Dementia TC 19
WCN Chile 2015

Cognitive complaint as a preclinical stage in dementias

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Conflicts of interest

I have no disclosures to announce in association with the contents of this presentation

Learning objectives

- Defining the preclinical stage
- Subjective cognitive decline
- Clinical evaluation
  Anamnesis or interview
  Neuropsychological tests
  Neurological examination
- Key remarks

Problems with biomarkers…

2014

THE COCHRANE COLLABORATION®

[11]C-PIB-PET for the early diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI) (Review)

Zhang S, Smailagic N, Hyde C, Noel-Storr AH, Takwoingi Y, McShane R, Feng J

Although the good sensitivity achieved in some included studies is promising for the value of PIB-PET, given the heterogeneity in the conduct and interpretation of the test and the lack of defined thresholds for determination of test positivity, we cannot recommend its routine use in clinical practice.

THE COCHRANE COLLABORATION®

Plasma and cerebrospinal fluid amyloid beta for the diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI) (Review)

Ritchie C, Smailagic N, Noel-Storr AH, Takwoingi Y, Flicker L, Mason SE, McShane R

The measure of abnormally low CSF Aβ levels has very little diagnostic benefit with likelihood ratios suggesting only marginal clinical utility. We conclude that when applied to a population of patients with MCI, CSF Aβ levels cannot be recommended as an accurate test for Alzheimer´s disease.

