Cognitive problems in the elderly

CPD meeting, Benoni, Department of Family Medicine, University of Pretoria
26th August 2022. 14:00 – 15:00

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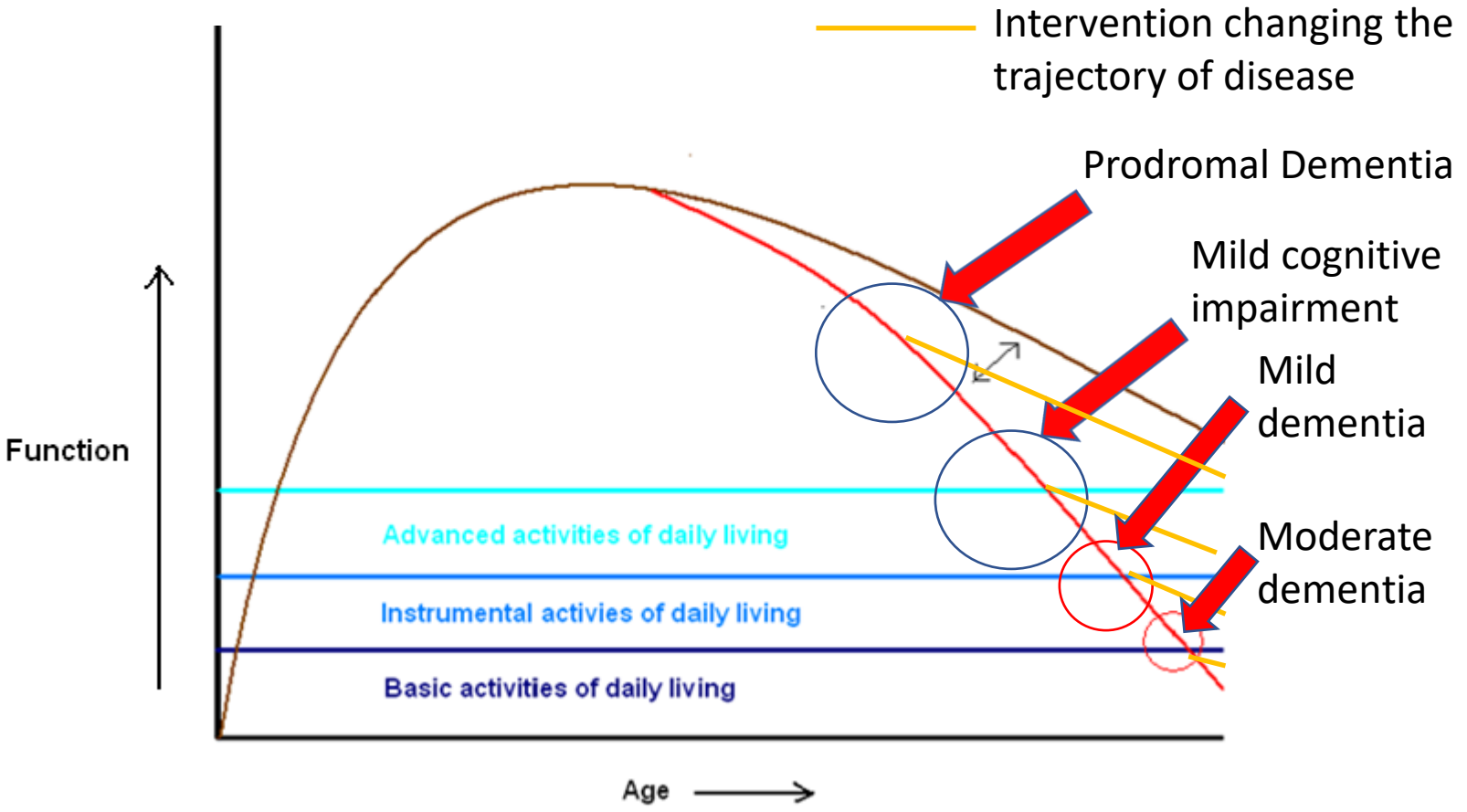
Disclosures – Brent Tipping

- Division of Geriatric Medicine at Wits University has received the following educational training grants:
  - 2012-2022 from Sir Donald Gordon and his Foundation
  - 2012-2013, 2019 from the Discovery Health Foundation
- I am a co-investigation on a National Institutes of Health R01-AG054066 project entitled: Cognitive Function, Alzheimer's Disease and Related Disorders in the HAALSI Cohort.
- I have received honoraria for presentations/ participation on advisory boards/travel or educational grants from:
  - Adcock Ingram (2014)
  - Astellas (2021)
  - Bayer (2016, 2018)
  - Boehringher Ingelheim (2012)
  - Janssen (2008, 2018)
  - Lilly (2016)
  - Novartis (2010, 2013, 2017)
  - Merck (2017)
  - Servier laboratories (2009-2018)

Functional decline with ageing and disease



"Normal" ageing is NOT associated with any functional impairment

Simplified scheme of the stages of memory and possible impairments

STIMULUS

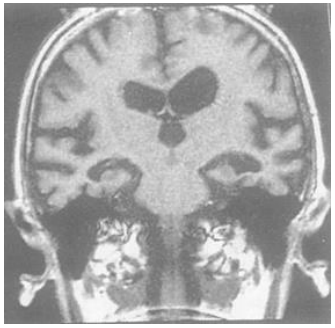
REGISTRATION → STORAGE → RETRIEVAL → Stimulus recall

<u>Attentional /concentration disorders:</u>

- **Delirium**
- Sleep
- Depression disorders
- Anxiety/Severe stress
- Hearing loss
- Medications

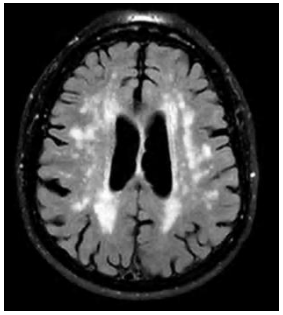
<u>Damage to cortical (grey matter) structures:</u>

- Alzheimer's Dementia



<u>Sub cortical (white matter connections) dysfunction:</u>

- Mini-stroke dementia



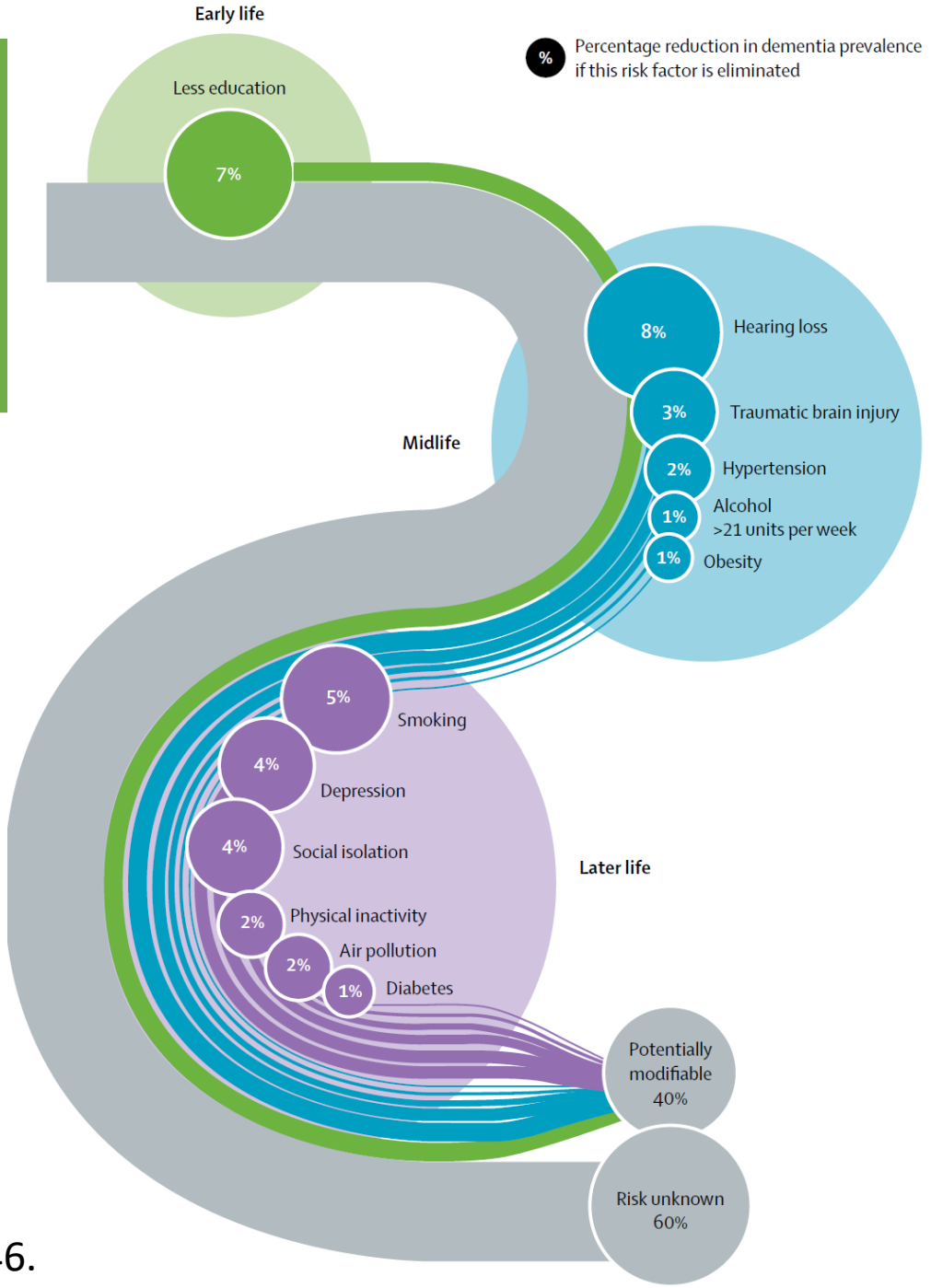
Dementia

A loss of mental ability severe enough to interfere with normal activities of daily living, lasting more than six months, not present since birth, and not associated with a loss or alteration of consciousness.

Dementia is a life-course illness

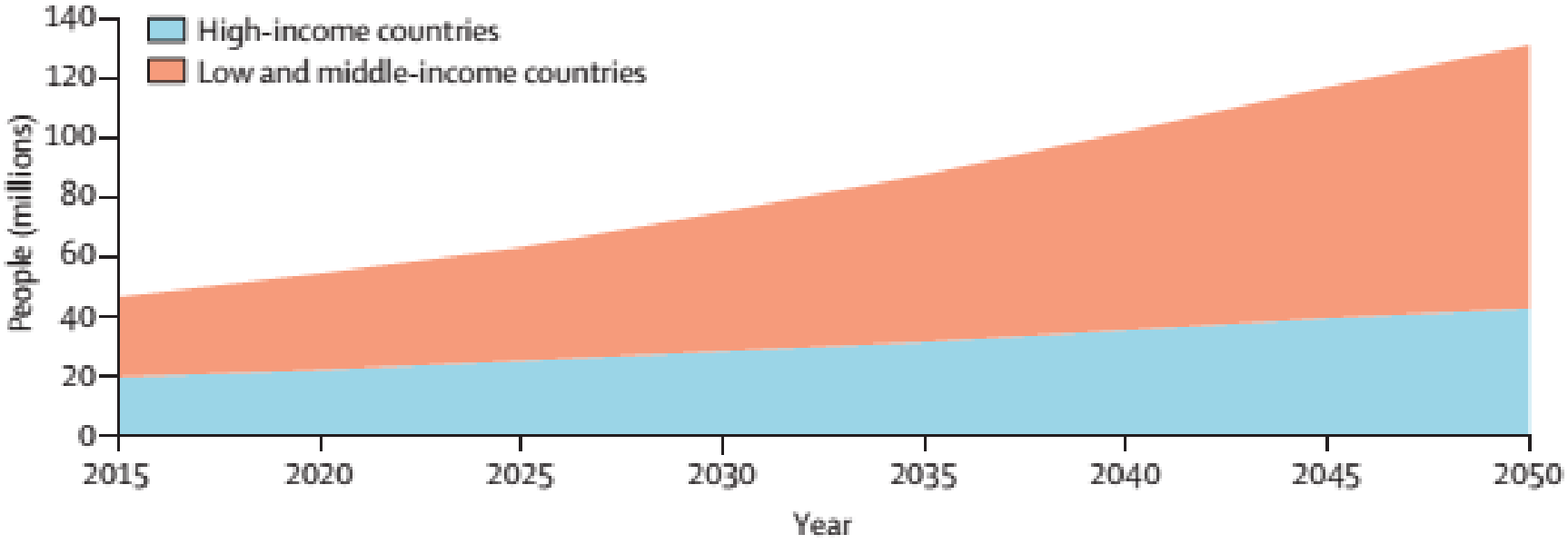
There is no one miracle cure at the end that will fix the problem!

Population attributable fraction of potentially modifiable risk factors for dementia



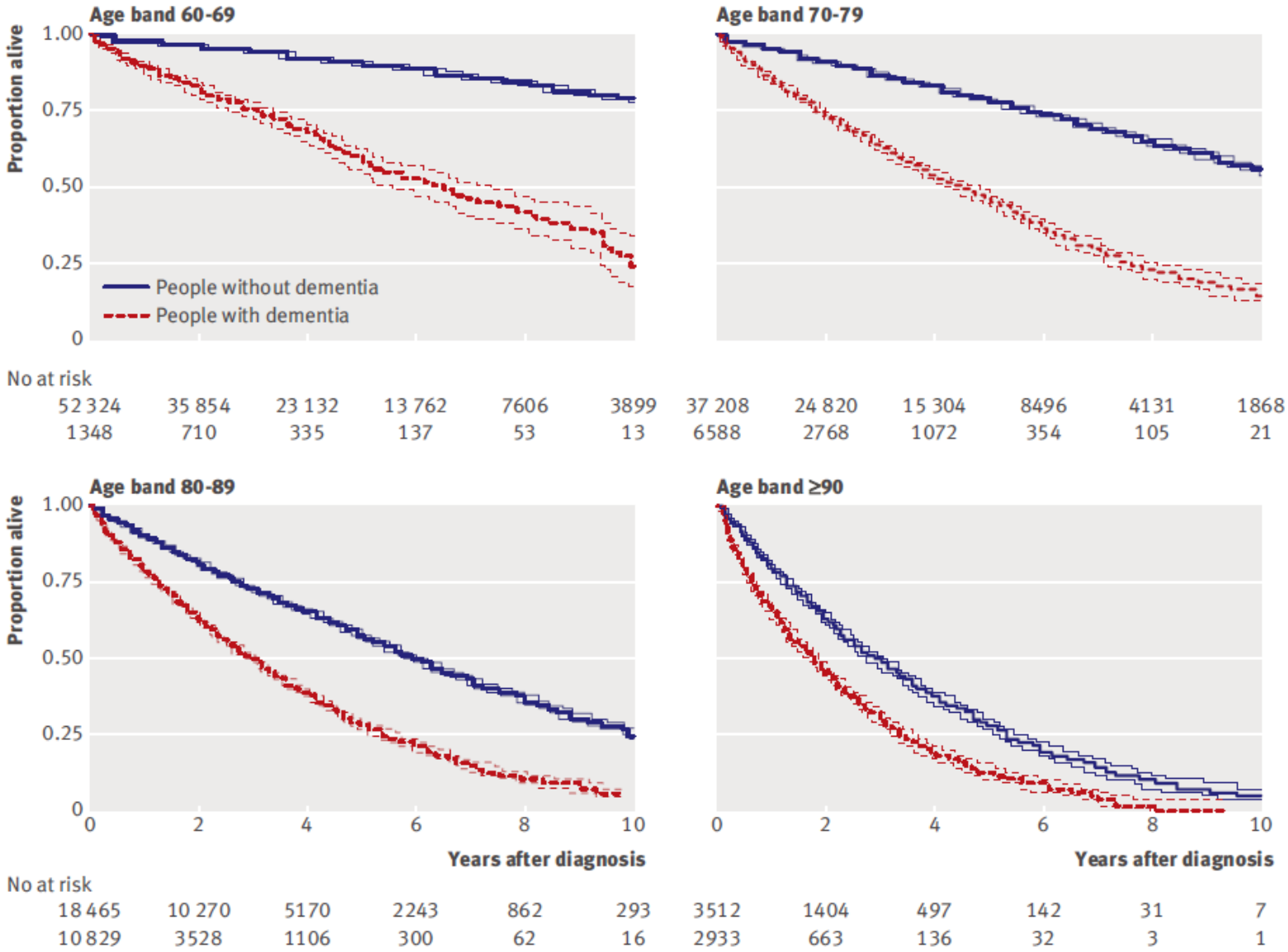
Livingston et al. Lancet 2020; 396: 413–46.

Growth in numbers of people with dementia in high-income and low and middle-income countries



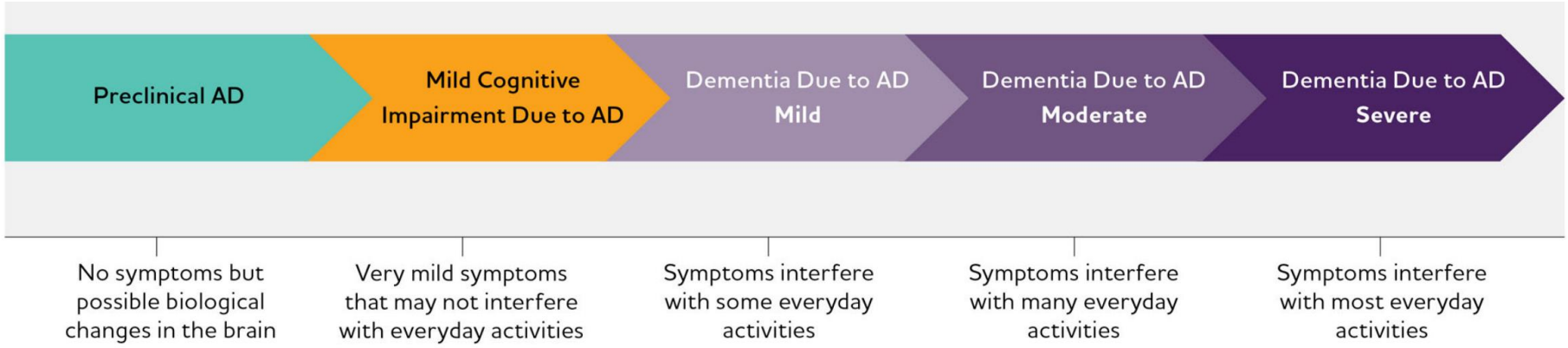
Prince et al. World Alzheimer report 2015. Alzheimer's Disease International, 2015.

