

# Dementia prevention, intervention, and care: 2024 report of the *Lancet* standing Commission



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## Executive summary

The 2024 update of the *Lancet* Commission on dementia provides new hopeful evidence about dementia prevention, intervention, and care. As people live longer, the number of people 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 2020 report of the *Lancet* Commission on dementia, prioritising systematic reviews and meta-analyses and triangulating findings from different studies showing how cognitive and physical reserve develop across the life course and how reducing vascular damage (eg, by reducing smoking and treating high blood pressure) is likely to have contributed to a reduction in age-related dementia incidence. Evidence is increasing and is now stronger than before that tackling the many risk factors for dementia that we modelled previously (ie, less education, hearing loss, hypertension, smoking, obesity, depression, physical inactivity, diabetes, excessive alcohol consumption [ie, >21 UK units, equivalent to >12 US units], traumatic brain injury [TBI], air pollution, and social isolation) reduces the risk of developing dementia. In this report, we add the new compelling evidence that untreated vision loss and high LDL cholesterol are risk factors for dementia.

We have completed new meta-analyses of the risk of hearing loss and depression for future dementia and 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 the population attributable fractions to generate a new comprehensive life-course perspective of dementia prevention incorporating these 14 risk factors. The potential for prevention is high and, overall, nearly half of dementias could theoretically be prevented by eliminating these 14 risk factors. These findings provide hope. Although change is difficult and some associations might be only partly causal, our new evidence synthesis shows how individuals can reduce their dementia risk and we discuss how policy interventions might improve dementia prevention. There is more potential for reduction in risk in low-income and middle-income countries and among minoritised and lower socioeconomic groups, for which new evidence shows that there is often a higher burden of modifiable risk than for higher-income countries and

majority populations within them, so dementia is more likely to develop at an earlier age.

Evidence for specific risk factors suggests that all children should be educated, and a long duration of education is beneficial. It is important to be cognitively, physically, and socially active in midlife (ie, aged 18–65 years) and late life (ie, aged >65 years), with novel evidence showing that midlife cognitive activity makes a difference even in people who received little education. The evidence that treating hearing loss decreases the risk of dementia is now stronger than when our previous Commission report was published. Use of hearing aids appears to be particularly effective in people with hearing loss and additional risk factors for dementia. New evidence also suggests that treating depression and smoking cessation might both reduce dementia risk.

We report the new finding that reducing air pollution is linked with improved cognition and a reduction in dementia risk. Policy makers should implement strategies to improve air quality, particularly in areas with high air pollution. TBI, at any age and from any source, continues to be a risk factor for dementia, and new and improved evidence suggests that contact sports pose a risk. This evidence suggests that protection from head injury, such as by use of appropriate head protection equipment, reducing high-impact collisions and heading practice in sports training, and avoiding playing sports immediately after TBI, should be an individual and public health priority.

New evidence suggests that reducing the risk of dementia increases the number of healthy years of life and compresses the duration of ill health for people who develop dementia. Prevention approaches should aim to decrease risk factor levels early (ie, the earlier, the better) and keep them low throughout life (ie, the longer, the better). Although addressing risk factors at an early stage of life 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 that midlife interventions are important, but some risk factors have their origins at societal levels and across the life course. All of the risk factors covered in this report have the potential for risk reduction at scale through policy changes that could affect risk across the life course. Additional evidence suggests that these changes are often cost saving and, for the first time, it is clear that risk can be modified even in people with increased genetic risk of dementia.

Published Online  
July 31, 2024  
[https://doi.org/10.1016/S0140-6736\(24\)01296-0](https://doi.org/10.1016/S0140-6736(24)01296-0)

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## Key messages

### Two new modifiable risk factors for dementia

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

### Modifying 14 risk factors might prevent or delay nearly half of dementia cases

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 groups at high risk are included. Actions to decrease dementia risk should begin early and continue throughout life. Risk is clustered in individuals; therefore, interventions should 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

We recommend several specific actions across the 14 risk factors:

- Ensure good quality education is available for all and encourage cognitively stimulating activities in midlife to protect cognition
- Make hearing aids accessible for people with hearing loss and decrease harmful noise exposure to reduce hearing loss
- Treat depression effectively
- Encourage use of helmets and head protection in contact sports and on bicycles
- Encourage exercise because people who participate in sport and exercise are less likely to develop dementia
- Reduce cigarette smoking through education, price control, and preventing smoking in public places and make smoking cessation advice accessible
- Prevent or reduce hypertension and maintain systolic blood pressure of 130 mm Hg or less from age 40 years
- Detect and treat high LDL cholesterol from midlife
- Maintain a healthy weight and treat obesity as early as possible, which also helps to prevent diabetes
- Reduce high alcohol consumption through price control and increased awareness of levels and risks of overconsumption
- Prioritise age-friendly and supportive community environments and housing and reduce social isolation by facilitating participation in activities and living with others
- Make screening and treatment for vision loss accessible for all
- Reduce exposure to air pollution

### Considerations for people with dementia

Interventions after 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.

Neuropsychiatric symptoms should be treated, and clear evidence exists that care-coordinated multicomponent interventions are helpful. Activity interventions also reduce neuropsychiatric symptoms and are important to maintain enjoyment and purpose for people with dementia. There is no evidence for exercise as an intervention for neuropsychiatric symptoms.

Cholinesterase inhibitors and memantine should be provided for people with Alzheimer's disease and Lewy body dementia. These drugs are cheap, with relatively few side-effects; attenuate cognitive deterioration to a modest extent, with good evidence of a long-term effect; and are available in most high-income countries, although less so in low-income and middle-income countries.

There is progress in and hope for disease-modifying treatments for Alzheimer's disease, with some trials of amyloid- $\beta$ -targeting antibodies showing modest efficacy in reducing deterioration after 18 months of treatment. However, effects are small and drugs have been trialled in people with mild disease and people with few other illnesses. These treatments have been licensed in some countries but have notable side-effects, with few data about long-term effects. The expense of these treatments and the precautions that must be taken, which have resource implications for staff, scanning, and specialist blood testing, could limit their use and be challenging for health systems. We recommend that full information is shared broadly about the unknown long-term effects, the absence of data about the effects in people with multimorbidity, and the scale of efficacy and side-effects, particularly for APOE  $\epsilon 4$  genotype carriers. We recommend that people on amyloid- $\beta$ -targeting antibodies are carefully monitored.

Cerebrospinal fluid or blood biomarkers should be used clinically only in people with dementia or cognitive impairment to help to confirm or exclude a diagnosis of Alzheimer's disease. Biomarkers are only validated in largely White populations, limiting generalisability and raising health equity concerns.

People with dementia who become acutely physically unwell and need to be admitted to hospital deteriorate faster cognitively than others with dementia. It is important to protect physical health and ensure that people have help if needed to ensure that they eat and drink enough and can take medication.

COVID-19 exposed the vulnerability of people with dementia. We need to learn from this pandemic and also protect people with dementia as their lives and wellbeing, and that of their families, have been valued less than that of people without dementia.

The field of biomarkers has moved on since the 2020 report, with fluid biomarkers more widely validated, although much of the work has been conducted in people seen in tertiary centres, who often differ from most people with dementia because they tend to be younger or have rarer dementias. Additionally, there is now more clarity about the meaning of biomarker changes. Amyloid  $\beta$  and tau biomarkers in people with cognitive impairment help to confirm the presence of Alzheimer's disease pathology but do not confirm that this pathology is the cause of symptoms. Amyloid plaques occur many years before clinical presentation of dementia. Amyloid  $\beta$  biomarkers are common in older individuals (ie, 10% positivity at age 70 years and 33% positivity at age 85 years in a US sample) who do not have cognitive impairment, most of whom will not develop dementia. The presence of both amyloid  $\beta$  and tau biomarkers increases the probability of dementia, and neuroimaging evidence of neurodegeneration further increases this risk. The vision of blood biomarkers, such as phosphorylated tau, as a scalable test to predict who will develop dementia is progressing but is not yet realised.

For people living with dementia, interventions after diagnosis can help to maximise physical health, improve quality of life, reduce hospitalisations, and plan for the future. Interventions should be individualised, consider the person's life circumstances, and include family and other carers. Considerably more evidence exists about multicomponent psychosocial interventions for family carers and managing neuropsychiatric symptoms than was available at the time of our last report. These interventions are important and should be person-centred.

New evidence exists for the beneficial effects of cholinesterase inhibitors for people with Alzheimer's disease and Lewy body dementia in both the long term and the short term. Although cholinesterase inhibitors should be available for treatment of these dementias based on evidence for their effectiveness, this treatment is still not available in many countries. Less is known about anti-amyloid  $\beta$  antibody treatments. Encouragingly, for the first time, a few trials have reported a small decrease in cognitive deterioration in people receiving anti-amyloid antibody treatments, with substantially reduced amyloid  $\beta$  in the brain. These treatments reduced deterioration after 18 months of treatment by 27–35%, but are expensive, burdensome to use, require intensive monitoring and follow-up, and can have clinically significant and sometimes serious side-effects. No evidence exists on their long-term effects and safety.

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

The substantial advances in understanding protection and risk and in pharmacological and non-pharmacological

interventions for people with dementia mean that, now more than ever, we can prevent, diagnose, and treat dementia, improving life for individuals, families, and society.

