Preventing Dementia

What risk factors should we target and in whom?

Dr Matthew Pase

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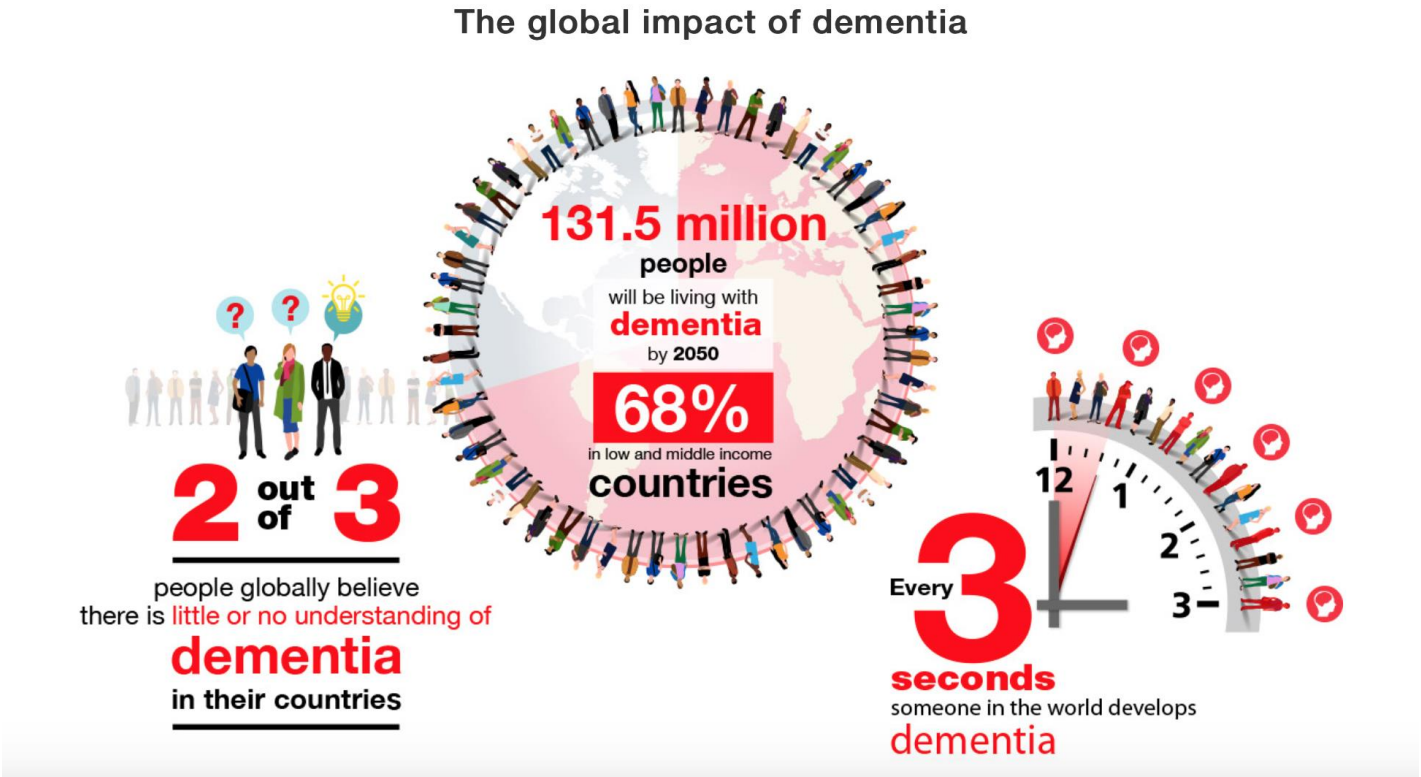
Head, Epidemiology of Dementia Lab, Monash University;

PI, the Brain and Cognitive Health (BACH) cohort study;

Overview

- The changing landscape of dementia
- Vascular risk factors and dementia
- Lifestyle and dementia
- Sleep and dementia
- Conclusions

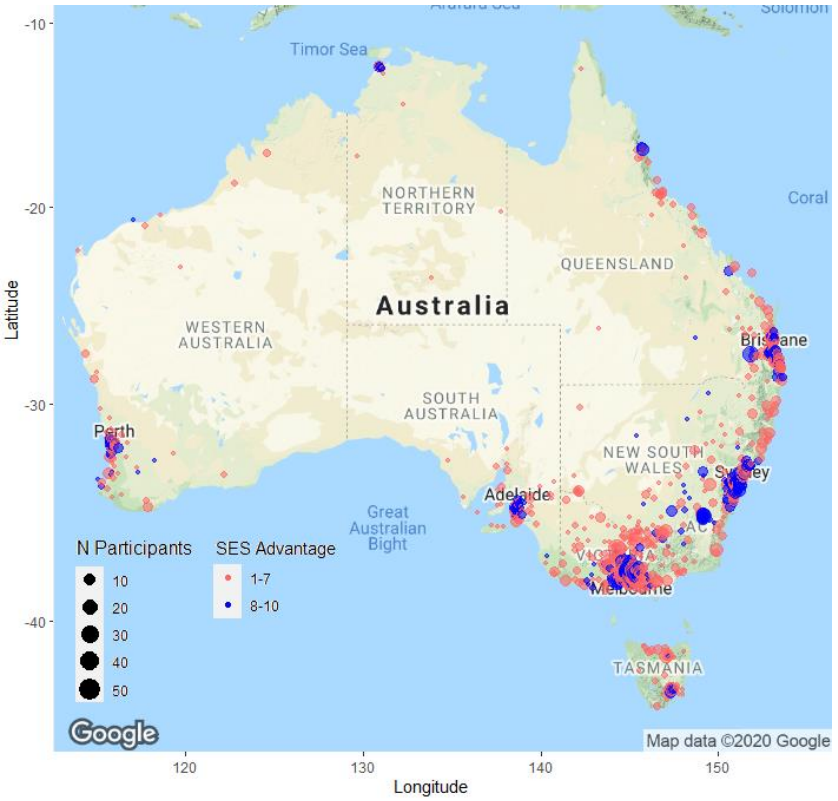
Dementia: A Growing Health Concern



Source: Dementia Alliance International

Neighbourhood Advantage & Dementia Risk

- Cross-sectional study of 4656 Australian adults aged 40 to 70 years
- Higher neighborhood-level SES was associated with better memory and lower dementia risk scores
- Findings were independent of rurality

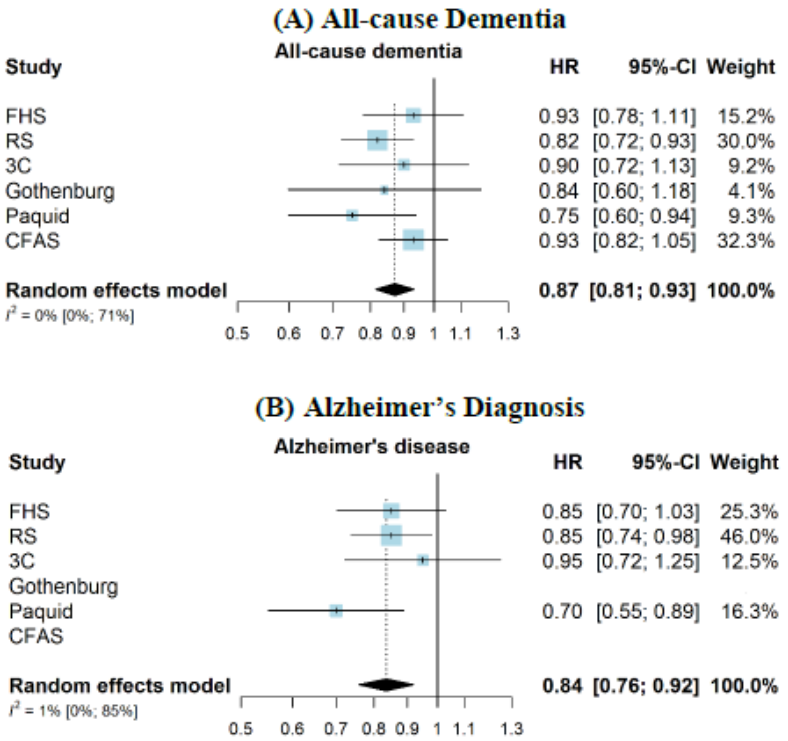


Pase et al JAMA Open, 2022

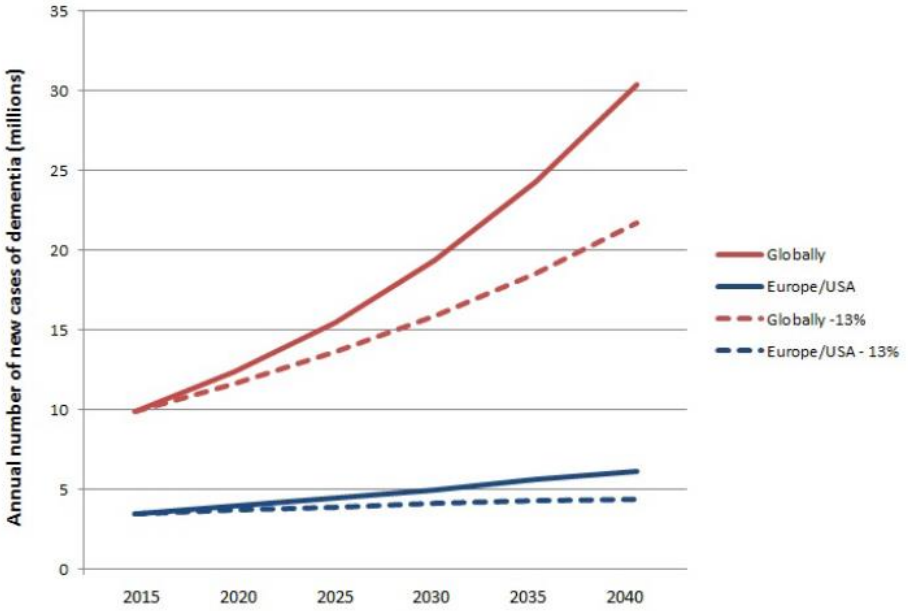
The Average Persons Risk of Dementia Is:

