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Executive summary

The 2024 update of the Lancet Commission on Dementia provides new, recent research evidence about dementia prevention, intervention, and care.

As people live longer, the numbers who live with dementia continues to rise even as the age-specific incidence *decreases* in high income countries emphasising the need to identify and implement prevention approaches. We have summarised the new research since the last Lancet Commission on Dementia in 2020, showing how cognitive and physical reserve develop across the lifecourse and how less vascular damage is likely to have contributed to a reduction in age-related dementia incidence. There is growing and stronger evidence that tackling many risk factors for dementia which we modelled previously (less education, hearing impairment, hypertension, smoking, obesity, depression, physical inactivity, diabetes, higher alcohol consumption, traumatic brain injury (TBI), air pollution and social isolation) reduces the risk of developing dementia. We have added the new additional, compelling evidence that uncorrected vision impairment and high LDL (low density lipoprotein) cholesterol are risk factors for dementia.

We have completed new meta-analyses of the risk of hearing impairment and depression for future dementia, reviewed and used the most recent literature on worldwide risk and prevalences of all risk factors to calculate new population attributable fractions for all risks. We have used these to generate a new comprehensive life-course perspective of dementia prevention incorporating these 14 risk factors. The potential for prevention is high and, overall, the 14 risk factors account for nearly half of dementias which theoretically can be prevented by eliminating these risks. This is very hopeful and although change is difficult, and some associations may be only partly causal, our new evidence synthesis shows how individuals can reduce their dementia risk and our new section about policy interventions which can improve dementia prevention. This is particularly so in low and middle-income countries (LMICs), minoritised and lower socio-economic groups where new evidence shows that there is often a higher burden of modifiable risk, so dementia is more likely to develop at an earlier age.

Evidence for specific risk factors suggests that all children should be educated, and longer duration of education is beneficial. It is important to be cognitively, physically, and socially active in mid- and late-life, with novel evidence showing that mid-life cognitive activity makes a difference even in those who received little education. The evidence that treating hearing loss decreases the risk of dementia is now stronger. Using hearing aids appears particularly effective in those with hearing loss and other risk factors for dementia. There is also new evidence that treating depression and smoking cessation may both reduce dementia risk.

We report the new evidence that reducing air pollution is linked with better cognition and less dementia. Policy makers should also improve air quality, particularly in areas with higher air pollution. Traumatic brain injury (TBI) at any age and from any source, continues to be a risk factor for dementia and there is now new and better evidence that this is true in contact sports. This leads to additional and new recommendations that protection from head injury by appropriate head protection equipment, limiting high-impact collisions and heading practice in sports training, and avoiding playing immediately after TBI, should be an individual and public health priority.

There is new evidence that reducing the risk of dementia increases healthy years of life and compresses the duration of ill health for people who develop it. Prevention approaches should aim to decrease risk factor levels early (the earlier, the better) and keep them low throughout life (the longer, the better). While starting early is desirable, there is also benefit from tackling risk throughout life, it is never too early or too late to reduce dementia risk. Much of the evidence suggests mid-life, interventions but some risk factors have their origins at societal levels and across the lifecourse. All the risk factors covered can be seen as having potential for risk

reduction at scale through policy changes that affect risk across the lifecourse. There is now additional evidence that these changes are often cost saving and clarity for the first time that risk can be modified even in those with higher genetic risk.

The field of biomarkers has moved on with fluid biomarkers more widely validated, although much of the work is in people seen in tertiary centres who differ from most people with dementia. There is more clarity about the meaning of these changes. Amyloid and tau biomarkers in those with dementia help confirm the presence of Alzheimer's disease pathology although not that it is the cause of symptoms. Amyloid accumulation occurs many years before dementia. Amyloid biomarkers are common in older individuals who do not have cognitive impairment, most of whom will not develop dementia over their lifetime. The presence of both amyloid and tau biomarkers increases the probability of dementia; markers of neurodegeneration further increase this risk**.** The vision of blood biomarkers as a scalable test to predict who will develop dementias is progressing but is not yet realised.

For those living with dementia, interventions post-diagnosis help, including maximising physical health, improving quality of life, reducing hospitalisations and planning for the future. Interventions should be individualised and consider the person's life circumstances and include family and other carers. There is considerably more evidence about multicomponent psychosocial interventions for family carers and managing neuropsychiatric symptoms. These are important and should be person-centred.

Cholinesterase inhibitors for Alzheimer's and Lewy Body dementias have new evidence of beneficial long as well as short-term effects and should be available but are still not in many countries. We know less about anti-amyloid antibody treatments. It is encouraging that for the first time a small number of trials have reported a small amount of decreased cognitive deterioration in the intervention group with substantially reduced amyloid in the brain. These have a small effect in reducing deterioration after 18-months of treatment (by 27-35%), but are expensive, burdensome to use, require intensive monitoring and follow-up and can have significant and sometimes serious side -effects. There is currently no evidence on longer-term effects and safety.

COVID-19 exposed the vulnerability of people with dementia. We need to learn from these new observations to ensure that those who are vulnerable are protected and that the lives and wellbeing of those with dementia, and their families, are valued.

Strapline

The substantial advances in understanding protection and risk, and pharmacological and non-pharmacological interventions in dementia means that now more than ever we can prevent, diagnose, and treat dementia, improving life for individuals, families, and society.

Key messages

Two new modifiable risk factors for dementia

- New evidence supports adding vision impairment and high cholesterol as potentially modifiable risk factors for dementia to add to the 12 risk factors identified in our 2020 Lancet Commission (less education, head injury, physical inactivity, smoking, excessive alcohol consumption, hypertension, obesity, diabetes, hearing impairment, depression, infrequent social contact, and air pollution).

14 risk factors account for nearly half of the risk for dementia. Modifying them may prevent or delay dementia.

- Be ambitious about prevention. Prevention involves both policy changes at national and international governmental levels and individually tailored interventions. Population-based policy should prioritise equity and ensure that high risk groups are included. Actions to decrease dementia risk should begin early and

continue throughout life. Risk is clustered in individuals and interventions therefore will often be multicomponent.

- Risk is modifiable irrespective of *APOE* genetic status. Multicomponent interventions addressing several risk factors potentially benefit individuals with either high or low genetic dementia risk.

Specific actions to reduce dementia risk across the life course.

- Good quality education for all. Cognitively stimulating activities in midlife also protect cognition.
- Hearing aids to be accessible for people with hearing loss. Reduce hearing loss by lowering harmful noise exposure.
- Treat depression effectively.
- Encourage use of helmets and head protection in contact sports and on bikes
- Encourage exercise. People who participate in sport and exercise are less likely to develop dementia.
- Reduce cigarette smoking by education, price control and preventing smoking in public places. Make smoking cessation advice accessible.
- Reduce hypertension. Aim to prevent hypertension and maintain systolic BP of 130 mm Hg or less from age 40 years.
- Detect and treat high cholesterol (low density lipoprotein cholesterol, LDL-C) from midlife.
- Maintain healthy weight. Treating obesity as early as possible also helps prevent diabetes.
- Reduce high alcohol consumption through price control and increased awareness of levels and risks of over consumption.
- Prioritise age-friendly and supportive community environments and housing. Reduces social isolation by facilitating participation in activities and living with others.
- Make screening and treatment for vision impairment accessible for all.
- Reduce exposure to air pollution.

For those with dementia, recommendations are:

- Interventions post-diagnosis help people to live well with dementia, including planning for the future. Multicomponent coping interventions for family carers and managing neuropsychiatric symptoms are important and should be person-centred.
- Treat neuropsychiatric symptoms. Activity interventions are important to maintain enjoyment and purpose for people with dementia and reduce neuropsychiatric symptoms. There is no evidence for exercise as an intervention for neuropsychiatric symptoms.
- Cholinesterase Inhibitors and memantine for Alzheimer's dementia are cheap with relatively few side-effects. They attenuate cognitive deterioration to a modest extent. There is good evidence that they have an effect for years. They are available in most high-income countries but less so in low- and middle-Income countries.
- There is progress in disease modifying treatment for Alzheimer's disease with some trials showing modest efficacy in reducing deterioration after 18-months of treatment. These findings are exciting and give hope, but effects are small, and drugs have been trialled in mild disease and people with few other illnesses. They have been licensed in some countries. They have significant side -effects with little data about longer term effects. Their expense and the precautions which must be taken, which have resource implications for staff, scanning and specialist blood testing will reduce their use now and will be challenging for health systems.
- CSF or blood biomarkers should currently only be used clinically in those with dementia or cognitive impairment to help confirm or exclude a diagnosis of Alzheimer's dementia. They are only validated in largely white populations, limiting generalisability, and raising health equity concerns.

- Covid-19 exposed the vulnerability of people with dementia. We need to learn from this and protect those with dementia as their (and their families) lives and wellbeing have been valued less than those without dementia.

Introduction

We reconvened the Lancet Commission on dementia prevention, intervention, and care (1, 2) with the aim of influencing policy, knowledge, clinical practice, and the research agenda. There has been exciting progress in dementia prevention, diagnosis, drug and non-pharmacological treatment. We now know that more can and should be done to prevent dementia and to help people living with dementia and their families. Our interdisciplinary, international, multicultural group of experts adopted a triangulation framework, prioritising systematic reviews and meta-analyses and performing new meta-analyses where needed. Each commissioner chosen from a wide geographical and cultural range to incorporate diverse viewpoints, wrote at least one section and each was presented and debated face to face as well as in multiple written versions. We unanimously agreed on the best available evidence and its consistency. We identified advances likely to have the greatest impact, performed new work to allow us to calculate potentially modifiable risk factors for dementia, (2, 3) report our new analyses, and consolidate current knowledge. We summarise the balance of evidence about prevention, intervention, and care.

The number of people living with dementia worldwide in 2019 was estimated at 57 million and is projected to increase to 153 million by 2050.(4) The overall numbers of people with dementia have increased more recently in lower income countries due to greater percentage increase in longevity. (5, 6)

In this third Lancet Commission on dementia report, we summarise what was already known by stating what we reported in previous commissions. This comes from research over decades by people from around the world. We then build on it, explain new evidence, reference it, and produce new evidence, integrating it all to make updated recommendations. We specifically consider populations in both high-income countries (HICs) and low- and middle-income countries (LMICs), and underrepresented, underserved and minoritised communities in all countries where evidence is available. The evidence is still disproportionately from HICs. Interventions may also be more likely in HICs as they depend on resource availability, despite potentially being cost-saving.(7) (8, 9) Most (31 of 46) countries' national dementia plans do not make specific recommendations for the consideration of diversity, equity or inclusion of those from underrepresented cultures and ethnicities,(10) and those that do usually confine their recommendations to interpretation of cognitive tests.(11) As we set out below, considering these factors for all cultures and ethnicities in all types of dementia is essential to target help to those who need it most.

Prevention

There has been an explosion of work on dementia prevention and risk reduction relating to reducing the 12 factors identified from the large research literature and added to by our work in our earlier Lancet commissions (2017, 2020), with the potential to prevent 40% of cases of dementia (less education, hearing loss, hypertension, physical inactivity, diabetes, social isolation, excessive alcohol consumption, air pollution, smoking, obesity, traumatic brain injury, depression).(2) We discussed mechanisms for these 12 risk factors which indicated that risk at any age might be reduced.

Here we update the evidence and consider other potential risk factors. We use a lifecourse approach to understand how to reduce risk or prevent dementia, as many risks operate at different timepoints in the lifespan. For example, obesity and high blood pressure (BP) represent risk factors in mid-life, often with earlier life origins, but in late-life may reduce if people are developing mild cognitive impairment (MCI) and dementia. (12-14) As before, we look for risk factors with high-quality, consistent, dose respondent, validly measured evidence, which precedes dementia and remain when measured a decade or more before onset. We only include those with convincing evidence, while acknowledging there are likely to be other risk and protective factors. The commissioners met and discussed the evidence and what to include and set out our discussions and

the evidence in the paper.. We discussed new biologically plausible evidence about mechanisms linking a risk factor to dementia and when there is new evidence, we present it and summarise previous evidence about mechanisms to give a balanced picture. We do not, however, aim to give a complete, detailed review of all mechanisms. We also discuss if evidence is from diverse populations and therefore generalisable, and if there is evidence that intervention makes a difference.

Compression of morbidity

Data from some HICs suggest a decline in age-specific incidence rates (15) highlighting the importance of prevention. There are less data from LMICs. Where these have examined the relationship with deprivation, the decline is primarily in those in socio-economically advantaged areas.(15) This suggests that many dementias are potentially preventable (and deferrable) but age-specific rates may increase if risks, such as diabetes or obesity, prevalence increases and this may be particularly in those with less education. A recent English study suggests this may be happening already although there is uncertainty with more evidence needed. (16) (17, 18)

Those with a healthy lifestyle, involving regular exercise, not smoking, avoiding excess alcohol, and late life cognitive activity, not only have a lower risk of dementia, but dementia onset was also pushed back further than life expectancy prolongation. (19) Overall, those living healthier lives can expect to live longer, and if they develop dementia, live less years with it – with significant quality of life implications for individuals and cost-saving implications for services.

Cognitive vulnerability, brain maintenance and cognitive reserve

As discussed in the last commission, neuropathological changes do not inevitably lead to dementia. Most older people with dementia have several types of neuropathology. One study of six community cohorts, comprising 4,354 people aged >80 years who had died in the US or UK, analysed six types of neuropathology and found 91% of people died with two or more types of neuropathology.(20) The more types of neuropathology people had the more likely they were to have dementia (see figure 1), but some people with many neuropathologies had not developed dementia.

The ability to withstand neuropathology before showing the symptoms of dementia is described as cognitive reserve. Sometimes the term resilience or brain reserve is also used as coping with pathology and resistance to neuropathology. People who are physically healthier are better able to withstand the effects of neuropathology. (21) Thus, while the age-related incidence of dementia has decreased in some countries over the last 25 years, one post-mortem study showed no differences in neurodegeneration but a reduction in vascular pathology.(22) A systematic review found that physical, cognitive and social activities increase cognitive reserve and attenuate the effect of neuropathology. (23) Overall, greater cognitive and physical reserve(21) developed across the lifecourse, preserving cognitive health despite neuropathology, and less vascular damage are likely to have contributed to the reduced age-related dementia incidence.(24) Nonetheless, the numbers of people with dementia continue to rise due to population ageing.

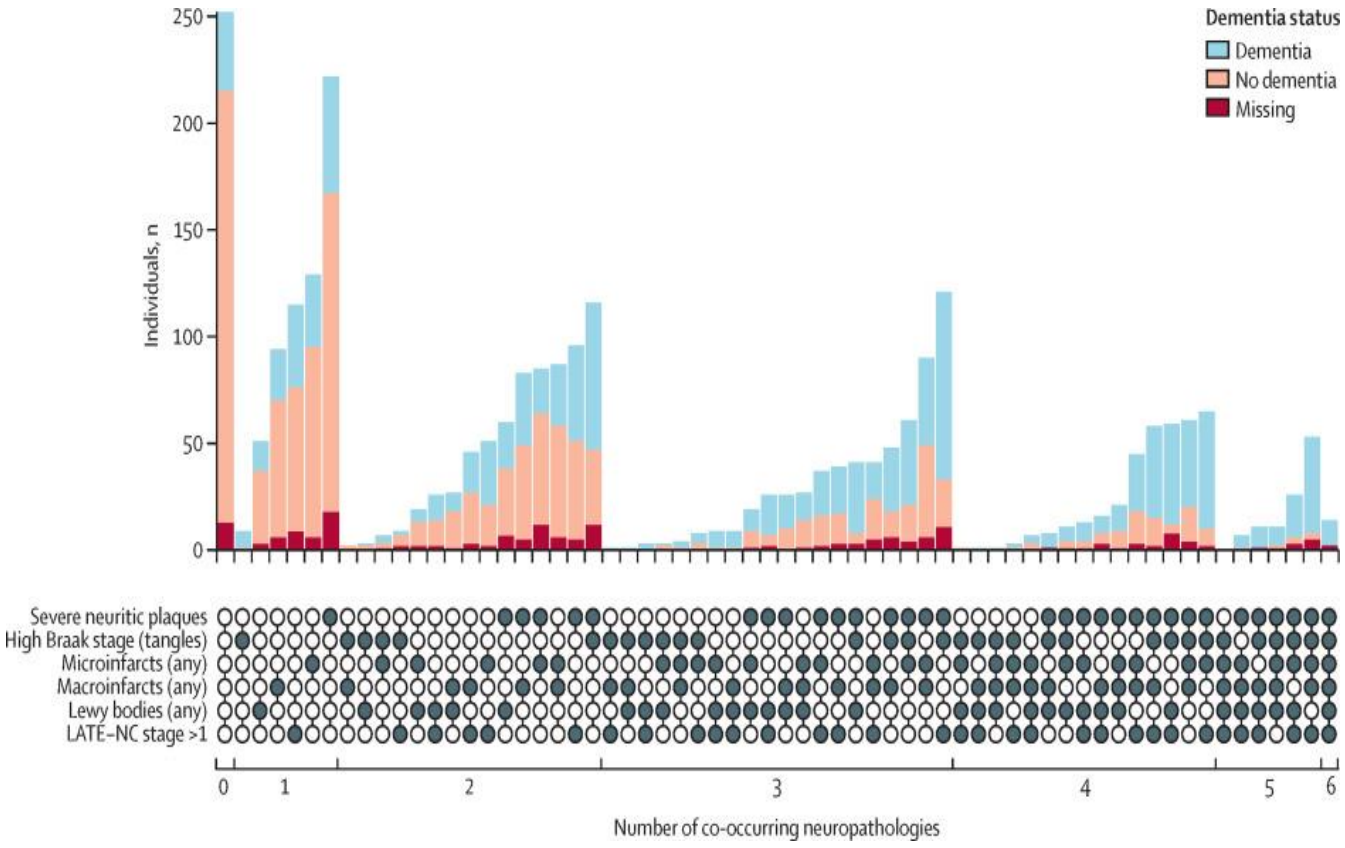


Figure 1 Co-occurrence of six key neuropathologies by clinical dementia status from data pooled across five cohorts (Adult Changes in Thought. Cambridge City over-75s Cohort Study. Cognitive Function and Ageing Studies. Framingham Heart Study. Limbic-predominant age-related TDP-43 encephalopathy neuropathologic change. Religious Orders Study and Memory and Aging Project). with permission **(20) LATE-NC=** Limbic-predominant age-related TDP-43 encephalopathy

The challenges of research into prevention and risk reduction in dementia

Lifecourse nature of exposures to protection and risk

There are many factors that operate across the lifecourse from pregnancy through to later life. These are challenging to track, and our evidence base is necessarily limited to what is studied at particular ages. Here, we look at evidence directly related to dementia. However, there is much broader evidence that we do not capture on early life optimal brain growth and exposure to adversity and its impact on cognition, vascular health and on physical and cognitive activities. Educational exposure has strong protective evidence. In this Commission we use the language of risk, and then discuss protection which can mitigate both the risks and illness arising from the risks and is an important opportunity for the future.

Effects of the long prodrome before dementia-identification and intervention

The long preclinical phase of some dementias over more than a decade is characterised by progressive neuropathological changes, such as amyloid or tau accumulation before Alzheimer's dementia (AD), which initially have few cognitive effects, that may increase over many years.(25) There can be changes in behaviour

and health long before dementia, so potential risks identified in the few years before dementia could be either or both a true causal effect or reverse causation. This can be the case even when studies report the mean cohort follow-up time, this may vary between those who develop dementia (as it is censored at dementia onset) and those who do not. Future studies should report the mean follow-up of those who develop and do not develop dementia separately or test the effect of excluding incident cases which develop within 5-10 years of follow-up.

There are many methodological difficulties with designing and conducting intervention trials in dementia prevention, including ensuring sufficient follow-up duration, recruitment of participants from high risk or excluded groups, and adherence to and making changes that are associated with better cognitive functioning trajectories,(26) but adherence decreases with increasing intervention complexity and intensity.(27) It can be more difficult to demonstrate an intervention's benefit in RCTs if the control group is highly motivated to also take up the intervention. Benefit may stop or decrease if the intervention does not continue.

Causes of dementia

Strokes (including those caused by atrial fibrillation), Parkinson's disease, HIV, and syphilis, are causes of dementia rather than risk factors, and we do not include them here as risk factors. Vascular dementia is usually related to stroke (and is specified in the diagnostic criteria) which can be both symptomatic or without motor symptoms and detected on imaging. These happens more often in people with many potentially modifiable risk factors, such as smoking, hypertension and diabetes. (28)

Length and timing of exposure to possible risk factors

The duration, consistency, and timing of exposure to possible risk may be important with recent studies finding, for example, that mid-life diabetes is a risk factor for dementia, but diabetes may not be a risk in those whose diabetes onset is in late-life. (29) It is unclear whether this is because of shorter duration of exposure in those who develop it in late-life, more severe diabetes or whether there is a critical period of exposure. It may be if people with late-life diabetes live long enough, they may also be at greater risk of dementia. Other risk factors, such as smoking, which the evidence now suggests is a risk factor in midlife, clearly also confers risk in late life.

Clustering of risk factors

Important social disadvantage such as less education, more social isolation and lower socioeconomic status tend to cluster with health factors that predict cognitive decline and dementia. (30) People therefore often have several risk factors which may act together, and this means it is important to consider communality. We have chosen to consider risks individually and correct for communality, rather than consider different risk profiles.

Diversity, Equity and Inclusivity

We have previously considered prevention and risk reduction on a global level using international data on prevalence of risk factors and relative risks (RR) from meta-analyses where possible.(1, 2) Consideration of equity is important, not only ethically but also to inform intervention targeting and accessibility to maximise preventative impact. (31) Many 'big data' sources from volunteers by their nature exclude those most at risk.(32) In addition, some of the big cohort studies like UK Biobank also recruit younger volunteers and while this is positive for the exclusion of reverse causality, currently most people have not reached the age where dementia is more common and therefore finding Cohort studies of dementia risk factors and therefore meta-analyses are overwhelmingly from HICs, and within these cohorts, recruit people of European origin, more education, and higher socioeconomic status, and more usually of older age groups with few people from minority ethnic groups. (33) This also applies to clinical trials and for both may relate to exclusion criteria,

specifying other significant medical and psychiatric illnesses, lack of a study partner, inability to shoulder research participation burden and lack of local language fluency. (34, 35)

Risk factor prevalence varies between countries(36) as well as within countries.(37) A meta-analysis of 31 studies from 15 Latin American countries showed twice as many people without any education compared to those with one or more year (21.4% versus 9.9%) had dementia and a slightly higher prevalence in rural than urban and women versus men.(31) Risk factors cluster within communities and individuals. Underserved ethnic groups, such as the Māori group in New Zealand, First Nation groups in Australia, Black individuals in the US and UK, and Hispanic individuals in the US, have higher prevalence of potentially modifiable risk factors.(38-45) Furthermore, the literature and therefore our commissions have assumed that the impact of having each risk factor is the same for everyone. In contrast, cardiovascular disease research has found that the effect of, for example, high BP effect on the risk of stroke is greater in minority ethnic groups in the UK compared to the White British population and risk factors effect for dementia may vary between ethnic groups.(46, 47)

Socio-economic status

The effect of socioeconomic status on prevalence of some risk factors can vary between countries. There is a higher prevalence of hypertension, diabetes, obesity, physical inactivity, smoking, excessive alcohol, less education, traumatic brain injury (TBI) and exposure to air pollution in those from lower socioeconomic groups in HICs, and with lower income level.(48-50) In LIC, reported lower prevalences of obesity or diabetes in those with less wealth or education are inconsistent.(51) (52) Social isolation is seen less in some LIC. [34]

Female sex and gender

Biological sex – the physical differences between people from sex chromosomes and reproductive organs is usually noted at birth and people are assigned a sex. Lived gender is how a person identifies on the spectrum of gender. They are increasingly recognised as separable in societies for some people. Biological sex, hormonal exposure and societal roles are all potentially important in influencing risk of dementia syndrome and its expression in later life. Findings about the effect of biological sex on risk of dementia are inconsistent.(53) Women have higher age-adjusted dementia incidence rates than men in some but not all countries.(54) One meta-analysis with nearly a million people from 205 studies in 37 countries found that increased rates of dementia in women compared to men were explained by differences in life expectancy and education. (54) An individual participant -analysis (IPA) found widely varying results in individual countries. (55) Overall 21 cohorts with 29,850 participants across Africa, Asia, Europe, North America, Australia, and South America found an HR of 1.12 (1.02, 1.23) of women compared to men. The first nationally representative dementia prevalence estimates in India found higher prevalence in women, people with less education, and rurality. (56, 57) In both HICs and LMICs there is evidence that risk is related to other factors than biological sex. It has been hypothesised that longer life span, less educational attainment and reduced oestrogen in postmenopausal women could cause sex differences in dementia development. A representative nationwide study in Japan of 2200 adults followed from age 60 for 12 years or until death, found that lower educational attainment and domestic work or manual labour occupations accounted for women's lower baseline cognitive scores and more cognitive decline over the years of follow-up. (58) A UK study of 15,924 participants found that women born more recently were catching up with men's higher memory and fluency scores, as women's access to education increases.(59) Analysis of 70,846 people aged ≥60 years in US, Mexico, Brazil, China, and India found adjustment for education attenuated men and women's cognitive difference and eliminated it in the high education group in high and middle-income countries.(60) This difference between countries suggests that increased risk in women is related in part to lack of opportunity in work and education, leading to more poverty and less access to medical care and discrimination, all of which vary between cultures rather than biology. (61) While there is relatively little

knowledge about risks of dementia in those who have the same sex partner, one US study of 23,669 adults aged over 50 found a higher risk of cognitive impairment in those with a same sex rather than opposite sex partner. (62) However, cisgender men and women have fewer risk factors for late-life dementia on average than transgender men or women. (63)

Methods to consider causality.

