BRESCIA, 10 MARZO 2018

Malattia di Alzheimer Aspetti diagnostici: Luci ed ombre

Orazio ZANETTI

Italian Society of Gerontology and Geriatrics

Alzheimer Unit – Memory Clinic – Clinical Trial Unit

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SOCIETÀ ITALIANA
DI GERONTOLOGIA
E GERIATRIA

Summary

- History
- Numbers
- Prevention
- Diagnosis
- Therapy
- Care (long term care)
- Ethical issues
- *Citizenschip*

Summary

- **History**
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THE LANCET *1997*

Department of medical history

Auguste D and Alzheimer's disease

The discover
(1906)

Konrad Maurer, Stephan Volk, Hector Gerbaldo

Figure 3: **Auguste D**

Editorial

The Prevalence and Malignancy of Alzheimer Disease

A Major Killer

An accompanying letter to the editor (p 304) provides another illustration of the malignancy of Alzheimer disease, a phenomenon well known to neurologists. Katzman and Karasu[1] estimate that the senile form of Alzheimer disease may rank as the fourth or fifth most common cause of death in the United States. Yet the US vital statistics tables do not list "Alzheimer disease," "senile dementia," or "senility" as a cause of death, even in the extended list of 288 causes of death.

The argument that Alzheimer disease is a major killer rests on the assumption that Alzheimer disease and senile dementia are a single process and should, therefore, be considered a single disease. Both Alzheimer disease and senile dementia are progressive dementias with similar changes in mental and neurological status that are indistinguishable by careful clinical analyses.[1-3] The pathological findings are identical—atrophy of the brain, marked loss of neurons, neurofibrillary tangles, granulovacuolar changes, and neuritic (senile) plaques. Ultrastructural studies have established the identity of the neurofibrillary tangle with its twisted tubule and the senile plaque with its amyloid core and degenerating neurites in the brains of patients with Alzheimer disease (under age 65) and senile dementia (over age 65). Most recent ultrastructural and neurochemical studies indicate that the neurofibrillary tangle in both disorders is characterized by the twisted tubule that represents two neurofilaments joined together in a helical fashion with a period of 800 Angstroms. The studies of Tomlinson et al[4] and Blessed et al[5] have established a quantitative correlation between the degree of dementia and the number of neurofibrillary tangles and senile plaques in the cerebral cortex. The evidence on which a distinction between senile dementia and Alzheimer disease can still be argued is the genetic analysis of Larsson et al.[6] In their analysis of the kindred of patients with senile dementia, numerous relatives were found with senile dementia, but none with a diagnosis of Alzheimer disease. However, the incidence of the Alzheimer senile dementia complex is strongly age-related, even among the elderly. Larsson et al[6] had suggested a predisposing, autosomal dominant gene with age-related penetrance, reaching a penetrance of 40% at age 90. Therefore, the absence of any relative with "Alzheimer disease" might be related to its relative infrequency in patients under 65. Moreover, in a genetic study carried out in Switzerland, Constantinidis et al[7] encountered the two diseases in the same family. Although further studies are clearly indicated, the fact remains that neither the clinician, the neuropathologist, nor the electron microscopist can distinguish between the two disorders, except by the age of the patient. Today, the majority of workers in the field accept the identity of the two disease.[8] We believe that it is time to drop the arbitrary age distinction and adopt the single designation, Alzheimer disease.

Precise epidemiological information is not available concerning the prevalence of Alzheimer disease in the United States. However, several excellent community surveys of the prevalence of organic dementias in persons over age 65 have been carried out in northern Europe.[9-13] In these series, care has been taken to include persons living at home as well as those receiving institutional care. The prevalence of "severe dementia" or organic "psychosis," terms used to describe patients in whom, in addition to intellectual deterioration, there was evidence of disorganization of the personality and inability to carry out the normal tasks of daily living, averaged 4.1%. The prevalence of "mild dementia" and "mild mental deterioration" or "chronic brain syndrome without psychosis," terms used to describe individuals with intellectual impairment who are still able to carry out activities of daily living, averaged 10.8%. Estimates of the incidence of Alzheimer disease (senile dementia) among patients over age 65 with organic dementia vary between 40%[10] and 58%.[9] Applying these figures to the United States, the prevalence of Alzheimer disease in persons over age 65 would have been between 360,000 and 510,000 in 1970. If the same ratio held for those with moderate dementia, then the prevalence of those with a chronic brain syndrome without psychosis due to Alzheimer disease would be between 850,000 and 1,200,000.

An estimate of the malignancy of Alzheimer disease may be made as follows. Studies of patients with this disorder show a marked decrease in life expectancy, depending on the age at onset of symptoms.[4,17-19] In a series from Stockholm analyzed by Kay,[17] the average survival period was 2.6 years for demented males compared to 8.7 years for the age-matched non-demented male population, and 2.3 years for demented females compared to an expected survival of 10.9 years. The data analyzed by Wang and Whanger,[21] who applied life tables, were somewhat more optimistic. In patients with senile dementia, the average age at onset was 74.1, with 5.1 remaining years of life as against an expectancy of 9.6 years. In arteriosclerotic brain disorders with an average age at onset of 66.3 years and a survival expectancy of 14.0 years, death occurred within an average of 3.8 years. In a small series of patients with the presenile form of Alzheimer disease whose average age at onset was 60, the life expectancy should have been 23.1 years, yet death occurred within 7.1 years.

Based only on the prevalence of the severe forms of dementia and the life expectancy as noted above, between 60,000 and 90,000 persons with senile dementia die each year, and these estimates do not take into account persons under age 65 or those within whom the moderate forms of dementia may shorten life expectancy. None of these estimates correspond to the US vital statistics tables,[22-24] as noted above. The death certificates of patients with senile dementia bear witness to the bronchopneumonia, myocardial infarct, pulmonary embolus, cerebrovascular accident, or other acute event occurring at death.[16,20,25] But such events also may mercifully end the life of patients with malignant neoplasms. Yet, the latter diagnosis enters the death certificate as the first cause of death while we officially ignore the existence of senile dementia.

Our estimate of the prevalence of Alzheimer disease has been based on conservative assumptions. We have not included in our estimate those patients with the presenile (under age 65) form of Alzheimer disease, nor have we corrected our figures for the increase in average age in the population over 65 that occurs decade-by-decade. But even if the true prevalence were double our estimate, one still might be surprised as how little was the incidence of true senility or Alzheimer disease.

A mild form of defect in memory storage or recall, a condition that Kral[26] has termed "benign senescent forgetfulness," may be relatively common as the population ages. However, these minor changes do not result in the functional disability or increased mortality that can be directly attributed to Alzheimer disease. The functional integrity in extreme old age is not confined to an Adenauer, Picasso, or a Casals but has been shown by the Duke longitudinal study.[27] In focusing attention on the mortality associated with Alzheimer disease, our goal is not to find a way to prolong the life of severely demented persons, but rather to call attention to our belief that senile as well as presenile forms of Alzheimer are a single disease, a disease whose etiology must be determined, whose course must be aborted, and ultimately a disease to be prevented.

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Bronx, NY

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THE NEW DISCOVER 1976

Summary

- History
- **Numbers**
- Prevention
- Diagnosis
- Therapy
- Care (long term care)
- Ethical issues
- Citizenschip

Ageing populations: the challenges ahead

Kaare Christensen, Gabriele Doblhammer, Roland Rau, James W Vaupel

Lancet 2009; 374: 1196–208
See Editorial page 1120

If the pace of increase in life expectancy in developed countries over the past two centuries continues through the 21st century, most babies born since 2000 in France, Germany, Italy, the UK, the USA, Canada, Japan, and other

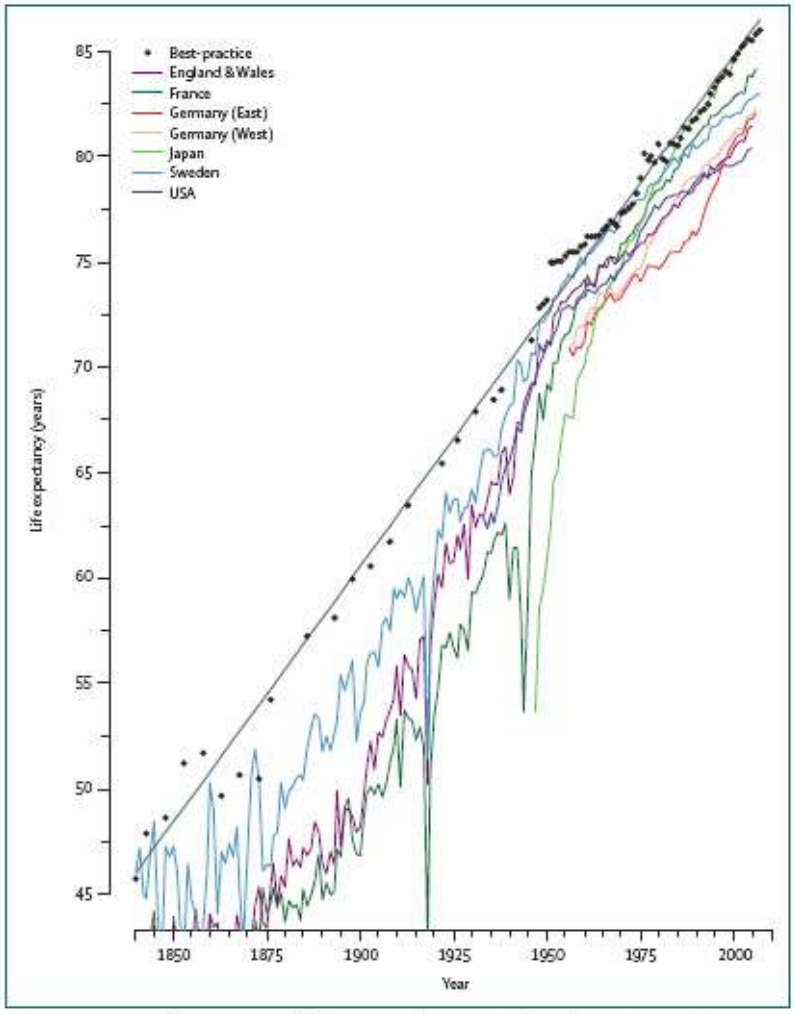
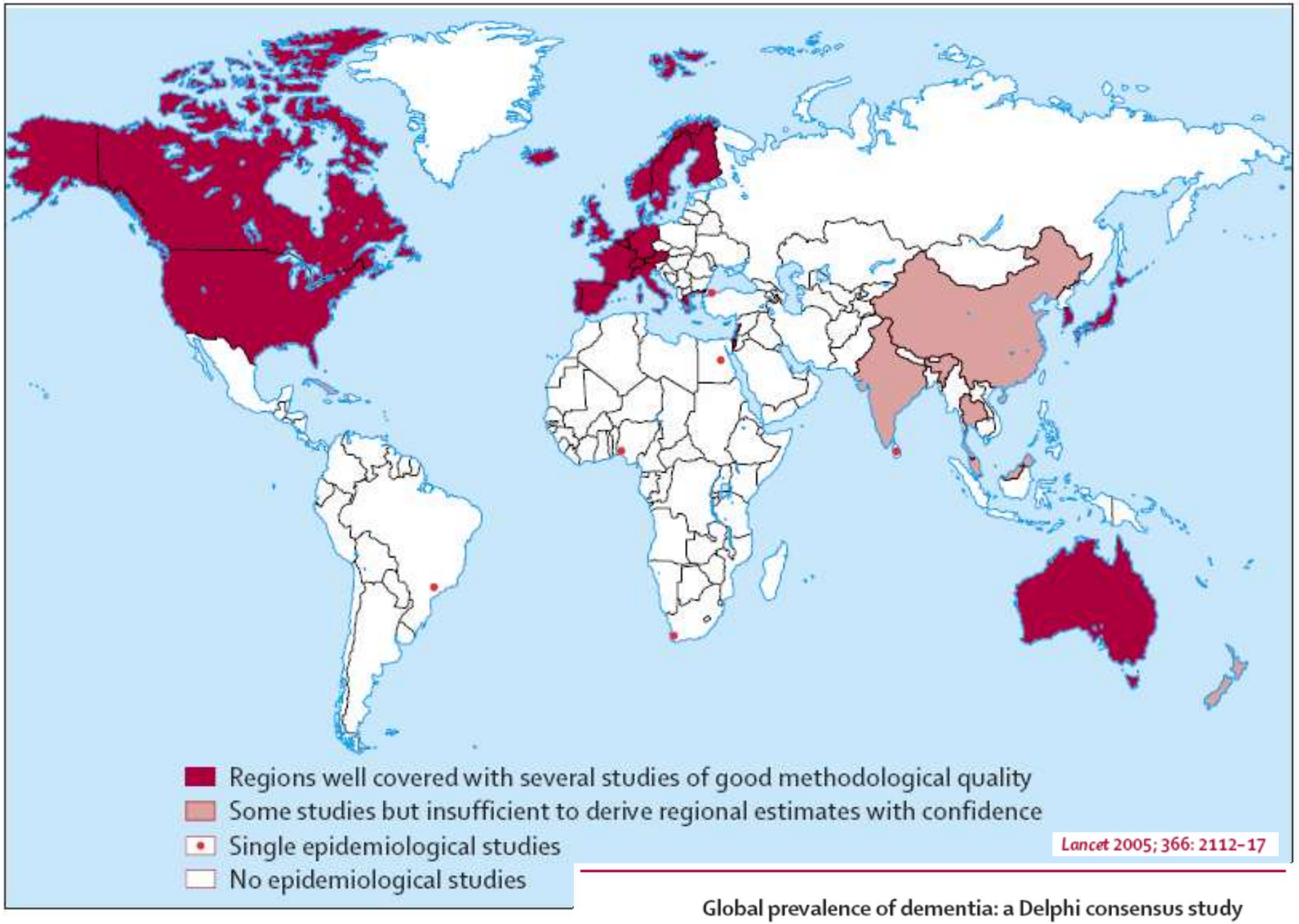