The continuum of Alzheimer´s disease

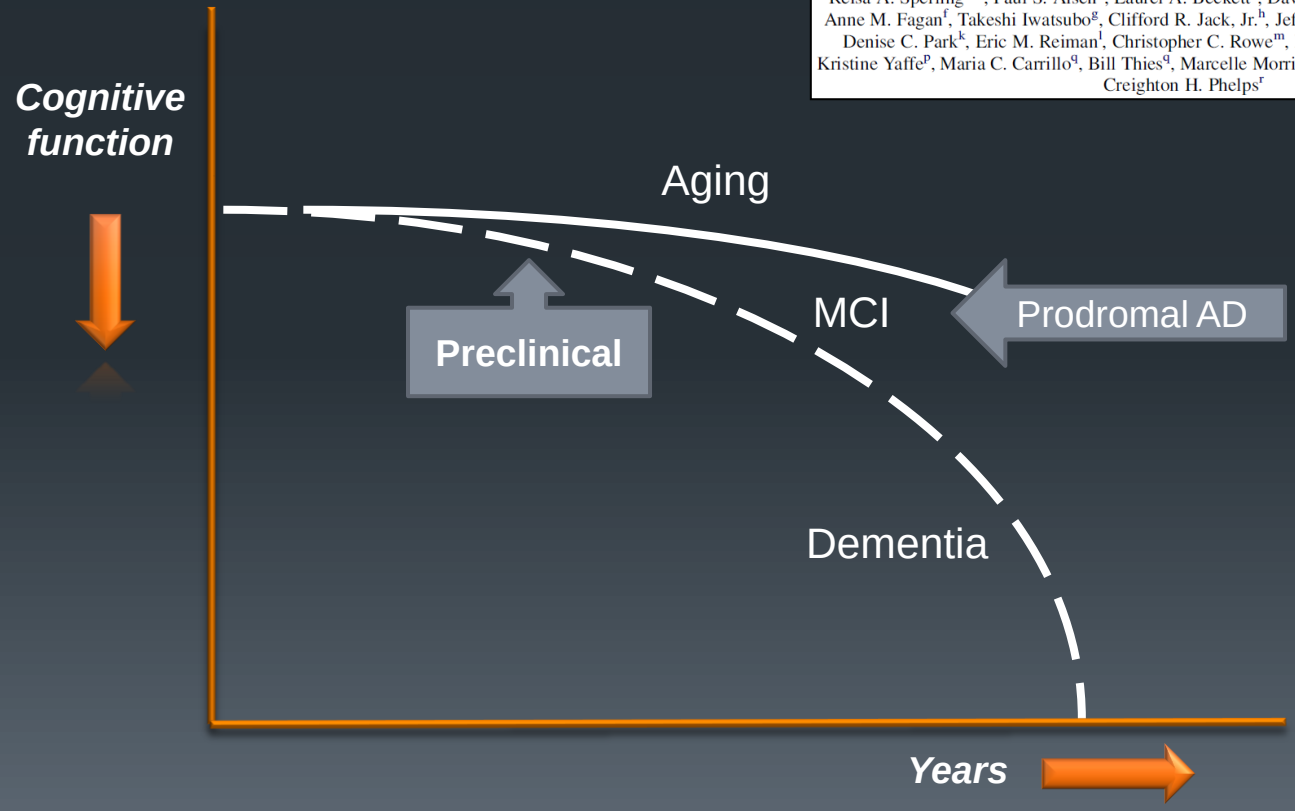
ELSEVIER

Alzheimer's & Dementia 7 (2011) 280–292

Alzheimer's & Dementia

Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease

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], Creighton H. Phelps[r]



Course of AD NIA/AA, 2011

- Preclinical Alzheimer´s disease

  No impairment in cognition on standard assessments and biomarker evidence for AD

ELSEVIER

Archives of Medical Research

Archives of Medical Research ■ (2012) ■

REVIEW ARTICLE

Clinical Diagnosis in Preclinical Stage of Alzheimer's Disease

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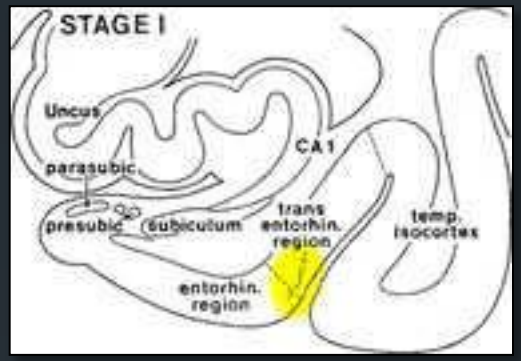
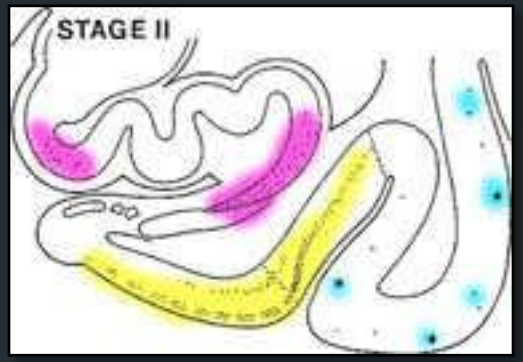
- Mild Cognitive Impairment (MCI) due to Alzheimer´s disease
- Dementia due to Alzheimer´s disease

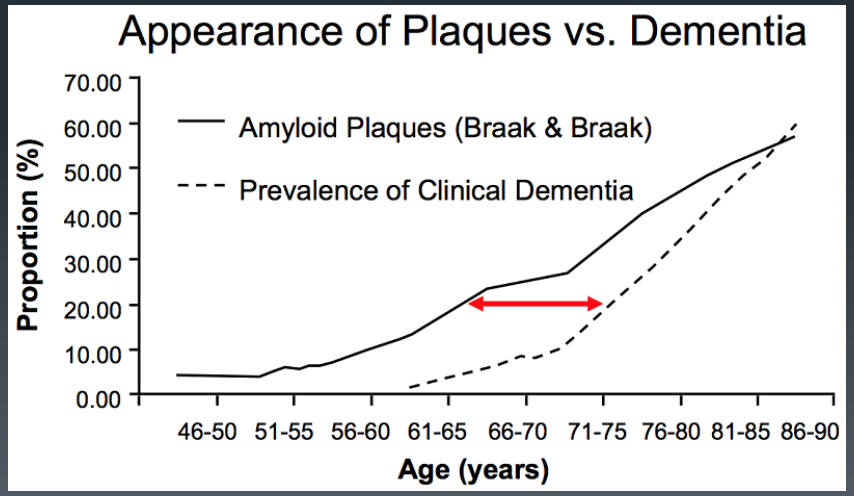
Can we detect clinical changes?



