

# Dementia prevention - what are the risks and does intervention help?



THE LANCET

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"It is never too early and never too late in the life course for dementia prevention."

See The Lancet Commission, page 413

Dementia prevention, intervention, and care: 2020 report of the Lancet Commission *The Lancet* 396 (10248), 413-446 doi.org/10.1016/S0140-6736(20)30367-6

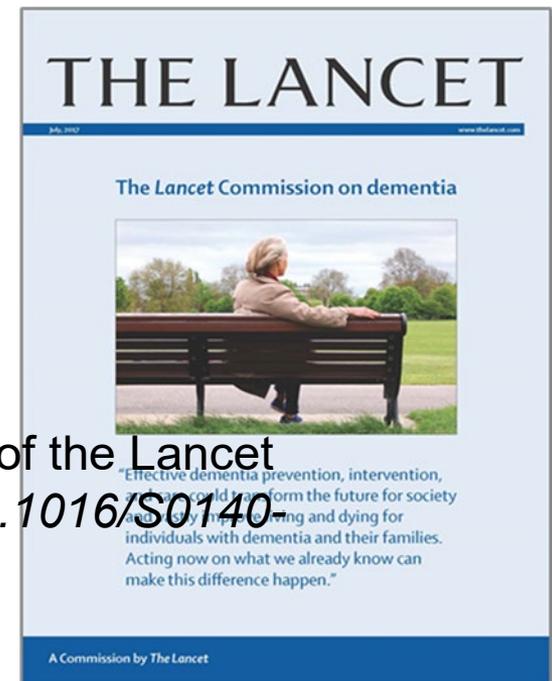
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Dementia prevention, intervention and care. Lancet 2017

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## What I will talk about

- Why consider dementia preventable
- Dementia risks
  - What are they
  - Worldwide
  - Between countries
  - within countries
- What should we do?