Figure 1: Best-practice life expectancy and life expectancy for women in selected countries from 1840 to 2007
Linear regression trend depicted by solid grey line with a slope of 0·24 per year. Data from supplementary material of reference 12 and the Human Mortality Database.

The good news



Lancet 2005; 366: 2112–17

Global prevalence of dementia: a Delphi consensus study

Claudia P Ferri, Martin Prince, Carol Brayne, Henry Brodaty, Laura Fratiglioni, Mary Ganguli, Kathleen Hall, Kazuo Hasegawa, Hugh Hendrie, Yueqin Huang, Anthony Jorm, Colin Mathers, Paulo R Menezes, Elizabeth Rimmer, Marcia Scazufca, for Alzheimer's Disease International

Figure 1: **Prevalence studies worldwide**

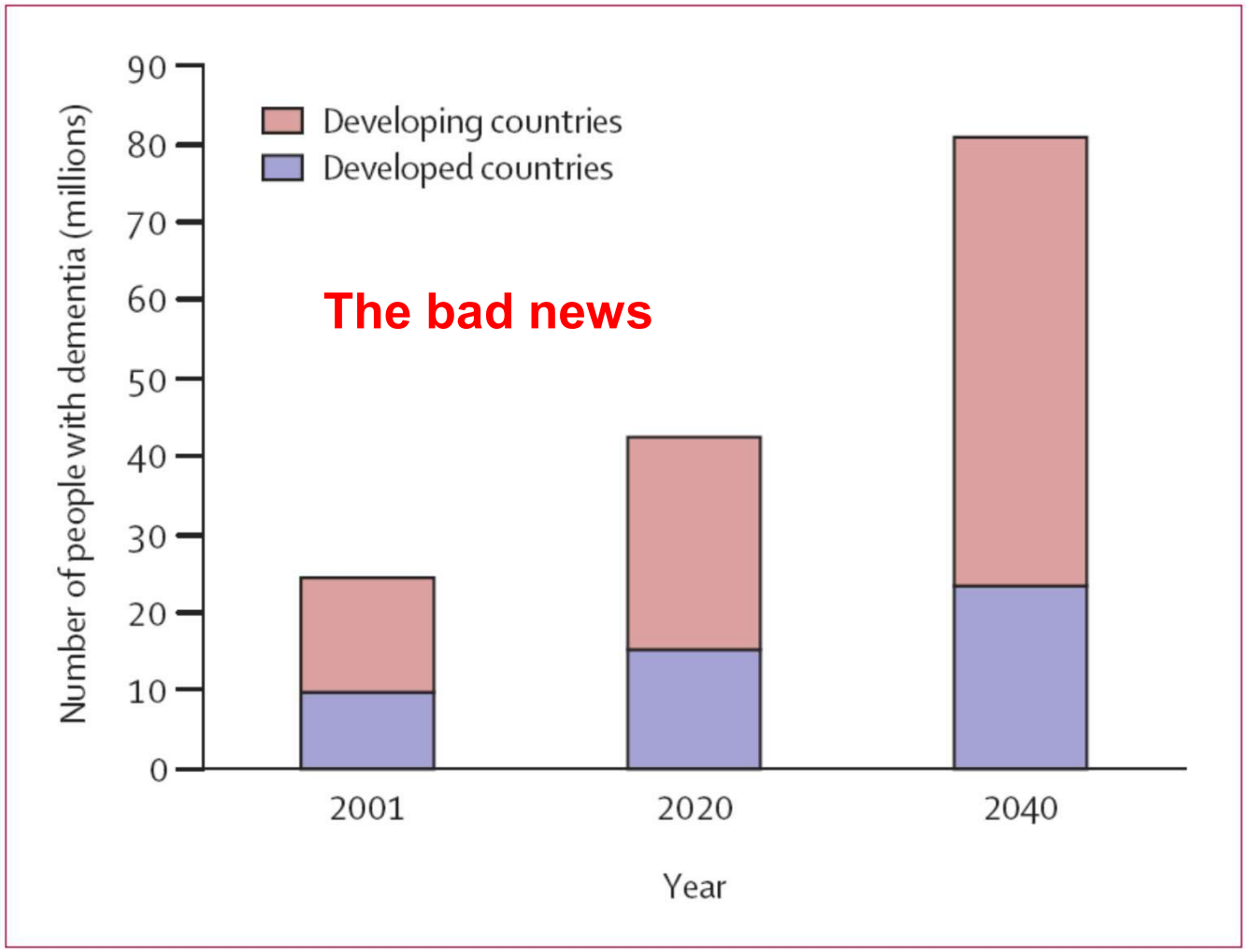


Figure 2: Number of people with dementia in developed and developing countries

Lancet 2005; 366: 2112–17

ELSEVIER

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Alzheimer's & Dementia

Review Articles

The global prevalence of dementia: A systematic review and metaanalysis

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The very bad news

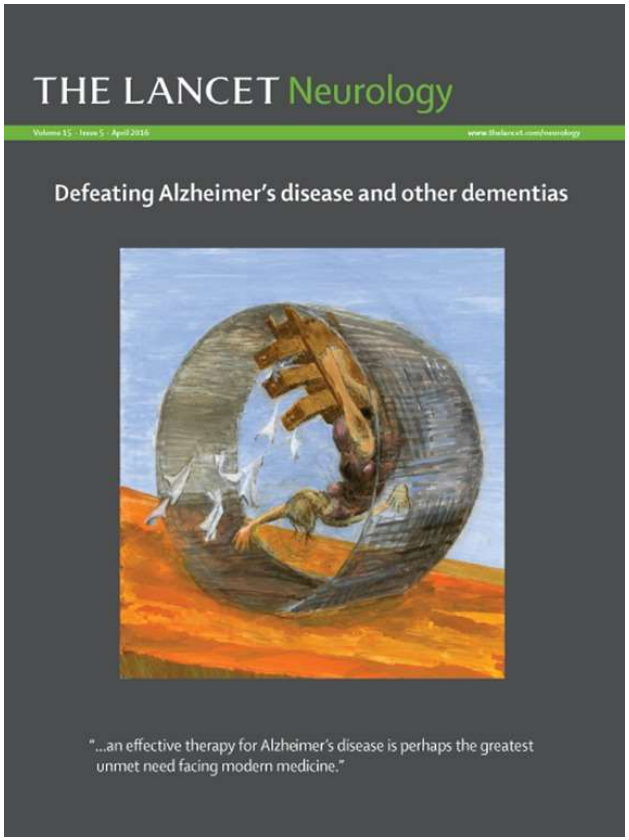
Table 4
Total population >60, crude estimated prevalence of dementia (2010), estimated number of people with dementia (2010, 2030 and 2050) and proportionate increases (2010–2030 and 2010–2050) by GBD world region

GBD region	Over 60 population (millions, 2010)	Crude estimated prevalence (%, 2010)	Number of people with dementia (millions)			Proportionate increases (%)	
			2010	2030	2050	2010–2030	2010–2050
Asia	406.55	3.9	15.94	33.04	60.92	107	282
Australasia	4.82	6.4	0.31	0.53	0.79	71	157
Asia Pacific	46.63	6.1	2.83	5.36	7.03	89	148
Oceania	0.49	4.0	0.02	0.04	0.10	100	400
Central Asia	7.16	4.6	0.33	0.56	1.19	70	261
East Asia	171.61	3.2	5.49	11.93	22.54	117	311
South Asia	124.61	3.6	4.48	9.31	18.12	108	304
South East Asia	51.22	4.8	2.48	5.30	11.13	114	349
Europe	160.18	6.2	9.95	13.95	18.65	40	87
Western Europe	97.27	7.2	6.98	10.03	13.44	44	93
Central Europe	23.61	4.7	1.10	1.57	2.10	43	91
Eastern Europe	39.30	4.8	1.87	2.36	3.10	26	66
The Americas	120.74	6.5	7.82	14.78	27.08	89	246
North America	63.67	6.9	4.38	7.13	11.01	63	151
Caribbean	5.06	6.5	0.33	0.62	1.04	88	215
Andean LA	4.51	5.6	0.25	0.59	1.29	136	416
Central LA	19.54	6.1	1.19	2.79	6.37	134	435
Southern LA	8.74	7.0	0.61	1.08	1.83	77	200
Tropical LA	19.23	5.5	1.05	2.58	5.54	146	428
Africa	71.07	2.6	1.86	3.92	8.74	111	370
North Africa/Middle East	31.11	3.7	1.15	2.59	6.19	125	438
Central SSA	3.93	1.8	0.07	0.12	0.24	71	243
East SSA	16.03	2.3	0.36	0.69	1.38	92	283
Southern SSA	4.66	2.1	0.10	0.17	0.20	70	100
West SSA	15.33	1.2	0.18	0.35	0.72	94	300
World	758.54	4.7	35.56	65.69	115.38	85	225

