Life-Course Strategies for Preventing Dementia

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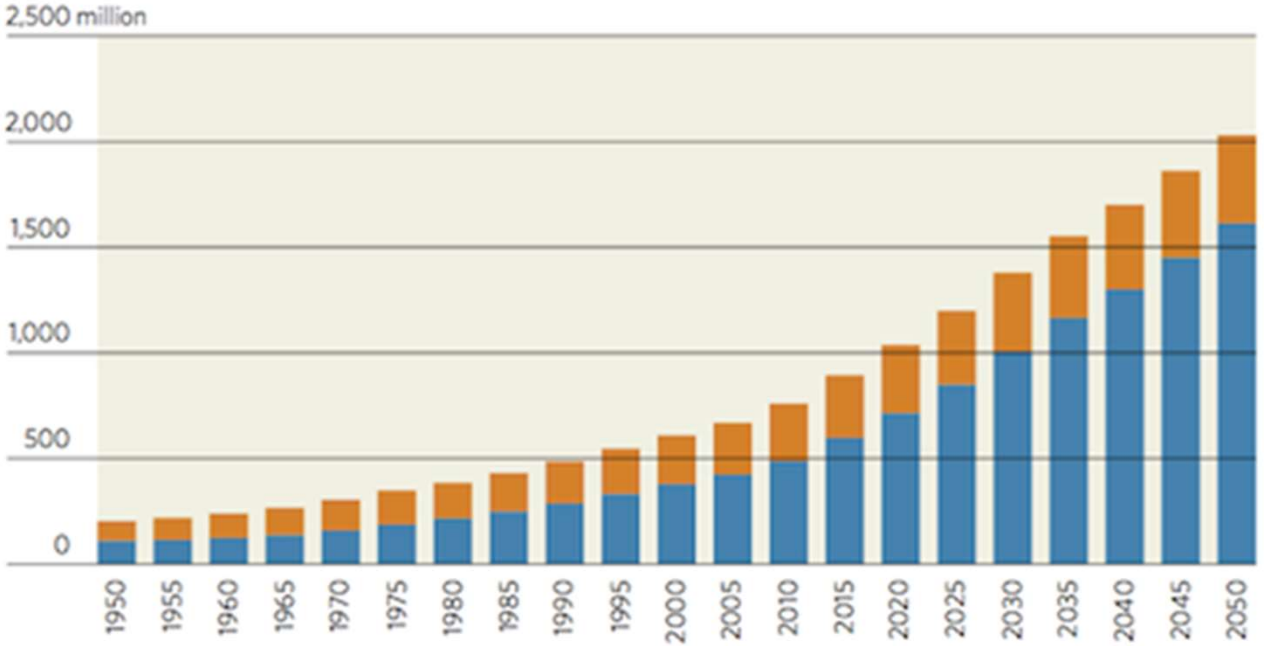
Global Aging Demographics

Number of people aged 60 or over: World, developed and developing countries, 1950-2050



Source: UNDESA, *World Population Ageing 2011* (2012; forthcoming), based on UNDESA Population Division medium projection scenario, *World Population Prospects: The 2010 Revision*.

Note: The group of "developed countries" corresponds to the "more developed regions" of the *World Population Prospects: The 2010 Revision*, and the group "developing countries" corresponds to the "less developed regions" of the same publication.

Background

- Approximately 11.2% of Americans over age 65 have probable dementia and 10.6% have possible dementia according to the National Health and Aging Trends Study;

- These estimates are expected to increase by 2050 and have significant implications for the health and function of older adults, as well as for their families, and the healthcare system;

- *Dementia significantly impairs daily functioning, with estimated costs in the United States of between $159 and $215 billion each year;*

Dementia is a multifactorial disease

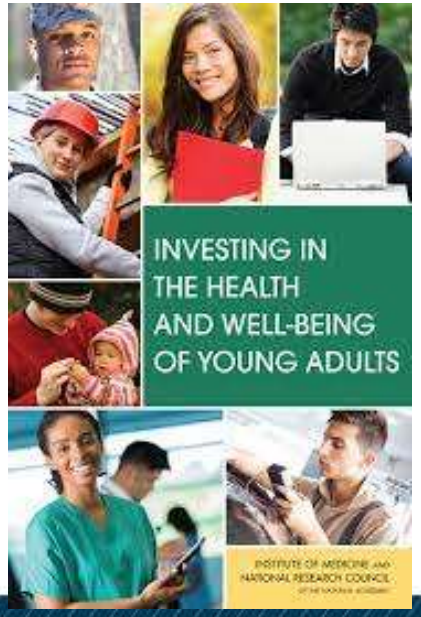
As much as **40%** of dementia may be attributable to twelve modifiable risk factors:

- low education
- physical inactivity
- obesity in mid-life
- depression
- social isolation
- traumatic brain injury
- air pollution
- current smoking
- hypertension
- diabetes
- hearing loss
- excessive alcohol use

Lancet Commission, 2020

A Life Course Approach to Preventing Dementia

Early Life **Mid-Life** **Later Life**



Lancet Commission, 2020

Population attributable fractions for 12 dementia risk factors

	Relative risk for dementia (95% CI)	Risk factor prevalence	Communality	Unweighted PAF	Weighted PAF*
Early life (<45 years)					
Less education	1·6 (1·3–2·0)	40·0%	61·2%	19·4%	7·1%
Midlife (age 45–65 years)					
Hearing loss	1·9 (1·4–2·7)	31·7%	45·6%	22·2%	8·2%
TBI	1·8 (1·5–2·2)	12·1%	55·2%	9·2%	3·4%
Hypertension	1·6 (1·2–2·2)	8·9%	68·3%	5·1%	1·9%
Alcohol (>21 units/week)	1·2 (1·1–1·3)	11·8%	73·3%	2·1%	0·8%
Obesity (body-mass index ≥30)	1·6 (1·3–1·9)	3·4%	58·5%	2·0%	0·7%
Later life (age >65 years)					
Smoking	1·6 (1·2–2·2)	27·4%	62·3%	14·1%	5·2%
Depression	1·9 (1·6–2·3)	13·2%	69·8%	10·6%	3·9%
Social isolation	1·6 (1·3–1·9)	11·0%	28·1%	4·2%	3·5%
Physical inactivity	1·4 (1·2–1·7)	17·7%	55·2%	9·6%	1·6%
Diabetes	1·5 (1·3–1·8)	6·4%	71·4%	3·1%	1·1%
Air pollution	1·1 (1·1–1·1)	75·0%	13·3%	6·3%	2·3%

