

Preventing Well & Treating Well

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What we will cover – two parts

Reducing risk / Preventing dementia

- Can we prevent dementia?
- Risk factors
- Evidence

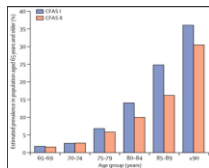
Medication

- Anticholinergic burden
- Current drugs for dementia
- New drugs for dementia

1

2

Can we prevent dementia?



Lancet. 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

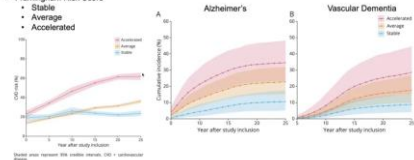
(shows drop in prevalence over 20 years. Note the total number which is not shown continues to increase as population is aging faster than incidence is dropping)

Better effect than any drug in development

3

It doesn't just affect vascular dementia

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



Van Gool et al. Neurology 2012

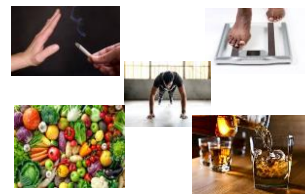
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Living Caerphilly

- 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...

5

Healthy Behaviours In Caerphilly



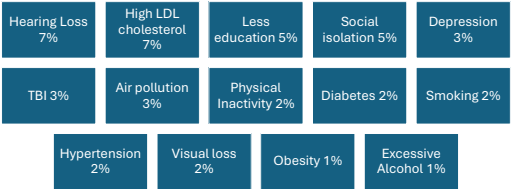
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Lancet Paper

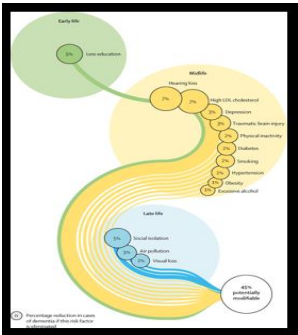


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Identified 14 modifiable risk factors and their PAF (Population Attributable Fraction) - the global percentage reduction in dementia prevalence if this risk factor is eliminated
TOTAL 45%



8



9

We can prevent dementia!

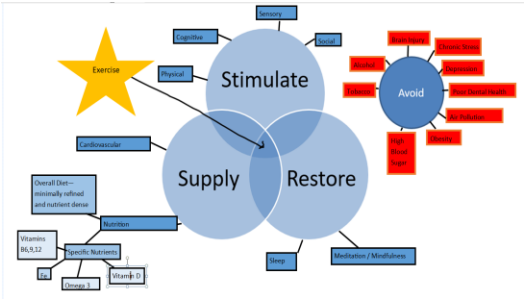
- Or at least 45% of it
- Cognitive reserve and decreased damage?
- Never too early, (almost) never too late
- Our brains are plastic and cognitive decline is not as inevitable as we thought
- Learning new things improves the brain's blood supply

10

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
 - Adaptability – enabling preservation despite neuropathology so networks continue

11



12

Vascular Supply

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

13

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 -with increased
 - free radicals,
 - AGEs
 - and a disruption in the ATPase pump;
 High blood sugar damages your brain directly, and not just through its effect on the vascular supply
- Specific nutrients important
- Avoid UPF

14

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

15

Specific nutrients



16

Physical Stimulation

- ie: Exercise!
- Probably one of the most important factors
- 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.

17

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

18

How does it work?



19

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

20

How much exercise?



21

Physical activity for adults and older adults



22

Cognitive Stimulation improves cerebral blood supply

- Demand coupling drives neurodegeneration: A model of age-related cognitive decline and dementia. Turckett 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

23

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

24

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

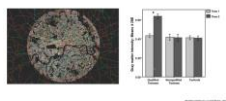
25

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 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.

26

Gaining 'The Knowledge' grows the hippocampus



27

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?

28

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 decline.
- 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

29

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)

30

How does Sleep help?

- REM – dream sleep helps store memories
- Non-REM – helps brain clear out its products of metabolism (waste). Glymphatic drainage helping large waste molecules cross BBB to leave brain
- Association does seem bidirectional.

