CONVEGNO CARD

***DEMENZE, DISTRETTO E TERRITORIO: COSTRUIAMO LE ALLEANZE***

Taranto, Cittadella della Carità, 26 febbraio 2016

# *L'Importanza della Diagnosi Precoce di Demenza*

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*Department of Basic Medicine Neuroscience and Sense Organs*
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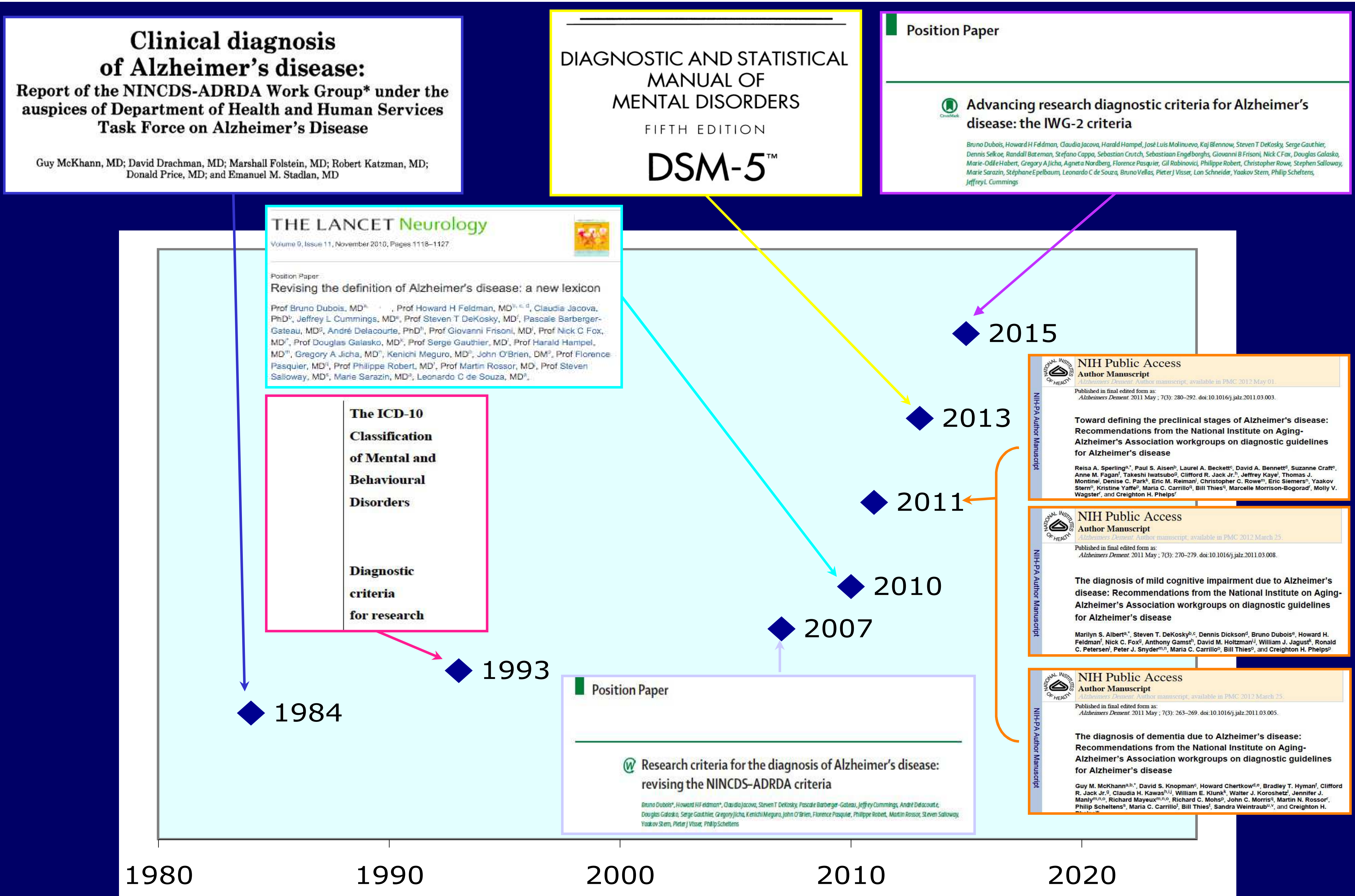
*at "Pia Fondazione Card G. Panico" Hospital Tricase (Le)*
*University of Bari*



**Clinical diagnosis of Alzheimer's disease:**

**Report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease**

Guy McKhann, MD; David Drachman, MD; Marshall Folstein, MD; Robert Katzman, MD; Donald Price, MD; and Emanuel M. Stadlan, MD

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DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS

FIFTH EDITION

**DSM-5™**

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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*

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THE LANCET Neurology

Volume 9, Issue 11, November 2010, Pages 1118–1127

Position Paper

Revising the definition of Alzheimer's disease: a new lexicon

Prof Bruno Dubois, MD[a], Prof Howard H Feldman, MD[b, c, d], Claudia Jacova, PhD[b], Jeffrey L Cummings, MD[e], Prof Steven T DeKosky, MD[f], Pascale Barberger-Gateau, MD[g], André Delacourte, PhD[h], Prof Giovanni Frisoni, MD[i], Prof Nick C Fox, MD[j], Prof Douglas Galasko, MD[k], Prof Serge Gauthier, MD[l], Prof Harald Hampel, MD[m], Gregory A Jicha, MD[n], Kenichi Meguro, MD[o], John O'Brien, DM[p], Prof Florence Pasquier, MD[q], Prof Philippe Robert, MD[r], Prof Martin Rossor, MD[j], Prof Steven Salloway, MD[s], Marie Sarazin, MD[a], Leonardo C de Souza, MD[a],

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**The ICD-10**
**Classification**
**of Mental and**
**Behavioural**
**Disorders**

**Diagnostic**
**criteria**
**for research**

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*Alzheimers Dement.* Author manuscript; available in PMC 2012 May 01.

Published in final edited form as:
*Alzheimers Dement.* 2011 May ; 7(3): 280–292. doi:10.1016/j.jalz.2011.03.003.

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**Reisa A. Sperling[a,*], Paul S. Aisen[b], Laurel A. Beckett[c], David A. Bennett[d], Suzanne Craft[e], Anne M. Fagan[f], Takeshi Iwatsubo[g], Clifford R. Jack Jr.[h], Jeffrey Kaye[i], Thomas J. Montine[j], Denise C. Park[k], Eric M. Reiman[l], Christopher C. Rowe[m], Eric Siemers[n], Yaakov Stern[o], Kristine Yaffe[p], Maria C. Carrillo[q], Bill Thies[q], Marcelle Morrison-Bogorad[r], Molly V. Wagster[r]**, and **Creighton H. Phelps[r]**

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*Alzheimers Dement.* Author manuscript; available in PMC 2012 March 25.

Published in final edited form as:
*Alzheimers Dement.* 2011 May ; 7(3): 270–279. doi:10.1016/j.jalz.2011.03.008.

**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]**, and **Creighton H. Phelps[p]**

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**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. Carrillo[t], Bill Thies[t], Sandra Weintraub[u,v]**, and **Creighton H.**

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Position Paper

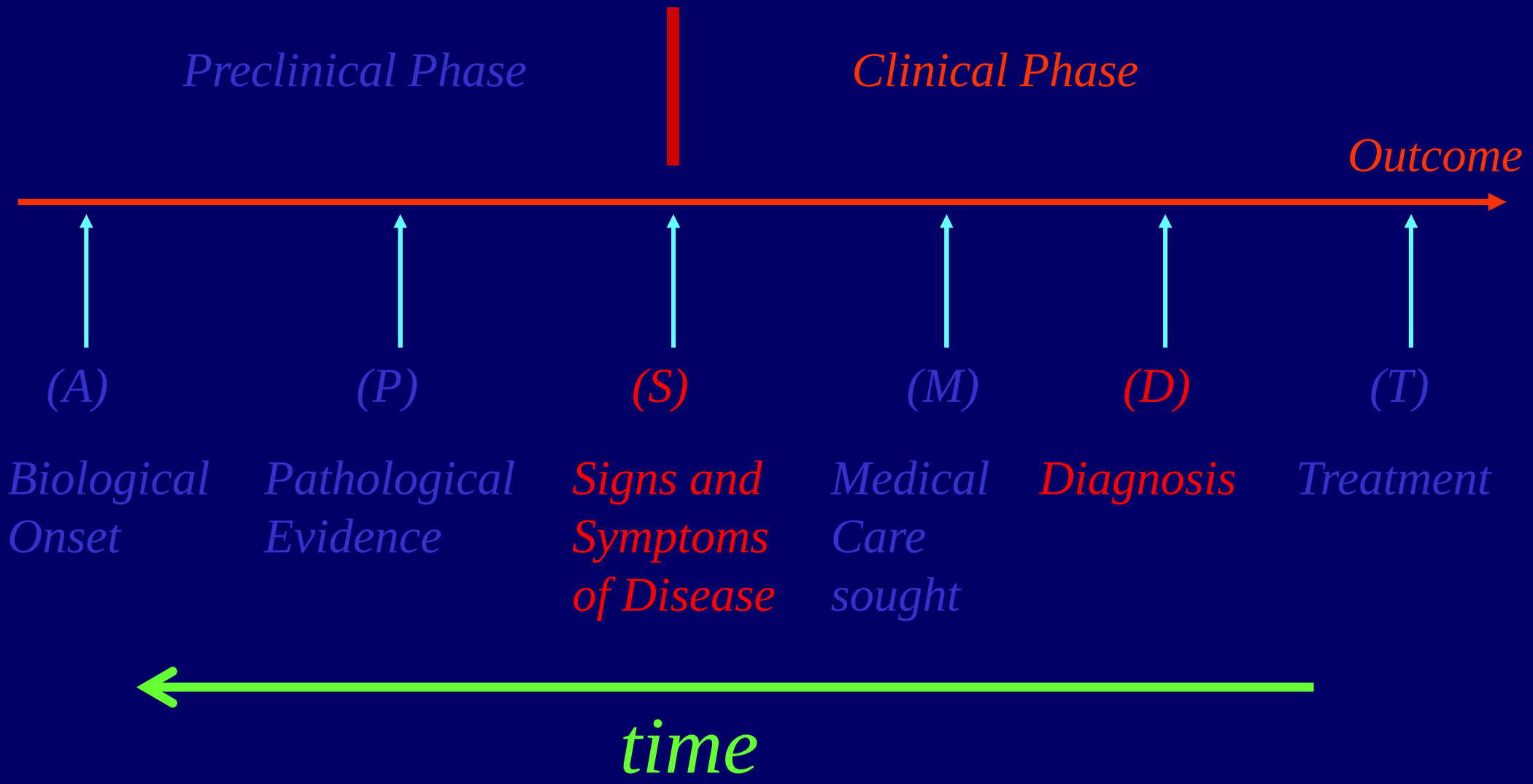
Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS–ADRDA criteria

*Bruno Dubois*, Howard H Feldman*, Claudia Jacova, Steven T DeKosky, Pascale Barberger-Gateau, Jeffrey Cummings, André Delacourte, Douglas Galasko, Serge Gauthier, Gregory Jicha, Kenichi Meguro, John O'Brien, Florence Pasquier, Philippe Robert, Martin Rossor, Steven Salloway, Yaakov Stern, Pieter J Visser, Philip Scheltens*

# *The Future:*

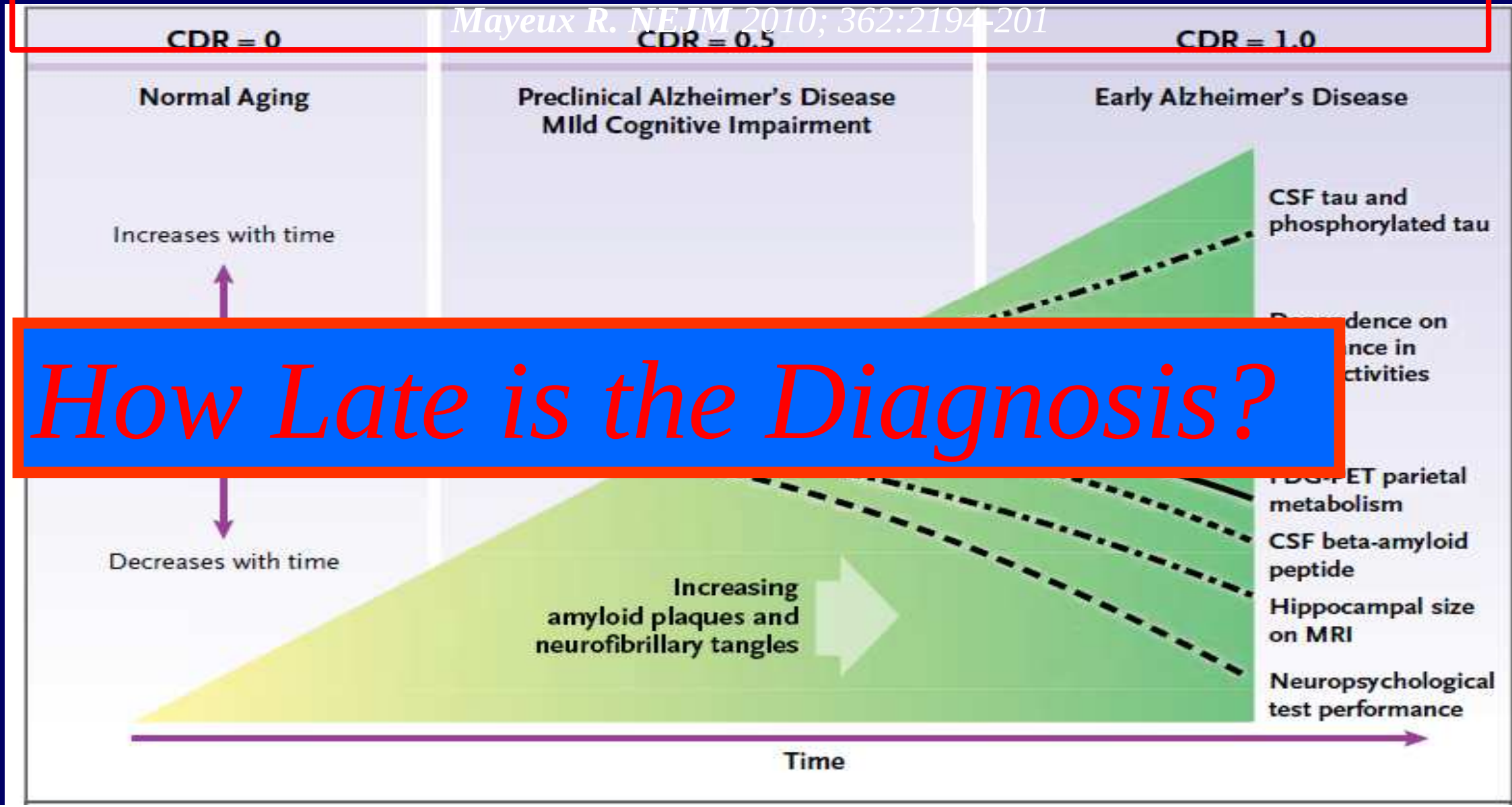
## *Reshaping The Natural History of a Disease*

*Gordis L, Epidemiology 2000 W. B. Saunders Company Philadelphia, PA*



# *Sequence of Pathological, Clinical, and Radiologic Changes from Normal Aging to Early AD*

*Mayeux R. NEJM 2010; 362:2194-201*




*How Late is the Diagnosis?*

# Clinical diagnosis of Probable AD NICDS-ADRDA Criteria

**NINCDS-ADRDA Criteria for Diagnosis of Alzheimer's Disease**

Dementia established by clinical examination and standardized brief mental status examination and confirmed by neuropsychologic tests

Deficits in two or more areas of cognition

Progressive worsening of memory and other cognitive function

No disturbance of consciousness

Onset between 40 and 90 years

Absence of other systemic or neurologic disorders sufficient to account for the progressive cognitive defects

**Features supporting diagnosis of Alzheimer's disease**

Progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia)

Impaired activities of daily living and altered patterns of behavior

Family history of a similar disorder, especially if confirmed neuropathologically

Normal lumbar puncture

Normal pattern or nonspecific changes in electroencephalogram

Evidence of cerebral atrophy on computed tomography, with progression on serial observation

**Features against diagnosis of Alzheimer's disease**

Sudden onset

Focal neurologic findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness

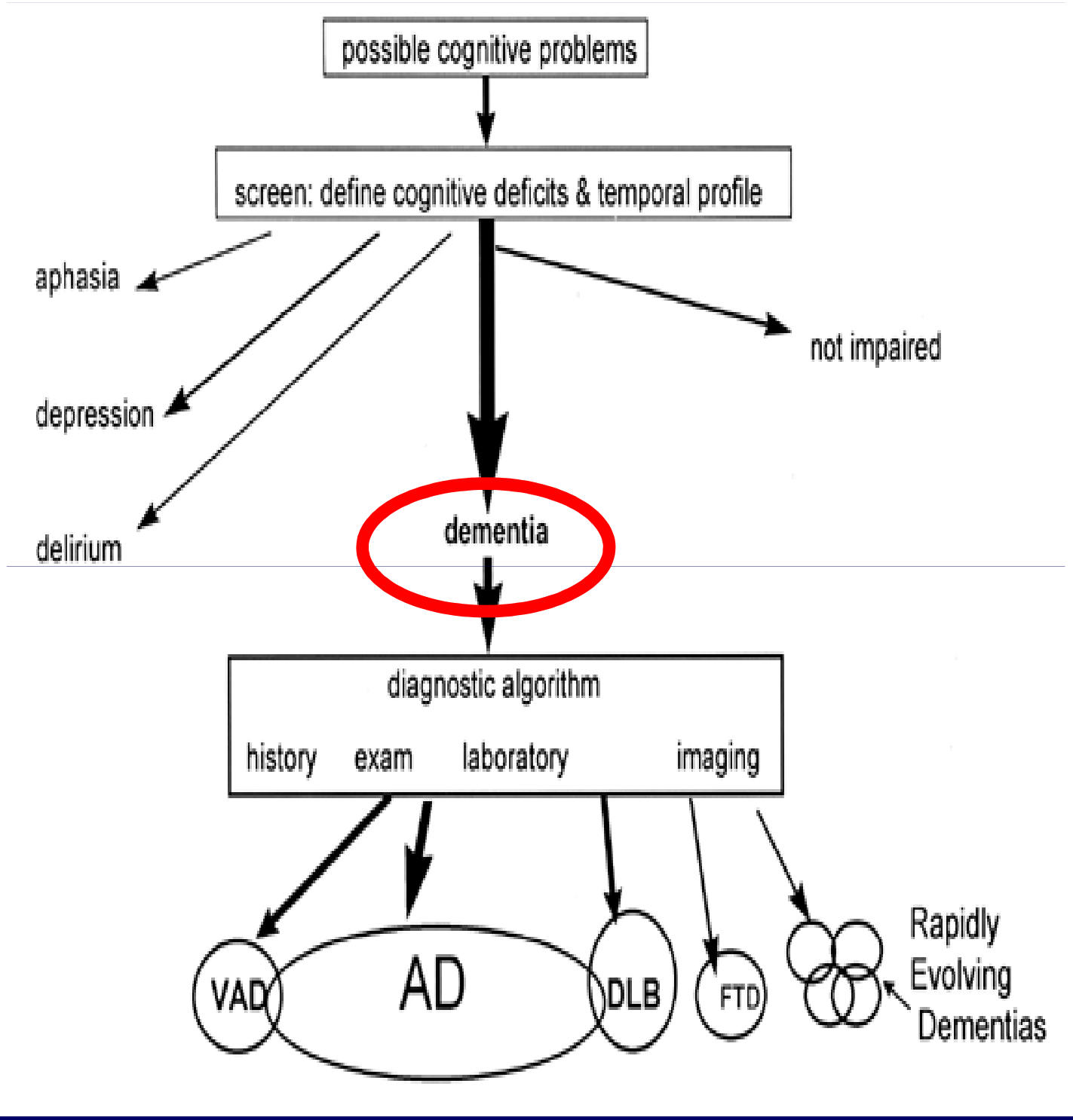
Seizures or gait disturbance at the onset or very early in the course of the illness