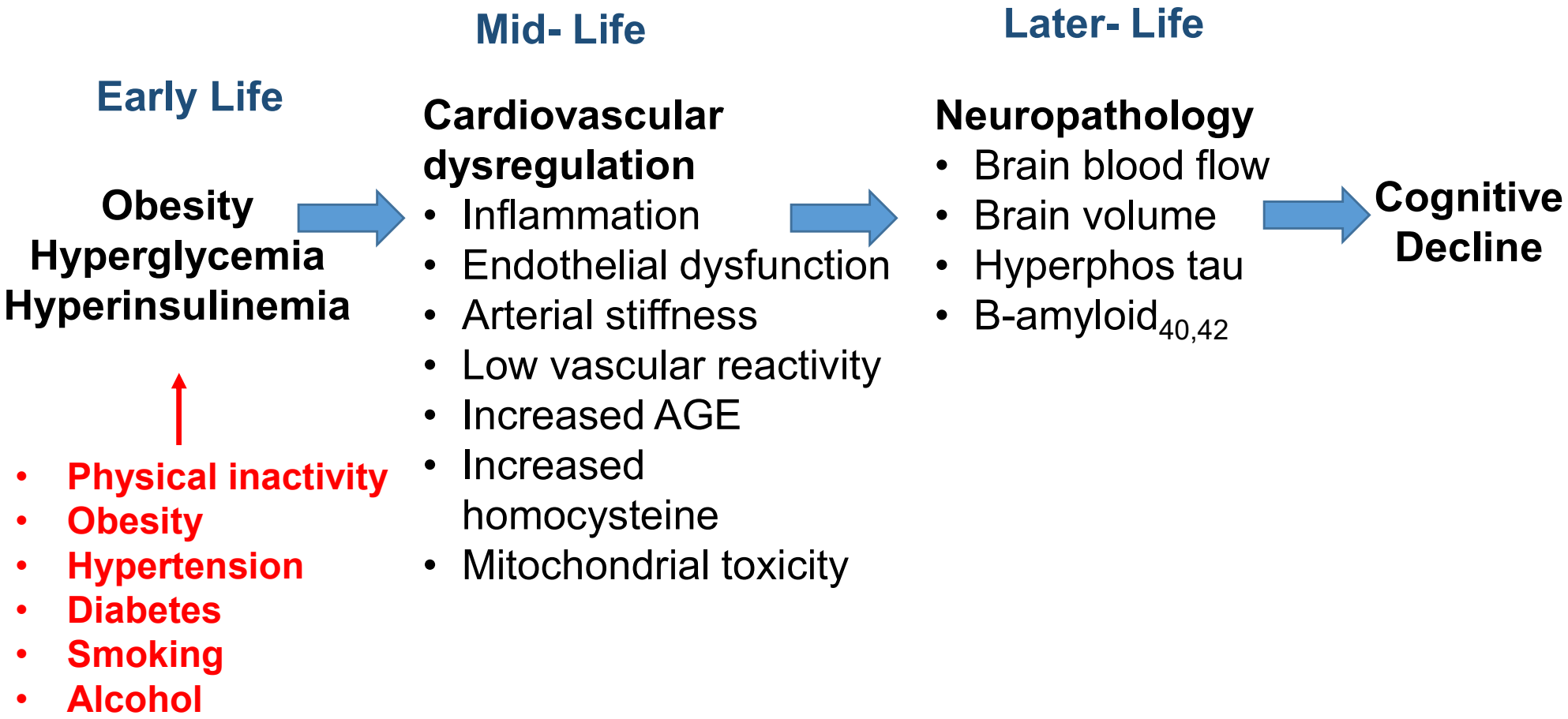
Data are relative risk (95% CI) or %. Overall weighted PAF=39·7%. PAF=population attributable fraction. TBI=traumatic brain injury. *Weighted PAF is the relative contribution of each risk factor to the overall PAF when adjusted for communality.

Table 1: PAF for 12 dementia risk factors

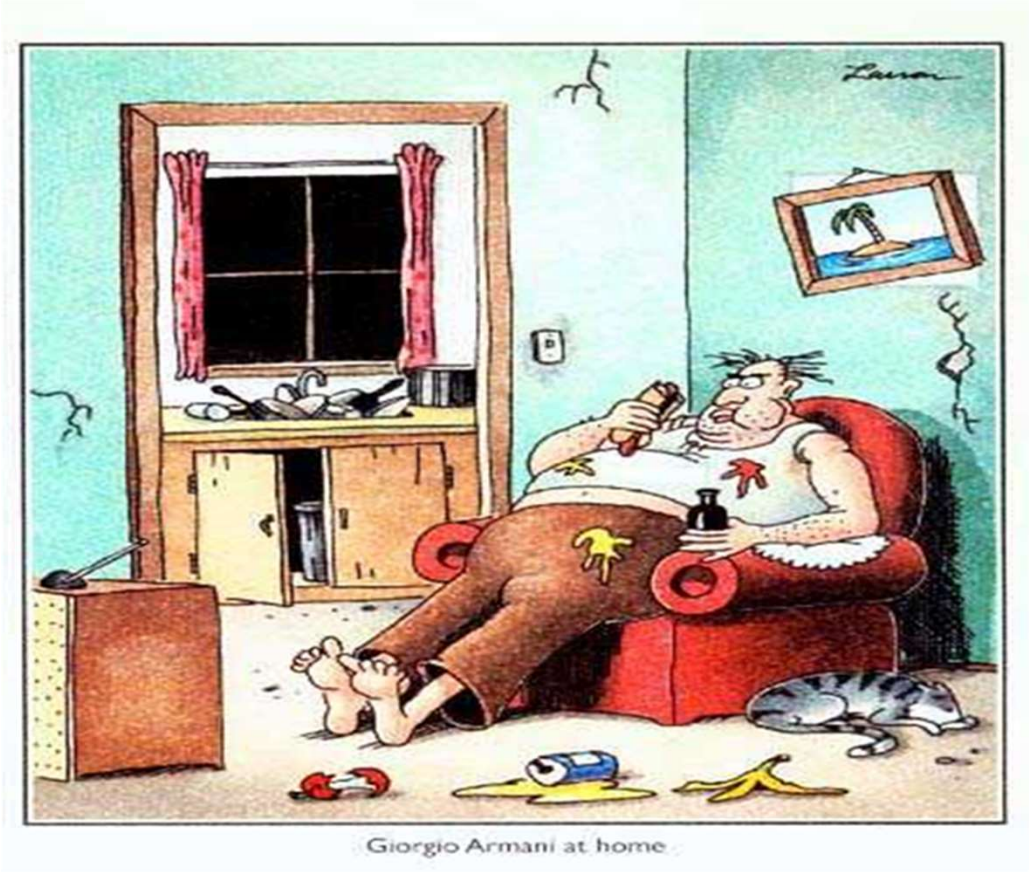
Preventive Pathways

- Preventing neuropathological damage;
- Increasing and maintaining cognitive reserve

Dysregulation of metabolic, inflammatory, and oxidative pathways



Life's Simple 7



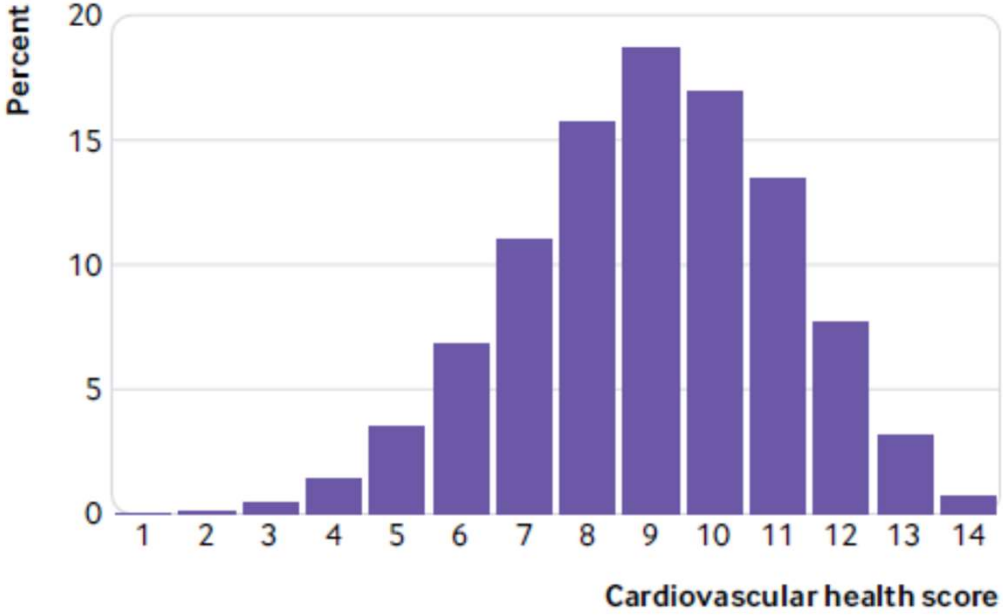
Giorgio Armani at home

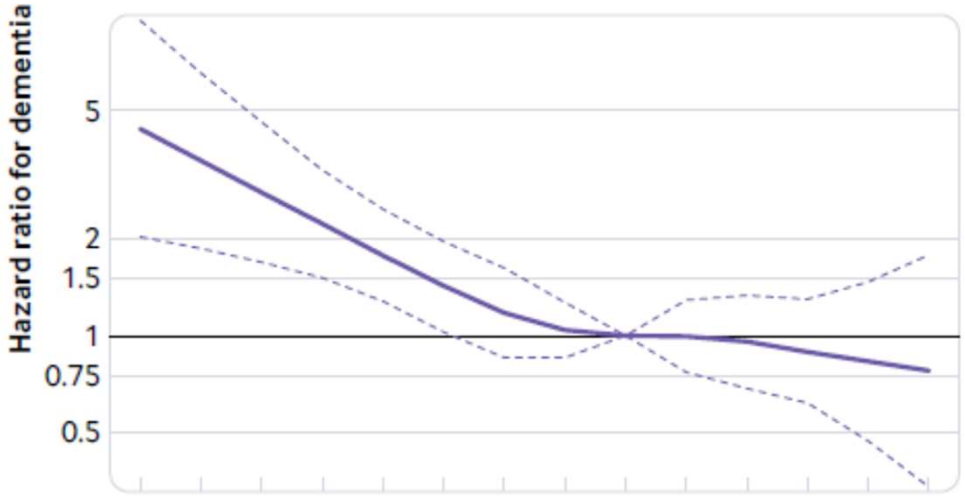
- Smoking
- Diet
- Physical activity
- BMI
- Fasting glucose
- Cholesterol
- SBP/DBP

