ENFERMEDAD DE ALZHEIMER PRECLÍNICA Y PRODRÓMICA

José Miguel Santonja Llabata

Real Academia de Medicina de la Comunidad Valenciana

Valencia 5 de Marzo de 2019

DIAGNÓSTICO

Anamnesis

Exploración neuropsicológica

Pruebas complementarias: exclusión de otras patologías

Criterios diagnósticos: NINCS-ADRDA (1984): S 81% E 70%

ORIGINAL CONTRIBUTION

Mild Cognitive Impairment

Clinical Characterization and Outcome

Ronald C. Petersen, PhD, MD; Glenn E. Smith, PhD; Stephen C. Waring, DVM, PhD; Robert J. Ivnik, PhD; Eric G. Tangalos, MD; Emre Kokmen, MD

Background: Subjects with a mild cognitive impairment (MCI) have a memory impairment beyond that expected for age and education yet are not demented. These subjects are becoming the focus of many prediction studies and early intervention trials.

Objective: To characterize clinically subjects with MCI cross-sectionally and longitudinally.

Design: A prospective, longitudinal inception cohort.

Setting: General community clinic.

Participants: A sample of 76 consecutively evaluated subjects with MCI were compared with 234 healthy control subjects and 106 patients with mild Alzheimer disease (AD), all from a community setting as part of the Mayo Clinic Alzheimer's Disease Center/Alzheimer's Disease Patient Registry, Rochester, Minn.

Main Outcome Measures: The 3 groups of individuals were compared on demographic factors and measures of cognitive function including the Mini-Mental State Examination, Wechsler Adult Intelligence Scale–Revised, Wechsler Memory Scale–Revised, Dementia Rating Scale, Free and Cued Selective Reminding Test, and Auditory Verbal Learning Test. Clinical classifications of dementia and AD were determined according to the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition* and the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria, respectively.

Results: The primary distinction between control subjects and subjects with MCI was in the area of memory, while other cognitive functions were comparable. However, when the subjects with MCI were compared with the patients with very mild AD, memory performance was similar, but patients with AD were more impaired in other cognitive domains as well. Longitudinal performance demonstrated that the subjects with MCI declined at a rate greater than that of the controls but less rapidly than the patients with mild AD.

Conclusions: Patients who meet the criteria for MCI can be differentiated from healthy control subjects and those with very mild AD. They appear to constitute a clinical entity that can be characterized for treatment interventions.

Arch Neurol. 1999;56:303-308

Criterios NIA-AA DCL:

Cambios cognitivos respecto al nivel previo de la persona

Deterioro en uno o más dominios cognitivos (el síntoma más común y el más típico de los pacientes que progresan a demencia es la afectación de memoria episódica)

Preservación de las actividades de la vida diaria, mantienen buena funcionalidad e independencia en el día a día, aunque pueden tener problemas en aquellas tareas más complejas que antes realizaban sin problemas como pagar facturas, preparar una comida etc.

No demencia

Neuropathology and Applied Neurobiology 1990, **16**, 111–121

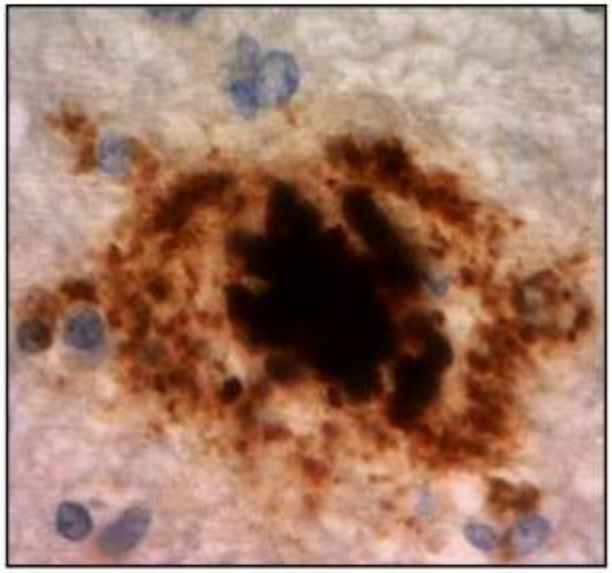
A quantitative histological study of early clinical and preclinical Alzheimer's disease

B. M. HUBBARD*, G. W. FENTON† AND J. M. ANDERSON*
**Departments of Pathology and †Psychiatry, Ninewells Hospital and Medical School, Dundee, DD1 9SY*

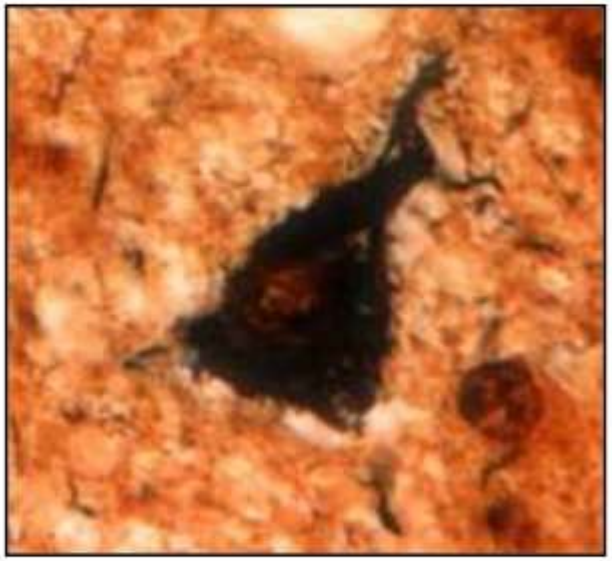
Hubbard B. M., Fenton G. W. & Anderson J. M. (1990) *Neuropathology and Applied Neurobiology* **16**, 111–121. **A quantitative histological study of early clinical and preclinical Alzheimer's disease.** Brains from 70 unselected general hospital necropsy cases aged 60–95 years were surveyed histologically for changes of Alzheimer's disease using Congo Red-Gallocyanin preparations. Counts were made of neurofibrillary tangles in two areas of the neocortex, the hippocampal formation and the substantia innominata. Neurons were counted

A further six cases (8.6%) showed excessive tangle accumulation which may represent preclinical Alzheimer's disease. Tangles were present in the temporal neocortex (Brodmann area 22), whereas they were absent in the remainder of the survey. Tangle density in the hippocampal formation (>50 tangles in a 10 μm section) was also above the baseline level of the majority of cases. However, neuron loss was not widespread in these cases and none had shown evidence of cognitive impairment.