1) Higher than that of their parents
2) Lower than that of their parents
3) The same as their parents

The Changing Landscape of Dementia

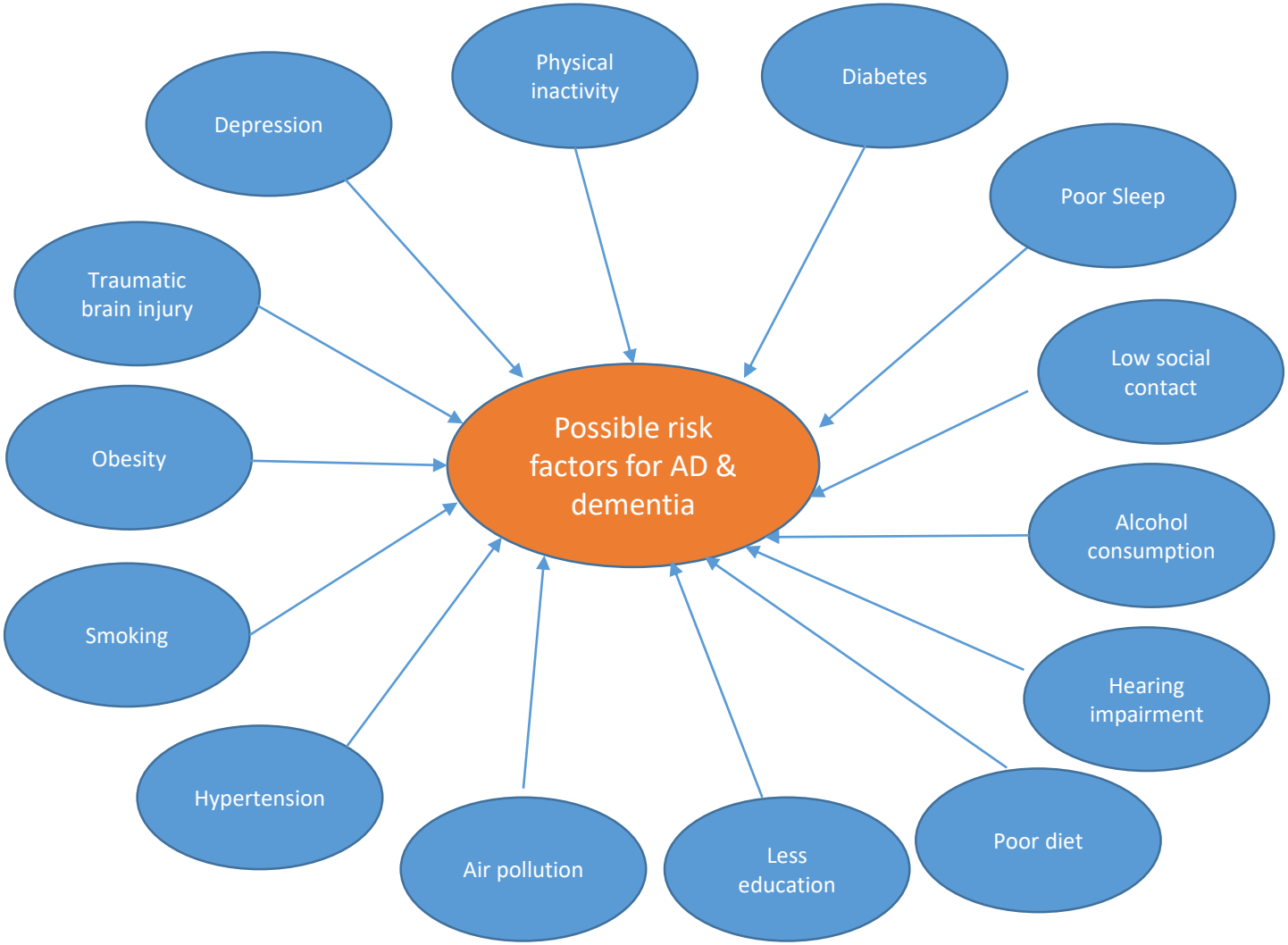


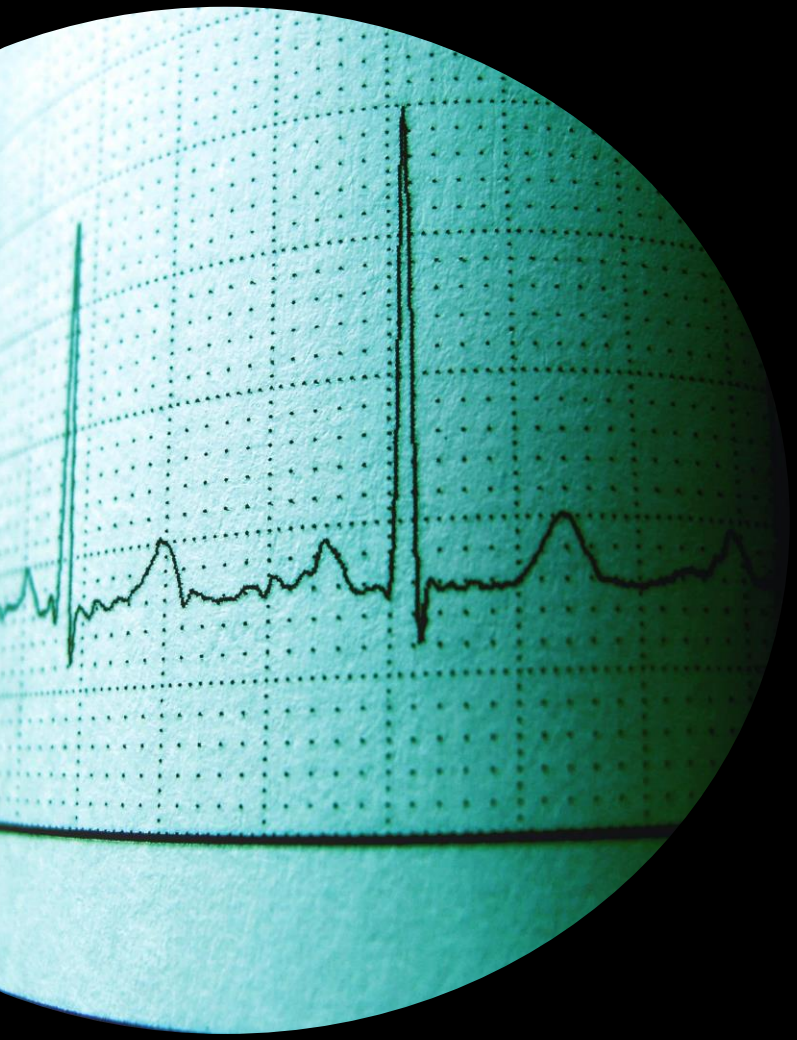
Incidence trends per decade
(*N = 59,230; 5,133 cases)*



Projected incidence of dementia in millions based on current rates (solid lines) and assuming a decreasing trend (dashed lines)