# *Dementia Diagnosis: A Three-Step Process*

1. *Identification of a Dementia Syndrome*

2. *Exclusion of Other Etiologies*

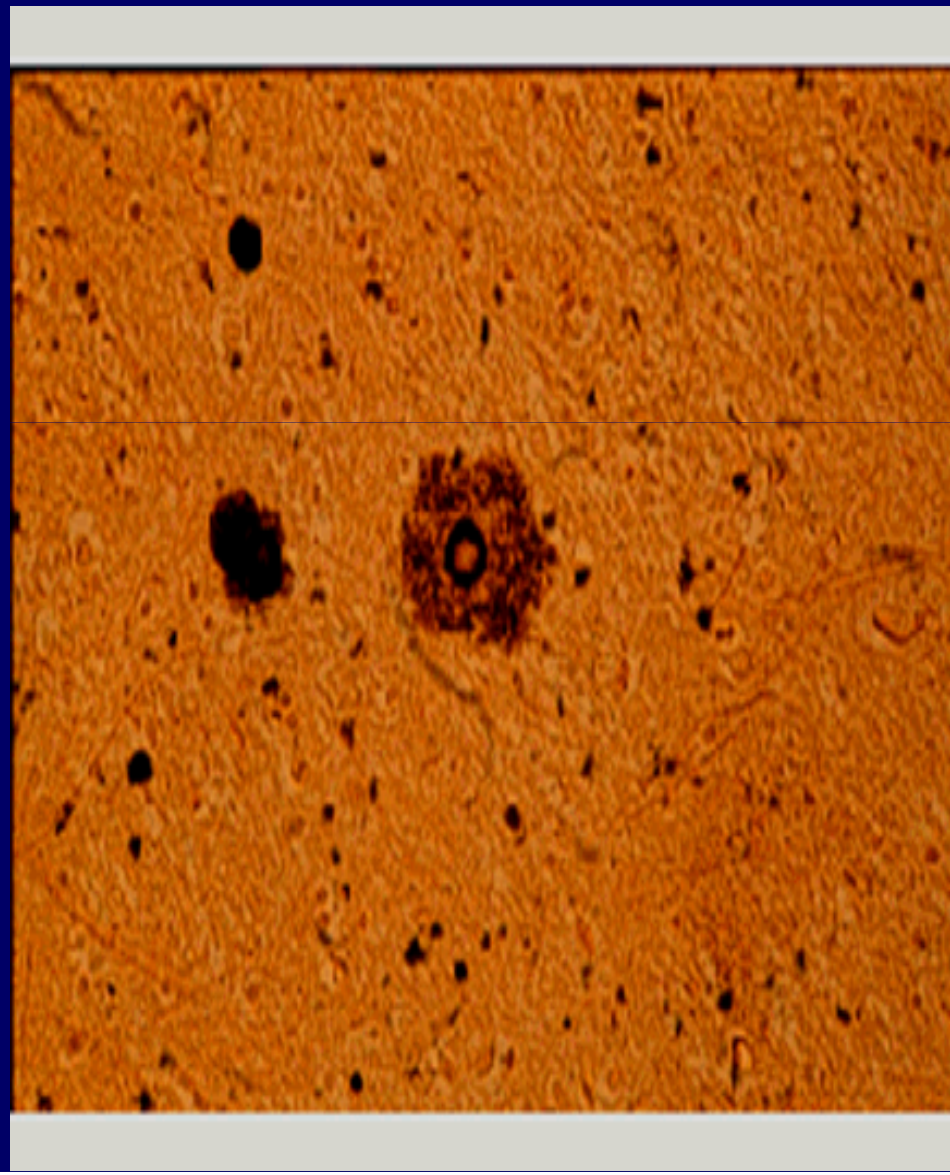
3. *Classification*



# *What is the Gold Standard?*

- 1984 NINCDS ADRDA Clinical Criteria

- The disease was caused by proven AD pathology



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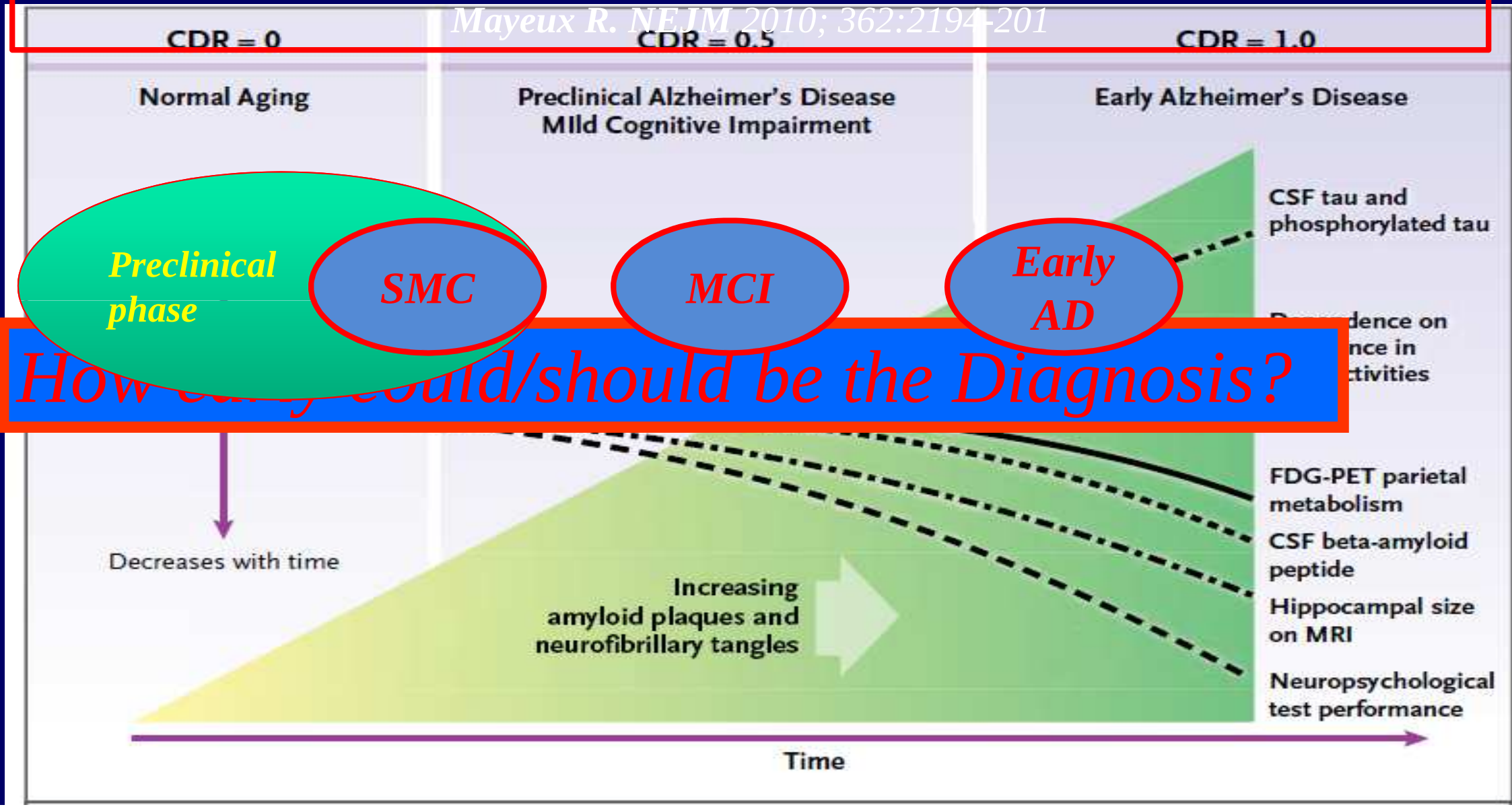


# *Diagnosis of MCI and Mild Dementia*

Table 1. Diagnosis of mild cognitive impairment (MCI) and mild dementia [1] [4].

| Criteria | MCI | Mild AD |
|---|---|---|
| Evidence of performance | 1 or more<br>performance<br>ains greater<br>age and<br>educational background | More than one<br>O<br>in<br>as<br>executive function |
| Interference with daily activities | Limited interference with daily activity; however, complex functional tasks may be completed less efficiently, e.g., preparing meals, shopping alone for clothes and groceries, planning a day's activity, remembering appointments or paying bills | Significant interference in being able to function effectively at work or during usual activity; however, still able to carry out less complex activity, e.g., ADLs—bathing, dressing and grooming and IADLs—completing chores or attending social functions |

[1] Concern about change in cognition, as compared with previous level based on information from the patient, clinician or corroborative informant. ADLs = Activities of Daily Living; IADLs = Instrumental Activities of Daily Living.

# *Differential Evolution of Cognitive Impairment in Nondemented Older Persons: Results From the Kungsholmen Project*

*Palmer K et al Am J Psychiatry 2002;159:436-442*

**TABLE 2. Outcome at 3-Year Follow-Up of Subjects in a Population-Based Study Who Were Aged 75–95 Years and Had Mild, Moderate, and Severe Cognitive Impairment, No Dementia (CIND), at Baseline**

| | Status at 3 Years | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Dead[a] | | | | Demented[a] | | | | Stable (Still Had CIND) | | Improved (No Longer Had CIND) | |
| | | | Adjusted Relative Risk[c] | | | | Adjusted Relative Risk[c] | | | | | |
| Baseline Severity of CIND | N | %[b] | Relative Risk | 95% CI | N | %[b] | Relative Risk | 95% CI | N | %[b] | N | %[b] |
| Mild (N=185) | 63 | 34 | 1.9[d] | 1.4–2.5 | 65 | 35 | 3.6[e] | 2.6–4.8 | 21 | 11 | 46 | 25 |
| Moderate (N=83) | 25 | 30 | 1.7[f] | 1.1–2.5 | 36 | 43 | 5.4[g] | 3.7–7.8 | 4 | 5 | 22 | 27 |
| Severe (N=48) | 11 | 23 | 1.3[h] | 0.7–2.4 | 24 | 50 | 7.0[i] | 4.5–10.8 | 1 | 2 | 13 | 27 |

[a] Death and dementia categories both include deceased subjects with a dementia diagnosis.

[b] Based on number of subjects with mild, moderate, or severe CIND. Percentages in each row do not add up to 100 because of the overlapping of the death and dementia categories.

[c] Relative risk was adjusted for age, education, and sex. Wald's chi-square statistics were estimated from three separate Cox regression models in which the subjects with mild, moderate, and severe baseline cognitive impairment, respectively, were compared to the subjects who had no baseline cognitive impairment.

[d] $\chi^2=19.2$, df=1, $p<0.001$.

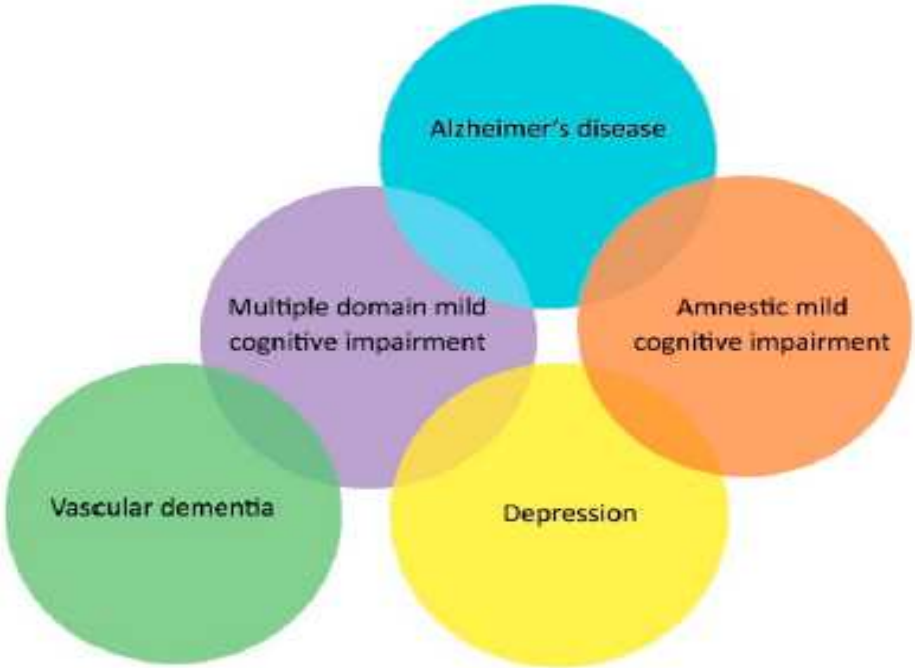
[e] $\chi^2=70.5$, df=1, $p<0.001$.

[f] $\chi^2=5.8$, df=1, $p<0.02$.

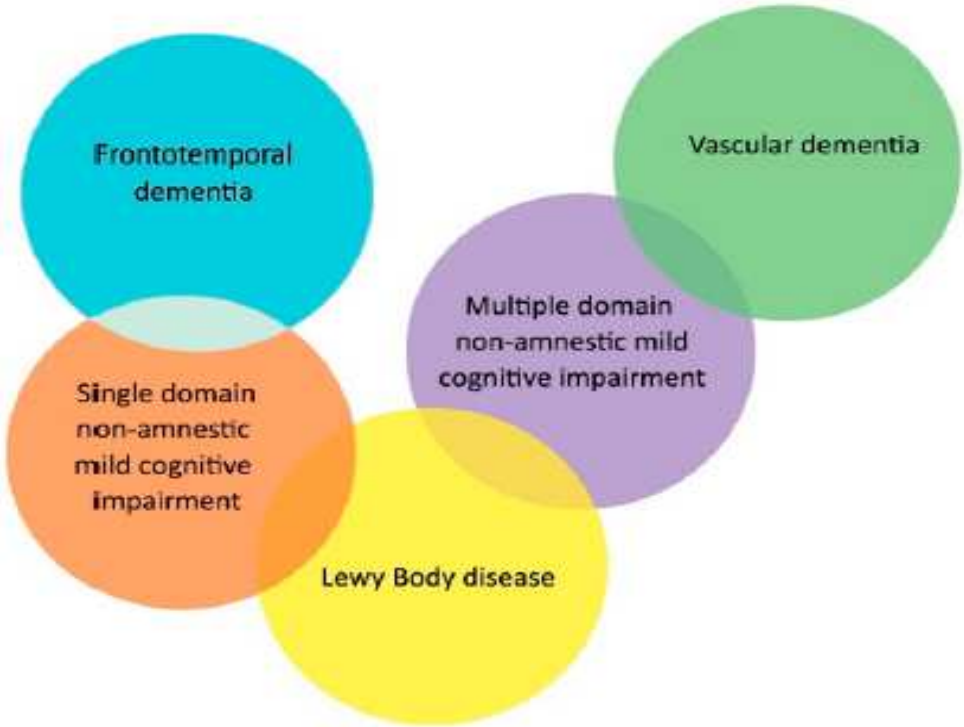
[g] $\chi^2=78.8$, df=1, $p<0.001$.

[h] $\chi^2=0.7$, df=1, $p<0.40$.

[i] $\chi^2=75.6$, df=1, $p<0.001$.


Alzheimer's disease
Multiple domain mild cognitive impairment
Amnestic mild cognitive impairment
Vascular dementia
Depression

(A)


Frontotemporal dementia
Vascular dementia
Multiple domain non-amnestic mild cognitive impairment
Single domain non-amnestic mild cognitive impairment
Lewy Body disease

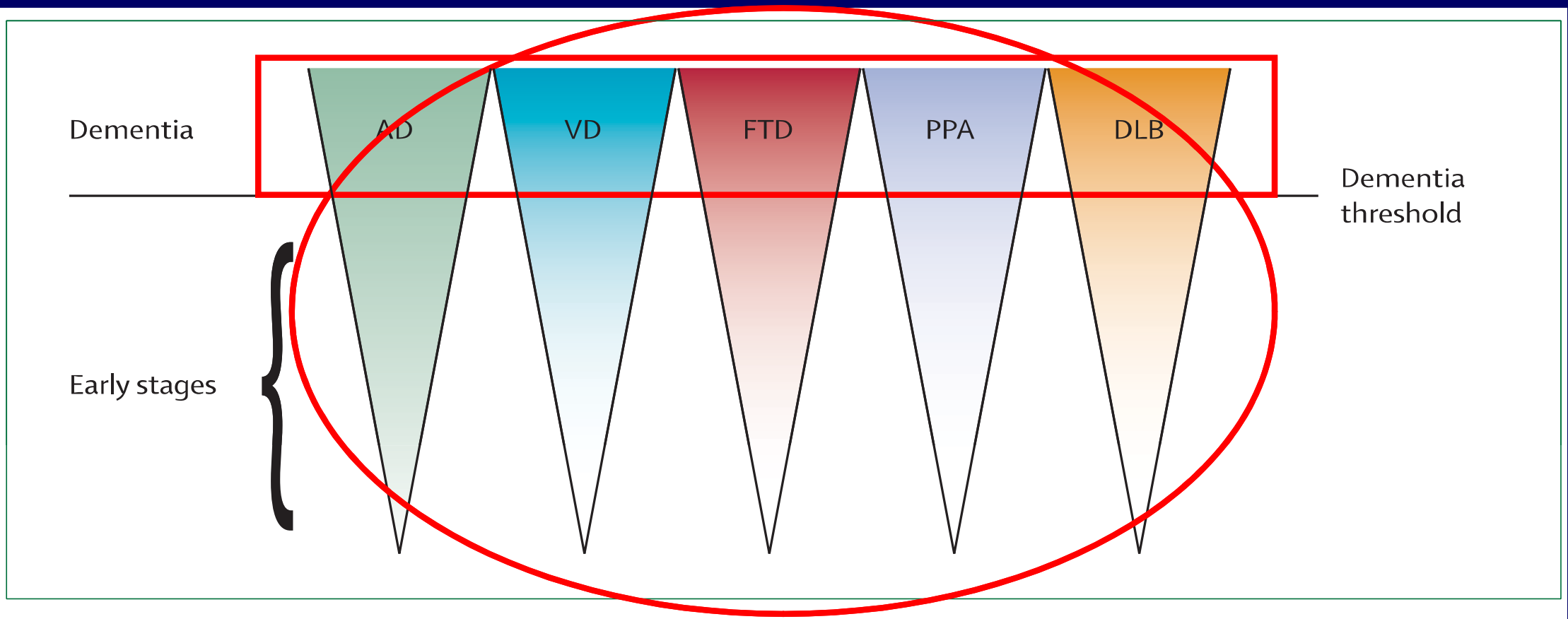



***Figure:*** **Alzheimer's disease starts and should be identified before the occurrence of full-blown dementia (as for other dementing conditions)**

AD=Alzheimer's disease; VD=vascular dementia; FTD=frontotemporal dementia; PPA=primary progressive aphasia; DLB=dementia with Lewy bodies.

