Preventing Well.
Can We Prevent Dementia?

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What we will cover

- Can we prevent dementia?
- Evidence
- Risk factors
- Motivating people to change
- Reaching the hard to reach

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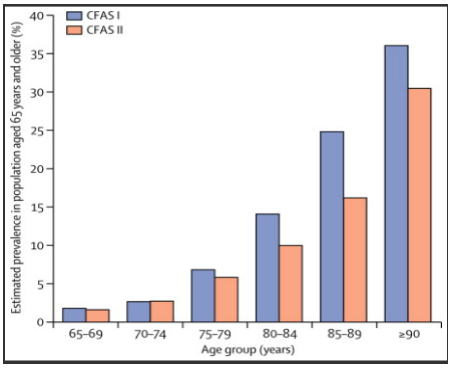
Can we prevent dementia?



Lancet 2013. A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from 3 geographical areas of England; results of the Cognitive Function and Aging Study I and II (CFAS I and CFAS II). CFAS I **1989-1994**, CFAS II **2008-2011**

(shows drop in prevalence over 20 years. Note the total number which is not shown continues to increase as population is aging faster than incidence is dropping)

Better effect than any drug in development

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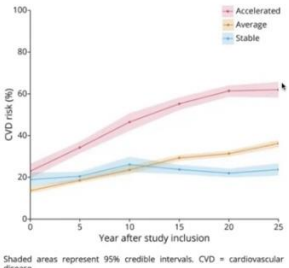
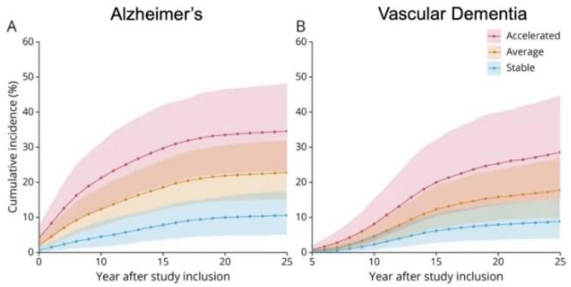
It doesn't just affect vascular dementia

- 1,244 Dementia-free adults (Sweden)
  - 50s-60s
- Framingham Risk Score
  - Stable
  - Average
  - Accelerated



Shaded areas represent 95% credible intervals. CVD = cardiovascular disease.



Von Cederland et al. Neurology 2022

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Living Caerphilly

- Epidemiological cohort study
- Prof Elwood, MRC
- Looked at 90% of the middle aged men in Caerphilly from 1979 (2,500+)
- Baseline health then detailed review every 5 years – GP and hospital records, incident analysis
- Found for those that had 4/5 or more healthy behaviours, there was reduction of dementia by up to 65%
- (similar reductions in diabetes, heart disease, overall mortality and a 30% reduction in cancer)
- Those healthy behaviours were…

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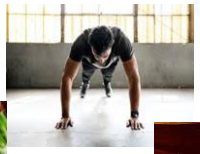
Healthy Behaviours In Caerphilly





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Lancet Paper

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Identified 14 modifiable risk factors and their PAF (Population Attributable Fraction)
- the global percentage reduction in dementia prevalence if this risk factor is eliminated

- Hearing Loss 7%
- High LDL cholesterol 7%
- Less education 5%
- Social isolation 5%
- Depression 3%
- TBI 3%
- Air pollution 3%
- Physical Inactivity 2%
- Diabetes 2%
- Smoking 2%
- Hypertension 2%
- Visual loss 2%
- Obesity 1%
- Excessive Alcohol 1%

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There are many other studies

The same risk factors

Other risk factors – diet (vit D, vit C, hyperhomocysteinuria), sleep, frailty, arrhythmias, stroke, cognitive activity, orthostatic hypotension, deprivation

Genetics and how they interact with other risk factors

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Paper – Effective Interventions for Potentially Modifiable Risk Factors for late onset dementia: a costs and cost effectiveness modelling study

- Lancet Healthy Longevity 2020; 1; e13-20
- Mukadam et al
- **Findings We found effective interventions for hypertension, smoking cessation, diabetes prevention, and hearing loss. Treatments for stopping smoking and provision of hearing aids reduced cost. Treatment of hypertension was cost-effective by reference to standard UK thresholds. The three interventions when fully implemented would save £1·863 billion annually in England, reduce dementia prevalence by 8·5%, and produce quality-adjusted life-year gains. The intervention for diabetes was unlikely to be cost-effective in terms of effect on dementia alone.**

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We can prevent dementia!

