

4th NARI Biennial Seminar – 10th September 2010

Exercise and Cognition in later life: an update

Nicola T Lautenschlager



THE UNIVERSITY OF
MELBOURNE

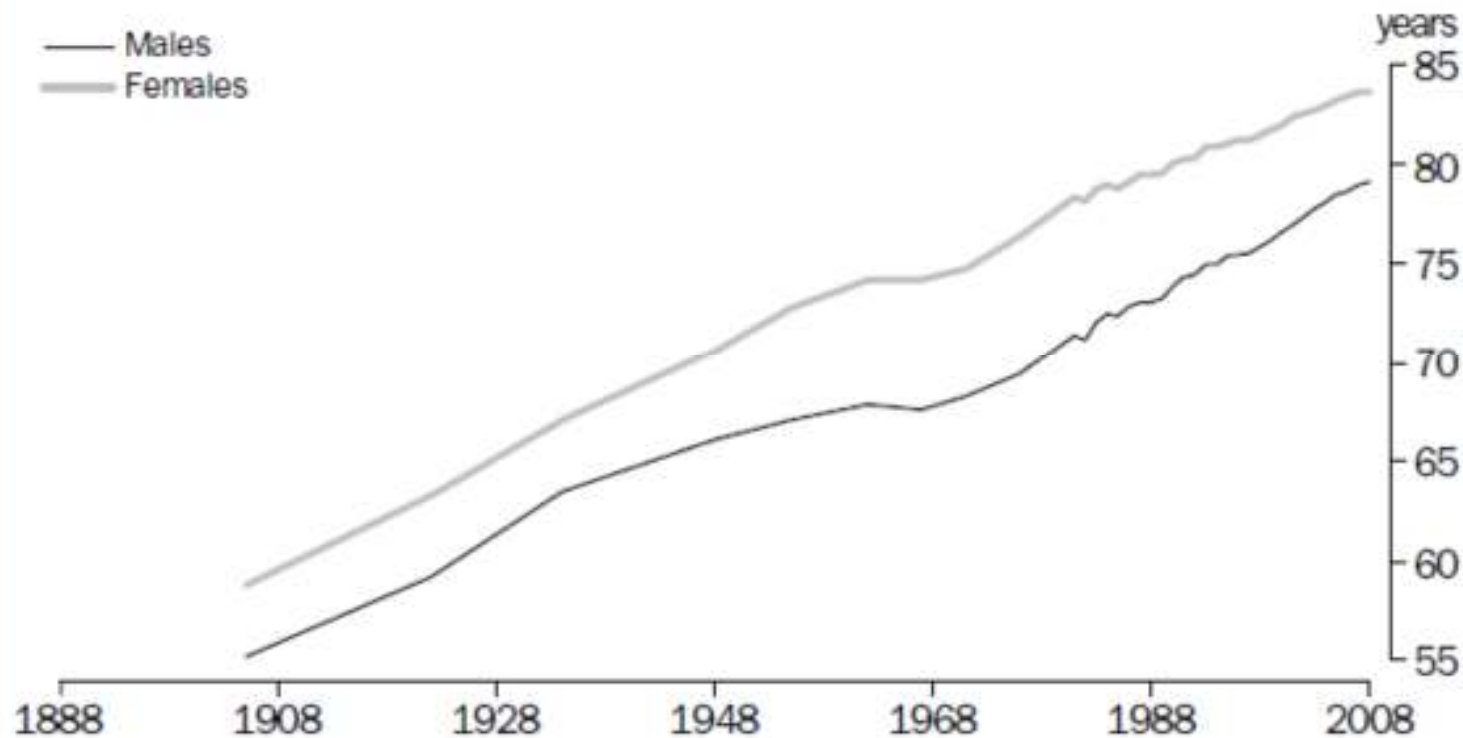
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2.11 LIFE EXPECTANCY AT BIRTH—1907–2008



Source: Australian Historical Population Statistics (3105.0.65.001); Deaths, Australia (3302.0)

Life expectancy at birth (2008)

men: 79.2 years (only higher in Iceland, Hong Kong and Switzerland)

women: 83.8 years (only higher in Japan, Hong Kong, Switzerland, France, Spain)

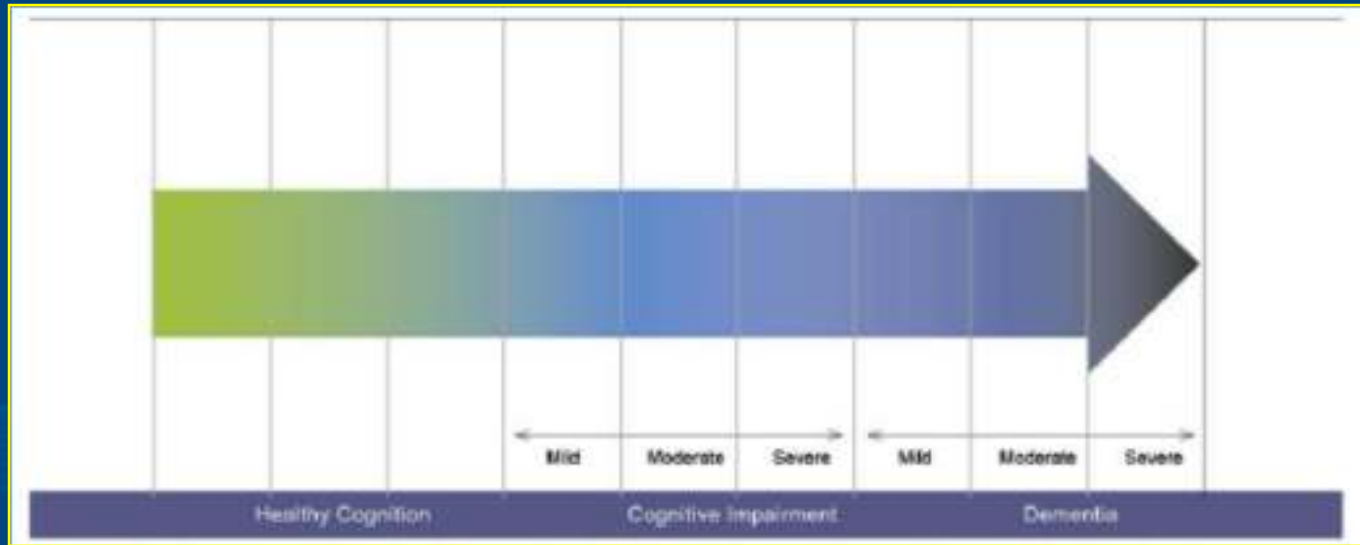
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Continuum of cognition