AHA, 2010

Association of ideal cardiovascular health at age 50 with incidence of dementia: 25 year follow-up of Whitehall II cohort study (N=7,899)

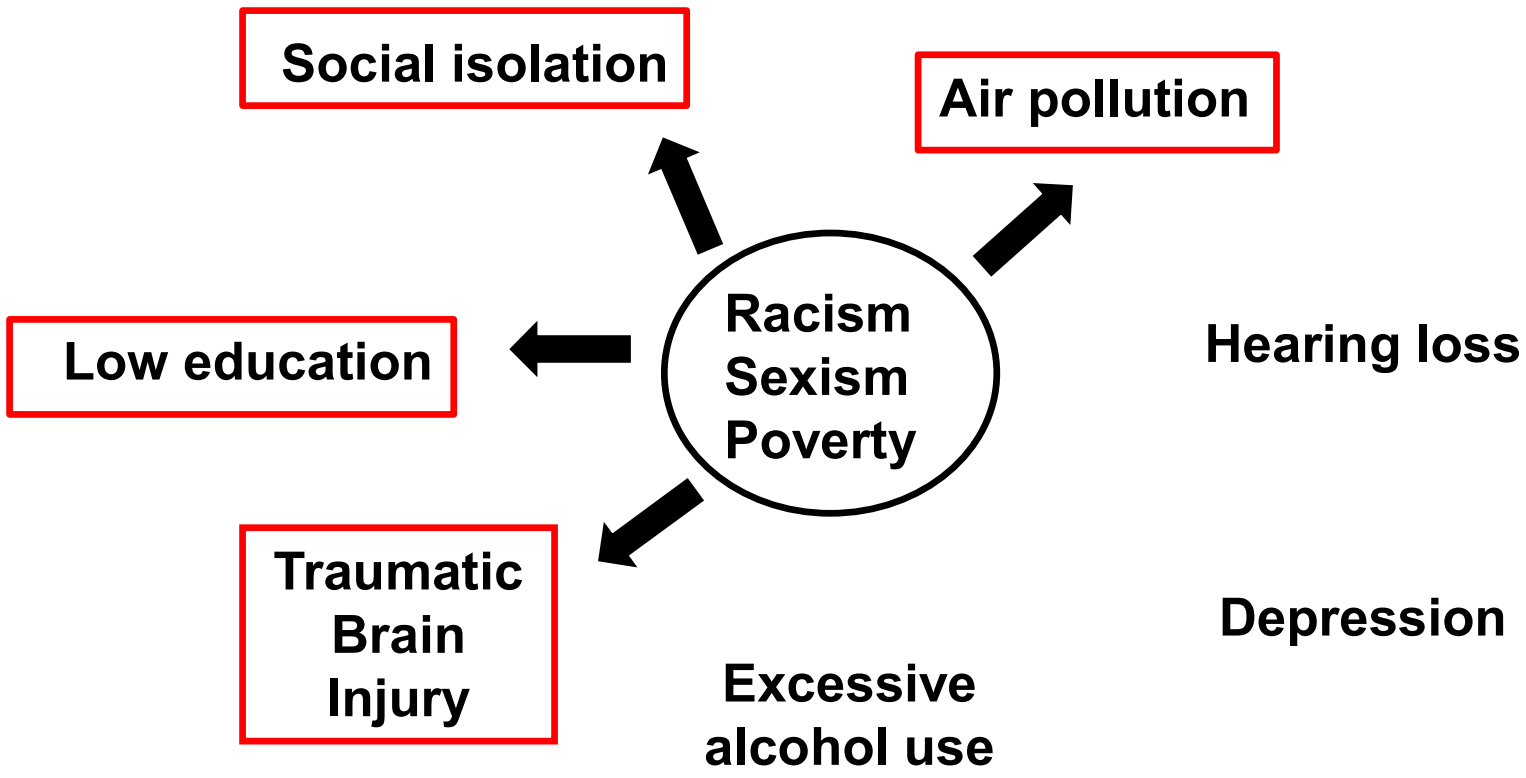
HR= 0.89 (95% CI: 0.85 to 0.95)





Sabia S, et al. BMJ 2019;366:l4414

Building and Maintaining Cognitive Reserve



Cognitive Reserve

- Educational attainment;
- Occupational complexity;
- Later-life engagement in cognitive-intellectual activities.

Association of Daily Intellectual Activities With Lower Risk of Incident Dementia Among Older Chinese Adults (N=15,582)

- Prospective study of community-dwelling older adults (≥65 y) living in China;
- Median follow-up time was 5 years;
- Late-life intellectual activities included reading books, newspapers, or magazines; playing board games, Mahjong, or card games; and betting on horse racing.

ATC Lee, et al. JAMA Psychiatry 2018

Estimated ORs for Incident Dementia After Excluding Participants Who Developed Incident Dementia Within 3 Years After Baseline (N=15,582)

Type of Leisure Activities	Model 1		Model 2[a]	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Intellectual	0.59 (0.50-0.68)	<.001	0.71 (0.60-0.84)	<.001
Social	1.00 (0.83-1.19)	.96	0.97 (0.81-1.17)	.78
Other recreational	1.50 (0.84-2.69)	.18	1.56 (0.86-2.81)	.14

[a] Adjusted for age, sex, educational level, cardiovascular risk factors, visual and hearing impairments, poor mobility, depression, smoking, adequate consumption of fruits and vegetables, regular physical exercise, and other types of leisure activities.

Education

Intellectual capacity gains due to education tend to plateau in late adolescence;

Reverse causation—those people with higher intellectual capacity tend to attain more education, achieve higher occupational status, and engage more in cognitive-intellectual activities.

Kremen WS, et al. PNAS. 2019;116:2021-2026

Vietnam Era Twin Study of Aging (VETSA) (N=1009 male veterans)

Table 3. Model 4: Predictors of late midlife (average age 62 y) cognitive function including age 20 y GCA and lifetime education (including only participants with exactly 12 y of education at the age 20 y GCA assessment)