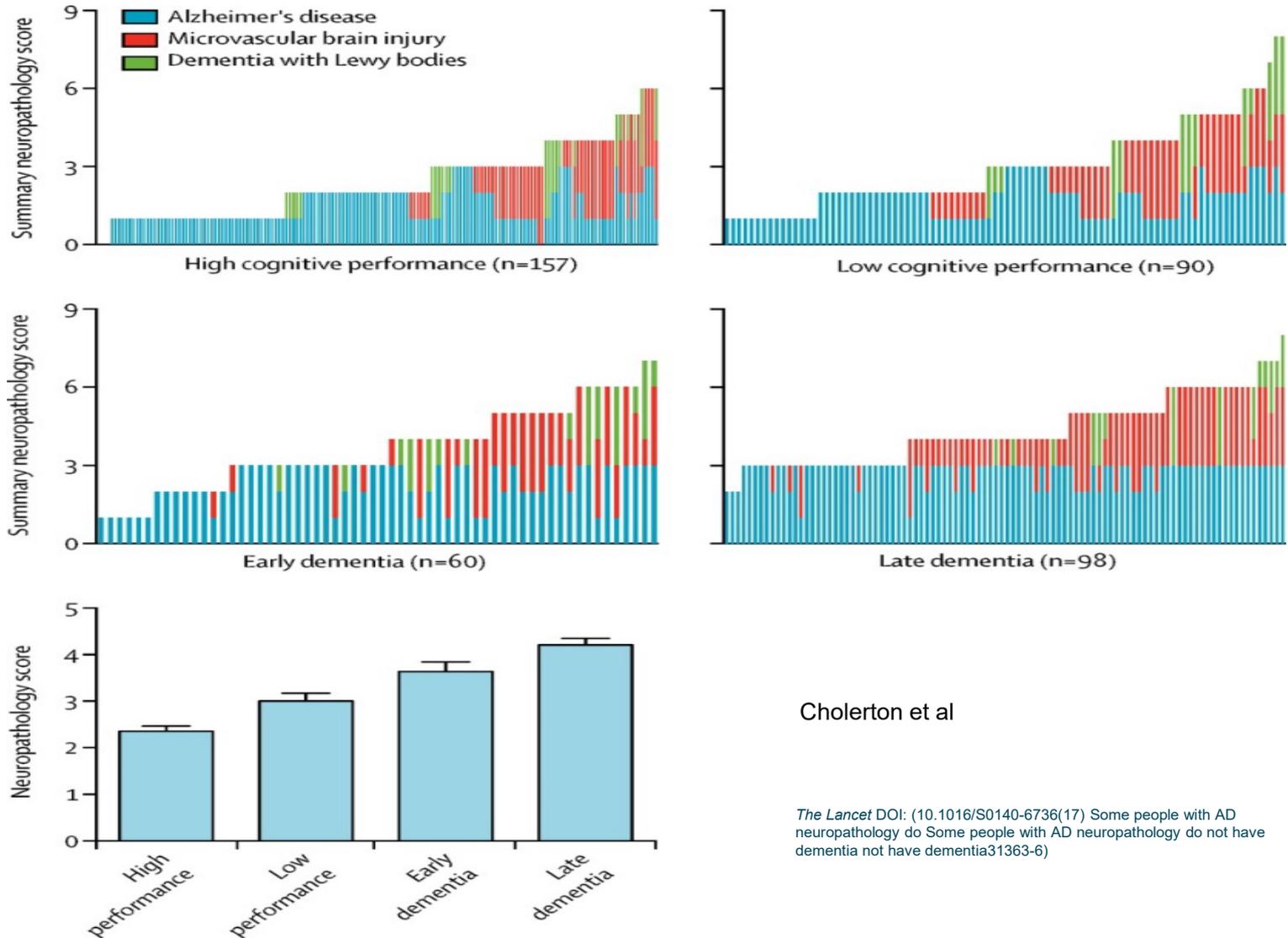
## Why consider dementia preventable

↑dementia as ↑ older people – 50 →132 million by 2050. Particularly in LMIC

- 25% incidence decrease in past 20 years; US and Europe
- Stable or increased in some countries -Japan, South Korea, Hong Kong, Brazil, India and Taiwan
  - So dementia potentially not inevitably preventable
- Mechanisms thought to be
  - Cognitive reserve
  - Reduction in damage
- Improvements
  - higher income, more educated people within HIC.
  - Men > woman (24 vs 8%)



# Some people with neuropathology do not have dementia – cognitive reserve



Cholerton et al

*The Lancet* DOI: (10.1016/S0140-6736(17) 31363-6) Some people with AD neuropathology do not have dementia

# Life course analysis

## – Lancet commissions

- When in life course?
- Defined mid life as age 45-65, Later life as >65



## – 2017

- 9 individual risk factors from NICE/ NIH in First analysis to include social isolation and hearing

## – 2020

- Added 3 with consistent, biologically plausible evidence
- TBI, pollution, alcohol,

## – 2024-

# Risk factors considered

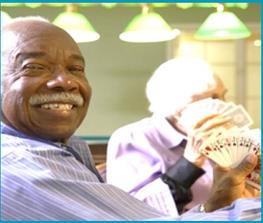
- 9 individual risk factors from NICE and NIH in 2017

## **Added 2020**

- Traumatic Brain Injury
- Pollution
- Alcohol

## **Not added**

- Sleep increased or decreased.
- Diet – no particular element, inconsistent



# Twelve risk factors

## Early life

- Less education



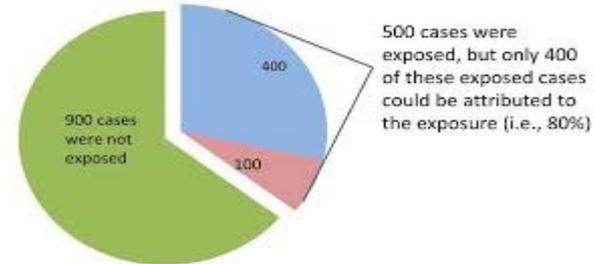
## Mid life (45-65)

- Peripheral hearing loss
- Hypertension
- Obesity
- Traumatic Brain Injury
- Excessive alcohol

## Late life (>65)

- Smoking
- Depression
- Physical inactivity
- Air Pollution
- Social isolation
- Diabetes

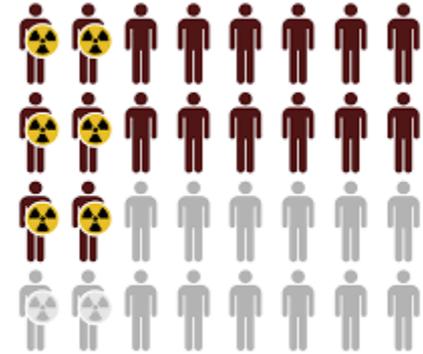
# PAF calculation



- Population Attributable Fraction
- Fraction theoretically prevented by eliminating risk factor
- $PAF = \text{Relative Risk (meta-analysis)} \times \text{Prevalence of risk factor}$
- Used all-cause dementia
- International data
- Twelve risks
- We know there are others

