Normal cognitive ageing to dementia

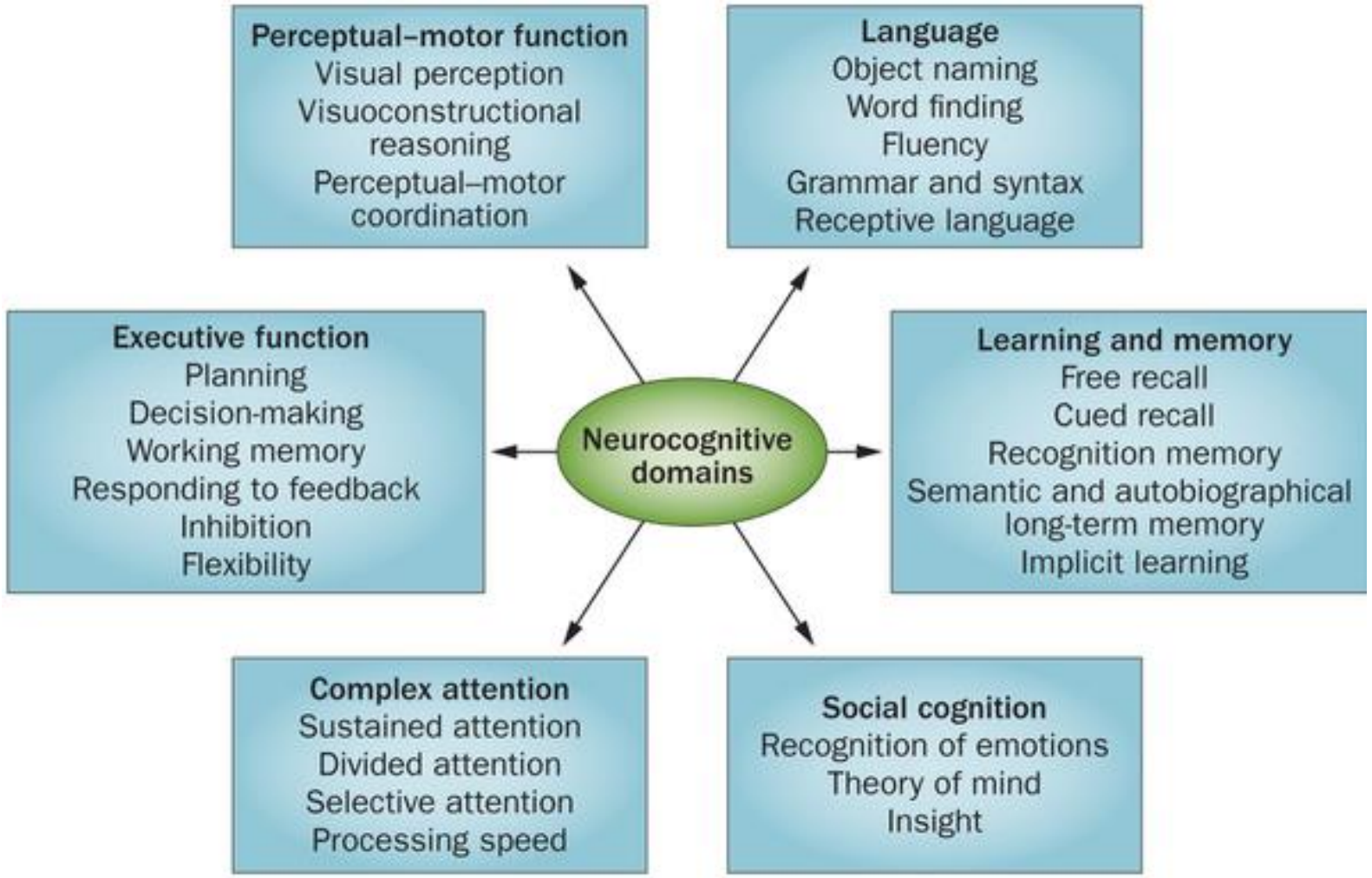
Stella-M Paddick Newcastle University

Overview

- Cognition
- Some changes in normal ageing
- Subjective cognitive decline (SCD)
- Mild cognitive impairment (MCI)
- Dementia
- An overview of potentially modifiable risk factors
- Concept of cognitive reserve

How we measure cognition – cognitive domains

Cognitive Domains- DSM5



Sachdev, P. S. *et al. Nat. Rev. Neurol.* **10**, 634–642 (2014)

How we measure cognition – crystallised versus fluid intelligence

Fluid intelligence

- cognitive abilities that **do not depend on what you know**.
- Speed and efficiency of solving novel problems.
- Remembering new information
- Speed of processing new information.
- (visuospatial ability, episodic memory, processing speed)

Crystalised intelligence

- cognitive abilities that **depend critically on what you know**.
- Professional knowledge
- World knowledge/facts
- Vocabulary
- Semantic memory
- ‘experience’

G – most cognitive performance inter-related

- Overall cognitive performance (G) – best single predictor of
- Job performance
- Economic success
- Health during the lifespan
- Longevity

- ‘Cognitive ability allows us to deal with complexity –
- Navigating society is a complex task. (Gottfried, 1997)

Normal ageing?

Mental Health and ‘Happiness’ in later life

Paradoxical Trend for Improvement in Mental Health with Aging: A Community-Based Study of 1,546 Adults Aged 21–100 Years. J Clin Psychiatry. 2016 Aug; 77(8): e1019–e1025 Michael L. Thomas, et al

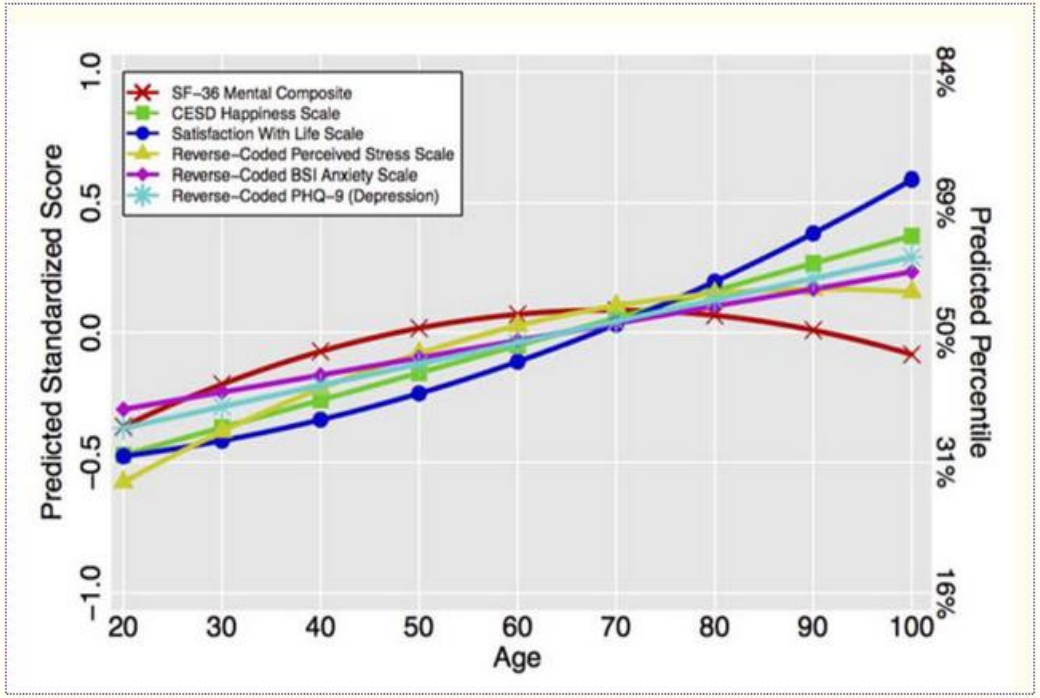
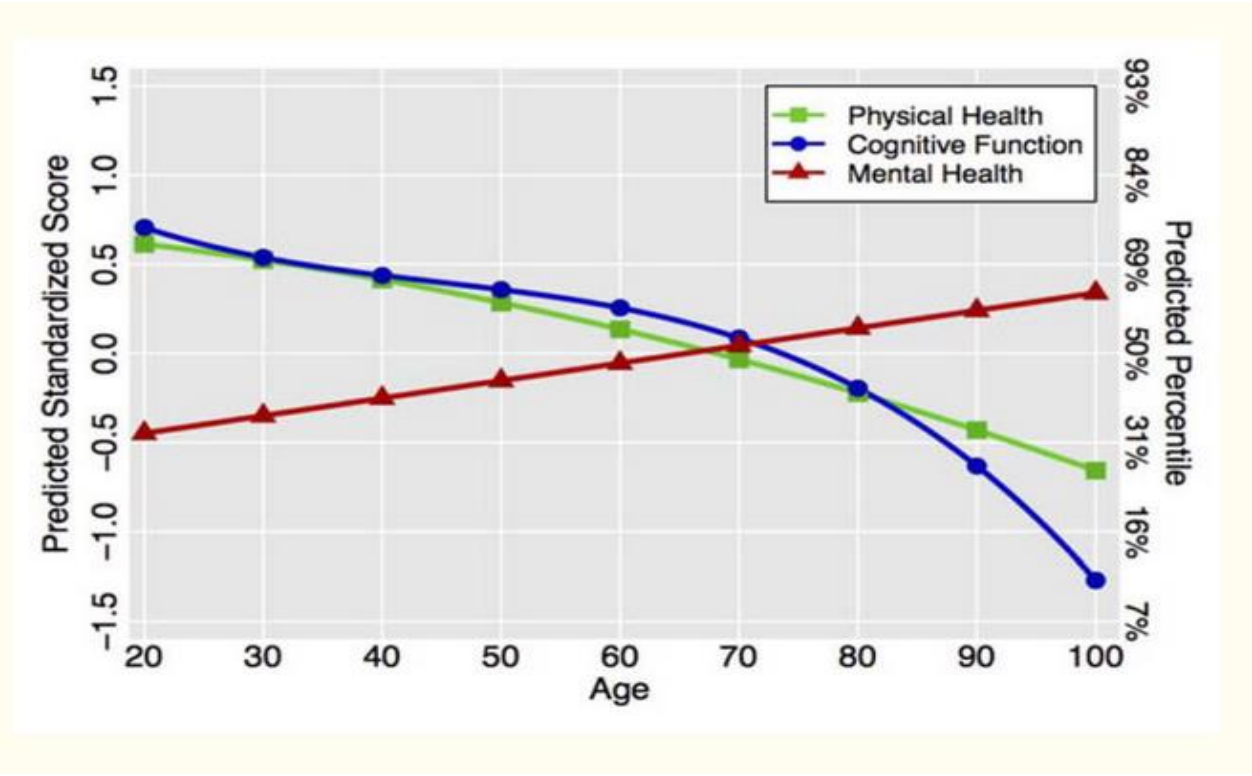


Figure 2

Predicted Values for Individual Measures of Mental Health

Abbreviations. BSI = Brief Symptom Inventory; CESD = Center for Epidemiological Studies – Depression scale; PHQ-9 = Patient Health Questionnaire Depression Module.



Trajectories of Big Five Personality Traits: A Coordinated Analysis of 16 Longitudinal Samples

N=60,000 people, 16 studies

Extraversion (declined)

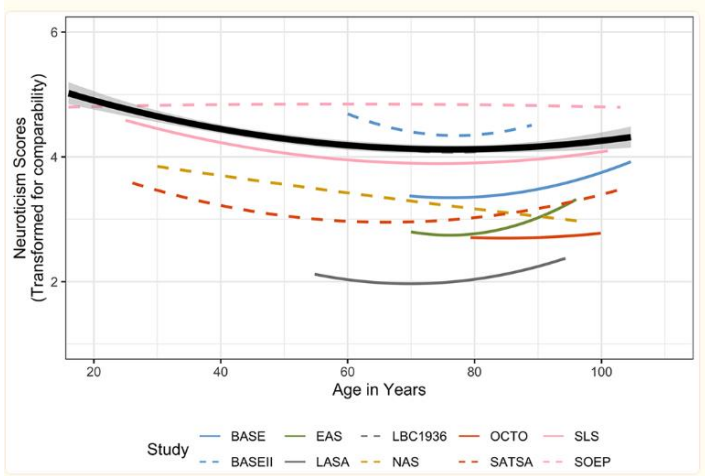
Openness (declined)

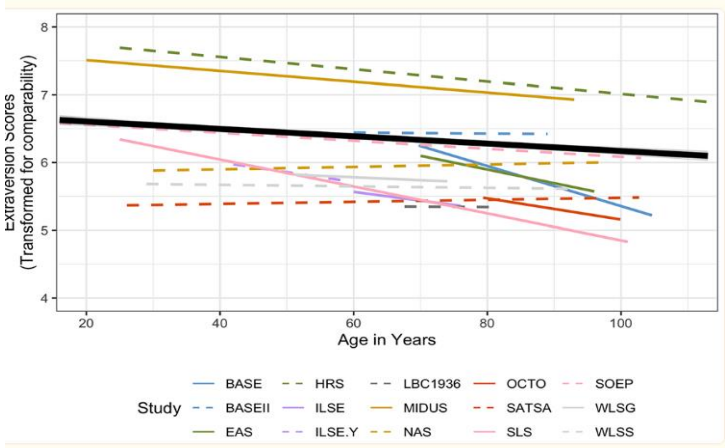
Conscientiousness (declined)

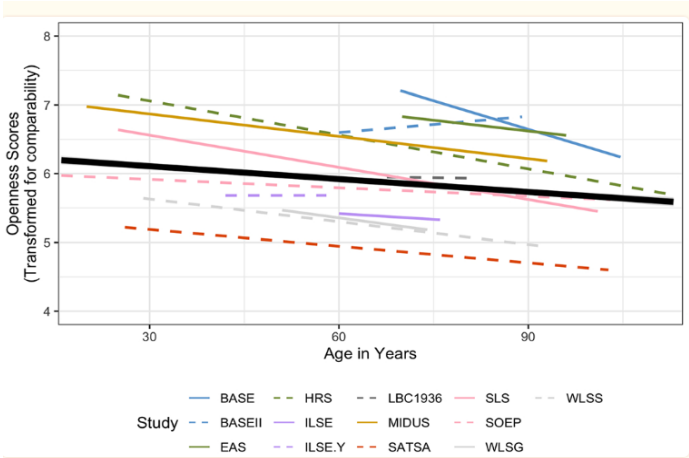
Agreeableness (? Improves)

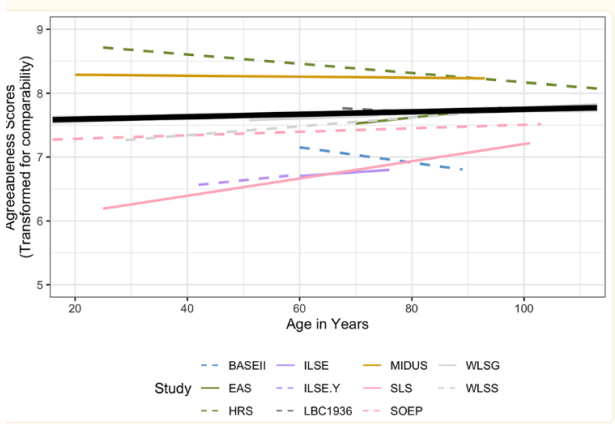
Neuroticism increases (on non linear model)

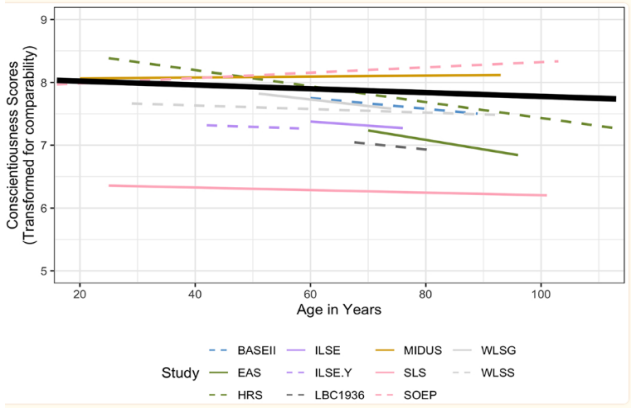
Much heterogeneity and challenges of measurement











Graham et al, 2020 E. J. Personality

Damian, (2019). Sixteen going on sixty-six: A longitudinal study of personality stability and change across 50 years. *J. Personality & Social Psych, 117*(3), 674–695.