While randomised controlled trials (RCTs) are the gold-standard in establishing intervention effectiveness, and therefore causality of risk factors, they are often impractical for dementia. Trials may require decades of intervention and follow-up before clinical dementia occurs, leading to prohibitive costs and bias because of selective drop-out. It may be unethical or impossible to randomise people. Causal inference methods, quasi-experimental or ecological studies may add to the evidence. (64) A Cochrane review comparing studies of healthcare outcomes (not dementia specifically) which assessed quantitative effects of RCTs and observational studies of interventions found 23/34 reported substantially the same effect estimates from RCTs and observational studies.(65) Differences were found when there was high heterogeneity in meta-analysis (>50%). One approach is to study the effects of intervention implemented at a particular time, such as reduction in air pollution or increase in education for a whole population. Another is Mendelian randomisation (MR) analyses which we have, for the first time, incorporated in our triangulation framework where possible, to help to establish causation. MR is a causal inference method, based on alleles being randomly allocated at conception, so their association with a risk cannot be caused by a later disease. This assumes that behaviours and mood are partly genetically driven and can only be used where there is sufficient genetic diversity influencing a particular risk factor in the population studied. MR is also limited by factors such as survival bias, which is likely to account for controversial MR findings which are in the opposite direction to RCT findings. (66) (67)

Specific potentially modifiable risk factors for dementia

Dementia prevention efforts should take a nuanced and tailored approach for different groups and seek to reduce structural and sociocultural barriers to engagement of higher risk groups. Trials and research databases should aim for sociodemographic diversity to reflect real life populations. In the next sections, we briefly describe relevant newly published and illustrative research studies that add to the 2020 commission's evidence base about protective and risk factors for the development of dementia. We discuss where in the life course the evidence suggests they begin to be important given the constraints of ages at which evidence is studied.(2) While some risk factors, like hypertension, evolve and change during the life course, others such as alcohol or smoking may be more consistent. We summarise potential mechanisms of protection from dementia in Figure 2.

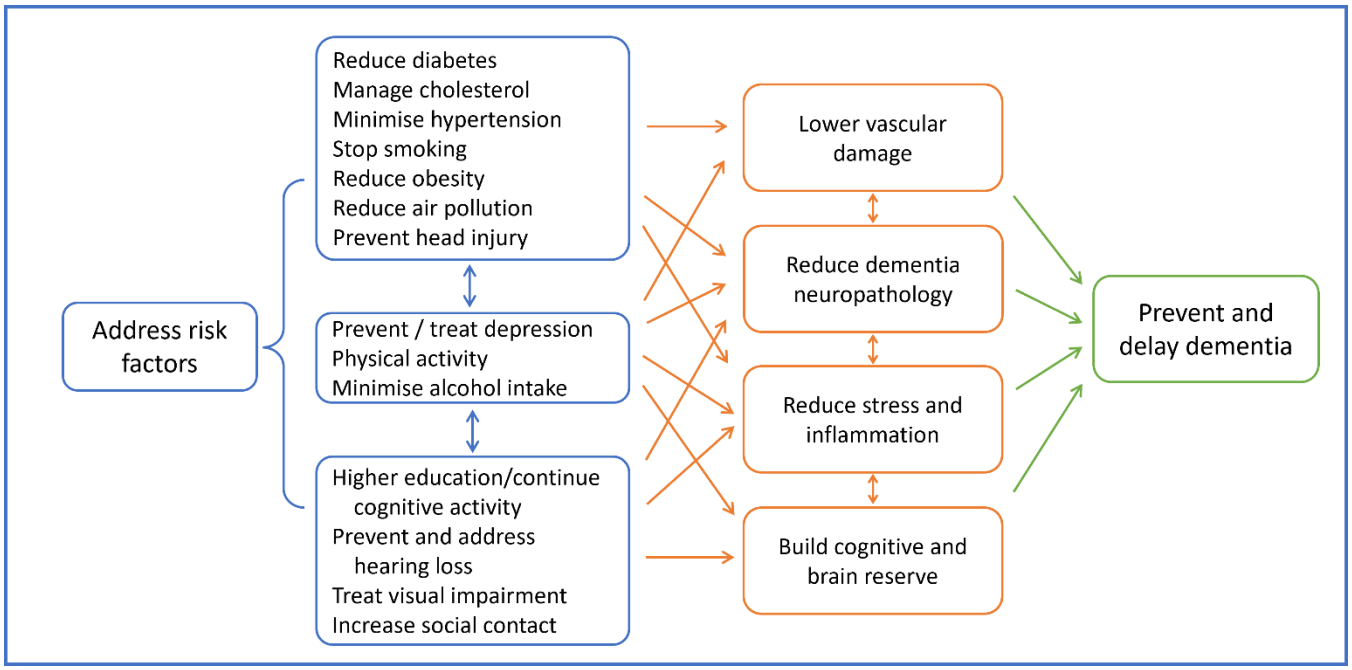


Figure 2. Possible brain mechanisms for enhancing or maintaining cognitive reserve and risk reduction of potentially modifiable risk factors in dementia.

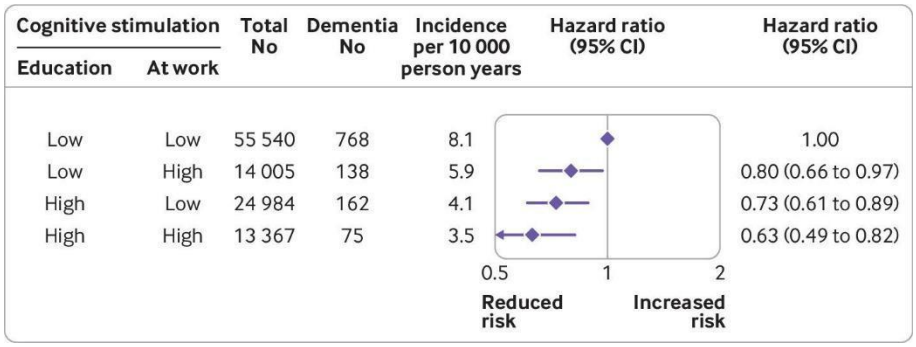
Education, educational attainment, and cognitive activity

We previously reported that those with more childhood education and higher educational attainment have a reduced dementia risk, and discussed whether effects of later cognitive stimulation might be due to people with more education having more cognitively stimulating occupations.(2) Differences in the quality of education, as measured by reading levels at age 14 to 15, have been estimated to account for about half of the US disparities in dementia prevalence across racial groups.(68) Overall, it appears to be educational attainment, not the related years of education, which drives the protective effect for future cognition and dementia. (69, 70)

In China, studies 20 years apart, using the same methods and geographical area, find that dementia incidence and prevalence has increased specifically in those with less than 6 years of education, possibly because this is a population that is now more likely to survive to older age. (71) In the US there has been a decline in dementia, in parallel with more education for all the diverse US population. Reported dementia prevalence has fallen more steeply in Black people aged 65 to 74 years, in line with the greater improvement in education.(72) In Asian Americans attaining a university degree is associated with lower dementia risk.(73)

A study of 107,896 people from HICs followed for 13.7-30.1 years found a lower risk of dementia in participants with high compared with low cognitive stimulation at work (10-year follow-up HR= 0.79, 0.66 – 0.95).(74) Those with high cognitive stimulation at work but little education had an 80% (0.66-0.97) risk of dementia and those with high cognitive stimulation and high education had a 63% (0.49-0.82) risk, compared to those with little education and low work cognitive stimulation (see Figure 3). There were similar results in a study from Asia, Australia, Europe, and North America following 10,195 people for 3.9 –6.4 years, where both high school education and occupational complexity were independently associated with increased dementia-free survival time, with 28% of the effect of education mediated by occupational complexity.(75) However, a US study found

that years of schooling predicted protection against the effect of MRI white matter lesions in White but not Black people. (76) Globally, educational attainment has increased over time but remains relatively low in some countries, so is of great relevance when considering dementia prevention and overall health. (77)



With permission ***Figure 3 Association of cognitive stimulation over the life course with incident dementia (74)***

Mechanism

Higher cognitive stimulation has been associated with cognitive reserve and the ability to maintain this through multiple mechanisms. These include the level of circulating proteins to allow brain repair through axonogenesis and synaptogenesis, (74) greater efficiency of and less decline in functional brain networks,(78, 79) increased occupational attainment linked with improved financial situation leading to choices about where to live, better physical health through better health care access and health awareness, and other health promoting behaviours. An MR study found the effect of years of education (measured by genes predicting this) was mediated by intelligence (measured by genes linked to IQ test performance).(80)

Education and cognitive interventions in normal cognition and mild cognitive impairment

In the previous Lancet commission, we reported that trials of computerised cognitive training (CCT) in healthy older people and those with mild cognitive impairment generally suggested a small positive effect on cognition, but it was unclear whether CCT was of clinical value because of the low standard and heterogeneity of studies.(81) An updated Cochrane review of CCT interventions for maintaining cognitive function in cognitively healthy older individuals, delivered over 12 to 26 weeks, also found low-quality evidence supporting immediate small benefits of CCT on global cognitive function versus active controls and on episodic memory versus inactive control, without long-term evidence of effect.(82) It is important to note that short term, low intensity CCT interventions, which can be financially costly, have only low quality evidence of short-term effectiveness and none of long term effectiveness in maintaining cognition. It is possible that the cognitive training in these trials does not cover the breadth of cognitive function or is not intensive or engaging enough or is too late in life to preserve cognitive function. Exposure to cognitive stimulation at work reduces risk of dementia and is of longer duration than cognitive interventions or cognitively stimulating hobbies. (74)

Hearing loss and hearing aids

Globally, an estimated 20% of people have hearing loss, sometimes related to occupational or environmental exposures to noise or untreated infections; 62% of them are aged over 50 years, and it is often untreated.(83) In our previous Lancet Commissions we performed a meta-analysis of high-quality cohort studies with participants free of dementia but with objectively measured peripheral hearing loss at baseline. (1, 2) We defined high quality as objective measures of hearing through pure-tone assessment, > 5 years follow-up, adjusted for age,

cardiovascular factors and cognition or education at baseline and an overall risk for the outcome of incident dementia. There are four further meta-analyses on the association between hearing loss and subsequent dementia, (84-87) one of which focussed on Sinitic tonal languages.(86) They all found a significant association between hearing loss and subsequent dementia ranging from 1.28 (1.02-1.5)(84) to 2.39 (1.58 – 3.61).(85) None of these included all the criteria that we judged ensured high-quality data in our previous meta-analysis. We also excluded studies comparing populations with varying severities of hearing loss, but not comparing hearing loss individuals with those with normal hearing. We searched again until March 20, 2023, on PubMed, Ovid Embase, PsycINFO, Web of Science, Cochrane Library, PROSPERO, and Centre for Reviews and Dissemination, contacting authors for clarification as needed and found six studies fitting the criteria (see appendix page 1-2 for search strategy and results)(88-93) We calculated totals if only subgroups were reported, generating an overall HR for studies.(89, 91, 92) We used results unadjusted for hearing aids as they are in the causal pathway between hearing loss and dementia. (92-94) The baseline age of study participants ranged from 59 to 77 years, average =59 with the largest study recruiting participants at age 18 to 20 but measuring hearing status at mean age 59. (91) Follow-up between baseline hearing and dementia status was between 6 and 12 years (average 7 years). In random effect meta-analysis, people with hearing loss had an increased risk of dementia compared to those with normal hearing (HR 1.37, 1.00-1.87, I^2 =80%, n=666,370) see figure 4. Four of the smaller studies reported hearing aid use, and between 18 and 64.5% of those with hearing loss wore hearing aids. (88-90, 93) All people with hearing loss were included, without considering use of hearing aids in the overall risk estimate, so it is a conservative estimate. In our meta-regression, studies with more people who wore hearing aids found a lower likelihood of dementia, but this had wide confidence intervals (-1.32; -3.34-0.71).

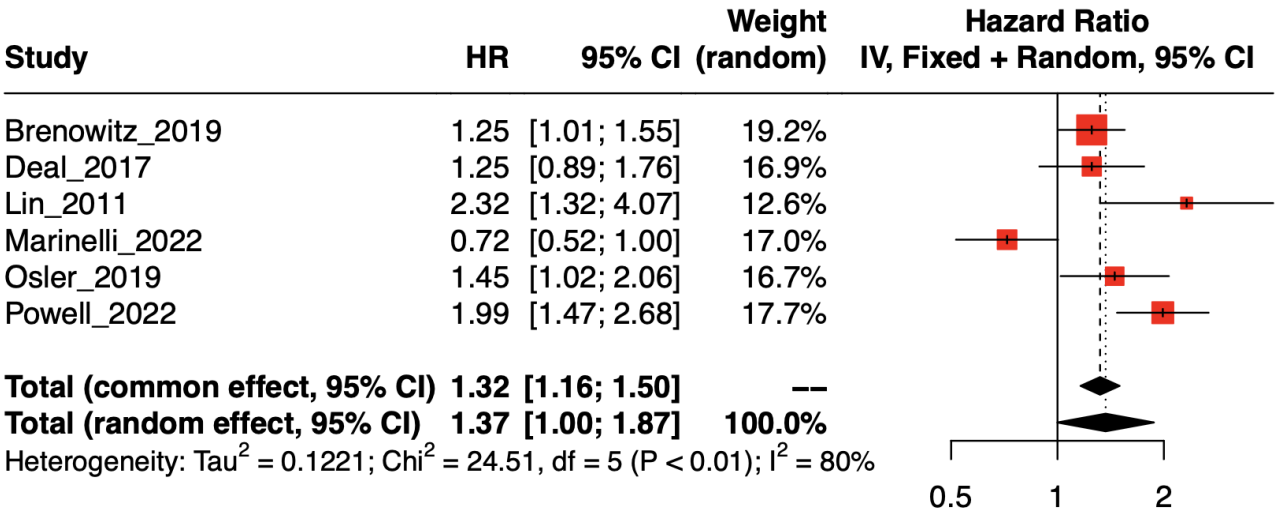


Figure 4 Relative risk of dementia for people with hearing impairment at baseline compared to those without hearing impairment.

As severity of hearing loss increases, dementia risk increases: all four studies which have investigated dose-response between hearing and dementia risk have found that every 10 dB decrease in hearing ability increases

dementia risk. (89, 90, 95, 96) The magnitude of this risk increase varies between studies, from 4%(95) to 24% (90) increase of dementia risk per 10 dB worse hearing.

Specific speech-in-noise (SiN) loss is rarer where the deficit is understanding speech where other sounds are present. The only large study to date where SiN was objectively measured is from UK Biobank, n=82 039; 100 people with SiN loss, followed for a median of 10 years). Compared to normal hearing, impaired SiN hearing was associated with a 61% (HR = 1.61, 1.41–1.84) and poor SiN with a 91% (HR 1.91, 1.55–2.36) increase in dementia.(97)

Mechanisms

There are several hypothesised mechanisms as to how hearing loss might increase dementia risk. Psychosocial factors such as loneliness, depression and social isolation may be involved. Other mechanisms include reduced cognitive reserve from lack of environmental stimuli, increased cognitive resources needed for listening and an interaction of these risks with brain pathology.(98) This is consistent with longer exposure to hearing loss being associated with higher dementia risk, with maximum risk in those diagnosed with hearing loss for more than 25 years. (99) Another postulated mechanism is that common cardiovascular pathology causes hearing loss and dementia, when cardiovascular health status or risks would substantially account for the association between hearing loss and dementia risk, but this has not been reported.(98)

Effect of correction of hearing impairment

This evidence raises the question of whether treating hearing loss with hearing aids can eliminate or mitigate this increased dementia risk. The ACHIEVE study, the first RCT of hearing aids recruited healthy volunteers from advertisements (N=739), or older adults from the Atherosclerosis Risk in Communities (ARIC, N=238) study.(100) There was no overall effect on the primary outcome, cognition at three-year follow-up (difference -0·002, –0·08 – 0·08). Importantly, a pre-specified analysis found substantial effects in the ARIC subgroup in cognition at three years, (difference 0·19, 0·02 -0·36). The ARIC population had more dementia risk factors (2.8 years older, lower baseline cognition, smoked more, less education, more often lived alone, more likely to have diabetes and hypertension). Cognitive decline was higher in the ARIC group (24%) than in people who answered adverts (8%) at 3 years follow-up. This volunteer response bias resulted in insufficient statistical power to detect any difference. Overall, there was a large (48%) protective effect of hearing aids on cognition in a high-risk population. The explanation of the large effect in ARIC may be that hearing aids in high risk groups also change social contact, low mood, cognitive stimulation and improve motivation and communication about medical treatment but as yet we do not have evidence of this.(101)

We previously discussed the evidence that hearing aid use is protective against dementia and reduces cognitive deterioration rates after hearing aid use began.(2) A more recent systematic review and meta-analysis of 8 cohort studies with 126,903 participants, followed for 2 to 25 years, reported that people with hearing impairment who used hearing aids had a 19% (0.76-0.87; I^2 = 0%) lower risk of cognitive decline and a 17% (0.77-0.90; I^2 = 0%, 4 studies) lower risk of dementia, compared to those with uncorrected hearing impairment (see figure 5).(102)

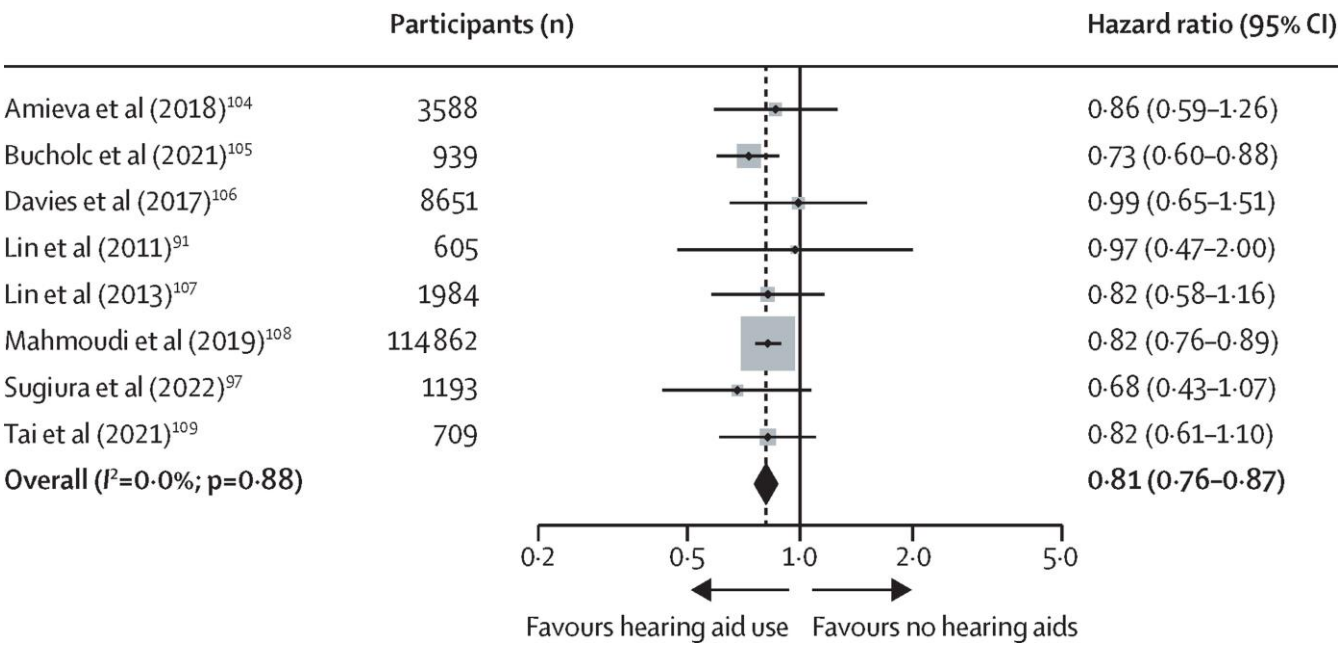


Figure 5. Longitudinal association of hearing aid use and cognitive decline

Pooled hazard ratio in random-effects meta-analysis. Weights are from random-effects analysis. Created with data

In another cohort of 2114 people aged >50 years, with self-reported hearing-impairment, 1154 had MCI and those that used hearing aids were at significantly lower risk of developing all-cause dementia over follow-up compared to those not using hearing aids (HR 0.73, 0.61 – 0.89).(103) The median time to incident dementia was 2 years for non–hearing aid users and 4 years for hearing aid users.

The observational evidence of the benefits of hearing aids for dementia risk is increasing. Even if we only consider the studies with long follow up to reduce reverse causality, the evidence on hearing aids reducing dementia risk is consistent and supportive. Implementing hearing aids, if effective in preventing dementia would likely be cost-saving.(7)

Depression

In the 2020 Lancet commission we concluded based on published studies that the relationship between depression and dementia was probably bidirectional and that in the years before dementia, depression can be a symptom of evolving dementia; a reaction to cognitive impairment; or a cause of cognitive impairment. We also noted that few studies had considered whether risk of dementia was affected by treatment.

A new meta-analysis found depression was associated with all-cause dementia although there was a high degree of between studies heterogeneity (RR 1.96, 1.59-2.43; I^2= 96.5%; 27 studies). (104) For this commission, we performed a random effects meta-analysis using the seven studies with a 10 to 14-year follow-up (104-111) and found an increased risk of dementia (RR 2.25, 1.69 -2.98 I^2= *82.8%*) see figure 6. Six studies which specified the age of participants had baseline average age of 63 years. Although the studies were heterogenous in the effect size, they consistently found a higher risk including in those which matched participants for age, sex, socioeconomic status, and comorbidities. Similarly, a later Danish case-control study of 246 499 adults diagnosed with depression at baseline, at median age 51, found a higher risk of dementia among those

diagnosed with depression (HR 2.41,2.35-2.47), after 20 to 39 years (HR 1.79, 1.58-2.04) and in those diagnosed with depression in early, middle, or late life (18-44 years: HR 3.08; 2.64-3.58; 45-59 years: HR 2.95; 2.75-3.17; 60 years: HR 2.31; 2.25-2.38).(112)

A Swedish nationwide study of 41,727 twins with 18-year follow up found that dementia risk was increased for mid- and late-life and lifelong depression: mid-life, OR 1.46 (1.09-1.95), late-life 2.16 (1.82-2.56), and lifelong depression 2.65 (1.17-5.98).(113)

Overall, these studies suggest that depression increases the risk of dementia at all adult ages, although in late life some of the association is caused by preclinical dementia. We are therefore classifying it as a midlife risk factor as there is clear mid-life risk. The findings about the effect of both medication and therapy treatment in reducing the risk now suggests it is important to treat depression both for quality of life and because it may reduce the risk of later dementia.

