Practical Points and Evidence Based in Diagnosis and Treatment of Mild Cognitive Impairment

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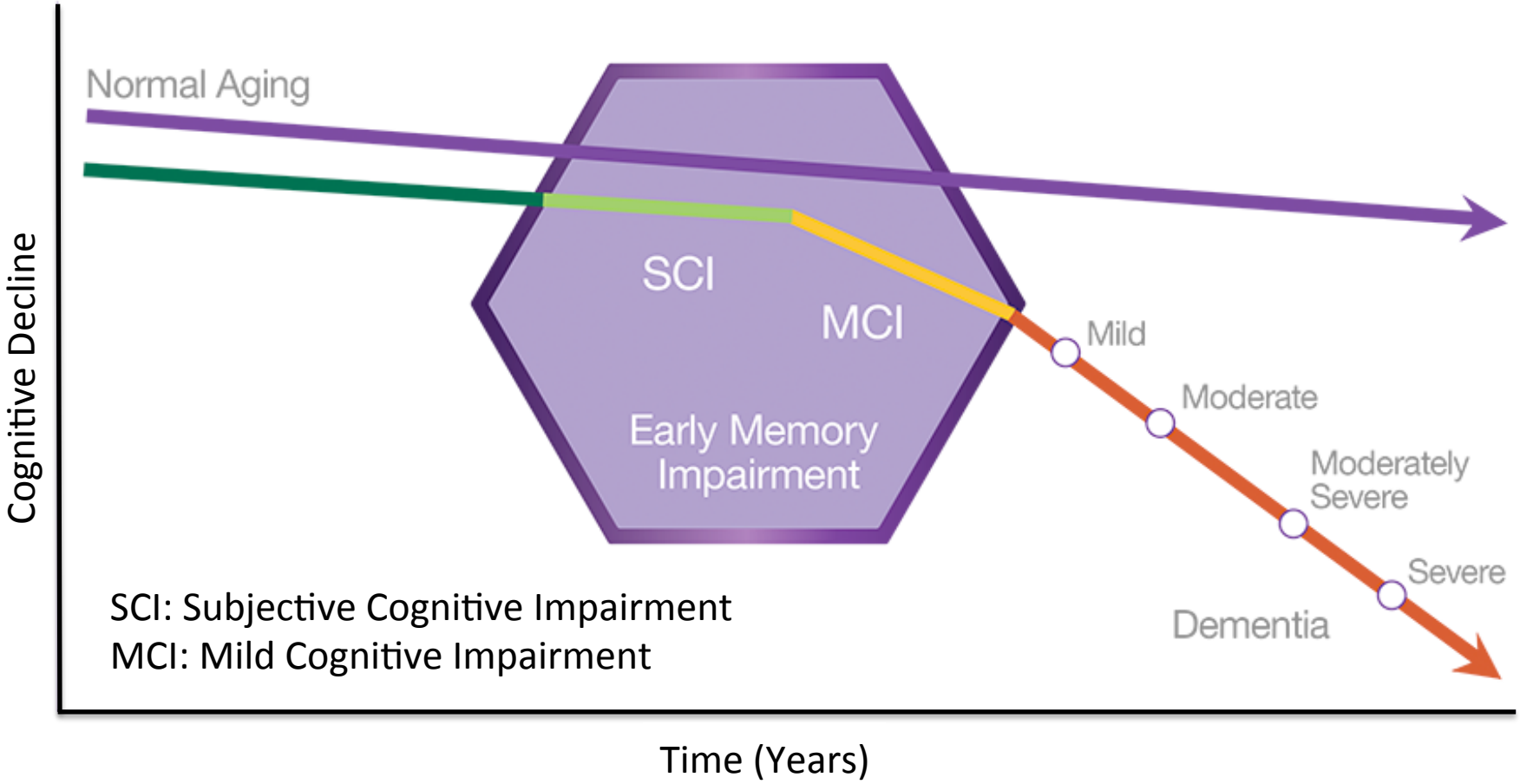
Mild cognitive impairment

- Terminology-definition
- Classification-criteria diagnosis
- Prognosis
- Treatment

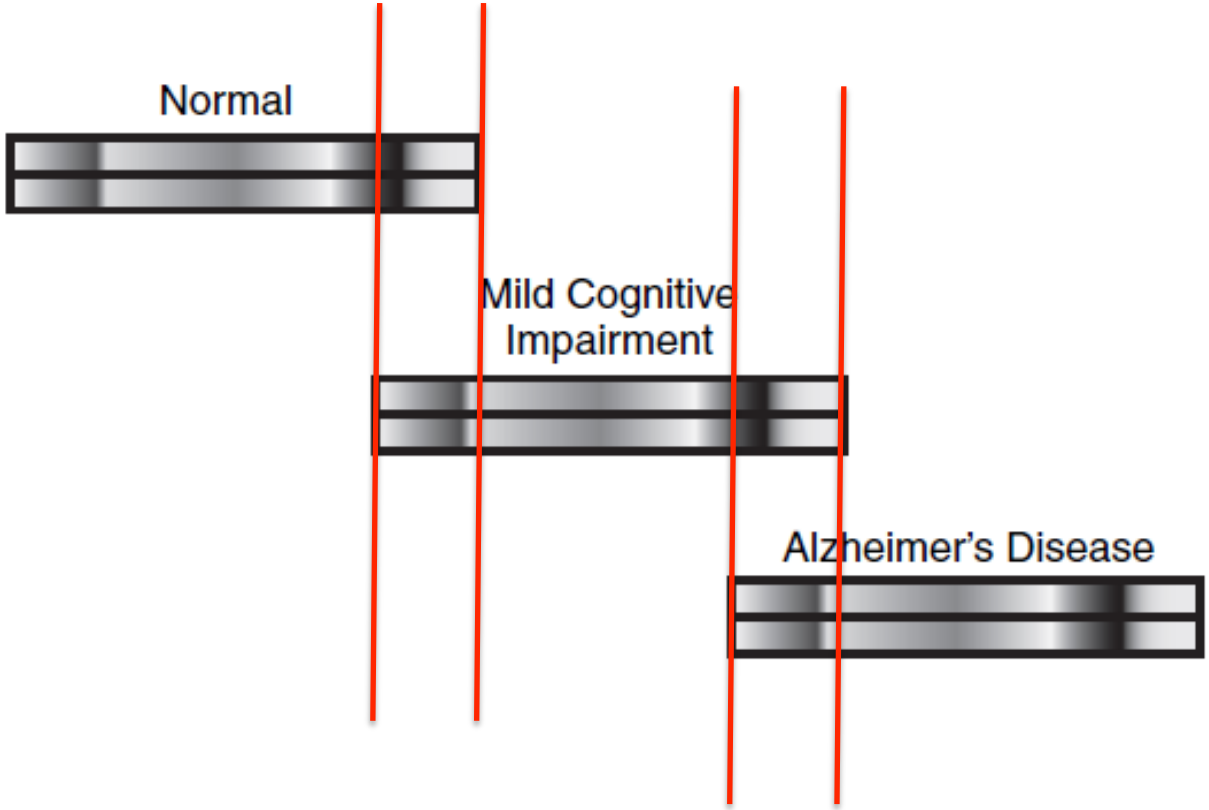
Hypothetical change in function



SCI: Subjective Cognitive Impairment
MCI: Mild Cognitive Impairment

Adapted from Golomb J. et.al. Dialogues Clin Neurosci, 2004, 6:351-64

Cognitive continuum



The overlap in the boundary between normal aging and MCI and AD

Journal of Internal Medicine 2004; 256: 183–194

TABLE 7-1 Criteria Developed to Characterize Cognitive Impairments in Nondemented Elderly Subjects

Criteria	Year
Benign senescent forgetfulness[14]	1962
Age-associated memory impairment[12]	1986
Late-life forgetfulness[11]	1989
Mild cognitive impairment[19]	1991
Mild cognitive decline[a20]	1993
Age-associated cognitive decline[16]	1994
Age-related cognitive decline[17]	1994
Mild neurocognitive decline[a17]	1994
Cognitive impairment no dementia[13,26]	1995
Mild cognitive impairment[15]	1996
Modified mild cognitive impairment (four subtypes[b])[21]	2004
Modified mild cognitive impairment (three subtypes[c])[22]	2004
Diagnostic guidelines for mild cognitive impairment due to Alzheimer disease from the National Institute on Aging and Alzheimer's Association[d24]	2011

Temporal evolution of criteria for MCI

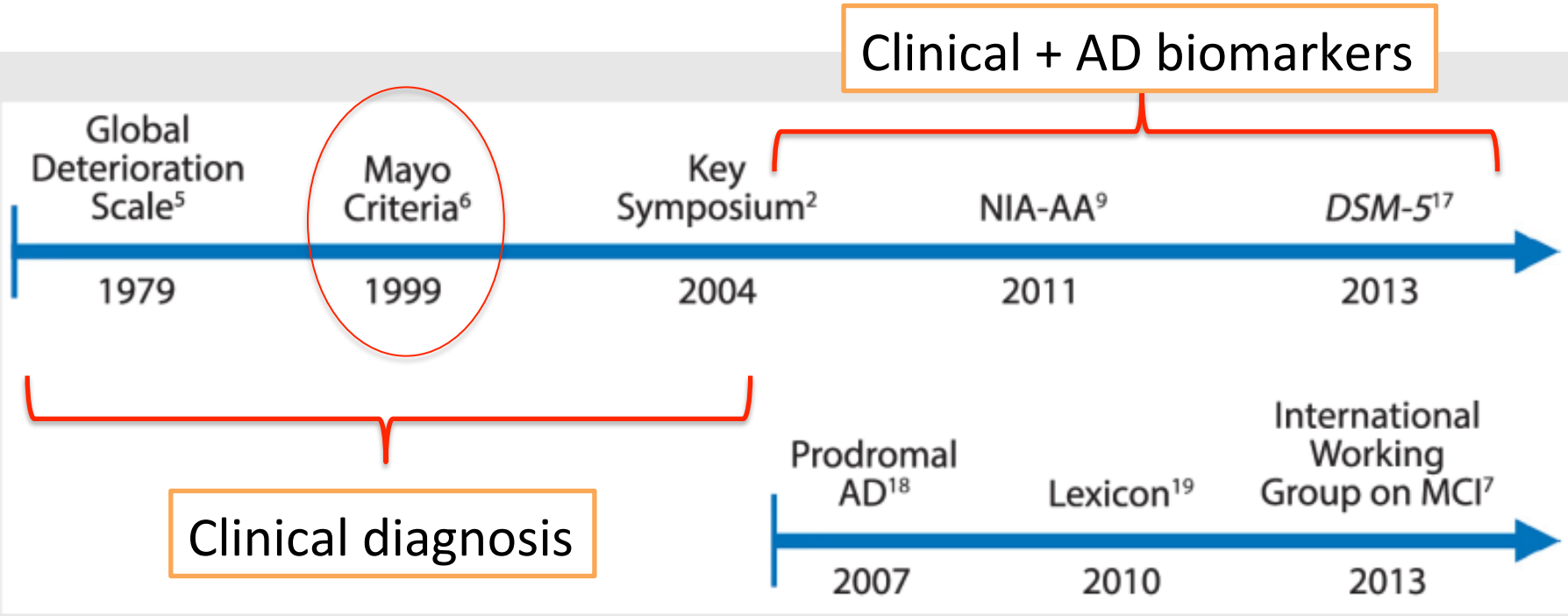


FIGURE 2-2 Temporal evolution of criteria for mild cognitive impairment (MCI) and prodromal Alzheimer disease (AD).

DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; NIA-AA = National Institute on Aging–Alzheimer's Association.

Petersen RC. Continuum (Minneap Minn) 2016; 22(2): 404-18

Mayo MCI criteria, 1999

(i) **Memory complaint**, preferably corroborated by an informant

(ii) **Objective** memory impairment for age

(iii) Relatively **preserved general cognition** for age

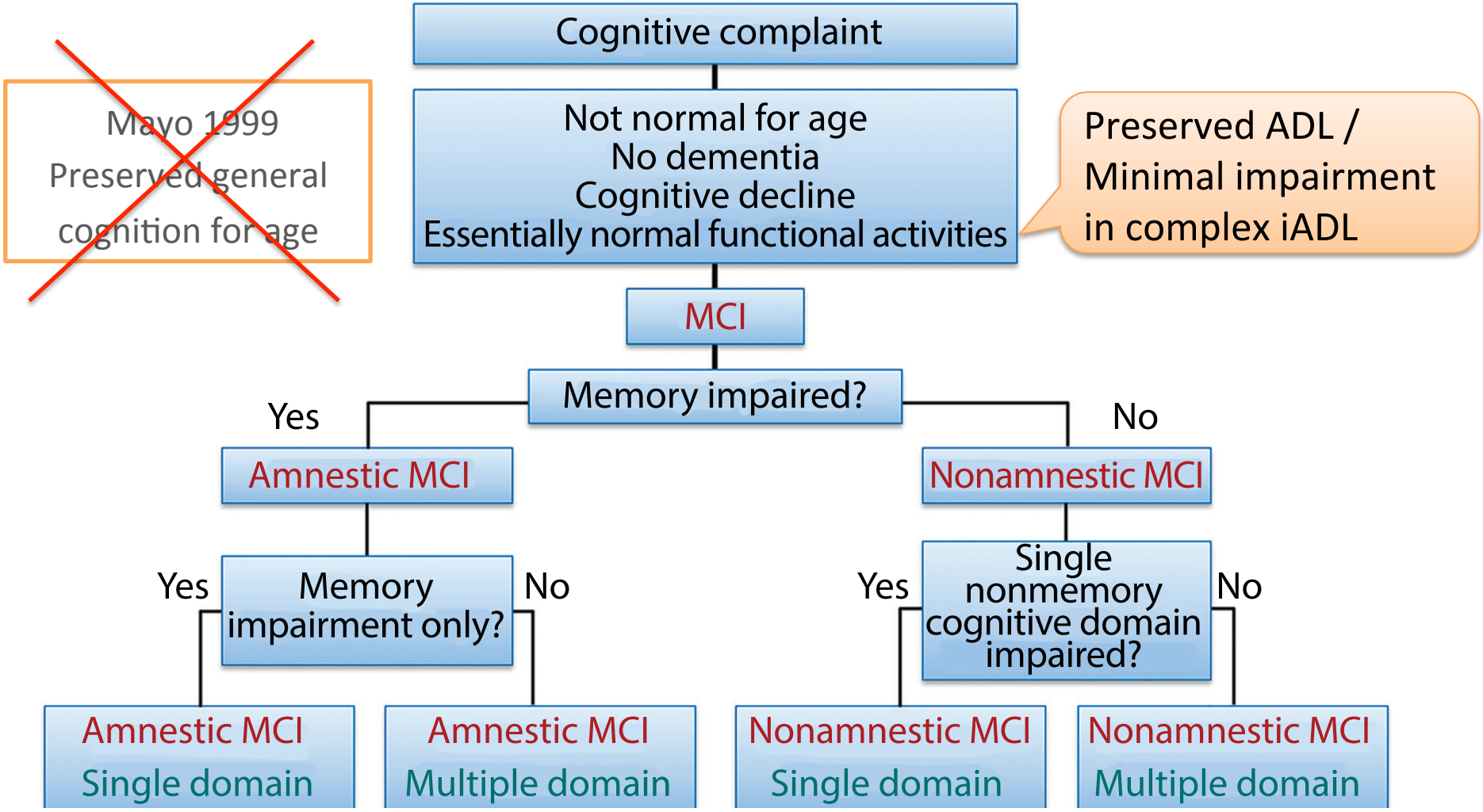
(iv) Essentially **intact activities of daily living**

(v) Not demented*

*Does not meet criteria (DSM IV, ICD 10) for a dementia syndrome

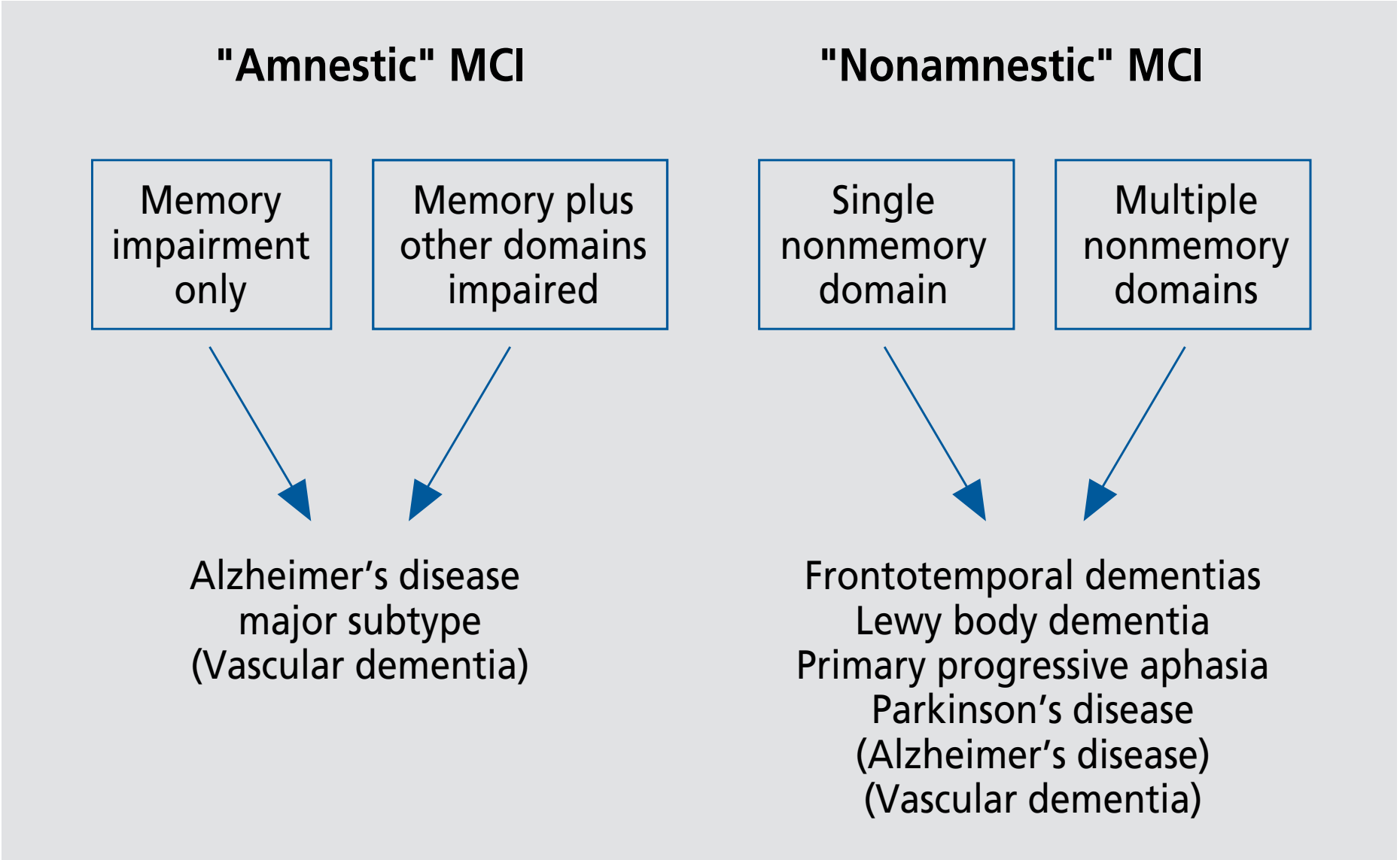
Petersen RC, Smith GE, Waring SC, et al. Arch Neurol 1999;56(3)