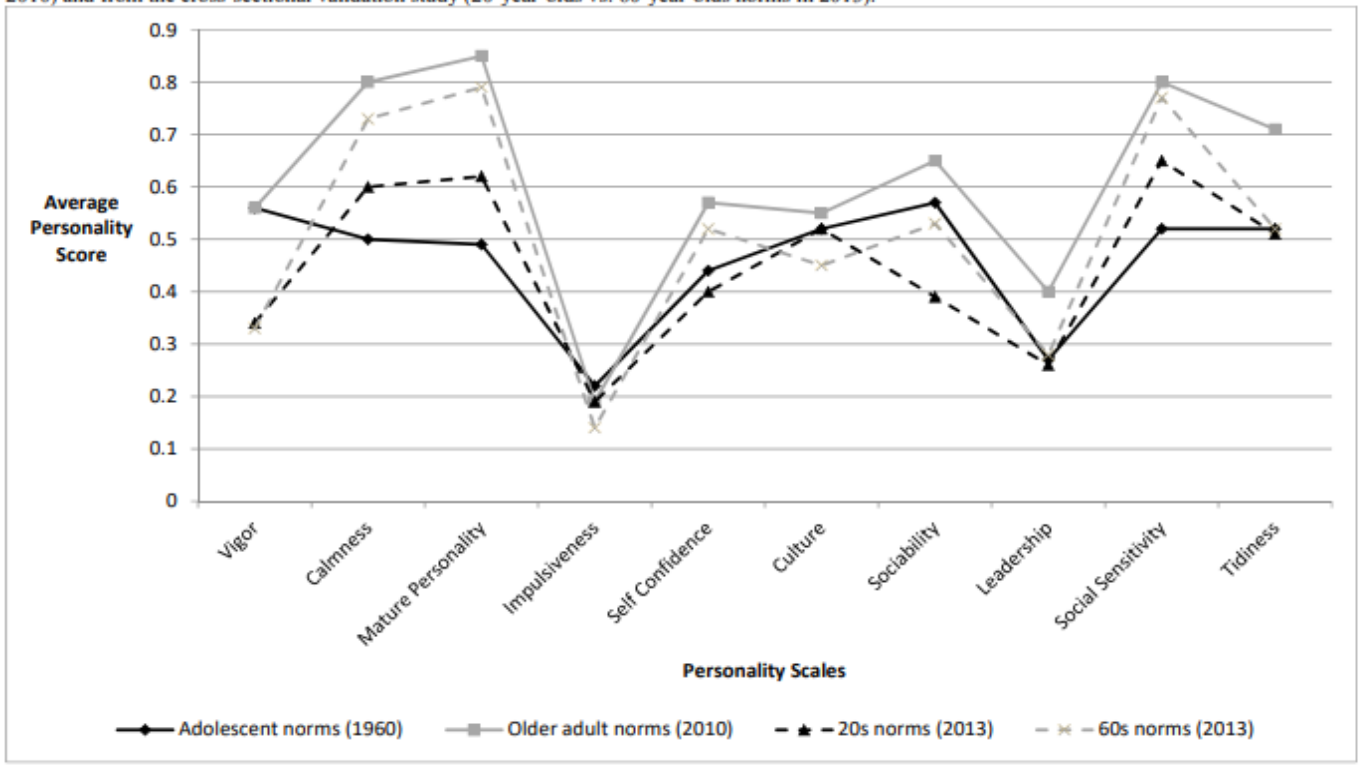
USA n=1760 50 year follow up

Cross sectional validation 2013 (measurement)

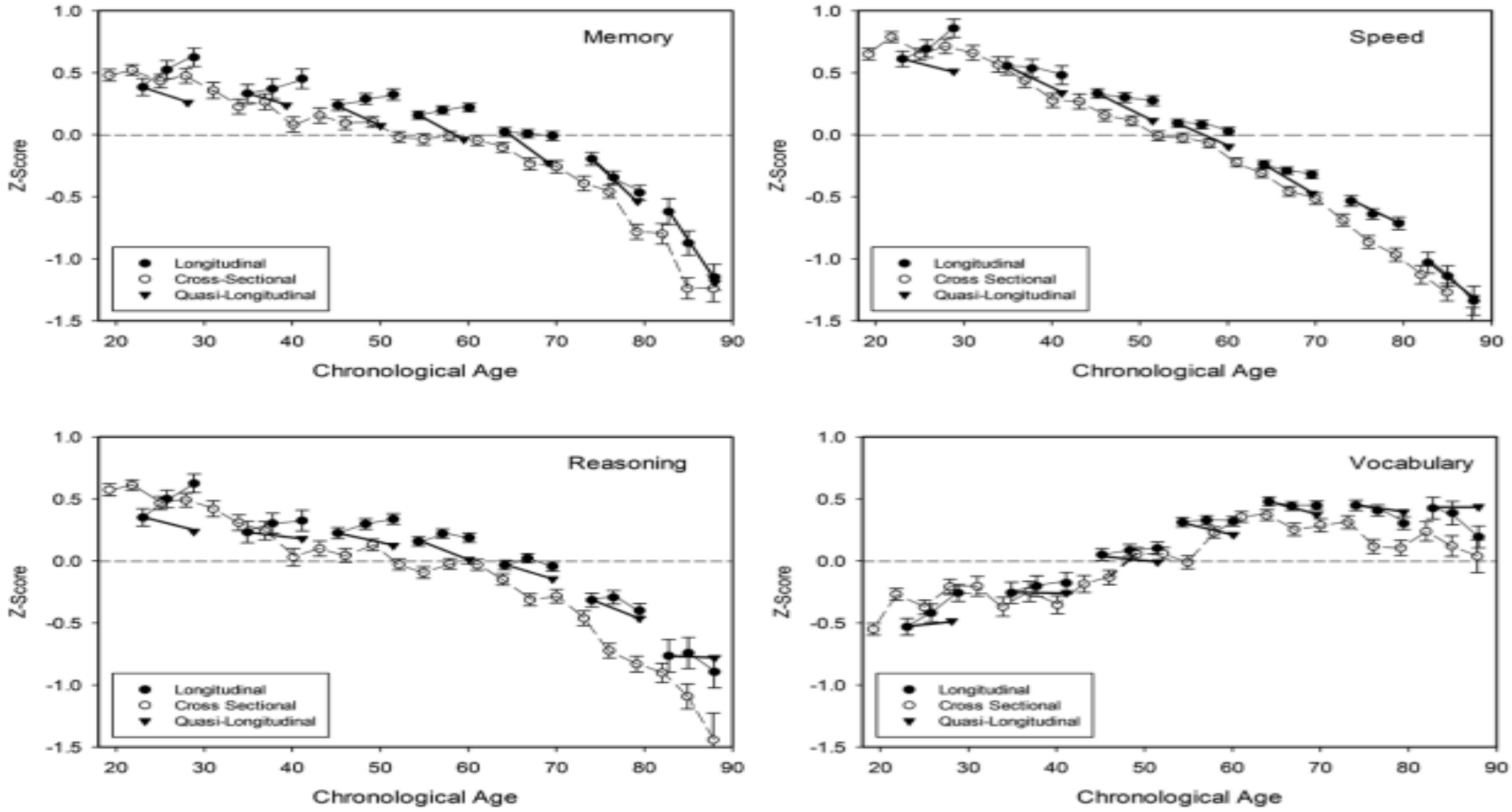
20-60% showed variance in each characteristic. Also showed stability.

Clear differences between older and younger adults

Figure 2. Normative Personality Trait Profiles from the main longitudinal study (baseline = adolescent norms in 1960; 50th year follow-up = older adult norms 2010) and from the cross-sectional validation study (20-year-olds vs. 60-year-olds norms in 2013).

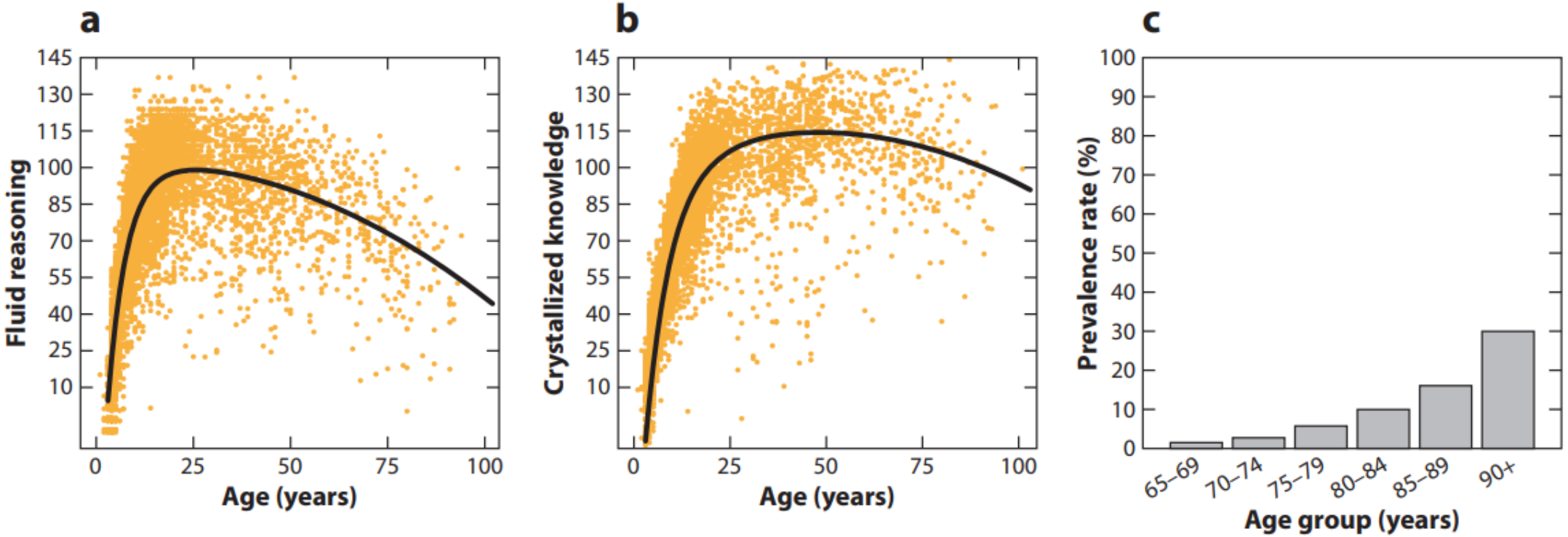


Cognitive trajectories in normal ageing (n=5000 + 1600)

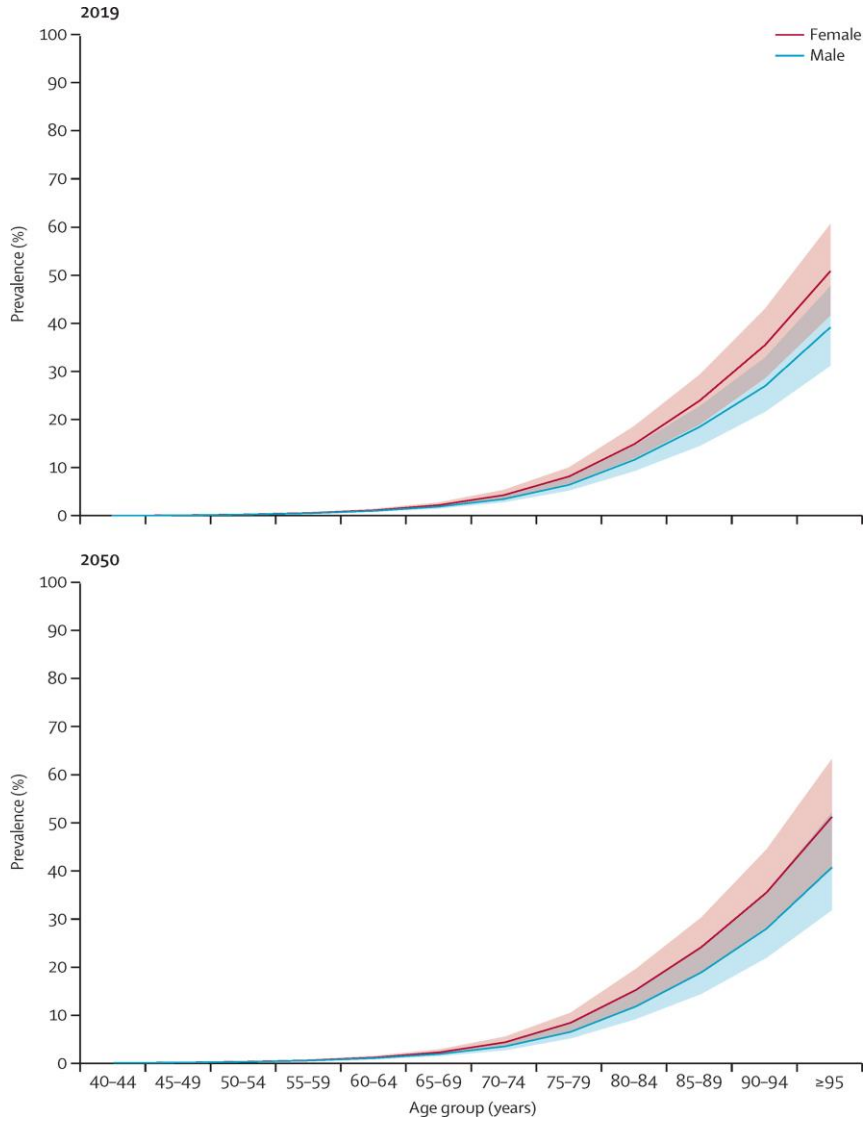


Salthouse, T. A. (2019). Trajectories of normal cognitive aging. *Psychology and aging*, *34*(1), 17.

Cognitive trajectories in normal ageing (and dementia risk by age)



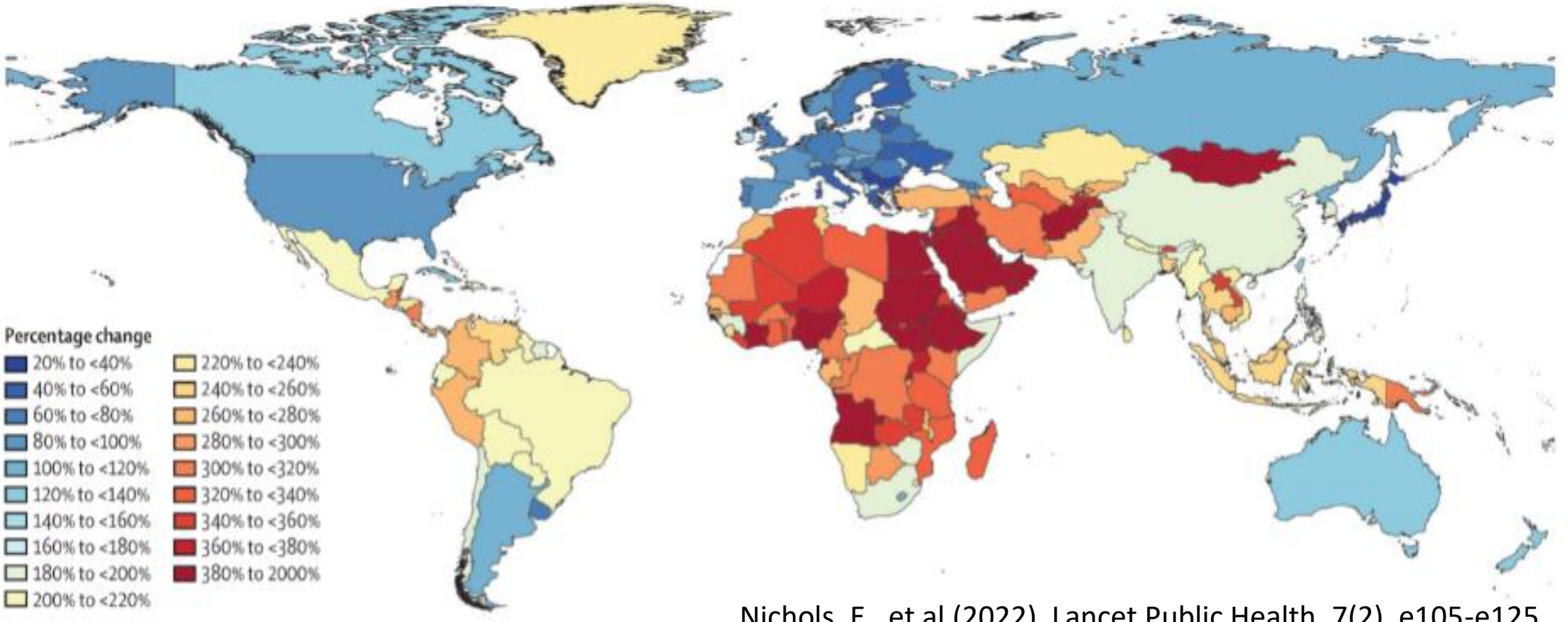
‘abnormal’ ageing. neurodegeneration and dementia



GBD estimates - 57·4 million 2019, 83·2 million 2030, 116·0 million in 2040, 152·8 million 2050

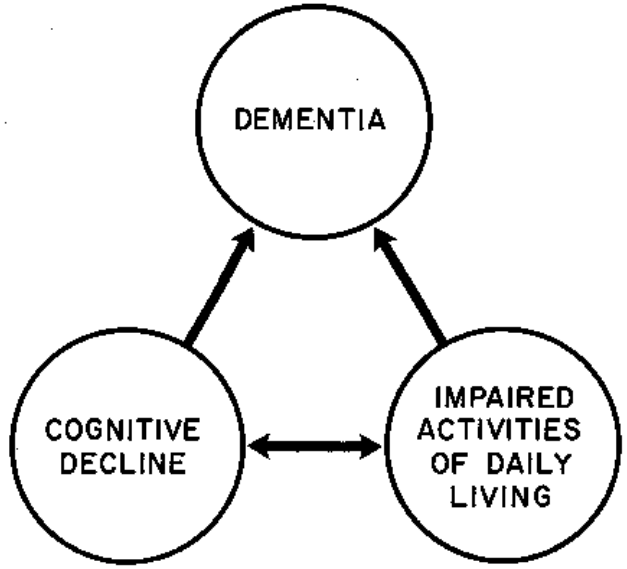
By age (2050), aged 40–69 years (0.5% men/0.6% women), 70–84 years (6·5% m/8.5% w), aged 85+ 23·5% M/30.5% w.) GBD 2019 Dementia Forecasting Collaborators

Worldwide projections dementia prevalence GBD



Nichols, E., et al (2022). Lancet Public Health, 7(2), e105-e125.