Cognitive ability/domain	Childhood SES	Age 20 y GCA	Lifetime education	Occupational complexity	Engagement in cognitive activities	Physical activity	Health status
Age 62 GCA (n = 663)	−0.047; P = 0.148	**0.645; P = 2.1e-55**	0.021; P = 0.570	0.060; P = 0.054	0.079; P = 0.018	0.041; P = 0.189	**−0.092; P = 0.002**
Abstract reasoning (n = 662)	0.049; P = 0.222	**0.324; P = 9.2e-17**	0.021; P = 0.646	0.072; P = 0.050	0.087; P = 0.029	0.023; P = 0.544	**−0.114; P = 0.001**
Episodic memory (n = 663)	−0.007; P = 0.875	**0.269; P = 7.7e-12**	0.074; P = 0.101	0.062; P = 0.086	0.066; P = 0.095	0.014; P = 0.707	0.007; P = 0.832
Processing speed (n = 662)	0.015; P = 0.733	**0.173; P = 0.000020**	0.035; P = 0.462	**0.134; P = 0.00040**	**0.109; P = 0.009**	0.086; P = 0.028	−0.075; P = 0.044
Verbal fluency (n = 663)	−0.029; P = 0.522	0.096; P = 0.020	0.101; P = 0.034	0.063; P = 0.097	**0.132; P = 0.002**	0.061; P = 0.116	−0.005; P = 0.902
Visual-spatial ability (n = 658)	0.023; P = 0.570	**0.409; P = 6.8e-27**	0.092; P = 0.035	0.056; P = 0.104	0.077; P = 0.043	0.034; P = 0.341	−0.075; P = 0.024
Short-term/working memory (n = 663)	0.015; P = 0.743	**0.318; P = 1.2e-15**	0.095; P = 0.036	**0.095; P = 0.008**	0.023; P = 0.551	0.059; P = 0.110	−0.033; P = 0.348
Executive function (n = 664)	0.004; P = 0.918	**0.305; P = 1.4e-15**	0.084; P = 0.055	**0.131; P = 0.00013**	−0.005; P = 0.896	0.043; P = 0.226	−0.084; P = 0.014

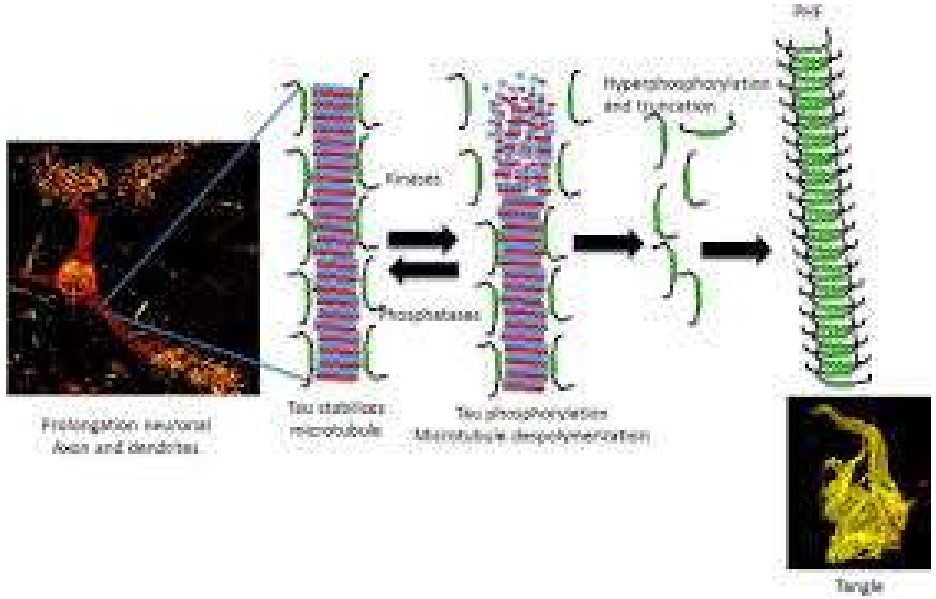
Engagement in cognitive activities, physical activity, and health status were assessed at average age 56 y. All outcomes were adjusted for age and race/ethnicity. Numbers in the table are β coefficients. Values in bold type are significant after correction for multiple testing. Sample sizes are 93–96% of the total number. Exact P values are shown to highlight differences in magnitude of effects. GCA, general cognitive ability; SES, socioeconomic status.

***GCA measured at age 20 and age 62 by the Armed Forces Qualification Test (AFQT)**

Kremen WS, et al. PNAS. 2019;116:2021-2026

Traumatic Brain Injury

- **Mild TBI**
  - Concussion
- **Severe TBI**
  - Skull fracture
  - Edema
  - Brain injury
  - Bleed



Hyperphosphorylated tau pathology

Relative risk of all-cause dementia associated with mid-life TBI

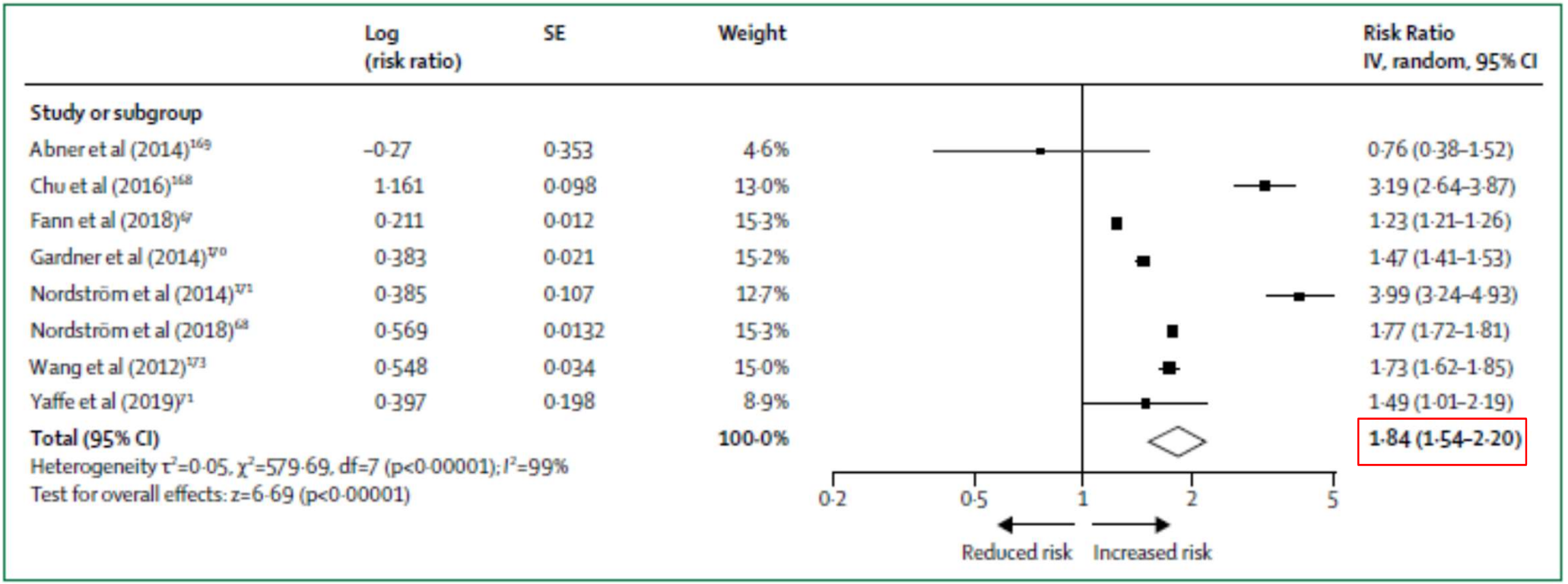


Figure 6: **Meta-analysis of relative risk of all-cause dementia associated with all severity midlife traumatic brain injury**

Lancet Commission, 2020

Table 2. Associations between TBI and the risk of dementia during follow-up in 491,252 Swedish citizens >50 years.