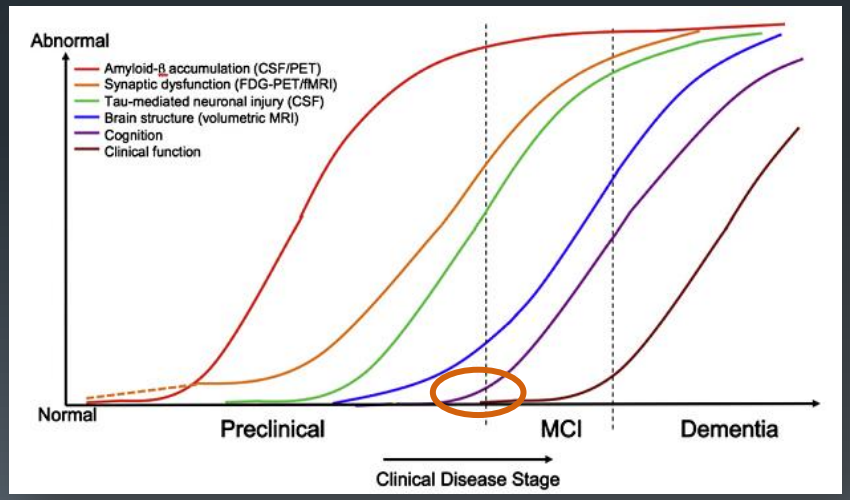
Braak & Braak I



Braak & Braak II

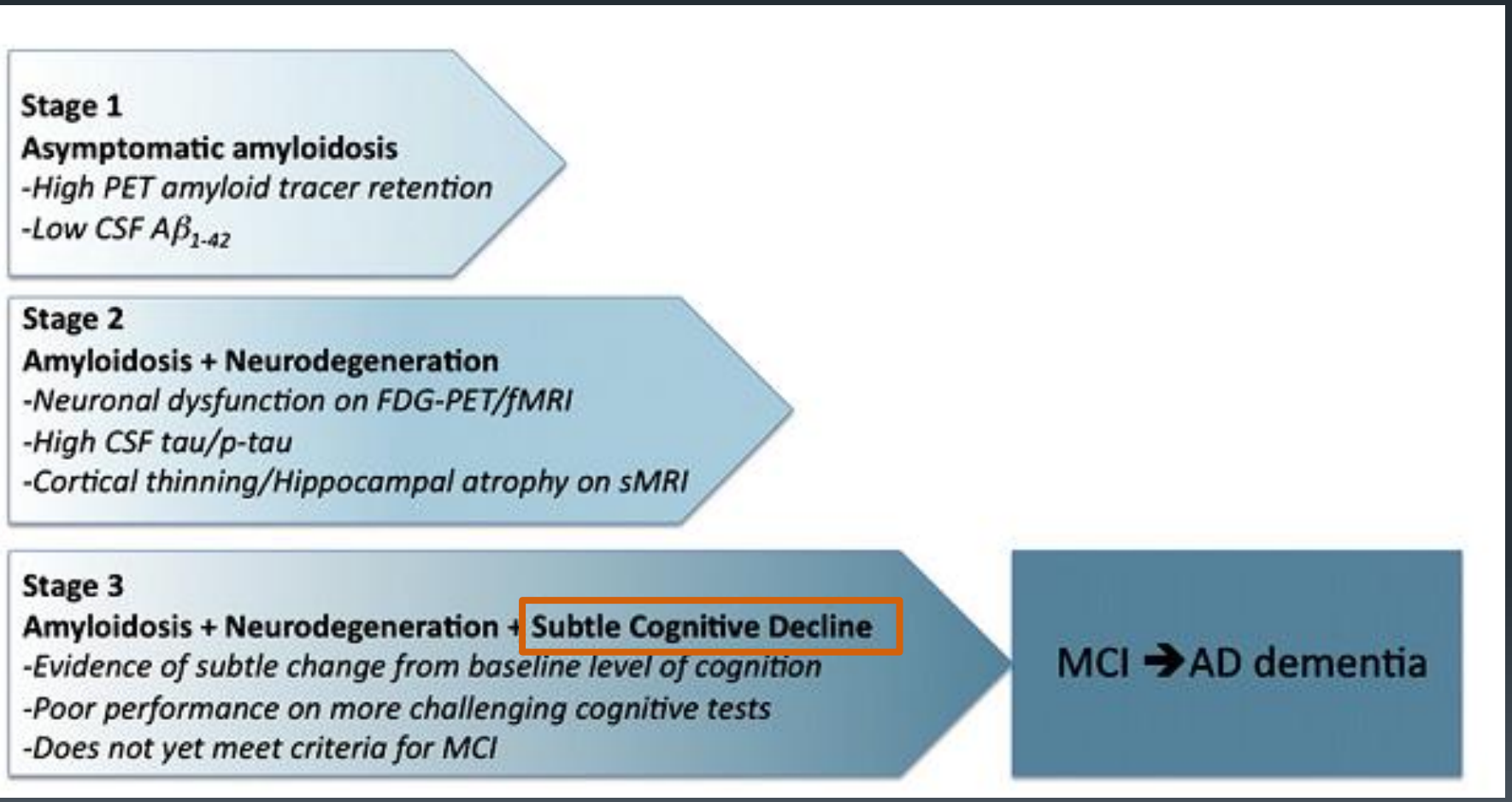


Lag of ten years



Opportunity window

The preclinical stages of AD Sperling R , 2011



If the decline is detected clinically then, by definition, how can be it a “preclinical” state ?