Dementia (Major Neurocognitive Disorder) - DSM 5 Criteria



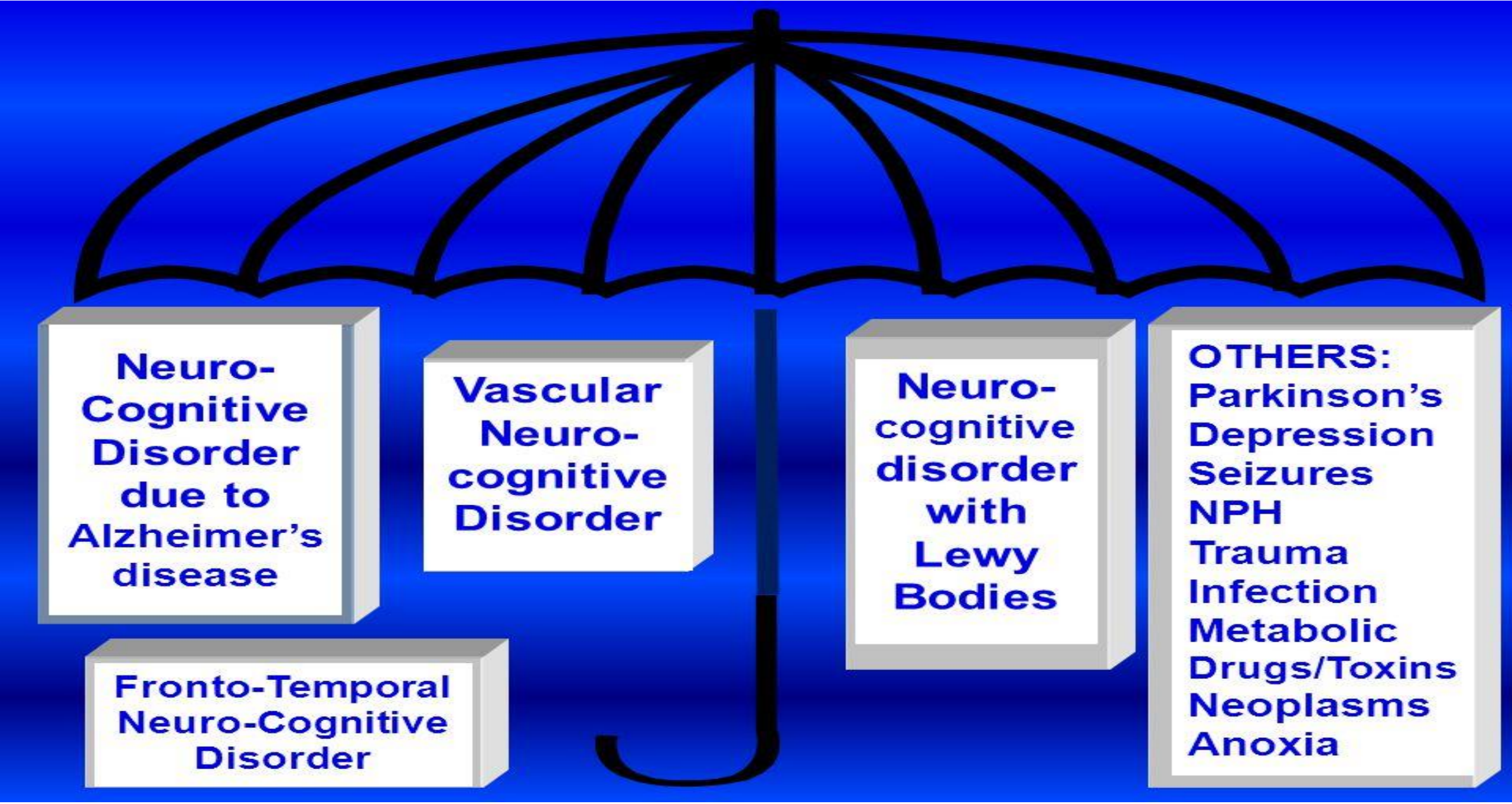
✓ Evidence of significant cognitive decline from a prev performance in one or more cognitive domains:

- Learning and memory
- Language
- Executive function
- Complex attention
- Perceptual-motor
- Social cognition

✓The cognitive deficits interfere with independence in everyday activities

✓The cognitive deficits do not occur exclusively in the context of a delirium

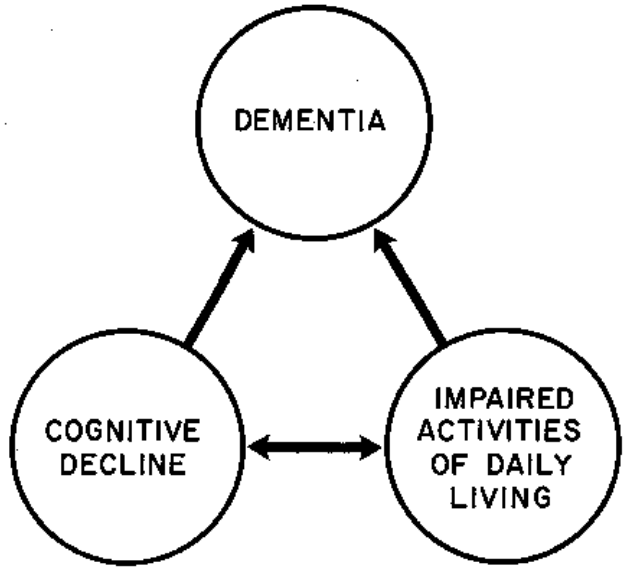
✓The cognitive deficits are not better explained by another mental disorder (eg, major depressive disorder, schizophrenia)



DSM 5 Classification (APA, 2013)

Spectrum of cognitive decline

Normal Cognition → **Mild Cognitive Impairment** → Dementia



ADL normal, Cognitive decline

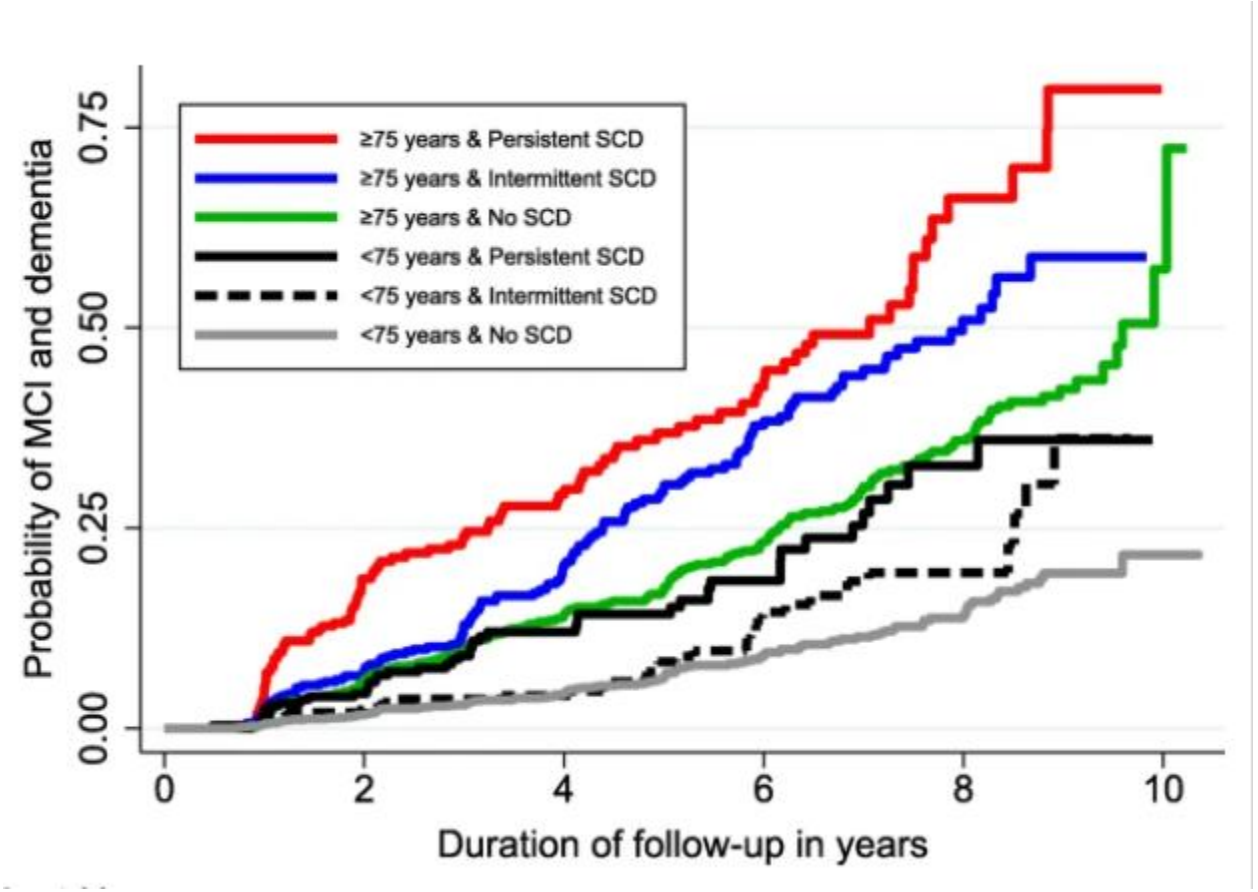
Severe cog. deficits
Impaired ADL
Need for support

Mild Neurocognitive Disorder	Major Neurocognitive Disorder

Subjective cognitive decline SCD
‘I have memory problems doctor’

Is subjective cognitive decline important?

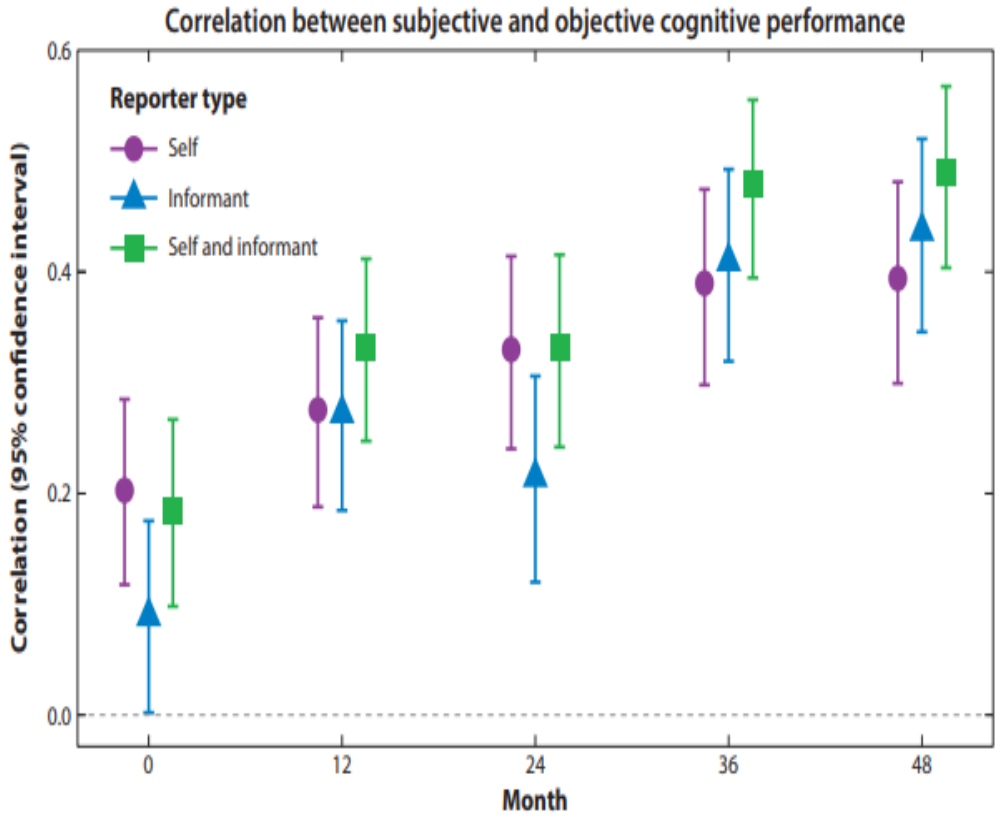
- Population-based studies- 50%-80% of 70+ with normal range cognitive testing report perceived cognitive decline when asked.
- All ages, meta analysis – 4 years follow-up 14% dementia, 27% MCI
- PM studies aged 60+ - association of SCD and amyloid/tau burden.
- On average, dementia occurs 10 years after onset SCD (longitudinal data)

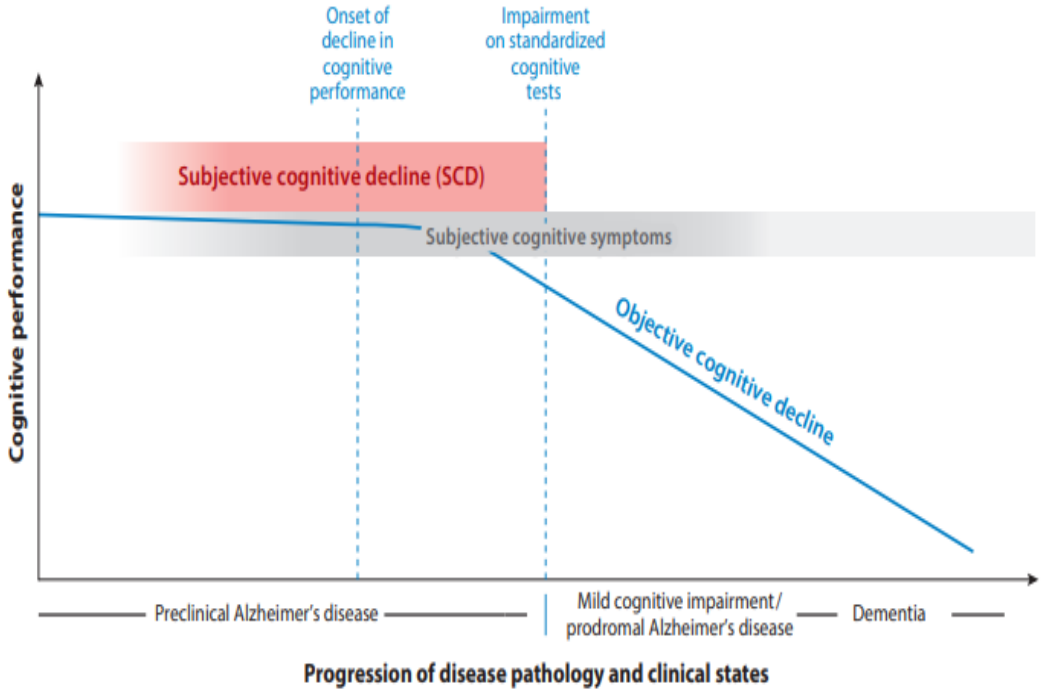


Kaplan-Meier curves reflecting the risk of MCI and dementia, stratified by age groups and trajectories of SCD (*n* = 5661) Liew, (2020). *Alzheimer's res & therapy*, *12*(1), 1-12.

Jessen F, et al. *Arch Gen Psychiatry* 2010; 67: 414–22., van Harten *Neurology* 2018; 91: e300–12
Mitchell A,. *Acta Psychiatr Scand* 2014; 130: 439–51. meta-analysis, Verlinden VJA, *Alzheimers Dement* 2016; 12: 144–53.

Progression (in those later with AD)

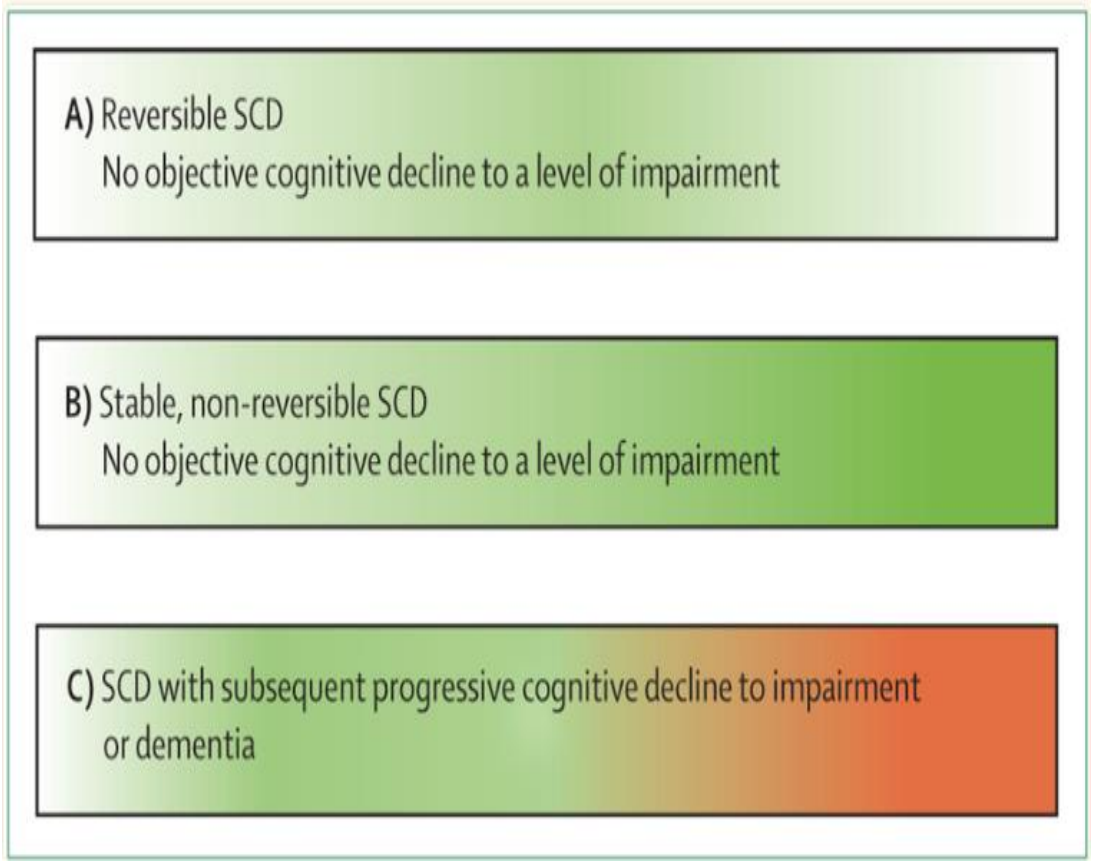




Rabin, Annu. Rev. Clin. Psychol. 2017. 13:369–96

SCD plus – those at potentially higher risk

- Subjective decline in memory over other cognitive domains
- Onset of SCD within the past 5 years
- Onset of SCD at 60 years and older
- Concern (worry) associated with SCD
- Persistence of SCD over time*
- **Confirmation of cognitive decline by an observer**
- **APOE4 allele**
- **Biomarkers for AD**