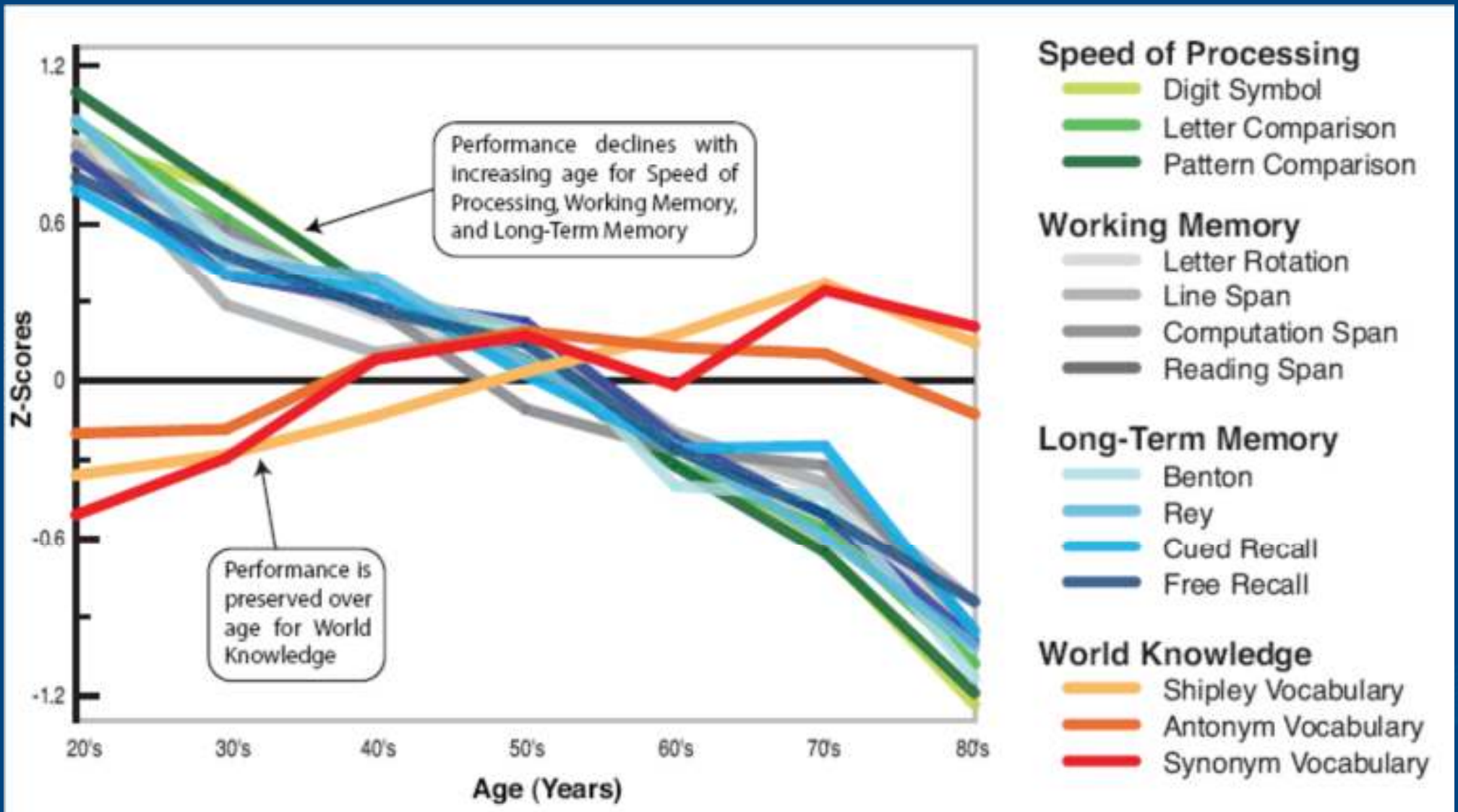
- Successful Ageing
- Normal Ageing
- Subjective Memory Complaints (SMC)
- Mild Cognitive Impairment (MCI)
- Dementia



Absence of chronic disease and disability
High cognitive and physical functioning
Active engagement with life



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Memory complaint preferably qualified by an informant

Memory impairment for age and education

Preserved general cognitive function

Intact activities of daily living

Not demented

Amnestic MCI

Petersen, 2007

Complaint from person or family member

Objective cognitive impairment

Change from normal functioning

Preserved overall general function, but some increased difficulty in activities of daily living

Not demented

MCI

Winblad et al., 2004

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Prevalence of Cognitive Impairment without Dementia in the United States

Brenda L. Plassman, PhD; Kenneth M. Langa, MD, PhD; Gwenith G. Fisher, PhD; Steven G. Heeringa, PhD; David R. Weir, PhD; Mary Beth Ofstedal, PhD; James R. Burke, MD, PhD; Michael D. Hurd, PhD; Guy G. Potter, PhD; Willard L. Rodgers, PhD; David C. Steffens, MD, MHS; John J. McArdle, PhD; Robert J. Willis, PhD; and Robert B. Wallace, MD

n=1770 approached; n=856 assessed

CIND

Consensus panel using clinical judgement
Mild cognitive or functional impairment
Cognitive performance below expectation and at least 1.5 SD below norms
Reported by participant or informant
Does not meet criteria of dementia

Prodromal AD

Consensus panel using clinical judgement
CIND present
Pattern of symptoms and neuropsychological test results suggestive of prodromal AD
No other medical or neuropsychiatric conditions present to preclude and eventual diagnosis of AD

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Cognitive Impairment without Dementia Subtype after Initial Assessment	Frequency, <i>n</i> (%)	Mean Age (SD), <i>y</i>
Prodromal Alzheimer disease	94 (34.2)	81.88 (5.94)
Medical conditions	55 (23.9)	80.28 (5.96)
Stroke	34 (15.5)	81.04 (5.41)
Vascular cognitive impairment without dementia	20 (10.1)	78.63 (6.25)
Depression and other psychiatric disorders	10 (5.1)	80.21 (3.59)
Neurologic conditions	10 (5.2)	82.71 (6.71)
Amnesic mild cognitive impairment	4 (2.8)	82.45 (12.52)
Past or current alcohol abuse	6 (1.7)	76.89 (1.34)
Low baseline intellect or presence of learning disorders	8 (1.4)	81.12 (4.66)
Total	241 (100)	80.92 (5.90)

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Age	All Cognitive Impairment without Dementia (<i>n</i> = 241)		Prodromal Alzheimer Disease (<i>n</i> = 98)†	
	Prevalence (95% CI), %	Population Estimate (95% CI)	Prevalence (95% CI), %	Population Estimate (95% CI)
71–79 y	16.0 (11.5–20.5)	2.29 (1.65–2.94)	5.5 (2.6–8.4)	0.79 (0.37–1.20)
80–89 y	29.2 (24.3–34.1)	2.41 (2.00–2.81)	9.7 (6.4–13.1)	0.80 (0.528–1.081)
≥90 y	39.0 (25.7–52.2)	0.73 (0.48–0.98)	22.4 (11.9–32.9)	0.42 (0.22–0.62)
Total	22.2 (18.7–25.7)	5.43 (4.57–6.29)	8.2 (6.5–10.0)	2.01 (1.59–2.45)

Vascular Cognitive Impairment without Dementia and Stroke (<i>n</i> = 54)†		Medical Conditions (<i>n</i> = 55)†	
Prevalence (95% CI), %	Population Estimate (95% CI)	Prevalence (95% CI), %	Population Estimate (95% CI)
3.5 (1.4–5.6)	0.50 (0.20–0.80)	4.7 (1.2–8.5)	0.674 (0.17–1.22)
10.1 (6.4–13.9)	0.83 (0.53–1.15)	5.4 (2.1–8.7)	0.45 (0.17–0.72)
2.9 (0.0–6.3)	0.05 (0.0–0.12)	9.2 (0.2–18.2)	0.17 (0.00–0.34)
5.7 (3.8–7.6)	1.39 (0.93–1.86)	5.3 (2.6–8.0)	1.30 (0.64–1.96)

8% died /a
12% demented /a

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Mild Cognitive impairment (MCI)

Minimal

What's in a name?

