¿Es la Enfermedad de Alzheimer prevenible?

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XII Congreso Iberoamericano Alzheimer
Ecuador 2019

Introducción:Prevención

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Enfermedad de Alzheimer no tiene cura o medicación modificadora

¿Podemos impedir que las persona desarrollen Enfermedad de Alzheimer ?

¿Podemos retrasar el inico de la Enfemedad de Alzheimer?

¿Porque es importante prevenir la EA ? : Problema económico

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1 billon de dólares

2018

2 billones de dólares

2030

¿Porque es importante prevenir la EA ?: Problema epidemiológico

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50 millones

- 60% Países de rentas bajas
- América Latina 3.4 millones
- Ecuador 59 mil personas y dentro de las pimeras causa de defunción

152 millones

- 72% Países de rentas bajas

2018 — **2030** — **2050**

82 milones

Epidemiología de la Demencia

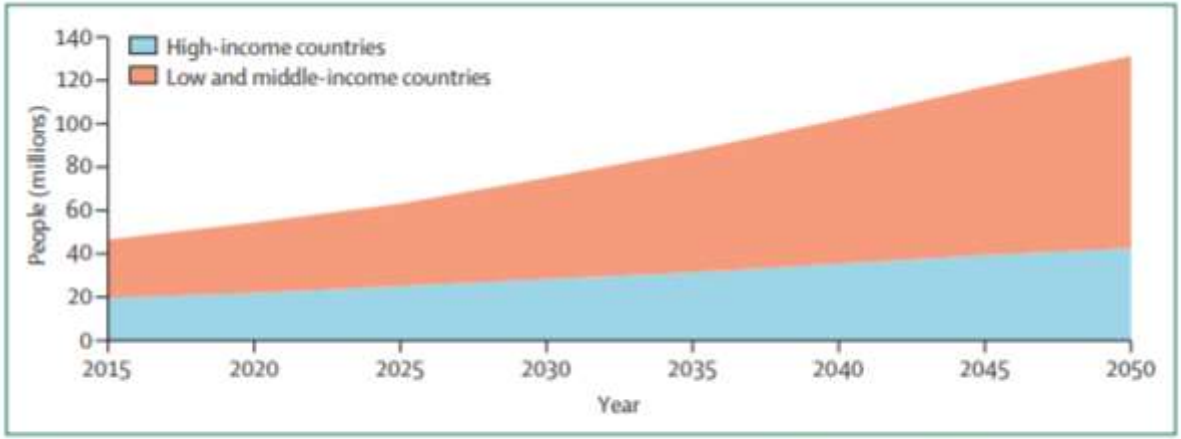

Figure 1: **Growth in numbers of people with dementia in high-income and low and middle-income countries**
Reproduced from Prince and colleagues,[2] by permission of Alzheimer's Disease International.

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❖Framingham Heart Study desde 1975. Se incluyen 5205 personas de 60 años o mayores.

El ratio de demencia ajustado por edad y sexo fue de
- 3.6 por 100 personas durante la primera época (1970s -1980),
- 2.8 por 100 personas durante la segunda época (1980s -1990)
- 2.2 por 100 personas durante la tercera época (1990 - 2000s)
- 2.0 por 100 personas durante la cuarta época (2000s -2010).

La incidencia durante la primera época se reduce a la
- la segunda epoca un 22%,
- la tercera epoca un 38%,
- la cuarta epoca un 44%.

Table 2. Temporal Trends in the Incidence of Dementia.*

Subtype	No. of Cases	Total No. of Observation Periods	5-Yr Cumulative Hazard Rate (95% CI)†				5-Yr Hazard Ratio (95% CI)‡				P Value for Trend
			Epoch 1	Epoch 2	Epoch 3	Epoch 4	Epoch 2	Epoch 3	Epoch 4	Trend§	
Overall dementia	371	9015	3.6 (2.9–4.4)	2.8 (2.2–3.5)	2.2 (1.8–2.8)	2.0 (1.5–2.6)	0.78 (0.59–1.04)	0.62 (0.47–0.83)	0.56 (0.41–0.77)	0.80 (0.72–0.90)	<0.001
Alzheimer's disease	264	9015	2.0 (1.5–2.6)	2.0 (1.5–2.6)	1.7 (1.3–2.3)	1.4 (1.0–1.9)	1.00 (0.70–1.43)	0.88 (0.62–1.25)	0.70 (0.48–1.03)	0.88 (0.77–1.00)	0.052
Vascular dementia	84	9014	0.8 (0.6–1.3)	0.8 (0.5–1.2)	0.4 (0.2–0.7)	0.4 (0.2–0.7)	0.89 (0.51–1.56)	0.46 (0.25–0.86)	0.45 (0.23–0.87)	0.71 (0.56–0.90)	0.004

N Engl J Med 2016;374:523-32.