Jessen F, *Alzheimers Dement* 2014; 10: 844–52 SCD criteria

Mild Cognitive Impairment (MCI)

Petersen Criteria for MCI
(Amnestic MCI)

- 5 criteria - most widely applied classification for MCI
- References: Petersen et al. (1999, 2001)

- 1) Memory complaints
  - Self, informant or health care provider
  - Concerned about vs. detected on questionnaire
- 2) Minimal or no functional impairment of usual ADLs
- 3) Normal general cognitive function
- 4) Abnormal memory test performance
  - relative to age norms, but considering est. baseline level
- 5) Does not meet criteria for clinical Dx of dementia

Various other criteria e.g. ICD/DSM/IWG

ICD-11

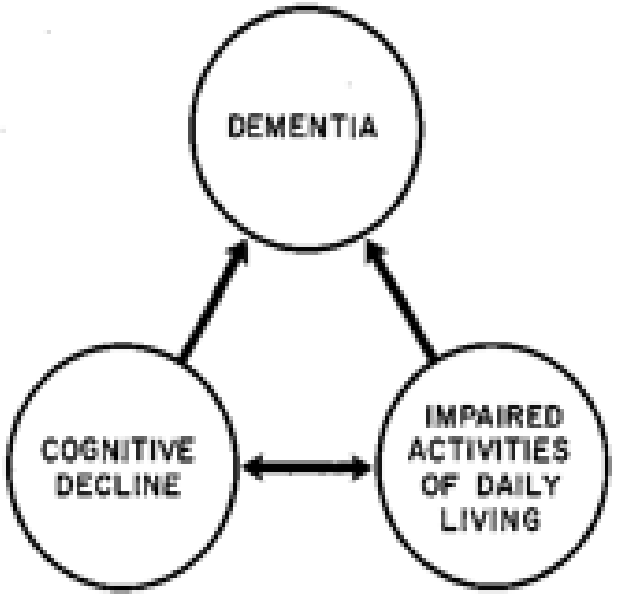
- mild impairment in one or more cognitive domains relative to that expected given age and general premorbid cognitive functioning, decline from the individual's previous level of functioning.
- report from the patient, informant, or clinical observation, accompanied by objective evidence of impairment by quantified clinical assessment or standardized cognitive testing.
- Cognitive impairment is not severe enough to significantly interfere with an individual's ability to perform activities related to personal, family, social, educational, and/or occupational functioning or other important functional areas.
- Cognitive impairment is not attributable to normal aging and may be static, progressive, or may resolve or improve depending on underlying cause or treatment.
- Cognitive impairment may be attributable to an underlying acquired disease of the nervous system, a trauma, an infection or other disease process affecting the brain, use of specific substances or medications, nutritional deficiency or exposure to toxins, or the etiology may be undetermined. T
- he impairment is not due to current substance intoxication or withdrawal.

DSM-5 minor neurocognitive disorder

- . modest cognitive decline from previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual–motor, or social cognition) based on
- : 1. Concern of individual, knowledgeable informant, or clinician re mild decline in cognitive function; and
- 2. modest impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.
- B. The cognitive deficits do not interfere with capacity for independence in everyday activities (complex instrumental activities of daily living such as paying bills or managing medications are preserved, but greater effort, compensatory strategies, or accommodation may be required).
- C. The cognitive deficits do not occur exclusively in the context of a delirium.
- D. The cognitive deficits are not better explained by another mental disorder (eg major depressive disorder or schizophrenia).

MCI

Normal Cognition → **Mild Cognitive Impairment** → Dementia



ADL normal, Cognitive decline

Severe cog. deficits
Impaired ADL
Need for support

Mild Neurocognitive Disorder	Major Neurocognitive Disorder

IMPORTANCE of MCI

- Amnestic MCI – 12-15% a year progress to dementia
- May reverse or not progress
- NB DSM-5 criteria assume this is AD and will progress (preclinical AD)
- Consider follow up, and if no progression discharge
- Higher risk of progression if multi domain

- Consider reversible causes –
- MCI secondary to a medical condition
- Depression/anxiety/drug effect ie anticholinergics

Need for normative values on cognitive tests – we have verbal learning/recall/category fluency for Tanzania and Nigeria

Dement Neuropsychol 2021 September;15(3):339-349

Original Article

https://doi.org/10.1590/1980-57642021dn15-030005

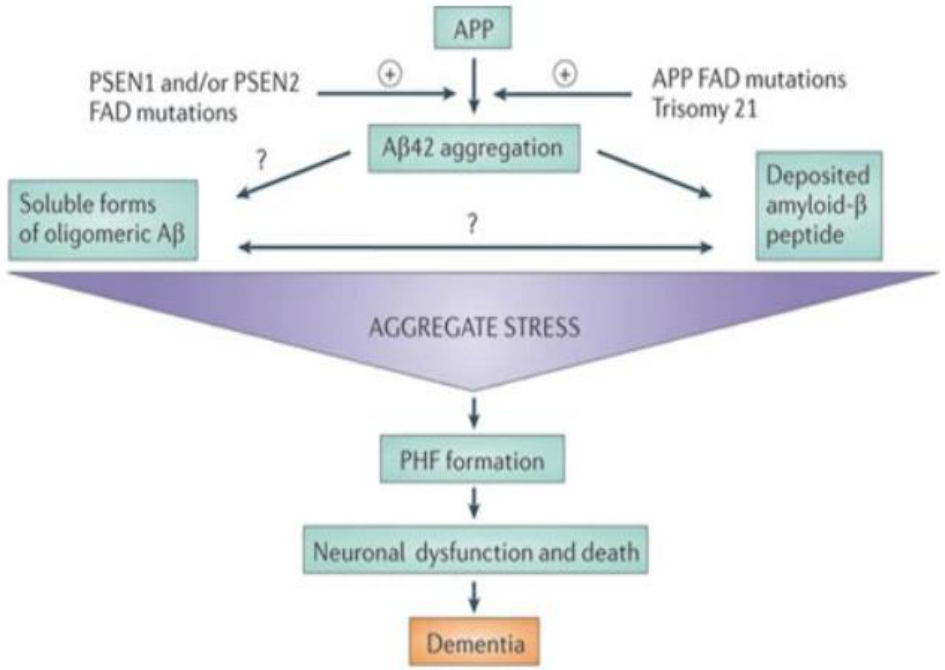
Population normative data for three cognitive screening tools for older adults in sub-Saharan Africa

William Keith Gray[1], Stella-Maria Paddick[2], Adesola Ogunniyi[3], Olaide Olakehinde[3], Catherine Dotchin[1,2], John Kissima[4], Sarah Urasa[5], Aloyce Kisoli[5], Jane Rogathi[5], Declare Mushi[5], Akindele Adebiyi[3], Irene Haule[4], Louise Robinson[2], Richard Walker[1,2]

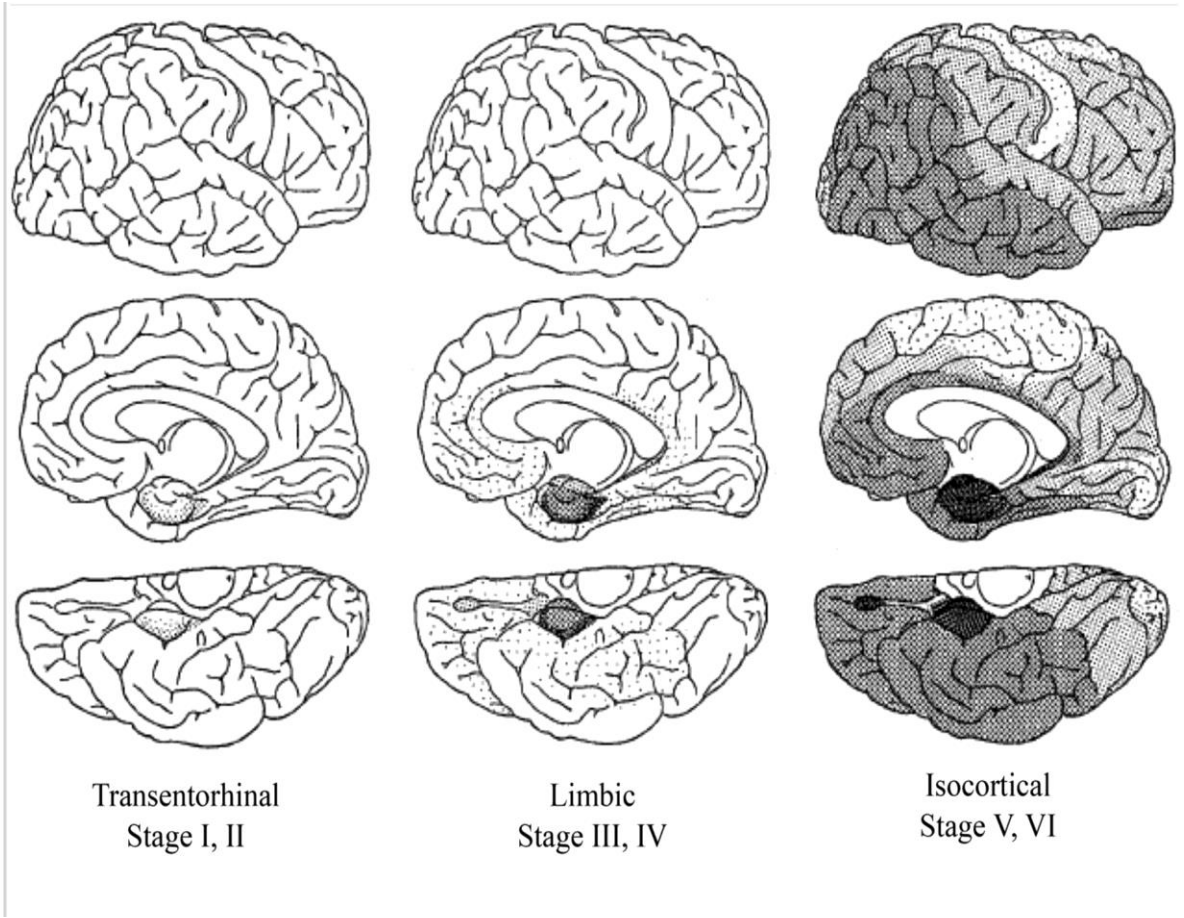
Degeneration and dementia subtypes

Neurodegeneration – amyloid cascade hypothesis of AD

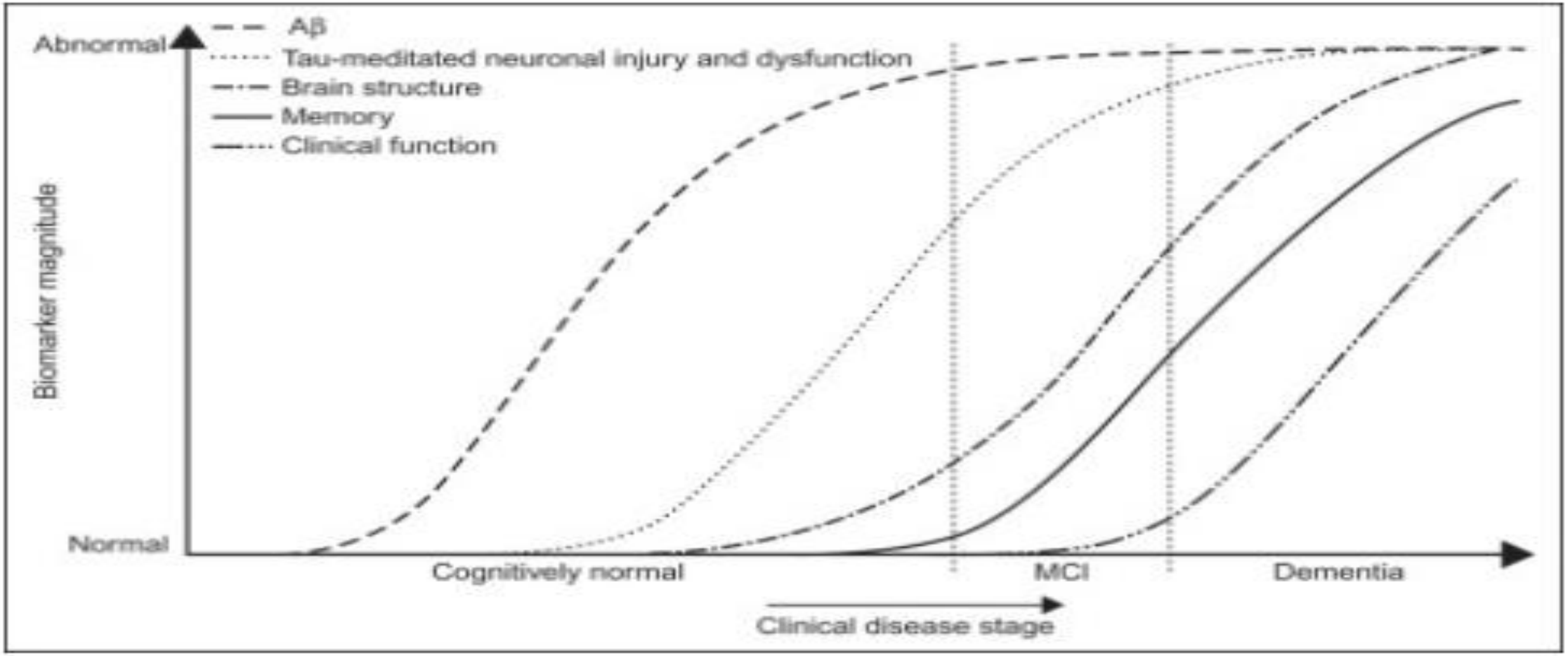
Figure 1: The amyloid cascade hypothesis.



Nature Reviews | Drug Discovery



Alzheimer's disease – progresses for many years before memory is impaired.



DSM5 vascular cognitive impairment (NB others inc VICCS/NINCDS-AIREN)

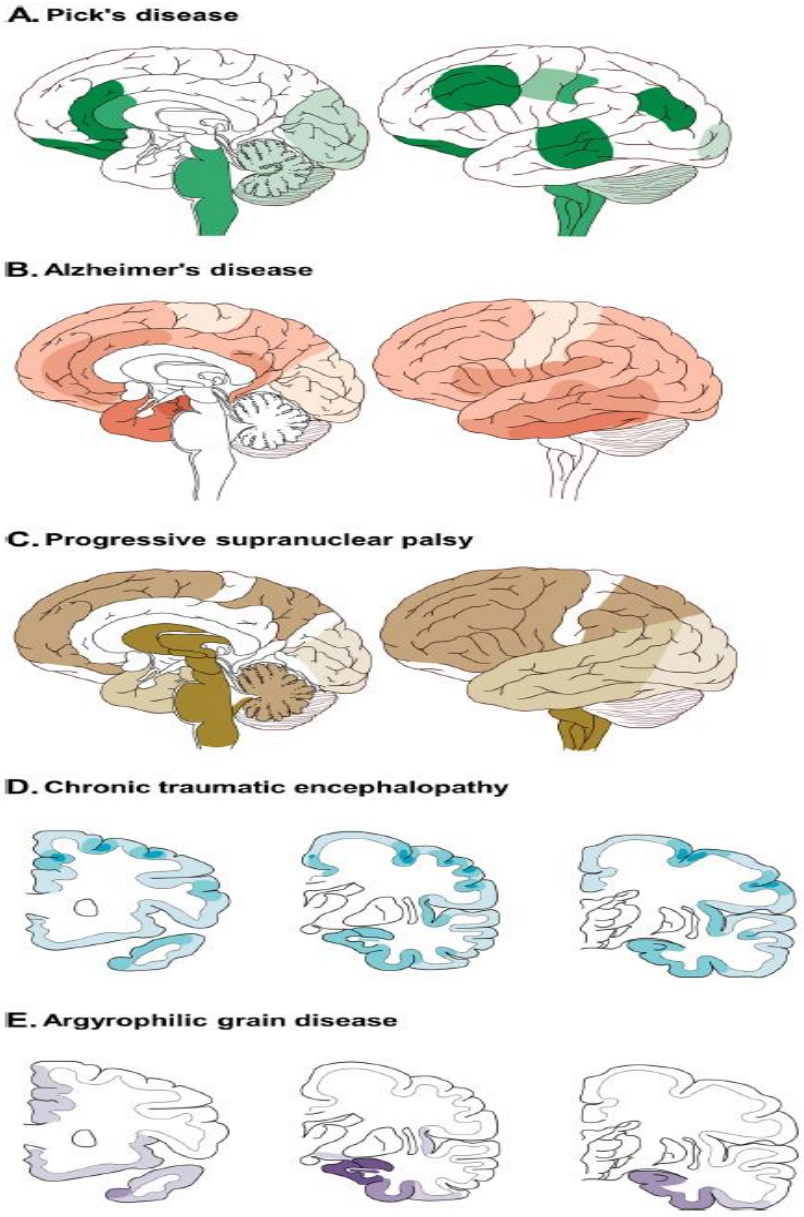
- A. Criteria are met for major or mild neurocognitive disorder.
- B Clinical features are consistent with a vascular etiology,

Onset temporally related to one or more cerebrovascular events.