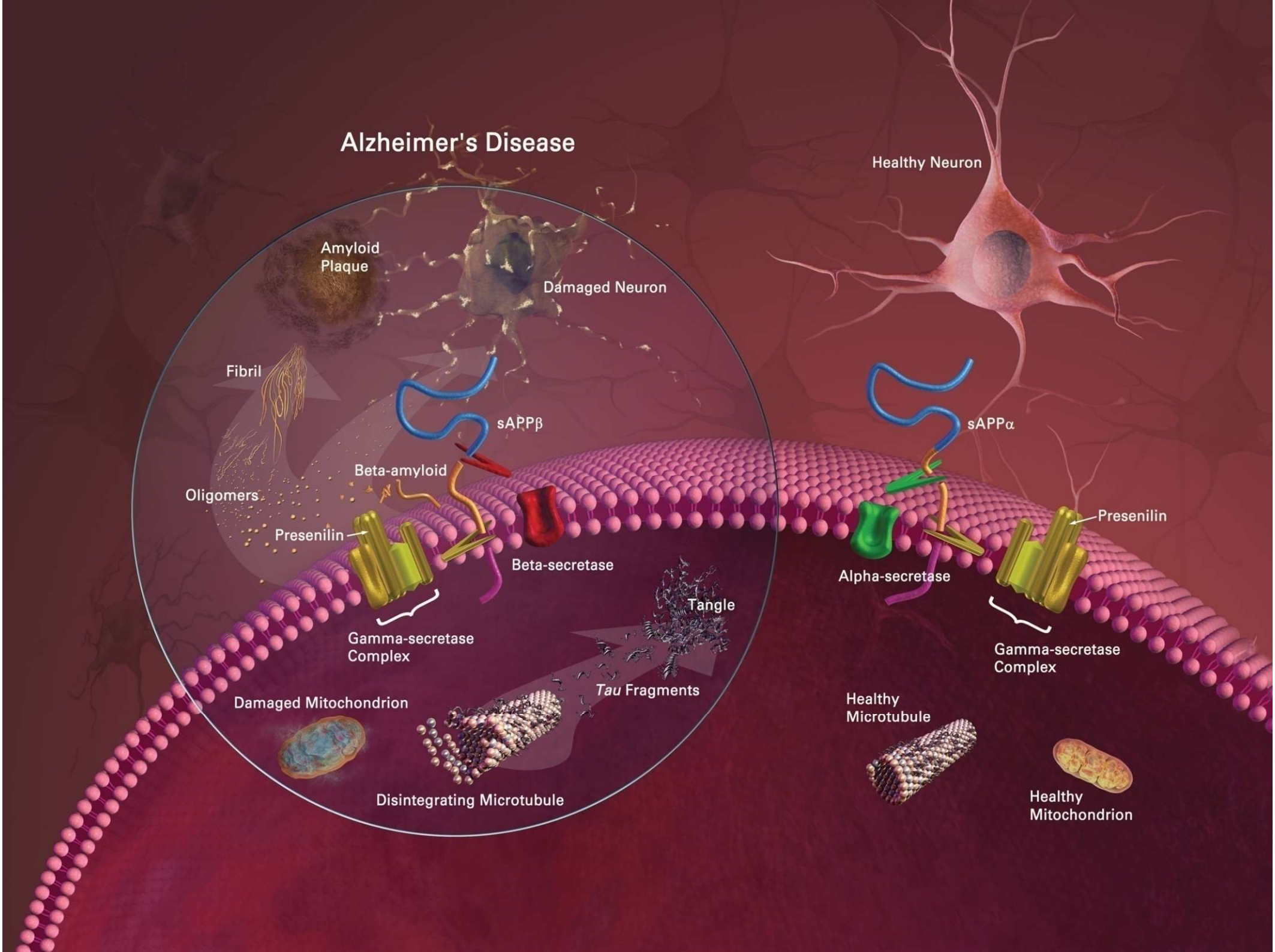
LESIONES HISTOPATOLÓGICAS



Placa Senil o neurítica
β Amiloide



Ovillo Neurofibrilar
Tau


Alzheimer's Disease
Amyloid Plaque
Damaged Neuron
Fibril
sAPPβ
Beta-amyloid
Oligomers
Presenilin
Beta-secretase
Gamma-secretase Complex
Tangle
Tau Fragments
Damaged Mitochondrion
Disintegrating Microtubule
Healthy Neuron
sAPPα
Presenilin
Alpha-secretase
Gamma-secretase Complex
Healthy Microtubule
Healthy Mitochondrion

BETA AMILOIDE 42 (Aβ42)

- Disminución de hasta el 50% de Aβ42 en LCR de pacientes con EA frente a sujetos sanos
- Descenso por depósito en las placas de amiloide
- No específico
- También disminuido en ECJ, ELA y otras enfermedades neurodegenerativas

PROTEÍNA TAU (Tτ)

Todos los estudios indican un claro aumento de la proteína tau en LCR de EA con respecto a lo sujetos sanos

Poco específico ya que aumenta también en el ictus agudo y de forma muy marcada en la enfermedad de Creutzfeldt-Jakob (ECJ)

Es normal en demencia vascular, frontotemporal o cuerpos de Lewy

Indica un daño neuronal axonal

TAU FOSFORILADA (Pτ)

- Más específica
- No aumenta en el ictus agudo
- Sólo aumenta ligeramente en la ECJ
- Aumenta de forma marcada en la EA
- Indica el estado de hiperfosforilación de la proteína tau

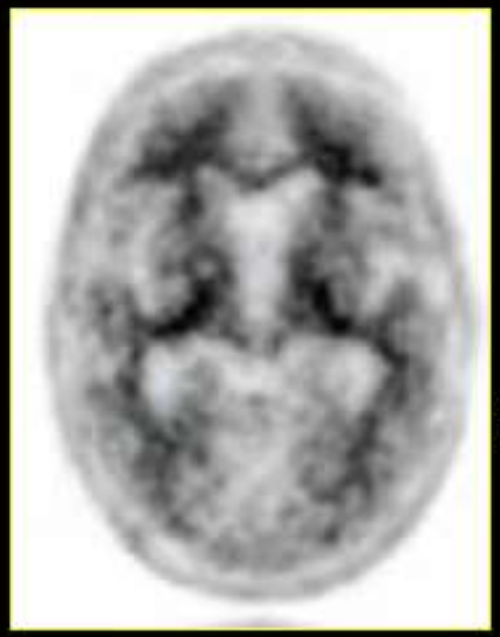
COMBINACIÓN

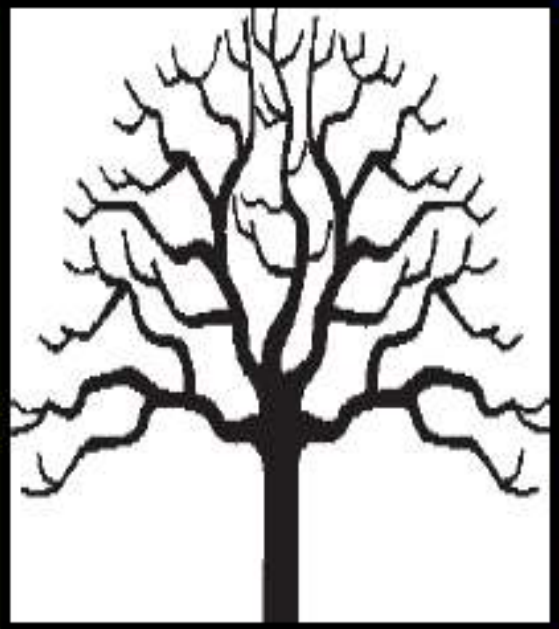
- El estudio combinado de los marcadores descritos anteriormente mejora la sensibilidad y especificidad para discriminar entre EA y otras demencias

- La combinación de Aumento de Tτ y disminución de Aβ42 consigue una sensibilidad del 89% y una especificidad del 90% aprox según diversos estudios

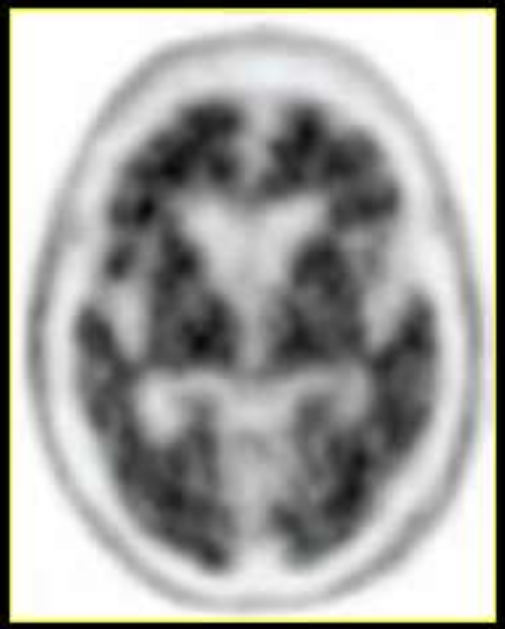
¿ Como se ve un de PET Amiloide.....?

