

El Manejo del Deterioro Cognitivo en el año 2030

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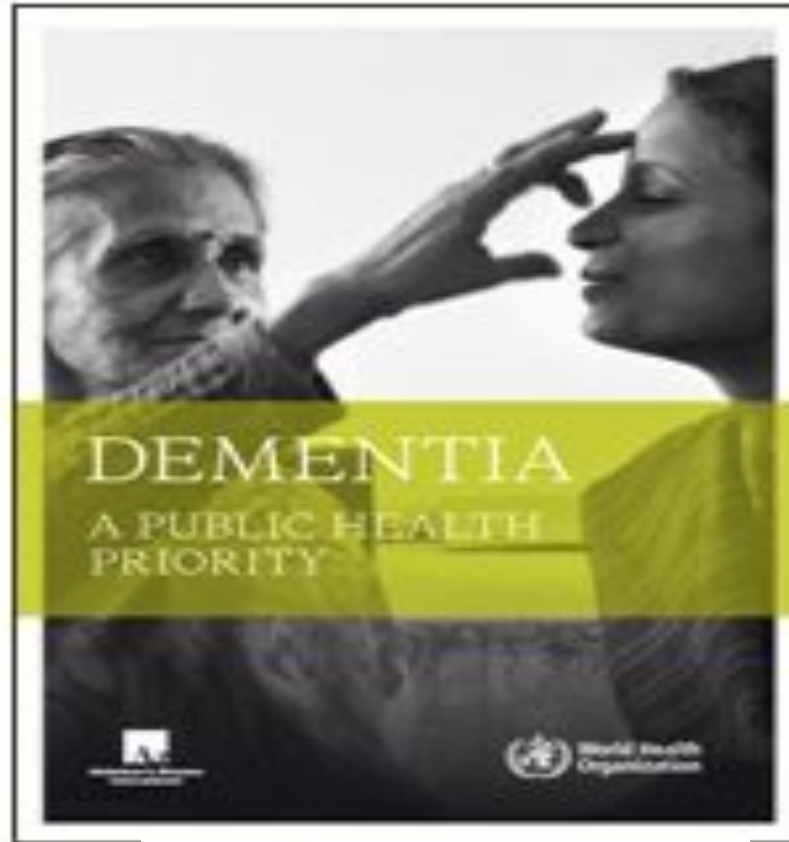
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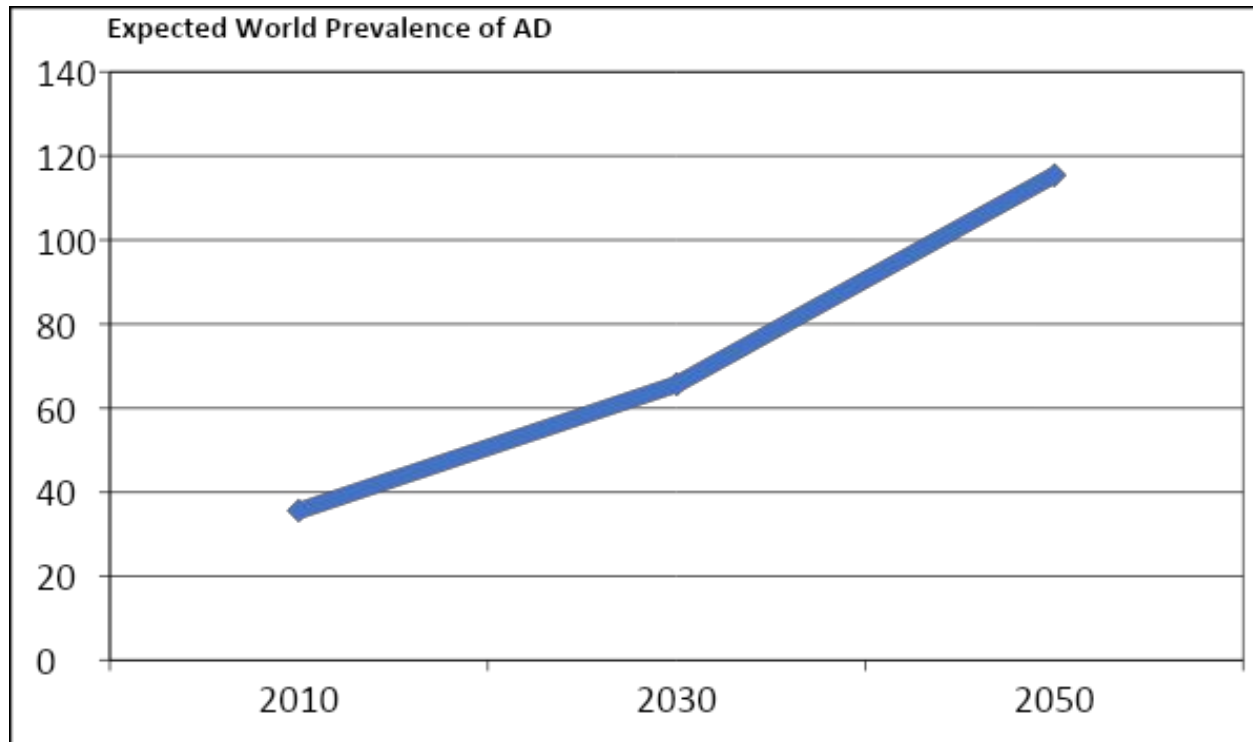


Situación actual global y en España

La demencia es el principal reto socio-sanitario al que nos enfrentamos.

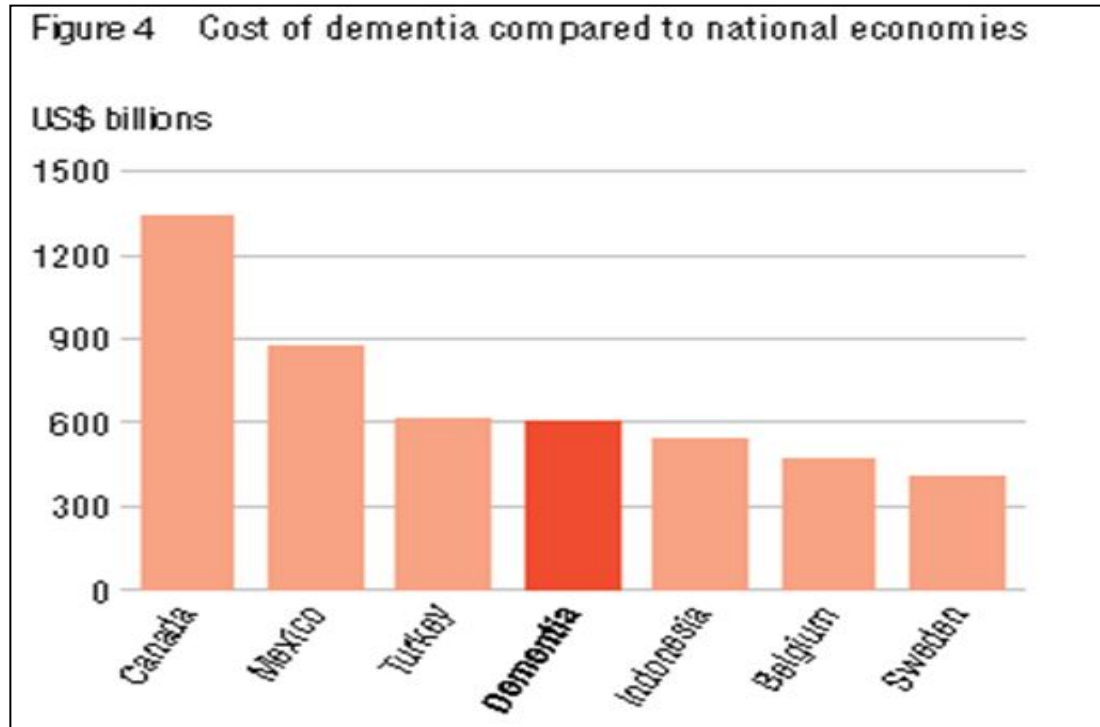


Casos de demencia globales



- En el **2020**: **47 millones** de personas padecen demencia
- Se estima que en el **2030** se incrementa hasta **75 millones**
- En **2050**: **131 millones**
- **Sobre todo en países en desarrollo se espera el principal incremento**

Impacto económico mundial



- **Coste anual medio** de un paciente con demencia: **€32,282.05** (Cantarero et al)
- Coste total estimado en 2010 de la demencia es de **604.000 millones de dólares**
- Si el coste de la demencia fuese un país, sería la **economía número 18**
- **Demencia consume más dinero que ictus, enfermedades cardiovasculares y cáncer .**



**HAY 800.000
PERSONAS EN
ESPAÑA CON
ENFERMEDAD DE
ALZHEIMER**



**ES LA PRINCIPAL
CAUSA DE
DISCAPACIDAD
EN PERSONAS
MAYORES**



**CADA AÑO SE
DIAGNOSTICAN
EN ESPAÑA 40.000
NUEVOS CASOS
DE ALZHEIMER**

Demencia no detectada y utilización de los servicios sanitarios: implicaciones para la atención primaria

M.V. Zunzunegui Pastor^a, T. del Ser^b, A. Rodríguez Laso^c, M.J. García Yébenes^c, J. Domingo^b y A. Otero Puime^c

Aten Primaria 2003;31(9):581-6

**TABLA
2**

Número de casos y casos detectados de demencia en personas mayores de 70 años, supervivientes de la cohorte de Leganés, 2000 (n = 527)

	Casos con demencia		
	Totales	Detectados	No detectados
Grado de demencia ^a			
Demencia leve	20	1 (5%)	19
Demencia moderada	29	9 (31%)	20
Demencia grave	14	9 (64%)	5
Causa de demencia ^b			
Enfermedad de Alzheimer	42	13 (31%)	29
Demencia vascular	12	4 (33%)	8
Demencia con cuerpos de Lewy	5	2 (40%)	3
Otra	4	0 (0%)	4
Total	63	19 (30%)	44

^aEl grado de demencia se estableció según criterios DSM-III-R ($\chi^2 = 13,76$; gl = 2; p = 0,001). ^bLa causa de demencia se estableció según los datos clínicos ($\chi^2 = 2,03$; gl = 3; p = 0,56). gl: grados de libertad..

Más de la mitad de las personas con demencia están sin diagnosticar

En el caso de la **demencia leve** los casos sin diagnosticar llegan a más del **80%**

Pablo Martínez-Lage

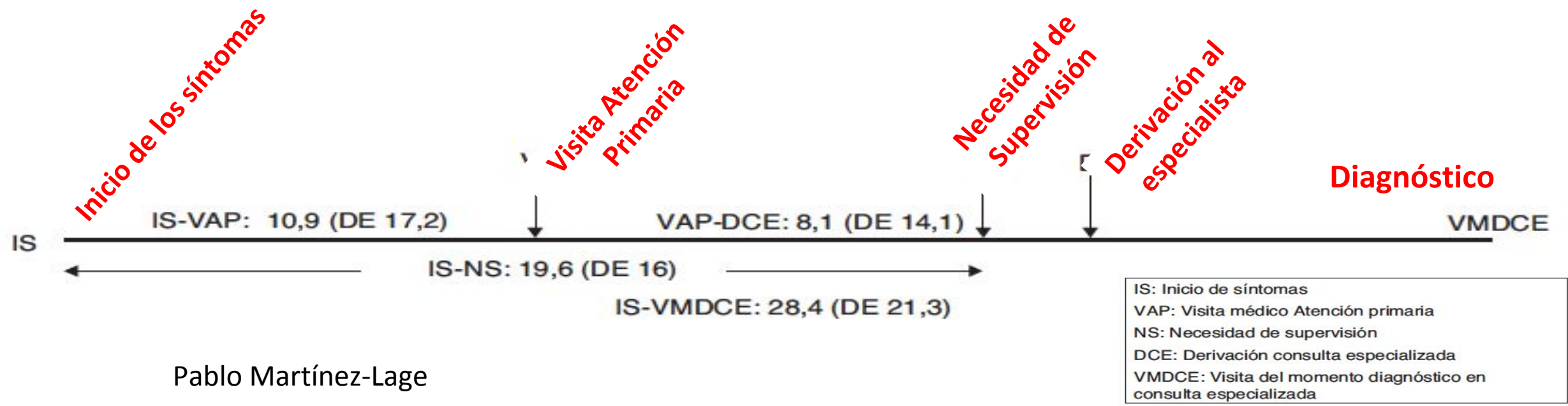
A. Patients seek medical attention late.

