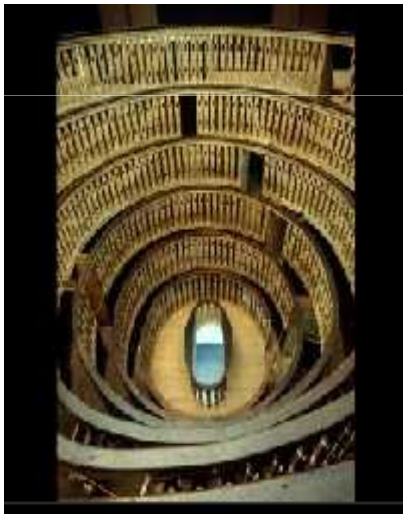
La Malattia di Alzheimer e le altre demenze

Milano 11 ottobre 2010

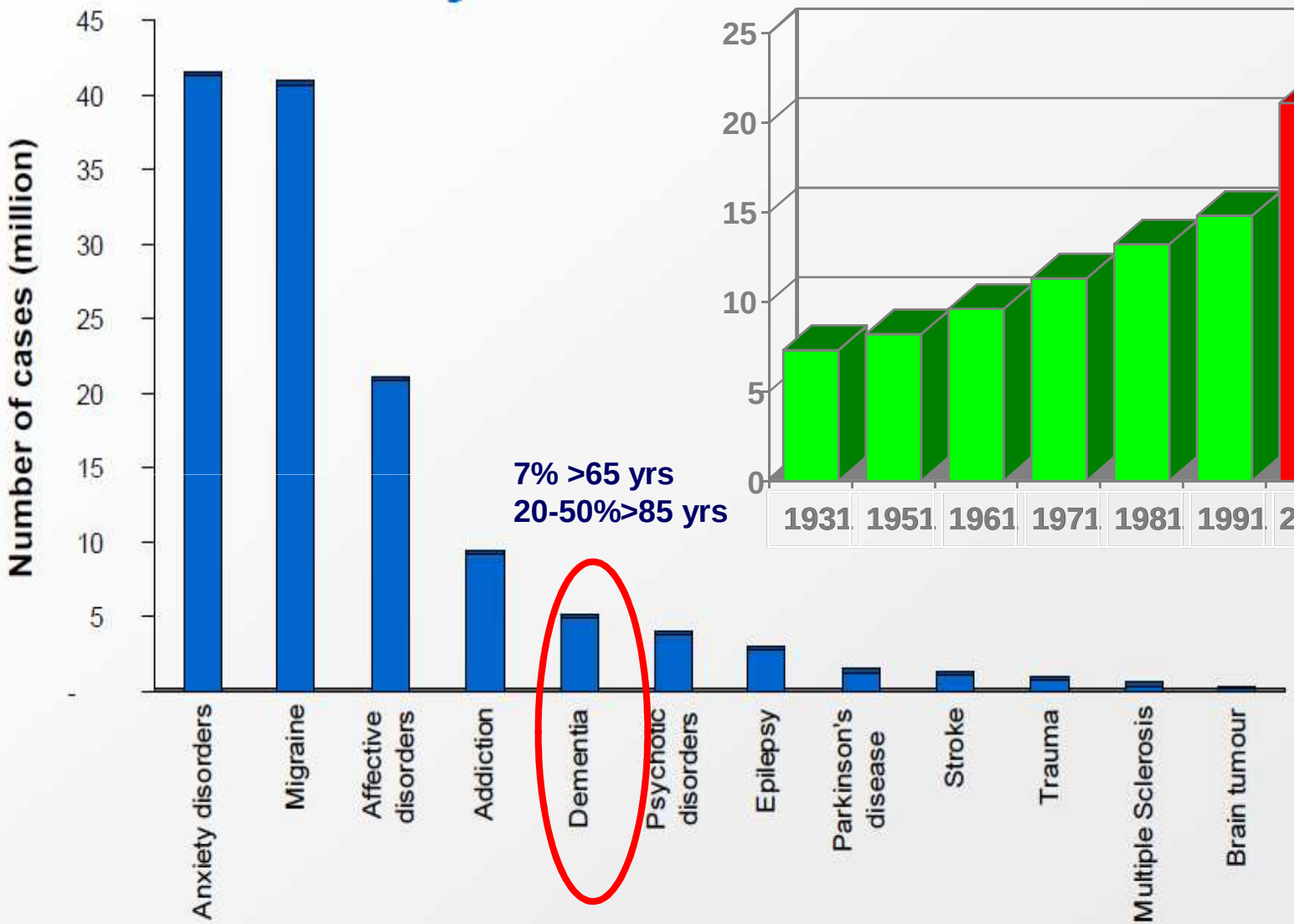


Annachiara Cagnin
Dipartimento di Neuroscienze
Padova

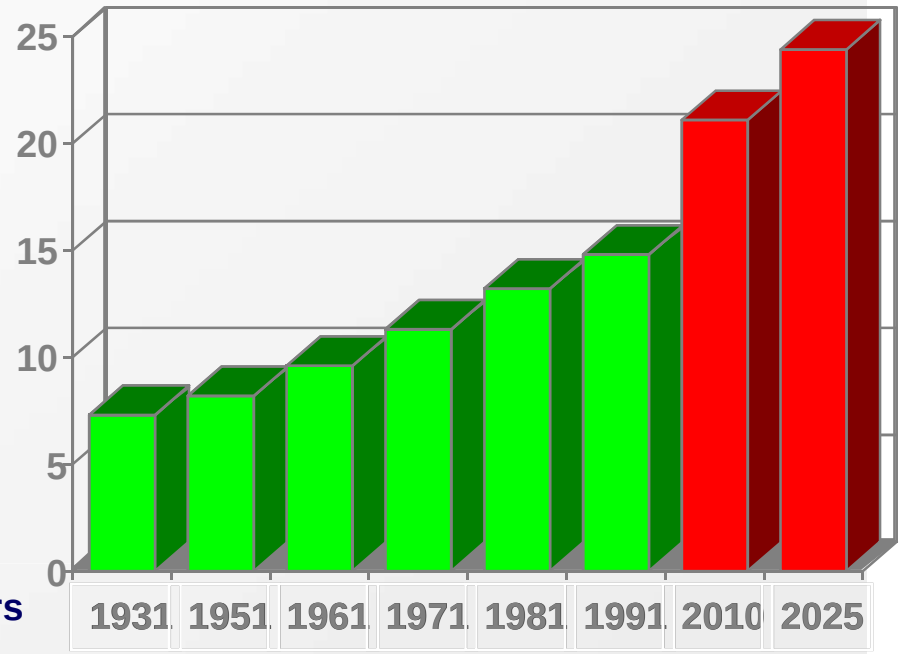
Focus on …

- Demenza : epidemiologia, disabilità, costi
- Diagnosi precoce di malattia di Alzheimer
- Diagnosi differenziale
- Terapia

Prevalence by disorder



% of subjects > 65yrs



Source: Figure 3 in Andlin-Sobocki et al (2005) Cost of Disorders of the Brain in Europe. Eur J Neurol 12 (Suppl 1): 1-27.

Alzheimer's Disease International

World Alzheimer Report 2009

Stima della prevalenza in Europa di ultrasessantenni affetti da demenza nel periodo 2010 -2050

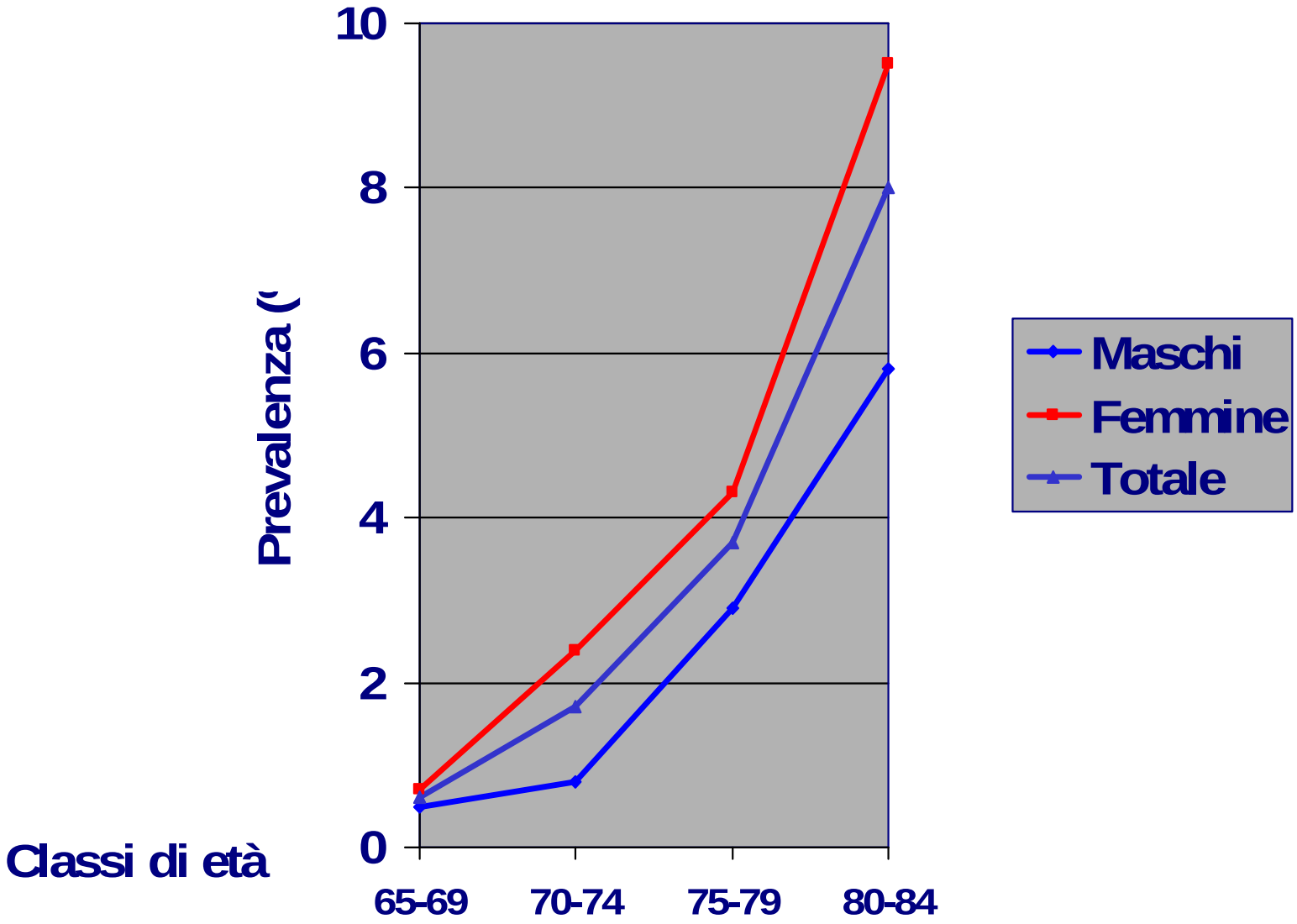
GBD Region	Over 60 population (millions)	Crude estimated prevalence (%)	Number of people with dementia (millions)			Proportionate increases (%)	
	2010	2010	2010	2030	2050	2010-2030	2010-2050
EUROPE	**160.18**	**6.2**	**9.95**	**13.95**	**18.65**	**40**	**87**
Europe, Western	97.27	7.2	6.98	10.03	13.44	44	93
Europe, Central	23.61	4.7	1.10	1.57	2.10	43	91
Europe, East	39.30	4.8	1.87	2.36	3.10	26	66

2 We estimate 35.6 million people with dementia in 2010, the numbers nearly doubling every 20 years, to 65.7 million in 2030 and 115.4 million in 2050.

