Dementia prevention: What do we know and where do we go from here?

UNSW AUSTRALIA

Never Stand Still | Science | Psychology

Kaarin J. Anstey and Ruth Peters

DCRC Dementia Centre for Research Collaboration

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What is the problem?

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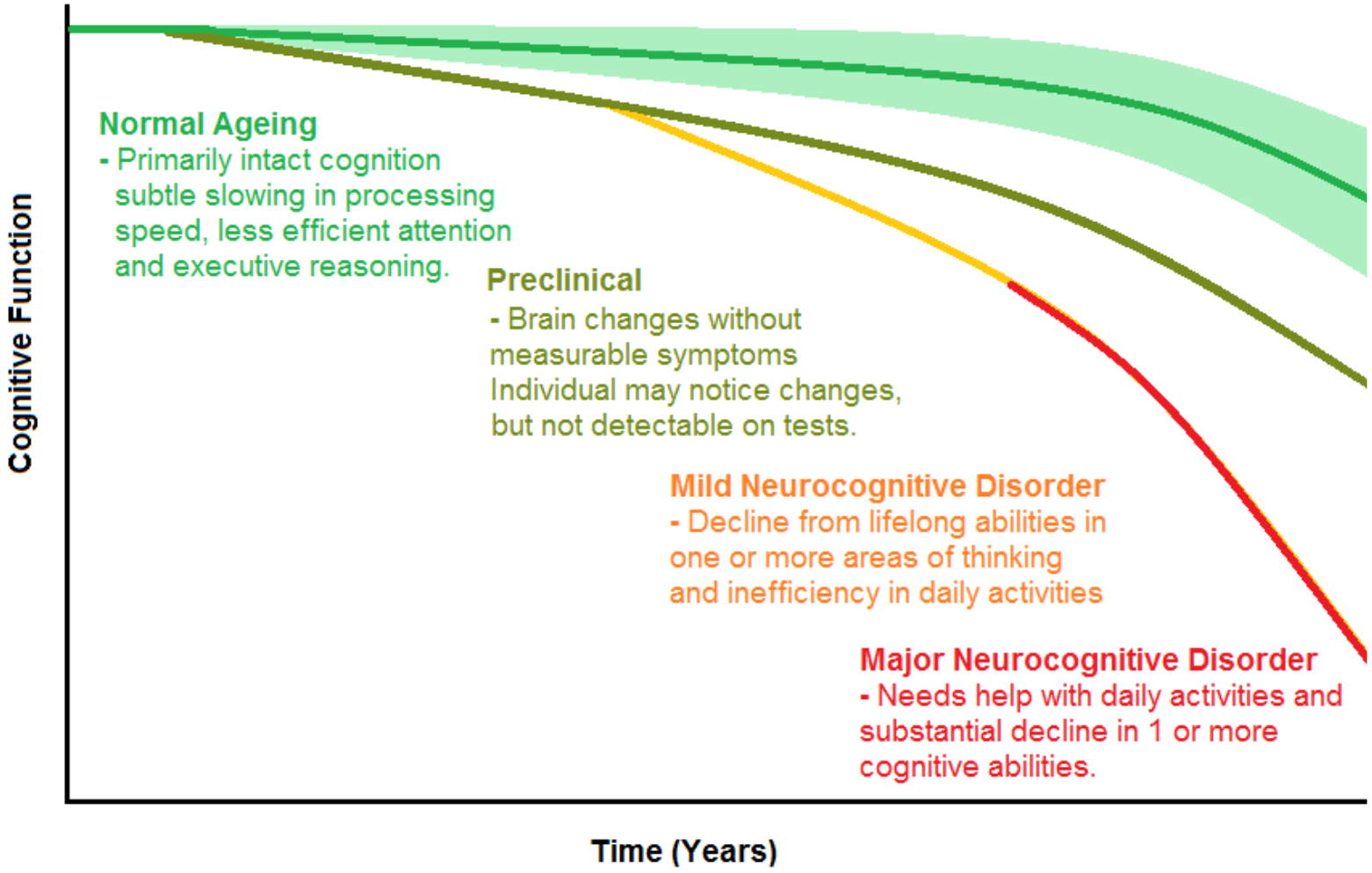
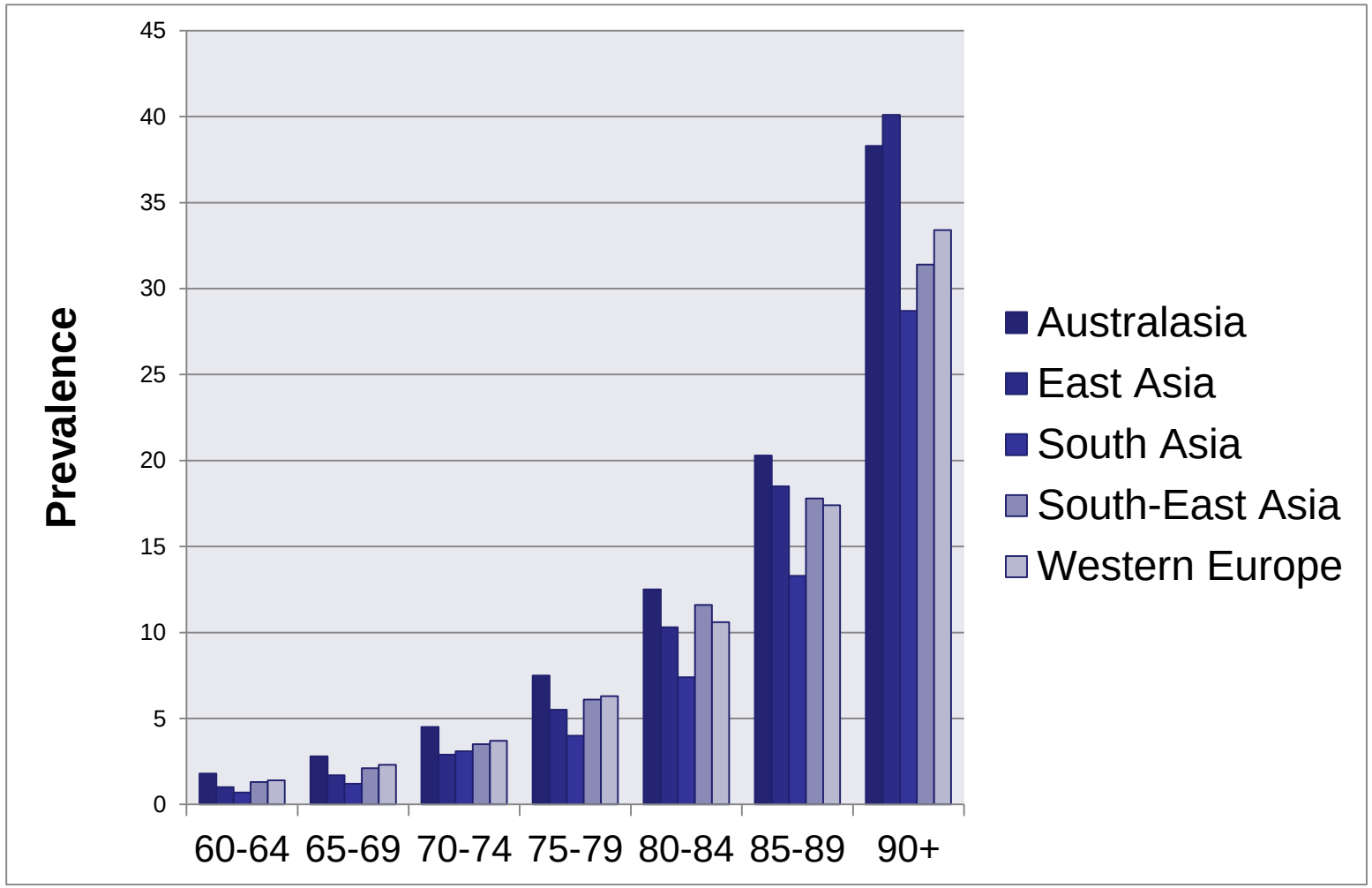
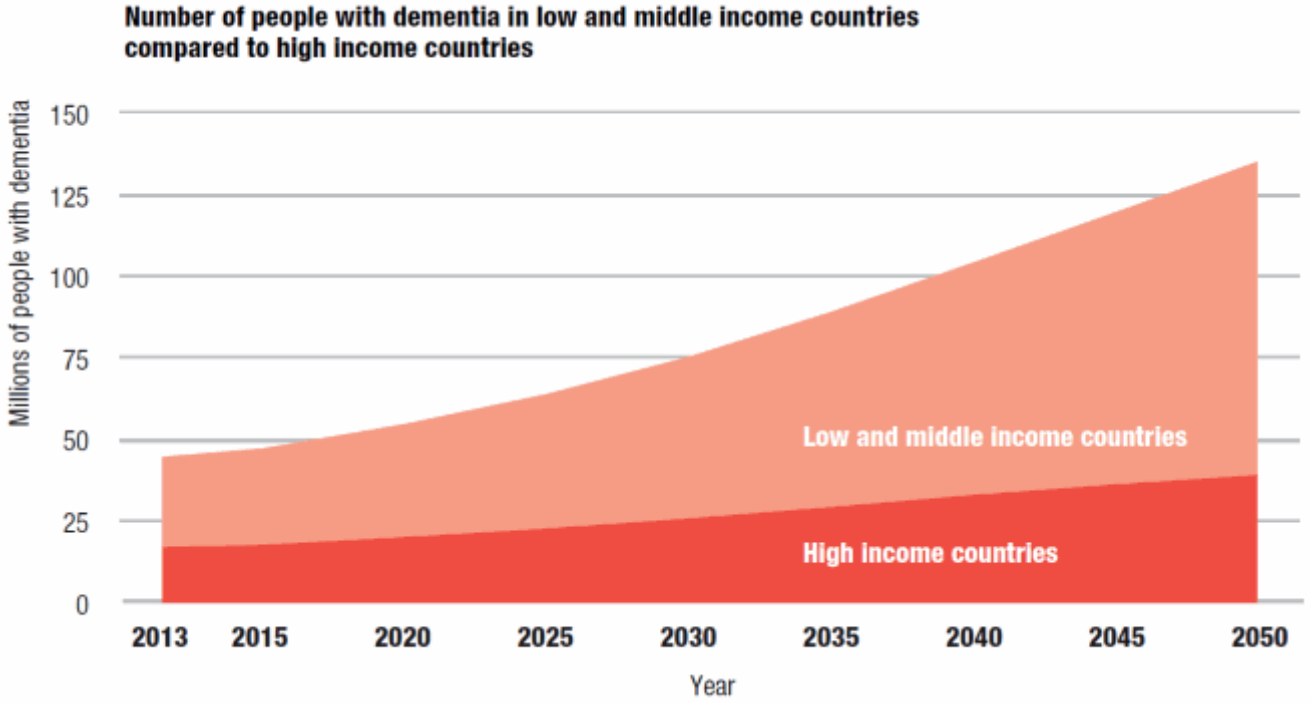