Incidence of Dementia over Three Decades in the Framingham Heart Study

Claudia L. Satizabal, Ph.D., Alexa S. Beiser, Ph.D., Vincent Chouraki, M.D., Ph.D., Geneviève Chêne, M.D., Ph.D., Carole Dufouil, Ph.D., and Sudha Seshadri, M.D.

¿Qué esta sucediendo en los países de renta alta?

Retos en prevención en Enfermedad de Alzheimer

Genética vs Esporádica

Fenotipos clínicos diferentes

Amnésico vs. No Amnésico

10-30% de adultos mayores sanos beta amiolodes en PET

Diferente grado de patología estructural y neuropatología

Enfermedad de Alzheimer es heterógenea

AD begins 2 to 3 decades before symptoms appear

Xu W, et al. *J Neurol Neurosurg Psychiatry*. 2015;86:1299-1306.
Bendlin BB, et al. *Maturitas*. 2010;65:131-137.

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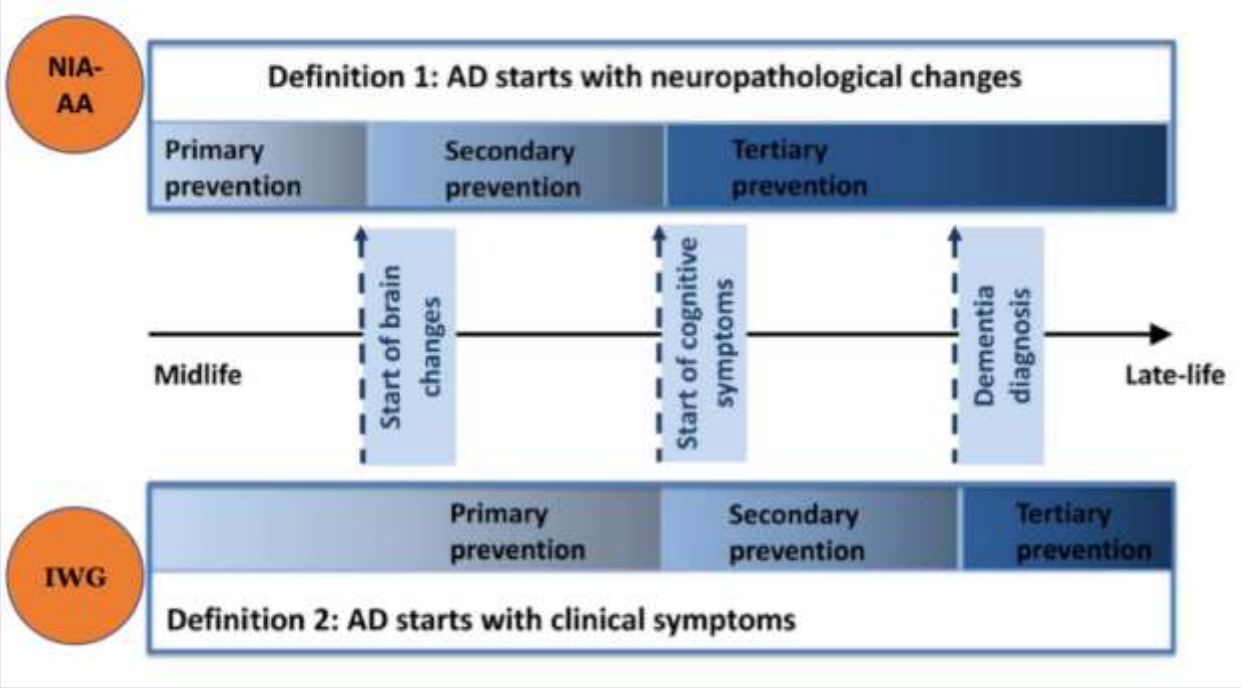
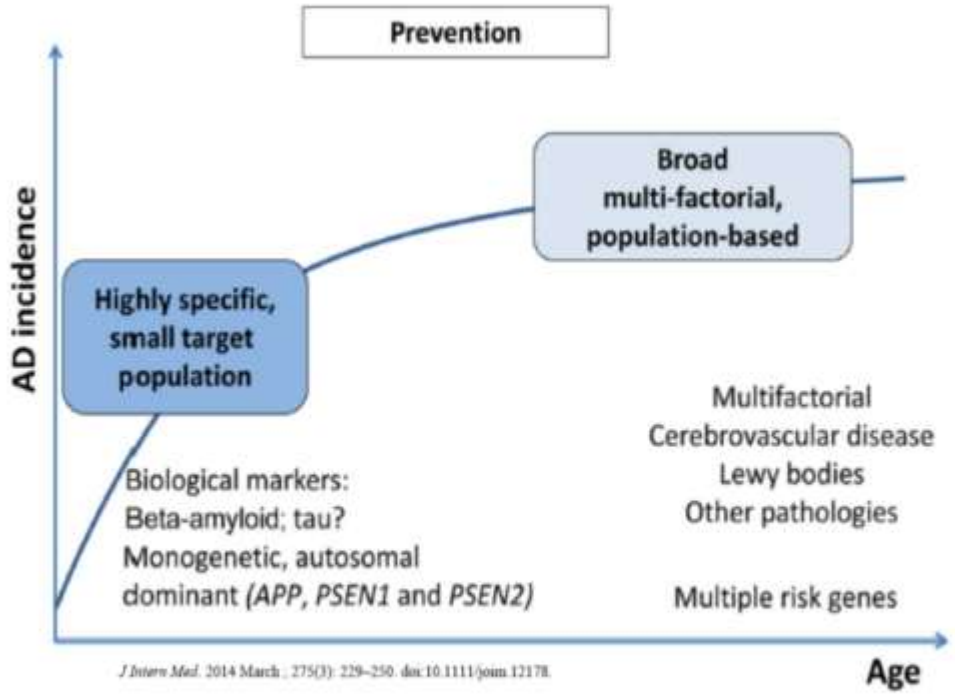
Prevención depende de la definición EA