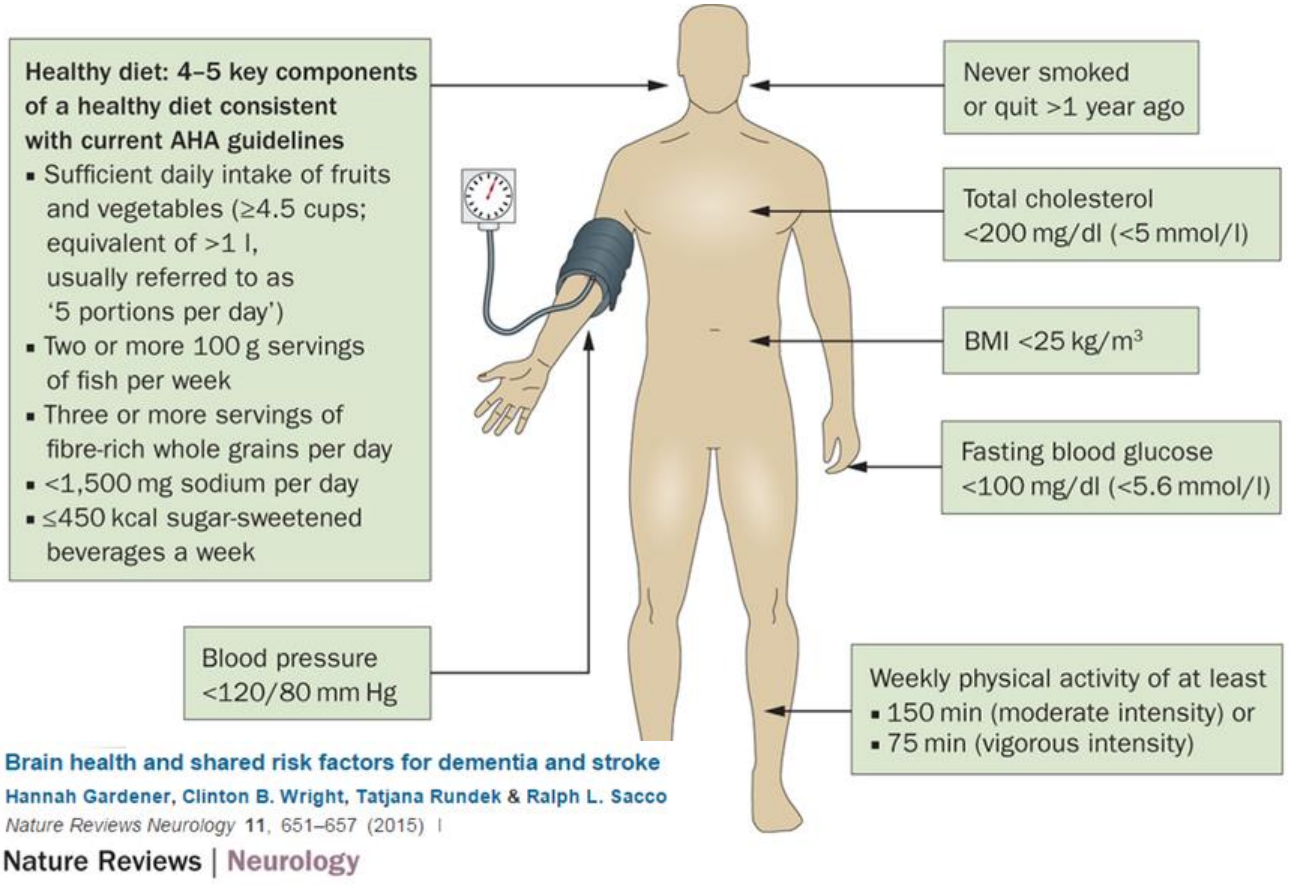
Wolters et al Neurology. 2020


Possible risk factors for AD & dementia
Depression
Physical inactivity
Diabetes
Poor Sleep
Traumatic brain injury
Low social contact
Obesity
Alcohol consumption
Smoking
Hearing impairment
Hypertension
Air pollution
Less education
Poor diet



What is the Relationship between Vascular Health and Dementia?

Ideal-CVH



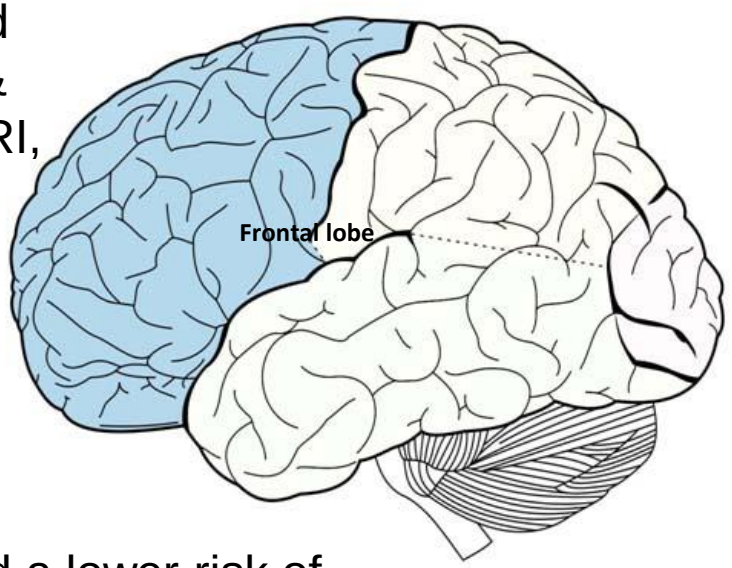
Brain health and shared risk factors for dementia and stroke
Hannah Gardener, Clinton B. Wright, Tatjana Rundek & Ralph L. Sacco
Nature Reviews Neurology **11**, 651–657 (2015) |
Nature Reviews | Neurology

AWARD 1 POINT FOR EACH:

1. Non Smoker
2. Optimal Cholesterol
3. Optimal BMI
4. Physically active
5. Optimal Blood Glucose
6. Optimal BP
7. Healthy Diet

Ideal-CVH Slows Vascular Brain Aging

Methods
Over 2,500 subjects followed for 10-years with uninterrupted surveillance for dementia & multiple rounds of brain MRI, and neuropsyc testing

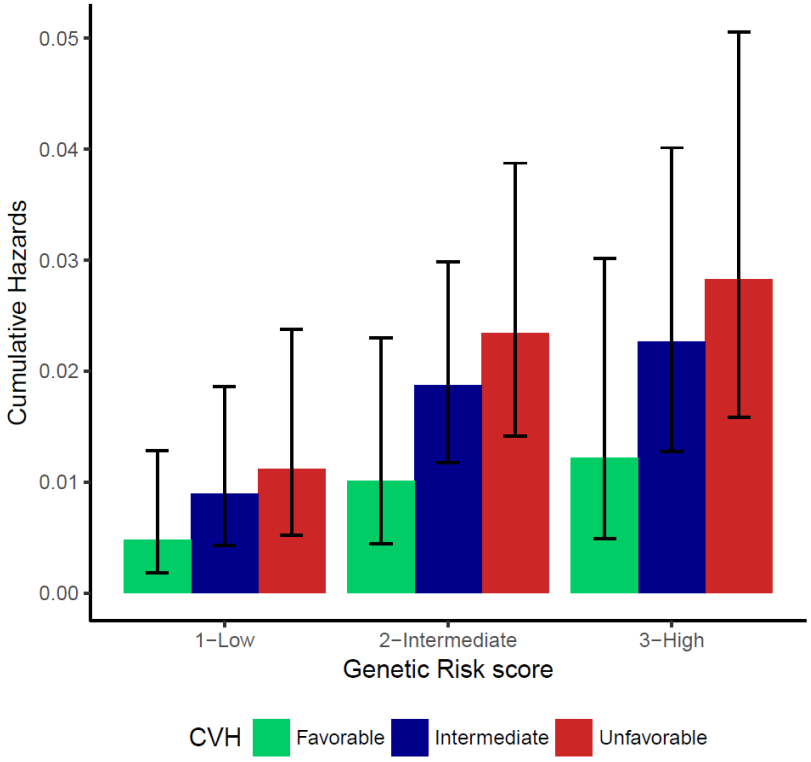


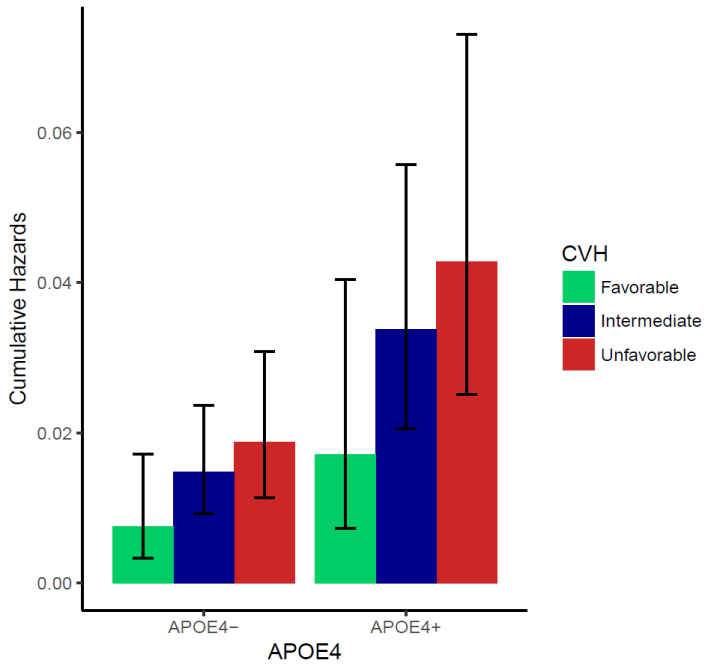
A 1-point higher CVH score reduced the rate of decline in frontal brain volume to that of someone 3.4 years younger

Results
Higher Ideal CVH predicted a lower risk of
-Incident **stroke** (HR = 0.83, 95% CI 0.71-0.97)
-Incident **VaD** (HR = 0.61, 95% CI 0.39–0.95)
-Incident **AD dementia** (HR = 0.79, 95% CI 0.64–0.98)
-less **cognitive decline** (particularly visual memory and reasoning)
-less **brain atrophy** on MRI

Pase et al Stroke. 2016

5-Year Cumulative Hazards for Dementia by Genetic Risk and Ideal CVH





Peloso et al Neurology. 2020

Is the Association between Vascular & Brain Health Age Dependent?

