New strategies for the management of dementia

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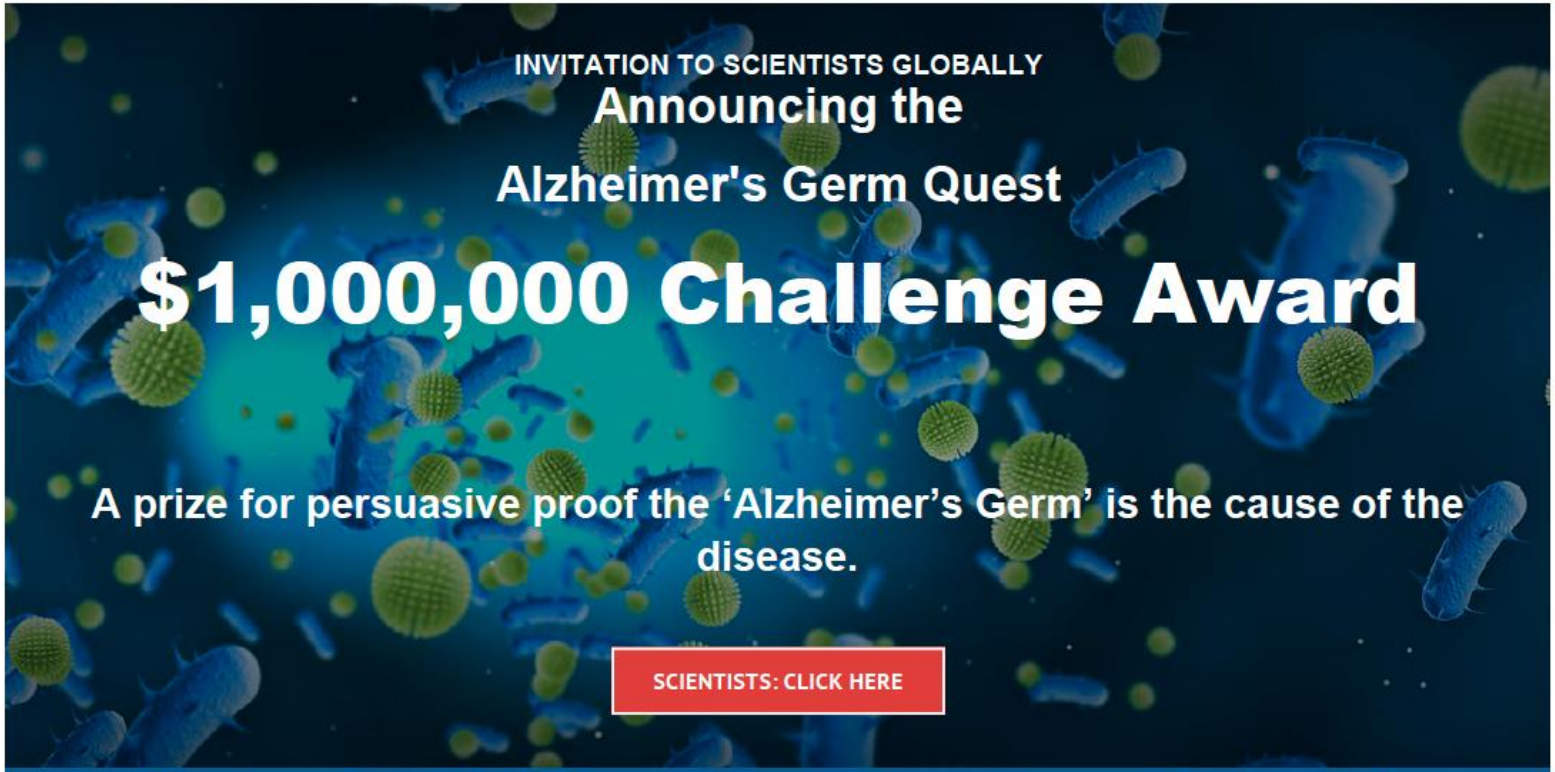
ALZgerm.org
ALZHEIMER'S GERM QUEST, INC.



Not a scientist? You too can encourage the quest!

SIGN PETITION

Alzheimer's is a public health emergency in the U.S.

RE FOR
ING

Your detective talents are needed!

World: more than 44 million suffering. Cause unknown. No cure. No preventive.

There are many clues a germ is the villain.

Decades of research and billions of dollars have investigated the amyloid plaques and tau protein tangles found in the brains of AD patients. Unfortunately, none of this has produced results useful for patients.

Good news: Researchers are finding increasing evidence that Alzheimer's is an infection caused by a germ—bacterium, virus, parasite, fungus, or prion.

Farfetched? Not at all. Germs were found to be the cause of other diseases once considered mysteries: tuberculosis, AIDS, Zika, Legionnaire's, malaria, kuru, etc.

Yet there has not so far been a thorough search for a causative microbe for AD. In fact, virtually none of today's $1.6 billion in AD research funding is dedicated to finding an Alzheimer's germ. Understand why a germ is likely by reading our White Paper.

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Summary

- There are a lot of people with dementia and the numbers are rapidly growing
- Assessment, disclosing a diagnosis and making sure that appropriate services are involved are the most important things we do at this stage
- There are no new medications and the “new” biomarkers and imaging tests have virtually no clinical utility
- Non-pharmacological interventions have been shown to work, are probably cost-effective but have poor uptake. We can do better.