# Diagnostic Criteria (Operational Criteria)

- Provide clear and reproducibile applications of definition ( based on clinical/test characteristics)
- Provide homogeneous groups of cases
- Possible identification of subgroups
- Starting point to predict prognosis and choose a therapy

# *Sequence of Pathological, Clinical, and Radiologic Changes from Normal Aging to Early AD*

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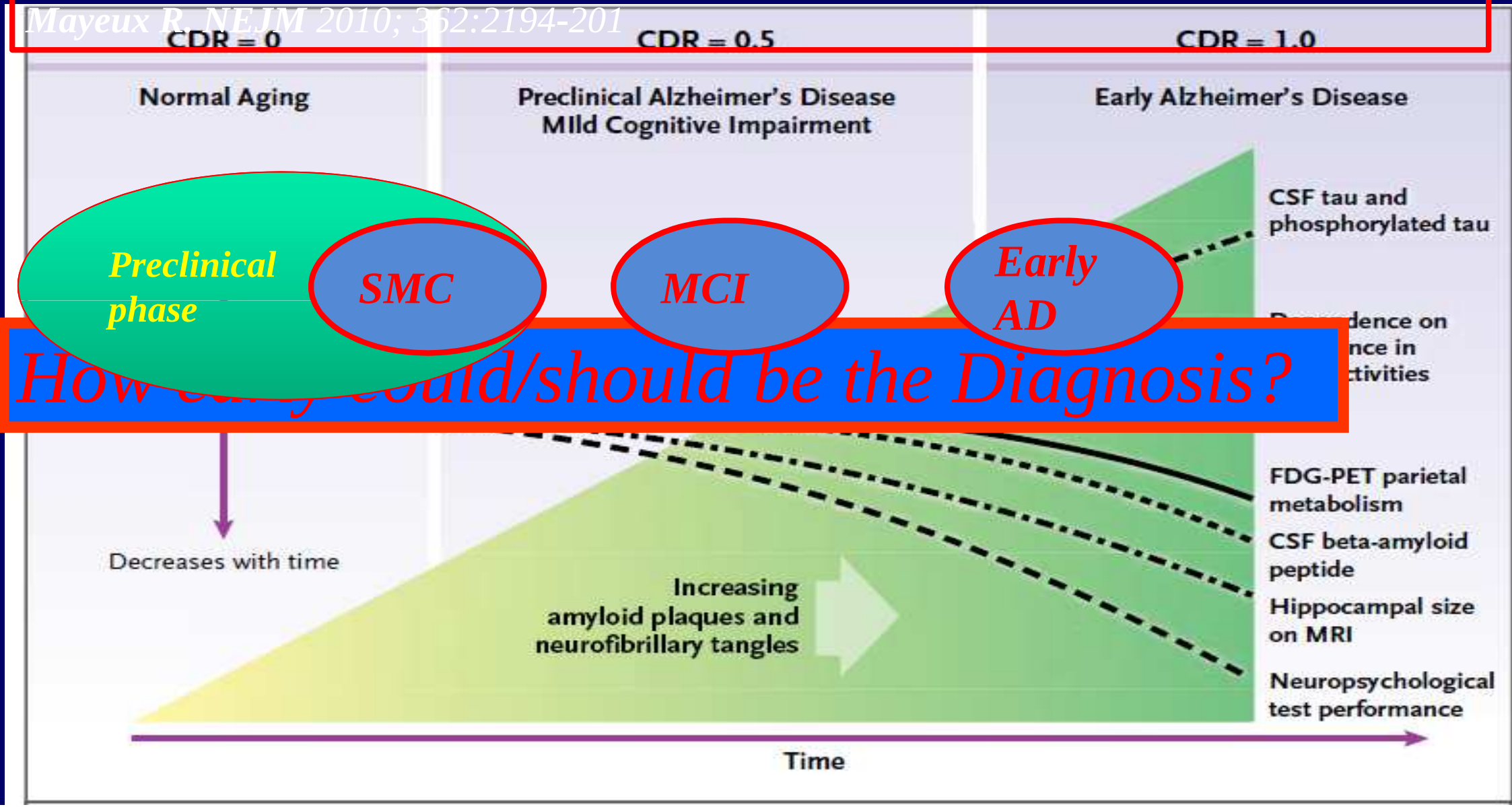


# A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease

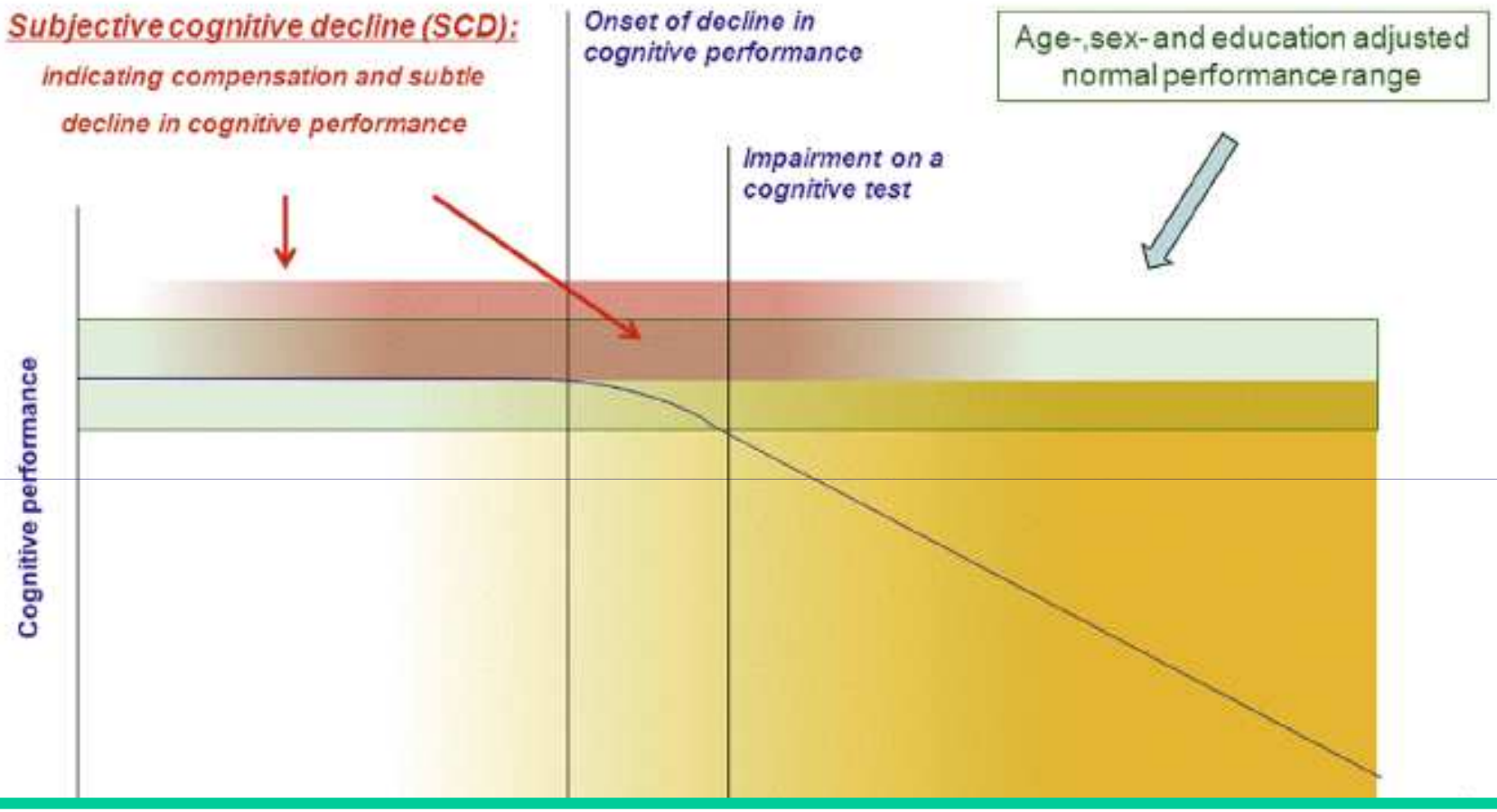



Table 1
Research criteria for pre-MCI subjective cognitive decline (SCD)

1. Self-experienced persistent decline in cognitive capacity in comparison with a previously normal status and unrelated to an acute event.
2. Normal age-, gender-, and education-adjusted performance on standardized cognitive tests, which are used to classify mild cognitive impairment (MCI) or prodromal AD.

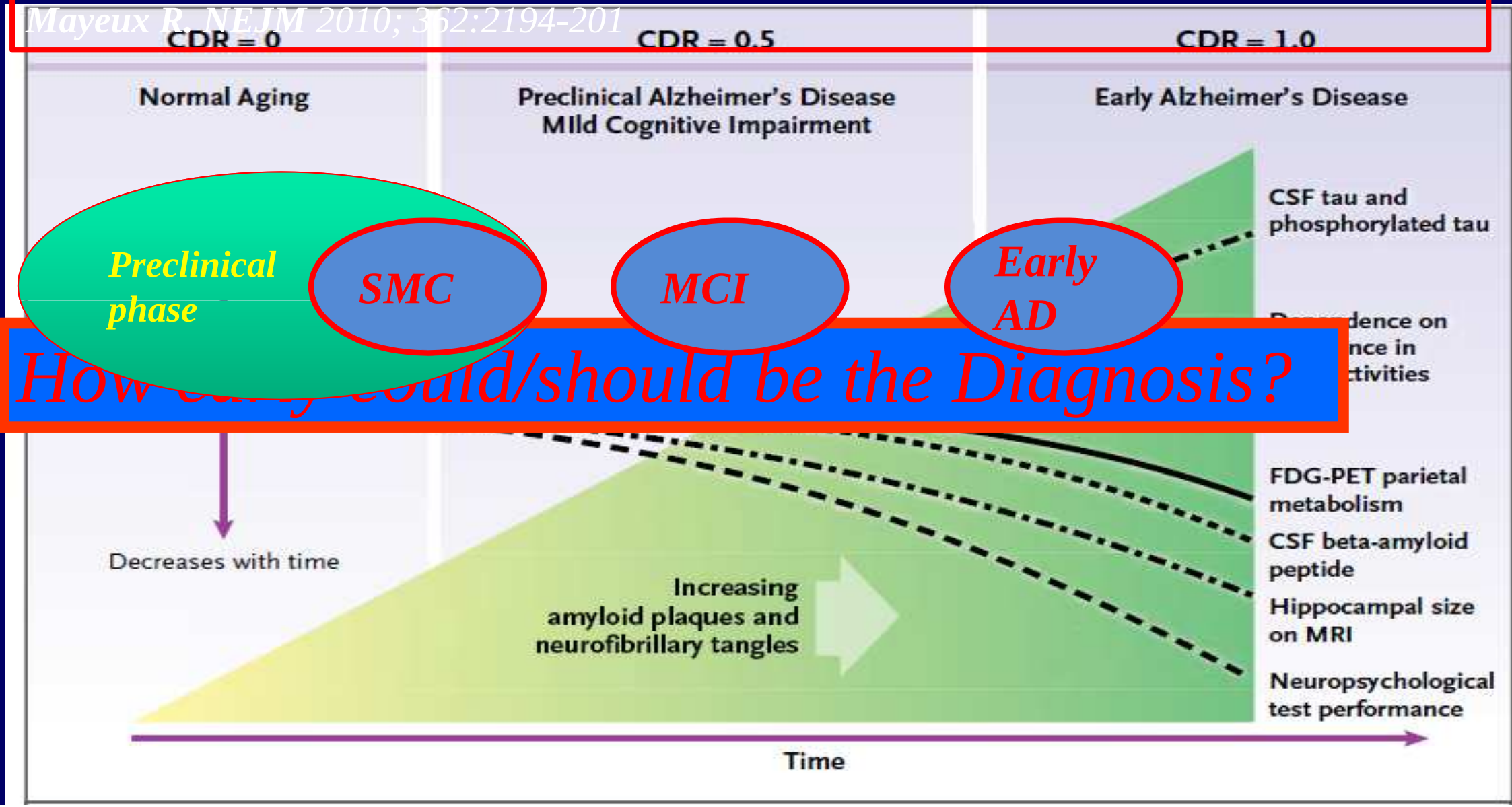
1 and 2 must be present

Exclusion criteria

- Mild cognitive impairment, prodromal AD, or dementia
- Can be explained by a psychiatric* or neurologic disease (apart from AD), medical disorder, medication, or substance use

# *Sequence of Pathological, Clinical, and Radiologic Changes from Normal Aging to Early AD*

*Mayeux R. NEJM 2010; 362:2194-201*



1. Aβ, including any of the isoforms of Aβ, plasma, or CSF samples.
2. Tau, including total or hyperphosphorylated tau, plasma, or CSF samples.
3. MRI, including any structural, functional, spectroscopic, or other techniques.
4. PET imaging of FDG uptake.
5. PET imaging of specific ligands for Aβ (Pittsburgh compound B [PiB], etc.).

# Multimodal work-up of neurodegeneration

Key parameters

Individual specific questions

**MRI:** Tumors, cerebrovascular lesions etc.

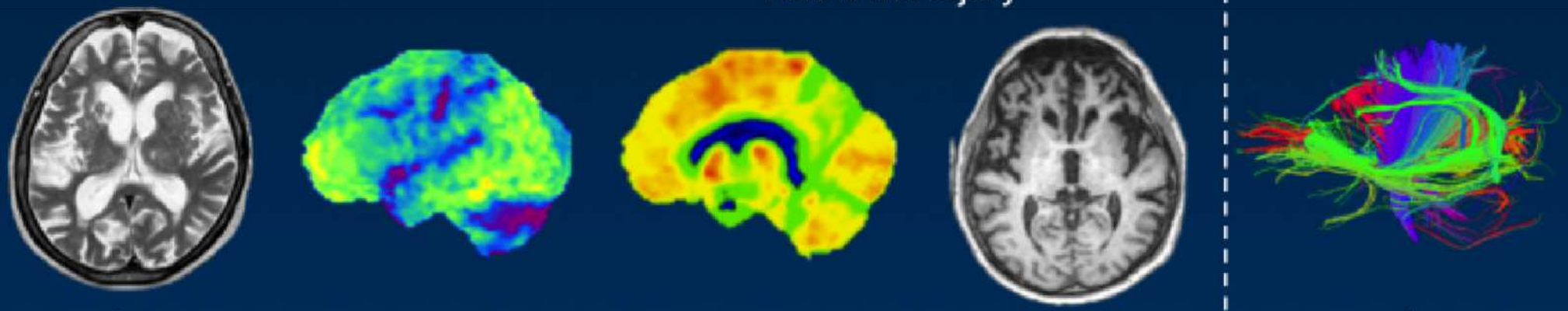
**PET:** Molecular pathology, amyloid/tau

**PET:** Neuronal dysfunction (metabolism/perfusion)

**MRI:** Atrophy, structural changes

**PET&/or MRI:** Inflammation receptor status connectivity, etc.

Neuronal injury



PET/MR:

Complete check-up in a one stop fashion in optimized quality (motion/atrophy correction)

# *New NIA Classification System*

**Stage 1**
**Asymptomatic amyloidosis**
*-High PET amyloid tracer retention*
*-Low CSF $A\beta_{1\text{-}42}$*

Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup

Reisa A. Sperling[a,*], Paul S. Aisen[b], Laurel A. Beckett[c], David A. Bennett[d], Suzanne Craft[e], Anne M. Fagan[f], Takeshi Iwatsubo[g], Clifford R. Jack[h], Jeffrey Kaye[i], Thomas J. Montine[j], Denise C. Park[k], Eric M. Reiman[l], Christopher C. Rowe[m], Eric Siemers[n], Yaakov Stern[o], Kristine Yaffe[p], Maria C. Carrillo[q], Bill Thies[q], Marcelle Morrison-Bogorad[r], Molly V. Wagster[r], Creighton H. Phelps[r]

Alzheimer's & Dementia ■ (2011) 1–13

**Stage 2**
**Amyloidosis + Neurodegeneration**
*-Neuronal dysfunction on FDG-PET/fMRI*
*-High CSF tau/p-tau*
*-Cortical thinning/Hippocampal atrophy on sMRI*

**Stage 3**
**Amyloidosis + Neurodegeneration + Subtle Cognitive Decline**
*-Evidence of subtle change from baseline level of cognition*
*-Poor performance on more challenging cognitive tests*
*-Does not yet meet criteria for MCI*

MCI → AD dementia

**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*)

**Exclusion criteria† for typical AD**

*History*

- Sudden onset
- Early occurrence of the following symptoms: gait disturbances, seizures, major and prevalent behavioural changes

*Clinical features*

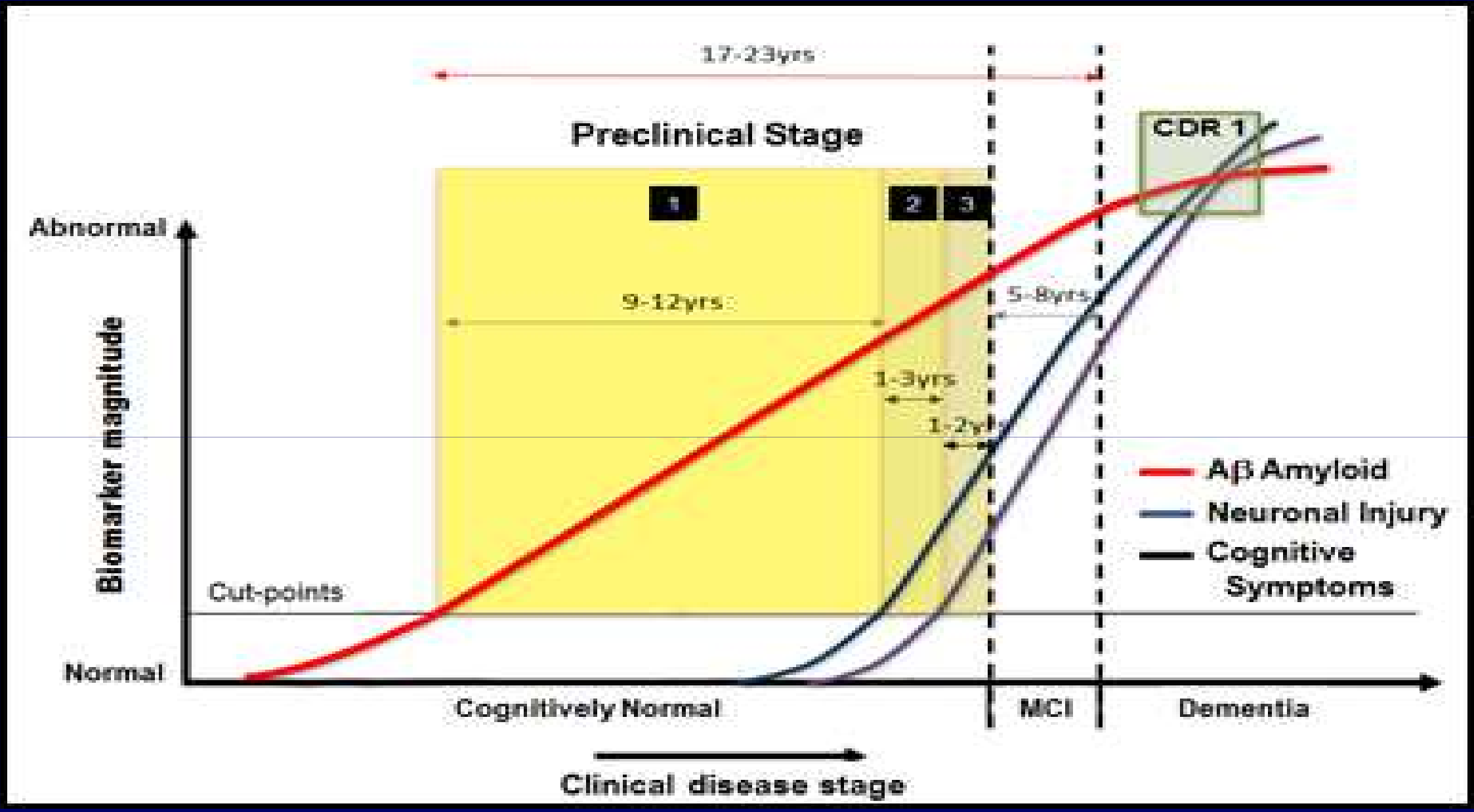
- Focal neurological features
- Early extrapyramidal signs
- Early hallucinations
- Cognitive fluctuations

