (Delayed word recall)	1.5	2.23	12	-0.15	2.23	13	3.2%	0.72 [-0.10, 1.53]
McMillan 2011 (41) (Word recognition accuracy %)	3.33	10.63	12	-0.26	10.63	13	3.4%	0.33 [-0.46, 1.12]
McMillan 2011 (41) (Delayed picture recognition %)	-2.09	9.1	12	-2.31	9.1	13	3.4%	0.02 [-0.76, 0.81]
Valls-Pedret 2015 (57) (Paired associates) Med EVOO	0.25	3.21	127	-0.09	3.21	48	9.5%	0.11 [-0.23, 0.44]
Valls-Pedret 2015 (57) (Paired associates) Med Nuts	0.41	3.2	112	-0.09	3.2	48	9.3%	0.16 [-0.18, 0.49]
Valls-Pedret 2015 (57) (RAVLT delayed recall) Med EVOO	1.47	2.95	127	0.95	2.95	48	9.5%	0.18 [-0.16, 0.51]
Valls-Pedret 2015 (57) (RAVLT delayed recall) Med Nuts	1.8	2.93	112	0.95	2.93	48	9.3%	0.29 [-0.05, 0.63]
Valls-Pedret 2015 (57) (RAVLT total learning) Med EVOO	4.5	7.91	127	2.1	7.91	48	9.4%	0.30 [-0.03, 0.64]
Valls-Pedret 2015 (57) (RAVLT total learning) Med Nuts	4.26	7.9	112	2.1	7.9	48	9.3%	0.27 [-0.07, 0.61]
Lee 2015 (42) (Delayed word recall-correct responses)	0.67	1.35	11	-0.48	1.35	11	2.8%	0.82 [-0.06, 1.70]
Lee 2015 (42) (Immediate word recall-correct responses)	1.14	1.03	11	-0.64	1.03	11	2.3%	1.66 [0.67, 2.66]
Lee 2015 (42) (Picture recognition-correct responses)	-0.14	3.31	12	-2.52	3.31	12	3.1%	0.69 [-0.13, 1.52]
Lee 2015 (42) (Word recognition accuracy %)	-8.87	15.32	12	-0.14	15.32	12	3.2%	-0.55 [-1.37, 0.27]
Knight 2016 (58) (BVRT)	-0.13	1.41	70	0.19	1.41	67	9.4%	-0.23 [-0.56, 0.11]
Knight 2016 (58) (RAVLT total score)	9.48	14.37	70	11.84	14.37	67	9.4%	-0.16 [-0.50, 0.17]
Total (95% CI)			951			520	100.0%	0.19 [0.03, 0.36]

Heterogeneity: Tau² = 0.04; Chi² = 27.88, df = 15 (P = 0.02); I² = 46%



The American Journal of Clinical Nutrition, Volume 107, Issue 3, March 2018, Pages 389–404, https://doi.org/10.1093/ajcn/nqx070

OXFORD UNIVERSITY PRESS

Evidence of interventions preventing dementia
Combination strategies in the prevention of dementia

FINGER

- **Objective: To reduce cognitive impairment in an at risk population through a 2-year multi-domain life-style intervention**

- **Target population: 60-77 year old persons (n= 1200) from previous population-based non-intervention studies (FINRISK, D2D)**

Ngandu T et al.
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.
Lancet. 2015 Jun 6;385(9984):2255-63.