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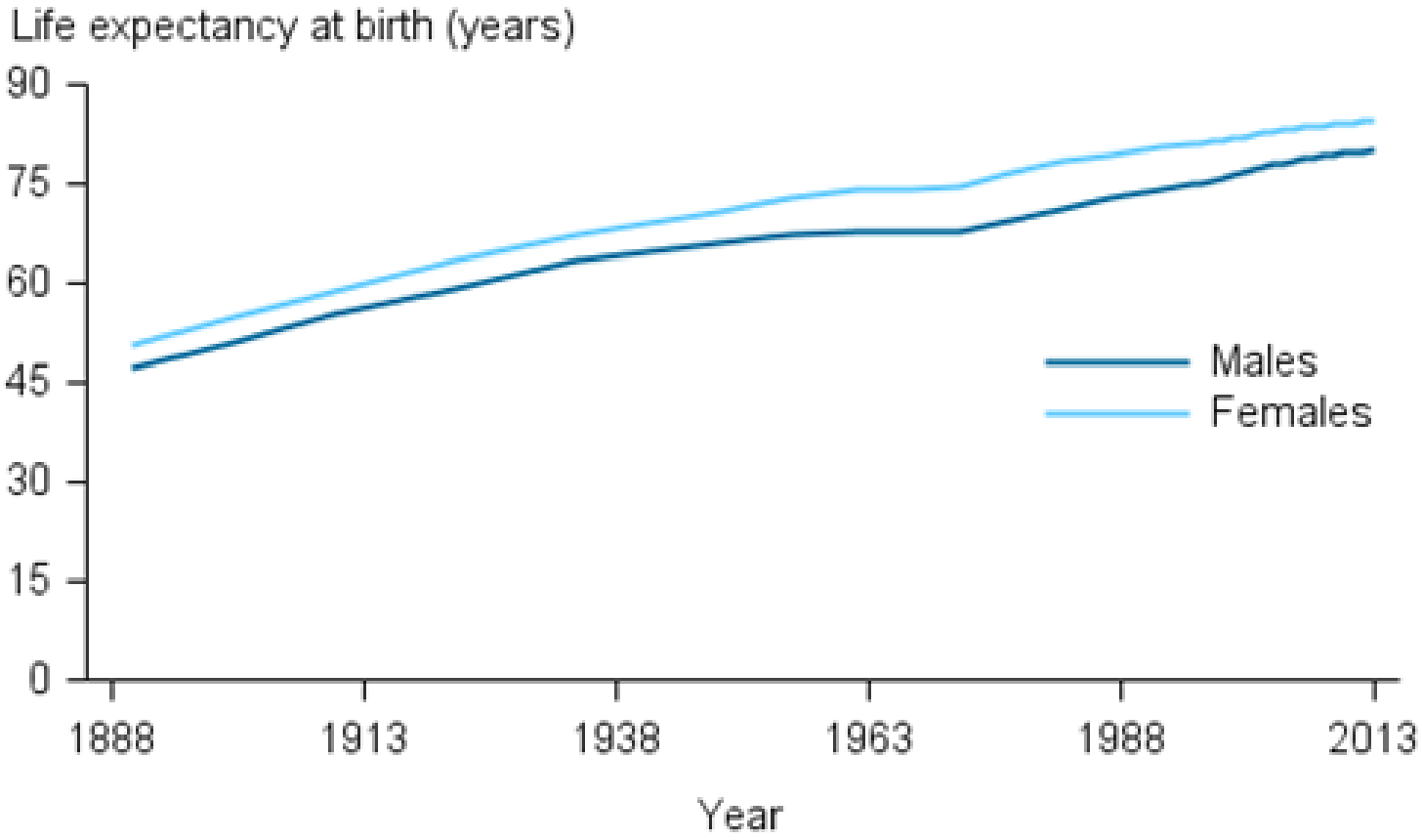
Life Expectancy in Australia and US
What a success story!



A boy born in 2011–2013 can expect to live to the age of 80.1 years and a girl would be expected to live to 84.3 years compared with 47.2 and 50.8 years in 1881–1890.

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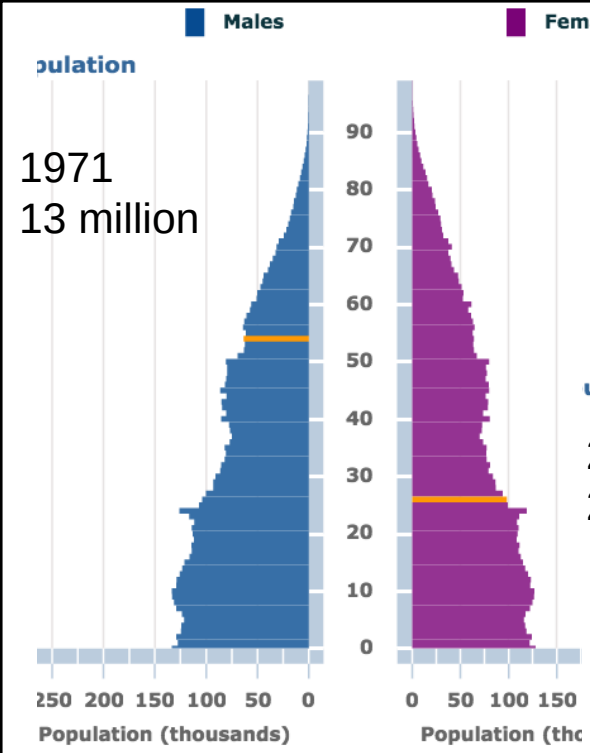
Cohort versus Period Life Expectancy

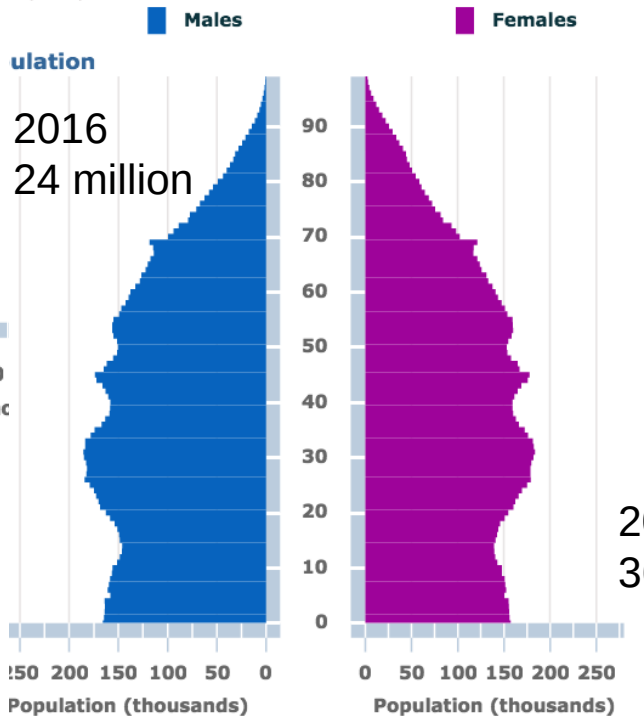
We live even longer (according to the Intergenerat. report)

Year of Birth	2015	2025	2035	2045	2055
Cohort LE					
Men	91.5	92.6	93.6	94.4	95.1
Women	93.6	94.5	95.3	96.0	96.6
Period LE					
Men	80.7	82.9	84.9	86.6	88.1
Women	84.8	86.4	87.9	89.3	90.5

- Based on the idea of modeling future expected health gains – that may never eventuate…..