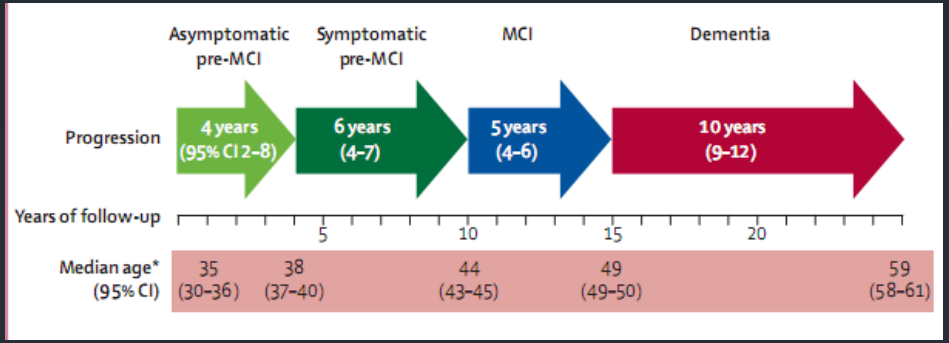
Level of cognition as a function of NIA-Reagan pathologic diagnosis Bennett DA et al, 2006

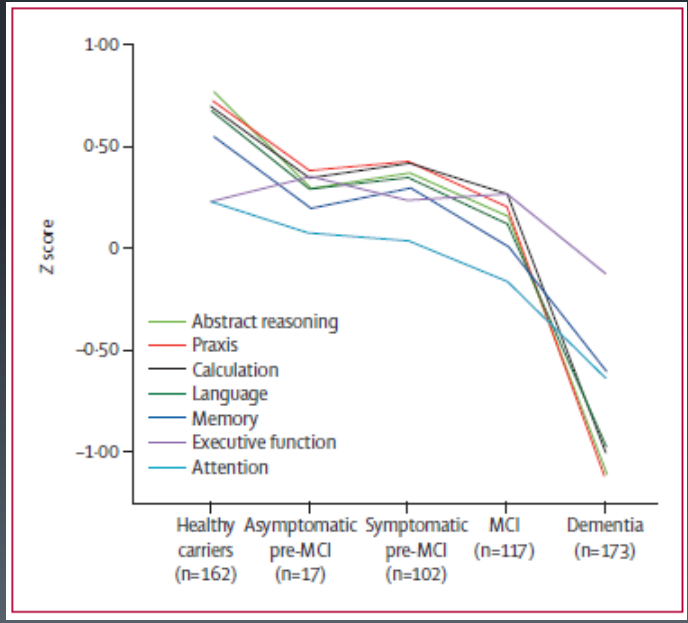
without cognitive impairment proximate to death N=134