Far from extreme

Not powerful or strong

Moderate in type or degree or effect or force

Faint

Slight

Not severe

Vague

Not acute

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What do patients think of the diagnosis MCI?

- „It is my age“
- „I am not interested“
- „I‘ve always been very absent-minded“
- „It‘s the medication“
- „It‘s because of my hearing problem“
- „I think the hip surgery is the cause...“
- „I wonder where it comes from“
- This is the beginning, but where will it end?“
- „Will I become demented?“
- „Many people of my age have this“
- „I have to resign myself to it“
- „After the consultation with the geriatrician I stopped looking for causes“
- „I keep worrying about becoming a burden to my children“
- „I am angry with myself, but I take it out on him“
- „I‘ve lost my self-confidence“
- „My husband thinks that I am getting senile which I resent“
- „I feel great when others don‘t notice it“

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Care giver, care partner or family member?

- „Please tell me about your experience that led up to your spouse being diagnosed with MCI and your experience since....“

Major Theme	Theme Cluster
Putting the puzzle pieces together: There really is something wrong	a. Short-term memory declining b. Difficulty in engaging in some familiar tasks c. Behavioral changes d. Emotional changes e. Changes in social activity engagement
A downward spiral into a world of silence	a. Best friend is gone b. My world is shrinking c. Rollercoaster distress
Consequences to caregivers of living in a world of silence	a. Taking on increasing obligation b. Decision-making challenge c. High cost to quality of life
Taking charge of care	a. Knowing major needs and concerns b. Finding care strategies

„Why can't you do this? He looks fine!“

„The diagnosis is MCI. A huge relief because still today there are many times that I ask myself am I just imagining this?“

„Would you want me to help you with the meds? No! You have taken enough stuff away from me already.“

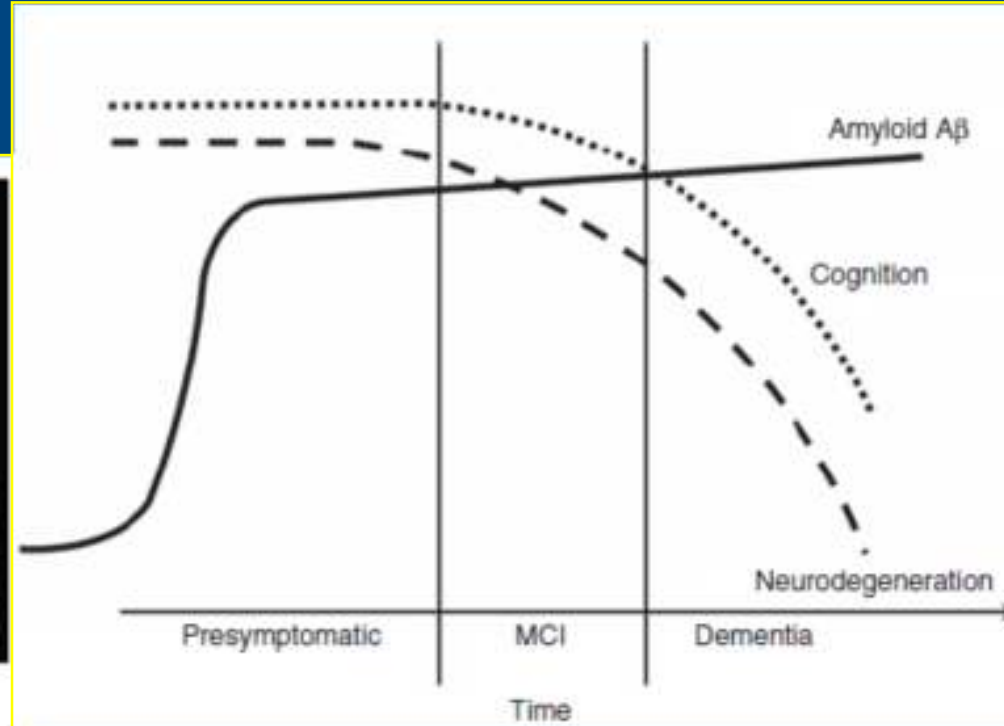
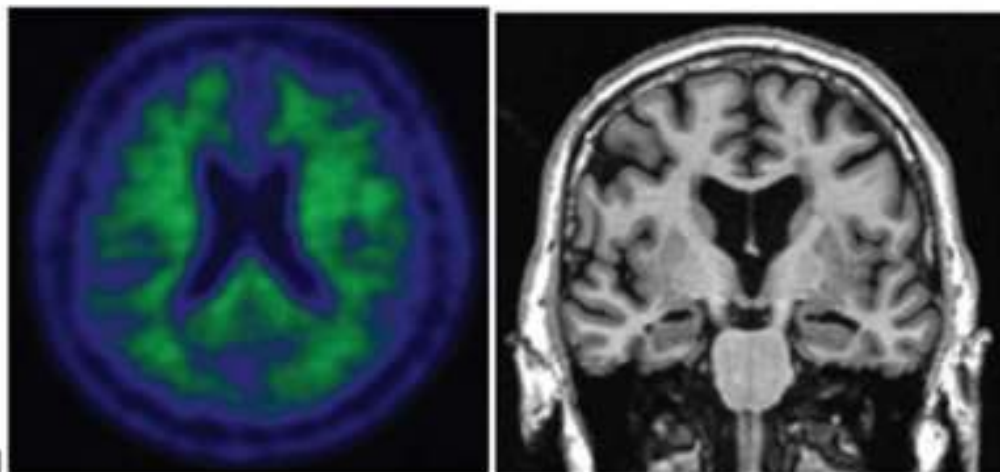
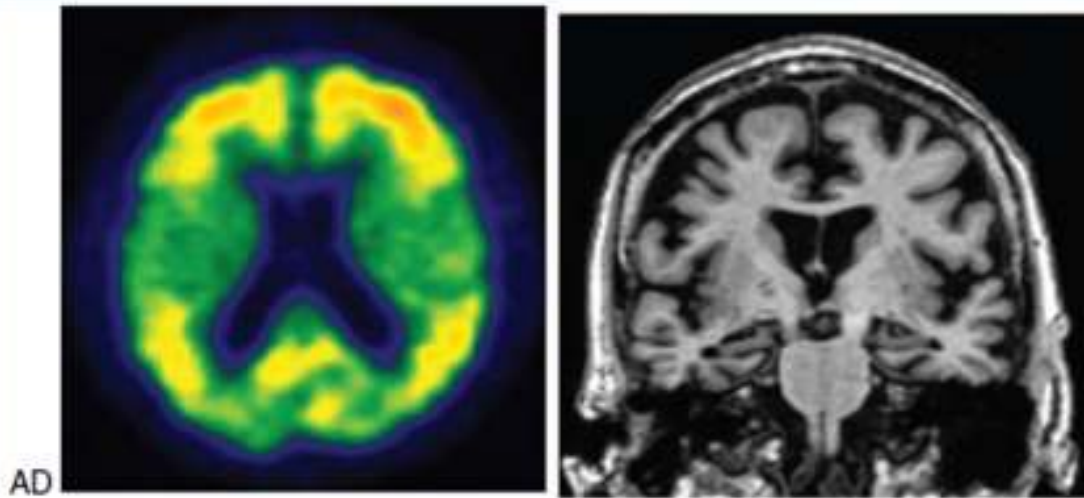
„So I have changed my definition of what is ethical behaviour and I trust God understands that...“