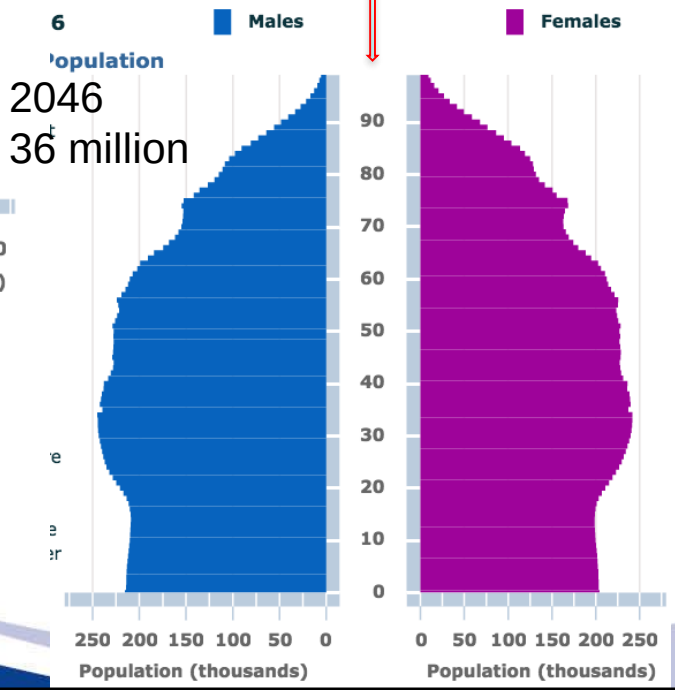
Australian Population 1971-2046

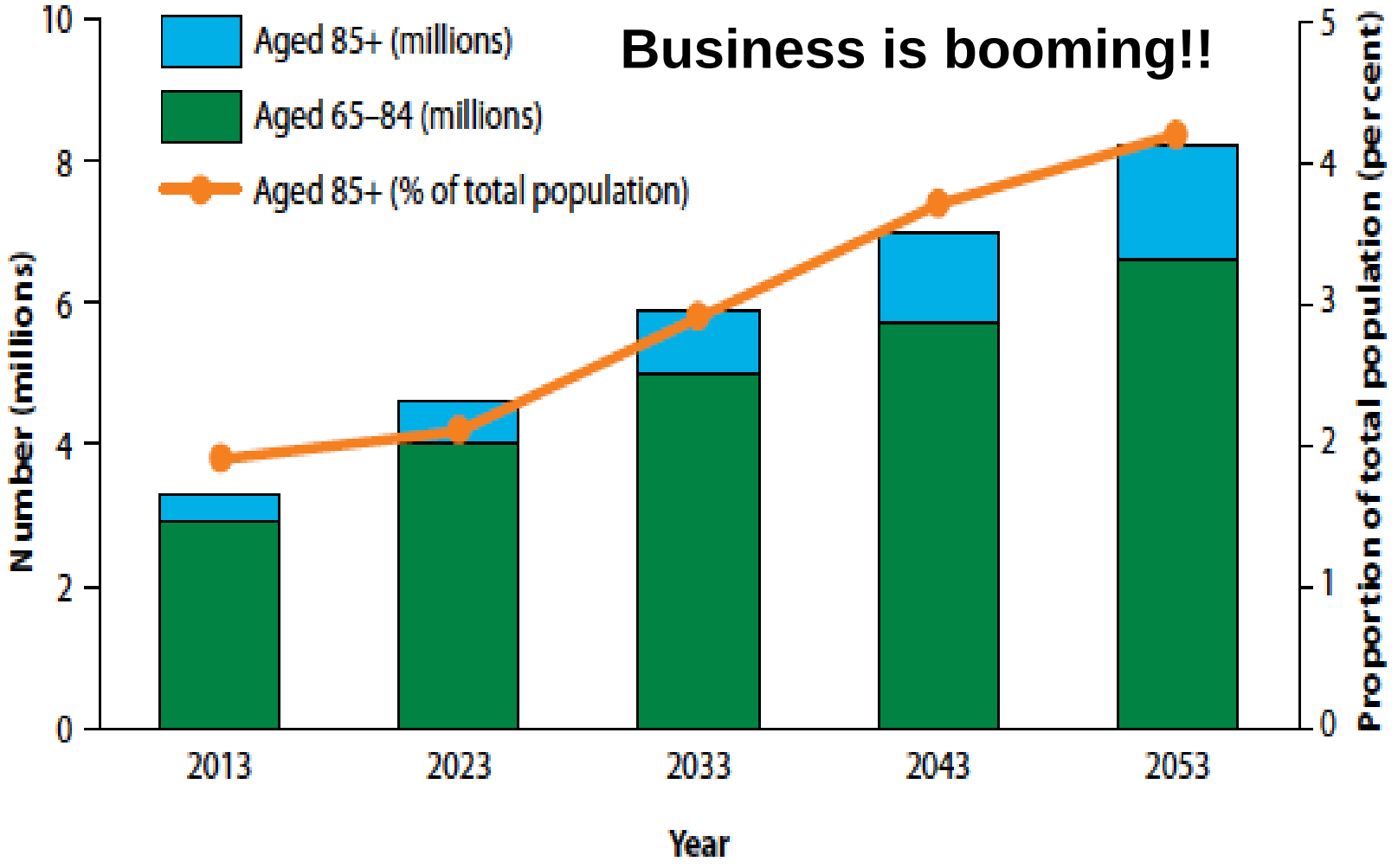




In 1971 we were
Under-Old
Post WW2 very large proportionate migration

These older people are already here – many are in the audience





Note: Data are as at 30 June. Data presented for 2023 onwards are based on population projections (series B).

Sources: AIHW analysis of ABS 2013a, 2013j.

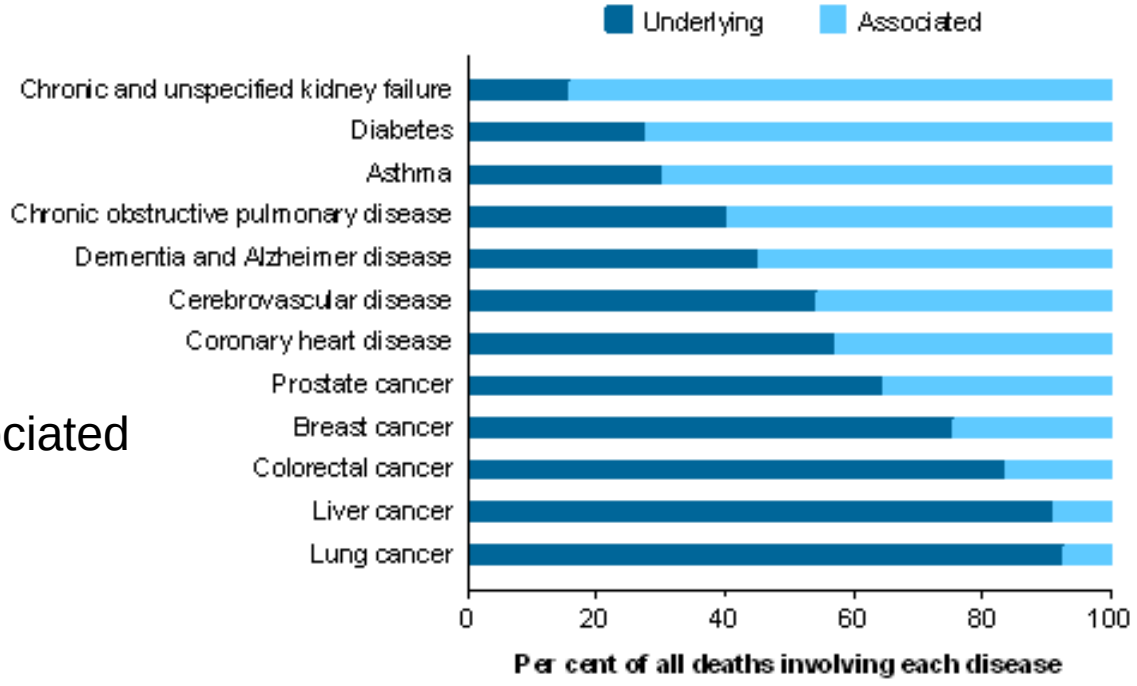
Scary?