Period after the TBI	Individuals at risk	Diagnosed with dementia	Unadjusted		Adjusted*	
			Odds ratio	95% CI	Odds ratio	95% CI
Overall	491,252	21,963	1.90	1.85–1.96	1.81	1.75–1.86
1–364 days	491,252	2,784 (0.6%)	3.69	3.40–3.99	3.52	3.23–3.84
1–4.9 years	458,525	5,893 (1.3%)	2.37	2.24–2.51	2.24	2.11–2.38
5–9.9 years	362,201	4,234 (1.2%)	1.86	1.74–1.99	1.75	1.63–1.88
10–19.9 years	272,328	4,644 (1.7%)	1.58	1.48–1.68	1.48	1.39–1.58
20–29.9 years	161,526	2,916 (1.8%)	1.50	1.39–1.63	1.40	1.29–1.52
30 years or more	83,034	1,492 (1.8%)	1.28	1.15–1.44	1.25	1.11–1.41

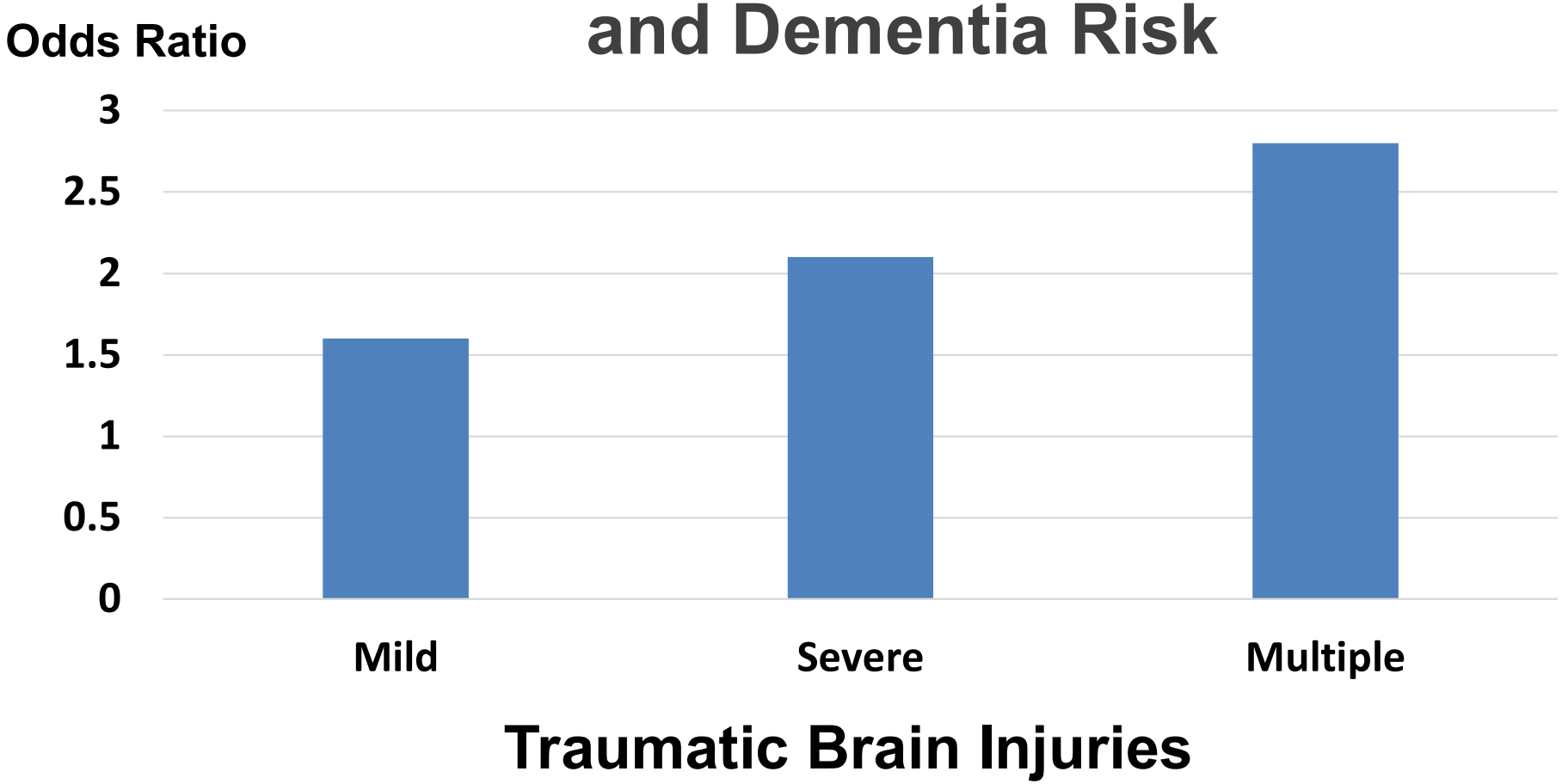
*Adjusted for age, civil status, education, early retirement pension, and diagnoses at baseline.

Abbreviations: CI, confidence interval; TBI, traumatic brain injury.

https://doi.org/10.1371/journal.pmed.1002496.t002

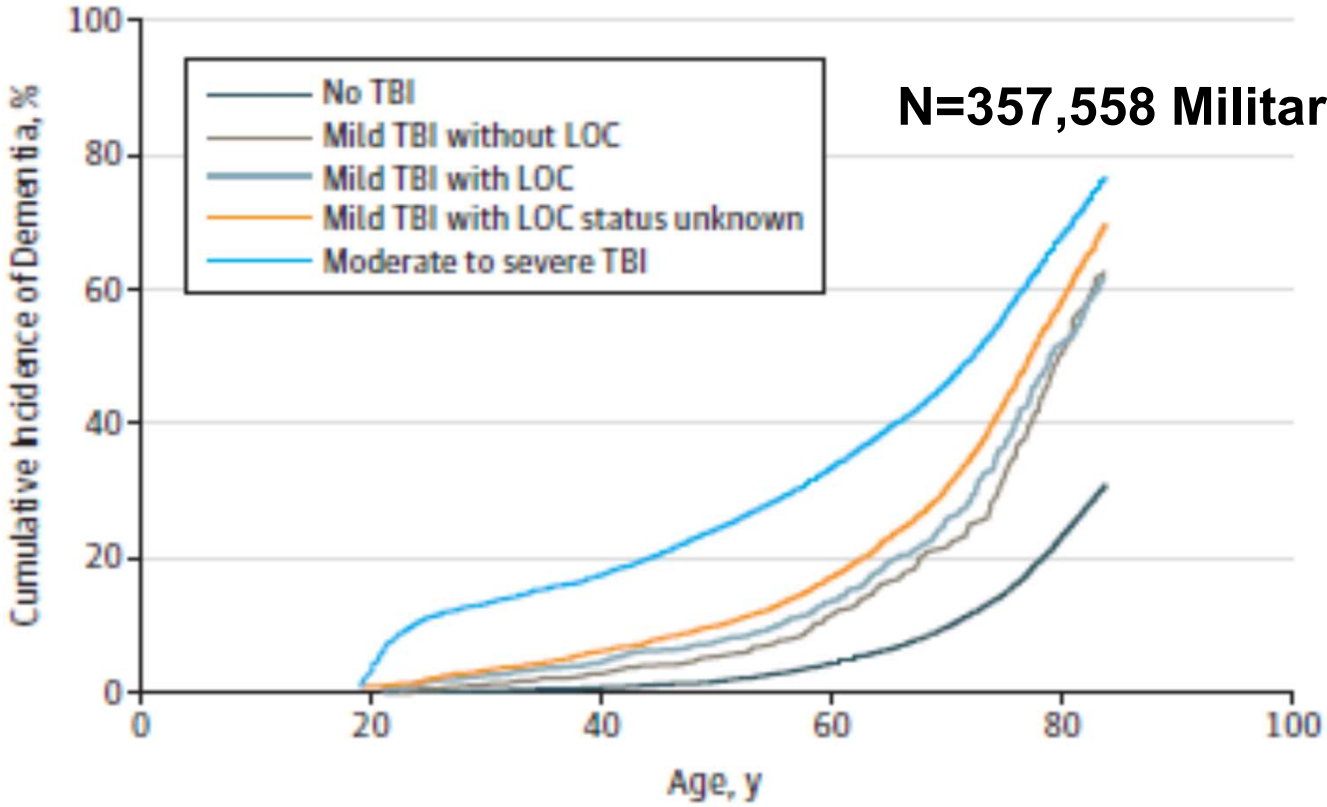
Nordström A, Nordström P (2018) Traumatic brain injury and the risk of dementia diagnosis: A nationwide cohort study. PLOS Medicine 15(1): e1002496. https://doi.org/10.1371/journal.pmed.1002496
https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002496

Dose Response Association between TBI and Dementia Risk



Nordström A, Nordström P (2018)

Figure. Cumulative Incidence of Dementia by Traumatic Brain Injury (TBI) Severity



N=357,558 Military Veterans

The unadjusted cumulative incidence of dementia (age at dementia diagnosis) is shown as a function of TBI severity. After adjustment for demographics, medical conditions, and psychiatric disorders, there was a dose-response relationship between TBI severity and dementia diagnosis with hazard ratios of 2.36 (95% CI, 2.10-2.66) for mild TBI without loss of consciousness (LOC); 2.51 (95% CI, 2.29-2.76) for mild TBI with LOC; 3.19 (95% CI, 3.05-3.33) for mild TBI with LOC status unknown, and 3.77 (95% CI, 3.63-3.91) for moderate to severe TBI.