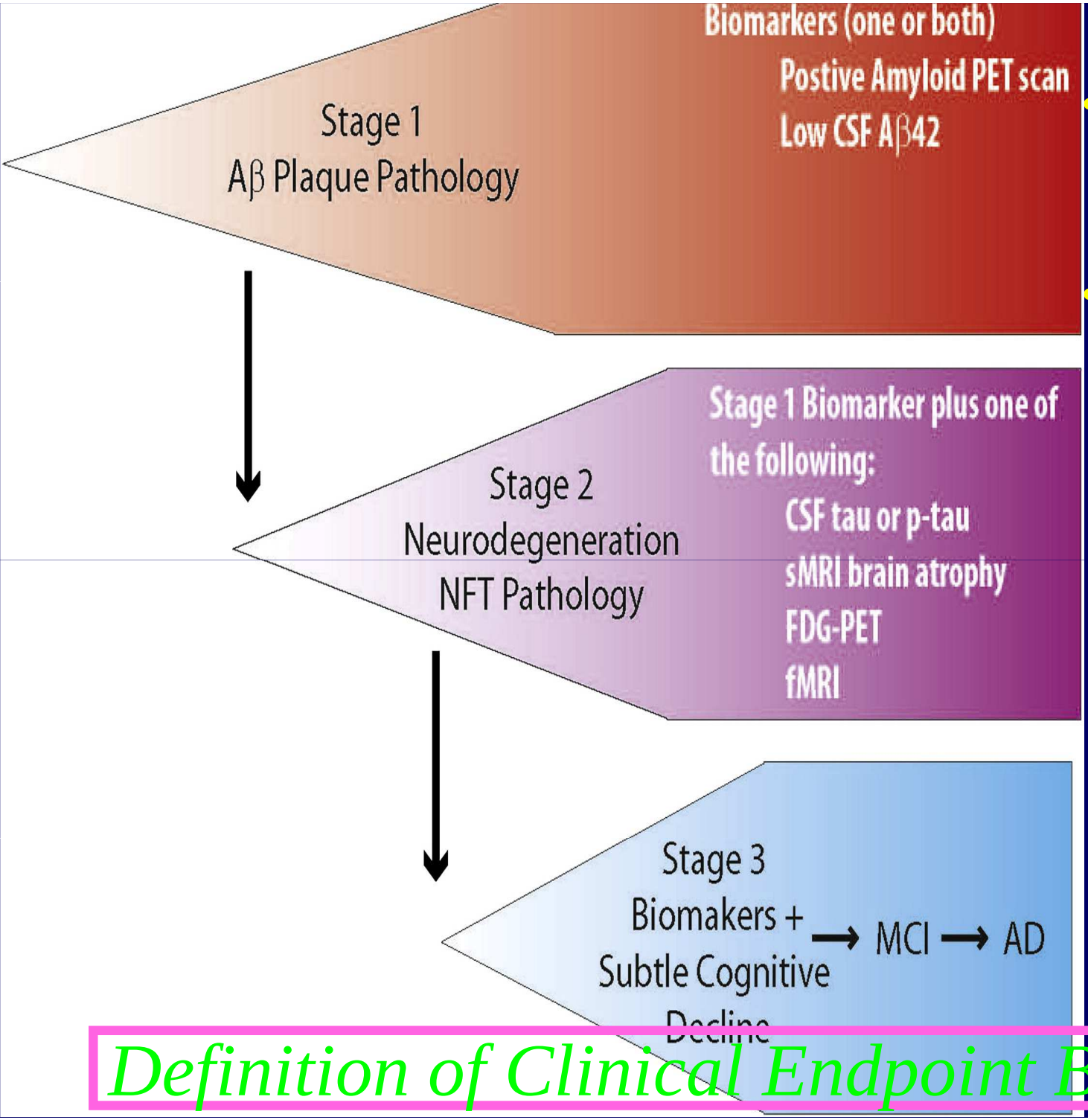
*Other medical conditions severe enough to account for memory and related symptoms*

- Non-AD dementia
- Major depression
- Cerebrovascular disease
- Toxic, inflammatory, and metabolic disorders, all of which may require specific investigations
- MRI FLAIR or T2 signal changes in the medial temporal lobe that are consistent with infectious or vascular insults

AD=Alzheimer's disease. *Hippocampal amnestic syndrome might be difficult to identify in the moderately severe to severe dementia stages of the disease, in which in-vivo evidence of Alzheimer's pathology might be sufficient in the presence of a well characterised dementia syndrome. †Additional investigations, such as blood tests and brain MRI, are needed to exclude other causes of cognitive disorders or dementia, or concomitant pathologies (vascular lesions).

*Symptom onset is important*


17-23yrs
Preclinical Stage
CDR 1
1
2
3
Abnormal
Biomarker magnitude
9-12yrs
5-8yrs
1-3yrs
1-2yr
Aβ Amyloid
Neuronal Injury
Cognitive Symptoms
Cut-points
Normal
Cognitively Normal
MCI
Dementia
Clinical disease stage

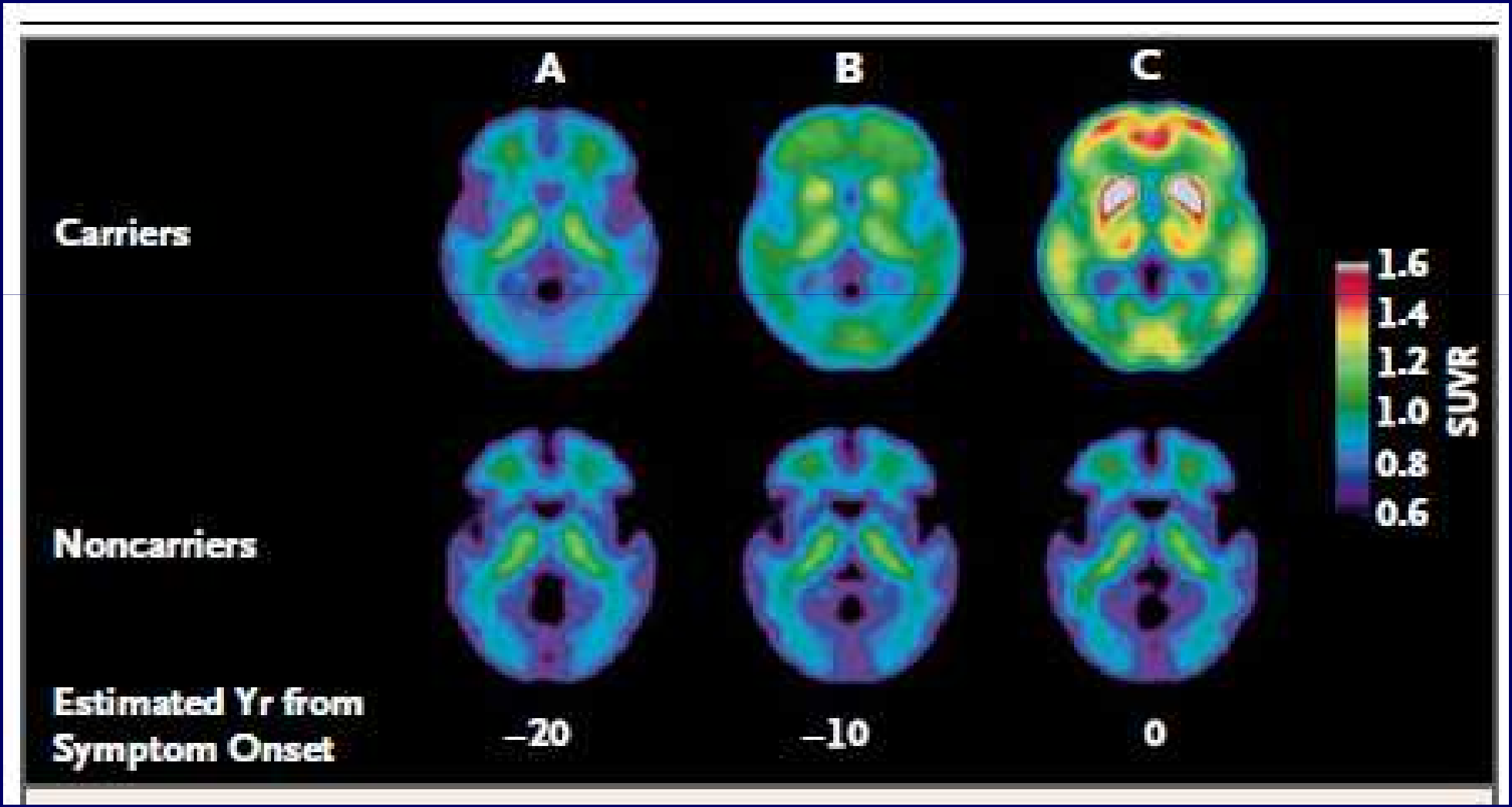


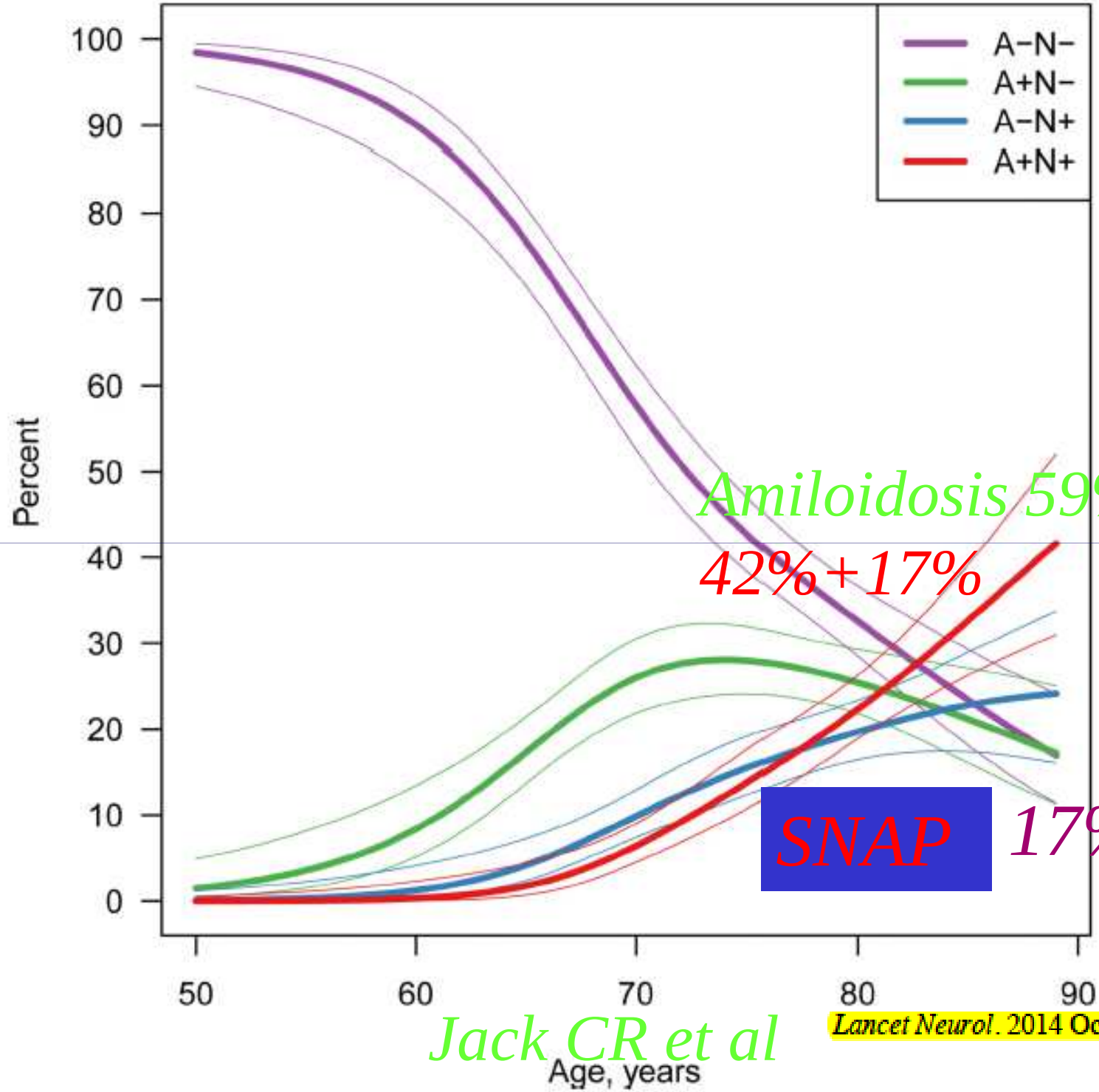

- "A biomarker that is intended to substitute for a clinical endpoint.
- It is expected to predict clinical benefit (or lack of benefit) based on epidemiologic, therapeutic, pathophysiologic or other scientific evidence."