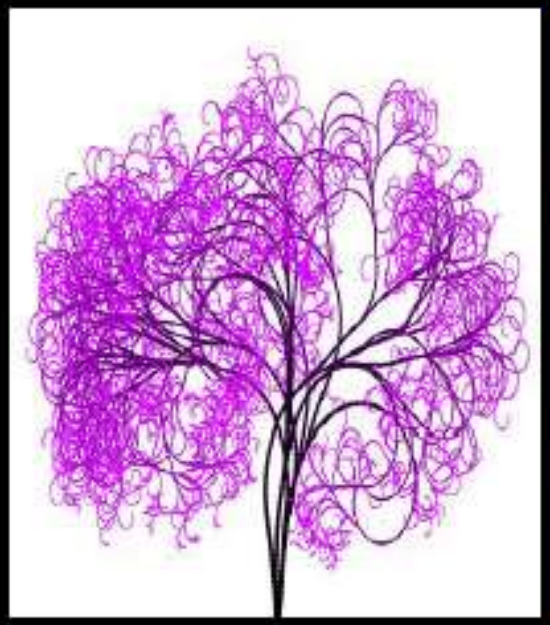
Negativo





Positivo



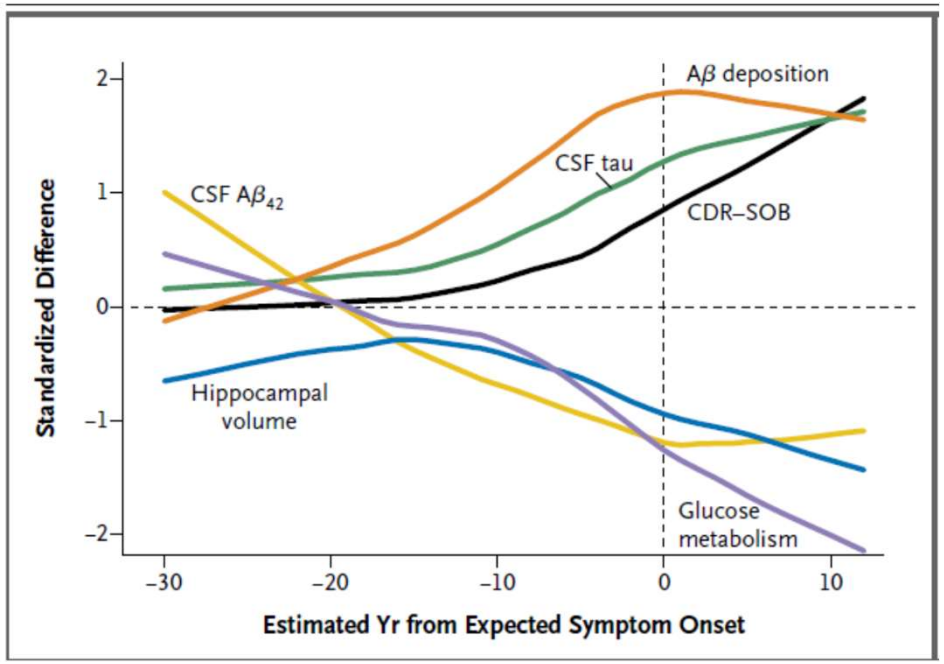


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 30, 2012 VOL. 367 NO. 9

Clinical and Biomarker Changes in Dominantly Inherited Alzheimer's Disease

Randall J. Bateman, M.D., Chengjie Xiong, Ph.D., Tammie L.S. Benzinger, M.D., Ph.D., Anne M. Fagan, Ph.D., Alison Goate, Ph.D., Nick C. Fox, M.D., Daniel S. Marcus, Ph.D., Nigel J. Cairns, Ph.D., Xianyun Xie, M.S., Tyler M. Blazey, B.S., David M. Holtzman, M.D., Anna Santacruz, B.S., Virginia Buckles, Ph.D., Angela Oliver, R.N., Krista Moulder, Ph.D., Paul S. Aisen, M.D., Bernardino Ghetti, M.D., William E. Klunk, M.D., Eric McDade, M.D., Ralph N. Martins, Ph.D., Colin L. Masters, M.D., Richard Mayeux, M.D., John M. Ringman, M.D., Martin N. Rossor, M.D., Peter R. Schofield, Ph.D., D.Sc., Reisa A. Sperling, M.D., Stephen Salloway, M.D., and John C. Morris, M.D., for the Dominantly Inherited Alzheimer Network



MODELO DE MARCADORES

AB42 en LCR 25 años antes

AB en PET 15 años antes

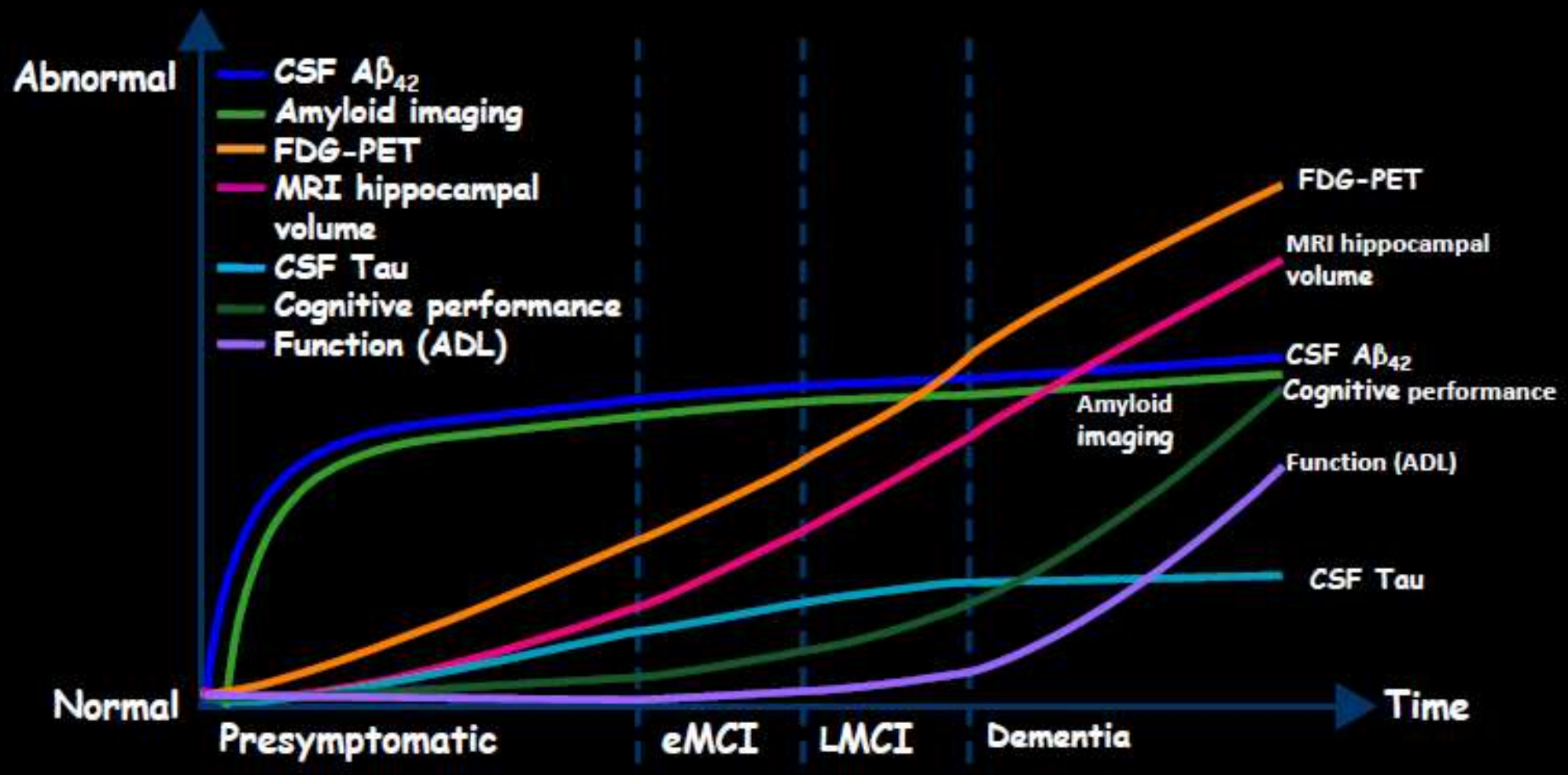
Tau en LCR y atrofia cerebral 15 años antes

Hipometabolismo en PET-FDG y alt memoria 10 años

Función global MMSE y CDR 5 años antes

Diag de demencia 3 años después

AD progression



Aisen PS, Petersen RC, Donohue MC, et al. *Alzheimers Dement.* 2010;6:239-246.

Criterios NIA-AA

DCL debido a enfermedad de Alzheimer con alto grado de certeza: si cumple los criterios centrales y además presenta un biomarcador positivo de depósito de amiloide y un biomarcador positivo de daño neuronal.

DCL debido a enfermedad de Alzheimer con grado intermedio de certeza: cumple los criterios centrales pero sólo tiene un biomarcador positivo (bien de amiloidosis o de neurodegeneración).

DCL probablemente no debido a EA: si cumple criterios centrales pero no tiene ningún biomarcador positivo.