Abbreviations: LA, Latin America; SSA, Sub-Saharan Africa

Defeating Alzheimer's disease and other dementias: a priority for European science and society

Bengt Winblad, Philippe Amouyel, Sandrine Andrieu, Clive Ballard, Carol Brayne, Henry Brodaty, Angel Cedazo-Minguez, Bruno Dubois, David Edvardsson, Howard Feldman, Laura Fratiglioni, Giovanni B Frisoni, Serge Gauthier, Jean Georges, Caroline Graff, Khalid Iqbal, Frank Jessen, Gunilla Johansson, Linus Jönsson, Miia Kivipelto, Martin Knapp, Francesca Mangialasche, René Melis, Agneta Nordberg, Marcel Olde Rikkert, Chengxuan Qiu, Thomas P Sakmar, Philip Scheltens, Lon S Schneider, Reisa Sperling, Lars O Tjernberg, Gunhild Waldemar, Anders Wimo, Henrik Zetterberg



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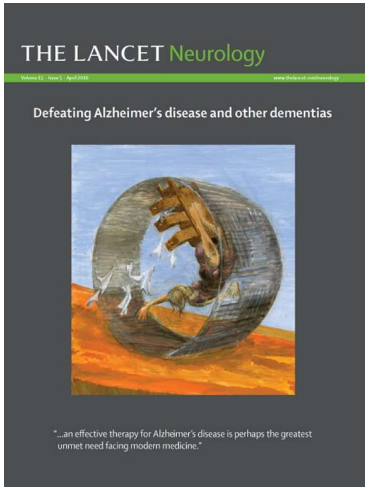


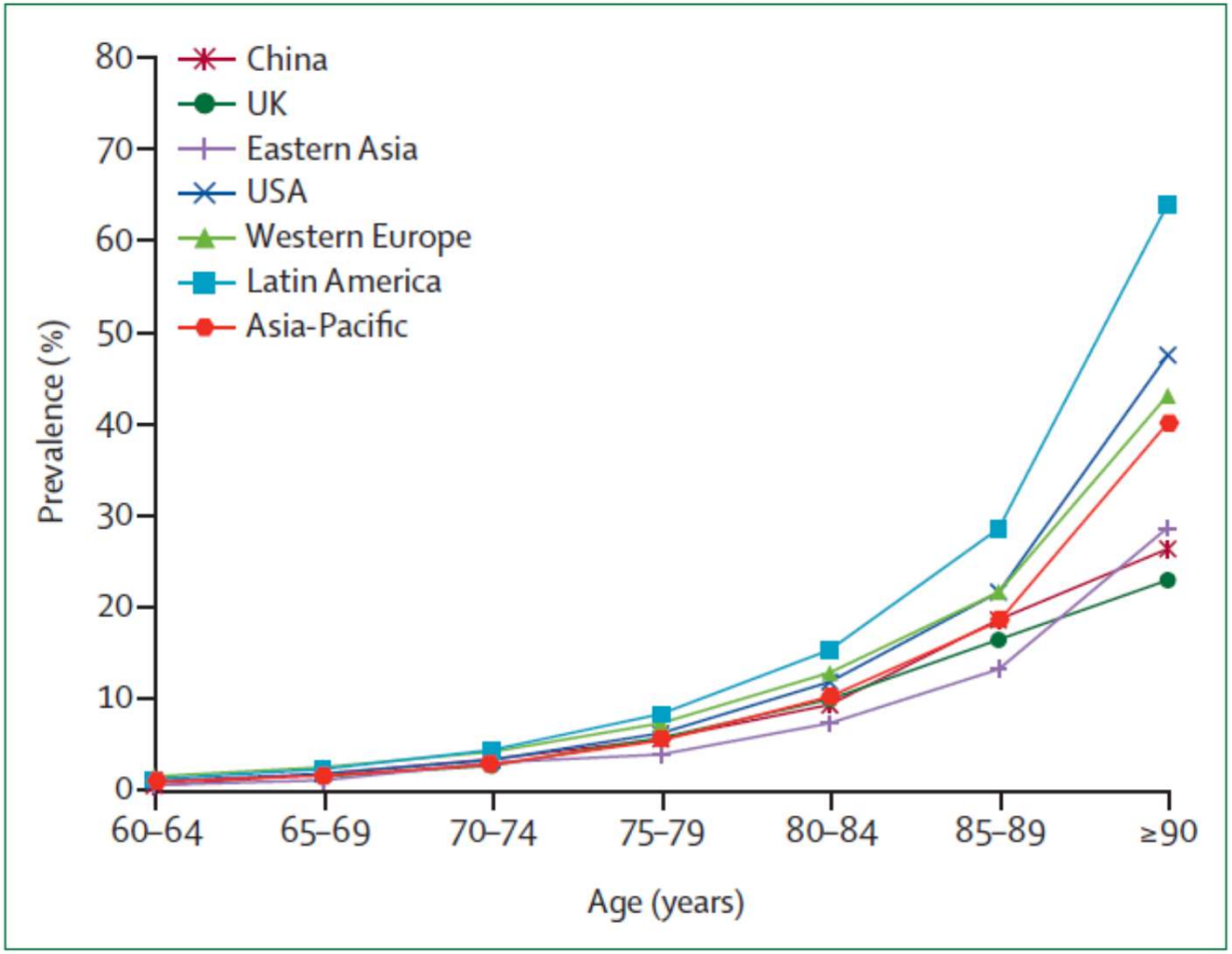
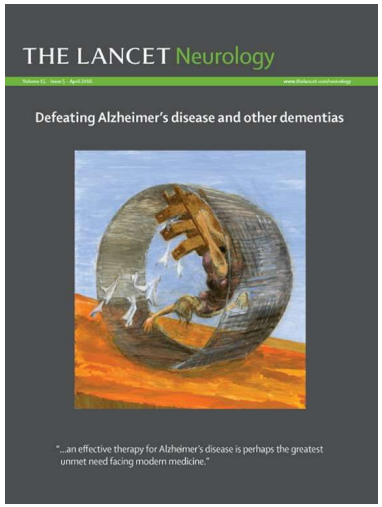
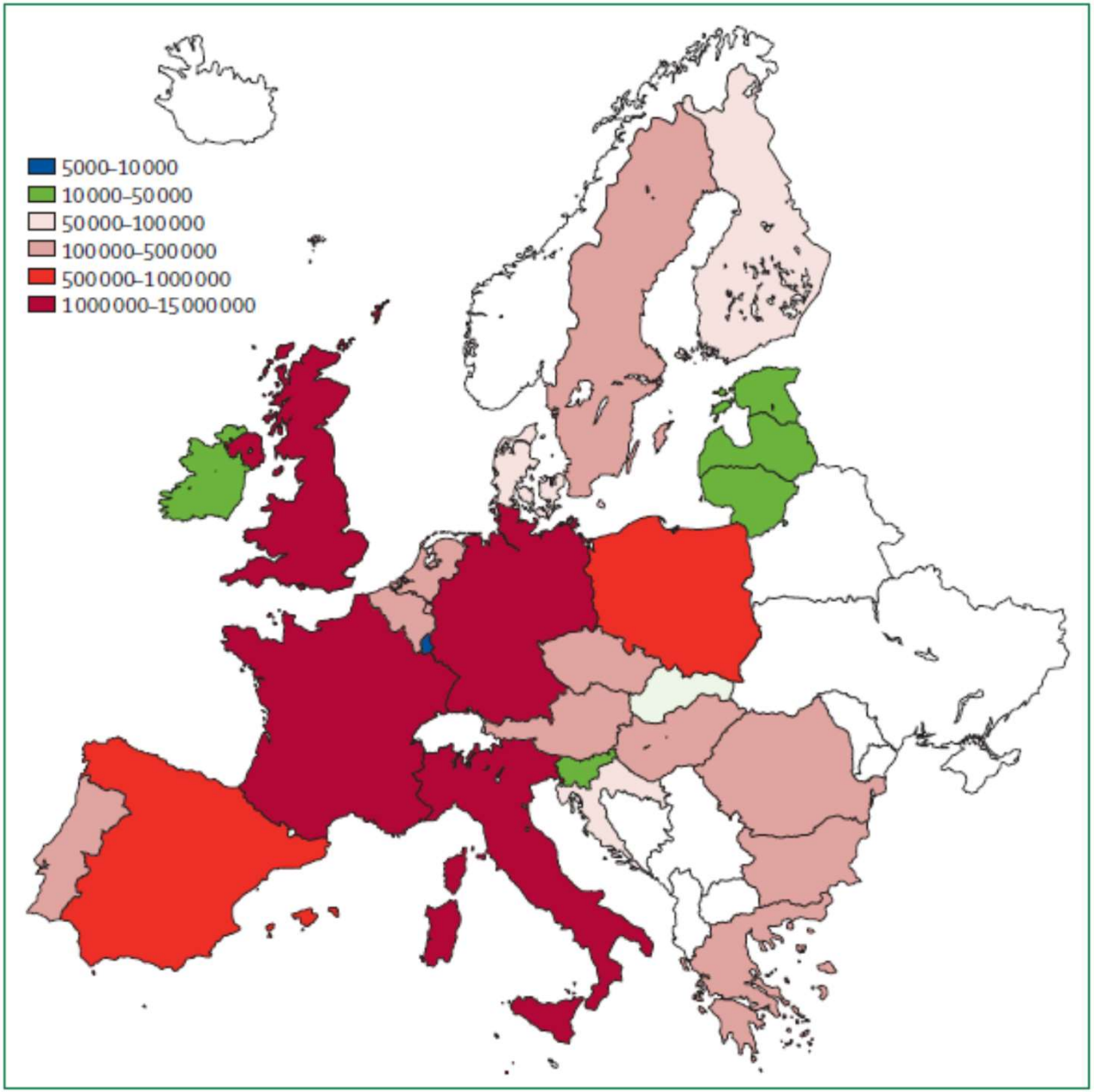


Figure 3: Age-specific prevalence of dementia by world region and in major countries





Total number of persons with dementia

ELSEVIER

Alzheimer's & Dementia 9 (2013) 1–11

Alzheimer's & Dementia

Featured Articles

The worldwide economic impact of dementia 2010

Anders Wimo[a,b,*], Linus Jönsson[c], John Bond[d], Martin Prince[e,†], Bengt Winblad[b,†]; on behalf of Alzheimer Disease International

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Table 4
Cost per person with dementia by World Bank income region

World Bank income region	Informal care (all ADLs), US$	Direct costs, US$		Total costs, US$
		Medical	Social	
Low	500	244	124	868
Lower middle	2012	717	380	3109
Upper middle	2879	2194	1755	6827
High	13,244	4766	14,855	32,865
All	7084	2711	7191	16,986

Abbreviation: ADLs, activities of daily living.

