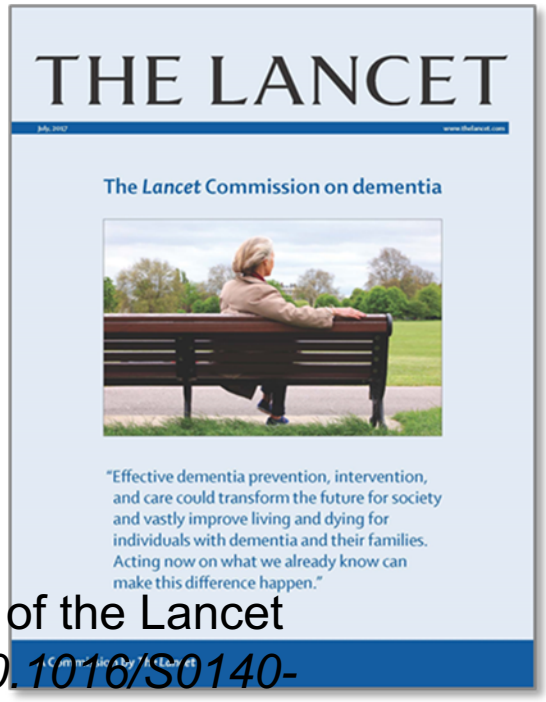
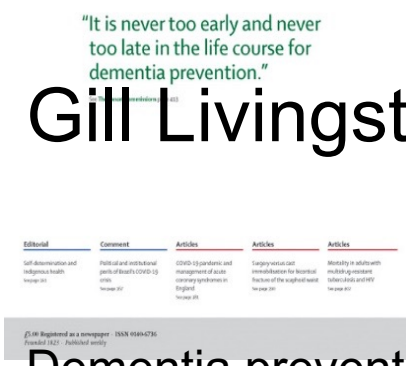
Prevention of Dementia?





Gill Livingston @ **gill_livingston**

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*

Dementia prevention, intervention and care. Lancet 2017

http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(17)31363-6.pdf

Andrew Sommerlad, Jonathan Huntley, Sergi Costafreda, David Ames, Clive Ballard, Sube Banerjee, Carol Brayne, Alistair Burns, Jiska Cohen-Mansfield, Claudia Cooper, Amit Dias, Nick Fox, Laura Gitlin, Robert Howard, Helen Kales, Mika Kivimaki, Eric Larson, Adesola Ogunniyi, Vasiliki Orgeta, Karen Ritchie, Kenneth Rockwood, Elizabeth Sampson, Quincy Samus, Lon Schneider, Geir Selbæk, Linda Teri, Naaheed Mukadam

Partners **UCL,** Alzheimer's Society Leading the fight against dementia; Improving Dementia Care ESRC·NIHR; Alzheimer's Research UK The Power to Defeat Dementia