31

How to improve sleep

- Investigate why its poor – sleep apnoea? Stress? Alcohol? Caffeine Menopause?
- Avoid hypnotics
- Exercise,
- Screen avoidance before bed
- Regular pattern of going to bed and rising,
- Change temp from warm to cooler as go to bed
- Sleepio - CBTi

32

Restore- Meditation and Mindfulness

- 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



33

34

The Mindful Life Group

The UK's only not-for-profit dedicated to older adult mental health

A FREE six-week programme starting online

Monday 2nd June 2025 from 10:30am-11:30am

MindCog:
A program designed to improve your brain health for people with Mild Cognitive Impairment

Designed by Clinical Psychologists

Visit our website
www.the-mindful-life.com
to find out more and apply

We are a Clinical Psychology led organisation and aim to provide robust interventions to support good mental health and reduce dementia risk.

- ✓ Clinician led
- ✓ Improve mental health
- ✓ Evidence-Based
- ✓ Tailored for over 65s

35

Avoid - toxins

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

36

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 their notes

37

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

38

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

39

Avoid – Air Pollution

- Animal models suggest airborne pollutants accelerate neurodegenerative processes
- High NO2 concentration, fine ambient particulate matter from traffic exhaust 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

40

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 diabetic, control of BM is important for brain as well as everywhere else

41

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 men 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. Better not to gain it in the first place

42

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

43

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

44

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, heterogeneous pathologies and outcomes (but a lot of tau)

45

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

46

Must remember that is not all preventable

- Somewhere between 45% 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 Parkinson's Disease Dementia or Lewy Body Dementia or Fronto-temporal dementias

47

What about genetics?

- Can't 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

48

APOE

- 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.....

49

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.

50

Any questions so far?



51

Medications

- Anticholinergic burden
- Antidementia drugs – those we have and those we have yet to have!

52

Anticholinergic burden

- Medical Research Council – cognitive function and aging study. 2011.
- Concept of anticholinergic burden
- Gives drugs a score 0-3
- Score more than 3 is significant, can get much higher with polypharmacy
- About more than risk to cognition
- Also falls
- Increased risk of death according to score (cause / effect?)

53

ACB3, not a complete list

Amitriptyline	Amoxapine	Atropine	Chlorphenamine
Clorpromazine	Clomipromine	Clozapine	Darifenacin
Desipramine	Doxepine	Hydroxyzine	Pyridoxine

54

More 3s

Imipramine	Nortriptyline	Olanzapine	Orphenadrine
Oxybutynin	Paroxetine	Quetiapine	Tolteridine
	Trifluoperazine	Tropium chloride	

55

ACB 2

Amantadine	Belladonna	Carbamazepine	Cyclobenzaprine
Cyproheptadine	Loxapine	Nefopam	Oxcarbazepine
	Pimozide		

56

ACB Score 1 – not a complete list

Alprazolam	Aripiprazole	Atenolol	Buprionon	Captopril
Cetirizine	Cimetidine	CODEINE	Diazepam	Digoxin
Dipyridamole	Fentanyl	Fluvoxamine	Furosemide	

57

ACB1 – continued – but still not complete

Haloperidol	Hydralazine	Hydrocortison	Isosorbide dinitrate
Isosorbide mononitrate	Levocetirizine	Loperamide	Metoprolol
Morphine	Nifedipine	Paliperidone	Prednisolone

58

A few more ACB 1

Quinidine	Ranitidine	Risperidone	Theophylline
Trazodone	Venlafaxine	Warfarin	

59

Antidementia drugs

- Acetyl Cholinesterase Inhibitors – Donepezil, Rivastigmine, Galantamine
- Memantine
- Monoclonal antibodies? Aducanumab, Donanumab, Lecanumab - not going to happen with these three, but no doubt others are in the pipeline. Problems – not enough benefit, not safe enough, a lot of (expensive) monitoring, drugs themselves not cheap and administered as day patient by infusion

60

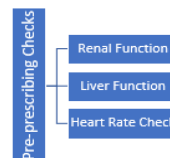
Before prescribing antedementia drugs

- Medication review – to reduce cholinergic burden, anything no longer necessary, reduce sedation
- Refer for care, support, non pharm treatment



61

Pre- Prescribing Checks



62

DEMENTIA TYPE	1 st LINE MEDICATION	2 nd LINE MEDICATION
Mild cognitive impairment/Disorder (not a dementia)	None – not advised	None – not advised
Alzheimer's Disease	CEI (Donepezil/Rivastigmine)	Memantine
Vascular Dementia	None (manage vascular risk factors)	None
Mixed Dementia (with Alz or PDD/LBD component)	CEI (Donepezil)	Memantine
Dementia in Parkinson's Disease PDD/Lewy Body Dementia LBD	(Donepezil/Rivastigmine)	Memantine
Fronto Temporal Dementia	None - Specialist Advice	None
Alcohol Related Dementia	None – advise alcohol abstinence and treatment with thiamine	None
Other e.g. MS, HD Hydrocephalus	None – specialist advice	None