## Introduction

We reconvened the *Lancet* Commission on dementia prevention, intervention, and care<sup>1,2</sup> with the aim of influencing policy, knowledge, clinical practice, and the research agenda. Exciting progress has been made in dementia prevention, diagnosis, and drugs and non-pharmacological treatments. More can and should be done to prevent dementia and to help people living with dementia and their families.<sup>3</sup> 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 section was presented and debated face to face and in multiple written versions. We unanimously agreed on the best available evidence and its consistency. We identified advances that are likely to have the greatest effects and performed new work to allow us to calculate the effects of potentially modifiable risk factors for dementia. Here, we report our new analyses and consolidate current knowledge, summarising 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.<sup>4</sup> The proportion of people with dementia has increased over time in lower-income countries due to a greater percentage increase in longevity than in high-income countries.<sup>5,6</sup>

In this third report of the *Lancet* Commission on dementia, we summarise what was already known by stating what we reported in previous commissions. This information comes from research over many decades by people around the world. We then build on this research, explain new evidence, reference it, and produce new evidence, integrating the information to make updated recommendations. We specifically consider populations in both high-income countries (HICs) and low-income and middle-income countries (LMICs) and under-represented, underserved, and minoritised communities in all countries where evidence is available. The evidence still disproportionately comes from HICs. The use of and research into interventions might also be more likely in HICs because they depend on resource availability, despite potentially being cost saving.<sup>7–9</sup> The national dementia plans in 31 of 46 countries do not make specific recommendations for the consideration of diversity, equity, or inclusion of people from under-represented cultures and ethnicities,<sup>10</sup> and plans that do consider these factors usually confine their recommendations to interpretation of cognitive tests.<sup>11</sup> As we set out in this

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report, ensuring consideration of all cultures and ethnicities for all types of dementia is essential to target help to people who need it most.

### Prevention

There has been a rapid expansion in the volume of work on dementia prevention and risk reduction related to the 12 risk factors that were identified from the existing research literature and discussed in our earlier *Lancet* Commission reports in 2017 and 2020.<sup>2</sup> The risk factors identified in our earlier reports were less education, hearing loss, hypertension, physical inactivity, diabetes, social isolation, excessive alcohol consumption, air pollution, smoking, obesity, traumatic brain injury, and depression—for which we reported that reductions have the potential to prevent 40% of cases of dementia.<sup>2</sup> We discussed the mechanisms for these 12 risk factors, which indicated that risk can be reduced at any age.

Here, we update the evidence and consider other potential risk factors. We use a life-course approach to understand how to reduce risk or prevent dementia because many risks operate at different timepoints in the lifespan. For example, obesity and high blood pressure are risk factors in midlife, often with earlier life origins, but in late life, the association with mild cognitive impairment (MCI) and dementia is reduced.<sup>12–14</sup> As in our previous reports, we look for risk factors with high-quality, consistent, dose-responsive, validly measured evidence; that precede dementia; and that are still present when measured a decade or more before onset. We include only those risk factors with convincing evidence but acknowledge that there are likely to be other risk and protective factors. The commissioners met and discussed the evidence, decided what to include, and set out our discussions and the evidence in the paper. Here, we discuss 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 view. We do not, however, aim to give a complete, detailed review of all mechanisms. We also discuss whether evidence is from diverse populations and therefore generalisable, and whether there is evidence that intervention to reduce the risk factor makes a difference to risk of dementia.

### Compression of morbidity

Data from some HICs suggest that age-specific dementia incidence rates have decreased over the past two decades,<sup>15</sup> emphasising that prevention is possible. There are fewer data from LMICs. Studies that have examined the association of dementia with socioeconomic deprivation suggest that the decrease in dementia incidence primarily occurs in people living in socioeconomically advantaged areas.<sup>15</sup> These findings suggest that many dementias are potentially preventable

(and deferrable), but age-specific rates might increase if risk prevalence (eg, prevalence of diabetes or obesity) increases, and this increase in age-specific rates might be particularly impactful in people with less education. An English study<sup>16</sup> suggests that an increase in age-specific dementia rates might be happening already, although there is uncertainty and additional evidence is needed.<sup>16–18</sup>

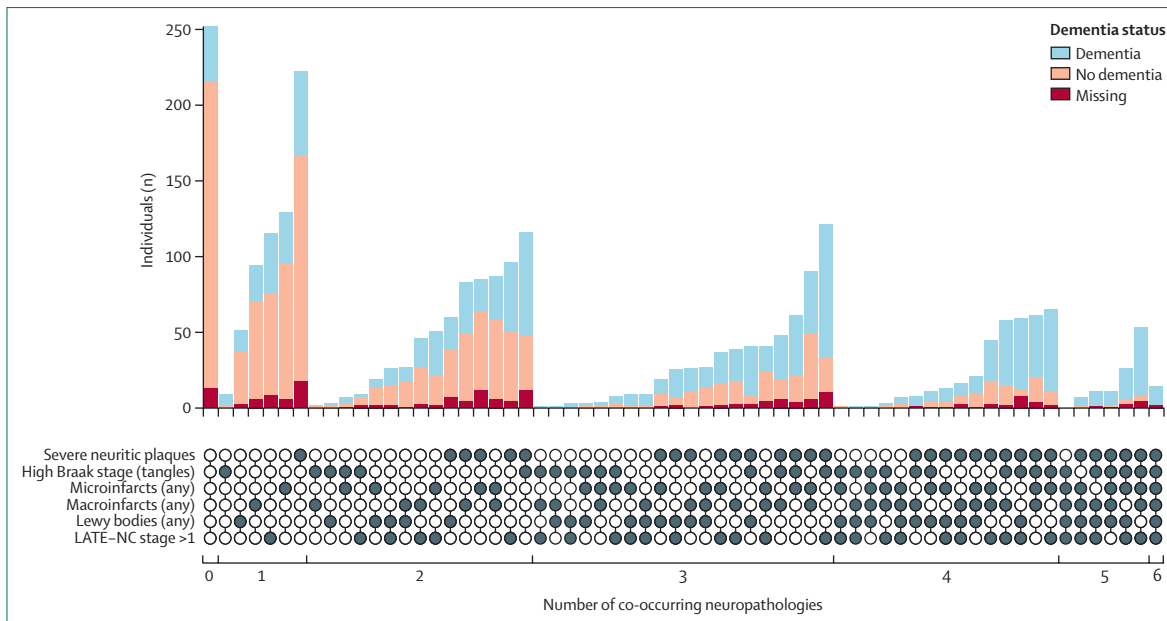
People with healthy lifestyles, involving regular exercise, not smoking, avoiding excess alcohol, and including cognitive activity in late life, were shown not only to have a lower risk of dementia than those with less healthy lifestyles but also to have dementia onset delayed for longer than their increased life expectancy, resulting in more healthy years and fewer years of illness.<sup>19</sup> Overall, people living healthier lives can expect to live longer than people with unhealthy lifestyles, and if they develop dementia, live fewer years with the disease, with notable quality-of-life implications for individuals and cost-saving implications for services.

### Cognitive vulnerability, brain maintenance, and cognitive reserve

As discussed in the 2020 *Lancet* 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 4354 people older than 80 years who had died in the USA or the UK, identified that 2443 (91%) of 2695 people analysed for six types of neuropathology died with two or more types of neuropathology.<sup>20</sup> The more types of neuropathology that people had, the more likely they were to have dementia (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 terms resilience or brain reserve are also used to describe coping with pathology and resistance to neuropathology. People who are physically healthier are better able to withstand the effects of neuropathology than people who are physically unhealthy.<sup>21</sup> For example, although the age-related incidence of dementia has decreased in some countries over the past 25 years, one post-mortem study showed no differences in neurodegeneration over that time but a reduction in vascular pathology.<sup>22</sup> A systematic review reported that physical, cognitive, and social activities increase cognitive reserve and attenuate the effect of neuropathology.<sup>23</sup> Overall, in the past two decades, a combination of greater cognitive and physical reserve<sup>21</sup> developed across the life course, preserving cognitive health despite neuropathology, and less vascular damage are likely to have contributed to the observed decreased age-related dementia incidence.<sup>24</sup> Nonetheless, the number of people with dementia continues to increase due to population ageing.





**Figure 1: Co-occurrence of six key neuropathologies by clinical dementia status from data pooled across five cohorts**

The five cohorts were Adult Changes in Thought, Cambridge City Over-75s Cohort Study, Cognitive Function and Ageing Studies, Framingham Heart Study, and Religious Orders Study, and Memory and Aging Project. LATE-NC=limbic-predominant age-related TDP-43 encephalopathy neuropathological change. Reproduced from Nichols et al.<sup>20</sup>

## The challenges of research into dementia prevention and risk reduction

### Life-course nature of exposures to protection and risk

Many factors operate across the life course from gestation through to late life. These factors are challenging to track, and our evidence base is limited to what is studied at particular ages. Here, we look at evidence directly related to dementia; however, broader evidence that we do not capture exists on optimal brain growth in early life (ie, in utero and infancy) and exposure to adversity and its effects on cognition, vascular health, and physical and cognitive activities. Educational exposure has strong protective effects. 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.