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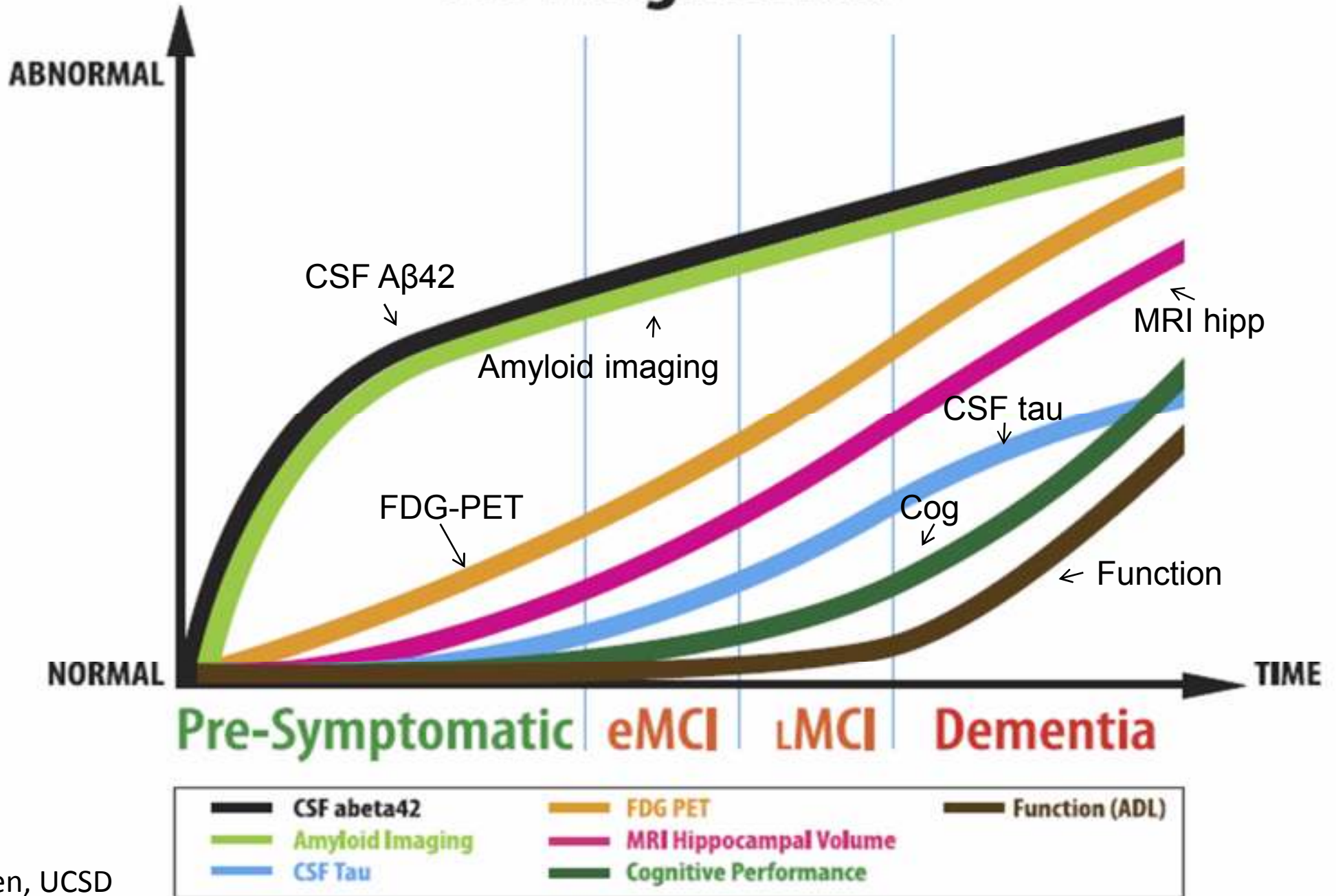
Potential causes for MCI:

1. Neurodegenerative brain disease (AD, PPD, LBD, FTD, etc.)
2. Cerebrovascular disease
3. Depression
4. Anxiety
5. Life events/ stressors/ personality
6. Organic factors
7. Post delirium
7. Various combinations of the above

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AD Progression



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National Institute on Aging and Alzheimer's Association Lead Effort to Update Diagnostic Criteria for Alzheimer's Disease

*- News briefing/Q&A: AAICAD 2010, Tuesday, July 13, 2010, 11:45 am-12:45 pm
Hawai'i Convention Center, Room 321A, 1801 Kalakaua Avenue, Honolulu -*

Honolulu, Hawaii, July 13, 2010 – Scientists at the Alzheimer's Association International Conference on Alzheimer's Disease 2010 (AAICAD 2010) today presented the first draft reports from three workgroups convened by the National Institute on Aging (NIA) and the Alzheimer's Association to update the diagnostic criteria for Alzheimer's disease for the first time in 25 years.

The current criteria for the diagnosis of Alzheimer's were established by a National Institute of Neurological Disorders and Stroke (NINDS)/Alzheimer's Disease and Related Disorders Association (ADRDA) workgroup in 1984. These criteria were almost universally adopted and have been useful; they have survived intact without modification for more than 25 years. However, experts note, the field has evolved to a great extent since then.

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www.alz.org/research/diagnostic_criteria

Pre-clinical – The group is laying out a research agenda to identify methods of assessment that may help predict risk for developing the disease. Biomarkers and other clinical assessment tools to identify early cognitive decline are being investigated to establish the presence of Alzheimer's brain changes in people with no overt symptoms and to identify those who may eventually develop the disease.

Mild cognitive impairment – The group is refining the MCI criteria, which will help to indicate cognitive change before dementia and better differentiate MCI from Alzheimer's. Research is underway to better understand the cognitive changes taking place, how they may relate to biomarkers, and which of these methods best indicate the likelihood of imminent progression to Alzheimer's dementia.

Alzheimer's dementia – The group is revising the existing criteria for diagnosing Alzheimer's to include possible biomarkers and other assessments that may aid in diagnosis

Operational Research Criteria for Defining Preclinical AD

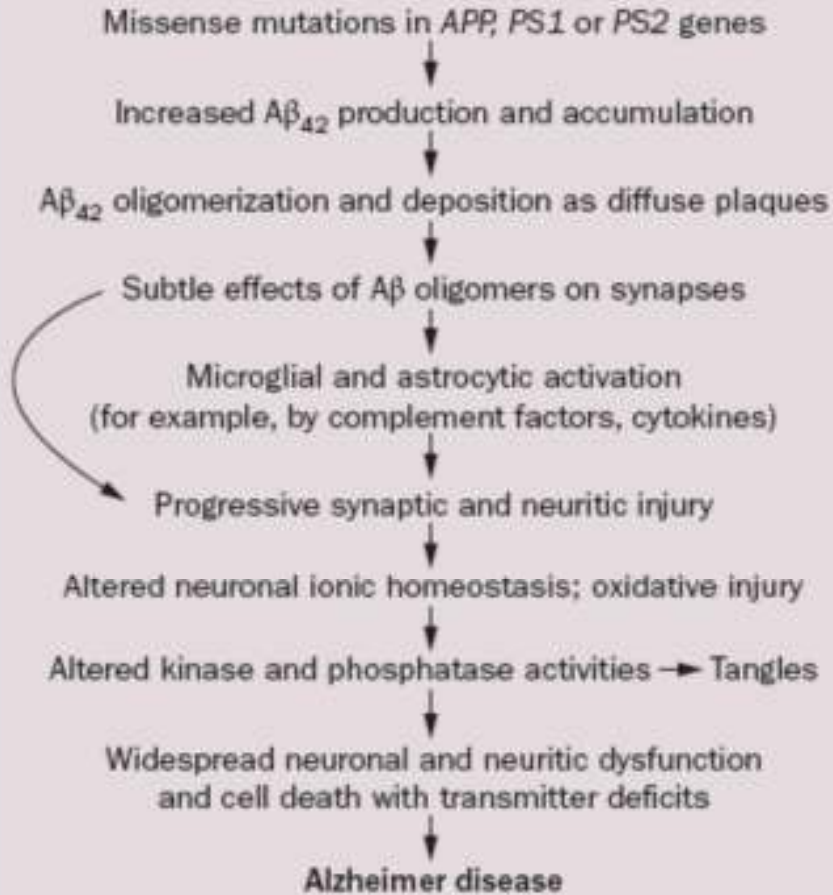
1. Biomarker evidence of amyloid- β accumulation (Stage 1 = asymptomatic cerebral amyloidosis)
 - a. Elevated tracer retention on PET amyloid imaging and/or low A β_{42} on CSF assay