INCLUSION CRITERIA:
persons at risk of cognitive decline/dementia

FINGER

Dementia Risk score ≥ 6

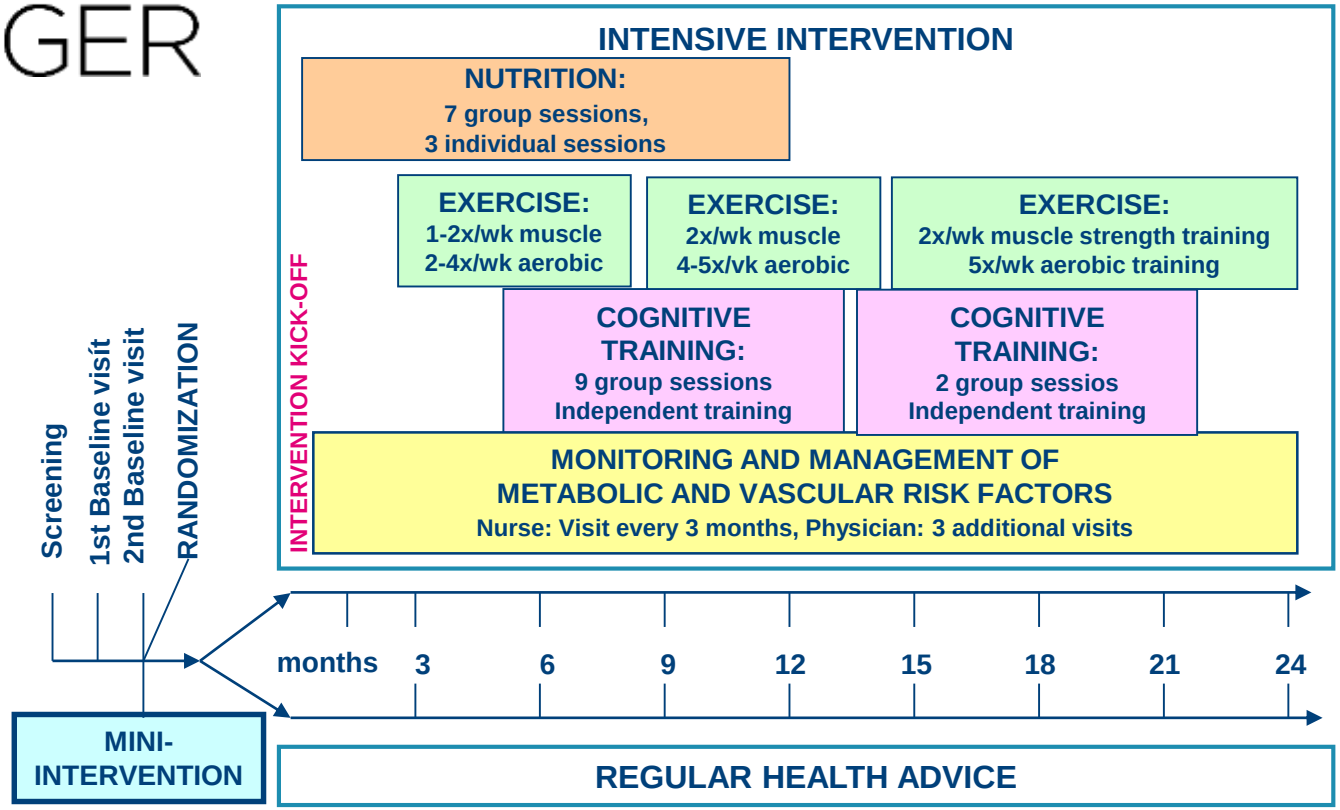
Based on risk factors assessed in earlier population surveys: Age, Education, Sex, SBP, Cholesterol, BMI, Physical Activity
(Kivipelto et al., Lancet Neurology 2006)

AND

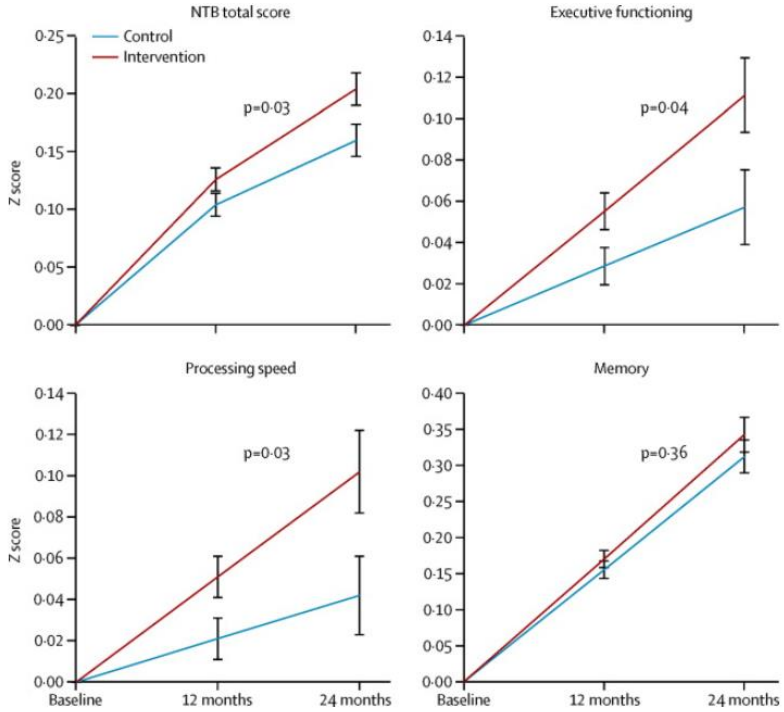
Cognitive performance at mean level or slightly lower than expected for age
(based on CERAD test battery)