Criterios IWG-2 para EA en cualquier estadío:

A) FENOTIPO CLÍNICO CLÁSICO

1. Presencia de déficit de memoria episódica (exclusivamente o asociada con otros déficits cognitivos o conductuales), en la que exista:

2. Cambio gradual y progresivo en la memoria episódica, reportado bien por el paciente o por un familiar fiable y con una duración mayor de 6 meses

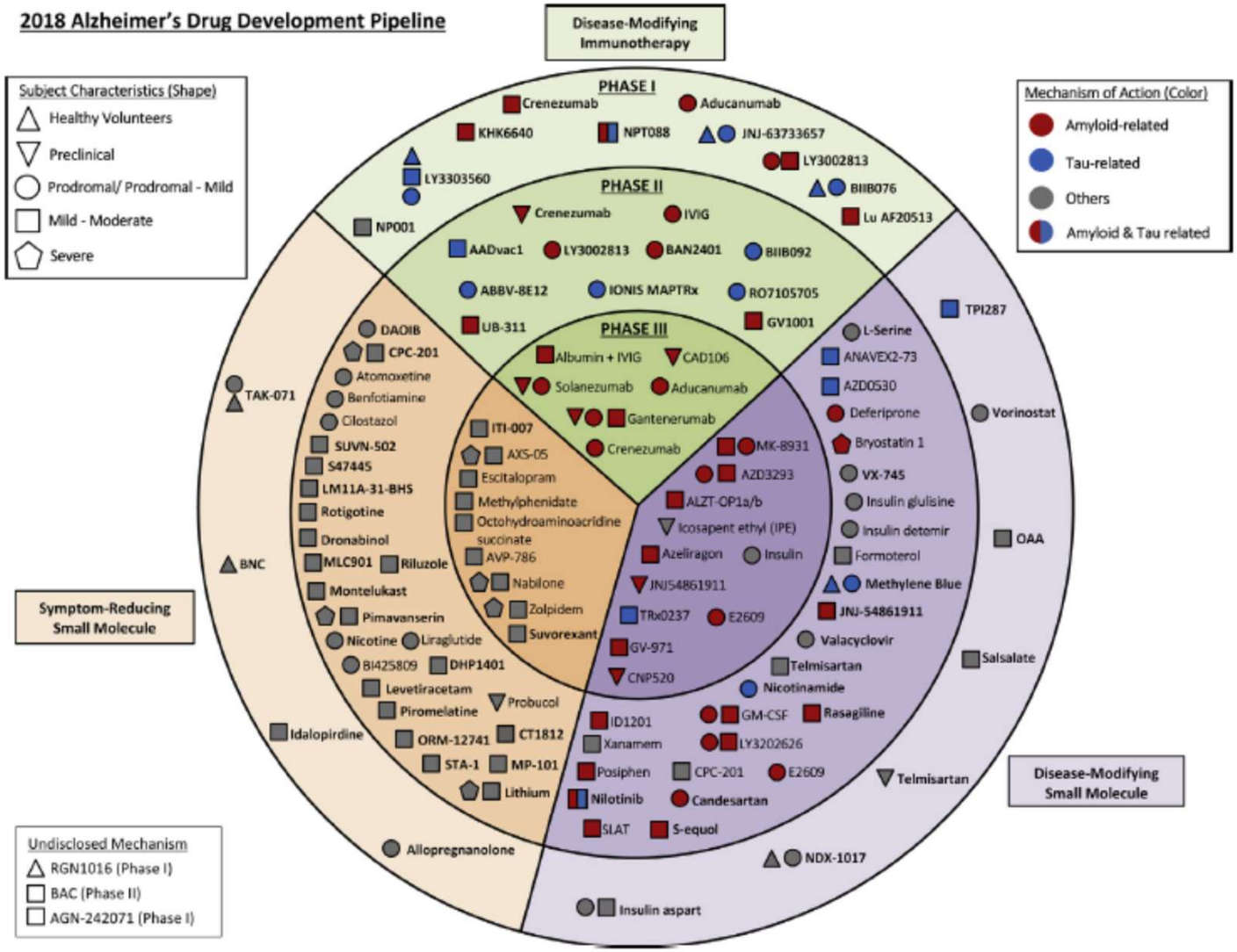
3. Evidencia objetiva de un síndrome amnésico hipocampal, basándose en tests establecidos

B) EVIDENCIA IN-VIVO DE PATOLOGÍA ALZHEIMER (uno de los siguientes)

1. A β 42 disminuida y T-Tau o P-Tau elevadas en LCR

2. Captación de trazador en PET amiloide

3. Mutación autosómica dominante conocida (PSEN1, PSEN2, APP)


2018 Alzheimer's Drug Development Pipeline
Disease-Modifying Immunotherapy
Subject Characteristics (Shape)
Healthy Volunteers
Preclinical
Prodromal/ Prodromal - Mild
Mild - Moderate
Severe
Mechanism of Action (Color)
Amyloid-related
Tau-related
Others
Amyloid & Tau related
PHASE I
Crenezumab
Aducanumab
KHK6640
NPT088
JNJ-63733657
LY3002813
LY3303560
BIIB076
Lu AF20513
NP001
PHASE II
Crenezumab
IVIG
AADvac1
LY3002813
BAN2401
BIIB092
ABBV-8E12
IONIS MAPTRx
RO7105705
UB-311
GV1001
PHASE III
Albumin + IVIG
CAD106
Solanezumab
Aducanumab
Gantenerumab
Crenezumab
TPI287
L-Serine
ANAVEX2-73
AZD0530
Deferiprone
Bryostatin 1
VX-745
Insulin glulisine
Insulin detemir
Formoterol
Methylene Blue
JNJ-54861911
Valacyclovir
Telmisartan
Nicotinamide
Rasagiline
Vorinostat
OAA
Salsalate
Telmisartan
NDX-1017
Insulin aspart
MK-8931
AZD3293
ALZT-OP1a/b
Icosapent ethyl (IPE)
Azeliragon
Insulin
JNJ54861911
TRx0237
E2609
GV-971
CNP520
GM-CSF
LY3202626
ID1201
Xanamem
Posiphen
CPC-201
E2609
Nilotinib
Candesartan
SLAT
S-equol
ITI-007
AXS-05
Escitalopram
Methylphenidate
Octohydroaminoacridine succinate
AVP-786
Nabilone
Zolpidem
Suvorexant
DAOIB
CPC-201
Atomoxetine
Benfotiamine
Cilostazol
SUVN-502
S47445
LM11A-31-BHS
Rotigotine
Dronabinol
MLC901
Riluzole
Montelukast
Pimavanserin
Nicotine
Liraglutide
BI425809
DHP1401
Levetiracetam
Piromelatine
Probucol
ORM-12741
CT1812
STA-1
MP-101
Lithium
TAK-071
BNC
Idalopirdine
Allopregnanolone
Symptom-Reducing Small Molecule
Disease-Modifying Small Molecule
Undisclosed Mechanism
RGN1016 (Phase I)
BAC (Phase II)
AGN-242071 (Phase I)

Ostrowitzki *et al. Alzheimer's Research & Therapy* (2017) 9:95
DOI 10.1186/s13195-017-0318-y