Estadio evolutivo de los pacientes con enfermedad de Alzheimer que acuden a la consulta especializada en España. Estudio EACE[☆]

J. Alom Poveda^a, M. Baquero^{b,*} y M. González-Adalid Guerreiro^c



Neurología. 2013;28(8):477–487



Pablo Martínez-Lage

The typical patient experiences symptoms for more than 2 years (26.1 mo) and visits an average of 2.3 doctors before diagnosis. Only 43% of patients are in the mild stage

Alzheimer's Foundation of America. I CAN: Investigating caregivers attitudes and needs.

<http://www.2f.biglobe.p.jp/~boke/ican2996.pdf>. Accessed march 5 2009

Prevalencia de uso de fármacos para el tratamiento de la enfermedad de Alzheimer y su evolución temporal: un estudio descriptivo con la base de datos de atención primaria BIFAP

Julio Bonis Sanz¹, María Canto de Hoyos Alonso², Ana Llorente García¹, Miguel Gil García¹, Dolores Montero Corominas¹ y Francisco de Abajo Iglesias^{1,3}

AMBOS SEXOS DE 65 A 110 AÑOS										
	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
n	248 568	361 342	415 706	444 241	427 499	412 083	383 074	351 628	343 261	270 470
Diagnóstico^a										
Demencia	2,97 %	3,23 %	3,43 %	3,61 %	3,74 %	3,97 %	4,05 %	4,12 %	4,15 %	4,17 %
Prevalencia de tratamiento en pacientes con demencia^b										
IACE (% del total)	23,13 % (100 %)	24,00 % (87 %)	25,41 % (80 %)	26,01 % (76 %)	27,08 % (72 %)	27,50 % (70 %)	28,05 % (70 %)	29,31 % (69 %)	28,74 % (68 %)	27,74 % (68 %)
Memantina (% del total)	N/A	1,89 % (7 %)	3,94 % (12 %)	5,02 % (15 %)	6,52 % (17 %)	7,25 % (18 %)	7,11 % (18 %)	7,52 % (18 %)	7,52 % (18 %)	7,09 % (17 %)
IACE + memantina (% del total)	N/A	1,69 % (6 %)	2,46 % (8 %)	2,92 % (9 %)	3,89 % (11 %)	4,87 % (12 %)	4,98 % (12 %)	5,59 % (13 %)	6,07 % (14 %)	6,29 % (15 %)
Prevalencia de uso en población mayor de 64 años^c										
IACE (% del total)	0,86 % (100 %)	0,99 % (87 %)	1,12 % (81 %)	1,24 % (78 %)	1,36 % (73 %)	1,49 % (71 %)	1,58 % (71 %)	1,71 % (71 %)	1,70 % (70 %)	1,68 % (70 %)
Memantina (% del total)	N/A	0,07 % (6 %)	0,15 % (11 %)	0,21 % (13 %)	0,29 % (16 %)	0,34 % (17 %)	0,36 % (16 %)	0,37 % (15 %)	0,37 % (15 %)	0,35 % (15 %)
IACE + memantina (% del total)	N/A	0,08 % (7 %)	0,11 % (8 %)	0,15 % (9 %)	0,20 % (11 %)	0,25 % (12 %)	0,28 % (13 %)	0,33 % (14 %)	0,36 % (15 %)	0,37 % (15 %)

>50% AD patients untreated

Planes de demencia

- A día de hoy NO existe en España un Plan nacional de Demencia.
- Existe una estrategia de enfermedades neurodegenerativas que no comporta financiación (o es mínima)
- Plan Nacional Redactado/aprobado pendiente de su implementación.
- En Cantabria estamos trabajando junto con la Oficina de Cronicidad del SCS en la Ruta Asistencial del paciente con Deterioro Cognitivo

Avances relevantes

Epidemiología

Prevalencia de la demencia a lo largo del tiempo

- Physical and cognitive functioning of people older than 90 years: a comparison of two Danish cohorts born 10 years apart (*Christensen The Lancet 2013*)
- 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 (*Matthews The Lancet 2013*)

Existe una disminución global de la prevalencia de demencia en los sujetos nacidos más tarde

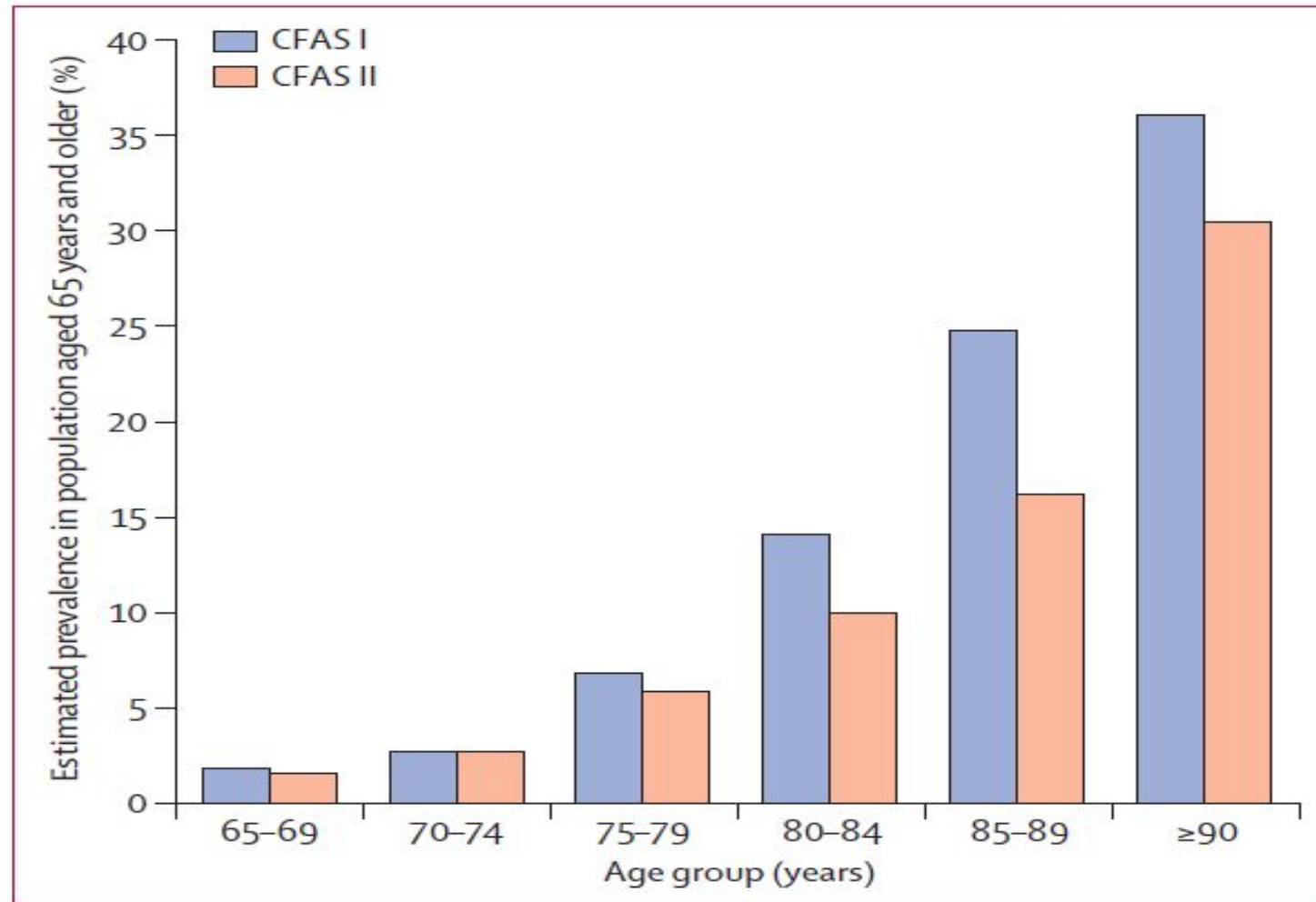


Figure 1: CFAS I and CFAS II age-specific dementia prevalence
CFAS=Cognitive Function and Ageing Study.

(Matthews The Lancet 2013)

Prevención

El riesgo de demencia es modificable

- **Reducción muy significativa de la prevalencia de demencia.**
- Probablemente en relación con:
 - Cambios en hábitos de vida
 - Mejoras en sanidad
 - Mejoras en educación

(Christensen The Lancet 2013)

(Matthews The Lancet 2013)

Table ES1. Summary of findings on potential risk factors and interventions for AD

Direction of association	Factors	Level of evidence‡
Increased risk	<ul style="list-style-type: none"> • APOE e4 genotype • Conjugated equine estrogen with methyl progesterone* 	Moderate
	<ul style="list-style-type: none"> • Some non-steroidal anti-inflammatory drugs* • Depressive disorder • Diabetes mellitus • Hyperlipidemia in mid-life • Traumatic brain injury in males • Pesticide exposure • Never married, less social support • Current tobacco use 	Low
Decreased risk	<ul style="list-style-type: none"> • Mediterranean diet • Folic acid • HMG-CoA reductase inhibitors (statins) • Higher levels of education • Light to moderate alcohol intake • Cognitively engaging activities • Physical activity, particularly high levels 	Low
No association	<ul style="list-style-type: none"> • Ginkgo biloba* 	High
	<ul style="list-style-type: none"> • Vitamin E* • Cholinesterase inhibitors* 	Moderate
	<ul style="list-style-type: none"> • Anti-hypertensive medication* • Conjugated equine estrogen • Omega-3 fatty acids* • Vitamins B12, C, beta-carotene • Homocysteine • Hypertension • Obesity • Metabolic syndrome • Early childhood factors • Occupational level • Lead 	Low
Inadequate evidence to assess association	<ul style="list-style-type: none"> • Saturated fat intake • Fruit and vegetable intake • Trace metals • High caloric intake • Memantine • Sleep apnea • Anxiety disorders • Resiliency • Non-cognitive, non-physical leisure activities • Agent Orange, Gulf War Syndrome • Solvents, aluminum • Genetic factors other than APOE 	(Not applicable)

* Data from observational studies and RCTs.

Abbreviations: APOE = apolipoprotein E gene; APOE e4 = epsilon 4 allele of the apolipoprotein E gene; HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A; RCTs = randomized controlled trials

‡GRADE criteria (see Methods section)

MÉDICOS

Diabetes

Hiperlipidemia en la edad media

Depresión

Traumatismo craneal

FARMACOLÓGICOS

Estatinas

Antihipertensivos

SOCIOECONÓMICOS

Dieta mediterránea

Ejercicio

Educación y actividades sociales

Tabaco

Uso moderado de alcohol

EXPOSICIONES AMBIENTALES

Pesticidas

El riesgo de demencia es modificable

- Por ejemplo, una revisión sistemática centrada en **siete factores modificadores** (bajo nivel de educación, tabaquismo, diabetes, la hipertensión, obesidad en edades medias de la vida, depresión y sedentarismo) sugiere que sólo **una reducción del 10%** en la exposición a estos factores de riesgo en edades medias de la vida podría potencialmente **prevenir** hasta al **1,1 millón de casos de AD por año** en todo el mundo.

Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurol* 2011; **10: 819–28.**

Tratamiento

No existen tratamientos que cambien el curso de la enfermedad

- Hay cuatro fármacos aprobados para uso clínico en Europa:
 - Memantina
 - Donepezilo
 - Rivastigmina
 - Galantamina
- Efecto sintomático-> retrasan deterioro funcional y mejoran aspectos conductuales

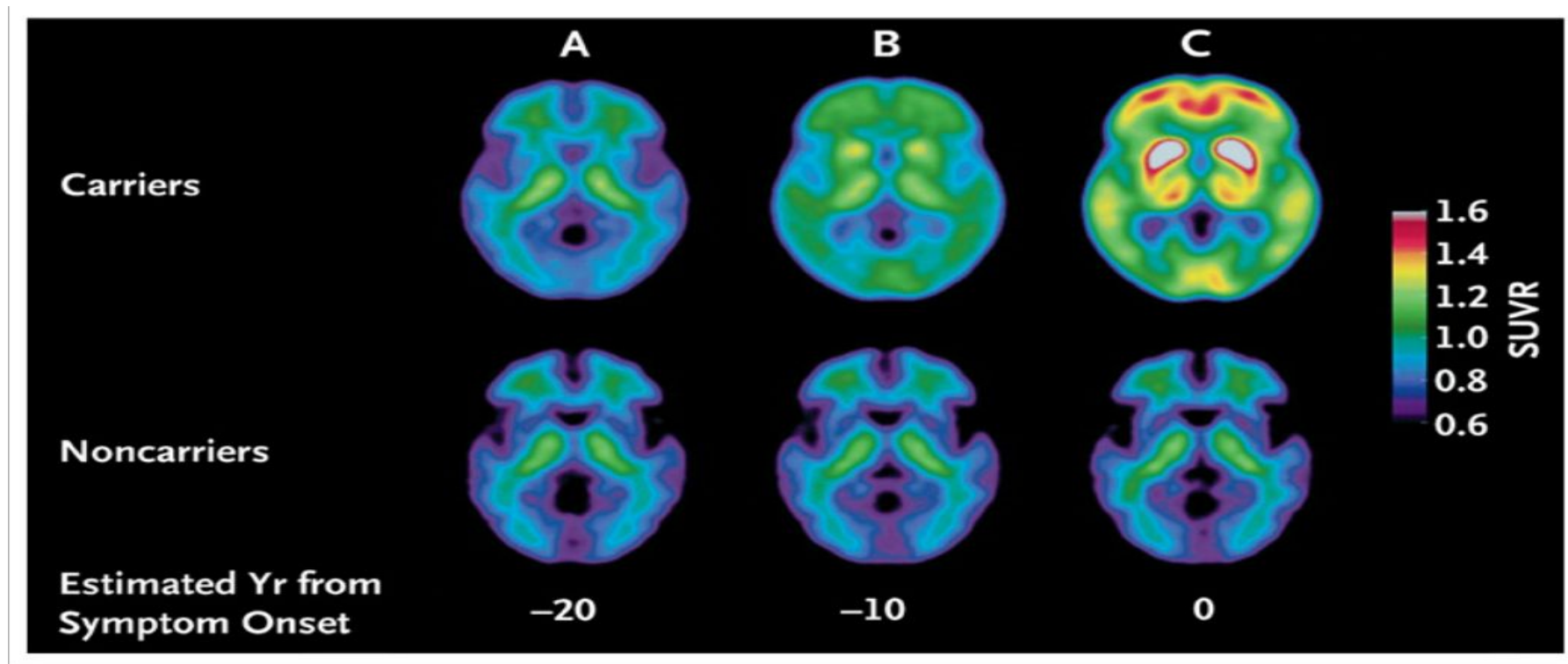
Tratamientos **modificadores del curso** de la enfermedad

- **Retrasando** el inicio de la clínica **5 años** reduciría a la **mitad la prevalencia** de la demencia

Brodaty H, Breteler MM, Dekosky ST, et al. The world of dementia beyond 2020. *J Am Geriatr Soc* 2011; **59: 923–27.**

La ventana terapéutica de la enfermedad de Alzheimer es muy grande

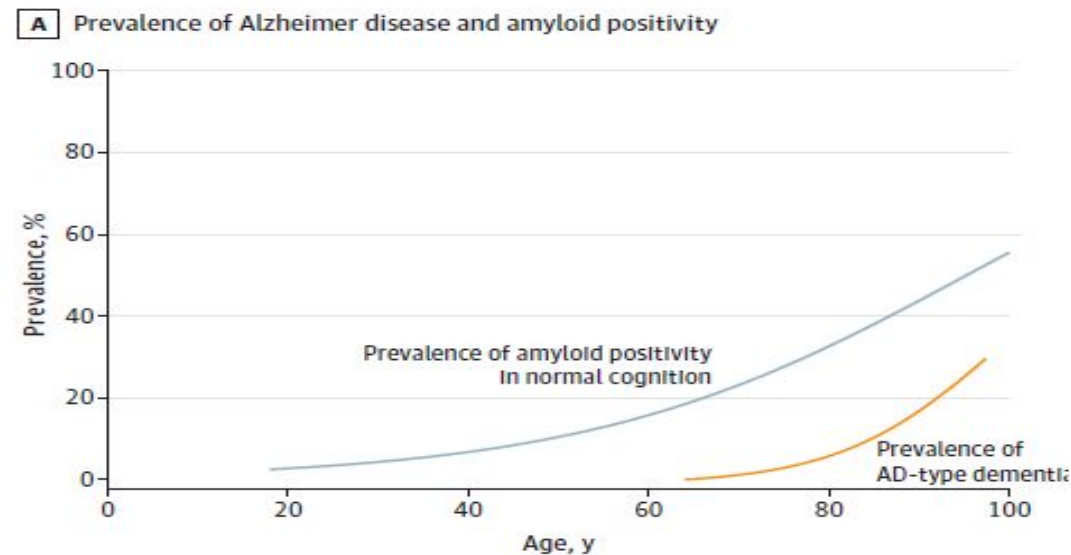
ESTUDIO DIAN: En los portadores de mutaciones de EA familiar se detecta **amiloide cerebral** hasta **20 años antes** de los síntomas



Bateman et al NEJM 2012

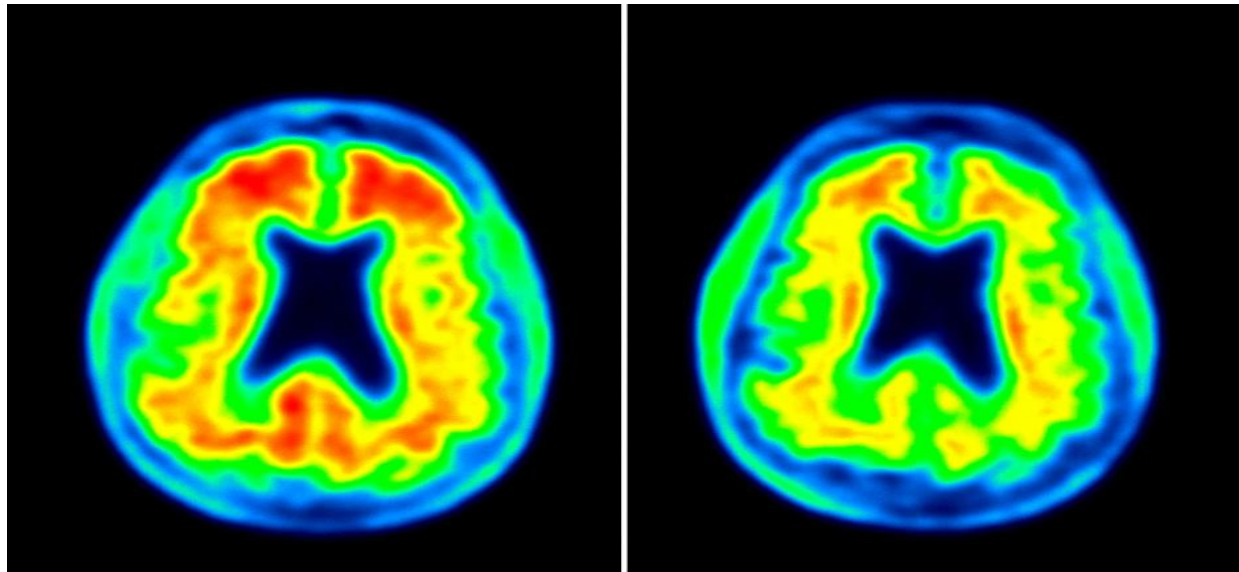
Los depósitos de amiloide se forman hasta 20 años del diagnóstico de EA

Figure 4. Comparison of the Prevalence of Amyloid Positivity With the Prevalence of and Lifetime Risks for Alzheimer Disease-Type Dementia



The prevalence estimates in panel A were estimated from a meta-analysis of 14 studies (eMethods in the Supplement). The prevalence estimates in panel B of amyloid positivity in participants with normal cognition are plotted against

Tratamientos modificadores del curso de la enfermedad



(12th International Conference on Alzheimer's and Parkinson's Diseases in Nice, France)

- A pesar de que los fármacos anti beta-amiloide tienen éxito eliminando esa proteína del cerebro, **no mejoran** a los pacientes.
- **Vías alternativas: tau, inflamación...**
- **Estudios en pre-sintomáticos**

Cohorte Valdecilla para el estudio de la memoria y el envejecimiento cerebral

- Voluntarios mayores de 55 años libres de demencia
- Estudio exhaustivo y seguimiento anual
- Determinación de individuos en riesgo de demencia
- Participación en ensayos clínicos con fármacos que prevengan el deterioro cognitivo