Barns DE, et al. 2018

Air Pollution

Exposure to ambient air pollution and the incidence of dementia: A population-based cohort study*

Table 2
Hazard ratios (HR) and 95% confidence intervals (95% CI) for the associations of incident dementia with every interquartile-range (IQR) increase in exposure to $PM_{2.5}$ (IQR = 4.8 μg/m^3), NO_2 (IQR = 14.2 ppb), and O_3 (IQR = 6.3 ppb) in Ontario, during the follow-up period 2001–2013.

PAF=6.1%
wPAF=2.3%

Model*	$PM_{2.5}$		NO_2		O_3	
	HR	95% CI	HR	95% CI	HR	95% CI
Adjusted for age and sex, and stratified region	1.06	1.05–1.07	1.14	1.12–1.16	0.97	0.94–0.98
Neighborhood-level income, education, unemployment rate, and immigrants†	1.04	1.03–1.05	1.11	1.09–1.13	0.98	0.96–0.99
Urban residency and a North/South indicator	1.04	1.03–1.05	1.11	1.09–1.13	0.98	0.96–1.00
Preexisting brain injury, stroke, diabetes, hypertension, coronary heart disease, heart failure, and arrhythmia‡	1.04	1.03–1.05	1.10	1.08–1.12	0.98	0.96–1.00
Indirectly adjusted for smoking, physical activity, obesity, and education	1.03	1.02–1.04	1.10	1.08–1.12	0.98	0.96–1.00

*A 12-y prospective study of over 2 million Canadian-born adults 55-85 y

Chen H, et al. Environment International. 2017

Burden of Dementia-Specific Mortality Associated With $PM_{2.5}$ Air Pollution in the United States

	PAF	Total Deaths	Rate/100,000	Age-standardized Rate/100,000
Dementia Mortality	8.2 (6.0-13.1)	19,852	6.1	5.1

- A cohort of 4,522,160 US veterans followed up between 2006 and 2016.
- ***The burden was particularly high in African Americans and those living in low socioeconomic communities.***

Bowe B, et al. JAMA Network Open, 2019

Air Pollution and Dementia: a Systematic Review

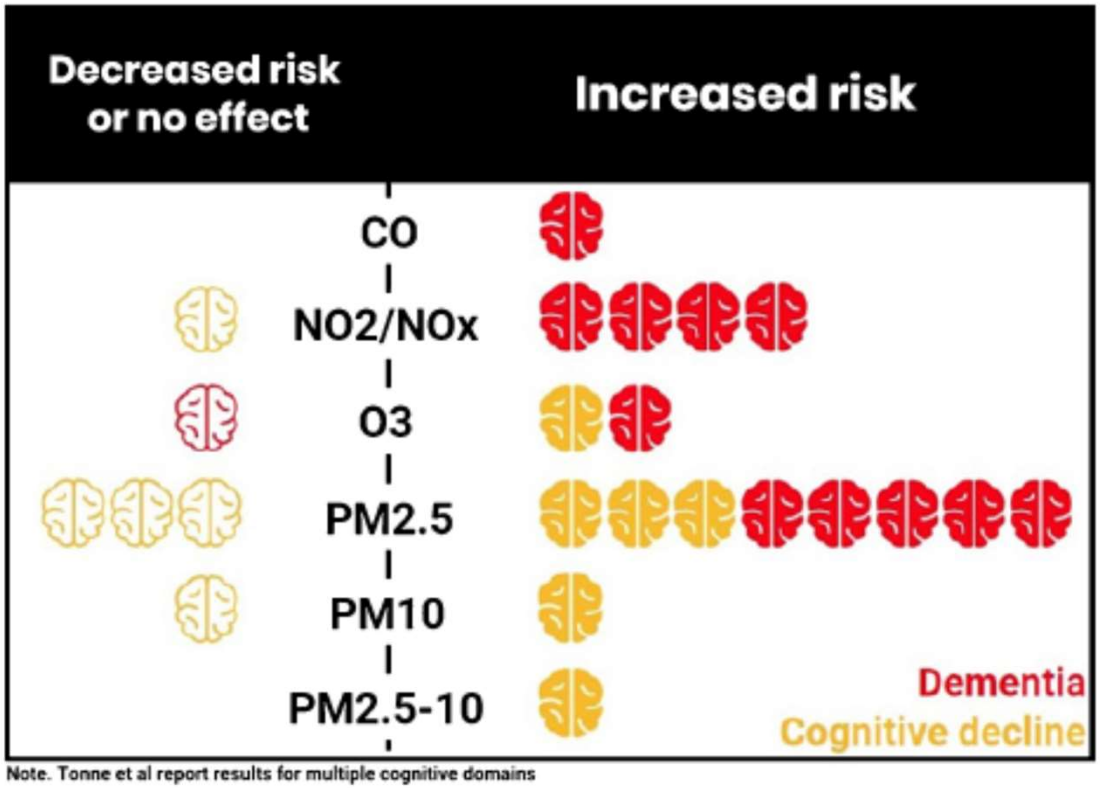
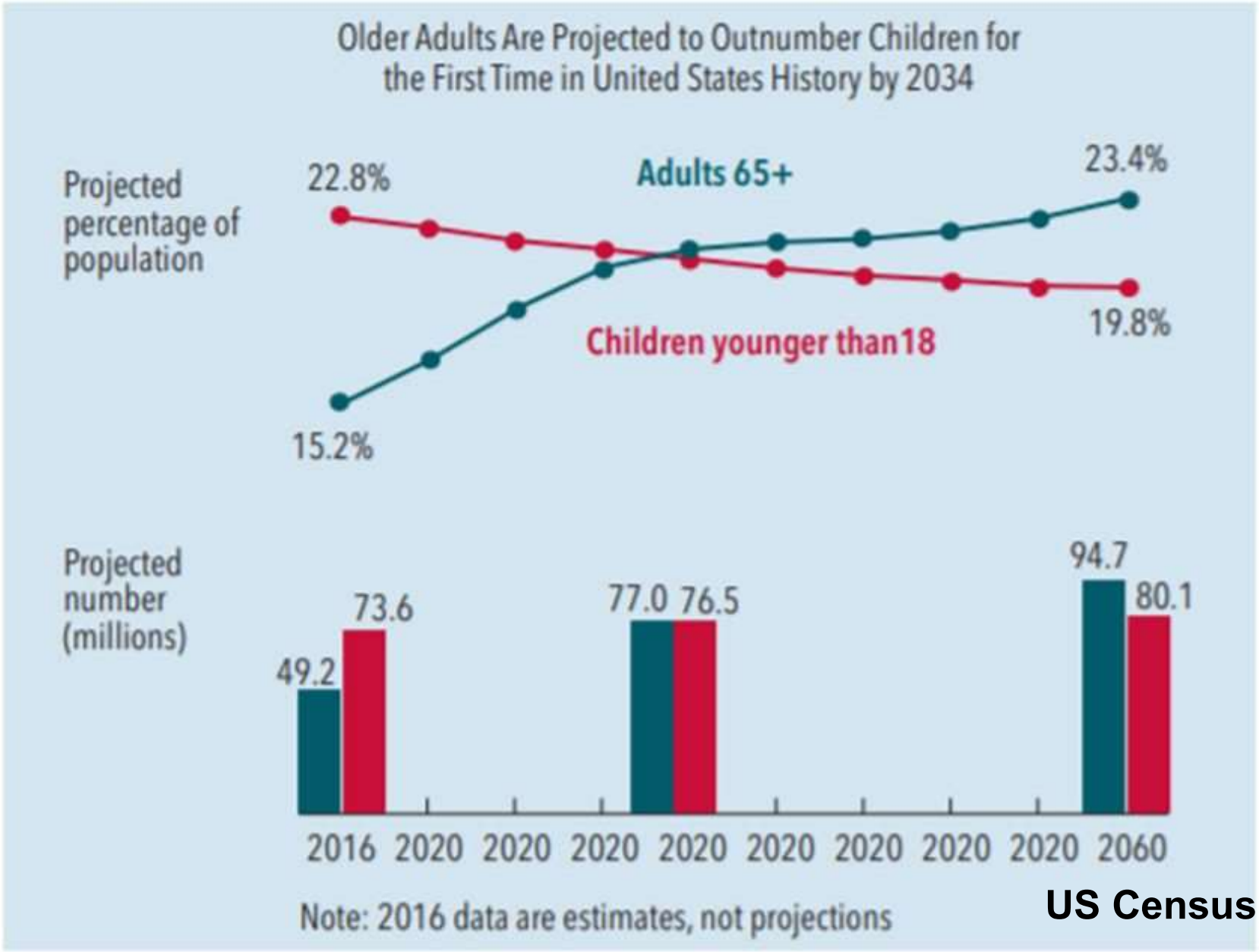