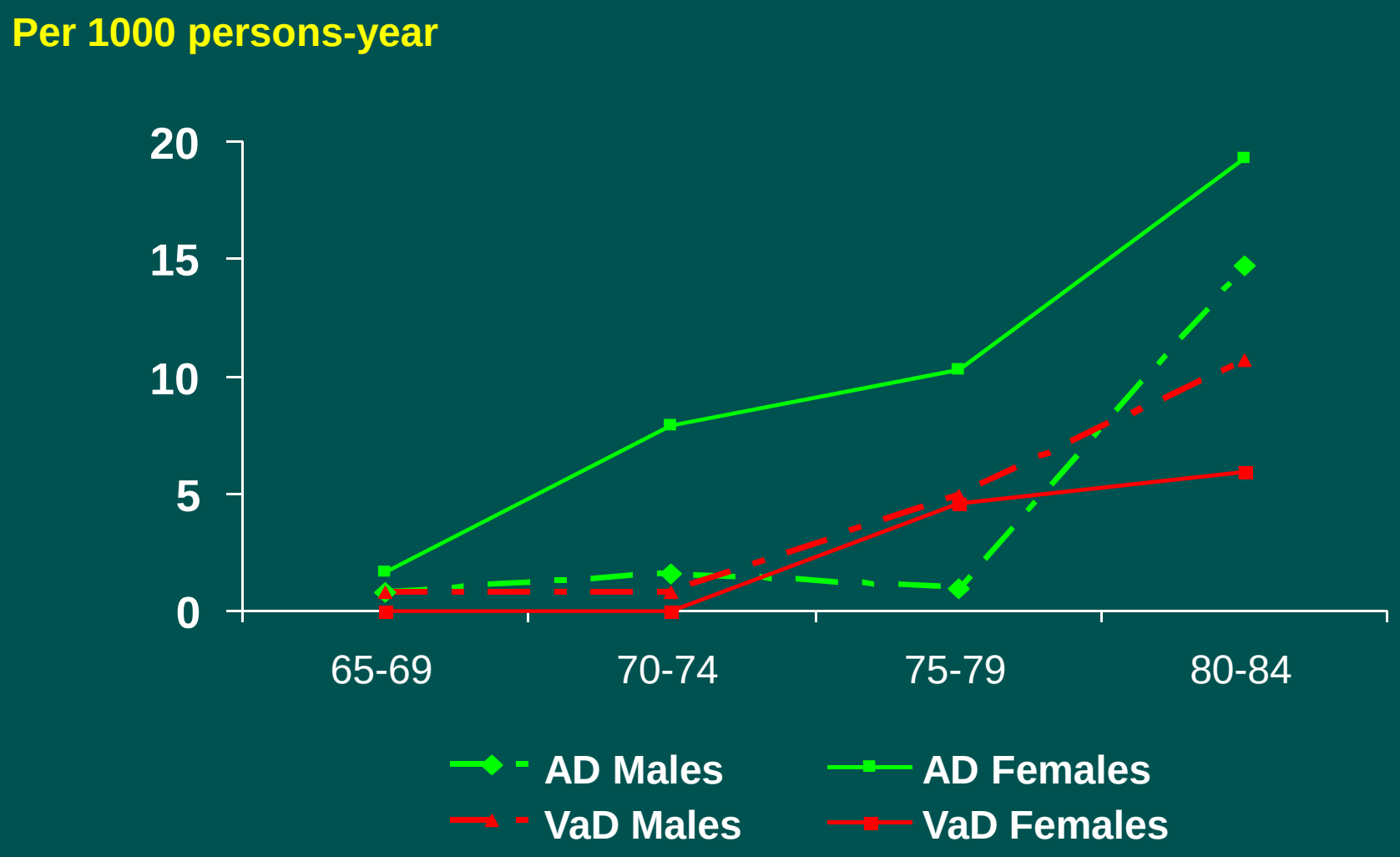
PREVALENZA (%) DI DEMENZA in ITALIA

Region	Study	Age	Prevalence all causes D	Prevalence AD	Prevalence VaD
Appignano (Firenze)	Rocca et al 1990	> 59 years	6,2 %	2,6 %	2,2 %
Sicily	Corso et al 1992	> 65 years	2,4 %	-	-
Centre - Italy	Prencipe et al, 1996	> 64 years	8,0 %	5.1 %	2,2 %
ILSA	Amaducci et al. 1996	>64 years	6,4 %	2,5 %	1,4 %
Vescovato (Cremona)	Ferini-Strambi et al 1997	>59 years	9,8 %	5,2 %	2,7 %
Granarolo (Ravenna)	De Ronchi et al, 2002	> 61 years	10,1 %	5,2%	2,5%
Conselice Study	Ravaglia et al, 2002	65-97 years	5,9 %	3,0%	2,7%
Buttapietra (Verona)	Benedetti et al.	> 74 years	15,8 %	6,7 %	3,6 %

PREVALENZA DELLA MALATTIA DI ALZHEIMER
STUDIO ILSA



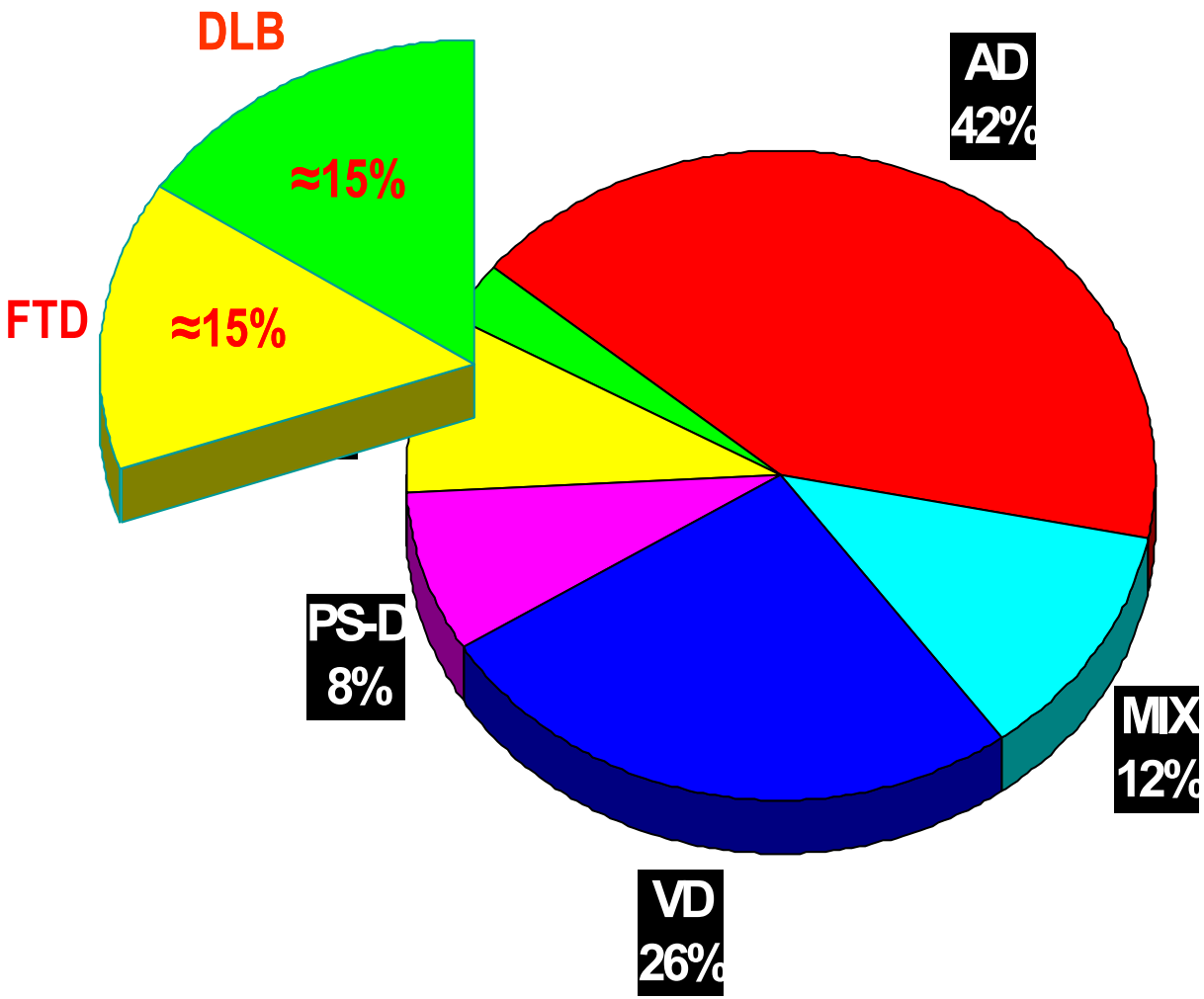
Incidenza di demenza ILSA STUDY



INCIDENZA MEDIA > 65 AA : 12 CASI X 1000 /ANNO

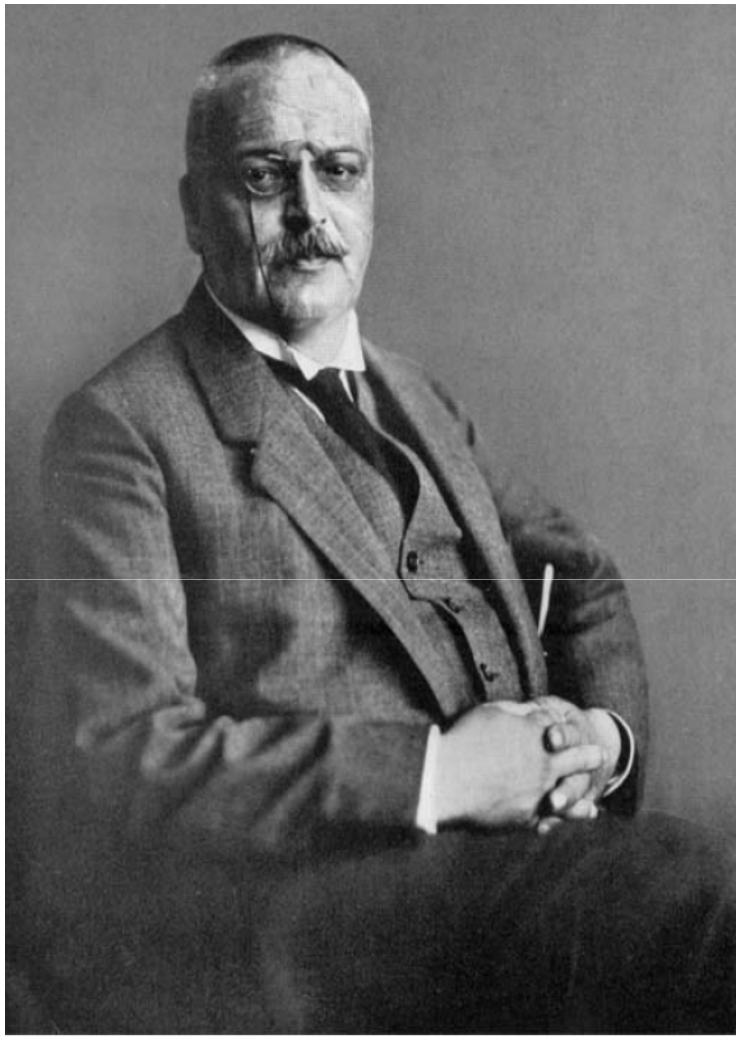
Main causes for dementia

(400 neuropathological exams)



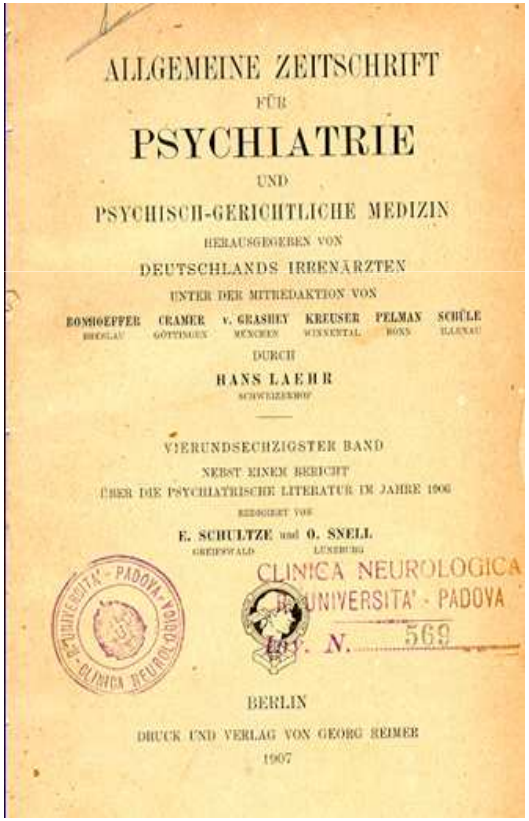
Aloys Alzheimer

1864-1915



Nel 1907 il Dr. Alzheimer descrisse i sintomi e i reperti neuropatologici di una paziente affetta da una malattia neuro-comportamentale che prese il nome di

Malattia di Alzheimer



ALLGEMEINE ZEITSCHRIFT
FÜR
PSYCHIATRIE
UND
PSYCHISCH-GERICHTLICHE MEDIZIN
HERAUSGEGEBEN VON
DEUTSCHLANDS IRRENÄRZTEN
UNTER DER MITREDAKTION VON
BONHOEFFER CRAMER v. GRASHEY KREUSER PELMAN SCHÜLE
DURCH
HANS LAEHR

VIERUNDSECHZIGSTER BAND
NEBST EINEM BERICHT
ÜBER DIE PSYCHIATRISCHE LITERATUR IM JAHRE 1906
REDIGIERT VON
E. SCHULTZE und O. SNELL

CLINICA NEUROLOGICA
UNIVERSITA' - PADOVA
Inv. N. 569

BERLIN
DRUCK UND VERLAG VON GEORG REIMER
1907

Alzheimer

Figure: Auguste D, June 18, 1902 at asylum for the insane and epileptics in Frankfurt on Main

Quadro clinico

Declino cognitivo

* Perdita di memoria
* Disorientamento temporale e spaziale
* Afasia
* Aprassia
* Agnosia
* Difficoltà delle funzioni esecutive