2. Biomarker evidence of synaptic dysfunction and or early neurodegeneration (Stage 2 = evidence of amyloid positivity + presence of one or more additional AD markers)
 - a. Elevated CSF tau or phospho-tau
 - b. Hypometabolism in an AD-like pattern (i.e. posterior cingulate, precuneus, and/or temporo-parietal cortices) on FDG-PET
 - c. Cortical thinning/grey matter loss in AD-like anatomic distribution (i.e. lateral and medial parietal, posterior cingulate and lateral temporal cortices) and/or hippocampal atrophy on volumetric MRI

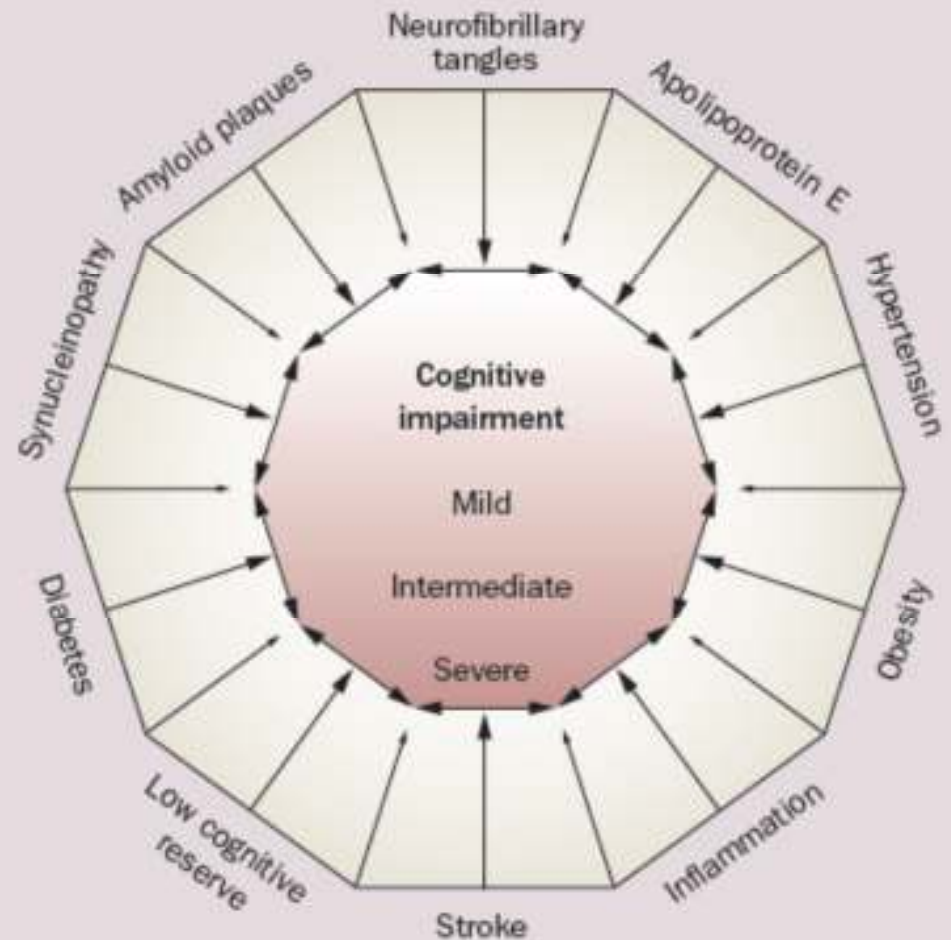
3. Evidence of subtle cognitive decline, but does not meet criteria for MCI or dementia (Stage 3 = amyloid positivity + markers of neurodegeneration + very early cognitive symptoms)
 - a. Demonstrated cognitive decline over time on standard cognitive tests, but not meeting criteria for MCI
 - b. Subtle impairment on challenging cognitive tests, particularly accounting for level of innate ability or cognitive reserve but not meeting criteria for MCI

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a The amyloid cascade hypothesis



b The dynamic polygon hypothesis



What to consider when managing MCI

- Disclosure of diagnosis
- Information on assessment results
- Individualised information on prognosis
- Pharmacological management options
- Non-pharmacological approaches
- Information on research trials in the area
- Monitoring health and vascular risk factors
- Neuropsychiatric symptoms
- Discuss ADLs (including driving)
- Planning the future (e.g. finances, travelling, etc.)
- Information on AD treatment in case of progression
- “Carer” burden
- Information on useful contacts (e.g. Alzheimer Association)
- Regular follow-up appointments

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Protective approach

- Choose your parents wisely...(genes and childhood)
- Healthy diet
- Cognitive activity
- Physical activity
- Social network and support
- Avoiding and monitoring vascular risk factors
- Avoiding head injury and other brain damage
- Manage depression

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Physical activity – the benefits

- Improved fitness
- Improved physical health (e.g. reduced risk of heart disease, diabetes, some types of cancer)
- Reduced morbidity & mortality
- Improved mental health
- Improved confidence and quality of life
- ? Protects brain health



THE HON JUSTINE ELLIOT MP

Minister for Ageing

MEDIA RELEASE

23 March 2009

First Physical Activity Recommendations for Older Australians

For the first time, the Australian Government has developed physical activity recommendations specifically for older Australians.

http://www.mednwh.unimelb.edu.au/research/health_promotion.htm

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Possible mechanism?