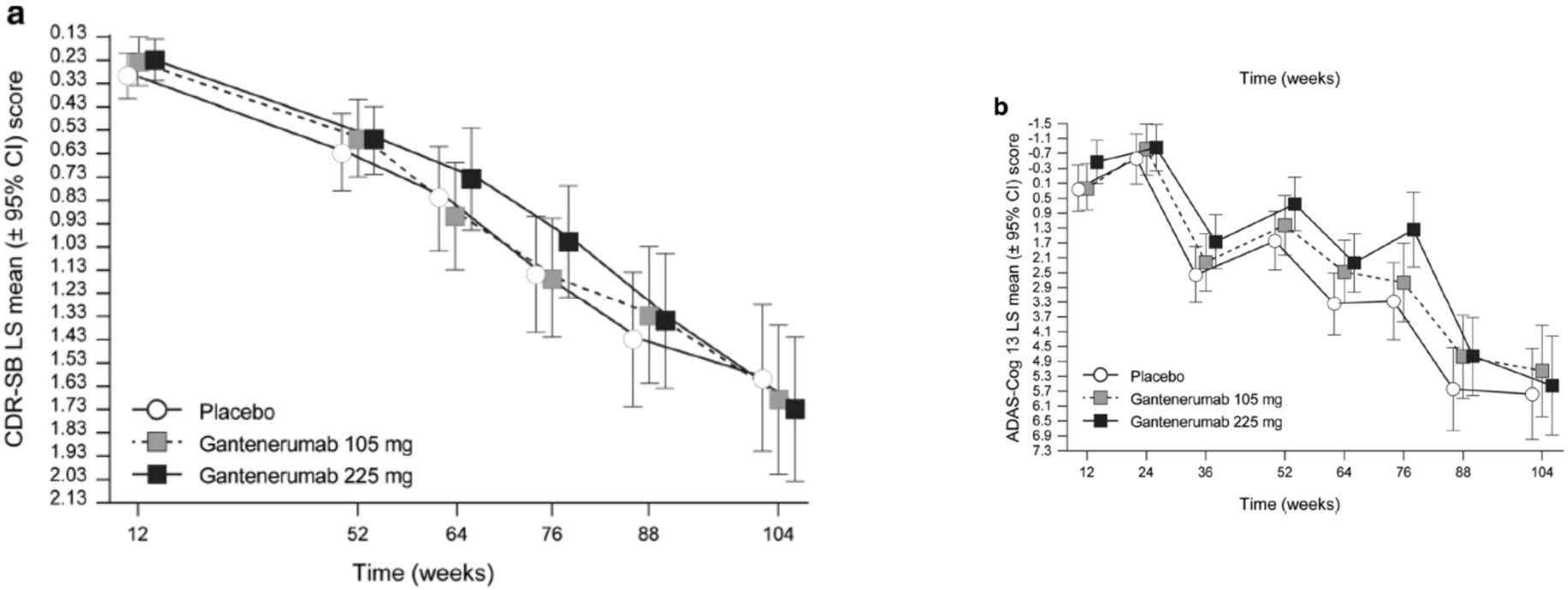
Alzheimer's
Research & Therapy

RESEARCH

Open Access

A phase III randomized trial of gantenerumab in prodromal Alzheimer's disease

Susanne Ostrowitzki[1], Robert A. Lasser[2], Ernest Dorflinger[3], Philip Scheltens[4], Frederik Barkhof[4,5,6], Tania Nikolcheva[6], Elizabeth Ashford[7], Sylvie Retout[8], Carsten Hofmann[8], Paul Delmar[9], Gregory Klein[6], Mirjana Andjelkovic[8], Bruno Dubois[10], Mercè Boada[11], Kaj Blennow[12], Luca Santarelli[13], Paulo Fontoura[9*] and for the SCarlet RoAD Investigators



MPR

Steve Duffy, Digital Content Editor
May 23, 2018

Studies Halted for Alzheimer's Candidate Atabecestat Due to Safety Concerns

Update on Phase 3 Clinical Trials of Lanabecestat for Alzheimer's Disease

Independent data monitoring committee advises lanabecestat is unlikely to meet primary endpoints, leading to decision to discontinue these trials

ELSEVIER

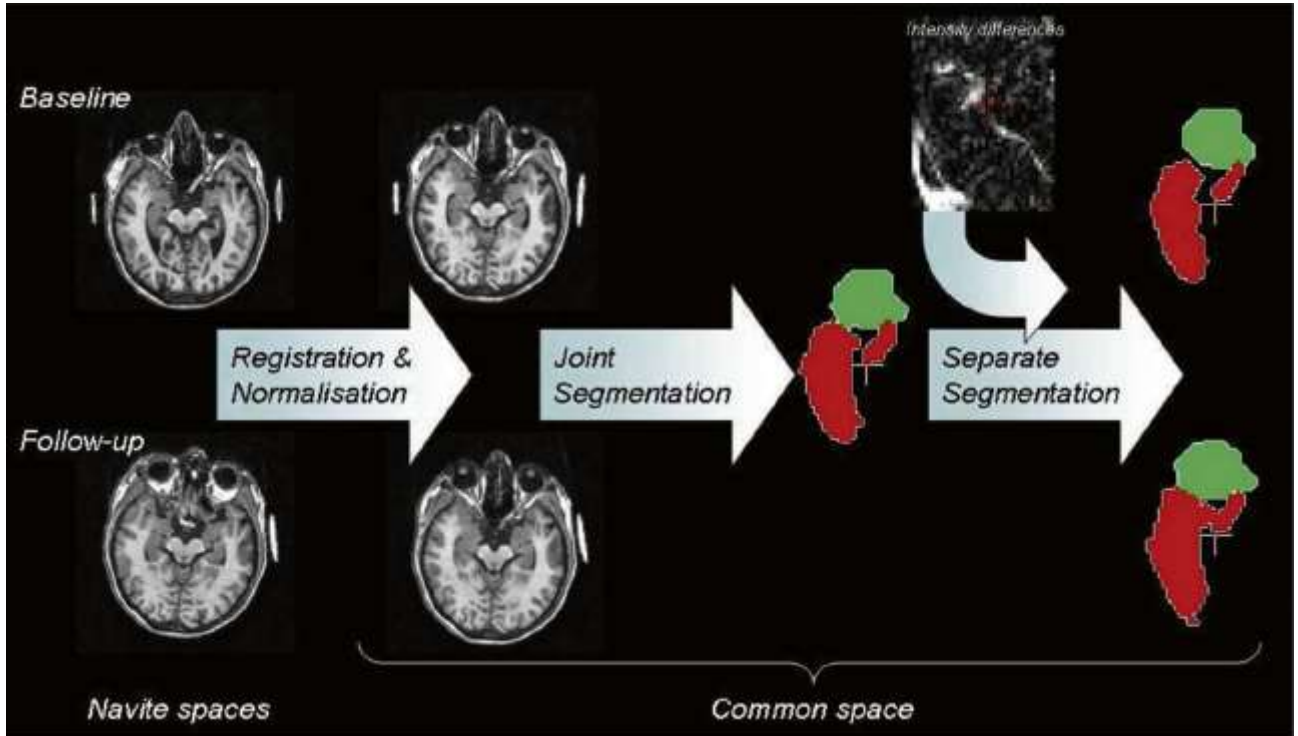
CrossMark

Alzheimer's & Dementia 11 (2015) 1041-1049

Alzheimer's & Dementia

Donepezil decreases annual rate of hippocampal atrophy in suspected prodromal Alzheimer's disease

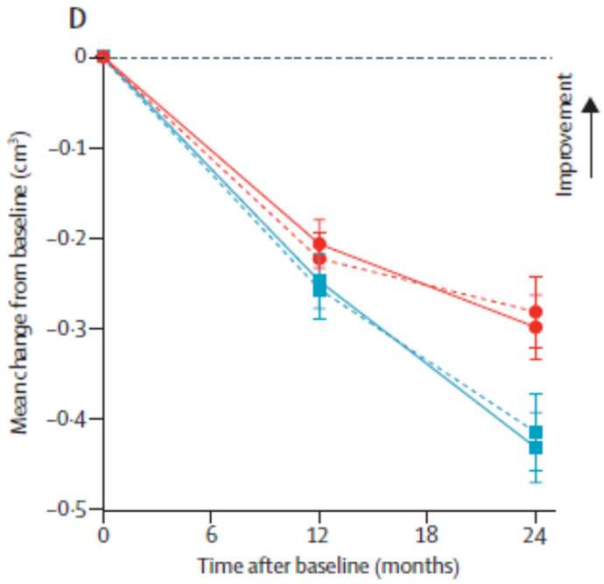
Bruno Dubois[a,b,c,*], Marie Chupin[b], Harald Hampel[a,b,c], Simone Lista[a,b], Enrica Cavedo[a,b], Bernard Croisile[d], Guy Louis Tisserand[d], Jacques Touchon[e], Alain Bonafe[e], Pierre Jean Ousset[f], Amir Ait Ameur[g], Olivier Rouaud[h], Fréderic Ricolfi[h], Alain Vighetto[d], Florence Pasquier[i], Christine Delmaire[j], Mathieu Ceccaldi[k], Nadine Girard[k], Carole Dufouil[l], Stéphane Lehericy[b,c,m], Isabelle Tonelli[n], Françoise Duveau[n], Olivier Colliot[b], Line Garnero[b], Marie Sarazin[a,b,c], Didier Dormont[b,c,o], and the "Hippocampus Study Group"