Demenza

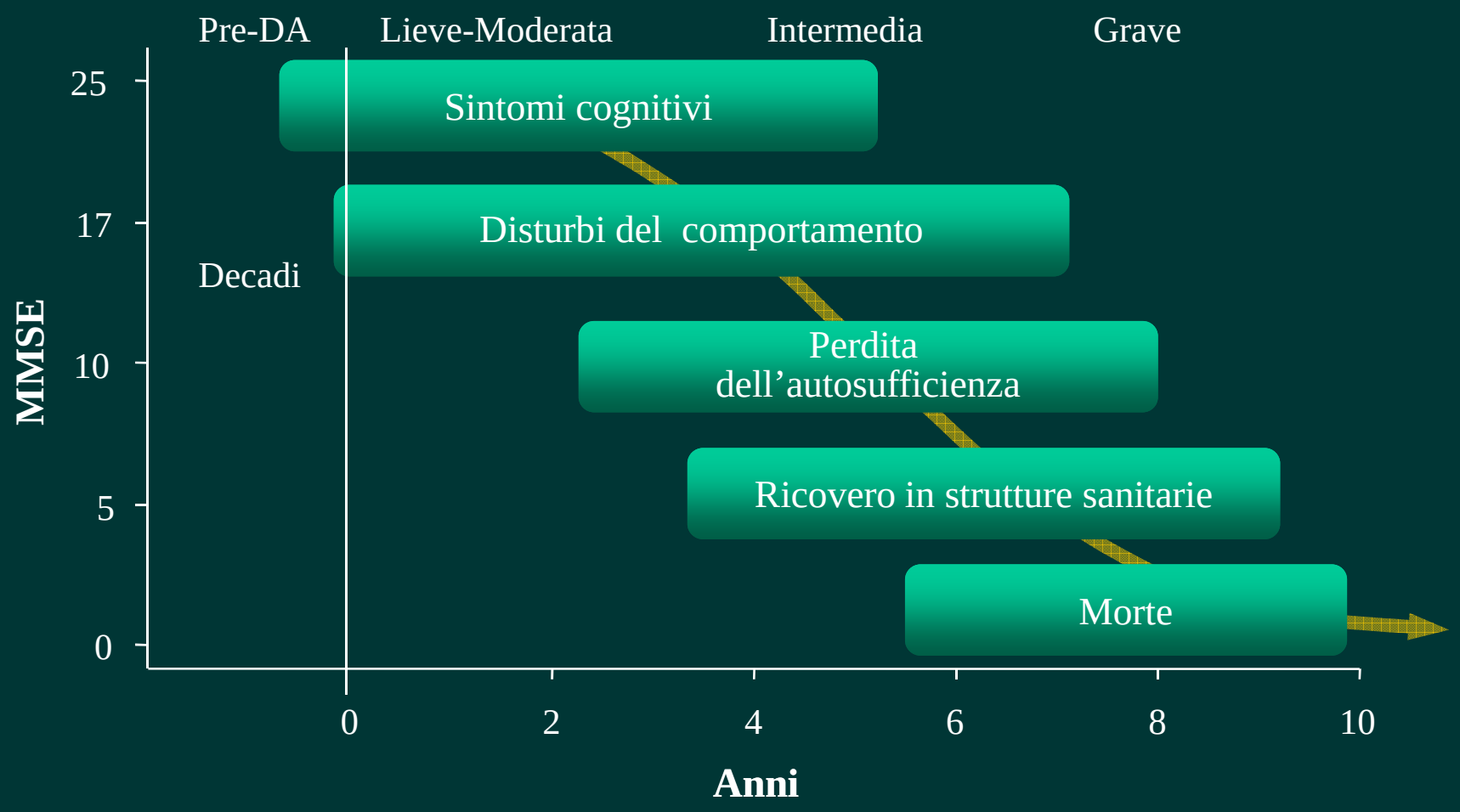
Disturbi del Comportamento

* Oscillazioni dell'umore
* Alterazioni della personalità
* Psicosi
* Agitazione
* Wandering
* Sintomi neurovegetativi

Compromissione funzionale

* IADL
* ADL

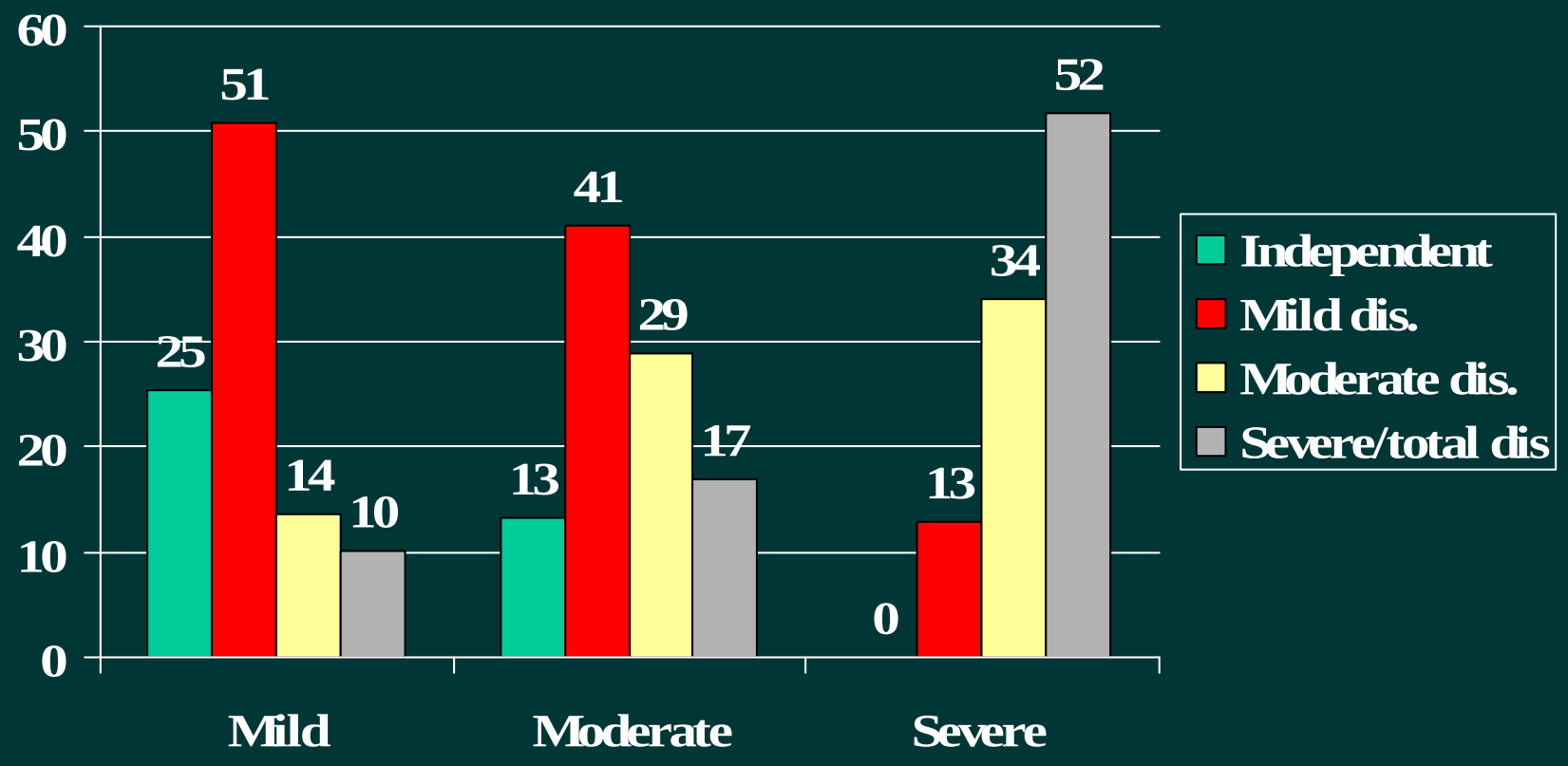
Storia naturale della demenza di Alzheimer



Adattata da Gauthier S. ed. Clinical Diagnosis and Management of Alzheimer's Disease. 1996.

Livelli (%) di disabilità per gravità della demenza.

ILSA Study



Chronic disease/ condition	Years lived with disability (YLD, millions) and % contribution to total chronic disease YLDs	Rank order (YLD)	Years of Life Lost (YLL, millions) and % contribution to total chronic disease YLLs	Rank order (YLL)
Blindness	13.3 (21.5%)	1	0.0 (0.0)	12
Dementia	7.4 (11.9%)	2	1.4 (1.1%)	8
Deafness	6.5 (10.6%)	3	0.0 (0.0%)	13
Stroke	6.2 (10.1%)	4	23.4 (17.8%)	3
Arthritis	5.8 (9.5%)	5	0.4 (0.3%)	10
Mental disorders	5.6 (9.1%)	6	1.7 (1.3%)	7
Digestive	3.4 (5.5%)	7	6.1 (4.6%)	4
Heart disease	3.3 (5.3%)	8	43.3 (32.9%)	1
Cancer	1.5 (2.5%)	9	29.6 (22.5%)	2
Diabetes	1.5 (2.5%)	10	4.9 (3.7%)	5
Genitourinary	1.1 (1.8%)	11	3.1 (2.4%)	6
Endocrine	0.5 (0.8%)	12	0.8 (0.6%)	9
Skin	0.4 (0.6%)	13	0.2 (0.2%)	11
Total chronic disease burden	61.8 (100%)		131.7 (100%)	

Alzheimer's Disease International
World Alzheimer Report
2009

Scale per la disabilità

- Scale self reported (sottostima del deficit)
- Scale ottenute dal caregiver (sovrastima del deficit)
- Valutazioni diretta (DAFS)

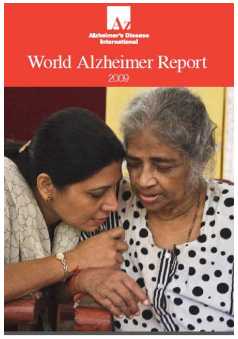
Scale per la disabilità

- IADL: Instrumental activities of daily living (0-8/5)
- BADL: Basic activities of daily living
- Barthel Index
- AADL: advance activities of daily living (attività voluttuarie o socio-culturali)
- DAD: disability assessment of dementia (fasi iniziali)
- Functional Assessment Staging Test
- DAFS: Direct Assessment of functional status

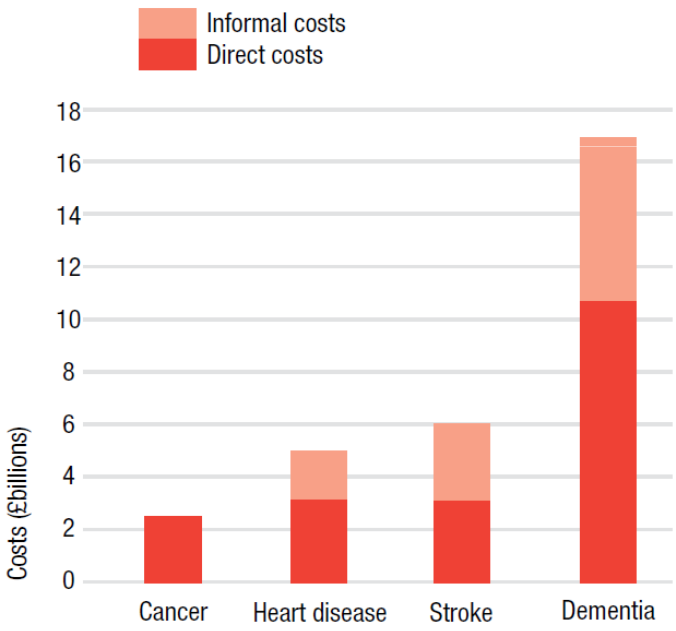
I costi sociali della demenza

- Costi economici
  - *Diretti* (visite, esami, trattamenti, ospedalizzazioni, interventi abitativi, supporto assistenziale, ecc.)
  - *Indiretti* (mancata produttività, assistenza della famiglia)

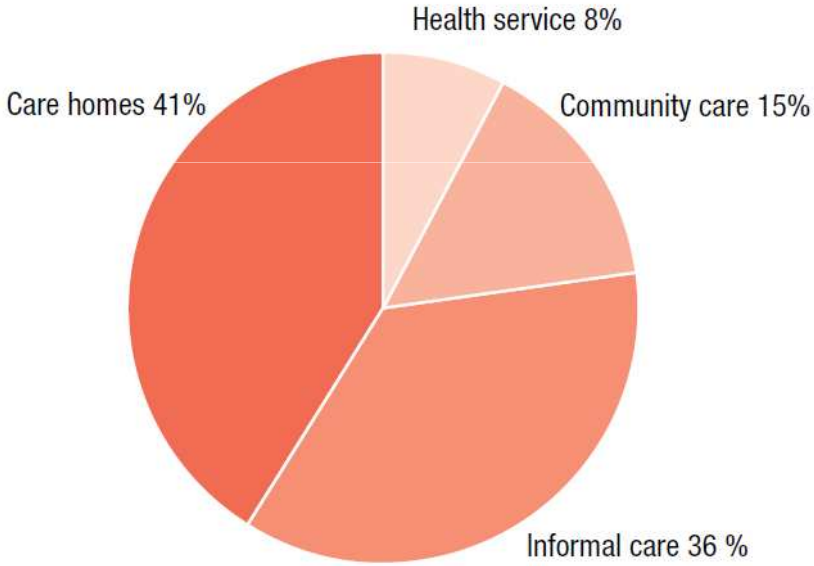
- Conseguenze del caregiving sulla famiglia (riduzione produttività, stress psicologico, impatto sulla salute)



The comparative societal costs of cancer, ischaemic heart disease, stroke and dementia in the United Kingdom



The breakdown of the total annual cost of dementia (£17 billion) in the United Kingdom [7]