What I will talk about

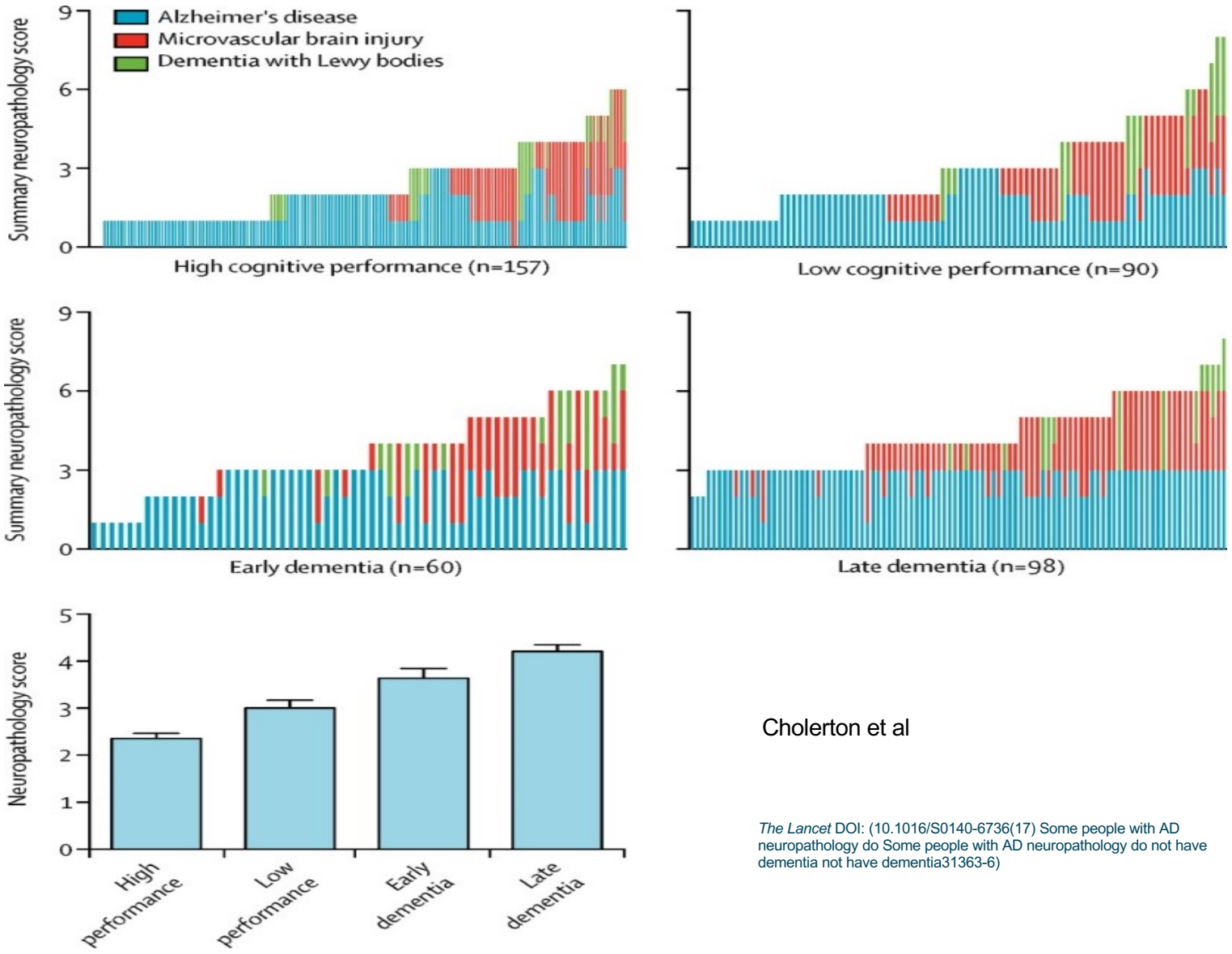
- Why should we consider dementia as preventable
- Lifecourse risk
- Discussion of individual risk factors
- Modification of risk
- What should we do?

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 is 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



Cholerton et al

The Lancet DOI: (10.1016/S0140-6736(17) Some people with AD neuropathology do Some people with AD neuropathology do not have dementia not have dementia31363-6)

Twelve risk factors

Early life

- Less education

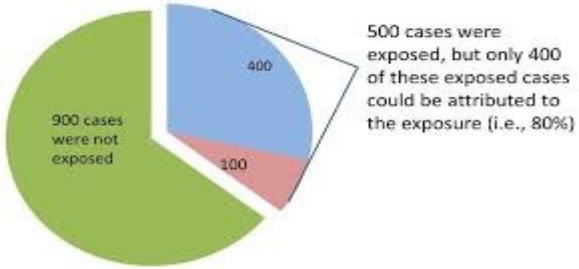
Mid life (45-65)

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

Late life (>65)

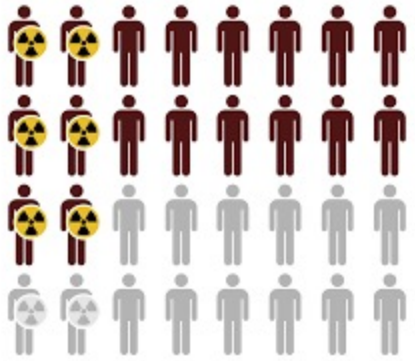
- Smoking
- Depression
- Physical inactivity
- Air Pollution
- Social isolation
- Diabetes

PAF calculation



- Population Attributable Fraction
- Fraction theoretically prevented by eliminating risk factor
- PAF = Relative Risk (meta-analysis) X Prevalence of risk factor
- Used all-cause dementia
- International data when available
- Twelve risks
- We know there are others