Kaplan-Meier survival curves for people with and without dementia



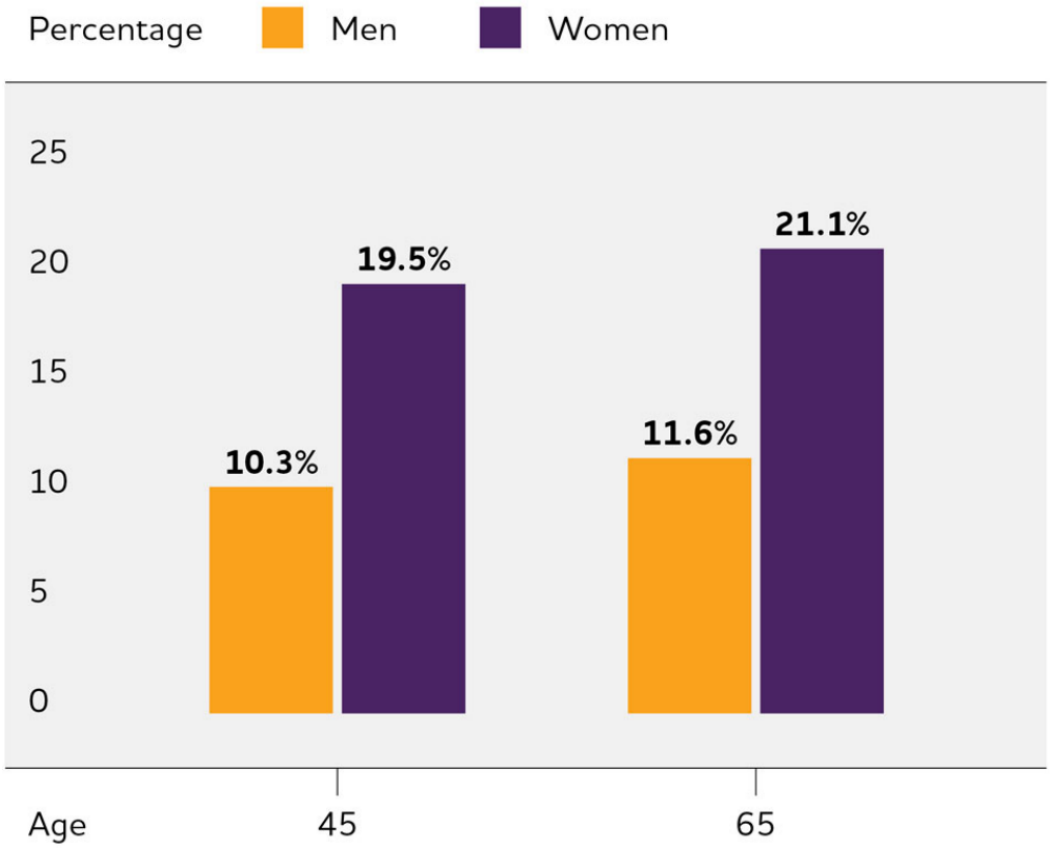
Rait et al. BMJ 2010;341:c3584

Healthy cognition–to–dementia continuum



DOI: 10.1002/alz.12638 ALZHEIMER'S ASSOCIATION REPORT

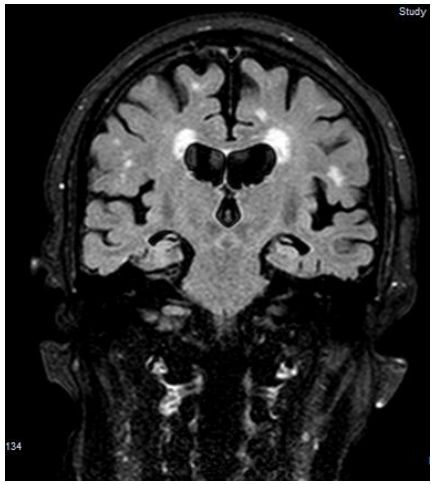
Estimated lifetime risk for Alzheimer's dementia, by sex, at ages 45 and 65. USA population.

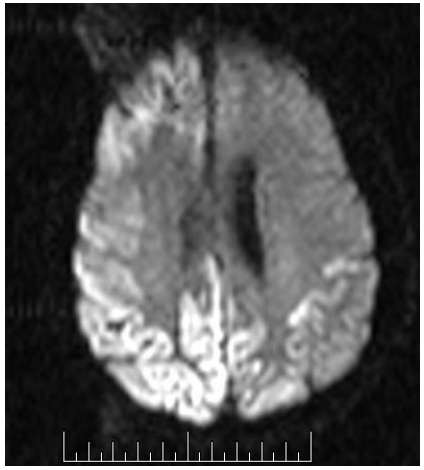


DOI: 10.1002/alz.12638 ALZHEIMER'S ASSOCIATION REPORT

Neuro-degenerative/Vascular causes dementia

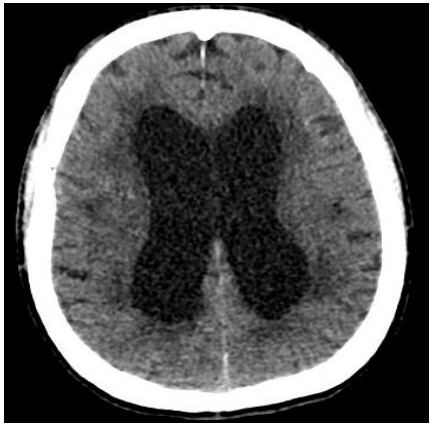
Alzheimer's type – early and late onset (common)
Vascular dementia – Sub cortical ischemia, post-stroke, multiple infarct (common)
Limbic-predominant age-related TDP-43 encephalopathy (uncommon)
Frontotemporal dementia – behavioural and semantic variants (rare)
Lewy Body Dementia and Parkinson's disease (uncommon)
Huntington's disease (very rare)
Prion disease (very rare)
Primary Progressive aphasia(rare)

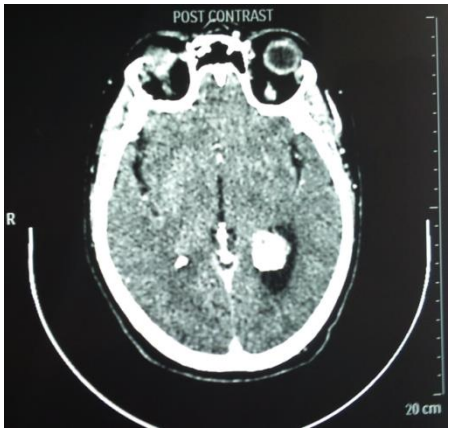


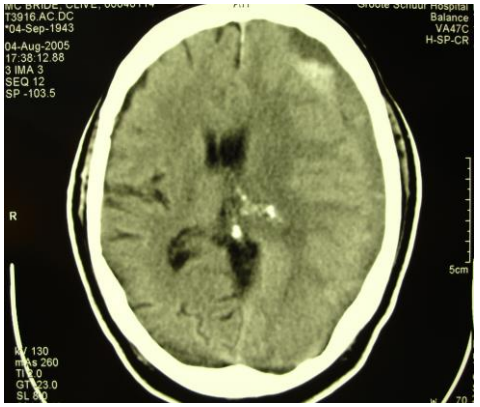


“Correctable/stabilisable” causes of cognitive problems

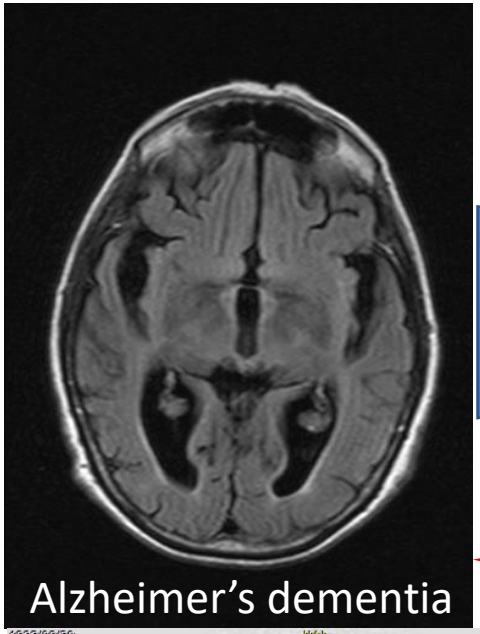
Brain tumours
Infection related – HIV associated neurocognitive disorder, tertiary syphilis
Normal pressure hydrocephalus
Recurrent hypoglycaemia
Vitamin deficiencies: Pellagra (B6), Thiamine (B1), Pernicious anaemia (B12)
Subdural haemorrhage
Chronic electrolyte imbalances – hypercalcemia, hyponatremia
Chronic hypoxia, obstructive sleep apnoea
Depression and anxiety disorders
Excessive alcohol intake
Dysthyroidism – hyper or hypo functioning
Poor vision: cataracts
Poor hearing







Not everything in life is clear cut



Alzheimer's dementia

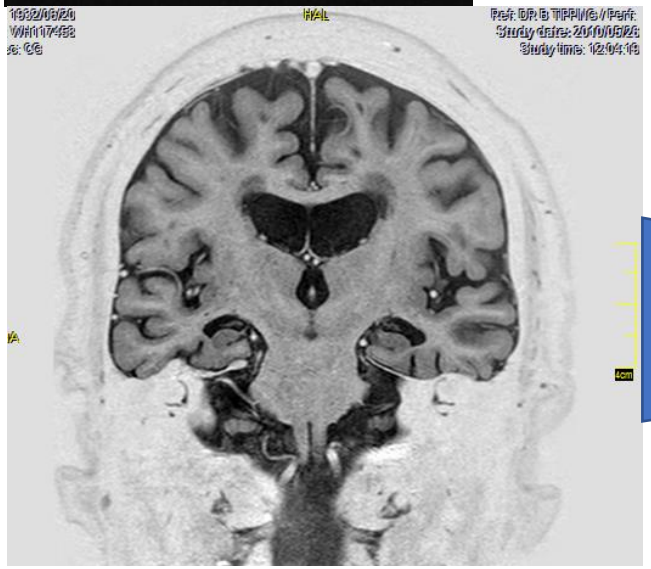
Alcohol

Head injury

Neurodegenerative burden

Vitamin B12

Vascular disease burden

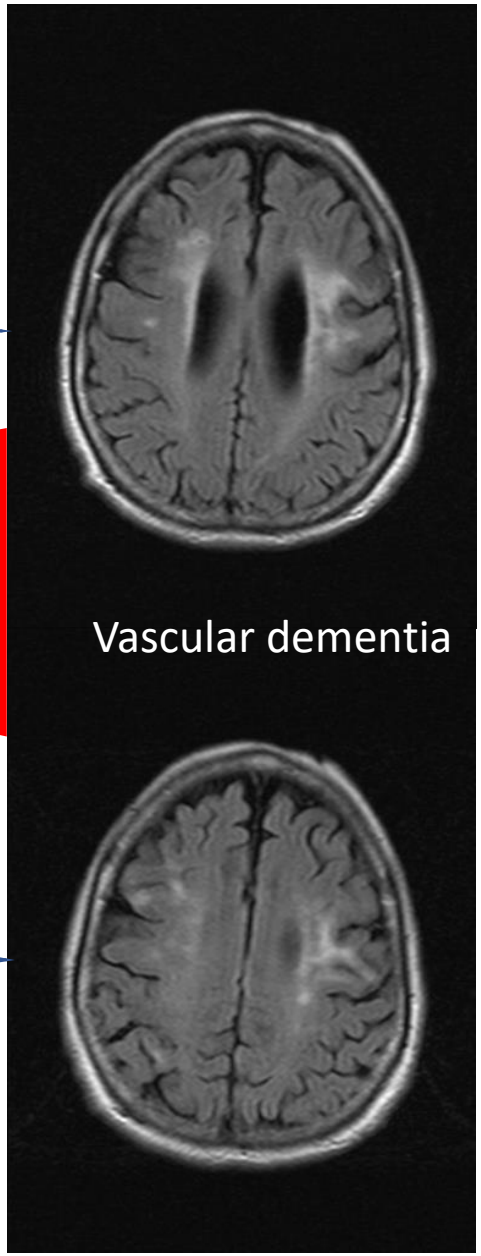


Dysglycaemia/diabetes mellitus

Neurodegenerative burden

Sleep apnoea/COPD

Depression



Vascular dementia

Early correct diagnosis of cognitive impairment in 2022 allows:

- Patient involvement in decision making.
- Exclusion of cognitively exacerbating illness.
- Implementation of cognitive protective strategies.
- Caregiver support and planning.
- Early detection and management of accelerators/co-morbidity e.g. depression, vitamin B12 deficiency, etc.

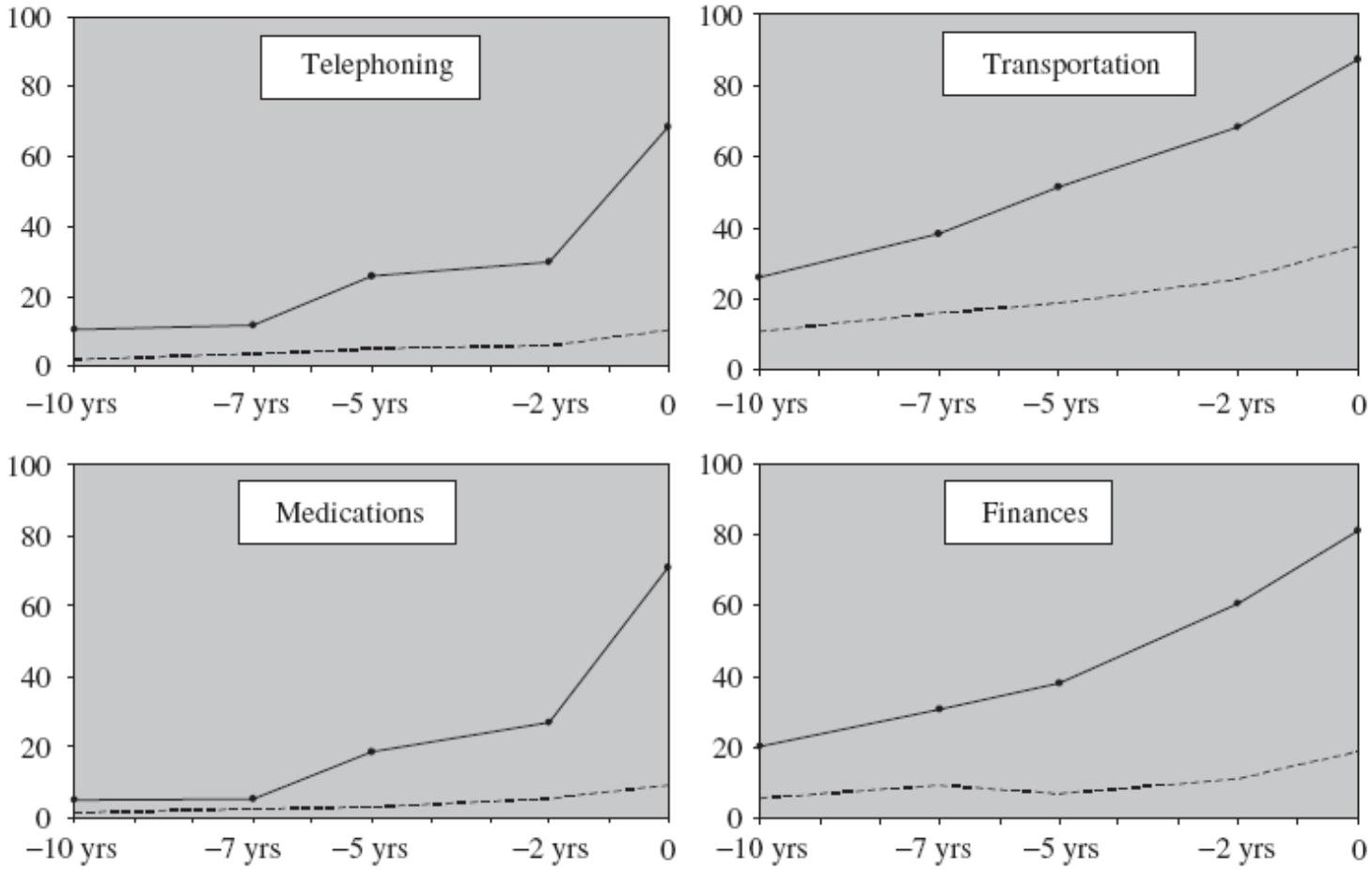
Diagnosis of a clinical sub-type in early dementia in 2022:

- Guides management in terms of:
  - Non-pharmacological strategies
  - Pharmacological strategies
  - Monitoring for adverse effects e.g. aspiration/falls
  - Caregiver support/planning
  - Advanced care planning