J Intern Med. 2014 March ; 275(3): 229–250. doi:10.1111/joim.12178.

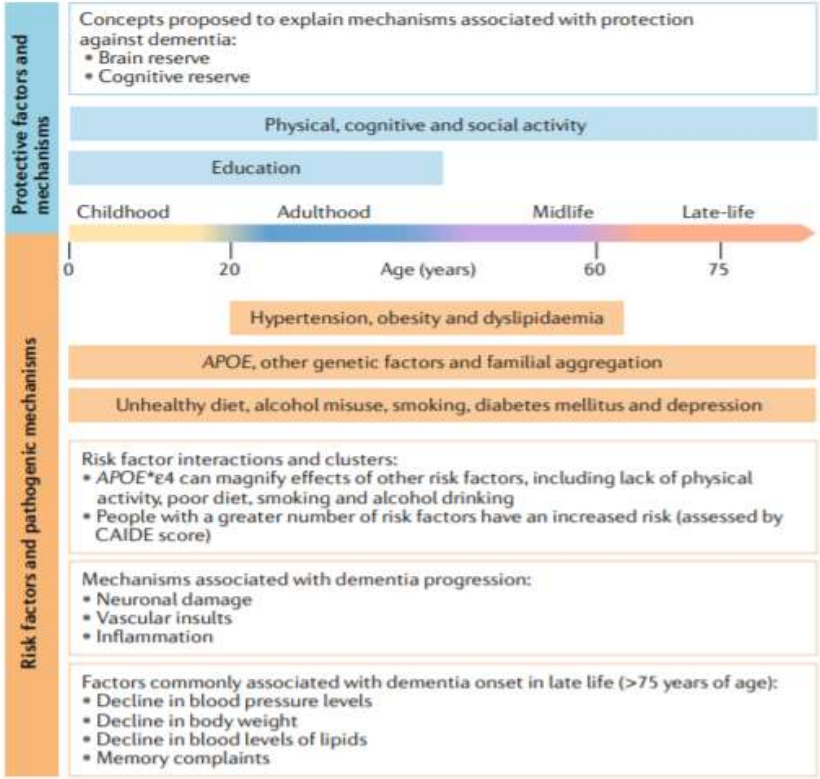
Advances in the prevention of Alzheimer's disease and dementia

Alina Solomon[1,2], Francesca Mangialasche[3], Edo Richard[4], Sandrine Andrieu[5], David A. Bennett[6], Monique Breteler[7], Laura Fratiglioni[3], Babak Hooshmand[3], Ara S. Khachaturian[8], Lon S. Schneider[9], Ingmar Skoog[10], and Miia Kivipelto[1,2,3]

¿En qué momento actuamos ?