Communality –people not lab rats

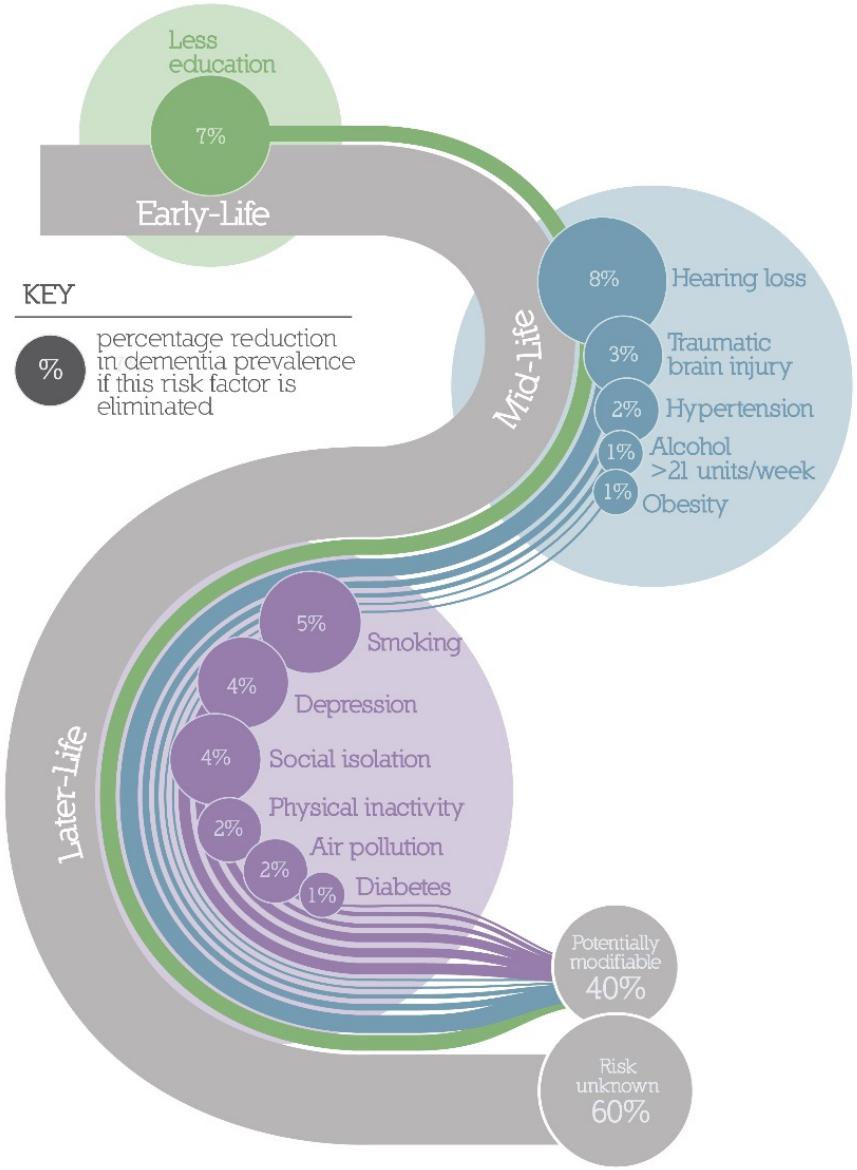


People tend to have clusters of risk factors

- 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 ≥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)

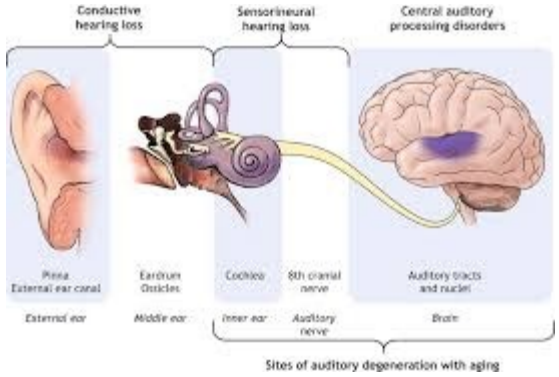
- Individual risk factor PAF = Pe (RRe-1) / [1 + Pe (RRe-1)]