- Or at least 45% of it
- Cognitive reserve and decreased damage?
- Never too early, (almost) never too late
- Our brains are plastic and cognitive decline is not as inevitable as we thought

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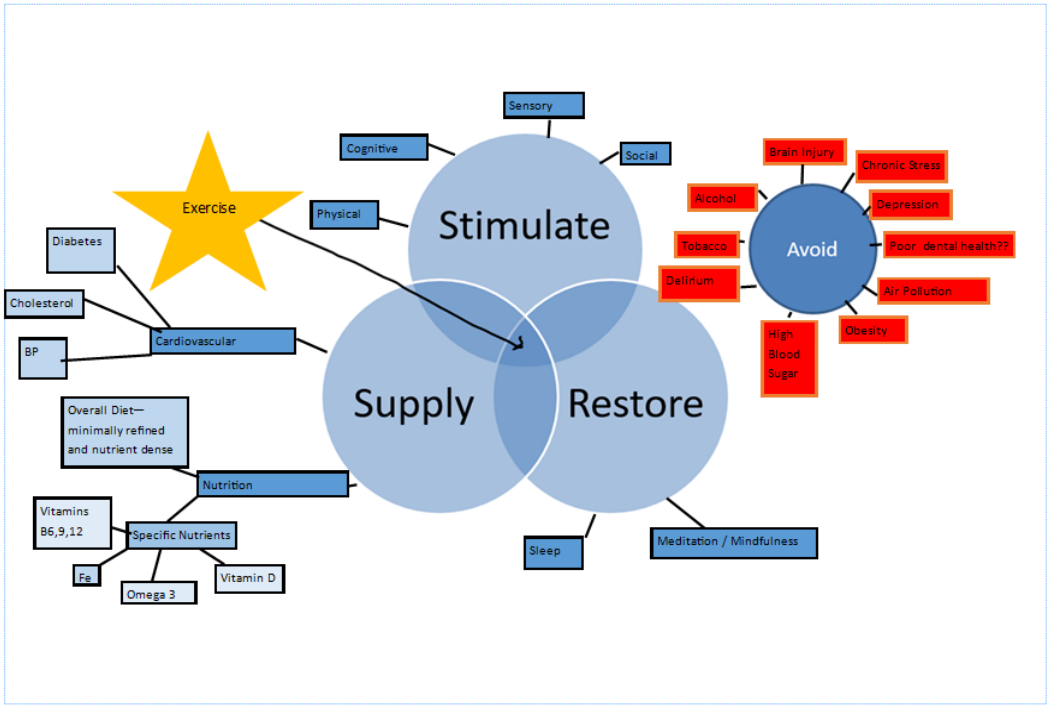

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Vascular Supply

- Protect cerebral vasculature against diabetes, hypertension, hyperlipidaemia
- Treat arrhythmias
- Physical exercise
- Healthy heart, healthy brain

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Nutrient Supply (not in Lancet)

- Overall diet quality – whole food, plenty of plants, minimally processed (almost no UPF), low GI
- **Eat Food. Mostly Plants. Not Too Much**.
- Mediterranean or MIND diets probably best for brain
- **Low GI** as neurons are sensitive to blood sugar spikes, causes stress and brain damage
- Specific nutrients important
- **Quality of diet is proportional to hippocampal size**

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MIND diet (Mediterranean / DASH combined)

- Leafy greens every day,
- Other veg every day
- Berries x2/week,
- Whole grains x 3/day
- Fish x1/week,
- Poultry x2/week,
- Beans x 3/week
- Nuts x 5/week
- Wine 1 glass/day
- Olive oil

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Avoid Ultra-Processed Food

- Association between consumption of ultra-processed foods and cognitive decline. Goncalves et al. JAMA Neurol. 5.12.2022
- 11,000 people f/u for 8 years
- Those with UPF consumption above the first quartile showed a 28% higher rate of global cognitive decline

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Meat?