Factores de Riesgo y Enfermedad de Alzheimer

Factores de Riesgo y Enfermedad de Alzheimer



Lifestyle interventions to prevent cognitive impairment, dementia and Alzheimer disease

Miia Kivipelto, Francesca Mangialasche and Tiia Ngandu

Factores de Riesgo

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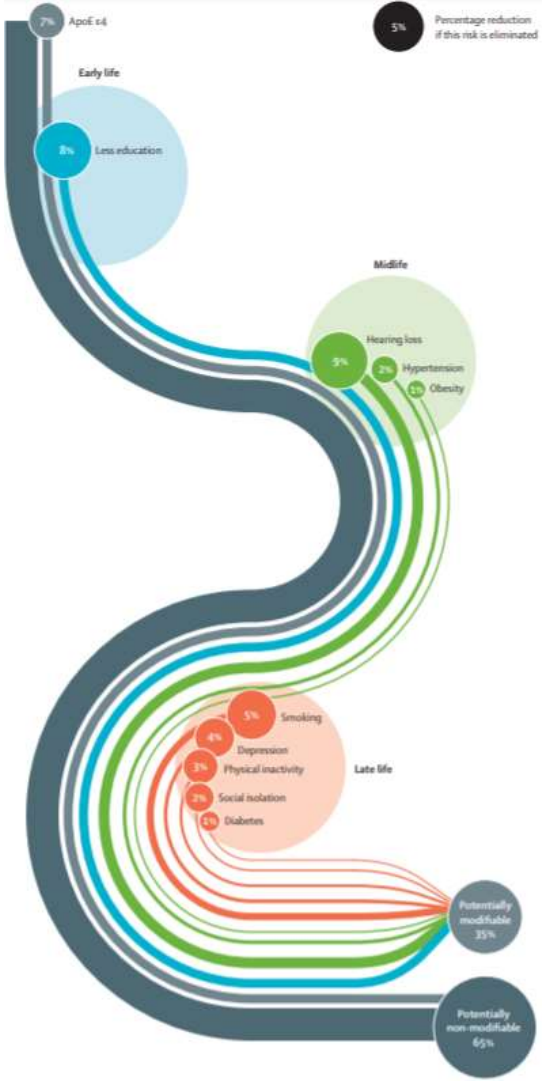
No modificables	Modificables
• Edad • Genero • Genética: APOE 4, Presenilina 1y 2 , APP	• HTA • DM2 • Obesidad • Fumador • Depresión • Inactvidad física • Baja educación



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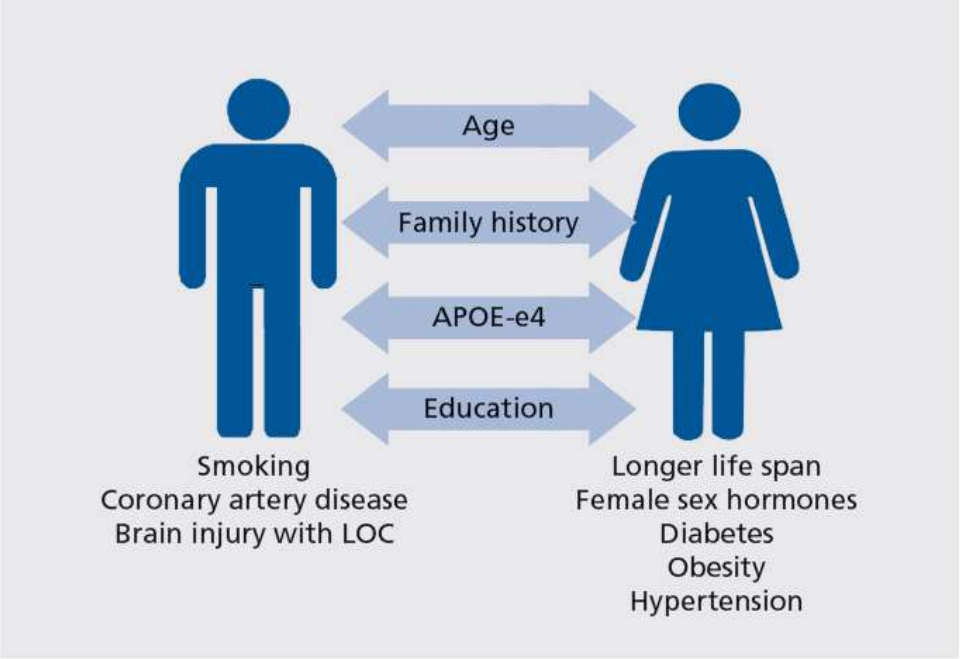
Dementia prevention, intervention, and care