Size of the problem by age



Size of problem by numbers

Worldwide prevalence > 65 is 5-7%
Estimated at 50 million living with dementia by 2017
75 Million expected by 2030
More prevalent in women, particularly at older ages
Increasing due to demographic change



What do we mean by ‘Prevention’?

Primary Prevention

Preventing disease or injury before it occurs – e.g. through vaccination, or removing exposure to risk factors – population level

Secondary Prevention

Reduce impact of disease that has already occurred, or stop progress of those with preclinical disease (e.g. MCI) – either population or patient level

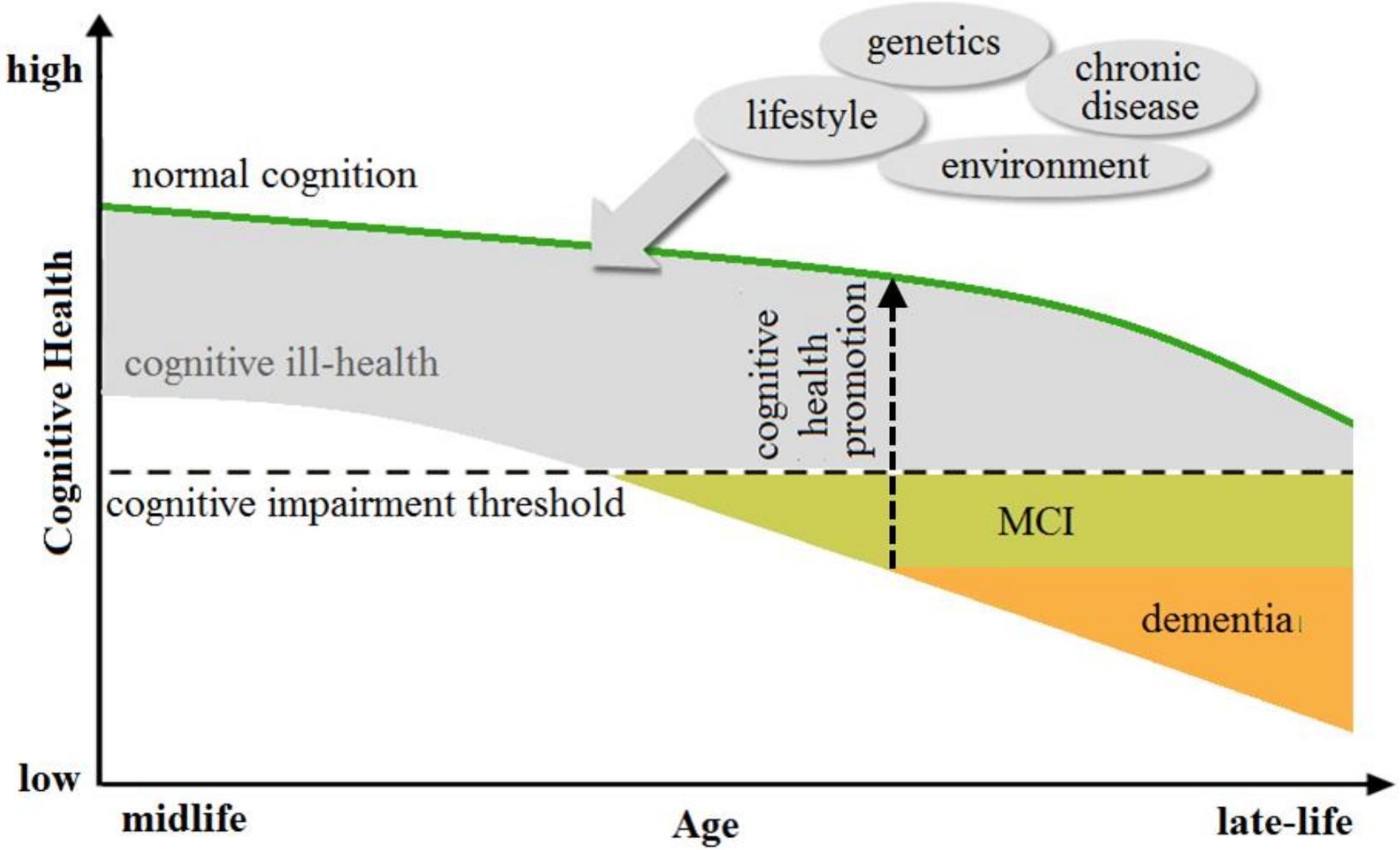
Tertiary Prevention

Reduce impact and or slow rate of progression of established disease – patient level

Responsible: Who? How? Why?

What do we know now?

A life course approach is required



Risk factors may be modifiable or non-modifiable

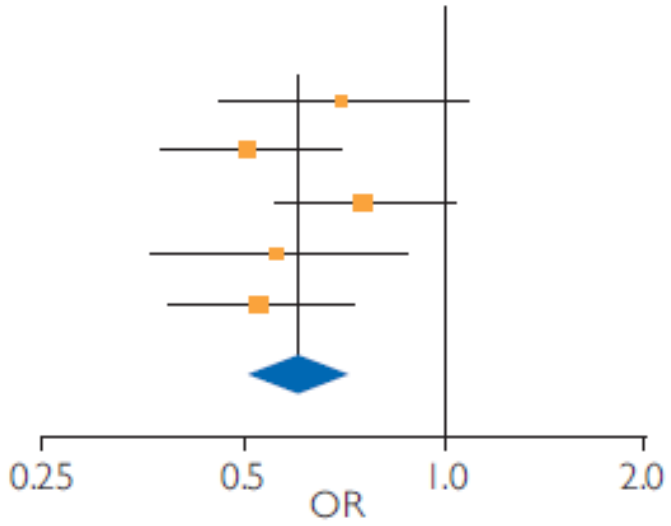
Non-modifiable – genetics, country of birth, gender, age