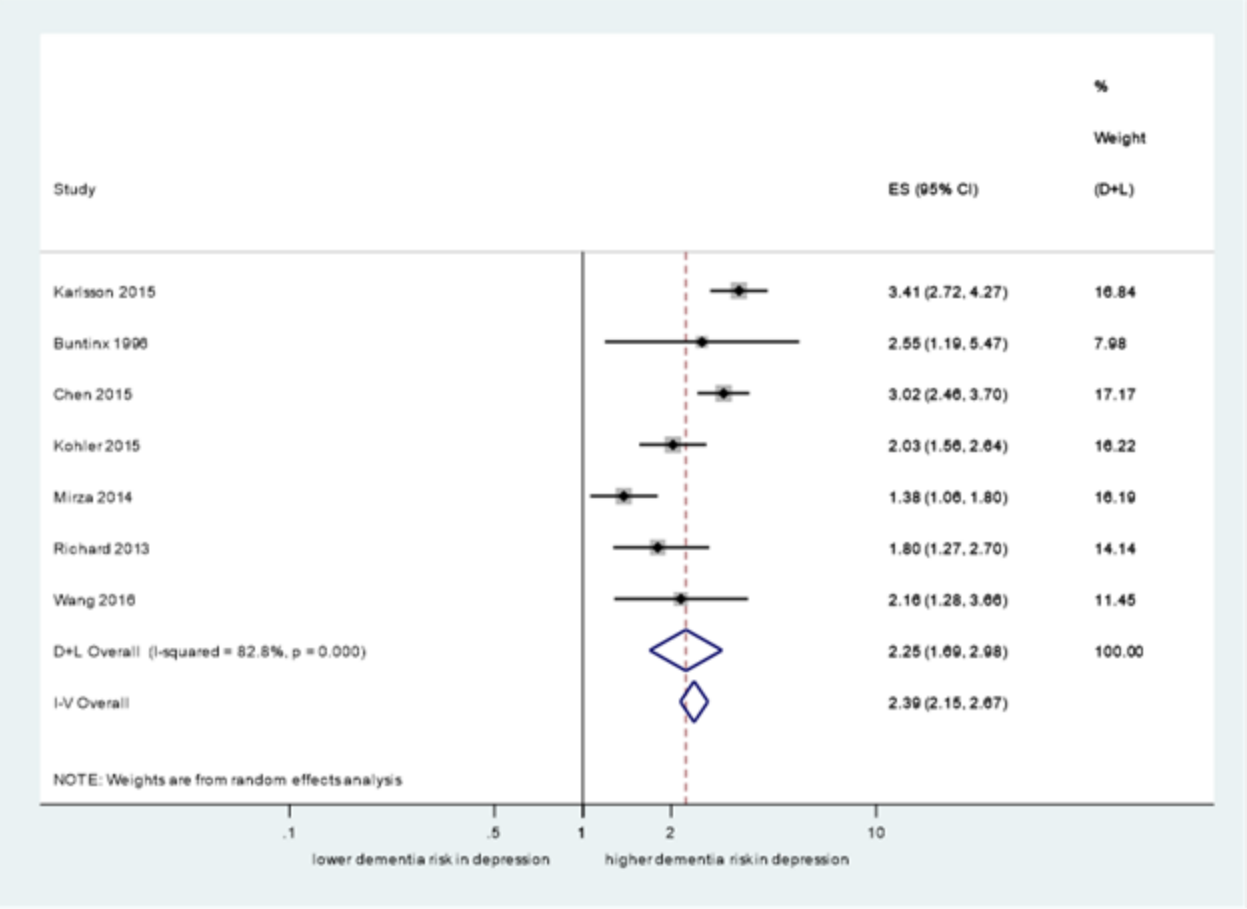


Figure 6 Meta-analysis of risk of developing dementia 10 to 14 years after depression diagnosis compared to those who were not depressed.

Mechanisms

There was no difference between identical or non-identical twins in the study above, leading to the conclusion that the risk was not accounted for by genetic risk or early life environment, but the risk of mid-life depression and future dementia was lower in those with more than eight years education. (113) Mechanisms linking depression to dementia risk remain unknown although depression is related to reduced self-care and social

contact. Another hypothesised mechanism by which depression might increase dementia could be over-secretion of cortisol leading to hippocampal atrophy or inflammatory response.(114)

Interventions for depression

A UKB study of interventions for depression included 354,313 participants aged 50–70 years without dementia, followed up for a median of 11.9 years,(115) finding that people with a diagnosis of depression (n=46,280) had a higher risk of developing dementia (HR 1.51, 1.38–1.63). Those who were treated for depression (medication 14695, psychotherapy=2151, combination = 5281) were less likely to develop dementia than the untreated group (overall HR 0.69, 0.62–0.77; pharmacotherapy HR 0.77, 0.65–0.91; psychotherapy HR 0.74, 0.58–0.94; and combination therapy HR 0.62, 0.53–0.73). The untreated group who remitted did not have a higher risk of dementia than the nondepressed group (HR 0.84, 0.56–1.24). This is a larger group and for a longer period compared to previous evidence(116, 117) but remains open to bias of observational studies. However, it is unlikely there will be such long term RCTs.

Traumatic Brain Injury

We meta-analysed the risk of all-cause dementia following TBI in the 2020 commission (RR 1·84, 1·54–2·20).(2) Subsequently two meta-analyses reported similar figures. The first, including 21 studies, totalling 8,684,485 people, reported OR 1.81 (1.53-2.14) for TBI and risk of dementia. (118) A meta-analysis of 32 studies (n= 7,634,844), which included 17 studies from the other meta-analysis, found a RR for dementia after TBI of 1.66 (1.42-1.93). (119) Both of these studies found that younger age (<65 years) and male sex were associated with higher risk.

In LMICs, TBI occurs most commonly from road traffic accidents but in HICs it is most commonly because of falls or violence, with alcohol a common contributory factor. (120) TBI risk is therefore linked to other health behaviours which are risk factors for dementia. A large (n= 32,385) national Finnish prospective longitudinal study found the association between major TBI (>3 days hospitalisation) and dementia was attenuated from HR 1.51 (1.03-2.22) to HR 1.30 (0.86-1.97) after adjusting for other risk factors for dementia including education, smoking status, alcohol consumption, physical activity and hypertension.(121)

Mild TBI and dementia

Concussion and mild TBI (mTBI) are often used interchangeably.(122) There remain relatively few studies of mTBI and dementia risk, and methodological issues include inconsistent definitions. A previous cohort study using a national patient register found increased risk, even with a single mTBI (OR 1.63; 1.57–1.70).(123) Since our last commission, a cohort study found no increased risk from mTBI over 15 years[229] but a systematic review and meta-analysis of 3,149,740 people reported a history of mTBI, fulfilling world Health organisation criteria, increased risk of AD (RR 1.18, 1.11-1.25) and a sensitivity analysis including the many fewer studies in which mTBI preceded AD by > 10 years also found higher risk, although with wider confidence intervals (RR 2.02, 0.66-6.21, n=2,307). (124)

TBI and sport

Some sports (e.g., rugby, American football, ice hockey) involve frequent head contact and whiplash events are associated with greater risk of repeated TBI than sports where low frequency individual TBI may occur in accidents or as part of the sport (e.g., cycling, horse-riding, boxing). There is increasing concern that professional and amateur soccer and rugby players live with and die more from neurodegenerative illnesses than the general population, which may be related to occasional severe TBI or frequent mTBI from physical contact with others or heading a football.(125) A meta-analysis which ranked concussion risk in contact sports, found 83 studies of reported concussion rates, mainly from the US (n=66) with 5 each from Canada and the UK.(126) Rugby had the highest concussion rate (28.3 concussions per 10,000 games; followed by American Football (8.7) ice hockey

(7.9), and wrestling (5.0). College sport had slightly higher concussion rates than high school sport; 3.8 concussions vs 3.7 per 10,000 games.

There is evidence that people who play professional soccer for longer and in positions where they head the ball more often and are more likely to incur head injuries are at higher risk of dementia. One small study (60 players) found cognitive ability in former professional soccer players was inversely associated with estimated heading frequency. (127) A large study from Scotland found 5.0% of 7676 former soccer players compared to 1.6% of 23,028 individuals matched on age, sex, and area socioeconomic status developed a neurodegenerative disease (HR, 3.66; 2.88-4.65).(128) This elevated risk was highest for defenders who have a greater frequency of headers and lowest for goalkeepers, and higher for those who had played professionally for >15 years. A study of French professional footballers found all-cause mortality lower than that of the national population (SMR 0.69, 0.64–0.75) but an excess of deaths with dementia (SMR 3.38, 2.49–4.50). (129, 130) A cohort study of 6007 male football players (but not goalkeepers) from Sweden's top division and controls matched for sex, area and region reported that football players had a higher risk of all-cause dementia (HR 1·62, 1·47–1·78) but not motor neuron or Parkinson's disease. (131) Risk of all-cause mortality (HR 0·95 0·91–0·99), was lower among football players than controls. Similarly, all-cause mortality was lower among former national team rugby players until 70 years of age but over a median of 32 years, 47 (11.4%) former rugby players and 67 (5.4%) controls were diagnosed with neurodegenerative disease (HR 2.67, 1.67-4.27).(129)

Mechanisms

TBI can cause or exacerbate dementia through direct trauma.(132) Plausible pathological mechanisms for longer term neurodegeneration following TBI include axonal injury promoting early generation of proteinopathies (hyperphosphorylated tau and amyloid B), microglial activation and cortical atrophy. (133, 134) We identified 3 cohort studies which assessed brain pathology in those with a history of TBI and loss of consciousness, with no consistency between studies for the association with neuropathologies. A study of 1589 people who had an autopsy found an increase in Lewy body pathology and hippocampal sclerosis but not plaques or tangles in those who had TBI with loss of consciousness. (135) An ADNI study of 241 participants, 41 of whom reported previous TBI, found a history of TBI was associated with increased B amyloid deposition, cortical thinning and onset of cognitive impairment 3-4 year earlier. (136) In contrast, a UK population study of 80 participants who had TBI with loss of consciousness before age 60, found no difference in amyloid deposition, hippocampal volume or cortical thickness but lower cognition and smaller brain volume at age around 70 than their 42 counterparts without injury.(137) Ongoing work using neuroimaging and fluid biomarkers of neurodegeneration may help identify both overlapping and distinct patterns of neuropathology in different subtypes of post-traumatic dementia or other neurodegenerative disorders, including chronic traumatic encephalopathy. (134, 138)

Overall, the evidence suggests that TBI increases dementia risk, possibly leading to earlier onset of dementia by 2-3 years, (139) which may be due to accumulation of underlying neuropathology. This risk of neurodegenerative disease should not obscure the message that sport is generally good for health. Protection from head injury, for example, by appropriate head protection equipment, limiting heading practice and high-impact collisions, preventing playing immediately after TBI and possibly adaptation of the rules, should now be an individual and public health priority. Some sports bodies and government bodies have begun to implement this policy.

Smoking

We previously reported that late-life smoking is associated with an increased risk of dementia (HR 1.6, 1.2-2.2).(2) new evidence shows that midlife smoking (compared to late-life) appears to be a stronger dementia risk

factor in more recent studies possibly because of improvements in treating cardiovascular disease and smoking-related cancers, so smokers now have an increased chance of living long enough to develop dementia. A large meta-analysis reported midlife smoking increased dementia risk (RR 1.30 118-1.45, 37 studies) but there was no increased risk in former smokers. (140) Long-term cohort studies, including the Framingham Heart Study (21-year follow-up which found strongest risk in those who were smokers starting in early adult life),(141) the Atherosclerosis Risk in Communities (ARIC, 25-year follow-up, n= 15,744 HR 1.41, 1.23-1.61*)*,(142) and the Whitehall II study (32-year follow-up, HR 1.36, 1.10-1.68),(143) have reported similar excess risks of dementia in midlife current smokers. A UKB study of 497,401 adults reported a HR 1.7 (1.2–2.5) for smokers aged <50 years at baseline.(144) In the Danish general population a pooled analysis of two prospective cohorts of 61,664 individuals, reported that risk of dementia for smokers in midlife were increased for men (HR 3.2, 1.4–7.4) and women (HR 1.7, 1.1–2.8).(145)

The effect of stopping smoking

A 32-year follow-up of the Whitehall II cohort, controlling for socioeconomic status, found that smokers (HR 1.36,1.10-1.68) but not ex-smokers (HR 0.95, 0.79-1.14) have an increased risk of dementia compared to those who have never smoked, and that socioeconomic inequalities in dementia risk were partially mediated by smoking. (143) The meta-analysis above also showed no increased risk in former smokers. Similarly, a Korean nationwide study of 789,532 participants who were assessed for smoking status over 2 years reported that ex-smokers had a lower risk of all cause dementia HR 0.92 (0.87-0.97) compared with continuing smokers and this was more pronounced among adults who smoked before age 65 (HR 0.8, 0.7–0.9) than those aged 65 years or older (HR 1.0, 0.9–1.0).(146) Another Korean population study examining dementia risk in people with atrial fibrillation, also found a reduced risk of dementia in those who quit smoking compared to current smokers (HR 0.83, 0.72-0.95).(147) These studies suggest that smoking cessation reduces dementia risk compared to continued smoking. Smoking should now be considered a midlife risk factor (in the 2020 commission it was considered as a late life risk factor) and the effect of stopping smoking is encouraging.

Cardiovascular risk factors

We have chosen to consider risk factors individually rather than overall cardiovascular morbidity. Vascular dementia usually occurs when people have a stroke (and is part of the diagnostic criteria) and happens more often in people who smoke or who have diabetes and hypertension. (28) Stroke and dementia share risk factors of less education, lack of exercise, hypertension, heart disease and less social contact (148) but some people with these risk factors will not develop dementia despite neuropathology, sometimes because they die younger.(23)

Several studies have examined a combination of cardiovascular risk factors. The Life's Simple 7 group defined ideal cardiovascular health factors (BMI, diet, smoking, physical activity, blood pressure, cholesterol and glucose levels), and better scores on this index are associated with lower dementia risk. (28) (149) Similarly, in China, a 10-year longitudinal study of 29,072 people with mean age 72, found that having four or more of six factors: a healthy diet (eating at least 7 of 12 eligible food items), physical exercise (≥150 min of moderate intensity or ≥75 min of vigorous intensity weekly), active social contact (≥ 2 per week), active cognitive activity (≥ 2 per week), never or former smoking, and never drinking alcohol was associated with slower memory decline in those with fewer protective cardiovascular risk factors. (150) This applied to both *APOE*ε4 carriers and non-carriers.

Cholesterol: Low Density Lipoprotein Cholesterol (LDL- C)

The evidence available at the time of previous commission reports on higher levels of low-density lipoprotein cholesterol (LDL-C) was a possible dementia risk factor was inconclusive. Meta-analytic evidence found

inconsistent evidence from HICs that high LDL-C in midlife, but not in later life, might be a risk factor for cognitive decline, all cause dementia and AD.(151) (152)

A newer meta-analysis of LDL-C in adults aged <65 years followed up for > 12 months, found 3 cohort studies with 1,138,488 participants, all from UK, and reported each 1mmol/l increase in LDL-C was associated with 8% increased incidence of all cause dementia (1.08; 1.03 - 1.14; I^2 = 0.3%). (153) A study of 1,189,090 participants found high LDL (>3mmol/l) was associated with an increased risk of dementia, HR 1.33, 1.26-1.41.(47) Higher baseline LDL-C in a large cohort from UK general practice cohort (n=1,853,954) followed up for a median of 7.4 years, was similarly associated with higher risk of all cause dementia (RR 1.05, 1.03–1.06 per SD increase in LDL-C, 1.01 mmol/L or 39 mg/dL increase). (154) This risk was greater in midlife, people aged <65 with high LDL-C had increased risk for dementia diagnosed within 10 years (RR 1·10, 1·04–1·15) and over 10 years after baseline (RR 1·17, 1·08–1·27). High LDL-C is sometimes associated with diet and in a Danish cohort study of 94,184 people followed from a mean age of 58 years, those who did not adhere to dietary guidelines (≥ 3 weekly servings of all of fruit, vegetables and fish, rarely drink sugar sweetened drinks, eat prepared meat like sausages or have takeaways) were more likely to have high levels of LDL-C. (155) After a median follow-up of 10 years, those with low adherence were more likely to develop non-AD dementia compared to high adherence (low adherence HR 1.54, 1.18–2.00), but not AD dementia although subtyping may not be accurate. There was no increased risk of dementia in people who took lipid lowering drugs. A US study of 4392 people found that higher high-density lipoprotein-cholesterol (HDL-C) protected against the development of dementia.(156)

Further evidence of causality comes from a MR meta-analysis which included 27 studies with 3136 people with dementia and 3103 healthy controls, which reported that high total cholesterol and low HDL-Cl were risk factors for dementia. (157) In contrast, an individual participant meta-analysis at baseline older age (>21,000 people, mean baseline age 76 years) found no association between total LDL or HDL-C and cognitive decline; this did not change if analysis was stratified by statin use or *APOE*ε4 status.(158)

Mechanisms

Excess brain cholesterol is associated with increased stroke risk and higher deposition of brain amyloid and tau. (153) HDL reduces cholesterol (159) and lowering cholesterol decreases Aβ levels.(152)

Interventions for high cholesterol

Individual counselling about diet and exercise has a small effect in reducing LDL-C.(160) Cholesterol-lowering statins have become a focus of research in AD and have potential benefit as they are anti-inflammatory and antioxidant as well as reducing cholesterol.(161) A meta-analysis of 36 cohort studies found statin use was associated with a reduced risk of all-cause dementia compared to untreated high cholesterol (OR 0.80, 0.75-0.86, I^2 =97.5) and AD (OR 0.68, 0.56-0.81 I^2 =94.5) with no difference between men and women. (162) A Cochrane review of RCTs of statins given in late life found only one study and no effect on dementia risk and two studies of cognitive outcome with no effect.(163) Repeat observational data can be used to emulate a target trial of statin use. Using data from 6373 participants aged 55-80 years an emulated trial found sustained statin use, but not statin initiation alone, to be associated with reduced 10-year risk of dementia or death.(164)

Decision

Overall, there is high quality consistent, biologically plausible, evidence that high LDL cholesterol in midlife is a risk factor for dementia. Earlier World Health Organisation guidelines suggested management of dyslipidaemias in mid-life may be offered to reduce the risk of cognitive decline and dementia but thought the evidence quality was low.(116) Although there are not long term high quality RCTs of statins to prevent dementia , these would be unethical and impractical. Meta-analyses observational studies are heterogenous but show benefit, possibly

because the benefit depends on age of initiation. Statins may mitigate this excess risk, but this is less clear in late life.

Physical inactivity, exercise, and fitness

We previously concluded that the balance of evidence is that the link between exercise and dementia is likely to be bidirectional.(2) Physical activity changes over a person's lifetime, decreasing when someone becomes ill and varies across cultures, socioeconomic status, and between sexes and can be at different levels of intensity making it complex to study. Since the 2020 commission, A systematic review and meta-analysis of 58 studies exploring the link between physical activity and dementia, found that physical activity was associated with a decreased risk of all-cause dementia (RR 0.80, 0.77 to 0.84, n=257,983) and dementia types in short and longer follow-ups ≥20 years, and at all ages. (165) A range of intensities of exercise were included in the meta-analysis. Reduction in risk was greatest when moving from extreme sedentariness to some physical activity .a cohort study (n=1,417) which recorded physical activity five times between age 36 and 69, found that being physically active at all ages was associated with better cognition at age 69; with the strongest association for sustained physical activity.(166) A prospective study of 29,826 people followed up for a median of 24.5 years, and assessed twice for weekly physical activity 10 years apart, found those who maintained an individually estimated optimal level of physical activity had a reduced risk of dementia compared to persistently inactive individuals (HR 0.75, 0.58-0.97 as did those who increased their physical activity to an optimal level (HR 0.83, 0.72-0.96).(167) A longitudinal study of 1718 women over a median time of 11.9 years, found more physical activity was associated with less cognitive decline but not when this was adjusted for diabetes and hypertension.(168)

Physical activity interventions

An RCT of 945 participants, mean age 78 years and 48% women, were randomised 2:1:1 to a 5-year control group, moderate-intensity continuous training or high-intensity interval training twice weekly.(169) At 5 years, 96% of the control group adhered to national guidance for physical activity, and 75% and 76% adhered to the interval training intervention. There was no significant difference in cognition between the groups (beta 0.26, −0.17 - 0.69) or odds of MCI (OR 0.86, 0.66-1.13). Men in the exercise group had a decreased risk of MCI (OR 0.65, 0.47-0.99) and slightly higher cognitive scores than controls. Those who decreased peak oxygen uptake, compared to maintaining or increasing it had higher odds of MCI (1.35, 0.98-1.87) compared to the control group although this was imprecisely estimated. Findings are in line with the small cognitive benefit shown in an umbrella review of RCTs on the effects of physical exercise on cognition.(170) Outcomes may depend on not only the duration but type and intensity of physical activity. At the policy-level, urban design interventions and provision of high-quality green spaces are recommended by the WHO to reduce physical inactivity across the population.(171)

Mechanisms

Exercise at any age appeared helpful for cognition, possibly through changes in blood flow and function from reduced hypertension and increased nitric oxide culminating in enhanced brain plasticity and reduced neuroinflammation. (172) People who engage in moderate to vigorous exercise on more days have relatively larger brain volumes than those who do less or no exercise. (173) (174) There is also evidence from mouse models that irisin, a myokine released during exercise, may be neuroprotective.(175)

Diabetes

We previously discussed type 2 diabetes as a risk factor for development of late-life dementia. New evidence suggests that age of onset makes a difference with midlife, but not necessarily late-life diabetes onset increasing the risk of dementia. In a prospective cohort study of 10,095 participants, the risk for dementia increased for every 5-year earlier age of type 2 diabetes onset (HR 1.24, 1.06-1.46) until aged over 70 years at onset).(29) It

now seems that diabetes should be classified as a midlife risk for dementia. It is unclear whether diabetes is no longer a risk factor for dementia at older ages or the lack of demonstrated significant risk is because of shorter follow-up and there are few studies. The WHO concludes that late life diabetes may have a detrimental effect on brain health and dementia risk. (116) Longer illness duration and poorly controlled diabetes increases the risk of dementia.