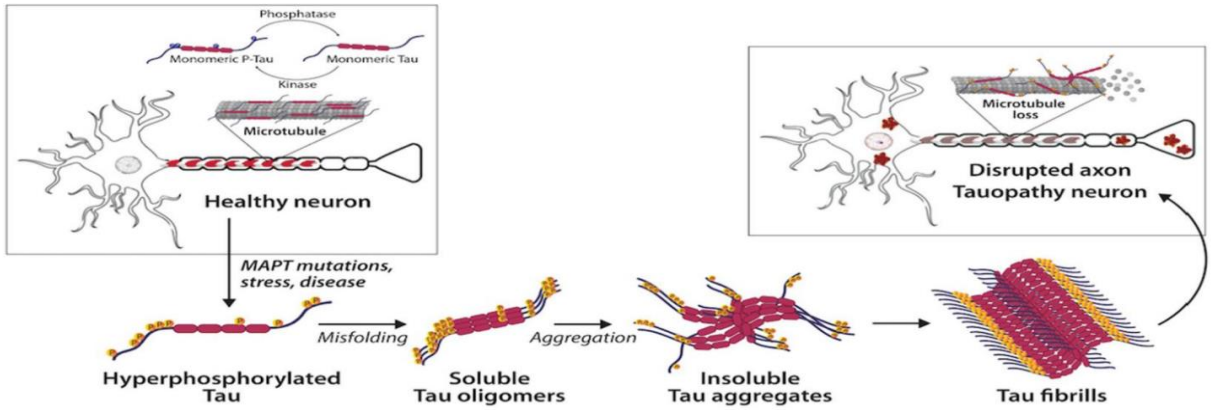
And/or

- Evidence for decline is prominent in complex attention (including processing speed) and frontal-executive function.
- C. Evidence of cerebrovascular disease from history, physical examination, and/or neuroimaging **considered sufficient to account for the neurocognitive deficits.**
- D.The symptoms are not better explained by another brain disease or systemic disorder

Tauopathies



- Spectrum of cognitive and movement disorders (much overlap/mixed pathology)
- Primary - Pick disease, corticobasal degeneration, progressive supranuclear palsy, argyrophilic grain disease.
- Secondary – AD (most common)
- Environmental - chronic traumatic encephalopathy
- geographically isolated -Guam-Parkinsonian-dementia complex.



Spectrum of pathologies resulting in FTD

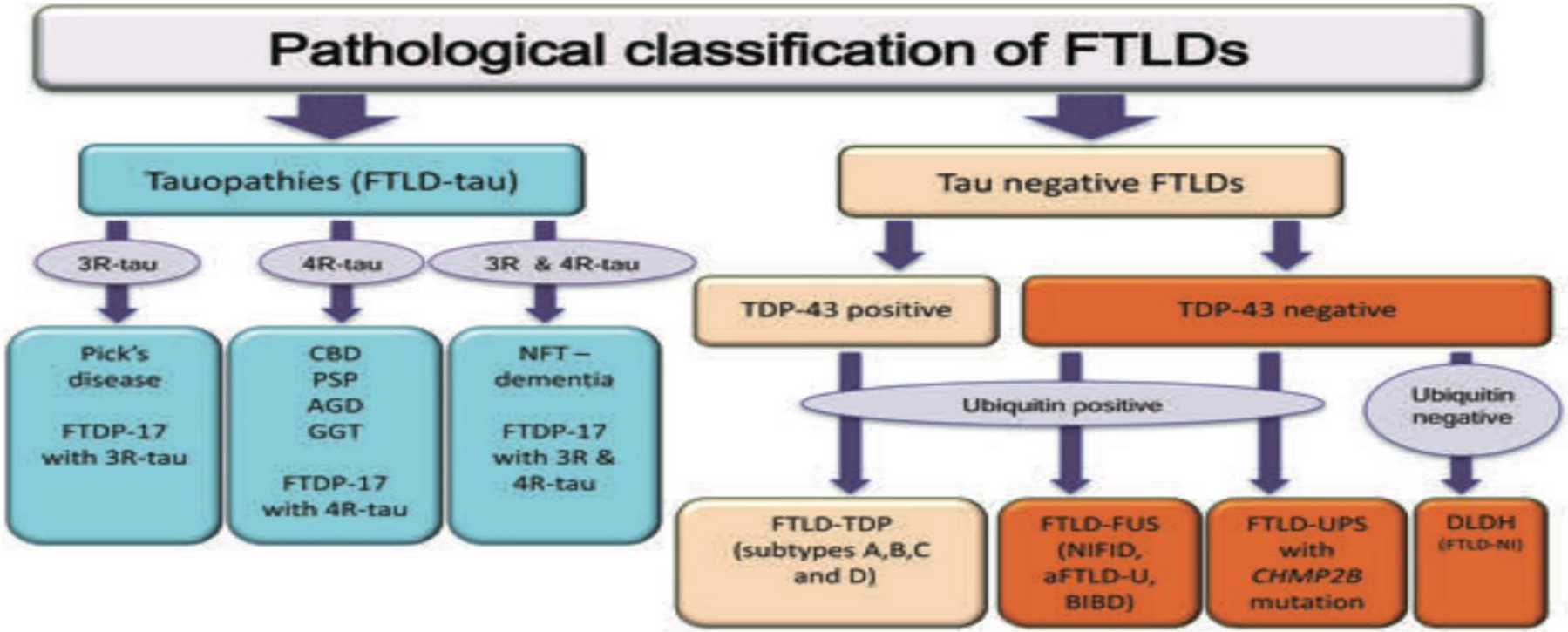
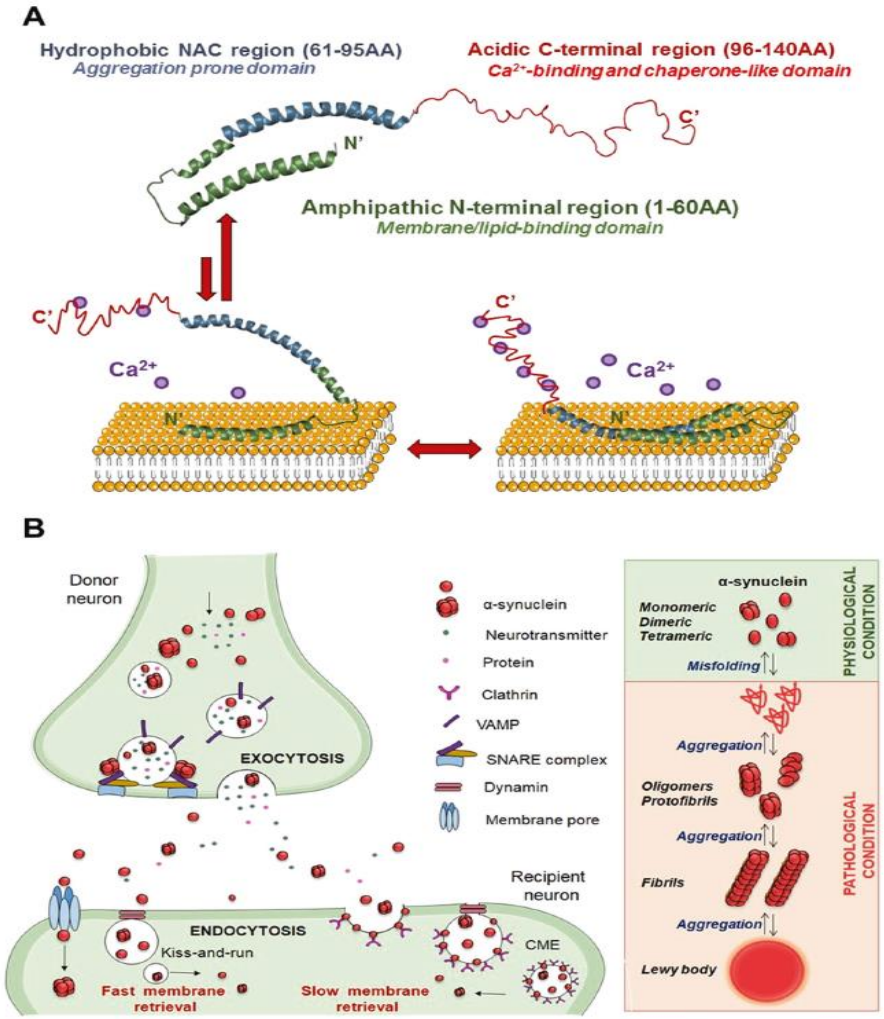


Figure 3. A schematic illustration of the pathological classification of frontotemporal lobar degenerations. Current classification is based on the molecular features of the disease-associated, inclusion forming proteins, morphological phenotypes and genetic data (for description of the different disease groups and individual diseases see text). 3R-tau, three-repeat tau; 4R-tau, four-repeat tau; aFTLD-U, atypical frontotemporal lobar degeneration with ubiquitin immunoreactive neuronal inclusions; AGD, argyrophilic grain disease; BIBD, basophilic inclusion body disease; CBD, corticobasal degeneration; DLDH, dementia lacking distinctive histology; FTLD, frontotemporal lobar degeneration; FTDP-17, frontotemporal dementia and parkinsonism linked to chromosome 17; GGT, globular glial tauopathy, NFT-dementia, neurofibrillary tangle dementia; NIFID, neuronal intermediate filament inclusion disease.

Synucleinopathies

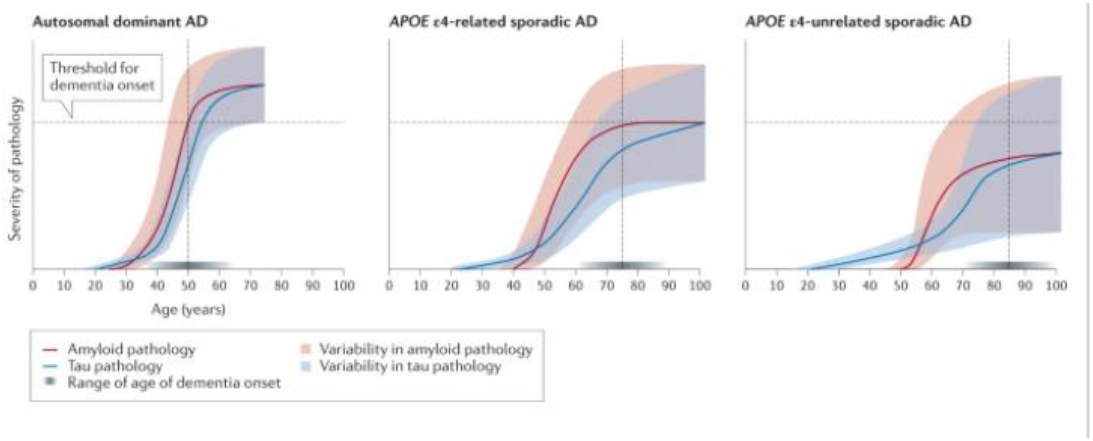


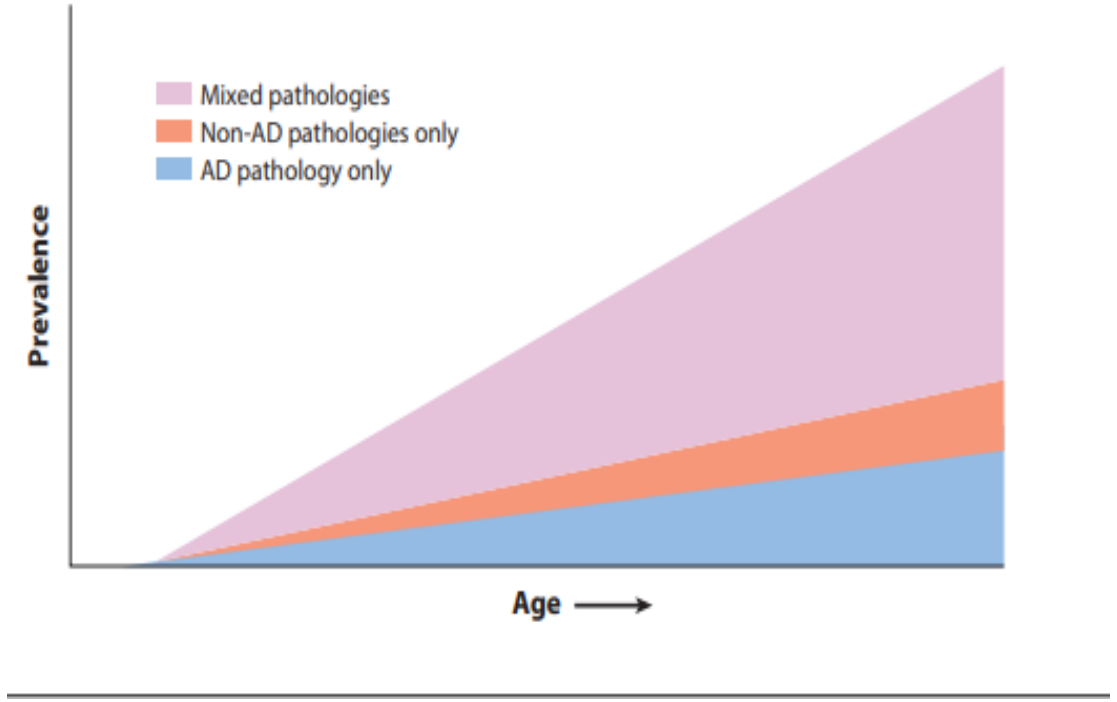
- Dementia with Lewy Bodies
- Parkinsons dementia
- PSP etc

Calabresi, Cell Death & Disease **vol. 14**, 176 (2023)

Most dementias are mixed – and this becomes more likely with increasing age.
Pure VAD relatively uncommon and often overdiagnosed
AD and CVD have a bidirectional relationship and worsen each other.

Aβ and tau threshold, manifest cognitive impairment 50 years in a.dominant AD, 75 years in *APOE* ε4-related sporadic AD and 85 years in *APOE* ε4-unrelated sporadic AD.





Frisoni, G. B.et al . (2022). The probabilistic model of Alzheimer disease: the amyloid hypothesis revised. *Nature Reviews Neuroscience*, *23*(1), 53-66. james & Bennet Annu. Rev. Public Health 2019. 40:65–84

How to proceed (we can discuss cases this PM)

- Is there objective cognitive decline? (ensure culturally appropriate test used)
- Is there evidence of delirium? CAM positive? Attentional deficit? Sudden onset/fluctuating confusion/clouding of consciousness
- Is there evidence of depression? If in doubt, treat and reassess
- Is there functional impairment?
- Have other causes been excluded? (check bloods, HIV, CT brain)
- (usually 6 months duration, though no longer in DSM)
- Think about ‘subtype’ as may affect trajectory and management

The concept of cognitive reserve

Ageing and neurodegeneration

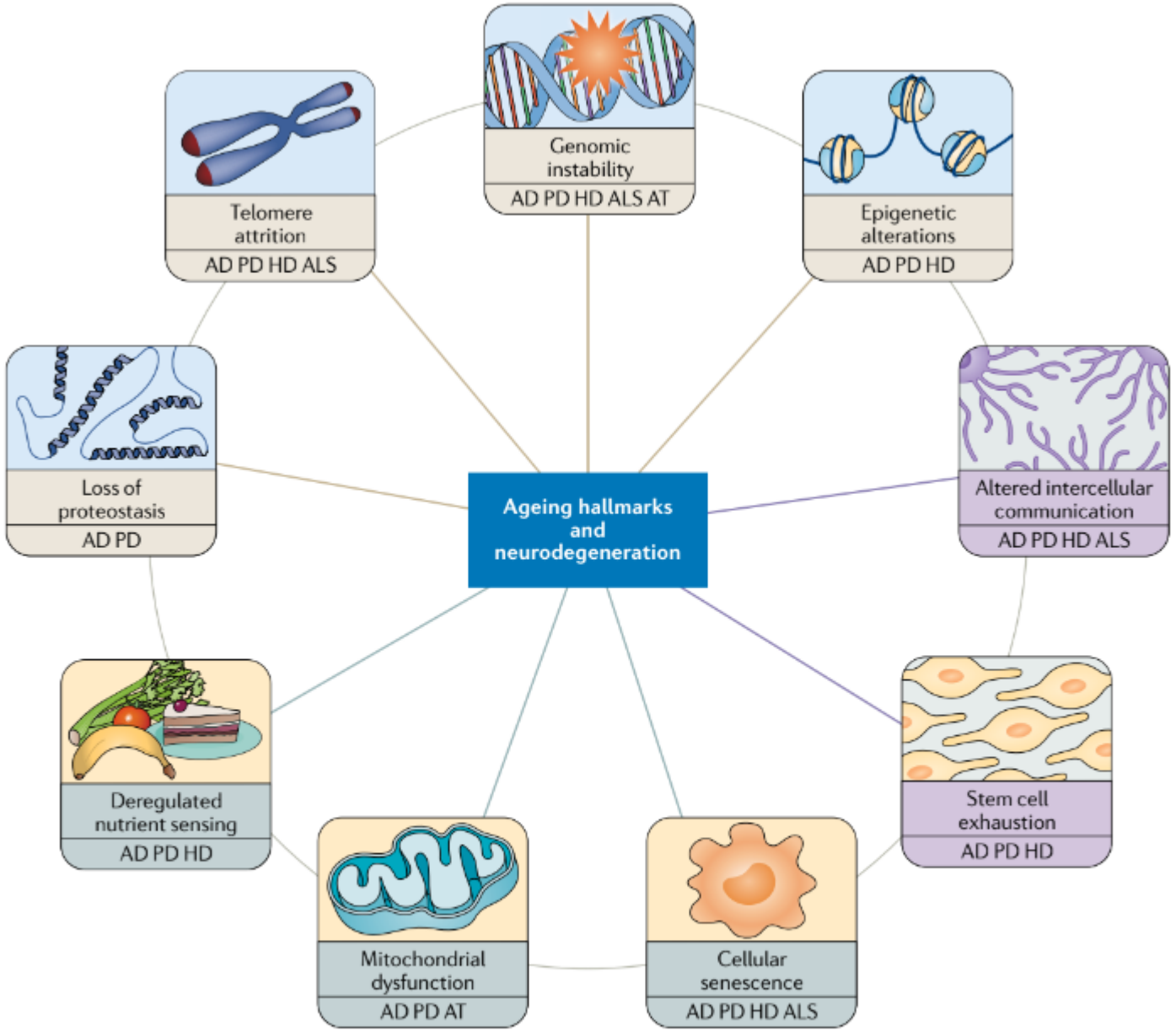
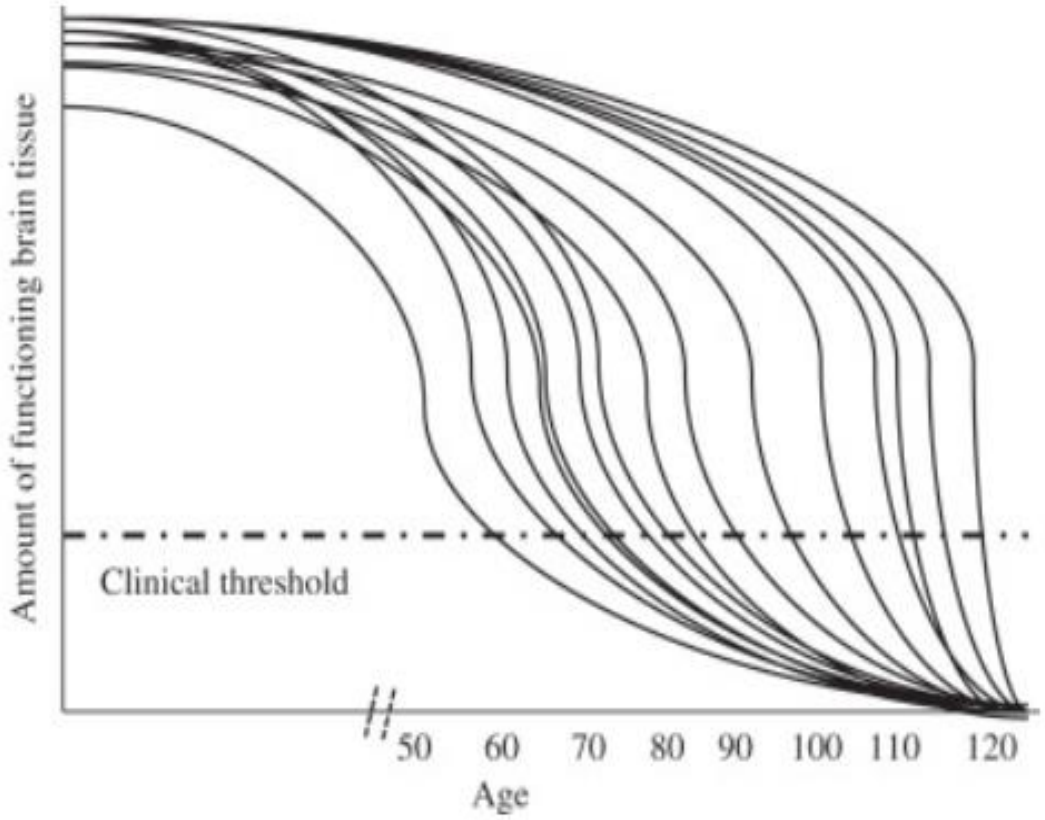