CENSIS 2007

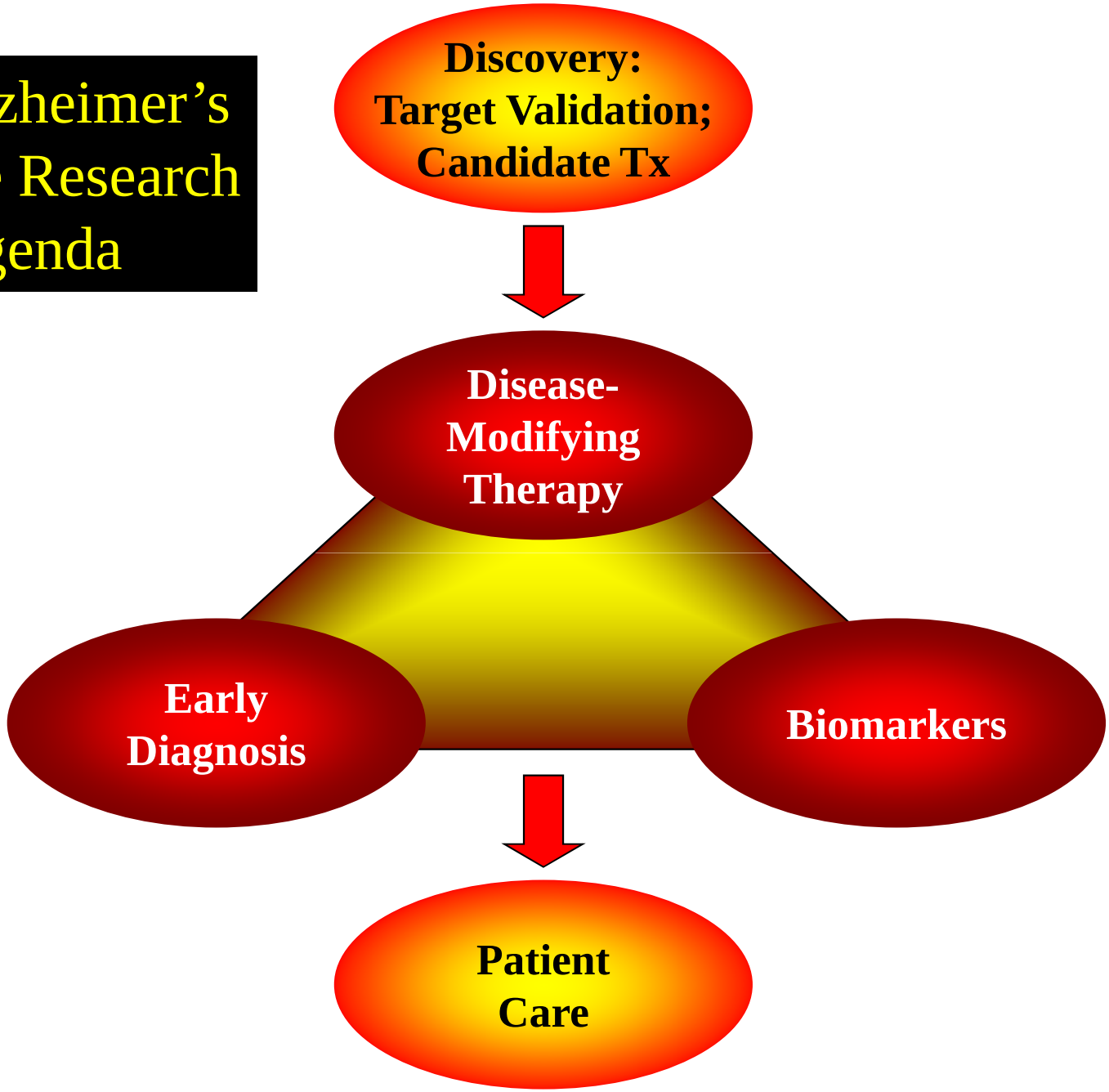
- Costo medio 60.000 Euro/anno
  - 14.800 Euro/anno (25%) costi diretti (71% a carico della famiglia)
  - 46.000 Euro/anno costi indiretti (95%) a carico della famiglia

LA DIMENSIONE ECONOMICA

- **Il costo totale annuo per la cura e assistenza di un paziente con AD varia da 15.000 a 50.000 €**
- **In Italia 2/3 dei costi sono rappresentati dai costi indiretti**
- **Ogni aumento di un punto al Neuropsychiatric Inventory corrisponde un incremento dei costi indiretti annuali compreso tra 247 e 409 US$**
- **Ogni punto perso di MMSE comporta un aumento del costo annuo che va da 700 (per MMSE di 20) a 2400 US$ (per MMSE di 12)**
- **Ogni funzione persa alle IADL comporta un incremento del costo annuo di 3700 US$**

Farlow, M. R. Neurology 2005;65:S1-4S

The Alzheimer's Disease Research Agenda



…Due decenni d'inferno avevano preceduto la diagnosi. All'inizio c'erano stati tanti piccoli segnali: trascinava i piedi, si stropicciava in continuazione le mani, si agitava all'improvviso, c'era qualcosa nel suo sguardo..., mi chiedevo come mai i suoi abiti erano finiti nel mio armadio….

Mild Cognitive Impairment (MCI)

(Amnestico)

1. Deficit della memoria riportato dal soggetto (confermato da un familiare)

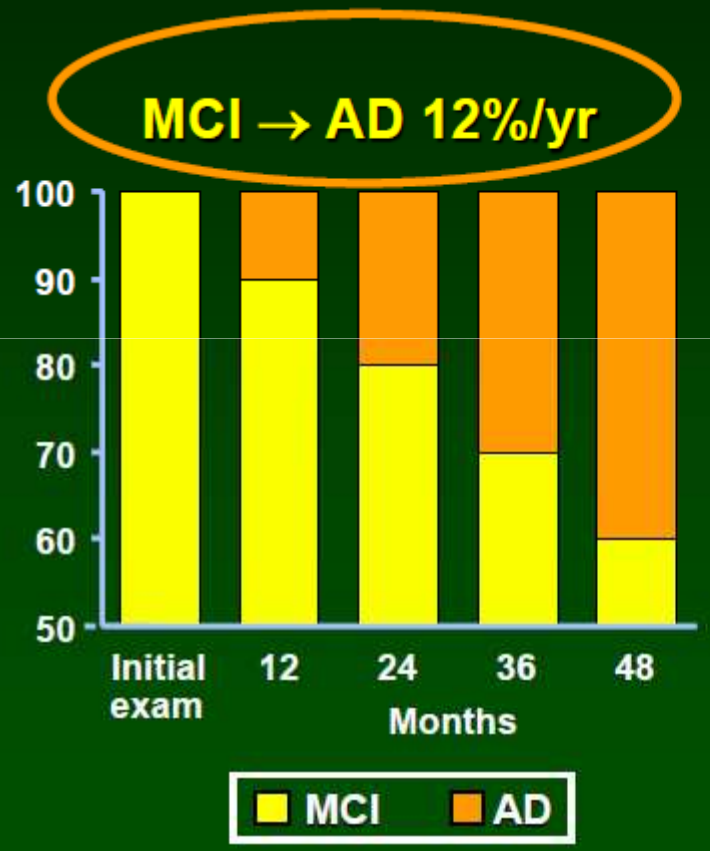
2. Deficit evidenziato con un test quantitativo di memoria episodica (racconto)

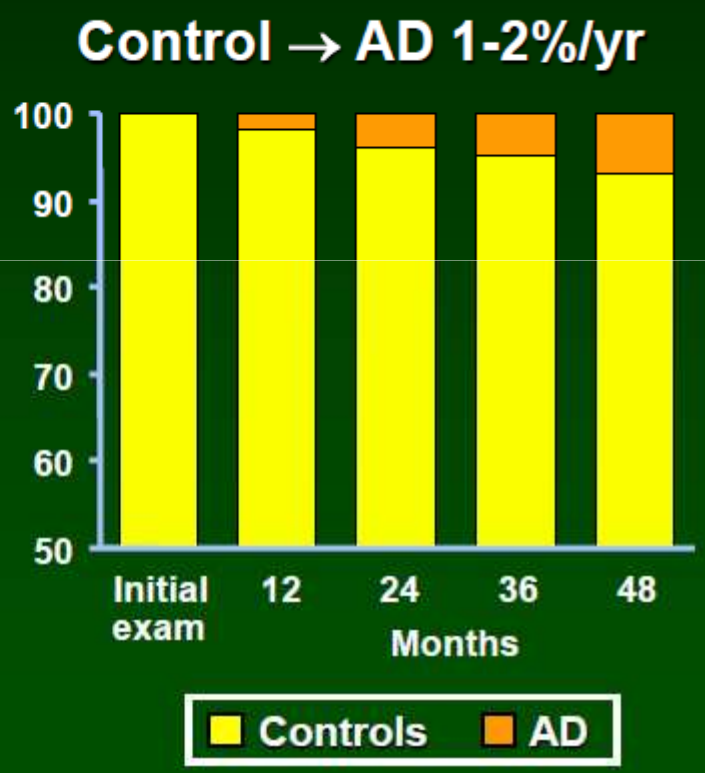
3. Altre funzioni cognitive normali

4. ADL mantenute

5. Assenza di demenza

Mild Cognitive Impairment (MCI)





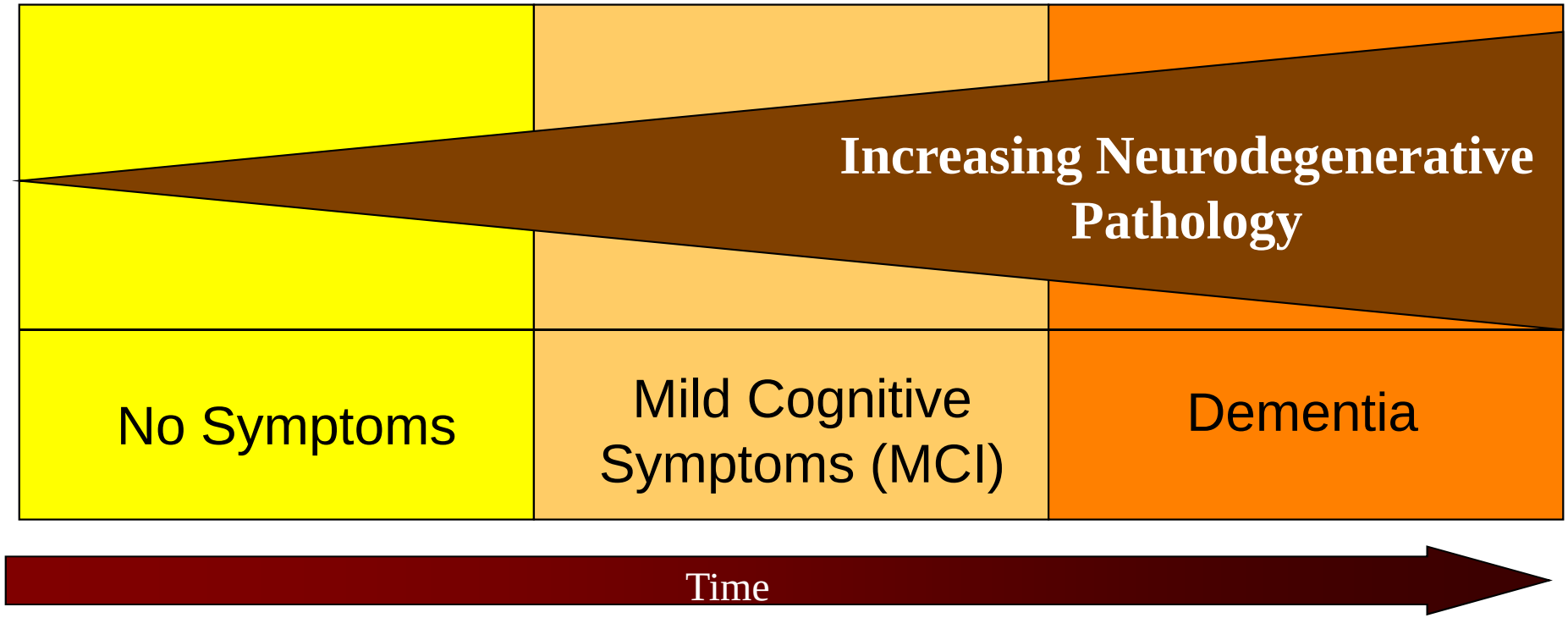
Petersen RC et al: Arch Neurol 56:303-308, 1999

Obiettivi della diagnosi precoce di MCI

- E' possibile che un intervento precoce sia in grado almeno di rallentare la progressione da MCI a demenza
- Un approccio integrato nei pazienti con MCI dovrebbe includere:
  - **Gestione dei fattori di rischio modificabili**
  - **Intervento sullo stile di vita**
  - **Valutazioni cognitivo-funzionali periodiche**
- **Gestione dei fattori di rischio modificabili per AD/MCI:**
  - ipercolesterolemia
  - ipertensione arteriosa
  - diabete mellito
  - obesità
  - abitudine al fumo