Genética

Hasta el 70% de las causas de la enfermedad de Alzheimer son heredables

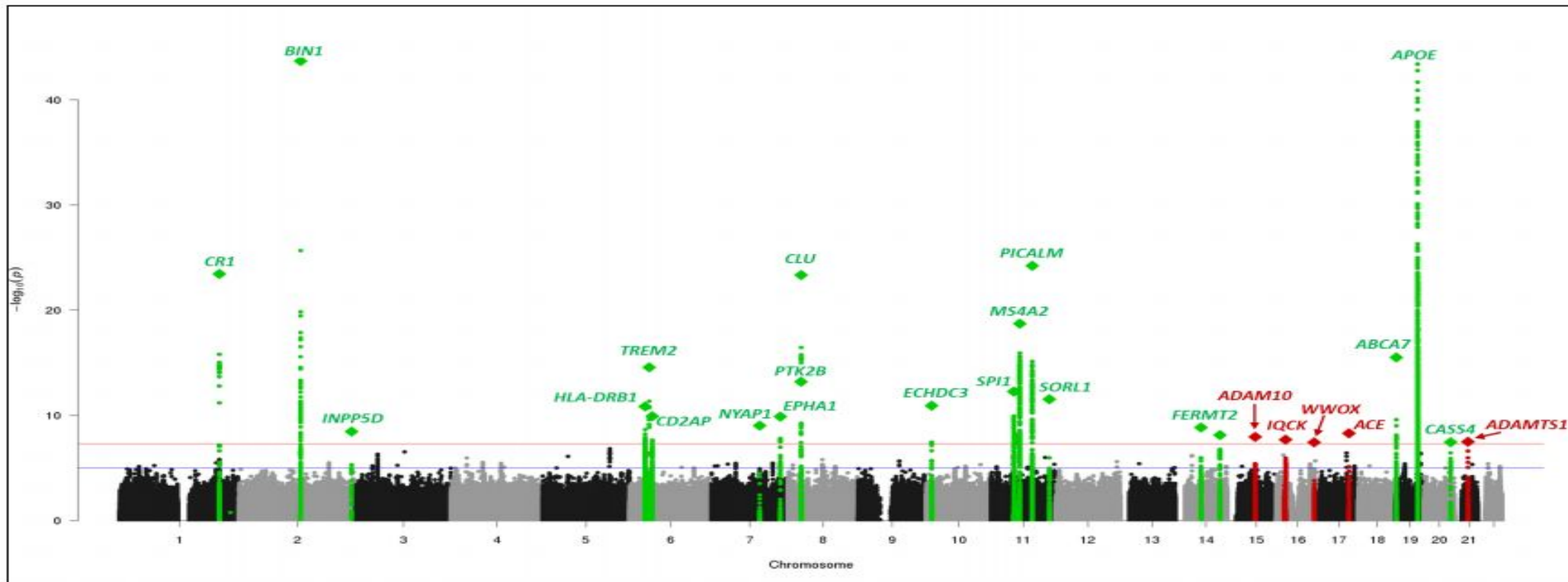
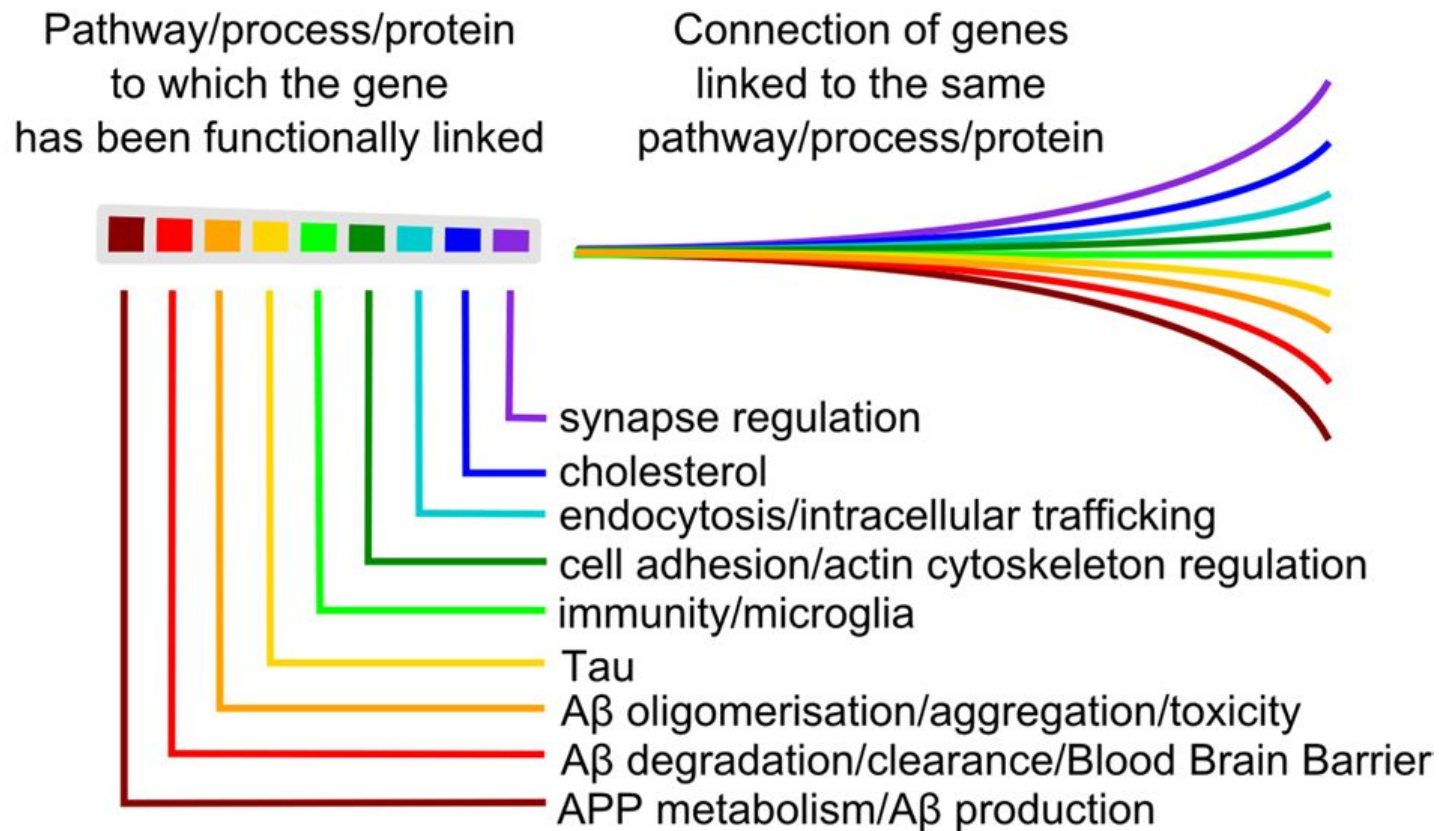


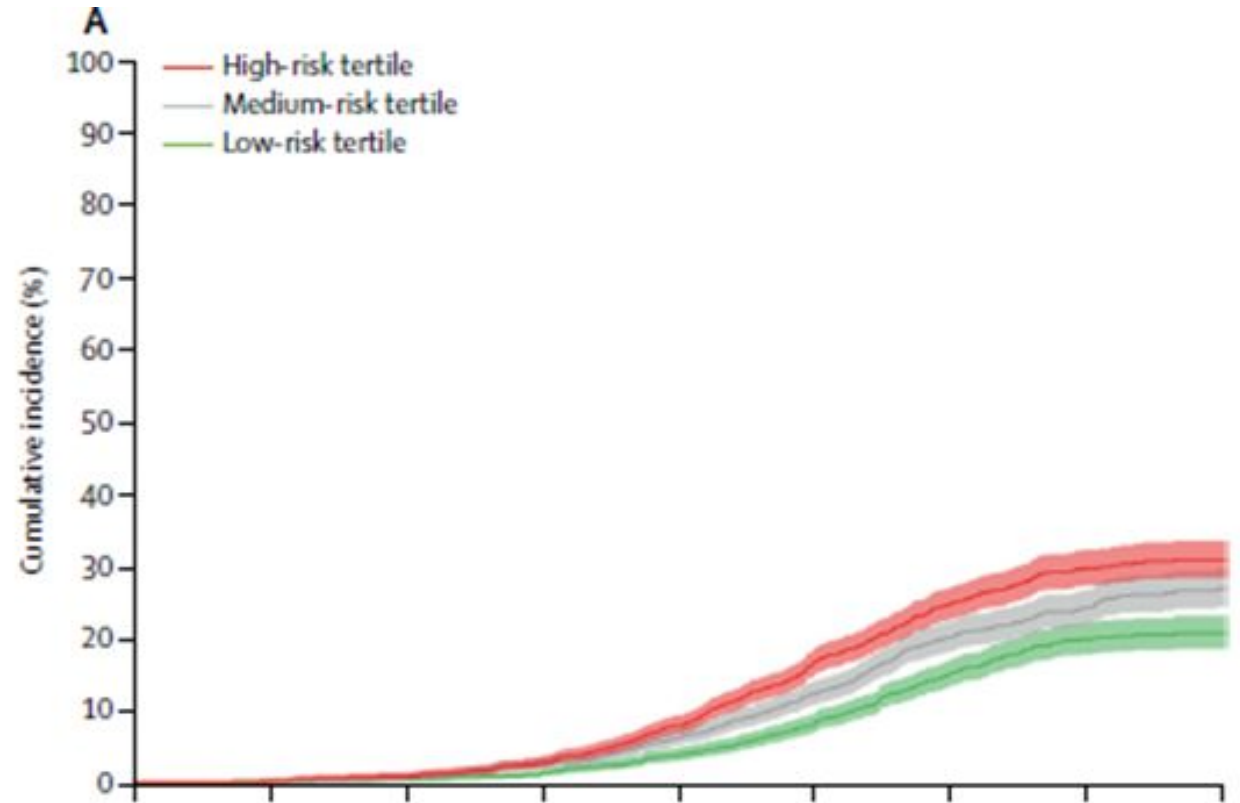
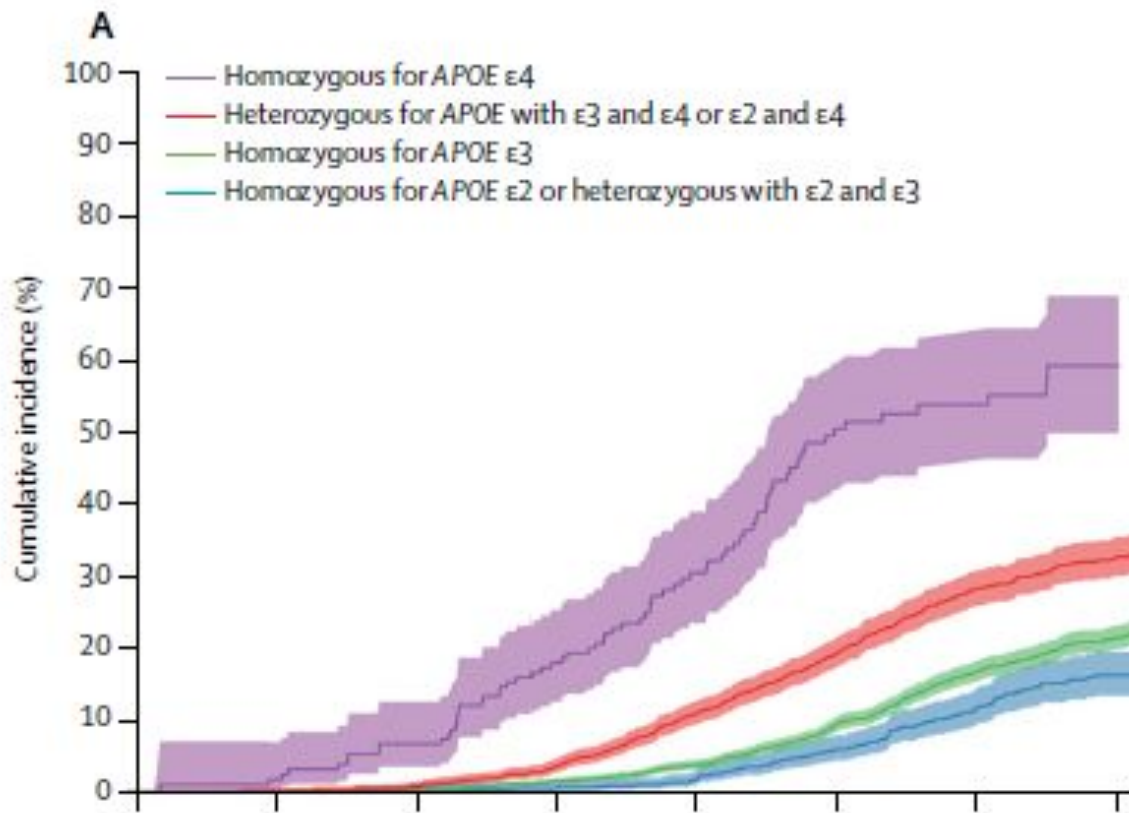
Figure 1. Manhattan plot of meta-analysis of Stage 1, 2 and 3 results for genome-wide association with Alzheimer's disease. The threshold for genome-wide significance ($P < 5 \times 10^{-8}$) is indicated by the red line, while the blue line represents the suggestive threshold ($P < 1 \times 10^{-5}$). Loci previously identified by the Lambert et al. 2013 IGAP GWAS are shown in green, and newly associated loci are shown in red. Loci are named for the closest gene to the sentinel variant for each locus. Diamonds represent variants with the smallest P values for each genome-wide locus.