Fig. 2 | **Hallmarks of ageing.** Nine hallmarks of ageing — genomic instability, telomere attrition, epigenetic alterations, mitochondrial dysfunction, deregulated nutrient sensing, loss of proteostasis, cellular senescence, stem cell exhaustion and altered intercellular communication — seen in the main neurodegenerative diseases. AD, Alzheimer disease; ALS, amyotrophic lateral sclerosis; AT, ataxia telangiectasia; HD, Huntington disease; PD, Parkinson disease.

Borenstein and Mortimer incidence of AD 2016 – everyone has their own trajectory but some escape it

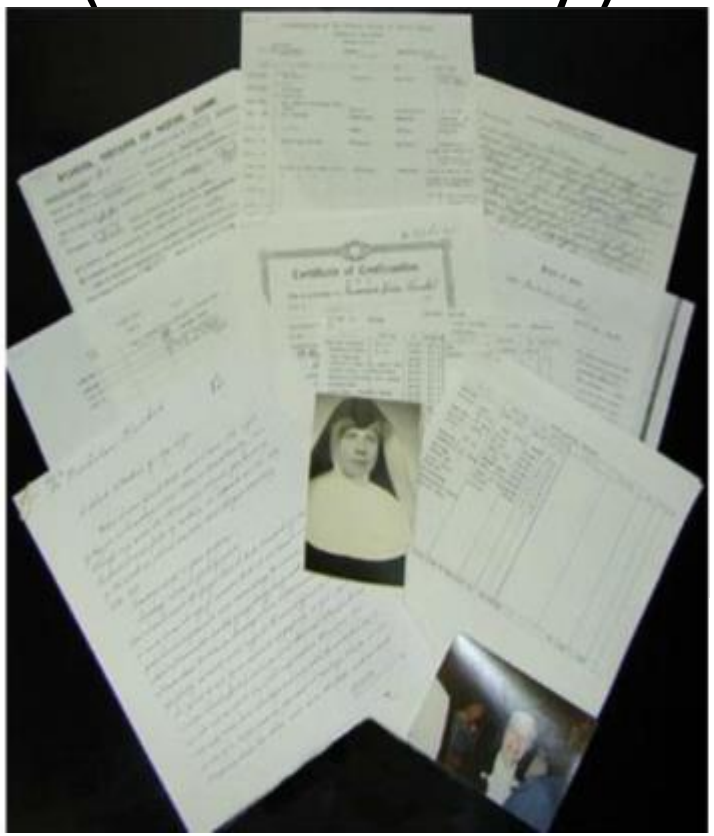
- Neurodegeneration
- Vascular damage
- Oxidative stress
- Inflammation
- Brain resilience

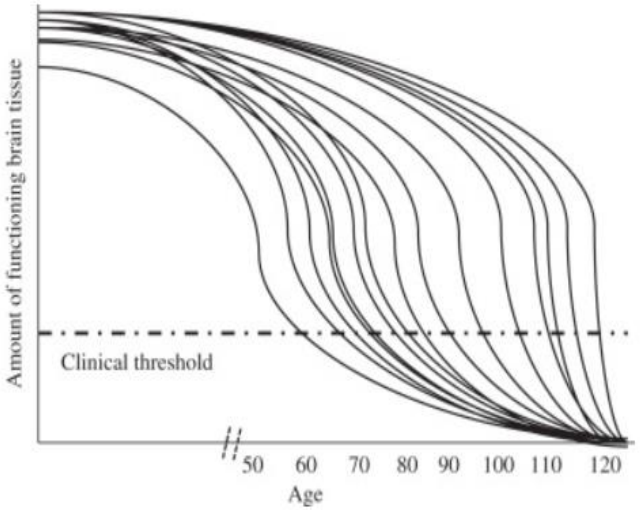
- (genetic risk etc)



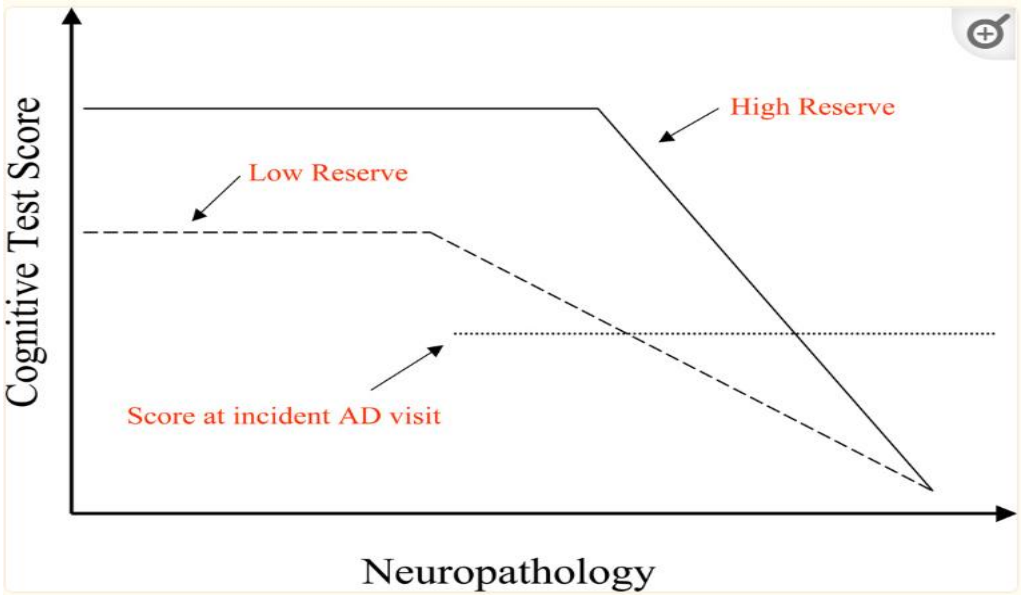
The Religious Orders (Nun Study)

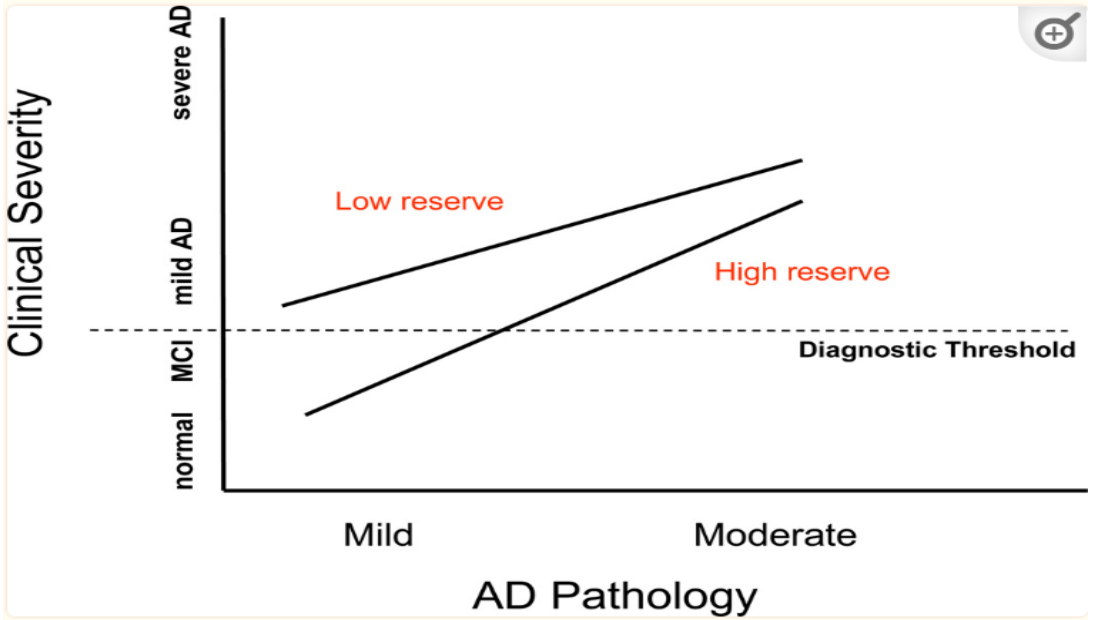
- No good relationship between presence of dementia in life, and AD (amyloid plaques/tangles) burden at autopsy.
- Protective effect of early linguistic ability/idea complexity
- Bilingualism

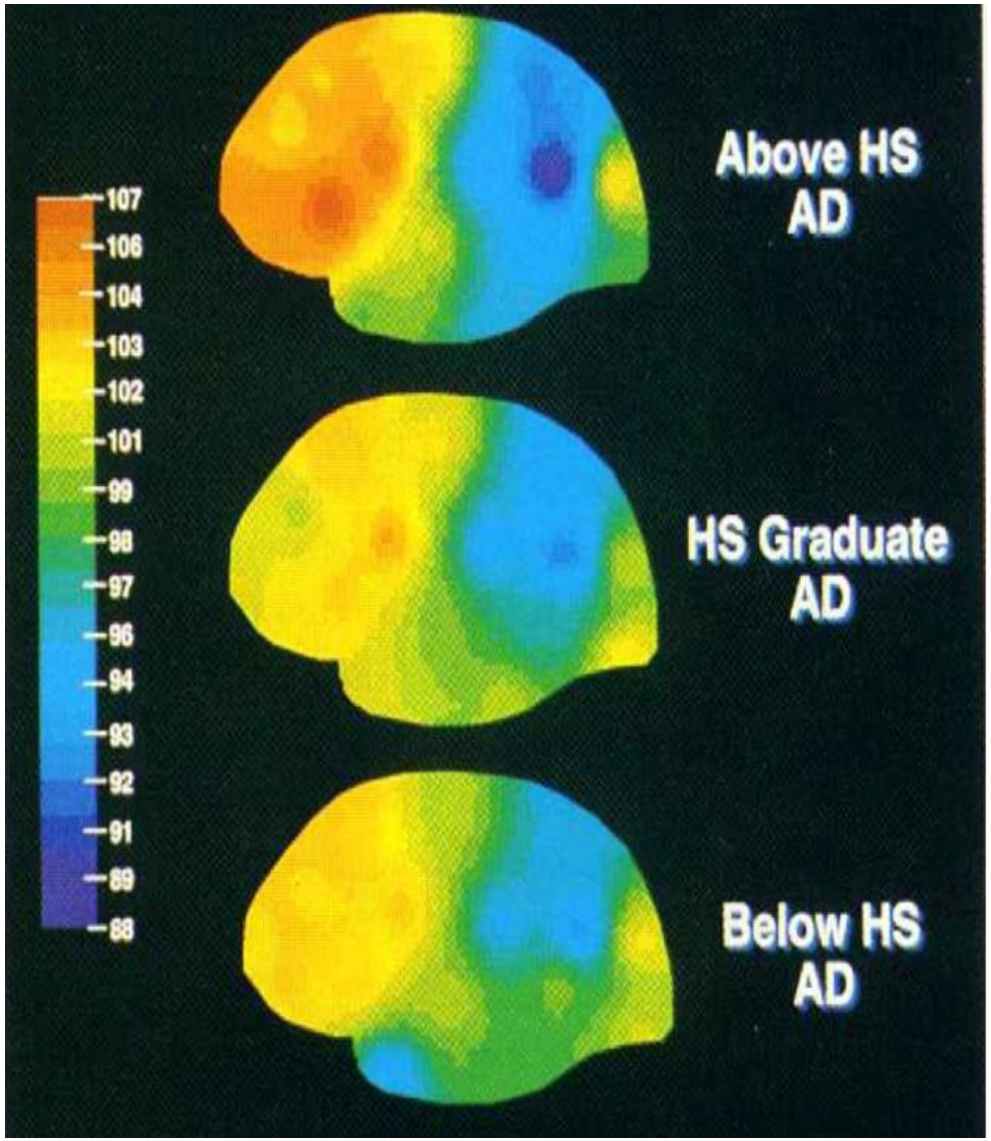




Cognitive reserve and AD pathology (Stern, 2012)