The duration, consistency, and timing of exposure to possible risk might be important, with one study reporting, for example, that midlife diabetes is a risk factor for dementia but might not be a risk in those whose diabetes onset is in late life.<sup>25</sup> It is unclear whether this difference in risk is because of shorter duration of exposure in people who develop diabetes in late life than in those who develop diabetes in midlife, whether severity of diabetes has an effect on risk, or whether there is a critical period of exposure. It is possible that, if people who develop diabetes in late life live long enough, they might also be at increased risk of dementia. Other risk factors, such as smoking, which evidence suggests is a risk factor in midlife, clearly also confer risk in late life.

### 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  $\beta$  or tau accumulation before Alzheimer's dementia. The neuropathological changes initially have few cognitive effects but these effects can increase over many years.<sup>26</sup> Changes in behaviour and health can occur long before dementia onset, so potential risks identified in the few years before dementia onset could be true causal effect or reverse causation, or the link could be bidirectional. This bidirectionality could be true even when studies report the mean cohort follow-up time, which might vary between people who develop dementia (due to censoring at dementia onset) and those who do not. Future studies should report the mean follow-up of people who develop and do not develop dementia separately or test the effect of excluding incident cases that develop within 5–10 years of follow-up.

There are many methodological difficulties in designing and conducting intervention trials for dementia prevention, including ensuring sufficient follow-up duration; recruitment of participants from groups at high risk or who are often excluded, such as people from minority ethnic groups (which vary by country); and adherence to the intervention and making associated lifestyle or behavioural changes that are associated with improved cognitive functioning trajectories,<sup>27</sup> considering adherence decreases with increasing intervention complexity and intensity.<sup>28</sup> It can

be more difficult to show the benefit of an intervention in a randomised controlled trial (RCT) if the control group is highly motivated to also take up the intervention. Benefit might stop or decrease if the intervention does not continue after the end of the trial.

### Diversity, equity, and inclusivity

We previously considered prevention and risk reduction on a global level, using international data for prevalence of risk factors and relative risks (RR) from meta-analyses where possible.<sup>12</sup> Consideration of equity is important, not only ethically but also to inform intervention targeting and accessibility to maximise preventive effects.<sup>29</sup> Many big data sources comprise data from volunteers, which by their nature exclude people who are most at risk.<sup>30</sup> Additionally, some of the big cohort studies, such as the UK Biobank, also recruit younger volunteers (ie, aged <50 years), and although their inclusion is useful for the exclusion of reverse causality, most people have not reached the age at which dementia is common and therefore findings might not be generalisable to older populations. Cohort studies of dementia risk factors, and therefore meta-analyses, are overwhelmingly from HICs, and these studies tend to recruit people of European origin with a high level of education and high socioeconomic status, who are usually from older age groups (ie, >65 years), with few people included from minority ethnic groups.<sup>31</sup> These limitations also apply to clinical trials and, for both types of study, might relate to exclusion criteria that specify other notable medical and psychiatric illnesses; lack of a study partner to accompany the participant to the trial visits and support them, such as a family carer; inability to handle research participation burden; and lack of local language fluency.<sup>32,33</sup>

Risk factor prevalence varies between countries<sup>34</sup> and within countries.<sup>35</sup> A meta-analysis of 31 studies from 15 Latin American countries showed that twice as many people without any education compared with those with 1 year or more of education had dementia (21.4% vs 9.9%) and reported a slightly higher prevalence in rural than urban settings and in women than in men.<sup>29</sup> Risk factors cluster within communities and individuals. People from underserved ethnic groups, such as the Māori people in New Zealand, First Nations Australians, Black individuals in the USA and the UK, and Hispanic individuals in the USA, have higher prevalence of potentially modifiable risk factors than the country's majority population.<sup>36–43</sup> Furthermore, the literature, and therefore our Commissions, have assumed that the effect of having each risk factor is the same for everyone. By contrast, cardiovascular disease research has identified, for example, that the effect of high blood pressure on the risk of stroke is greater in south Asian people in the UK than in the White British population and the effects of risk factors for dementia might also vary between ethnic groups.<sup>44,45</sup>

Important social disadvantage factors, such as less education, more social isolation, and low socioeconomic

status, tend to cluster with health factors that predict cognitive decline and dementia.<sup>46</sup> Therefore, people often have several risk factors, which might act together, meaning it is important to consider communality. We have chosen to consider risks individually and correct for communality, rather than consider various risk profiles.

The effect of socioeconomic status on prevalence of some risk factors can vary between countries. The prevalence of hypertension, diabetes, obesity, physical inactivity, smoking, excessive alcohol consumption, less education, traumatic brain injury (TBI), and exposure to air pollution is higher in people from low socioeconomic groups and with a low income in HICs.<sup>47–49</sup> In low-income countries, the reported lower prevalences of obesity or diabetes in people with less wealth or education are inconsistent.<sup>50,51</sup> Additionally, social isolation is less common in some low-income countries than in high-income countries.<sup>32</sup>

Biological sex—ie, the physical differences between people due to their 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. Sex and gender are increasingly recognised as separable concepts in some societies. Biological sex, hormonal exposure, and societal roles are all potentially important in influencing risk of dementia and its expression in late life. Findings about the effect of biological sex on risk of dementia are inconsistent.<sup>52</sup> Women have higher age-adjusted dementia incidence rates than men in some but not all countries.<sup>53</sup> One meta-analysis with nearly a million people from 205 studies in 37 countries identified that increased incidence and prevalence of dementia in women compared with in men were explained by differences in life expectancy and education.<sup>53</sup> An individual participant analysis reported widely varying results in individual countries.<sup>54</sup> Across 21 cohorts with a total of 29850 participants in Africa, Asia, Europe, North America, Australia, and South America, the risk of developing dementia was greater in women than in men (hazard ratio [HR] 1.12, 95% CI 1.02–1.23). The first nationally representative dementia prevalence estimates in India indicated a higher prevalence in women, people with less education, and in rural settings.<sup>55,56</sup>

In both HICs and LMICs, evidence suggests that risk is related to factors other than biological sex. Longer life span and less educational attainment in women than in men, and reduced oestrogen in postmenopausal women, could cause sex differences in dementia development. A representative nationwide study in Japan of 2200 adults followed up from age 60 years for 12 years, or until death, reported 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.<sup>57</sup> A UK study of 15924 participants identified that women born more recently in the cohort were catching up with men's

higher memory and fluency scores, as women's access to education increases.<sup>58</sup> An analysis of 70 846 people aged 60 years or older in the USA, Mexico, Brazil, China, and India found that poorer cognitive function in women than men was more pronounced in middle-income countries than in the USA. Adjustment for education attenuated the difference in cognition between men and women in all countries and eliminated the difference in the group that received a high level of education.<sup>59</sup> This difference between countries suggests that increased risk in women is partly related to lack of opportunity in work and education, leading to increased poverty, decreased access to medical care, and discrimination, all of which vary between cultures rather than between biological sexes.<sup>60</sup> Although little knowledge exists about the risks of dementia in people who have a same-sex partner, one US study of 23 669 adults older than 50 years identified a higher risk of cognitive impairment in those with a same-sex partner than in those with an opposite-sex partner.<sup>61</sup> Additionally, cisgender men and women generally have fewer risk factors for developing dementia in late life than do transgender men and women.<sup>62</sup>

#### Methods to consider causality

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, which can be either symptomatic or detected on imaging in the absence of motor symptoms, and stroke is specified in the diagnostic criteria for vascular dementia. Stroke happens more often in people with many potentially modifiable risk factors, such as smoking, hypertension, and diabetes, than in people without risk factors.<sup>63</sup>

Although RCTs are the gold standard in establishing efficacy of an intervention, and therefore causality of risk factors, they are often impractical for studying dementia. Trials might require decades of intervention and follow-up before clinical dementia occurs, leading to prohibitive costs and bias because of selective drop-out. Additionally, it might be unethical or impossible to randomly assign people to a treatment group. Causal inference methods, quasi-experimental studies, or ecological studies could add to the evidence.<sup>64</sup> A Cochrane review comparing studies of health-care outcomes (although not dementia specifically), which assessed quantitative effects of RCTs and observational studies of interventions, identified that 23 of 34 studies reported similar effect estimates from RCTs and observational studies.<sup>65</sup> Differences were identified when there was high heterogeneity in the meta-analysis (ie, >50%). One approach for assessing causality 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 approach is mendelian randomisation analyses, which

we have, for the first time, incorporated into our triangulation framework where possible, to help to establish causation. Mendelian randomisation is a causal inference method that is based on alleles being randomly allocated at conception, so their association with a risk cannot be caused by a later disease. This approach assumes that behaviours and mood are partly genetically driven and can be used for causal inference only where there is sufficient genetic diversity influencing a particular risk factor in the population studied. Mendelian randomisation is also limited by factors such as survival bias, which is likely to account for controversial mendelian randomisation findings that oppose RCT findings.<sup>66,67</sup>

#### 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 groups at high risk. 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 evidence base of the 2020 Commission about protective and risk factors for the development of dementia. We discuss where in the life course the evidence suggests that these factors begin to be important, given the constraints of ages for which evidence is available.<sup>2</sup> Whereas some risk factors, such as hypertension, evolve and change during the life course, other factors, such as alcohol or smoking, might be more consistent. We summarise the potential mechanisms of protection from dementia in figure 2.