La genética a multiplicado nuestro conocimiento de las causas de la enfermedad

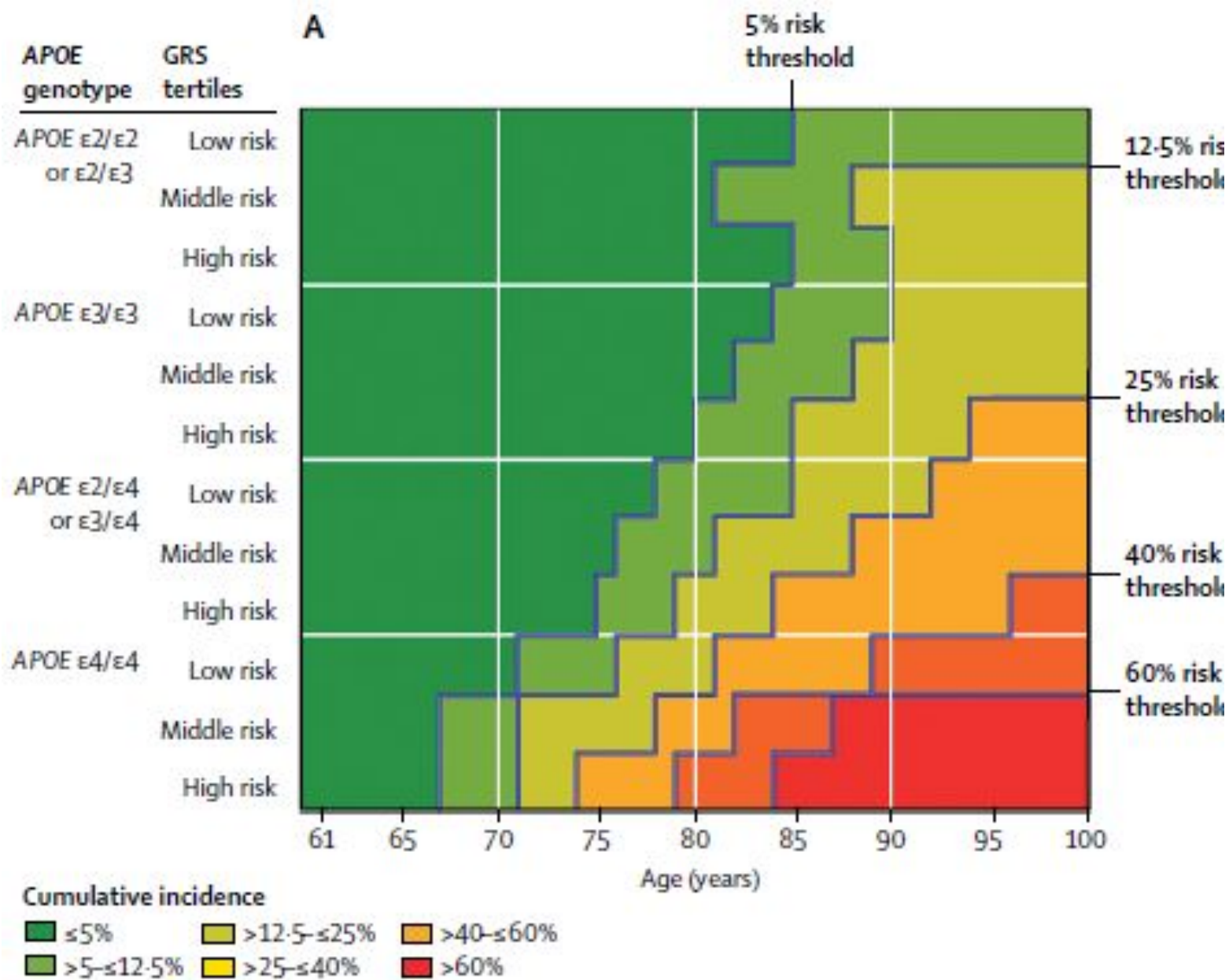
- Papel clave de diversas rutas metabólicas:



Categorización de riesgo de EA



Sven van der Lee Lancet Neurology 2018

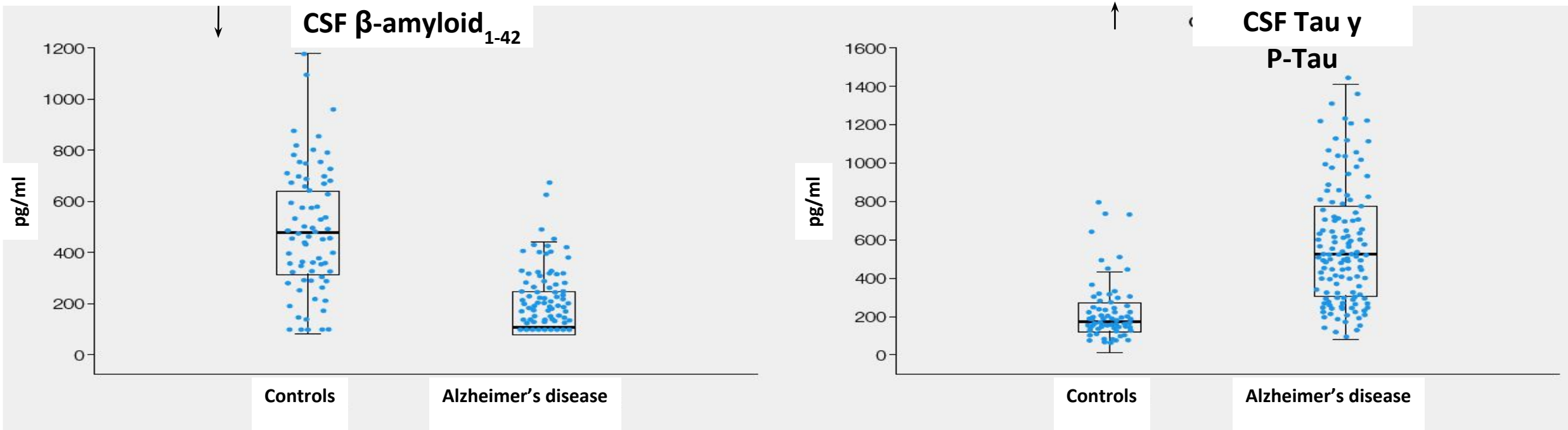


La edad y los genes predicen el riesgo de Alzheimer

Biomarcadores

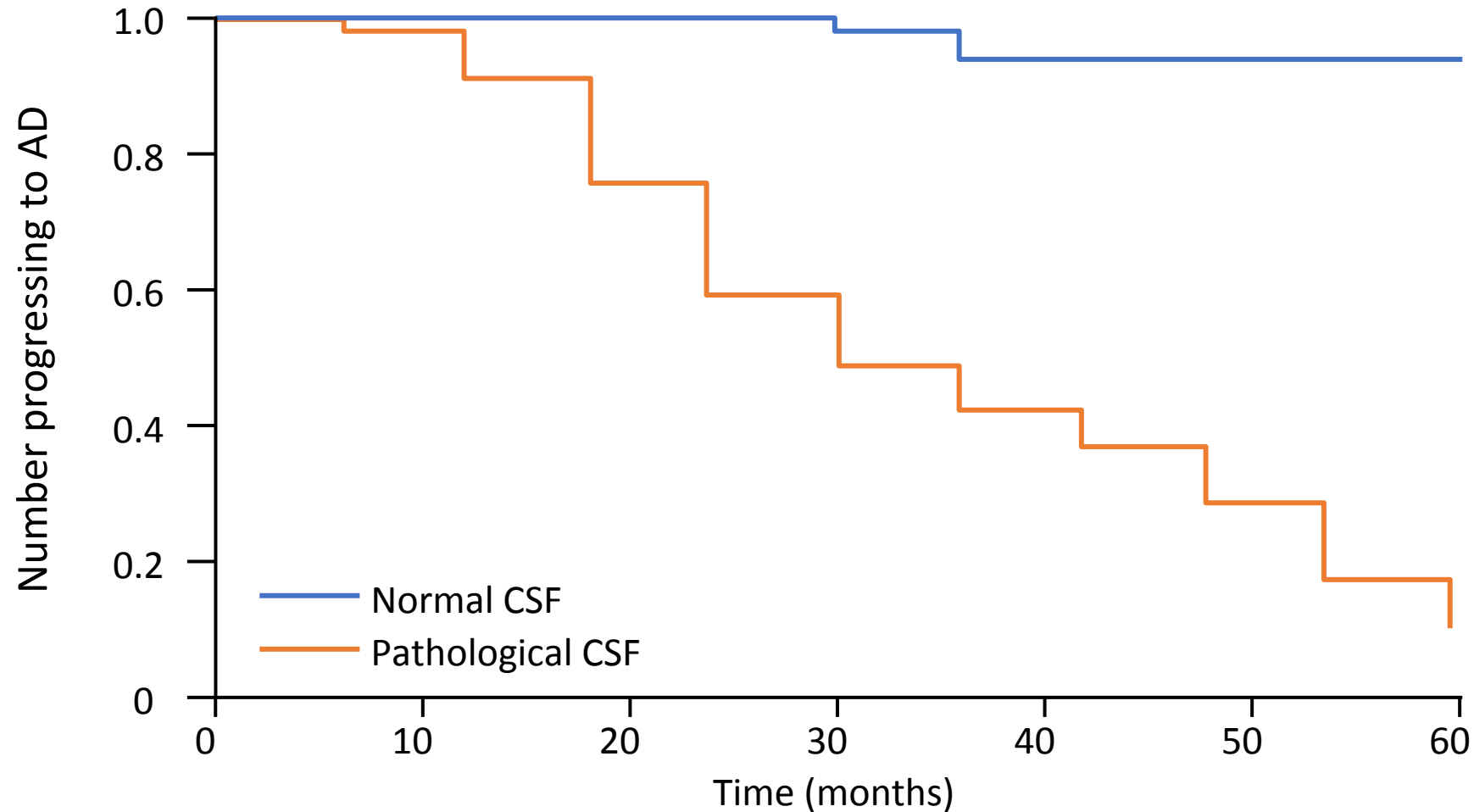
Biomarcadores “core” de EA en LCR

- Existen **patrones específicos** de alteraciones químicas en la composición del **LCR** característicos de algunas demencias



Sunderland JAMA 2003

Progresión a EA de pacientes con **DCL**



Marcadores de LCR

- Punción Lumbar: procedimiento seguro- 9% cefalea post puncion (**Duits et al 2015 Alzheimer's &Dementia**)
- Problemas de reproducibilidad: cada laboratorio debe generar sus puntos de corte (**Mattsson 2013 Alzheimer's &Dementia**)
- Problemas de interpretación (resultados contradictorios)
- Los biomarcadores de LCR se han limitado a centros de referencia
- Nuevas **técnicas automatizadas** (Fujirebio, Elecsys...) viene a solventar este problema

CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis

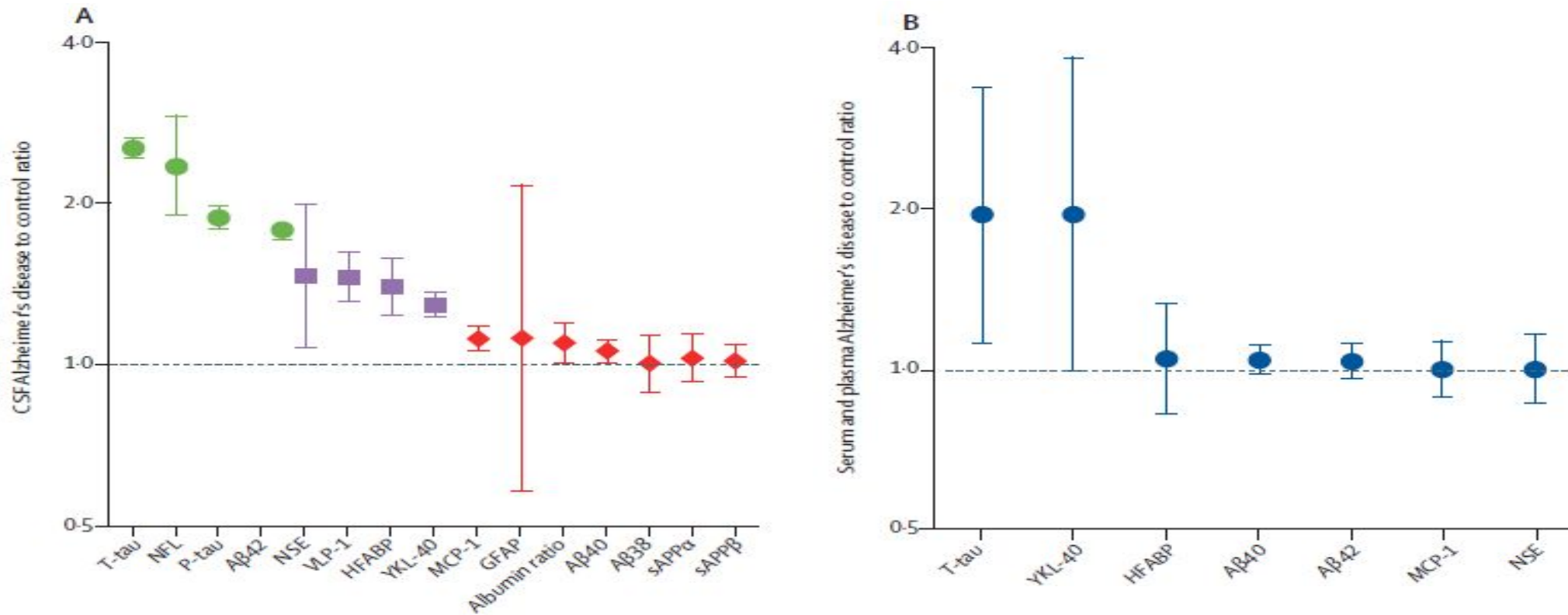


Bob Olsson, Ronald Lautner, Ulf Andreasson, Annika Öhrfelt, Erik Portelius, Maria Bjerke, Mikko Hölttä, Christoffer Rosén, Caroline Olsson, Gabrielle Strobel, Elizabeth Wu, Kelly Dakin, Max Petzold, Kaj Blennow, Henrik Zetterberg