Key symposium/revised Mayo MCI criteria 2004



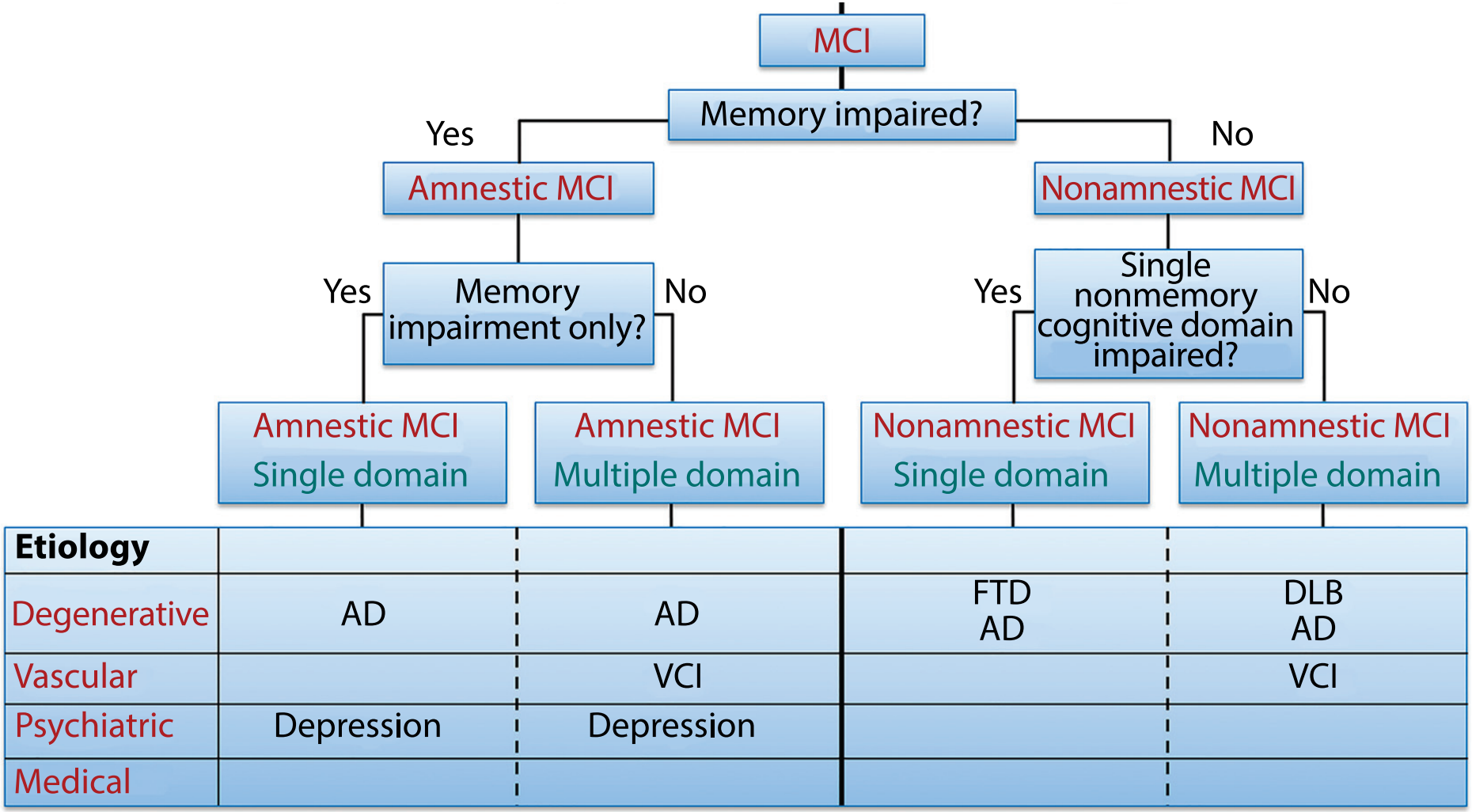
Journal of Internal Medicine 2004; 256: 183–194

Why do we need to classify MCI?



Golomb J. et.al. Dialogues Clin Neurosci, 2004, 6:351-64

The syndromic phenotype can be paired with possible etiologies

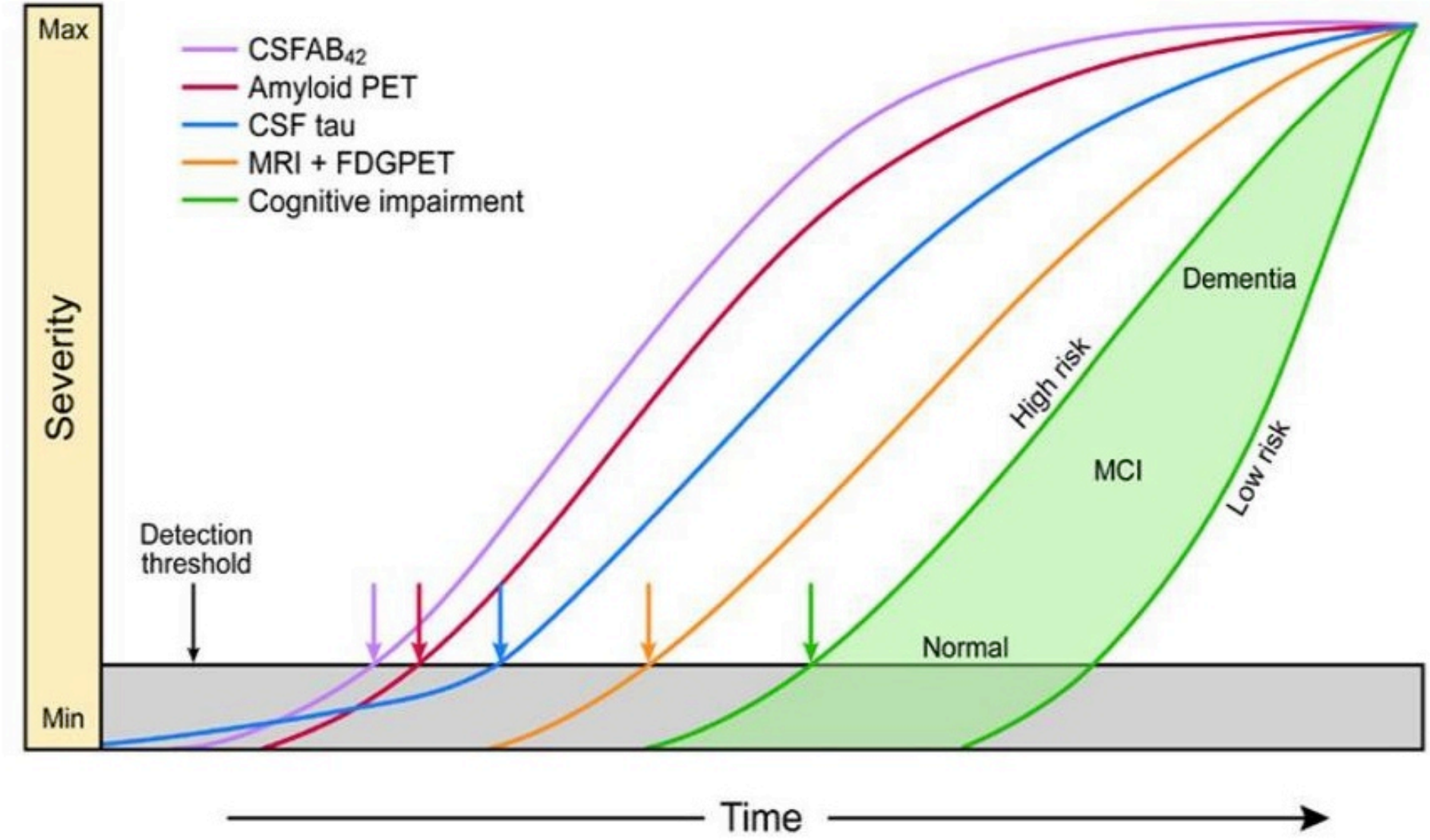


Etiology				
Degenerative	AD	AD	FTD AD	DLB AD
Vascular		VCI		VCI
Psychiatric	Depression	Depression		
Medical				

AD = Alzheimer disease; DLB = dementia with Lewy bodies; FTD = frontotemporal dementia; MCI = mild cognitive impairment; VCI = vascular cognitive impairment

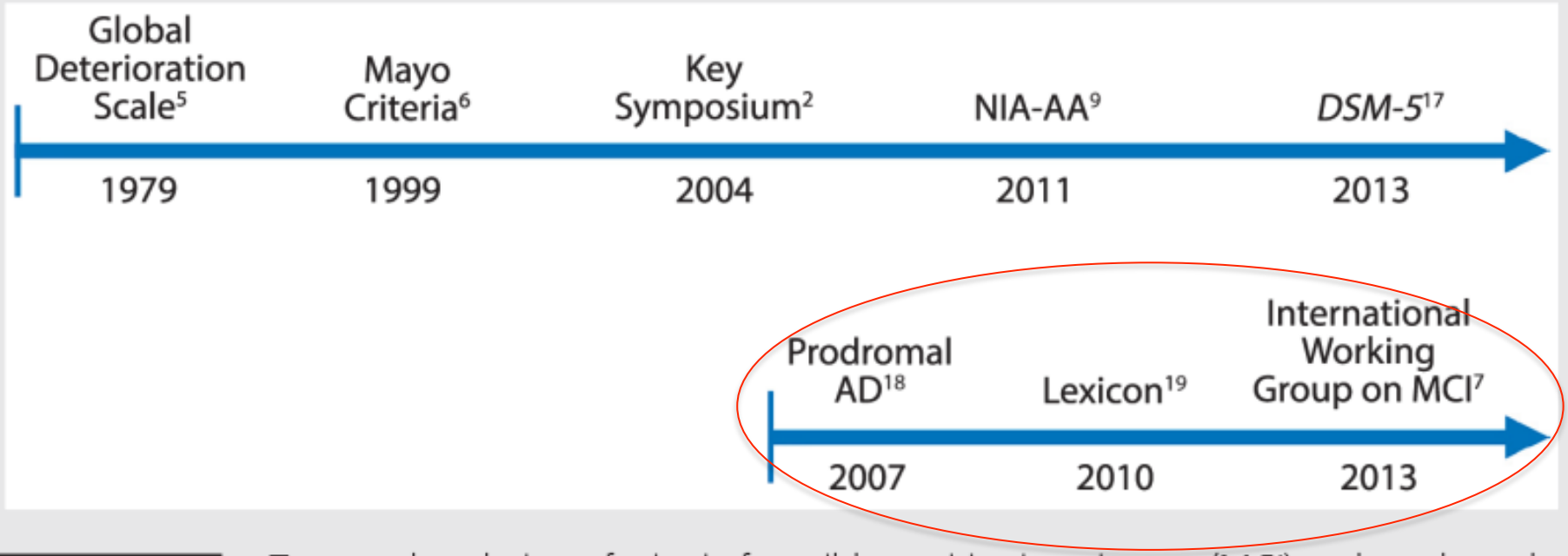
Petersen RC. Continuum (Minneap Minn) 2016; 22(2): 404-18

Alzheimer's disease progression



REACHING FOR A CURE: Alzheimer's Disease and Related Dementias Research at NIH 21 Bypass Budget Proposal for Fiscal Year 2017

Temporal evolution of criteria for MCI



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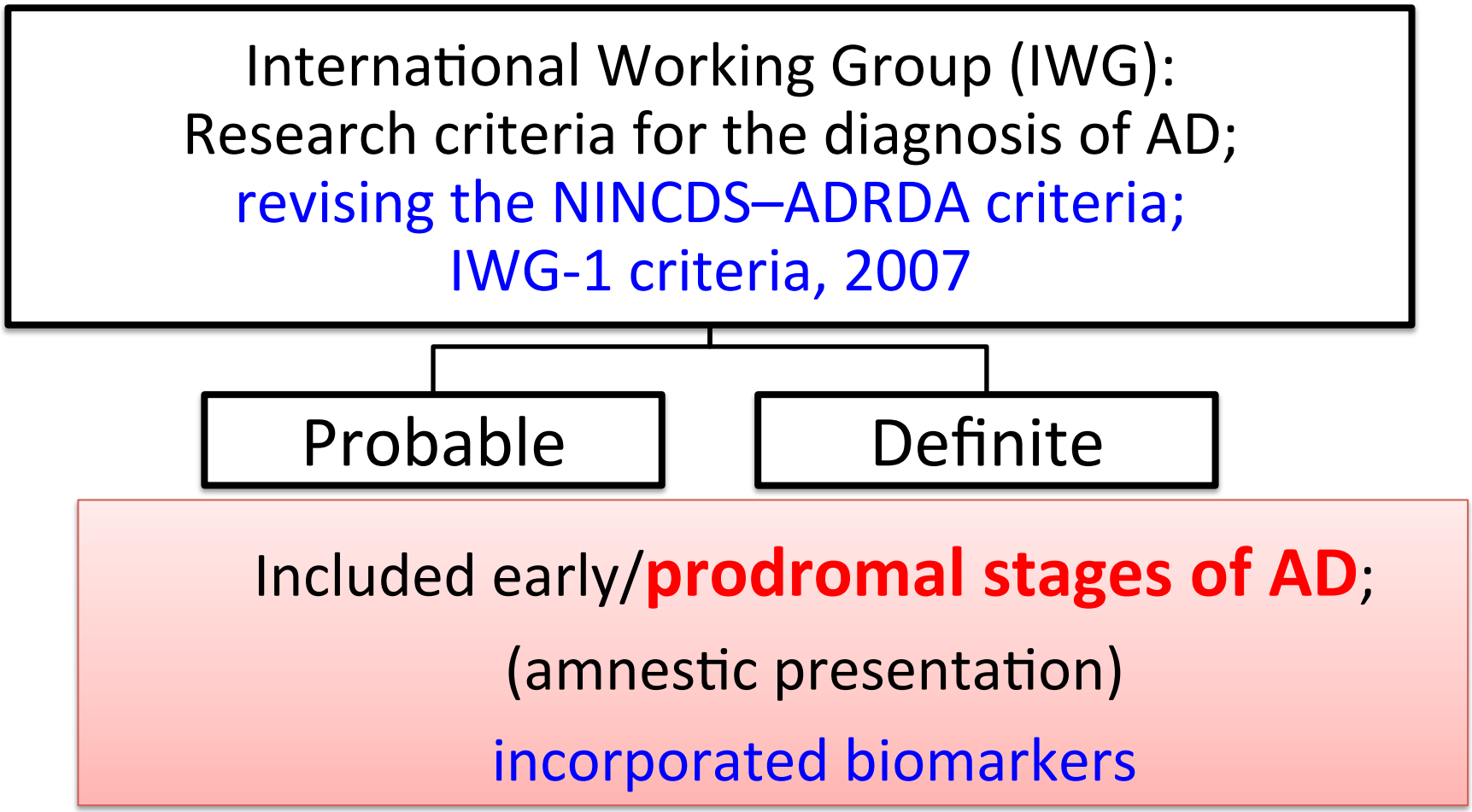
Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS–ADRDA criteria

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*



Dubois B et al. Lancet Neurol 2007;6(8):734-46.