# *Definition of Clinical Endpoint Biomarker*

# *Comparison of A-Beta Deposition with PET-PIB in Carriers and not Carriers in Dominantly Inherited AD*

*Bateman RJ NEJM July 23 2012*

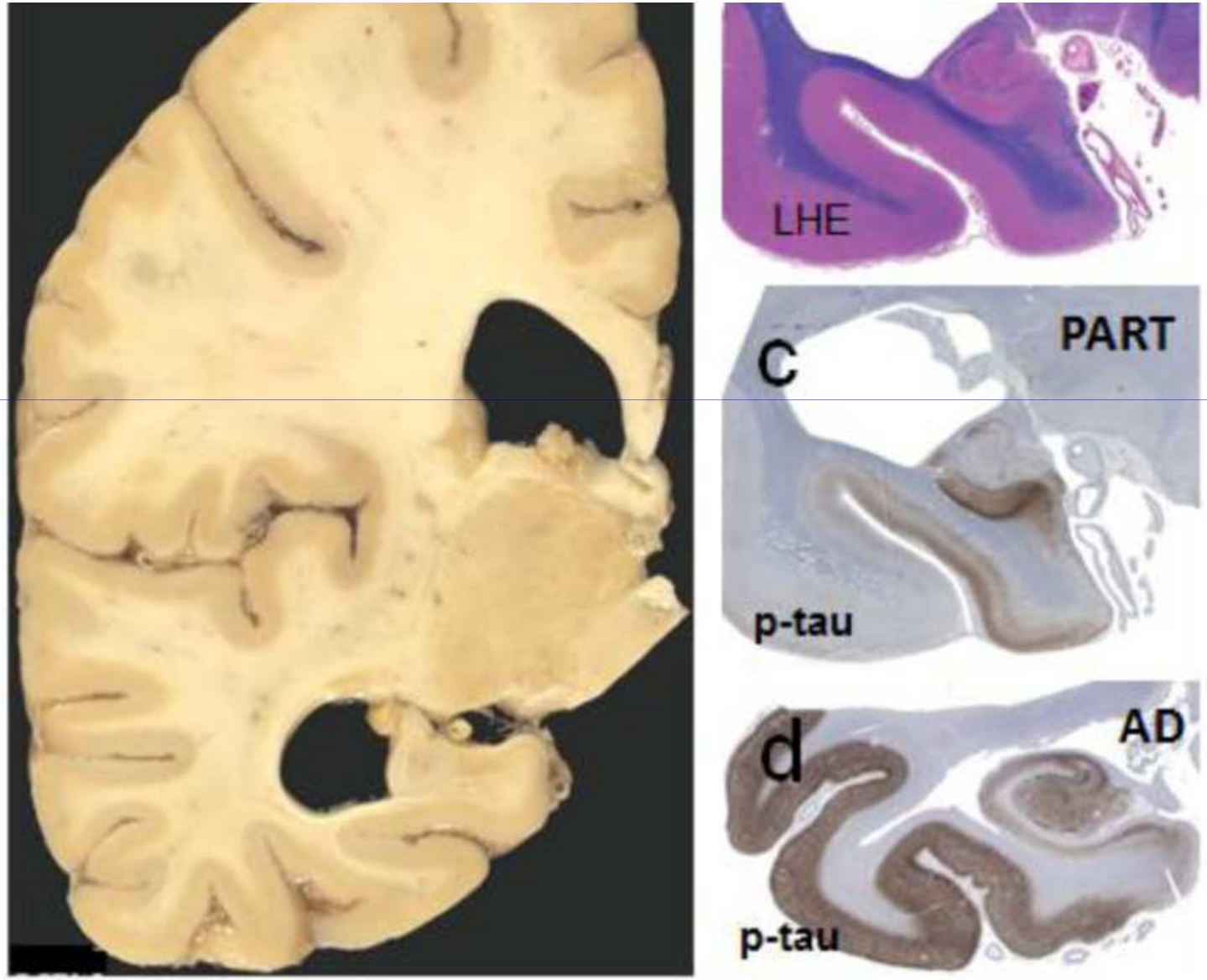


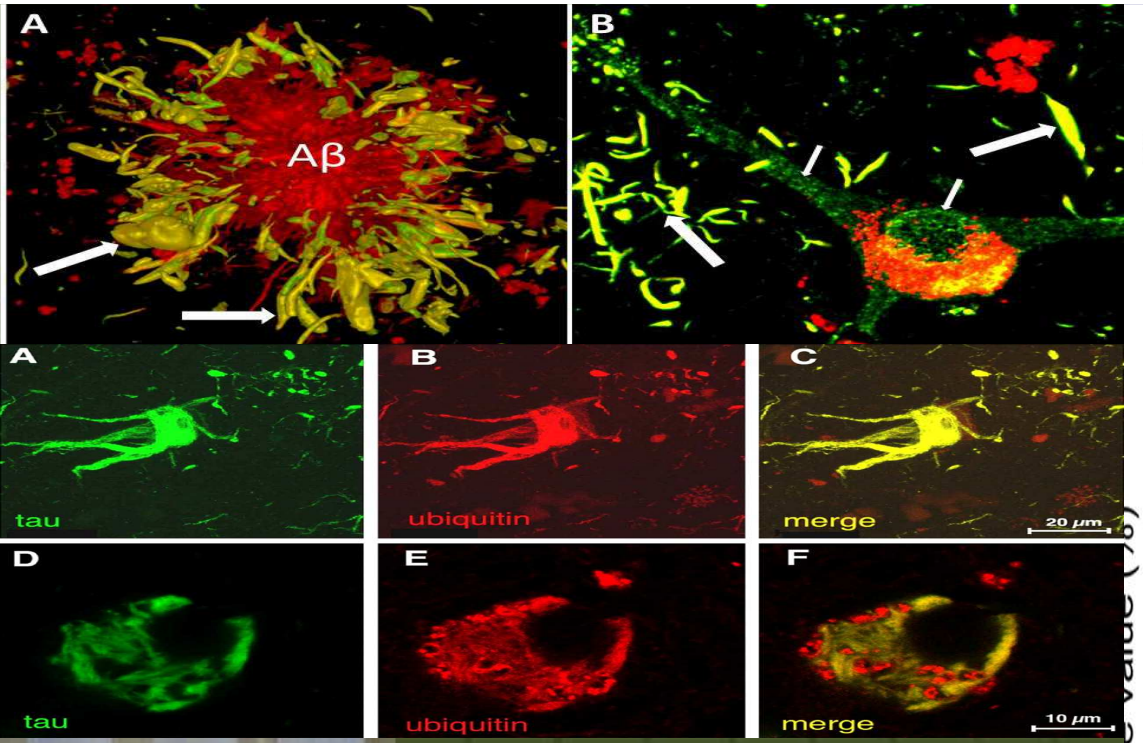


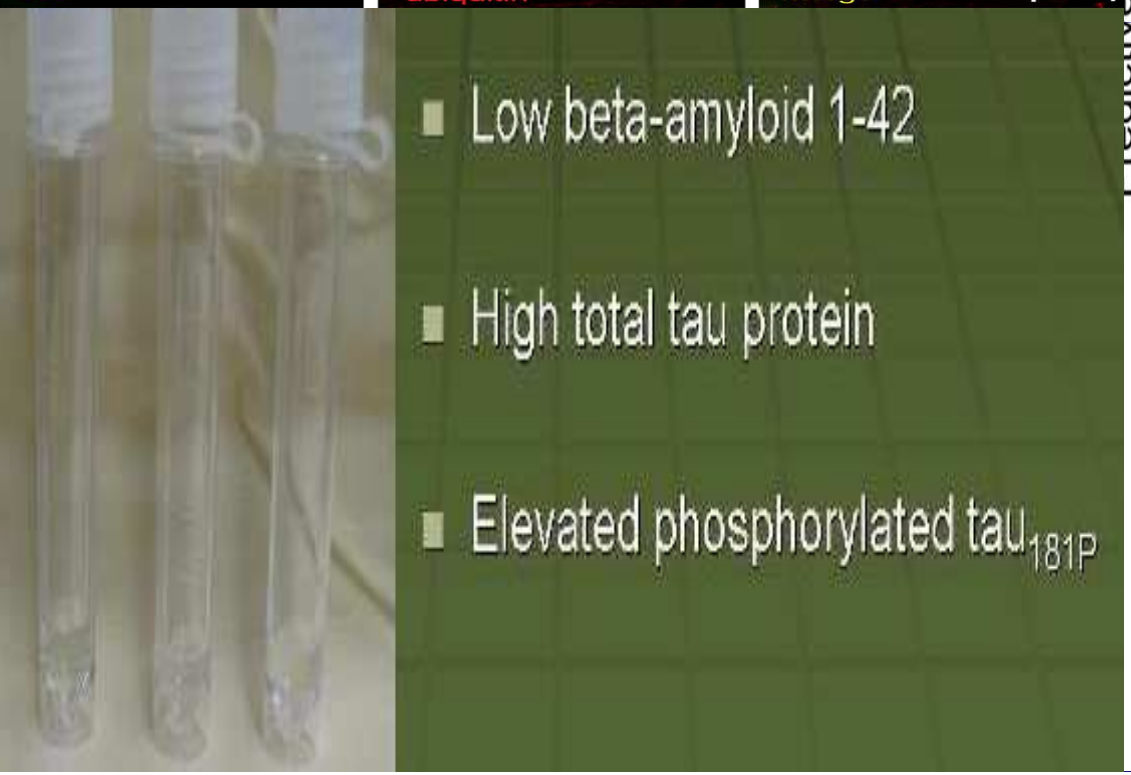

Jack CR et al

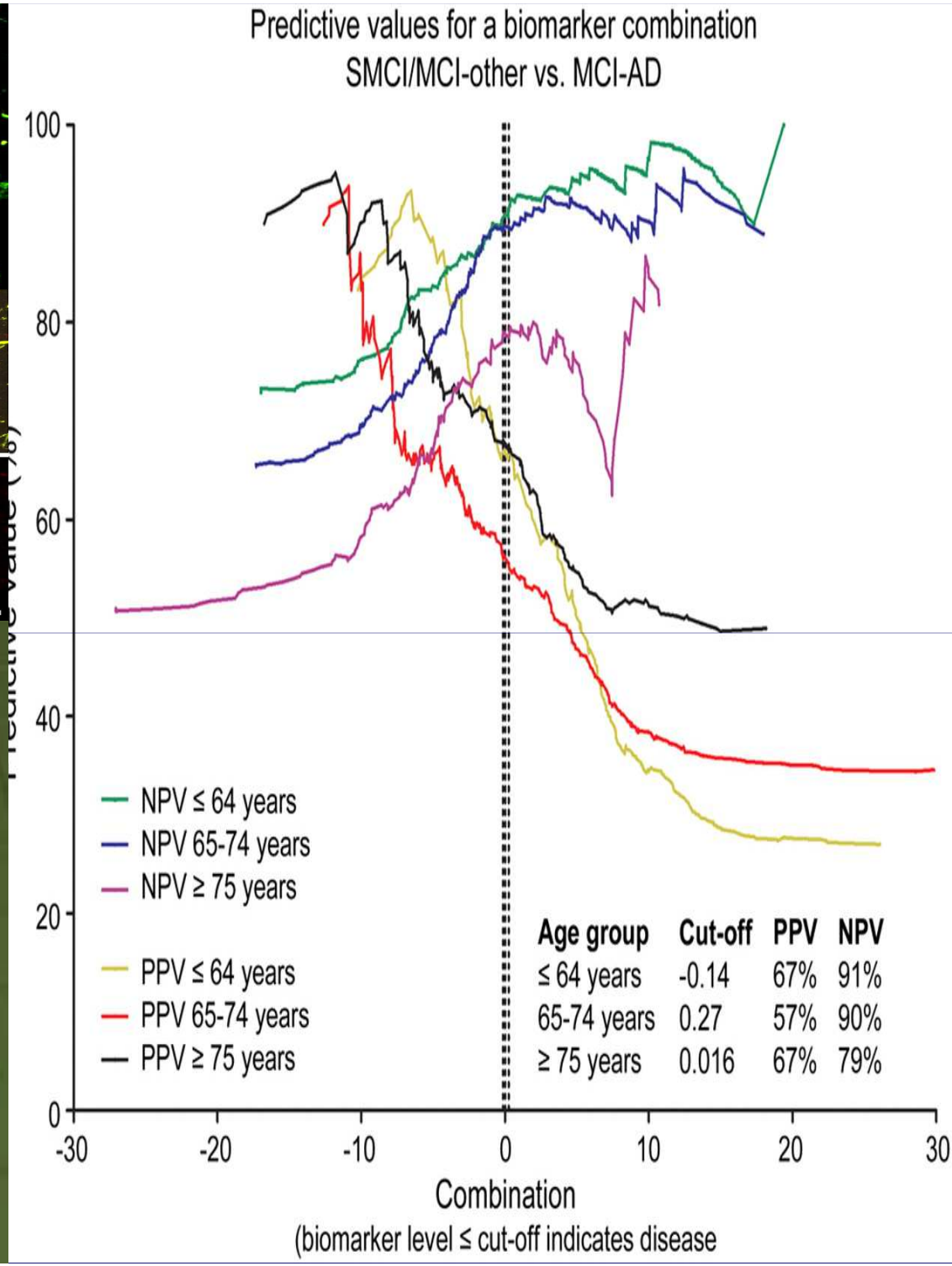
*Lancet Neurol*. 2014 October ; 13(10): 997–1005.

# Primary age-related tauopathy (PART): a common pathology associated with human aging




A
Aβ
B
A
tau
B
ubiquitin
C
merge
20 μm
D
tau
E
ubiquitin
F
merge
10 μm


Low beta-amyloid 1-42
High total tau protein
Elevated phosphorylated tau181P


Predictive values for a biomarker combination
SMCI/MCI-other vs. MCI-AD
100
80
60
40
20
0
-30
-20
-10
0
10
20
30
Combination
(biomarker level ≤ cut-off indicates disease
NPV ≤ 64 years
NPV 65-74 years
NPV ≥ 75 years
PPV ≤ 64 years
PPV 65-74 years
PPV ≥ 75 years
Age group Cut-off PPV NPV
≤ 64 years -0.14 67% 91%
65-74 years 0.27 57% 90%
≥ 75 years 0.016 67% 79%

# Conclusioni

- Nuovi sistemi classificatori
- Diagnosi precoce importante per RCT
- Markers sono molto più efficaci in età basse (>75aa)
- Nuove entità cliniche in fase precoce:SNAP e PART

# Diagnostic Criteria (Operational Criteria)

- Provide clear and reproducibile applications of definition ( based on clinical/test characteristics)
- Provide homogeneous groups of cases
- Possible identification of subgroups
- Starting point to predict prognosis and choose a therapy


*The Single Patient*

*Diagnosis*

*Prognosis*

*Treatment*

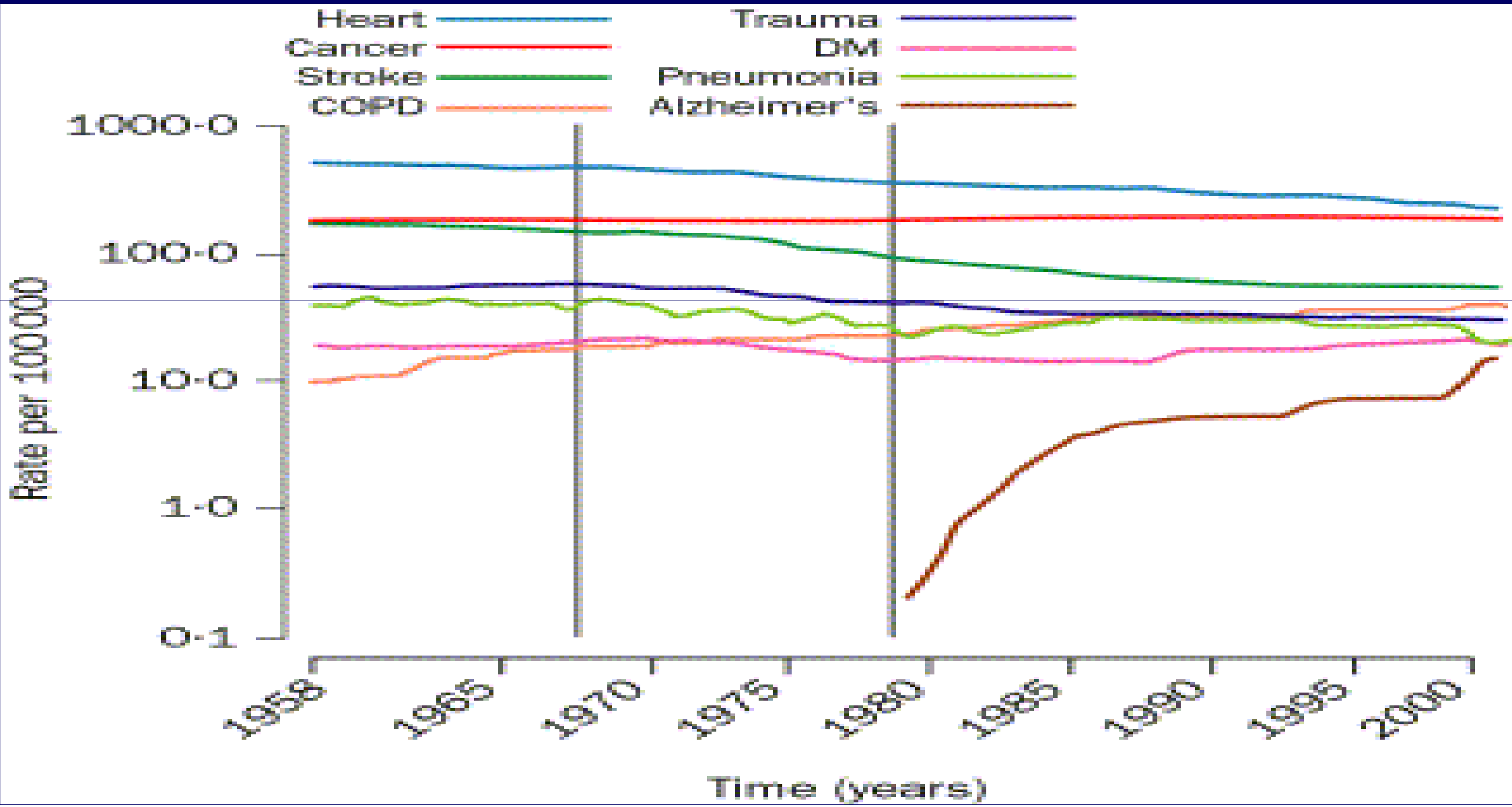
*Groups of Patients*

*Participating to Studies*

*OBS or RCT*

# *Mortality from leading causes of death over the past five decades*

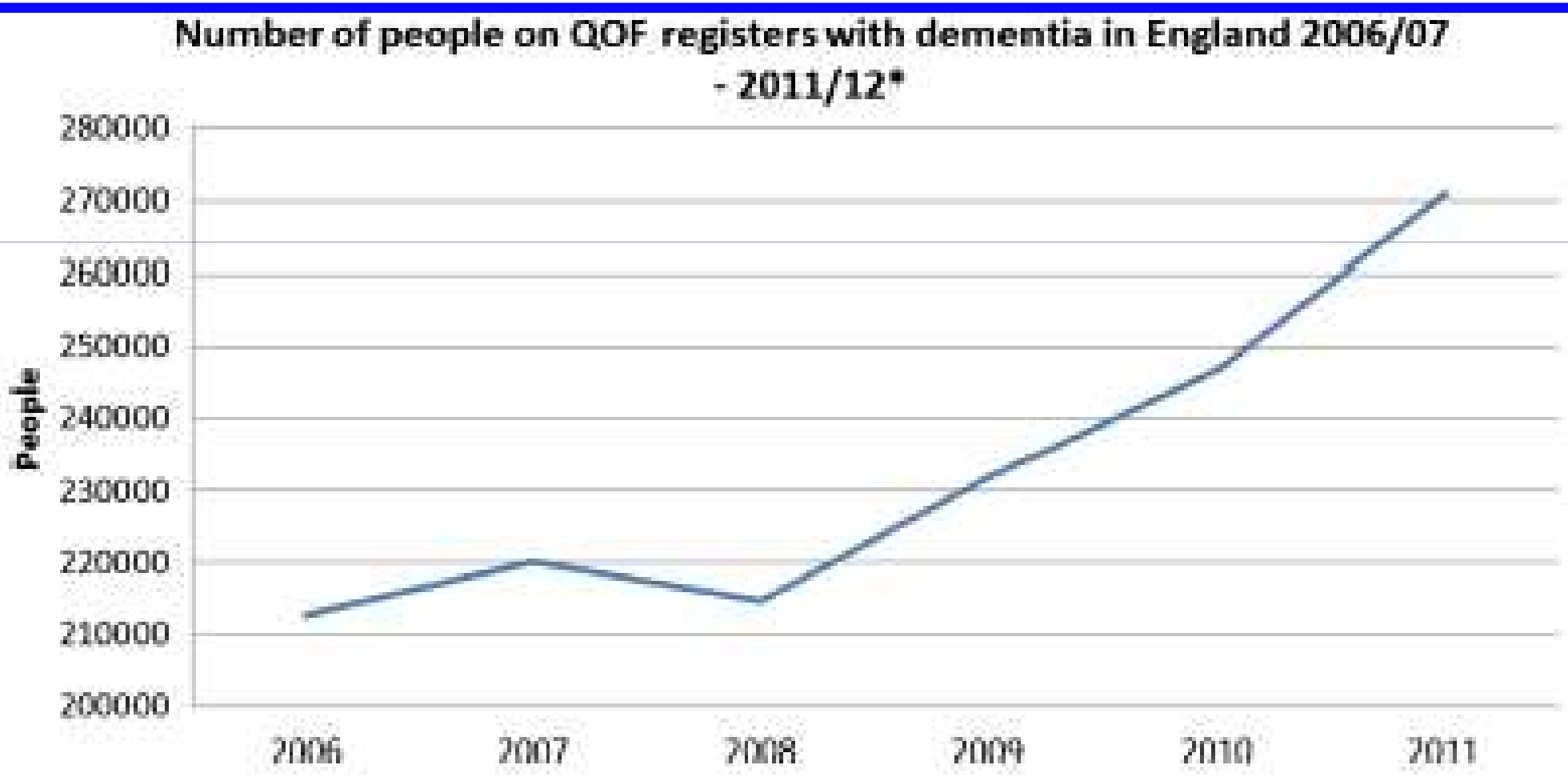
*Casserly I. et al Lancet 2004; 363:1139-46.*

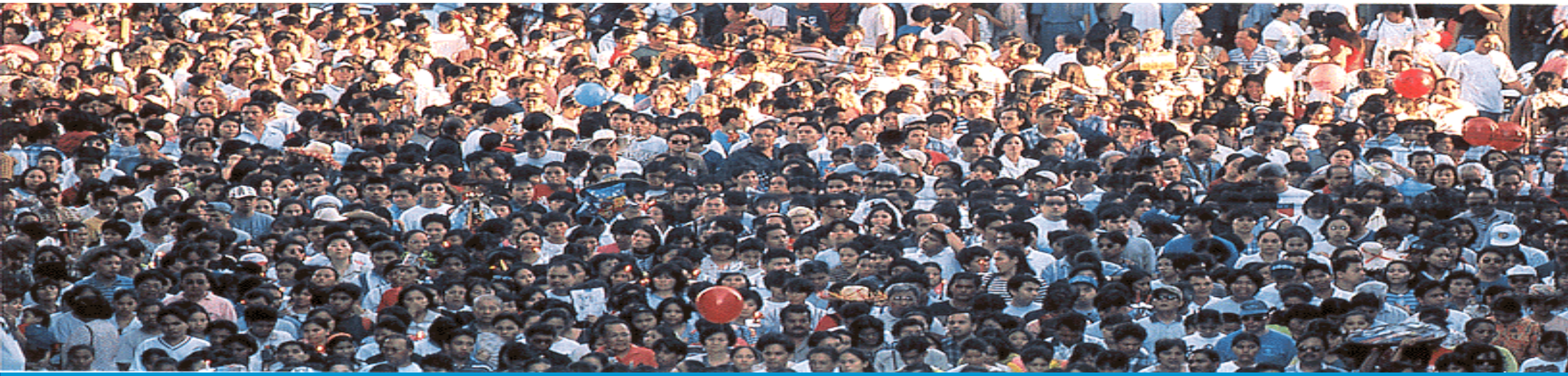


BMJ Open

# Diagnostic rates and treatment of dementia before and after launch of a national dementia policy: an observational study using English national databases

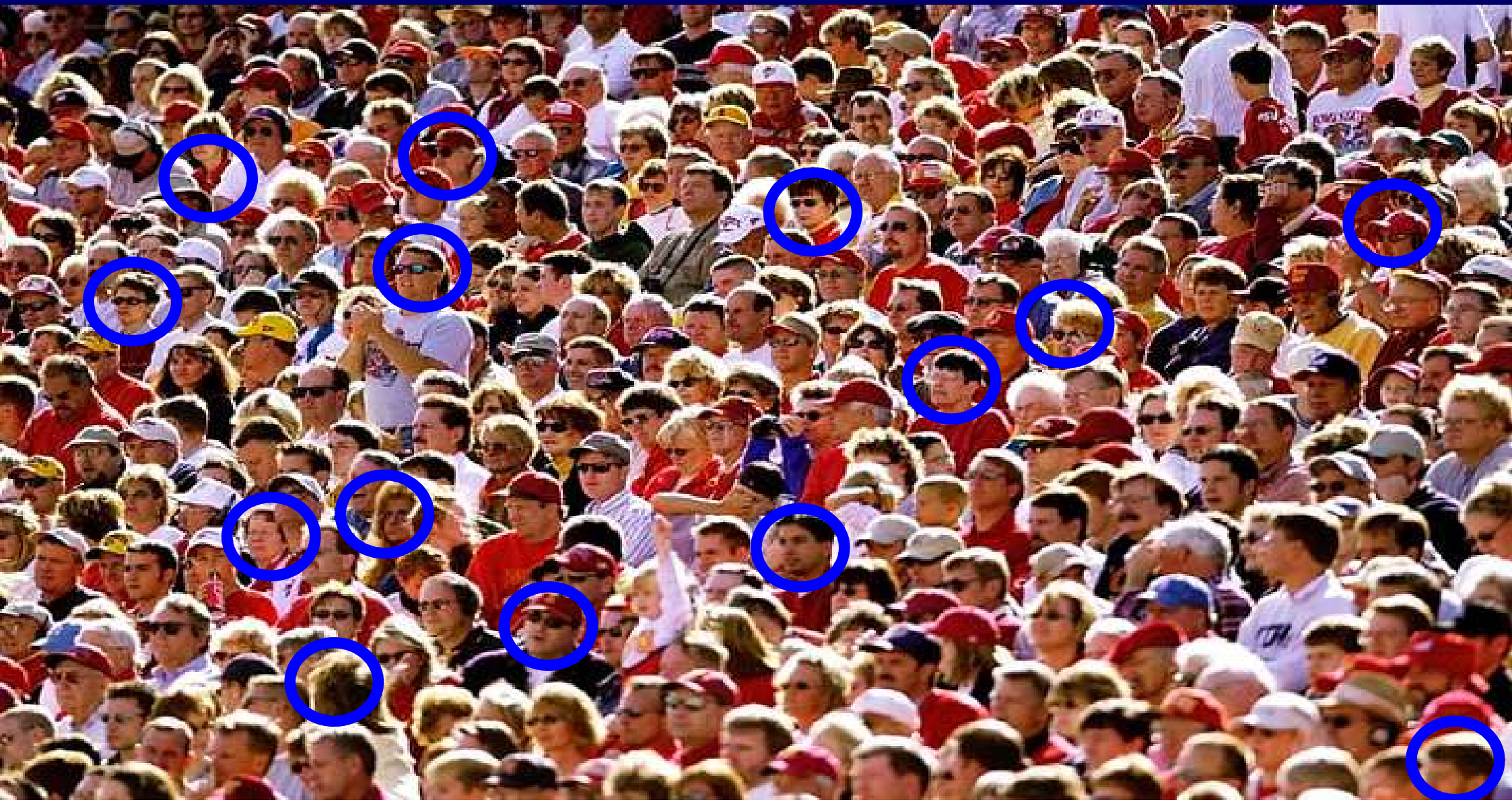
Naaheed Mukadam,[1] Gill Livingston,[1] Khadija Rantell,[2] Sam Rickman[1]



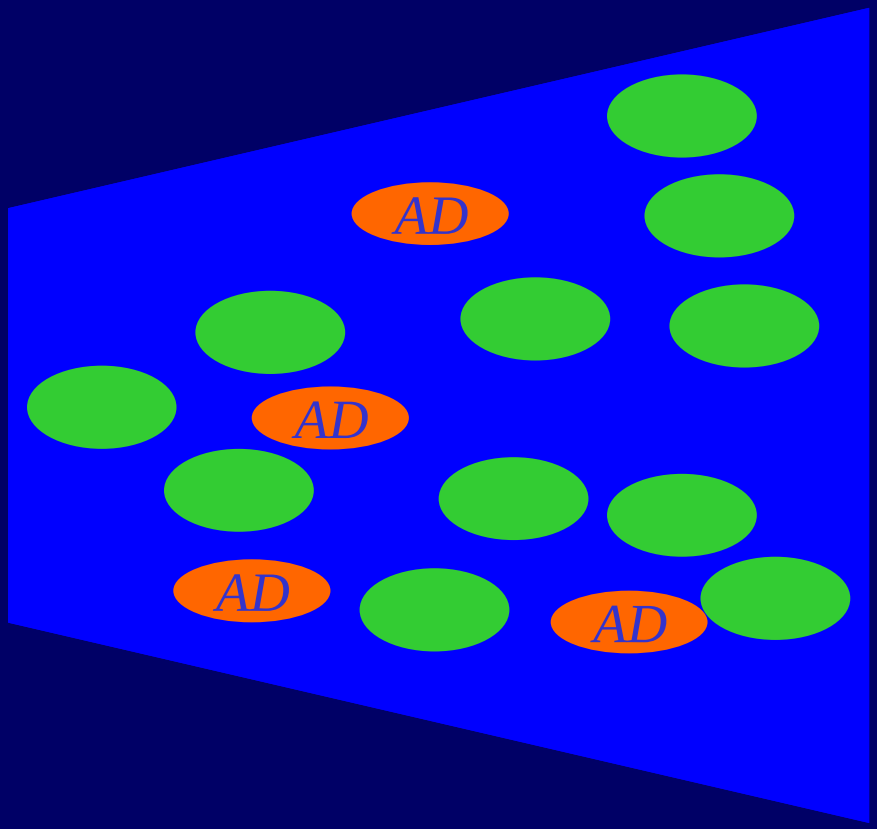


MORE
SCIENCE.
LESS
FEAR.