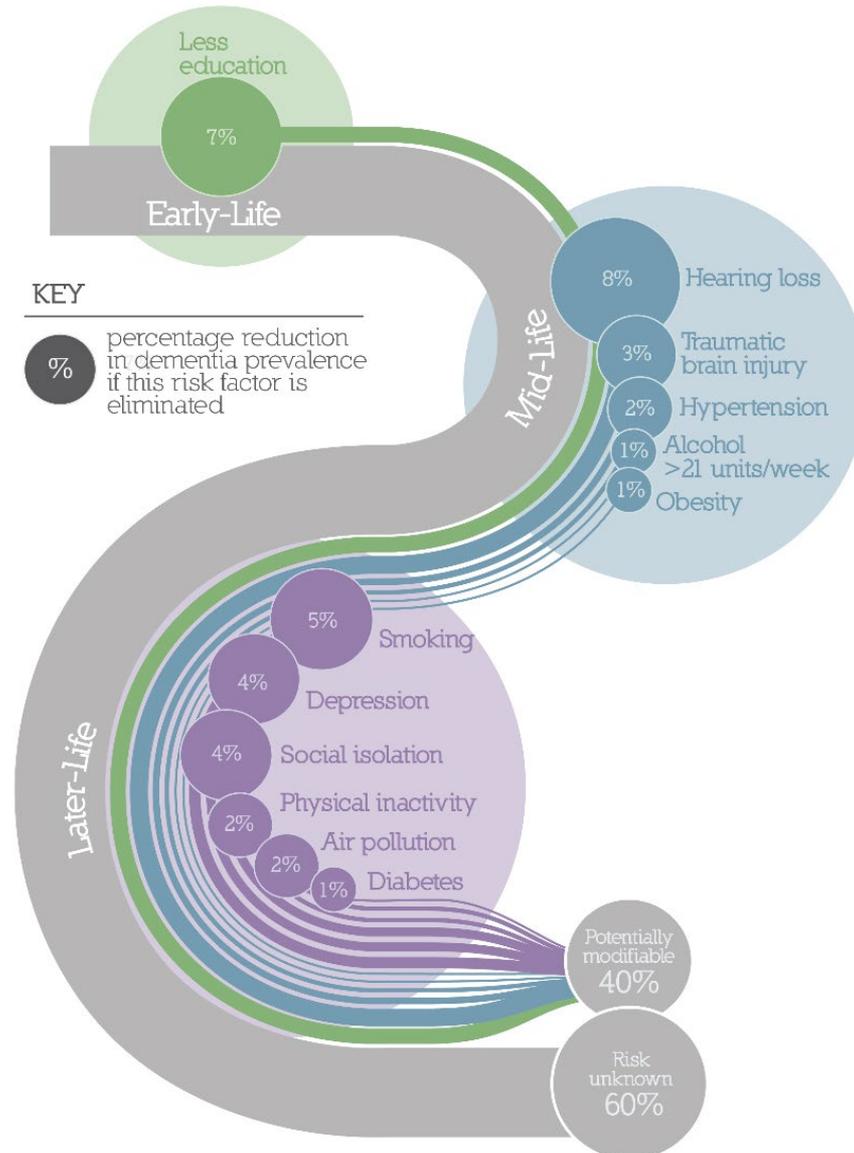
# Communality –people not lab rats

People tend to have clusters of risk factors



- Input data on all risk factors
- Calculate tetrachoric correlation to generate correlation matrix
- Conduct principal-component analysis on the matrix to generate eigenvectors (directions mapped onto the datapoints from which variance to the data is measured)
- unobserved factors underlying the variables that explain the variance
- Retain components with eigenvalues  $\geq 1$  in model
- Communality is the sum of the square of all factor loadings (how much each unobserved component explained each measured variable)
- Weighting (1-communality)
- Individual risk factor PAF =  $P_e (RRe-1) / [1 + P_e (RRe-1)]$

# Population Attributable Fraction- 40%

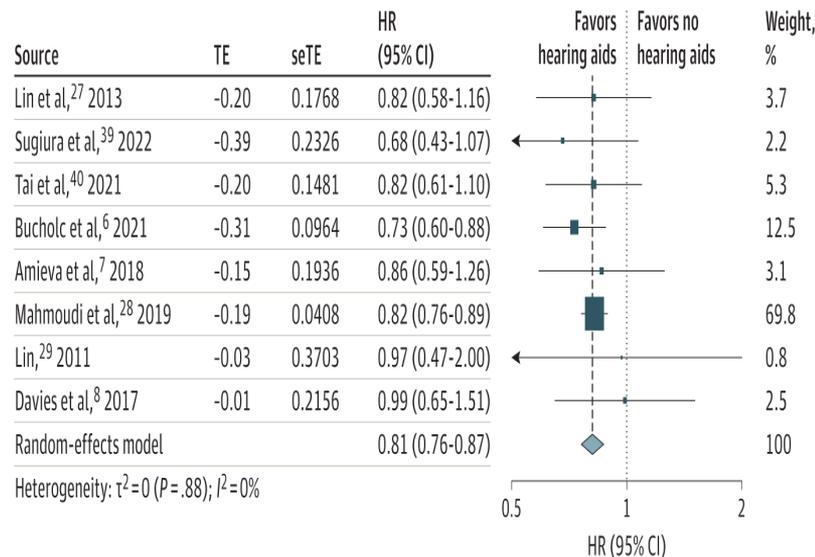


	Relative risk for dementia (95% CI)	Risk factor prevalence	Communality	Unweighted PAF	Weighted PAF*
<b>Early life (&lt;45 years)</b>					
Less education	1.6 (1.3–2.0)	40.0%	61.2%	19.4%	7.1%
<b>Midlife (age 45–65 years)</b>					
Hearing loss	1.9 (1.4–2.7)	31.7%	45.6%	22.2%	8.2%
Traumatic brain injury	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%
<b>Later life (age &gt;65 years)</b>					
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)	17.7%	55.2%	9.6%	3.5%
Physical inactivity	1.4 (1.2–1.7)	11.0%	28.1%	4.2%	1.6%