Mechanism

Our understanding of the mechanism is incomplete. Long-term micro- and macro-vascular complications are well-established in diabetes, and it is likely that causal mechanism incorporates a strong vascular component, including stroke risk. (176) Peripheral insulin resistance leads to decrease insulin signalling in the central nervous system, followed by alteration in brain metabolism. Insulin resistance is a common molecular mechanism linking diabetes and AD; it leads to increased Aβ toxicity, Tau hyperphosphorylation, oxidative stress and neuroinflammation. (177) Elevated systemic inflammatory markers (such as CRP) were associated with the diabetes-associated increased dementia risk. (29)

Interventions for diabetes

It is unclear if effective treatment of diabetes ameliorates dementia risk, particularly as taking more oral medication and insulin is related to having more severe diabetes. Strict, intensive compared to standard diabetic control, however, does not decrease the risk of dementia.(2) Some evidence suggests that those taking certain types of anti-diabetic medication may be less at risk of dementia. A systematic review meta-analysis and network analysis of 27 studies (1,590,757 patients) which did not report heterogeneity found cohort studies indicated that Sodium-glucose Cotransporter-2(SGLT-2) inhibitors(OR 0.41, 0.22–0.76),glucagon-like peptide 1 receptor agonists (GLP-1 RAs) (OR 0.34, 0.14–0.85]) and dipeptidyl peptidase (DPP)-4 (OR 0.78 [0.61–0.99]) were associated with dementia risk reduction while sulfonylureas (OR 1.43, 1.11–1.82]) were found to be associated with increased risk.(178) Metformin was not associated with a decreased or increased risk (OR 0.71; 0.46–1.08). A study in UK primary care found that 114,628 people with diabetes initiating metformin compared to 95,609 on no medication for their diabetes had a significantly lower risk of dementia HR 0.88 (0.84-0.92) (179) Another meta-analysis of 819,511 people with type 2 diabetes and a mean follow up of 4.5 years had similar findings with less subsequent dementia in users of three classes of drugs but reported high heterogeneity; SLGT-2 - (3 studies, RR, 0.62; 0.39–0.97, I^2 82.5%) ; GLP-1RA (4 studies, RR 0.72; 0.54–0.97 I^2 91.3 %) and DPP-4 inhibitors (RR 0.84; 0.74–0.94; I^2 88.6%). (180) People with diabetes may not be taking medication because their diabetes is well controlled without medication or because it is not well treated which may account for the heterogeneity between studies. There is also RCT evidence for the protective effect of GLP-1 RAs. (181) In a Taiwanese population of 31,384 propensity-matched pairs (including matching for chronic kidney disease with diabetes) followed for five years, those who were adherent to metformin had a 72% lower risk of developing dementia. (182) I Novel study designs like MR or target trial emulation might help address potential confounding by indication, where high blood sugar leads to particular prescriptions or harms those who do not take medication. (183)

Weight loss might also help diabetes control and therefore cognition. One RCT recruited 3,751 people aged 45 to 76 with type 2 diabetes mellitus, who were overweight or obese, to a 10 year increased exercise and decreased calorie intake intervention versus diabetes support and education (the look AHEAD study).(184) This study was terminated as in the interim analysis it had no effect on death from vascular outcomes or myocardial infarction, stroke or severe angina.. Cognitive outcome was measured at follow up controlling for baseline education but not cognition. There was a strong inverse relationship between HbA1c concentration and

cognition over both groups. Cognitive function was not related to group allocation or to weight loss. Overall tighter control of diabetes, but not very low blood sugar, or weight loss without improved diabetic control may attenuate the risk and be a way of decreasing dementia.

Hypertension and its trajectory

Our commission has previously discussed the evidence that midlife hypertension increases the risk for all-cause dementia, AD and vascular dementia, but that nearer the time of dementia people's BP tends to fall.(2) Blood pressure across the lifecourse rises in western societies, with evidence of rises associated with socioeconomic circumstance. A systematic review of longitudinal studies estimated that BP first rises then starts to decrease 5 years prior to dementia diagnosis while weight falls around 10 years before diagnosis.(185) However, an individual participant data (IPD) meta-analysis finds that high blood pressure may continue to be a risk in older age(186) but some people who are developing dementia have a lower blood pressure and therefore the picture is mixed. These meta-analyses do not cover blood pressure variability but a cohort study (n=2234, ≥ 65 years) measured blood pressure variability, with assessments over 3, 6, 9 and 12 years, and found that higher systolic variability increased the risk of dementia with HRs ranging from 1.02 (1.01-1.04) to 1.10 (1.05-1.16). (187)

African Americans have higher recorded BP than other US groups and this may be a contributor to a higher risk of dementia than in White Americans. This is considered in an IPD meta-analysis of five cohort studies of 19,378 people with mean age 59.8, where black African Americans had significantly faster global cognition decline but there was no significant difference after adjustment for cumulative mean systolic BP. (188)

Interventions for high blood pressure

There are three meta-analyses of antihypertensive medication RCTs. Two found they were protective(189) (12) against cognitive impairment and dementia and one with short (1 year) follow-up did not.(190) The meta-analysis of 12 RCTs (n=96,158) with a mean follow-up of 4.1 years found a lower risk of dementia or cognitive impairment compared with controls (OR 0.93, 0.88-0.98) and of cognitive impairment alone (OR 0.93, 0.88-0.99). (189) The second study used IPD from 5 RCTs (n=28,008) with placebo controls, three of which were in the first study, and found a lower risk of dementia in the treatment group (OR 0.87, 0.75-0.99). (12) A Cochrane review with three studies overlapping with the previous study, included 12 RCTs (8 placebo controlled, n=30,412) with interventions lasting at least 12 months. It concluded that there was a modest benefit on cognitive change measured with MMSE (5 studies, MD 0.20 (0.10-0.29) but duration was too short to show a difference in dementia incidence (4 studies; OR 0.89, 0.72-1.09).(190) An IPD meta-analysis of 17 studies including people in LMICs and HICs (mean age72.5, follow-up 4.3 years) found that that those with untreated hypertension had a 42% higher risk of dementia than healthy controls (HR 1.42; 1.15-1.76), but this risk was attenuated or lost with treatment (HR 1.13; 0.99-1.28 vs. healthy controls). (186) One meta-analysis of IPD cohorts comprising 31,090 dementia free adults at baseline with follow-up of ≥ 5 years found those with hypertension taking any antihypertensive were at lower risk than those not (HR 0.88 0.79-0.98) but no difference between classes of drugs. (191)While there is a lack of direct comparison of the effect of different antihypertensives, a network analysis and systematic review found that treatment with angiotensin receptor 11 blockers and calcium channel blockers (CCBs), were associated with lower dementia risk after 7 and 10 years compared with other antihypertensives.(192) MR findings of high BP being protective (193-196) are inconsistent with RCTs findings and MR studies' findings are likely to be influenced by survival bias. (12, 189, 197)

Obesity and weight

We previously discussed that obesity in midlife is a risk factor for dementia.(2) A further systematic review and meta-analyses examining the relationship between obesity and dementia included 14 studies with 77,890

participants, and found that midlife obesity was associated with subsequent all cause dementia (RR 1.31, 1.02-1.68).(198) Another study on central obesity, measured through waist circumference or waist to hip ratio, included 5,060,687 participants from 16 studies, and showed that higher versus lower waist circumference was associated with a greater risk of cognitive impairment and dementia (HR 1.10, 1.05-1.15) and the risk was greater in those aged >65 years.(199) Obesity is more common in those who exercise less and is associated with diabetes and hypertension which also cause cardiovascular disease,(200) so it is possible that this association is mediated by other risk factors for dementia. Nonetheless, most studies in these meta-analyses adjusted for health conditions such as hypertension, stroke, blood lipid levels and diabetes, as well as demographic characteristics so this should have minimised the effect of these intermediaries.

Interventions for excess weight

A meta-analysis of interventional studies for weight loss identified 13 longitudinal studies (total of 551 participants) and 7 RCTs (total of 468 participants) of overweight and obese participants. Intentional modest weight loss of even 2 kg amongst trial participants was associated with improvements in cognition at median follow-up of 6 months, (201) indicating that health behaviours could have a beneficial effect even if weight loss is not sufficient to alter obesity status. These improvements were more pronounced in people who changed their diet or who exercised to lose weight, than in those who had bariatric surgery. The average weight loss from non-surgical interventions is around 2kg.(202)

An additional suggested mechanism is stigma in people with higher Body Mass Index (BMI), which is associated with higher cortisol levels, inflammation and negative health consequences and may contribute to the association with dementia.(203) Further work is needed to understand mechanisms by which excess adiposity contributes to dementia risk.

Being underweight

A systematic review of 19 prospective studies where data were pooled, also found an increased risk of dementia in underweight individuals (BMI <18.5; HR: 1.26, 1.20-1.31).(204) An IPD meta-analysis of 1.3 million people from 39 prospective cohort studies found that obesity was a risk factor for dementia in cohorts where baseline was >15 years before but appeared protective if <10 before dementia. [193] Their interpretation was that increased risk in the weight loss group was due to reverse causation, as people often lose weight before they develop dementia. Being underweight is also potentially linked with malnutrition, although it can occur for many reasons.

Excessive alcohol consumption

In the previous Lancet Commission, we found that drinking >21 UK units (14 US drinks, 168g) of ethanol weekly in midlife compared with lighter drinking (<14 units) was associated with an increased risk of dementia (RR 1.18, 1.06-1.31).(2) Similarly, a subsequent individual participant meta-analysis of 131,415 participants from France, UK, Sweden and Finland found, after adjusting for confounders, heavier drinking (> 21 units/week) in midlife, compared to lighter drinking, was associated with an increased risk of dementia (HR 1.22, 1.01-1.48).(205) In line with this a review of 28 systematic reviews concluded that heavy alcohol use was associated with increased risk of all-cause dementia and reduced grey matter volume in imaging studies. (206) Alcohol-induced loss of consciousness increased dementia risk in those with either moderate or heavy consumption. (205)

Non-drinkers

Some cross-sectional studies of older adults have found a similar dementia risk in heavy alcohol drinkers and non-drinkers but some people who are counted as non-drinkers were previously heavy drinkers. (207) A

Japanese prospective study following 42,870 participants for 14.9 years, found both non-drinking and drinking >450 g alcohol/week from midlife compared to light drinking, were associated with increased risk of dementia (HR 1.29, 1.12-1.47, HR 1.34, 1.12-1.60 respectively).(208) An IPD meta-analysis of 24,478 older adults from 15 prospective cohort studies reported that during 151, 636 person years of follow-up, dementia risk was lower in occasional (HR 0.78, 0.68-0.89), light-moderate (1.3–24.9 g/day; HR =0.78, 0.7-0.87), and moderate-heavy drinkers (25–44.9 g/day; HR 0.62, 0.51-0.77) than non-drinkers but not in heavy drinkers (> 45g/day). (209) MR also finds a causal relationship between alcohol consumption and earlier age of onset of AD, and suggests that any relationship between not drinking and AD is due to survivor bias.(210) Observational studies usually find a j-shaped dose-response, such that non-drinking is associated with increasing dementia risk compared to light drinking. This is probably because many non-drinkers have previously had high alcohol consumption or other illnesses which prevent them drinking and studies which correct for this find there is no excess mortality in the non- drinking group. (207, 211)

Reduction of excessive alcohol consumption

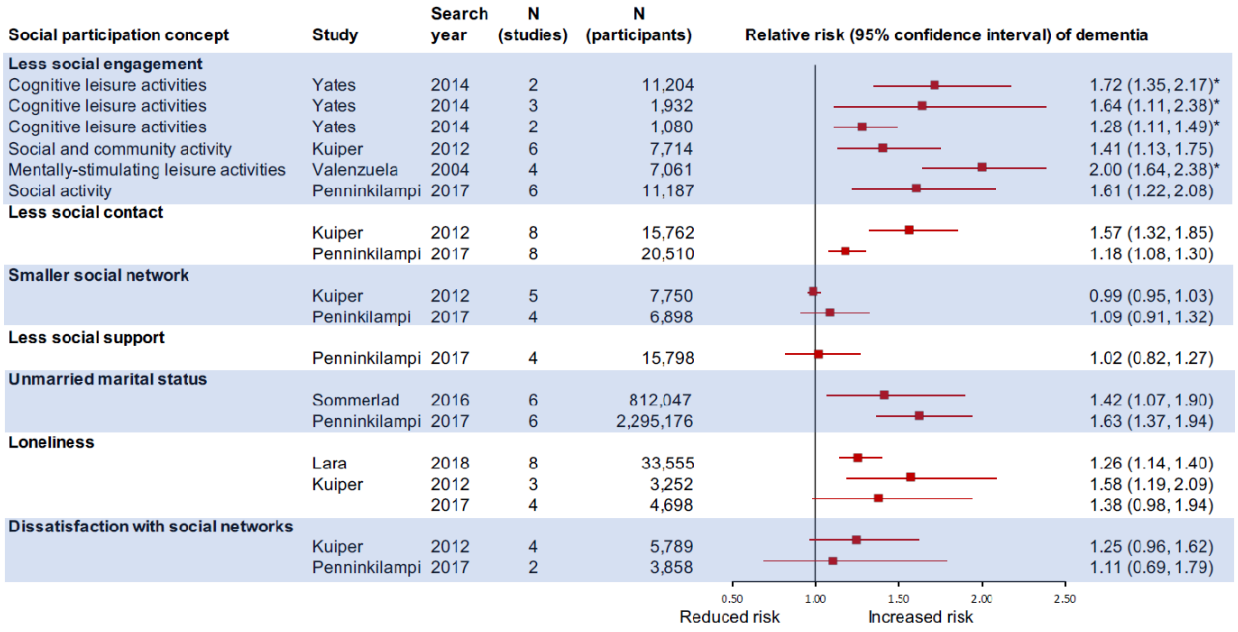
A study of a nationwide South Korean cohort of 3,933,382 participants that serially assessed alcohol consumption over 3 years, found sustained heavy drinkers (≥30grams or 3 units/day) had an increased risk of all-cause dementia (HR 1.08, 1.03-1.10), and reducing drinking from heavy to moderate levels (15.0-29.9g/day) reduced the risk of all cause dementia (HR 0.92, 0.86-0.99) compared to sustained abstinence. (212) Sustained mild (<15 g/day) or moderate alcohol consumption, or initiating mild alcohol consumption versus sustained non-drinkers, was also associated with lower risk of all cause dementia (HR 0.79 0.77-0.8; HR 0.83, 0.79-0.88; HR 0.93, 0.9-0.96 respectively) but as above, some non-drinkers may have been former heavy drinkers. Overall, reduction of excessive alcohol or sustained light drinking is associated with a lower dementia risk than excessive alcohol. There is a lack of clear evidence that not drinking alcohol increases the risk of dementia. The observational evidence of excess risk for non-drinkers may be due to people who have previously drunk large amounts, abstained at the time when data was gathered (and been classified as non-drinkers) and then may return to drinking.

Social isolation

We have previously discussed social isolation or lack of social contact as a risk factor for dementia.(2) Since then, two systematic reviews found less frequent social contact was associated with higher risk of dementia. The first, which included eight studies with a total of 15,762 participants, reported higher dementia risk (RR 1.57, 1.32-1.85) for those with less compared to more frequent social contact,(213) while the second (with one overlapping paper) reported a smaller increased risk (RR 1.18, 1.08-1.30). (214) Duration of follow-up may partly explain inconsistent results from these studies; seven of the eight studies in one of the reviews had less than 4 years' follow-up making reverse causation likely. (213) However, two subsequent studies of participants in UKB, with 9 (215) and 12(216) years mean follow-up, found that dementia risk was higher in those who were more socially isolated at baseline.

Loneliness is linked to, but differs from, social isolation as it is about people's feelings that their social contact is inadequate. (217) Loneliness was also associated with elevated dementia risk in three reviews comprising 3-8 studies (RR 1.26, 1.14-1.40; 1.38, 0.98–1.94 and 1.58, 1.19-2.09 respectively). (213) Elevated dementia risk of 34-91% was reported in subsequent studies, in the US over 10 years, in Netherlands and Sweden over 14 years and in Japan over 5 years. (218-222) Some, but not all, of these studies found the association persisted after adjustment for potential confounders, including lack of social contact. These results are summarised in figure 7.

Participation in social activities is also linked, but distinct, from social isolation and has been linked with lower dementia risk. Two studies with serial social activity measurement found that declining social activity participation was associated with higher dementia risk in the short term but not but with a longer follow-up. (223, 224) This suggests that the link with participation may be at least partly due to reverse causation whereby decline occurs during the preclinical phase of dementia.



(216)

Figure 7 Different aspects of social participation and risk of dementia. With permission(217)

Mechanisms

Social contact in any form has a potentially beneficial effect on dementia risk by building cognitive reserve, promoting healthy behaviours, and reducing stress and inflammation. (217) Risk has been reported to be consistent across individuals with different polygenic risk scores (215) and social isolation linked to lower grey matter volume in the temporal, frontal, and other brain regions.(217)

Interventions to increase social contact and activity participation.

Interventions to increase social contact and participation in activities through facilitator-led group activities have yielded inconsistent results on general cognitive function. One Finnish RCT of a three-month intervention with a primary outcome of cognition recruited 235 people who were lonely aged ≥75 and showed a small, significant improvement on ADAS-cog performance (mean difference in change -2.6 /100 points)(225) but studies from the US (226) and China(227) did not find that facilitator-led group activities were beneficial. Studies of multidomain interventions which included group components suggested small cognitive benefits (Cohen's d = 0.13 (228) and mean mini-mental state examination (MMSE) difference 0.99 points) for highly intensive interventions. A subsequent pilot RCT of a multidomain intervention, including social activities through group meetings and additional scheduled monthly social activities, led to general cognitive improvement at 24 weeks despite small numbers (Repeatable Battery for the Assessment of Neuropsychological Status score between group difference 6.2 points (p=0.004). (229) The contribution of the social component of multidomain intervention is unclear. Existing studies are too small and follow-up too short to identify if they have any effect on dementia incidence.

Air pollution

Exposure to particulates in domestic and external environments is now of intense concern and interest. Exposure is lifelong and a potential contributor to many long-term conditions across the lifecourse. In the 2020 commission, we found agreement that fine particulate matter air pollution, $PM_{2.5}$ (diameter ≤ 2.5µm) and PM_{10} (diameter ≤ 10µm) were risk factors for dementia and cognitive impairment, despite substantial heterogeneity across studies in durations of exposure, covariates in the analysis, outcomes, and variable risk of bias.(2) Continuing research interest on this is reflected by the publication of at least nine further systematic reviews and meta-analyses since 2019, which have all reported that air pollution is associated with increased dementia risk. To manage study heterogeneity, some meta-analyses have narrowed inclusion criteria, e.g., one review analysed only studies providing hazard ratios (HR), comprising 20 studies involving 91,391,296 people, and reported a pooled higher dementia risk of 3% per 1 µg/m^3 increment in $PM_{2.5}$ (HR 1.03, 1.02–1.05).(230) A conservative pooled estimate, obtained from a meta-analysis of five studies that used active case ascertainment of high quality studies, reported a 17% increase in dementia risk per 2 µg/m^3 increment in $PM_{2.5}$, although confidence intervals were wide and included the null (HR 1.17, 0.96- 1.43).(231) Pooled HRs were reported from five studies each of nitrogen dioxide (HR per 10µg/m^3 1.0,; 0.98 - 1.06) and nitrogen oxides (HR per 10 µg/m^3 1.05, 0.98 - 1.13), and four of ozone (HR per 5 µg/m^3 1.00, 0.98 -1.05), none of which were statistically significant. Other pollutants had been studied by too few studies for meta-analysis.(231)

In both HICs and LMICs, where air pollution levels are often high and increasing, $PM_{2.5}$ and PM_{10} levels have also been associated with dementia, MCI, and AD.(232-235) There may be distinct or synergistic risks from ambient (outdoor) and household (indoor) air pollution. Studies in LMICs have demonstrated that solid fuel use, a proxy for household (indoor) air pollution, is associated with higher dementia risk and accelerated cognitive decline among middle-aged and older adults.(236, 237) Residential wood and coal burning stoves can also be a source of indoor air pollution, and are reported to currently contribute 38% of the UK's $PM_{2.5}$ emissions and associated health risks.(238)

A US 7-year cohort study of >18 million participants found that the $PM_{2.5}$ constituent with the strongest association with dementia risk was black carbon (HR per 1µg/m^3 increment 1.12; 1.11, 1.14).(239) The studies have mainly been in older adults at baseline but does not rule out an effect earlier in life.

Mechanism of air pollution's effect on dementia

A longitudinal study with a mean follow-up of 6 years of 2,927 Swedish residents (63% women, free from dementia at baseline, baseline mean age 74) considered $PM_{2.5}$ and NOx yearly from 1990, to examine if CVD (atrial fibrillation, ischemic heart disease, heart failure, and stroke) modified or mediated the association between pollution and dementia and found it did.(240) The effect of air pollution is worst among people with these pre-existing conditions.

The effects of changing air pollution

There is emerging evidence on the potential effects of improved air quality on cognitive decline and dementia incidence. A French cohort study with 12-years' follow-up, reported a reduction in $PM_{2.5}$ between 1990-2000 was associated with a lower risk of dementia (HR, 0.85; 0.76 -0.95 for median $PM_{2.5}$ reduction of 12.2 µg/m^3).(241) Older US women living in an area with improved air quality ($PM_{2.5}$ and NO_2 reduced over ten years) had a lower risk of dementia.(242) In a quasi-experimental study, the China's Clean Air Act mitigated cognitive decline in older adults, indicating that strict clean air policies may reduce the risk of cognitive ageing measured by mini-mental state examination associated with air pollution.(243) A north-south difference in China's central

heating policies led to differences in air pollution concentrations; higher air pollution (PM_{10}, NO_2, SO_2, CO, O_3) was associated with a 42.4% higher dementia risk.(244)

As the evidence base grows, it would be valuable to standardize study design, reporting and analyses to allow comparisons, and achieve a more granular understanding of the association between air pollution and dementia.(245) Given the close link between socioeconomic circumstances, household conditions and exposure to air pollution, minimising residual confounding in these studies is difficult.

Overall, there is much stronger support for the implementation of World Health Organization global air quality guidelines that ultimately aim for average annual $PM_{2.5}$ concentrations of less than 5 $\mu g/m^3$.(246, 247) It is unclear if there is any 'safe' level of air pollution, as each 1 $\mu g/m^3$ unit increment in $PM_{2.5}$ is associated with higher dementia risk, and the lowest annual $PM_{2.5}$ concentration in global mega-cities was reported to be 6.7 $\mu g/m^3$ in Miami, whilst the top five most polluted cities had an annual average concentration of $PM_{2.5}$ greater than 89 $\mu g/m^3$.(248) There is little known about risk in relation to dementia subtypes, and whether individual PM constituents are important (e.g., black carbon, sulphates, nitrates and ammonium).

Uncorrected visual impairment

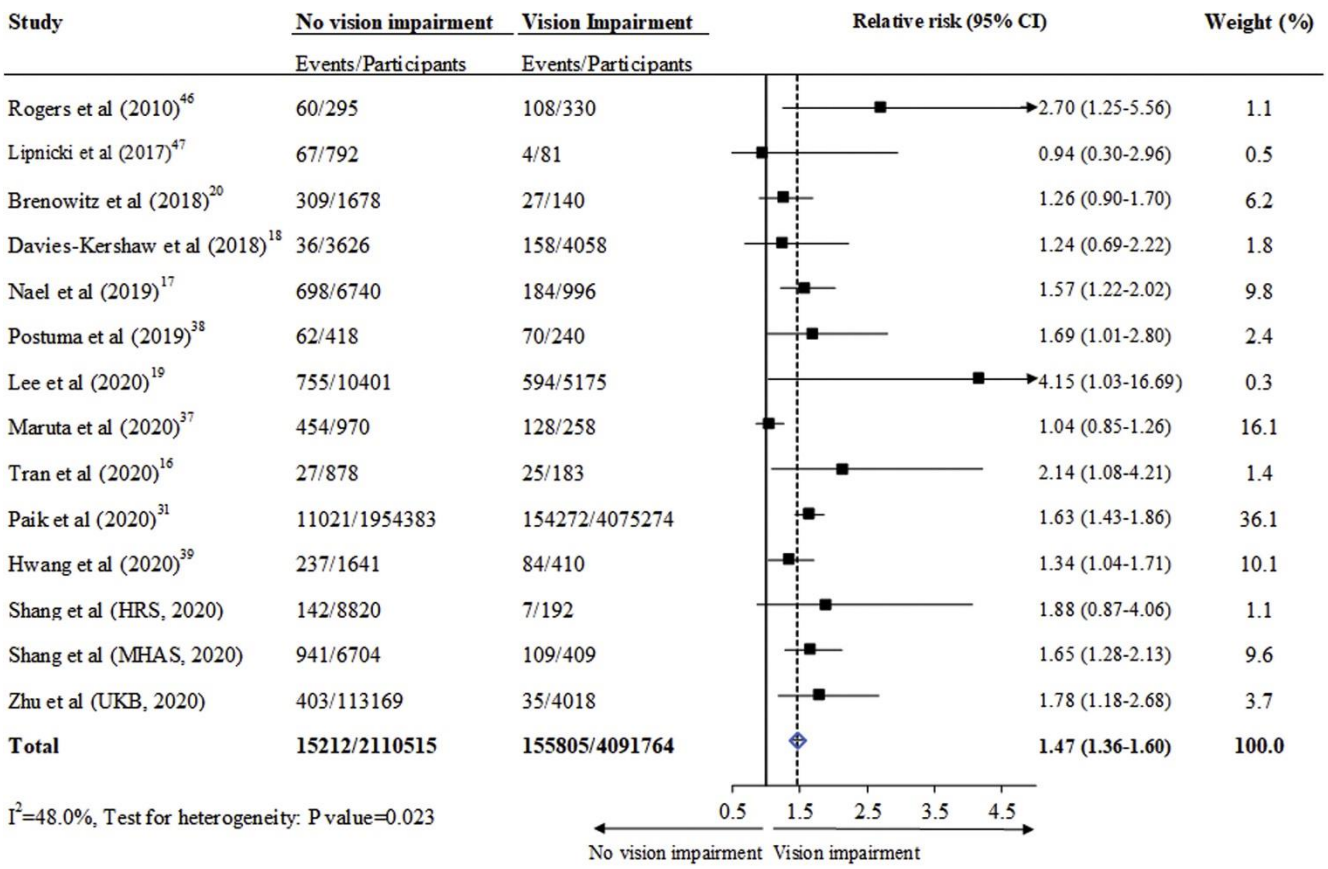
The global prevalence of avoidable vision impairment and blindness, including uncorrected refractive error and cataracts, in adults aged ≥50 years is has been estimated to be 12.6%, with prevalence much higher in LMICs than in HICs.(249) (249) This is distinct from cortical blindness seen in posterior cortical atrophy, usually due to AD, but often initially misdiagnosed as ocular disease.(250)

Visual impairment, cataract, diabetic retinopathy, glaucoma and macular degeneration and dementia risk

Our commission has not previously considered vision impairment as a risk factor for dementia but there is now considerable new evidence. This includes a meta-analysis of 14 prospective cohort studies, with follow-up between 3.7 to 14.5 years, including 6,204,827 older adults who were cognitively intact at baseline, of whom 171,888 developed dementia. (251) Vision impairment was associated with a pooled RR for dementia of 1.47 (1.36 -1.60 see figure 8). In an accompanying meta-analysis of 12 prospective cohort studies with 45,313 participants, 13,350 of whom developed cognitive impairment, the RR for vision impairment was 1.35 (1.28 - 1.41).