Summary

Background Alzheimer's disease biomarkers are important for early diagnosis in routine clinical practice and research. Three core CSF biomarkers for the diagnosis of Alzheimer's disease (A β 42, T-tau, and P-tau) have been assessed in numerous studies, and several other Alzheimer's disease markers are emerging in the literature. However, there have been no comprehensive meta-analyses of their diagnostic performance. We systematically reviewed the literature for 15 biomarkers in both CSF and blood to assess which of these were most altered in Alzheimer's disease.

Lancet Neurol 2016
Published Online
April 8, 2016
[http://dx.doi.org/10.1016/S1474-4422\(16\)00070-3](http://dx.doi.org/10.1016/S1474-4422(16)00070-3)
Department of Psychiatry



Biomarcadores en sangre



nature
biotechnology

LETTERS

Single-molecule enzyme-linked immunosorbent assay detects serum proteins at subfemtomolar concentrations

David M Rissin^{1,3}, Cheuk W Kan^{1,3}, Todd G Campbell¹, Stuart C Howes¹, David R Fournier¹, Linan Song¹, Tomasz Piech¹, Purvish P Patel¹, Lei Chang², Andrew J Rivnak¹, Evan P Ferrell¹, Jeffrey D Randall¹, Gail K Provuncher¹, David R Walt² & David C Duffy¹

The ability to detect single protein molecules^{1,2} in blood could accelerate the discovery and use of more sensitive diagnostic biomarkers. To detect low-abundance proteins in blood, we captured them on microscopic beads decorated with specific antibodies (one target protein molecule per bead) and then labeled the immunocomplexes with an enzymatic reporter capable of generating a fluorescent product. After isolating the beads in 50-fL reaction chambers designed to hold only a single bead, we used fluorescence imaging to detect single protein molecules. Our single-molecule enzyme-linked immunosorbent assay (digital ELISA) approach detected as few as ~10–20 enzyme-labeled complexes in 100 μ l of sample (~10⁻¹⁹ M) and routinely allowed detection of clinically relevant proteins in serum at concentrations (<10⁻¹⁵ M) much lower than conventional ELISA^{3–5}. Digital ELISA detected prostate-specific antigen (PSA) in sera from patients who have undergone radical prostatectomy at concentrations as low as 14 fg/ml (0.4 fM).

The clinical use of protein biomarkers to differentiate between healthy and disease states, and to monitor disease progression, requires the measurement of low concentrations of proteins in complex samples. Current immunoassays typically measure proteins at concentrations above 10⁻¹⁷ M⁶. The serum concentrations of the majority of proteins important in cancer⁷, neurological disorders^{8,9}, and the early stages of infection¹⁰, however, are thought to range from 10⁻¹⁶ to 10⁻¹² M. For instance, a 1-mm³ tumor composed of a million cells that each secrete 5,000 proteins into 5 liters of circulating blood translates to a concentration of ~2 \times 10⁻¹⁵ M (or 2 fM). Moreover, serum from individuals recently infected with HIV contains 10–3,000 viruses per ml, resulting in estimated concentrations of the p24 capsid antigen ranging from 30 \times 10⁻¹⁸ M (50 aM) to 15 \times 10⁻¹³ M (15 fM)¹¹. Attempts to develop methods capable of measuring these concentrations of proteins have focused on the replication of nucleic acid labels on proteins^{12,13}, or on measuring the bulk, ensemble properties of labeled protein molecules^{14–16}. The work of Mirkin *et al.*^{12,17} and others¹⁸ using labels based on gold nanoparticles and DNA barcodes has pushed the detection of proteins into the low femtomolar range; a recent report

using this technology demonstrated the detection of 10 fM of PSA in serum¹⁷. Nonetheless, the sensitivities achieved by methods for detecting proteins still lag behind those for nucleic acids, such as PCR, limiting the number of gene products that have been detected in blood^{19,20}. The isolation and detection of single protein molecules provides a promising approach for measuring extremely low concentrations of proteins²¹. For example, Todd *et al.*⁷ have developed flow-based methods for serially detecting single fluorescently labeled detection antibodies that have been released from immunocomplexes formed on solid substrates. Here, we report an approach for detecting thousands of single protein molecules simultaneously using the same reagents as the gold standard for detecting proteins, namely, the ELISA. This method has been used to detect proteins in serum at subfemtomolar concentrations.

Our approach makes use of arrays of femtoliter-sized reaction chambers (Fig. 1)—which we term single-molecule arrays (SIMoAs)—that can isolate and detect single enzyme molecules^{22–24}. This approach builds from the work of Walt *et al.*^{25–27}, who used these arrays to study the kinetics²⁷ and inhibition²⁸ of single enzymes. Our objective was to exploit the ability of SIMoAs to trap and detect single enzymes to detect single enzyme-labeled proteins. In the first step of this single-molecule immunoassay (Fig. 1a) a sandwich antibody complex is formed on microscopic beads (2.7 μ m diameter), and the bound complexes are labeled with an enzyme, as in a conventional bead-based ELISA. When assaying samples containing extremely low concentrations of protein, the ratio of protein molecules (and the resulting enzyme-labeled complex) to beads is small (typically <1:1) and, as such, the percentage of beads that contain a labeled immunocomplex follows a Poisson distribution. At low concentrations of protein, the Poisson distribution indicates that beads carry either a single immunocomplex or none. For example, if 50 aM of a protein in 0.1 ml (3,000 molecules) is captured and labeled on 200,000 beads, then 1.5% of the beads will carry one protein molecule and 98.5% will not carry any protein molecules (Fig. 1b)²⁹. It is not possible to detect these low numbers of enzyme labels using standard detection technology (for example, a plate reader), because the fluorophores generated by each enzyme diffuse into a large assay volume (typically 0.1–1 ml), and it takes hundreds of thousands of enzyme labels to generate a

¹Quantiris Corporation, Cambridge, Massachusetts, USA. ²Department of Chemistry, Tufts University, Medford, Massachusetts, USA. ³These authors contributed equally to this work. Correspondence should be addressed to D.C.D. (dduffy@quantiris.com).

Received 1 February; accepted 29 April; published online XX XXXX 2010; doi:10.1038/nbt.100

Single MOlecule Analysis

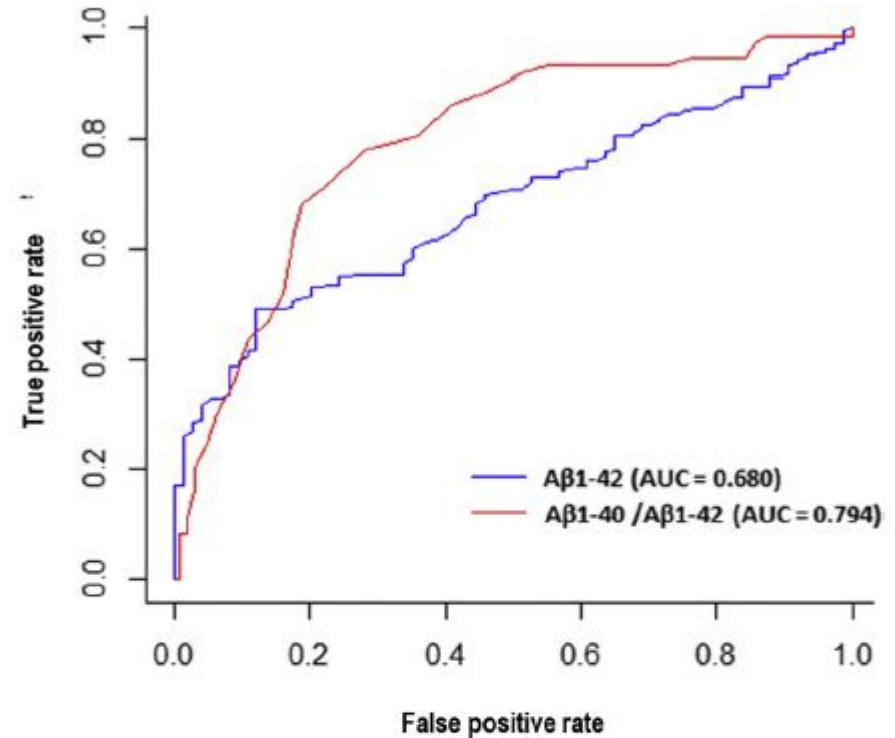


Fig. 1. ROC of plasma Aβ₁₋₄₂ levels and of the plasma Aβ₁₋₄₀/Aβ₁₋₄₂ ratio in predicting the individual Aβ-PET status. Baseline diagnostic performance test ROCs show for Aβ₁₋₄₂ at the best cutoff point an AUC 68.1% with a sensitivity of 52.3% and a specificity of 79.7% (balanced accuracy of 66%), whereas the ratio Aβ₁₋₄₀/Aβ₁₋₄₂ shows an AUC of 0.794 with a sensitivity of 78.1% and a specificity of 74.9% (balanced accuracy of 76.5%), at the best cutoff point (17.82). The DeLong's test discloses a statistically significant difference between the two ROCs ($P = .006$). Abbreviations: AUC, area under the curve; Aβ₁₋₄₀, plasma concentrations of 40 amino acid-long amyloid-β; Aβ₁₋₄₂, plasma concentrations of 42 amino acid-long Aβ; Aβ-PET, amyloid-β positron emission tomography; ROC, receiver operating characteristic curve.