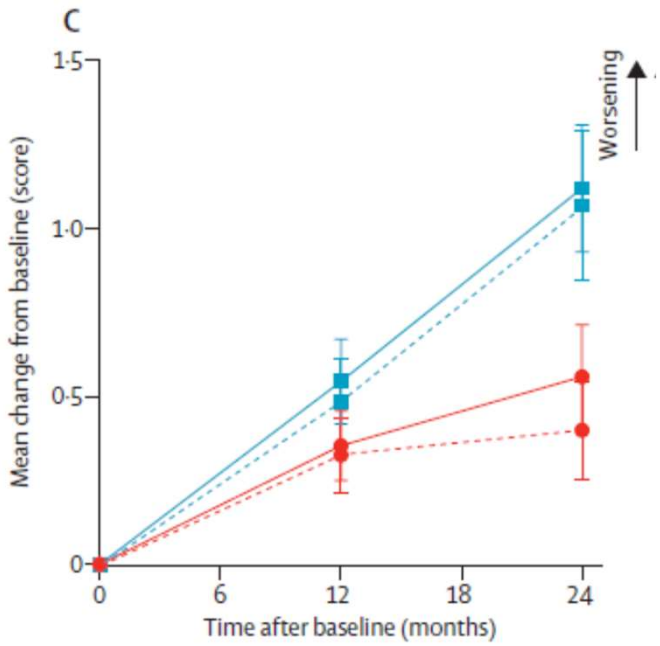


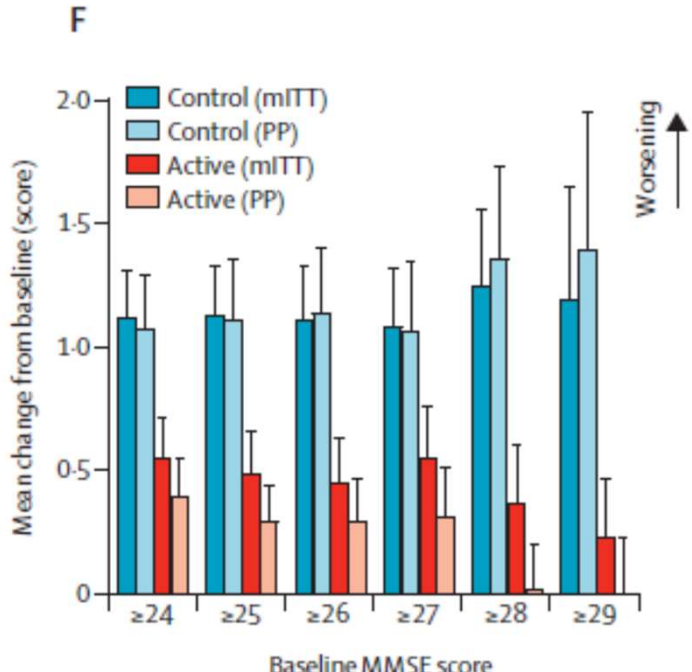
24-month intervention with a specific multinutrient in people with prodromal Alzheimer's disease (LipiDiDiet): a randomised, double-blind, controlled trial

*Hilkka Soininen, Alina Solomon, Pieter Jelle Visser, Suzanne B Hendrix, Kaj Blennow, Miia Kivipelto, Tobias Hartmann, on behalf of the LipiDiDiet clinical study group**

Lancet Neurol 2017; 16: 965–75







EA PRODRÓMICA MANEJO

Participar en ensayos clínicos

Anticolinesterásicos

Souvenaid

Evitar nihilismo terapéutico

Criterios IWG-2 para estadíos preclínicos

CRITERIOS IWG-2 PARA PACIENTES ASINTOMÁTICOS EN RIESGO DE EA (A+B)

A) Ausencia de fenotipo clínico específico (los dos)

-Ausencia de síndrome amnésico hipocampal

-Ausencia de cualquier fenotípico atípico EA

B) evidencia In-vivo de patología Alzheimer (uno de los dos)

-A β 42 disminuida y T-Tau o P-Tau elevadas en LCR

-Captación de trazador en PET amiloide

CRITERIOS IWG-2 PARA ENFERMEDAD DE ALZHEIMER PRESINTOMÁTICA (A+B)

A) Ausencia de fenotipo clínico específico (los dos)

-Ausencia de síndrome amnésico hipocampal

-Ausencia de cualquier fenotípico atípìco EA

B) Mutación autosómica dominante en PSEN1, PSEN2, APP o otros genes, incluído síndrome de Down

NUEVOS CRITERIOS

Criterios NIA-AA EA preclínica

Estadío 1: Amiloidosis asintomática. Los pacientes presentan un biomarcador de amiloidosis positivo sin evidencia de neurodegeneración, ni de déficits cognitivos sutiles

Estadío 2: Amiloidosis +evidencia de disfunción sináptica o neurodegeneración

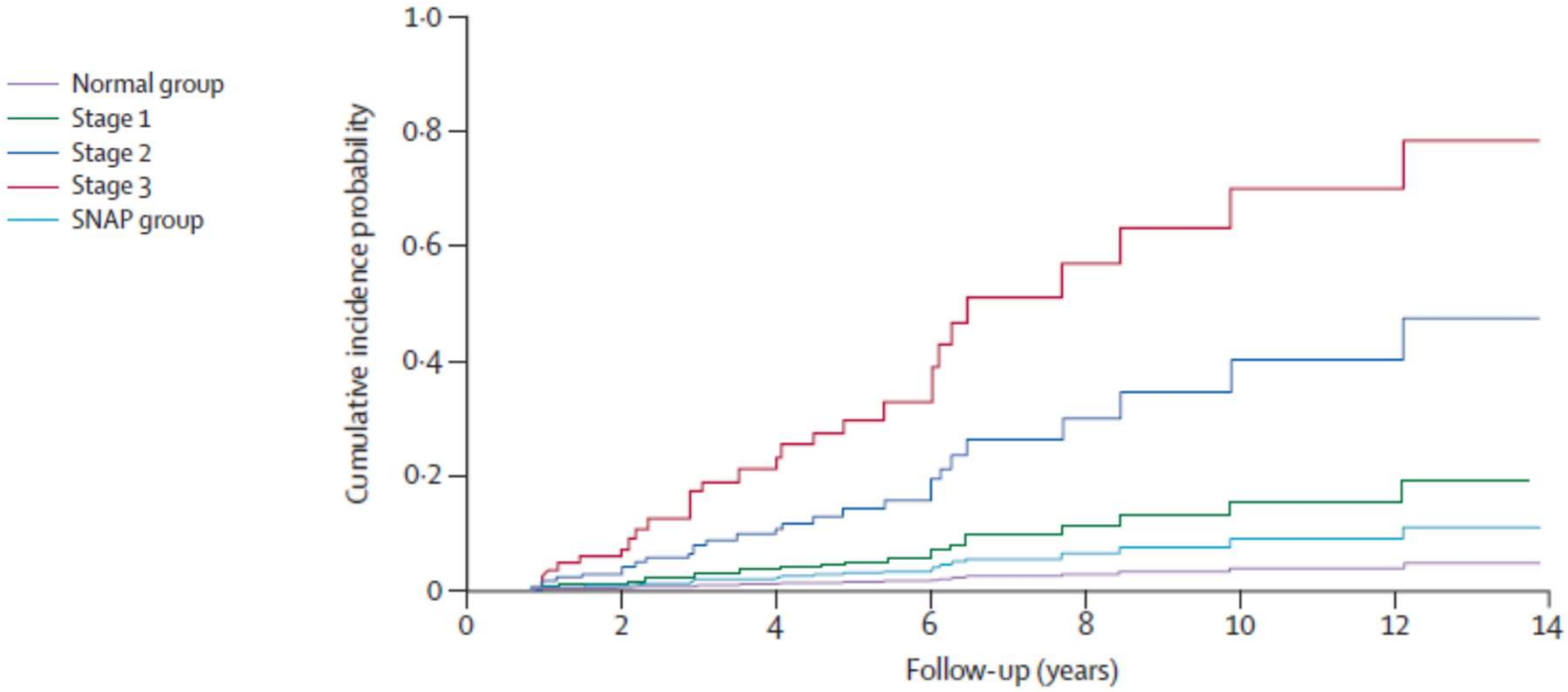
Estadío 3: Amiloidosis+ neurodegeneración + deterioro cognitivo sutil

Preclinical Alzheimer's disease and its outcome: a longitudinal cohort study

Stephanie J B Vos, Chengjie Xiong, Pieter Jelle Visser, Mateusz S Jasielec, Jason Hassenstab, Elizabeth A Grant, Nigel J Cairns, John C Morris, David M Holtzman, Anne M Fagan

Lancet Neurol 2013; 12:957–65

Findings Of 311 participants, 129 (41%) were classed as normal, 47 (15%) as stage 1, 36 (12%) as stage 2, 13 (4%) as stage 3, 72 (23%) as SNAP, and 14 (5%) remained unclassified. The 5-year progression rate to CDR at least 0·5, symptomatic Alzheimer's disease was 2% for participants classed as normal, 11% for stage 1, 26% for stage 2, 56% for stage 3, and 5% for SNAP. Compared with individuals classed as normal, participants with preclinical Alzheimer's disease had an increased risk of death after adjusting for covariates (hazard ratio 6·2, 95% CI 1·1–35·0; p=0·040).