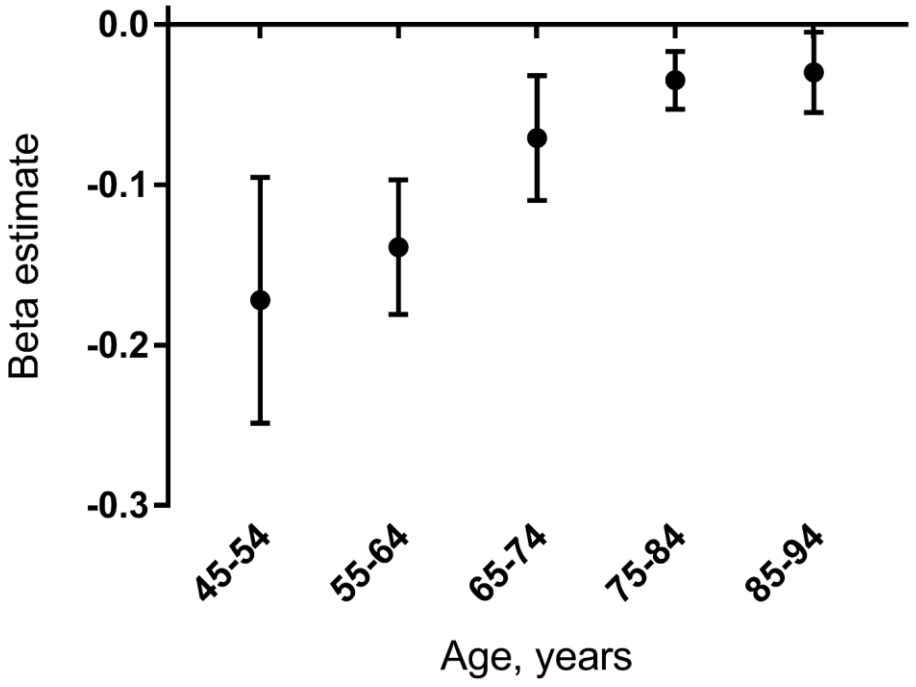
HTN associated with 7 years of brain ageing

Mean age, 42 years

HTN associated with 2 years of brain ageing

Mean age, 62 years

Association between VRF burden and Brain Volume is Age Dependent



(P for trend < 0.0001)

A lower value indicates a stronger link between vascular risk factors and smaller brain volume.

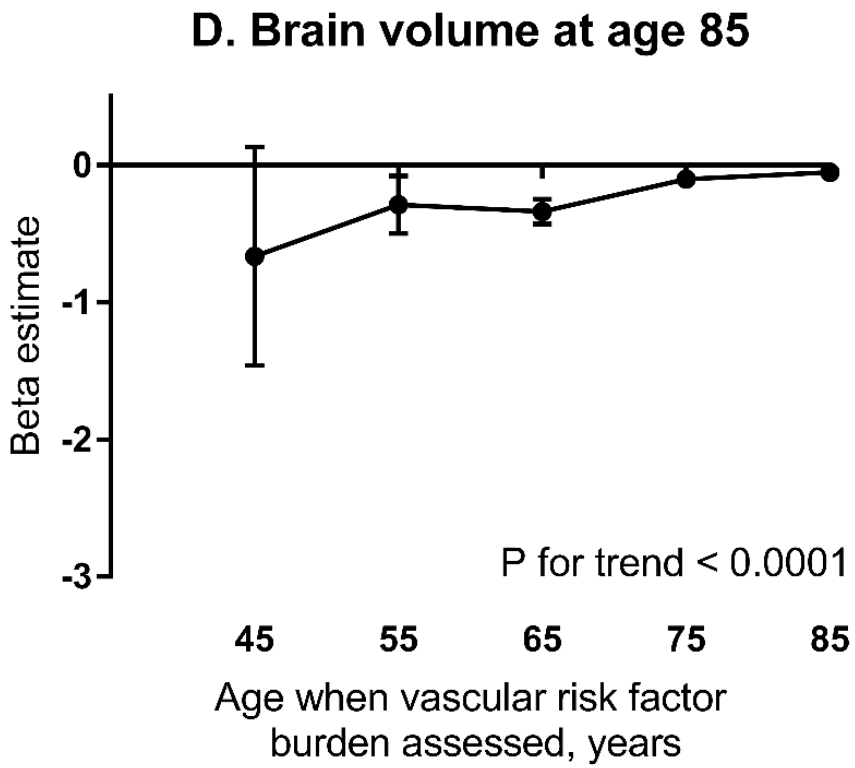
N = 2,887

Pase et al Neurology. 2018

What Best Predicts MRI Brain Volume at Age 85?

- Vascular risk factors measured at the same time as the MRI (i.e. age 85)
- Vascular risk factors measured 10 years ago (i.e. age 75)
- Vascular risk factors measured 20 years ago (i.e. age 65)
- Vascular risk factors measured 40 years ago (i.e. age 45)

Past VRF Burden & Brain Volume

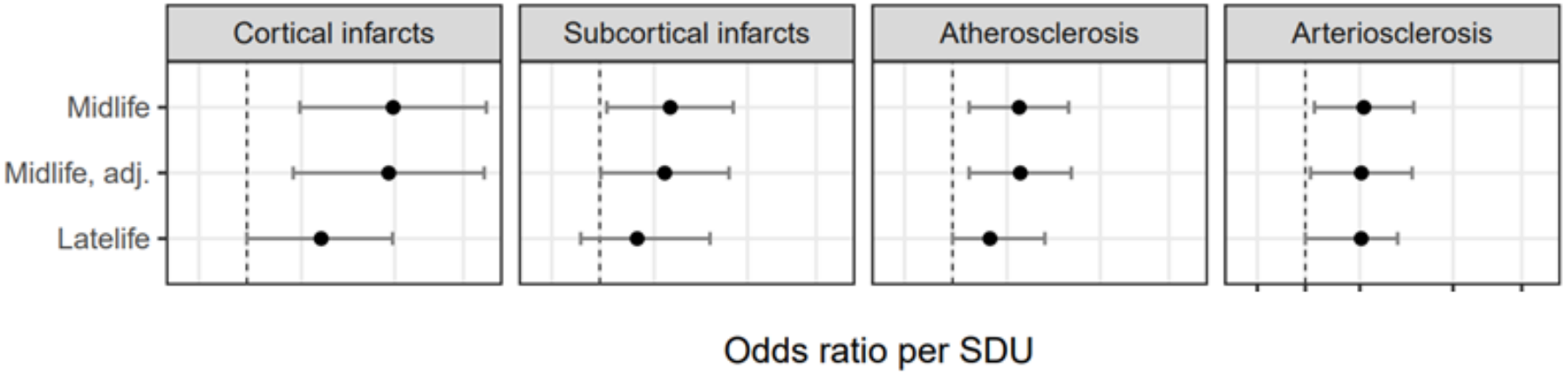


N = 7,868

Pase et al Neurology. 2018

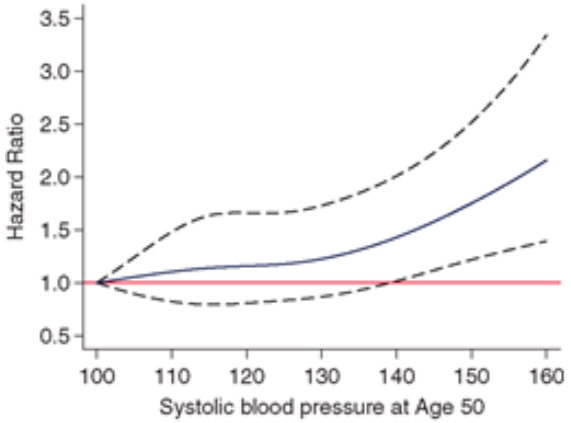
VRF Burden & Neuropathology

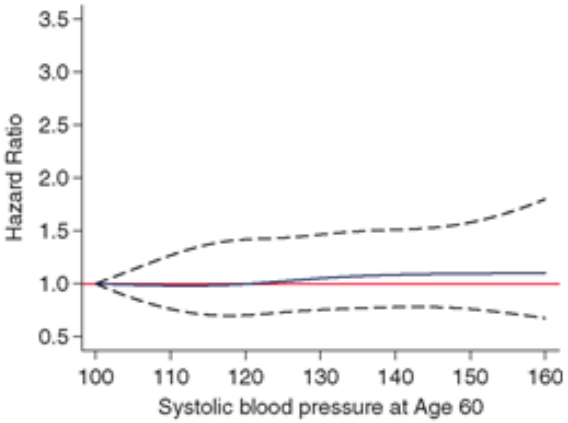
- **Objective:** To examine the association between VRF burden and neuropathology at autopsy (N, 129)
- **Design:** VRF burden was measured in midlife (mean, 33 years < death) and as close to death as possible (mean, 4 years < death)