# *Cohort Design for Common Diseases*
# *High Incidence and Prevalence*



# Common Neurodegenerative Diseases : Study Design

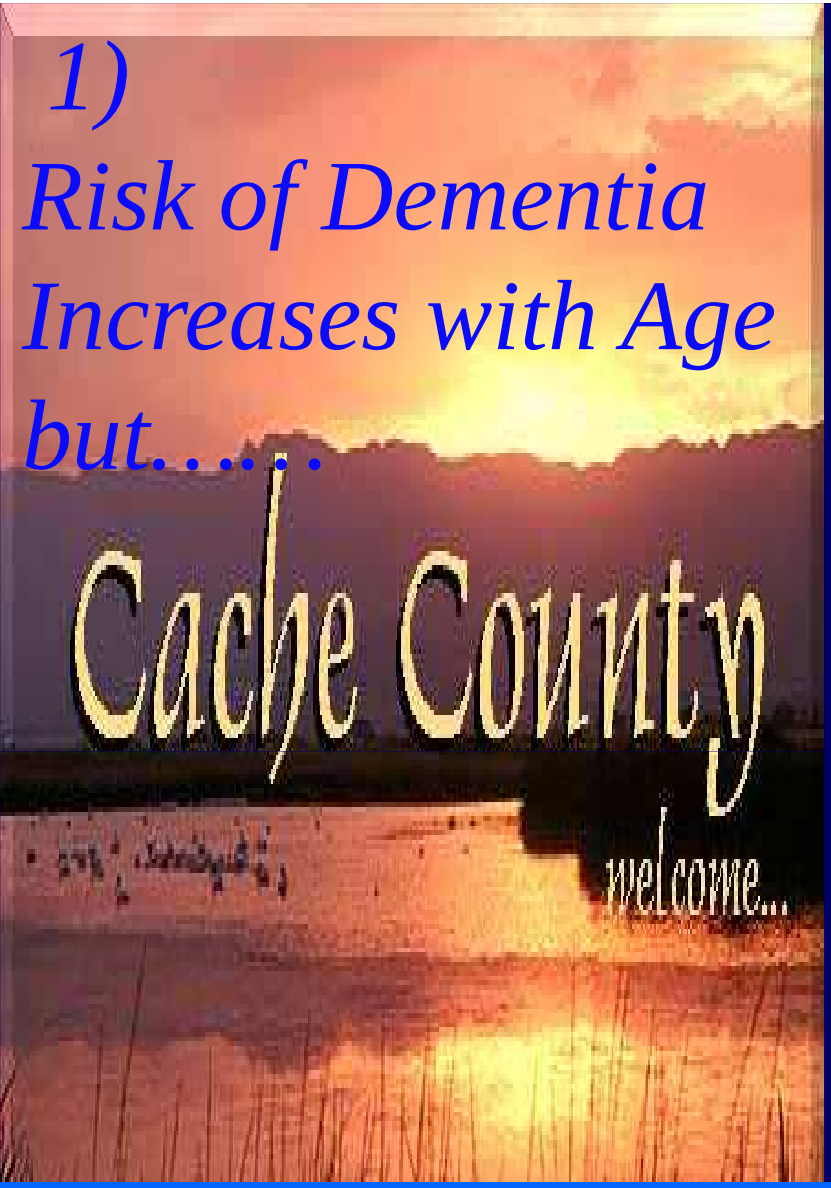



- Small geographical area
- Door to door survey
- Do not rely on previous medical diagnosis
- 2-3 phases design
- Limited sampled population

  500-10000

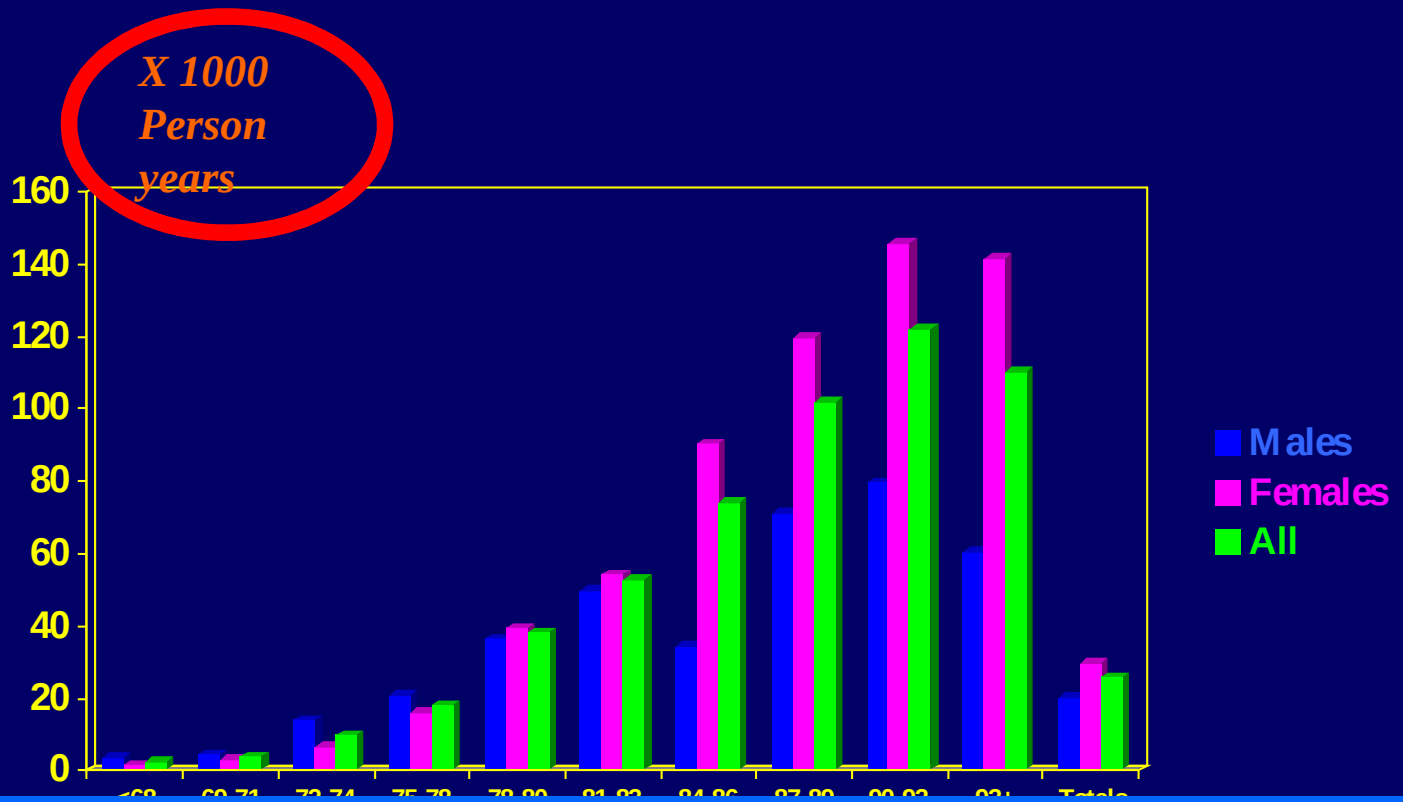
*1)*

*Risk of Dementia Increases with Age but……*




# The Cache County Study
# Incidence of Dementia by Sex and Age

*Miech R A, Breitner J C S, Zandi P P et al. Neurol 2002; 58:209-218.*

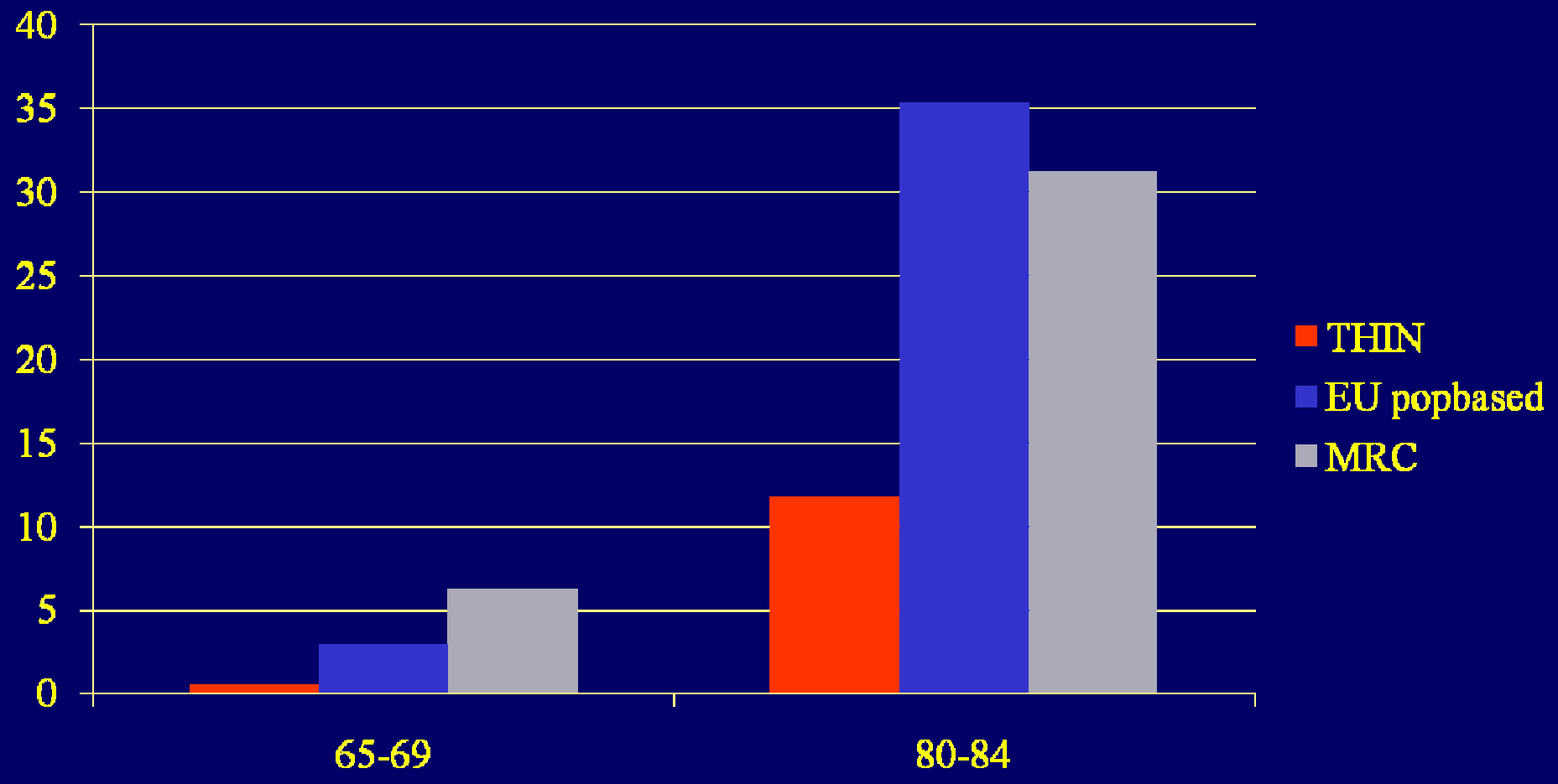



*1)Risk of Dementia Increases with Age but…… and AD is a common Disease*

Incidenza in tre studi

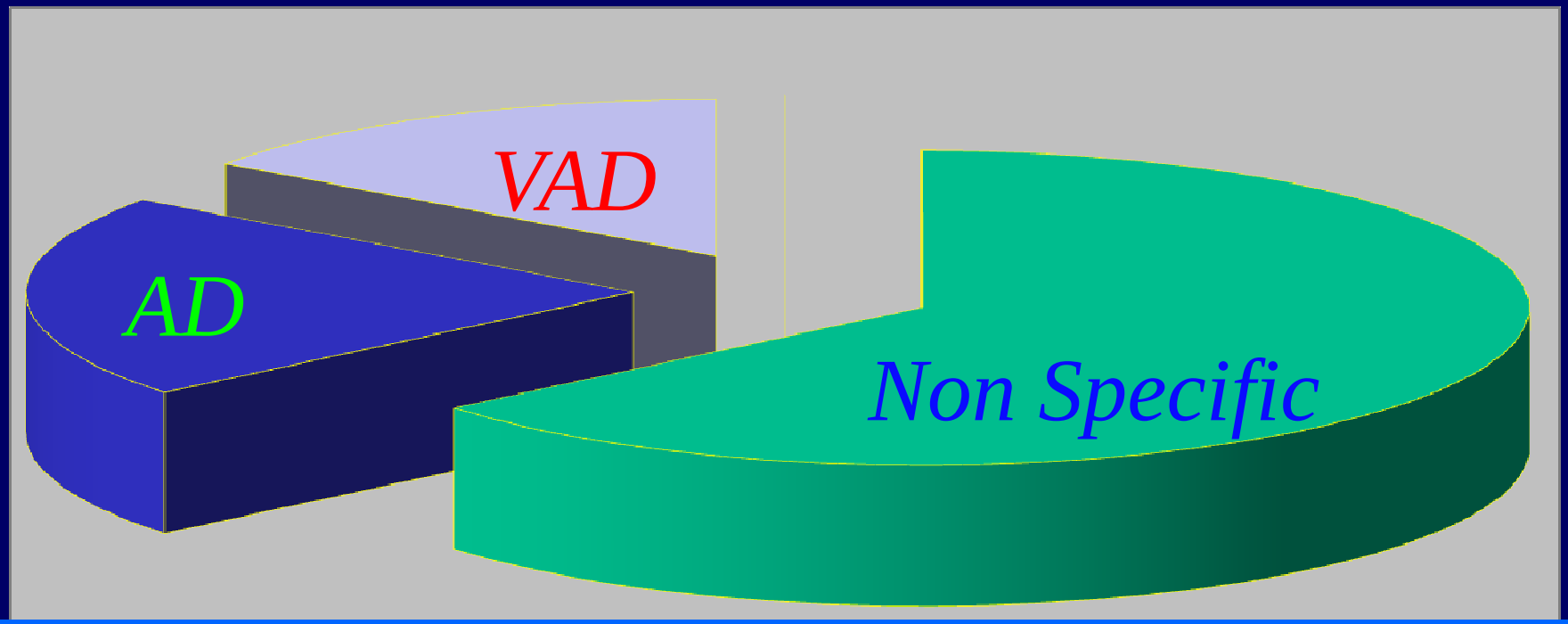
Confronto tra la diagnosi di demenza nello studio del MMG e Ricerca attiva di Demenza negli Studi Epidemiologici

Rait G et al BMJ. 2010 5;341:c3584




*2) Half of Dementia Cases are not Diagnosed*

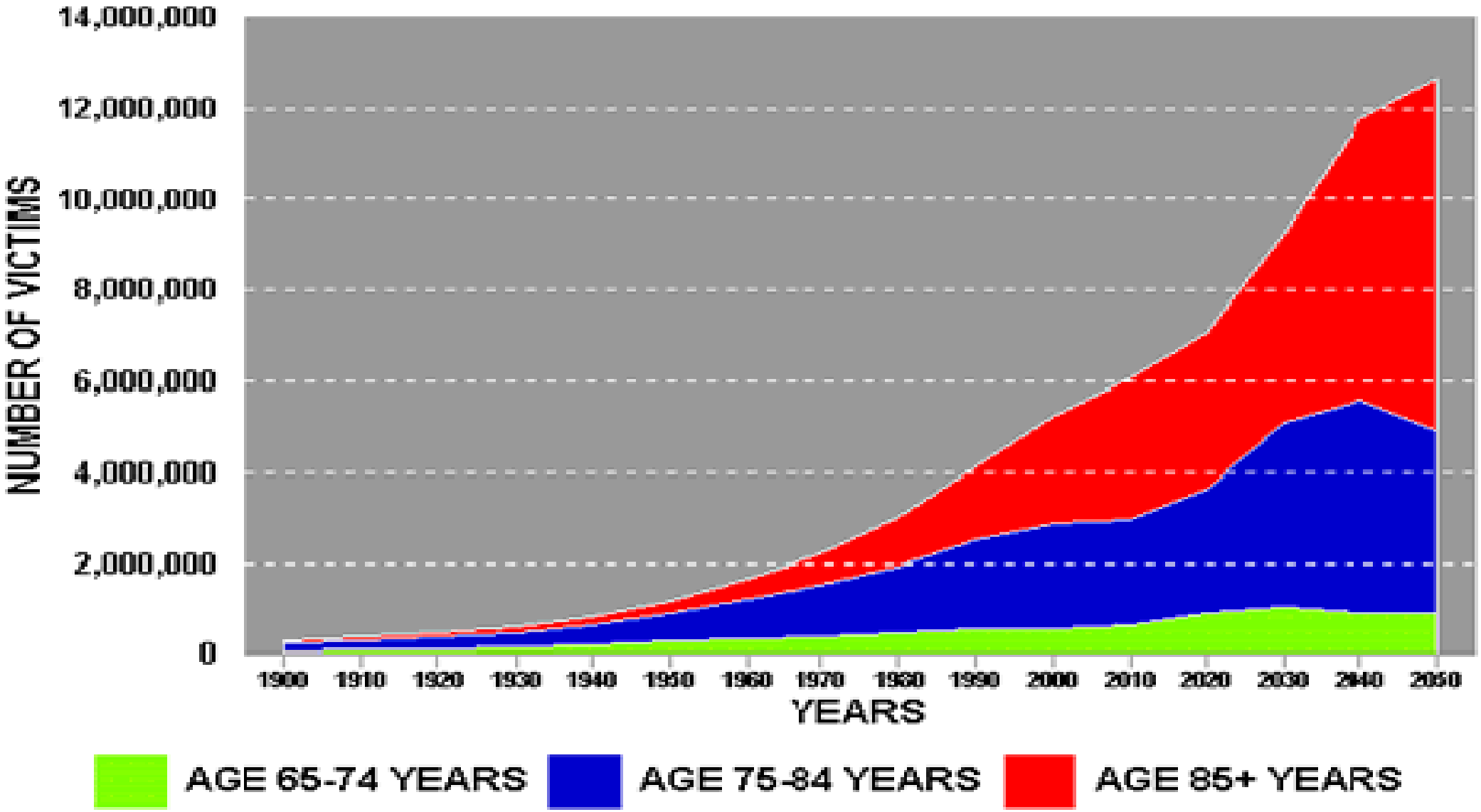
*Rait G et al BMJ. 2010 5;341:c3584*




*3) The Diagnosis of Subtypes of Dementia is done only in 1/3 of the cases in UK GP Practices*