Gill Livingston, Andrew Sommerlad, Vasiliki Orgeta, Sergi G Costafreda, Jonathan Huntley, David Ames, Clive Ballard, Sube Banerjee, Alistair Burns, Jiska Cohen-Mansfield, Claudia Cooper, Nick Fox, Laura N Gitlin, Robert Howard, Helen C Kales, Eric B Larson, Karen Ritchie, Kenneth Rockwood, Elizabeth L Sampson, Quincy Samus, Lon S Schneider, Geir Selbæk, Linda Teri, Naaheed Mukadam

Edad: Aumenta de forma exponencial a los 65 años incidencia y prevalencia se duplica cada 5 años

Genero no hay una clara relación

2:1 M:H



Factores de riesgo y EA

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- HTA
  - Systolic Hypertension in Europe (Syst-Eur) 1988-1997
    - Objetivo presión menor 150 mm Hg
    - Se redujo la incidencia de demencia en un 50%
    - 7.7 casos por 1000 pacientes-años a 3.8 casos
    - 1000 personas tratados HTA x 5 años 19 casos de demencia se pueden prevenir.
  - Factores de riesgo en edad media y protector en edad avanzada

Hiperlipidemia

- 2 estudios PROSPER y Heart Protection study negativos

DM

- 2-5 aumento del riesgo relacionado con amiloidogenesis
- ACCORD-MIND grupo de control intensivo tenia mayor volumen cerebral

Fibrilación auricular

- Aumenta riesgo por micro sangrados

Estilo de vida

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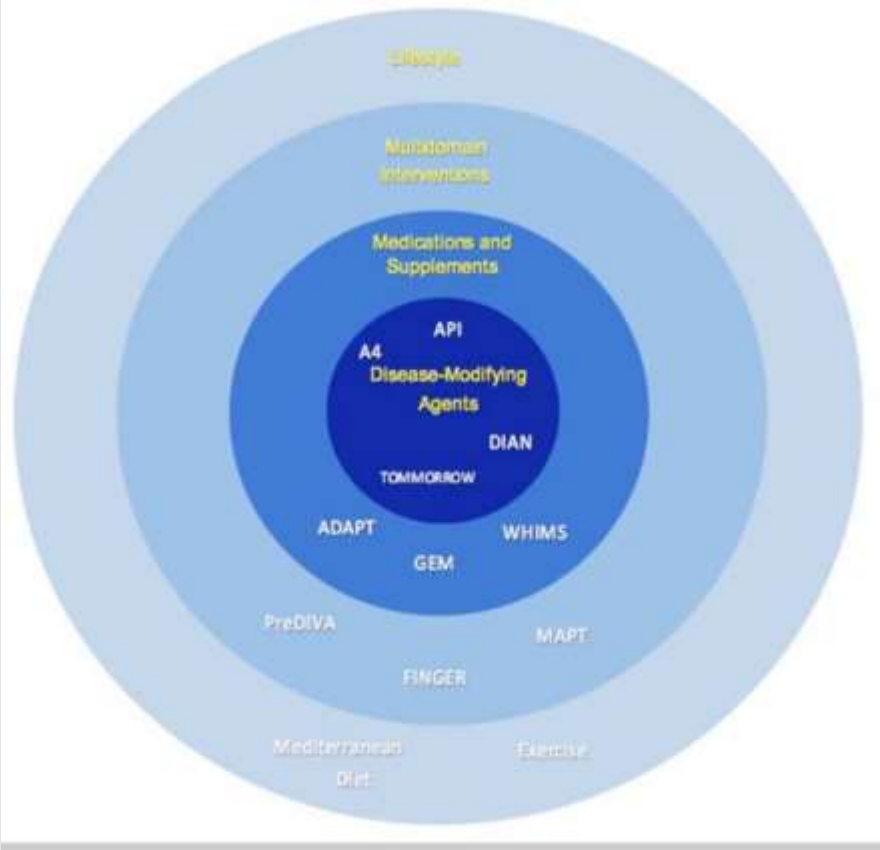
Actividad física	•Tipo de ejercio, cantidad e intesidad •Aumenta el volumen cerebral , el factor derivado de crecimiento neuronal, aumenta la eliminación del amioloide
Tabaquismo	• Estres oxidativo
Consumo de Alcohol	• Neurotoxicidad, Deficiencia nutricional, Neuroinflamación
Dieta	• Nutrientes únicos a Patrones Dietéticos (Dieta Mediterranea)
Depresión	• Hormonas de Estres y factores de crecimiento neuronal • Disminuye el volume del Hipocampo
Baja Educación	• Estudios menores secundaria • Reserva cognitiva
Aislamiento Social	