Figure 8

Meta-analysis of risk ratios of at least visual impairment compared to no visual impairment on incident all-cause dementia. CI, confidence interval. With permission (252)



A second meta-analyses found increased risk of all-cause dementia (RR 1.38, 1.19–1.59, n=37705) with visual impairment.(252) Breaking this down into different eye conditions, there was increased dementia risk associated with cataracts (3 studies, 6,659 participants, 1,312 cases, (HR 1.17, 1.00–1.38, $I^2 = 0.0\%$) and diabetic retinopathy (43,658 participants, 7,060 cases, HR 1.34, 1.11–1.61, $I^2 = 63.9\%$), but not with glaucoma (6 studies, 175,357 participants, 44,144 cases, HR 0.97, 0.90–1.04, $I^2 = 51.5\%$) or age-related macular degeneration (3 studies, 800,692 participants, > 2,559 cases, HR 1.15, 0.88–1.50, $I^2 = 91.0\%$).

One US study of 16,690 participants, investigated the inclusion of vision impairment as an additional potentially modifiable risk factor in the life-course model based on the 2020 Lancet Commission, and found that the population attributable fraction (PAF) of vision impairment was 1.8% in that population. (253) As the prevalence of vision impairment was higher in minority groups (9.9% of the Black non-Hispanic population and 11% of the Hispanic population compared to 7.7% of the White non-Hispanic population), the risk and potential benefit may be greater in these populations.

Effect of cataract treatment

A US study followed 3038 older adults (age >65 years) with cataracts and normal cognition at baseline for over 20 years. (254) The analysis controlled for age, race, *APOE* genotype, education, smoking, and an extensive list of comorbidities and reported that those who had cataract extraction had significantly reduced dementia risk compared to those who did not (HR, 0.71; 0.62-0.83; 23,554 person-years of follow-up). Although a UKB study of 300,823 people found that those with cataracts had an increased risk of dementia (HR, 1.2, 1.01–1.46), but that there was no difference in dementia risk between those who had cataract surgery and healthy controls.(255)

Mechanism of link between vision impairment and dementia

The mechanisms behind these associations may be related to underlying illness such as diabetes which is a risk factor for dementia, (2) vision loss itself, as might be suggested by a possible effect of cataract surgery, or shared neuropathological processes in both the retina and the brain.(256) A Korean longitudinal health insurance database study of 6,029,657 people, found that dementia risk increased with visual impairment severity, supporting the hypothesis that vision loss in itself may be causal or that there is a dose-response effect to a shared aetiological factor.(257) A study of diabetic retinopathy and dementia found that the association between retinopathy and dementia remained after adjusting for diabetes severity, as measured by five years of glucose levels control and renal function after >5 years of diabetic retinopathy. (258)

Decision

increasing evidence supports an association between uncorrected visual impairment and dementia risk, and potential modification by treatment. We have therefore included it as a risk factor in our analysis. Treatment for visual impairment is effective and cost-effective for an estimated 90% of people but across the world, particularly in those living in LMICs visual impairment is often not treated.(253) (249) There is a clear prevention opportunity.

Multicomponent dementia prevention studies

Multidomain interventions address multiple dementia risk factors through health-related and behavioural changes so, in principle, are appropriate for a multifactorial condition. They vary in approach, from detailed individualised approaches supported by goal setting in person, or those linked to digital platforms or mobile apps. Others are based more on group activities. The existing evidence is preliminary as there are few completed studies but over 40 ongoing trials.(259) A 2021 Cochrane review identified nine multi-domain interventions for the prevention of dementia or cognitive decline RCTs with 18,452 participants.(260) There was high certainty of a small benefit on overall cognition (3 RCTs; composite z score mean difference (MD) 0.03, 0.01- 0.06, n = 4,617, over 18-36 months), (228, 261, 262) particularly in people with the *APOE*ε4 genotype (2 RCTs; n = 2,043, follow-up 24-36 months, carriers MD 0.14, 0.04 -0.25, noncarriers MD 0.04, -0.02 to 0.10,), but the effect on dementia incidence had wide confidence intervals (2 RCTs; n = 7256, follow-up 6 to 13 years RR 0.94, 0.76 -1.18). (263, 264) Similarly, the pre-DIVA trial addressing cardiovascular risk factors longer term follow-up (median 10.3 years, participants aged 70 -78 years at baseline showed similar results regarding dementia incidence.(265) Since then two further RCTs have reported. Age Well, recruited 1030 vascular at-risk adults in Germany. Nurses instructed intervention participants, to follow a multidomain intervention with two follow-up visits and five phone calls over two years. (266) The intervention was nutrition and medication optimisation, and physical, social, and cognitive activity with goals set, and had no effect on cognition over 24 months compared to controls given general health advice. The investigators thought the intervention was not targeted enough or intense enough. The SMARRT trial ran for two years and recruited 172 adults aged 70-89 and addressed personalised risk reduction goals with health coaching and nurse visitors over 2 years and found a cognitive improvement in the intervention group of 0.14 standard deviations; 0.03-0.25, a 74% improvement compared to Health Education control. (267)

Multicomponent Interventions in MCI

A systematic review and meta-analysis of multidomain interventions in MCI found 28 RCTs of older adults with MCI receiving non-pharmacological multi-domain interventions over up to a year (n=2711) and a moderate effect on global cognition (standardised mean difference 0.41, 0.23-0. 59, ($I^2 = 62\%$) with improvements in executive function and memory compared to single intervention active control. (268) The authors considered

reasons for the heterogeneity including some studies being underpowered but could not draw firm conclusions. One smaller systematic review of lifestyle RCTs in people with MCI found only three small RCTs (total n=156) and a significant benefit for cognition with low heterogeneity.(269)

Difficulties in multicomponent intervention studies

Studies have often recruited participants based on high cardiovascular risk.(262) A systematic review reported that the 10-year dementia risk for individuals eligible for four large-scale trials of multidomain (2+ domains) interventions(228, 261, 262, 264, 270) was similar to those deemed ineligible, thus future trials may need to more accurately identify people at higher dementia risk.(271)

Some studies have employed strategies to boost efficacy and adherence, including intervention coaches to support behaviour change, digitally delivered personalised and scalable self-management interventions, and targeting people of lower SES and people in LMICs. (229, 272-275) These should clarify whether the cognitive benefits reported in existing trials can be replicated or increased and whether they are likely to be scalable and clinically significant in preventing dementia. It is currently unclear whether the cognitive benefits identified are sustainable after intervention cessation, if they translate into a reduction in dementia incidence, or if they can be implemented with similar adherence and effectiveness in more resource-deprived in higher risk groups.
A review of trials for dementia prevention found that only 62% of studies reported any ethnicity data and in those, minority ethnic groups accounted for a relatively low percentage of participants.(276) The FINGERS study(228) did not report ethnicity or dementia incidence but reported that effects of the intervention on cognitive function were the same across socio-economic categories (albeit within a relatively affluent cohort). All but 2% of participants in the HATICE study (a computer platform, coach supported goal setting approach) were White.(261) Results were not disaggregated by ethnicity but the impact of the intervention was greatest in those with the lowest baseline educational attainment.
Overall, even interventions with modest effects could theoretically have significant preventative effects at the population level, including those less affluent or in LMICs. Interventions for individual and multiple risks would potentially be cost-effective but scalability is challenging, (7, 277-279) and they may need to be repeated at intervals to achieve sustained benefits.

Total PAF calculation

We incorporated the two new risk factors - high LDL-C and uncorrected vision impairment and the 12 factors in our previous model into our life-course model of dementia. We used the largest recent worldwide meta-analyses for risk factor prevalence and relative risk and if not available the best data, and sources and justifications are detailed in appendix page 2-6. We performed new meta-analyses for the relative risk for depression and hearing loss as explained above.

PAF calculation

We used all 37,000 participants aged ≥ 45 years from the HUNT study which is a longitudinal population-based health study among residents aged 20 years or older in the county of Nord-Trøndelag, Norway (167) (280) (281) to estimate communalities (clustering of risk factors) of the 14 risk factors. Appendix 3 (page 5-9) - shows the PAF formula, risk factor definitions and steps including Stata code in calculating communality and PAF. Our analysis found five principal components, explaining 54 % of the total variance between the 14 risk factors, indicating there was substantial overlap in risk factor prevalence, so we accounted for this in our weighted PAF estimates. We estimated that the PAF for all 14 risk factors was 45.3%. Figure 9 shows the life-course model of 14 potentially modifiable risk factors for dementia. Table 1 displays the prevalence, communality, relative risk, unweighted and weighted PAFs adjusted for communality for all 14 potentially modifiable dementia risk factors. Numbers in both are rounded so the total is the nearest whole number.

Population attributable fraction of potentially modifiable risk factors for dementia

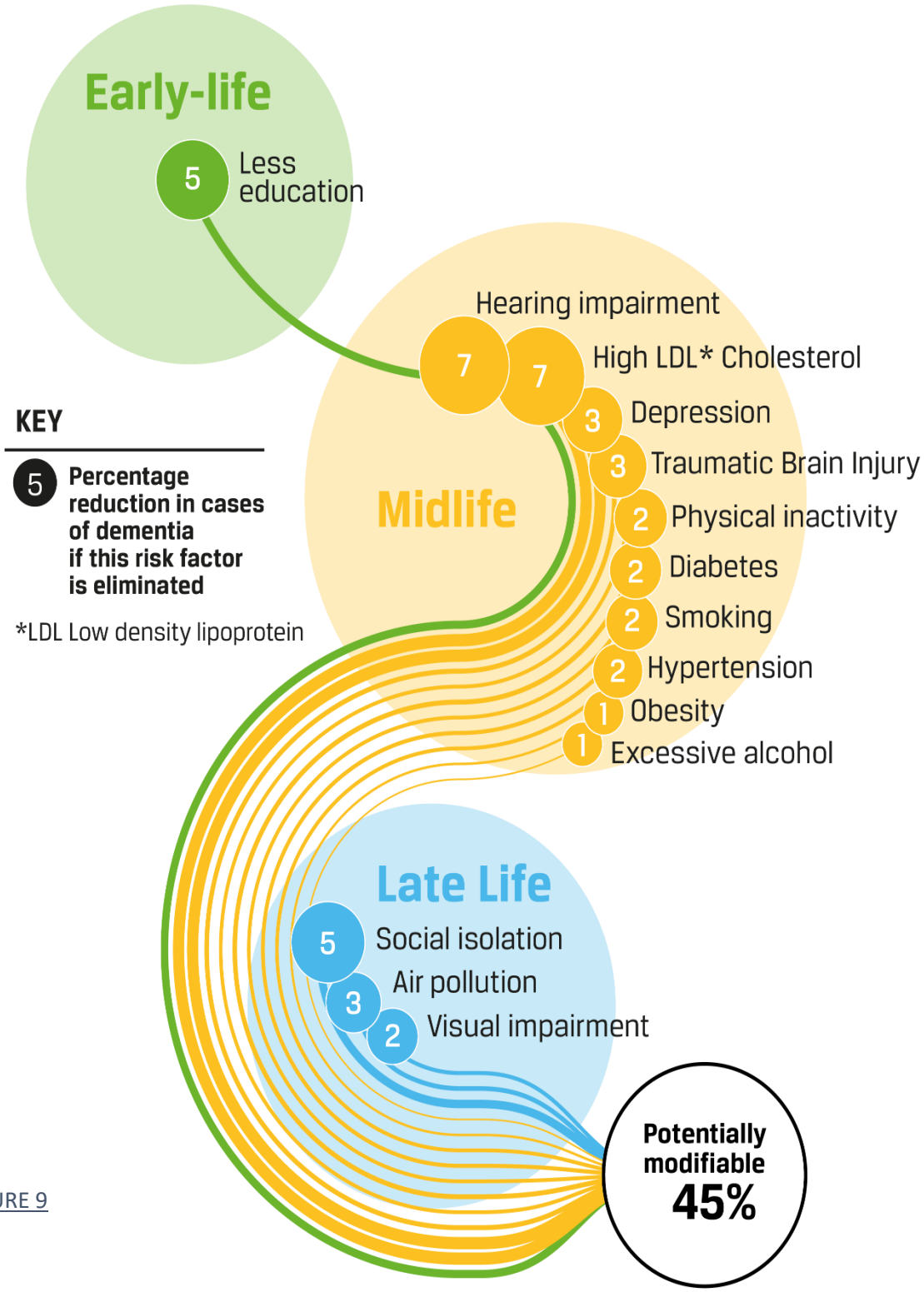


FIGURE 9

Strengths and limitations

This is the most comprehensive analysis to date of the PAF for potentially modifiable risk factors for dementia and updates previous calculations with newly incorporated risk factors with convincing evidence, and updated worldwide estimates of relative risks and prevalence for the risk factors. Selection criteria always have a degree of subjectivity which can affect conclusions, so we have presented the evidence on which they were built for transparency. We have used the best current evidence for magnitude of risk, but this may have over or under-estimated it. We used systematic reviews for the chosen risk factors, identified data to calculate communality for 14 risk factors and provided new meta-analyses where required for our synthesis. We only did new meta-analyses for depression and hearing loss (as there were no recent reviews) and may therefore have missed some new evidence. We have detailed how we did these but had not pre-registered them. We find a hopeful picture with an estimate of nearly half of all cases of dementia being associated with 14 potentially modifiable risk factors.

We used worldwide figures of prevalence where possible, which include disproportionate numbers from HICs although we have included evidence that risk factors prevalence varies between countries.(32) (33) Most global research is from HICs, so LMICs remain under-represented due to lack of data. We have assumed risk factors cause dementia and have included more evidence that changing them has the potential to change the prevalence of dementia. We have also not included other risks with less certain evidence and know there will be others. There is a lack of evidence on how risk and protective factors might cluster or vary within and across different nations. Participants in HUNT reported a lower prevalence of alcohol abuse than worldwide figures and are living in a HICs with a lack of ethnic diversity. Additionally, we could not find a worldwide estimate of prevalence of LDL cholesterol and acknowledge that the use of an estimate from a single cohort study is not ideal. Many risk factors are linked to deprivation, for example, where people live and exposure to air pollution, or the possibility of finding reasonably priced healthy food within reasonable walking distance and having the resources and skills to prepare it, linked to obesity and diabetes. Deprivation is strongly linked to education and its incorporation in our communality calculations will reduce the individual effects of these. We remained unable to meta-analyse data on air pollution, although the data remains consistent that it is a risk for dementia.

We have more evidence that longer exposure to a risk has more effect, for example in diabetes, and that risks act more strongly in people who are vulnerable, for example air pollution. Thus, it is important to redouble efforts to treat existing conditions in the best possible way for all at risk. However, this risk modification affects the population but does not guarantee any individual will avoid dementia. In addition, it is vital to think about communities and people with multiple risks where approaches beyond the individual treatment or exhortation of behaviour change have potentially larger impact over the longer term. The length or intensity of an intervention required to make a difference is unknown, but it is hopeful that that risk associated with smoking can be reduced across time, and indeed may be one of the factors associated with prevalence reductions seen in some populations. While association is not causation, the effect on cognition of multicomponent, hearing aid and hypertensions RCTs, and the naturalistic changes with reduction in air pollution, cigarette smoking, social contact, hearing and vision corrections and increases in cognitive stimulation through work, continue to suggest a causal relationship with the clinical expression of dementia. More socially disadvantaged groups in both LMICs and HICs are more at risk and should be a priority for intervention. There is considerably more evidence that these changes are important for people whether or not they are at increased genetic risk. We have summarised key points to highlight our recommendations based on reflecting on the literature we have presented. Although

there are major gaps in our understanding of risk, these should not wait, as there are ways to reduce the chances of developing dementia and benefit individuals, families, and society.

Public health approach

Though dementia is a leading public health challenge, a public health lens is a relatively novel approach to dementia prevention. Risks can be conceptualised as something the individual can change but a public health approach recognises the lifecourse generation of ill-health associated with deprivation or disadvantage. The socioeconomic patterning of conditions such as type 2 diabetes and obesity, as well as behaviours such as smoking and excess alcohol consumption starts in early life.[282] Understanding the cause of risk inequalities such as unequal access to education, to healthy and safe environments, and poor occupational conditions can compel change in societal conditions to maximise the population reach, cost-effectiveness, and health equity of interventions.(283, 284) Since cardiovascular health and smoking partially mediate the relationship between socioeconomic deprivation and dementia,(285-288) life-course, population-level approaches to support physical activity, not smoking and a non-obesogenic, healthy diet which could also impact and diabetes are expected to have a profound effect on inequalities in dementia prevalence.

Demonstrating a link between changes in these risk factors and subsequent reduced dementia risk is difficult because of the life course accumulation of dementia risk and the long pre-symptomatic build-up of pathology means that many years or decades may be necessary to show a difference. Another approach is to use the risk (and protective) factors as proxy-outcomes, with assumed causality leading to reduced dementia prevalence. Other study designs, such as quasi-experimental studies, also have the potential to provide clarity as to the impact of such initiatives on dementia risk. (289)There are several population-level interventions with appropriate tailoring to cultural and economic contexts, which could theoretically significantly reduce dementia prevalence, inequalities, and system-wide costs, including:

- Fiscal policies such as subsidies to increase affordability of healthy foods and taxation to reduce the affordability of alcohol, tobacco and unhealthy food; levies to encourage product reformulation; removing financial barriers to continuing education and cleaner fuels.(171, 277, 290)
- Marketing policies – e.g., reducing advertising exposure to unhealthy products, well designed mass media campaigns that shift sociocultural norms. (171, 277, 290, 291)
- Legislative and availability policies – e.g., smoking bans in public places, reducing hours of alcohol sales, making healthy food more accessible, reducing density of fast-food outlets, provision of safe and high-quality green spaces and active travel infrastructure, noise exposure reduction and hearing protective equipment provision in workplaces, low emission zones to reduce air pollution, and mandating helmet use in active travel and sports. (171, 277, 290)
- Physical environmental adaptations to make exercising and socialising accessible and safe by optimising urban planning, accessibility, and infrastructure, as recommended in the WHO's Global Age Friendly Cities Guide.
- Housing policies: Provision of adequate-socially connected housing for older people is a focus of several governmental and third sector organisations, with potential to reduce social isolation and loneliness and provide support networks for older people.

Potential risk factors considered with insufficient evidence to include.

We know there are other potentially modifiable risk factors and there are several others we considered but on balance currently we judged that there is not enough consistent evidence to meet our high bar of being included as modifiable risk factors. These include too little sleep, an unhealthy diet, infections, and mental health conditions.

Sleep

As we discussed in the last commission, it was unclear whether the association of short and long sleep duration (usually defined as ≤5 hours and ≥10 hours respectively) is associated with increased risk of cognitive decline and dementia or is because people who are developing dementia have disturbed sleep in the prodromal stage. (2, 292-294) Two meta-analyses included studies using varying definitions, from short being <7 hours and long being >8 hours and had a follow-up of <10 years until incident dementia, and their findings of an inverted U-shaped association between sleep duration and dementia risk remain subject to potential reverse causation bias. (293, 295) Some studies are noteworthy because of longer follow-up but no studies reported those who developed dementia soon after sleep duration ascertainment separately from those who developed it after longer periods. (280, 296-301) The reverse causation hypothesis is supported by a longitudinal MRI brain imaging study of 3893 healthy adults which found that brain atrophy rates were not associated with either longer or shorter sleep duration nor quality of sleep when controlling for BMI, socio-economic status and mood.(302) However cross -sectionally sleep duration was associated with cortical thickness and the authors suggest that normal brains support normal sleep duration.

Short sleep duration

In the million-woman study of 830,716 women (mean age 60 years at baseline) with a 17-year follow-up, there was a slightly higher risk of dementia (RR 1.08, 1.04-1.12) among those who reported shorter but not very short sleep duration (<7 hours). In the Whitehall II study, persistent short sleep duration ≤6 hours at age 50, 60, and 70 compared to persistent normal sleep duration (7 hours) was associated with a 30% increased dementia risk independently of sociodemographic, behavioural, cardiometabolic, and mental health factors.(303) In a Norwegian cohort of 7492 people with follow-up of 11 years, insomnia (which may differ from short sleep duration), was not associated with all-cause dementia, AD or cognitive score.

Shift work.

Shift work, where some work is outside the normal working day, may disrupt the circadian rhythm and this may increase the risk of cardiovascular disease and some other illnesses. A systematic review found heterogenous evidence of dementia risk and could not draw conclusions.(304) A subsequent UKB study examined whether shift work might be related to dementia and followed 170,722 people, aged in their early 50s at baseline, for a median of 12.4 years, of whom 27,450 (16.1%) did shift work. It was associated with an increased risk of dementia (HR 1.30, 1.08–1.58) but this was not increased further in night shift compared to day shift workers, although the power to detect differences was low. (305)

Long sleep duration and napping

In a Swedish cohort of 28,775 individuals aged 65 years and older, the association between long sleep duration and dementia over a 13-year follow-up was completely attenuated after cases occurring in the first 5 years of follow-up were excluded from the analysis, highlighting the role of reverse causation bias.(300) Similarly, in the US million woman study there was no association between long sleep duration (>8 hours) or daytime napping and dementia on longer term follow-up after the first five years.(306) A UKB MR study found a small association between habitual napping and higher brain volume (unstandardized ß 15.80 cm^3, 0.25- 31.34) but no difference in hippocampal volume or cognitive tests.(307)

Sleep apnoea.

Along with duration of sleep, emerging evidence suggests that quality of sleep, specifically sleep apnoea, may be associated with dementia. A systematic review and meta-analysis of eleven studies including 1,333,424 participants follow up of up to 14.9 years found people with sleep apnoea had an increased risk of developing dementia (HR 1.43, 1.26–1.62). (308) Few of these studies adjusted for obesity. It may be worth considering screening questions about dementia in people with sleep apnoea.