Revising the NINCDS–ADRDA criteria: IWG criteria, 2007

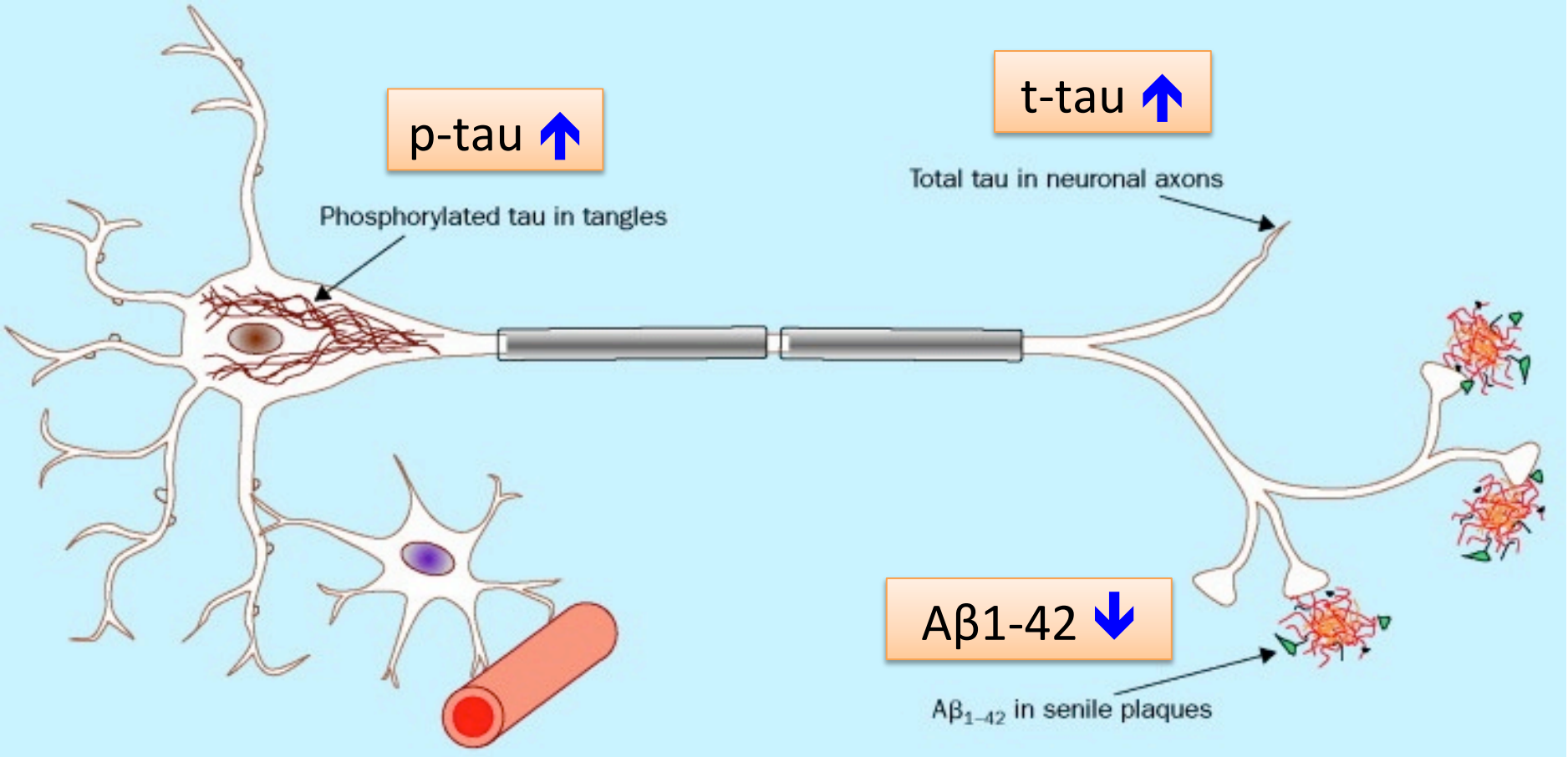
- **Prodromal AD** (Clinical + biomarkers)
  - Subjective/objective memory impairment, preserved function

    Plus
  - At least one or more abnormal biomarkers among
    - Pathophysiological markers
      - Cerebrospinal fluid analysis: Aβ-42, t-tau, p-tau
      - Amyloid PET
    - Topographical markers
      - Structural neuroimaging: hippocampal atrophy
      - FDG PET: hypometabolism
    - Genetic study
      - AD autosomal dominant mutation on chromosome 1, 14, or 21)

Dubois B et al. Lancet Neurol 2007;6(8):734-46.

Pathophysiological markers

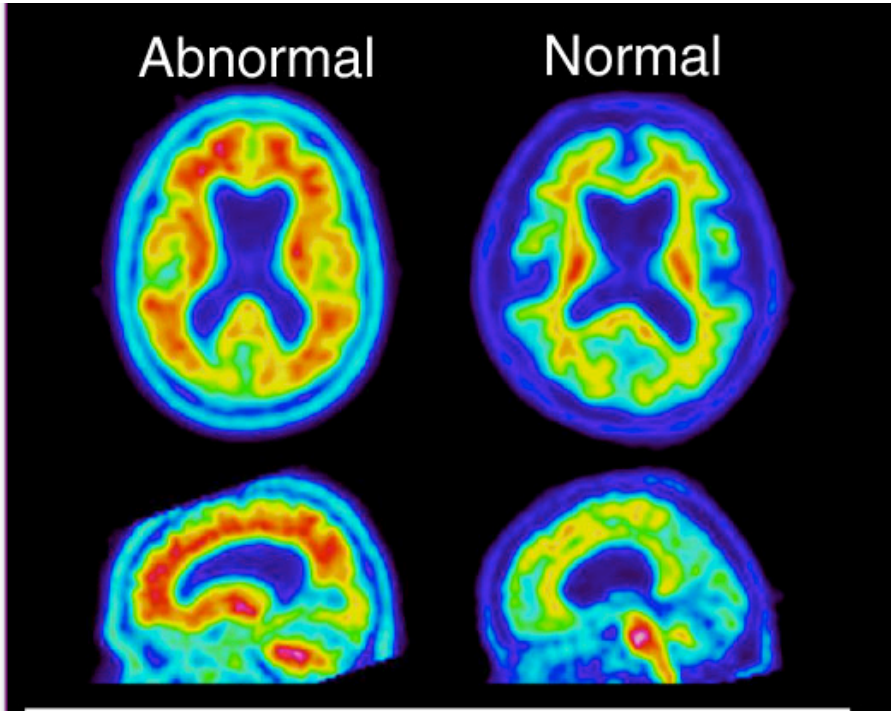
CSF biomarkers



Blennow K, Hampel H. Lancet Neuro 2003

Pathophysiological markers

Amyloid PET imaging



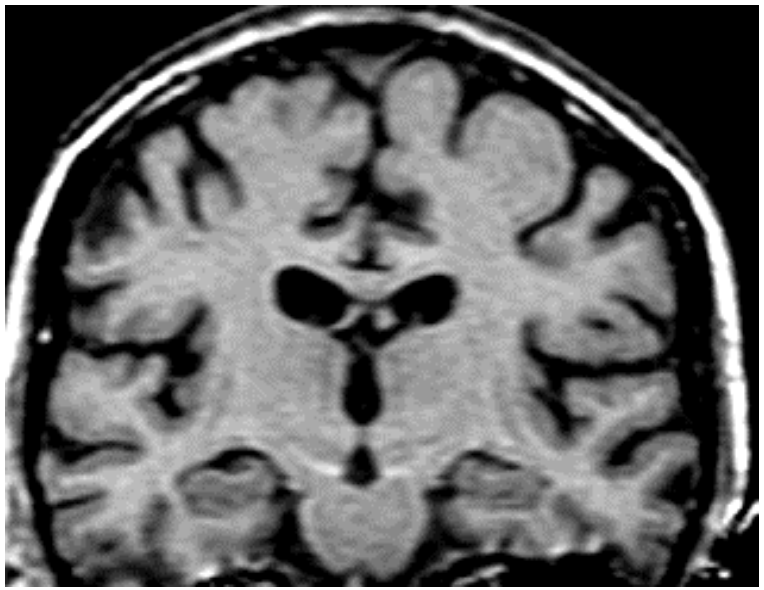
Amyloid ligands

- ^{11}C-Pittsburgh Compound B (PiB)
- Fluorine-18-labeled
  - ^{18}F-florbetapir
  - ^{18}F-flutemetamol
  - ^{18}F-florbetaben

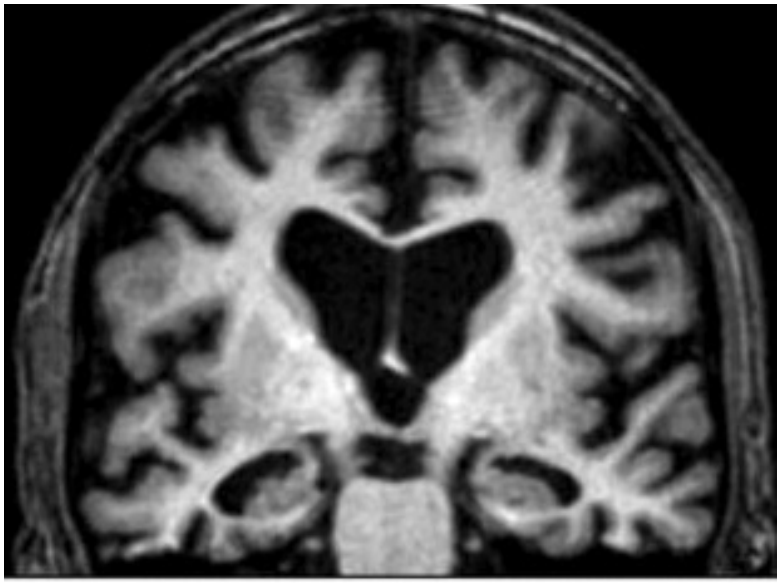
[1]Leinonen et al. Acta Neuropathologica Communications 2014

Topographical markers

Structural MRI



Normal

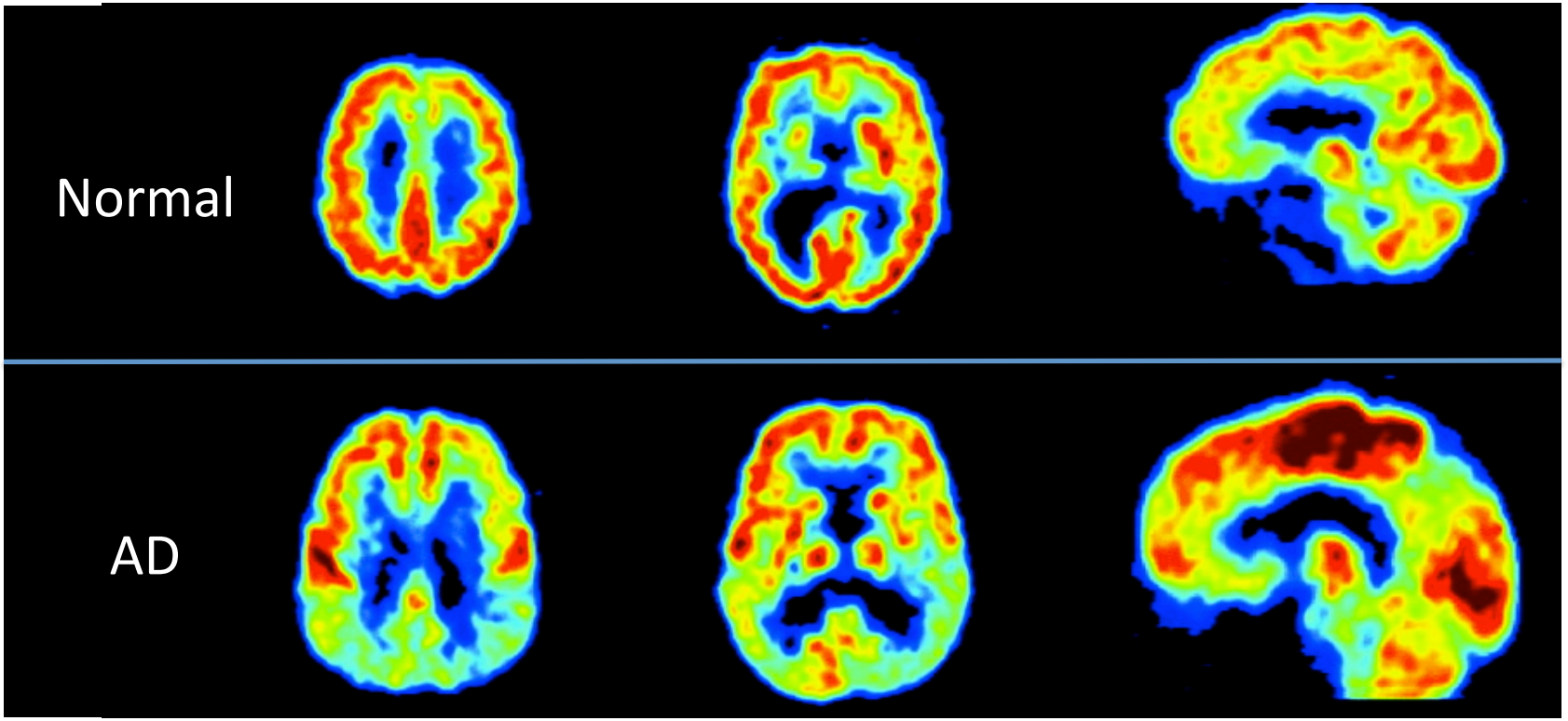


AD

Bilateral hippocampal atrophy

Topographical markers

FDG-PET imaging



Hypometabolism in lateral temporal-parietal, posterior cingulate, precuneus

Jagust W, et al. *Neurology* 2007; **69:** 871–77.

IWG criteria: New lexicon for AD, 2010

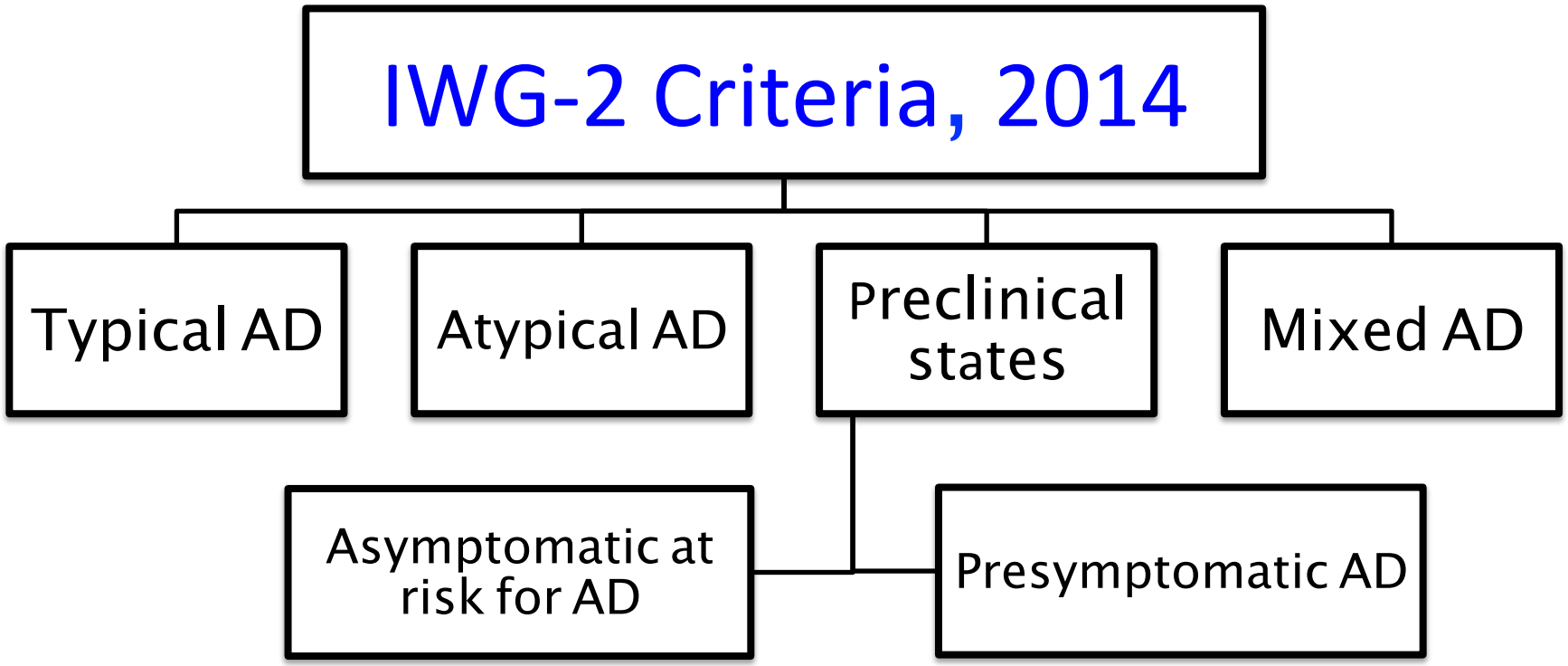
- Alzheimer's disease (AD)
- Prodromal AD (predementia stage): episodic memory loss, not effects function + AD biomarkers
- AD dementia: episodic memory loss, effects function + AD biomarkers
- Typical AD
- Atypical AD
- Mixed AD: AD + clinical/biomarkers of other disorders (Vascular/LBD)
- Preclinical states of AD
  - Asymptomatic at risk for AD: evidence of amyloidosis in the brain
  - Presymptomatic AD (will develop AD): monogenic AD mutation
- Alzheimer's pathology: SP, NFT, synaptic loss, vascular amyloid deposits
- Mild cognitive impairment:
  - Memory / not memory presentation
  - Absence of functional impairment
  - Negative/undone AD biomarkers

Dubois B et al. Lancet Neurol 2010;9(11):1118-27.

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

Lancet Neurol 2014; 13: 614–29

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



Dubois B et al. Lancet Neurol 2014; 13: 614–29.

IWG-2 Criteria, 2014

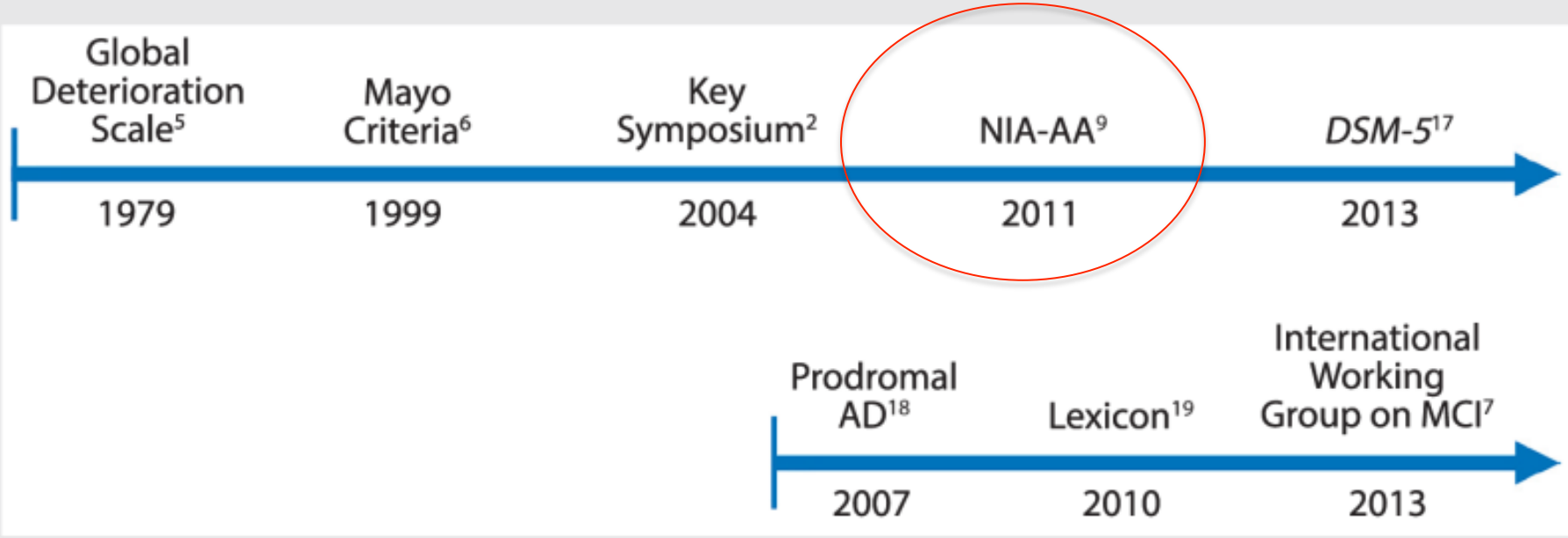
	Pathophysiological markers	Topographical markers
Cerebrospinal fluid		
Amyloid β_{42}	Yes	No
Total tau, phospho-tau	Yes	No
PET		
Amyloid tracer uptake	Yes	No
Fluorodeoxyglucose	No	Yes
Structural MRI		
Medial temporal atrophy	No	Yes

AD=Alzheimer's disease.