Modifiable – lifestyle, clinical, environmental

Physical activity

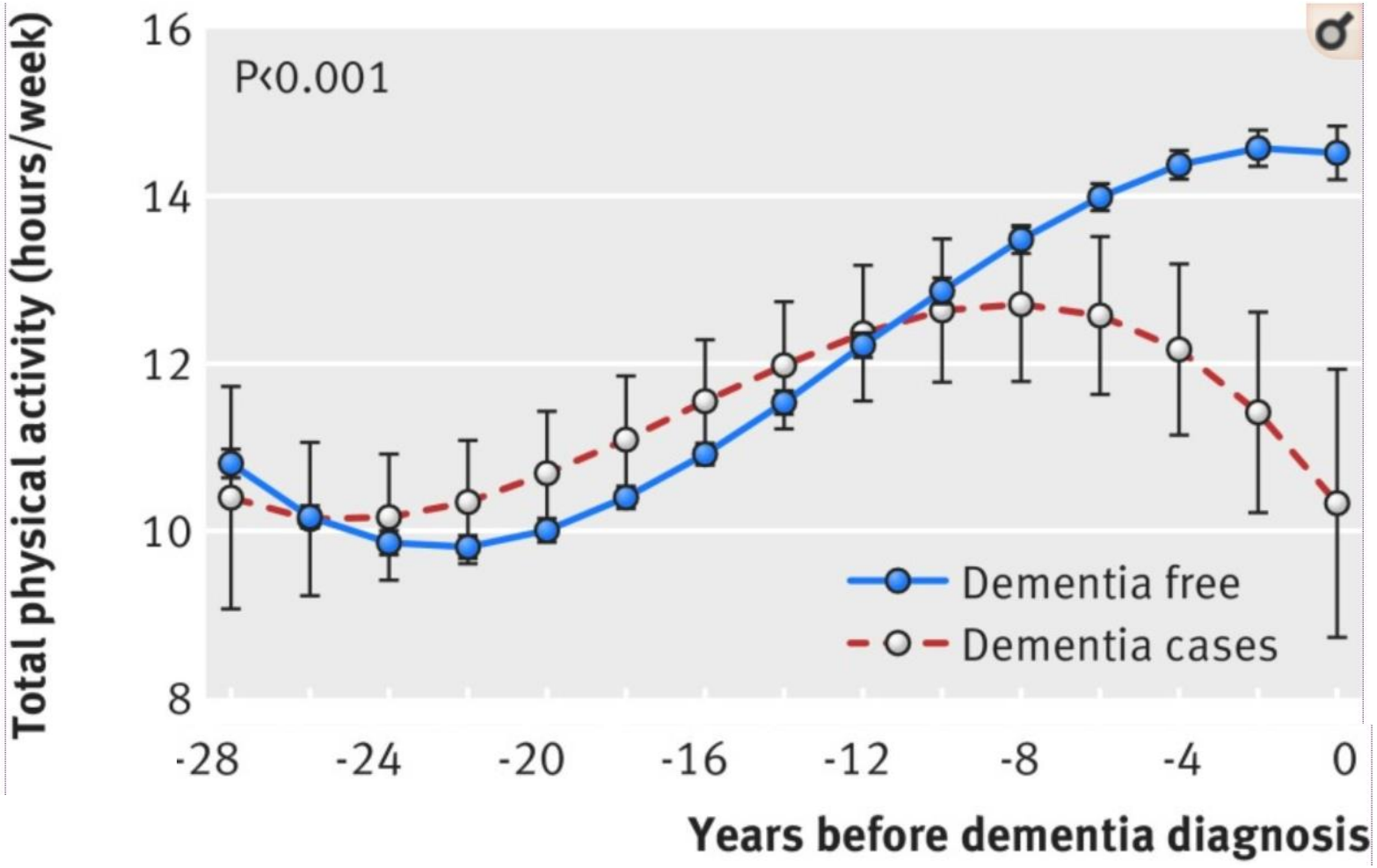
Adhering to international PA guidelines, (150 min/wk of MVPA, or brisk walk for 20-30 minutes most days) during the previous approximately 5 + years
Has 40% reduced risk of AD.

Study	Sample size	OR (95% CI)	Weight(%)	*P* value
Abbott et al[21]	2257	0.70 (0.46-1.08)	13.8	.11
Laurin et al[27]	3848	0.51 (0.37-0.70)	24.75	<.001
Podewils et al[38]	2531	0.75 (0.55-1.03)	24.63	.08
Ravaglia et al[33]	749	0.56 (0.36-0.88)	12.46	.01
Scarmeas et al[31]	1230	0.53 (0.38-0.72)	24.37	<.001
Synthesis	**10,615**	**0.60 (0.51-0.71)**	**100**	**<.001**



Santoz-Lozano et al, 2016 Mayo Clinic Proceedings

Exercise and risk of dementia



Whitehall study

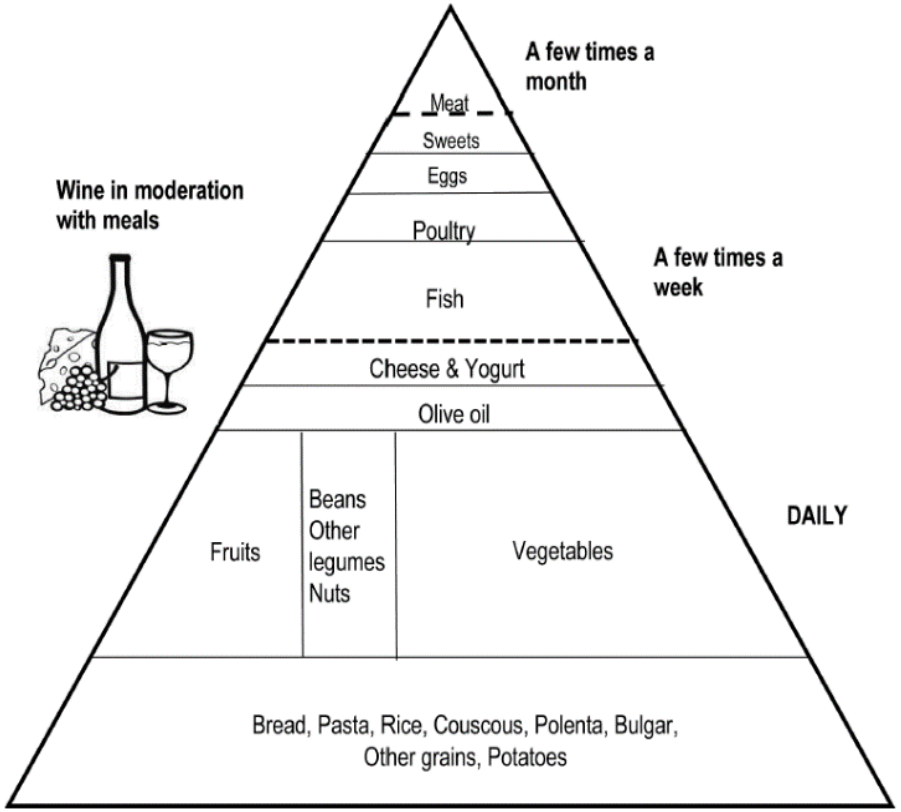
Physical activity no different at baseline

Activity reduced prior to dementia

Association may be due to reverse causality!