# Hearing loss

- Hearing loss → ↑ RR future dementia
- Meta-analysis of hearing aids vs not wearing HA
  - 8 cohort studies, 126,903 participants, FU 2-25 years,
  - HA 19% lower risk of cognitive decline
  - and a 17% lower risk of dementia
  - $I^2 = 0\%$

- Yeo et al Jama Neurol 2022





# Hearing aids

- **ACHIEVE study - RCT** of hearing aids recruited healthy volunteers from advertisements (N=739), or older adults from the Atherosclerosis Risk in Communities (ARIC, N=238) study.
- Substantial effects in ARIC -older, 48% less deterioration - 2.8 years older, lower baseline cognition, smoked more, less education, more often lived alone, more diabetes and hypertension). Healthy volunteers did not deteriorate.
  - Lim et al 2023
- UK Biobank (n=437,554) found no increased dementia risks if HI using hearing aids vs normal hearing.
  - Sensitivity analysis restricted to dementia >10 years later found
  - no evidence for reverse causation
  - no difference in mitigation according to
    - cardiovascular disease, APOEε4 alleles, income level, education.

Jiang et al TLPH 2023
- MCI – hearing loss 2 years to dementia, using HA 4 years.

# Education and cognitive stimulation

- Education important for cognitive reserve.
- Education till age 20 is additionally protective

- People with cognitively stimulating vs non-stimulating jobs ~20% ↓dementia risk.
- Cognitive stimulation at work associated with ↓proteins that inhibit central nervous system axonogenesis & synaptogenesis
- Lower levels of these proteins also associated with lower dementia risk.

- Kivimaki et al 2021 BMJ

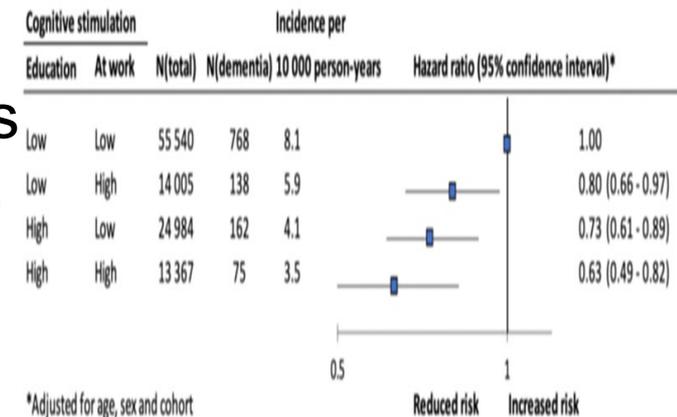


Figure 4. Association of lifecourse cognitive stimulation with incident dementia (a post hoc analysis)

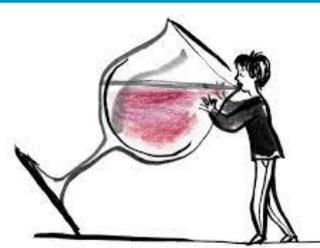
- Some evidence that retirement may increase deterioration even allowing for ill health