Mechanisms

Sleep disturbances are postulated to increase dementia risk through several processes.(292) They often co-occur with other conditions affecting dementia risk (e.g., diabetes, depression, alcohol consumption). In addition, people with impaired sleep may be treated with benzodiazepines which may be related to cognitive decline. One systematic review and meta-analysis found very low quality evidence of an increased risk of dementia in people taking benzodiazepines in 11 studies with follow-up over 72–264 months (OR 1.38, 1.07–1.77; I^2 = 98%; n=980,860).(309) A prospective cohort study found that the risk was higher in those with low benzodiazepines dosage compared to those taking higher doses, suggesting the relationship is not causal.(310) Experimental studies support a detrimental effect of acute sleep deprivation on immediate cognitive performance.(311)

Biological mechanisms include neuroinflammation,(312) atherosclerosis,(313) alpha-synucleinopathies (dementia with Lewy bodies and Parkinson disease dementia),(314) and impaired amyloid-β clearance.(315) However, this usually occurs during deep sleep at the beginning of the night, which lasts one to two hours so is unlikely to be affected in those reporting sleep disturbances. (316-318) Amyloid plaque build-up contributes to poor sleep in older adults through its direct impact on sleep-wake regulator brain regions.(319, 320) There is also some evidence of an association of Aβ accumulation with disruption of the circadian rhythm and sleep pattern in cognitively normal adults.(321)

Decision

Since the last commission, further evidence indicates that prolonged sleep is not a risk factor for dementia, although dementia and its prodrome may cause prolonged sleep. People should not curtail their sleep to reduce dementia risk. Benzodiazepines do not appear to cause dementia.

Overall, current evidence appears to indicate that short sleep duration may be associated with a small, increased risk of dementia but there is a lack of evidence about the characterisation of short sleep, and no information on sleep quality or circadian rhythm disturbance which may be the factors associated with increased risk of developing dementia rather than length of sleep. Therefore, the evidence about short sleep has not yet been clarified enough to be sure of causation. We are unable to make recommendations on sleep as a risk factor.

Diet

As we previously discussed, nutrition and individual dietary components are challenging to research and there are contradictory findings regarding their link with cognition and dementia.(2) A diet encompasses multiple healthy and unhealthy food and drinks and is often part of a way of life, so observed effects may be related to lifestyle or be independent of them.(322) The Mediterranean and similar diets tend to be less available in LMICs.

Observational studies of whole diets, dementia, AD pathology and brain atrophy

Similar healthy diets include the Mediterranean diet, dietary approaches to stop hypertension (DASH) diet, and the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet which is the Mediterranean diet plus specific healthy foods. The WHO makes a conditional recommendation of Mediterranean diet for risk reduction in dementia meaning they were unsure about the balance of evidence between desirable and undesirable effects. (116) Since then there have been several new studies. One systematic review and meta-analysis identified 16 cohort studies with follow-up from 2.2 to 41 years.(323) High diet quality relative to low diet quality was associated with lower dementia risk (RR 0.8, 0.7 -0.95; n=66,930; 12 studies). This risk was similar when only studies which had follow-up for >10 years were included (RR 0.78, 0.62-0.99, 6 studies) or when restricted to the outcome of AD. In contrast, they reported that studies using a continuous Mediterranean

diet score found no significant association between Mediterranean diet adherence and risk of dementia. A subsequent larger meta-analysis of three cohort studies with 224 049 participants found higher adherence to the MIND diet score was associated with lower risk of dementia (HR for every 3-point increment, 0.83; 0.72-0.95; I^2 = 0%).(324) A third systematic review reported protection in 10 of 21 studies of the Mediterranean diet against global cognitive decline; 3 of 8 studies against incident dementia and 2 of 4 studies against AD in particular.(325)

Since these reviews, a Swedish prospective cohort of 28,025 people in midlife (mean age at first assessment 58 years, median follow-up 19.8 years) reported neither adherence to dietary recommendations nor to the modified Mediterranean diet lowered the risk of dementia, AD or VD or AD pathology. (326) These results remained the same when those who developed dementia in the five years after baseline were excluded. In contrast, a UKB study (n=60,298, mean age at baseline 63.8, mean follow up 9.1 years) reported adherence to the Mediterranean diet was associated with lower dementia risk independent of *APOE* status. (327)A US cohort of older people (n =581, mean age at first assessment =84) found MIND and Mediterranean dietary patterns, particularly consumption of green leafy vegetables, inversely correlated with beta-amyloid load, phosphorylated tau tangles and global AD pathology at post-mortem. (328)

Ultraprocessed foods

Ultraprocessed food (UPF) are formulations of processed food substances (oils, fats, sugars, starch, and protein isolates) containing little or no whole foods. Classifications of food vary as the definition is vague. A cross-sectional US study of 3,632 participants aged ≥60 years found overall cognitive performance and memory were not associated with the percentage of daily energy intake dietary from UPF after correction for confounders. (329) A longitudinal study from Brazil (n= 10, 775, mean age at baseline 51.6, 5,880 participants (54.6%) women, 5723 (53.1%) White, median follow-up 8 years) where individuals whose UPF consumption was in the highest three quartiles, reported a 28% faster rate of global cognitive decline (β -0.004; -0.006 to -0.001) and a 25% faster rate of executive function decline (β -0.003, -0.005 to 0.000) compared with those in the lowest quartile after adjustment for relevant sociodemographic and clinical variables. (330) These studies are not long enough to rule out reverse causation bias.

Omega fats

A French study (n=1279, mean age at baseline 74.3, follow-up 17 years) found higher levels of omega-3 index in plasma were associated with a lower risk of dementia (HR for 1 standard deviation 0.87, 0.76–0.98), and a lower decline in medial temporal lobe volume.(331)

Microbiome

Gut microbiome encompasses all microbes in the gut. Changes in it occur as people age or from obesity, diet, infection, CVD, sleep issues or lack of physical activity. It has been suggested that the changes in the microbiome mediate the effects of diet on the brain(322) and facilitate neuro-inflammation and cell death and are a risk factor for dementia. (332) Few studies have examined the associations of gut microbiome with dementia, and we cannot draw any conclusions.

Dietary interventions

Designing dietary interventions is difficult as the right doses, forms, timing in life and duration remain unclear.(322) The caveats in long term RCTs outlined above in terms of practicality, ethics and bias are particularly salient here. The commission previously found convincing evidence that vitamins did not prevent cognitive deterioration in the general population as did the WHO (2, 116) Since then further studies have not produced convincing benefit.

A three-year RCT of a dietary educational intervention - dietary counselling and either MIND diet or mild calorie-controlled diet testing in 604 older people without cognitive impairment, a positive family history of dementia, a BMI >25, and a suboptimal diet, found no between group differences in global cognition and a secondary brain MRI outcome. (333) Both groups improved in cognitive score, had a similar weight loss of around 5kg and similar MRI outcomes.

COSMOS-MIND, was a three-year RCT, nested in the cardiovascular COSMOS RCT in 2262 volunteer participants (mean age = 73). The trial tested separately daily cocoa extract (primary analysis) and multivitamin-mineral (MVM).(334) Cocoa extract (plus or minus MVM) had no effect on global cognition and MVM supplementation led to a small, not clinically, but statistically significant, global cognition benefit (mean z 0.07, 0.02- 0.12) in memory and executive function. The authors suggested further studies in those at greater risk.
COSMOS-WEB was a subset of COSMOS that substantially overlapped with COSMOS-MIND but examined only those randomized to cocoa extract or placebo and found that the flavanol intervention did not enhance memory over 1 to 3 years.(335) A 24 week RCT of anthocyanins (flavonoid found in berries and fruit, thought to be anti-inflammatory, antioxidant and to improve lipid profile) in 206 people age 60 to 80 years old without dementia found no difference in cognitive outcomes.(336) They thought this may be because of lack of power and duration as there was a difference between the slopes of cognitive decline.

Decisions

Nutritional epidemiology studies often but inconsistently report an association between diet and biomarkers, cognitive decline, dementia, or AD. Studies are of few, mostly Western diets. Clinical trials have generally reported that nutritional and dietary interventions do not reduce cognitive impairment. Intervention results are small, heterogenous, usually not statistically significant, and, at best could be considered hypothesis generating findings, but do not support the primary hypotheses. Positive results in some subgroups indicate that future investigation may be useful. There is indication that interventions may need to be longer to have an effect.

Eating a diet high in fruit and vegetables and low in ultra-processed foods is good for many health conditions and impacts dementia risk factors of obesity, diabetes, and hypertension but there is not enough evidence to say they are directly useful for dementia prevention. There is a lack of data on the effect of malnutrition in early life.

Infections and systemic inflammation

In one IPD meta-analysis, severe peripheral systemic infections requiring hospitalisation were linked to higher dementia risk and associations persisted after adjustment for age, sex, SES, health behaviours, BMI, hypertension, diabetes and *APOE* genotype (HR 1·22,1·09-1·36). (337) This may partly be explained by higher rates of dementia and brain vulnerability in people hospitalised with infection who have a smaller brain volume and lower white matter integrity than age-matched controls who are not hospitalised. (338, 339) A subsequent electronic register study of almost 1 million UK adults, showed that infections resulting in hospitalisation, but not those treated in primary care, were associated with a higher risk of dementia or AD. (340) Several viruses and bacteria were associated with dementia risk and risk was elevated more in those with CNS infections but also with extra-CNS infection. (337, 341, 342) (337) In the Baltimore Longitudinal Study of Aging (N=1009), accelerated white matter atrophy was observed among individuals with a history of symptomatic herpetic infections. (343) although another study found no association between Herpes Simplex infection and cognitive decline or brain atrophy. (344)

Sepsis, pneumonia, lower respiratory tract infections, skin and soft tissue infections and urinary tract infections are all associated with higher rates of dementia in people and animal studies. (340) Similarly, raised peripheral

inflammatory markers are linked to higher dementia risk with one meta-analysis of 10 studies with follow-up ranging from two to 25 years. reporting the highest compared to lowest quartile C reactive protein (CRP) had a higher dementia risk (HR 1.34, 1.05-1.71) with similar results for Interleukin 6 (IL-6) in four studies (HR 1.40, 1.13-1.74] and a1-antichymotrypsin in three studies (HR 1.54, 1.14-2.08) but not Lp-PLA2 (HR 1.06, 0.94-1.18). (345) Higher inflammatory marker levels are also associated with more cognitive decline.(346)

There is currently little longitudinal evidence on the long-term impact of COVID-19 and evidence in this area is about the effect of COVID-19 on cognitive function and biomarkers, not on dementia risk. COVID-19 may increase the risk of cognitive impairment with one meta-analysis finding slightly more impairment in global cognition 7 months after infection in adults with no known history of cognitive impairment than in controls (MOCA score MD-0.94; -1.59- -0.29).(347) In addition, declines in grey matter thickness and total brain size have been reported 6 months after SARS-CoV-2 infection in 785 UKB participants compared to those not infected. (348) It may also increase risks by changing population habits, for example, so people take less exercise or are more likely to be obese. (349)

Mechanisms of the effects of infection and inflammation

The mechanisms by which infections may contribute to higher dementia risk remain poorly understood and are likely to be bidirectional, with people with cognitive impairment and dementia more severely affected by infection and more likely to be admitted to hospital. Although the blood-brain barrier (BBB) protects the brain, there are multiple mechanisms for peripheral and central immune communication, including direct pathways of peripheral immune cell infiltration across the BBB and indirect pathways of systemic inflammation-driven modulation of CNS microglial function. (350, 351) Animal and in-vitro studies demonstrate that inflammatory stimuli may initiate long-term priming of the microglia, peripheral CD4+ and CD8+ T cells to a proinflammatory state, (352-354) potentially increasing amyloid plaque deposition.(355) Long-term immune activation and systemic inflammation can also adversely affect brain capillaries, increasing BBB permeability and related entry of neurotoxic plasma components, blood cells, and pathogens into the brain. (356, 357) As hospital-treated infections are more strongly associated with vascular than Alzheimer's dementia, mechanisms may involve vascular inflammatory pathways. (337, 340) BBB dysfunction has been linked to microbleeds and perivascular oedema, compromising microcirculation and inducing ischaemic damage.(358) Furthermore, infections and related systemic inflammation can trigger macrovascular events, including stroke, further increasing dementia risk.

Interventions with vaccines, anti-inflammatory or antibiotic drugs

Meta-analyses of observational studies suggest that vaccinations against rabies, tetanus, diphtheria, pertussis, herpes zoster, influenza, hepatitis A, typhoid and hepatitis B are associated with lower dementia risk, although this may be partly due to confounding factors as people who receive vaccinations may have different health behaviours and access to health care compared to those who do not.(359) One population cohort study using UK GP records of 13,383,431 adults age >50 years old found no effect of vaccines on the risk of dementia when adjusted for potential confounders. (360)

One systematic review and meta-analysis concluded there was no strong evidence from larger RCTs of interventions which modify infection and inflammation, reduce cognitive impairment, or risk or progression of dementia. (361) Non-steroidal anti-inflammatory medication for AD, such as naproxen and celecoxib in older adults with a family history of AD over 1 to 3-years or aspirin 100mg for older people over 9.6 years did not decrease dementia risk, (362) although they did increase adverse events. (363) Minocycline, a tetracycline antibiotic which protects against the toxic effects of β-amyloid in vitro and in animal models of AD, did not delay

the progression of cognitive impairment in people with mild AD over a 2-year period in a multicentre clinical trial.(364)

Interventions such as vaccinations, hand washing and ventilation that avoid infection and therefore reduce risk or severity of inflammation and vascular events are good for general health and may lower dementia risk.

Dental disease

Dental disease, including gum inflammation (periodontal) disease is associated with chronic, inflammation-driven disorders and has been suggested to be a risk factor for dementia.(365) People with better childhood cognitive function have better dental health and, throughout life, use more preventative dental care and lose fewer teeth than their counterparts, and this precedes by many decades potential mechanisms of compromised nutrition, chronic periodontitis and inflammation related to dental disease.(366)

A nationwide Swedish study controlling for demographic, socioeconomic and wider health conditions of people aged 40 to 80, did not find a higher incidence of dementia in 7992 individuals with caries and periodontal disease than 29,182 matched controls over 7.6 years.(367) A US study controlling for demographic, vascular health and SES, found that in 3521 people aged ≥ 65 years different (but not the same) periodontal disease were associated with either all cause dementia or AD or AD death over 26 years of follow-up.(368) The dental disease group had had less education, lower disposable income, and more comorbidities. Currently there is not consistent, high-quality evidence that dental and periodontal disease is a risk factor for dementia.

Decisions

The extent to which infections and inflammation are modifiable dementia risk factors remains unclear, as most studies are in older people with relatively short follow-up. Specific pathogens cross the BBB, such as syphilis, HIV and herpes and are diseases which directly cause dementia. This is not the same as infection being a risk itself. Inflammation may be a common pathway for many risks factors for dementia.

Bipolar disorder

A review of five longitudinal studies examined associations between bipolar disorder and dementia, with follow-up durations from 4 to 11 years.(104) There was no meta-analysis as several studies used the same database and were based on one of two population-based cohorts (in Western Australia or Taiwan), but there was a consistent association between bipolar disorder and dementia risk (HR between 2.31 to 4.55). One included study found greater illness severity related to higher dementia risk, the rate of dementia was higher in individuals who had 1-2 psychiatric admissions (RR 2.4, 1.9–3.1) and >2 admissions (5.7, 4.8–6.8) per year. Compared to those with no admissions. There was heterogeneity in the extent to which studies adjusted for factors such as cardiovascular risk, comorbidities, and alcohol consumption.

Psychotic disorders including schizophrenia.

A 2022 systematic review of 11 population-based cohort studies including 13 million people found an overall increased risk of all-cause dementia over median 11 years (RR 2.52, 1.67–3.80), although heterogeneity was high (I^2 99.7%).(369) Most included studies were of individuals with schizophrenia, and only one study specifically reported findings for early onset schizophrenia (<40 years), which showed higher dementia risk than controls but lower risk than late-onset schizophrenia (>40 years).(370) Another lifespan study included in the review also found lower dementia risk in younger (18-49 years) versus older individuals with schizophrenia.(371) However, a third lifespan study found higher dementia risk in the youngest (18-60 years) versus older age of onset groups with psychotic disorders,(372) potentially attributable to more deaths in older cohorts. Studies varied in the degree of adjustment for age, sex, comorbidities, alcohol, smoking, medications, income and education levels and there was

no conclusive evidence on the potential impact of specific comorbidities or antipsychotic medication on dementia risk, or risk for specific dementia types.

Mechanisms

People with schizophrenia have lower brain volumes at illness onset than the age-matched population suggesting a neurodevelopmental cause, (373) and cognitive impairment, a core feature of schizophrenia, is already present at illness onset.(374) There is no clear link between this cognitive impairment and specific AD-related neuropathology.(375) (376) and despite mainly experiencing normal age-related trajectories of cognitive functioning during mid-life, they show accelerated brain aging (in neuroimaging) compared to healthy controls and people with depression and bipolar disorder.(377) One systematic review found that cardiovascular risk factors including metabolic syndrome (13 studies; n = 2800; effect size [ES] 0.31; 0.13-0.50), diabetes (8 studies; n = 2976; ES = 0.32; 0.23-0.42), or hypertension (5 studies; n = 1899; ES0.21; 0.11-0.31) in people with schizophrenia were associated with significantly worse cognition. This higher prevalence of known dementia risk factors throughout mid-life, such as cardiovascular disease, hyperlipidaemia, obesity, smoking and social isolation contribute to further cognitive decline in older age.(378) People with very late-onset (>60 years) schizophrenia-like psychosis (VLOSLP) have a particularly high risk of developing dementia with a HR 4.22.(379) Although some of this can be explained by potential misdiagnosis of psychosis symptoms in dementia as VLOSLP, dementia diagnosis rates remain higher in this group for 20 years following diagnosis, and it may represent a dementia prodrome.

Decisions

Overall, there is consistent evidence that people with schizophrenia have more and earlier dementia than others, including those with depression and bipolar disorder. (380) People with schizophrenia have high cardiovascular morbidity and less education as well as cognitive impairment related to schizophrenia. We currently judge that it is unclear that schizophrenia independently predisposes to dementia beyond the fact that people with schizophrenia more often have other risk factors. We do not know if early intervention can modify pre-existing cognitive impairment specific to schizophrenia. There is relatively evidence on dementia risk in bipolar disorder, but findings have been consistent regarding an increased risk. We recommend, in line with policy in some countries, that people with schizophrenia and bipolar disorder are considered at risk and enhanced attention is paid to treating modifiable dementia risk factors.

Anxiety

A review of seven longitudinal studies found no increased risk of dementia in people with anxiety disorders (RR 1.18, 0.96-1.45) although individual studies had mixed findings and results were not adjusted for depression. (104) A subsequent study of 2551 adults aged 60 to 64 followed for 12 years, found no association of anxiety disorders themselves with cognition (after adjusting for depression) or with cognitive decline.(381) Those who responded to psychological treatment for anxiety had a lower incidence of all-cause dementia (median 3 years later, HR 0.83, 0.78-0.88) than those who did not.(382) This may suggest that those who are anxious as part of preclinical dementia are less likely to respond to treatment. A meta-analysis found no association between anxiety symptoms and Aβ (N = 5141, 13 studies) or tau (N = 1126, 4 studies) in cognitively healthy adults.(383)

Post-traumatic stress disorder

A systematic review of the associations between post-traumatic stress disorder (PTSD) and dementia found three studies in US, Denmark and Taiwan with sample sizes from 8750 to 489,994 and all observed higher risk of dementia in 11 to 17 years follow-up, ranging from HR 1.70 to 4.37.(104) The risk was more marked in those with depression but remained after adjustment for depression. An earlier systematic review and meta-analysis

which included these studies and another five studies suggested PTSD is a risk factor for dementia, although there was considerable heterogeneity between the included studies(HR 1.61, 1.43–1.81, I^2=85.8).(384) Despite the increased dementia risk, a follow-up study over 5 years found no increase in AD pathology in people with PTSD and suggested the increased dementia risk is from other causes. (385) There is only one meta-analysis and evidence is too heterogenous to generalise and conclude at this stage that PTSD is a modifiable risk factor for dementia.

Menopause and hormone replacement therapy

The role of hormone replacement therapy (HRT) was not discussed in the last commission, but it has been suggested that menopause and HRT may partially explain the higher prevalence of dementia in women than men. Meta-analytic data found that woman with menopause occurring after age 45 had a lower risk than those who had younger age, RR: 0.87, 0.78-0.97, I-2 =56.0%. (386)

Two nested case-control studies, using routinely collected primary care data from 16,291 women with dementia and 68,726 controls who had taken HRT for ≥3 years found increased risks of developing AD in women who had used oestrogen-progestogen therapy for between five and nine years (RR 1.11, 1.04-1.20) and for 10 years or more (RR 1.19, 1.06-1.33). (387, 388) In line with this, 5589 Danish women who had used oestrogen-progestogen therapy aged 50 to 60 compared to those who had never used it had an increased risk of all cause dementia and AD (HR 1.24, 1.17-1.33). Risk increased with more years of use, ranging from HR 1.21 for ≤1 year to 1.74 for >12 years of use. (389) Those taking HRT had increased risk whether they started it at younger or older ages (>age 55 years). The same risk was not found for progesterone-only or oestrogen-only therapy, and another study showed a lower risk of all cause dementia among those aged <80 years old who had been taking oestrogen-only therapy for ≥10 years (OR 0.85; 0.76 - 0.94) but not in those who had taken it for less time.(388)

Intervention studies

A meta-analysis of 23 heterogenous RCTs, 9 of which combined oestrogen and progesterone use, reported any HRT had a small but statistically significant negative effect on global cognition (MD −0.04, −0.08 to −0.01, I^2 = 0.0%).(390) Subgroup analysis found no positive effect in short or long term use of HRT in different age groups but a more negative effect if initiated after age 60. A further meta-analysis of RCTs found high quality evidence that post-menopausal women should not take oestrogen-only therapy to prevent dementia and some evidence that it increased the risk. (361)

Decisions

Overall, it is unclear whether menopause and HRT are causally related to dementia risk. There is some evidence that oestrogen-only therapy, and later-initiation of HRT, may increase dementia risk.

Multimorbidity and frailty

People who have more chronic illnesses and more severe illness are at higher risk of dementia, particularly if these illnesses begin in midlife.(391, 392) Up to 24% of people aged 50 and over are estimated to have frailty and this is more common in women.(393) In older Americans more frailty was associated with lower neuropsychological test score, (394) and a higher risk of developing MCI and dementia (HR 1.66, 1.55-1.78 and HR 1.14, 1.02-1.28 respectively per 0.1 increase on frailty index). (395) A further study of 1.7 million New Zealand adults over 30 years follow-up found that physical illness (defined as coronary heart disease, gout, chronic obstructive pulmonary disease, diabetes, cancer, traumatic brain injury, stroke and myocardial infarction), was associated with dementia risk (RR 1.19, 1.16-1.21).(372) In a UKB study of 206,960 participants, multimorbidity was associated with a 1.63-fold (1.55-1.71) increased risk of incident dementia over 15 years follow-up after adjusting for age, sex, ethnicity, education, socioeconomic status, and *APOE*ε4 status.(392) The

risk was highest in individuals with cardiovascular and cardiometabolic clusters of disease and those with the lower genetic risk of dementia. Outcome-wide studies, such as the Danish disease trajectory,(396) Finnish community-dwelling studies(397) and the Health Improvement Network in French and UK GP-records, (397) linked dementia risk to a wide range of diseases, which may be related to other risk factors, including sequelae of cerebrovascular disease, osteoporosis, severe infections, and mental disorders. Overall health, quantified by the degree of frailty, independently contributes to the risk of dementia in relation to neuropathology,(398) Alzheimer disease biomarkers (399) and polygenic risk score,(400) so dementia risk conveyed by each of these is higher in frailer individuals.

Interventions and care in dementia

Diagnosis

The path to diagnosis

Timely diagnosis of dementia is a priority in many countries because a diagnosis and identification of underlying causes and contributors is beneficial in enabling management and planning.(401) This is distinct from screening and as set out in the last commission, the only trial of dementia screening showed neither benefit nor harm and so we do not recommend it.(402)

A review of people seeking diagnosis from 32 studies across 13 countries, found that people with suspected dementia and family carers reported multiple barriers and facilitators to diagnosis.(403) Barriers included: denial, stigma and fear, lack of knowledge, normalisation of symptoms, desire to preserve autonomy, lack of perceived need, unawareness of changes, lack of family and friends network support, carer difficulties, problems accessing help and lack of preparedness of services to make a diagnosis. Enablers included: recognition of symptoms as a problem, prior knowledge and contacts, and support from informal networks.