- *Numero di casi di demenza incrementa in maniera esponenziale in tutto il mondo*
- *La diagnosi è inadeguata*
- *Le demenze (AD in particolare) sono la più probabile causa di disabilità nella fase avanzata della vita*

# PREVALENCE OF ALZHEIMER'S DISEASE
## (BY DECADES IN U.S.A. FROM 1900-2050)

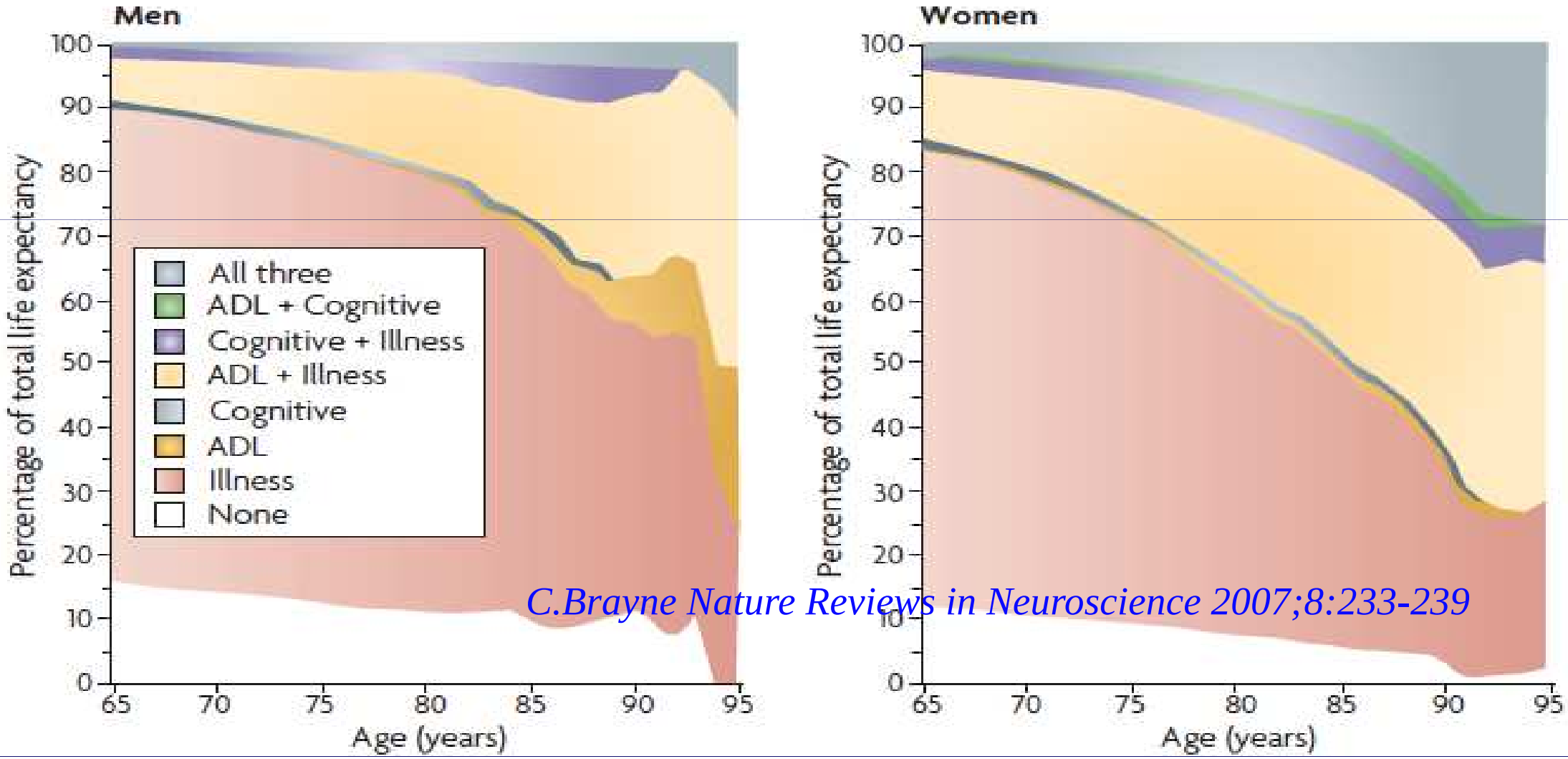



This graph portrays how many Americans over the age of 65 are currently affected by Alzheimer's, and a projection of how many more will become affected with it as time passes.

w3.ouhsc.edu

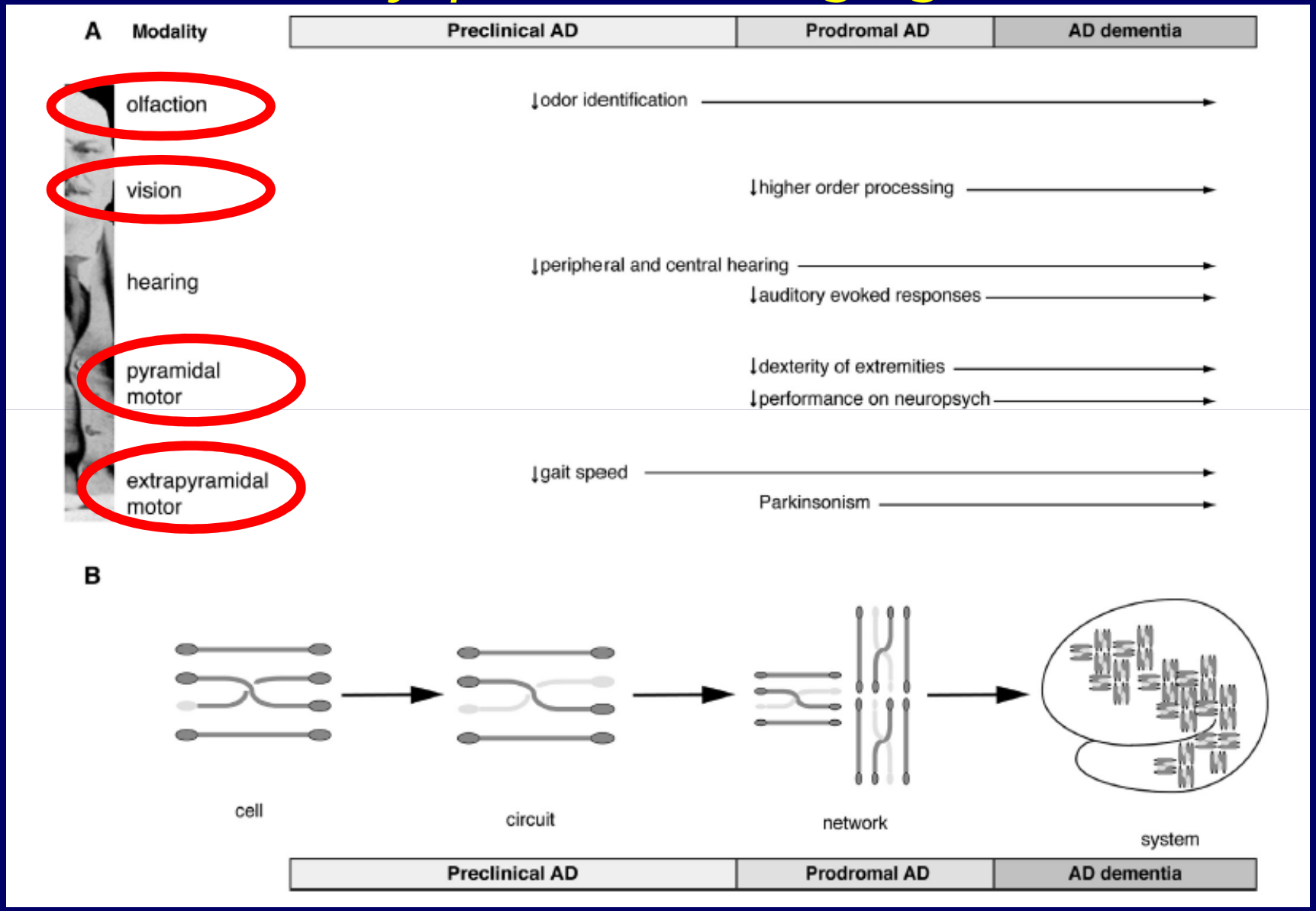
SCIENCE AND SOCIETY

# The elephant in the room — healthy brains in later life, epidemiology and public health




*C.Brayne Nature Reviews in Neuroscience 2007;8:233-239*

# National Institute on Aging Exploratory Workshop Sensory and Motor Dysfunctions in Aging and AD

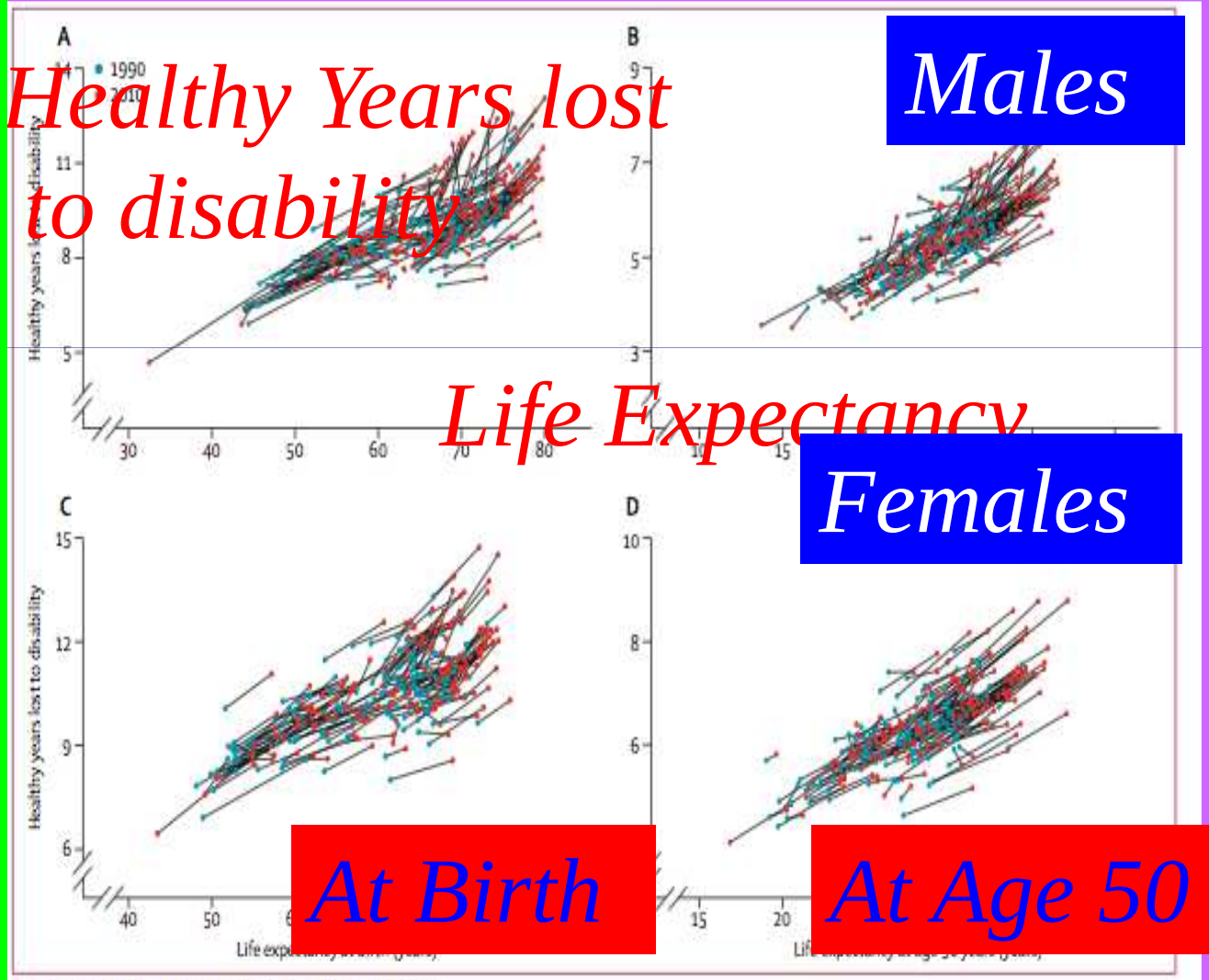



*Alzheimers Dement 2015;11:70-98*

# The Global Burden of Disease Study: #5

## Differential Increase in Healthy Years Lost to Disability vs Life Expectancy 1970-2010

Wang H et al Lancet 2012;380: 2071-94



***The Medical Research Council Cognitive Function and Ageing Study (MRC CFAS)***

***Brain Biopsies***

Random samples 65th year and above from Family Health Service Authority

Cambridgeshire
Gwynedd
Newcastle
Nottingham
Oxford
Liverpool

stratified by age group
(65-74 years and 75 years and over)

2500 in each of the areas but Liverpool sample size of 6000.

# A comparison of health expectancies over two decades in England: results of the Cognitive Function and Ageing Study I and II

Carol Jagger, Fiona E Matthews, Pia Wohland, Tony Fouweather, Blossom C M Stephan, Louise Robinson, Antony Arthur, Carol Brayne, on behalf of the Medical Research Council Cognitive Function and Ageing Collaboration*

*Would you say for one of your age your health is generally excellent/good/fair poor?*

*Come giudicheresti per uno della tua età il tuo stato di salute? Eccellente, buono, modesto, cattivo*

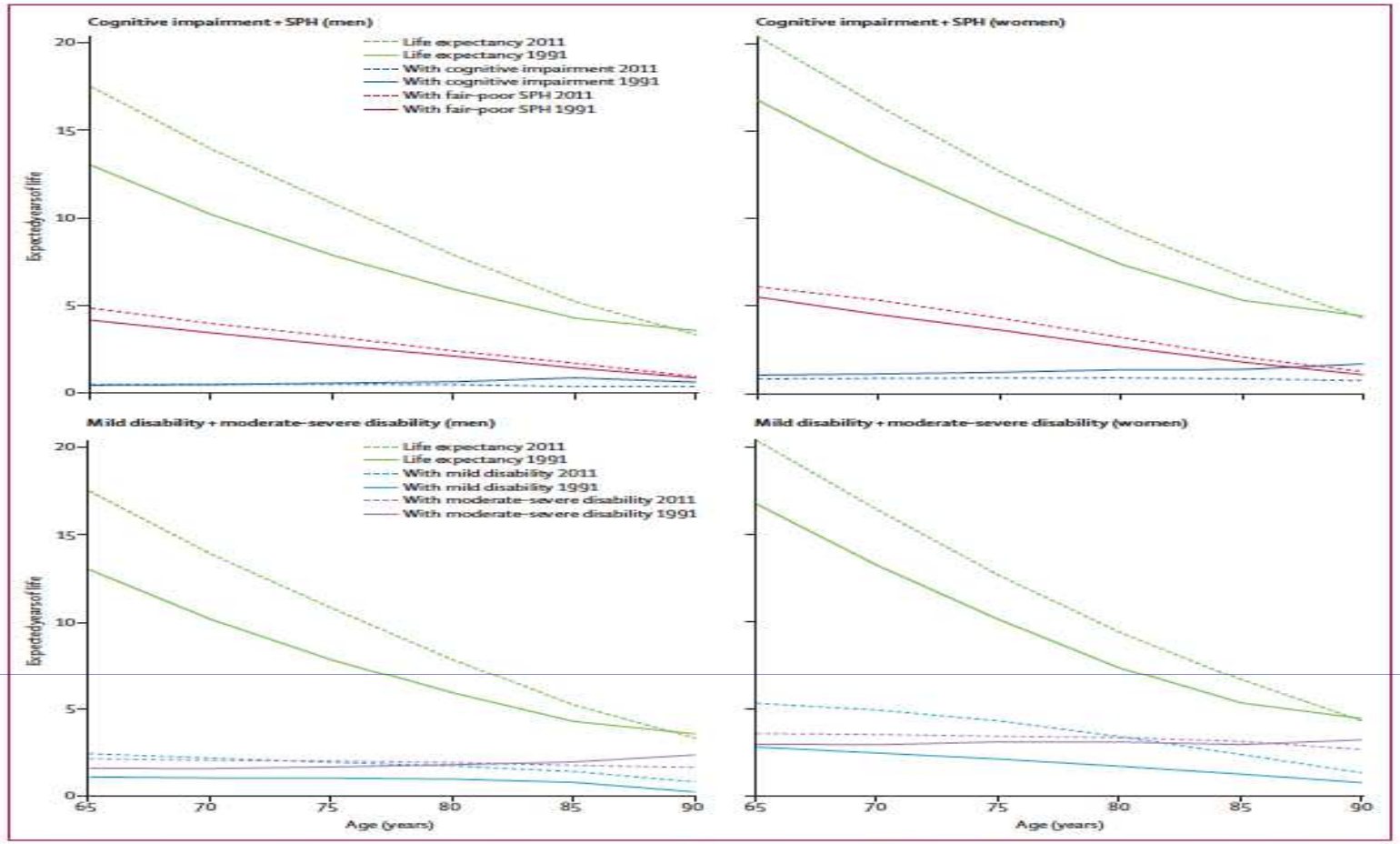


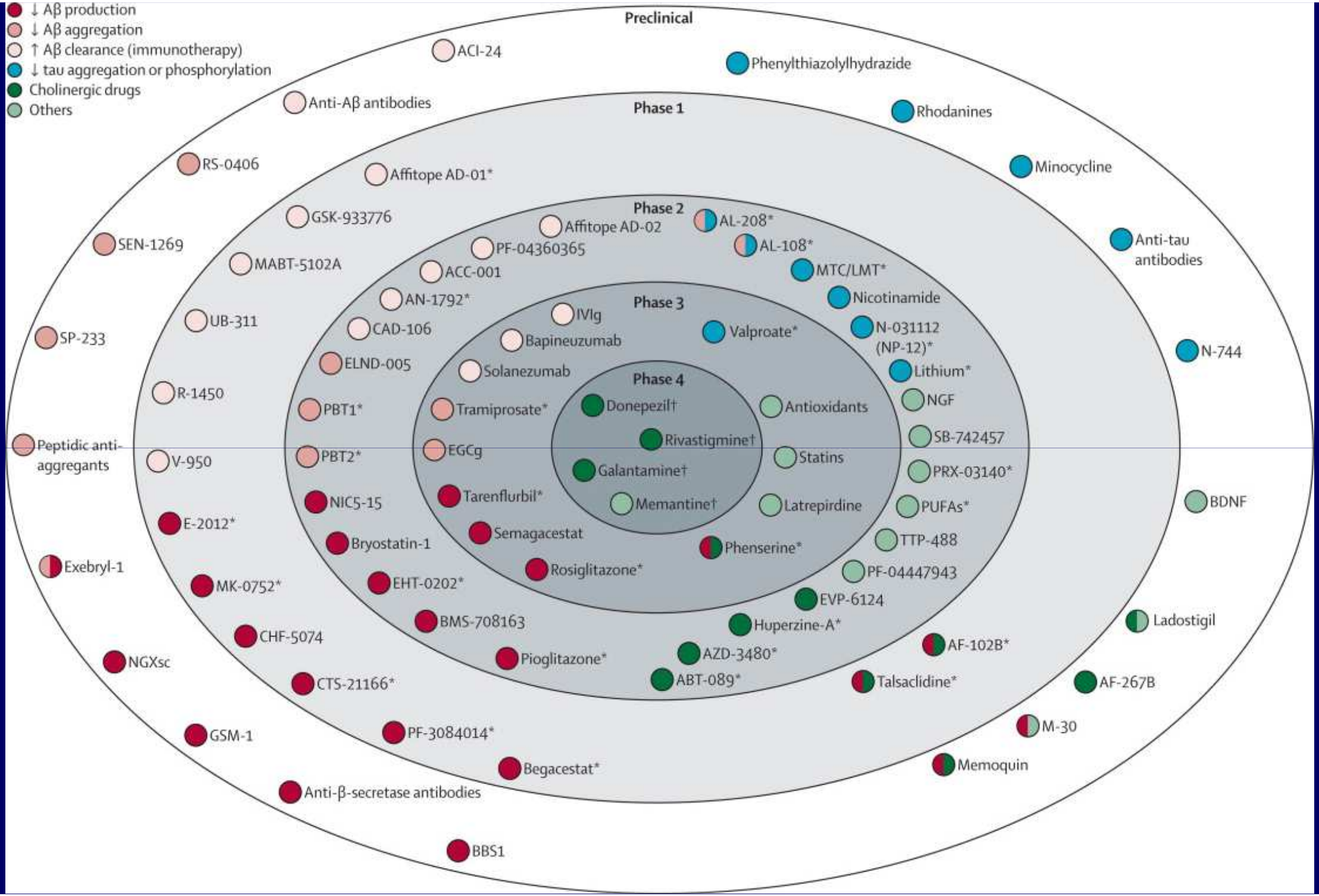

**Figure:** Life expectancy and years lived with cognitive impairment, fair-poor self-perceived health (SPH), mild disability, and moderate-severe disability in 1991 and 2011, all regions combined

**Findings** Between 1991 and 2011, gains in life expectancy at age 65 years (4·5 years for men and 3·6 years for women) were accompanied by equivalent gains in years free of any cognitive impairment (4·2 years [95% CI 4·2–4·3] for men and 4·4 years [4·3–4·5] for women) and decreased years with mild or moderate–severe cognitive impairment. Gains were also identified in years in excellent or good self-perceived health (3·8 years [95% CI 3·5–4·1] for men and 3·1 years [2·7–3·4] for women). Gains in disability-free years were much smaller than those in excellent–good self-perceived health or those free from cognitive impairment, especially for women (0·5 years [0·2–0·9] compared with 2·6 years [2·3–2·9] for men), mostly because of increased mild disability.