COSTS

Summary

- History
- Numbers
- **Prevention**
- Diagnosis
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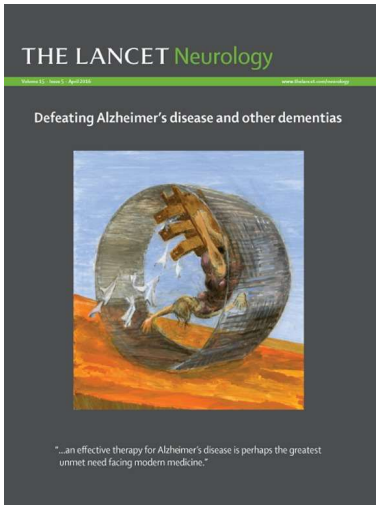
- Care (long term care)
- Ethical issues
- Citizenschip



Panel 4: Putative risk and protective factors for late-onset dementia and Alzheimer's disease

Risk factors

Older age

Genetic factors

- Familial aggregation (two or more family members with the disease)
- *APOE* ε4 allele
- Other susceptibility genes (eg, *CR1*, *PICALM*, *CLU*, *TREM2*, *TOMM40*)

Vascular risk and metabolic factors

- Atherosclerosis
- Cerebral macrovascular and microvascular lesions
- Cardiovascular diseases
- Diabetes mellitus and pre-diabetes
- Midlife hypertension
- Midlife overweight and obesity
- Midlife high serum cholesterol

Lifestyle factors

- Sedentary lifestyle
- Smoking
- Heavy alcohol consumption

Diet and nutritional factors

- Saturated fats
- Hyperhomocysteinaemia
- Deficiencies in vitamin B6, B12, and folate

Other factors

- Depression
- Traumatic brain injury
- Occupational exposure (eg, heavy metals, extremely-low-frequency electromagnetic fields)
- Infectious agents (eg, herpes simplex virus type I, *Chlamydophila pneumoniae*, spirochetes)

Protective factors

Genetic factors

- Some genes proposed (eg, *APP*, *APOE* ε2 allele)

Psychosocial factors

- High education and socioeconomic status
- High work complexity
- Rich social network and social engagement
- Mentally stimulating activity

Lifestyle factors

- Physical activity
- Light-to-moderate alcohol intake

Diet and nutritional factors

- Mediterranean diet
- Polyunsaturated fatty acid and fish-related fats
- Vitamin B6, vitamin B12, and folate
- Antioxidant vitamins (A, C, E)
- Vitamin D

Drugs

- Antihypertensive drugs
- Statins
- Hormone replacement therapy
- Non-steroidal anti-inflammatory drugs

Many risk and protective factors for dementia and Alzheimer's disease have been proposed and investigated; however, the evidence to support the factors listed here is variable, and the relevance of several proposed factors is open to debate. The most pronounced risk factors are advancing age and carrying one or two *APOE* ε4 alleles.

APOE=apolipoprotein E. *CR1*=complement component receptor 1. *PICALM*=phosphatidylinositol-binding clathrin assembly protein. *CLU*=clusterin. *TREM2*=triggering receptor expressed on myeloid cells 2. *TOMM40*=translocase of outer mitochondrial membrane 40 homologue. *APP*=amyloid precursor protein.

2014

Dementia

World Alzheimer's Month

September

Alzheimer's Disease International

Can we reduce the risk?

Summary

- History
- Numbers
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La Commissione accelera gli interventi sul morbo di Alzheimer e altre malattie neurodegenerative

Oggi (22 luglio 2009) la Commissione ha adottato proposte concrete per il morbo di Alzheimer e altre forme di demenza e malattie neurodegenerative.
(http://ec.europa.eu/health/ph_information/dissemination/diseases/alzheimer_en.htm)

Quattro settori principali di intervento:

1) Interventi tempestivi per diagnosticare la demenza (e ridurne i rischi)

2) Migliore coordinamento delle attività di ricerca tra i paesi dell'UE

3) Condivisione delle buone prassi

4) Creazione di un forum di riflessione sui diritti, l'autonomia e la dignità dei pazienti.

LA DIAGNOSI PRECOCE MIGLIORA GLI OUTCOME PER PAZIENTE E FAMIGLIA

World Alzheimer's Day™ - September 21, 2009

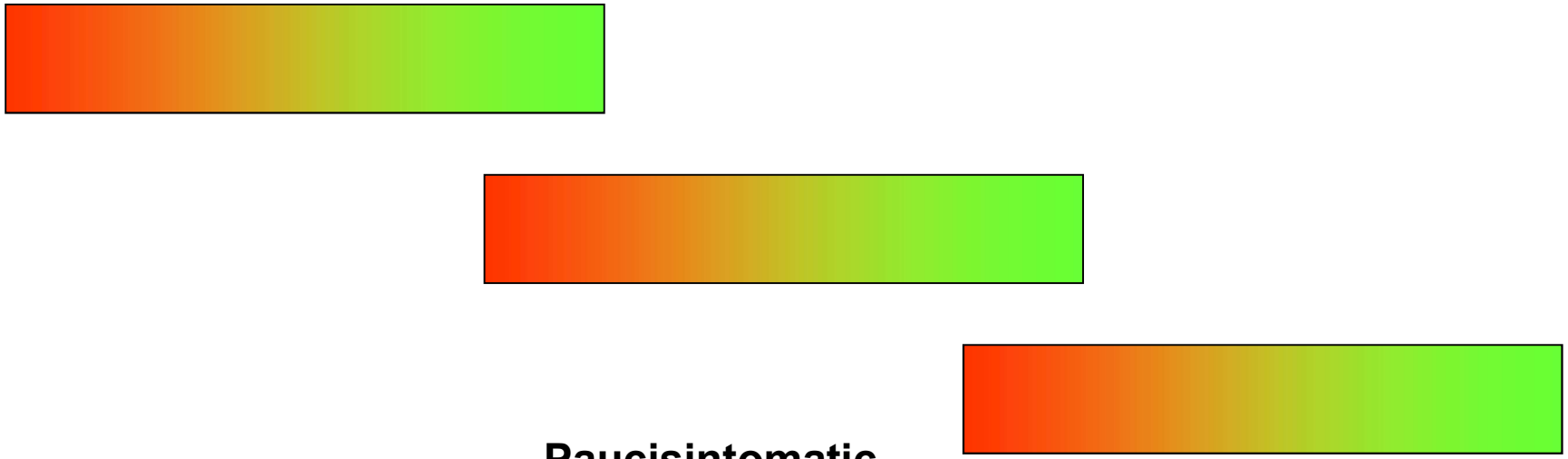
Diagnosi della Demenza:
See It Sooner

DIAGNOSI PRECOCE !

The theme for World Alzheimer's Day™ 2009 is 'Diagnosing Dementia: **See It Sooner**'.

The range of cognitive impairment

Normal **“MCI”** **Dementia**



Asintomatic

Preclinical phase-presintomatic

Paucisintomatic

Predementia phase

Prodromal dementia

Sintomatic

Clear dementia

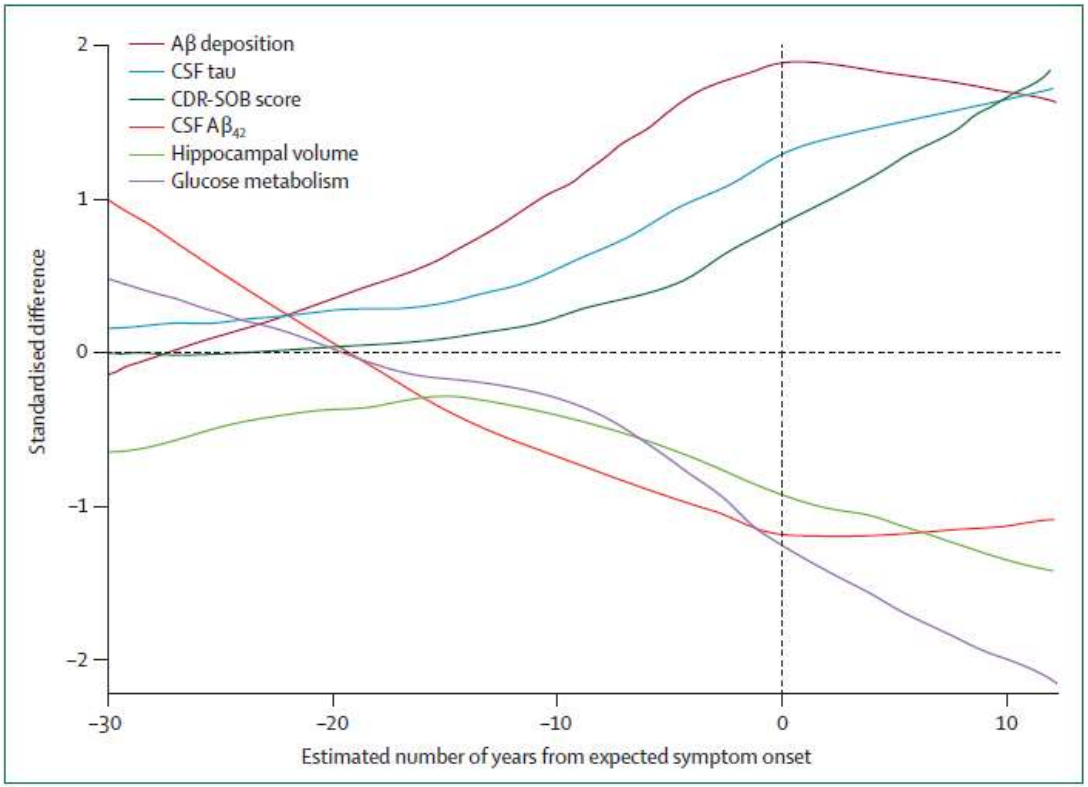


Figure 4: **Temporal ordering of biomarkers in carriers of autosomal-dominant mutations**
Cross-sectional data from the Dominantly Inherited Alzheimer's Network (DIAN) study.[54] Temporal ordering is inferred by anchoring each individual's current age to the age of dementia onset in his or her affected parent. The proposed order in which biomarkers become abnormal is: CSF $A\beta_{42}$; amyloid PET; CSF tau; fluorodeoxyglucose PET and structural MRI; followed by clinical symptoms. Aβ=amyloid β. CDR-SOB=Clinical Dementia Rating Scale Sum of Boxes. Reproduced from Bateman et al,[54] by permission of the Massachusetts Medical Society.