- A long term diet high in processed meat eg sausages, spam, bacon increases your risk of dementia by 25%
- **But**
- Unprocessed meat decreases your risk of dementia
- Probably a B12 effect.

- Some vegan food is ultra-processed

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Specific nutrients

- Evidence that all the following are modifiable risks for dementia
- Iron (Hb<120, 40% increased risk)
- B6 (pyridoxine) , (B9) folate and B12 (cobalamins) both work to reduce homocysteine, which causes damage to arterial walls
- Vitamin D (<29ng/ml increases risk 30%)
- Choline
- Omega 3s
- Get a better response to omega 3 if have enough B vits (the B vits perform the methylation that helps the omega 3 get into the cell membrane)

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Specific nutrients

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How does diet affect brain?

- B vitamins to generate energy
- B vitamins necessary for omega 3 to get into cell wall
- Quality of diet is proportional to BDNF and hippocampal size
- Diet can increase or decrease inflammation (sugars and some proteins and fats increase inflammation)
- Diet can increase or decrease free radicals
- Sugar in particular increases AGEs and free radicals, disrupts ATP pump
- Diet affects gut microbiome, gut bugs make SCFAs which communicate with brain, regulate inflammation
- Diet affects mucus lining of gut and what is absorbed into the body
- Gut communicates directly with brain

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Physical Stimulation

- ie: Exercise!
- Probably one of the most important factos
- It affects supply by increasing the strength of the vascular system
- It improves sleep quality, so improves the brain's ability to restore itself
- It affects your body's ability to avoid the toxic effects of glucose because muscle is powerfully effective at regulating it.

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But its more than that……

- The first study showing the brain can regenerate was an exercise intervention
- Exercise training increases size of hippocampus and improves memory Erickson et al. Proc Natl Acad Sci. 2011

- Took 120 older adults, Half stretched, half aerobically exercised
- Those who exercised increased hippocampal volume by 2%, those who stretched lost 1.4% over the same 1 year period – though those who were fitter lost less

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Where are the changes?

- Hippocampal volume
- Cortex
- Prefrontal

- Also reduced white matter atrophy and smaller volume of white matter lesions

Exercise- mediated neurogenesis in the hippocampus via BDNF. Liu et al. Front Neurosci 2018; 12:52

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How does it work?

Exercise increases the volume of muscles

Muscles produce myokines

Increases secretion of BDNF – drives growth of cortex, hippocampus

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What type of exercise?

- Aerobic exercise
- Resistance exercise
- Physical exercise has greater effect than cognitive when directly compared
- But the best effect is with the two combined, where there is skill based movement – dancing, badminton, tai chi better than walking

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How much exercise?