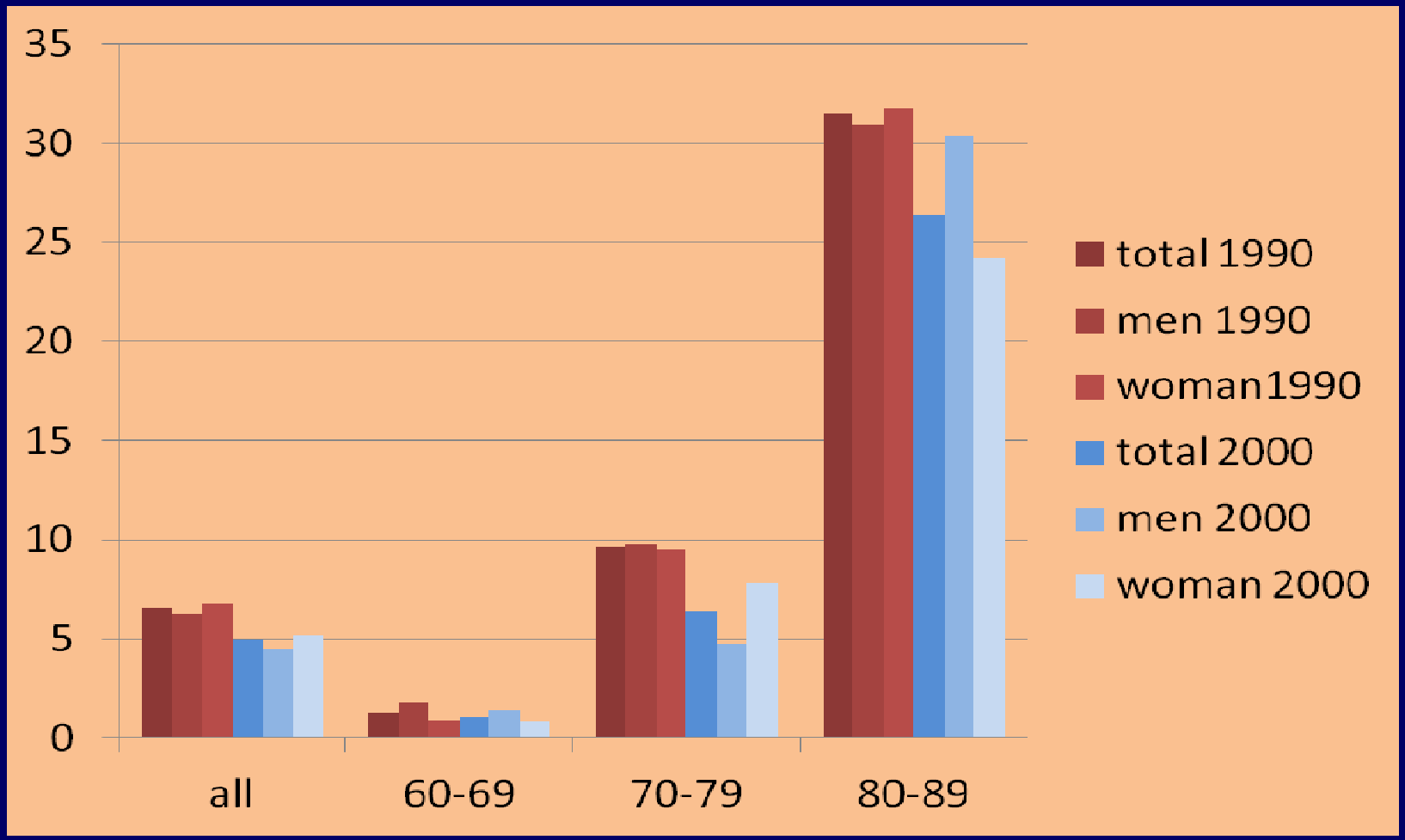
# Alzheimer's drugs show some promise in recent studies

## One of 2 treatments cited; Study data warn of possible side effects


BIOGEN/AP/FILE


↓ Aβ production
↓ Aβ aggregation
↑ Aβ clearance (immunotherapy)
↓ tau aggregation or phosphorylation
Cholinergic drugs
Others
Preclinical
Phase 1
Phase 2
Phase 3
Phase 4
ACI-24
Phenylthiazolylhydrazide
Anti-Aβ antibodies
Rhodanines
RS-0406
Minocycline
Affitope AD-01*
GSK-933776
Affitope AD-02
AL-208*
AL-108*
SEN-1269
Anti-tau antibodies
PF-04360365
MABT-5102A
ACC-001
MTC/LMT*
AN-1792*
Nicotinamide
IVIg
UB-311
CAD-106
Valproate*
N-031112 (NP-12)*
SP-233
Bapineuzumab
N-744
ELND-005
Solanezumab
Lithium*
R-1450
NGF
PBT1*
Tramiprosate*
Donepezil†
Antioxidants
Rivastigmine†
SB-742457
Peptidic anti-aggregants
PBT2*
EGCg
Statins
V-950
Galantamine†
PRX-03140*
NIC5-15
Tarenflurbil*
Memantine†
Latrepirdine
PUFAs*
BDNF
E-2012*
Semagacestat
Bryostatin-1
Phenserine*
TTP-488
Exebryl-1
Rosiglitazone*
PF-04447943
MK-0752*
EHT-0202*
EVP-6124
BMS-708163
Huperzine-A*
Ladostigil
CHF-5074
AF-102B*
NGXsc
Pioglitazone*
AZD-3480*
CTS-21166*
ABT-089*
Talsaclidine*
AF-267B
M-30
GSM-1
PF-3084014*
Memoquin
Begacestat*
Anti-β-secretase antibodies
BBS1

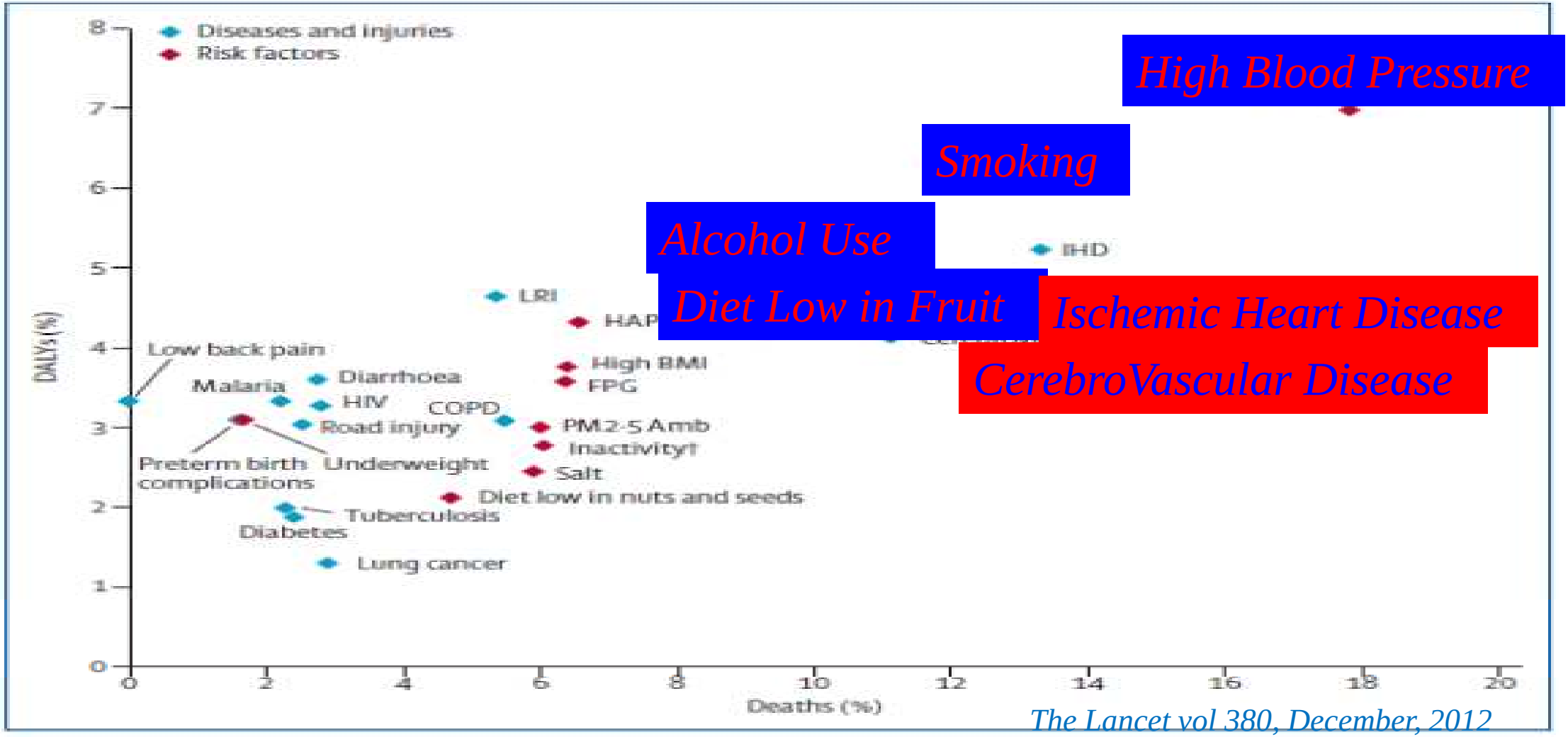
*The Rotterdam Study:*
*AD Incidence (Number of New Cases/ Year is Decreasing*
*Schrijvers EMC et al Neurology 2012; 78: 1456-1463*



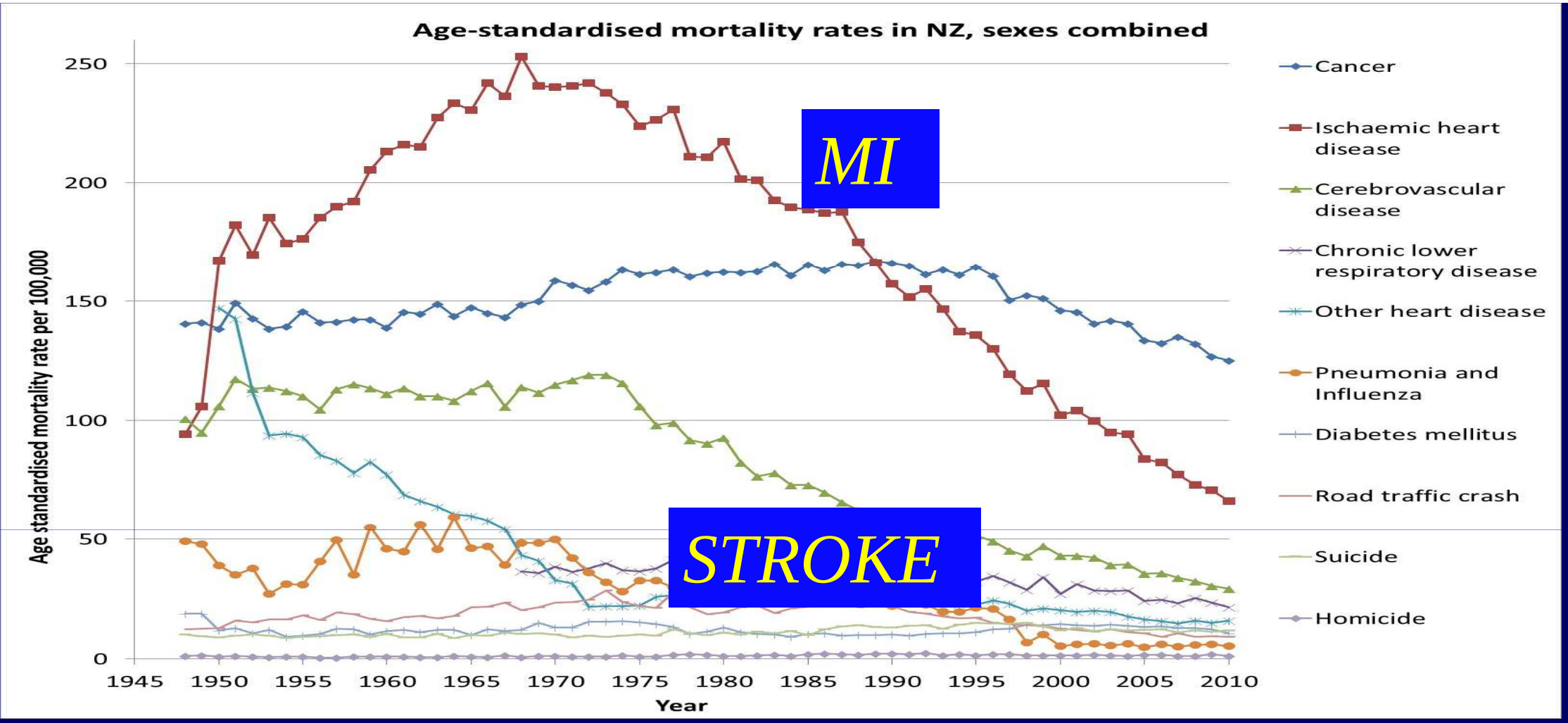
# *GBD 2010:*

# *Risk Factors are more Dangerous than Diseases*

*Comparison of the 10 leading diseases and injures and the 10 risk factors based on the percentage of Global Deaths and Global DALY*




*The Lancet vol 380, December, 2012*




# *Possible Causes of Reduction in AD Incidence*

*Reduction Incidence Stroke*

*Reduction of Incidence MI*

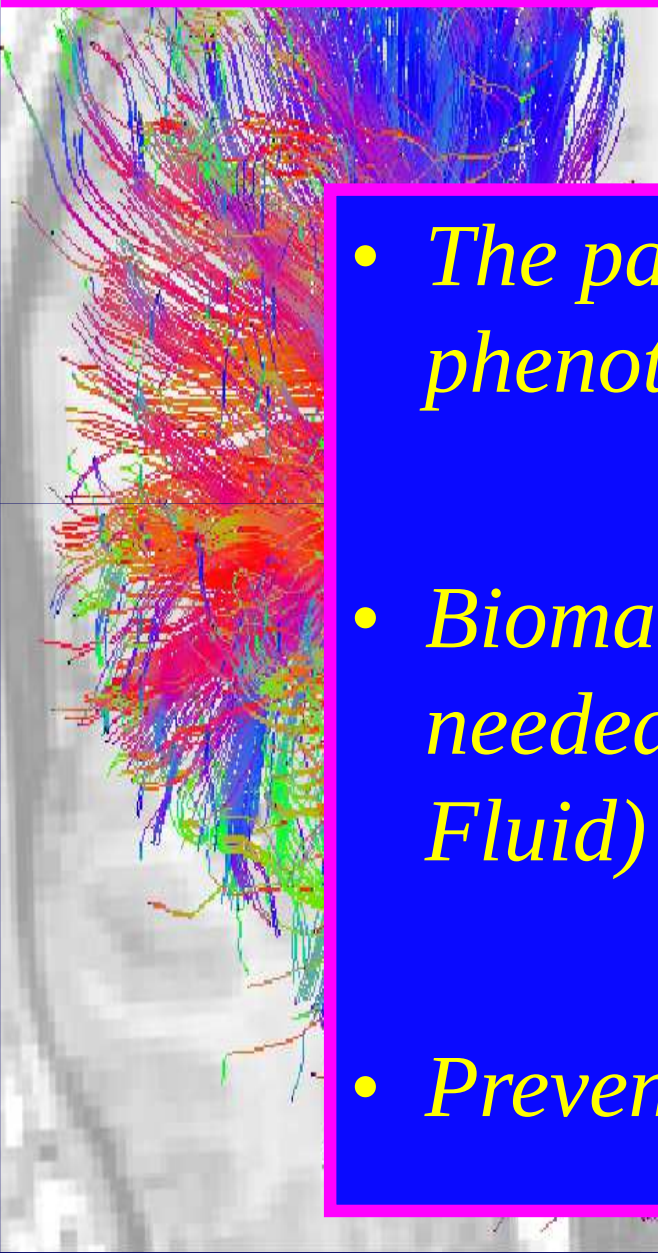
*Better control of High Blood Pressure*

# *Estimated Percent and Number of AD cases Attributable to Potentially Modifiable Risk Factors*

*Barnes&Jaffe Lancet Neurology 2011;10: 819-28*

| RISK FACTOR | POPULATION PREVALENCE | RELATIVE RISK (95% CI) | PAR% (Confidence Range) | NO. CASES ATTRIBUTABLE, Millions (Confidence Range) |
|---|---|---|---|---|
| Low education | 40.0% | 1.59 (1.35, 1.86) | 19.1% (12.3%, 25.6%) | 6.5 (4.2, 8.7) |
| Smoking | 27.4% | 1.59 (1.15, 2.20) | 13.9% (3.9%, 24.7%) | 4.7 (1.3, 8.4) |
| Physical inactivity | 17.7% | 1.82 (1.19, 2.78) | 12.7% (3.3%, 24.0%) | 4.3 (1.1, 8.1) |
| Depression | 13.2% | 1.90 (1.55, 2.33) | 10.6% (6.8%, 14.9%) | 3.6 (2.3, 5.1) |
| Mid-life hypertension | 8.9% | 1.61 (1.16, 2.24) | 5.1% (1.4%, 9.9%) | 1.7 (0.5, 3.4) |
| Diabetes | 6.4% | 1.39 (1.17, 1.66) | 2.4% (1.1%, 4.1%) | 0.8 (0.4, 1.4) |
| Mid-life obesity | 3.4% | 1.60 (1.34, 1.92) | 2.0% (1.1%, 3.0%) | 0.7 (0.4, 1.0) |
| Combined (maximum) | | | 50.7% | 17,187,028 |

# *AD: From Epidemiology to the Clinic*



- *The patient with AD is changing (Complex phenotype)*
- *Biomarkers specific of the neuropathology are needed but every results from the lab (Imaging or Fluid) is not sufficient for diagnosis*
- *Prevention (primary, secondary, tertiary ) works*

# *UVA : in Puglia e Basilicata (MT)*

Accordo ai sensi dell'art. 9 del decreto legislativo 28 agosto 1997, n. 281, tra il Governo, le Regioni e le Province autonome di Trento e Bolzano, le Province, i Comuni e le Comunità montane sul documento recante "**PIANO NAZIONALE DEMENZE – Strategie per la promozione ed il miglioramento della qualità e dell'appropriatezza degli interventi assistenziali nel settore delle demenze**"

**LA CONFERENZA UNIFICATA**

*22 novembre 2014*