Number and proportion of older people, 2013–2053

2.1 LEADING CAUSES OF DEATH(a), Australia - Selected years - 2006, 2010, 2015(b)

Cause of death and ICD code	2006 no.	2006 Rank	2010 no.	2010 Rank	2015 no.	2015 Rank	Median Age (2015) years
Ischaemic heart diseases (I20-I25)	23 132	1	21 721	1	19 777	1	85.1
Dementia, including Alzheimer disease (F01, F03, G30)	6 550	4	9 003	3	12 625	2	88.6
Cerebrovascular diseases (I60-I69)	11 479	2	11 200	2	10 869	3	86.6
Trachea, bronchus and lung cancer (C33-C34)	7 353	3	8 102	4	8 466	4	73.5
Chronic lower respiratory diseases (J40-J47)	5 463	5	6 129	5	7 991	5	81.7
Diabetes (E10-E14)	3 669	8	3 948	7	4 662	6	82.1

"In fact, a simple mathematical projection ….dementia deaths will outnumber those from heart disease as soon as 2021"



Underlying or Associated cause of death

	Age-specific rates[a] (per 100 population)			Number[a][b]			Per cent		
Age	Males	Females	Persons	Males	Females	Persons	Males	Females	Persons
Under 65	0.1	0.1	0.1	13,000	11,800	24,700	10.2	5.7	7.4
65–74	3.0	3.3	3.2	29,200	33,200	62,400	23.0	16.2	18.8
75–84	8.7	10.3	9.6	42,600	60,100	102,800	33.6	29.3	31.0
85+	24.7	33.1	30.0	42,300	99,900	142,100	33.3	48.7	42.8
Total: 65+	7.0	10.3	8.8	114,100	193,200	307,300	89.8	94.3	92.6
Total all ages	**1.1**	**1.8**	**1.4**	**127,000**	**204,900**	**332,000**	**100.0**	**100.0**	**100.0**

Prevalence of dementia doubles every 5 years past 60

60-64 1% **65-69 2%**

70-74 4% **75-79 8%**

80-84 16% **85+ 32%**

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Dementia - ICD 10

- Syndrome due to disease of the brain
- Usually chronic and progressive - at least 6 months for a confident diagnosis
- Involves a decline in multiple higher cortical functions including memory.
- Should attempt to avoid false positive diagnoses, especially depression.
- Decline in intellectual functioning affecting personal activities.
- No clouding of consciousness (delirium)

Dementia ICD 11

- Acquired brain syndrome characterized by a decline from a previous level of cognitive functioning with impairment in two or more cognitive domains (such as memory, executive functions, attention, language, social cognition and judgment, psychomotor speed, visuoperceptual or visuospatial abilities).
- Cognitive impairment not entirely attributable to normal aging
- Significantly interferes with independence in the person's performance of activities of daily living.
- The cognitive impairment is attributed or assumed to be attributable to a neurological or medical condition that affects the brain (including) trauma, nutritional deficiency, chronic use of specific substances or medications, or exposure to heavy metals or other toxins.

Alzheimer's Disease (ICD 10)

- Primary degenerative cerebral disease with characteristic neuropathological and neurochemical features.
  - Presence of dementia
  - Insidious Onset with slow deterioration
  - Absence of clinical evidence or findings from special investigations to suggest that the mental state may be due to other systemic or brain disease which can induce a dementia
  - Absence of a sudden, apoplectic onset or of neurological signs of focal damage such as hemiparesis, sensory loss, visual field defects and incoordination occurring early in the illness (although these phenomena may be superimposed later)

Vascular Dementia (ICD10)

- General criteria for dementia are met.
- Deficits in higher cognitive functions are unevenly distributed. Thus memory may be quite markedly affected while thinking, reasoning and information processing may show only mild decline.
- Clinical evidence of focal brain damage ($\geq$ 1).
  - Unilateral spastic weakness
  - Unilateral increased tendon reflexes
  - Extensor plantar response
  - Pseudobulbar palsy
- Evidence from history, examination or tests of significant cerebrovascular disease which may be reasonably judged to be aetiologically related to the dementia (eg history of stroke, evidence of cerebral infarction).

Dementia due to Lewy Body Disease (ICD11)

- Second most common form in the “elderly”
- Precise etiology is unknown but involves abnormal alpha-synuclein protein folding and aggregation with Lewy body formation primarily in the cortex and brainstem
- Onset is insidious with attentional and executive functioning initial deficits
- These cognitive deficits are often accompanied by visual hallucinations and symptoms of REM sleep behaviour disorder.
- Hallucinations in other sensory modalities, depressive symptoms, and delusions may also be present.
- Symptom presentation usually varies significantly over the course of days necessitating longitudinal assessment and differentiation from Delirium.
- Spontaneous onset of Parkinsonism within approximately 1 year of the onset of cognitive symptoms is characteristic of the disease. (DSM5 pretty similar)

Commonest form of dementia is Mixed

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Dementia in LATE Life – Where to from here?

"Brains of older individuals with ADD commonly contain a variety of pathological changes including amyloid plaques, tau tangles, vascular lesions, Lewy bodies/neurites, neuronal loss and transactive response DNA binding protein 43 kDa (TDP-43)."

"Not only does LATE neuropathology lead to a characteristic amnestic dementia syndrome closely resembling ADD, but the co-existence of LATE and Alzheimer's neuropathology has an additive effect"

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Frontotemporal dementia

- Rare!
- Largely defined by the presence or absence of language disturbance
  - Behavioural variant
  - Progressive nonfluent aphasia (PFNA)
  - Semantic dementia (SD)
- Disordered executive functioning (initiation, planning) and disinhibited behaviour
- Relatively little memory disturbance
- Anosognosia is common

Mild neurocognitive disorder (ICD11)

- Subjective experience of a decline from a previous level of cognitive functioning
- Accompanied by objective evidence of impairment in performance on one or more cognitive domains relative to age and general level of intellectual functioning
- Not sufficiently severe to significantly interfere with independence in person's performance of activities of daily living.
- The cognitive impairment is not entirely attributable to normal aging.
- May be attributable to an underlying disease of the nervous system, a trauma, an infection or other disease process affecting specific areas of the brain, or to chronic use of specific substances or medications, or the etiology may be undetermined.