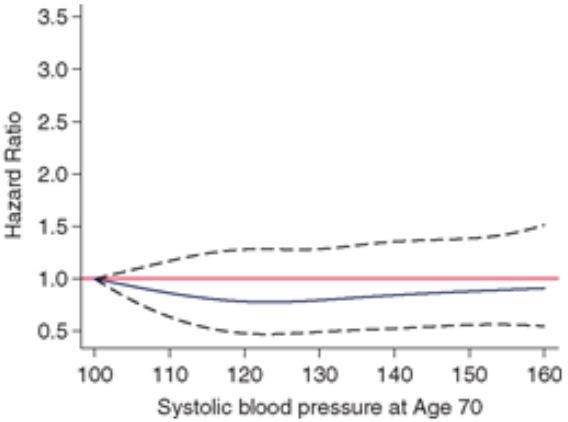


Conner, Pase, et al. ACTN.2019

Findings in Context







ESC European Society of Cardiology
European Heart Journal (2018) 0, 1–7
doi:10.1093/eurheartj/ehy288
CLINICAL RESEARCH
Hypertension

Association between systolic blood pressure and dementia in the Whitehall II cohort study: role of age, duration, and threshold used to define hypertension

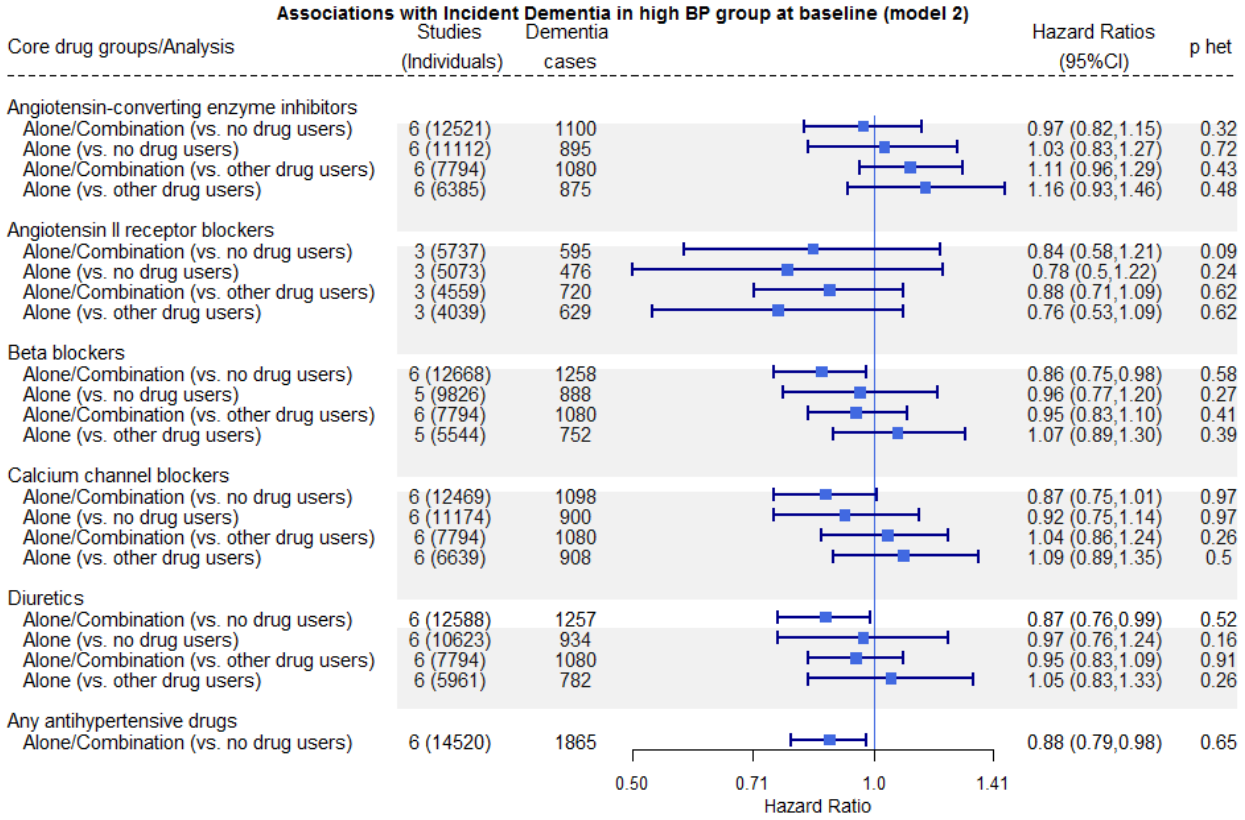
Jessica G. Abell[1,2], Mika Kivimäki[2], Aline Dugravot[1], Adam G. Tabak[1,3], Aurore Fayosse[1], Martin Shipley[2], Séverine Sabia[1,2†], and Archana Singh-Manoux[1,2*†]

Singh-Manoux. EHJ, 2018 0, 1-7.

What BP lowering meds are most effective for dementia prevention?

- 1) ACE Inhibitors
- 2) ARBs
- 3) Beta-blockers
- 4) CCB
- 5) Any

Can Treating High BP Reduce Dementia Risk?



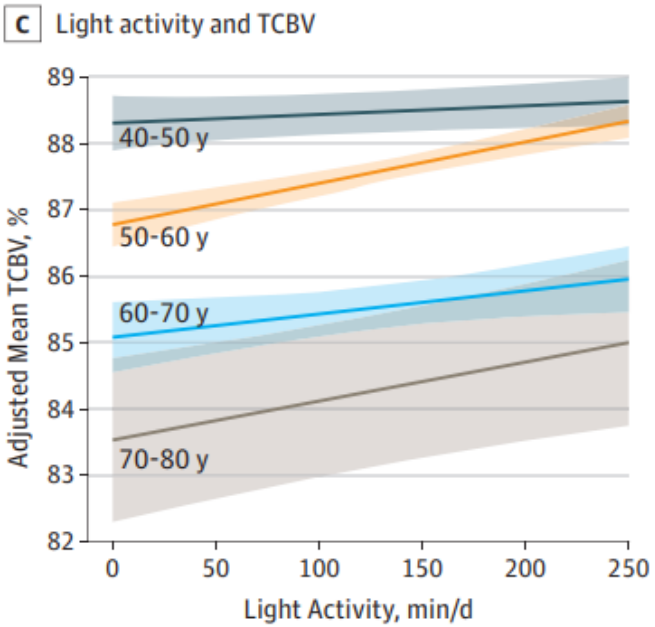
In people with high BP, treatment for high BP was associated with a reduced risk of developing (HR, 0.88; 95% CI 0.79-0.98)

Ding et al Lancet Neurology. 2020

What is the Relationship between Lifestyle Risk Factors and Dementia?

Light Intensity PA & Brain Volume

- **Background**: Most adults do not meet the recommended PA guidelines (150min moderate to vigorous PA/week)
- **Design:** Cross-sectional assessment of MRI brain volumes and accelerometry-derived total activity (steps/d) and intensity.
- **Results**: Each additional hour of light intensity PA was associated with larger brain volumes (equiv. to 1.1y of aging), even among persons not meeting current PA guidelines.
- **Importance:** Benefits of PA on brain aging may accrue at a lower more achievable level of intensity or duration



JAMA Network Open

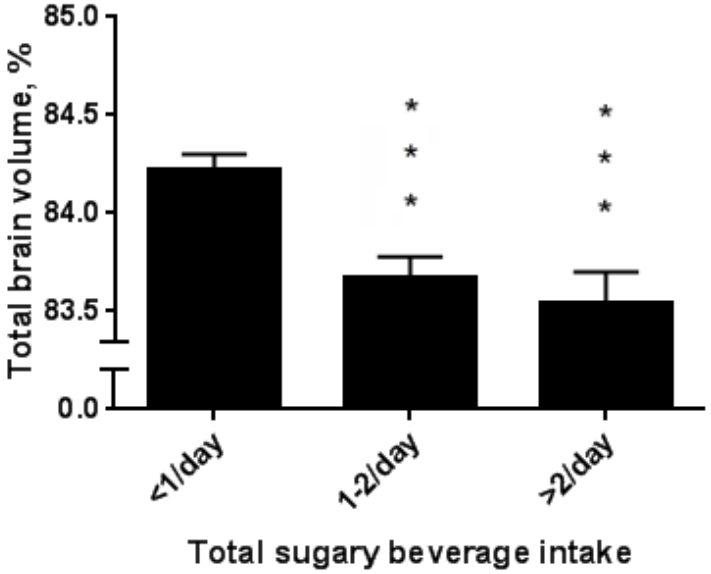
Original Investigation | Neurology

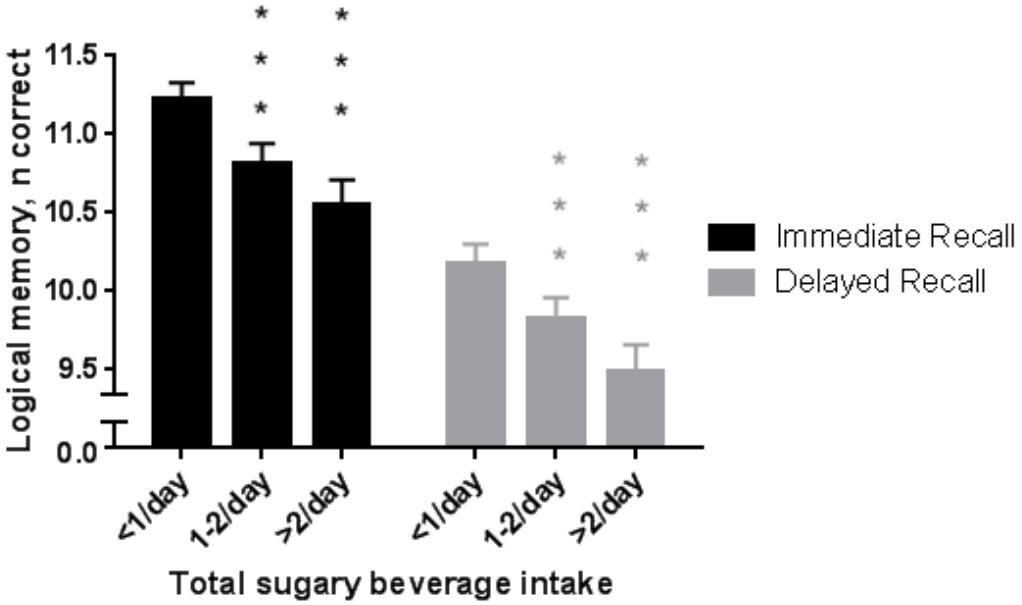
Association of Accelerometer-Measured Light-Intensity Physical Activity With Brain Volume