The NEW ENGLAND JOURNAL of MEDICINE

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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

Bateman et al. N Engl J Med 2012;367:795-804;
Jack et al. Lancet Neurol 2010;9:119-28

Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade

Clifford R Jack Jr, David S Knopman, William J Jagust, Leslie M Shaw, Paul S Aisen, Michael W Weiner, Ronald C Petersen, John Q Trojanowski

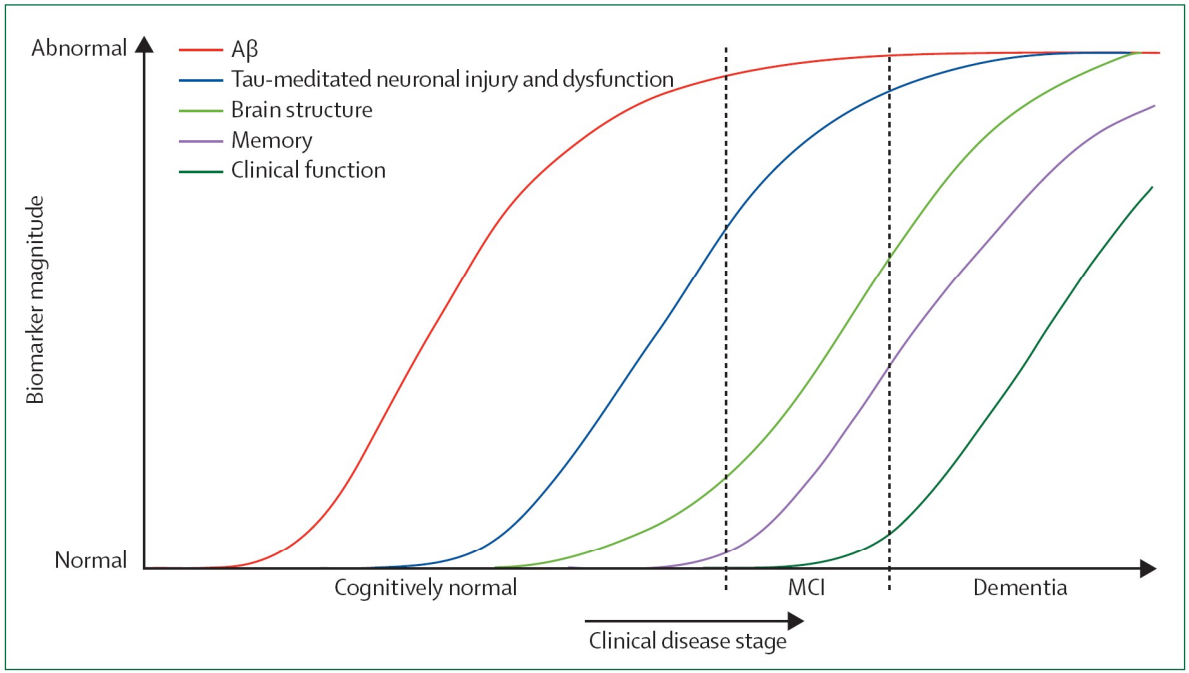


Figure 2: **Dynamic biomarkers of the Alzheimer's pathological cascade**
Aβ is identified by CSF $A\beta_{42}$ or PET amyloid imaging. Tau-mediated neuronal injury and dysfunction is identified by CSF tau or fluorodeoxyglucose-PET. Brain structure is measured by use of structural MRI. Aβ=β-amyloid. MCI=mild cognitive impairment.

Jack et al. Lancet Neurol 2010;9:119-28

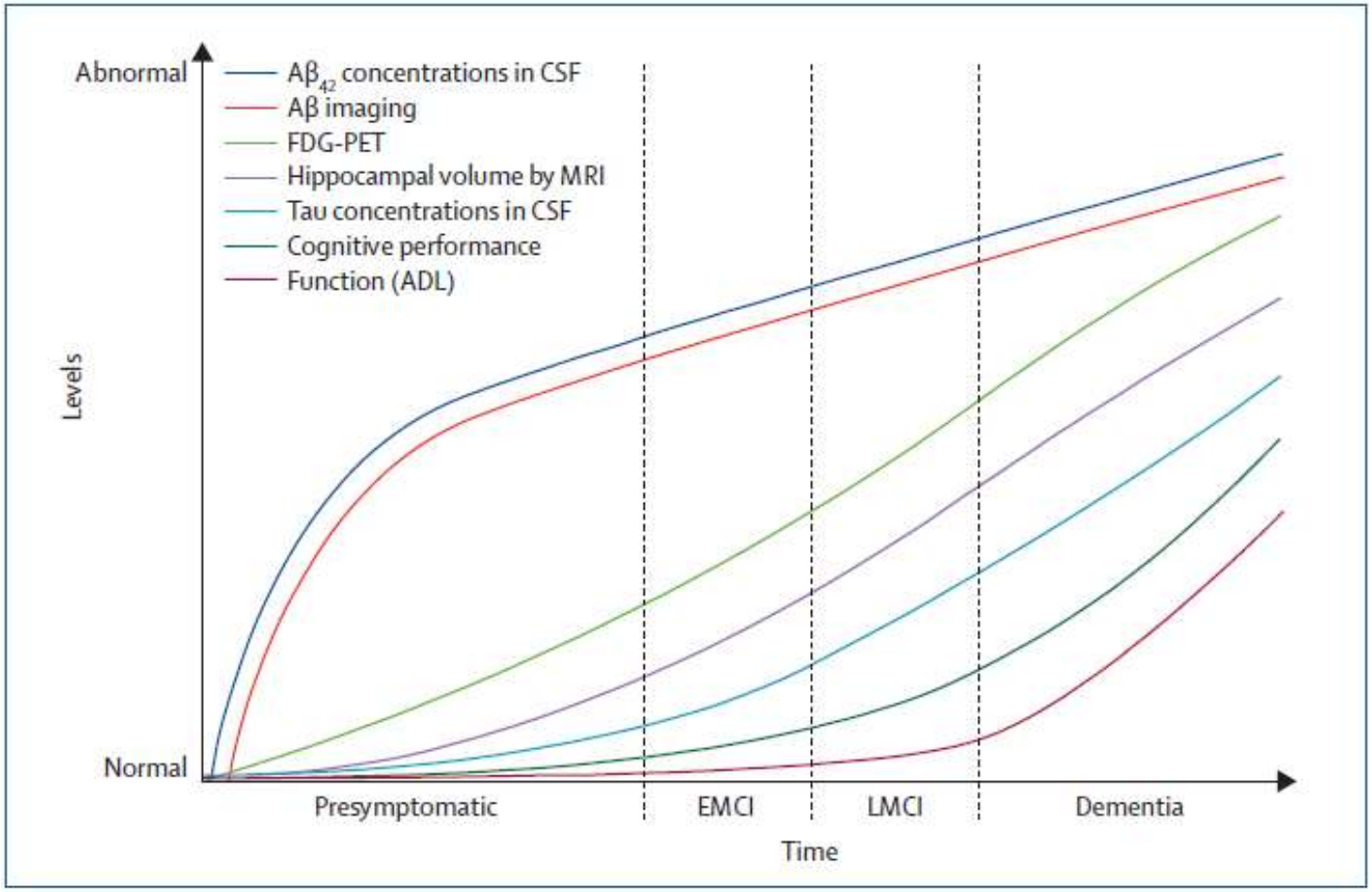
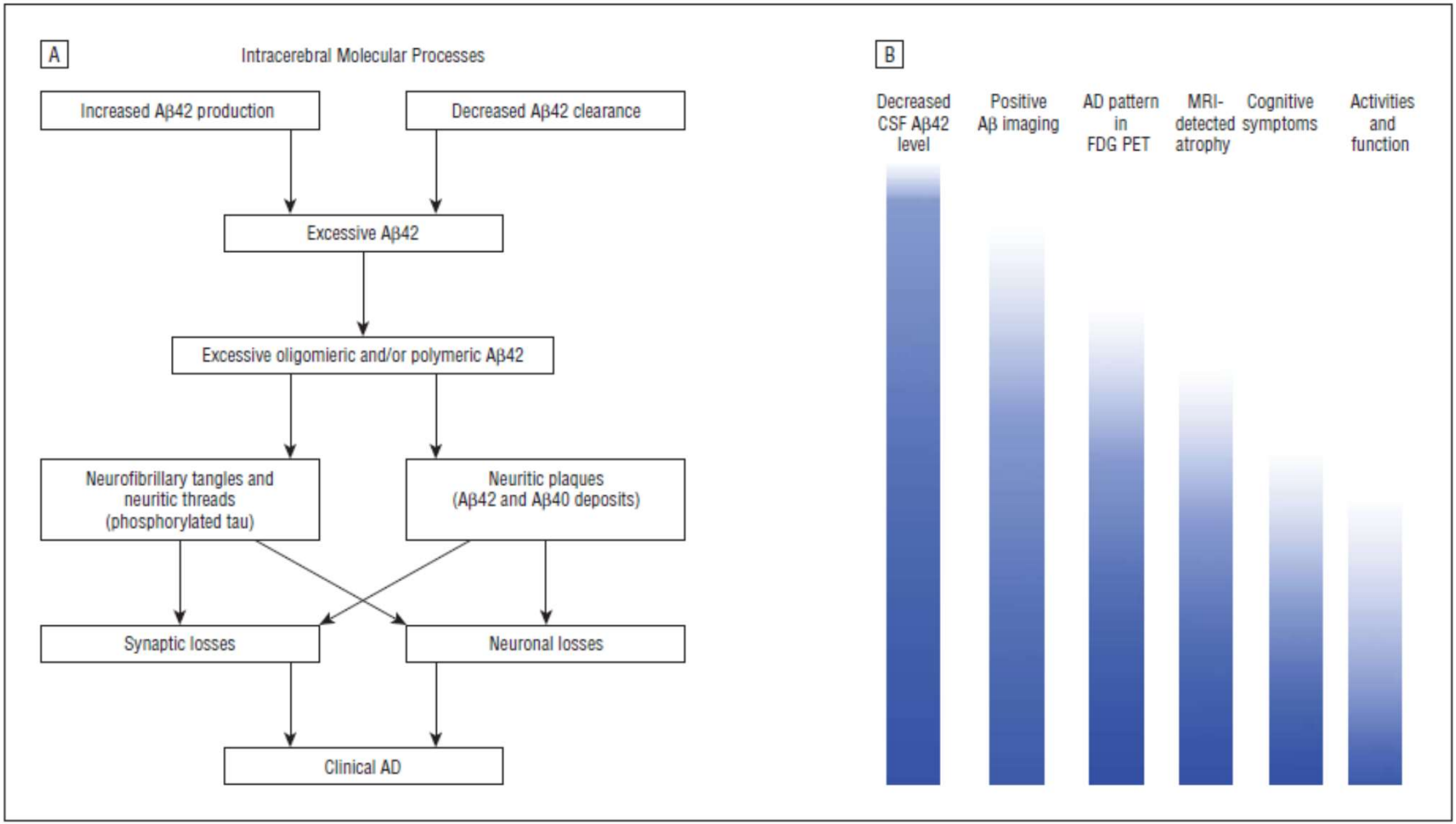


Figure: **Hypothetical progression of pathological and clinical events that lead to Alzheimer's disease, as detected by use of different imaging techniques, functional measures, or biomarkers**

Increases in the extent of pathological abnormality are shown for each imaging measure and biomarker. ADL=activities of daily living. EMCI=early MCI. FDG-PET=^{18}F-fluorodeoxyglucose PET. LMCI=late MCI.

Jack et al. Lancet Neurol 2010;9:119-28



Arch Neurol.
Published online April 2, 2012. doi:10.1001/archneurol.2011.2883

ARTICLE IN PRESS

ELSEVIER

Alzheimer's & Dementia ■ (2011) 1–6

Alzheimer's & Dementia

Introduction to the recommendations from the National Institute on Aging and the Alzheimer's Association workgroup on diagnostic guidelines for Alzheimer's disease

Clifford R. Jack, Jr.,[a,*], Marilyn S. Albert[b], David S. Knopman[a], Guy M. McKhann[b], Reisa A. Sperling[c], Maria C. Carrillo[d], Bill Thies[d], Creighton H. Phelps[e]

Three diagnostic pakages:

1. Alzheimer's disease (AD)
2. Prodromial AD (paucisintomatic)(MCI due to AD)
3. Preclinical AD (asintomatic, only for reseach)

Jack et al. Alzheimers Dement 2011;7:257-62

ELSEVIER

Alzheimer's & Dementia ■ (2011) 1–7

Alzheimer's & Dementia

The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup

Guy M. McKhann[a,b,*], David S. Knopman[c], Howard Chertkow[d,e], Bradley T. Hyman[f], Clifford R. Jack, Jr.[g], Claudia H. Kawas[h,i,j], William E. Klunk[k], Walter J. Koroshetz[l], Jennifer J. Manly[m,n,o], Richard Mayeux[m,n,o], Richard C. Mohs[p], John C. Morris[q], Martin N. Rossor[r], Philip Scheltens[s], Maria C. Carillo[t], Bill Thies[t], Sandra Weintraub[u,v], Creighton H. Phelps[w]

Alzheimer's & Dementia 2011; 7: 263-269

2. Criteria for all-cause dementia: Core clinical criteria

In this section, we outline core clinical criteria to be used in all clinical settings. Because there are many causes of dementia, we will first outline the criteria for all-cause dementia.