Population Attributable Fraction- 40%

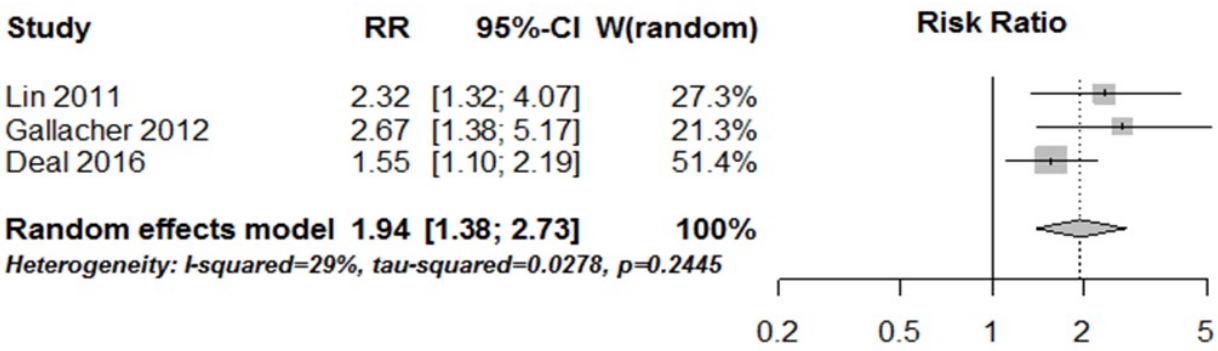


Risk factor	Relative Risk for dementia	Risk factor prevalence	Communality (%)	Unweighted PAF (%)	Weighted PAF* (%)
Early life (<45)					
Less education	1·6 (1·3 -2·0)	40.0	61.2	19.4	7.1
Mid -life (age 45 -65)					
Hearing loss	1·9 (1·4 -2·7)	31.7	45.6	22.2	8.2
Traumatic brain injury	1.8 (1.5 -2.2)	12.1	55.2	9.2	3.4
Hypertension	1·6 (1·2 -2·2)	8.9	68.3	5.1	1.9
Alcohol >21units/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)					
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

Hearing loss



- High quality papers
  - FU ≥ 5 years,
  - objective measure peripheral hearing (pure-tone audiometry)
  - Outcome incident dementia adjusted for age & CV risk



Hearing- highest PAF

- 3,777 people aged ≥65 with self-reported hearing problems- ↑dementia incidence 25-year later except if using hearing aids (Amieva et al 2017).
- 2114 hearing impaired MCI (mean age 78). Using hearing aids→ ↓ dementia risk (HR= 0.73). Mean time to dementia 2 vs 4 years (Bucholic et al 2021)
- 3811/7385 people hearing loss (mean age 65). ↓cognition when not using hearing aids.(Ray et al 2018)
- National representative survey of 2040 people aged >50, tested two-yearly for 18 years
  - Hearing aid biggest protection from cognitive decline. Maharani et al 2018
- Hearing loss associated temporal lobe volume loss

Education and cognitive stimulation

- Education is 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

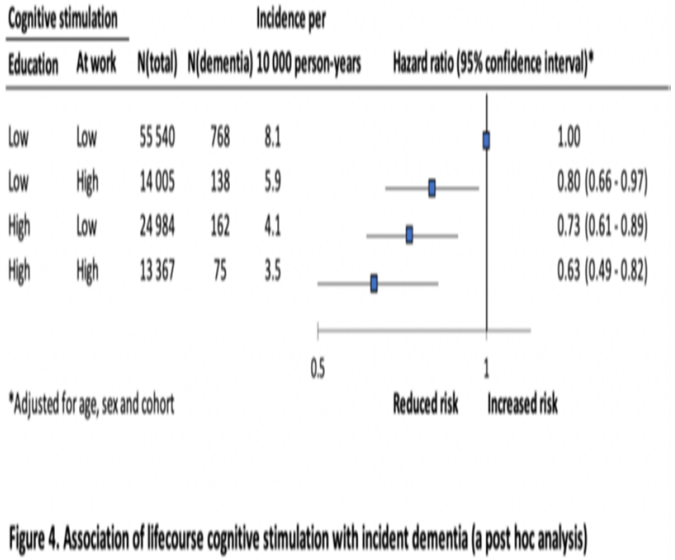


Figure 4. Association of lifecourse cognitive stimulation with incident dementia (a post hoc analysis)