## Social contact

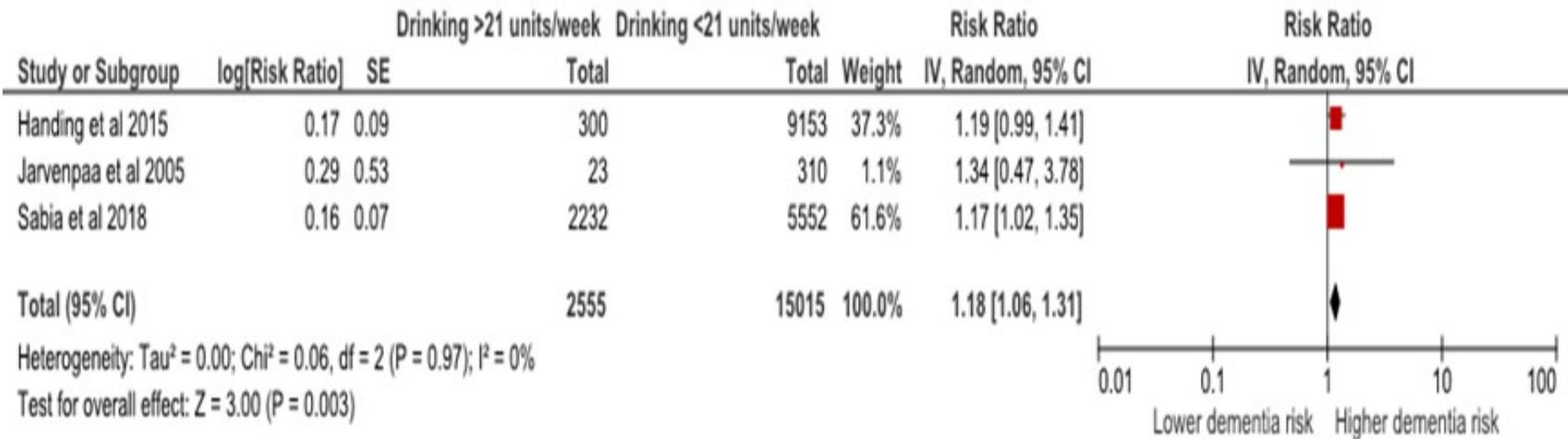


- PAF similar to HBP and inactivity.
  - ↑cognitive reserve and ↑ beneficial behaviours
- Dementia risk compared with married- 812000 people
  - ↑lifelong single (RR 1.4; 1.1-1.9), ↑Widow/ers (RR 1.2; 1.0-1.4)
- 28-year follow-up of 10,308 people
- ↑ social contacts age 60 years → ↓dementia risk (& 50 & 40)
  - (adjusted HR one SD social contact frequency 0.9 (0.79, 0.98),  $p=0.02$ ),
- High social contact (102K) associated with better late-life cognitive function ( $r=0.05$ , 95% CI: 0.04–0.065)
- Studies >10 years good social engagement ↓dementia ( $n=8876$ , RR=0.9, 95% CI 0.8–1.0).
  - [Penninkilampi et al 2018](#), [Evans et al 2019](#), [Sommerlad et al 2018](#).19

# Excessive alcohol



- Heavy drinking effects the brain
- Non-linear effect: ↑dementia risk drinking **>21 units/week alcohol** (14 drinks) vs <14 New meta-analysis Relative Risk 1.18





## Reduction in Alcohol consumption

South Korean cohort of 3,933,382 participants serially assessed for alcohol consumption over 3 years.

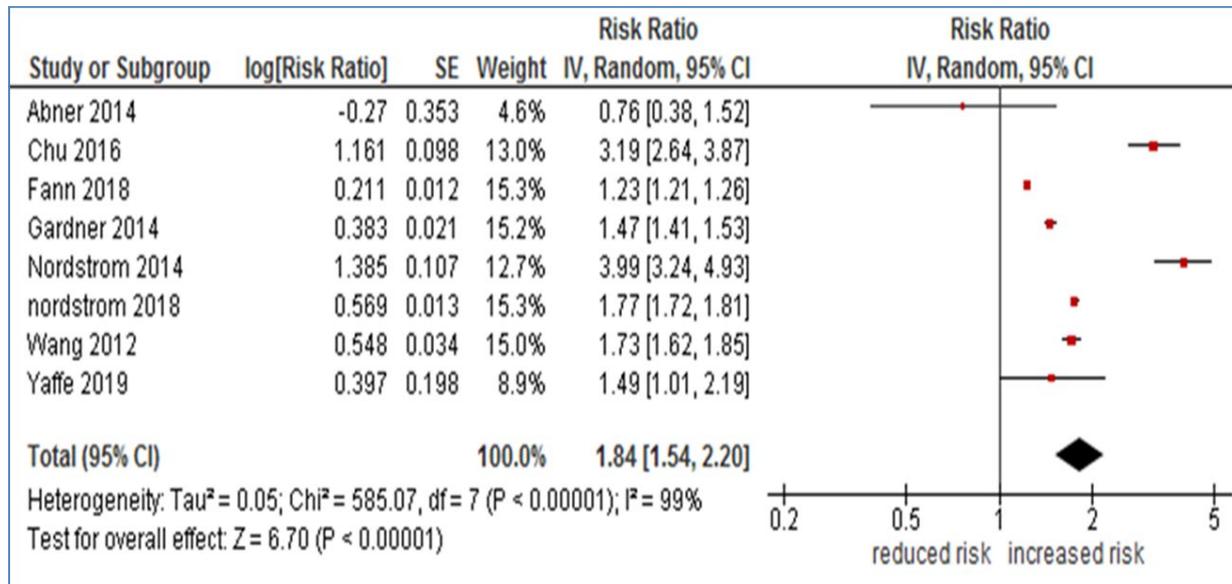
Sustained heavy drinkers (>3units/day) had an increased risk of all-cause dementia (HR 1.08, 1.03-1.1).