Sabia, Dugravot, Dartigues, Abell, Ebaz, Kivimaki, Singh-Manoux, BMJ, 2017

Mediterranean diet



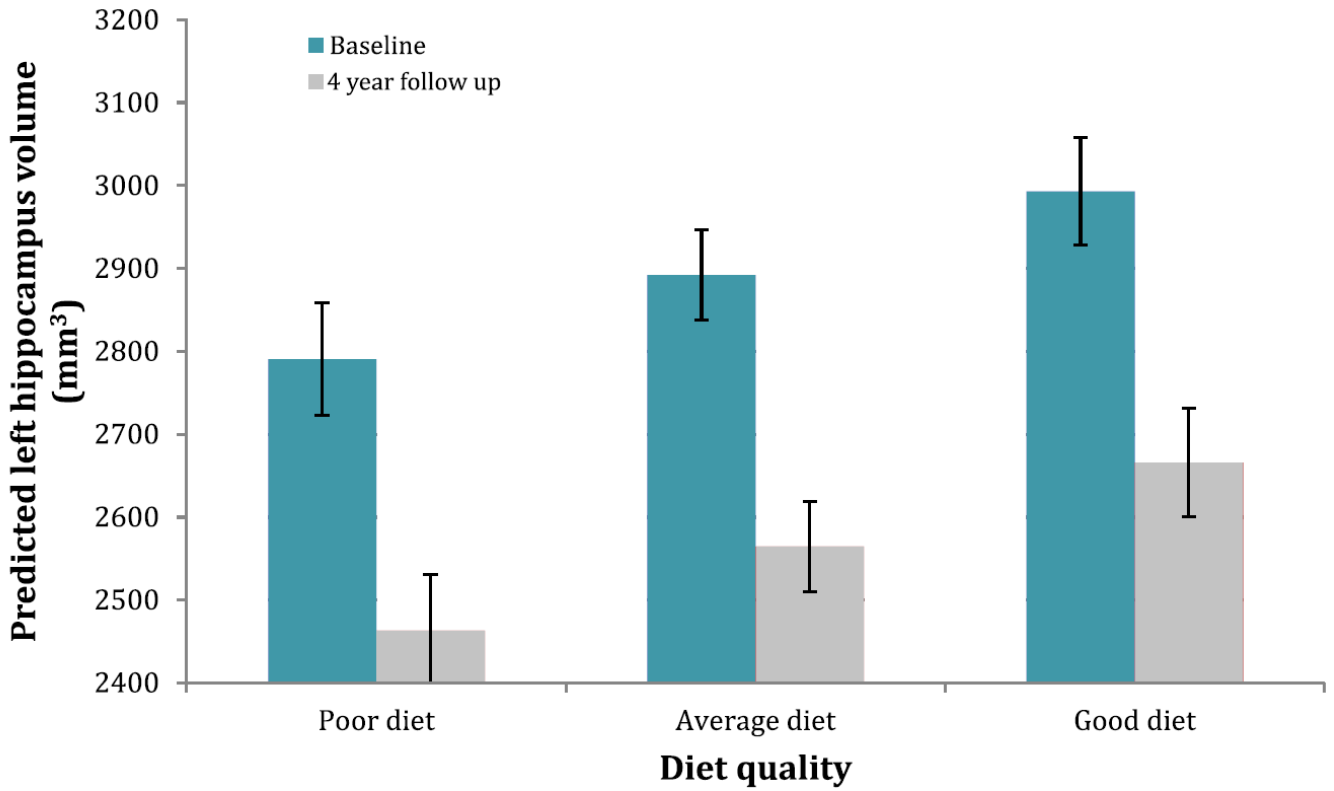
- Meta-analysis: 33% reduced risk of MCI or AD over 2-8 years
  (Singh et al 2014).
- DASH diet (Dietary Approaches to Stop Hypertension) protective against cognitive decline
  (e.g., Tangney et al 2014).

Western diet and brain

PATH Through Life Study

Dietary pattern high in meat, potatoes and soft drinks, low in fruits, vegetables, grains, fish (poor diet) linked to smaller hippocampal volume

(Jacka et al, PLoS Medicine 2015)



Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND)

Table 1
MIND diet component servings and scoring

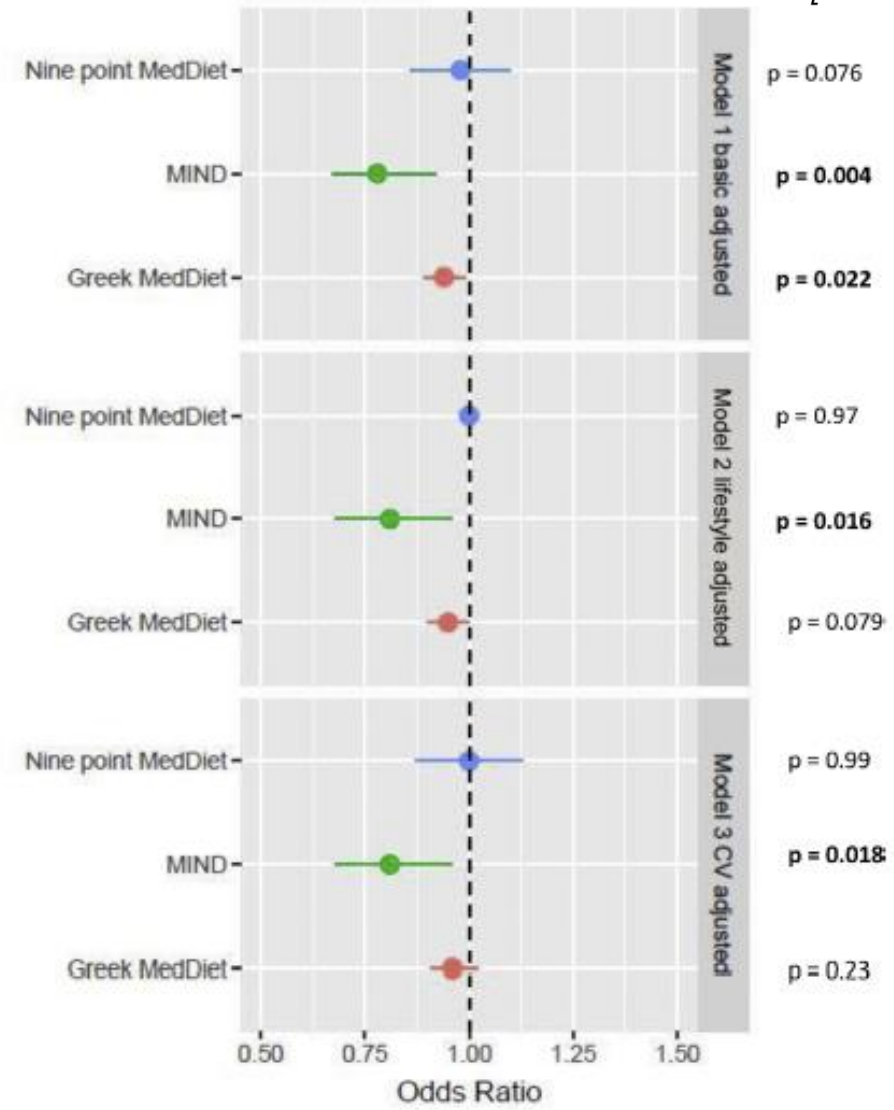
Diet component	0	0.5	1
Green leafy* vegetables	≤2 servings/wk	>2 to <6/wk	≥6 servings/wk
Other vegetables†	<5 serving/wk	5 to <7 wk	≥1 serving/d
Berries‡	<1 serving/wk	1/wk	≥2 servings/wk
Nuts	<1/mo	1/mo to <5/wk	≥5 servings/wk
Olive oil	Not primary oil		Primary oil used
Butter, margarine	>2 T/d	1–2/d	<1 T/d
Cheese	7 + servings/wk	1–6/wk	<1 serving/wk
Whole grains	<1 serving/d	1–2/d	≥3 servings/d
Fish (not fried)‖	Rarely	1–3/mo	≥1 meals/wk
Beans§	<1 meal/wk	1–3/wk	>3 meals/wk
Poultry (not fried)¶	<1 meal/wk	1/wk	≥2 meals/wk
Red meat and products#	7 + meals/wk	4–6/wk	<4 meals/wk
Fast fried foods**	4 + times/wk	1–3/wk	<1 time/wk
Pastries and sweets††	7 + servings/wk	5–6/wk	<5 servings/wk
Wine	>1 glass/d or never	1/mo–6/wk	1 glass/d
Total score			15

- Adapted the Medi and Dash diets
- Protective against Alzheimer's pathology
- Uniquely specifies consumption of berries and green leafy vegetables.
- 2 observational studies showed greater adherence to MIND diet reduced risk of developing Alzheimer's disease and less cognitive decline over 10 years.

(Morris et al., 2015, Alz Dem)

MIND Diet – PATH Through Life Project

- 1220 Australians aged 60-64 followed for 12 years
- CSIRO Food Frequency questionnaire
- Coded for MEDI and MIND diets
- MCI and dementia diagnosed at each wave
- MIND Diet (OR = 0.47, 95% CI 0.24-0.91) not MEDI, associated with reduced risk of cognitive impairment and dementia



Hosking, D, Eramudugolla, R., Cherbuin, N, Anstey, KJ, *Alzheimer's and Dementia*, 2019

Smoking

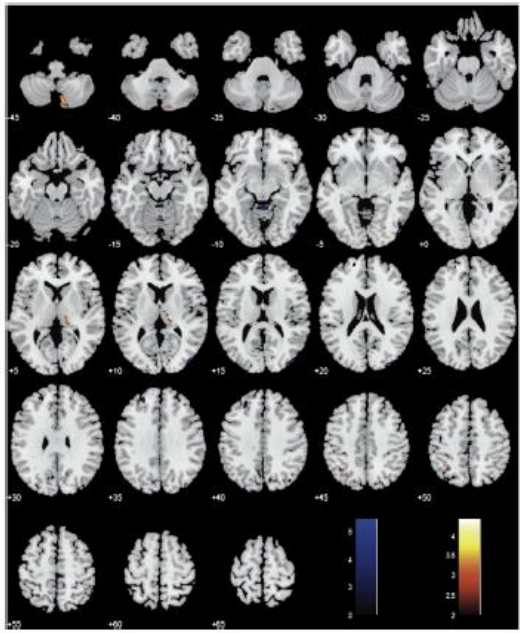
- Meta-analysis 19 prospective studies with at least 12 months of follow-up.
- Mean study age 74 years.