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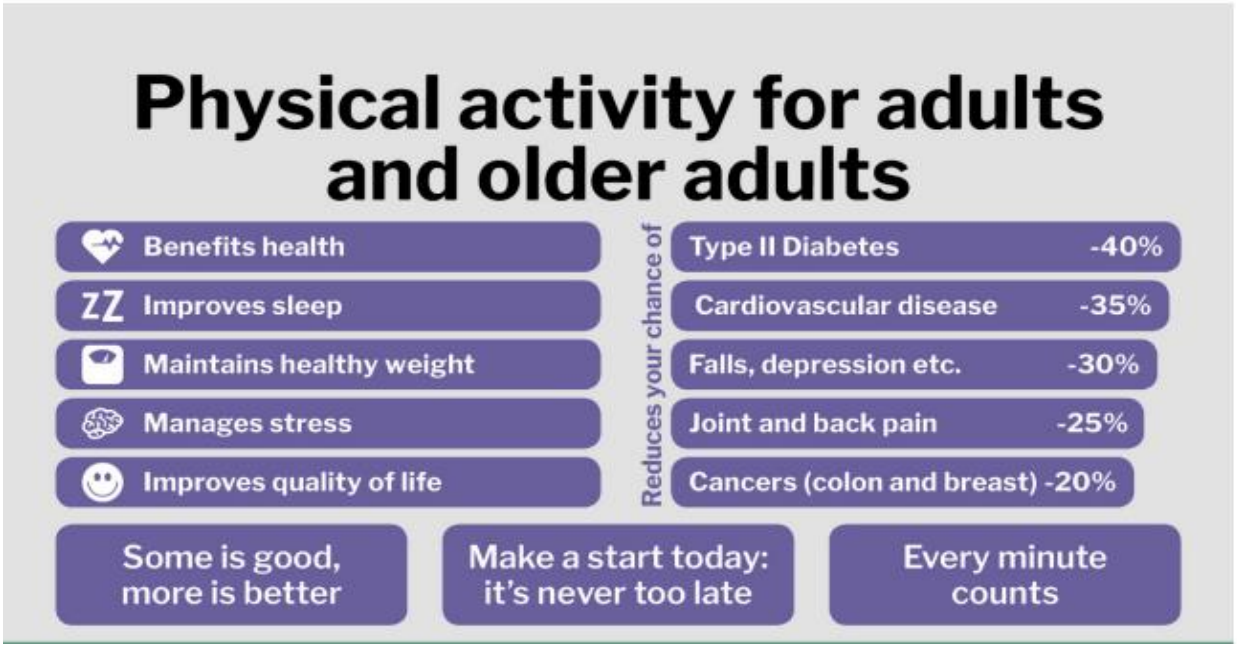

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Cognitive Stimulation improves cerebral blood supply

- Demand coupling drives neurodegeneration: A model of age-related cognitive decline and dementia. Turknett and Wood
- Cells 2022.11 (18) 2789
- Demand is a critical stimulus of cerebro-vascular maintenance and growth – as neurons fire, it activates chemical signals (adenosine, prostaglandins), driving the growth of blood vessels around them. **Demand coupling**
- Cognitive demand upregulates cellular repair and autophagy
- Using your brain to think helps maintain / grow the vascular support
- Poor vascular supply makes it hard to respond to a challenge

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Retirement

- Retirement later is associated with lower dementia risk
- Does postponing retirement affect cognitive function? Hale et al. SSM-Population Health. Vol 15, Sept 2021
- Substantial effect from ongoing employment, particularly for the highest educated

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Cognitive Reserve

- Cognitive reserve is what allows people to function normally despite having a significant degree of pathology in their brains.
  - Neurobiological – more neurones and synapses from early life
  - Brain maintenance – lifestyle and genes make brain less likely to deteriorate
  - Adapatability – enabling preservation despite neuropathology so networks continue

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Music

- Musicians have brains that look younger than non musical people
- Effect is greater for amateurs
- **Something being difficult, failing at it seems very important.**
- Learning music as a child is protective decades later.
- Strong et al. The cognitive functioning of older adult instrumental musicians and non-musicians. Aging, Neuropsychology and Cognition. Vol 26. 2019

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The Knowledge

- Woollett et al Acquiring the Knowledge of London's Layout drives structural brain changes. Current Biology. Vol 21, Issue 24
- Adults of average IQ, studying the intricate detail of London to be become taxi drivers over 4 years
- Those who qualified had gained an increase in grey matter volume in posterior hippocampi compared to non learners. This change was lasting over time.