ANNALS of Clinical and Translational Neurology
Open Access
AMERICAN NEUROLOGICAL ASSOCIATION

RESEARCH ARTICLE

Pre-amyloid stage of Alzheimer's disease in cognitively normal individuals

Betty M. Tijms[1], Lisa Vermunt[1], Marissa D. Zwan[1], Argonde C. van Harten[1], Wiesje M. van der Flier[1,2], Charlotte E. Teunissen[2], Philip Scheltens[1] & Pieter Jelle Visser[1,3] for ADNI*

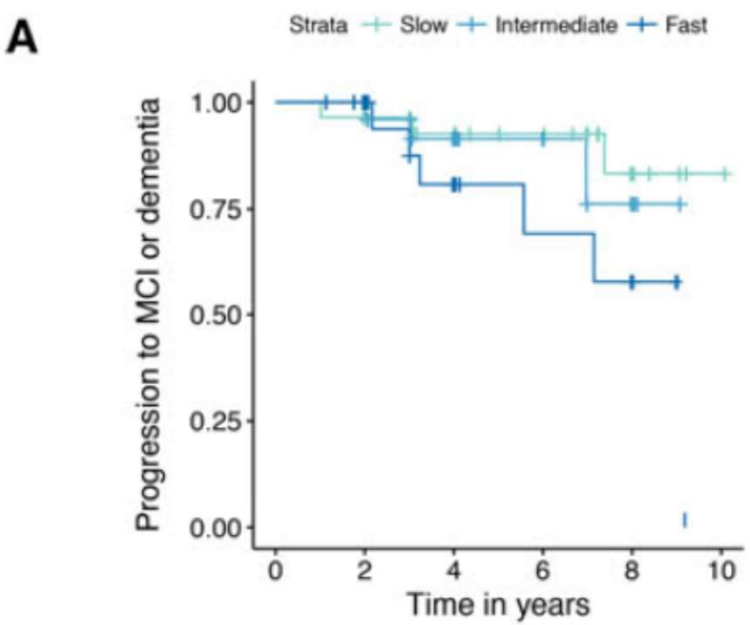
[1]Alzheimer Center, Department of Neurology, VU University Medical Center, Amsterdam Neuroscience, Amsterdam, The Netherlands
[2]Department of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam Neuroscience, Amsterdam, The Netherlands
[3]Department of Psychiatry & Neuropsychology, School for Mental Health and Neuroscience, Maastricht University, Maastricht, The Netherlands

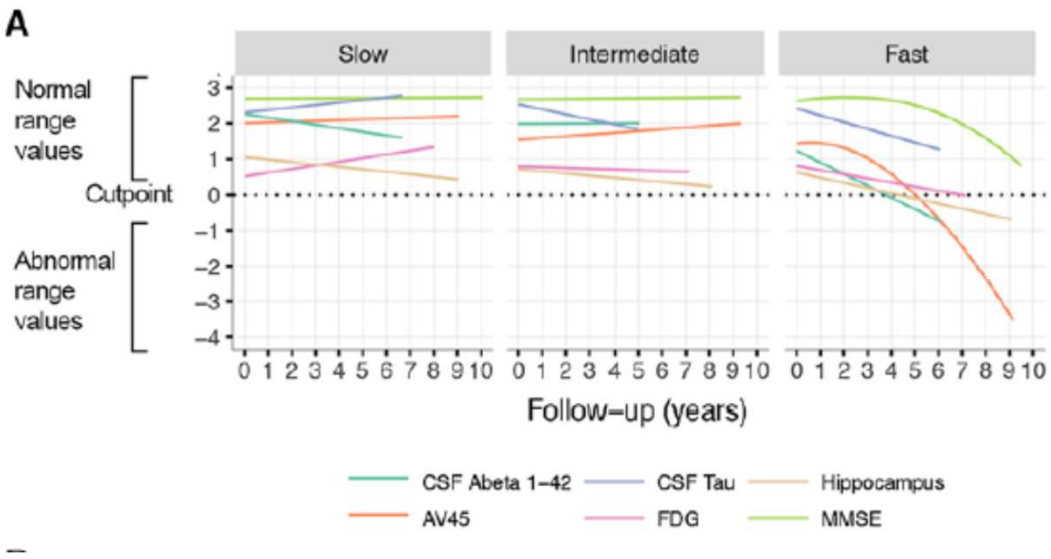
Table 2. Baseline and annual change effects for amyloid precursor protein (APP) processing markers measured in cerebrospinal fluid (CSF) as predictor and aβ 1–42 CSF levels as outcome variable.

Predictor variable	Baseline aβ 1–42 β (SE)	Annual change aβ 1–42 β (SE)
Aβ_{1-40}	0.19 (0.11)	–0.11 (0.03[b]
Aβ_{1-38}	0.17 (0.11)	–0.11 (0.03)[b]
BACE1	–0.04 (0.12)	–0.06 (0.03)[a]
sAPPβ	–0.03 (0.12)	–0.05 (0.03)

Pre-Amyloid Stage of Alzheimer's Disease

Pre-Amyloid Stage of Alzheimer's Disease





EVOLUCIÓN A EA

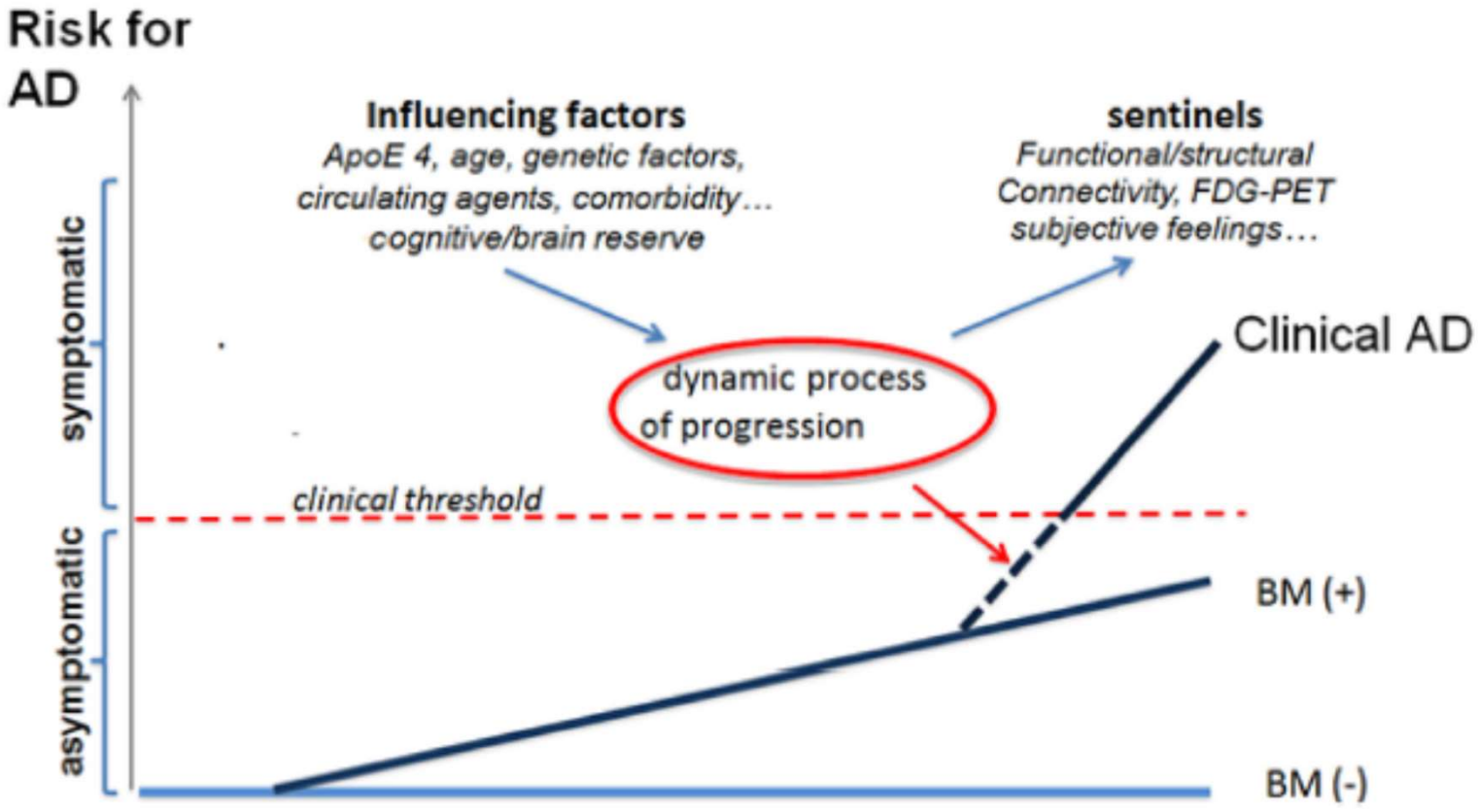


Fig. 2. The risk of clinical AD–hypothetical model. Abbreviation: AD, Alzheimer's disease; BM, pathophysiological biomarkers.