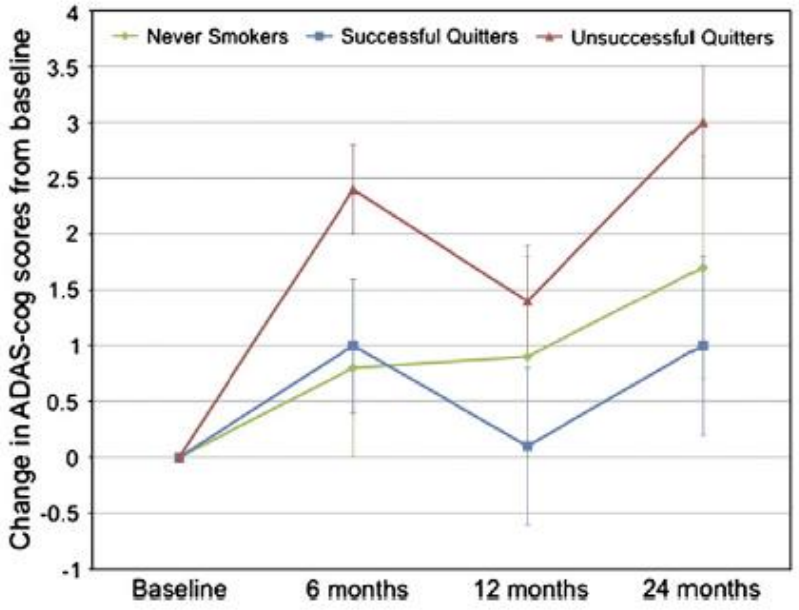
- Current smokers at baseline, relative to never smokers....
  - 1.27 (95% CI: 1.02, 1.60) for any dementia.
  - 1.79 (95% CI: 1.43, 2.23) for Alzheimer's Disease
  - 1.78 (95% CI: 1.28, 2.47) for vascular dementia (Anstey et al Am J Epidemiol 2007).

- Similar results from further meta-analysis (Peters et al BMC Geriatr 2008).
  - Current smokers relative to never or non-smokers....
  - 1.59 (95% CI 1.15, 2.20) for Alzheimer's Disease and
  - 1.35 (95% CI 0.90, 2.02) for vascular dementia

Cognitive and brain change in quitters

Trial of smoking cessation: 36 Never smokers, 48 unsuccessful quitters, 36 successful quitters. Quitters showed no cognitive decline but UQ did. Unsuccessful quitters showed more atrophy





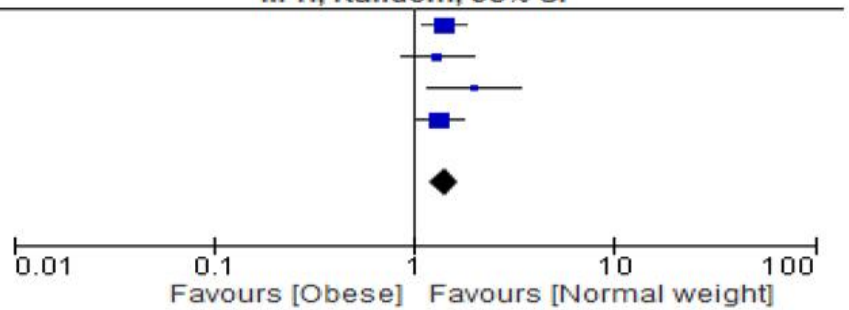
(Almeida et al., 2011, *Neuroimage)*

Obesity

Study or Subgroup	Obese (Midlife) Events	Total	Normal Weight Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Fitzpatrick et al	58	261	200	1263	37.8%	1.40 [1.08, 1.82]
Rovona-Springer et al	19	82	119	671	14.1%	1.31 [0.85, 2.00]
Tolppanen et al	23	199	27	464	9.1%	1.99 [1.17, 3.38]
Whitmer et al	66	891	307	5581	39.0%	1.35 [1.04, 1.74]
Total (95% CI)		**1433**		**7979**	**100.0%**	**1.41 [1.20, 1.66]**
Total events	166		653			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.85$, df = 3 (P = 0.60); $I^2 = 0\%$

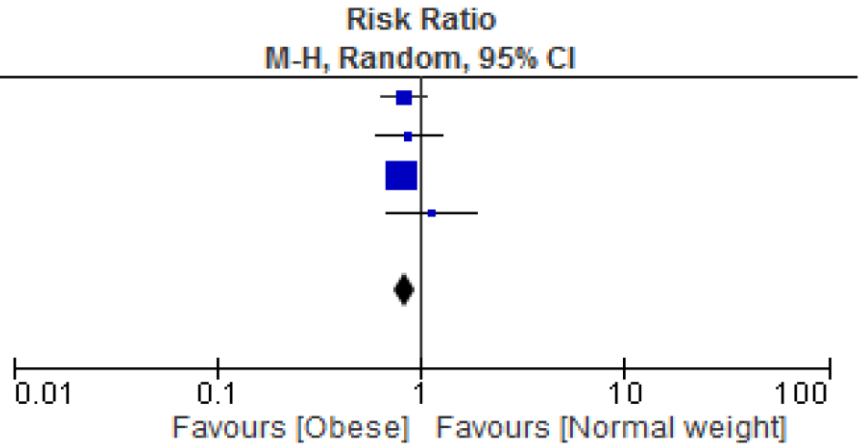
Test for overall effect: Z = 4.22 (P < 0.0001)



Study or Subgroup	Obese Events	Total	normal (Late life) Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Fitzpatrick et al	78	520	168	920	23.7%	0.82 [0.64, 1.05]
Luchsinger et al	42	223	48	222	10.5%	0.87 [0.60, 1.26]
Power et al	214	2180	450	3706	60.5%	0.81 [0.69, 0.94]
Tolppanen et al	28	340	25	342	5.3%	1.13 [0.67, 1.89]
Total (95% CI)		**3263**		**5190**	**100.0%**	**0.83 [0.74, 0.94]**
Total events	362		691			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.52$, df = 3 (P = 0.68); $I^2 = 0\%$

Test for overall effect: Z = 3.00 (P = 0.003)



Pedditzi et al Age Ageing 2016

Abdominal fat a risk in normal BMI women

- Women's Health Initiative Study
- Aged 65-80 (n = 7163)
- Examined BMI, waist to hip ratio
- 4-5 years follow-up
- Abdominal obesity associated with dementia, even in normal weight women

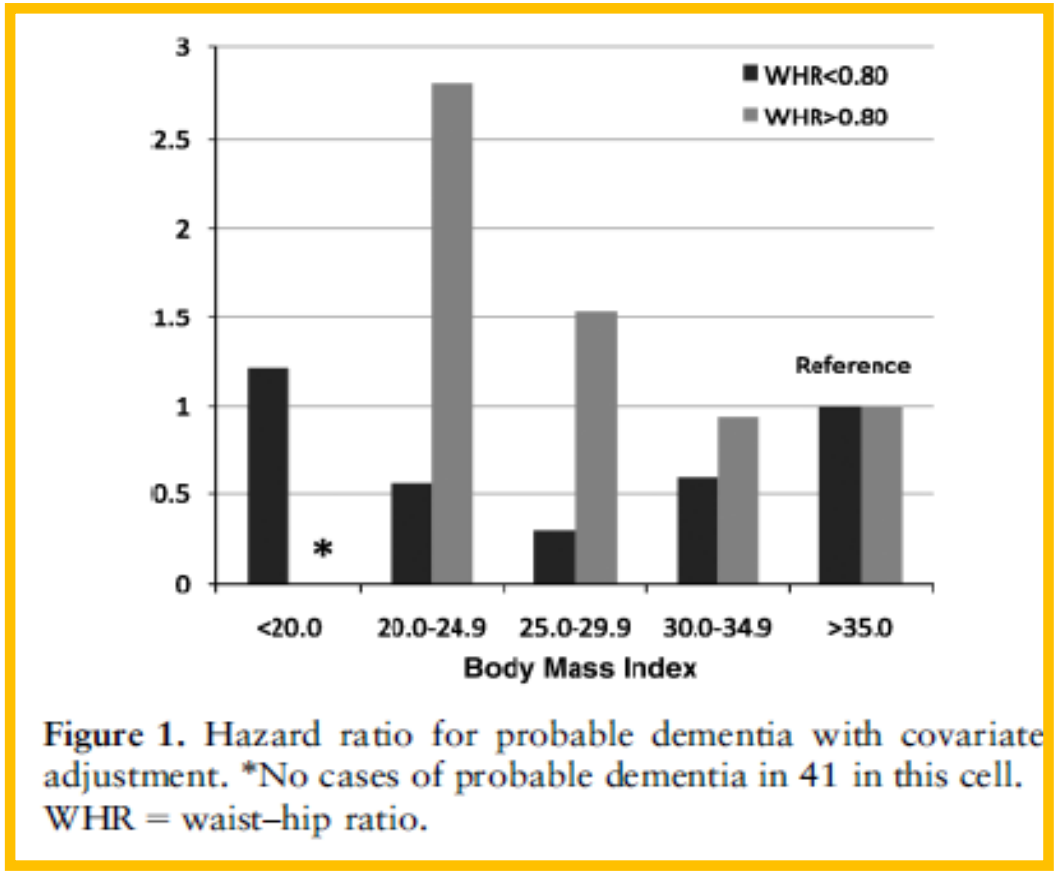


Figure 1. Hazard ratio for probable dementia with covariate adjustment. *No cases of probable dementia in 41 in this cell. WHR = waist–hip ratio.