Estrategias de Prevención



Niveles de prevención

Study, country	Intervention; duration	Number of participants and inclusion criteria; recruitment strategy	Outcome measure	Primary outcome results	Secondary cognitive outcomes
Dietary interventions					
OPAL[10], United Kingdom	Capsules providing 200 mg EPA plus 500 mg DHA versus olive oil placebo; 24 months	867 participants aged 70–79 years; recruited from general practice records	California Verbal Learning Test	No significant differences between trial arms	No significant differences between groups in any outcome (two memory tests, three processing speed tests, two executive function tests, three prospective memory tests and a reaction time test)
Physical activity interventions					
LIFE[80], United States	Moderate-intensity intervention including walking, resistance training and flexibility exercises versus health education control; 24 months	1,635 patients aged 70–89 years who were sedentary and at risk of mobility disability; recruited using various recruitment strategies	• Primary outcome: major mobility disability • Secondary outcomes: Digit Symbol Coding task and the revised Hopkins Verbal Learning Test • Tertiary outcomes: global and executive cognitive function and incident MCI or dementia at 24 months	Intervention reduced incident major mobility disability	No significant differences between groups in any cognitive outcomes; in subgroup analyses, intervention had a beneficial effect among those aged ≥80 years and among those with a low level of physical activity at baseline
Cognitive stimulation interventions					
ACTIVE[81,82,101,102], United States	Memory training versus reasoning training versus speed of processing versus control; ten sessions of training during 5–6 weeks + four booster sessions for a subsample at months 11 and 35; 2-year outcome and follow-up at 5 years and 10 years	2,802 participants aged ≥65 years; recruited using a variety of sampling strategies	• Proximal outcomes: memory (episodic verbal memory tasks), reasoning (identification of patterns) and speed of processing • Primary outcome: daily function	Each intervention improved targeted cognitive ability compared with baseline, durable to 2 years; effects of interventions on the targeted cognitive ability were maintained through 5 years	Cognitive training did not affect rates of incident dementia after 5 years of follow-up; reasoning training and speed of processing training but not memory training improvement in trained cognitive ability was retained after 10 years
IHAMS[85], United States	Computerized visual speed of processing training; 10 hours on-site versus 10 hours + 4-hour booster on-site versus 10 hours at home versus attention training (control); five sessions of training for 5 weeks + two booster sessions for a subsample at month 11; 1-year outcome	681 participants aged ≥50 years who had made two or more visits to the clinic in the past year and had a PC and Internet connection at home; identified from general internal or family medicine clinics	• Primary outcome: UFOV test (measure of attention) • Secondary outcomes: TMT A and B, SDMT, Stroop, COWAT and DVT (measures of attention, processing speed and executive function)	All intervention groups had small to medium improvements in UFOV	All intervention groups had small to medium improvements in TMT A, TMT B, SDMT and Stroop Word but not on other Stroop tasks, COWAT or DVT

wasAZ

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Intervenciones Unimodales

Lifestyle interventions to prevent cognitive impairment, dementia and Alzheimer disease

Miia Kivipelto[1,2,3,4,*], Francesca Mangialasche[1] and Tiia Ngandy[1,2]

INTERVENCIONES MULTIMODALES

Intervenciones Multimodales

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European Dementia Prevention Initiative

- **FINGER** Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability
- **preDIVA** Prevention of Dementia by Intensive Vascular Care
- **MAPT** Multidomain Alzheimer Preventive Trial