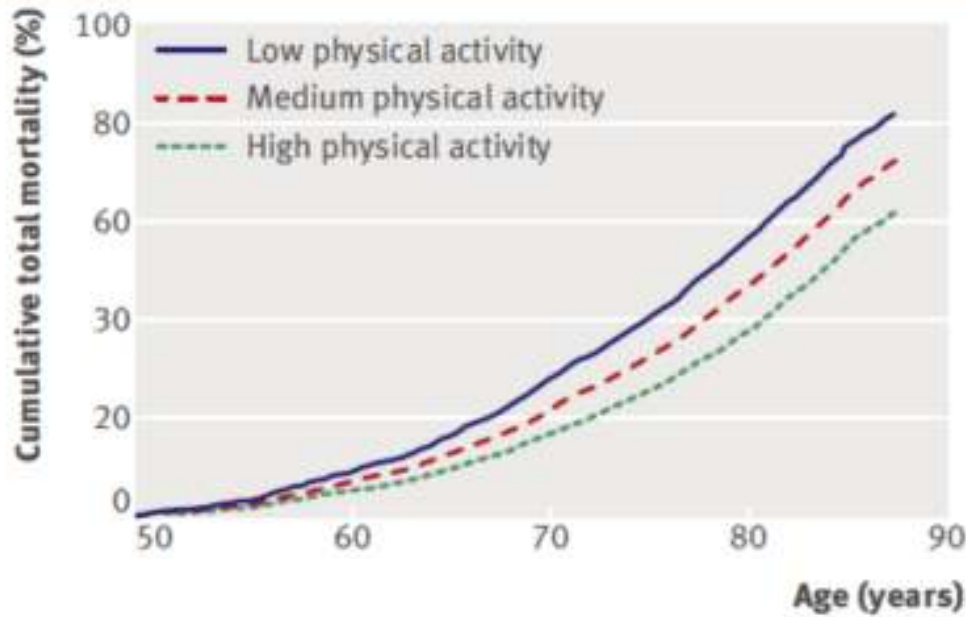
- Alteration in cerebral vascular function and brain perfusion
- Supports survival & function of neurons
- Neuroendocrine responses to stress
- Reduces brain amyloid burden
- Reduces inflammation
- Stimulates synaptogenesis & neurogenesis
- Influenced by genetic factors (e.g. APOE e4 allele)
- Psychological factors

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Physical activity and mortality

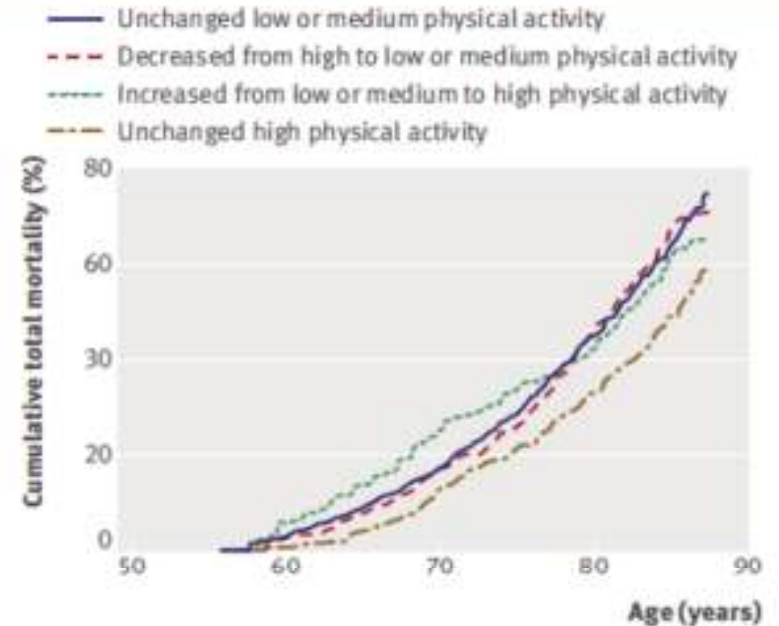
- Uppsala longitudinal study of adult men, n= 2322 aged 49-51, follow-up at age 60, 70, 77 and 82 y
- 15% sedentary, 36% medium PA (e.g. walks and cycling), almost 50% high level of PA (3h+ sport/week) at age 50y. At end of follow-up 60% had died
- High level PA men lived 3.8 y longer than sedentary men and 1.8 y longer than medium PA men. Effect of sedentary behaviour was similar to smoking and obesity
- Those who changed to high PA during follow-up had same survival after 10 years like baseline high PA men, but had initially increased mortality in the first 5 years after change
- Mechanism: metabolic syndrome, hypertension, inflammatory and hormonal responses, gut mobility, neuromuscular and brain function, genetics

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Age	50	60	70	77	82	End of study
Men at risk	2205	1904	1406	1123	933	876

Fig 2 | Cumulative mortality from age 50 (Cox regression) according to leisure time physical activity level and total mortality. At end of follow-up, estimated proportions of deaths were 81.4 (95% confidence interval 80.8 to 82.0) for low physical activity, 72.0 (71.5 to 72.5) for medium, and 61.8 (61.4 to 62.2) for high



Age	60	70	77	82	End of study
Men at risk	1759	1261	996	816	761

Fig 3 | Cumulative mortality from age 60 (Kaplan-Meier) according to changes in leisure time physical activity level and total mortality. Slopes of curves correspond to mortality rates. Parallel curves indicate equal rates of death. At the end of follow-up, rates were 74.0 (95% confidence interval 67.0 to 80.6) for unchanged low-medium, 70.5 (64.8 to 76.0) for decreased from high to low-medium, 64.7 (57.4 to 71.9) for increased from low-medium to high, and 58.5 (50.8 to 66.3) for unchanged high

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Tan et al.: “Physical activity and the risk of dementia: The Framingham Study”

Longitudinal epidemiological study

N=1,211; age: 76 years +

Physical activity Index (1986/87)

Follow-up: 2 decades; n=242 developed dementia

HR=0.55 for moderate/heavy physical activity

Effect mainly for men

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ICAD 2010

Symposium: “Behavioural Interventions to enhance cognitive functions and delay dementia onset”

- T'ai Chi helps cognition in sedentary Chinese
- The FABS trial (physical activity) - positive
- The MAX trial (cognitive/physical activity) – all improved
- The Finger trial (multi-domain) - ongoing
- The MAPT trial (multi-domain) - ongoing

Challenges:

Control group

Outcome measures

Theoretical models for understanding and predicting health-related behaviour

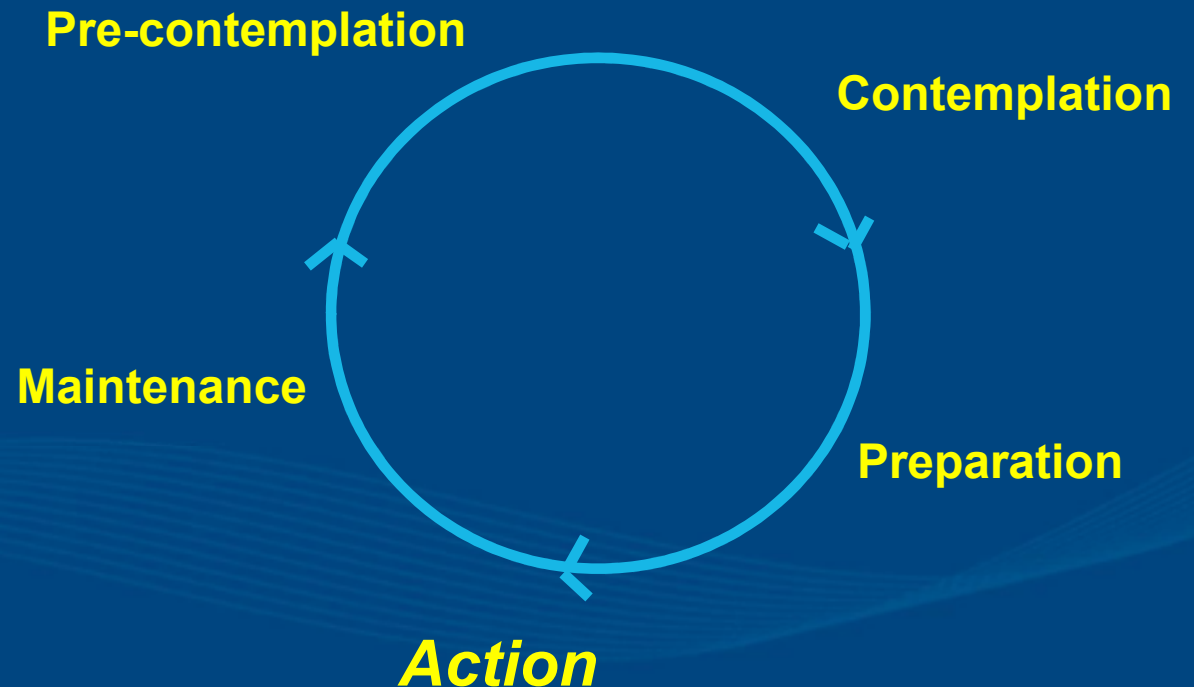
- Stages-of-change model
- Self-efficacy theory
- Both theories are based on a dynamic model