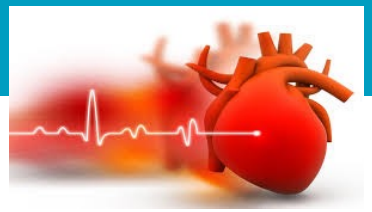
- Some evidence that retirement may increase deterioration even allowing for ill health

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
- Passive smoking also a risk
- Probably late life as more time smoking =more risk

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 (also 50 and 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



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 aiming to decrease systolic BP to <120 (control 140) in 9361 people aged 50+ without diabetes
- Five years later significant ↓MCI HR = 0.8, and combined MCI or dementia (HR, 0.9)
  - JAMA. 2019;321(6):553-561

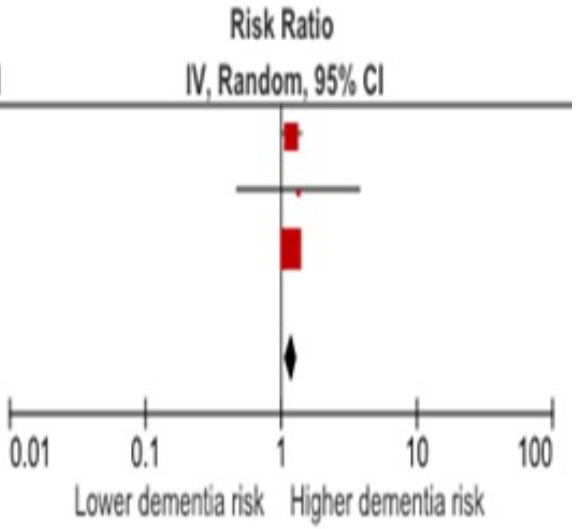
Alcohol

- Heavy drinking effects the brain
- Non-linear effect: ↑dementia risk drinking >21 UK units/week alcohol (14 US drinks) vs <14 (10 here) . New meta-analysis RR =1.18

Study or Subgroup	log[Risk Ratio]	SE	Drinking >21 units/week Total	Drinking <21 units/week Total	Weight	Risk Ratio IV, Random, 95% CI
Handing et al 2015	0.17	0.09	300	9153	37.3%	1.19 [0.99, 1.41]
Jarvenpaa et al 2005	0.29	0.53	23	310	1.1%	1.34 [0.47, 3.78]
Sabia et al 2018	0.16	0.07	2232	5552	61.6%	1.17 [1.02, 1.35]
Total (95% CI)			2555	15015	100.0%	1.18 [1.06, 1.31]

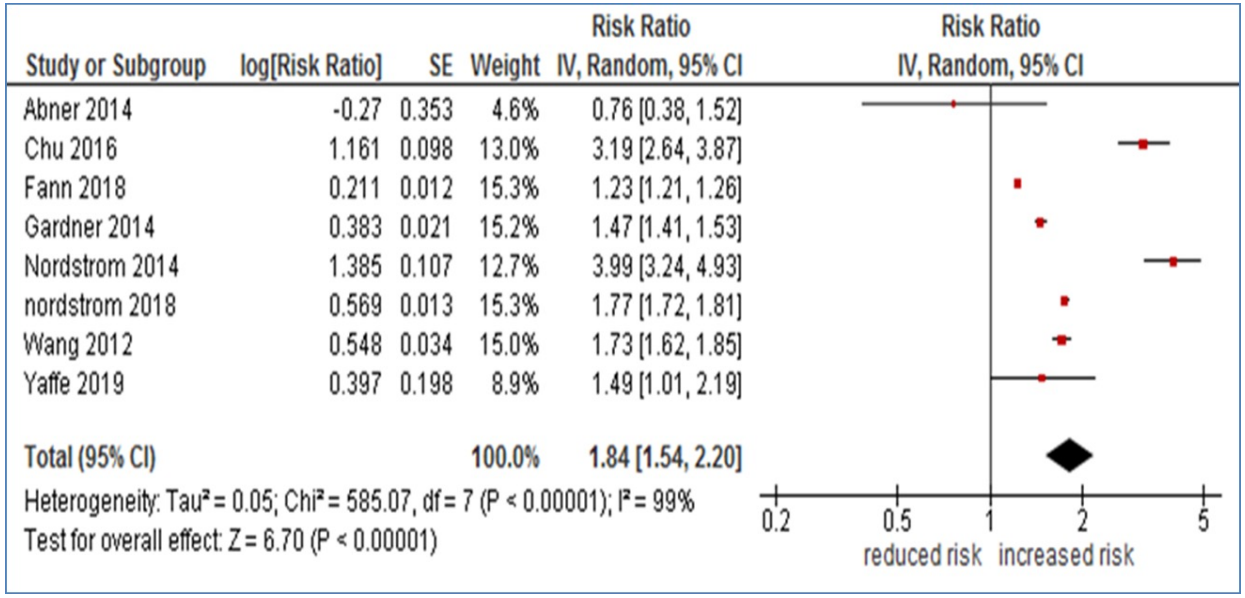
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.06$, $df = 2$ ($P = 0.97$); $I^2 = 0\%$