Reducing drinking from heavy to moderate levels (<21 units) reduced the risk of all cause dementia HR 0.92 (0.86-0.99).



# Traumatic Brain Injury

- TBI -car, motorcycle, bike injuries; military incidents, recreational sports, firearms & falls
- Risk ↑↑most in first 6 months but↑ over 30 years.
- Risk ↑with severity and number of TBI
- New meta-analysis. **TBI & all dementia RR 1.84**





# Air pollution

- 13 heterogeneous cohorts with 1-15 years follow-up of air pollutants exposure and incident dementia.
- All found  $PM_{2.5}$ ,  $NO_2$  and CO  $\uparrow$  dementia risk
- Data from Canada- only study of all-cause air pollution/ all cause dementia N=2,066,639; baseline mean age =67
- Canada pollutant concentrations among world lowest
- We calculated RR of dementia for those in the 3 highest quartiles compared to 4th = **1.09;1.07-1.11**
- Meta-analysis of 20 studies; n= 91,391,296,  $\uparrow$  dementia risk of 3% per  $1 \mu g/m^3 \uparrow$  in  $PM_{2.5}$  (HR, 1.03; 1.02–1.05].
  - Abolhasani et al 2023
- UK residential wood and coal burning stoves produce 38% of the country's  $PM_{2.5}$  emissions are reported to originate
  - Chakraborty et al 2020

# The effects of changing air pollution



- Chinese longitudinal survey - Clean Air Act implementation mitigates cognitive decline (MMSE 2.45 points/4 years)
  - Yao Yao et al 2022. TLHL
- French cohort study with 12-years' follow-up reported  $\downarrow$ PM<sub>2.5</sub> between 1990-2000 was associated with a  $\downarrow$ risk of dementia (HR 0.85; 0.76 -0.95 for median PM<sub>2.5</sub>  $\downarrow$  12.2  $\mu$ g/m<sup>3</sup>)
  - Letellier et al 2022
- Older US women living in an area with improved air quality (PM<sub>2.5</sub> and NO<sub>2</sub> reduced over ten years) had  $\downarrow$  risk of dementia
  - Wang et al 2022
- A north-south differences in China's central heating policies led to differences in air pollution concentrations;  $\uparrow$  air pollution (PM<sub>10</sub>, NO<sub>2</sub>, SO<sub>2</sub>, CO, O<sub>3</sub>) was associated with a  $\uparrow$  42.4% dementia risk
  - Xie et al 2022



# Hypertension

- Persistent mid-life hypertension increases risk of late life dementia (18-year FU HR 1.6)
- Falling BP without intervention in later life may be caused by dementia development (HR 2.4).
- SPRINT MIND aimed to decrease systolic BP to <120 (control 140)
- Five years later ↓MCI HR = 0.8), combined MCI or dementia (HR, 0.9)

– JAMA. 2019;321(6):553-561

# Hypertension



- Individual participant data from 5 placebo controlled RCTs (n=28,008) - ↓risk of dementia in treatment group (OR 0.87, 0.75-0.99)
  - Peters et al *Eur Heart* 2022
- Meta-analysis of 14 RCTs (n=96,158) mean follow up of 4.1 years found ↓risk of dementia compared with controls (7.0% vs 7.5%, OR 0.93 (0.88-0.98,  $I^2=0\%$ )
  - Hughes et al *Jama*, 2020
- Cochrane review did not find a difference but thought evidence was low standard as some FU were a year (OR 0.89, 0.72 -1.09)
  - Cunningham et al 2021



## Smoking

- Smoking
  - leads to cardiovascular pathology,
  - Cigarette smoke contains neurotoxins
- High prevalence contributes to the high PAF.
- Interventions to reduce cigarette smoking, which is declining in most countries;
- However, smoking increasing in China, Middle East, south Asia and Africa

# The effect of stopping smoking



- A 32-year follow-up of the Whitehall 2 cohort, controlling for SES, found that smokers (HR 1.36, 1.10-1.68) but not ex-smokers (HR 0.95, 0.79-1.14) have an increased  $\uparrow$  dementia risk compared to never smokers
  - Raggi et al 2022
- Social inequalities in dementia risk was partially mediated by smoking
  - Korean nationwide population cohort study of 789 532 participants who were assessed for smoking status over 2 years reported that smoking quitters had a lower risk of all cause dementia HR 0.92 (0.87-0.97) compared with continuing smokers
    - Jeong et 2023