63

Donepezil (Aricept)

- Cheapest
- Once daily dosing
- Two commonly used doses (5mg and 10mg)
- Long half life (70 hours)

64

Rivastigmine (Exelon)

- Short half life – must be given twice daily if used orally
- Has most GI SEs if used orally
- 1.5mg bd, 3mg bd, 4.5mg bd, 6mg bd oral dose regime
- Can use patch once daily, which has fewest SEs, but more expensive
- 4.6, 9.5, 13.3mg /24hours,

65

Galantamine?

- Don't bother about it
- We never use it

66

Side Effects of AChEIs

- Cardiac - Syncope, bradycardia, conduction defects (check pulse before initiation and at review)
- GI - nausea, vomiting, diarrhoea, hypersalivation
- Neuro - seizure, hallucinations, headache, disturbed sleep
- Use with caution in people with bladder outflow obstruction
- Most people tolerate very well.
- If SEs try giving with food or change timings

67

Memantine

- Works as an NMDA receptor blocker
- Alters flow of Ca through cellular pores, thought to affect ability to learn
- Preferred if there are cardiac problems
- Can be given with AChEI
- Starter pack - 5,10,15,20mg weekly, then 20mg thereafter
- Check renal function before prescribing - if eGFR <60, don't go above 10mg unless sx free.

68

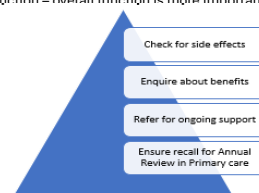
Memantine SEs

- Constipation
- Hypertension
- Dizziness
- Interacts with other drugs as competes for metabolism at enzyme 2D6
- It is usually very well tolerated

69

Review within one month of initiation

- Looking for benefits if present, but with AChEIs, keep taking if able to tolerate and no obvious benefit as may be reducing rate of decline - no need to test cognitive function - overall function is more important



70

When to stop

- If not tolerated
- If two AChEIs have been tried, there is no point trying another
- If reached the stage of reducing medication

71

Monoclonal Antibodies in AD.

- Although MHRA has approved licensing
- NICE has not approved and neither has EMA
- So available privately in theory - would need enormous infrastructure, but not on NHS

72

Monoclonal Antibodies for Alzheimer's

- Only licensed for AD, need to confirm pathology before treatment
- (CSF, possibly blood, PET)
- Given by infusion. For lecanemab, it's given in eg a chemo centre. Bag is diluted, given over an hour, repeated every 2/52
- MRI scans done before starting and then after first infusion, then before 5th, 7th and 14th infusions to check for ARIA (Amyloid Related Imaging Abnormalities). ARIA-E (Oedema) – headache, confusion, vomiting, nausea, tremor, gait disturbance. ARIA-H (microhaemorrhages)
- Risk of bleeding, serious allergic reaction, headache, dizziness, visual changes, increased confusion, shrinkage and rarely death
- Some question about the way evidence presented for aducanumab in US

73

Lifestyle Medicine for Dementia

- Ornish et al. Alzheimers Research & Therapy. 2024. June 7; 16;122
- Effects of intensive lifestyle changes on the progression of mild cognitive impairment or early dementia due to Alzheimer's disease: a randomised controlled trial.
- First trial like this
- Limitations – small numbers (50 people, half active), short time (20 weeks)
- Diet delivered, Exercise in person and online, resistance and cardio, stress management, sleep support, group support

74

- Omega 3
- Multivit and minerals
- Coenzyme Q10
- Vits C, B12
- Magnesium
- Lions mane
- Probiotic
- (all references in the paper)

75

Results of LM intervention

- Stat significant difference from control group in
- Cognitive function on CGIC (p=0.001), CDR-SB (p=0.032), CDR (p=0.037) and borderline signif on ADAS cog ((p=0.053)
- They also checked biomarkers. CRP and LDL decreased in intervention group, little change in the neuro ones. Also positive change in microbiome of intervention group

76

Unanswered questions

- What would the two groups look like now?
- Did people like the intervention? Did they keep it up?
- Would it make any difference to behaviour?

77