Components of the clinical evaluation of a patient with cognitive impairment

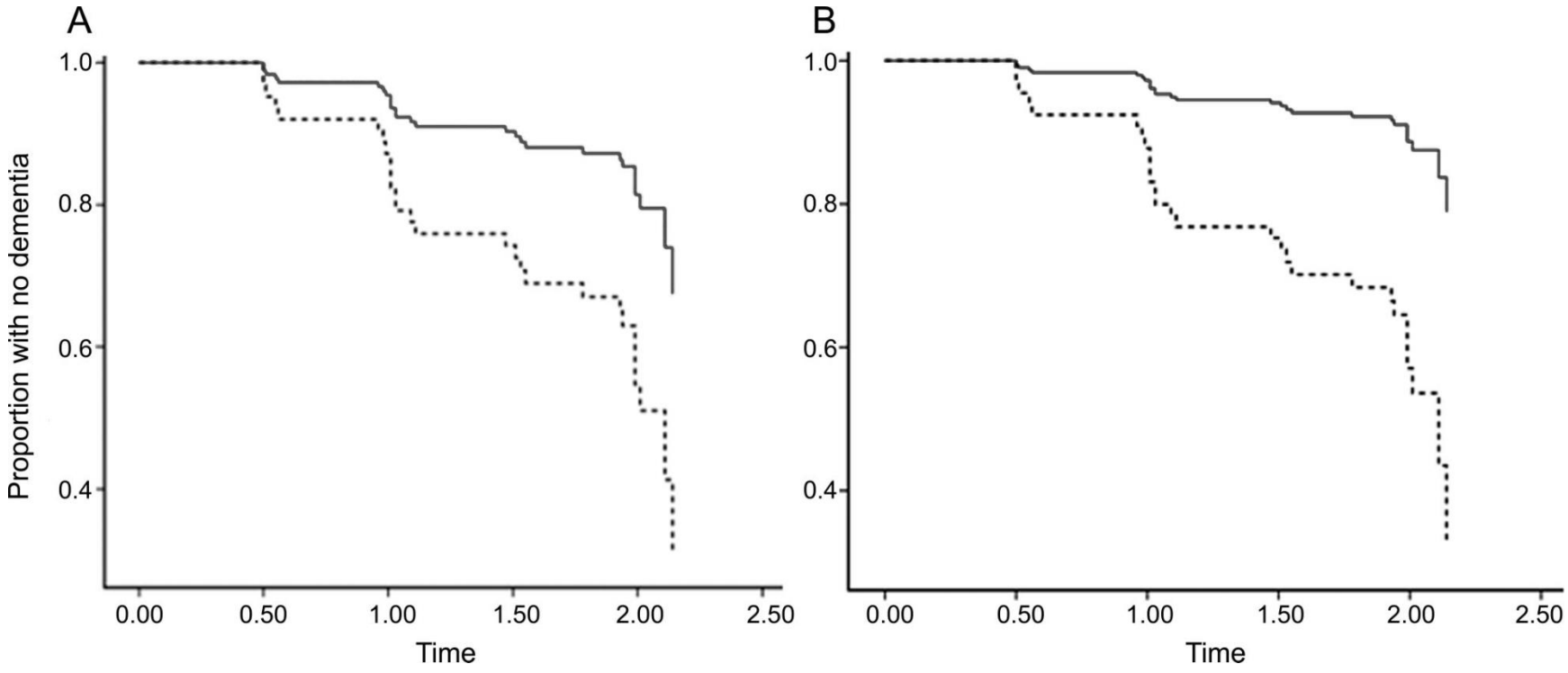
- Functional status – pre morbid vs. current
- Clinical course
- Neuropsychiatric symptoms
- Hearing and vision
- Cognitive assessment (MOCA/MMSE)
- Gait /falls – timed up and go, gait speed or watching the commute into the consulting room
- Continence
- Vascular risk factors – BP, DM, smoking, cholesterol, atrial fibrillation, OSA
- Alcohol intake
- Support structures/safety issues
- Bloods – Sodium, calcium, glucose, haemoglobin, urea, vitamin B12, CRP, HIV, RPR, GGT, MCV
- Neuroimaging

Prevalence of restriction in the four specific instrumental activities of daily living over the 10 years preceding dementia



Peres et al. J Am Geriatr Soc 2008;56:37-44

Survival curves in MCI patients show increased conversion over time for abnormal relative to normal subjects for PET and episodic memory



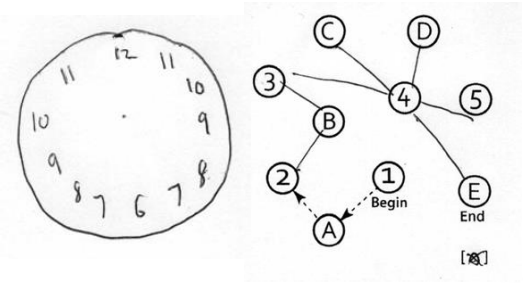
FDG-PET

Episodic memory (AVLT)

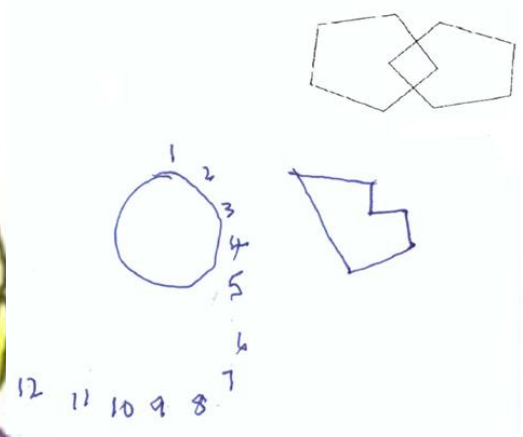
Neurology 2010;75:230–238

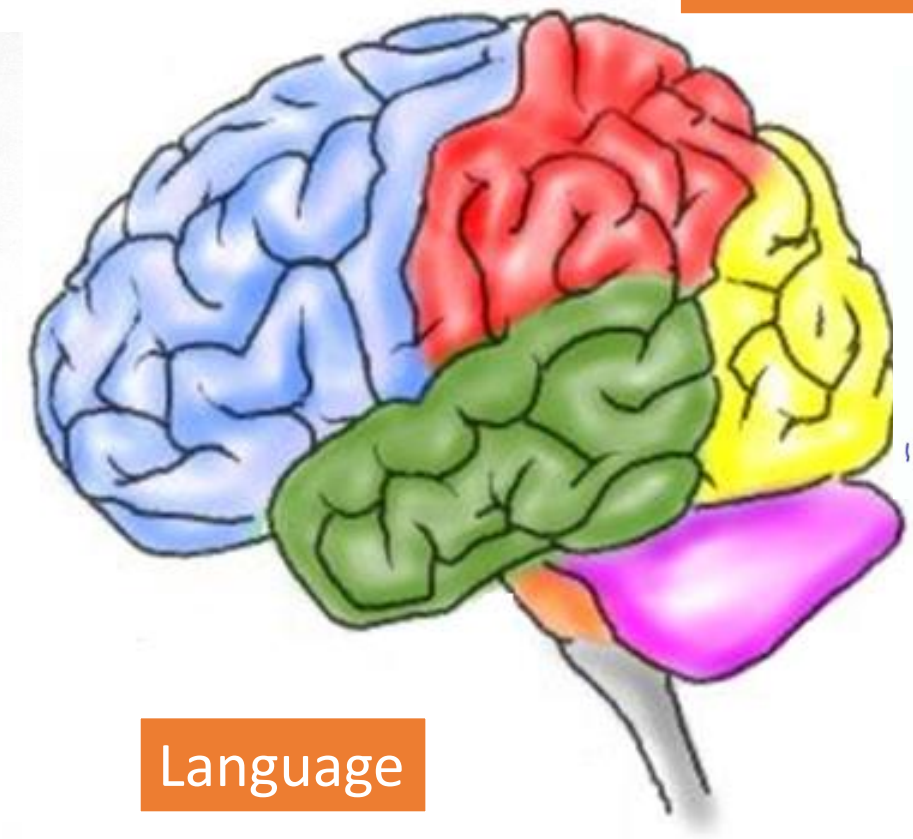
Bedside cognitive testing

Executive function

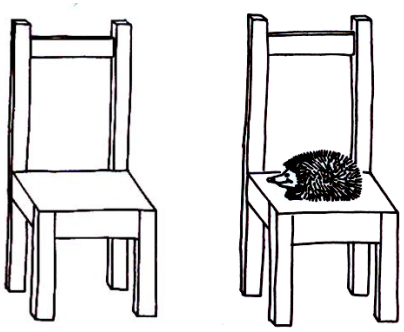


Visuospatial/calculation





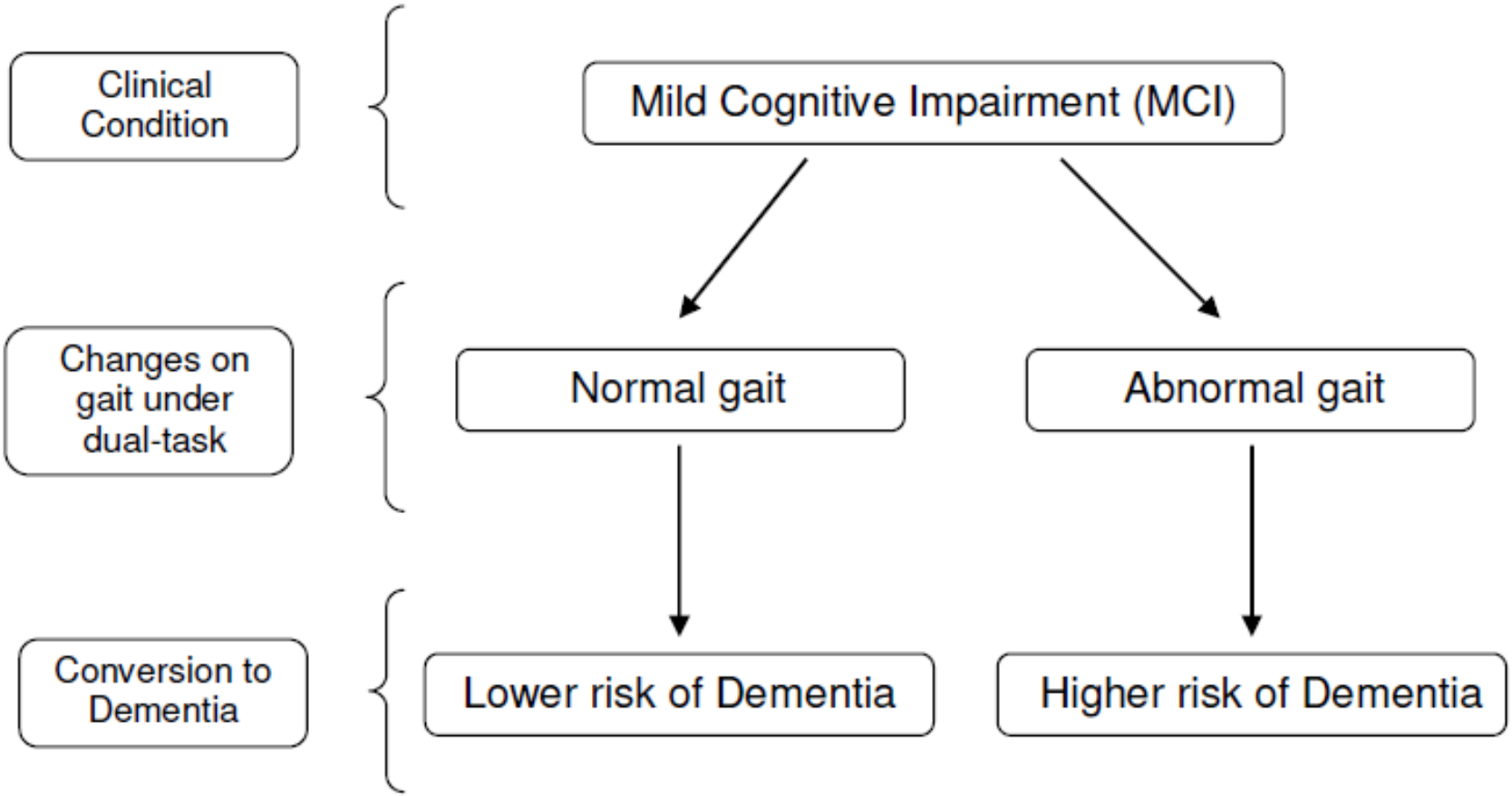
Memory



Attention

Language

Gait and cognition



BMC Geriatrics 2009; 9: 41

Abnormality of gait as a predictor of non-Alzheimer's dementia

INCIDENCE OF DEMENTIA AMONG 337 SUBJECTS WITH NORMAL GAIT AND 85 SUBJECTS WITH ABNORMAL GAIT AT BASE LINE.

Clinical Diagnosis	No. of Subjects with Diagnosis		Incidence per 100 Person-Years of Follow-up		Unadjusted Relative Risk (95% CI)*
	Normal Gait	Abnormal Gait	Normal Gait	Abnormal Gait	
Any dementia	88	37	4.07	8.28	2.03 (1.39–2.99)
Alzheimer's disease	57	13	2.64	2.91	1.10 (0.60–2.01)
Non-Alzheimer's dementia	31	24	1.43	5.30	3.75 (2.20–6.38)
Vascular	26	21	1.20	4.70	3.91 (2.20–6.94)
Other	5	3	0.23	0.67	2.90 (0.69–12.14)

Verghese et al. N Engl J Med 2002;347:1761-8.

Association between severity of cerebral small vessel disease and impaired gait

Severity of Cerebral SVD		Impaired Gait Velocity*		Impaired TUG Test†	
		OR (95% CI)	No./Total‡	OR (95% CI)	No./Total‡
WML volume in quintiles (range in mL)					
First+second	(0.5–5.1)	1.0 (reference)	5/172	1.0 (reference)	4/172
Third	(5.1–8.9)	4.1 (1.3–12.5)§	12/87	2.7 (0.8–9.8)	8/87
Fourth	(8.9–20.6)	2.0 (0.6–6.6)	10/86	2.5 (0.7–8.9)	11/86
Fifth	(20.6–139.7)	4.3 (1.3–14.1)§	23/86	4.4 (1.2–15.8)§	22/86
Lacunar infarcts					
0		1.0 (reference)	23/299	1.0 (reference)	22/299
1 or 2		1.4 (0.6–3.1)	13/93	1.0 (0.4–2.4)	11/93
>2		4.5 (1.7–12.0)§	14/39	3.1 (1.1–8.7)§	12/39

Adjusted for age, sex, height, TBV, and no. of lacunar infarcts or WMLs.
*Defined as <1 m/s in gait velocity.
†Defined as a TUG test of >12 seconds.
‡No. represents the absolute no. of subjects with an impaired gait velocity or TUG test in that group.
§$P<0.05$.

Karlijn F. de Laat et al. Stroke 2010, 41:1652-1658

Prevalence of cognitive impairment syndromes

Mild cognitive impairment

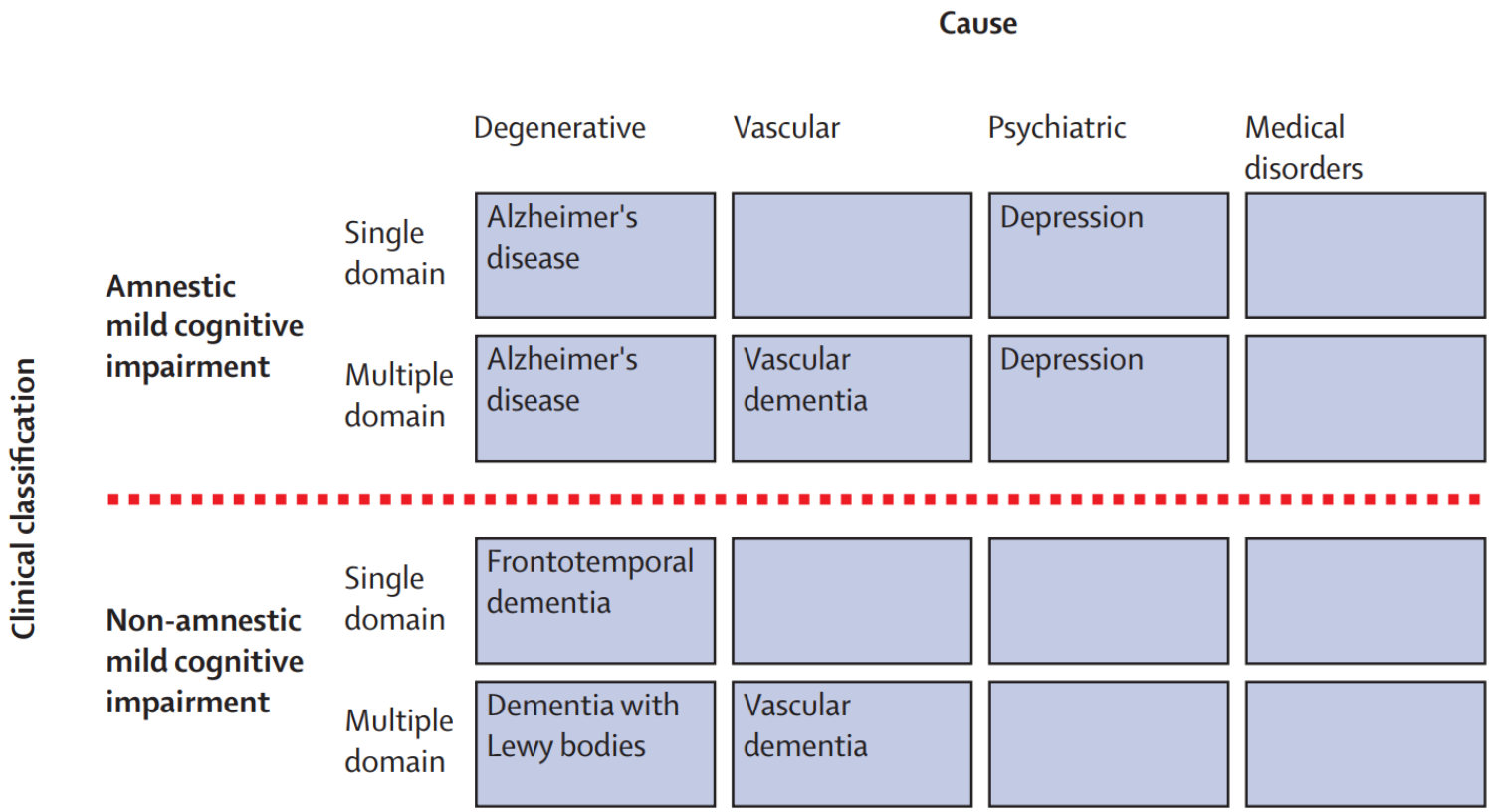
Age	Prevalence
60-64	6.7%
65-69	8.4%
70-74	10.1%
75-79	14.8%
80-84	25.2%