Fig. 2. Number of studies investigating relationship between exposure to pollutants and cognitive function or dementia.

Peters R. et al., J Alzheimer's Disease. 2019

FIGURE 1. An Aging Nation: Projected Number of Children and Older Adults



US Census, 2018

Social Isolation

- 25% of older adults live alone;
- 20% of older adults report feeling lonely;
- Social isolation among older people is associated with an extra $6.7 billion in Medicare spending per year

Meals on Wheels America, 2020

Influence of social relationship domains and their combinations on incident dementia: a prospective cohort study (N=13,984)*

Table 2 Cox proportional hazards model estimating the association between social relationship variables and incident dementia

Variables	Categories	Model 1*	Model 2†	Model 3‡
	(n, %)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Married	Yes (10 232, 73.2)	0.50 (0.46 to 0.54)	0.85 (0.76 to 0.94)	0.88 (0.79 to 0.99)
Contact (relatives)	Yes (12 990, 92.9)	0.74 (0.64 to 0.87)	0.85 (0.73 to 1.00)	0.89 (0.76 to 1.05)
Contact (friends)	Yes (12 291, 87.9)	0.55 (0.49 to 0.62)	0.78 (0.69 to 0.88)	0.83 (0.73 to 0.94)
Group participation	Yes (8671, 62.0)	0.61 (0.56 to 0.67)	0.85 (0.77 to 0.94)	0.89 (0.80 to 0.98)
Work engagement	Yes (3480, 24.9)	0.52 (0.47 to 0.59)	0.85 (0.76 to 0.97)	0.88 (0.77 to 0.99)
Support (family)	Yes (11 507, 82.3)	0.68 (0.62 to 0.75)	0.84 (0.76 to 0.94)	0.88 (0.79 to 0.99)
Support (relatives)	Yes (7372, 52.7)	0.92 (0.84 to 1.00)	1.02 (0.93 to 1.11)	1.03 (0.95 to 1.13)
Support (friends)	Yes (6121, 43.8)	0.75 (0.69 to 0.82)	0.96 (0.87 to 1.05)	0.98 (0.89 to 1.08)

*Unadjusted model.
†Association with each social variable and incident dementia is estimated. All covariates (age, gender, education, household income, Geriatric Depression Scale, subjective cognitive complaints, instrumental activities of daily living, stroke, diabetes, daily walking time and hobbies) are adjusted.
‡All social variables are simultaneously entered into the model with all covariates.

*13,984 community-dwelling Japanese older adults followed for 9.4 years.

Saito T, et al. J Epidemiol Community Health, 2018

Influence of social relationship domains and their combinations on incident dementia: a prospective cohort study (N=13,984)

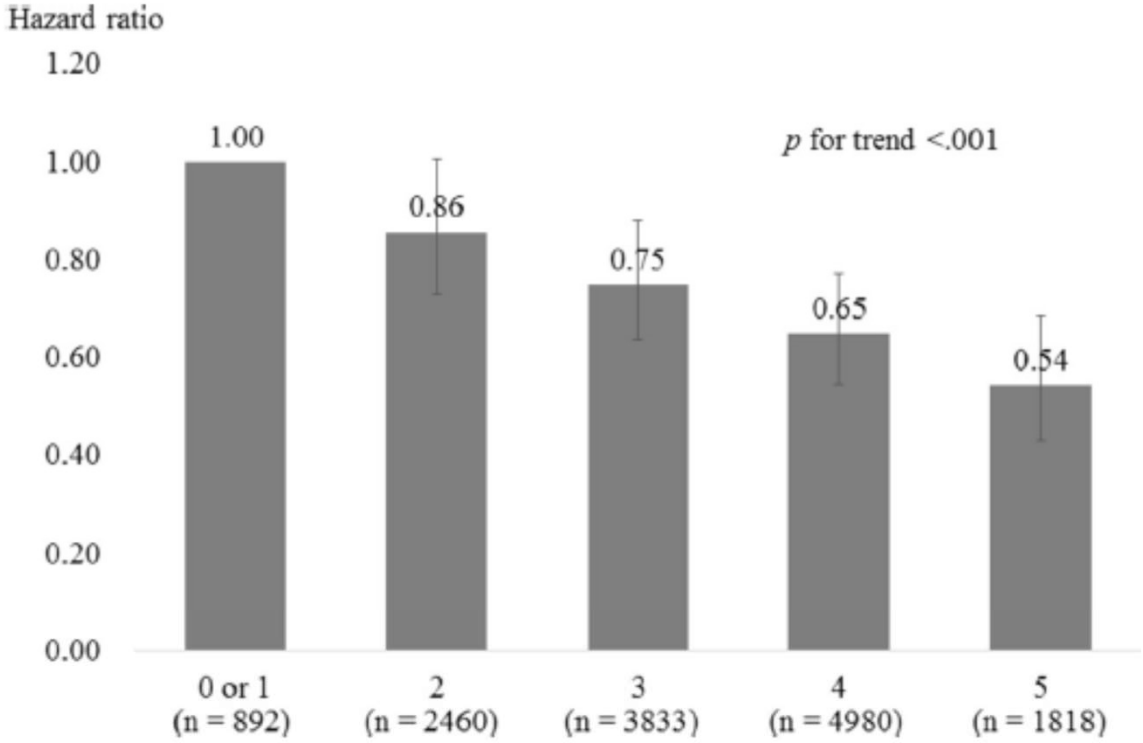


Figure 1 Hazard risks for incident dementia by diverse social relationship engagement score. The scores are calculated by adding the number of selected social relationship variables in which respondents engaged. The five social relationship variables are selected according to model 3: married, contact with friends, group participation, work engagement and social support exchanges with family. All covariates (age, gender, education, household income, Geriatric Depression Scale, subjective cognitive complaints, instrumental activities of daily living, stroke, diabetes, daily walking time and hobbies) are adjusted.