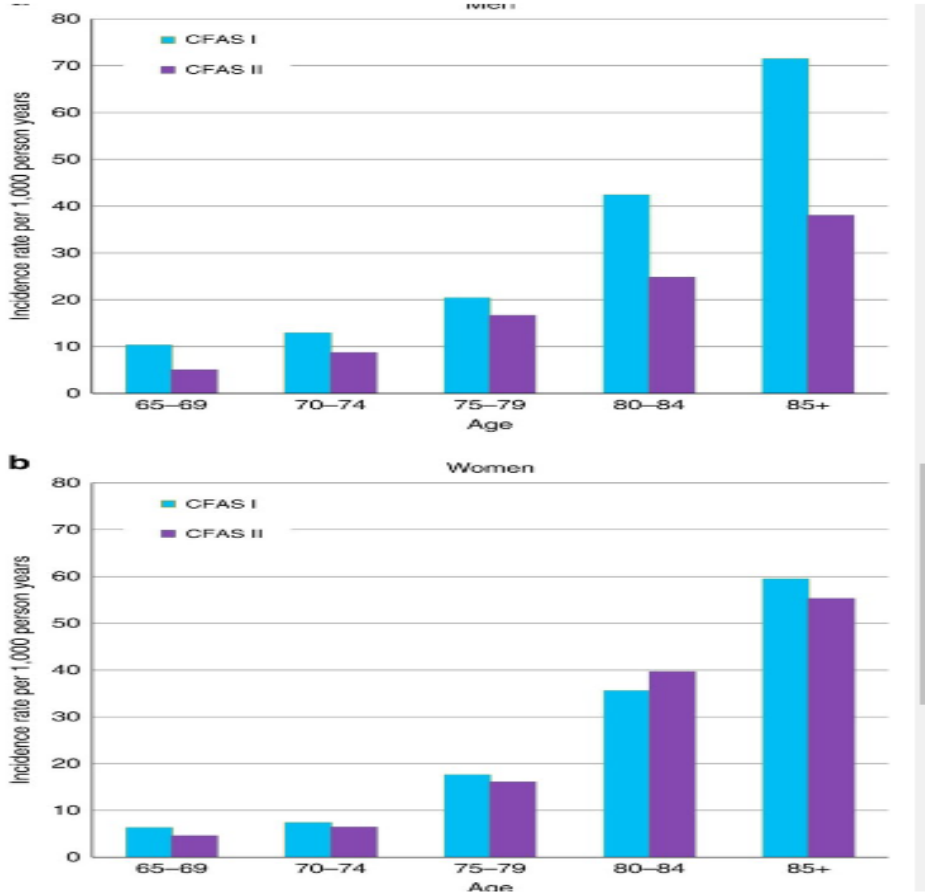


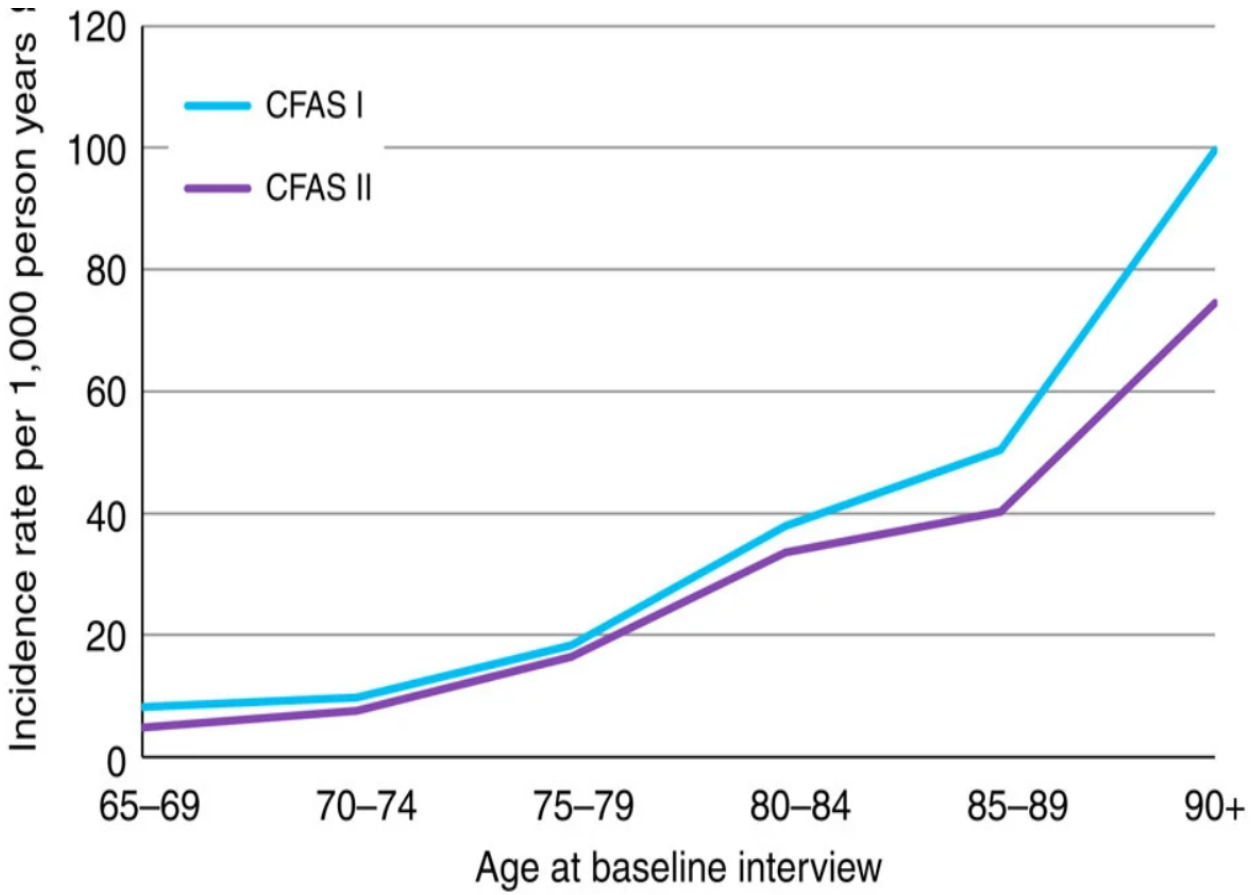




Potentially modifiable risk factors and prevention

Changing incidence rates of dementia -UK





Lancet commission 2020

Up to 40% of dementias preventable

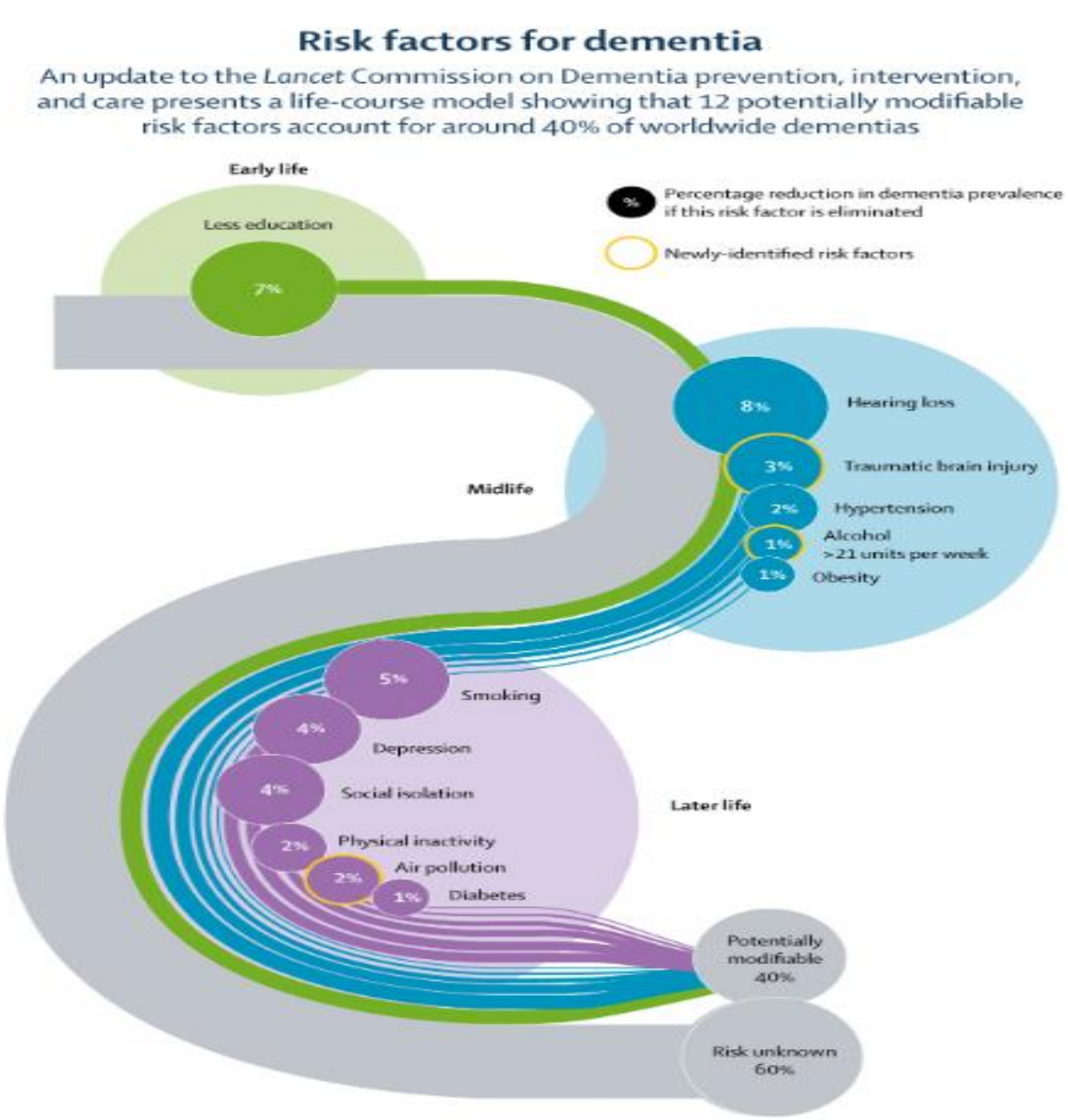
12 ‘potentially modifiable’ risk factors

Early –low education

Midlife – alcohol hearing impairment hypertension, TBI, obesity

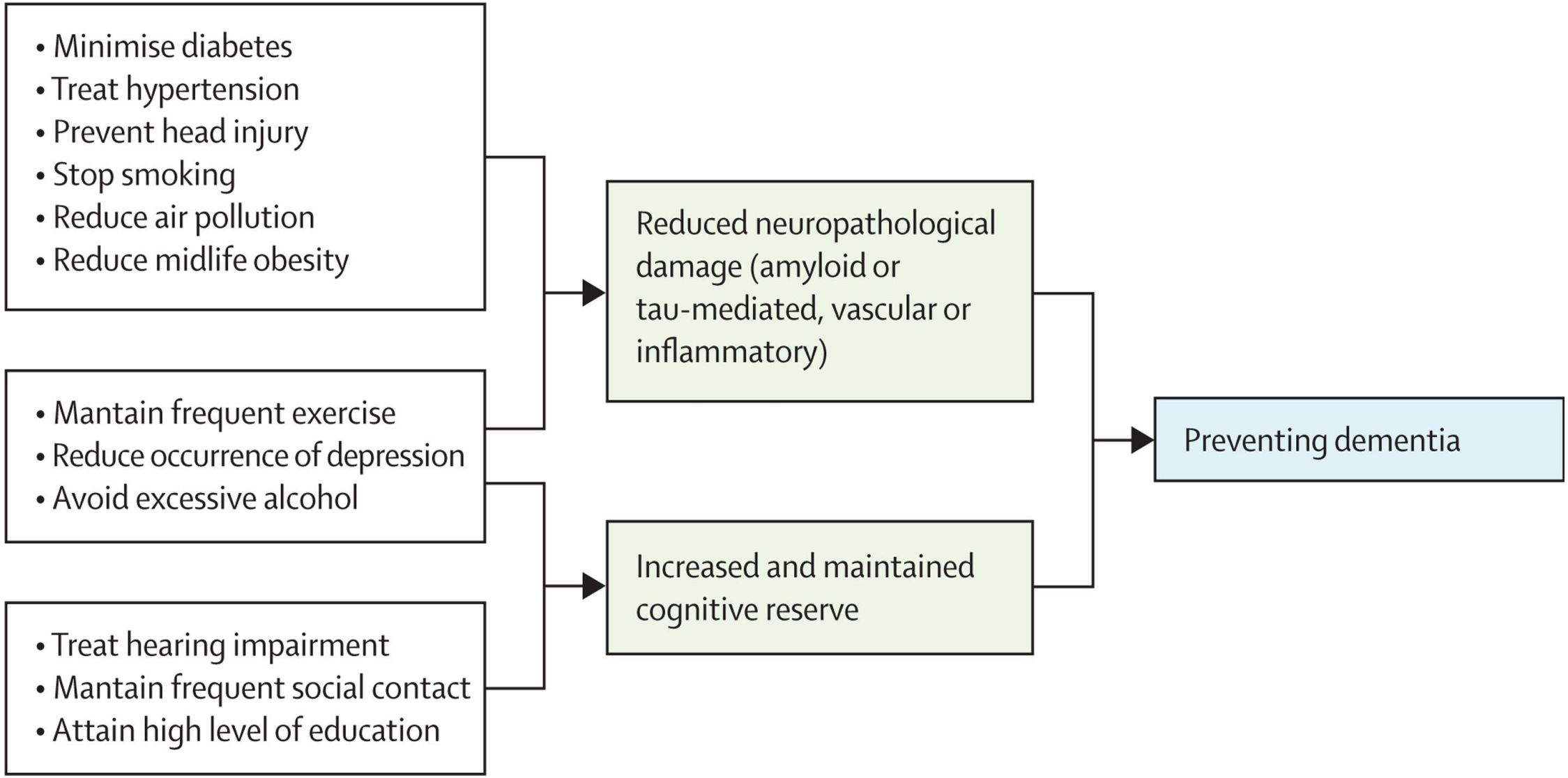
Late life – depression, smoking,

social isolation, inactivity, air pollution, diabetes

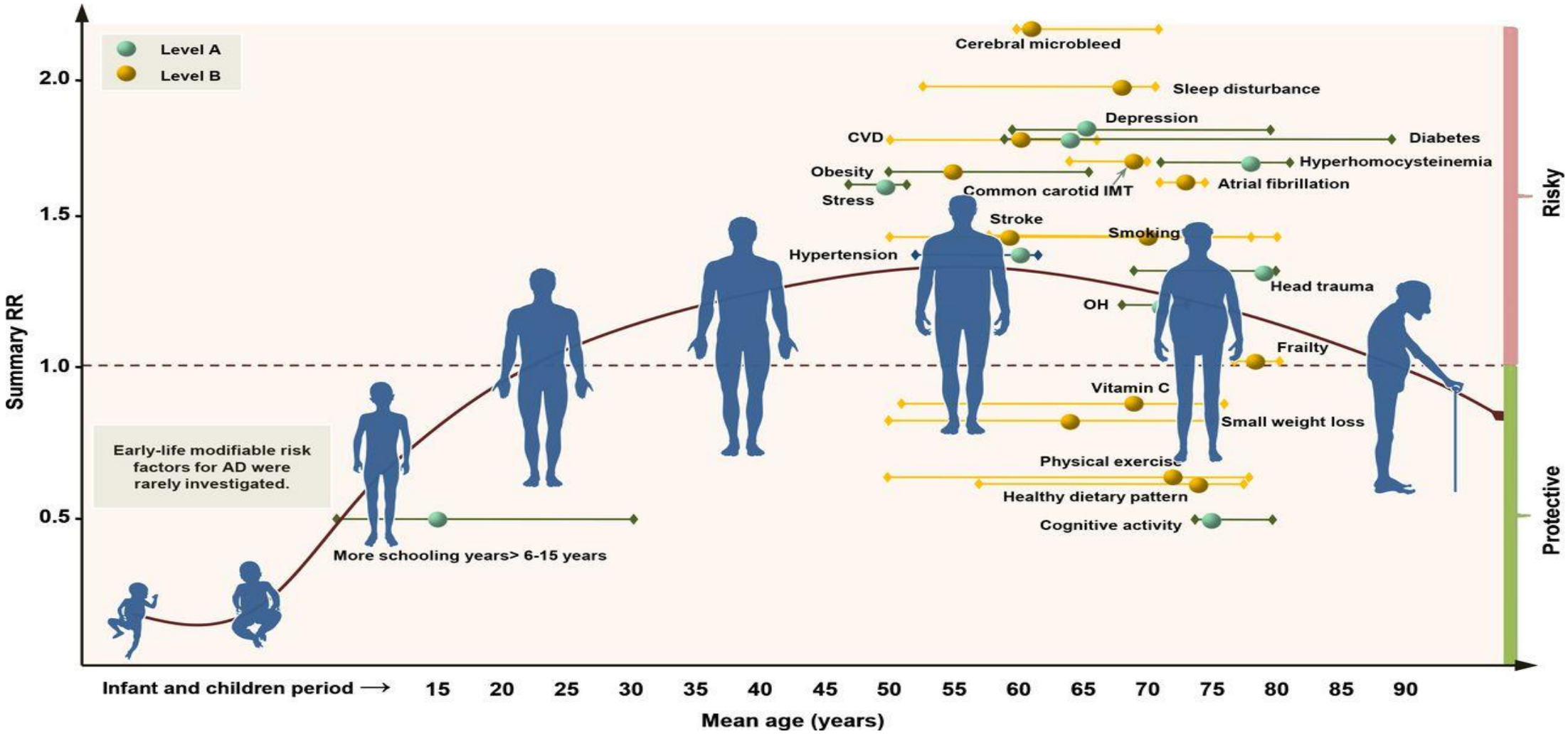


Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. The Lancet 2020.

Summary of lancet commission findings on dementia prevention 2020



Distribution of modifiable factors with Class I recommendation throughout the course of life.



Jin-Tai Yu et al. J Neurol Neurosurg Psychiatry 2020;91:1201-1209

JNNP

Summary

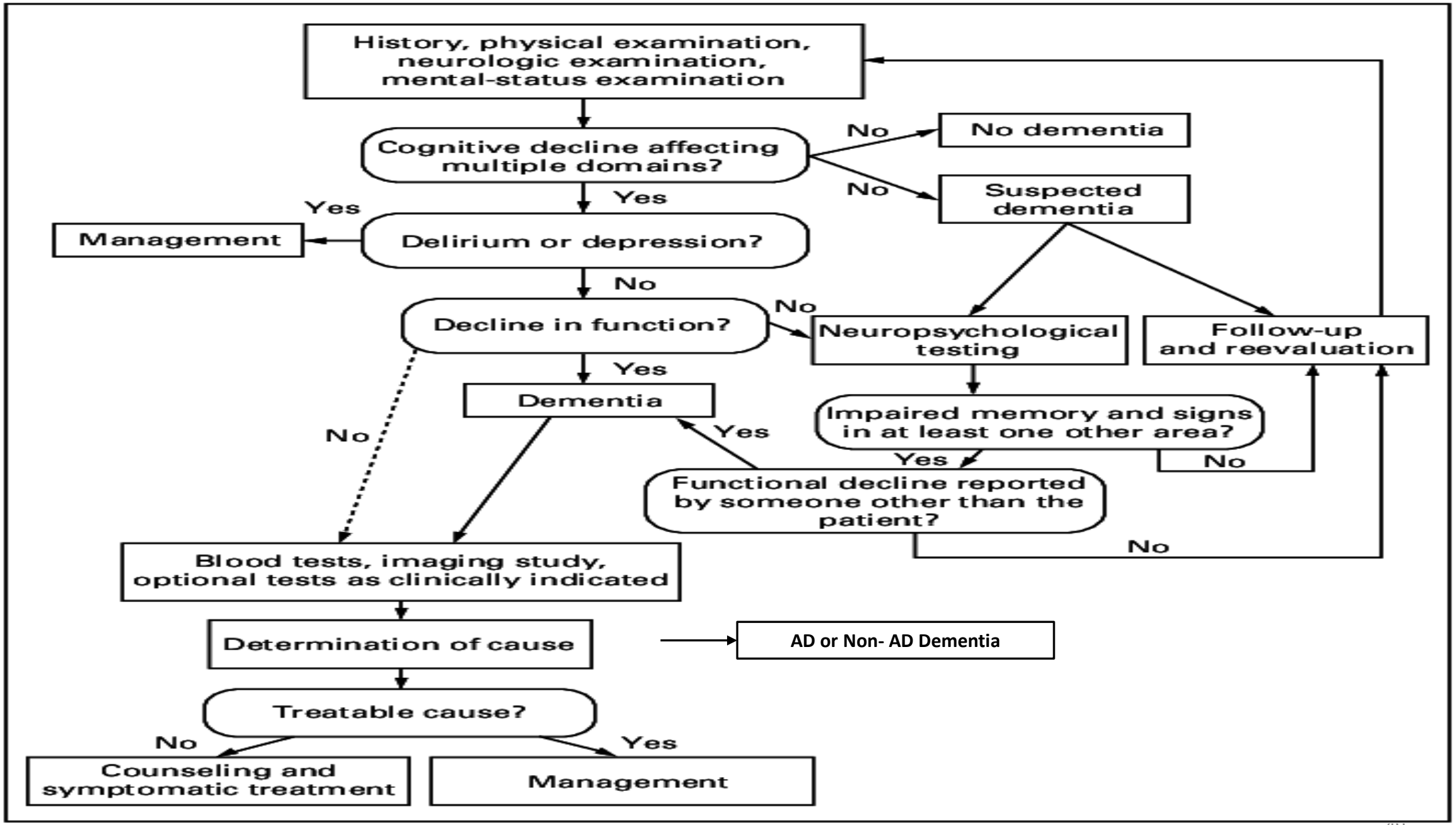
- There are some positives to normal cognitive ageing.
- SCD is common, identify and follow up those at higher risk
- MCI may be reversible, may progress. Consider follow-up, assertively identify and treat any exacerbating factors (depression/medications)
- Dementia is often mixed but most commonly AD and VAD (slides on subtypes added at end)
- Remember dementia is a terminal illness, think about psychosocial and carer support and safety (avoid antipsychotics if you can)
- Up to 40% of dementias may be preventable. 12 worldwide risk factors.