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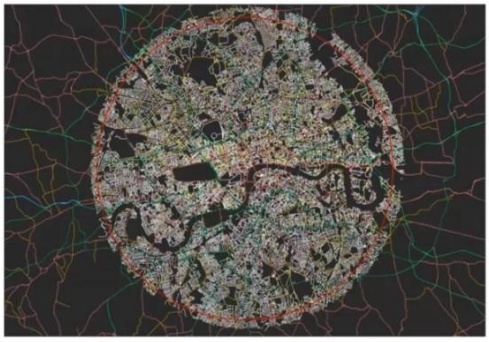
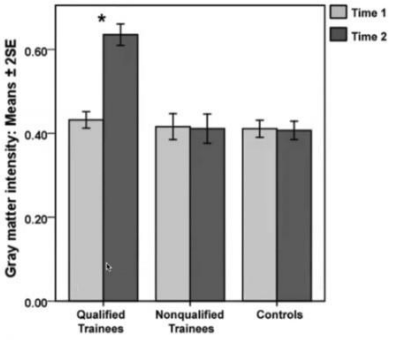
Gaining ‘The Knowledge’ grows the hippocampus





Woollett and Maguire. Current Biology. 2011

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Sensory loss

- Hearing loss is associated with dementia, treating it reduces the risk
- In the Lancet 2024 paper, PAF of 7% for hearing loss!
- Loss of vision has PAF of 2%.Reversed by cataract surgery
- Covid effects?

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Social Stimulation

- Late life engagement in social and leisure activities is associated with a decreased risk of dementia; A longitudinal study from the Kungsholmen Project. Am J Epid. Vol 155, Issue 12.
- Swedish study looking at data before death, found association between social contacts and reduced dementia.
- With a PAF of 5%, its as important as hypertension (2%), physical inactivity (2%) and obesity (1%) combined
- Seems to work on increasing cognitive reserve and increasing beneficial behaviours – people with more social contact exercise more, eat better, get more cognitive stimulation

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Restore – Sleep (not in Lancet)

- The Lancet paper does not include sleep, saying its hard to tease out cause and effect.
- Association of sleep duration in middle and old age with incidence of dementia. Sabia et al. Nature Communications. 12. Article no 2289(2021)
- 8000 people, up to 30 year f/u, using data from Whitehall Cohort Study
- 30% higher risk of dementia associated with a sleep duration of < 6 hours at 50, 60 and 70 (and also some increase if sleep > 9 hours)

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How does Sleep help?

- REM – dream sleep helps store memories
- Non-REM – helps brain clear out its products of metabolism (waste) – probably via glymphatic system which gets larger molecules out, bypassing BBB, but only works during sleep

- Association does seem bi-directional

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How to improve sleep

- Investigate why its poor – sleep apnoea? Stress? Alcohol? Caffeine Menopause?
- Avoid hypnotics
- Exercise,
- Blue light in morning, red at night (currently unsure)
- Regular pattern of going to bed and rising,
- Change temp from warm to cooler as go to bed
- Sleepio - CBTi

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Restore- Meditation and Mindfulness (not in Lancet)

- Not mentioned in Lancet, but might be useful for people who can't avoid poor sleep.
- People who meditate have younger brains
- Older meditators have bigger brains
- Estimating brain age using high-resolution pattern recognition: younger brains in long-term meditation practitioners. Luders et al. Neuroimage. 2016. Jul 1
- Meditation experience is associated with increased cortical thickness. Neuroreport. 2005. Nov 28

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Avoid - toxins

- Alcohol
- Tobacco
- Other recreational drugs (not in Lancet)
- Air pollution
- High blood sugar
- (Gum disease)

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Avoid - Alcohol

- Have always known about risks of alcohol on cognition
- French 5 year study **of 31 million people** (Schwarzinger M et al Contribution of alcohol use disorders to the burden of dementia in France 2008-13: a nationwide prospective cohort study. Lancet Public Health 2018 **3** 124-132)
- Found alcohol use disorders (as defined by ICD10) were associated with increased dementia risk. Especially clear for YOD – 56% had an alcohol use disorder in ther notes

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No Safe level of alcohol

- Topiwala A et al. Moderate alcohol consumption as risk factor for adverse brain outcomes and cognitive decline: longitudinal cohort study. BMJ 2017:357.
- Observational study over 30 years, looked at brain size on MRI v drinking history. Atrophy was in proportion to alcohol consumed, and there was no safe lower limit. No protection from light drinking compared to abstinence.
- Takeaway message is to drink as little as possible, definitely less than 12 units per week