#### Education, educational attainment, and cognitive activity

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

In China, studies 20 years apart using the same methods and geographical area reported that dementia incidence and prevalence have increased specifically in people with less than 6 years of education, possibly because this population is now more likely to survive to older age than in previous years due to generally improved population health.<sup>71</sup> In the USA, prevalence

has decreased, in parallel with increased education for all of the diverse US population. Reported dementia prevalence decreased most in Black people aged 65–74 years, in line with the greater improvement in education for this population than the non-Hispanic White population.<sup>72</sup> For Chinese, Filipino, and Japanese Americans, attaining a university degree was associated with decreased dementia risk.<sup>73</sup>

A study of 107 896 people from HICs who were followed up for 13.7–30.1 years reported a lower risk of dementia in participants with high cognitive stimulation at work than in participants with low cognitive stimulation at work (10-year follow-up HR 0.79, 95% CI 0.66–0.95).<sup>74</sup> Compared with people with little education and low cognitive stimulation at work, the HR for dementia in people with high cognitive stimulation at work but little education was 0.80 (0.66–0.97) and for people with high cognitive stimulation and high education was 0.63 (0.49–0.82; figure 3). Similar results were reported in a study conducted in Asia, Australia, Europe, and North America, which followed up 10 195 people for 3.9–6.4 years, which found that 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.<sup>75</sup> However, a US study reported that years of schooling predicted protection against the effect of MRI white matter lesions in White people but not Black people.<sup>76</sup> Globally, educational attainment has increased over time but is still low in some countries so is of great relevance when considering dementia prevention and overall health.<sup>77</sup>

High cognitive stimulation has been associated with cognitive reserve. The ability to maintain cognitive reserve could be mediated by many mechanisms, including higher concentrations of circulating proteins to allow brain repair through axonogenesis and synaptogenesis,<sup>74</sup> greater efficiency of and less decline in functional brain networks,<sup>78,79</sup> increased occupational attainment linked with improved financial situation leading to more choices about where to live, better physical health through better health-care access and health awareness, and other health promoting behaviours. A mendelian randomisation study identified that the effect of years of education (measured by predictive genes) was mediated by intelligence (measured by genes linked to intelligence quotient test performance).<sup>80</sup>

In the 2020 *Lancet* Commission, we reported that trials of computerised cognitive training in healthy older people and people with mild cognitive impairment generally suggested a small positive effect on cognition, but it was unclear whether computerised cognitive training was of clinical value because of the low quality and heterogeneity of studies.<sup>81</sup> An updated Cochrane review of computerised cognitive training interventions for maintaining cognitive function in cognitively healthy older individuals, delivered across 12–26 weeks, also identified low-quality evidence supporting immediate small benefits of computerised cognitive training on global cognitive function versus active controls and on episodic memory versus inactive controls, without long-term evidence of effect.<sup>82</sup> Notably, short-term computerised cognitive training interventions at low intensity, which can be financially costly, have only low-quality evidence of short-term effectiveness and no

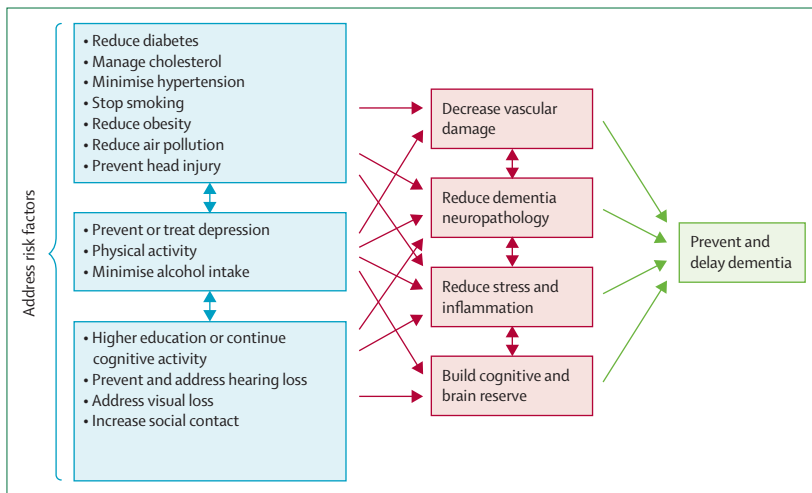


Figure 2: Possible brain mechanisms for enhancing or maintaining cognitive reserve and risk reduction of potentially modifiable risk factors in dementia

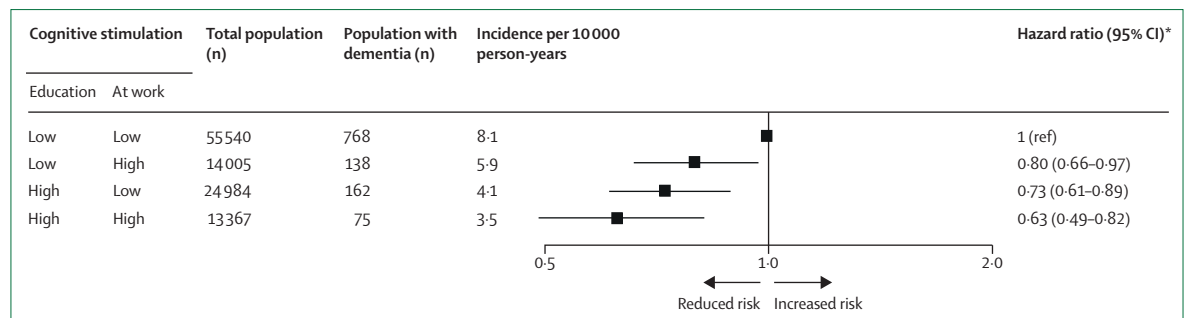


Figure 3: Association of cognitive stimulation over the life course with incident dementia  
Reproduced from Kivimäki et al.<sup>74</sup> \*Adjusted for age, sex, and cohort.



See Online for appendix

evidence 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, is not intensive or engaging enough, or is delivered 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.<sup>74</sup>

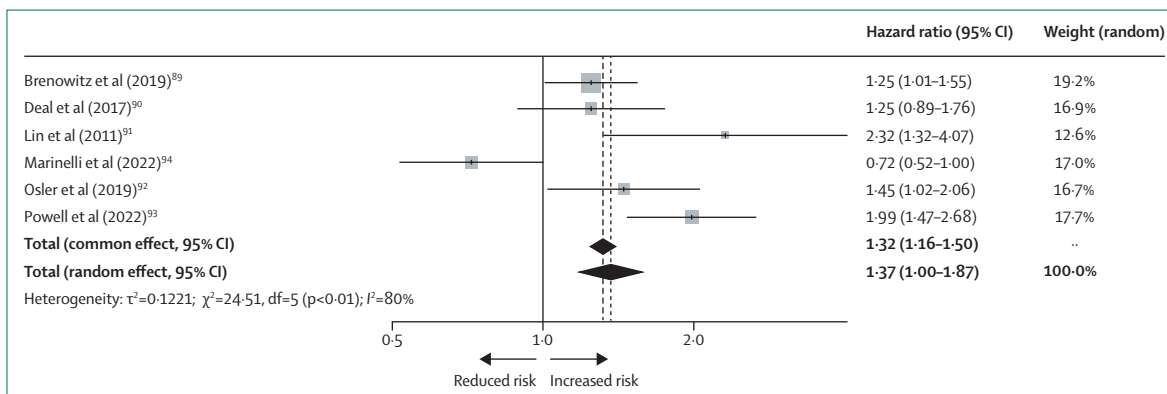
**Hearing loss and hearing aids**

Globally, an estimated 20% of people have hearing loss, sometimes related to occupational or environmental exposures to noise or untreated infections.<sup>83</sup> 62% of people worldwide with hearing loss are older than 50 years, and hearing loss is often untreated.<sup>83</sup> In our previous *Lancet* Commissions, we performed a meta-analysis of high-quality cohort studies with participants who were free of dementia but had objectively measured peripheral hearing loss at baseline.<sup>12</sup> We defined high-quality studies as those with objective measures of hearing through pure-tone assessment; more than 5 years of follow-up; adjustment for age, cardiovascular factors, and cognition or education at baseline; and an overall risk for the outcome of incident dementia. There are five further meta-analyses on the association between hearing loss and subsequent dementia,<sup>84–88</sup> one of which focused on Sinitic tonal languages.<sup>86</sup> All of these analyses reported significant associations between hearing loss and subsequent dementia, ranging from RR 1.28 (95% CI 1.02–1.58) to 2.39 (1.58–3.61).<sup>85</sup> In the most recent study, incident hearing loss was associated with incident dementia risk (HR 1.35, 95% CI 1.26–1.45) and was related to dose, as each 10-dB worsening of hearing was associated with a 16% increase in dementia risk (95% CI 1.07–1.27).<sup>88</sup>