The Framingham Heart Study

Nicole L. Spartano, PhD; Kendra L. Davis-Plourde, MA; Jayandra J. Himali, PhD; Charlotte Andersson, MD, PhD; Matthew P. Pase, PhD; Pauline Maillard, PhD; Charles DeCarli, MD; Joanne M. Murabito, MD, ScM; Alexa S. Beiser, PhD; Ramachandran S. Vasan, MD; Sudha Seshadri, MD

Sugary Drinks & Brain Aging





Pase et al. Alzheimer's & Dementia. 2017

Sugary Drinks & Brain Aging

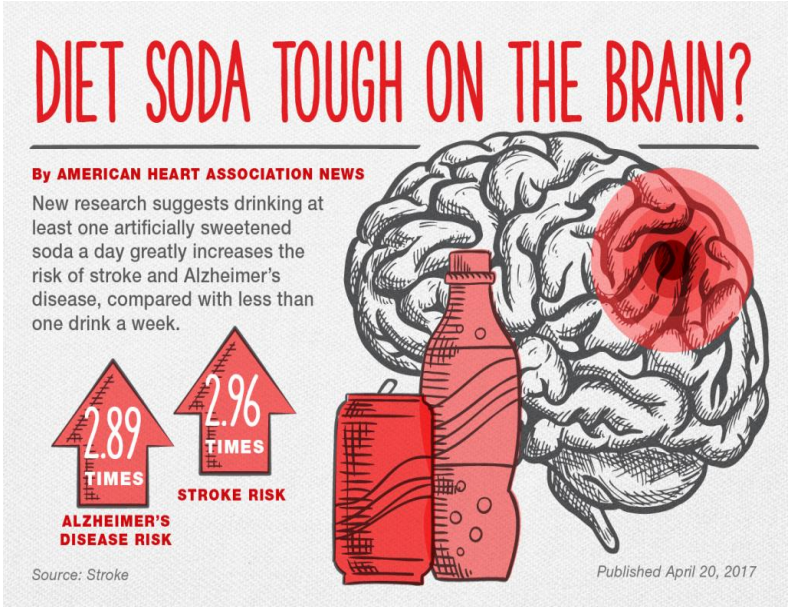
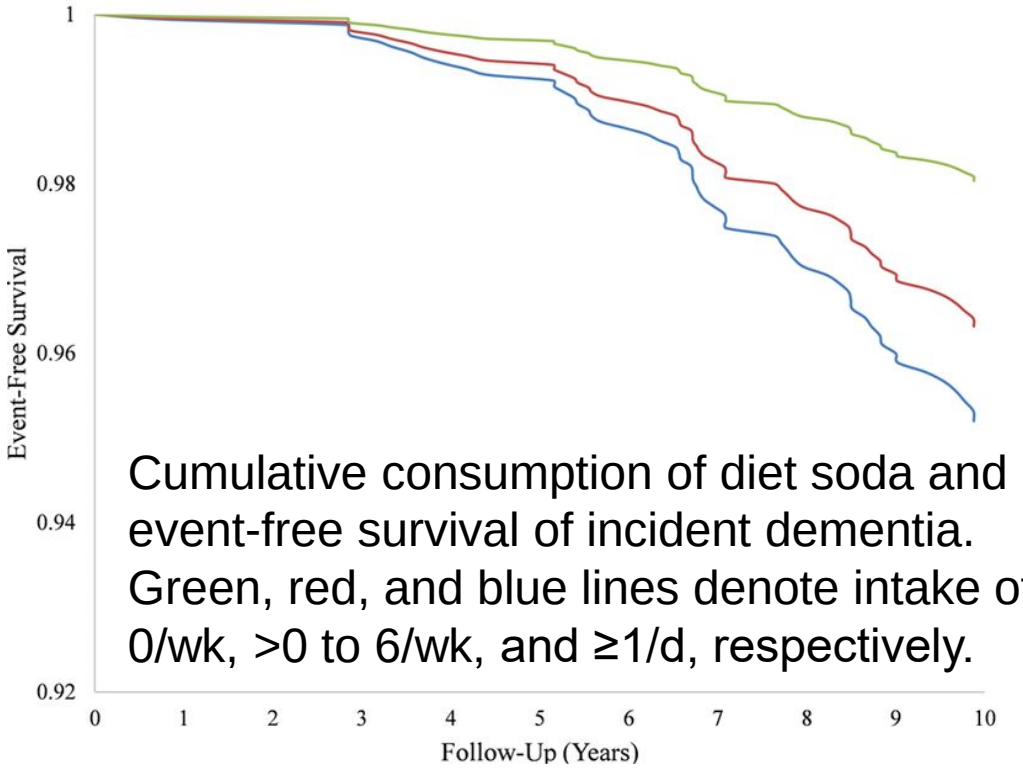


Photo Source: American Heart Association



Cumulative consumption of diet soda and event-free survival of incident dementia. Green, red, and blue lines denote intake of 0/wk, >0 to 6/wk, and ≥1/d, respectively.

Pase et al. Stroke, 2017

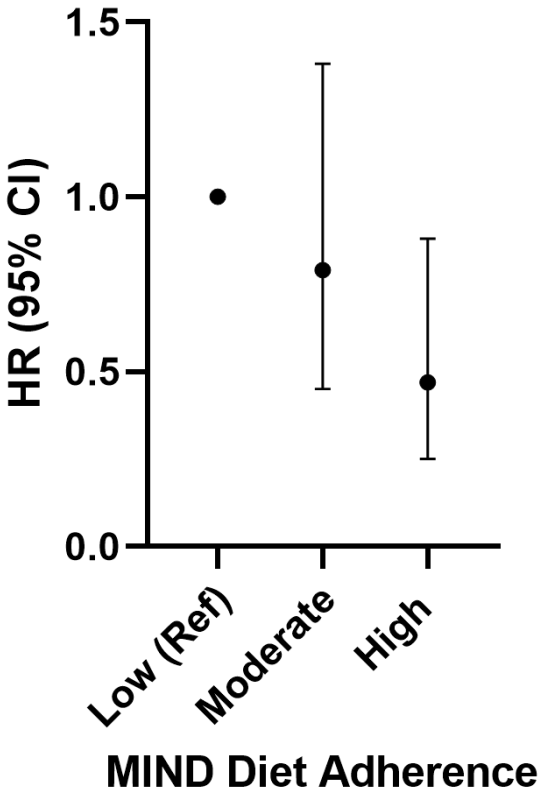
MIND Diet & the Brain

Table 1
Dietary component servings and maximum scores for the DASH, Mediterranean, and MIND diet scores

DASH*		MedDiet†		MIND	
DASH components	Max score	Mediterranean diet components	Max score	MIND components	Max score
Total grains ≥7/d	1	Nonrefined Grains >4/d	5	Whole Grains ≥3/d	1
Vegetables ≥4/d	1	Vegetables >4/d	5	Green Leafy ≥6/wk	1
		Potatoes >2/d	5	Other Vegetables ≥1/d	1
Fruits ≥4/d	1	Fruits >3/d	5	Berries ≥2/wk	1
Dairy ≥2/d	1	Full-fat Dairy ≤10/wk	5		
Meat, poultry and fish ≤2/d	1	Red meat ≤1/wk	5	Red Meats and products <4/wk	1
		Fish >6/wk	5	Fish ≥1/wk	1
		Poultry ≤3/wk	5	Poultry ≥2/wk	1
Nuts, seeds & legumes ≥4/wk	1	Legumes, nuts & beans >6/wk	5	Beans >3/wk	1
				Nuts ≥5/wk	1
				Fast/fried food <1/wk	1
Total fat ≤27% of kcal	1				
Saturated fat ≤6% of kcal	1				
		Olive oil ≥1/d	5	Olive Oil primary oil	1
				Butter, margarine <1 T/d	1
				Cheese <1/wk	1
Sweets ≤5/wk	1			Pastries, sweets <5/wk	1
Sodium ≤2400 mg/d	1				
		Alcohol <300 mL/d but >0	5	Alcohol/wine 1/d	1
Total DASH Score	10	Total MedDiet Score	55	Total MIND Score	15

Alzheimer Dement. 2015;11(9):1007-14

MIND Diet & the Brain



- We studied 2092 dementia-free participants followed for 10-years
- MIND diet scores were averaged across 3 timepoints
- Higher MIND diet scores also predict superior global cognition, verbal memory, visual memory, processing speed, verbal comprehension, and larger brain volume on MRI

Mind Diet Adherence and Cognitive Performance in the Framingham Heart Study

Debora Melo van Lent[a,b,c,d,*], Adrienne O'Donnell[c,e], Alexa S. Beiser[b,c,e], Ramachandran S. Vasan[c,f], Charles S. DeCarli[h], Nikolaos Scarmeas[i,j], Michael Wagner[d,k], Paul F. Jacques[c,l], Sudha Seshadri[a,b,c], Jayandra J. Himali[a,b,c,e,l] and Matthew P. Pase[c,m,n,l]

What is the Relationship between Sleep and Dementia?