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Avoid - smoking

- Smoking has negative effect on all circulation
- Smoking is associated with an increased risk of dementia; a meta-analysis of prospective cohort studies with investigation of potential effect modifiers. Zhong et al. PLOS one. 2015. March 12.
- Showed not just that smoking increases the risk of dementia, stopping smoking decreases the risk to that of never smokers.
- Risk of smoking worse in people apoE4 positive
- Second hand smoke is also a risk

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Avoid – Air Pollution

- Animal models suggest airbourne pollutants accelerate neurodegenerative processes
- High NO2 concentration, fine ambient particulate matter from traffic exhaust and and wood burning are assoc with increased dementia incidence. Traffic produces both
- Wood burners are more in residential areas, so though produce less than traffic, its where the people are
- Poorer people more exposed to traffic fumes
- CO also increases dementia risk

- B vitamins may have some small protection

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Avoid–Gum disease?(less evidence than rest)

- Meta-analysis by Asher in JAGS 2022
- Avoided reverse causation by making sure all studies at least 10 years long
- Very variable quality of studies, not well controlled, showed association, but not necessarily causal
- 24 studies looking at link between cog decline and periodontitis, and 23 looking at link between dementia and periodontitis
- Tooth loss was also independently linked to cognitive decline and dementia, with severity linked to proportion of teeth lost
- If there is a link, could be due to increased inflammation linked to oral bacteria acting as nidus for formation of plaques

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Avoid – High Blood Sugar

- High glucose toxic for the brain
- Importance of both diet and exercise
- Muscle regulates glucose – grow more if you can
- If you are diabetic, control of BM is important for brain as well as everywhere else

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Avoid - Obesity

- Obesity but not overweight associated with increased risk of dementia (Albanese et al BMI in midlife and dementia: systematic review and meta-regression analysis of 589,649 mean and women followed in longitudinal studies. Alzheimers Dement (Amst) 2017; **8**:165-178) – followed up for up to 42 years

- Not sure if losing the weight prevents dementia.

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Avoid - Depression

- Depression is complicated because of its interaction with dementia
- Nevertheless, its clear depression in midlife increases the risk of dementia in later life.
- And that treating the midlife depression reduces that increased risk
- Also small associations with anxiety and PTSD?

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Avoid – Toxic Stress

- Some stress good for our brains, helps learning
- But chronic stress of the type that is associated with loss of autonomy is associated with increased risk of dementia.
- Eg long term caring of relatives, especially if don't want to be doing it
- Eg work in which you feel you have no control

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Avoid – Traumatic Brain Injury

- Single, severe TBI is assoc with widespread phosphorylated tau
- Mostly caused by car, bike and motorbike injuries, military exposure, boxing, horse-riding, fire-arms and falls
- Fractures of skull more assoc with dementia than fractures of other bones, and is a long term risk
- Risk remain elevated over 30 years later (and maybe more)
- Severity of TBI associated with risk of dementia

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Avoid – Chronic Traumatic Encephalopathy

- Sports head injury- rugby, football. Footballers get more dementia than controls, but not goalkeepers. Girls more vulnerable
- Domestic violence
- In early days of understanding, not fully characterised, broad range of pathologies and outcomes
- Study on Scottish football players (Mackay DF et al, Neurodegenerative disease mortality among former professional soccer players.*N Engl J Med.* 2019; **381**: 1801-1808) – more likely than controls to have AD on death certificate, and more likely to have had anti-dementia drugs.