Table 1: **Categorisation of the current, most-validated AD biomarkers**

Dubois B et al. Lancet Neurol 2010;9(11):1118-27.

Temporal evolution of criteria for MCI



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DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; NIA-AA = National Institute on Aging–Alzheimer's Association.

Petersen RC. Continuum (Minneap Minn) 2016; 22(2): 404-18

ELSEVIER

Alzheimer's & Dementia 7 (2011)

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

1. Preclinical stages
2. MCI
3. Dementia

Due to AD

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]

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]

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

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], Creighton H. Phelps[w]

NIA-AA Criteria of MCI due to AD, 2011

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

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[p]*National Institute on Aging, Bethesda, MD, USA*

NIA-AA MCI due to AD criteria, 2011
incorporating biomarkers

Diagnostic category

1. MCI – core clinical criteria
2. MCI due to AD – intermediate likelihood
3. MCI due to AD – high likelihood
4. MCI – unlikely due AD

M.S. Albert et al. / Alzheimer's & Dementia 7 (2011) 270–279

NIA-AA MCI due to AD criteria, 2011 incorporating biomarkers

Biomarkers of Aβ deposition

- Low CSF Aβ42
- PET amyloid imaging

Biomarkers of neuronal injury

- Hight CSF tau/p-tau
- Structural MRI – medial temporal atrophy
- Functional imaging
  - FDG-PET imaging – hypometabolism
  - SPECT perfusion imaging - hypoperfusion

M.S. Albert et al. / Alzheimer's & Dementia 7 (2011) 270–279

NIA-AA MCI due to AD criteria, 2011 incorporating biomarkers

MCI likelihood due to AD	Evidence of Aβ42	Evidence of Neuronal Injury
Unknown	Not tested	Not tested
Low	Negative	Negative
Intermediate	Positive	Not tested
	Not tested	Positive
High	Positive	Positive

M.S. Albert et al. / Alzheimer's & Dementia 7 (2011) 270–279

DSM-5, 2013

Major neurocognitive disorder

A. Significant cognitive decline in ≥ 1 cognitive domains based on:
- Concern of the individual, informant, or clinician; and
- A substantial impairment in cognitive performance

B. Interfere with independence in everyday activities

C. Not delirium

D. Not better explained by another mental disorder

Minor neurocognitive disorder

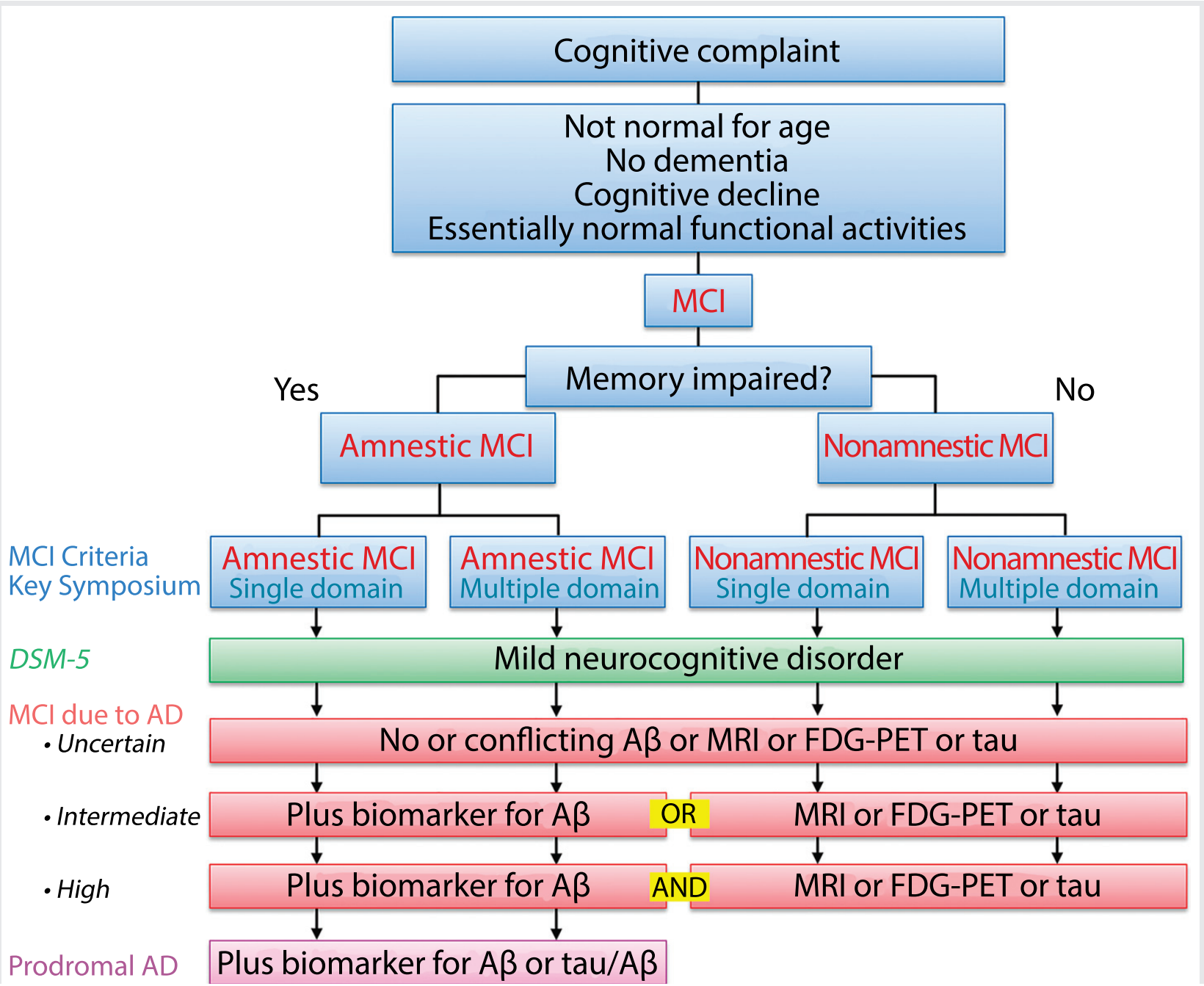
A. Modest cognitive decline in ≥ 1 cognitive domains based on:
- Concern of the individual, informant, or clinician
- A modest impairment in cognitive performance

B. Do not interfere with independence in everyday activities

C. Not delirium

D. Not better explained by another mental disorder

American Psychiatric Association. DSM-5, 2013.

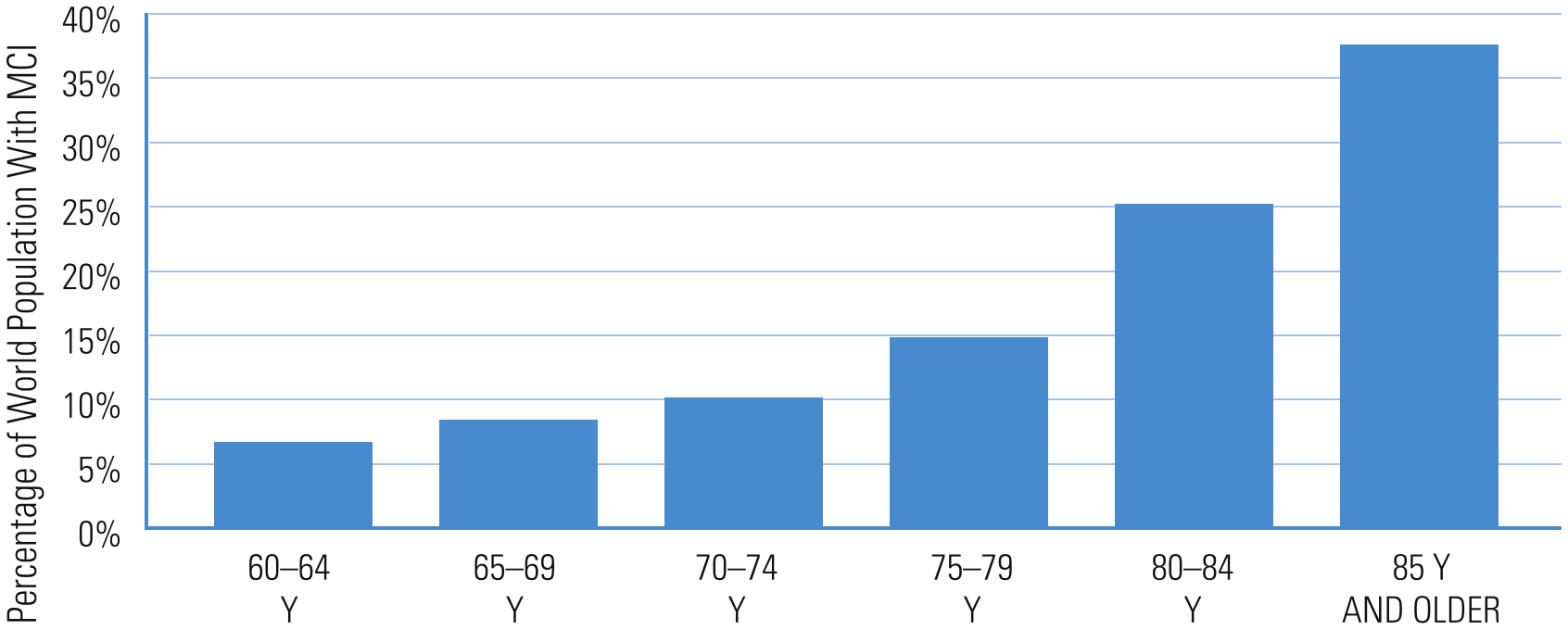


Petersen RC. Continuum (Minneap Minn) 2016; 22(2): 404-18

Non-degenerative/treatable etiologies of MCI

- Depression or other disorders of mood
- Medications: anticholinergics, antihistamines, benzodiazepines, and nonbenzodiazepine Z-class of sedative hypnotics
- Endocrine dysfunction: hypothyroidism
- Nutritional deficiency: vitamin B12 deficiency
- Alcohol and other recreational drug use
- Sleep disorders: OSA
- Other medical problems: uremia, hepatic encephalopathy

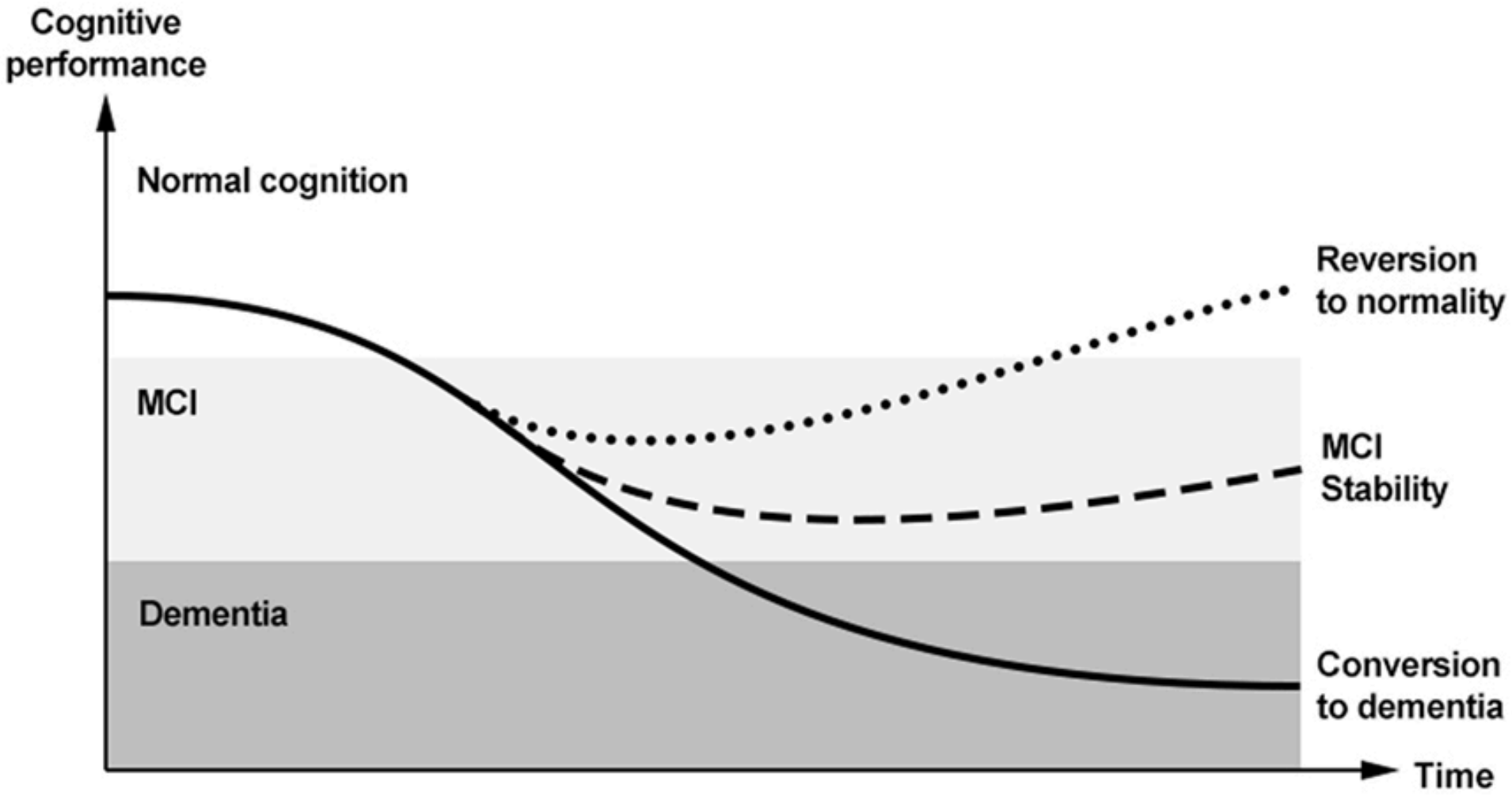
Prevalence of MCI



MCI is common starting at age 60 – 64 y
prevalence increases with age and lower educational level

Neurology® 2018;90:126-135

Prognosis of MCI



Front. Med., 30 October 2017

Reversion to normal aging

- In approximately 16% of individuals with MCI, cognition reverts to normal in a year.
- The predictors of reversions are
  - less severe symptoms
  - an absence of apolipoprotein E4 (ApoE4)
  - absence of involvement of episodic memory problems
  - attribution to a medical or psychiatric condition

MCI reversion group have higher change to develop dementia than normal aging

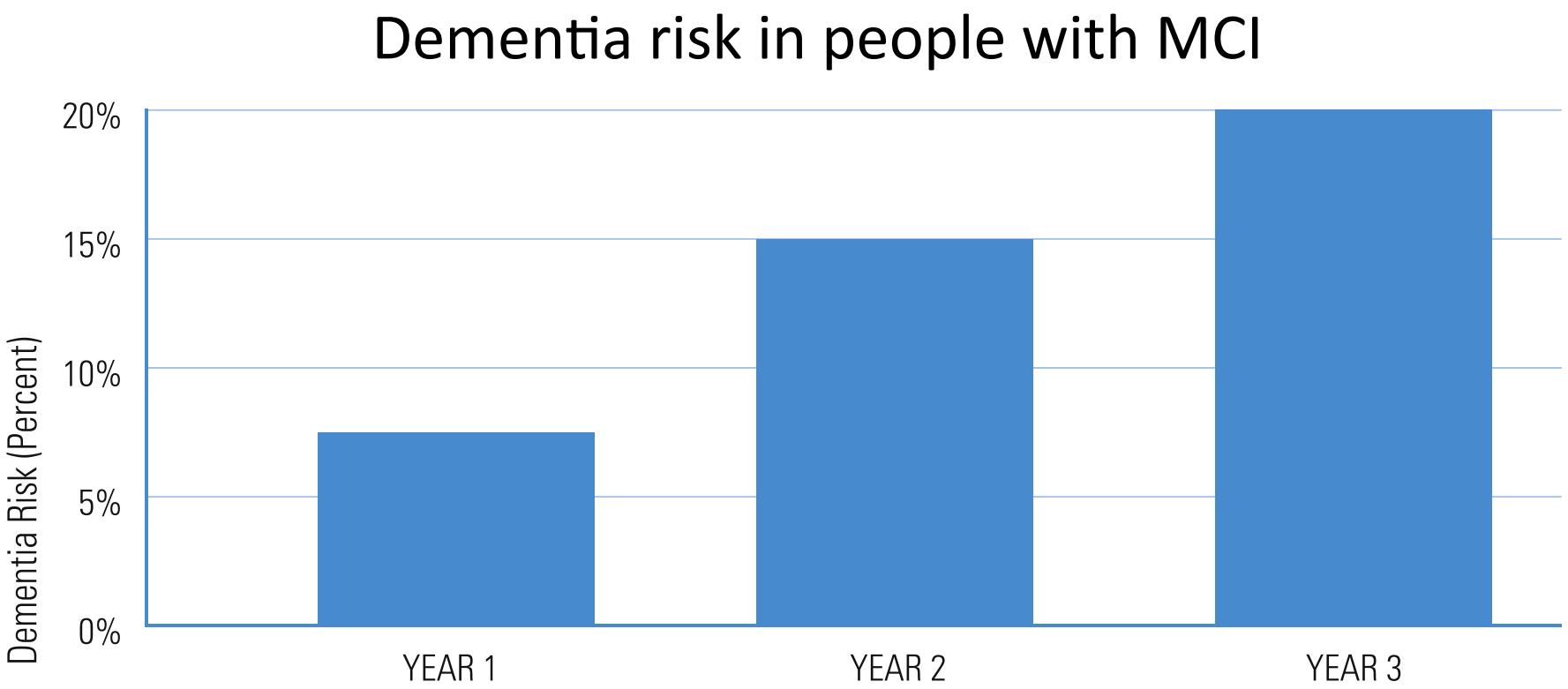
Koepsell TD, Monsell SE. Neurology 2012;79(15):1591–1598