Dementia

Age	Prevalence
60-64	1%
65-74	5%
75-84	15%
>85	35%

Petersen et al. Practice guideline update summary: Mild cognitive impairment. Neurology 2018;90(3):126- 135

Syndrome of Mild Cognitive Impairment (MCI)



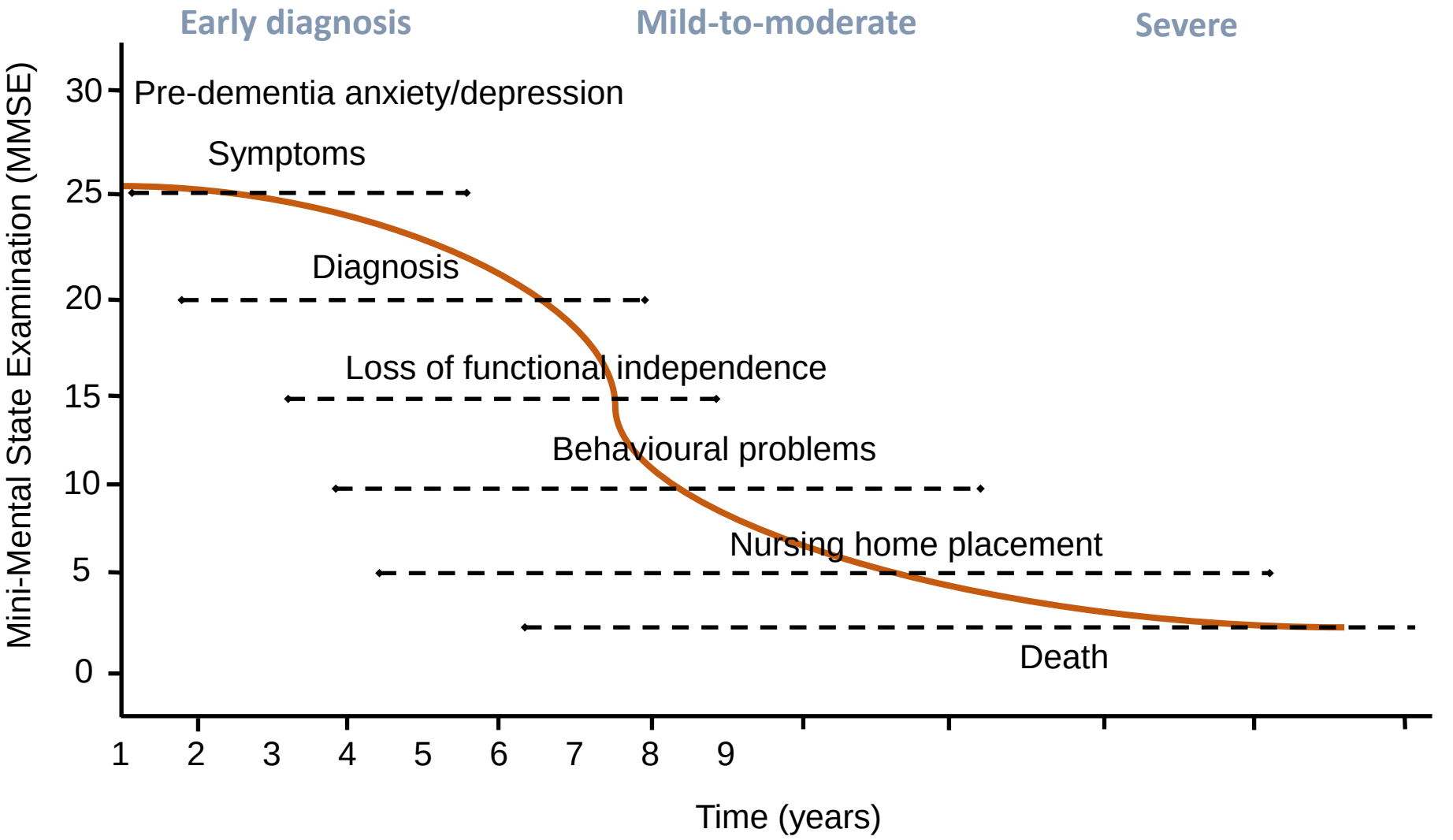
Presumed outcome of the subtypes of MCI when combined with the presumed pathogenesis

Gauthier et al. Lancet 2006; 367: 1262–70

Alzheimer's type dementia

- Cognitive testing – episodic memory deficits which don't correct with cueing, visuospatial
- Function – congruent with MMSE score.
- Neuropsychiatric – early on = mood problems, later on behaviour problems related to patient/environment mismatch
- Gait – "mobile enough to wander off and get lost"
- Continence – preserved until late when can't find the toilet
- Present via – children, self (when insight preserved early in disease)
- Clinical course: slow and steadily/predictably progressive
- Differential: early disease – mood disorder
- 10% rule – atypical presentation, seizures, hallucinations, rapid decline

Natural history of Alzheimer's dementia



Feldman and Gracon. The Natural History of Alzheimer's Disease. London: Martin Dunitz, 1996

Severity of Dementia (Alzheimer's)

(according to MMSE Score)

- 20-24 – Mild – medications, driving, finances, cooking.
- 19-15 – Moderate – help dressing, shaving.
- 10-14 – Moderately Severe – incontinence, lost at home, misidentifying family members.
- <10 – Severe – poor speech, poor mobility, poor eating

Frontotemporal dementia

- Cognitive testing – executive, language (particularly naming), memory. NB visuospatial always preserved initially.
- Function – much worse than the cognitive tests suggest. Often marked early impact on ability to work as mainly “younger patients 55-70 years”
- Neuropsychiatric – often few years lead in of psychiatric type problems – apathy, can appear “bipolar”, loss empathy with strained family relations, marked personality changes. Sweet tooth.
- Gait – very well preserved.
- Continence – urinary/faecal accidents without concern from moderate disease.
- Present via – family. Every one has had enough!
- Clinical course – slowly progressive
- Differential: alcohol, Alzheimer’s, late onset bipolar disease.

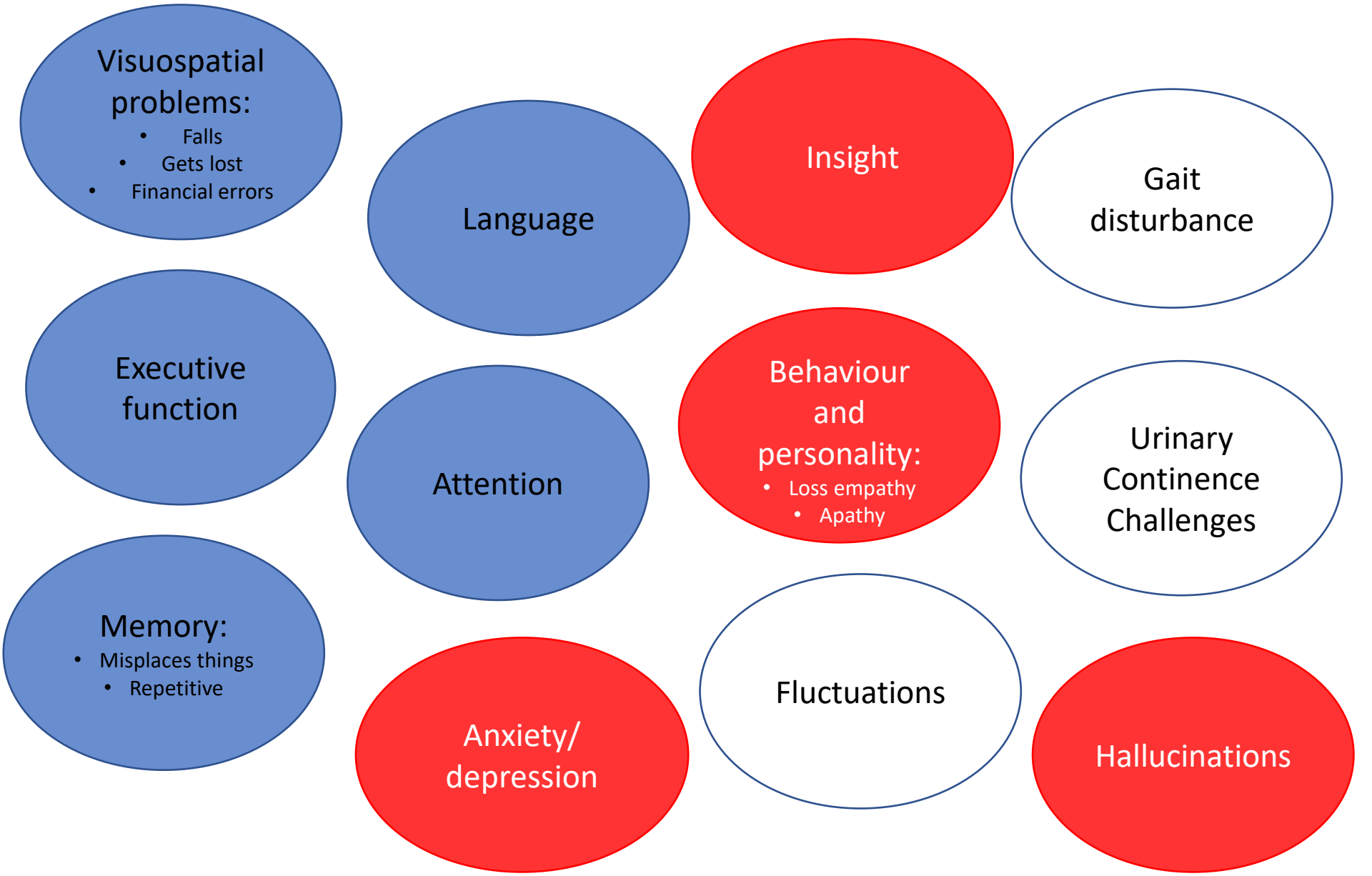
Lewy Body Dementia

- Cognitive testing – visuospatial, attention, executive function.
- Function – worse than the cognitive tests suggest – finances particularly poor.
- Neuropsychiatric – visual hallucinations, REM sleep disorder
- Gait – parkinsonian, falls
- Continence – bladder and bowel changes in moderate disease
- Present via – cardiologist, neurologist
- Clinical course: unpredictable and fluctuating
- Differential: delirium, alcohol related cognitive impairment, atypical Alzheimer's
- Inadvertent "trial of life" if given neuroleptics.

Vascular dementia – sub cortical ischemic type

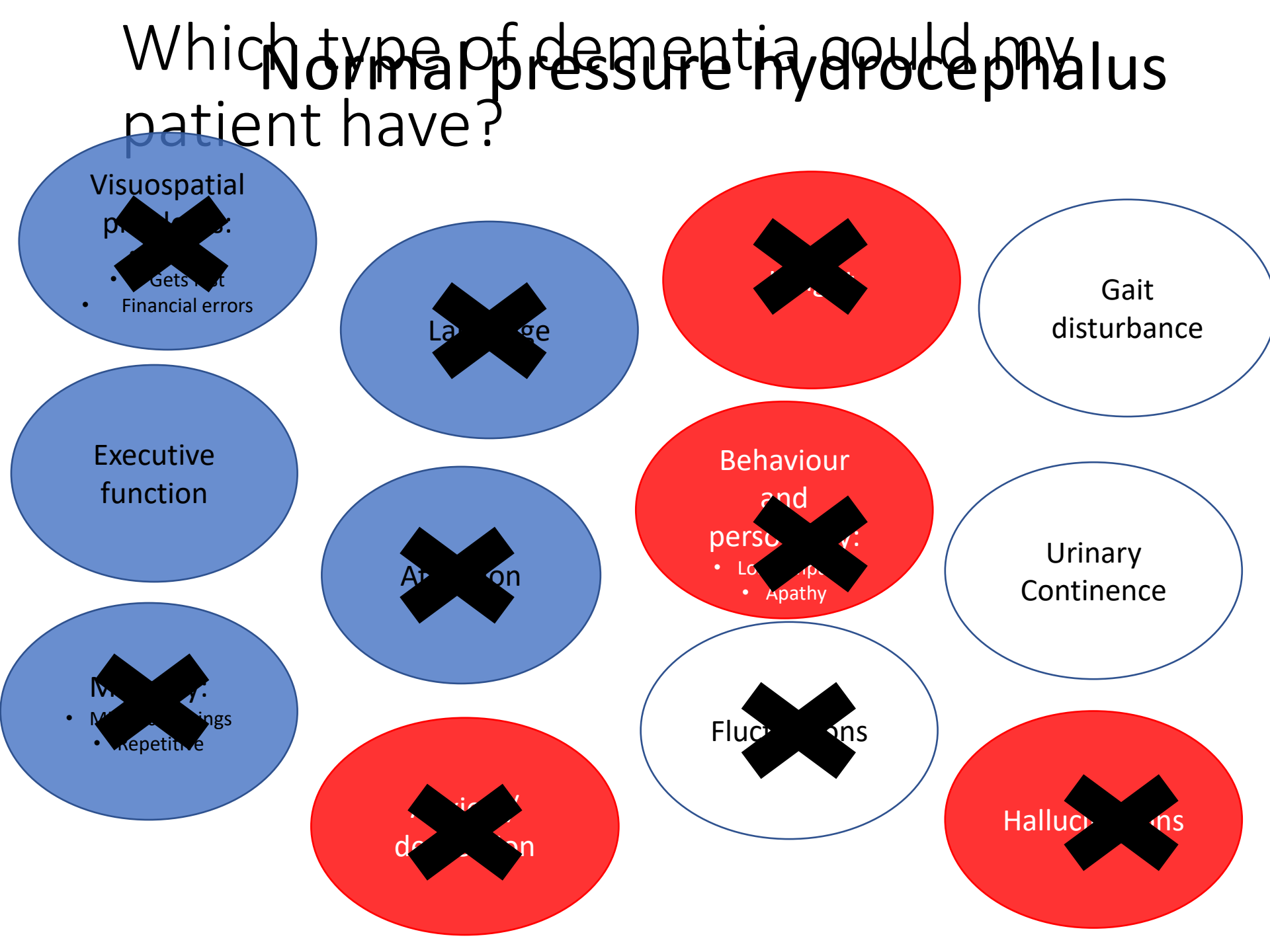
- Cognitive testing – executive function, visuospatial, language, memory (improves with cueing).
- Function – much worse than the cognitive tests suggest.
- Neuropsychiatric – “problem patients”, apathy, mood disorders
- Gait – poor gait initiation, “feet glued to floor”
- Continence – urinary/faecal accidents due to being caught short.
- Present via – family practitioner, vascular surgeon, cardiologist, neurologist, endocrinologist
- Clinical course: unpredictable, “step-wise”
- Differential: delirium, alcohol related cognitive impairment, atypical Alzheimer’s
- Vascular risk factors – DM2, smoker, hypertension (though can “settle” in later disease), OSA, AF, COPD, hyperlipidaemia.

Clinical assessment



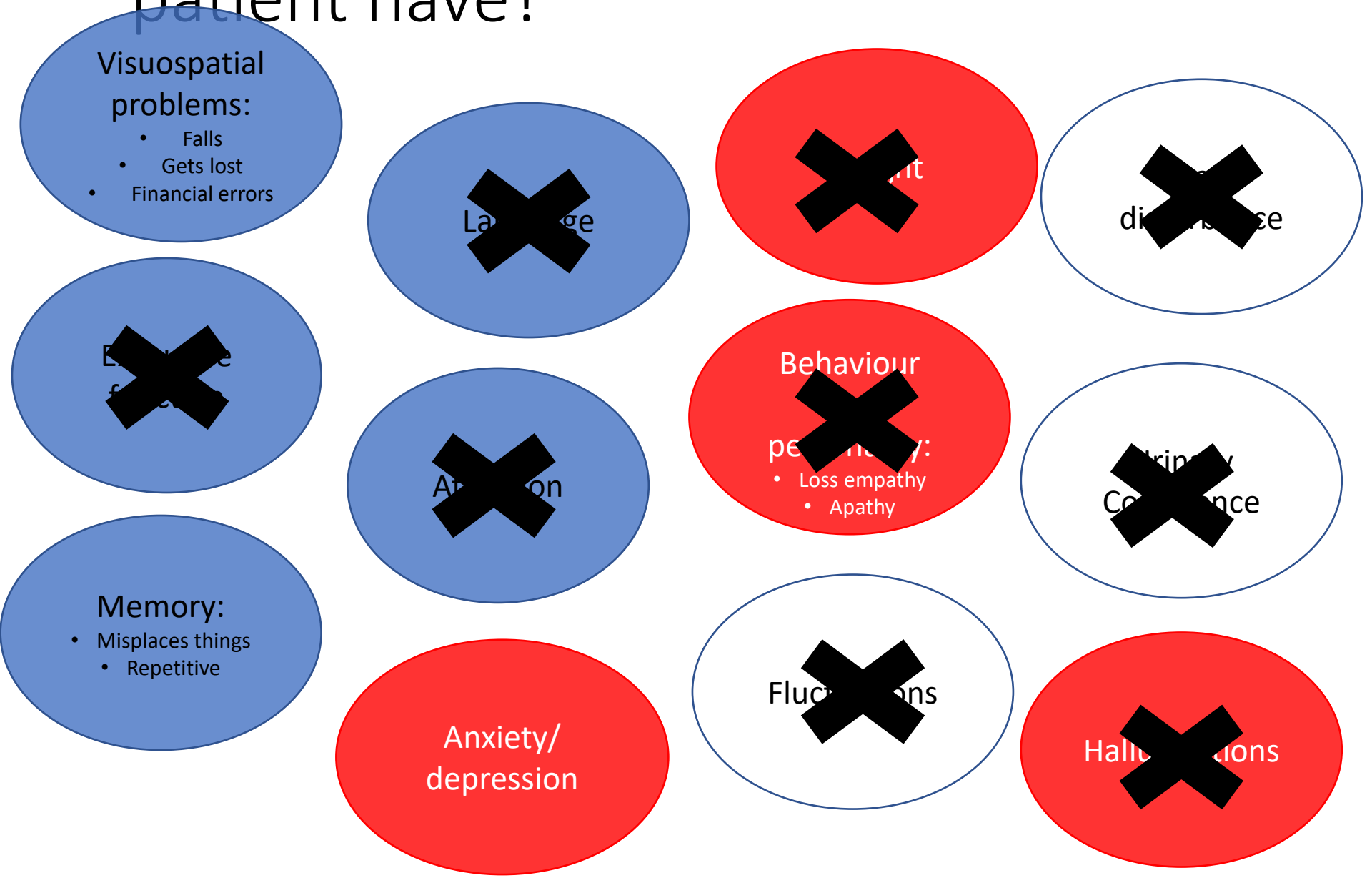
Which type of dementia could my patient have?