	NIA-Reagan pathologic AD		p Value
	No	Yes	
Episodic memory	**0.44 (0.45)**	**0.18 (0.46)**	**0.01 0.004**
Semantic memory	0.11 (0.47)	–0.05 (0.50)	0.16 0.17
Working memory	0.18 (0.71)	0.00 (0.58)	0.12 0.12
Perceptual speed	–0.15 (0.92)	–0.27 (0.77)	0.62 0.86
Visuospatial ability	0.03 (0.62)	0.12 (0.59)	0.26 0.85

Cognitive impairment subtypes in PSEN1 E280A carriers

Acosta-Baena et al, 2011





Variability of cognitive domains during clinical progression

Trajectories of decline in cognition in preclinical dementia

- Dementia cases first reported memory complaints 16 years before diagnosis, followed by decline in MMSE, IADL, and finally BADL.

  Vascular dementia related to earlier decline in daily functioning but later in cognition, compared with Alzheimer's disease

  Jacobus V, 2015
- There is consensus that incident AD persons show accelerated cognitive decline during the last 2-3 years before diagnosis

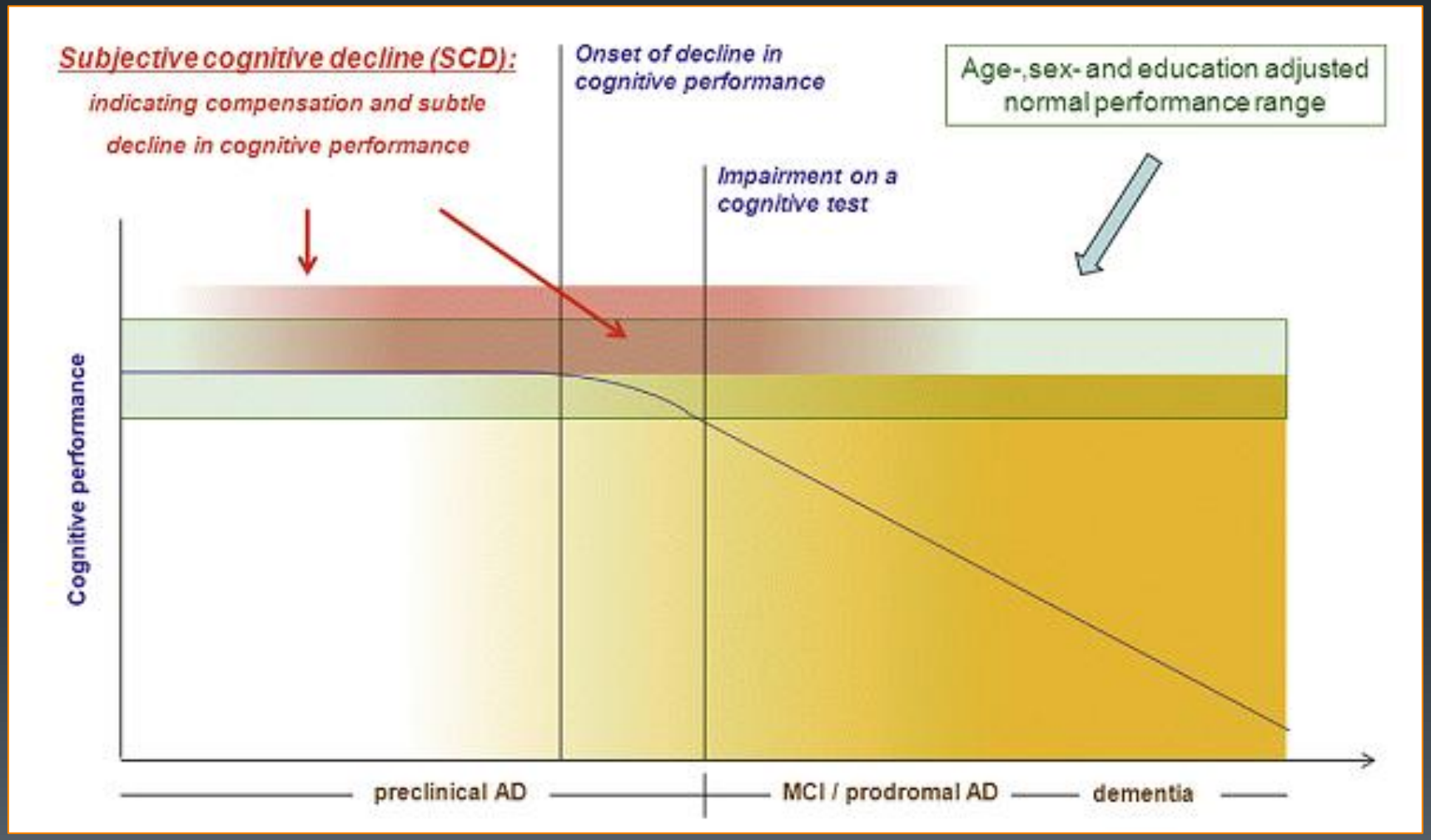
  Backman, 2001

Cognitive impairment 18 years before clinical diagnosis of AD dementia Rajan K et al, 2015

Years before diagnosis	Episodic memory[b]	Executive function[c]	Global cognition[d]
0.1-0.9	1.57 (1.48, 1.67)[e]	1.11 (1.10, 1.12)[e]	1.46 (1.39, 1.53)[e]
1.0-3.9	1.36 (1.29, 1.44)[e]	1.09 (1.08, 1.10)[e]	1.46 (1.38, 1.54)[e]
4.0-6.9	1.31 (1.23, 1.40)[e]	1.07 (1.05, 1.08)[e]	1.39 (1.31, 1.48)[e]
7.0-9.9	1.16 (1.07, 1.26)[f]	1.06 (1.04, 1.08)[e]	1.28 (1.19, 1.37)[e]
10.0-12.9	1.14 (1.02, 1.28)[g]	1.06 (1.04, 1.09)[e]	1.35 (1.20, 1.52)[e]
13.0-17.9	1.15 (1.00, 1.32)[g]	1.04 (1.02, 1.07)[f]	1.28 (1.11, 1.47)[e]

OR for cognitive test scores predicting the development of AD over an 18-year period

Progression of disease pathology and clinical states



Jessen F, 2014

Research criteria for SCI SCI-D Working Group 2014