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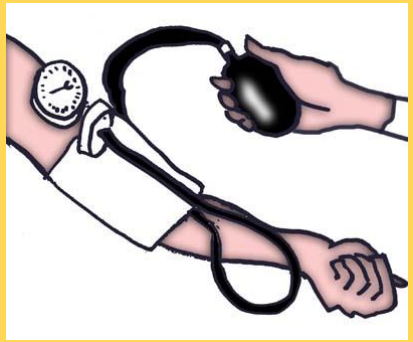
Clinical risk factors

Blood Pressure

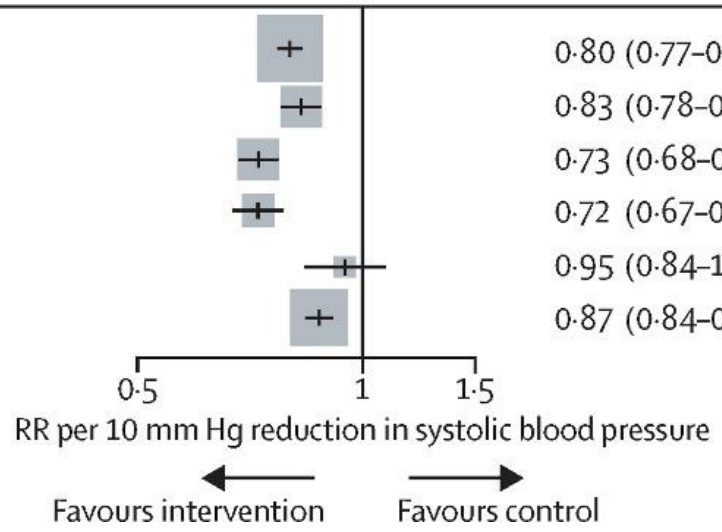


Diabetes Mellitus

Blood pressure

Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis

	Studies	Intervention		Control		RR (95% CI) per 10 mm Hg reduction in systolic blood pressure
		Events	Participants	Events	Participants	
Major cardiovascular events	55	13209	137319	14068	128259	0·80 (0·77–0·83)
Coronary heart disease	56	4862	136986	5301	128548	0·83 (0·78–0·88)
Stroke	54	4635	136682	5378	128641	0·73 (0·68–0·77)
Heart failure	43	3284	115411	3760	107440	0·72 (0·67–0·78)
Renal failure	16	890	39888	834	39043	0·95 (0·84–1·07)
All-cause mortality	57	9775	138298	9998	129700	0·87 (0·84–0·91)



Ettehad et al Lancet 2016

Blood pressure and incident dementia

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Source	n	Age at baseline	Follow up/yrs	Higher blood pressure associated with increased risk of dementia..
Skoog et al 1996	382	70	15	Yes
Lindsay et al 1997	5747	>=65	5	Yes
Launer et al 2000	3703 men	45-68	~22	Yes
Kivipelto et al 2002	1449	44-58	21	Yes
Ninomiya et al 2011	668	65-79	17	Yes

Honolulu Asia Aging Study

Cohort of Japanese American men born between 1900 and 1919

High Systolic blood pressure and incident dementia

Untreated:

All dementia Odds Ratio (OR) 3.88 (95% Confidence Intervals(CI 1.50-10.02)

Alzheimer's Disease OR 1.22 (0.37-4.04)

Vascular dementia OR 11.80 (3.52-39.50)

Treated:

All dementia OR 1.07 (0.53-2.17)

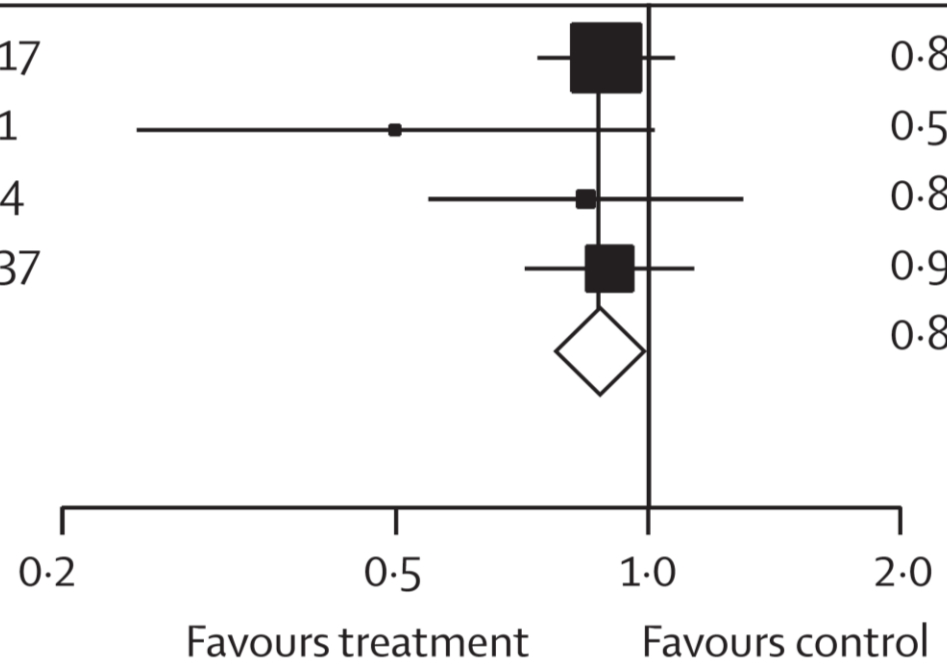
Alzheimer's Disease OR 0.65 (0.20-2.15)

Vascular dementia OR 1.46 (0.60-3.53)

Launer et al 2000 Neurobiology of Aging

Blood Pressure lowering trials with antihypertensive medication

	Active (N/n)	Placebo (N/n)	Hazard ratio (95% CI)
PROGRESS RR[12]	3051/193	3054/217	0·89 (0·74–1·07)
Syst-Eur RR[10]	1238/11	1180/21	0·50 (0·25–1·02)
SHEP RR[14]	2365/37	2371/44	0·84 (0·55–1·30)
HYVET RR	1687/126	1649/137	0·90 (0·71–1·13)
Combined (random)			0·87 (0·76–1·00)
Cochran Q=2·409; p=0·491			
Test for overall effect; p=0·045			