Sleep is Vital for Brain Health

Sleep Drives Metabolite Clearance from the Adult Brain

Lulu Xie,[1]* Hongyi Kang,[1]* Qiwu Xu,[1] Michael J. Chen,[1] Yonghong Liao,[1] Meenakshisundaram Thiyagarajan,[1] John O'Donnell,[1] Daniel J. Christensen,[1] Charles Nicholson,[2] Jeffrey J. Iliff,[1] Takahiro Takano,[1] Rashid Deane,[1] Maiken Nedergaard[1]†

www.sciencemag.org **SCIENCE** VOL 342 18 OCTOBER 2013

'The restorative function of sleep may be a consequence of the enhanced removal of potential neurotoxic waste products that accumulate in the awake CNS' (Xie et al., 2013 *Science)*

Insomnia & Cognition

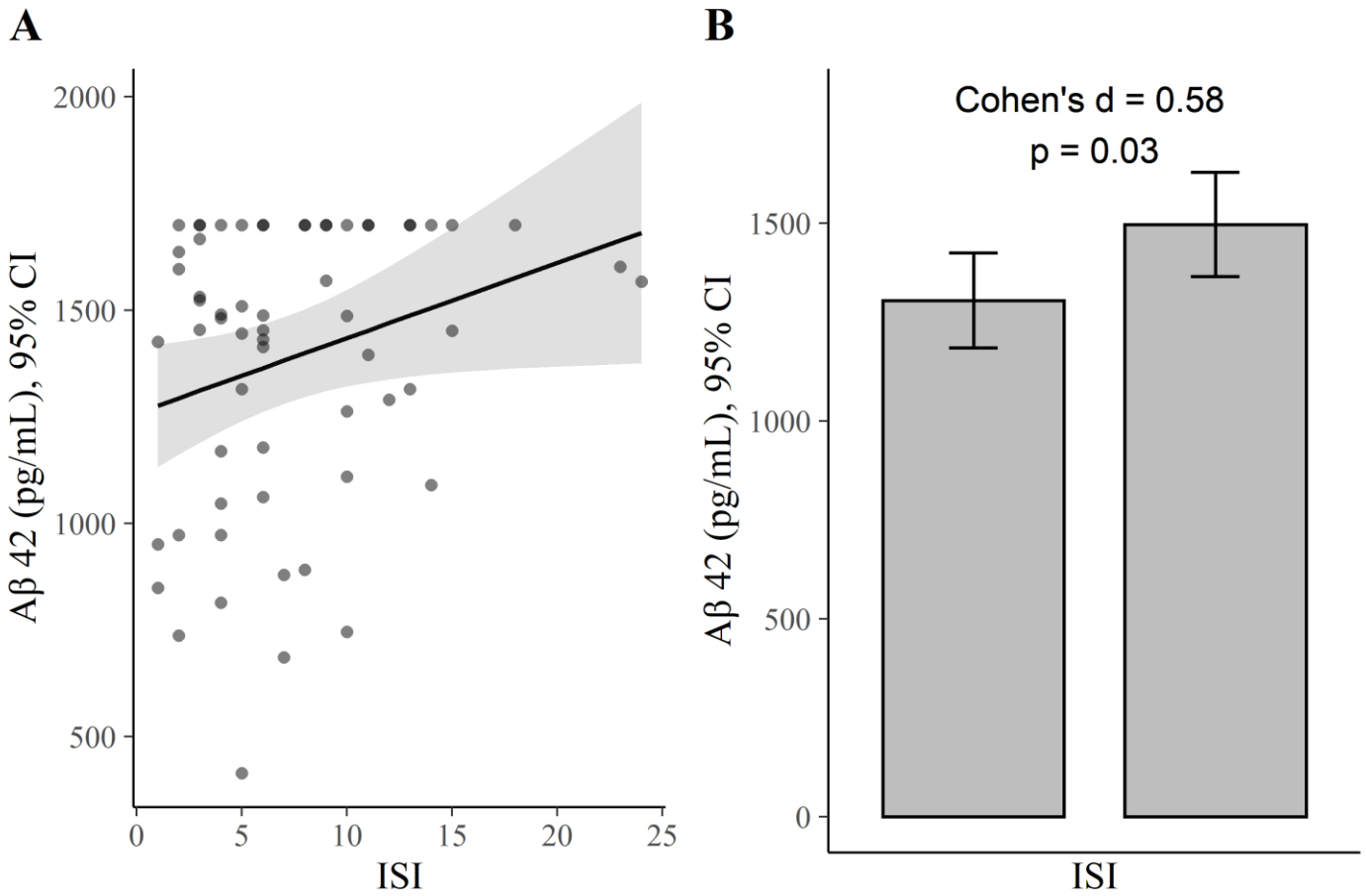
- 511 participants (aged 59±9 years; 49% men) from the community with self reported insomnia symptoms and cognition 3 years later
- Increased severity of insomnia symptoms was associated with poorer global cognition and verbal episodic memory measured approximately 3 years later
- The effect was particularly apparent in APOE e4 carriers

Baril…Pase, *Alzheimer's & Dementia* (2021)

TABLE 3

Cognitive performance	Insomnia symptom severity, five questions	
	β (standard error)	P*
Composite global cognitive score		
Model 1	−0.098 (0.035)	**.020**
Model 2	−0.098 (0.038)	**.023**
Logical Memory, immediate recall		
Model 1	−0.382 (0.140)	**.020**
Model 2	−0.447 (0.150)	**.014**
Logical Memory, delayed recall		
Model 1	−0.452 (0.146)	**.014**
Model 2	−0.521 (0.156)	**.013**
Trail Making Test, Part A (inverted)		
Model 1	−0.006 (0.014)	.812
Model 2	0.005 (0.015)	.812
Trail Making Test, Part B minus A (inverted)		
Model 1	−0.009 (0.009)	.470
Model 2	−0.007 (0.010)	.657
Similarities		
Model 1	−0.279 (0.154)	.123
Model 2	−0.326 (0.162)	.090
Hooper Visual Organization Test		
Model 1	−0.002 (0.023)	.935
Model 2	−0.009 (0.025)	.812

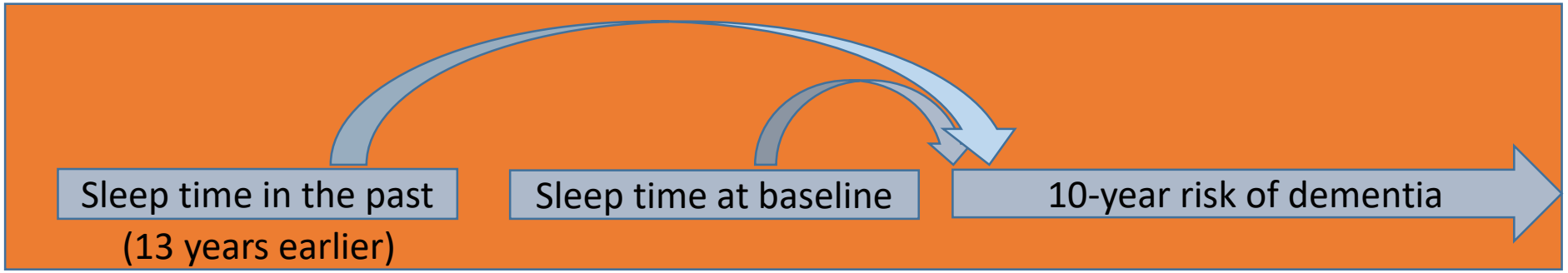
Insomnia & AD biomarkers



(A) Association between Insomnia Symptom Severity (ISI) score (continuous variable) and Aβ42 **(B)** Association between ISI score (high vs low) and Aβ42. Models are adjusted for age and sex.