The diagnosis of dementia is intended to encompass the spectrum of severity, ranging from the mildest to the most severe stages of dementia. The methodology for staging of dementia severity was beyond the charge of the workgroup. Dementia is diagnosed when there are cognitive or behavioral (neuropsychiatric) symptoms that:

1. Interfere with the ability to function at work or at usual activities; and
2. Represent a decline from previous levels of functioning and performing; and
3. Are not explained by delirium or major psychiatric disorder;
4. Cognitive impairment is detected and diagnosed through a combination of (1) history-taking from the patient and a knowledgeable informant and (2) an objective cognitive assessment, either a "bedside" mental status examination or neuropsychological testing. Neuropsychological testing should be performed when the routine history and bedside mental status examination cannot provide a confident diagnosis.

5. The cognitive or behavioral impairment involves a minimum of two of the following domains:

   a. Impaired ability to acquire and remember new information—symptoms include: repetitive questions or conversations, misplacing personal belongings, forgetting events or appointments, getting lost on a familiar route.

   b. Impaired reasoning and handling of complex tasks, poor judgment—symptoms include: poor understanding of safety risks, inability to manage finances, poor decision-making ability, inability to plan complex or sequential activities.

   c. Impaired visuospatial abilities—symptoms include: inability to recognize faces or common objects or to find objects in direct view despite good acuity, inability to operate simple implements, or orient clothing to the body.

   d. Impaired language functions (speaking, reading, writing)—symptoms include: difficulty thinking of common words while speaking, hesitations; speech, spelling, and writing errors.

   e. Changes in personality, behavior, or comportment—symptoms include: uncharacteristic mood fluctuations such as agitation, impaired motivation, initiative, apathy, loss of drive, social withdrawal, decreased interest in previous activities, loss of empathy, compulsive or obsessive behaviors, socially unacceptable behaviors.

4. Probable AD dementia: Core clinical criteria

4.1. Probable AD dementia is diagnosed when the patient

1. Meets criteria for dementia described earlier in the text, and in addition, has the following characteristics:

A. Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days;

B. Clear-cut history of worsening of cognition by report or observation; and

C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories.

   a. Amnestic presentation: It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, as defined earlier in the text.

b. Nonamnestic presentations: II°

- Language presentation: The most prominent deficits are in word-finding, but deficits in other cognitive domains should be present.
- Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present.
- Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present.

Note: All patients who met criteria for "probable AD" by the 1984 NINCDS–ADRDA criteria [1] would meet the current criteria for probable AD dementia mentioned in the present article.

6. Probable AD dementia with evidence of the AD pathophysiological process

In persons who meet the core clinical Criteria for probable AD dementia biomarker evidence may **increase the certainty that the basis of the clinical dementia syndrome is the AD pathophysiological process.** However, we do not advocate the use of AD biomarker tests for routine diagnostic purposes at the present time. There are several reasons for this limitation: (1) the core clinical criteria provide very good diagnostic accuracy and utility in most patients; (2) more research needs to be done to ensure that criteria that include the use of biomarkers have been appropriately designed, (3) there is limited standardization of biomarkers from one locale to another, and (4) access to biomarkers is limited to varying degrees in community settings. Presently, the use of biomarkers to enhance certainty of AD

ELSEVIER

Alzheimer's & Dementia 7 (2011) 270–279

Alzheimer's & Dementia

The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease

Marilyn S. Albert[a,*], Steven T. DeKosky[b,c], Dennis Dickson[d], Bruno Dubois[e], Howard H. Feldman[f], Nick C. Fox[g], Anthony Gamst[h], David M. Holtzman[i,j], William J. Jagust[k], Ronald C. Petersen[l], Peter J. Snyder[m,n], Maria C. Carrillo[o], Bill Thies[o], Creighton H. Phelps[p]

ferred to in this article as mild cognitive impairment due to AD. The workgroup developed the following two sets of criteria: (1) core clinical criteria that could be used by healthcare providers without access to advanced imaging techniques or cerebrospinal fluid analysis, and (2) research criteria that could be used in clinical research settings, including clinical trials. The second set of criteria incorporate the use of biomarkers based on imaging and cerebrospinal fluid measures. The final set of criteria

AD prodromal

Table 1
Summary of clinical and cognitive evaluation for MCI due to AD

Establish clinical and cognitive criteria
Cognitive concern reflecting a change in cognition reported by patient or informant or clinician (i.e., historical or observed evidence of decline over time)
Objective evidence of Impairment in one or more cognitive domains, typically including memory (i.e., formal or bedside testing to establish level of cognitive function in multiple domains)
Preservation of independence in functional abilities
Not demented
Examine etiology of MCI consistent with AD pathophysiological process
Rule out vascular, traumatic, medical causes of cognitive decline, where possible
Provide evidence of longitudinal decline in cognition, when feasible
Report history consistent with AD genetic factors, where relevant

Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment.

Biomarkers (I)

Table 2
Biomarkers under examination for AD

Biomarkers of Aβ deposition
CSF $A\beta_{42}$
PET amyloid imaging
Biomarkers of neuronal injury
CSF tau/phosphorylated-tau
Hippocampal volume or medial temporal atrophy by volumetric measures or visual rating
Rate of brain atrophy
FDG-PET imaging
SPECT perfusion imaging
Less well validated biomarkers: fMRI activation studies, resting BOLD functional connectivity, MRI perfusion, MR spectroscopy, diffusion tensor imaging, voxel-based and multivariate measures
Associated biochemical change
Inflammatory biomarkers (cytokines)
Oxidative stress (isoprostanes)
Other markers of synaptic damage and neurodegeneration such as cell death

Biomarkers (II)

Table 3
MCI criteria incorporating biomarkers

Diagnostic category	Biomarker probability of AD etiology	Aβ (PET or CSF)	Neuronal injury (tau, FDG, sMRI)
MCI–core clinical criteria	Uninformative	Conflicting/indeterminant/untested	Conflicting/indeterminant/untested
MCI due to AD—intermediate likelihood	Intermediate	Positive	Untested
		Untested	Positive
MCI due to AD—high likelihood	Highest	Positive	Positive
MCI—unlikely due to AD	Lowest	Negative	Negative

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid beta peptide; PET, positron emission tomography; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; sMRI, structural magnetic resonance imaging.

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Alzheimer's & Dementia 7 (2011) 270–279

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The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease

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Position Paper

Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria

Bruno Dubois, Howard H Feldman, Claudia Jacova, Harald Hampel, José Luis Molinuevo, Kaj Blennow, Steven T DeKosky, Serge Gauthier, Dennis Selkoe, Randall Bateman, Stefano Cappa, Sebastian Crutch, Sebastiaan Engelborghs, Giovanni B Frisoni, Nick C Fox, Douglas Galasko, Marie-Odile Habert, Gregory A Jicha, Agneta Nordberg, Florence Pasquier, Gil Rabinovici, Philippe Robert, Christopher Rowe, Stephen Salloway, Marie Sarazin, Stéphane Epelbaum, Leonardo C de Souza, Bruno Vellas, Pieter J Visser, Lon Schneider, Yaakov Stern, Philip Scheltens, Jeffrey L Cummings

Lancet Neurol 2014; 13: 614–29

June 2014

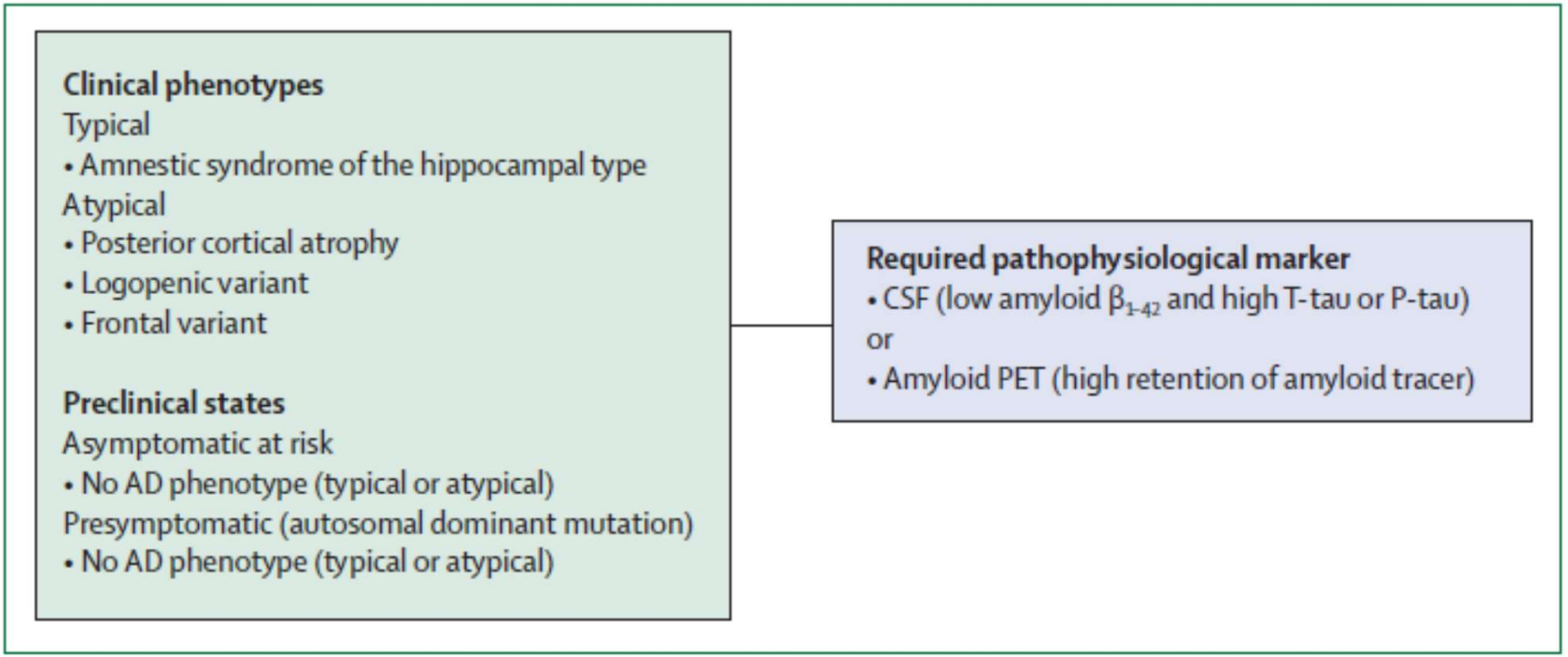


***Figure*: AD is defined as a clinicobiological entity**

A simplified algorithm is proposed: in any condition and at any stage of the disease, the diagnosis of AD relies on the presence of a pathophysiological marker. AD=Alzheimer's disease.