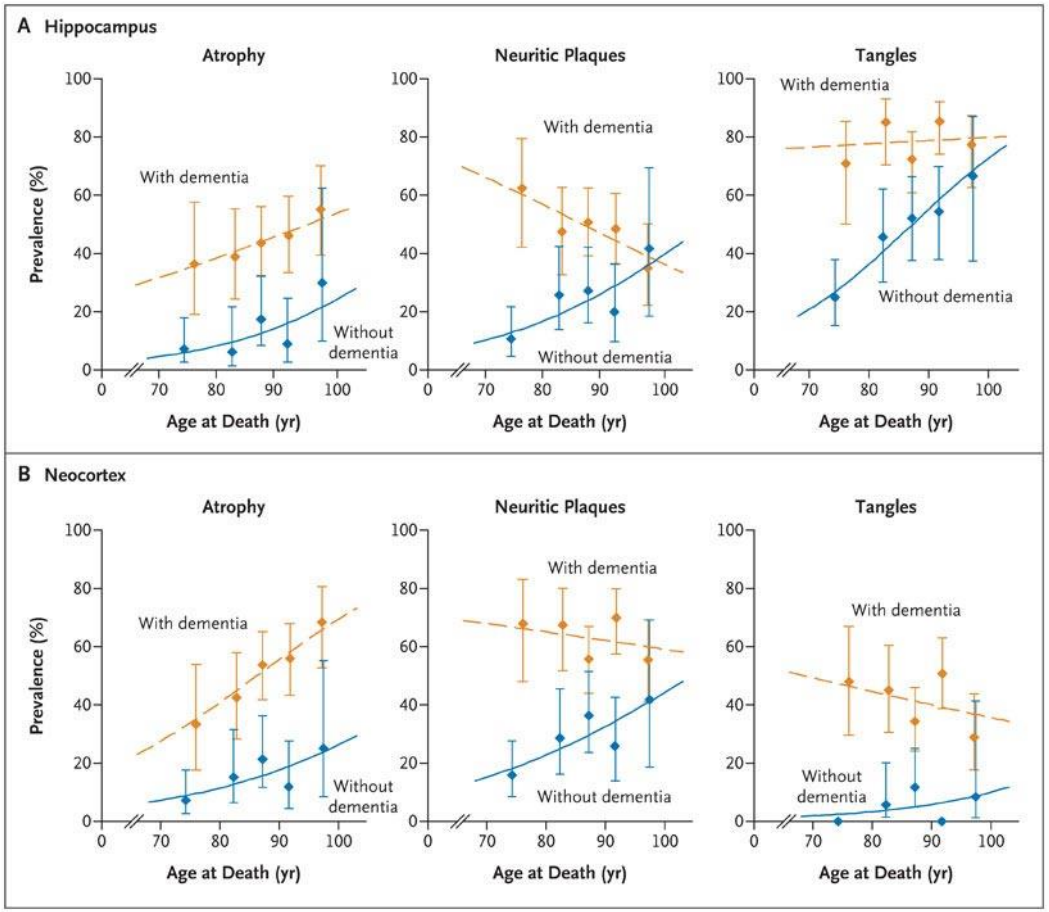
Alzheimers or Cognitive Frailty?

- Amyloid as the “cause” of Alzheimers dementia Masters et PNAS 1985
- Hopes were raised that within 10 years, effective interventions that alter disease progression would be available.
- Some 30 years later, such hopes are somewhat diminished.
- Interventions were duly tested but removing amyloid protein did not result in any clinical improvement, and in one trial of a gamma secretase inhibitor, semagacestat, worsening.
- May be that amyloid accumulates as part of the brain’s repair mechanism.
- Not all people progress to dementia from MCI and that some actually improve over time Song et al J Neur, Neurosurg Psych 2013
- Would explain high rates in Indigenous Australians, effects of physical activity, education, dementia following delirium etc

Dementia or Cognitive Frailty?

Age, neuropathology and dementia Savva et al N Engl J Med 2009; 360:2302

The association between the presence of dementia and Alzheimer pathology decreases with age



MOST COMMON FORM OF DEMENTIA - MIXED

- 5 separate pathologies associated with "Alzheimers-type dementia"
- Plaques and tangles
- Microvascular Lesions
- Atrophy
- Hippocampal sclerosis
- Cortical Lewy Bodies

(White L 2009)

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Early or Timely Diagnosis?

- A diagnosis should be made as soon as possible in every individual case - Driven by personal and professional experiences of delays in access to diagnosis and support.
- Currently no high quality evidence that diagnosis before the usual point of clinical presentation leads to long term improvements for people with dementia and their families. "policy cart before the research horse."
- "Early" versus "screening"
- Potential harms of premature diagnosis
  - Diversion of resources from activities of proven value
  - Misclassification of substantial numbers of people
  - Overdiagnosis and overtreatment
  - Raising levels of anxiety in the population, particularly among older people.

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

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

Main results

Alzheimer's disease dementia was evaluated in 14 studies. Of the 1349 participants included in the meta-analysis, 436 developed Alzheimer's dementia. Individual study estimates of sensitivity were between 36% and 100% while the specificities were between 29% and 91%..... At the median specificity of 64%, the sensitivity was 81% (95% CI 72 to 87).

Authors' conclusions

.. From our review, the measure of abnormally lowCSF Aß levels has very little diagnostic benefit …..We conclude that when applied to a population of patients with MCI, CSF Aß levels cannot be recommended as an accurate test for Alzheimer's disease.

18F PET florbetapir for the early diagnosis of ADD and other dementias

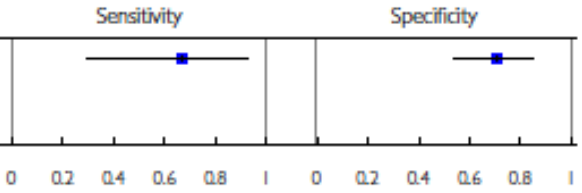
Gabriel Martínez, Robin WM Vernooij, Paulina Fuentes Padilla, Javier Zamora, Xavier Bonfill Cosp, Leon Flicker

Test 1. MCI to ADD by visual assessment from 2 to less than 4 years of follow-up.

Review: 18F PET with florbetapir for the early diagnosis of Alzheimer' s disease dementia and other dementias in people with mild cognitive impairment (MCI)

Test: 1 MCI to ADD by visual assessment from 2 to less than 4 years of follow-up

Study	TP	FP	FN	TN	Sensitivity	Specificity
Doraiswamy 2014	6	11	3	27	0.67 [0.30, 0.93]	0.71 [0.54, 0.85]

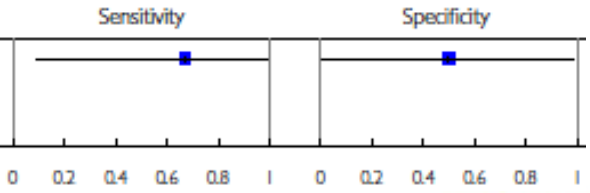


Test 4. MCI to any form of dementia.