MCI stability

- About 34% of individuals with MCI are cognitively stable at the end of 3 years after diagnosis.
- Predictors of stability include
  - better neuropsychological test results (especially in speed of mentation and memory recall)
  - younger age at diagnosis
  - an absence of ApoE4

Clem MA, et al. Cogn Behav Neurol 2017;30(01):8–15

Conversion to dementia



For MCI aged >= 65, dementia risk are
7.5% in the 1st year, 15% in the 2nd year and 20% risk in the 3rd year

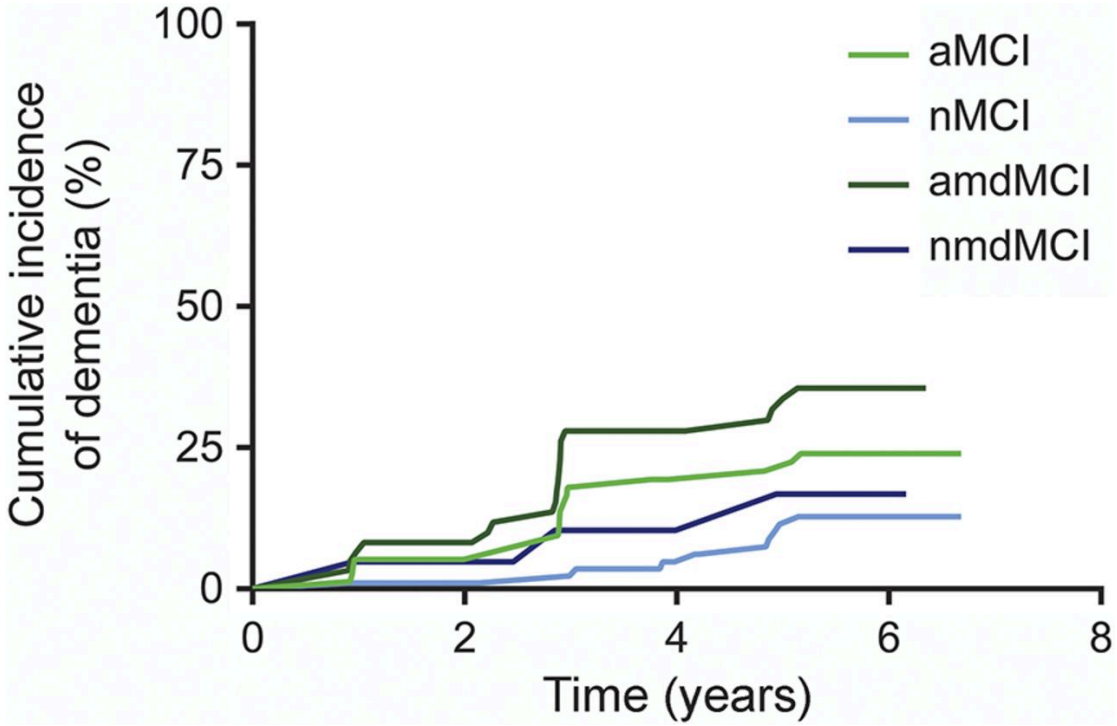
Neurology® 2018;90:126-135

Predictors of MCI progression

- MCI severity and subtype
- Cardiovascular risks factors
- Biomarkers of AD pathology
- Non-cognitive prodrome of dementia
  - Olfactory dysfunction
  - Slow gait – motoric cognitive risk syndrome

Predictors of MCI progression

- MCI severity and subtypes
  - Amnestic subtype

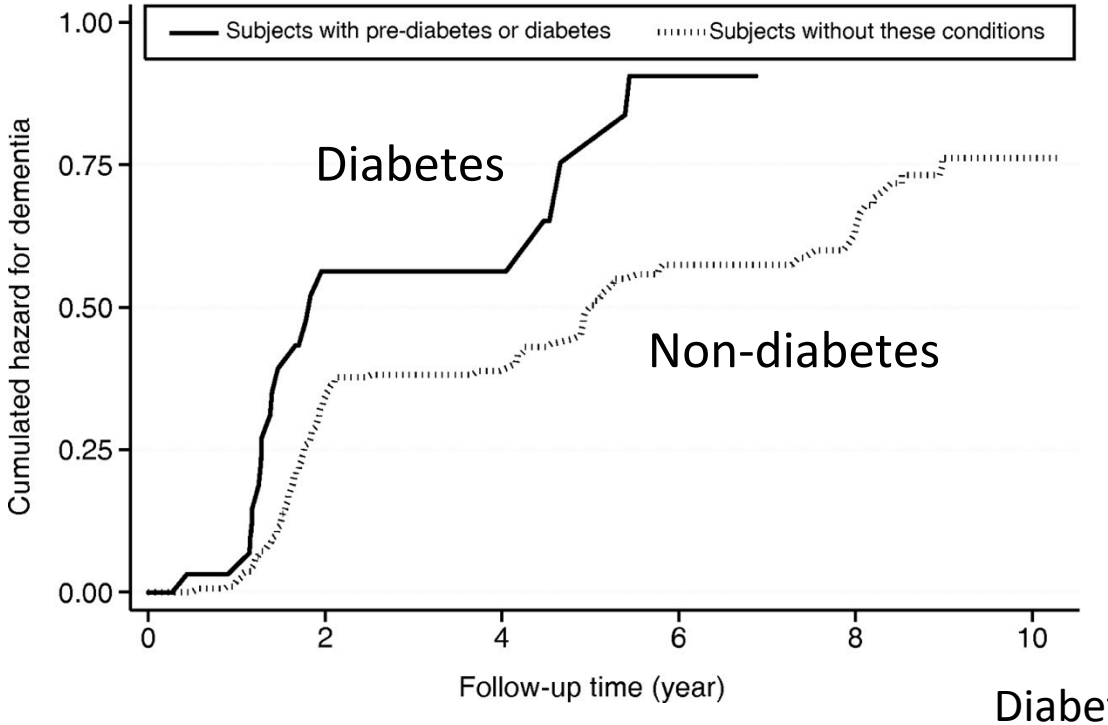


  - Severity of cognitive dysfunction (>1.5 SD)

Semin Neurol 2019;39:179–187. Liesbeth Aerts, et al. Neurology, June 06, 2017; 88

Predictors of MCI progression

- Cardiovascular risk factors
  - hypertension, diabetes, smoking, cerebrovascular disease, hypercholesterolemia, metabolic syndrome



Diabetes or pre-diabetes accelerated the progression from MCI to dementia by an average of 3.18 years

Diabetes 2010 Nov; 59(11): 2928-2935

Predictors of MCI progression

- Biomarkers of AD pathology
  - Genetic: ApoE4, AD mutation
  - CSF biomarkers
  - Neuroimaging
    - Structural MRI
    - FDG-PET, SPECT, fMRI
    - Amyloid

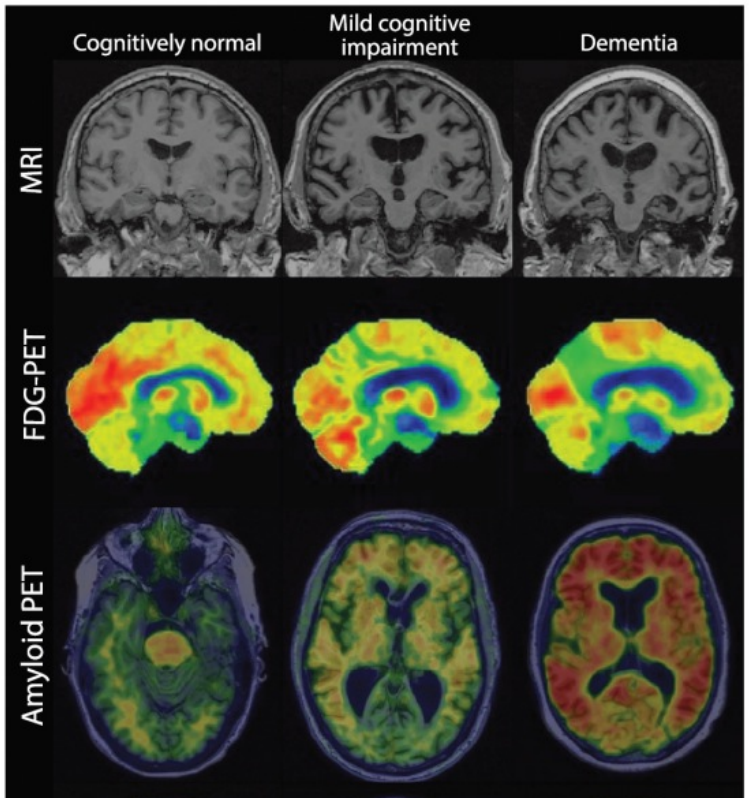
Apolipoprotein E (APOE) epsilon 4 (ε4)

- Carriers of ApoE4 genotype are more likely to progress rapidly
- However, ApoE4 can be found in normal individuals
- In clinical practice APOE testing does not add significantly to the diagnostic evaluation

Petersen RC. Continuum (Minneap Minn) 2016; 22(2): 404-18

Biomarkers of AD pathology

- CSF biomarkers
  - Low Aß42 levels
  - Elevated total tau and phosphorylated tau protein
  - Low ratio of Aß42 to tau
- Structural imaging
  - Temporal lobe and hippocampal atrophy
- Function imaging
  - FDG-PET: hypometabolism in temporal area
  - Amyloid PET: positive



MCI individuals with **one of the AD biomarkers** have an **increased risk for progressing** more rapidly than those subjects with the same clinical phenotype but normal biomarkers

Amyloid PET and CSF biomarkers in MCI

- Asymptomatic amyloid deposition is common in older (e.g., > 75 years) individuals and may not be related to a patient's presenting symptoms
- Positive result may cause psychological impact as predictive value is uncertain

Alzheimers Dement. 2013 Jan; 9(1): e–1-16.

Indication to use amyloid imgaing

a) A cognitive complaint with objectively confirmed impairment
b) Alzheimer's disease as a possible diagnosis, but when the diagnosis is uncertain after a comprehensive evaluation by a dementia expert
c) When knowledge of the presence or absence of amyloid-beta pathology is expected to increase diagnostic certainty and alter management.

Alzheimers Dement. 2013 Jan; 9(1): e–1-16.

Predictors of MCI progression

- Non-cognitive prodrome of dementia
  - Olfactory dysfunction
  - Motoric cognitive risk (MCR) syndrome

Original Investigation

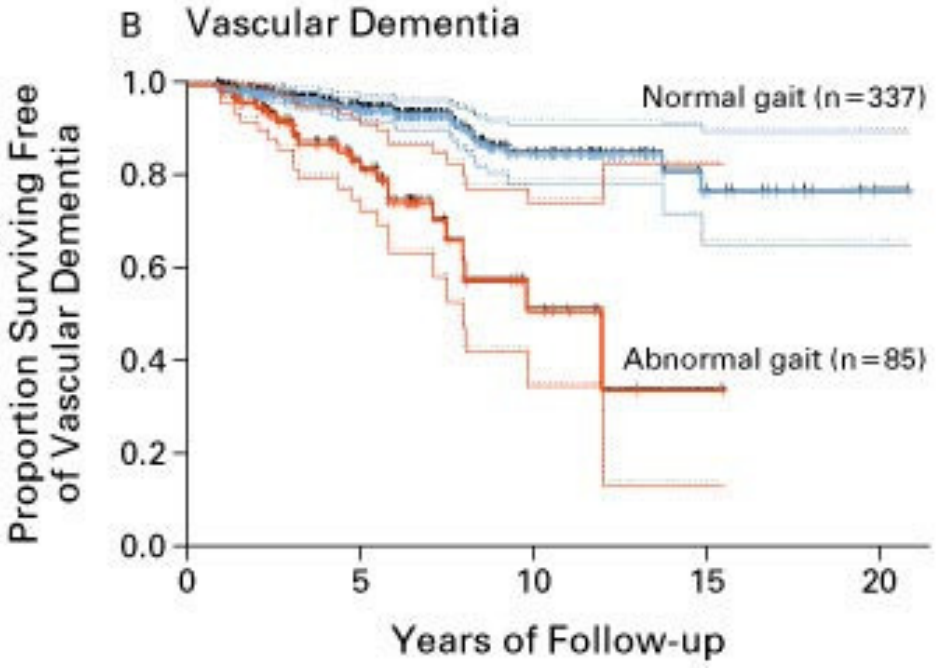
Association Between Olfactory Dysfunction and Amnestic Mild Cognitive Impairment and Alzheimer Disease Dementia

Rosebud O. Roberts, MB, ChB; Teresa J. H. Christianson, BS; Walter K. Kremers, PhD; Michelle M. Mielke, PhD; Mary M. Machulda, PhD; Maria Vassilaki, MD, PhD; Rabe E. Alhurani, MBBS; Yonas E. Geda, MD; David S. Knopman, MD; Ronald C. Petersen, MD, PhD

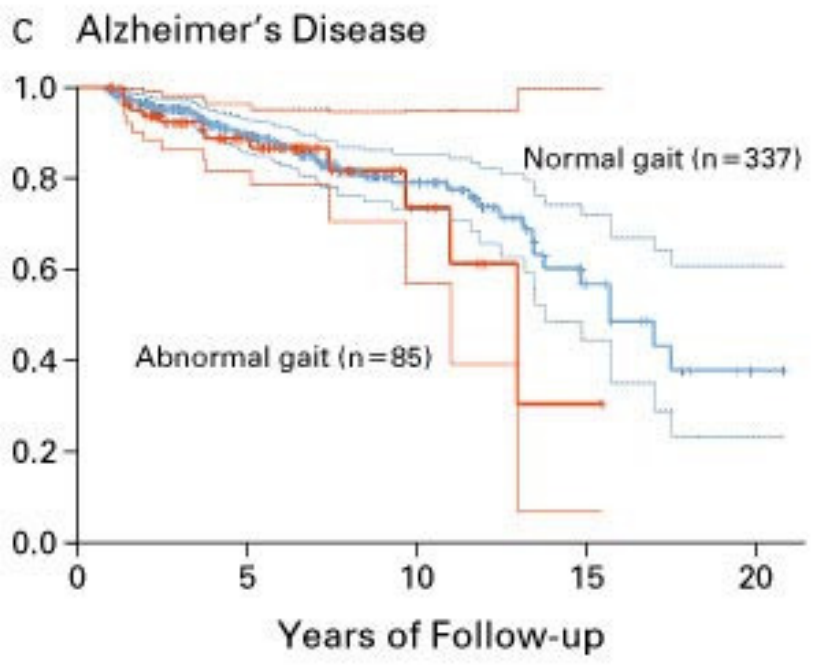
JAMA Neurol 2016; 73: 93-101

- Brief Smell Identification Test (BSIT) in adults aged 70-89
  - Normal baseline cognition (n=1430)
  - MCI (n=221)
- 3 years F/U: patients with amnestic MCI in the lowest quartile of olfactory function had 5-fold higher risk of progression to AD dementia compared with those in the highest quartile. (after adjusting for baseline cognitive scores and other risk factors)
- Olfactory dysfunction has been identified as a predictor of subsequent AD dementia, in both normal cognition / MCI

Abnormality of Gait as a Predictor of Non-Alzheimer's Dementia



hazard ratio, 3.46
[95% CI, 1.86 to 6.42]

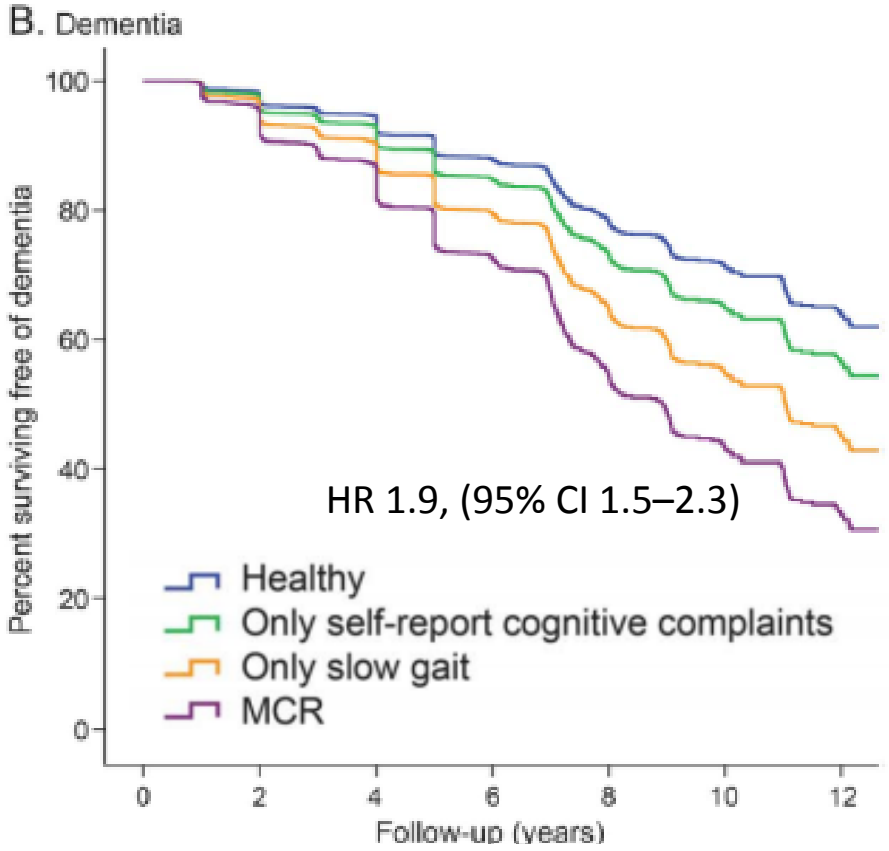


hazard ratio, 1.07
[95% CI, 0.57 to 2.02]

N Engl J Med. 2002 Nov 28;347(22):1761-8

Motoric cognitive risk (MCR) syndrome

- MCR syndrome = subjective cognitive complaints and slow gait > 1 SD
- The pooled prevalence of MCR among older adults is 9.7%
- MCR also predicted dementia in the pooled sample (adjusted Hazard Ratio 1.9)