Normal pressure hydrocephalus



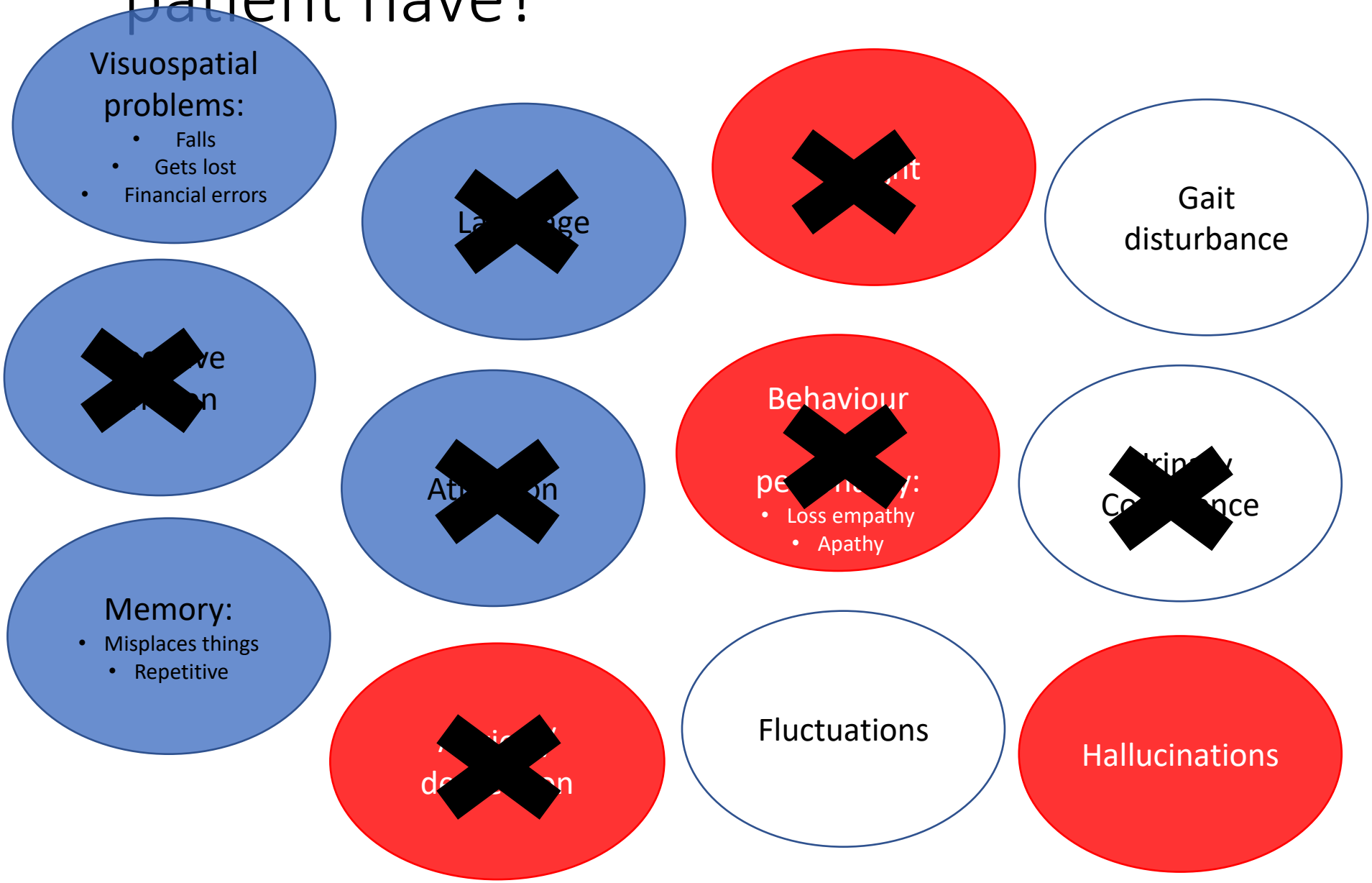
Which type of dementia could my patient have?

Alzheimer type dementia



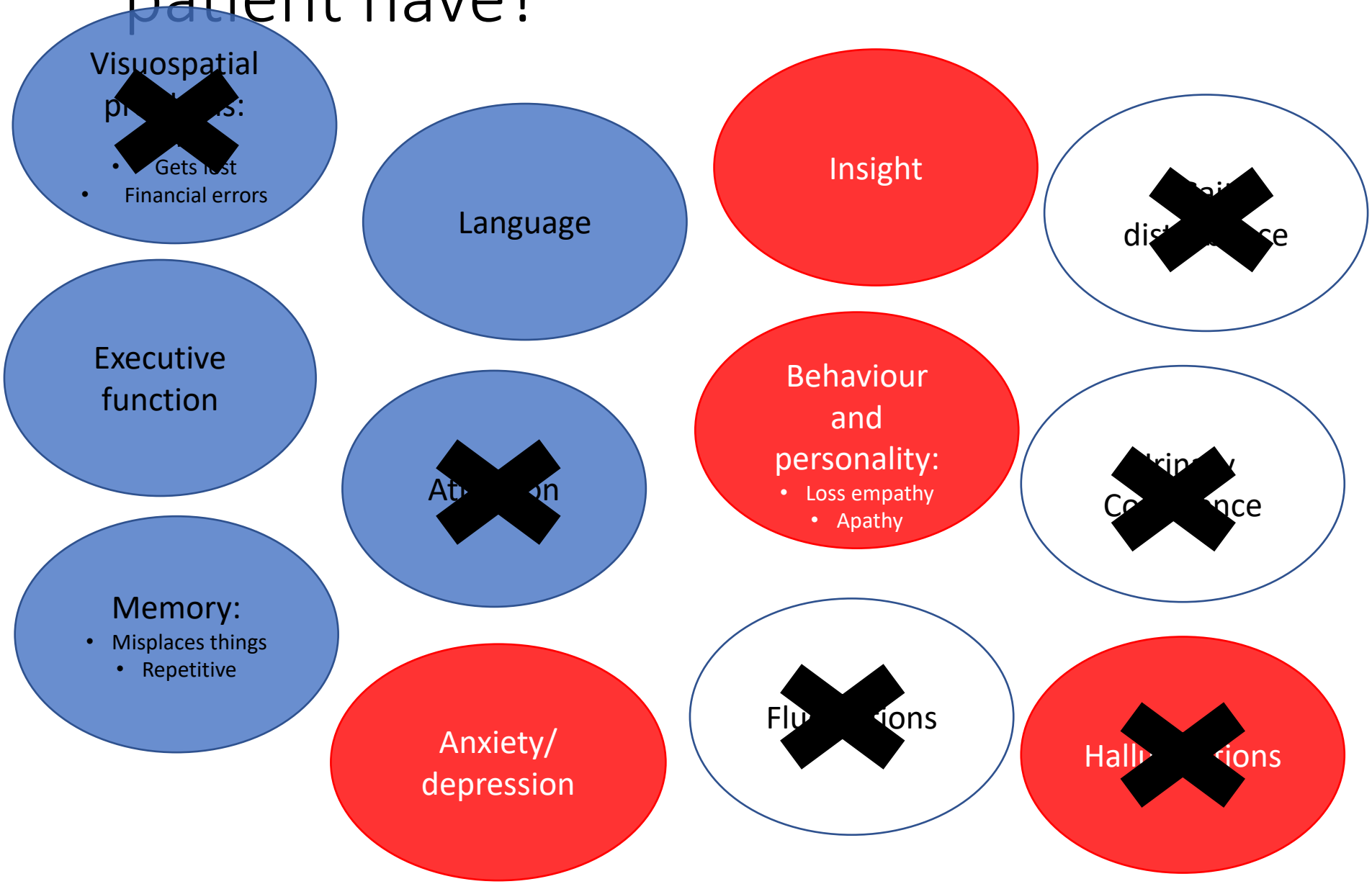
Which type of dementia could my patient have?

Lewy Body type dementia



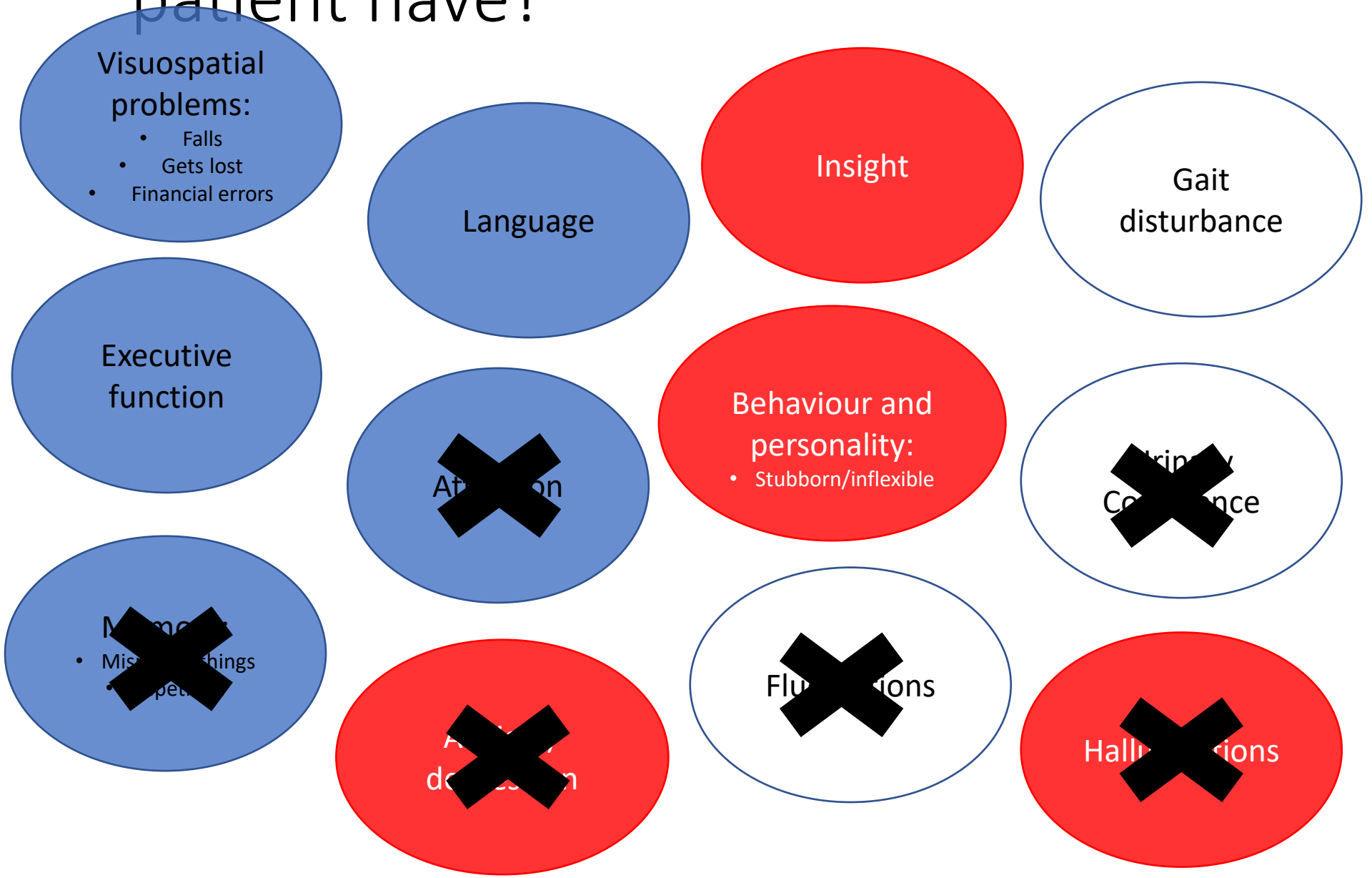
Which type of dementia could my patient have?

Frontotemporal dementia



Which type of dementia could my patient have?

Vascular dementia



Pharmacological management differs with dementia type

- Alzheimer's and Lewy Body – cholinesterase inhibitors (was R1000 now R215) and memantine (was R1200 now R285)
- Frontotemporal – SSRI's
- Vascular dementia – tailored vascular risk factor management

G.W. Blair, J.P. Appleton, K. Flaherty, et al., Tolerability, safety and intermediary pharmacological effects of cilostazol and isosorbide mononitra..., , https://doi.org/10.1016/j.eclinm.2019.04.001

Consensus** on current treatments for overall BPSD and agitation

TREATMENT OF OVERALL BSPD WITHIN AND AGITATION*	% AGREEMENT ACROSS PANEL +/−1 RANK SCORE	RANK
Thorough assessment and management of underlying causes	100%	1
Caregiver problem –solving/information/education	91%	2
Environmental adaptation/approaches	70%	3
Person-centered care	70%	4
Tailored activity program	70%	5
Citalopram	81%	6
Treat pain – Paracetamol/Analgesia	81%	7
Risperidone	64%	8

** Predominantly psychiatrists

Kales et al. International Psychogeriatrics: 2018; 1-8. doi:10.1017/S1041610218000534

BLACK BOX WARNING

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at increased risk of death. Analysis of seventeen placebo controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in the drug-treated patients of 1.7 times the risk in placebo treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug – treated patients was about 4.5% compared to a rate of about 2.6% in the placebo group. Although the cause of death were varied, most of the deaths appeared to be either cardiovascular or infectious in nature.

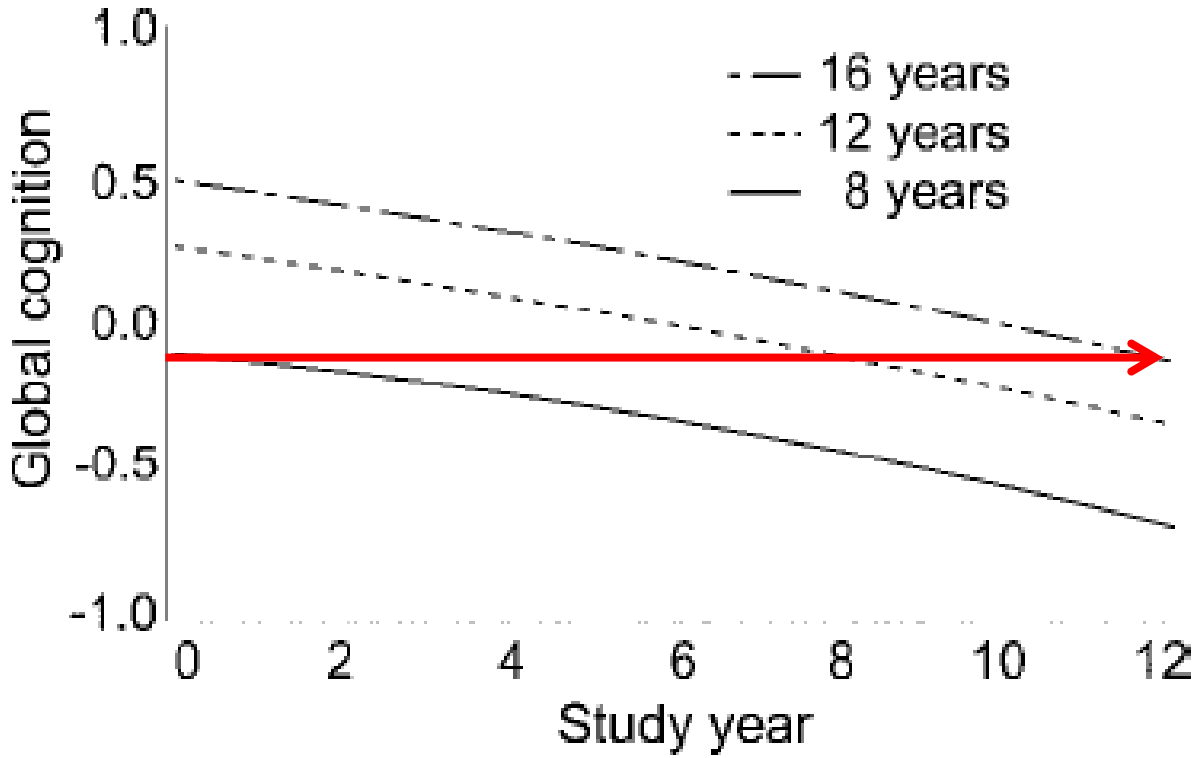
Antipsychotics, first (conventional) and second (atypical) generation Increased risk of cerebrovascular accident(stroke) and greater rate of cognitive decline and mortality in persons with dementia. Avoid antipsychotics for behavioural problems of dementia or delirium unless nonpharmacological options (e.g., behavioural interventions) have failed or are not possible and the older adult is threatening substantial harm to self or others.