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 MCI or prodromal AD

1 and 2 must be present

Exclusion criteria

- MCI, prodromal AD or dementia
- Can be explained by a psychiatric* or neurological disease (apart of AD), medical disorder, medication, or substance use

Subjective declination in cognition is unspecific…

- Normal aging
- Personality traits
- Psychiatric conditions
- Neurological and medical disorders
- Substance use
- Medications
- Sleep disorders

Alzheimer´s disease diagnosis

Original criteria NINCDS-ADRDA (1984)

- Clinical judgement
- Cognitive testing
- General neurological assessment

Recent memory
Is it hard to remember what you did yesterday?
Language
Is it difficult to find the name of some things?
Orientation
Do you know well where are you now?
Executive skills
Is it difficult for you to make decisions?

AD8 Dementia Screening Interview Galvin J et al, 2010

Remember, "Yes, a change" indicates that there has been a change in the last several years caused by cognitive (thinking and memory) problems.	**YES, A change**	**NO, No change**	**N/A, Don't know**
1. Problems with judgment (e.g., problems making decisions, bad financial decisions, problems with thinking)			
2. Less interest in hobbies/activities			
3. Repeats the same things over and over (questions, stories, or statements)			
4. Trouble learning how to use a tool, appliance, or gadget (e.g., VCR, computer, microwave, remote control)			
5. Forgets correct month or year			
6. Trouble handling complicated financial affairs (e.g., balancing checkbook, income taxes, paying bills)			
7. Trouble remembering appointments			
8. **Daily** problems with thinking and/or memory			
TOTAL AD8 SCORE			

AD8 score ≥ 2
had abnormal PIB binding and CSF biomarkers ($P<0.001$) compared with AD8 (-) subjects and scored in the impaired range of the WLM story A