None of these analyses included all of the criteria that we judged to ensure high-quality data in our previous meta-analysis. We also excluded studies comparing populations with varying severities of hearing loss, but not comparing individuals with hearing loss with those

without hearing loss. We searched again from database inception until March 20, 2023, on PubMed, Ovid Embase, PsycINFO, Web of Science, Cochrane Library, PROSPERO, and the Centre for Reviews and Dissemination, contacting authors for clarification as needed, and found six studies fitting the criteria (appendix pp 1–2).<sup>89–94</sup> We searched “all fields” using the search terms “dementia” or “cognitive decline” or “Alzheimer’s disease” or “mild cognitive impairment” AND “hearing” or “auditory” or “aural” or “presbycusis”. We calculated totals if only subgroups were reported, generating an overall HR for studies.<sup>90,92,93</sup> We used results unadjusted for hearing aids because hearing aids are part of the causal pathway between hearing loss and dementia.<sup>93–95</sup> The mean baseline age of study participants ranged from 59 years to 77 years, with the largest study recruiting men when they enrolled in the mandatory conscription board at age 18–20 years but measuring hearing status at a median age of 59.9 years (IQR 54.6–65.4).<sup>92</sup> Follow-up in all studies between baseline and dementia status was between 6 years and 12 years. We conducted a random-effects meta-analysis of these studies, in which people with hearing loss had an increased risk of dementia compared with those without hearing loss (HR 1.37, 95% CI 1.00–1.87;  $I^2=80\%$ ;  $n=666\ 370$ ; figure 4). Four of the smaller studies reported hearing aid use, and 18–64.5% of people with hearing loss wore hearing aids.<sup>89–91,94</sup> All people with hearing loss were included in our meta-analysis, without considering the use of hearing aids in the overall risk estimate, so the estimate is conservative. In our meta-regression, studies with a higher proportion of people who wore hearing aids reported a lower likelihood of dementia than those with a lower proportion of people who used hearing aids, but the confidence interval was wide (–1.32, –3.34 to 0.71).

As severity of hearing loss increases, dementia risk increases: all four studies that investigated dose–response between hearing and dementia risk reported that every 10 dB decrease in hearing ability increased dementia



**Figure 4: Relative risk of dementia for people with hearing loss at baseline compared with those without hearing loss**

A hazard ratio of less than 1 shows a reduced risk in people with baseline hearing loss compared with those without hearing loss, and a hazard ratio of more than 1 shows an increased risk in people with baseline hearing loss compared with those without.

risk.<sup>90,91,96,97</sup> The magnitude of this risk increase varied between studies, from a 4% increase<sup>96</sup> to a 24% increase<sup>91</sup> in dementia risk per 10 dB decrease in hearing ability.

Specific speech-in-noise hearing loss, in which the deficit is understanding speech when other background noises are present, is rare. The only large study to date in which speech-in-noise hearing loss was objectively measured used data from the UK Biobank (n=82039; 100 people with speech-in-noise loss, followed up for a median of 10 years). Compared with people with typical speech-in-noise hearing (ie, speech reception threshold in noise [SRTn] <-5.5 dB), there was an increased risk of dementia in people with insufficient (SRTn ≥-5.5 dB to <-3.5 dB; HR 1.61, 95% CI 1.41-1.84) and poor (SRTn ≥-3.5 dB; 1.91, 1.55-2.36) speech-in-noise hearing.<sup>98</sup>

Several mechanisms have been hypothesised to explain how hearing loss might increase dementia risk. Psychosocial factors, such as loneliness, depression, and social isolation, might be involved. Other mechanisms include reduced cognitive reserve from decreased environmental stimuli, increased cognitive resources needed for listening, and an interaction of these risks with brain pathology.<sup>99</sup> A causal link between hearing loss and dementia is supported by longer exposure to hearing loss being associated with higher dementia risk, with maximum risk in people who were diagnosed with hearing loss for more than 25 years.<sup>100</sup> Another postulated mechanism is common cardiovascular pathology, whereby vascular disease affects the cochlea or the ascending pathway, causing hearing loss, and the medial-temporal lobe, causing dementia. This mechanism would suggest that confounding by cardiovascular health status or risks would substantially account for the association between hearing loss and dementia risk, which has not been shown in meta-analyses.<sup>99</sup>

The evidence described here raises the question of whether the use of hearing aids in people with hearing loss can eliminate or mitigate the increased dementia risk. The ACHIEVE study, the first RCT of hearing aids and cognition, recruited people aged 70-84 years. The participants were healthy volunteers with hearing loss who were recruited with advertisements (n=739) and people from an existing cohort, the ARIC study (n=238).<sup>101</sup> There was no overall effect of the use of hearing aids on the primary outcome of cognition at 3-year follow-up (difference -0.002, 95% CI -0.08 to 0.08). Importantly, a prespecified sensitivity analysis identified substantial effects of hearing aid use on cognition at 3 years in the ARIC group (difference 0.19, 0.02 to 0.36). The ARIC population had more risk factors for dementia (ie, the mean population age was 2.8 years older, lower baseline cognition, smoked more, less education, more often lived alone, and more likely to have diabetes and hypertension) than the healthy volunteer population with hearing loss. Incident cognitive impairment was higher in the ARIC group (57 [24%] of 238 participants) than in people who

were recruited via advertisements (61 [8%] of 739 participants) at 3-year follow-up. Notably, the authors emphasised that volunteer participants who are recruited through this type of method generally represent a healthier subset of the target population. Overall, there was a large protective effect of hearing aids on cognition in the population at high risk in the ARIC cohort (48% reduction in 3-year global cognitive decline compared with the control population). The slower rate of cognitive decline in the healthy volunteer group compared with the ARIC cohort might have limited any effect on cognition in this group within a 3-year follow-up period. The explanation of the large effect in the ARIC cohort might be that hearing aids in groups at high risk of dementia also change social contact, low mood, cognitive stimulation, and improve motivation and communication about medical treatment, but this evidence does not exist yet.<sup>102</sup>

We previously discussed the evidence that hearing aid use is protective against dementia and reduces cognitive deterioration rates after beginning hearing aid use.<sup>2</sup> Since then, a systematic review and meta-analysis of eight cohort studies with 126 903 participants, followed up for 2-25 years, reported that people with hearing loss who used hearing aids had a significantly lower risk of cognitive decline (HR 0.81, 0.76-0.87;  $I^2=0\%$ ) and dementia (0.83, 0.77-0.90;  $I^2=0\%$ ; four studies) than those who did not use assistive devices (figure 5).<sup>103</sup>

In another cohort of 2114 people older than 50 years with self-reported hearing loss, 1154 people had MCI and those that used hearing aids were at significantly lower risk of developing all-cause dementia during the follow-up than those not using hearing aids (HR 0.73, 0.61-0.89).<sup>105</sup> 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 only the studies with long follow-up are considered, to reduce the chance of reverse causality, the evidence on hearing aids reducing dementia risk is consistent and supportive. Implementing the use of hearing aids, if effective in preventing dementia, would likely be cost saving.<sup>7</sup>

### Depression

In the 2020 *Lancet* Commission, we concluded based on published studies that the link between depression and dementia was probably bidirectional and that, in the years before dementia presentation, 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 for depression.

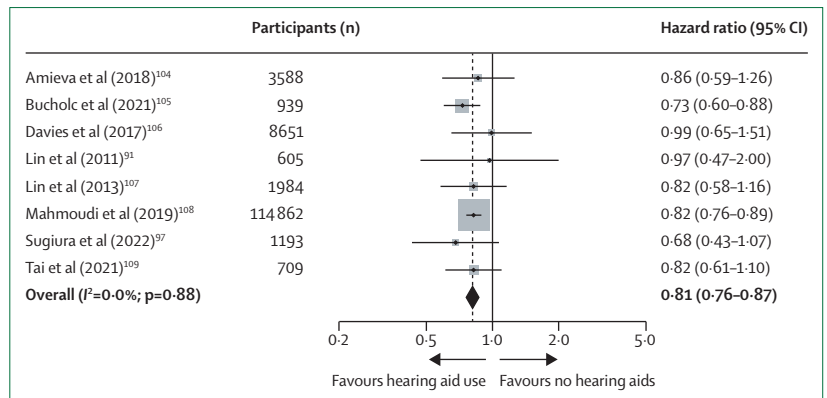
A new meta-analysis identified that depression was associated with all-cause dementia, although there was a high degree of heterogeneity between studies (RR 1.96, 95% CI 1.59-2.43;  $I^2=96.5\%$ ; 27 studies).<sup>110</sup> For this Commission, we chose the seven studies included by

Stafford and colleagues with a 10–14-year follow-up<sup>110–117</sup> and performed a random-effects meta-analysis of the results from these. We identified an increased risk of dementia for people with depression compared with those without depression (RR 2.25, 95% CI 1.69–2.98;  $I^2=82.8\%$ ; figure 6). Six studies that specified the age of participants had an overall baseline mean age of 63 years. Although the studies were heterogeneous in the effect size, they consistently reported an increased risk of dementia for people with depression, including in studies that matched participants for age, sex, socioeconomic status, and comorbidities. Similarly, a Danish case-control study of 246 499 adults diagnosed with depression (at median age 50.8 years, IQR 34.7–70.7) and 1190 302 individuals without depression reported a higher risk of dementia overall among those with depression (HR 2.41, 95% CI 2.35–2.47) compared with those without depression. The association was also seen in people for whom the interval between index date for depression assessment and dementia was longer than 20–39 years (1.79, 1.58–2.04), and in those diagnosed with depression in early (ie, 18–44 years; 3.08, 2.64–3.58), middle (ie, 45–59 years; 2.95, 2.75–3.17), or late life (ie, 60 years; 2.31, 2.25–2.38) compared with people without depression.<sup>120</sup> A Swedish nationwide study of 41727 twins, with an 18-year follow-up, reported that dementia risk was increased for midlife (odds ratio [OR] 1.46, 95% CI 1.09–1.95), late-life (2.16, 1.82–2.56), and lifelong (2.65, 1.17–5.98) depression.<sup>121</sup>