Beers List of inappropriate medications 2019, American Geriatrics Society

Brain protective strategies

Education level has the biggest bearing on cognitive reserve

Predicted 12-year paths of change in global cognition in persons with different years of education, adjusted for age, sex, and race



Neurology 2009;72:460–465

What is the biggest problem of oldest age?

Too old for school!
More frequent cognitive activity is associated with reduced incidence of dementia - risk lowered by 42%

- Good activities – playing board games, reading, playing a musical instrument.
- How much activity per week?
  - reading 3 newspapers and one book
  - playing chess/cards 3 times a week
  - "book" club once a week
  - 4-5 emails/letters a week

Wilson et al. Neurology 2007;69:1911-1920.
Verghese et al. N Engl J Med 2003;348:2508-16.
Spector et al. Br J Psychiatry 2003;183:248-54.

Social engagement – Optimise your eyes and your ears

Cataract extractions and risk of developing all cause-dementia and Alzheimer's disease dementia in patient

- Cohort study assessing 3038 adults 65 years of age or older with cataract enrolled in the Adult Changes in Thought study.
- Based on 23 554 person-years of follow-up, cataract extraction was associated with significantly reduced risk (hazard ratio, 0.71; 95% CI, 0.62-0.83; P < .001) of dementia compared with participants without surgery after controlling for years of education, self-reported White race, and smoking history and stratifying by apolipoprotein E genotype, sex, and age group at cataract diagnosis.
- In comparison, risk of dementia did not differ between participants who did or did not undergo glaucoma surgery, which does not restore vision (hazard ratio, 1.08; 95% CI, 0.75-1.56; p = 0.68).
- Suggests that cataract extraction is associated with lower risk of developing dementia among older adults.

Lee et al. JAMA Intern Med. 2022;182(2):134-141. doi:10.1001/jamainternmed.2021.6990

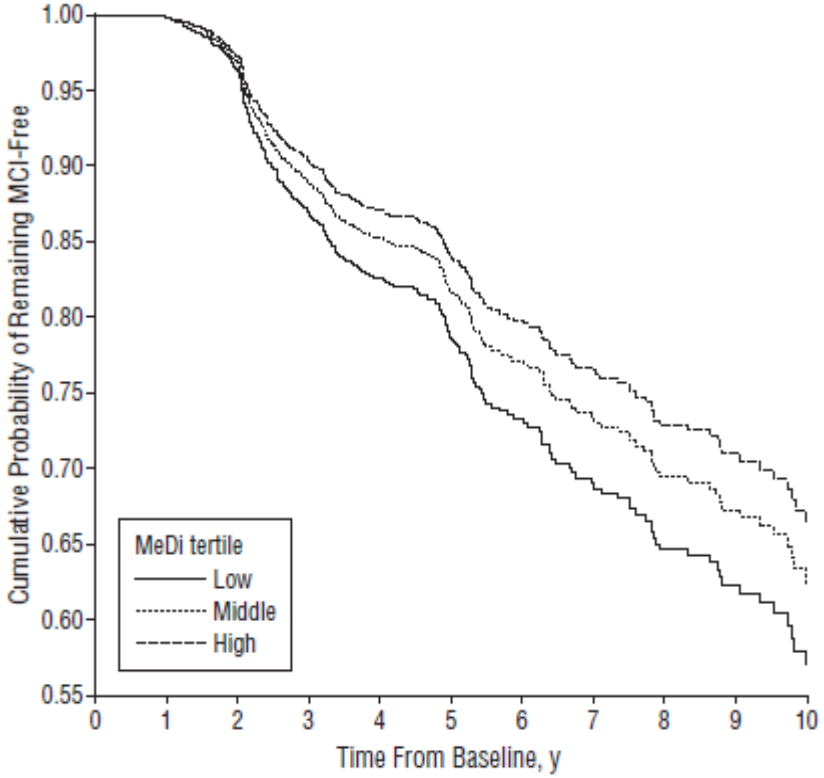
Hearing

- Midlife hearing impairment measured by audiometry, is associated with steeper temporal lobe volume loss, including in the hippocampus and entorhinal cortex.
- Immediate and delayed recall deteriorated less after initiation of hearing aid use and two longitudinal studies (18 and 25 years) show lower dementia incidence.

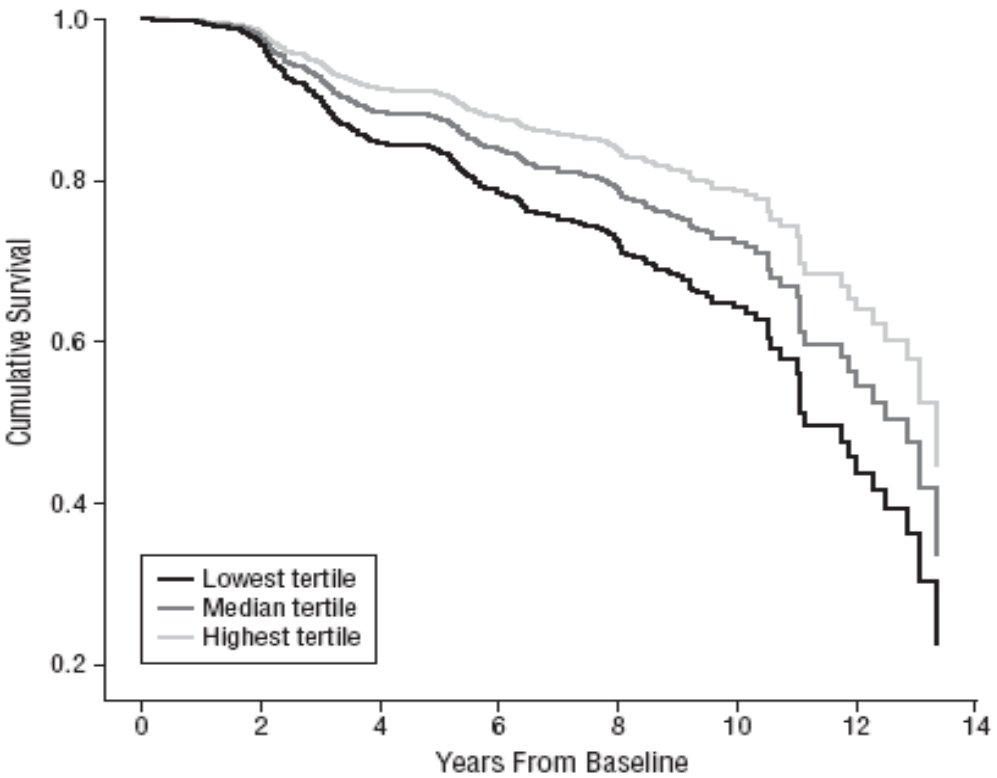
Livingston et al. Lancet 2020; 396: 413–46.

Food Combinations and Progression to Dementia Risk

- Higher intakes of salad dressing (olive oil based), nuts, fish, tomatoes, poultry, cruciferous vegetables, fruits, and dark and green leafy vegetables
- Lower intake of high fat dairy products, red meat, organ meat, and butter.



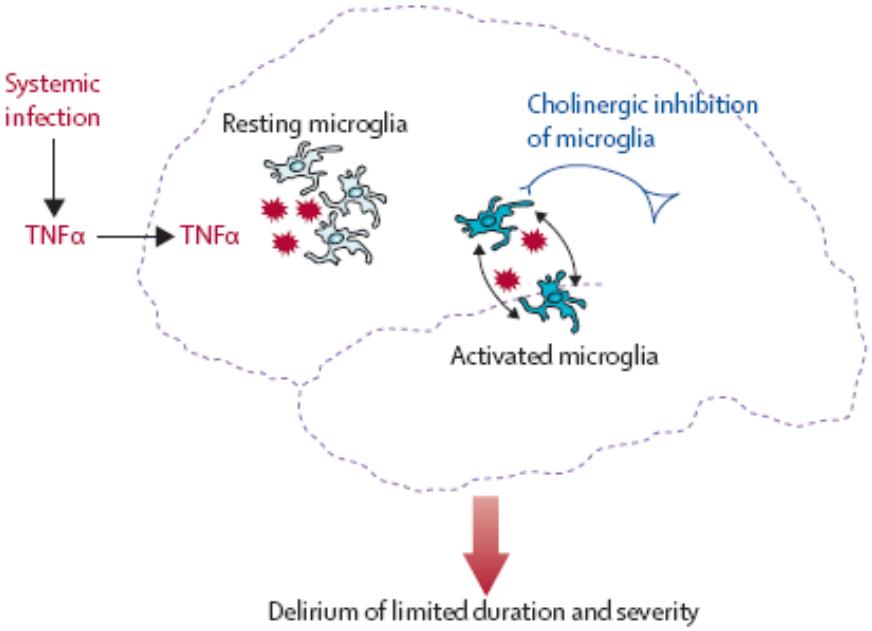
Arch Neurol. 2009;66(2):216-225



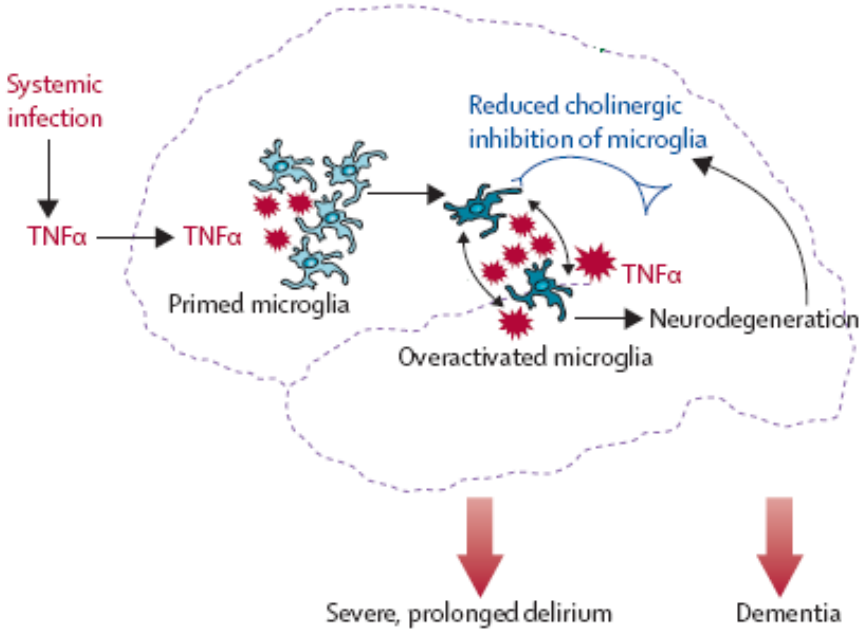
Arch Neurol. 2010;67(6):699-706

Relationship between Acute and Chronic Brain Failure

Normal Situation



Old age, incipient neurodegenerative disease, or anticholinergic therapy



Lancet 2010; 375: 773–75.

Adjusted odds ratios (OR) of dementia by prescription of anticholinergic drugs by period before a diagnosis of dementia

Drug class	Exposure period (years before index date)								
	15-20*			10-15†			4-10‡		
	No of cases (n=10 684)	No of controls (n=74 145)	OR§ (95% CI)	No of cases (n=23 959)	No of controls (n=166 735)	OR§ (95% CI)	No of cases (n=40 770)	No of controls (n=283 933)	OR§ (95% CI)
Any use									
Prescriptions (ACB score):									
None	3638	27 905	1.00	5602	44 790	1.00	4492	38 579	1.00
1	6789	44 564	1.05 (1.00 to 1.10)	17 867	118 973	1.06¶ (1.02 to 1.10)	35 722	242 210	1.06¶ (1.02 to 1.09)
2	193	1057	1.07 (0.91 to 1.25)	493	2556	1.14¶ (1.03 to 1.26)	1054	5734	1.11¶ (1.03 to 1.18)
3	1972	11 321	1.17¶ (1.10 to 1.24)	5242	30 303	1.15¶ (1.10 to 1.19)	12 338	72 335	1.13¶ (1.10 to 1.15)

Richardson et al. BMJ 2018;360:k1315

Cumulative Use of Strong Anti-cholinergic drugs and Incident Dementia

- 3434 persons who had their cumulative anti-cholinergic medication use assessed 10 years before entry into cognitive assessment study in Seattle Washington. Median age 75 at entry into study.
- 10-year cumulative dose-response relationship was observed for dementia and Alzheimer disease (test for trend, *P < .001).*
- *For dementia, adjusted hazard* ratios for cumulative anti-cholinergic drug use compared with non-use were:
  - 8% lower risk (not statistically significant) for 1 to 90 doses
  - 19% higher risk (not statistically significant) for 91 to 365 doses
  - 23% higher risk (not statically significant) for 366 to 1095 doses
  - 54% higher risk (VERY statistically significant) for greater than 1095 doses
- 24/1000 person years in control and 46/1000 person years in >1095 dose groups. Absolute risk increased 2.2% per 100 person years.

Grey et al. JAMA Intern Med. doi:10.1001/jamainternmed.2014.7663 Published online January 26, 2015

Using medications with definite anticholinergic effects increases risk of cognitive decline

- 2-year longitudinal study of participants enrolled in the Medical Research Council Cognitive Function and Ageing Study between 1991 and 1993. 13004 community-dwelling and institutionalized participants aged 65 and older.
- Use of medication with definite anticholinergic effects was associated with a 0.33-point greater decline in MMSE score (95% confidence interval (CI) 0.03–0.64, p=0.03) than not taking anticholinergics.

Fox et al. J Am Geriatr Soc 2011.

Effect of Total Number of Anticholinergic Medications Taken on Risk of Hospitalization for Confusion or Dementia

	Number of Anticholinergic Medications			
Number and Rate of Hospital Admissions	**0**	**1**	**2**	**≥3**
Hospital admissions, n[a]	368	220	51	7
Person-years	30,474	15,824	1,680	161
Rate per 10 years (95% CI)	0.12 (0.11–0.13)	0.14 (0.12–0.16)	0.30 (0.23–0.40)	0.43 (0.21–0.91)
IRR (95% CI)	1.00 (1.00–1.00)	1.15 (0.97–1.36)	2.51 (1.87–3.37)	3.58 (1.69–7.58)
Adjusted IRR (95% CI)[b]	1.00 (1.00–1.00)	1.17 (0.99–1.39)	2.58 (1.91–3.48)	3.87 (1.83–8.21)

CI = confidence interval; IRR = incidence rate ratio.

[a]Hospital admissions were identified over a 2-year period (July 1, 2010 to June 30, 2012).

[b]Adjusted for age, sex, socioeconomic index for areas, time-varying comorbidities, number of medications, prescribers, specialist visits, and prior hospitalizations.

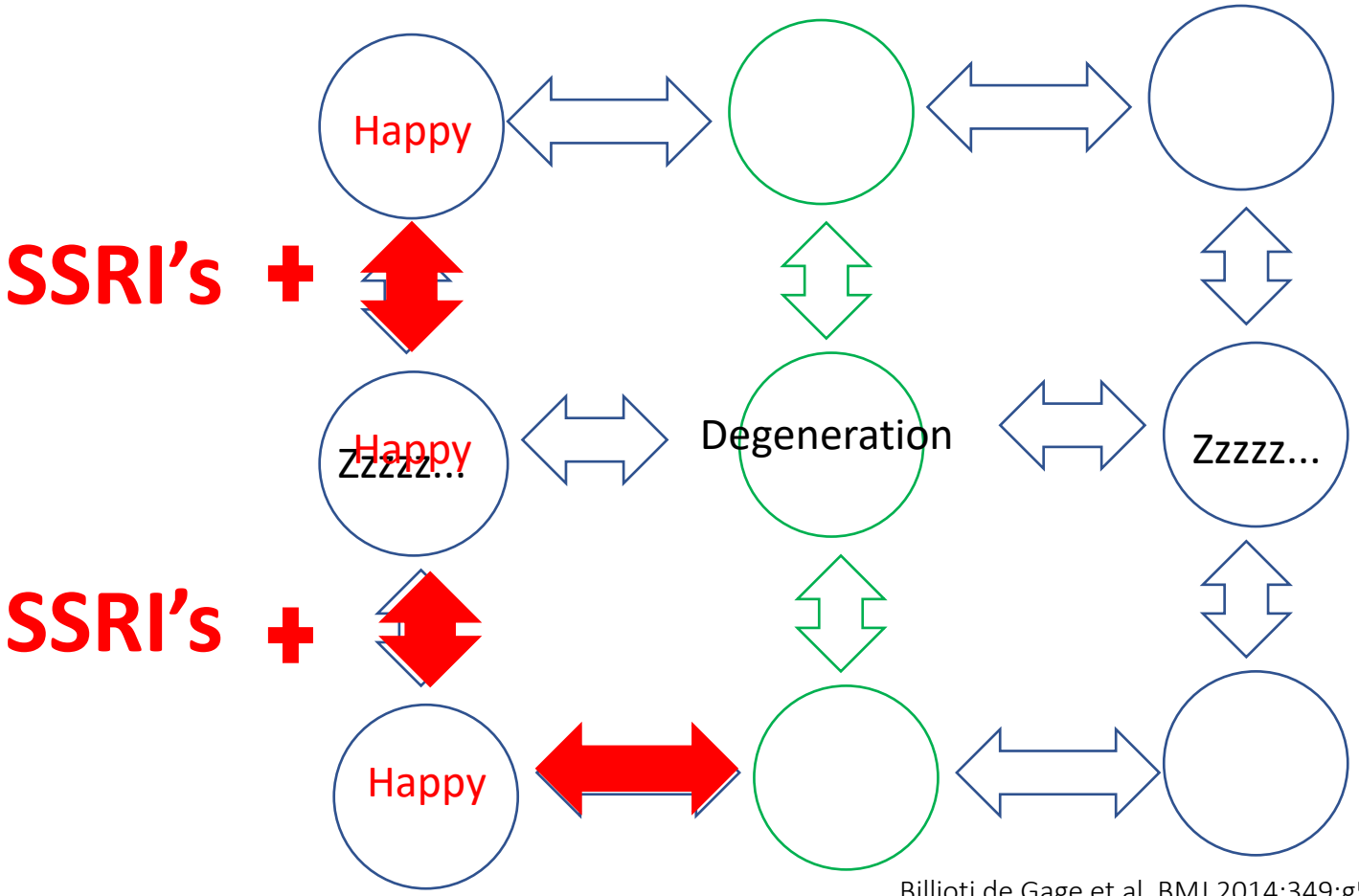
Kalish et al. J Am Geriatr Soc 62:1916–1922, 2014.