June 2014

Panel 1: IWG-2 criteria for typical AD (A plus B at any stage)

A Specific clinical phenotype

- Presence of an early and significant episodic memory impairment (isolated or associated with other cognitive or behavioural changes that are suggestive of a mild cognitive impairment or of a dementia syndrome) that includes the following features:
  - Gradual and progressive change in memory function reported by patient or informant over more than 6 months
  - Objective evidence of an amnestic syndrome of the hippocampal type,* based on significantly impaired performance on an episodic memory test with established specificity for AD, such as cued recall with control of encoding test

B In-vivo evidence of Alzheimer's pathology (one of the following)

- Decreased $A\beta_{1-42}$ together with increased T-tau or P-tau in CSF
- Increased tracer retention on amyloid PET
- AD autosomal dominant mutation present (in *PSEN1*, *PSEN2*, or *APP*)

June 2014

Panel 4: IWG-2 criteria for the preclinical states of AD

IWG-2 criteria for asymptomatic at risk for AD (A plus B)

A Absence of specific clinical phenotype (both are required)

- Absence of amnestic syndrome of the hippocampal type
- Absence of any clinical phenotype of atypical AD

B In-vivo evidence of Alzheimer's pathology (one of the following)

- Decreased $A\beta_{1-42}$ together with increased T-tau or P-tau in CSF
- Increased retention on fibrillar amyloid PET

June 2014

IWG-2 criteria for presymptomatic AD (A plus B)

A Absence of specific clinical phenotype (both are required)

- Absence of amnestic syndrome of the hippocampal type
- Absence of any clinical phenotype of atypical AD

B Proven AD autosomal dominant mutation in *PSEN1*, *PSEN2*, or *APP*, or other proven genes (including Down's syndrome trisomy 21)

June 2014

DIAGNOSTIC AND PROGRESSION MARKERS

Panel 5: Definition of AD biomarkers

Diagnostic marker

- Pathophysiological marker
- Reflects in-vivo pathology
- Is present at all stages of the disease
- Observable even in the asymptomatic state
- Might not be correlated with clinical severity
- Indicated for inclusion in protocols of clinical trials

June 2014

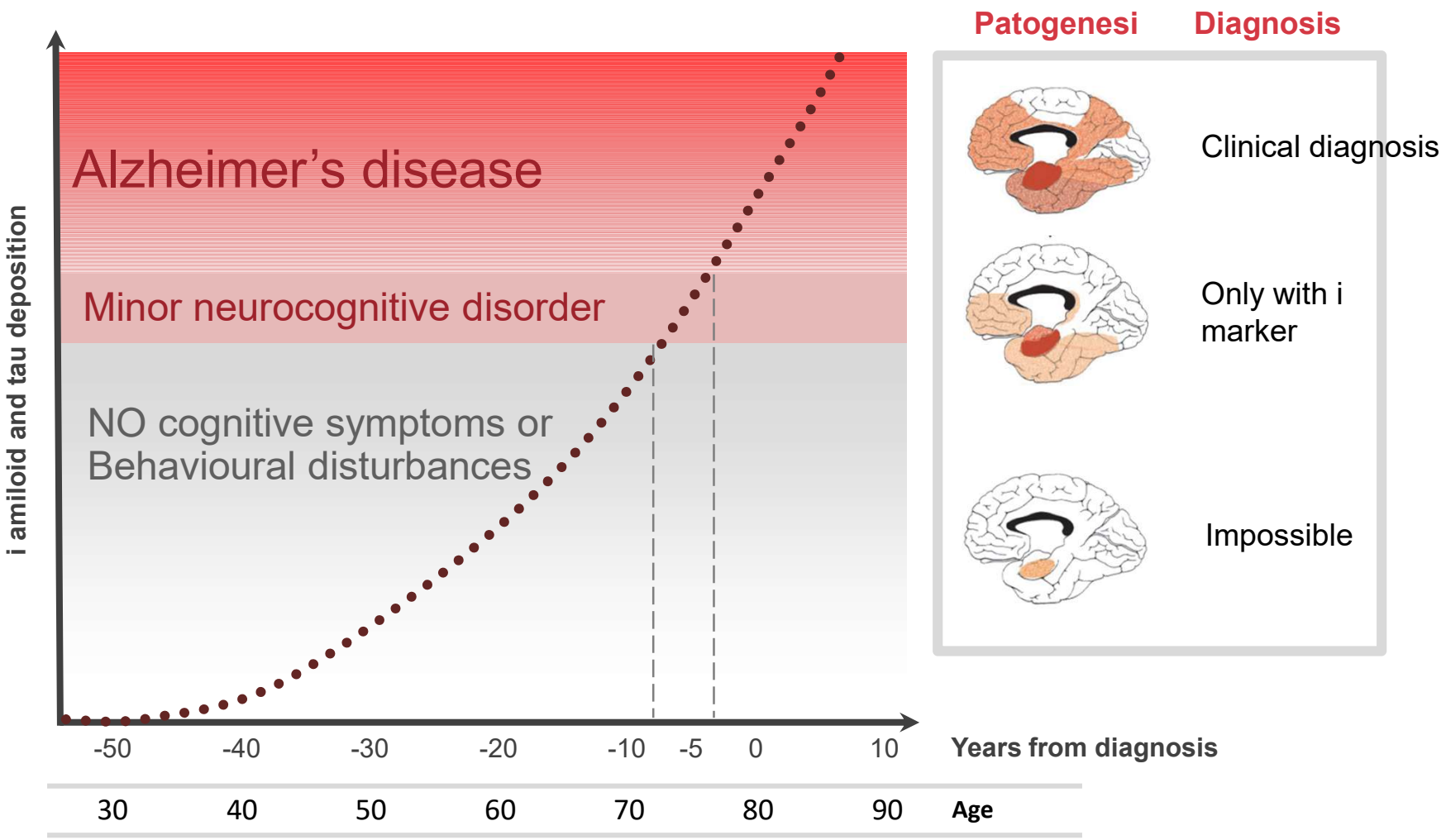
DIAGNOSTIC AND **PROGRESSION** MARKERS

Progression marker

- Topographical or downstream marker
- Poor disease specificity
- Indicates clinical severity (staging marker)
- Might not be present in early stages
- Quantifies time to disease milestones
- Indicated for disease progression

June 2014

Patogenesis and clinical diagnostic aspects of AD



Recommendations of the Italian Psychogeriatric Association (AIP) and Italian Society for the Study of Dementia (SINDEM) on Early Diagnosis of Alzheimer Disease

Presidents:

M. Trabucchi (AIP)
A. Padovani (SinDem)

May 2014

BIOMARKER VALIDITY IN THE DIAGNOSIS OF AD

Recommendations (I)

Structural imaging *should be carried out at least once in the diagnostic work-up of patients with cognitive impairment*

MRI is currently the imaging modality of choice for assessing subjects with suspected dementia; however, where MRI is not available or contraindicated, CT scans can usefully exclude major space occupying lesions, large infarcts and hydrocephalus.
The authors recommend to assess specific patterns of focal atrophy.

The authors strongly encourage the utilisation of standardised software programs to quantitatively analyse brain MRI to aid visual analysis.

AIP, SinDem, 2014

BIOMARKER VALIDITY IN THE DIAGNOSIS OF AD

Recommendations (II)

In persons with core clinical criteria for MCI and negative structural brain imaging a ***18F-FDG PET scan*** *can be considered for diagnosis purposes.*

The overall regional pattern of metabolic impairment of the ***posterior cingulate/precuneus*** *and lateral* ***temporoparietal cortices****, more accentuated than frontal cortex deficits, together with the relative preservation of the primary sensorimotor and visual cortices, basal ganglia and cerebellum defines the* ***distinct metabolic phenotype of typical AD.***

In persons with core clinical criteria for MCI the presence of an AD-like metabolic pattern at 18-FDG-PET is highly predictive of conversion to AD dementia within two years.

AIP, SinDem, 2014

BIOMARKER VALIDITY IN THE DIAGNOSIS OF AD

Recommendation (III)

Amyloid imaging should not be considered a routine test.

The authors recommend that ***amyloid imaging*** *can be considered for early diagnosis in individuals with core clinical criteria for MCI with a cognitive complaint objectively confirmed that is in persistent or progressive.*

These patients should satisfy the core clinical criteria for possible (not probable) AD.

The authors recommend that amyloid imaging can be considered in patients with progressive dementia and atypically early age of onset (usually defined as 65 years or less in age).

AIP, SinDem, 2014

BIOMARKER VALIDITY IN THE DIAGNOSIS OF AD

Recommendations (IV)

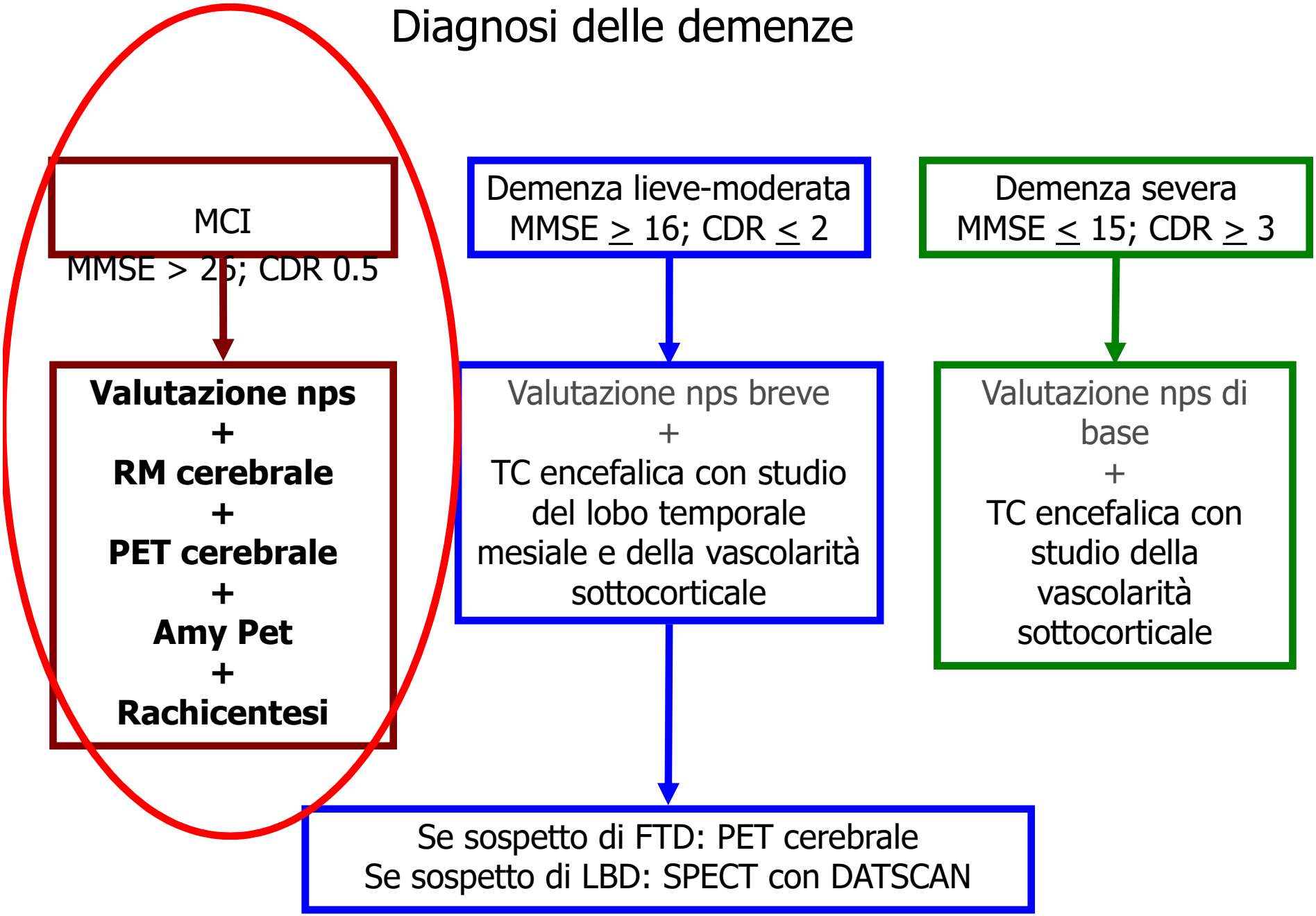
The combined pattern of low levels of ***Aβ42 together with high levels of T-tau and P-tau in CSF*** *has been shown to be specific to patients with AD.*

CSF determinations of substances that may play a pathogenetic role in dementias (beta-amyloid, tau protein) should be performed within the framework of research protocols.