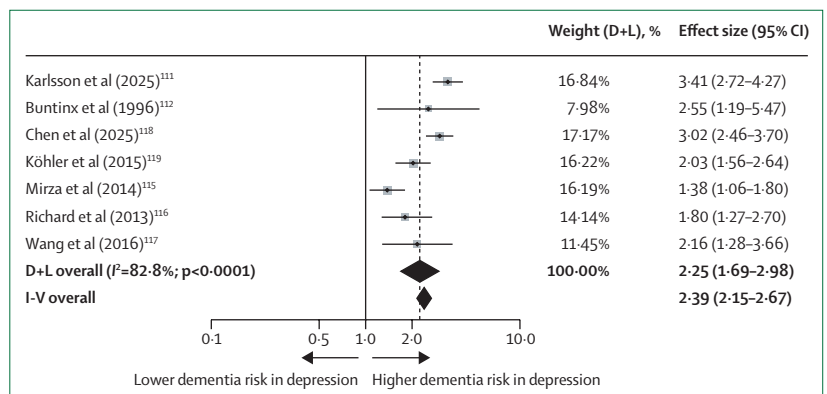
Overall, these studies suggest that depression increases the risk of dementia at all adult ages, although in late life, some of the association is caused by preclinical dementia. We are therefore classifying depression as a midlife risk factor because there is clear midlife risk.

There was no difference between identical or non-identical twins in the Swedish study described, leading to the conclusion that the risk of dementia was not accounted for by genetic risk or early life environment; however, the risk of midlife depression and future dementia was lower in those with 8 or more years of education than in those with less than 8 years of education.<sup>121</sup> Mechanisms linking depression to dementia risk are unknown, although depression might lead to reduced self-care and social contact. Another hypothesised mechanism by which depression might increase dementia could be oversecretion of cortisol leading to hippocampal atrophy or inflammatory response.<sup>122</sup>

A UK Biobank study of interventions for depression included 354 313 participants aged 50–70 years without dementia at baseline, followed up for a median of 11.9 years (IQR 11.2–12.6),<sup>123</sup> and reported that people with a diagnosis of depression (n=46 280) had a higher risk of developing dementia (HR 1.51, 95% CI 1.38–1.63). People who were treated for depression by pharmacotherapy (n=14 695; 0.77, 0.65–0.91), psychotherapy (n=2151; 0.74, 0.58–0.94), or combination therapy (n=5281; 0.62, 0.53–0.73) were less likely to develop dementia than the



**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 from Yeo et al.<sup>103</sup>



**Figure 6: Meta-analysis of risk of developing dementia 10–14 years after depression diagnosis compared with those who were not depressed**  
Weights are from random-effects analysis. D+L=DerSimonian and Laird method for meta-analysis. I-V=inverse-variance method for meta-analysis.

untreated group (overall treatment HR 0.69, 0.62–0.77). The untreated group who remitted did not have a higher risk of dementia than the group without depression (0.84, 0.56–1.24). This study provided data for a larger group and for a longer period than previous evidence<sup>124,125</sup> but is still open to the bias of observational studies. However, it is unlikely there will be such long-term RCTs. The findings on the effect of medication and therapy for depression in reducing the risk of dementia suggest the importance of treating depression both for quality of life and because it might reduce the risk of dementia in the future.

**TBI**

We performed a meta-analysis of the risk of all-cause dementia following TBI in the 2020 *Lancet* Commission (RR 1.84, 1.54–2.20).<sup>2</sup> Subsequently, two meta-analyses reported similar estimates. The first analysis, including 21 studies totalling 8 684 485 people, reported an OR of 1.81 (95% CI 1.53–2.14) for TBI and the risk of dementia.<sup>126</sup> A meta-analysis of 32 studies (n=7 634 844), which included 17 studies from the other meta-analysis, reported an RR for dementia after TBI of 1.66 (95% CI

1.42–1.93).<sup>127</sup> Both of these studies identified that younger age at TBI (ie, aged <65 years) and male sex were associated with higher risk of dementia.

In LMICs, TBI occurs most commonly from road traffic accidents, but in HICs, TBI is most commonly due to falls or violence, with alcohol being a common contributory factor.<sup>128</sup> TBI risk is therefore linked to other health behaviours that are risk factors for dementia. A large, national, Finnish, prospective, longitudinal study (n=32 385) reported that the association between major TBI (ie, >3 days' hospitalisation) and dementia was attenuated (from HR 1.51 [95% CI 1.03–2.22] to 1.30 [0.86–1.97]) after adjusting for other risk factors for dementia, including education, smoking status, alcohol consumption, physical activity, and hypertension.<sup>129</sup>

Concussion and mild TBI (mTBI) are terms that are often used interchangeably.<sup>130</sup> There are few studies of mTBI and dementia risk, and methodological issues include inconsistent definitions. A previous cohort study using a national patient register reported an increased risk of dementia even with a single mTBI (OR 1.63, 95% CI 1.57–1.70).<sup>131</sup> Since the 2020 *Lancet* Commission, a cohort study reported no increased risk of dementia from mTBI over 15 years,<sup>129</sup> but a systematic review and meta-analysis of five studies, including 3 149 740 people who reported a history of mTBI fulfilling WHO criteria, identified an increased risk of Alzheimer's disease (RR 1.18, 95% CI 1.11–1.25), and a sensitivity analysis including the few studies in which mTBI preceded Alzheimer's disease by more than 10 years (n=2307) also identified an increased risk of dementia following TBI, although with wider confidence intervals (2.02, 0.66–6.21).<sup>132</sup>

Some sports (eg, rugby, American football, and ice hockey) involve frequent head contact and whiplash events and are associated with greater risk of repeated TBI than sports in which low-frequency individual TBI might occur in accidents or as part of the sport (eg, cycling, horse riding, and boxing). There is increasing concern that professional and amateur soccer and rugby players live with and die more from neurodegenerative illnesses than do the general population, which might be related to occasional severe TBI or frequent mTBI from physical contact with others or heading a football.<sup>133</sup> A meta-analysis that ranked concussion risk in contact sports identified 83 studies of reported concussion rates, mainly from the USA (n=66), with five studies each from Canada and the UK.<sup>134</sup> Rugby had the highest concussion rate (28.3 concussions per 10 000 games), followed by American Football (8.7 concussions per 10 000 games), ice hockey (7.9 concussions per 10 000 games), and wrestling (5.0 concussions per 10 000 games). College sport had slightly higher concussion rates than high school sport (3.8 concussions vs 3.7 concussions per 10 000 games).

Evidence suggests that people who play professional soccer for longer, in positions where they head the ball more often, are more likely to incur head injuries and are

at higher risk of dementia. One small study of 60 players reported that cognitive ability in former professional soccer players was inversely associated with estimated heading frequency.<sup>135</sup> A large study in Scotland, UK, reported that 386 (5.0%) of 7676 former soccer players compared with 366 (1.6%) of 23 028 individuals matched on age, sex, and area socioeconomic status developed a neurodegenerative disease (HR 3.66, 95% CI 2.88–4.65).<sup>136</sup> This increased risk was highest for defenders who had a high frequency of headers or who had played professionally for more than 15 years and lowest for goalkeepers. A study of French professional soccer players reported that all-cause mortality was lower than that of the national population (standardised mortality rate 0.69, 95% CI 0.64–0.75) but soccer players who died had a higher rate of deaths with dementia than non-players (3.38, 2.49–4.50).<sup>137,138</sup> A cohort study of 6007 male soccer players (excluding goalkeepers) from Sweden's top division and control participants matched for sex, area, and region reported that soccer players had a higher risk of all-cause dementia (HR 1.62, 95% CI 1.47–1.78) but not motor neuron disease or Parkinson's disease.<sup>139</sup> Risk of all-cause mortality was lower among soccer players than controls (0.95, 0.91–0.99). 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%) of 412 former rugby players and 67 (5%) of 1236 participants in the control group were diagnosed with neurodegenerative disease (2.67, 1.67–4.27).<sup>137</sup>

TBI can cause or exacerbate dementia through direct trauma.<sup>140</sup> Plausible pathological mechanisms for long-term neurodegeneration following TBI include axonal injury promoting early generation of proteinopathies (eg, hyperphosphorylated tau and amyloid  $\beta$ ), microglial activation, and cortical atrophy.<sup>141,142</sup> We identified three cohort studies that assessed brain pathology in people 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 reported an increase in Lewy body pathology and hippocampal sclerosis but not plaques or tangles in people who had TBI with loss of consciousness.<sup>143</sup> An Alzheimer's Disease Neuroimaging Initiative study of 241 participants, 41 of whom reported previous TBI, identified that a history of TBI was associated with increased amyloid  $\beta$  deposition, cortical thinning, and onset of cognitive impairment 3–4 years earlier than for those without previous TBI.<sup>144</sup> By contrast, a UK population-based study that included 80 participants who had TBI with loss of consciousness before age 60 years found no difference in amyloid  $\beta$  deposition, hippocampal volume, or cortical thickness but lower cognition and smaller brain volume compared with their 395 counterparts without head injury by about age 70 years.<sup>145</sup> Ongoing work with neuroimaging and fluid biomarkers of neurodegeneration might help to identify



both overlapping and distinct patterns of neuropathology in people with different subtypes of post-traumatic dementia or other neurodegenerative disorders, including chronic traumatic encephalopathy.<sup>142,146</sup>

Overall, the evidence suggests that TBI increases dementia risk, possibly leading to earlier onset of dementia by 2–3 years than in people without TBI,<sup>147</sup> which might 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 to limit injury, should now be an individual and public health priority. Some sports bodies and government bodies have begun to implement these policies.