Drugs with anti-cholinergic activity commonly used in older persons

Type of Drug	Examples
Antihistamine	Hydroxyzine, diphenhydramine
Antispasmodic	Hyoscyamine
Tricyclic/some SSRI antidepressants	Amitriptyline, paroxetine
Benzodiazepine	Diazepam, temazepam, zolipdem, zopiclone
Analgesic	Codeine
Antiarrythmic	Digoxin
Diuretic	Furosemide
Antiparkinsonian	Orphenadrine
Bladder stabilisers	Oxybutinin, tolteridine, solifenacin, darifenacin.
Bronchodilator	Theophylline
Antibiotic	Levofloxacin
Antacids	Cimetidine, ranitidine

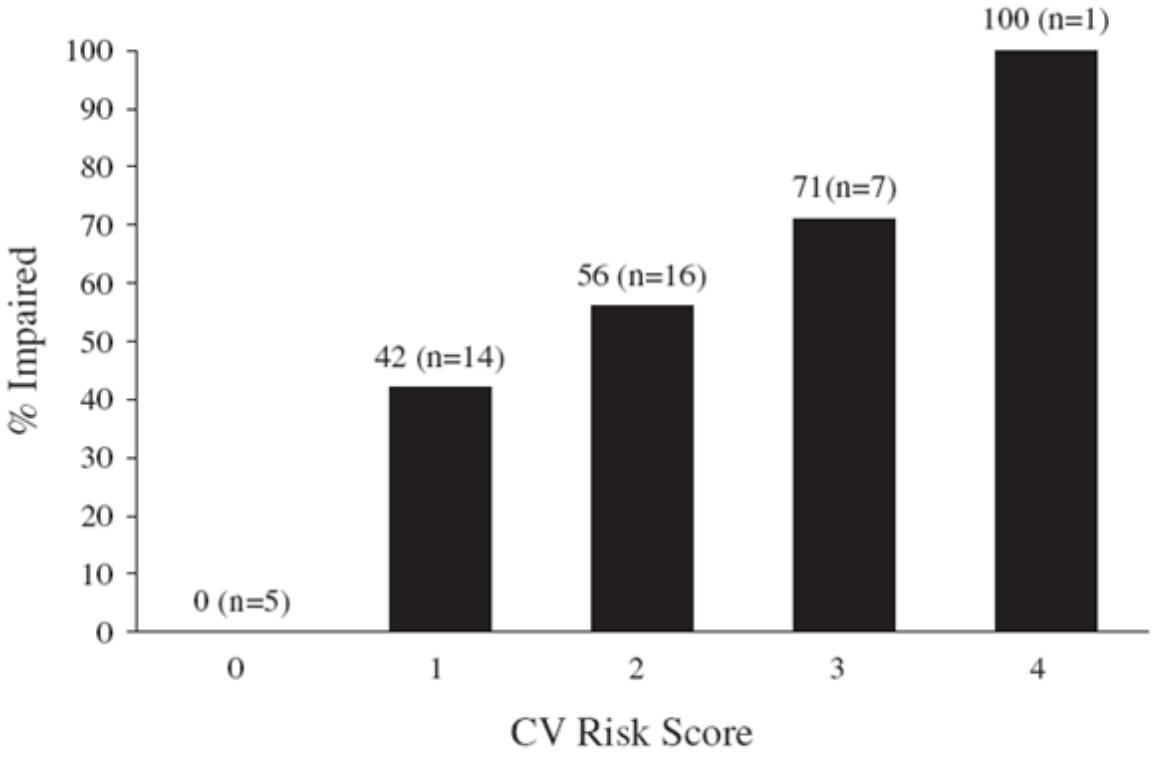
Beer's criteria
J Am Geriatr Soc.
2012; 60:616–631, 2012

Benzodiazepines (and their derivatives) limit cognitive reserve capacity when used long term. This reduces a person's ability to cope with early phase brain lesions by soliciting accessory neuronal networks.
Persons using benzodiazepines for more than 2-3 months have a 36-69% higher risk of developing Alzheimer's disease.



Billioti de Gage et al. BMJ 2014;349:g5205 doi: 10.1136/bmj.g5205
Launay J.M. et al.. Translat Psychiatry 2011; Nov 22; 1e56.

CVS risk factors and Executive impairment



Percentage of subjects classified by cardiovascular (CV) risk score as having frontal-executive impairment.

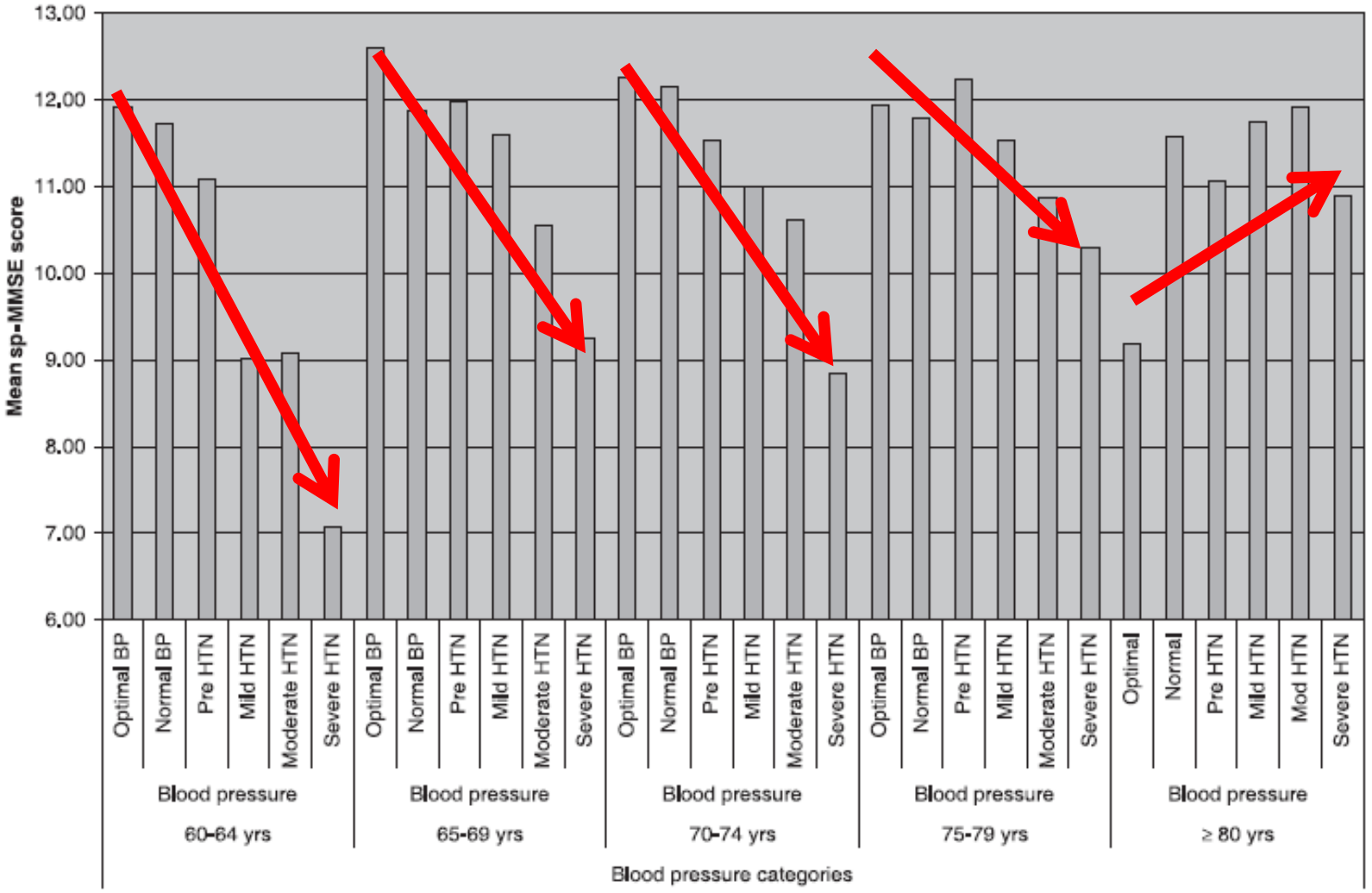
CV Risk Score

- Blood pressure
- Diabetes
- Myocardial infarction
- Coronary Artery Disease
- LVH
- Smoker
- Obesity
- Heart failure

Odd Ratio 2.44 (1.06-5.65) for association on Multivariate analysis

Pugh et al. J Am Geriatr Soc 2003;51:1439-1444.

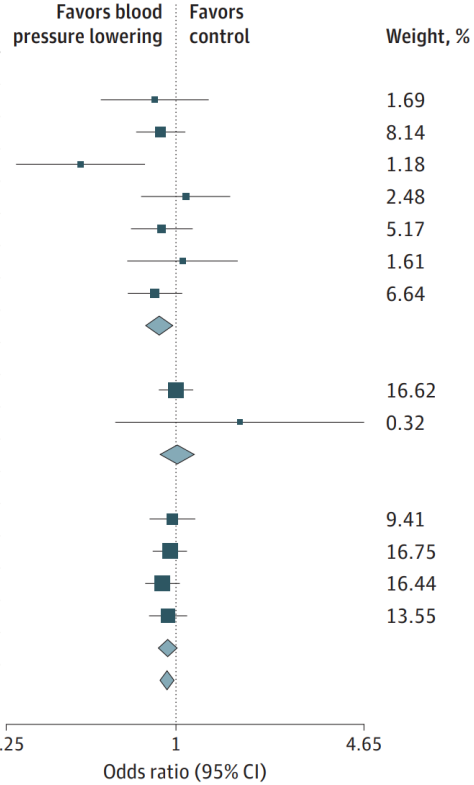
Association of blood pressure with cognition in patients >60 years



Obisesan et al. J Am Geriatr Soc 2008;56:501-9.

Association of Blood Pressure Lowering With Dementia or Cognitive Impairment

Study	Participants with dementia or cognitive impairment/total No.		Absolute risk reduction (95% CI), %	Odds ratio (95% CI)	Weight, %
	Blood pressure lowering group	Control group			
Dementia (criterion-referenced)					
SHEP,[22] 1994	37/2365	44/2371	0.29 (-0.45 to 1.03)	0.84 (0.54 to 1.31)	1.69
PROGRESS,[23] 2003	193/3051	217/3054	0.78 (-0.48 to 2.04)	0.88 (0.72 to 1.08)	8.14
Syst-Eur,[5] 2002	21/1485	43/1417	1.62 (0.54 to 2.70)	0.46 (0.27 to 0.78)	1.18
SCOPE,[24] 2003	62/2477	57/2460	-0.19 (-1.04 to 0.67)	1.08 (0.75 to 1.56)	2.48
HYVET-COG,[6] 2008	126/1687	137/1649	0.84 (-0.99 to 2.67)	0.89 (0.69 to 1.15)	5.17
ADVANCE,[25] 2009	39/5569	37/5571	-0.04 (-0.34 to 0.27)	1.05 (0.67 to 1.66)	1.61
SPRINT MIND,[12] 2019	149/4278	176/4285	0.62 (-0.18 to 1.43)	0.84 (0.67 to 1.05)	6.64
Random-effects model for subgroup ($Q_6 = 7.92$; $P = .24$; $I^2 = 0.0\%$)				0.87 (0.78 to 0.97)	
Dementia (clinical-based)					
PRoFESS,[26] 2008	408/8624	409/8646	0.00 (-0.63 to 0.63)	1.00 (0.87 to 1.15)	16.62
HOPE-3,[13] 2019	10/811	6/815	-0.50 (-1.46 to 0.46)	1.68 (0.61 to 4.65)	0.32
Random-effects model for subgroup ($Q_1 = 0.99$; $P = .32$; $I^2 = 0.0\%$)				1.01 (0.88 to 1.16)	
Dementia and mild cognitive impairment (composite)					
TRANSCEND,[7] 2011[a]	239/2694	245/2689	0.24 (-1.29 to 1.77)	0.97 (0.81 to 1.17)	9.41
ON TARGET (Dual),[7] 2011[a]	618/7807	326/3932.5	0.37 (-0.68 to 1.42)	0.95 (0.83 to 1.09)	16.75
ON TARGET (ARB),[7] 2011[a]	584/7797	326/3932.5	0.80 (-0.24 to 1.84)	0.90 (0.78 to 1.03)	16.44
SPS3,[27] 2014[a]	506/1323	535/1345	1.53 (-2.17 to 5.23)	0.94 (0.80 to 1.10)	13.55
Random-effects model for subgroup ($Q_3 = 0.57$; $P = .90$; $I^2 = 0.0\%$)				0.93 (0.87 to 1.01)	
Test for overall effect: $z = -2.50$; $P = .01$ Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 12.14$; $P = .43$; $I^2 = 0.0\%$			0.39 (0.09 to 0.68)	0.93 (0.88 to 0.98)	



The squares and bars represent the mean values and 95% CIs of the effect sizes and the area of the squares reflects the weight of the studies. Diamonds represent the combined effects and the vertical dotted line represents the line of no association.

[a] Composite of dementia and cognitive impairment.

Hughes et al. JAMA. 2020;323(19):1934-1944

Diabetes Mellitus

- Uncontrolled diabetics have higher risk of both vascular and Alzheimer's dementia.
- Low sugar is more dangerous than high sugars so avoid tight control strategies.
- Can't not won't – remember executive function

	Executive impairment		
	Absent (*N*=47)	Present (*N*=51)	
Age (mean±SD)	56.2±10.0	59±10.7	NS
Years of education (mean±SD)			
HBA_{1c} <7.0%	9.8±3.3	8.7±1.2	NS
HBA_{1c} ≥7.0%	9.5±2.9	8.0±2.1	*p*=0.013
Diabetic control (*N* (%))			
HBA_{1c} <7.0%	11 (23%)	3 (6%)	*p*=0.019
HBA_{1c} ≥7.0%	36 (77%)	48 (94%)	
Patient reported adherence (*N* (%))			
Dietary	20 (43%)	27 (53%)*	NS
Medication	36 (77%)	36 (71%)	NS
Mean No. of target organs damaged (±SD)	1.4±1.3	1.7±1.2	NS
Drugs used (*N* (%))			
Metformin	32 (68%)	32 (63%)	NS
Sulphonylureas	18 (38%)	16 (31%)	NS
Insulin	37 (79%)	39 (76%)	NS
Aspirin	36 (77%)	32 (63%)	NS
Statin	18 (38%)	17 (33%)	NS
ACE inhibitors	36 (77%)	28 (71%)	*p*=0.041

*In 2 patients dietary adherence was unknown.
NS = not significant.

de Wet et al. S Afr Med J 2007; 97: 1074-1076

Statins

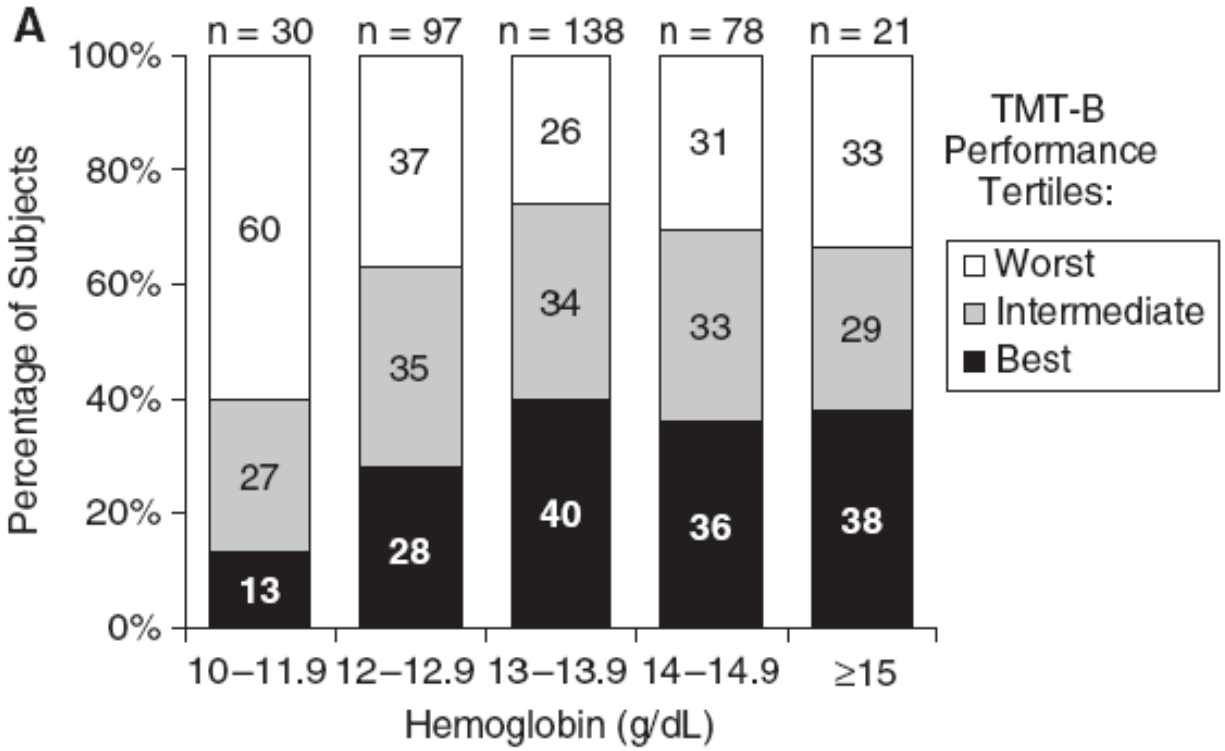
Statins

- Use of statins has been associated with a 37 to 87% lower risk of developing dementia (p=0.002).
- Statins have beneficial effects on the microvasculature, including increasing endothelial nitric oxide synthase (eNOS) and reducing endothelin-1 thereby dilating capillaries and increasing blood flow.
- Isolated case reports of statin related cognitive dysfunction – tends to be rare and of short duration.