Saito T, et al., 2018

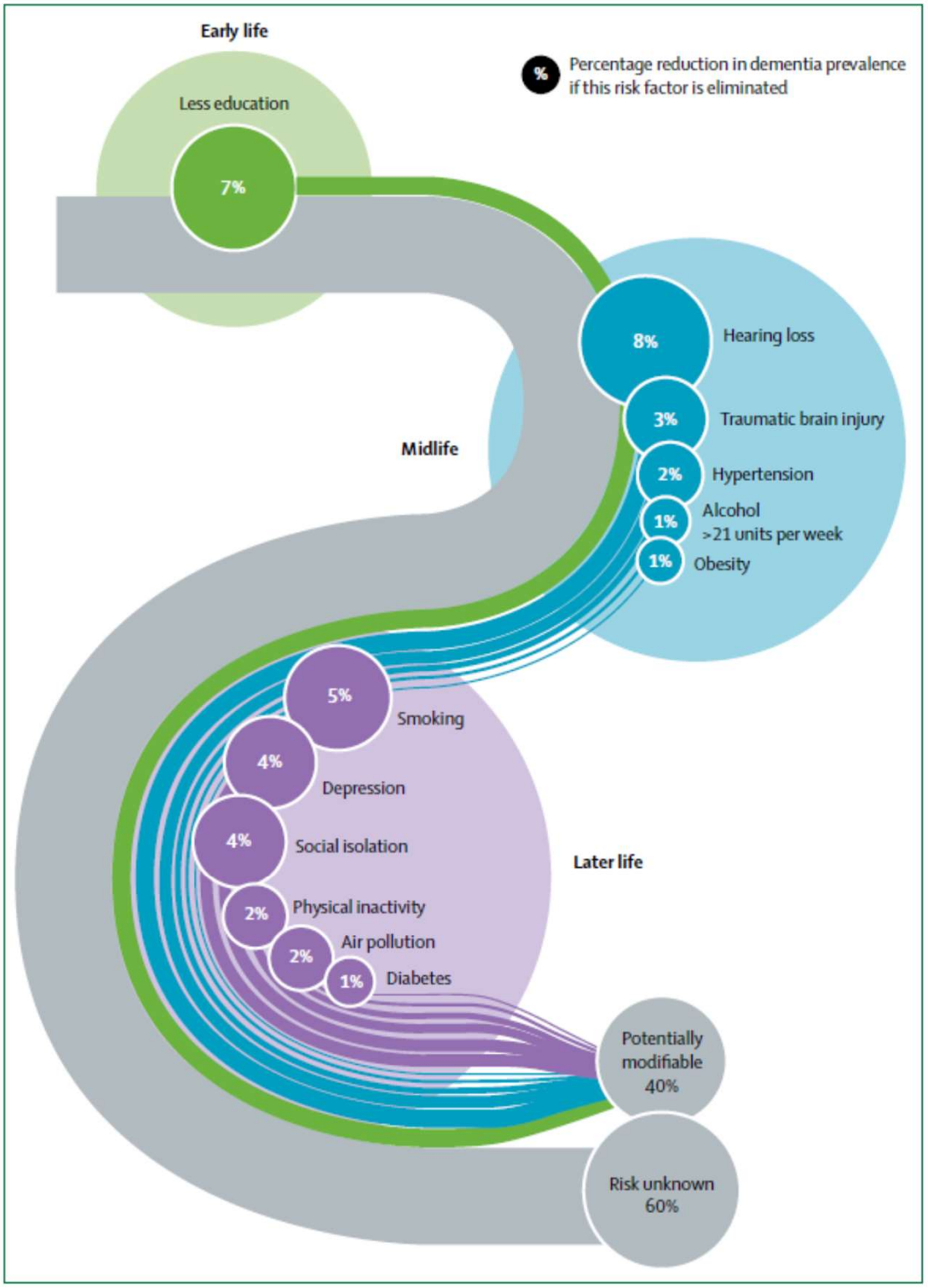


Figure 7: Population attributable fraction of potentially modifiable risk factors for dementia

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Preventive strategies targeted toward the individual

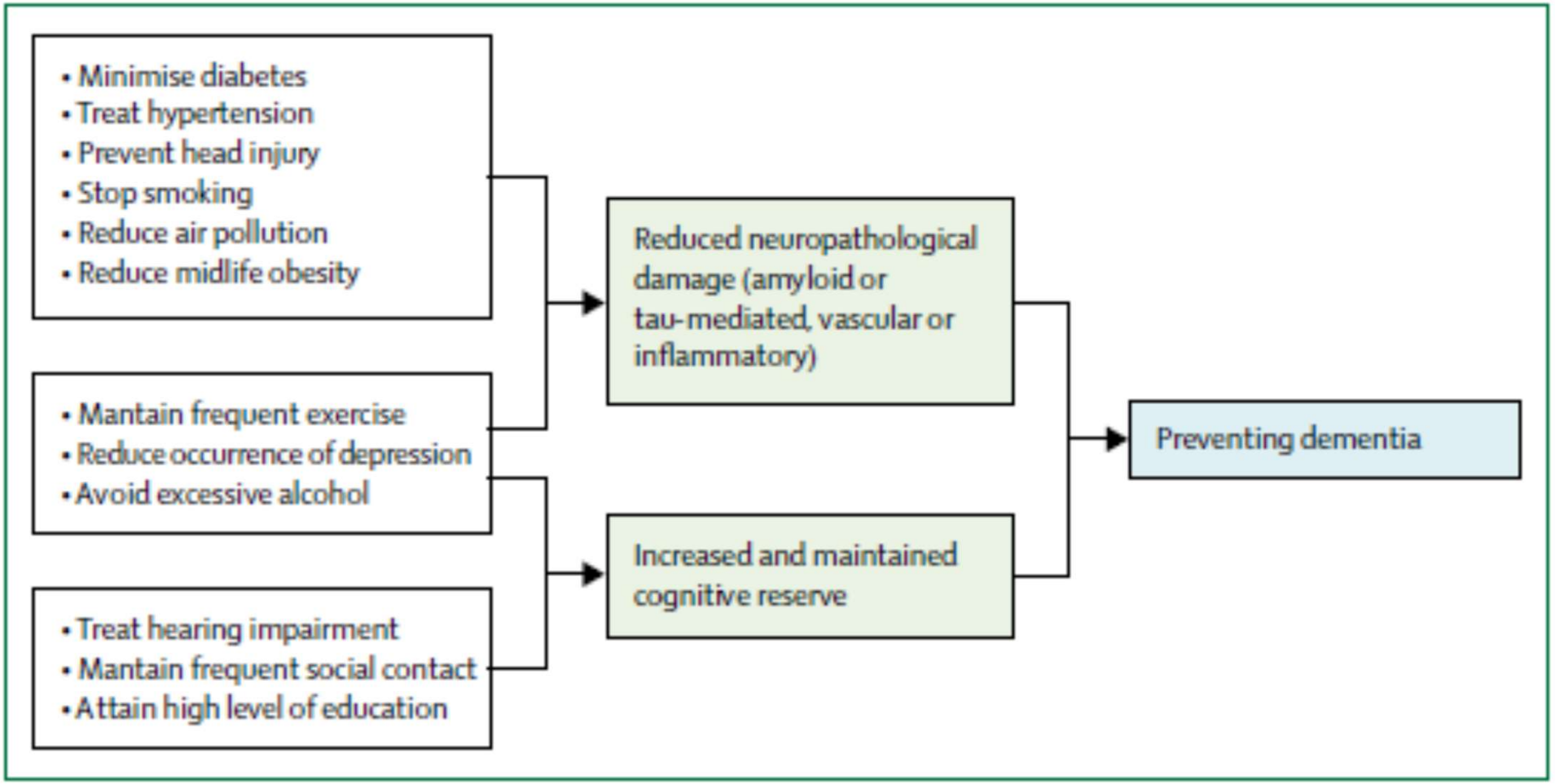

Figure 2: **Possible brain mechanisms for enhancing or maintaining cognitive reserve and risk reduction of potentially modifiable risk factors in dementia**

Lancet Commission, 2020

Policy, Systems, Environment (PSE) Approach

- Working at a more foundational level to address causes and improve environments where we live, work, learn, play, and receive health care, we can prevent many people from becoming chronically ill

- Can help public health advocates create sustainable, comprehensive measures to improve public health

Policy	Systems	Environment
Written statement of organizational position, decision or course of action. (such as ordinances, resolutions, mandates, guidelines, or rules)	Changes in organizational procedures (such as personnel, resource allocation, programs)	Physical, observable changes in the built, economic, and/or social environment.

PSE Priorities

- Prioritize education across the life-span;
- Create healthy food and built environments;
- Create stricter laws to reduce sport-, occupational-, and transportation-related TBIs;
- Create stricter air pollution regulations –especially in low-income neighborhoods;
- Create stricter occupational and environmental noise pollution regulations;
- Strengthen national efforts to reduce exposure to SHS – especially among children;
- Create more Age-Friendly environments


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