### Smoking

We previously reported that smoking in late life is associated with an increased risk of dementia (HR 1.6, 1.2–2.2).<sup>2</sup> New evidence now shows that midlife smoking appears to be a stronger risk factor for dementia than is smoking in late life, possibly because of improvements in treating cardiovascular disease and smoking-related cancers, leading to an increased chance of smokers living long enough to develop dementia. A large meta-analysis by Zhong and colleagues reported that midlife smoking increased dementia risk (RR 1.30, 95% CI 1.18–1.45; 37 studies) but there was no increased risk in former smokers.<sup>148</sup> The Framingham Heart Study (n=4015; 21-year follow-up) identified the strongest risk for dementia in people who started smoking in early adult life (ie, aged 33–44 years; HR 1.42, 95% CI 0.05–3.60).<sup>149</sup> Other long-term cohort studies, such as the ARIC study (25-year follow-up; n=15744; 1.41, 1.23–1.61)<sup>150</sup> and the Whitehall II study (32-year follow-up; n=9951; 1.36, 1.10–1.68),<sup>151</sup> have reported similar excess risks of dementia in midlife (ie, mean age 44.9 years [SD 6.0]) current smokers. A UK Biobank study of 497401 adults reported an HR for dementia of 1.7 (1.2–2.5) for smokers younger than 50 years at baseline.<sup>152</sup> In the Danish general population, a pooled analysis of two prospective cohorts, including a total of 61664 individuals, reported that risk of dementia for midlife smokers was increased for men (3.2, 1.4–7.4) and women (1.7, 1.1–2.8) compared with non-smokers.<sup>153</sup>

A 32-year follow-up of the Whitehall II cohort, controlling for socioeconomic status, identified that current smokers (HR 1.36, 95% CI 1.10–1.68) but not ex-smokers (0.95, 0.79–1.14) have an increased risk of dementia compared with people who have never smoked and that socioeconomic inequalities in dementia risk were partly mediated by smoking.<sup>151</sup> The study by Zhong and colleagues also showed no increased risk in former smokers. Similarly, a Korean nationwide study of 789532 participants who were

assessed for smoking status over 2 years reported that ex-smokers had a lower risk of all cause dementia (0.92, 0.87–0.97) than continuing smokers, which was more pronounced among adults who smoked before age 65 years (0.8, 0.7–0.9) than those who smoked at age 65 years or older (1.0, 0.9–1.0).<sup>154</sup> Another Korean population study examining dementia risk in people with atrial fibrillation also reported a reduced risk of dementia in people who had quit smoking (0.83, 0.72–0.95) compared with current smokers.<sup>155</sup> These studies suggest that smoking cessation reduces dementia risk compared with continued smoking. Smoking should now be considered a midlife risk factor (rather than a late-life factor, as in the 2020 *Lancet* Commission),<sup>2</sup> and the beneficial 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 stroke is part of the diagnostic criteria), and vascular dementia happens more often in people who smoke or who have diabetes and hypertension.<sup>63</sup> Stroke and dementia share the risk factors of less education, infrequent exercise, hypertension, heart disease, and social isolation,<sup>156</sup> but some people with these risk factors will not develop dementia despite neuropathology, sometimes because they die at a young age, before dementia develops.<sup>23</sup>

Several studies have examined the effect of a combination of cardiovascular risk factors on dementia risk. The Life's Simple 7 group defined ideal cardiovascular health factors (ie, BMI, diet, smoking, physical activity, blood pressure, cholesterol, and glucose concentrations), and higher scores on this index are associated with lower dementia risk.<sup>63,157</sup> Similarly, in China, a 10-year longitudinal study of 29072 people with mean age of 72 years at follow-up (SD 6.6) reported that slow memory decline was associated with being in the healthy group, which meant having at least four of six factors: healthy diet (ie, eating at least seven of 12 eligible food items), physical exercise (ie,  $\geq 150$  min of moderate intensity or  $\geq 75$  min of vigorous intensity exercise weekly), active social contact (ie,  $\geq 2$  social contacts per week, including online), active cognitive activity (ie, engaging in  $\geq 2$  cognitive activities per week), never or previously smoking (ie, quit smoking  $\geq 3$  years ago), and never drinking alcohol (ie, drinking less than a small glass of wine daily).<sup>158</sup> This association applied to both *APOE*  $\epsilon 4$  carriers and non-carriers.

### LDL cholesterol

At the time of the previous *Lancet* Commissions on dementia, the evidence available on whether a high concentration of LDL cholesterol was a possible dementia risk factor was inconclusive.<sup>2</sup> Meta-analytic evidence identified inconsistent evidence from HICs that high



LDL cholesterol in midlife, but not in late life, might be a risk factor for cognitive decline, all-cause dementia, and Alzheimer's disease.<sup>159,160</sup>

Since then, a meta-analysis of three cohort studies with a total of 1138488 participants, all from the UK, looking at LDL cholesterol in adults younger than 65 years followed up for more than 12 months reported that each 1 mmol/L increase in LDL cholesterol was associated with an 8% increase in incidence of all-cause dementia (effect size 1.08, 95% CI 1.03–1.14;  $I^2=0.3\%$ ).<sup>161</sup> A study of 1189090 participants reported that high LDL cholesterol (ie, >3 mmol/L) was associated with an increased risk of dementia (HR 1.33, 95% CI 1.26–1.41).<sup>45</sup> In a large cohort from the UK Clinical Practice Research Datalink (n=1853954) who were followed up for a median of 7.4 years (IQR 4.6–10.4), higher baseline LDL cholesterol was similarly associated with increased risk of all-cause dementia (adjusted rate ratio 1.05, 95% CI 1.03–1.06 per SD increase in LDL cholesterol [ie, 1.01 mmol/L or 39 mg/dL increase]).<sup>162</sup> This risk was stronger in people younger than 65 years at baseline for dementia diagnosed within 10 years (1.10, 1.04–1.15) and more than 10 years after baseline (1.17, 1.08–1.27) than for people who were older than 65 years at baseline. In a Danish cohort study of 94184 people followed up from a mean age of 58 years (SD 13.0), people who did not adhere to dietary guidelines (ie, eat at least three weekly servings of all of fruit, vegetables, and fish; rarely drink sugar-sweetened drinks; rarely eat prepared meat like sausages or have takeaways) were more likely to have high LDL cholesterol.<sup>163</sup> After a median follow-up of 9 years (range <1–15), people with low adherence to these guidelines were more likely to develop dementia types other than Alzheimer's disease than were people with high adherence (HR 1.54, 95% CI 1.18–2.00), but were not more likely to develop Alzheimer's disease, although subtyping of dementia might not have been accurate. People who took lipid-lowering drugs did not have an increased risk of dementia. A US study of 4392 people reported that increased HDL cholesterol protected against the development of dementia.<sup>164</sup>

Further evidence of causality comes from a mendelian randomisation meta-analysis that included 27 studies, including 3136 people with dementia and 3103 healthy controls, which reported that high total cholesterol and low HDL cholesterol were risk factors for dementia.<sup>165</sup> By contrast, an individual participant meta-analysis of more than 21000 people (mean baseline age 76 years) identified no association between total cholesterol, LDL cholesterol, or HDL cholesterol and cognitive decline. This result did not change when the analysis was stratified by statin use or APOE  $\epsilon 4$  status.<sup>166</sup>

Excess brain cholesterol is associated with increased stroke risk and deposition of brain amyloid  $\beta$  and tau, suggesting a potential mechanism for the link between LDL cholesterol and dementia.<sup>161</sup> HDL reduces excessive cholesterol and is inversely correlated with brain amyloid  $\beta$  concentration.<sup>167</sup>

Individual counselling about diet and exercise has a small effect in reducing LDL cholesterol.<sup>168</sup> Statins have become a focus of research in the field of Alzheimer's disease and have potential benefit due to their anti-inflammatory and antioxidant properties as well as reducing cholesterol.<sup>169</sup> A meta-analysis of 36 cohort studies identified that statin use was associated with a reduced risk of all-cause dementia (OR 0.80, 95% CI 0.75–0.86;  $I^2=97.5\%$ ) and Alzheimer's disease (0.68, 0.56–0.81;  $I^2=94.5\%$ ) compared with untreated high cholesterol, with no difference between men and women.<sup>170</sup> A Cochrane review of RCTs of statins given in late life found no effect on either dementia risk (one study) or cognitive outcomes (two studies).<sup>171</sup> Repeat observational data can be used to emulate a target trial of statin use. By use of data from 6373 participants aged 55–80 years, an emulated trial identified that sustained statin use, but not statin initiation alone, was associated with reduced 10-year risk of dementia or death.<sup>172</sup>

Overall, high-quality, consistent, biologically plausible evidence exists that high LDL cholesterol in midlife is a risk factor for dementia. The 2019 WHO guidelines suggested that management of dyslipidaemia in midlife could be offered to reduce the risk of cognitive decline and dementia but that the quality of evidence was low.<sup>124</sup> Although long-term, high-quality RCTs of statins to prevent dementia do not exist, these studies would be unethical and impractical to run. Meta-analyses of observational studies are heterogenous but show benefit of statins on dementia risk, possibly because the benefit depends on age of initiation.