Study, country	Intervention; duration	Number of participants; inclusion criteria; recruitment strategy	Outcome	Primary outcome results	Secondary cognitive outcome results	Other results on cognitive outcomes
FINGER[71], Finland	Multidomain intervention including dietary counselling, exercise and cognitive training, and vascular risk factor monitoring versus regular health advice (control); 2-year intervention, 7-year follow-up	1,260 participants aged 60–77 years with an elevated risk of dementia based on CAIDE score ≥6 points, and cognitive function at or slightly below average level; participants were from previous population-based national surveys; individual randomization	Cognition measured with NTB (a composite measure of 14 standard cognitive tasks)	Intervention had beneficial effect on NTB; between-group (intervention versus control) difference for NTB change was 0.022 ($P = 0.030$) per year	Beneficial effect of intervention on executive functioning ($P = 0.039$) and processing speed ($P = 0.029$) but not on memory ($P = 0.36$)	Beneficial effect of intervention on memory when including more complex memory tasks ($P = 0.036$) and higher risk of decline in cognition in the control group than in the intervention group
PreDIVA[72], the Netherlands	Multidomain cardiovascular intervention (advice) versus usual care (control); 6-year intervention	3,526 participants aged 70–78 years; recruited from general practices; cluster randomization of 116 general practices	Incidence of dementia	No effect of intervention on dementia: HR 0.92 ($P = 0.54$)	No effect of intervention on MMSE and VAT, no effect of intervention on AD and reduced risk of non-AD dementia in the intervention group ($P = 0.007$)	Reduced risk of dementia in participants with untreated hypertension at baseline who were adherent to the intervention ($P = 0.02$)
MAPT[73], France	Multidomain intervention including integrated cognitive training, physical activity and dietary advice and preventive consultations plus omega-3 PUFAs versus multidomain versus omega-3 PUFAs versus placebo capsule; 3-year intervention	1,680 participants aged ≥70 years with memory complaint, IADL limitation or slow gait speed; recruited using diverse strategies including patient databases and advertisements; individual randomization	Cognition measured with a composite Z score combining four cognitive tests	No significant difference between any of the three intervention groups compared with placebo: between-group difference was 0.093 ($P = 0.142$) for multidomain + PUFA, 0.079 ($P = 0.179$) for multidomain and 0.011 ($P = 0.812$) for PUFA compared with placebo	Multidomain + PUFA ($P = 0.036$) had less decline in ten MMSE orientation items than the placebo group; other group comparisons and other cognitive outcomes (FCSRT, DSST, Category Naming Test, COWAT, MMSE, TMT A, TMT B and CDR-SB) showed no effect	Less cognitive decline in those who received multidomain intervention (two groups pooled) than in those who did not (other two groups pooled) ($P = 0.015$); beneficial effect of multidomain plus PUFA versus placebo among those with CAIDE score ≥6; beneficial effect of multidomain + PUFA ($P < 0.001$) and multidomain ($P = 0.003$) groups versus placebo among those with amyloid positivity

Intervencion Multimodales en marcha…

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HATICE	Australian Mind Your Brain (MYB)	World Wide Fingers
US- POINTER Protect Brain Health Trought LifeStyle Intervation to Reduce Risk	MIND-China	SINGER (Singapore intervention study to prevent cognitive impairment and disability)

Intervenciones: Modificadores de la Enfermedad

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

Cuál es la población objetivo

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Población con factores genéticos

Historia familiar de EA

Personas en edad media con FRCV

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The CAIDE dementia risk score

Risk factor		Points
Age	<47 years	0
	47–53 years	3
	>53 years	4
Education	≥10 years	0
	7–9 years	2
	<7 years	3
Sex	Female	0
	Male	1
Blood pressure	≤140 mmHg	0
	>140 mmHg	2
BMI	≤30 kg/m²	0
	>30 kg/m²	2
Total cholesterol	≤6.5 mmol/l	0
	>6.5 mmol/l	2
Physical activity	Yes	0
	No	1

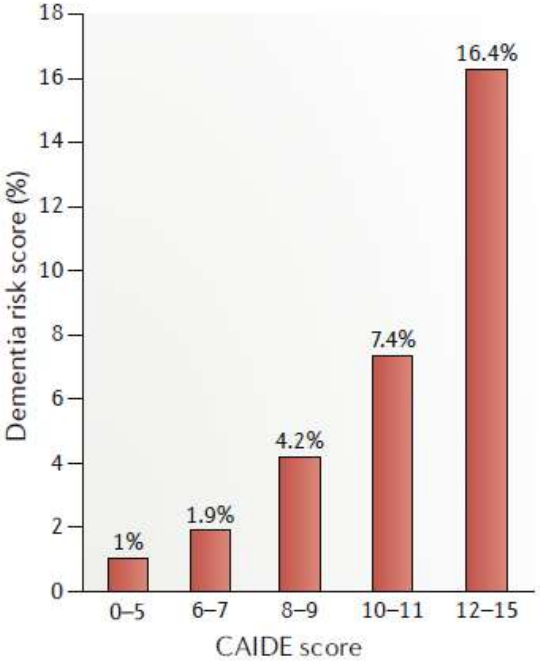


Fig. 2 | **CAIDE risk score.** The Cardiovascular Risk Factors, Aging and Dementia (CAIDE) risk score enables the prediction of the later risk of dementia on the basis of the risk factor profile present in midlife (age 40–65 years).