Equity in Diagnosis

Much of the work on the pathways to diagnosis comes from HICs. The identification of dementia as a medical condition has been challenging in LMICs, where despite a paucity of studies we know health care is under-resourced and tends to focus on infectious disease, with mental health disorders often stigmatised and hence hidden and where some people are still unaware of the illness of dementia. (404) (405) More people in LMICs present in late stages than in HICs, perhaps due to several factors including good support at home as well as lack of public health education, awareness, resources, accessibility, stigma and belief.(404, 406) Additionally, many research instruments, even when termed cross-cultural, were developed in HICs and are unsuitable for people with low levels of literacy or are culturally biased.(407) (408)

Dementia incidence(409-411) and prevalence (38) is higher in some minority ethnic groups in countries such as the US and UK. Notably, this is when measured by population-based survey rather than using electronic health records, indicating an under-recording or under use of services by some groups in routine data.(412) Cognitive screening tools that have primarily been developed in White, English-speaking populations, may be unsuitable in more diverse populations as they are affected by education and cultural background.(413) It is therefore key that cognitive assessment includes awareness of cultural diversity within the populations they serve, using tools that are not dependent on literacy and education level as appropriate.(414) One possible quality indicator for dementia care is the diagnosis proportion, but recording of dementia is lower for some ethnic groups, so any assumption of a similar prevalence is likely to be inaccurate for many of the minoritised population. These measures are therefore likely unfit to determine access to diagnosis.

Timely diagnosis

There has been little evaluation of the relative clinical and cost-effectiveness of different models of service delivery.(415) This means a lack of clarity about 'what good looks like' in terms of diagnostic services and care, and there is only indirect evidence that diagnosis of dementia is beneficial.(416)

The rationale for early or timely diagnosis is to sustain people with dementia and their family's well-being and health by opening the door to care and treatment. A diagnosis upholds an individual's right to know about their illnesses.(401) One review found that up to 92% of people with a diagnosis of dementia said they wanted to know their diagnosis, (417) and another that 91% of those diagnosed saw benefits in getting the diagnosis, and 60% wished they had known the diagnosis earlier.(418) These were people who had a diagnosis although not necessarily those who sought one early. The views of those people without a diagnosis were not represented in these studies.

Diagnosis can provide psychological benefits and time to adjust. It facilitates access to services when they are available that provide practical information, advice, guidance, and psychological and drug treatments. These can support people's ability to better manage their condition, plan for the future, and make decisions about care, support, financial and legal affairs whilst they have capacity.(419) Potential economic benefits from reducing health and social care costs by preventing unnecessary admissions to hospitals and care-homes have been modelled.(418, 420, 421) It is currently unknown whether any therapies can modify the disease course in AD to reduce dementia risk.

There are theoretical harms of a diagnosis of dementia,(419, 422) for example, early diagnosis might be associated with increased risks of depression, anxiety, or social withdrawal, particularly if post-diagnostic interventions and care are unavailable. There is evidence from a US national cohort of a lower risk of suicide in people with a diagnosis of dementia (HR 0.71, 0.53-0.94) but an increase in short-term suicide attempts after people were informed they had MCI or dementia (RR 1.73, 1.34-2.22; RR 1.44, 1.17-1.77 respectively).(423) There was no long-term increase in suicide attempts.

Mobile and wearable devices hold promise for detection and diagnosis of neurodegenerative disease as their routine use in the general population is widespread and increasing, and they can contain multiple sensors to study physical changes and cognitive abilities. (424) Nonetheless, a review of 20 mobile phone applications (apps) (425) reported none met criteria for use as a screening tool. Another review of 275 apps (426) suggested that those with artificial intelligence capabilities and use of machine learning had potential for detection and monitoring and should be further evaluated. There will be challenges in the existing data that inform such AI, particularly from the lack of representation of diversity.

The balance of evidence and ethical principles finds that people should have access to timely and accurate diagnosis with appropriate interventions when they are seeking help, but the evidence does not justify screening the whole population for dementia.

Biomarkers in AD

Research on biomarkers for Alzheimer pathology has progressed since the last commission. Biomarkers that measure amyloid (A), tau (T), and neurodegeneration (N) are now incorporated in some definitions of AD pathology, the "amyloid–tau–neurodegeneration" or A/T/N approach, but the presence of these biomarkers does not mean that someone has dementia.(427, 428) However, their absence indicates the likely absence of Alzheimer's pathology (but does not exclude other causes of dementia).(429)

Neuroimaging

Computer Tomography (CT) can show vascular changes, atrophy and other reasons for neurodegeneration and is cheaper and more accessible, but the precision is lower than Magnetic Resonance Imaging (MRI). Although several modalities of MRI exist, the simplest is structural MRI (for cerebral atrophy, primarily in the hippocampus, entorhinal cortex, and medial temporal lobe.)

More advanced techniques include diffusion tensor imaging, arterial spin labelling, magnetic resonance spectroscopy, functional MRI, and Positron Emission Tomography (PET, in vivo measurement of disease pathology using ligands). The limitations of all these advanced imaging techniques include cost, patient's consent and suitability, expertise required to interpret the results, although automated assessment performs nearly as well.(430) Amyloid-PET and tau-PET correlate with post-mortem amyloid plaques and neurofibrillary tangles.

CSF biomarkers

A low cerebrospinal fluid CSF Abeta42/Abeta40 ratio alone or combined with high phosphorylated tau (p-tau) is correlated with amyloid plaques and Alzheimer pathology. There is also potential to use amyloid and p-tau molecular (fluid) biomarkers as a way to evaluate underlying Alzheimer disease pathology as a potential cause of dementia or cognitive impairment, and in an asymptomatic population to determine those at higher risk of developing AD for inclusion in clinical trial populations (431, 432) but there are important considerations in their interpretation. Biochemical changes in the brain are reflected in the CSF because of its contact with the extracellular space in the brain. These biomarkers are essentially proteins (total tau, phosphorylated tau, and Aβ42, neurofilament light, neurogranulin) that have been validated against imaging modalities. The advantage of CSF biomarkers is their ability to detect early phases of disease and they have recently been related to cognitive decline and clinical conversion in studies changing 9-18 years before diagnosis. (433) (434, 435) Their disadvantages are cost, the need for specialized health care services, and the patient's perception of its invasiveness.

CSF-based assays are well-established in the clinical diagnosis of Creutzfeldt-Jakob disease A similar approach has been developed for Lewy body disease and assays to detect neuronal α-synuclein (n-αsyn) in CSF show great promise. (436, 437) A recent meta-analysis showed pooled sensitivities of 0.88 and specificities of 0.95 in distinguishing synucleinopathies from controls. (438) As with AD, biomarkers of Lewy body pathology become positive before dementia or parkinsonism and so may be not necessarily be the cause of cognitive symptoms, especially in older adults. Further work is needed to clarify the position of n-αsyn assays in clinical practice, but they are likely to play growing roles. As with other assays data are lacking from diverse cohorts.

Meaning and measurement of predictive markers

Multiple neuropathologies are common in older populations and more common than Alzheimer pathology alone (see figure 1). **(20)** Amyloid prevalence is age-related (>20% over age 70years; >30% by age 80).(439) This means that in older individuals a positive amyloid biomarker must be interpreted cautiously: it reflects amyloid pathology, but it may not be causing any impairment. Nonetheless, if someone is negative for amyloid biomarkers it means AD is unlikely – irrespective of age. As amyloid accumulation occurs many years before the onset of neurodegeneration or cognitive symptoms a positive amyloid biomarker *alone* is not a strong predictor of future impairment.

As discussed in the last commission, most cognitively normal people who are amyloid positive, do not develop Alzheimer's dementia over the next 10 years, or during their lifetime. In a US volunteer sample, at age 70, 10% of women were amyloid positive but 1% had Alzheimer's dementia. (440) By age 85 these figures were 33%

positive versus 9% Alzheimer's dementia with figures similar for men. One community-based autopsy cohort study of amyloid (A), tauopathy (T), and neurodegeneration (N) markers found only 8% of (A+T–[N]) compared t68% of (A+T+[N]) were associated with incident dementia in the last 5 years of life.(441)

Tau PET uptake occurs at a later stage and age than amyloid Pet and is more closely associated with cognitive dysfunction than amyloid-PET.(442, 443) Biomarkers of neurodegeneration, such as hippocampal atrophy, medial cortex thinning, low glucose uptake on fluorodeoxyglucose (FDG)-PET, or raised CSF neurofilament light (NFL- a non-specific marker of neurodegeneration), are more closely associated temporally with cognitive decline than amyloid and tau fluid biomarkers.(444) Cognitively unimpaired people who have amyloid and tau in the medial temporal lobe or temporal neocortex are more likely to decline cognitively compared to people who have neither and, over 6 years, the risk in those that are tau positive in temporal neocortex may approach 50% but samples are small and estimates imprecise. (445) Other biomarkers and progress in proteomics and metabolomics may uncover new pharmacological targets.(446-448)

Blood based biomarkers.

Since the last Lancet Commission, research has progressed into the validity of blood-based biomarkers for the specific diagnosis of AD in someone with dementia. It may be that blood-based biomarkers substitute for CSF or PET markers in determining eligibility for clinical trials and cohort studies in future and for staging the extent of Alzheimer-related pathology, although more evidence of validity in each specific populations of people with dementia is needed. Some have suggested they may be useful in future to identify people with dementia who do not need more invasive or expensive investigation, either because of very low or very high probability of having AD. (449) The ratio of plasma Aβ42:Aβ40 using a high precision assay has a high correlation with amyloid PET. (450, 451) Plasma p-tau181, p-tau217, and p-tau231 have a good or better accuracy than amyloid CSF Abeta and tau and PET measures of tau and amyloid pathology in discriminating people with amyloid pathology who may have clinical symptoms.(452-454) They theoretically overcome some cost, scalability and acceptability limitations of PET- and CSF biomarkers with lower patient and clinician burden, through local sample collection with potential central quality-controlled processing, increasing access to a pathology-specific AD diagnosis.

Clinically, they may not add value to prediction of whether people are developing Alzheimer's dementia. A combination of multiple blood-based biomarkers and demographic information, like age and sex, may allow for determining individualised risk of developing AD dementia and this has been done in an MCI population.(455) Yet, when blood-based biomarkers of p181-tau + Abeta42/40 were used in France in a clinical population of 2323 people with subjective cognitive impairment or MCI that were followed for 5 years, blood-based biomarkers added little to predictions of AD/mixed dementia vs no dementia, relative to a clinical model that used demographics and neuropsychological assessment alone. (456) Concordance (c-index) of prediction rose from 0.88 (0.86-0.9) to 0.90 (0.88-0.92).

In addition, most research has been in almost exclusively White populations, with a systematic review finding five studies and none were in Black Africans.(457) Participants are often younger than most people with dementia. Small studies in African Americans report lower levels of p-tau in both cognitively normal individuals and people with dementia and so the generalisability of biomarkers from White populations is unclear. A subsequent review found seven studies and again reported lower tau levels in Black individuals with dementia, but none found this was explained by greater vascular burden. (458) However, a recent study of a biracial, community-based sample of adults found no independent association of plasma AD biomarkers based on self-reported race, with age, sex, chronic kidney disease and vascular risk factors contributing to observed variation. (459)

Patient selection in AD trials: biomarker and genetic testing

Biomarkers in AD trials

Another development since the last Commission has been the use amyloid-PET as an eligibility criterion and as a surrogate clinical outcome for anti-amyloid antibody clinical trials of disease-modifying therapies for participants with early AD. Phase 2 and phase 3 trials of the monoclonal antibodies -- aducanumab, lecanemab, and donanemab, as well as the discontinued gantenerumab – that target Aβ plaques, fibrils, soluble protofibrils, and oligomeric Aβ species all required PET or CSF evidence of amyloid pathology for trial enrolment. (460-463) A phase 3 trial showed modest efficacy in slowing cognitive decline in early AD (MCI and dementia). The phase 3 trial of donanemab, monoclonal antibody that target Aβ plaques, fibrils, soluble protofibrils, and oligomeric Aβ species all targeting Aβ plaques, required people with early AD to have both positive amyloid PET and tau-PET, further dividing participants into low and intermediate/high positive tau burden groups.(464) Both used amyloid PET to assess amyloid lowering and it was a stopping criterion in the donanemab trial. Blood biomarkers could be used to assess whether to perform a PET scan and thus lower the cost of such trials. (465, 466)

Genetic testing

Knowledge about genetic testing in dementia has advanced rapidly but is not widely useful as most dementias are not caused by autosomal dominant genes. A positive genetic test for one of the alleles that leads to the rare autosomal dominant, early-onset AD increases the precision of the diagnosis and helps family members determine personal risk, may inform reproductive choices and can assist in clinical trials. A relatively larger proportion (up to a third in some estimates) of all frontotemporal dementias are due to a genetic mutation, and testing in the appropriate clinical setting may be important. (467)

Genetic testing for the *APOE*ε4 allele is not used diagnostically and many people with AD do not have it. *APOE* alleles contribute to the heterogeneity of the AD disease course. A post-mortem study (N= 1109) found a 10% faster rate of cognitive decline yearly in *APOE*ε4 carriers (−3.45 vs −3.03 MMSE points per year) and a 20% lower rate of decline in e2 carriers (−2.43 vs −3.03 points per year) compared to *APOE*ε3/ε3 carriers.(468)

APOE ε4 is an important predictor of ARIA-E and ARIA-H with treatment with anti-amyloid antibodies. Participants who are *APOE* ε4 homozygous and treated with lecanemab have a 33% incidence of vasogenic oedema, ARIA-E, compared to an 11% incidence in participants who are *APOE* ε4 heterozygous, and 5% who are not *APOE* ε4 carriers. (460) Thus, the boxed warning for lecanemab recommends APOE genotyping and patient counselling before treatment. Figures are similar with donanemab: 41%, 23%, and 16% incidences of ARIA-E for *APOE* ε4, homozygotes, heterozygotes, and non-carriers, respectively.

Summary of biomarkers now and in the future

Biomarkers look for a particular pathology not for a clinical syndrome and a biomarker is not a diagnostic test for dementia. Amyloid-PET is FDA approved for marketing and reimbursement, as an AD diagnostic aid, to help establish the presence of amyloid plaques and Alzheimer pathology. There are clear ethical implications if used in people without cognitive impairment as markers of people with (asymptomatic) Alzheimer's disease, as they have the potential to increase the measured rates of Alzheimer's' disease without there being any increase in people with cognitive impairment or dementia, and misidentify people who will not develop dementia potentially causing harm. Currently, biomarkers should not be used alone for diagnosis to determine treatment as most people with positive Abeta biomarker by itself will never develop dementia. The stated hope is that if effective pre-symptomatic therapies are developed then accessible, cost-effective biomarkers for AD or other dementias may become important predicting who are likely to progress to illness and when, or as a surrogate endpoint for efficacy and to increase equity, but they have not reached this stage (see figure 10). (466)

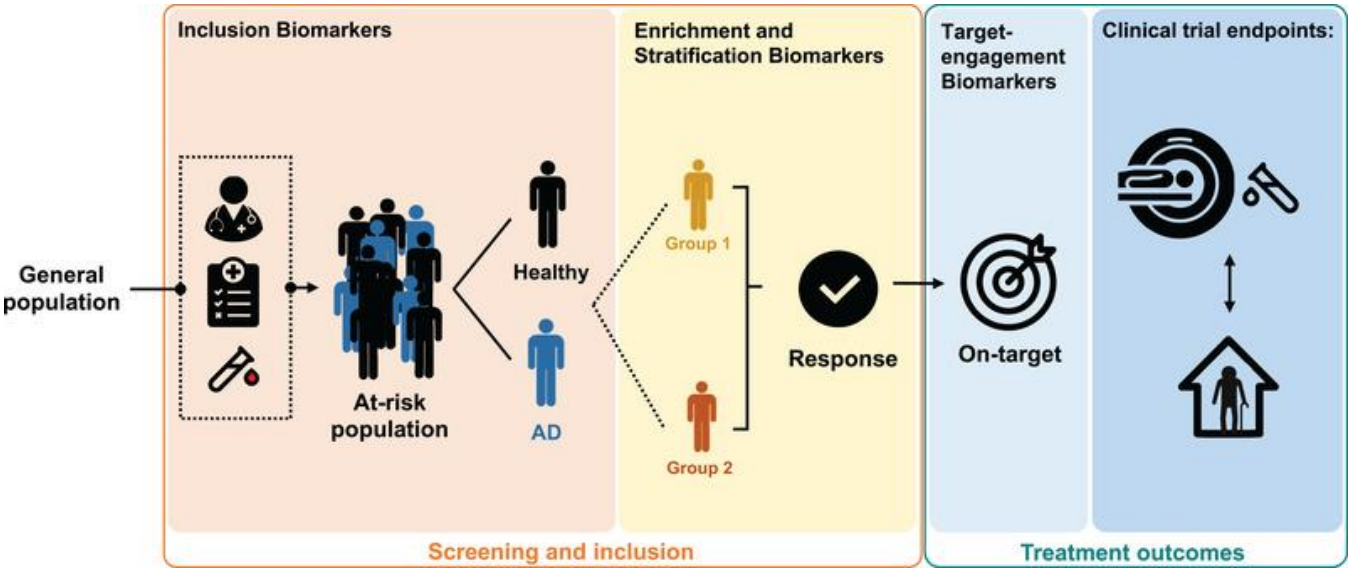


Figure 10 Vision of future use of biomarkers for dementia in clinical trials. by identifying those with elevated risk, a condition of interest, or stratification and predictive markers; and surrogate outcome measures (466) with permission.

Interventions once a diagnosis has been made.

Principles of intervention in people with dementia

The progressive nature of dementia means that people living with dementia require re-assessment and the application of tailored approaches to address their changing care needs over time. These needs can be complex and include physical multimorbidity, psychological, behavioural, and cognitive symptoms and possible risks arising from these.

Individualising interventions

People with dementia are individuals, whose support and intervention needs are influenced by their own lifecourse, family, friendship, culture and environment as well as changing cognitive, neuropsychiatric, functional and physical symptoms, as we discussed in the last commission.(2) Despite the availability of evidence-based practices, dementias continue to be under-detected and many individuals' and family carers' needs are unevaluated and unmet.(3)

Published best practices for dementia care globally include managing medical problems like high BP, diabetes, and COPD; preventing and treating infections and delirium; environmental accommodations for safety, preventing falls and maintaining function; medication management including simplifying and reducing daily medications, for example, reducing or stopping antihypertensives if BP is falling; treatment of symptoms through behavioural interventions; use of supportive and social services including assistance with activities of daily living, physical activity, meaningful activities, social engagement, healthy nutrition and hydration and addressing family carer needs. (2, 3, 469)

Culturally appropriate or adapted interventions.

Most interventions are developed in high-income countries (HICs). Interventions should be co-designed with local communities to ensure appropriateness for the context, culture, beliefs and practises which vary within and between countries.(470) In LMICs, dementia is often not recognised and diagnosed and, when it is, people

living with dementia are often faced with a lack of resources for treatment and care, including treatment of other illnesses and support for families. (471) The appropriateness of use of evidence-based interventions in LMICs can be uncertain, not only because of the lack of healthcare infrastructure and resources to deliver them, but also because of cultural differences that may make them inappropriate or less effective.

Effectiveness of interventions developed in one place will vary with acceptability and feasibility in different populations and thus while active ingredients should remain the same in different countries, interventions must be tailored in language and culture. (472) (473) Cultural adaptation is important for psychosocial interventions for various mental health conditions, and meta-analyses have shown that such interventions are more effective than non-culturally adapted interventions. (474-476)

A systematic review considering culturally tailored interventions for people living with dementia and family carers, found that culturally adapted interventions were as acceptable, feasible and effective when used in LMICs as in their original context as long as the interventions' core components are not compromised in the process.(472) Adaptation involves considering local cultures, needs and resources and identifying barriers and facilitators to their implementation. There are different opinions as to whether it is then necessary to conduct a full RCT in a new setting when an intervention has already been found to be effective as there may be biological, ethnic, cultural, and socioeconomic heterogeneity that influences treatment response and safety.(472, 477) Following cultural adaptation, interventions need to be tested and their components evaluated in the local context, to determine their acceptability and feasibility and to help define and refine the delivery characteristics of the intervention. It is important to include key stakeholders in the adaptation process and report the processes and outcomes considered. (472) Important other considerations are cultural appropriateness of outcome measures, many of which are developed in HICs, and scalability of the intervention.

Multicomponent dementia care interventions

Multicomponent dementia care models with person-centred care coordination aim to target assessment of risk and need for the person living with dementia and family carer using evidence-based approaches, which may include neuropsychiatric symptoms and carer quality of life. (478) Individual studies of care coordination have shown reduced care home admission, and cost-effectiveness from a societal and individual perspective,(479) but a meta-analysis of 14 care coordination RCTs did not show a statistically significant reduction in care home admission or hospitalisation. (478) Models that include a partnership between primary and specialised care may lead to reduced health care costs.(480)

Interventions for family carers

Although some people have found joy and humour associated with dementia, caring for a family member with a deteriorating illness such as dementia is usually increasingly difficult. This can vary across the course of dementia with greater anxiety and depression at outset than later for some. A meta-analysis (43 studies, 19911 participants) found a pooled prevalence of family carer depression of 31.2% (27.7 - 35.0).(481) There is evidence that some multicomponent carer interventions are effective in the short and long-term; and these usually include information about medical and community-based resources, skills training, stress reduction and coping techniques, providing emotional support and future planning. (2, 482-486) They reduce family carer depression, depression, burden, or stress and are cost-effective and cost saving. There is evidence that they are effective in Western and Asian HICs but little evidence in LMICs.(487) They can be culturally adapted and delivered by trained facilitators without clinical qualifications The START (Strategies for relatives) intervention developed and found to be clinically and cost effective in the UK, has been adapted for use to widen access, by making it culturally appropriate for Black and South Asian carers, and was successfully delivered in the third sector.(488,

489) intervention delivered by day care staff reduced carer depression at one year.(490) A Cochrane review of RCT reported that remote delivery of interventions for family carers of information or support found 26 studies and is not more effective than usual care. (491) A meta-analysis of internet-based psychoeducation for carers showed a small effect on depressive symptoms (SMD −0.19, −0.03−0.35) but not on anxiety, burden, and quality of life.(492)

Interventions for cognitive symptoms

Symptomatic treatment: Cholinesterase inhibitors and memantine

In the previous commissions we discussed cholinesterase inhibitors (ChEIs) and memantine, the currently available drugs for symptomatic treatment of cognitive symptoms in AD and dementia with Lewy bodies (DLB). While they were initially evaluated for people with mild-to-moderate AD, meta-analyses indicate that they are also related to better outcomes compared to placebo in severe dementia in severity of symptoms (SMD 0.37, 0.26–0.48; 4 studies), activities of daily living (SMD 0.15, 0.04–0.26; 5 studies) and decreased mortality compared to placebo (RR 0.60, 0.40–0.89; 6 studies).(493)

Longer-term, real-world studies are now published. These include a study demonstrating that 11,652 Swedish propensity-matched patients with AD who took ChEIs, compared to 5,826 who did not, performed slightly and persistently better during mean 5-years follow-up (MMSE 0.13; 0.06–0.20 points per year better), with a dose-response effect.(494) A similar propensity-matched, more long term study reported larger differences between people who did and did not take ChEIs; in 1,572 patients with dementia, the average decrease in MMSE in those taking ChEIs was 5.4 points and 10.8 points in those not at the end of 13.6 years follow-up ($p < 0.001$).(495) There was a strong association between ChEIs and lower all-cause mortality (HR 0.59, 0.53–0.66). Additionally, in a study of 592 patients with DLB, the 100 patients who took ChEIs and 273 who took ChEIs and memantine had significantly lower risk of death (HR 0.67; 0.48-0.93; HR 0.64; 0.50-0.83 respectively) than 219 who took neither, after controlling for sociodemographic factors, physical and cognitive health, and medication use. Those taking ChEIs or both ChEIs and memantine had significantly less time in unplanned hospitalisation for physical disorders.