"the currently available data suggest the use of high-dose statins as relatively simple therapy to lessen the severity of developing de*mentia*"
Lionel H Opie, Lancet Vol 384 September 13, 2014

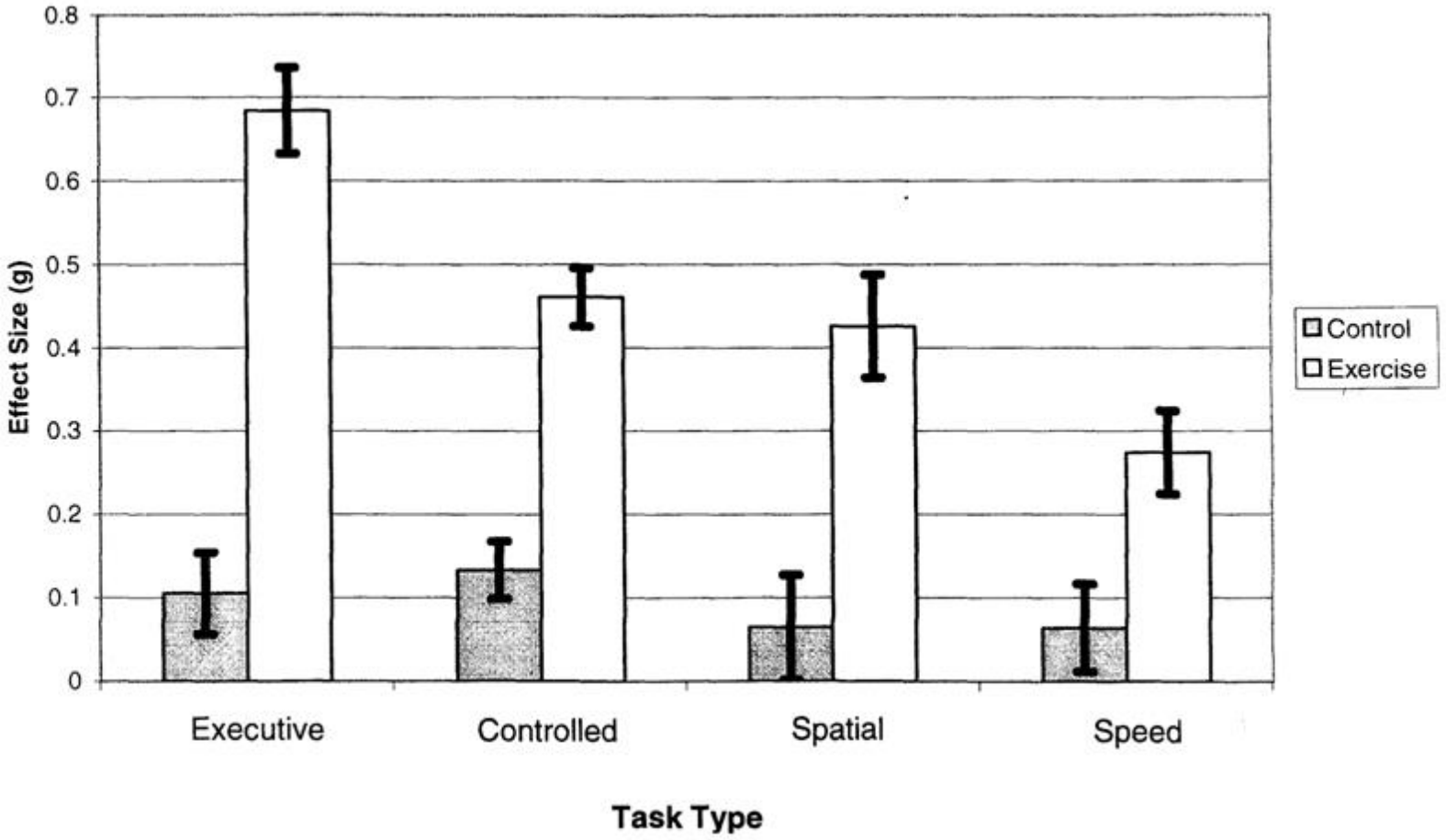
Jick et al. Lancet 2000; 356: 1627–31

Haemoglobin level is associated with executive impairment



Paulo et al. J Am Geriatr Soc 2006;54:1429-1435.

Aerobic exercise



Colcombe et al. Psych Sci 2003;14:125-130.

Exercise as a protector of cognition

Frequency of Exercise Intensity	No. (%) Mild Cognitive Impairment (n=198)		No. (%) Normal Cognition (n=1126)	OR (95% CI)[a]	*P* Value
Physical Exercise in Midlife					
Light					
None	25 (12.6)		104 (9.2)	1.00 [Reference]	
Any	173 (87.4)		1022 (90.8)	0.90 (0.55-1.47)	.68
Moderate					
None	58 (29.3)	39% reduction	193 (17.1)	1.00 [Reference]	
Any	140 (70.7)		933 (82.9)	0.61 (0.43-0.88)	.008[b]
Vigorous					
None	127 (64.1)		670 (59.5)	1.00 [Reference]	
Any	71 (35.9)		456 (40.5)	0.82 (0.59-1.15)	.25
Physical Exercise in Late Life					
Light					
None	52 (26.3)	31% reduction	184 (16.3)	1.00 [Reference]	
Any	146 (73.7)		942 (83.7)	0.69 (0.47-1.00)	.048
Moderate					
None	103 (52.0)	32% reduction	426 (37.8)	1.00 [Reference]	
Any	95 (48.0)		700 (62.2)	0.68 (0.49-0.93)	.02[c]
Vigorous					
None	171 (86.4)		969 (86.1)	1.00 [Reference]	
Any	27 (13.6)		157 (13.9)	1.14 (0.72-1.81)	.58

Arch Neurol. 2010;67(1):80-86

Folic Acid

- Supplementation for 3 years significantly improved:
  Memory (p=0.033), Information processing speed (p=0.016), Sensori-motor speed (p=0.055)
- Meta-analysis shows supplementation for stroke prevention:

	Stroke events/total patients		Relative risk (95% CI)	p value
	Intervention group	Control group		
Overall	373/8949	405/7892	0·82 (0·68–1·00)	0·045
Duration of intervention				
≤36 months[15,16,34,35]	224/4078	193/3015	1·00 (0·83–1·21)	0·95
>36 months[17,34,36,37]	149/4871	212/4877	0·71 (0·57–0·87)	0·001
Homocysteine lowering				
<20%[15,33,36]	179/2325	174/2180	0·89 (0·55–1·42)	0·62
≥20%[16,17,34,35]	172/4967	196/4051	0·77 (0·63–0·94)	0·012
Grain fortification				
Yes[15,33,36]	179/2325	174/2180	0·89 (0·55–1·42)	0·62
No[16,17,34,35,37]	194/6624	231/5712	0·75 (0·62–0·91)	0·003
History of stroke				
Yes[35]	152/1827	148/1853	1·04 (0·84–1·29)	0·71
No[16,17,33–37]	221/7122	257/6039	0·75 (0·62–0·90)	0·002

- In seniors with normal vitamin B12 status a high serum folate is associated with protection against cognitive impairment.
  - OR relating high versus normal serum folate 0.4 (95% CI 0.2-0.9) (p<0.05).
- Recommended that patients have vitamin B12 level checked and are replete prior to commencing folic acid supplementation.

Durga et al. Lancet 2007;369:208-216. Wang et al. Lancet 2007;369:1876-1882.
Connelly et al. Int J Geriatr 2008;23:155-160. Savaria et al. Am J Clin Nutr 2007;85:193-200.
Tangney et al. Neurology 2009;72:361–367.

Vitamin B12

- Lower level is associated with slightly higher rate of brain loss
- In clinical practice 15% of patients over 75 years will be deficient (<138pmol/l)

Odds ratios for PBVL per year over 5 years for loss in the highest tertile vs the other two tertiles by plasma vitamin B_{12}, holoTC, and TC saturation levels

	PBVL over 5 y			
	Simple model*		Adjusted model 2†	
Tertiles of dependent variable	OR (95% CI)	p Value	OR (95% CI)	p Value
Vitamin B_{12}				
>386 pmol/L	1.00 (reference)		1.00 (reference)	
308–386 pmol/L	2.89 (0.90–9.33)	0.076	4.39 (1.01–19.03)	0.048
<308 pmol/L	3.35 (1.02–11.00)	0.047	6.17 (1.25–30.47)	0.026
p Trend		0.053		0.028

*Adjusted for age and sex.
†As simple model plus adjustment for initial Cambridge Mental Disorders of the Elderly Examination (CAMCOG) score, serum creatinine, years of further education, systolic blood pressure, initial brain volume, ApoE ε4 polymorphism.
PBVL = percentage of brain volume loss; holoTC = holotranscobalamin; TC = transcobalamin; OR = odds ratio.

Neurology 2008;71:826-832

Thyroid function

- Studies in both overt and pre-clinical hypothyroidism support executive functioning, speed of processing and aspects of memory as being vulnerable.
- Full reversibility of mood and cognition with replacement is rare but improvement is common.
- Pre/Sub-clinical hyperthyroidism was associated with impaired cognition.
- Hyperthyroidism induced reduction in thyrotropin releasing hormone (TRH) secretion may lead to an impairment of brain acetylcholine metabolism.

J Am Geriatr Soc 2009;57:89–93.

Davis et al. Minerva Endocrinol. 2007;32:49-65.

Depression

- SSRI's class antidepressants are shown to have efficacy against the executive cognitive impairments of depression.
- Depression is an early marker of progression from mild cognitive impairment to dementia.
- Hippocampal subfield volume loss in older adults with amnestic mild cognitive impairment (aMCI) and depression history are associated with amyloid beta and tau pathology, thereby increasing the risk for Alzheimer's disease. This association is not present for non-amnestic subtype (naMCI).

Palmer et al. Neurology 2007;68:1596–1602.
Hoi Kei Leung et al. Eur J Neurosci. 2021;54:4953–4970.

Alcohol

- Alcohol causes brain damage by poisoning neurons and de-conditioning neural networks.
- Alcohol consumption of more than one drink per day in non-pregnant woman is deleterious to brain health.
- One drink = one beer 340ml OR one glass of wine 125ml OR one tot of spirits 25ml

"TWO IS TOO MANY"

Man Hormones

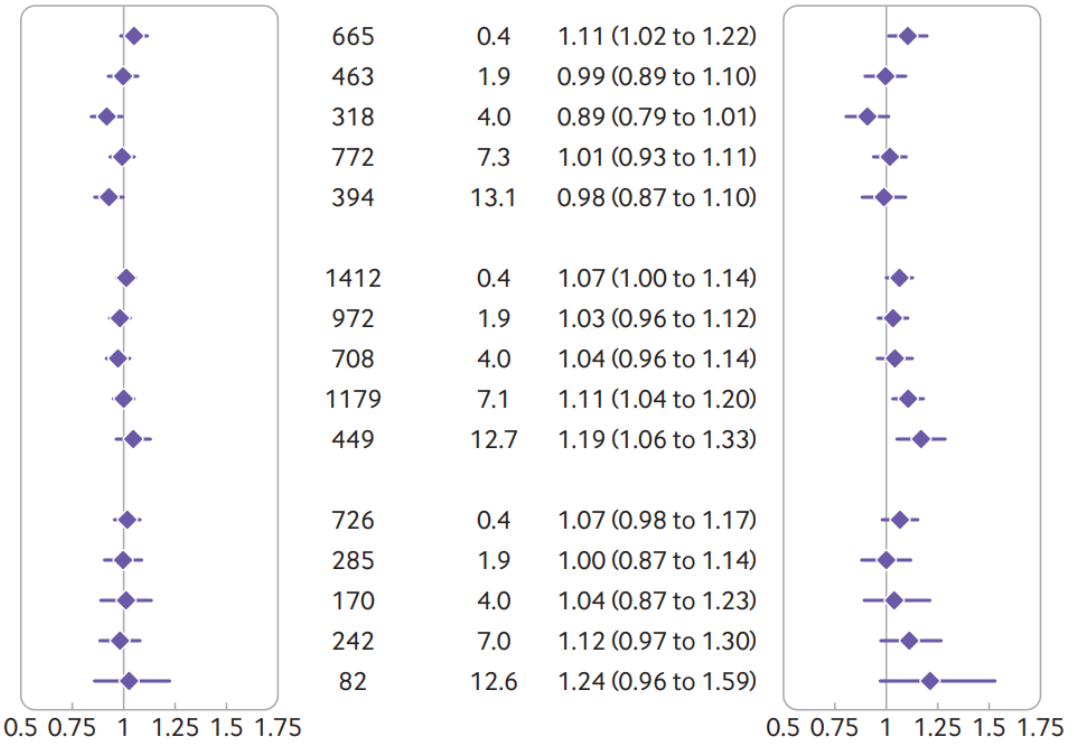
- Androgen deprivation therapy exposure is associated with dementia among elderly patients with prostate cancer.
- The number needed to harm was 18 patients (95% CI, 17-19 patients) and 10 patients (95% CI, 9.5-11 patients) for Alzheimer disease and dementia, respectively.
- I'm not aware of any data supporting supplementation of androgens as a strategy to protect brain function.
- In patients with clinically proven multiple system involvement of a testosterone deficiency there may be mood and mild symptomatic memory benefits with supplementation.

Jayadevappa et al. JAMA Network Open. 2019;2(7):e196562. doi:10.1001/jamanetworkopen.2019.6562

Woman hormones

Use of menopausal hormone therapy and risk of dementia

Years of use	All cases and controls: No of cases	Mean duration of use	Odds ratio (95% CI)	Odds ratio (95% CI)	Cases with Alzheimer's disease and controls: No of cases	Mean duration of use	Odds ratio (95% CI)	Odds ratio (95% CI)
Oestrogen only								
<1 year	1608	0.4	1.05 (0.99 to 1.12)		665	0.4	1.11 (1.02 to 1.22)	
1 to <3 years	1096	1.9	1.00 (0.93 to 1.07)		463	1.9	0.99 (0.89 to 1.10)	
3 to <5 years	778	4.0	0.92 (0.85 to 1.00)		318	4.0	0.89 (0.79 to 1.01)	
5 to <10 years	1773	7.3	0.99 (0.94 to 1.05)		772	7.3	1.01 (0.93 to 1.11)	
≥10 years	934	13.1	0.93 (0.86 to 1.00)		394	13.1	0.98 (0.87 to 1.10)	
Oestrogen and progestogen								
<1 year	3118	0.4	1.01 (0.97 to 1.06)		1412	0.4	1.07 (1.00 to 1.14)	
1 to <3 years	2101	1.9	0.98 (0.93 to 1.03)		972	1.9	1.03 (0.96 to 1.12)	
3 to <5 years	1513	4.0	0.97 (0.92 to 1.03)		708	4.0	1.04 (0.96 to 1.14)	
5 to <10 years	2445	7.1	1.00 (0.95 to 1.05)		1179	7.1	1.11 (1.04 to 1.20)	
≥10 years	925	12.7	1.05 (0.97 to 1.13)		449	12.7	1.19 (1.06 to 1.33)	
Tibolone								
<1 year	1591	0.4	1.02 (0.96 to 1.08)		726	0.4	1.07 (0.98 to 1.17)	
1 to <3 years	636	1.9	1.00 (0.91 to 1.09)		285	1.9	1.00 (0.87 to 1.14)	
3 to <5 years	376	3.9	1.01 (0.90 to 1.14)		170	4.0	1.04 (0.87 to 1.23)	
5 to <10 years	514	7.0	0.98 (0.89 to 1.09)		242	7.0	1.12 (0.97 to 1.30)	
≥10 years	162	12.3	1.03 (0.86 to 1.22)		82	12.6	1.24 (0.96 to 1.59)	



Vinogradova et al. BMJ 2021;375:n2182 | doi:10.1136/bmj.n2182

COFFEE

If mice were humans?

- Caffeine protects Alzheimer's mice against cognitive impairment and reduces brain beta amyloid production (equivalent of five cups per day).

Humans?

- Caffeine consumption is associated with a wide range of sociodemographic, lifestyle, and clinical variables which may also affect cognitive decline.
- The psychostimulant properties of caffeine appear to reduce cognitive decline (verbal retrieval (33%) and visuospatial memory (18%) in women without dementia, especially at higher ages.

Arendash et al. Neuroscience 2006;142:941-952.

Ritchie et al. Neurology 2007;69:536–545

What I wouldn’t endorse in 2022

- Blood genetic test markers for “risk” of Alzheimer’s.
- Cannabis products.
- Fad diets (excluding the Mediterranean diet).
- Following unproven/ disproven/ risky/expensive “alternative therapies” e.g. ginko biloba or any supplement costing more than R150 per month.
- Excessive alcohol, and any form of smoking.
- Use of anticholinergic and all hypnotic drugs.
- The hunt for the miracle cure!

Dementia in 2022

- No cure but……
- DEMENTIA does remain a manageable condition
- BIG PROBLEM:

PATIENTS AND FAMILIES SPEND SO MUCH TIME AND EFFORT DESPERATELY SEARCHING FOR A CURE THAT DOESN'T EXIST THAT MANAGEMENT IS NEGLECTED!!

- Research problem: research driven by well established agendas of the people who's livelihoods depend on the research.

The hard slog ahead

- Living and maintaining a healthy lifestyle with optimal chronic disease management during a persons life course.
- Affordable patient-centred support structures/facilities.
- Caregiver support and planning.
- Advanced care planning.
- National recognition of the nature, burden and management of persons with dementia:
  - Reimbursement/support for dementia care including carers
  - Safety – finances, driving, abuse
  - Advanced care planning