Review: 18F PET with florbetapir for the early diagnosis of Alzheimer' s disease dementia and other dementias in people with mild cognitive impairment (MCI)

Test: 4 MCI to any form of dementia

Study	TP	FP	FN	TN	Sensitivity	Specificity
Kawas 2013	2	1	1	1	0.67 [0.09, 0.99]	0.50 [0.01, 0.99]



the poor specificity, limited data available we cannot recommend routine use of 18F-florbetapir PET in clinical practice

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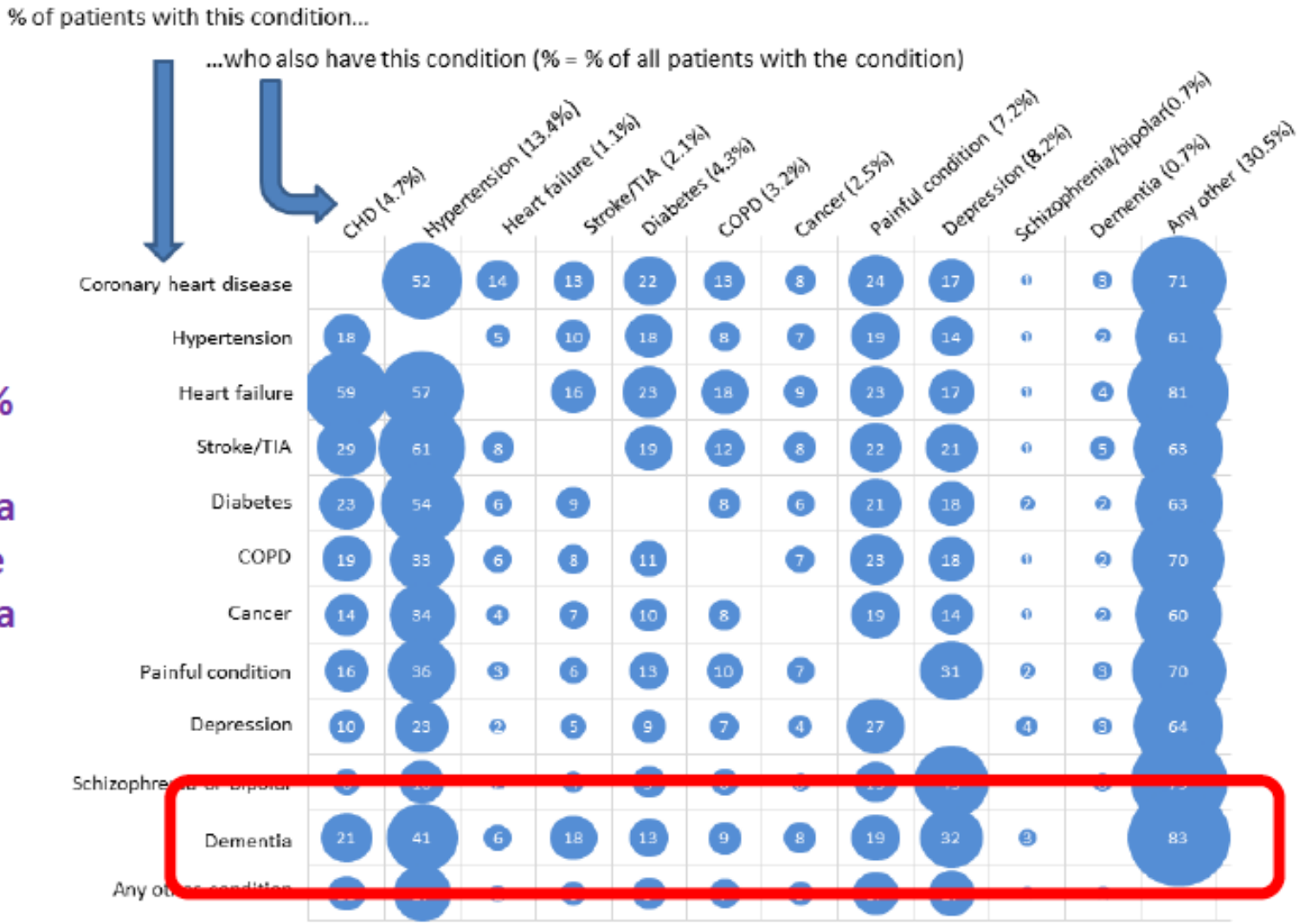
Domains of Assessment

- Cognition
- Functioning
  - Activities of daily living
  - Instrumental Activities of Daily Living
- Informant information
  - Related to cognitive decline
  - Abnormal behaviour
- Carer Assessment
  - (Medical) Type of dementia & medical co-morbidities

Most people of any age with any long term condition have multiple conditions *(Scottish School of Primary Care, 2012)*



Only 17% with dementia *just* have dementia

CLINICAL PRACTICE GUIDELINES AND PRINCIPLES OF CARE FOR PEOPLE WITH DEMENTIA

NEW practice guidelines for the diagnosis and treatment of dementia in Australia promise to help frontline health care professionals to improve the quality and consistency of the care they offer their dementia patients, according to a Clinical Focus published online (March 14 2016) by the Medical Journal of Australia

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Background

- Guidelines synthesise existing evidence.
- Guidelines can improve health outcomes and increase the efficiency and quality of care. (Grimshaw 2004)
- The NHMRC and ACSQHC agreed that Guidelines for Dementia should be prioritised.
- Funding received via the NHMRC Cognitive Decline Partnership Centre to review existing guidelines and adapt for the Australian context.

Dignity in Care

Recommendation: "Health and aged care professionals should provide person-centred care, by identifying and responding to the individual needs and preferences of the person with dementia, their carer(s) and family. The 10 Principles of Dignity in Care should be used as the standard by which care is delivered and evaluated" (PP)

1	Zero tolerance of all forms of abuse.
2	Support people with the same respect you would want for yourself or a member of your family.
3	Treat each person as an individual by offering a personalised service.
4	Enable people to maintain the maximum possible level of independence, choice and control.
5	Listen and support people to express their needs and wants.
6	Respect people's privacy.
7	Ensure people feel able to complain without fear of retribution.
8	Engage with family members and carers as care partners.
9	Assist people to maintain confidence and a positive self-esteem.