Verghese J, et al. Neurology 2014; 83: 718-726

Treatment

- Pharmacological treatment
- Non-pharmacological treatment

SPECIAL ARTICLE LEVEL OF RECOMMENDATION

Practice guideline update summary: Mild cognitive impairment

Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology

Ronald C. Petersen, MD, PhD, Oscar Lopez, MD, Melissa J. Armstrong, MD, MSc, Thomas S.D. Getchius, Mary Ganguli, MD, MPH, David Gloss, MD, MPH&TM, Gary S. Gronseth, MD, Daniel Marson, JD, PhD, Tamara Pringsheim, MD, Gregory S. Day, MD, MSc, Mark Sager, MD, James Stevens, MD, and

Correspondence
American Academy of Neurology
guidelines@aan.com

Neurology® 2018;90:126-135

Evidence for pharmacological treatment for MCI

Table 1 Evidence and conclusions for pharmacol

Agent	Classification of evidence	
Donepezil	3 Class II studies (Petersen 2005,[e10] Doody 2009,[e11] Salloway 2004[e12])	
Galantamine	2 Class II studies (Winblad 2008,[e13] both studies reported in 1 article)	
Rivastigmine	1 Class II study (Feldman 2007[e14])	
Flavonoid-containing drink	1 Class II study (Desideri 2012[e15])	In patients with MCI, there is insufficient evidence to support or refute the cognitive
Homocysteine-lowering B vitamins	1 Class II study (Smith 2010[e16])	In patients with MCI, there is insufficient evidence to support or refute the use of homocysteine-lowering therapies in patients with MCI (very low confidence in the evidence based on a single Class II study with decreased confidence in the evidence owing to use of a primary endpoint with unclear clinical significance).
Transdermal nicotine patch	1 Class I study (Newhouse 2012[e9])	Six months of transdermal nicotine (15 mg/d) use possibly improves cognitive test performance but not Clinical Global Impression of Change in patients with aMCI who do not smoke (low confidence in the evidence based on 1 Class I study with decreased confidence in the evidence owing to uncertain clinical significance of the outcome of hit reaction time).
Piribedil	1 Class III study (Nagaraja 2001[e19])	Data are insufficient to support or refute an effect of piribedil on cognitive measures in MCI (very low confidence in the evidence based on 1 Class III study).
Rofecoxib[a]	1 Class II study (Thal 2005[e17])	Rofecoxib possibly increases the risk of progression to AD in patients with MCI (low confidence in the evidence based on 1 Class II study).
Tesamorelin injections	1 Class II study (Baker 2012[e18])	In patients with MCI, treatment with tesamorelin injections over 20 weeks is possibly effective to improve performance on various cognitive measures (low confidence in the evidence based on 1 Class II study).[b]
V0191	1 Class III study (Dubois 2012[e20])	Data are insufficient to support or refute an effect of V0191 use on ADAS-Cog response rates in patients with MCI (very low confidence in the evidence based on 1 Class III study).
Vitamin E	1 Class II study (Petersen 2005[e10])	In patients with MCI, use of vitamin E 2,000 IU daily is possibly ineffective for reducing progression to AD (low confidence in the evidence based on a single Class II study).
Vitamin E + vitamin C	1 Class III study (Naeini 2014[e21])	In patients with MCI, combined use of oral vitamin E 300 mg and C 400 mg daily over 12 months is of uncertain efficacy (very low confidence in the evidence based on 1 Class III study).

Cholinesterase inhibitors for mild cognitive impairment

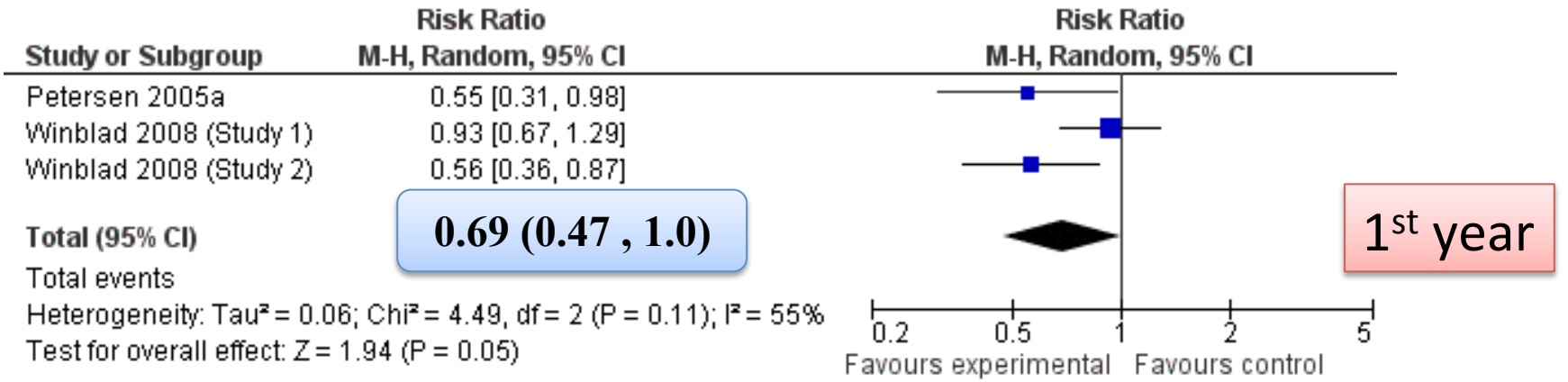
Russ TC, Morling JR

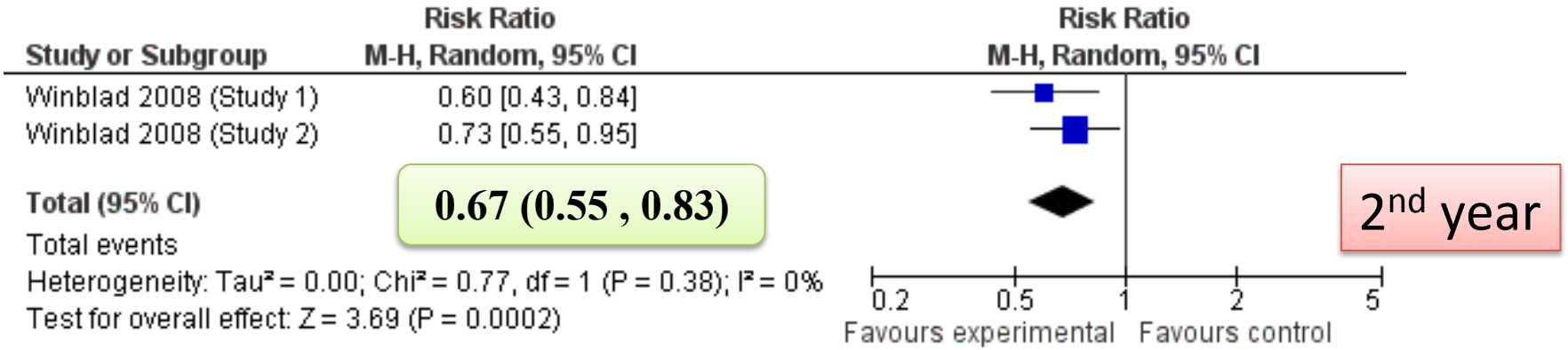
9 studies, 5149 MCI individuals

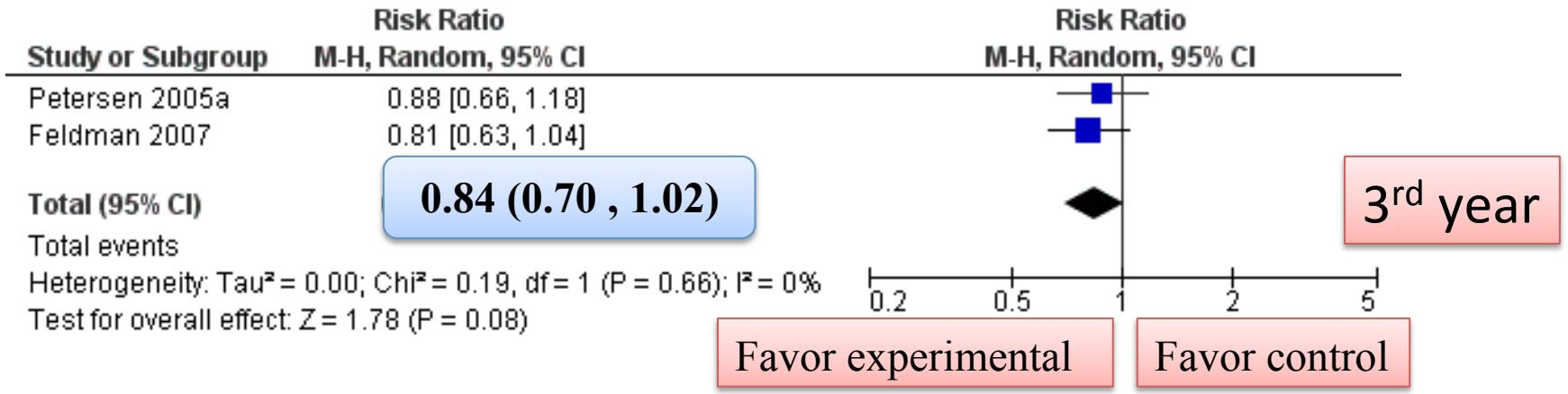
- 4 Donepezil
- 3 Galantamine
- 2 Rivastigmine

Cochrane Database of Systematic Reviews 2012, Issue 9

MCI conversion to dementia in 1, 2 and 3 years







Favor experimental

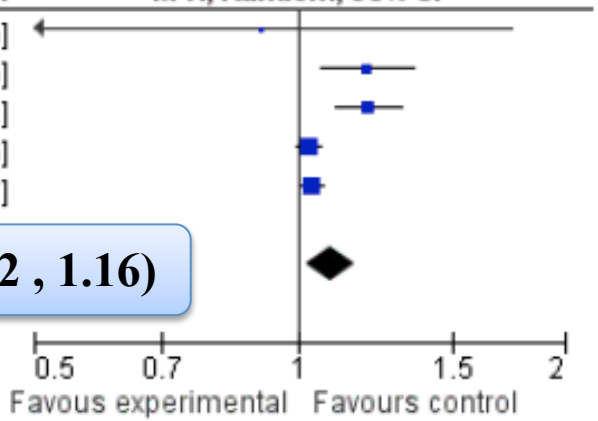
Favor control

Any adverse events

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Narasimhalu 2010	10	25	11	25	0.9%	0.91 [0.47, 1.75]
Salloway 2004	116	133	100	137	15.3%	1.19 [1.06, 1.35]
Doody 2009	318	409	267	412	20.7%	1.20 [1.10, 1.31]
Feldman 2007	483	508	472	510	31.5%	1.03 [1.00, 1.06]
Winblad 2008 (combined)	922	1026	887	1022	31.5%	1.04 [1.00, 1.07]
Total (95% CI)		**2101**		**2106**	**100.0%**	**1.09 (1.02 , 1.16)**
Total events	1849		1737			

Heterogeneity: Tau² = 0.00; Chi² = 19.32, df = 4 (P = 0.0007); I² = 79%

Test for overall effect: Z = 2.57 (P = 0.01)

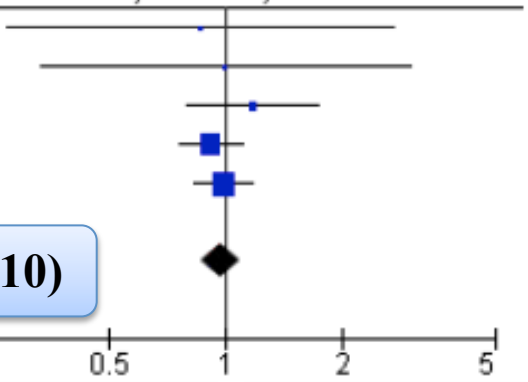


Serious adverse events

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Salloway 2004	5	133	6	137	1.1%	0.86 [0.27, 2.75]
Narasimhalu 2010	5	25	5	25	1.2%	1.00 [0.33, 3.03]
Doody 2009	48	409	41	412	9.8%	1.18 [0.80, 1.75]
Feldman 2007	141	508	155	510	41.0%	0.91 [0.75, 1.11]
Winblad 2008 (combined)	192	1026	194	1022	46.9%	0.99 [0.82, 1.18]
Total (95% CI)		**2101**		**2106**	**100.0%**	**0.97 (0.86 , 1.10)**
Total events	391		401			

Heterogeneity: Tau² = 0.00; Chi² = 1.41, df = 4 (P = 0.84); I² = 0%

Test for overall effect: Z = 0.47 (P = 0.64)



Cochrane Database of Systematic Reviews 2012, Issue 9

Cholinesterase inhibitors (ChEIs) for MCI

- No strong evidence of a beneficial effect on the progression to dementia at one, two or three years (only two studies reported reduced risk ratio for conversion at two years)
- No effect on cognitive test scores
- More adverse events in the ChEIs groups
  - GI: diarrhea, nausea, vomiting
  - Other: leg cramps/muscle spasm, headache, syncope or dizziness, insomnia, abnormal dream
- But no more serious adverse events or deaths
  - Cardiac problems were no more likely in either group

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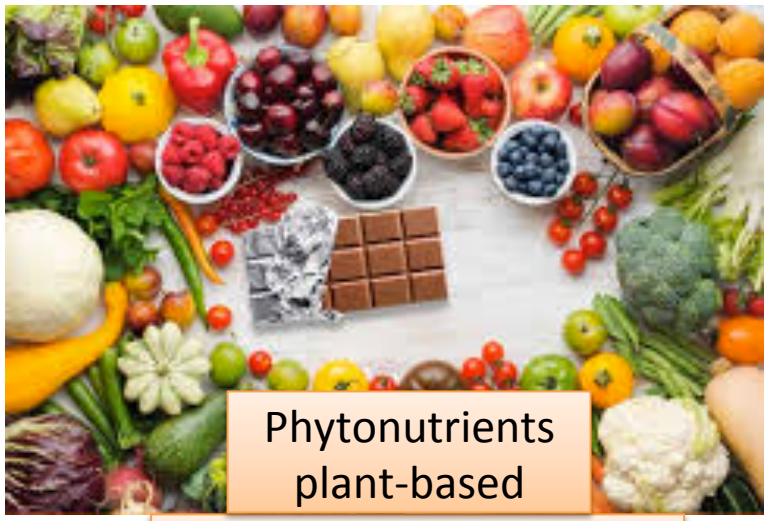
Flavonoid-containing drink



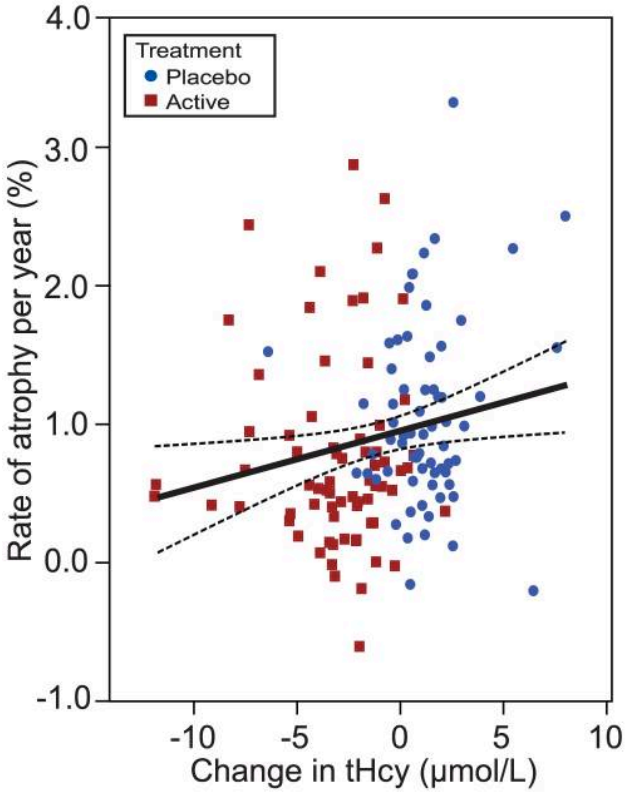
- 90 elderly with MCI randomized cocoa flavanols for 8 weeks
  - High dose = 990 mg/d
  - Intermediate dose = 520 mg/d
  - Low dose = 45 mg/d of
- High flavanols group had significant better score on Trail Making Test A, TMT B and verbal fluency test

- However, there is insufficient evidence to support or refute the cognitive benefits of a drink with high-dose flavonoids with very low confidence in the evidence based on a single Class II study with CIs including unimportant effects

Desideri et al, Hypertension. 2012 Sep;60(3):794-801.

Homocysteine-lowering B vitamins

- Homocysteine is a risk factor for brain atrophy, cognitive impairment and dementia
- B vitamins can reduce plasma homocysteine
- 168 MCI participants x 24 months
  - 85 in active treatment group
    (folic acid, vitamin B12, vitamin B6)
  - 83 receiving placebo
- Mean rate of brain atrophy per year
  - 0.76% [0.63–0.90] in active group
  - 1.08% [0.94–1.22] in the placebo group
    (P = 0.001)
- Homocysteine lowering B vitamins may reduce rate of brain atrophy in MCI

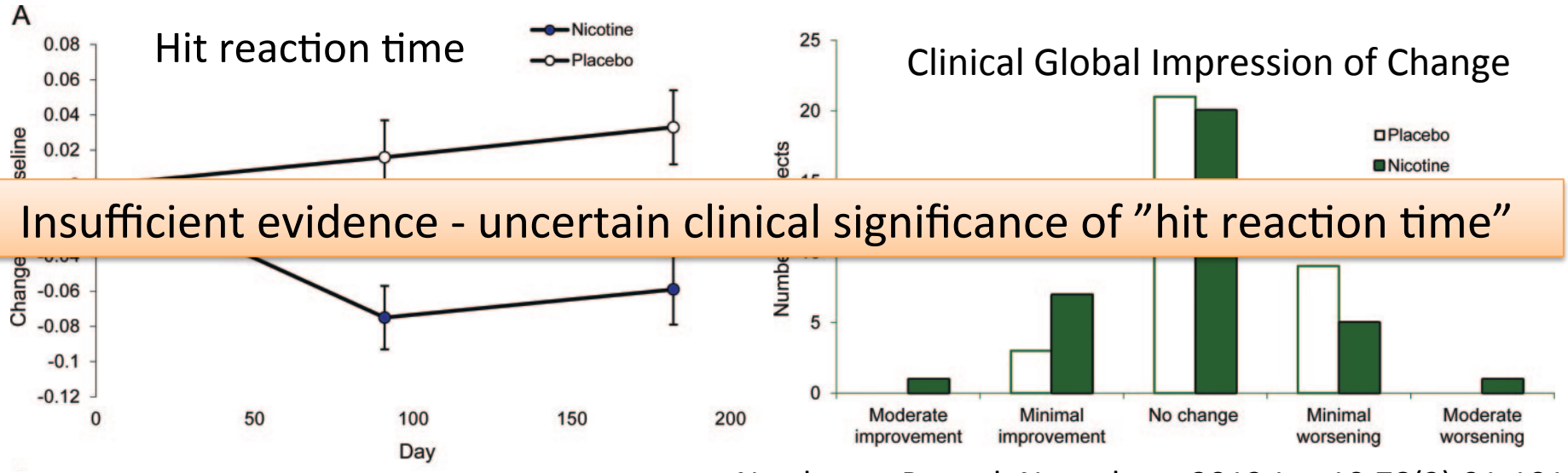


- Insufficient evidence and unclear clinical significance.