Stages-of-change-model and physical activity

- Developed in 1983 by Prochaska & DiClemente
- Aim was to describe the different phases involved in the change and maintenance of health-related behaviour
- Theory is that individuals engaging in a new behaviour move in an orderly procession through the stages
- The time they need to move from stage to stage can vary and they also can get “stuck” at a stage or relapse to an earlier stage

Stages-of-change-model and physical activity

- The progress individuals can make as a result of an intervention depends on which stage they are at the beginning of the intervention
- Approach often used by clinicians to encourage change in behaviour (e.g. stop smoking, weight control etc).



Self-efficacy

- Definition: the belief that one has the ability to perform a task
- Theory is that self-efficacy is strongly related to one's actual ability to perform the behaviour
- Self-efficacy has been shown to be superior to past performance in predicting future behaviour
- Self-efficacy and stages-of-change theories are connected (the lower stages correlate with lower self-efficacy)
- Increasing self-efficacy has been found to facilitate movement up the stages

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Self-efficacy in adverse conditions questionnaire

How confident are you that you could exercise in each of the following situations:

- a. When you are tired, how sure are you that you would do exercise
- b. When you are in a bad mood, how sure are you that you would exercise
- c. When you feel you don't have the time, how sure are you that you would exercise
- d. When you are on vacation, how sure are you that you would exercise
- e. When it is raining/or cold, how sure are you that you would exercise

Not at all sure

Moderately sure

Very sure

1 2

3 4

5

Self-efficacy in older adults with memory complaints and Mild Cognitive Impairment

- Can older adults with memory complaints be motivated to participate in physical activity and what is the role of self-efficacy?
- What is the effect of a 6-months individualised home-based physical activity and behavioural intervention program on self efficacy?

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JAMA[®]

Online article and related content
current as of September 2, 2008.

Effect of Physical Activity on Cognitive Function in Older Adults at Risk for Alzheimer Disease: A Randomized Trial

Nicola T. Lautenschlager; Kay L. Cox; Leon Flicker; et al.

JAMA. 2008;300(9):1027-1037 (doi:10.1001/jama.300.9.1027)

Participants: 170, 50 years and older with Subjective Memory Complaints (SMC) with or without Mild Cognitive Impairment (MCI)

Primary outcome: ADAS-cog

Aim: to perform for 24 weeks at least 150 min of moderate intensity physical activity in blocks of 3 sessions per week

Results: 1.3 points difference on the ADAS-cog

Steps: 9000 more

Adherence: 78.2%

Mary's Physical Activity Program

3 TIMES THIS WEEK

- | | |
|-----------------------------|---------|
| 1. Warm-up (slow pace walk) | 5 mins |
| 2. Stretch | 5 mins |
| 3. Moderate/brisk pace walk | 40 mins |
| 4. Cool down walk | 5 mins |
| 5. Stretch | 5 mins |

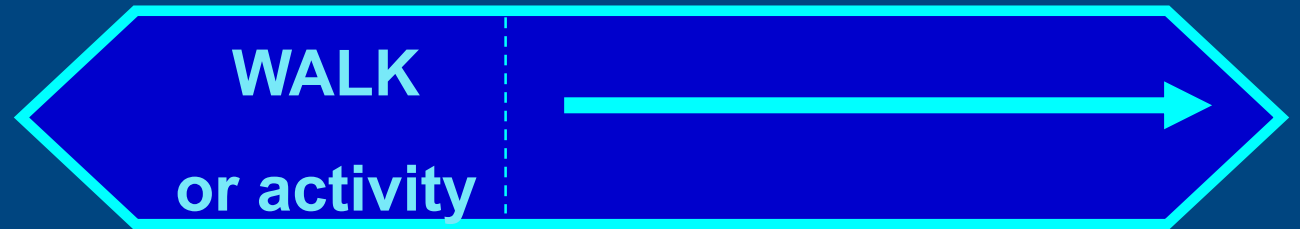
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Control



Unsupervised

Exercise



Monitored

Unsupervised

Time (Months)



Behavioural Intervention

Manual

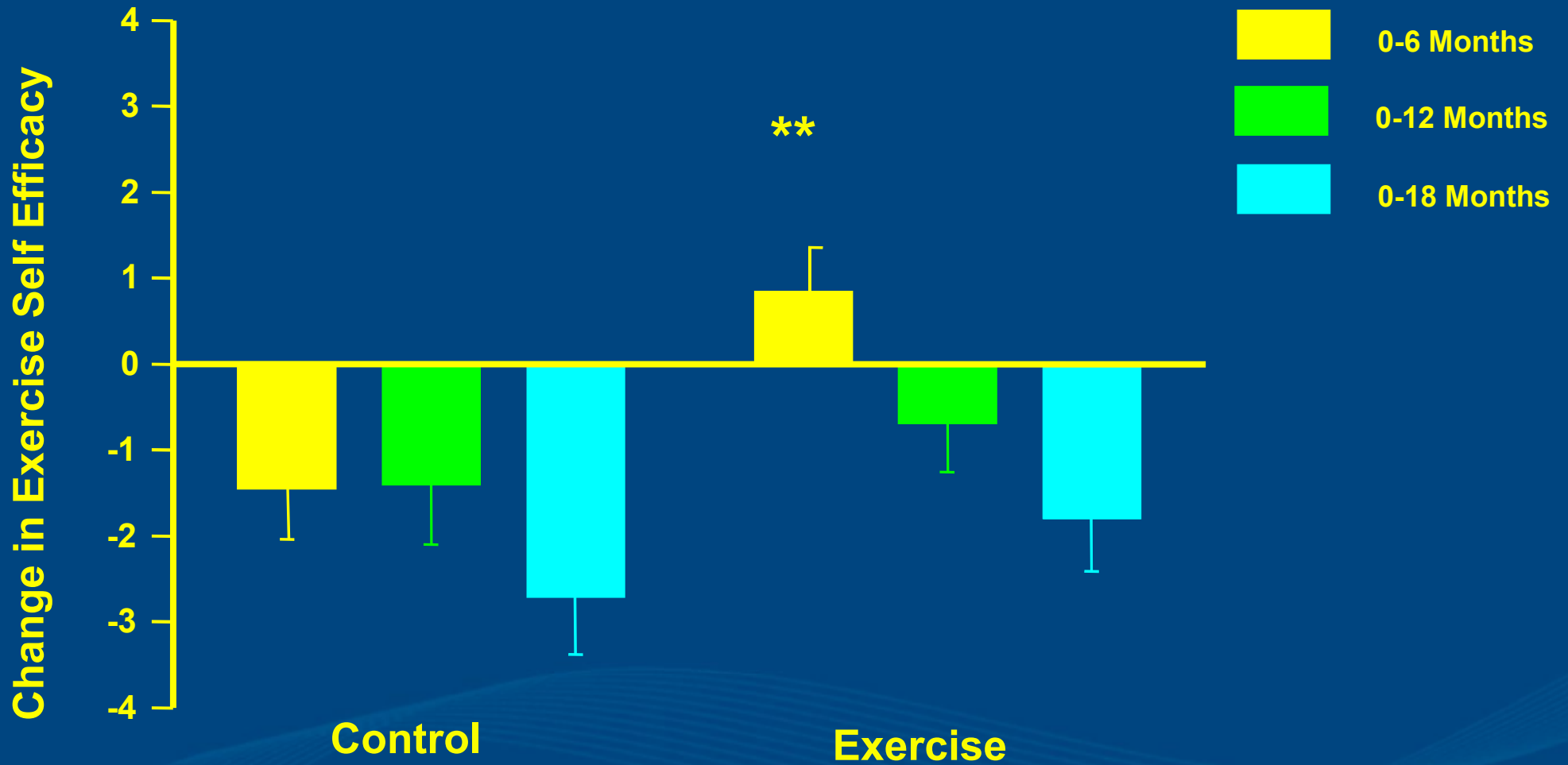
- ◆ Benefits and costs
- ◆ Rewards
- ◆ Goal setting
- ◆ Time management
- ◆ Identifying barriers
- ◆ Overcoming hurdles
- ◆ Injury prevention
- ◆ Exercise partners