## Changing risk factors -does it change outcomes ?

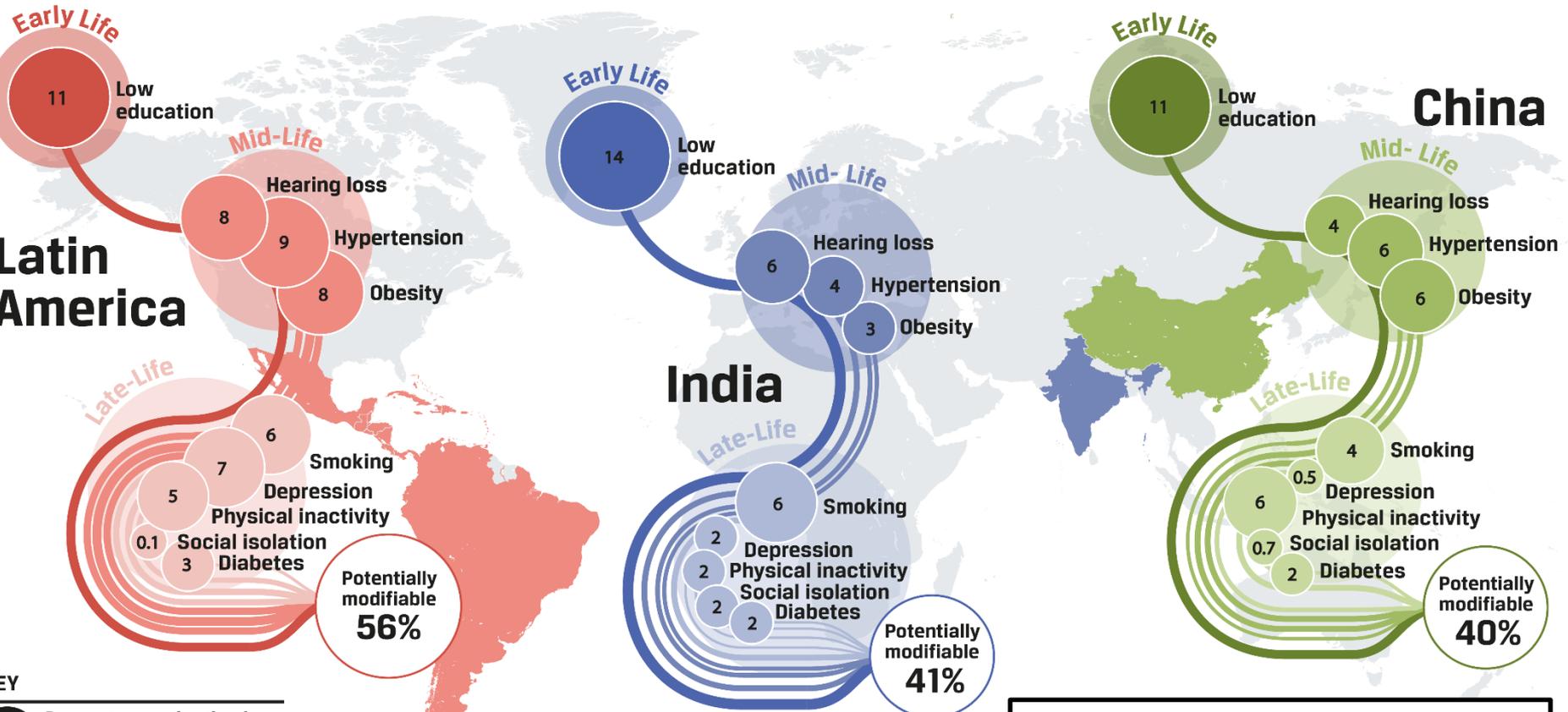
- Use of hearing aids decreases risk
- When air pollution reduces – cognition better than in comparator areas
- When hypertension treated then less dementia
- People without much education relatively protected by jobs with high cognitive demands
- Stopping smoking reduces risk
- Treating depression –reduces risk
- Important to make changes with people at risk.
- RCTs tend to recruit low risk people.
- Need to target those at risk



# Is the risk the same for everyone?

- Cohort studies primarily
  - White participants
  - High income countries
  - Risk varies between countries
  - Risk factors cluster around inequalities
    - Minority ethnic groups
    - Lower socio-economic groups
    - LMIC