The authors recommend to assess concurrently levels of Abeta 42, Total Tau and Phospho Tau and to utilize CSF biomarkers in the setting of the entire clinical and instrumental picture.

AIP, SinDem, 2014

Diagnosi delle demenze



Summary

- History
- Numbers
- Prevention
- **Diagnosis**
- Therapy
- **Care (long term care)**
- **Ethical issues**
- Citizenschip

INTERNATIONAL JOURNAL OF GERIATRIC PSYCHIATRY
Int J Geriatr Psychiatry 2005; **20**: 377–386.
Published online in Wiley InterScience (www.interscience.wiley.com). **DOI**: 10.1002/gps.1302

Factors affecting timely recognition and diagnosis of dementia across Europe: from awareness to stigma

Myrra J. F. J. Vernooij-Dassen[1]*, Esme D. Moniz-Cook[2], Robert T. Woods[3], Jan De Lepeleire[4], Antonio Leuschner[5], Orazio Zanetti[6], Joycelyn de Rotrou[7], Geraldine Kenny[8], Manuel Franco[9], Vincent Peters[10], Steve Iliffe[11] and the INTERDEM group

Stigma, no treatment,
”There is nothing to do”

PERSPECTIVES

OPINION

Preclinical Alzheimer disease —the challenges ahead

Reisa A. Sperling, Jason Karlawish and Keith A. Johnson

Abstract | There is growing recognition that the pathophysiological process of Alzheimer disease (AD) begins many years prior to clinically obvious symptoms, and the concept of a presymptomatic or preclinical stage of AD is becoming more widely accepted. Advances in biomarker studies have enabled detection of AD pathology *in vivo* in clinically normal older individuals. The predictive value of these biomarkers at the individual patient level, however, remains to be elucidated. The ultimate goal of identifying individuals in the preclinical stages of AD is to facilitate early intervention to delay and perhaps even prevent emergence of the clinical syndrome. A number of challenges remain to be overcome before this concept can be validated and translated into clinical practice.

Sperling, R. A. *et al. Nat. Rev. Neurol.* 9, 54–58 (2013); published online 27 November 2012; doi:10.1038/nrneurol.2012.241

- Ethical and practical concerns about disclosure of biomarker status in asymptomatic or very early symptomatic individuals need to be addressed. Solutions may vary by country. For example, in Australia, the current policy is nondisclosure of amyloid PET status, but as more is learned about the meaning of a positive amyloid scan, individuals may wish to be informed of their test results.

Alzheimer's Prevention Initiative: A Plan to Accelerate the Evaluation of Presymptomatic Treatments; Eric M. Reiman, MD, JessicaB.S. Langbaum, PhD, Adam S. Fleisher, MD,Richard J. Caselli, MD, Kewei Chen, PhD, Napatkamon Ayutyanont, PhD, Yakeel T.Quiroz, MA, Kenneth S. Kosik, MD, Francisco Lopera, MD, and **Pierre N. Tariot, MD**

Lancet Neurol 2013; 12: 207–16

Personal View

Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers

Clifford R Jack Jr, David S Knopman, William J Jagust, Ronald C Petersen, Michael W Weiner, Paul S Aisen, Leslie M Shaw, Prashanthi Vemuri, Heather J Wiste, Stephen D Weigand, Timothy G Lesnick, Vernon S Pankratz, Michael C Donohue, John Q Trojanowski

Not all patients with MCI have AD pathology and progress to dementia.

MCI negative to amyloidosis and/or neurodegeneration should not progress to dementia.

Not all patients with AD pathology progress to dementia. → **[etical aspects]**

Lancet Neurol 2013; 12: 207–16

Personal View

Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers

Clifford R Jack Jr, David S Knopman, William J Jagust, Ronald C Petersen, Michael W Weiner, Paul S Aisen, Leslie M Shaw, Prashanthi Vemuri, Heather J Wiste, Stephen D Weigand, Timothy G Lesnick, Vernon S Pankratz, Michael C Donohue, John Q Trojanowski

1) Amyloid deposition
2) Neurodegeneration - synaptic dysfunction
3) Neuronal loss – brain atrophy

Not all patients with MCI have AD pathology and progress to dementia. MCI negative to amyloidosis and/or neurodegeneration should not progress to dementia.

Not all patients with AD pathology progress to dementia.

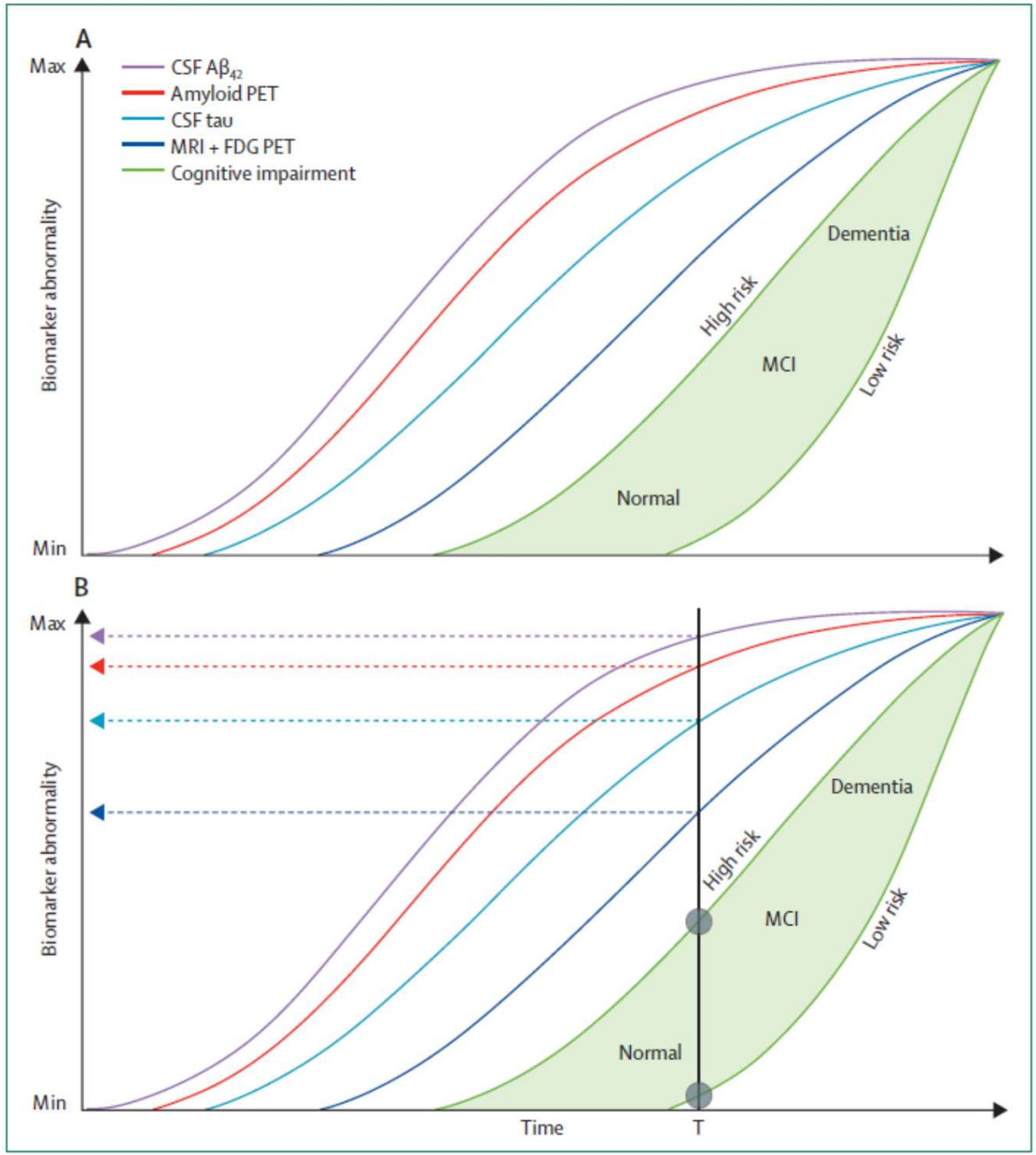


Figure 5: Revised model of dynamic biomarkers of the Alzheimer's disease pathological cascade

Lancet Neurol 2013; 12: 207–16

“Sapessi tu quanti mulini, a guardar meglio sono veramente giganti; quante lucciole sono veramente lanterne!”

G. Bufalino: Qui pro quo.
Bompiani, Milano, 1991, p.48

Uncertain progress on the fuzzy boundaries od AD

Whitehouse P.J., George D.R.

JAD, 2011;26:1-5

"The myth of Alzheimer's"

What you aren't being told about today's most dreaded diagnosis (2008)

Summary

- History
- Numbers
- Prevention
- **Diagnosis**
- Therapy
- **Care (long term care)**
- **Ethical issues**
- **Citizenschip**

Jeanne Calment

RC PSYCH ROYAL COLLEGE OF PSYCHIATRISTS
The British Journal of Psychiatry
BJPsych

Eugeria, longevity and normal ageing.

K Ritchie
BJP 1997, 171:501.
Access the most recent version at DOI: 10.1192/bjp.171.6.501

On 4 August 1997 Jeanne Calment, aged 122 years and considered to be the oldest human being in the history of our species, died in Arles of 'natural causes'. Not only was she the oldest person, she was probably also the most healthy. Living independently until the age of 110, with no previous history of illness, she had entirely escaped the principal current causes of mortality and morbidity; cancer, cardiovascular disease and senile dementia. Despite visual and hearing loss, she maintained autonomy in the face of the dependence imposed by the regulations of a nursing home – refusing care and visitors she did not want, smoking in a public place, and insisting on her daily glass of port.

Journal of Alzheimer's Disease 9 (2006) 447–453
IOS Press

Quality of life: The bridge from the cholinergic basal forebrain to cognitive science and bioethics

Peter J. Whitehouse*
Case Western Reserve University, OH, USA

field. We are all human beings living on the same planet who age and die. We must develop a global bioethic, not a narrow superficial bioethics like the one that currently dominates medicine. This global bioethic must include a concern for social justice and sustainability of diversity of life [30].

"The diseases have symptoms: the symptoms suggest the organic foundation of all that we are. They make us think of the brain like a piece of meat. And where should I recognize that, yes, the brain is a piece of meat, I look instead to keep a blind spot where I put stories that emphasize the most soul-related aspects of the self "

Jonathan Franzen: My father's brain.

Ferruccio
Sangiacomo, 2008