Workshop
Phone monitoring
Newsletters

- Aim to improve self-efficacy by promoting practical strategies to enhance PA and self-management skills (via individual program & feedback)
- Self-efficacy was measured at baseline, 6, 12 and 18 months

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Self efficacy scores were 2.11 point higher (0.70, 3.52, < 0.01)

ANCOVA ** P<0.01

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Table 1. Linear regression model for steps at 6 months

	B	SE B	t	P
Age	-21.52	200.21	-0.10	0.91
Gender	5383.0	3108.73	1.73	0.08
Baseline steps	0.61	0.06	9.73	0.00
Exercise group	8796.52	3029.17	2.90	0.00
Baseline self-efficacy	893.62	340.18	2.62	0.01



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Table 2. Linear regression model for steps at 12 months

	B	SE B	t	P
Age	36.04	263.64	0.13	0.89
Gender	4061.51	4074.81	0.99	0.32
Baseline steps	0.61	0.08	7.47	0.00
Exercise group	10467.06	3965.66	2.63	0.01
Baseline self-efficacy	402.43	443.14	0.90	0.36



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Table 3. Linear regression model for steps at 18 months

	B	SE B	t	P
Age	138.76	279.39	0.49	0.62
Gender	-3033.00	4262.51	-0.71	0.47
Baseline steps	0.68	0.08	7.88	0.00
Exercise group	3554.53	4116.32	0.86	0.39
Baseline self-efficacy	481.93	453.58	1.06	0.29



Summary

- Self-efficacy was significantly higher in the PA group at 6 months, but not at 12 or 18 months
- PA group, higher baseline pedometer scores and self-efficacy scores predicted the 6 months activity
- PA group and higher baseline pedometer scores predicted the 12 months activity
- Only higher baseline pedometer scores predicted the 18 months activity

Conclusions - 1

- The behavioural intervention program increased self-efficacy in the short term, but not in the long term
- These findings suggest that to sustain self-efficacy and achieve long term improvement in physical activity a continuing minimal intervention program is necessary
- This could include booster phone calls, newsletters, workshops, social events etc

Do we need to focus more on the dynamic nature of the theories ?

- The cognitive and behavioural processes are of different relevance depending of the stage
- Sedentary individuals tend to prefer cognitive processes
- Active individuals prefer behavioural processes
- Cognitive themes: increasing knowledge, consequences to others, warning of risks, considering benefits and barriers, etc.
- Behavioural themes: reminding yourself, rewarding yourself, enlisting social support, replacing sedentary activities with more active behaviours, etc.
- Participants respond better to individual approaches tailored to the stage the are at

Conclusions - 2

- To sustain self efficacy effectively is a key factor for multi-domain long-term trials with individuals at risk, especially for home-based programs
- Additionally this is relevant to clinical programs which are not based on a volunteer approach
- Therefore continuous cost-effective self-efficacy support will be crucial to translate research PA programs into clinical practice successfully as part of a multi-domain health promotion approach to reduce the risk of cognitive decline

Cochrane's evidence:

„There is insufficient evidence to determine the effectiveness of physical activity programs in managing or improving cognition, function, behaviour, depression, and mortality in people with dementia...Further well designed research is required.“

Alzheimer's Disease?

Would you be interested in participating in a research study?

The National Ageing Research Institute (NARI) and the University of Melbourne are conducting a research study to find out if physical activity can help memory and quality of life.

We are looking for volunteers who have been diagnosed with Alzheimer's Disease and their relative or close friend who would be interested in participating.

The study involves three assessments at NARI within 12 months which include questionnaires for memory and other health factors, as well as physical fitness tests.

Half of the participants will be randomised to a home-based physical activity program (like walking).

If you are interested, please phone **Dr Elizabeth Cyarto** on 8387 2332.



FABS II

12 months NH&MRC funded RCT with physical activity for AD

In Melbourne, Perth, Brisbane

Runs at NARI

Please suggest to suitable patients:

AD, MMSE > 9, carer available

Lives in the community, can exercise, fluent in English

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AIBL Focus groups: has physical activity any impact on cognition and dementia?

- „If someone asked me I wouldn't have thought necessarily so. Thinking Oh goody because my mother had dementia. A year ago my husband and I started ballroom dancing. For us it's so difficult to remember the sequences.“
- I'd be happy to believe that there is some exercise effect on memory..but if you think of exercise promoting blood flow around the body, and it's good for your brain..then it's quite believable that there's some good effect.“
- „Personally it makes me feel much better, much calmer, more rational – thinking is clearer.“
- You have to be organised to do your exercises – maybe that is how it helps the memory.“
- Physical activity is good for your emotional health. The more intense your exercise the more likely you stop thinking about anything.“

AIBL Focus groups: what are the barriers towards physical activity?

- „If you don't know what is available.“
- „Lack of motivation in my opinion. People should get out of their chairs and do something. My late father just sat around and snoozed.“
- „People are different. For some people it is not what they like.“
- „Sometimes distance is a problem.“
- „Some people are joiners other are shy. Fact that you have to join a group might be a barrier.“
- „Physical ability“
- „Weather, resources, costs.“

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Lost in translation:

From prospective study to randomised controlled trial to clinical management

- Occam's razor: "all things being equal, the simplest solution is best"
- Whitehead's caution: "seek simplicity and distrust it"
- Many prospective studies show positive association for protective factors
- However RCTs often fail to replicate findings (e.g. estrogen, ginkgo, etc.)
- Complex methodological challenges with interpreting and translating epidemiological findings (often over-simplification)
- Challenges: selection of population, trial methodology, timing of intervention, dose effect, duration, complexity of AD, genetics, etc.
- Are they relevant in every-day life and how to make them cost effective?

Ganguli & Kukull, 2010

Conclusions

- Exercise is a promising candidate for a protective factor for cognition
- Exciting research in the field of physical and cognitive activity
- Need for more translational research