INTERVENTION SCHEDULE

FINGER



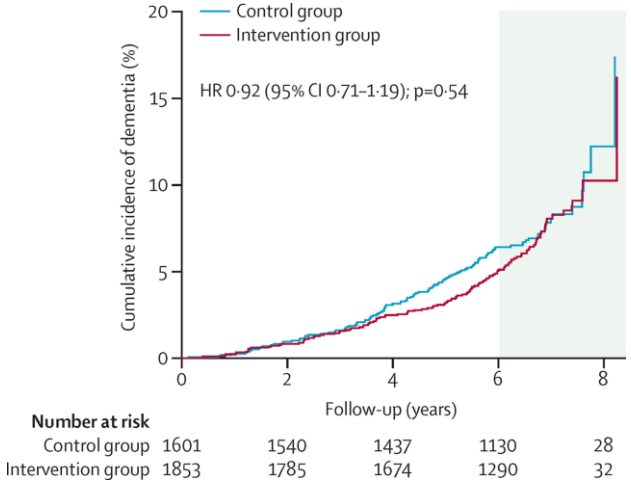
FINGER



Ngandu T et al.
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.
Lancet. 2015 Jun 6;385(9984):2255-63.

PreDIVA study

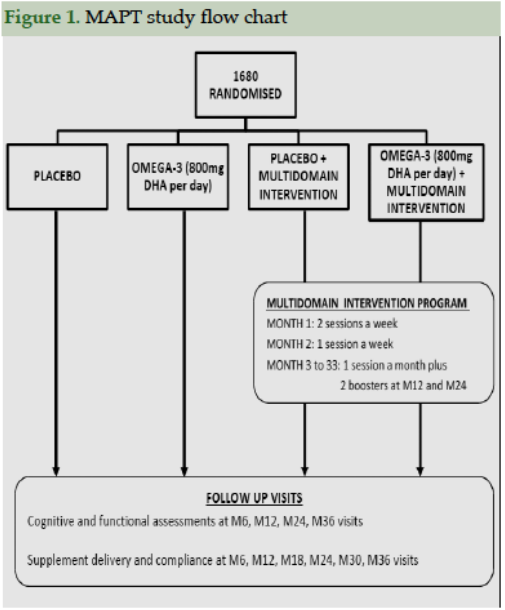
- P- 3526 70-79 yr olds with normal cognition
- I- Nurse-led CV intervention
- 0- No significant change in 6 year incidence of dementia, 7% vs 7%