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



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 longitudinal studies with 1-15 years follow-up of air pollutants exposure and incident dementia
- Exposure to $PM_{2.5,}$ $NO_{2,}$ and CO all ↑ dementia risk
- Too heterogeneous for meta-analysis
- Data from only study of all-cause air pollution and 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
- Chinese longitudinal survey that Clean Air Act implementation mitigates cognitive decline (difference MMSE 2.45 points/4 years) Yao Yao et al 2022. TLHL

The Lancet commissions about diet

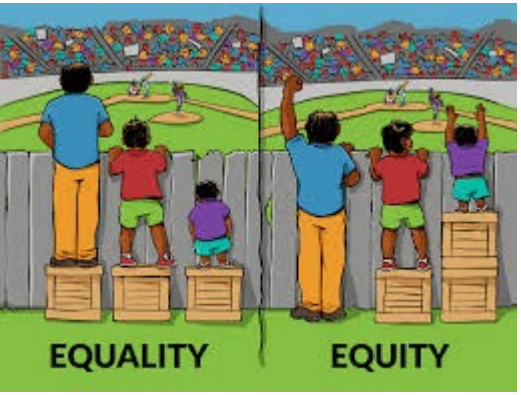
- Pattern of risk and the individual's other health, both physical and mental might be especially important.
- A Mediterranean or Scandinavian diet might help prevent cognitive decline in people with intact cognition,
  - particularly as one component of a healthy lifestyle,
  - although how long the exposure has to be
  - or at what age is unclear.

We do not recommend

- vitamins, oils or dietary supplements to prevent dementia
- extensive trials has not led to signals of benefit

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



Not just about individual intervention

- Culture, poverty and inequality are obstacles to, or drivers of, the need for change.
- Those who are most deprived need the changes most and will derive the highest benefit.
- As societies we need to think beyond promoting individual health and begin to improve circumstances in which people live

RCTs to prevent dementia

WORLD WIDE FINGERS

- FINGER RCT - 2-year Finnish multidomain intervention to prevent cognitive decline and dementia. 1260 people age 60–77 with CV risks
  - small reduction in cognitive decline vs control
- Healthy Ageing Through Internet Counselling in the Elderly (HATICE) - 18 months, 2724 people ≥65
  - Small improvement in CV primary outcome Vs control mainly through weight loss, and the dementia risk
  - Larger effect in younger age group (65–70 years) and those with less education, higher risk.
  - Targeting high-risk populations might be more effective

United States

- Laura Gitlin invited to give Lancet evidence to US congress end 2020
- **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

https://aspe.hhs.gov/sites/default/files/2021-09/NAPA-2021-Risk-Reduction-Recommendations.pdf

PHE risk reduction in dementia

"A recent Lancet commission has shown that some of the modifiable risk factors for dementia include: smoking, weight, physical activity and blood pressure."

- dementia risk reduction messaging should be communicated to all individuals having an NHS Health Check; and

 Included as a mandated part of the programme

Be ambitious about prevention

- Aim for systolic BP ≤130 mmHg from around age 40
- Encourage hearing aids for hearing loss. ↓hearing loss
- Reduce exposure to air pollution & second-hand smoke.
- Prevent head injury
- Limit alcohol -drink <14 AU units (21 UK) weekly
- Avoid smoking uptake & support smoking cessation
- Give all children with primary & secondary education.
- Reduce obesity and the linked condition of diabetes

Most vulnerable stand to gain most

Thank you