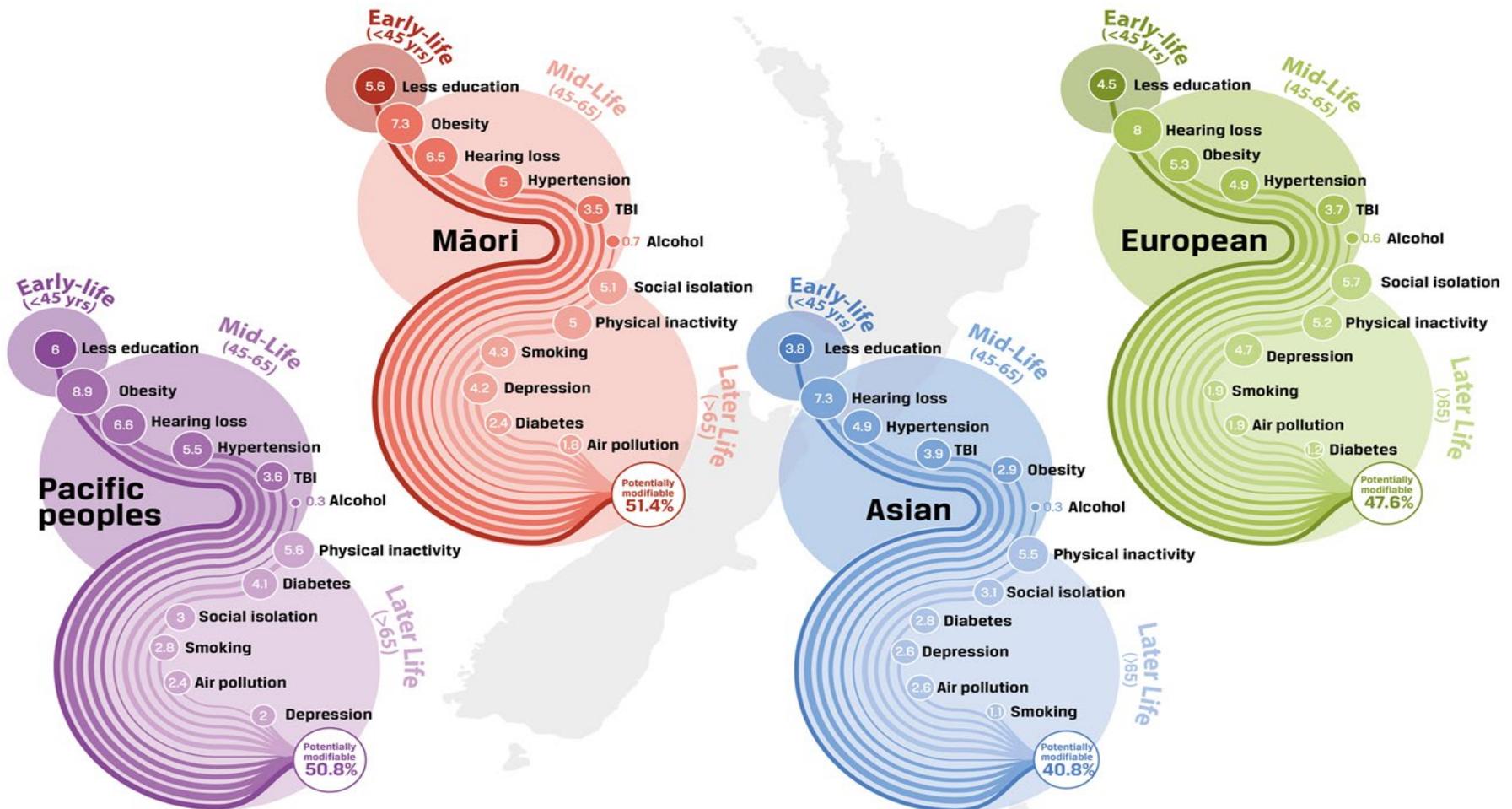
# Effects in Lower and Middle Income Countries

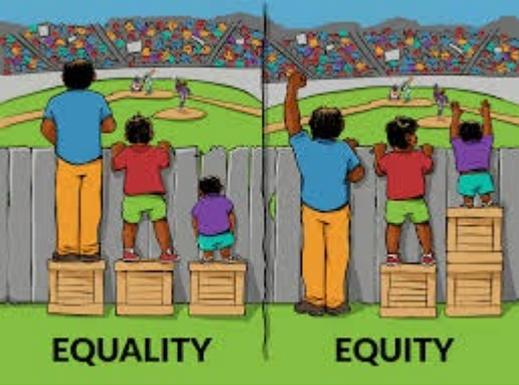


5 Percentage reduction in cases of dementia if this risk factor is eliminated

Mukadam..Livingston 2019  
Lancet Global Health

# Relative PAF contribution across four ethnic groups in New Zealand





## Not just about individual intervention

- Risk clusters - minoritized cultures, poverty and inequality
- As societies we need to think beyond individual health
- Disease modifying treatments do not remove need for prevention
- 40% potentially preventable.
- More in LMIC
- Tackling risk
  - provide more years of healthy life
  - or prevent dementia ever occurring



# United States



- **US congress** The National Alzheimer's Project Act (NAPA) Advisory Council create and advance a National Plan to address Alzheimer's disease and related dementias
- Added new goal (in 2021) to Reduce the Burden of Risk Factors
- To aggressively address 10 potential risk factors (↓15% by 2030)
- **CDC** consulted in 2021 on making a US policy with targets of the risk factors on prevention
- 15% per decade = ↓1.2 million people with AD in 2050

Thank you