These studies are observational, not randomised, and may reflect residual confounding based on willingness to initiate treatment so people taking ChEIs have unmeasured factors which may lead to better outcomes. Trials show that ChEIs do not cure or stop cognitive decline but have short-term modest positive effects and that stopping them is associated with worse outcomes in the longer term. Clinicians can offer these relatively affordable (in HICs but not LMICs), readily available, low side-effect medications for people with AD and DLB.

Anti-amyloid antibodies for Alzheimer's disease

Clinical trials have investigated disease-modifying therapies (DMTs), drugs intended to affect AD pathological processes by targeting amyloid-β (Abeta) or tau protein, inflammatory pathways, or metabolic dysfunction,(496) as they may alter illness expression and progression. The hypothesis is Abeta is characteristic of AD, so amyloid-β-targeting immunotherapy studies aim to treat those with Abeta, who are cognitively unimpaired, or have MCI or mild Alzheimer's dementia. For older individuals with sporadic AD (which accounts for >95% of AD cases), it remains unclear how strongly early differences or longitudinal changes in AD biomarkers influence lifetime dementia risk or clinical progression to dementia.

Since our last commission there have been positive trials of three anti-amyloid-β monoclonal antibodies for treatment of MCI due to AD and mild AD dementia in those with positive amyloid-beta biomarkers as well as three negative trials. In two conflicting, identically designed phase 3 trials, aducanumab was associated with

less decline than placebo of 0.39 (0.09-0.69) Clinical Dementia Rating scale-Sum of Boxes (CDR-SB) points (out of a total possible score of 18) at 18 months in one study, and a statistically non-significant outcome favouring placebo in the other. (461) Lecanemab was associated with less worsening by 0.45 (0.23-0.67) CDR-SB points compared to placebo worsening after 18 months' treatment and in secondary cognitive, activities of daily living, and compositive outcomes. (460) Donanemab reported less worsening in integrated Alzheimer Disease Rating Scale (cognition and functioning) in the drug group −10.19 (−11.22 to −9.16) compared to placebo worsening −13.11 (−14.10 to −12.13) after 18 months' treatment and in secondary cognitive, activities of daily living, and composite outcomes. (462) Since these studies were published two new studies of the subcutaneously administered antibody, gantenerumab with two year follow-up have shown similar biomarker clearance with reduction in amyloid plaques but no statistically significant effect on CDR-SB (-0.31 and -0.19). (463) (497) The effects were of similar magnitude in some domains to the more positive trials but did not reach statistical significance. (497) Similarly a trial of solanezumab did not slow cognitive decline in people with pre-clinical Alzheimer's disease, did not affect amyloid plaque level but influenced CDR-SB in line with the other studies (-0.34). (498) (497)

Aducanumab received FDA accelerated approval in June 2021, (499) with the post-marketing requirement to perform a phase 4 trial, though one such attempt has been abandoned due to low uptake. Biogen, the manufacturer of aducanumab have subsequently announced that they are withdrawing it from the market and that the phase 4 trial will be stopped. The FDA approved lecanemab in July 2023. (460) The approvals were based partly on the "reasonable expectation" that a reduction in amyloid- PET load, or plaques, were likely to predict clinical benefit, although correlations between reduction in plaques and change on clinical ratings scales are very weak. These antibodies have not been tested in those with moderate or severe dementia, with lowest score as MMSE 22 for lecanemab, and MMSE 20 for donanemab. Those in the trial needed biomarker-evidence of amyloid positivity, access to health facilities for biweekly intravenous treatment administration and regular MRI and clinical monitoring for up to 18 months, or potentially longer.

The clinical importance of these differences is controversial.(500-503) There is excitement about positive results but no consensus about whether these treatments are an advance or not, or whether observed effects are worthwhile given the known burden, risks and costs. (504)

Clinical implications

In those that are effective, we do not yet know whether clinical benefits with treatment beyond 18-months will increase, remain steady or reduce; currently the effect remains less than that of donepezil.(505). Adverse effects such as vasogenic oedema and brain haemorrhage, known as ARIA-E and ARIA-H, as well decreased brain volume on MRI are continuing concerns for anti-amyloid antibody treatment. Future results from open label extensions of trials may help answer these questions but there will be substantial dropouts and competing morbidity and mortality. The small effect makes it harder to discount the potential of unblinding from adverse effects, These include ARIA-E (oedema or effusions) and ARIA-H (micro-haemorrhages, macro-haemorrhages (i.e., strokes), or superficial siderosis) in over 20% decreased brain volume on MRI are continuing concerns for anti-amyloid antibody treatment and infusion-related reactions, in about 26% of patients on lecanemab, and only 7.4% of patients on placebo. (507) (460, 461) There are ongoing safety concerns because of accelerated brain atrophy and deaths with amyloid plaque-lowering immunotherapies. (508, 509) Lecanemab has a boxed warning for serious and symptomatic ARIA and requires testing for *APOE*ε4 prior to initiation as homozygosity increases risk.(510)

Generalisability

The stringent eligibility criteria for clinical trials of drugs for AD made study population's health better than the general AD population (511) and historically excluded racial and ethnic backgrounds were under-represented, although there were higher numbers of minoritised groups in the lecanemab trial. Only 8% (19/237) of a community-based Mayo Clinic Study of Aging who had a positive amyloid-PET scan and met criteria for MCI or mild dementia, would have met the lecanemab trial eligibility criteria. (512)

A meta-analysis of 101 drug trials in AD reported that 94.7% of the population were White and most excluded people with psychiatric illness (78%) cerebrovascular disease (68%) and cardiovascular disease (71%) and needed a family carer to attend infusions (80%).(513) It is difficult to generalise findings to most people with AD who have high levels of multimorbidity and mixed neuropathology and to those who live in countries where healthcare systems could not support this level of intervention.

Costs and provisions

So far, the only marketing authorisation outside the US has been for lecanemab in Japan. Aducanumab, although freely available in the US by prescription is rarely prescribed. In the US, Medicare and CMS will provide usual coverage or lecanemab and donanemab, if physicians enter patients' data into a CMS-facilitated registry. (514) Lecanemab is nominally priced at $26,500 per patient per year.(515) It is unknown what price that Medicare, the US Veterans Administration, and private insurers will pay. In addition, there are costs for the many physician visits, biweekly infusions, lab tests, MRIs, and PET scans and management of side-effects. Medicare patients are typically required to co-pay up to 20% for all of this. The US Institute for Clinical and Economic Review (ICER) reported the cost-effective annual pricing was lower for lecanemab, between $8900-21,500.(516) Treatment costs if lecanemab was available in the 27 EU countries, for those qualifying for it, at US pricing are estimated at 133 billion EUR per year, equivalent to over half of the total pharmaceutical expenditures in the EU(517) before treatment-related costs are considered. However, historically the EU and UK pay a fraction of the US list price for new and expensive medications.

Summary of Disease Modifying Treatments (see Box 1)

Finding amyloid-targeting treatments which influence cognition is an important milestone which may be the beginning of the development of drugs that can make a bigger difference.(518) Effects are small in all drugs. (497) The resources required to support earlier biomarker-based diagnosis and supervision of administration and safety as well as to buy the drugs, will mean that roll-outs into many health systems will be slow or not at all. If approved for this group, we recommend that they are used in research centres to find out more about adverse effects in more typical patients and whether the long-term effects support disease modification or not.

Cognitive interventions for people with dementia

We previously reported that the literature suggested that people completing cognitive interventions had improvements in general and specific cognitive abilities such as verbal fluency which lasted for a few months to one year.(2) A 2023 Cochrane review of 25 studies using the MMSE, with 1893 participants, found that there was moderate-quality evidence of a clinically important difference of 1.99 (1.24-2.74) points between cognitive stimulation and control groups, and clinically relevant improvements in communication and social interaction.(519) Improvements were larger when sessions were twice, rather than once weekly, and where people had mild compared to moderate dementia.

Box 1 Summary of current controversies about amyloid-targeting antibodies

Efficacy

Unclear if benefit is clinically meaningful. or the duration of effect

Difficulties in implementation

Monthly or fortnightly infusions, requiring visits to an infusion centre over a typical 18-month treatment period. Frequent MRIs needed for safety surveillance. Significant restructuring of existing healthcare infrastructure may be needed for the required physician visits, infusions, lab tests, MRIs, and PET scans and management of adverse effects. Lack of infrastructure in many healthcare systems that could support this level of intervention.

Costs

Lecanemab is nominally priced at $26,500 per patient per year, not including associated costs of eligibility screening, administration and monitoring. Historically the EU and UK pay less than US list price for new and expensive medications.

Monitoring and side effects

Regular clinical and radiological monitoring for oedema and haemorrhage that may occur in 20% of lecanemab patients and nearly twice that in donanemab patients.

Exclusions

Most existing community-based patients would not meet trial eligibility criteria. It is therefore difficult to generalise findings to most people with AD who are racially and ethnically diverse and have high levels of multimorbidity and mixed neuropathology.

Interventions for neuropsychiatric symptoms of dementia

Activity interventions

RCTs since 2018 of the tailored activity program (TAP) and other activity interventions are shown in Table 2. A systematic review and meta-analysis of 7 studies of the TAP interventions found a moderate effect on improving quality of life (standardised ES Cohen's d 0.79, 0.39–1.18; 7 studies, n=160) , decreasing neuropsychiatric symptoms (0.62; 0.40–0.83) and decreasing carer burden (0.68, 0.29–1.07).(520) " This included small pilot trials in LMICs which showed similar effects and validate the effectiveness of the transcripts.(521) (522) They may also be cost saving because of lower use of healthcare systems. (523) Good quality RCTs of exercise interventions for people with dementia found they did not improve neuropsychiatric symptoms, cognition or functioning.(524, 525)

Studies vary in the quality of evidence and design strategies, from feasibility studies and small RCTs to large multi-site, cluster randomized trials (Table 2). Overall, the evidence supports earlier trials showing that different types of activities and being actively engaged reduced depression, neuropsychiatric symptoms and improved overall well-being in people with dementia and in some cases had important benefits for carers, such as saving time in caregiving. Successful activity-oriented interventions tend to be tailored to individual's interests, preferences and abilities and involve the family carer. The scalability and implementation of tailored activity interventions, and the potential cost of these interventions need additional evidence with only two studies

evaluating cost effectiveness. In contrast, RCTs of exercise as an activity did not find any mental health domain improvement in either community or care homes. (524-526)

Sleep disturbance in people with dementia.

Dysregulation of the sleep-wake cycle is common in people with dementia, due to multiple mechanisms including the pathophysiological processes affecting the hypothalamus and the brainstem, lack of activity and light, pain, anxiety and the environment. (527) A meta-analysis reported the pooled prevalence of clinically-significant sleep disturbance in community-dwelling people with dementia to be 19% (13-25; n = 2753) and there has been no change in prevalence over time, suggesting treatment has not improved sleep.(528) Sleep disturbance was less common among people with AD (24 %, 16-33, n = 310) than DLB (49%, 37-61 n = 65). The prevalence was similar in a meta-analysis of care home residents (55 studies n= 22,780; 20% 16-24).(529)

There continues to be little evidence that medication is effective. One review of nine RCTs rated to be low-quality (530) found low-certainty evidence in a small trial (n=30) that trazadone 50 mg for two weeks may improve time asleep but no clear effect on other sleep parameters (MD 42.5 minutes, 0.9 -84.0). An orexin antagonist for four weeks in 274 people with mild-to-moderate AD increased time asleep (MD 28.2 minutes, 11.1- 45.3) and decreased time awake after sleep onset (MD –15.7 minutes, –28.1- –3.3) without increasing adverse effects but did not affect number of awakenings. There was no evidence of melatonin efficacy. There are no RCTs of benzodiazepines or Z-drugs for sleep in people with dementia, but they may cause significant harms. In longitudinal primary care studies, higher dose Z-drug or benzodiazepine use (equivalent to ≥ 7.5 mg zopiclone or >5 mg diazepam) in dementia was associated with increased fracture and stroke risks and so should be avoided for this purpose.(531) There is no conclusive evidence that non-pharmacological interventions improve sleep in dementia, although trials are underway.(532)

Depression

We described in our previous commission the evidence that antidepressants are no more effective than placebo for depression in people with dementia.(2) People in both groups improve and it can be argued that drug treatments are held to a higher standard than non-drug interventions when the non-intervention group usually receives treatment as usual. It is likely that for many people, depression in dementia differs from depression in those without dementia as brain changes in dementia, which vary between different subtypes of dementia, may mean that antidepressants which are effective in depression without dementia do not work. (533) A Cochrane review of RCTs of psychological treatments for depression and anxiety in MCI or dementia found what they labelled CBT-based treatments (four CBT, eight behavioural activation and two problem solving therapy) added to usual care for people with dementia or MCI and depressive symptoms or depressive diagnosis had a large effect (SMD -0.84, -1.14 - -0.54; I^2 = 24%; 4 studies- 3 of which were problem solving therapies, 194 participants) but there was little or no effect for those without depressive symptoms or diagnosis at baseline. (534) Supportive and counselling treatments were not effective.

Psychosis

Aetiology

Psychosis can precede dementia and as discussed in the risk section; very late onset schizophrenia may be a dementia prodrome. (535) Psychotic symptoms in dementia are associated with a particular tauopathy and neocortical synaptic disruption but it is not known if these are causal.(535) There is also a modest association between psychosis in AD and *APOE*ε4, which does not account for all of the risk.(536)

Management

We previously discussed how comprehensive clinical assessment is essential in suspected psychosis in dementia, as misremembering experienced by individuals with dementia is distinct from delusions, and new psychotic symptoms may be due to delirium.(1)

If a person with dementia is not distressed by psychosis, they may not require treatment. Management should continue to start with non-pharmacological interventions, to maximise stimulation such as improving hearing and sight and increasing social and other stimulation.

ChEIs have a minute effect on improving psychosis in AD with a meta-analysis of IPD from 12 RCTs of ChEIs for psychotic symptoms as secondary outcomes in AD (delusions −0.08, −0.14 - −0.03, I^2=0; hallucinations 0.09, −0.14- −0.04; I^2=0, n= 5580). (537) Caveats remain about any antipsychotic use, which include increased dementia-specific mortality, and these may be appropriate for those whose psychosis creates distress or functional impairment and should be prescribed in as low a dose and for the shortest time possible. Meta-analyses find risperidone and aripiprazole are the antipsychotics with the best evidence, with evidence that there is less risk of stroke with risperidone for delusions than other indications. (535) (2)

An RCT of pimavanserin (an atypical antipsychotic with selective serotonin 5-HT2a inverse agonist effect) withdrawal in dementia-related psychosis was stopped early due to lower rates of relapse in the treatment versus placebo groups, which appeared to be driven by effects in people with Parkinson's disease.(538) A US retrospective cohort study comparing pimavanserin (n=3227) with atypical antipsychotics (n=18442) in Parkinson's disease with or without dementia, found a 35% lower mortality rate in those treated with pimavanserin(539). An earlier RCT of efficacy in AD psychosis showed differences favouring pimavanserin at week 6 but not at 2, 4, 9 or 12 weeks.(540) Pimavanserin is approved as a treatment for psychosis in Parkinson's disease, but the FDA rejected it for treatment in AD.

Agitation

We have previously, and still recommend, an approach for the comprehensive assessment and management of agitation in dementia, which is common, heterogenous, distressing and associated with increased carer burden and costs of care.(1) Immediate action requires assessment of underlying reasons for agitation, such as pain and distress and management of these before using medication.

Certain antipsychotics, such as risperidone, are licensed in UK, Australia, Canada and EU for treating agitation in dementia. In May 2023, brexpiprazole became the first antipsychotic to obtain US FDA marketing approval for treating agitation in AD but does not afford better efficacy or safety than other atypical antipsychotic drugs for this indication.(541, 542) (543) A phase 3 study (N=433) showed that treatment with brexpiprazole 2mg per day for agitation in AD was associated with an improvement of -3.77 Cohen-Mansfield Agitation Inventory (CMAI) points versus placebo at 12 weeks.(542) The most recent larger 12-week phase 3 RCT of brexpiprazole 2-3mg per day for agitation in AD (n=345) reported an improvement of -5.3 CMAI points compared to placebo. (544) In comparison, a pooled analysis of RCTs of risperidone that used the CMAI (n=1150) showed a mean dose of 1mg/day was associated with an improvement of -5.4 CMAI points at 12 weeks.(545) The main concern with antipsychotic drugs in dementia is increased risk for cardiovascular adverse events and mortality.(546) Brexpiprazole treatment was associated with numerically more deaths compared to placebo (6 versus 1). Risperidone remains the atypical antipsychotic with the largest RCT evidence base in the treatment of agitation. These medications should only be used after a thorough assessment and management of underlying causes of agitation, a trial of non-pharmacologic strategies with careful consideration and after potential risks have been shared and discussed with the person with dementia and their family carers depending on capacity.

Hospital admissions and delirium

Delirium is common, under-recognised and under-treated in older people and occurs in people who are more cognitively impaired prior to an acute illness.(547) In the last Lancet commission, we discussed how delirium and dementia frequently occur together but there is no definitive evidence that any medication improves delirium; sedating benzodiazepines are ineffective and like antipsychotics, are associated with increased mortality and morbidity.(2)

Delirium superimposed on dementia is associated with longer length of hospitalisation, worse cognitive and functional outcomes, and a higher risk of care home admission and mortality.(548) A recent meta-analysis found that delirium was significantly associated with future cognitive decline (ES Hedges g 0.45; 0.34-0.57).(549) In a London study quantifying this, 209/1510 (13.6%) participants in a prospective cohort with median age 77 years, were admitted to hospital at least once over a follow-up of 30 months or more. (550) Those who were more cognitively impaired were more likely to be admitted and both more likely to develop delirium and the delirium was more severe than their comparators. Cognitive impairment is a risk factor for delirium which is a risk factor for further cognitive deterioration and functional decline.(551)

It is important to energetically treat delirium, both treating the underlying illness and using non-pharmacological means of increasing orientation, vision and hearing maximisation, management of pain and hypoxia, fluid support and ensuring food intake. In addition, it is essential to monitor the health of people discharged from hospital with delirium. They are often cognitively impaired or have dementia and cannot be expected to initiate and work on a treatment plan at home without help. Preventing and treating delirium in those without dementia might decrease dementia risk but currently we cannot be sure.(552)

Lessons learned from COVID-19 and dementia.

COVID-19 by itself and the associated social isolation and lockdown has had a significant, disproportionate, negative impact on symptoms and mortality of people with dementia and on their families, and carers.(553) People with dementia had around five times the mortality from COVID-19 (meta-analysis of 10 studies OR 5.17, 2.31- 11.59; n=119,218) compared to those without dementia (554) A systematic review of the effects of social isolation in COVID-19 found 9/15 (60%) studies with 6,442 participants reported worse than expected deterioration in cognition and 14/15 (93%) worsening or new onset of non-cognitive symptoms. (555)

Care home residents usually need personal care, and thus cannot be isolated from staff. Family were frequently restricted or forbidden to visit during the pandemic to contain risk, thus leaving people isolated.(553, 556) Larger care homes, those who used more agency staff, transferred staff between settings, tested less for COVID-19 and had less access to personal protective equipment (PPE) had higher levels of infection and mortality.(557)

Long term lessons about pandemics and end-of-life management for people with dementia

Longer term lessons for other pandemics include policy ensuring that people are not admitted to a care home when their infection status is positive or unknown, as this exposes people who have no say in it to danger. We now know the positive impact of care homes restricting movement of staff between homes and ensuring staff have priority access to and wear PPE to reduce infection. People with dementia require access to care which is appropriate for them, and it is impossible to completely isolate people who need 24-hour care.

People with dementia should be encouraged to make legal decisions about what they want while they have capacity to make these decisions. As we discussed in detail in the last commission, people with dementia have other illnesses and die earlier. (2) They or another decision-maker like a family member, if they do not have capacity to make decisions, should decide about possible curative and palliative care, rather than blanket

decisions being made for people with dementia. People with dementia should have the same access to palliative care as the remainder of the population.

Technology and delivery of interventions

Technology has several potential roles in dementia management, including in diagnosis and assessment, monitoring to promote safety, assistance in activities of daily living and cognition, facilitating social interaction and leisure activities, and supporting family carers.(558) There is a dearth of high-quality research on emerging technologies, due to novelty and a rapidly evolving field, meaning that evidence for their use is often lacking.

Monitoring symptoms

Technologies to assess dementia symptoms have limited evidence. A review of 14 studies of sensing technologies for dementia symptoms showed that, in 7 studies, actigraphy correlated with agitation and aggression in people with dementia, but there was a lack of evidence for other technologies .(559) A review of 55 studies of assessments of sleep quality in dementia found no benefit of actigraphy in five studies, compared to questionnaire-based instruments. (529)

Technological interventions

A scoping review indicated that smart-home technologies, which are appliances and devices in the home connected via the internet to enhance the living environment, are not ready for implementation for people with dementia, and that there was not clear evidence of efficacy .(560) An RCT in 495 people with dementia of assistive technology and telecare recommended by a health or social care professional to meet assessed needs was not better than a basic package of safety-related devices in length of time that participants remained in the community, carer burden, depression or anxiety, health and social care or societal costs and quality-adjusted life-years. (561) In a systematic review of 66 studies, socially assistive robots were generally feasible and acceptable to people with dementia and their carers, and to healthcare professionals, but there was no evidence of effect on cognition, neuropsychiatric symptoms, or quality of life. (562)

Summary of technology in dementia

In general, there is a lack of evidence to recommend specific technologies for dementia management. Technologies should, where possible, supplement rather than replace existing care leading to harmful social isolation. There is concern that future technology may reduce equity by being less accessible to those with less financial resources.

Conclusions

The number of people living with dementia is going to increase in all countries and policy makers should prioritise resources to enable risk reduction and to help people with dementia and their families. There is much more evidence that interventions can help retain cognition and prevent dementia. These should be targeted at those who need them most.

The prevention approach should be directed at addressing midlife risk factor levels early enough (the earlier, the better) and maintaining them low throughout life (the longer, the better). Key individual interventions are preventing and treating hearing loss, treating vision loss and depression; cognitive stimulation throughout life, decreasing smoking, reducing and treating vascular risk factors (cholesterol, diabetes, obesity, blood pressure), reduce head injury, maintaining and encouraging physical activity. Policy changes can reduce air pollution, salt and sugar in food thus targeting obesity, hypertension and diabetes and make structural changes to increase exercise and reduce social isolation. There is still an effect of changing the risk throughout life. "*It's never too early to start and never too late to start*".

Much can be done for people with dementia and their families, but in many countries, it is not available or a priority. Good quality diagnosis, care planning and tailored post-diagnostic support enables the prevention of harm, treatment of neuropsychiatric symptoms, and protection of quality of life for people with dementia and their family carers. We have interventions that work, but do not deliver them at scale to everyone that would benefit from them.

We have a long-awaited scientific breakthrough with some modestly positive (and some negative) results for potentially disease modifying drugs, but the clinical implications are still unclear. There is exciting progress in biomarkers but by themselves they are not enough to justify diagnosis. Clinically should be used only to help classify whether people with dementia have Alzheimer's. Drug and psychosocial treatment are progressing. It is even more important therefore that we make things better for people with dementia and their families.

Conflict of interest

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AB acts as a consultant for Lilly, Taurx pharmaceuticals and Eisai. He also carries out medico legal work for solicitors.

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Contributors

GL wrote the first draft of the whole paper and revisions of drafts. All authors contributed to sections of the report, and all revised the paper for important intellectual content. SC, AS and GL conceptualised and performed new meta-analyses. GL, NM, GS and AS conceived the new PAF calculation and defined variables. GL and NM updated prevalence and RR for the PAF. NM carried out the analysis for weighted PAF. GL, SC, AS, JH, NM, KL, SA, DA, SB, NCF, CPF, LG, RH, HCK, MK, EBL, NN, KR, QS, KS, AS-M, LS, YY and SW attended the conference to discuss the content.

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