Nicolazzo…Pase. Under review

Sleep Time & Dementia Risk



Prolonged sleep duration as a marker of early neurodegeneration predicting incident dementia

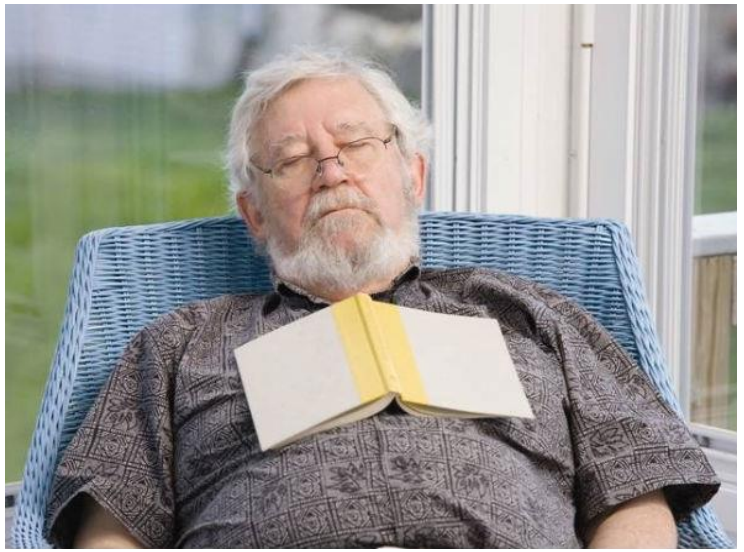
Andrew J. Westwood, MD
Alexa Beiser, PhD
Nikita Jain
Jayandra J. Himali, PhD
Charles DeCarli, MD
Sanford H. Auerbach, MD
Matthew P. Pase, PhD*
Sudha Seshadri, MD*

ABSTRACT

Objective: To evaluate the association between sleep duration and the risk of incident dementia and brain aging.

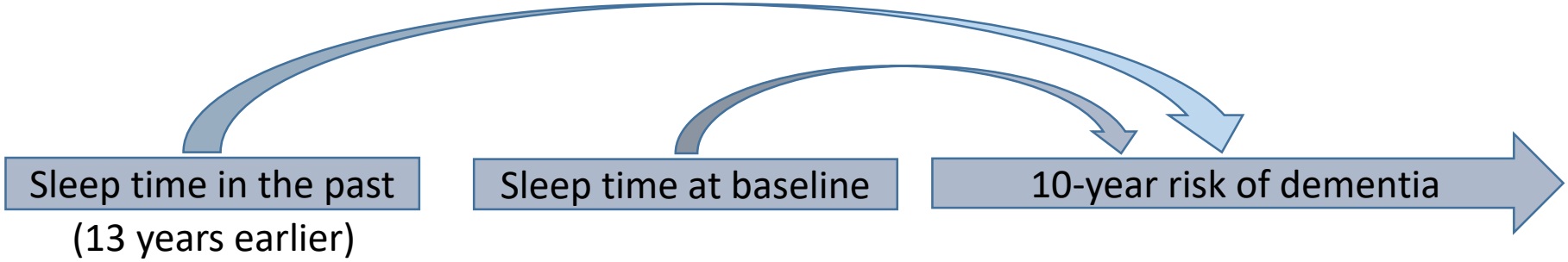
Methods: Self-reported total hours of sleep were examined in the Framingham Heart Study (n = 2,457, mean age 72 ± 6 years, 57% women) as a 3-level variable: <6 hours (short), 6–9 hours (reference), and >9 hours (long), and was related to the risk of incident dementia over 10 years, and cross-sectionally to total cerebral brain volume (TCBV) and cognitive performance.

Results: We observed 234 cases of all-cause dementia over 10 years of follow-up. In multivariable analyses, prolonged sleep duration was associated with an increased risk of incident dementia (hazard ratio [HR] 2.01; 95% confidence interval [CI] 1.24–3.26). These findings were driven



Neurology. 2017.88(12):1172-1179

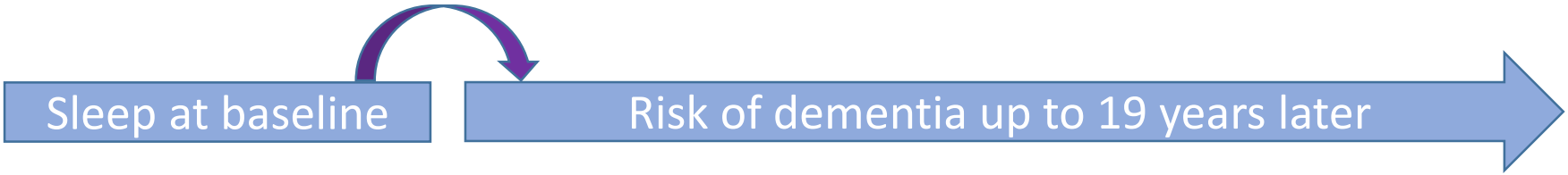
Sleep Time & Dementia Risk



Sleeping >9 hrs:	x 2 ⇧ risk of dementia	HR, 2.04 (95% CI: 1.26-3.30)
Always sleeping >9 hrs:	no ⇧ in risk of dementia	HR, 1.34 (95% CI: 0.42-4.26)
Recently sleeping >9 hrs:	x2.4 ⇧ in risk of dementia	HR, 2.43 (95% CI: 1.44-4.11)
Recently sleeping >9 hrs + having thinking problems:	x 6 ⇧ in risk of dementia	HR, 6.01 (95% CI: 1.48-24.43)

Neurology. 2017.88(12):1172-1179

Sleep Architecture & Dementia Risk



	All-Dementia			AD Dementia	
	HR (95% CI)	p		HR (95% CI)	p
Stage 1, %	1.08 (0.99, 1.17)	0.10		1.05 (0.94, 1.17)	0.37
Stage 2, %	1.01 (0.98, 1.04)	0.70		1.01 (0.97, 1.04)	0.71
SWS, %	1.07 (0.82, 1.40)	0.61		1.10 (0.80, 1.52)	0.56
REM, %	**0.91 (0.86, 0.97)**	**0.004**		**0.92 (0.86, 0.99)**	**0.02**

Models are adjusted for age and sex. Results were unchanged with adjusting for BMI, education level, APOE ε4, smoking, SBP, Rx for hypertension, DM, CHD, depressive symptoms, sleeping meds, antidepressants, & anxiolytics.

Pase et al. Neurology. 2017;89(12):1244-1250

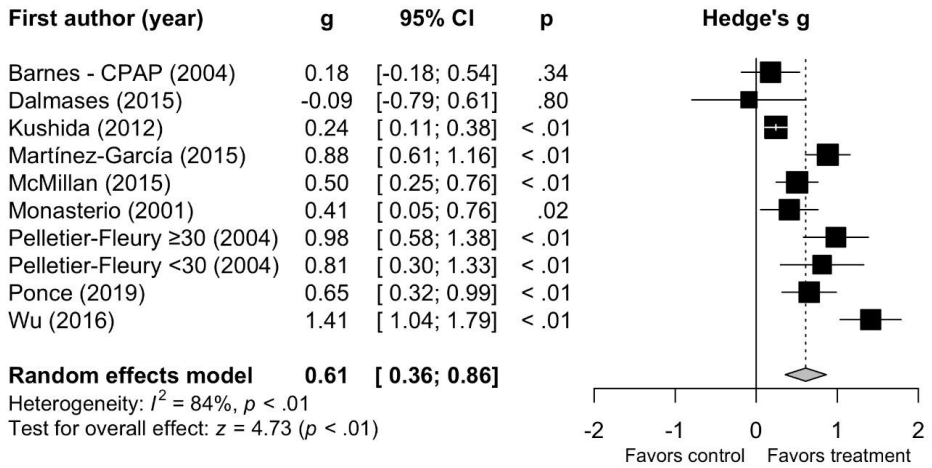
Slow Wave Sleep & Brain Aging

- **Methods**. N = 492 with a brain MRI and in-home overnight PSG
- **Results:** Longer SWS duration associated with higher cortical and subcortical brain volume, and lower WMHV volume. SWS duration did not associate with hippocampal volume.
- **Interpretation:** More SWS was associated with a healthier brain

	Absolute SWS duration		SWS percent	
	β (SE)	p	β (SE)	p
Total brain volume, % of ICV	0.08 (0.03)	**0.017**	0.12 (0.07)	0.056
Cortical GM volume, % of ICV	0.08 (0.03)	**0.003**	0.15 (0.06)	**0.008**
Subcortical GM volume, % of ICV	0.009 (0.005)	0.082	0.02 (0.01)	**0.047**
Hippocampal volume, % of ICV	-0.001 (0.001)	0.590	-0.001 (0.002)	0.465
WMHV, % of ICV	-0.05 (0.02)	**0.002**	-0.08 (0.03)	**0.009**

Baril…Pase,* Himali*. *Neurology*, 2021

Does Treating Sleep Apnea Improve Cognition?



Treating sleep apnoea reduces daytime sleepiness but has no effect on cognition

Pooled effects CPAP treatment on cognition

		Pooled effect				
	Studies	Hedge's g	95% CI lower	95% CI upper	p	I^2 %
Long-term storage/retrieval	5	-0.08	-0.41	0.25	.64	80
Short-term memory	5	0.00	-0.22	0.22	.98	44
Reaction time	2	0.09	-0.13	0.31	.42	0
Processing speed	9	-0.05	-0.14	0.03	.23	0
Visual processing	2	0.21	-0.28	0.70	.40	75

Franks…Pase. Under review

Summary

Dementia risk differs by age, geographic location, advantage, and time

Maintaining a healthy heart at an early age is important for preserving brain health with advancing age

Aspects of lifestyle, such as adequate sleep, may be involved in dementia pathogenesis

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BACH brain and cognitive health cohort study
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