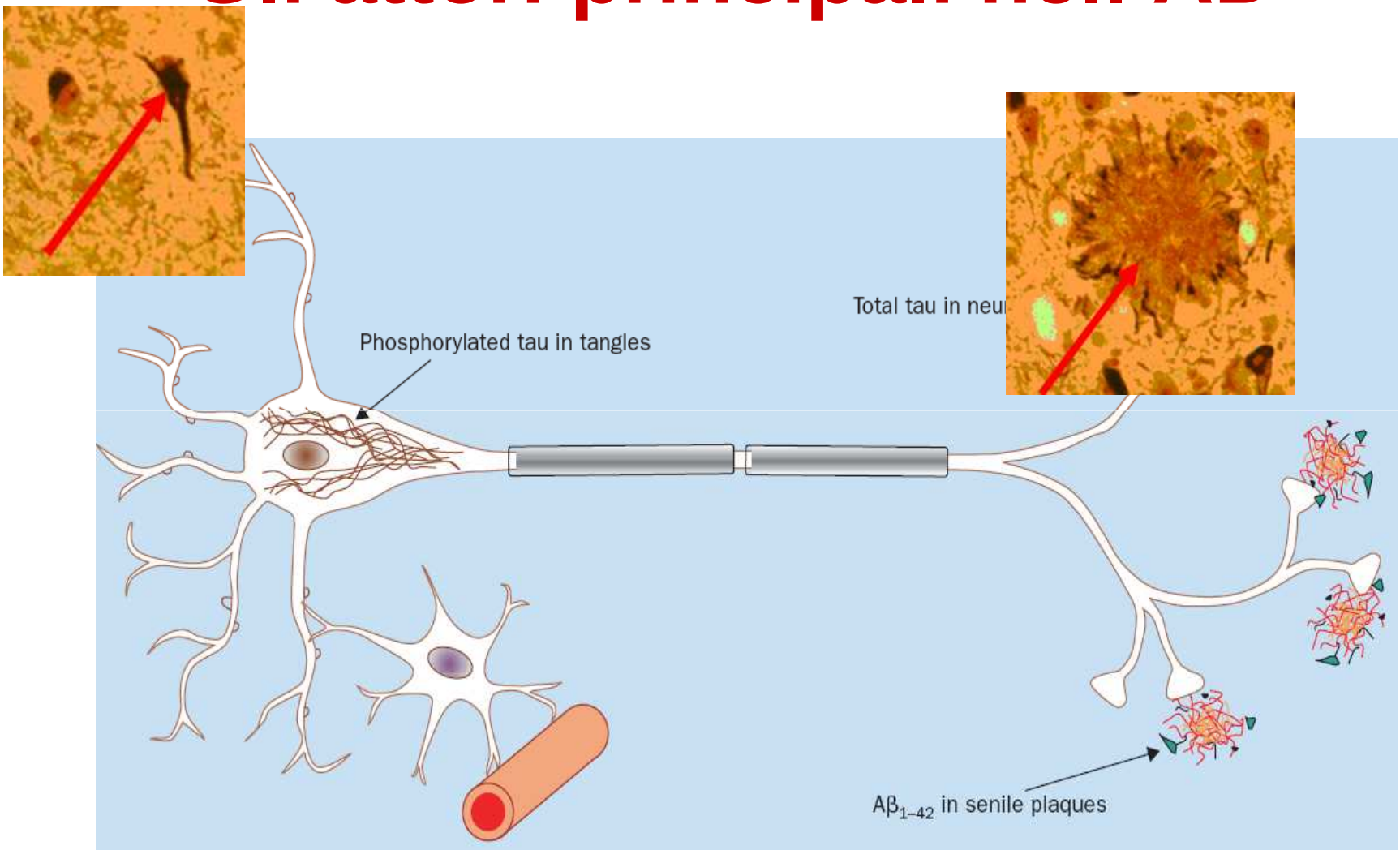
Kidd P. Alternative Medicine Review. 2008

Need of diagnostic/prognostic biomarker

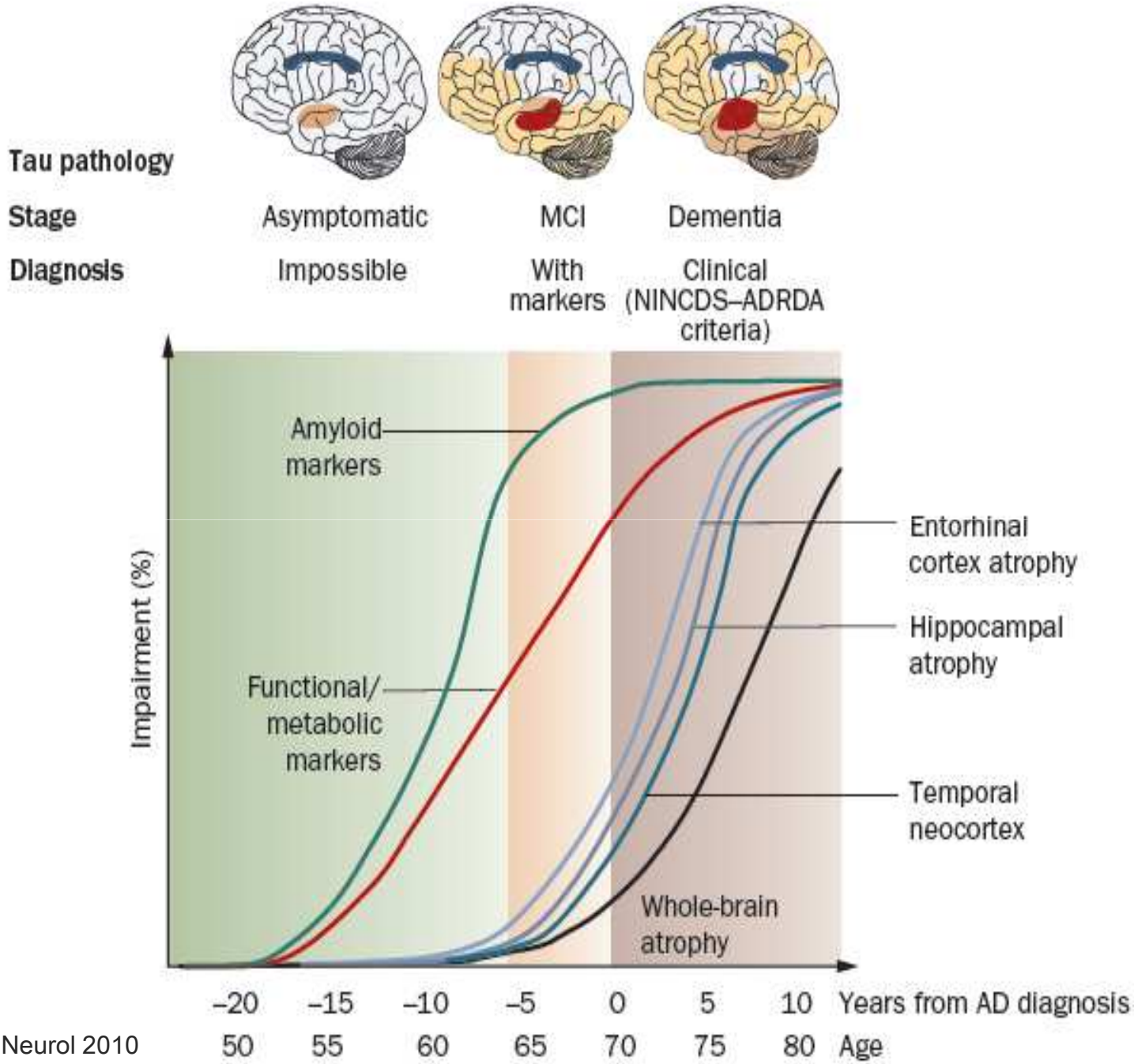


- Biomarkers assist in identifying the underlying pathology
- Biomarker changes may precede clinically detectable changes

Gli attori principali nell'AD



LIQUOR: Abeta ↓ TAU ↑



Frisoni, Nature Neurol 2010

Position Paper

Lancet Neurol 2007; 6:734-46

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

A. An episodic memory disorder

- Progressive change in memory function (patient or informant)
- Evidence of a recall deficit that does not normalize with cueing
- Deficit isolated or associated with other cognitive changes

+

B. Structural: atrophy of medial temporal lobe (MRI)

or

C. Biochemical: changes in biomarkers (CSF)

or

D. Functional: neuroimaging pattern on PET or SPECT

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

Supportive features

B. Presence of medial temporal lobe atrophy

- Volume loss of hippocampi, entorhinal cortex, amygdala evidenced on MRI with qualitative ratings using visual scoring (referenced to well characterised population with age norms) or quantitative volumetry of regions of interest (referenced to well characterised population with age norms)

C. Abnormal cerebrospinal fluid biomarker

- Low amyloid β_{1-42} concentrations, increased total tau concentrations, or increased phospho-tau concentrations, or combinations of the three
- Other well validated markers to be discovered in the future

D. Specific pattern on functional neuroimaging with PET

- Reduced glucose metabolism in bilateral temporal parietal regions
- Other well validated ligands, including those that foreseeably will emerge such as Pittsburg compound B or FDDNP

E. Proven AD autosomal dominant mutation within the immediate family

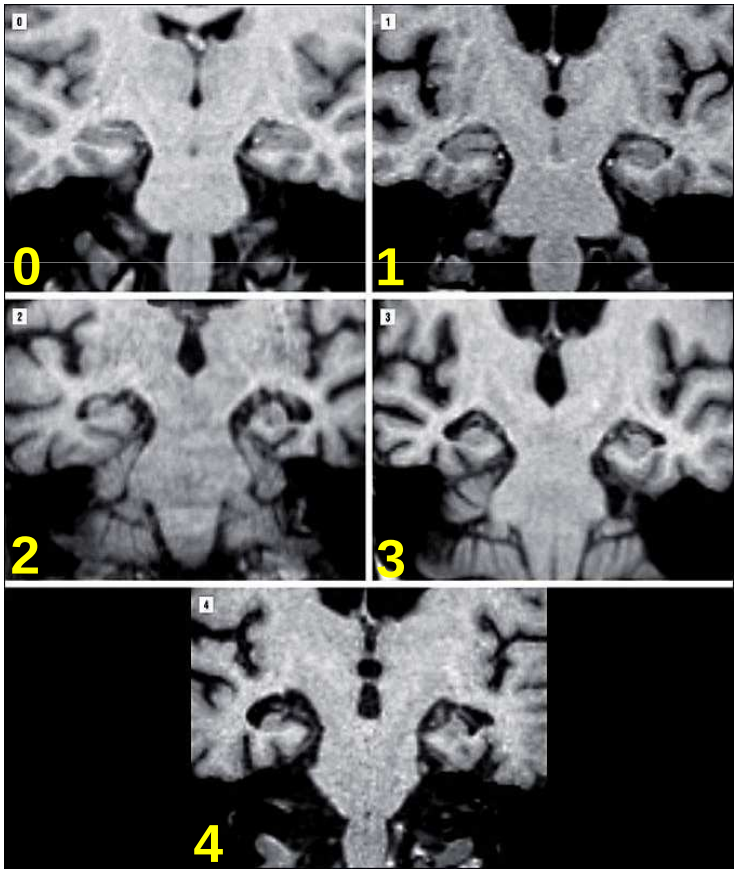
Dubois, Lancet Neurol 2007

Qualitative rating of temporal atrophy

Sheltens scale

Medial Temporal Atrophy Rating Algorithm

Score	Width of Choroidal Fissure	Width of Temporal Horn	Height of Hippocampus
0	Normal	Normal	Normal
1	Mildly widened	Normal	Normal
2	Moderately widened	Mildly widened	Mildly reduced
3	Markedly widened	Moderately widened	Moderately reduced
4	Markedly widened	Markedly widened	Markedly reduced



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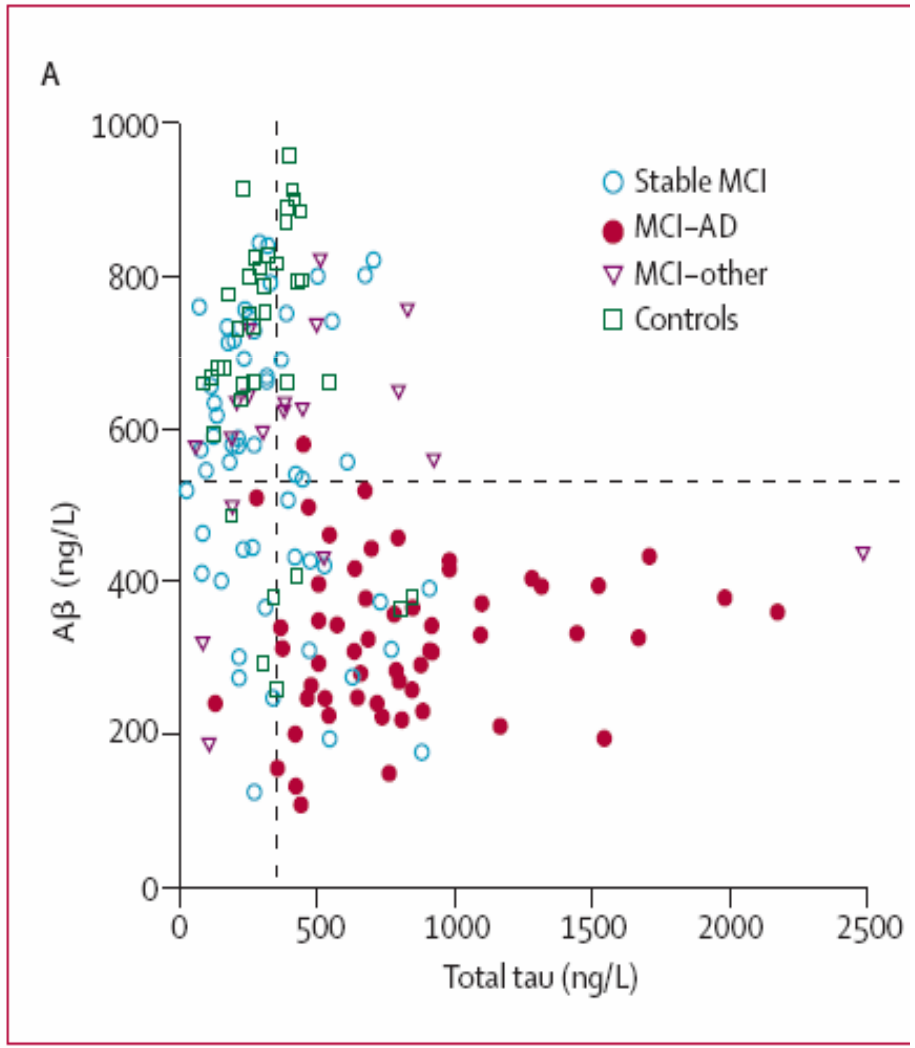
Dubois, Lancet Neurol 2007

Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study



Sensitivity 93%
Specificity 83-89%

Lancet Neurol 2006; 5: 228–34

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

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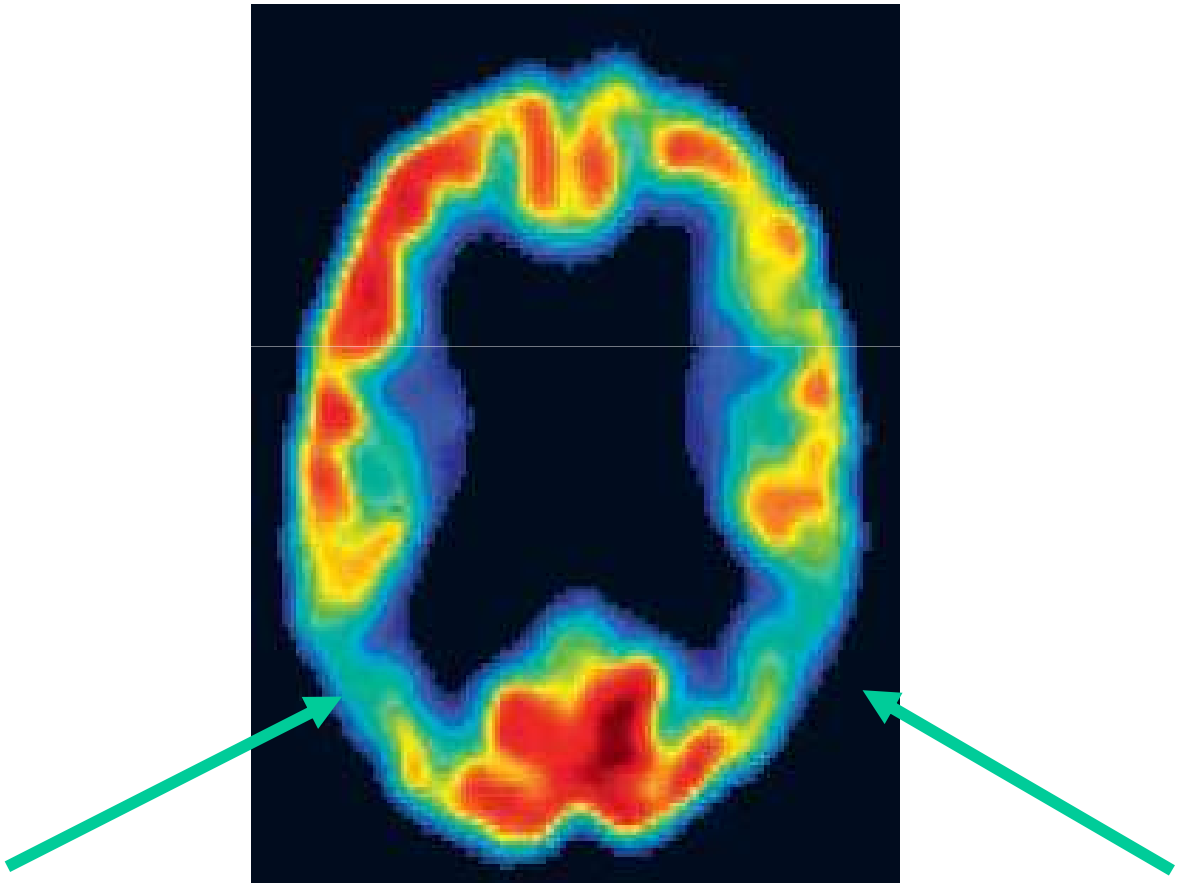
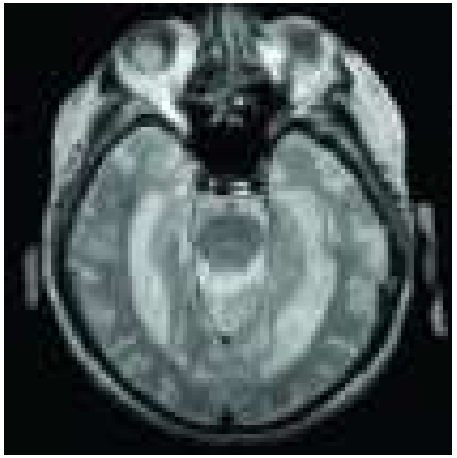
FDG-PET SCANS



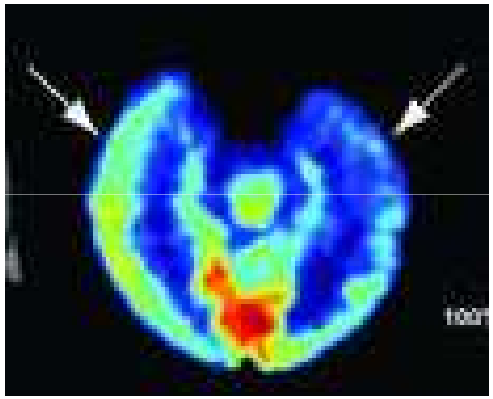
Neuroimaging

MRI



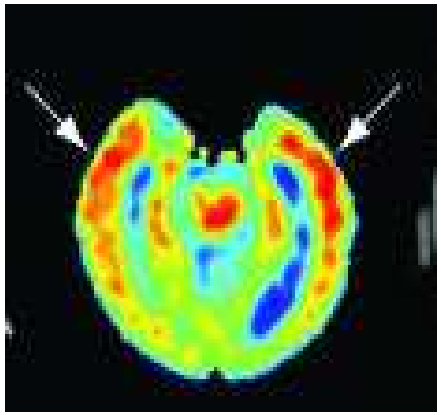
Atrofia cerebrale

FDG-PET



Metabolismo glucidico

F-FDDNP-PET



Placche amiloidi

STRUTTURALE

FUNZIONALE

NEUROPATOLOGICO

Diagnosi differenziale

- Demenza fronto-temporale
- Demenza a corpi di Lewy diffusi
- Demenze secondarie
  - Demenza vascolare
  - Idrocefalo normoteso

Demenza fronto-temporale

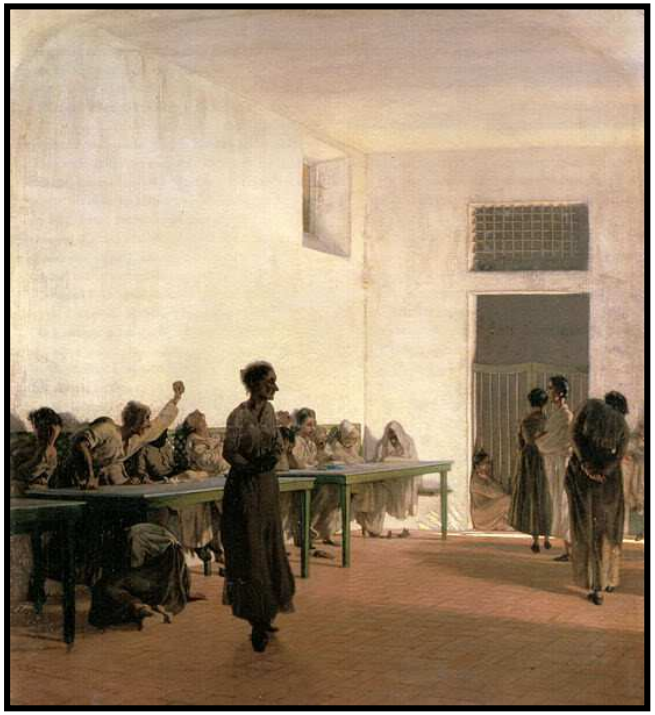
1° Sintomi Comportamentali

Personalità e **condotta sociale**

Sindrome Disinibita

Sindrome Apatica

Sindrome DOC–like



2° Sintomi Cognitivi

Sindrome **disesecutiva**

Alterazioni del **linguaggio**

3° Sintomi Motori

Variante con **Malattia del Motoneurone** o **Parkinsonismo**

FTD *versus* AD

- Alterata condotta sociale e personale
- Iperoralità e alterazione dell'alimentazione
- Comportamenti e pensieri stereotipati

- Precoce alterazione dell'eloquio
- Preservate abilità visuo-spaziali e memoria episodica

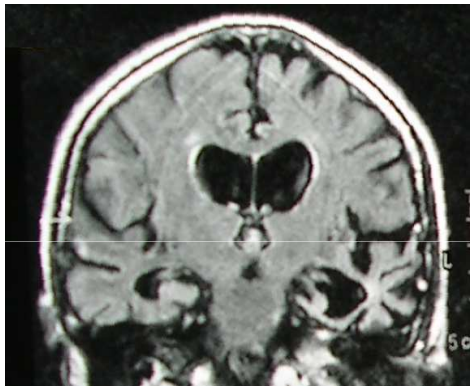
- Acinesia

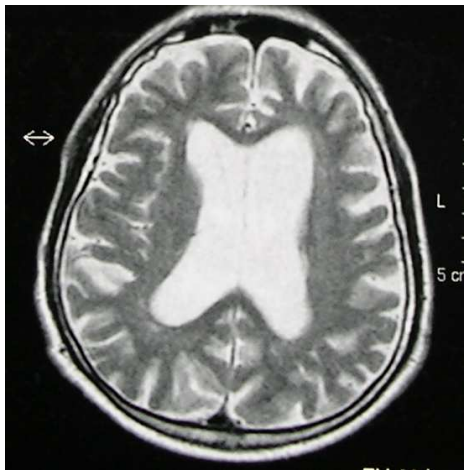
Classificazione corretta
93% di FTD
97% di AD

Rosen et al., Neurology 2002

Pattern di atrofia cerebrale in FTD

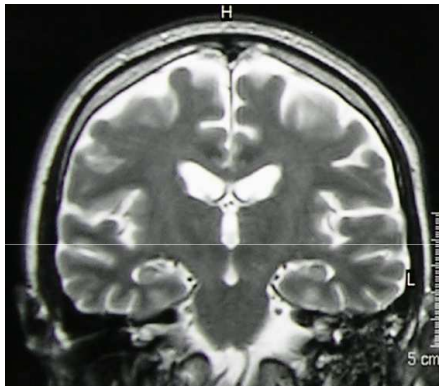
Asimmetria frontotemporale

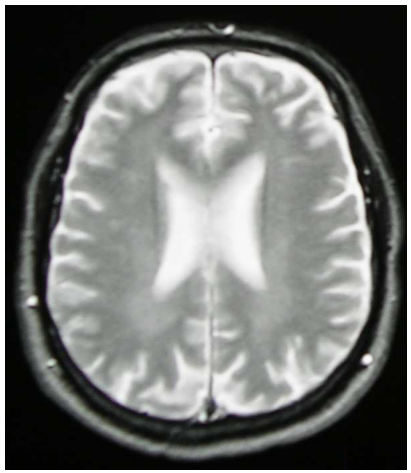




Frontale bilaterale

(1/3 di FTD)