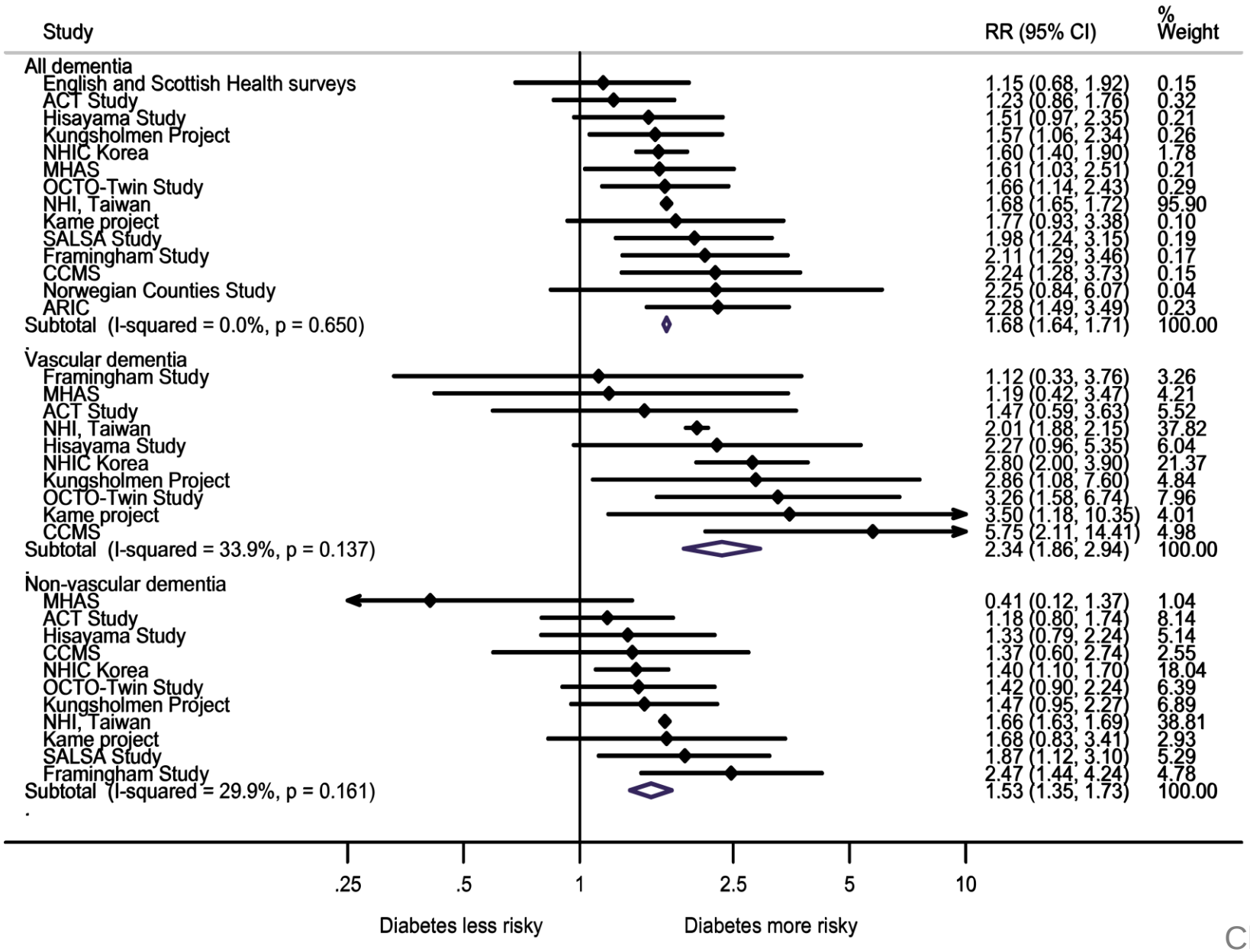


Peters et al Lancet Neurol 2009

Systolic blood Pressure Intervention Trial - Memory and Cognition IN Decreased Hypertension (SPRINT-MIND)

- Blood pressure goals <120mmHg versus <140mmHg
- 8563 (91.5%) participants completed at least 1 follow-up cognitive assessment.
- The mean age 67.9 years
- Median follow-up of 5.11 years,
- combined rate of mild cognitive impairment or probable dementia HR, 0.85; 95% CI, 0.74-0.97).

Williamson et al JAMA 2019



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Diabetes and dementia risk

14 studies, 2,310,330 individuals
women:
RR 1.62 [95% CI 1.45–1.80];
men:
RR 1.58 [95% CI 1.38–1.81]).

Chatterjee et al Diabetes Care 2016

But hypoglycaemia is associated with increased risk…

Compared with patients with no hypoglycemia,

- 1 episode……. ……(HR, 1.26; 95% CI, 1.10-1.49);
- 2 episodes…… ……(HR, 1.80; 95% CI, 1.37-2.36); and
- 3 or more episodes…… (HR, 1.94; 95% CI, 1.42-2.64).

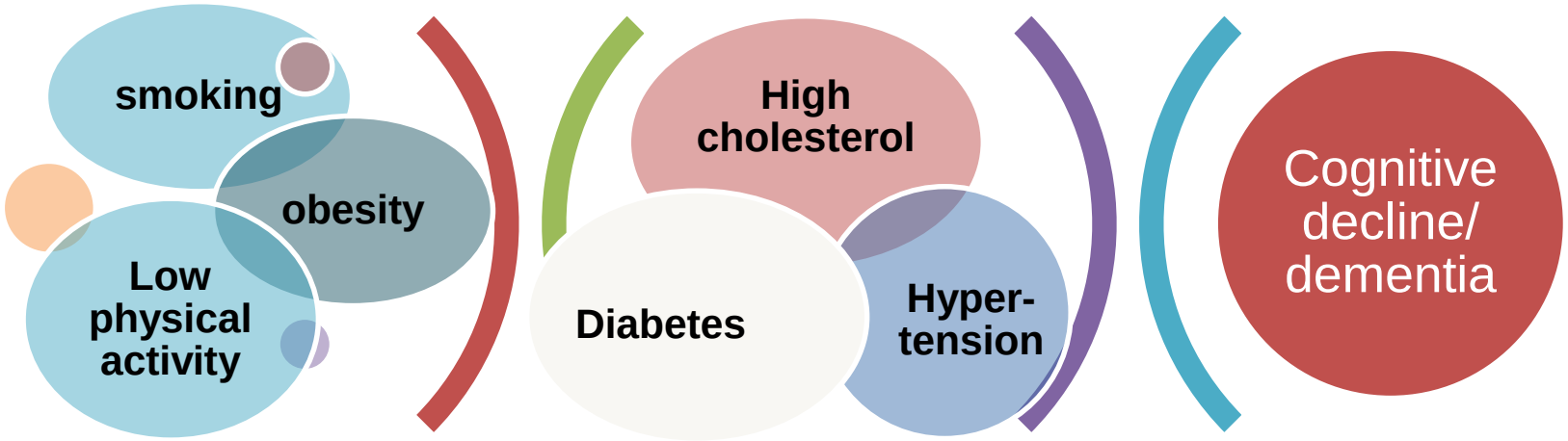
Whitmer et al JAMA 2009

Trials of treatments for type 2 diabetes

- Cochrane review
- 4 trials reporting cognitive outcomes
- 2 larger trials both comparing standard to intensive blood glucose lowering
- No evidence for treatment reducing risk of dementia
- Intensive treatment was more likely to cause hypoglycaemia

Areosa Satre Cochrane Collaboration et al 2017

Applicability of the current evidence, …the real world



BMJ Open

Combining modifiable risk factors and risk of dementia: a systematic review and meta-analysis

Ruth Peters,[1,2,3] Andrew Booth,[4] Kenneth Rockwood,[5] Jean Peters,[4] Catherine D'Este,[6,7] Kaarin J Anstey[1,3]

Objective: to systematically examine the literature addressing clustering or co-occurring modifiable risk factors for incident cognitive decline and dementia within individuals, and to estimate, using meta-analysis, the impact of exposure to one or more modifiable risk factors compared to absence of risk factors on the risk of future cognitive decline and dementia.

Risk factor clustering - systematic review

- Longitudinal studies with an explicit aim to examine the impact of additive or clustered modifiable risk factor burden for combinations of multiple core modifiable dementia risk factors (hypertension or high blood pressure, hypercholesterolemia or high cholesterol, diabetes, high body mass index, smoking, excess alcohol, low physical activity and poor diet).
- Some evidence or clear implication that participants were free of cognitive decline or dementia at baseline assessment.
- Use of formal assessment of cognitive function or dementia or clear implication that formal dementia diagnosis took place.
- Report of cognitive decline or dementia outcomes.

What has been published?