Diagnostic criteria for subtypes and diagnostic algorithms

Supplementary section

How to proceed

- Is there objective cognitive decline? (ensure culturally appropriate test used)
- Is there evidence of delirium? CAM positive? Attentional deficit? Sudden onset/fluctuating confusion/clouding of consciousness
- Is there evidence of depression? If in doubt, treat and reassess
- Is there functional impairment?
- Have other causes been excluded? (check bloods, CT brain)
- (usually 6 months duration, though no longer in DSM)
- Think about ‘subtype’ as may affect trajectory and management


History, physical examination, neurologic examination, mental-status examination
Cognitive decline affecting multiple domains?
No
No dementia
No
Suspected dementia
Yes
Yes
Management
Delirium or depression?
No
Decline in function?
No
Neuropsychological testing
Follow-up and reevaluation
Yes
Dementia
Impaired memory and signs in at least one other area?
Yes
No
Yes
No
Functional decline reported by someone other than the patient?
No
Blood tests, imaging study, optional tests as clinically indicated
Determination of cause
AD or Non- AD Dementia
Treatable cause?
No
Yes
Counseling and symptomatic treatment
Management

Dementia with Lewy Bodies (DLB)

McKeith et al 2017.

Diagnosis Requires

- ≥ 2 core features or
- 1 core feature plus 1 suggestive feature

Core Features

- Fluctuating cognition
- Recurrent visual hallucinations
- Parkinsonism

Suggestive Features

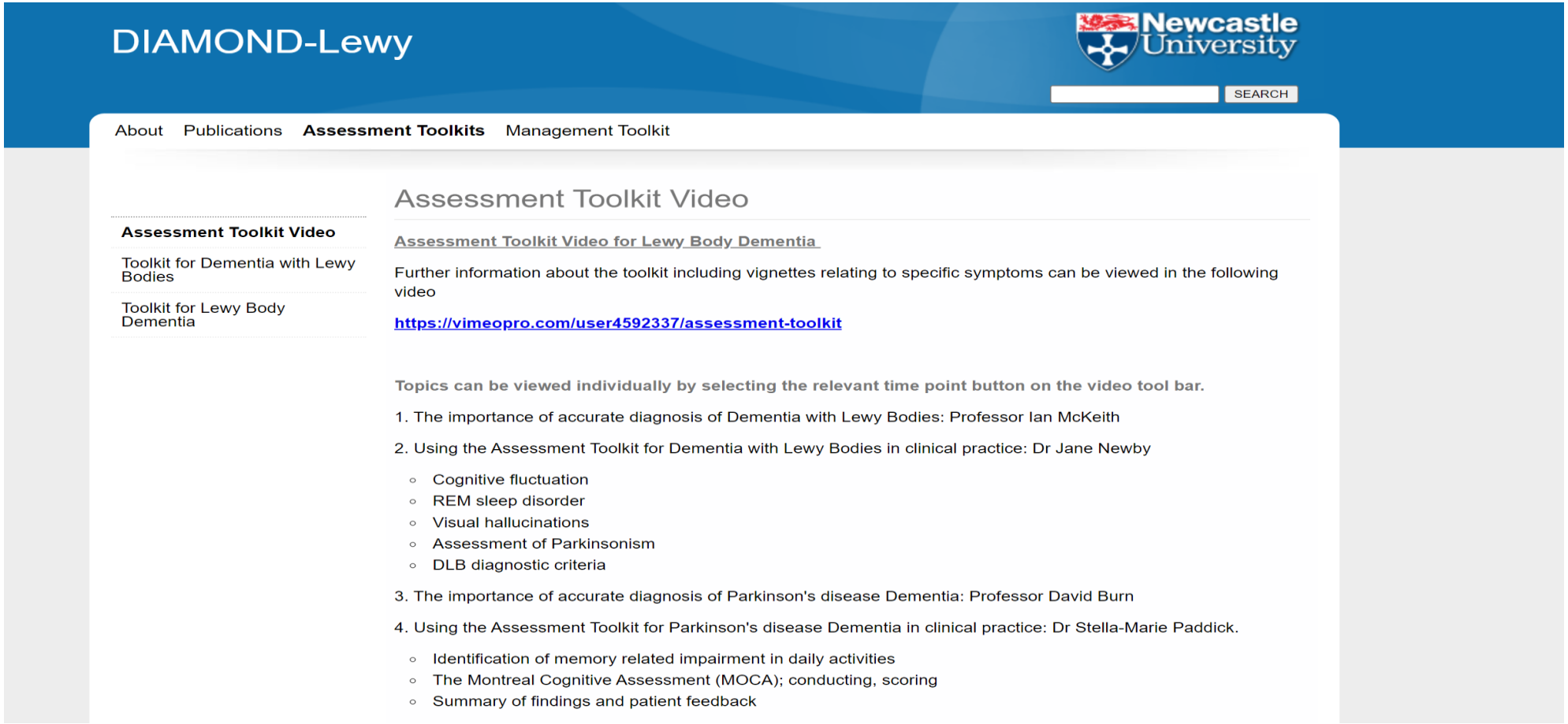
- REM sleep behavior disorder
- Severe neuroleptic sensitivity
- Low dopamine activity in basal ganglia on dopamine transporter SPECT or PET

Supportive Features (add no diagnostic specificity)

- Severe autonomic dysfunction
- Depression
- Generalized low uptake on perfusion SPECT or ^{18}F-FDG PET with relatively reduced occipital activity

DLB/PD assessment toolkit

https://research.ncl.ac.uk/diamondlewy/assessmenttoolkits/assessmenttoolkitvideo/



Diagnostic criteria for dementia in Parkinson's disease

MDS-proposed criteria for dementia in PD[1-3]

1. **Core features:** Diagnosis of PD & dementia syndrome
2. **Associated clinical features:** Impairment of at least 2 of 4 cognitive domains (may be supported by behavioural symptoms)

Features which make diagnosis uncertain

- Coexistence of any abnormality that could itself cause cognitive impairment, but not cause dementia
- Unknown time interval between onset of motor and cognitive symptoms

Features which make diagnosis impossible

Cognitive and behavioural symptoms presenting as a result of other conditions, for example:

- Acute confusion due to systemic diseases/abnormalities or drug intoxication
- Major depression according to DSM-IV
- Features of 'probable vascular dementia' according to NINDS–AIREN

- The risk of developing dementia for patients with PD, at any time, is approximately 4–6 times that for people of a similar age without PD[2]
- Dementia also seems to be more prevalent in patients with motor symptoms dominated by postural instability–gait difficulty symptoms, rather than in those for whom tremor is dominant[2]
- Drawing from these findings, the MDS task force proposed a simple set of diagnostic criteria that could be used by clinicians without specialist training[1-3]
- The criteria particularly focus on the timing of dementia symptoms; they should follow the onset of motor symptoms by ≥1 year[3]
- This distinguishes PD-related dementia from dementia with Lewy bodies (DLB), which has a different disease course[1]

AIREN=Association Internationale pour la Recherche et l'Enseignement en Neurosciences; DLB=dementia with Lewy bodies; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, fourth edition; MDS=Movement Disorder Society; NINDS=National Institute of Neurological Disorders and Stroke

1. Poewe et al. Int J Clin Pract 2008;62(10):1581–1587; 2. Emre et al. Mov Disord 2007;22(12):1689–1707;
3. Dubois et al. Mov Disord 2007;22(16):2314–2324

Frontotemporal Dementia

- Preferentially involves the frontal and temporal lobes.

- Symptoms depend on the region (lobe) involved:

- 3 variants
- Behavioral Variant
- Primary Progressive Aphasia
- Semantic Dementia

Common pathological inclusions include:

- hyperphosphrylated tau protein
- TDP- 43 protein

Frontotemporal dementia

- Lund Manchester criteria

Behaviour disorder Insidious onset, slow progression, early loss of insight, loss of social and personal awareness ,mental rigidity ,disinhibition ,lack of judgement, impulsivity , stereotyped repetitive behaviour, Impulsivity.

Affective symptoms Depression ,Hypochondriasis, emotional bluntness, lack of empathy,

Speech disorder reduction of speech ,stereotypy ,echolalia . Receptive speech preserved, late mutism.

Physical signs –Early incontinence ,Rigidity, Tremor, Low and labile blood pressure.

Neary et al , 1998.

Behavioral variant frontotemporal dementia	*Semantic dementia*	*Progressive nonfluent aphasia*
Core features		
Insidious onset and gradual progression	Insidious onset and gradual progression	Insidious onset and gradual progression
Early decline in social and interpersonal conduct	Language disorder characterized by progressive, fluent, empty, spontaneous speech; loss of word meaning; impaired naming and comprehension; semantic paraphasia*	Nonfluent, spontaneous speech with at least one of the following: agrammatism, phonemic paraphasia*, anomia
Early impairment in regulation of personal conduct	Perceptual disorder characterized by impaired recognition of familiar faces and/or objects	—
Early emotional blunting	Preserved perceptual matching and drawing reproduction	—
Early loss of insight	Preserved single-word repetition and ability to read aloud	—
Supportive features		
Behavioral disorder, with decline in personal hygiene; distractibility and impersistence; hyperorality; dietary changes; repetitive stereotypic behavior; utilization behavior	Behavioral changes with loss of sympathy and empathy; narrowed preoccupations; parsimony	Behavioral changes with early preservation of social skills; late behavioral changes similar to behavioral variant frontotemporal dementia
Speech and language changes with altered speech output; echolalia†; perseveration‡; mutism	Speech and language changes with press of speech; idiosyncratic word usage; absence of phonemic paraphasia*; dysgraphia§;	Speech and language changes with stuttering; impaired repetition; alexia‖; dysgraphia§; early preservation of word

Frascati Criteria for the diagnosis of HIV – Associated Neurocognitive Disorder (HAND)

Asymptomatic Neurocognitive Impairment (ANI)	Mild Neurocognitive Disorder (MND)	HIV-Associated Dementia (HAD)
No interference with ADLs	At least mild interference with ADLs	Marked interference with ADLs
At least 1.0 SD below mean of normative population in at least two cognitive domains	At least 1.0 SD below mean of normative population in at least two cognitive domains	At least 2.0 SD below mean of normative population in at least two cognitive domains

Clinical vs disease/specific classification (debate)

- Probable Alzheimer Disease Dementia

  Criteria for dementia are met

  Insidious onset

  Gradual progression

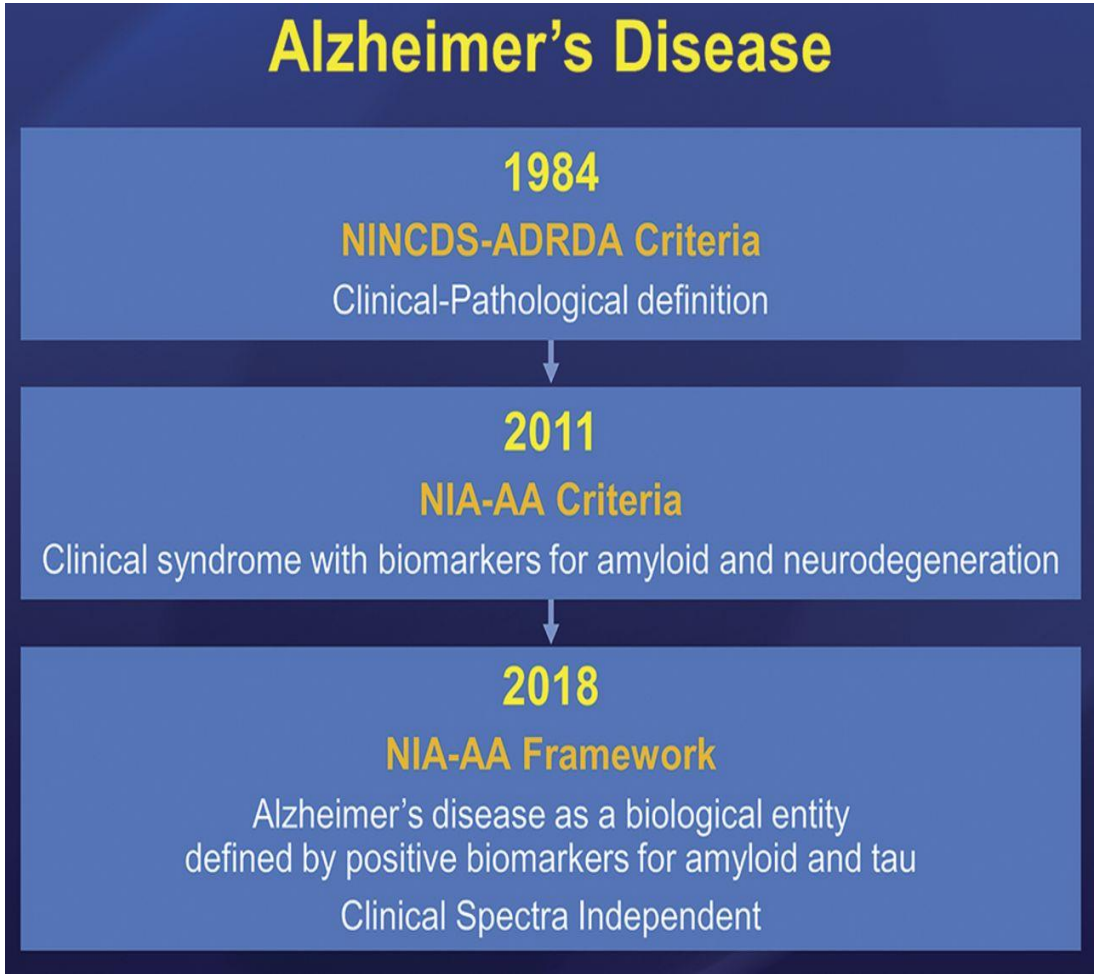
  Initial symptoms

    Amnestic

    Nonamnestic (language, executive)

  No other neurologic, psychiatric, or general medical disorders of severity that can interfere with cognition

  Positive biomarkers (eg, CSF amyloid-β [Aβ]/tau, amyloid positron emission tomography [PET], hippocampal atrophy on MRI) increase diagnostic certainty



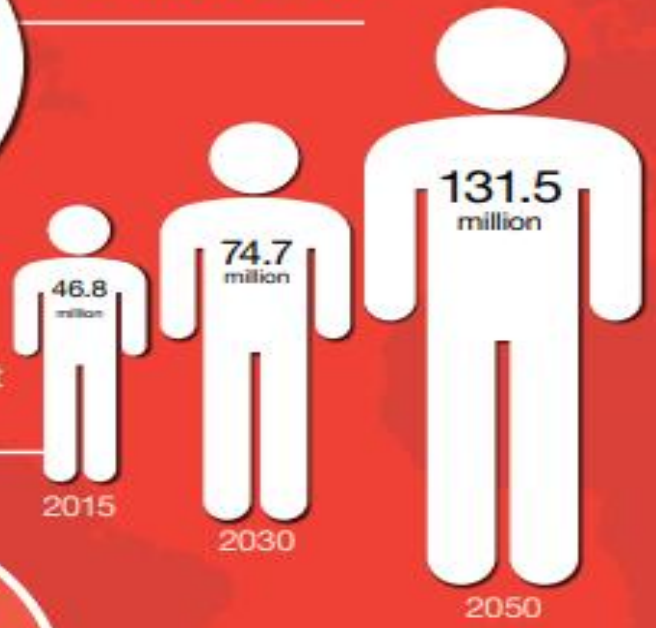
NIA/AA McKhann Criteria 2011

INFOGRAPHIC

The global impact of dementia

Around the world, there will be 9.9 million new cases of dementia in 2015,

one every 3 seconds



46.8 million people worldwide are living with dementia in 2015.

This number will almost double every 20 years.

Much of the increase will take place in low and middle income countries (LMICs): in 2015, 58% of all people with dementia live in LMICs, rising to 63% in 2030 and 68% in 2050.

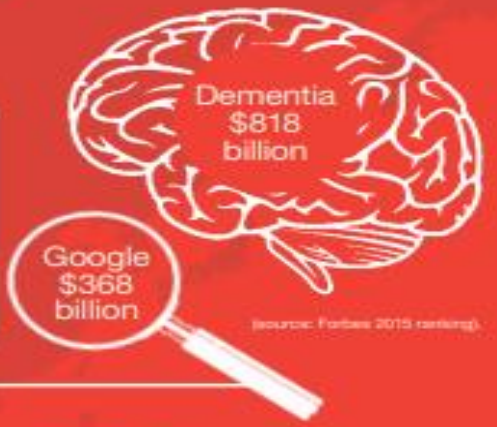
The total estimated worldwide cost of dementia in 2015 is US$ 818 billion. By 2018, dementia will become a trillion dollar disease, rising to

US$ 2 trillion by 2030

If global dementia care were a country, it would be the

18th largest economy

in the world exceeding the market values of companies such as Apple and Google



(source: Forbes 2015 ranking)

This map shows the estimated number of people living with dementia in each world region in 2015.

We must now involve more countries and regions in the global action on dementia.