Se puede predecir la población en riesgo

CAIDE (Cardiovascular Risk Factors Aging and Dementia)

Dementia prevention, intervention, and care

Gill Livingston, Andrew Sommerlad, Vasiliki Orgeta, Sergi G Costafreda, Jonathan Huntley, David Ames, Clive Ballard, Sube Banerjee, Alistair Burns, Jiska Cohen-Mansfield, Claudia Cooper, Nick Fox, Laura N Gitlin, Robert Howard, Helen C Kales, Eric B Larson, Karen Ritchie, Kenneth Rockwood, Elizabeth L Sampson, Quincy Samus, Lon S Schneider, Geir Selbæk, Linda Teri, Naaheed Mukadam

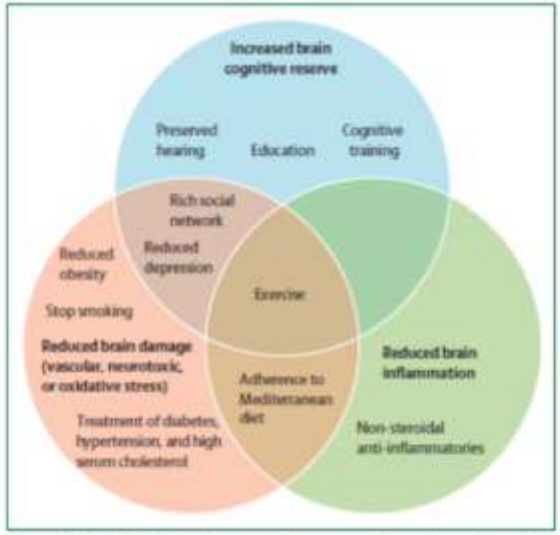
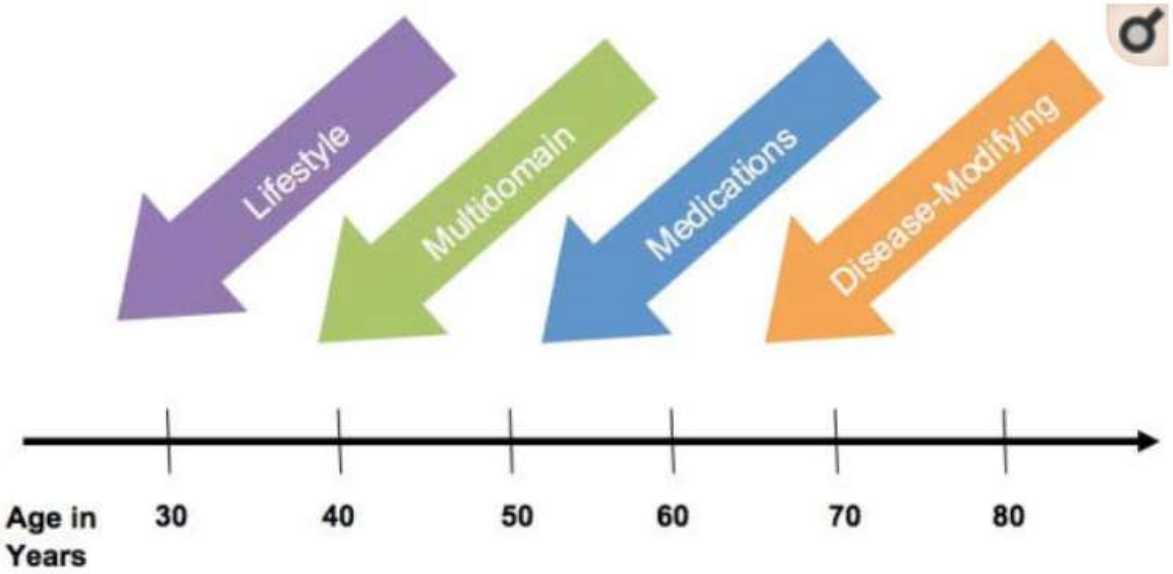


Figure 5: Potential brain mechanisms for preventive strategies in dementia

Momentos para prevenir



Primary and Secondary Prevention Trials in Alzheimer Disease: Looking Back, Moving Forward

David C. Hsu, M.D.[a,c,d,*] and Gad A. Marshall, M.D.[b,c,d]

Conclusiones

- EA es potenciablemente prevenible si se modifican factores de riesgo
- Las intervenciones multimodales
- Se deben de hacer de forma precoz y en población sana
- Posponener la EA en 5 años disminuye la prevalencia en 50% en 50 años
- Intervenciones de prevención deben ser realizadas en todo el continuum de la EA fases asintomáticas hasta avanzadas
- Estrategias de prevención mutidomnio son efectivas y sostenibles en países geograficamente, economicamente y culturalmente diferentes

- Neurodegeneración