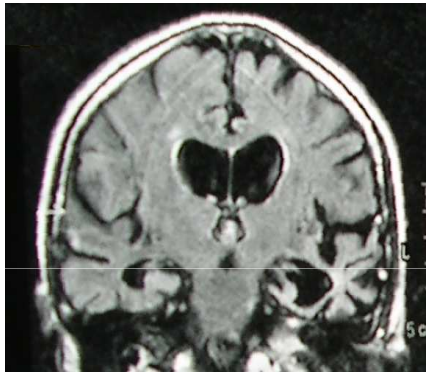


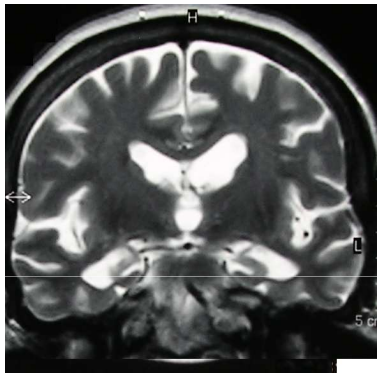


Pattern di atrofia FTD *vs* AD

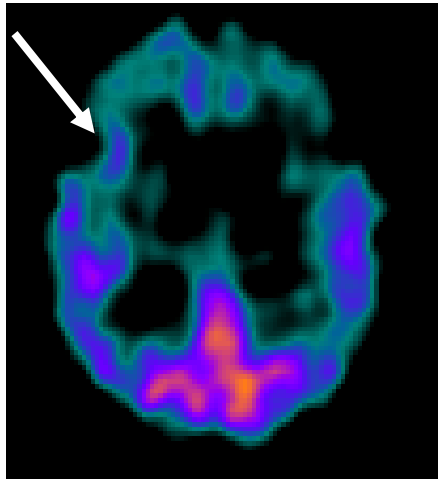
FTD **AD**

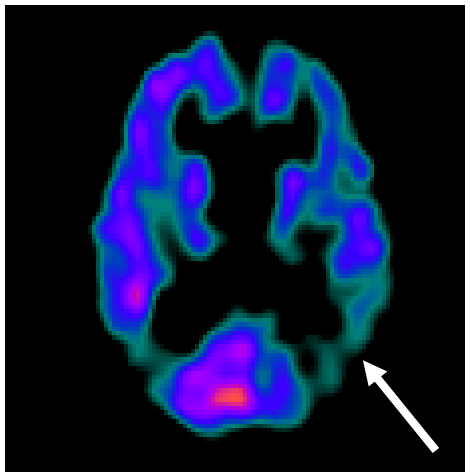
RMN



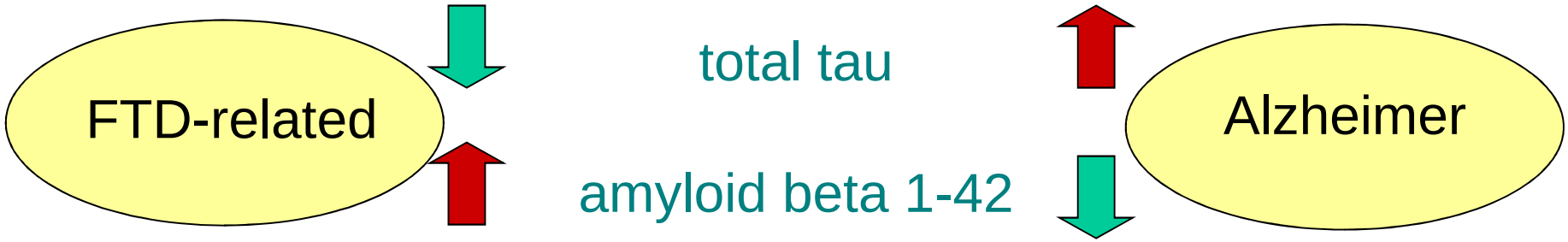


SPECT CBF





CSF biomarkers

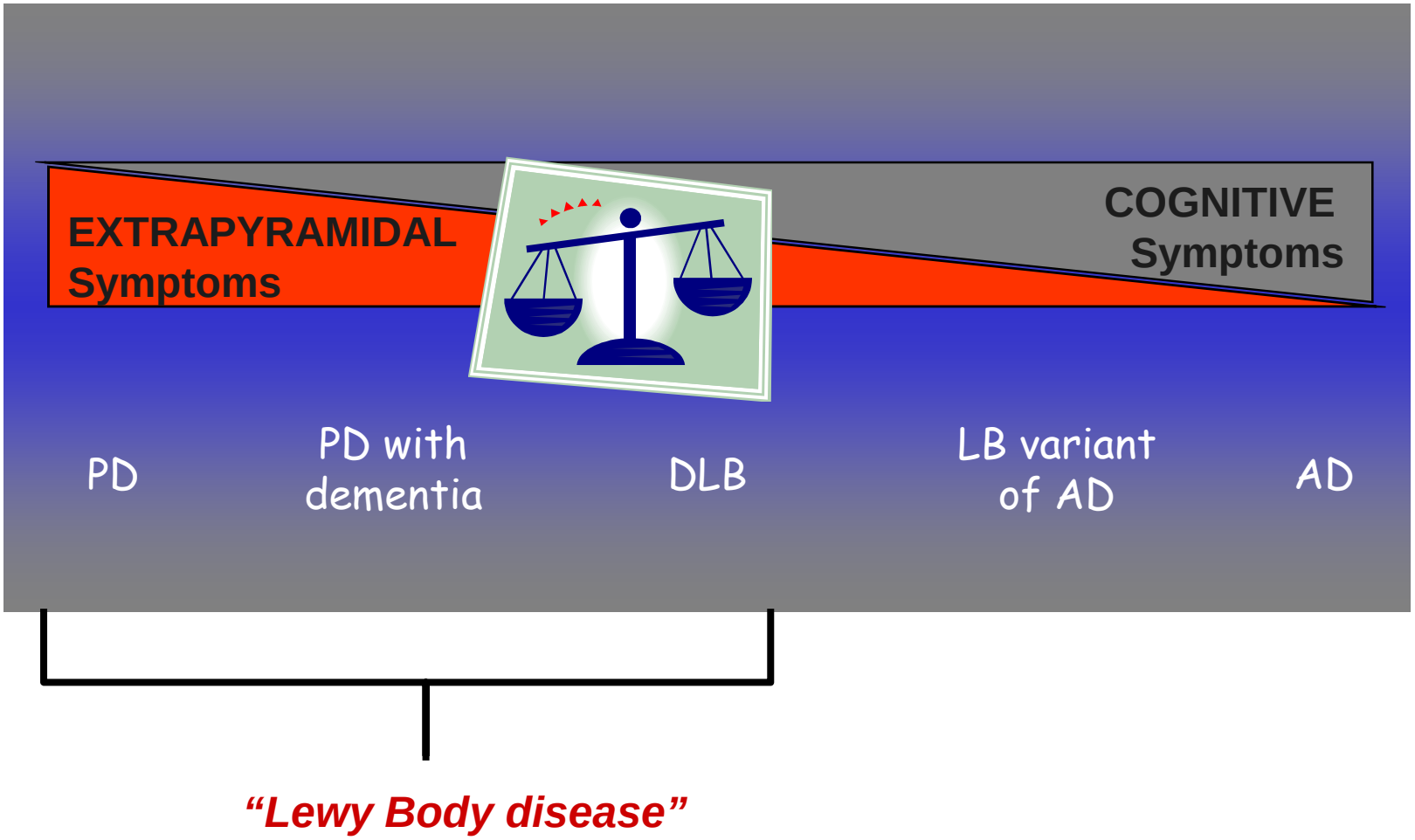


Due biomarkers classificano correttamente 88.5% di FTD e AD.

Utilità nell'identificare presentazioni atipiche di AD

Grossman, Ann Neurol 2005

Demenza e disturbi extrapiramidali
Lo spettro clinico



Demenza a Corpi di Lewy (DLB)

Criteri diagnostici

Central feature: Dementia

(deficits on attention, executive function, visuo-spatial abilities)

Core features: two of the following: probable; one: possible DLB

- Fluctuating cognition with pronounced variations in attention
- Recurrent visual hallucinations (well formed and detailed)
- Spontaneous features of parkinsonism

Suggestive features

- RBD
- Severe neuroleptic sensitivity
- Low dopamine transporter uptake in BG (PECT/PET imaging)

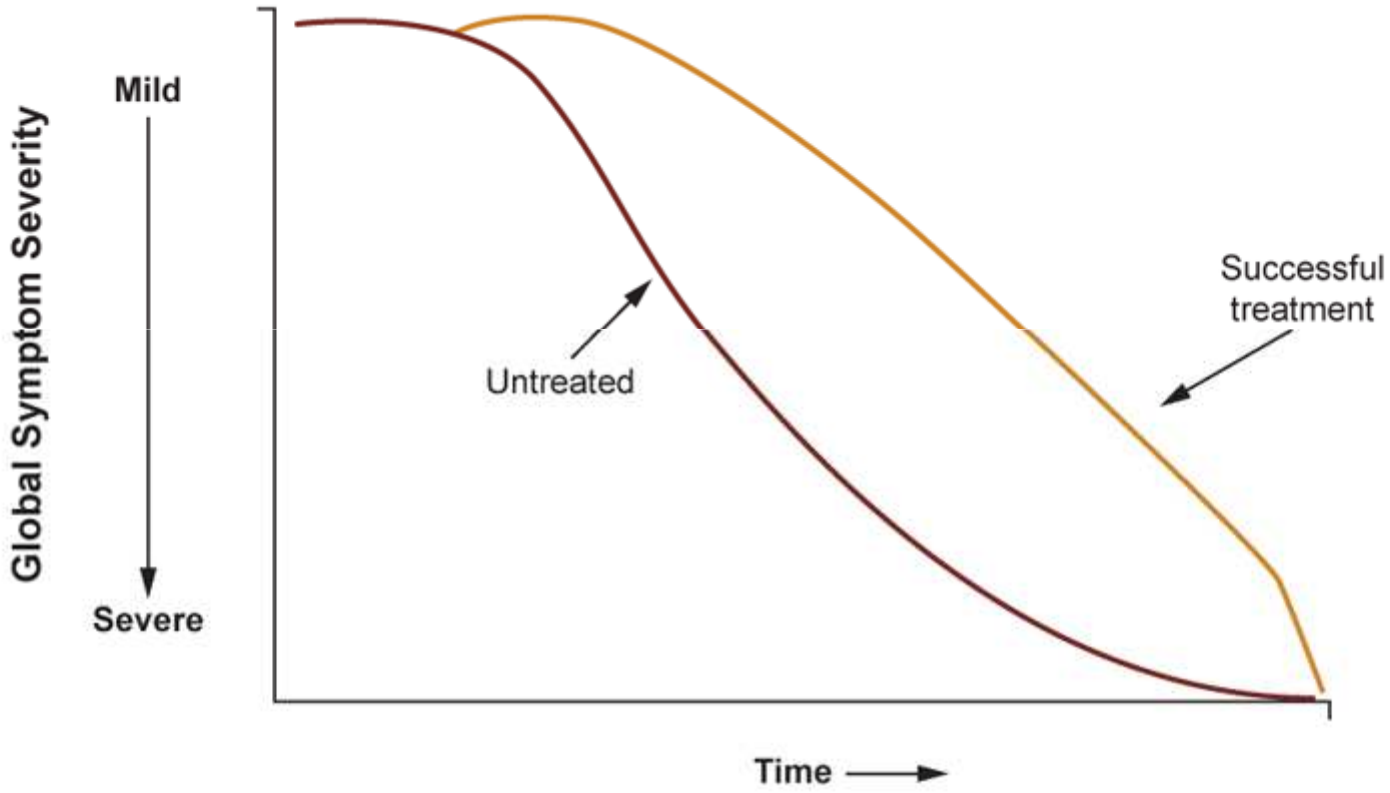
McKeith, Neurology 2005

Il trattamento del paziente demente: aspetti principali

- Fornire interventi riabilitativi e psicosociali specifici
- Utilizzare farmaci attivi sul declino cognitivo
- Trattare i sintomi non cognitivi
- Valutare e trattare le patologie co-occorrenti
- Prevenire e trattare le complicanze
- Definire un piano complessivo di trattamento

mod.da *A Bianchetti, M Trabucchi: Alzheimer's Disease.*
S Govoni, CL Bolis, M Trabucchi. Dementias. Springer Verlag Ed, 1999

Hypothetical Treatment Expectations vs Expected Decline in AD



PeerView press

Current standard of care

Table 1. Clinical Pharmacology of Agents Useful for Reducing the Signs of Dementia.*

Characteristic	Donepezil	Rivastigmine	Galantamine	Memantine
Time to maximal serum concentration (hr)	3–5	0.5–2	0.5–1	3–7
Absorption affected by food	No	Yes	Yes	No
Serum half-life (hr)	70–80	2†	5–7	60–80
Protein binding (%)	96	40	0–20	45
Metabolism	CYP2D6, CYP3A4	Nonhepatic	CYP2D6, CYP3A4	Nonhepatic
Dose (initial/maximal)	5 mg daily/ 10 mg daily	1.5 mg twice daily/ 6 mg twice daily	4 mg twice daily/ 12 mg twice daily	5 mg daily/ 10 mg twice daily
Mechanism of action	Cholinesterase inhibitor	Cholinesterase inhibitor	Cholinesterase inhibitor	NMDA-receptor antagonist