REVIEW ARTICLE

Int J Geriatr Psychiatry 2014

International Journal of Geriatric Psychiatry

Target risk factors for dementia prevention: a systematic review and Delphi consensus study on the evidence from observational studies

Kay Deckers[1], Martin P. J. van Boxtel[1], Olga J. G. Schiepers[1], Marjolein de Vugt[1], Juan Luis Muñoz Sánchez[2], Kaarin J. Anstey[3], Carol Brayne[4], Jean-Francois Dartigues[5], Knut Engedal[6], Miia Kivipelto[7], Karen Ritchie[8], John M Starr[9], Kristine Yaffe[10], Kate Irving[11,†], Frans R. J. Verhey[1] and Sebastian Köhler[1]

Table 3 Second Delphi round: ranking of dementia risk and protective factors

Risk/protective factors	Frequency[a]	Score[b]	Final rank[c]
Depression	8	120	1
Diabetes	8	115	2
High cognitive activity	8	113	3
(High) physical activity	8	111	4
Hypertension	8	108	5
Mediterranean diet	8	64	6
Obesity (midlife)	8	50	7
Smoking	8	46	8
Low/moderate alcohol	8	37	9
High cholesterol	7	31	10
Coronary heart disease	1	5	11

[a]Frequency = number of times risk factor is mentioned by the eight Delphi experts.
[b]Score = total number of points assigned by the eight Delphi experts.
[c]Final rank = final rank based on score.

A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: results of the Cognitive Function and Ageing Study I and II

Lancet 2013; 382: 1405–12

Fiona E Matthews, Antony Arthur, Linda E Barnes, John Bond, Carol Jagger, Louise Robinson, Carol Brayne, on behalf of the Medical Research Council Cognitive Function and Ageing Collaboration

Twenty-year changes in dementia occurrence suggest decreasing incidence in central Stockholm, Sweden

Neurology® 2013;80:1888-1894

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ABSTRACT

Objective: To explore whether prevalence, survival, and incidence of dementia have changed from 1987-1994 to 2001-2008 in Stockholm, Sweden.

Methods: This study is based on 2 cross-sectional surveys of people aged 75 years or over conducted in central Stockholm: the Kungsholmen Project (KP) (1987-1989, n = 1,700) and the Swedish National study on Aging and Care in Kungsholmen (SNAC-K) (2001-2004, n = 1,575). In both surveys we diagnosed dementia according to *DSM-III-R* criteria, following the identical diagnostic procedure. Death certificates were used to determine survival status of KP partici-

ORIGINAL CONTRIBUTION

Association of Lifetime Cognitive Engagement and Low β-Amyloid Deposition

Arch Neurol. 2012;69(5):623-629.

Susan M. Landau, PhD; Shawn M. Marks, BS; Elizabeth C. Mormino, PhD; Gil D. Rabinovici, MD; Hwamee Oh, PhD; James P. O'Neil, PhD; Robert S. Wilson, PhD; William J. Jagust, MD

Cognitive reserve in ageing and Alzheimer's disease

Yaakov Stern

Lancet Neurol 2012; 11: 1006–12

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The concept of cognitive reserve provides an explanation for differences between individuals in susceptibility to age-related brain changes or pathology related to Alzheimer's disease, whereby some people can tolerate more of these changes than others and maintain function. Epidemiological studies suggest that lifelong experiences, including educational and occupational attainment, and leisure activities in later life, can increase this reserve. For example, the risk of developing Alzheimer's disease is reduced in individuals with higher educational or occupational attainment. Reserve can conveniently be divided into two types: brain reserve, which refers to differences in the brain structure that may increase tolerance to pathology, and cognitive reserve, which refers to differences between individuals in how tasks are performed that might enable some people to be more resilient to brain changes than others. Greater understanding of the concept of cognitive reserve could lead to interventions to slow cognitive ageing or reduce the risk of dementia.

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Physical Activity, Mediterranean Diet and Biomarkers-Assessed Risk of Alzheimer's: A Multi-Modality Brain Imaging Study

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J Prev Alzheimers Dis. 2014 June ; 1(1): 23–32.

Mediterranean Diet and Magnetic Resonance Imaging-Assessed Brain Atrophy in Cognitively Normal Individuals at Risk for Alzheimer's Disease

L. Mosconi, **J. Murray**, **W.H. Tsui**, **Y. Li**, **M. Davies**, **S. Williams**, **E. Pirraglia**, **N. Spector**, **R.S. Osorio**, **L. Glodzik**, **P. McHugh**, and **M.J. de Leon**
New York University School of Medicine, New York, NY 10016

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; 385: 2255–63

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

DIETA

EJERCICIO FÍSICO

ACTIVIDAD COGNITIVA

CONTROL DE FACTORES DE RIESGO VASCULAR

DOS AÑOS

FRENTE A CONSEJOS DE SALUD GENERAL

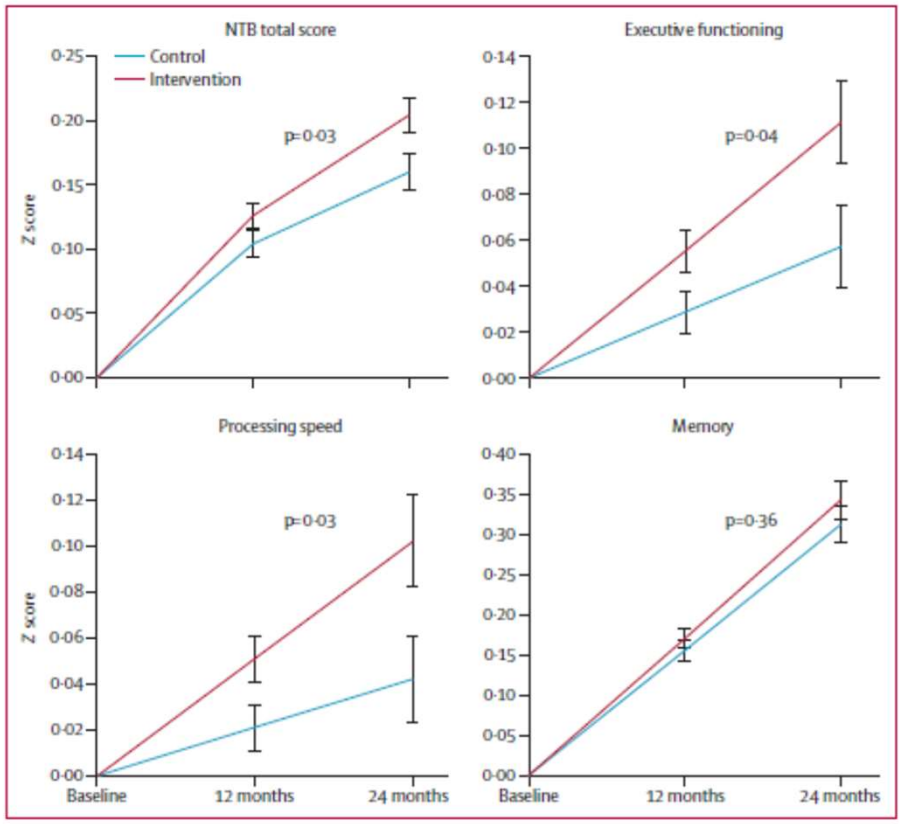

Figure 2: Change in cognitive performance during the 2 year intervention
Figure shows estimated mean change in cognitive performance from baseline until 12 and 24 months (higher scores suggest better performance) in the modified intention-to-treat population. Error bars are SEs. Mixed-model repeated-measures analyses were used to assess between-group differences (group x time interaction) in changes from baseline to 24 months based on data from all participants with at least one post-baseline measurement. NTB=neuropsychiatric test battery.

MEDIDAS PREVENTIVAS

Realizar una continua y variada actividad intelectual y física desde edades tempranas hasta las más avanzadas.

Prevenir y tratar adecuadamente los síntomas depresivos

Participar con entusiasmo en actividades sociales y de ocio.

Consumir una dieta baja en grasas saturadas, con vegetales y frutas con contenido antioxidante, sin exceso de calorías y con contenido de ácidos grasos omega-3 al menos una vez a la semana.

Abandonar el tabaco y consumir como máximo un vaso diario de vino a partir de edades medias.

Controlar y tratar la HTA desde edades medias, evitando la hipotensión en mayores de 75 años.

Detectar la hipercolesterolemia y tratarla con estatinas desde edades medias.