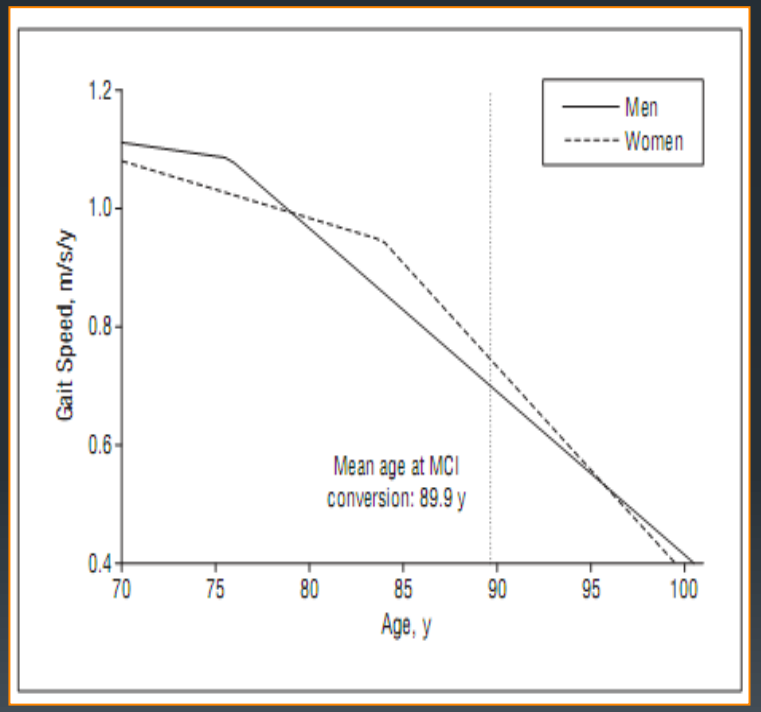
Neuropsychiatric impairments as predictors of MCI or dementia

- Almost 2/3 of persons > 65 with new onset depression or anxiety developed MCI or dementia in a subsequent 12 year period Geda YE, 2006
- Non-psychotic symptoms predicted incident MCI (follow up 5 ys) Agitation HR 3.06 Apathy HR 2.26 Anxiety HR 1.87 Geda YE, 2014

Gait and cognitive impairments in older adults

Motor Cognitive Risk (MCR) syndrome

- Cognitive complaints
- Slow gait
- Preserved ADL
- Absence of dementia



Trajectory of gait speed preceding MCI
Buracchio T et al, 2010

Key messages

- Data suggest that AD pathology may be associated with subtle cognitive deficits even in persons with pre MCI, but still is pending to define all the clinical borders present in normal aging
- Diagnosis in stages before dementia may serve to formulate advance directives and to define the population for targeted dementia prevention trials
- Without biomarkers would be key to optimize the classic clinical method with an emphasis on a good interrogation about cognitive complaints

Key references

- Acosta-Baena N, Sepulveda-Falla D, Lopera-Gomez C, Jaramillo-Elorza M, Moreno S, Aguirre-Acevedo D et al. Pre-dementia clinical stages in presenilin 1 E280A familial early-onset Alzheimer´s disease: a retrospective cohort study. *Lancet Neurol* (2011); 10:213-220
- Backman L, Small B & Fratiglioni L. Stability of preclinical memory episodic déficit in Alzheimer´s disease. *Brain* (2001) 124:96-102
- Bennett DA, Schneider JA, Arvanitakis Z, Kelly JF, Aqqarwal NT, Shah RC et al. *Neurology* (2006); 66(12):1837-44
- Buracchio T, Dodge H, Howleson D, Wasserman D, Kaye J. The trajectory of gait preceding mild cognitive impairment. *Arch Neurol* (2010) 67; (8):980-986
- Jessen F, Amariglio R, van Boxtel M, Breteler M, Ceccaldi M, Chetelat G et al. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer´s disease. *Alzheimer´s and Dementia* (2014) 1-9
- Parihar R, Mahoney J, Verghese J. Relationship of gait and cognition in elderly. *Current Transl Geriatr Exp Gerontol Rep* (2013) Sep 1; 2(3)
- Rajan K, Wilson R, Weuve J, Barnes L, Evans D. Cognitive impairment 18 years before clinical diagnosis of Alzheimer dementia. *Neurology* (2015) 85:898-904