Arrival of PiB PET

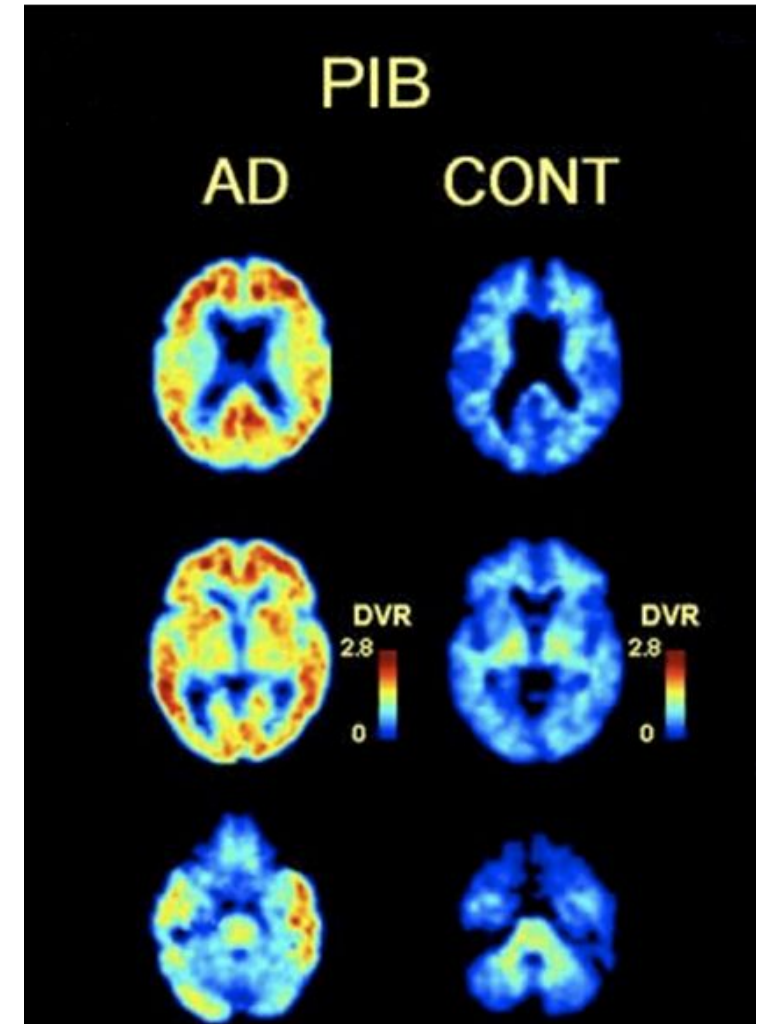
ORIGINAL ARTICLES

Imaging Brain Amyloid in Alzheimer's Disease with Pittsburgh Compound-B

William E. Klunk, MD, PhD,¹ Henry Engler, MD,² Agneta Nordberg, MD, PhD,^{3,4} Yanming Wang, PhD,⁵ Gunnar Blomqvist, PhD,² Daniel P. Holt, BS,⁵ Mats Bergström, PhD,² Irina Savitcheva, MD,² Guo-feng Huang, PhD,⁵ Sergio Estrada, PhD,² Birgitta Ausén, MSCI,⁴ Manik L. Debnath, MS,¹ Julien Barletta, BS,⁶ Julie C. Price, PhD,⁵ Johan Sandell, PhD,² Brian J. Lopresti, BS,⁵ Anders Wall, PhD,² Pernilla Koivisto, PhD,² Gunnar Antoni, PhD,² Chester A. Mathis, PhD,⁵ and Bengt Långström, PhD^{2,6}

This report describes the first human study of a novel amyloid-imaging positron emission tomography (PET) tracer, termed Pittsburgh Compound-B (PiB), in 16 patients with diagnosed mild AD and 9 controls. Compared with controls, AD patients typically showed marked retention of PiB in areas of association cortex known to contain large amounts of amyloid deposits in AD. In the AD patient group, PiB retention was increased most prominently in frontal cortex (1.94-fold, $p = 0.0001$). Large increases also were observed in parietal (1.71-fold, $p = 0.0002$), temporal (1.52-fold, $p = 0.002$), and occipital (1.54-fold, $p = 0.002$) cortex and the striatum (1.76-fold, $p = 0.0001$). PiB retention was equivalent in AD patients and controls in areas known to be relatively unaffected by amyloid deposition (such as subcortical white matter, pons, and cerebellum). Studies in three young (21 years) and six older healthy controls (69.5 ± 11 years) showed low PiB retention in cortical areas and no significant group differences between young and older controls. In cortical areas, PiB retention correlated inversely with cerebral glucose metabolism determined with ^{18}F -fluorodeoxyglucose. This relationship was most robust in the parietal cortex ($r = -0.72$; $p = 0.0001$). The results suggest that PET imaging with the novel tracer, PiB, can provide quantitative information on amyloid deposits in living subjects.

Ann Neurol 2004;55:306-319



Clinical utility of Amyloid PET

Practical utility of amyloid and FDG-PET in an academic dementia center

11

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ABSTRACT

Objective: To evaluate the effect of amyloid imaging on clinical decision making.

Methods: We conducted a retrospective analysis of 140 cognitively impaired patients (mean age 65.0 years, 46% primary β -amyloid (A β) diagnosis, mean Mini-Mental State Examination 22.3) who underwent amyloid (Pittsburgh compound B [PiB]) PET as part of observational research studies and were evaluated clinically before and after the scan. One hundred thirty-four concurrently underwent fluorodeoxyglucose (FDG)-PET. We assessed for changes between the pre- and post-PET clinical diagnosis (from A β to non-A β diagnosis or vice versa) and Alzheimer disease treatment plan. The association between PiB/FDG results and changes in management was evaluated using χ^2 and multivariate logistic regression. Postmortem diagnosis was available for 24 patients (17%).

Results: Concordance between scan results and baseline diagnosis was high (PiB 84%, FDG 82%). The primary diagnosis changed after PET in 13/140 patients (9%) overall but in 5/13 (38%) patients considered pre-PET diagnostic dilemmas. When examined independently, discordant PiB and discordant FDG were both associated with diagnostic change (unadjusted $p < 0.0001$). However, when examined together in a multivariate logistic regression, only discordant PiB remained significant (adjusted $p = 0.00013$). Changes in treatment were associated with discordant PiB in patients with non-A β diagnoses (adjusted $p = 0.028$), while FDG had no effect on therapy. Both PiB (96%) and FDG (91%) showed high agreement with autopsy diagnosis.

Conclusions: PET had a moderate effect on clinical outcomes. Discordant PiB had a greater effect than discordant FDG, and influence on diagnosis was greater than on treatment. Prospective studies are needed to better characterize the clinical role of amyloid PET. *Neurology*® 2014;82:230-238

GLOSSARY

A β = β -amyloid; AD = Alzheimer disease; AUC = appropriate use criteria; CBS = corticobasal syndrome; CDR = Clinical Dementia Rating; ChE-I = cholinesterase inhibitor; CMS = Centers for Medicare & Medicaid Services; DLB = dementia with Lewy bodies; FDG = fluorodeoxyglucose; FTLD = frontotemporal dementia; MCI = mild cognitive impairment; PiB = Pittsburgh compound B; UCSF = University of California, San Francisco.

PET ligands that bind to fibrillar β -amyloid (A β) enable the in vivo detection of amyloid plaques, a core feature of Alzheimer disease (AD) pathology.¹ Use of the first A β -specific tracer, Pittsburgh compound B (PiB), has been limited to research centers because of the short half-life of the carbon-11 radiolabel (20 minutes). A β tracers labeled with fluorine-18 (¹⁸F, $t_{1/2} = 110$ minutes) have subsequently been developed for clinical use, with one recently approved by the US Food and Drug Administration.² Few studies have evaluated the effect of amyloid PET on patient diagnosis and treatment.³⁻⁶ In a recent decision, the US Centers for Medicare & Medicaid Services (CMS) concluded that there are insufficient data that amyloid imaging affects clinical outcomes to justify reimbursing scans.⁷

Our center has conducted research studies applying PiB and ¹⁸F-fluorodeoxyglucose (FDG)-PET to evaluate the utility of PET in differential diagnosis⁸ and to study mechanisms of AD.⁹⁻¹²

From the Memory and Aging Center and Department of Neurology (P.S.-J., P.M.G., J.H., B.G., M.H., L.T.G., M.G.-T., W.W.S., A.L.B., H.J.R., J.H.K., L.M.W.), G.D.R.) and Department of Pathology and Laboratory Medicine (E.J.H.), University of California, San Francisco, University Hospital 'Marqués de Valdecilla' (IFIMAV and Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (P.S.-J.), Santander, Spain; Helen Wills Neuroscience Institute (P.M.G., W.J.), G.D.R.), University of California, Berkeley, Lawrence Berkeley National Laboratory (P.M.G., J.P.O., M.J., W.J.), G.D.R.), Berkeley, CA; Center for Neurodegeneration Research (J.Q.T.), University of Pennsylvania, Philadelphia, and Department of Pathology and Laboratory Medicine (H.V.V.), University of California, Los Angeles.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of this article.

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Supplemental data at
www.neurology.org

Utility of Amyloid and FDG-PET in Clinical Practice: Differences Between Secondary and Tertiary Care Memory Units

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Accepted 7 March 2018

Abstract. The clinical utility of amyloid positron emission tomography (PET) has not been fully established. Our aim was to evaluate the effect of amyloid imaging on clinical decision making in a secondary care unit and compare our results with a previous study in a tertiary center following the same methods. We reviewed retrospectively 151 cognitively impaired patients who underwent amyloid (Pittsburgh compound B [PiB]) PET and were evaluated clinically before and after the scan in a secondary care unit. One hundred and fifty concurrently underwent fluorodeoxyglucose (FDG)-PET. We assessed changes between the pre- and post-PET clinical diagnosis and Alzheimer's disease treatment plan. The association between PiB/FDG results and changes in management was evaluated using χ^2 and multivariate logistic regression. Concordance between classification based on scan readings and baseline diagnosis was 66% for PiB and 47% for FDG. The primary diagnosis changed after PET in 17.2% of cases. When examined independently, discordant PiB and discordant FDG were both associated with diagnostic change ($p < 0.0001$). However, when examined together in a multivariate logistic regression, only discordant PiB remained significant ($p = 0.0002$). Changes in treatment were associated with concordant PiB ($p = 0.009$) while FDG had no effect on treatment decisions. Based on our regression model, patients with diagnostic dilemmas, a suspected non-amyloid syndrome, and Clinical Dementia Rating < 1 were more likely to benefit from amyloid PET due to a higher likelihood of diagnostic change. We found that changes in diagnosis after PET in our secondary center almost doubled those of our previous analysis of a tertiary unit (9% versus 17.2%). Our results offer some clues about the rational use of amyloid PET in a secondary care memory unit stressing its utility in mild cognitive impairment patients.