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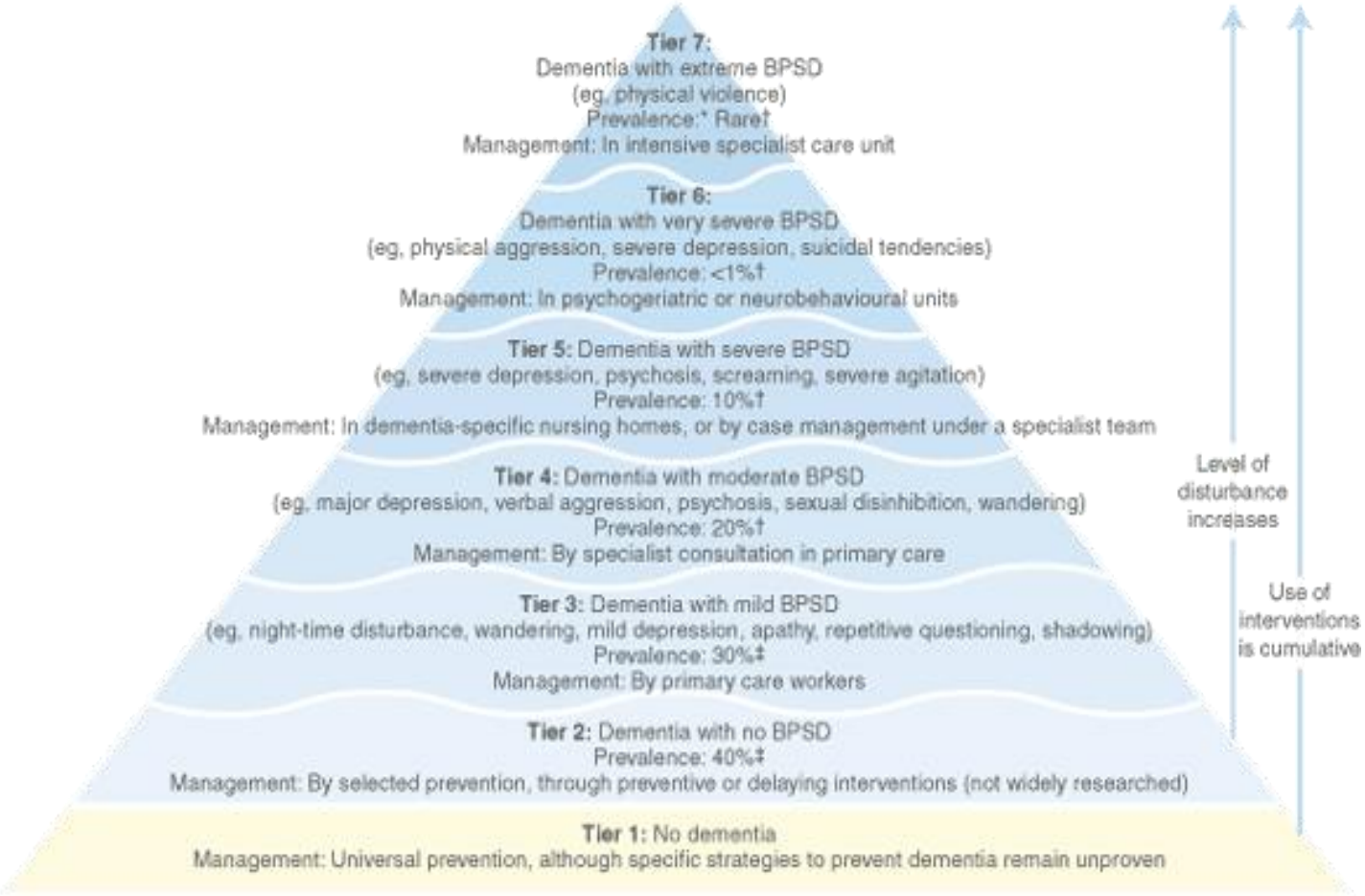
Brodaty et al

MJA 2003 178: 231-234



*Prevalence is expressed as estimated percentage of people with dementia who currently fall into this category.
†Estimate based on clinical observation. ‡Estimate based on Ballard et al.[2]

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Why disclose dementia diagnosis?

- Patient has a right to know (or not to know)
- Helps to avoid later confusion and ambiguity
- Starting point for sharing information
- Fosters a collaborative relationship between the patient and healthcare professional
- Makes future communications easier
- Enables patient and carer to plan for the future
- Enables patient to start sorting out legal, financial and practical issues
- Maintains openness in the relationship with the patient

Foy et al, 2007

What was the evidence for ChIs?

Saturday 6 March 1999

BMJ

Acetylcholinesterase inhibitors for Alzheimer's disease

More benefit may arise from the assessments they necessitate

Editorial 1999

- “The evidence to date is that treatments based on the cholinergic hypothesis are essentially symptomatic. No substantial data support the hypothesis that these medications modify the disease - that is, delay its progression.”
- “The effect is modest but may be more prominent in some patients than others”
- “concerns have been raised about how these modest increases in cognition and global impression translate into clinical effects that can be used in a total care package for people with dementia”
- “there is at least some evidence of a modest improvement in carer rated quality of life, but an average change of 2.8 points in a scale with a mean disability score of 54 points does not appear dramatic”
- “Delays to institutionalisation or extreme dependency …. may be more appropriate end points for this type of analysis. “

Memantine

(Cochrane review McShane et al 2006)

- Low affinity N-methyl-D-aspartate (NMDA) type receptor antagonists, such as memantine, might prevent excitatory amino acid neurotoxicity without interfering with the physiological actions of glutamate necessary for learning and memory.
- Memantine has a small beneficial, clinically detectable effect on cognitive function and functional decline measured at 6 months in patients with moderate to severe Alzheimer's Disease (AD). (PBS MMSE 10-14)
- In patients with mild to moderate dementia, the small beneficial effect on cognition was not clinically detectable in those with vascular dementia and barely detectable in those with AD.
- It is well tolerated. Slightly fewer patients with moderate to severe AD taking memantine develop agitation, but there is no evidence either way about whether it has an effect on agitation which is already present.

Training staff

- *"Health and aged care organisations should ensure that all staff working with people with dementia receive dementia-care training (attitude, knowledge and skill development) that is consistent with their roles and responsibilities. Training should reflect programs that have been shown to optimise care for people with dementia. Effective programs tend to be: delivered face-to-face by someone experienced in dementia care; scheduled over several training sessions; involve ongoing mentoring or support from someone experienced in dementia care; and, utilise active learning techniques such as problem solving, case based training and role plays." (EBR)*

- *"Training programs should be comprehensive and have a strong focus on communicating effectively with the person with dementia and his or her carer(s) and family and recognising, preventing and managing behavioural and psychological symptoms of dementia. Staff should be trained in the principles of person-centred care and how these principles are applied in practice." (EBR)*

Evidence: There are a number of RCTs that demonstrate that training programs in residential care settings (as described above) can reduce symptoms such as agitation, reduce restraint use and improve the quality of care.

Management of symptoms

Recommendations support:

- Attempting to minimise symptoms by considering unmet needs and lowered stress threshold
- Comprehensive assessment by a professional with skills in this area (eg ABC approach)
- Objective measurement to monitor the type and patterns
- Non-pharmacological approaches in the first instance

Management of symptoms

"To assist the carer(s) and family help the person with dementia who is experiencing behavioural and psychological symptoms of dementia, carer(s) and family should be offered interventions which involve:

- *carer skills training in managing symptoms and communicating effectively with the person with dementia*
- *meaningful activity planning*
- *environmental redesign and modification to improve safety and enjoyment*
- *problem solving and management planning." (EBR)*

Management of symptoms - pharmacological

The Guidelines recommend:

- Trial of analgesic medication where the person is suspected to be in pain due to distress
- Trial of SSRI antidepressants for agitation (citalopram has the strongest evidence)
- Avoiding antipsychotics in people with mild to moderate symptoms

- There is uncertainty around the efficacy of antidepressants in the treatment of depression in people with dementia. Larger trials have not shown benefit.