Smith AD, et al. PLoS One. 2010 Sep 8;5(9):e12244

Transdermal nicotine patch

- Nicotine improves performance in smokers on cognitively demanding attentional tasks
- Nicotine improved cognitive function in AD subjects
- 64 nonsmoking, amnestic MCI were randomized to
  - 34 transdermal nicotine (15 mg /d) vs 33 placebo x 6 months
- Active group possibly improves cognitive test performance (hit reaction time) but not Clinical Global Impression of Change



Insufficient evidence - uncertain clinical significance of ”hit reaction time”

Newhouse P, et al. Neurology. 2012 Jan 10;78(2):91-101

The American Journal of Psychiatry

Piribedil = Dopamine agonist

From: Randomized Study of the Dopamine Receptor Agonist Piribedil in the Treatment of Mild Cognitive Impairment

American Journal of Psychiatry 2001 Sep;158(9):1517-9

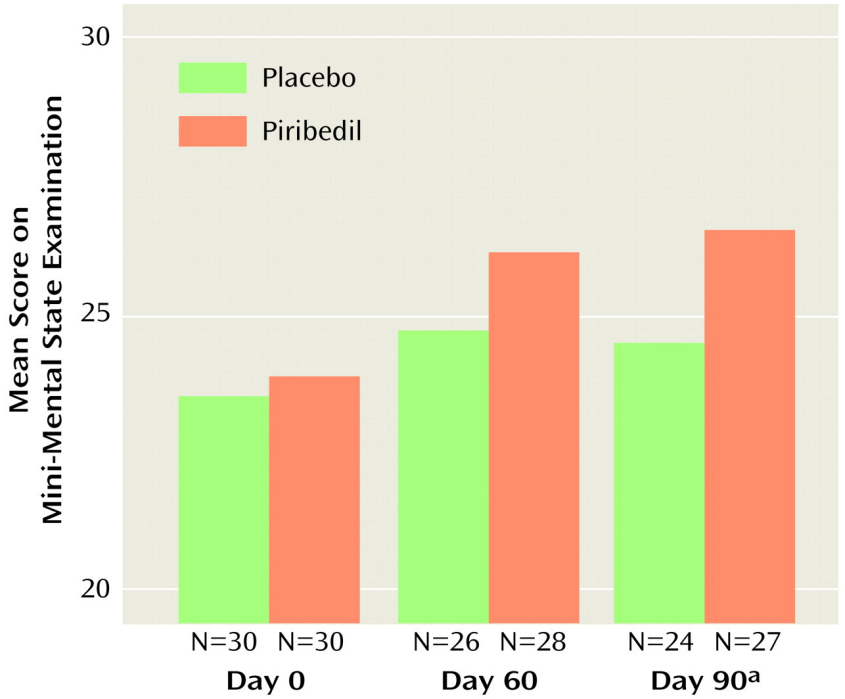
Age-related decrease in dopamine D(2) receptors is associated with cognitive decline in healthy elderly individuals

90-day randomized double-blind study in 60 MCI baseline MMSE 21-25
piribedil (50 mg/d) vs placebo

19 (63.3%) of piribedil group and eight (26.7%) of placebo had increases in MMSE scores, to 26 or more.

The response rate and the mean increase in MMSE scores were significantly greater with piribedil.

Data are insufficient, very low confidence in the evidence based on 1 Class III study



Significant group effect on change from day 0 ($t=2.83$, $df=49$, $p<0.01$).

Rofecoxib – selective COX-2 inhibitors

- Inflammatory mechanisms have been implicated in AD and might be mediated via the COX-2 enzyme.
- 4-year randomized controlled study of MCI patients aged > 65
  - Rofecoxib 25 mg daily (N = 725) vs placebo (N= 732)
- The estimated annual AD diagnosis rate was
  - 6.4% in the rofecoxib group
  - 4.5% in the placebo group (p = 0.011)
- No difference in cognitive outcome and global function
- Rofecoxib possibly increases the risk of progression to AD in patients with MCI

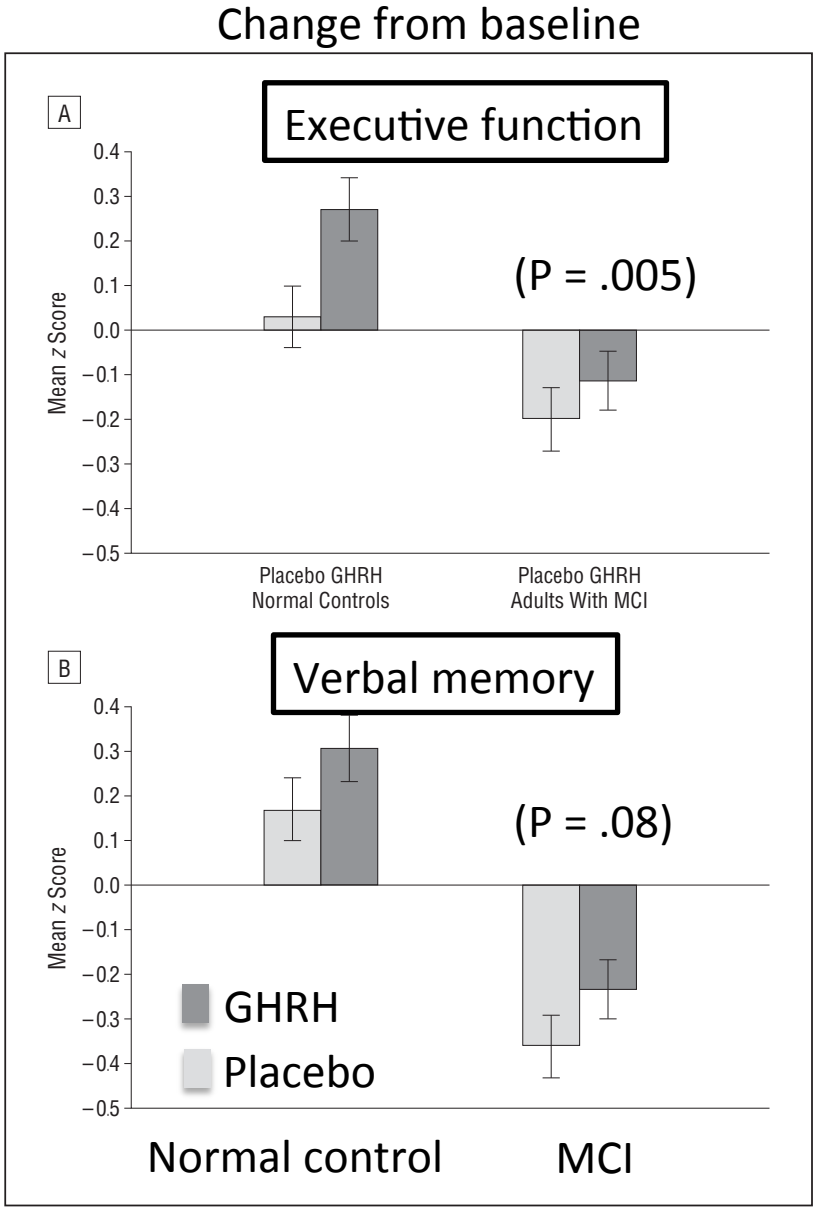
Neuropsychopharmacology. 2005 Jun;30(6):1204-15.

Tesamorelin injections

- Growth hormone–releasing hormone (GHRH) have potent effects on brain function, their levels decrease with advancing age

- 61 amnestic MCI (GHRH vs placebo)
- Treatment with tesamorelin (GHRH) (1 mg/d) over 20 weeks is possibly effective to improve performance on executive function and verbal memory

- Low confidence in the evidence based on 1 Class II study.



Baker, L. D., et al Archives of Neurology, 69(11), 1420.

Vitamin E

The NEW ENGLAND JOURNAL of MEDICINE

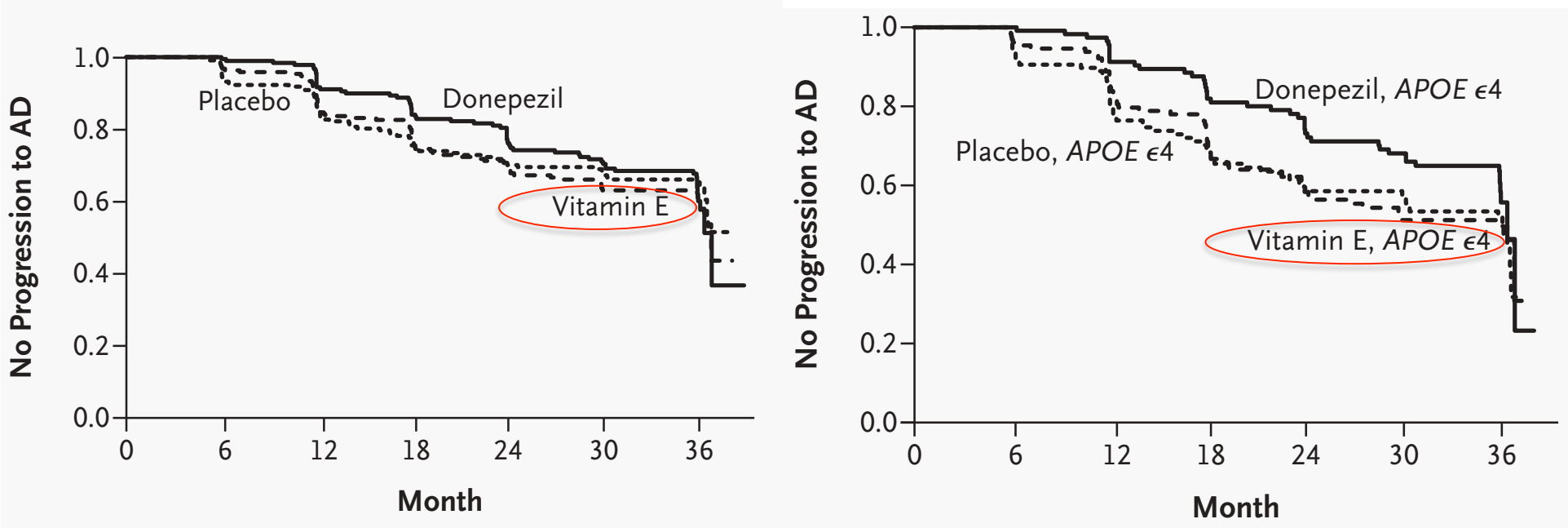
ESTABLISHED IN 1812 JUNE 9, 2005 VOL. 352 NO. 23

Vitamin E and Donepezil for the Treatment of Mild Cognitive Impairment

Ronald C. Petersen, Ph.D., M.D., Ronald G. Thomas, Ph.D., Michael Grundman, M.D., M.P.H., David Bennett, M.D., Rachelle Doody, M.D., Ph.D., Steven Ferris, Ph.D., Douglas Galasko, M.D., Shelia Jin, M.D., M.P.H., Jeffrey Kaye, M.D., Allan Levey, M.D., Ph.D., Eric Pfeiffer, M.D., Mary Sano, Ph.D., Christopher H. van Dyck, M.D., and Leon J. Thal, M.D., for the Alzheimer's Disease Cooperative Study Group*

Vitamin E is the most potent lipophilic chain- breaking antioxidant

769 amnestic MCI aged 55-90 were randomly assigned to receive 2000 IU of vitamin E daily, 10 mg of donepezil daily, or placebo for three years.



Vitamin E had no benefit for reducing progression to AD in overall and APOE4 carriers

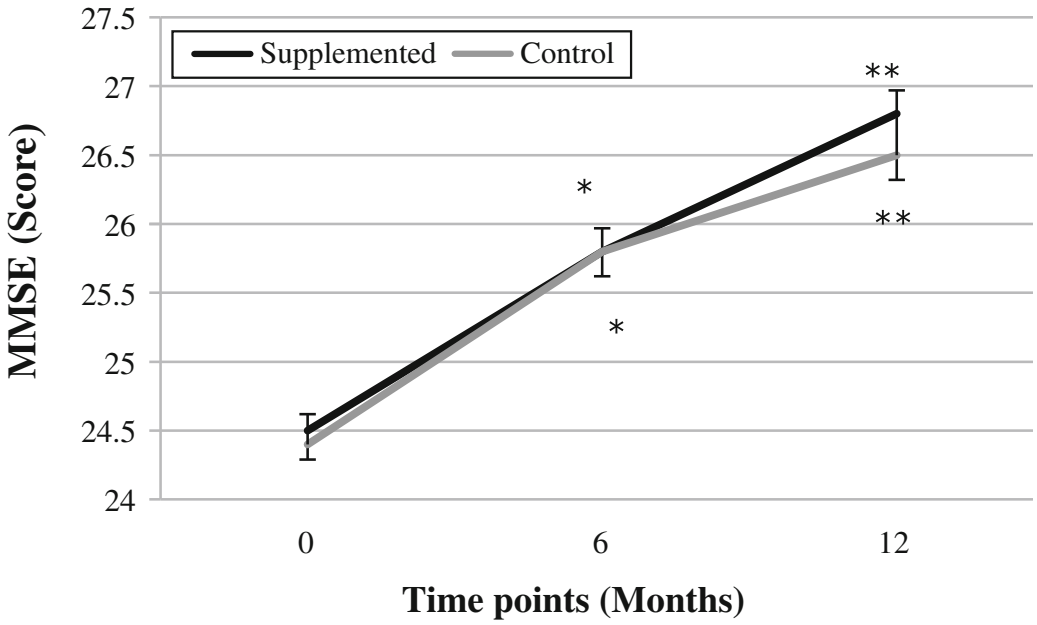
Peterson, et. al. 2005. N Engl J Med. 2005 Jun 9;352(23):2379-88

Vitamin E + vitamin C

Vitamins E and Vitamin C (potent antioxidant) are expected to reduce neuronal damage

256 elderly with MCI, aged 60–75 years, received vitamin E 300 mg + vitamin C 400 mg/d vs placebo for 12 months

After adjusting for the covariates effects, MMSE scores following 6- and 12-month antioxidant supplementation did not differ from control group



Alavi Naeini, A. M., et al. 2013. European Journal of Nutrition, 53(5), 1255–1262.

Pharmacological treatment

- Currently, there are no approved medications for the treatment of MCI.

- Numerous studies of pharmacologic or dietary agents show no benefit either improve cognition or delay progression in patients with MCI.

Neurology® 2018;90:126-135

Non-pharmacological treatment

- Exercise
- Cognitive intervention
- Mediterranean diet

A Randomized Controlled Trial of Multicomponent Exercise in Older Adults with Mild Cognitive Impairment

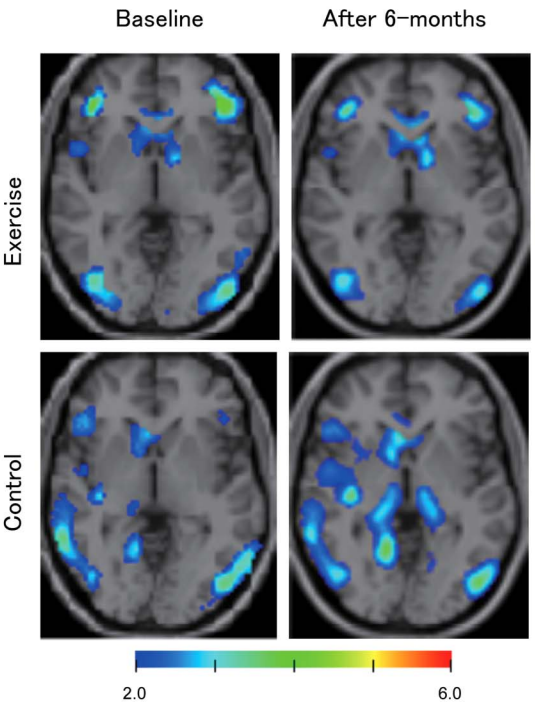
Takao Suzuki[1]*, Hiroyuki Shimada[2], Hyuma Makizako[2], Takehiko Doi[2], Daisuke Yoshida[2], Kengo Ito[3], Hiroshi Shimokata[4], Yukihiko Washimi[5], Hidetoshi Endo[6], Takashi Kato[3] PLoS ONE 2013;8:e61483.

100 subjects with MCI (50 aMCI) mean age, 75 years

90-min x 2 days/week for 6 months

aerobic exercise, muscle strength training, postural balance retraining, dual-task training

	aMCI subjects (n = 50)				
	Mean Difference From Baseline (95% CI) in aMCI Group		*P* Value ANOVA for Repeated Measures		
	Exercise Group (n = 24)	Control Group (n = 23)	Group	Time	Group × time interaction
MMSE	0.3 (−0.8, 1.3)	−1.4 (−2.5, −0.3)	0.03	0.14	.04[b]
ADAS-cog	−1.2 (−2.1, −0.3)	−0.1 (−1.0, 0.8)	0.1	0.06	0.1
WMS-LM I	3.8 (1.6, 5.9)	0.5 (−1.6, 2.7)	0.14	<.01	.04[a]
WMS-LM II	3.8 (1.8, 5.7)	2.1 (0.1, 4.2)	0.11	<.01	0.26
MTA-ERC	0.1 (0, 0.2)	0 (−0.1, 0.1)	0.91	0.03	0.27
WBC	−0.1 (−0.8, 0.6)	0.9 (0.2, 1.6)	0.86	0.08	<.05[b]



Exercise improved logical memory and maintaining general cognitive function and reducing whole brain cortical atrophy in older adults with amnestic MCI

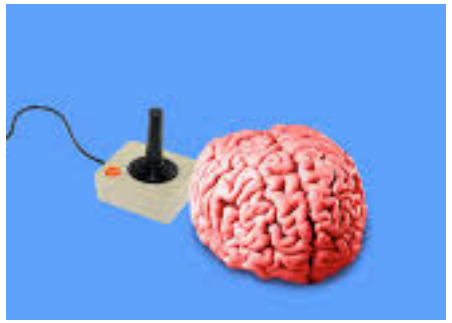
Arch Intern Med. 2012 April 23; 172(8): 666–668. doi:10.1001/archinternmed.2012.379.