Keywords: Alzheimer's disease, amyloid, dementia, FDG, PET, PiB

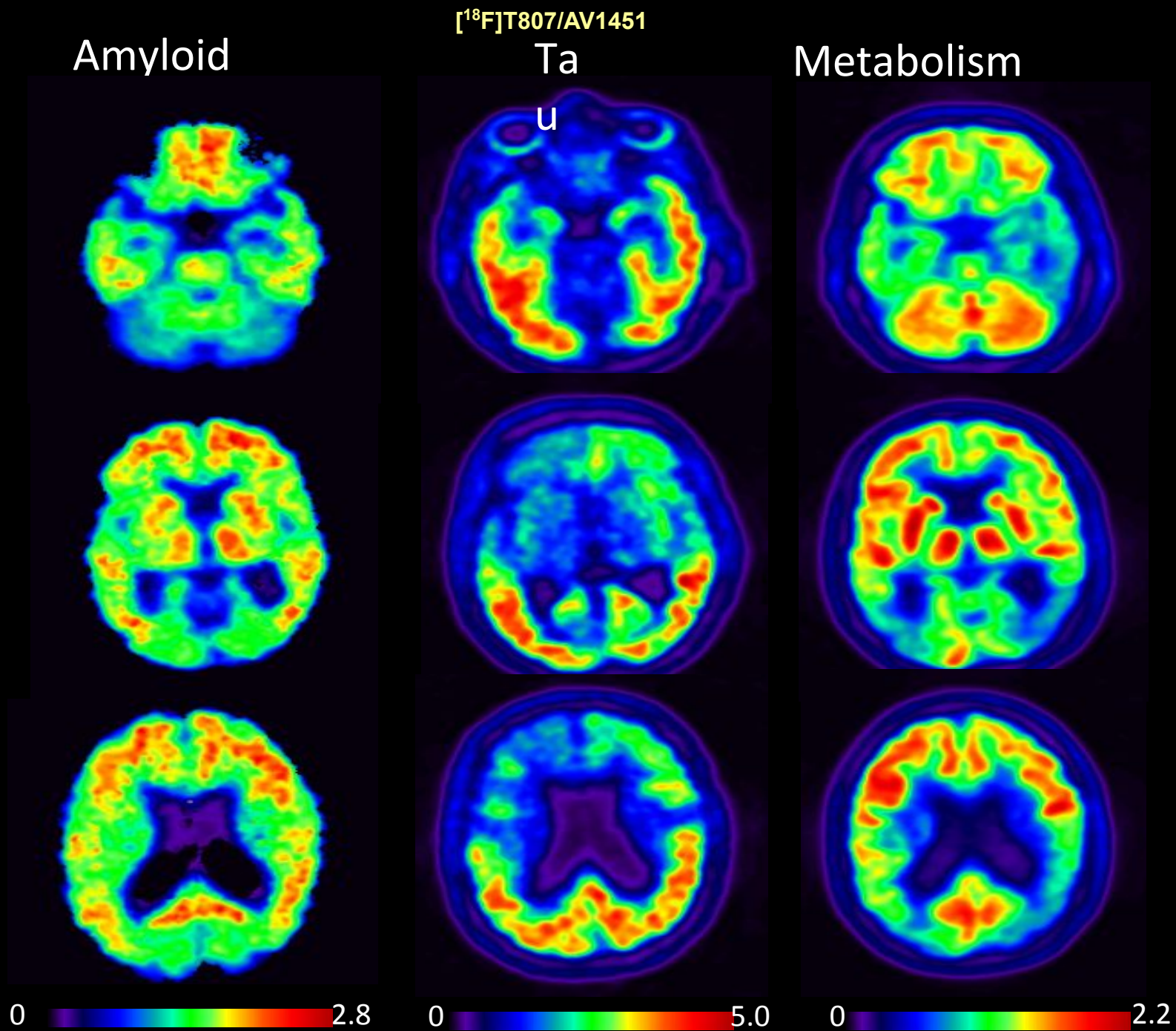
INTRODUCTION

Positron emission tomography (PET) tracers allow moderate to frequent amyloid- β (A β) plaques to be detected in the brain. There is abundant evidence of the relationship between the risk of mild cognitive

Paradoxically these test are more valuable in secondary centers than in tertiary (9% vs 17.2% diagnostic change).

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**54 yo
probable AD
(PCA)
MMSE 21**



Slide courtesy of Gil Rabinovici

Dynamic measurements of A β

EDITORIAL

Dynamic measurements of β -amyloid accumulation

The early effect of *APOE*

Pascual Sánchez-Juan,
MD, PhD
Sudha Seshadri, MD

Despite many disappointments, the strongest current in Alzheimer disease (AD) research remains the pursuit of anti-amyloid therapies. There is increasing rec-

availability of PET methods, longitudinal data in individuals without dementia is still scarce.

In this issue of *Neurology*[®], Lim and Mormino⁴

EDITORIAL

Amyloid “accumulators”

The next generation of candidates for amyloid-targeted clinical trials?

Corey T. McMillan, and Gael Chételat

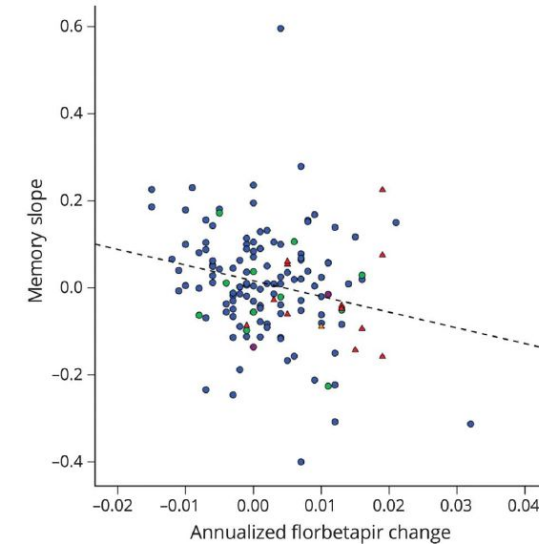
Neurology[®] 2018;0:1-2. doi:10.1212/WNL.0000000000005362

Correspondence

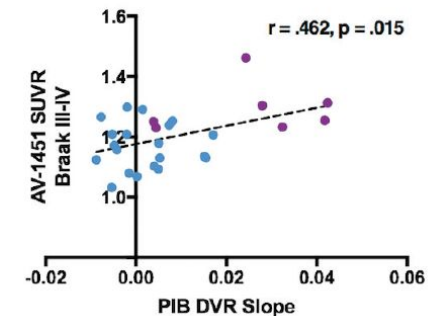
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Dynamic measurements of A β

- (Landau 2018):
 - ADNI A β - cognitively normal at baseline.
 - Sequential amyloid PET.
 - Mean follow up 4 years.
 - A β -accumulators/Non-accumulators (60%/40%)
 - Accumulation rate -> Memory deterioration
- (Leal 2018)
 - “A β -accumulators” were related to higher PET tau levels



Landau 2018



Leal 2018

FUTURO

Prevención primaria

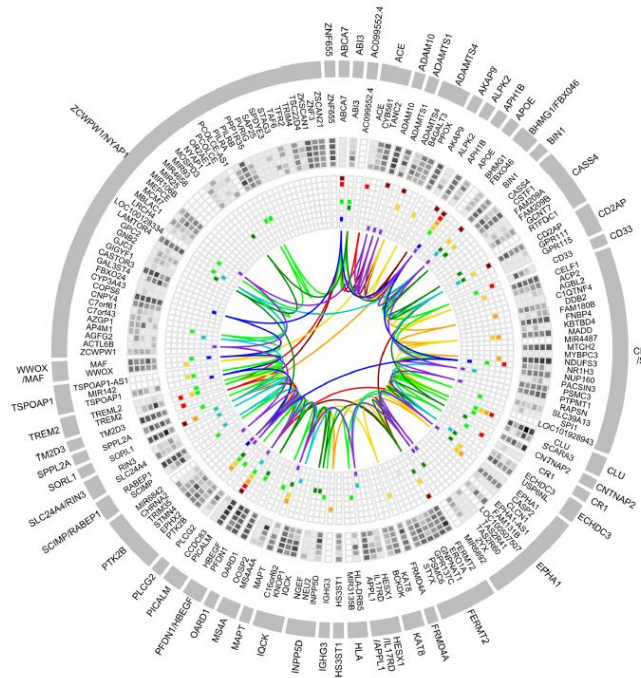
(No hay depósito de amiloide
en el cerebro)

Planes Nacionales/Regionales de Demencia

- Hasta 1/3 de los casos son evitables.
- Haciendo énfasis en educación sobre costumbres cerebro-saludables y control de riesgos comenzando –como tarde- en edades medias de la vida
- Potenciar:
 - Deporte
 - Vida activa...
- Prevenir (Estudio FINGERS)
 - Control Factores de Riesgo Cerebro-Vasculares
 - Evitar aislamiento sensorial
 - Mejorar sueño
 - Corregir procesos inflamatorios crónicos...

Prevención primaria personalizada

- Prevención primaria personalizada basada en nuestro perfil genético de riesgo



Individuos con susceptibilidad en determinadas rutas metabólicas (inflamación, colesterol, homeostasis proteínas...) deberán seguir medidas preventivas personalizadas.

Prevención secundaria

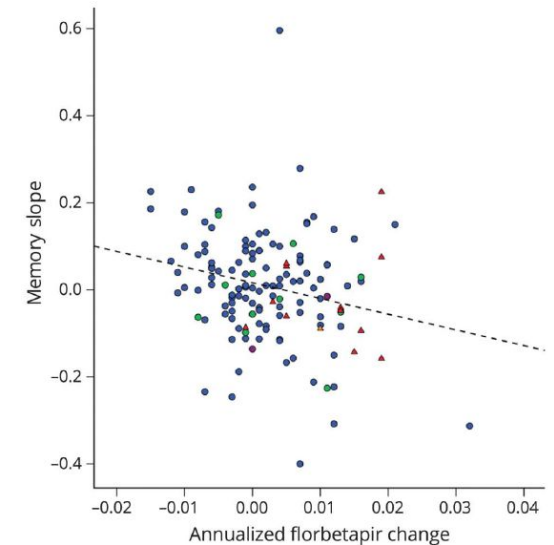
(hay depósito de amiloide en el cerebro)

Screening de individuos con acumulo de amiloide en su cerebro.

- Según el conocimiento actual el **depósito de amiloide** en el cerebro sería el primer evento patogénico.
- A día de hoy la mayoría de los **sistemas sanitarios no lo recomienda** basado en:
 1. No clara la trayectoria de los individuos Amiloide positivo (A+)
 2. Los test disponibles son muy caros (PET amiloide) o poco fiables/invasivos (LCR)
 3. No existe tratamiento que modifique la enfermedad

1. No clara la trayectoria de los individuos Amiloide positivo (A+)

- En buena medida desconocemos la evolución de estos individuos.
- Cada vez más información:
 - Cohortes prospectivas (ADNI, EPAD...**Valdecilla**)



Landau 2018

1. No clara la trayectoria de los individuos Amiloide positivo (A+)

- Efecto de la IQ en individuos con Amiloide +

PREQX

POSTQX

A- A+

A-

A+

LMT-WMSIII: 8.4 diferencia media (p 0.004)

CERAD Auditory Verbal Recall: 2.9 diferencia media (p 0.023)

Lage C en preparación

2. Los test disponibles son muy caros (PET amiloide) o poco fiables/invasivos (LCR)

A día de hoy:

- Si bien PET sigue siendo un prueba cara, hoy día su uso clínico se está extendiendo.
- Los biomarcadores de LCR se han automatizado y estandarizado y son reproducibles.
- Los biomarcadores de sangre son ya una realidad

3. No existe tratamiento que modifique la enfermedad

- FINGER (Miia Kivipelto)-> multidomain intervention
- **Necesitamos:**
 - **Fármacos/Intervenciones que cambien el curso de la enfermedad**

Manejo demencia 2023:

Screening de amiloidosis cerebral

- 1) Determinación de perfil genético de riesgo
 - Población de riesgo (población general en el futuro?)
- 2) Programas de Seguimiento
 - Marcadores en sangre secuenciales
 - E-test/Autotest

-> RESULTADO NUMÉRICO: **Puntuación de riesgo de Alzheimer**
- 3) Confirmación con marcadores de LCR o PET

E-test

- Autotest
- Dificultad para detectar cambios sutiles evitando efecto práctica
- Teléfonos móviles que repiten periódicamente ciertos test y con ayuda de inteligencia artificial detectan primeros signos de deterioro
- Altavoz inteligente que te pregunta cada mañana si recuerdas una serie de palabras
- Sensores que detectan sutiles cambios en el patrón sueño
- Alfombras y sensores ópticos que miden si tu marcha y equilibrio han cambiado ligeramente.

Cuidados por la 'habitación inteligente'



La Universidad, el Idival y la empresa Ambar trabajan en un innovador proyecto de «salud digital» para mejorar la calidad asistencial de las personas mayores

Tratamientos prevención secundaria en 2030

Ejemplo de las estatinas como prevención infarto

- ... pero AD es mucho más complejo y participan varias proteínas y vías metabólicas (tau, amiloide, tdp43, inflamación, homeostasis de proteínas...)
- Necesario por tanto:
 - **Medicina de precisión:** Fármacos específicos de acuerdo al perfil de susceptibilidad (Ej: ANAVEX Phase 2^a; Target Sigma -1Receptor (SIGMAR1))
 - Aproximación compleja con **múltiples estrategias farmacológicas y NO farmacológicas**

Resumen

- Prevención primaria **macro** (planes de demencia) y **micro** (prevención personalizada en individuos de riesgo)
- Prevención secundaria: detección precoz de individuos en riesgo
 - Genética
 - E-test
 - Biomarcadores
- Profilaxis secundaria con estrategias **combinadas** farmacológicas y no farmacológicas dirigidas de forma **individual** según el perfil del individuo.

En el futuro, la llegada del paciente al neurólogo con una demencia sin diagnóstico previo debería ser un fracaso del sistema.



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UDC