Management of symptoms - pharmacological

- People with severe symptoms causing distress to themselves or others may be offered treatment with an antipsychotic. Risperidone and olanzapine have the strongest evidence for agitation/aggression. Conditions of use are outlined in the recommendations.
- Recommendations provided regarding use of parenteral medication (noting that oral medication should be offered first).

Management of symptoms

"Where people with dementia have moderate to severe behavioural and psychological symptoms of dementia that puts themselves or others at risk, referral to a specialist service for the management of behavioural and psychological symptoms should occur." (PP)

DBMAS, new Severe Behaviour Response Teams (SBRTs)

Support for carers

"Carer(s) and family should have access to programs designed to provide support and optimise their ability to provide care for the person with dementia. Programs should be tailored to the needs of the individual and delivered in the home or at another accessible location. Programs should be delivered over multiple sessions and include:

- *education regarding dementia and its consequences*
- *information regarding relevant services including respite*
- *referral to support organisations such as Alzheimer's Australia or Carers Australia*
- *development of individualised strategies and building carer skills to overcome specific problems experienced by the person with dementia as reported by the carer*
- *training in providing care and communicating most effectively with the person with dementia*
- *support and information regarding coping strategies to maintain their own wellbeing including stress management*
- *training in the use of pleasant and meaningful activities as a strategy to engage the person with dementia" (EBR)*

Carers should be offered respite and be provided with information on how to join a mutual support group

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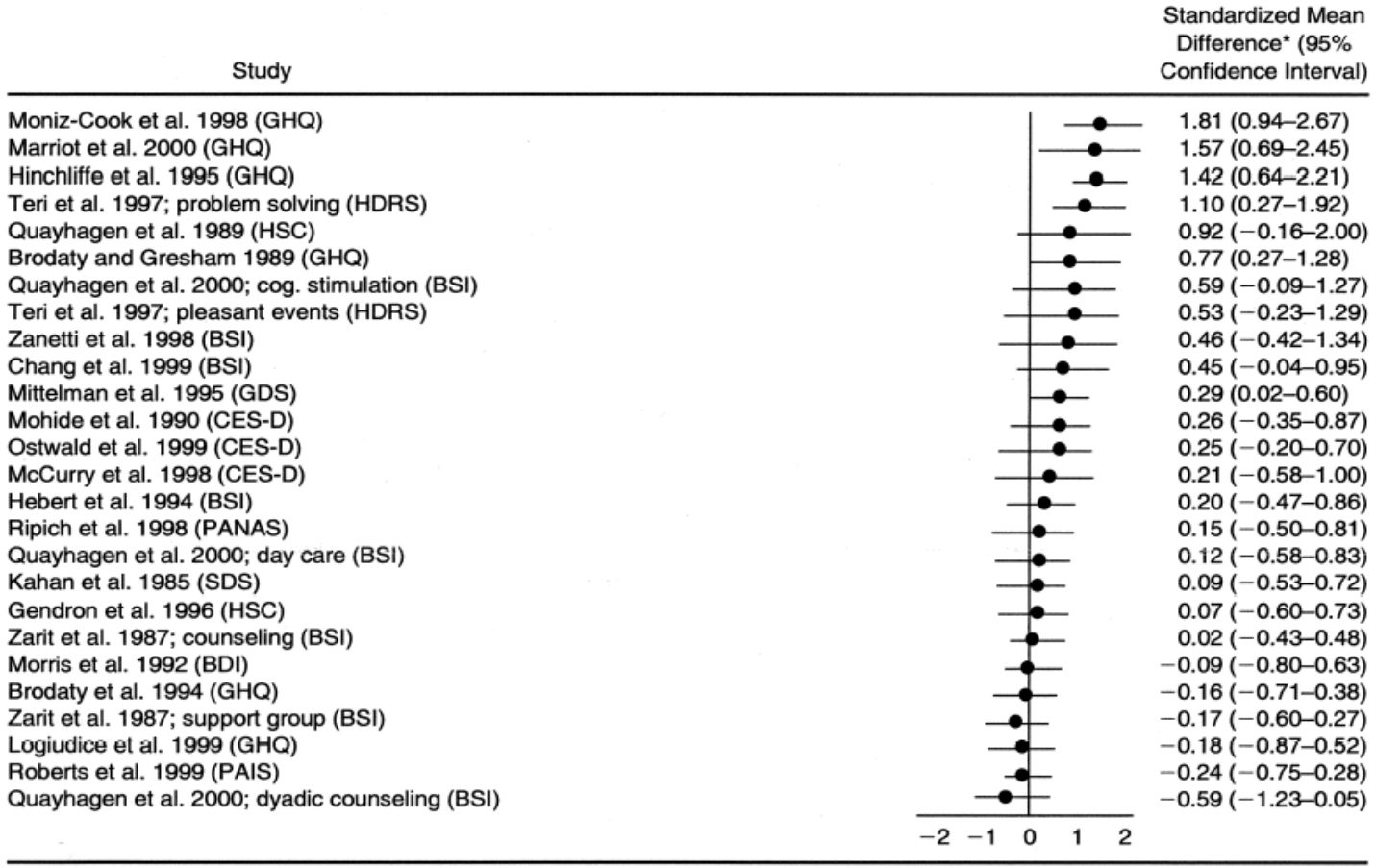
Effect Size for Psychological Morbidity at Most Current Follow-Up Assessment 0.31 [0.13, 0.50] Brodaty et al JAGS 2003; 51:657



*Effect size measured as standardized mean difference between treatment and control group.

GHQ = General Health Questionnaire (Goldberg & Williams, 1988); BSI = brief symptom inventory (Derogatis et al. 1983); SDS = Self-rating Depression Scale (Zung, 1965); HSC = Hopkins Symptom Checklist (Derogatis et al. 1974); CES-D = Center for Epidemiological Studies Depression Scale (Radloff, 1977); PANAS = Positive and Negative Affect Scale (modified version; Watson et al. 1988); PAIS = Psychosocial Adjustment to Illness Scale.

End of life care

- Should be consistent with the person's Advance Care Plans.
- Health and aged care staff and carers and families should continue to offer people with dementia food and drink by mouth.
- Nutritional support, including artificial (tube) feeding, should be considered if dysphagia is thought to be a transient phenomenon, but artificial feeding should not generally be used in people with severe dementia
- Any decision about rehydration should be made in conjunction with the carer(s) and family after providing them with up-to-date information on the potential benefits and harm.
- Ethical and legal principles should be applied in all decision making (see NHMRC Guide on ethics and decision making in palliative care for older people)