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Avoid - Delirium

- Every episode of delirium increases risk of dementia
- Be alert for signs of ill health, treat as aggressively as is appropriate to prevent delirium
- If at risk, consider rescue antibiotics for UTI, RTI, skin infection
- If person is delirious, try to shorten the episode, if possible

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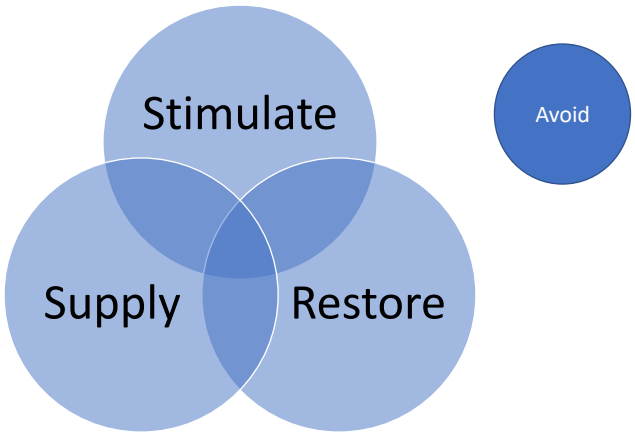
Preventing dementia



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Putting it together

- There are many trials that put these risk factors together, and show that the more you do, the greater the benefit
- For some its synergistic
  - Exercise and learning
  - B12 and omega 3

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Must remember that is not all preventable

- Somewhere between 40 and 70% is preventable
- There are some people whose dementia could never be prevented, though bad luck, unlucky genes, factors we can't change, and things we don't understand
- We don't know much about preventing Parkinsons Disease Dementia or Lewy Body Dementia or Fronto-temporal dementias

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What about genetics?

- Cant modify the genes, but can perhaps influence how they are expressed
- Several known AD genes – APP, PSEN1, PSEN2 and APOE4. There is widespread variance in distribution around the world

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APOE4

- As an example, take the APOE gene. It codes for a protein important for cholesterol transport.
- Each of us has 2 versions of the APOE gene, one from Mum, one from Dad
- 6 possible combinations 2+2, 2+3, 2+4, 3+3, 3+4, 4+4
- About 1 in 7 people have one copy of APOE4 – they have roughly 3x the risk of dementia
- About 1 in 50 people have two copies of APOE4 - they have roughly 9x the risk of dementia BUT……

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The Nigerian Paradox

- The population with the highest rate of APOE4 in the world is in Nigeria
- Yet Nigeria has a low rate of Alzheimer's disease. A 1992 study couldn't find a single case
- Lots of factors – young population (17.2 years compared to UK where its 40.1), different lifestyle, different diet
- Diet is low in animal fat (where cholesterol comes from), high in vegetables and unprocessed grains
- Much more physically active
- But slowly becoming westernised and rate is increasing.

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How to motivate people to change?

- Involvement
- Education
- Clinical
- Political
- Built environment
- At an individual level, find out what matters to them, meet them where they are.

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How to motivate people to change?

- Education
  - How many people know its preventable?
  - What are risk factors? What is ultraprocessed food?
  - Cycle helmets
  - Avoiding mixed messaging
  - What are the best times to reach people?

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How to motivate people to change?

- Clinical
  - Nudging, brief interventions
  - Person-centred,
  - Endorsement by clinician and referral in clinical setting
  - Motivational interviewing? Not as effective as would hope
  - Targetted health coaching

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How to motivate people to change?

- Political
  - Labelling,
  - Subsidies – meat, dairy, wheat, maize, sugar, oil
  - Taxes
  - Ultra-processed foods
  - Access
  - Supermarkets
  - Food poverty
  - Rugby, football, boxing

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How to motivate people to change

- Built environment
  - Stairs v lifts v escalators
  - Making people feel safe to walk and run
  - Cycle safety
  - Availability of public transport
  - Access to gyms and pools

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What makes people hard to reach?

- Education
- Language
- Culture and meaning
- Socio-economic status
- Social isolation
- People in institutions
- IT literacy and access

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And how to reach them

- Involve people
- Educate the professionals who interact with excluded people– midwives, teachers
- Build trust
- Reach people where they are
- Look at Hero of Health – the work of Dr Linda Mizun

- The Lancet commission shows that those who are hardest to reach are most likely to benefit

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Resources

- British Society of Lifestyle Medicine
- Kernow Branch of British Society of Lifestyle medicine – can join Whats App group if message me on 07771 576099. I also manage a Preventing Dementia WhatsApp group if you are interested.
- Hero of Health – Linda Mizun

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