Resistance training promotes cognitive and functional brain plasticity in seniors with probable mild cognitive impairment: A 6-month randomized controlled trial

Lindsay S. Nagamatsu, MA[1,2,3], **Todd C. Handy, PhD**[1,2], **C. Liang Hsu, BSc**[2,3,4], **Michelle Voss, PhD**[5], and **Teresa Liu-Ambrose, PT, PhD**[2,3,4]

- 86 MCI aged 70–80 years
- Exercise 60 min x 2 days/week for 26 weeks
    1. Resistance training (RT; n=28)
    2. Aerobic training (AT; n=30)
    3. Balance and tone training (control) (BAT; n=28)
- Compared with BAT, RT group significantly improved on the Stroop Test (p=0.04) and associative memory task (p=0.03)
- Twice-weekly resistance training is a promising strategy to alter the trajectory of cognitive decline in seniors with MCI.

Cognitive Intervention



- Cognitive stimulation (CS)
  - social and cognitive activities to stimulate multiple cognitive domains
- Cognitive training (CT)
  - repeated practice of standardized tasks targeting a specific cognitive function
- Cognitive rehabilitation (CR)
  - takes a person-centred approach
  - target impaired function activity planning
  - training in self-assertiveness, stress management, relaxation techniques
  - the use of external memory aids, memory training

Cognitive intervention in MCI

- There is insufficient evidence to support or refute the use of any individual cognitive intervention strategy
- Cognitive interventions may improve select measures of cognitive function
  - improvements in strategy knowledge, internal strategy use, and well-being but not external strategy or memory (Kinsella 2016e25)
  - improvement on multiple cognitive measures (Tsolaki 2011)
  - improvement on the MMSE but with some limitations (Nakatsuka 2015)
  - improvements in the integrated cognitive–physical training groups when considering the ADAS- Cog, fluency, and recall in patients with single-domain MCI and fluency in patients with multidomain MCI but no differences when all patients with MCI are considered (Lam 2015)

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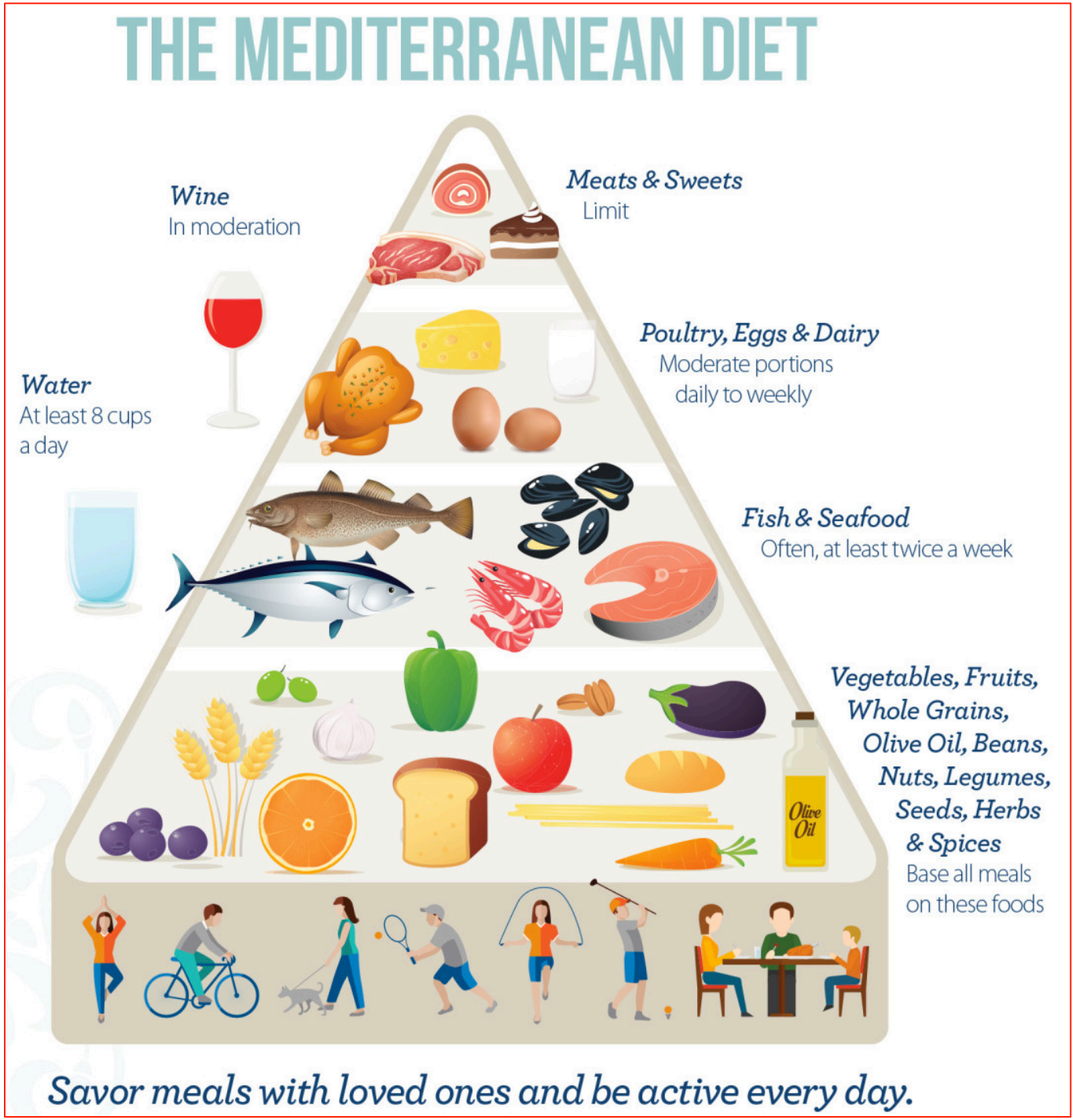
THE MEDITERRANEAN DIET

Greece, southern Italy, France, and Spain.



Association of Mediterranean Diet with Mild Cognitive Impairment and Alzheimer's Disease: A Systematic Review and Meta-Analysis

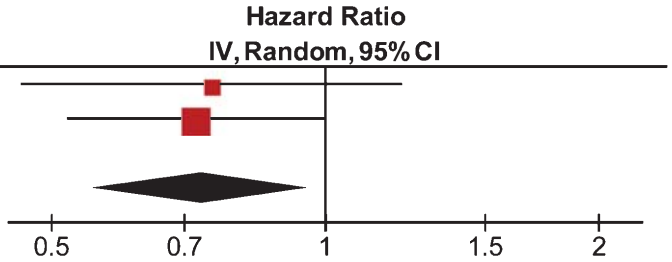
High adherence vs low adherence to Mediterranean diet

2.3 Highest vs Lowest MeDi tertile

Cognitively normal → MCI

Study or Subgroup	log[Hazard Ratio]	SE	MCI Total	CN Total	Weight	Hazard Ratio IV, Random, 95% CI
Roberts 2010	-0.2889	0.2467	93	1141	31.4%	0.75 [0.46, 1.21]
Scarmeas 2009 MCI	-0.3285	0.1668	241	1199	68.6%	0.72 [0.52, 1.00]
Total (95% CI)			**334**	**2340**	**100.0%**	**0.73 [0.56, 0.96]**

Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.89); I² = 0%
Test for overall effect: Z = 2.29 (P = 0.02)

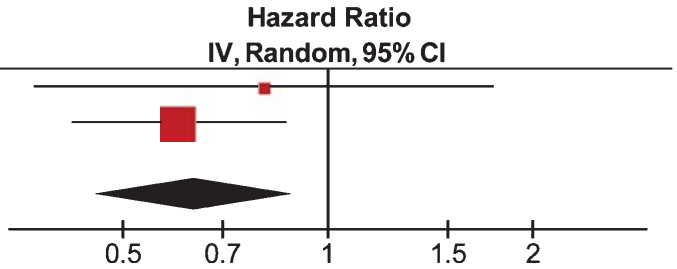


3.3 Highest vs Lowest MeDi tertile

Cognitively normal → Alzheimer's disease

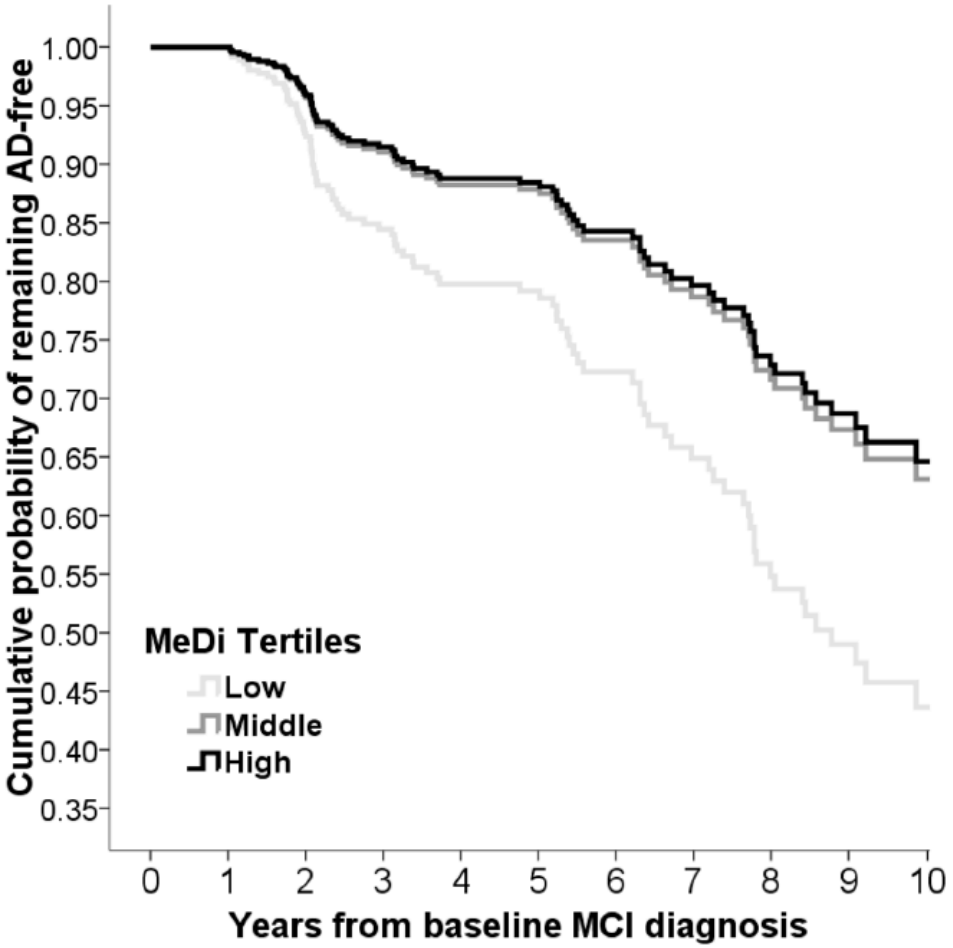
Study or Subgroup	log[Hazard Ratio]	SE	AD Total	CN Total	Weight	Hazard Ratio IV, Random, 95% CI
Feart 2009	-0.2169	0.3966	51	1410	18.0%	0.81 [0.37, 1.75]
Scarmeas 2006	-0.5034	0.1858	219	1759	82.0%	0.60 [0.42, 0.87]
Total (95% CI)			**270**	**3169**	**100.0%**	**0.64 [0.46, 0.89]**

Heterogeneity: Tau² = 0.00; Chi² = 0.43, df = 1 (P = 0.51); I² = 0%
Test for overall effect: Z = 2.69 (P = 0.007)



Journal of Alzheimer's Disease 39 (2014) 271–282

Mediterranean diet and progression from MCI to AD



Higher adherence to the Mediterranean diet is associated with a trend for reduced risk for MCI conversion to AD.

Scarmeas N, et al. Arch Neurol 2009; 66(2): 216-25

Non-pharmacological treatment

- Exercise
  - Exercise training (60-90 min x 2 d/wk) for 6 months is likely to improve cognitive measures
  - Exercise also has general health benefits and generally limited risk
- Cognitive intervention
  - Cognitive interventions may be beneficial in improving measures of cognitive function.
  - It is good practice to offer non-medication approaches to care.
- Mediterranean diet
  - Higher adherence to the Mediterranean diet is associated with a reduced risk of developing MCI and AD, and a reduced risk of progressing from MCI to AD

Practical points in diagnosis MCI

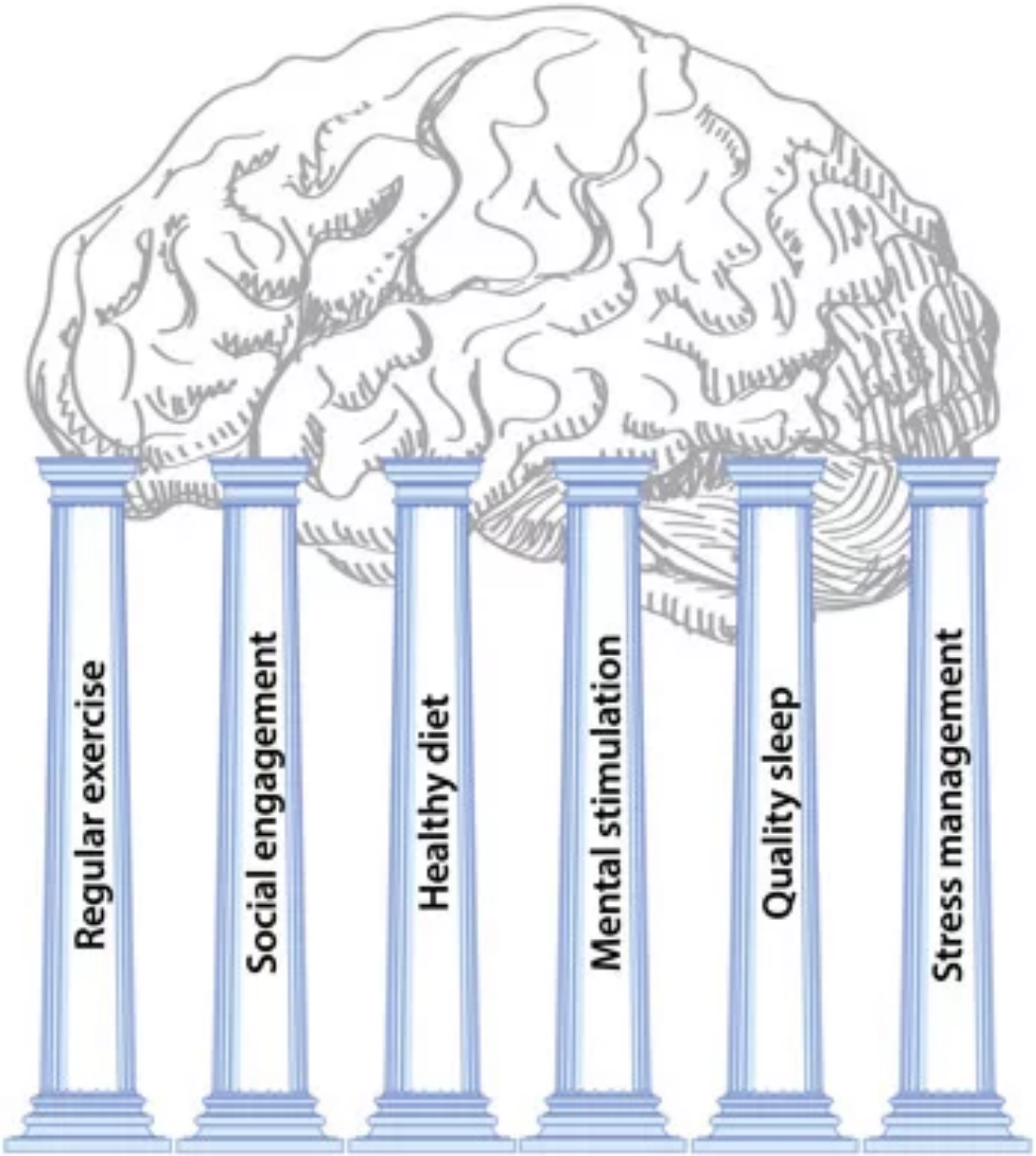
- Don't ignore subjective cognitive concerns
- Assess for objective cognitive impairment using validated tools
- Assess for functional impairment related to cognition
- Perform clinical assessment for diagnosis of MCI and evaluate for MCI risk factors/causes that are modifiable/treatable.
  - Physical examination, investigation (blood test, neuroimaging,…)
- There are no accepted biomarkers for clinical use in MCI available at this time. (only for research purpose)
- Perform serial assessments over time to monitor for changes in cognitive status

Practical points for MCI Management

- Wean patients from medications that can contribute to cognitive impairment
- Treat modifiable risk factors/ cardiovascular risk factors to prevent stroke and brain injury
- Treat treatable causes
  - OSA
  - Depression, anxiety,.. but avoid antidepressant with anticholinergic property
  - Other..
- Choose not to offer cholinesterase inhibitors or other cognitive enhancers (off-label prescription no empirical evidence)

Practical points for MCI Management

- Lifestyle modification
  - Regular exercise (twice per week)
  - Stop smoking
  - Avoid heavy alcohol or illicit drug use
  - Mediterranean diet
  - Cognitive interventions
  - Social engagement / encourage mental activity
- Patient education
  - No pharmacologic or dietary agents currently shown to have symptomatic cognitive benefit
  - Discuss diagnosis and uncertainties regarding prognosis
  - Discuss long-term planning: home safety, driving safety, finances, and estate planning.



https://www.helpguide.org/articles/alzheimers-dementia-aging/preventing-alzheimers-disease.htm