>40,000 participants

High income countries

Sample size from 322 to 8845

Two recruited men only

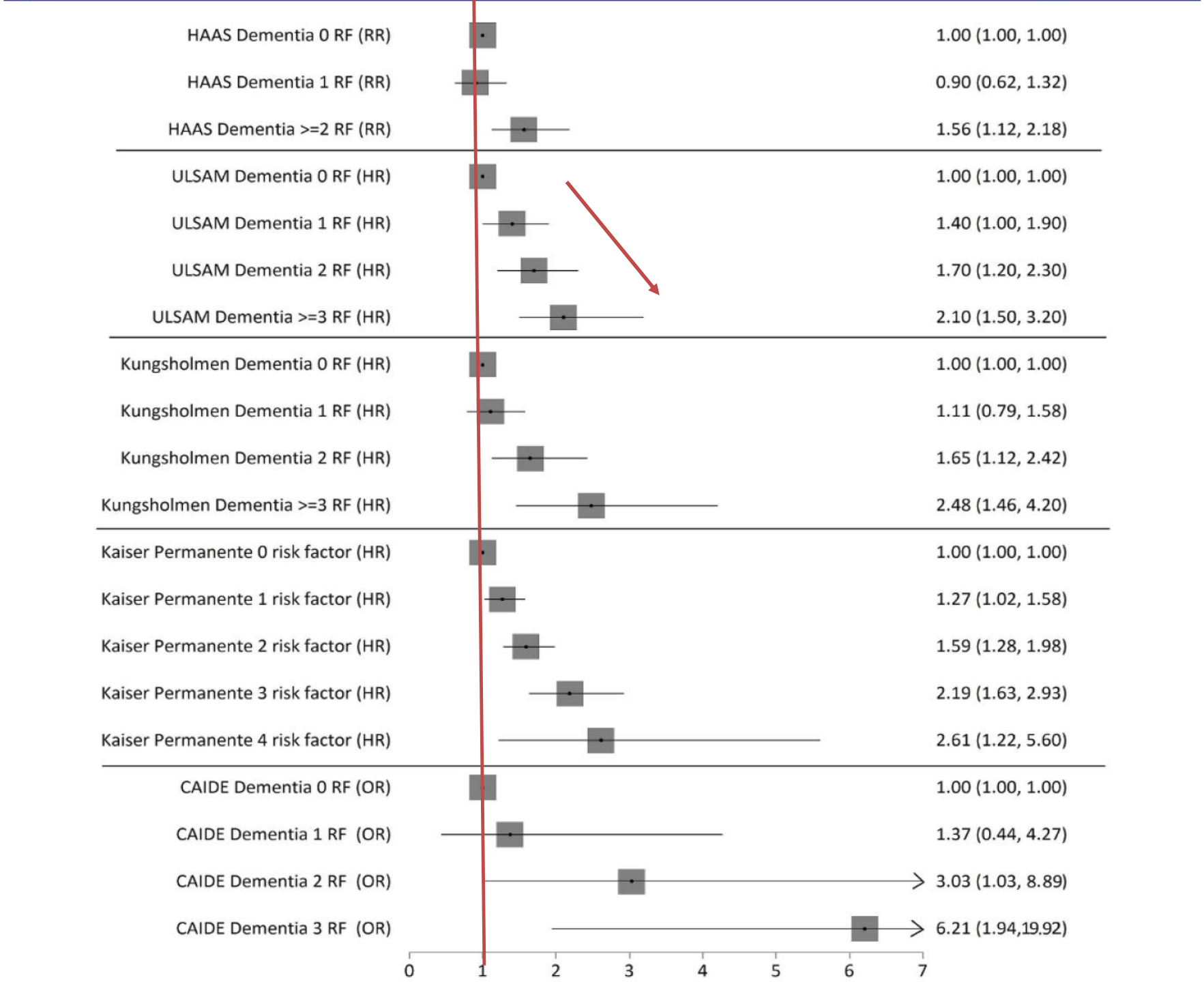
Follow up from 22 months to >20 years

- Very short follow up (<5 years) n=2
- Short follow up (5-10 years) n=8
- Moderate follow up (10-20 years) n=7
- Long follow up (>20 years) n=5

- Baseline in midlife (40-65 year) n=12
- Baseline in late life (>65 year) n=9
- One study baseline <30 years
- Outcomes
  - dementia (n=10),
  - Alzheimer's Disease (n=5),
  - cognitive function (n=12)

- **Higher numbers of risk factors or unhealthy behaviours were associated with increased risk**

- **Higher numbers of protective factors or health behaviours associated with decreased risk**



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Meta-analysis, per additional risk factor

Compared to those with no risk factors

1 risk factor

20% increase

2 risk factors

65% increase

>= 3 risk factors

200% increase

Future directions

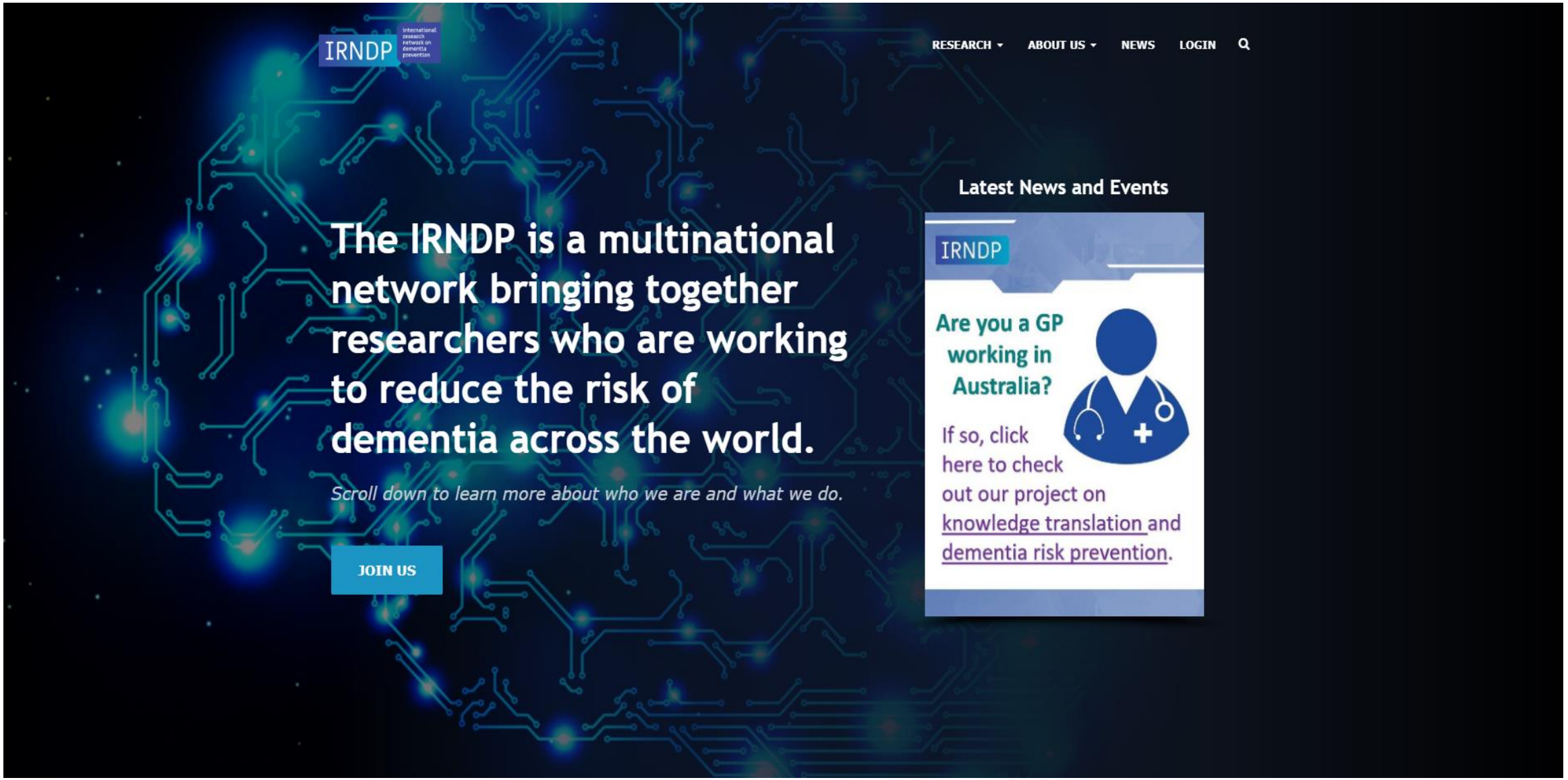
- Understand whether there are critical windows or ages when risk modification is most effective Better information on targets e.g. for blood pressure, glucose, BMI
- Identify who is at risk and where – identify subpopulations, regional differences, sex differences, clinical groups

What else do we need to achieve this?

- Improved quality of measures to enable results are valid and translatable
- Better cognitive measures that are sensitive to change in younger and mid-adulthood
- Include cognitive measures as secondary outcomes in trials
- Maintain cohort studies and trial cohorts to gather the long term follow-up data

What to do now?

- Don’t’ smoke
- Meet physical activity guidelines
- Medi or MIND dietary pattern
- Manage vascular risk factors
- Cognitive and social engagement
- Increase population level education
- Conduct more detailed research on risk and outcomes


IRNDP
international research network on dementia prevention
RESEARCH
ABOUT US
NEWS
LOGIN
The IRNDP is a multinational network bringing together researchers who are working to reduce the risk of dementia across the world.
Scroll down to learn more about who we are and what we do.
JOIN US
Latest News and Events
IRNDP
Are you a GP working in Australia?
If so, click here to check out our project on knowledge translation and dementia risk prevention.

Funding Acknowledgements

- NHMRC Centre of Research Excellence in Cognitive Health
- NHMRC Dementia Centre for Research Collaboration
- NHMRC Principal Research Fellowship
- ARC Centre of Excellence in Population Ageing Research

IRNDP international research network on dementia prevention

https://coghealth.net.au/

IRNDP.com