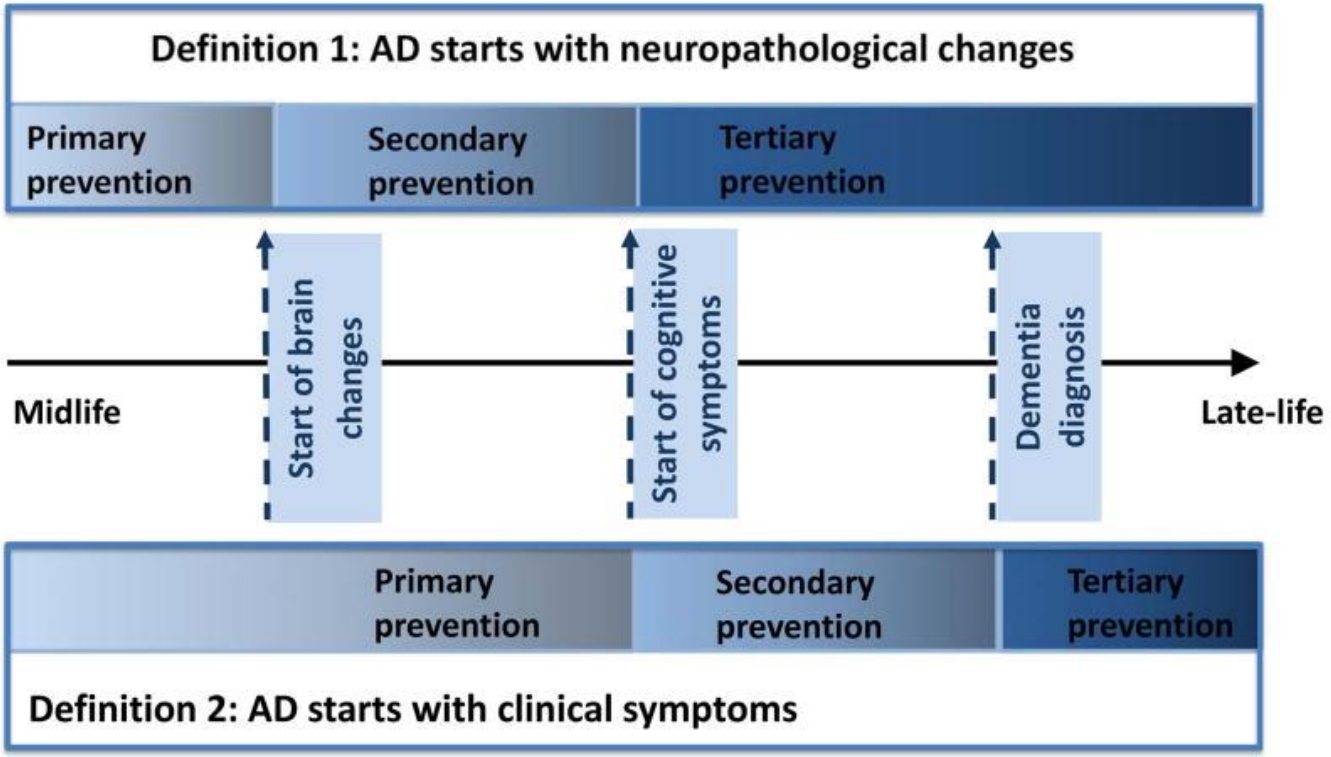
EP Moll van Charante, E Richard, LS Eurelings, J-W van Dalen, SA Ligthart, EF van Bussel, MP Hoevenaar-Blom, M Vermeulen, WA van Gool
Effectiveness of a 6-year multidomain vascular care intervention to prevent dementia (preDIVA): a cluster-randomised controlled trial
The Lancet 10046(388):797-805 (2016)

MAPT trial

- P- 1525 >70, ‘memory complaints’
- I- 4 arms 0- 2 yr, no difference in cognition
- Beneficial if high CV risk or pathology on imaging



S Andrieu, et al
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
Lancet Neurol. 2017:16(5):377-89



Solomon, et al

Advances in the prevention of Alzheimer's disease and dementia

J Intern Med. 2014 Mar; 275(3): 229–250.

Anticholinergic drugs

- Nested Case Control study in UK

Exposure during DEP	No of cases (%)	No of controls (%)	Odds ratio (95% CI) Unadjusted	Odds ratio (95% CI) Adjusted at end of DEP* ‡
Any use				
Prescriptions (ACB score):				
None	4295 (10.5)	36 329 (12.8)	1.00	1.00
1	36 437 (89.4)	247 406 (87.1)	1.25§ (1.21 to 1.29)	1.10§ (1.06 to 1.15)
2	1429 (3.5)	7909 (2.8)	1.27§ (1.20 to 1.35)	1.10§ (1.03 to 1.16)
3	14 453 (35.5)	86 403 (30.4)	1.27§ (1.24 to 1.30)	1.11§ (1.08 to 1.14)

Richardson, et al
Anticholinergic drug use and risk of dementia: a case control study
BMJ. 2018;361:k1315.

Take home



- What is good for your heart is likely also good for your brain
- Robust evidence to recommend and preventive strategy is limited (Observational evidence is not translating into RCTs)
- Studies to date suggest that a multifactorial intervention comprising regular exercise and healthy diet, along with the amelioration of vascular risk factors and psychosocial stress, may be most promising for the prevention of cognitive decline
- Results from ongoing trials awaited (World Wide Fingers)