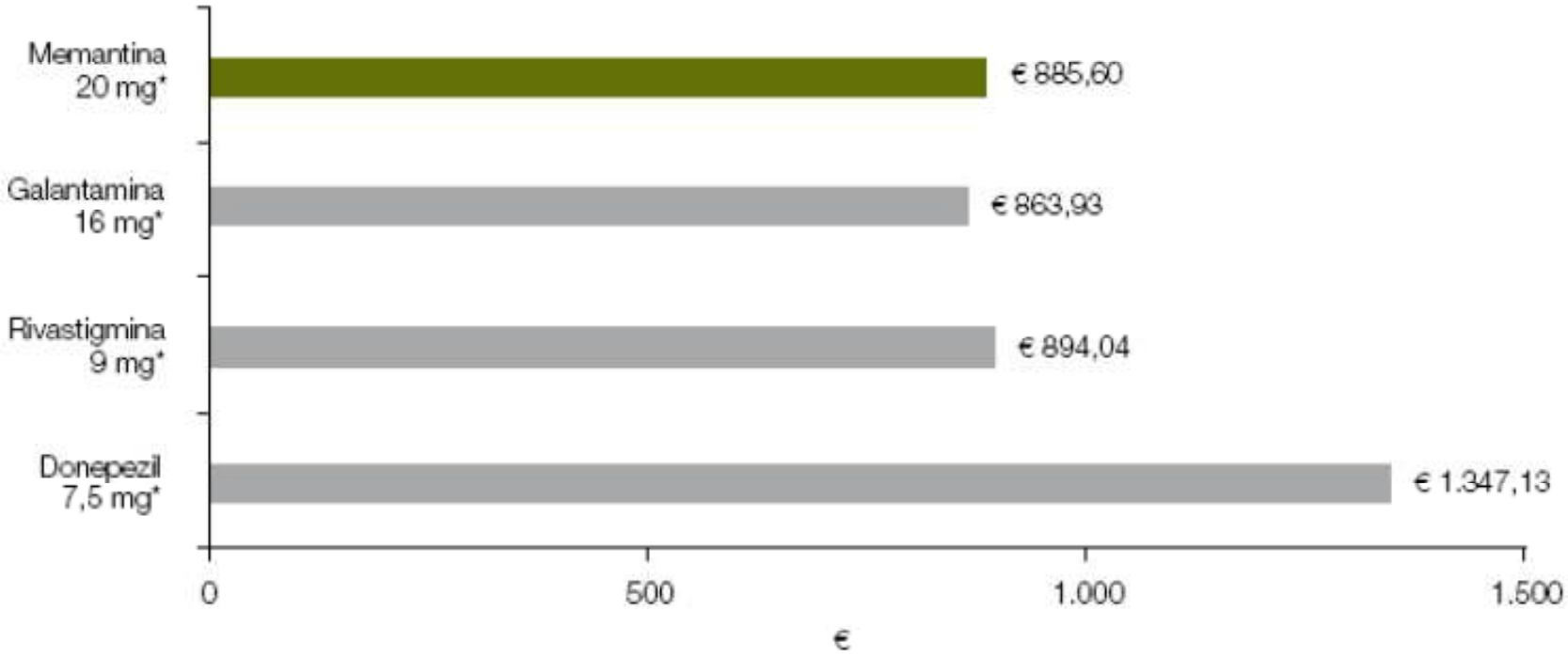
* CYP2D6 denotes cytochrome P-450 enzyme 2D6, CYP3A4 cytochrome P-450 enzyme 3A4, and NMDA *N*-methyl-D-aspartate.

† Rivastigmine is a pseudo-irreversible acetylcholinesterase inhibitor that has an eight-hour half-life for the inhibition of acetylcholinesterase in the brain.

Cummings; N Engl J Med 2004;351:56-67

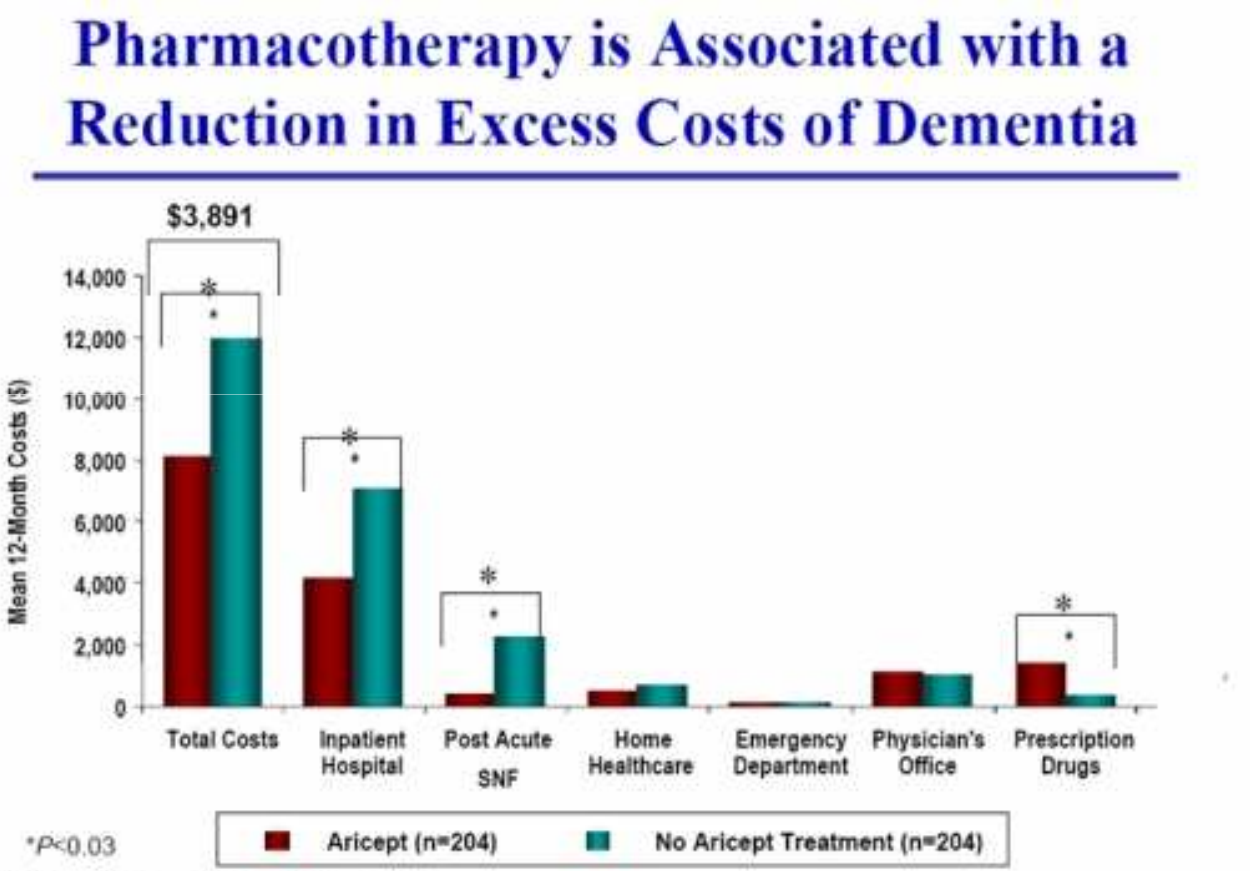
grafico 1

CONFRONTO DEI COSTI PER I PRIMI 12 MESI DI TERAPIA



* sono state considerate le DDD (Defined Daily Dose)

Cost-effectiveness



Fillit et al. Family Medicine, 2002
Lu, et al, Am J Geriatr. Pharmacotherapy, 2005

Alzheimer's Drug Discovery Foundation

JNNP

2009

Long-term effects of the concomitant use of memantine with cholinesterase inhibition in Alzheimer disease

O L Lopez, J T Becker, A S Wahed, J Saxton, R A Sweet, D A Wolk, W Klunk and S T DeKosky

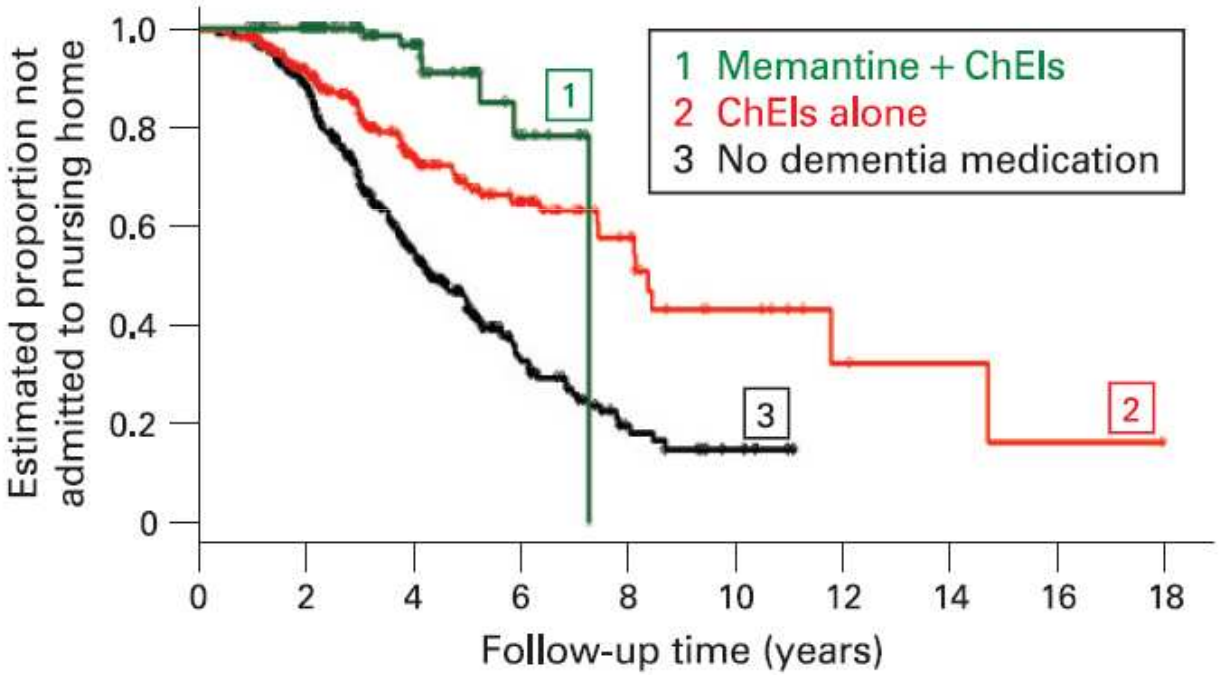
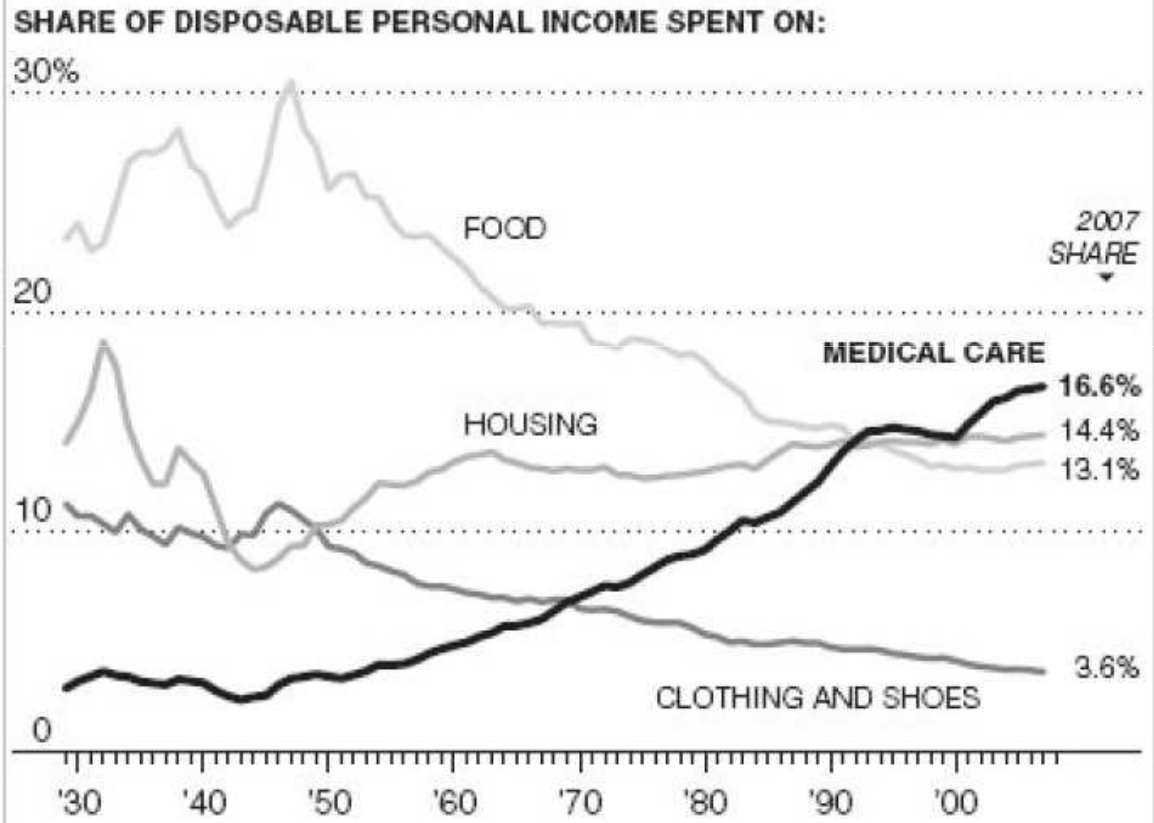


Figure 2 Time to nursing home admission in Cohort 1. ChEIs, cholinesterase inhibitors.

The Mounting Burden for Health Care

Spending on health care, which takes up more of consumers' income than housing, food or clothing, has risen siginificantly since 2000. As the economy slows and medical costs continue to rise, millions of people may be unable to afford care.



Sources: Bureau of Economic Analysis; Deloitte Center for Health Solutions Analysis

THE NEW YORK TIMES

The New York Times

May 4, 2008