### 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.<sup>2</sup> Physical activity changes over a person's lifetime, decreasing when someone becomes ill; varies across cultures, socioeconomic status, and between sexes; and can occur at different levels of intensity, making it complex to study. Since the 2020 *Lancet* Commission, a systematic review and meta-analysis of 58 studies (n=257983) exploring the link between physical activity and dementia identified that physical activity was associated with a decreased risk of all-cause dementia (RR 0.80, 95% CI 0.77–0.84) and Alzheimer's disease (0.86, 0.80–0.93) in short and long follow-ups of at least 20 years, regardless of baseline age.<sup>173</sup> There was decreased risk of vascular dementia in shorter follow-ups (0.79, 0.66–0.95) of a mean of 10.9 years (SD 8.5). A range of intensities of exercise were included in the meta-analysis, and reduction in risk was greatest when moving from extreme sedentariness to some physical activity. A cohort study (n=1417) that recorded physical activity five times between ages 36 years and 69 years reported that being physically active at all ages was associated with better cognition at age 69 years than no physical activity, with

the strongest association for sustained physical activity.<sup>174</sup> A prospective study of 29 826 people who were followed up for a median of 24·5 years (IQR 24·1–25·0) and whose weekly physical activity was assessed twice, 10 years apart, reported that people who maintained an individually estimated optimal level of physical activity had a reduced risk of dementia compared with persistently inactive individuals (HR 0·75, 95% CI 0·58–0·97), as did those who increased their physical activity to an optimal level (0·83, 0·72–0·96).<sup>175</sup> A longitudinal study of 1718 women over a median of 11·9 years (range 0·6–13·5) reported that higher physical activity level was associated with less cognitive decline, but not when the estimate was adjusted for diabetes and hypertension.<sup>176</sup>

In an RCT, 945 participants, with a mean age of 78 years (SD 2) and 450 (48%) women and 495 (52%) men, were randomly assigned (2:1:1) to a 5-year control group, moderate-intensity continuous training twice a week, or high-intensity interval training twice a week.<sup>177</sup> At 5 years, 474 (96%) of 494 participants in the control group adhered to national guidance for physical activity, 176 (75%) participants adhered to the moderate-intensity interval training intervention, and 164 (76%) adhered to the high-intensity interval training intervention. There was no significant difference in cognition ( $\beta$  0·26, 95% CI –0·17 to 0·69) or odds of MCI (OR 0·86, 95% CI 0·66 to 1·13) between the groups. Men in the combined moderate or high intensity exercise group had a decreased risk of MCI (0·68, 0·47 to 0·99) and slightly higher cognitive scores than male participants in the control group. Participants who decreased their peak oxygen uptake, rather than maintained or increased their uptake, had increased odds of MCI (1·35, 0·98 to 1·87) compared with those with stable oxygen uptake levels, although this result 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.<sup>178</sup> Outcomes might depend on not only the duration but also the type and intensity of physical activity. At the policy level, urban design interventions and provision of high-quality green spaces are recommended by WHO to reduce physical inactivity across the population.<sup>179</sup>

Exercise at any age appears to be 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.<sup>180</sup> People who engage in moderate-to-vigorous exercise on more days have relatively larger brain volumes than those who do less or no exercise.<sup>181,182</sup> Evidence from mouse models also suggests that irisin, a myokine released during exercise, might be neuroprotective.<sup>183</sup>

## Diabetes

We previously discussed type 2 diabetes as a risk factor in late life for development of 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 decrease in age of type 2 diabetes onset (HR 1·24, 95% CI 1·06–1·46), until aged over 70 years at onset.<sup>25</sup> Diabetes should be classified as a midlife risk for dementia. It is unclear whether diabetes is not a risk factor for dementia at older ages or whether the absence of evidence showing significant risk is because of short follow-ups and few studies. WHO concludes that diabetes in late life might have a detrimental effect on brain health and dementia risk.<sup>124</sup> Long illness duration and poorly controlled diabetes increase the risk of dementia.

Our understanding of the mechanism by which diabetes increases the risk of dementia is incomplete. Long-term microvascular and macrovascular complications are well established in diabetes, and the causal mechanism likely incorporates a strong vascular component, including stroke risk.<sup>184</sup> Peripheral insulin resistance leads to decreased insulin signalling in the CNS, followed by alteration in brain metabolism. Insulin resistance is a common molecular mechanism linking diabetes and Alzheimer's disease: it leads to increased amyloid  $\beta$  toxicity, tau hyperphosphorylation, oxidative stress, and neuroinflammation.<sup>185</sup> Increased concentrations of systemic inflammatory markers (eg, CRP) were associated with the diabetes-associated increased dementia risk.<sup>25</sup>

It is unclear whether effective treatment of diabetes ameliorates dementia risk per se, particularly as taking large quantities of oral medication and insulin is related to increased severity of diabetes. Strict, intensive treatment compared with standard diabetic control, however, does not decrease the risk of dementia.<sup>2</sup> Some evidence suggests that people taking some types of anti-diabetic medication might be less at risk of dementia. A systematic review, meta-analysis, and network analysis of 27 studies (1 590 757 participants), which did not report heterogeneity, identified that cohort studies indicated that SGLT2 inhibitors (OR 0·41, 95% CI 0·22–0·76), GLP-1 receptor agonists (0·34, 0·14–0·85), and DPP-4 inhibitors (0·78, 0·61–0·99) were associated with dementia risk reduction, whereas sulfonylureas were associated with increased risk (1·43, 1·11–1·82).<sup>186</sup> Metformin was not associated with a decreased or increased risk (0·71, 0·46–1·08). A study in UK primary care reported a significantly lower risk of dementia in 114 628 people with diabetes initiating metformin than in 95 609 people who were not on medication for their diabetes (HR 0·88, 95% CI 0·84–0·92).<sup>187</sup> A meta-analysis of three RCTs and a cohort study of GLP-1 receptor agonists in people with type 2 diabetes identified a lower dementia rate in people who were randomly assigned to the drug than in those on placebo (15 820 participants; HR 0·47, 95% CI 0·25–0·86) and in people on GLP-1 receptor agonists in the nationwide Danish cohort

(120054 individuals; 0.89, 0.86–0.93).<sup>188</sup> Another meta-analysis of observational studies of 819 511 people with type 2 diabetes and a mean follow-up of 4.5 years (range 1.3–7.2) reported similar findings, with less subsequent dementia in users of SGLT2 inhibitors (three studies; RR 0.62, 95% CI 0.39–0.97;  $I^2=82.5\%$ ), GLP-1 receptor agonists (four studies; 0.72, 0.54–0.97;  $I^2=91.3\%$ ), and DPP-4 inhibitors (seven studies; 0.84, 0.74–0.94;  $I^2=88.6\%$ ) than in people not using these medications, but the analysis reported high heterogeneity.<sup>189</sup> People with diabetes might not be taking medication because their diabetes is well controlled without medication or because it is not well treated, which might account for the heterogeneity between studies. Evidence from RCTs also exists for the protective effect of GLP-1 receptor agonists.<sup>189</sup> In a Taiwanese population of 31 384 propensity-matched pairs (including matching for chronic kidney disease with diabetes) who were followed up for 5 years, people who were adherent to metformin had a 72% lower risk of developing dementia than people who did not adhere.<sup>190</sup> Novel study designs, such as mendelian randomisation or target trial emulation, might help to address potential confounding by indication, whereby high blood sugar leads to particular prescriptions or harms people who do not take medication.<sup>191</sup>

Weight loss might also help to control diabetes and therefore might also affect cognition. The Look AHEAD study recruited 3751 people aged 45–76 years with type 2 diabetes and overweight or obesity and randomly assigned them to a 10-year intervention of increased exercise and decreased calorie intake or diabetes support and education.<sup>192</sup> This RCT was terminated because the interim analysis showed that the intervention 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 HbA<sub>1c</sub> concentration and cognition over both groups. Cognitive function was not related to group allocation or to weight loss. Overall improved control of diabetes, but not very low blood sugar or weight loss without improved diabetic control, might attenuate the risk of dementia and be a way of decreasing dementia risk.

### Hypertension and its trajectory

We previously discussed the evidence that midlife hypertension increases the risk for all-cause dementia, Alzheimer's disease, and vascular dementia but that, nearer the time of dementia, people's blood pressure tends to decrease.<sup>2</sup> Blood pressure increases across the life course in high-income societies, with evidence of increases being associated with socioeconomic circumstance. A systematic review of longitudinal studies estimated that blood pressure first increases then starts to decrease 5 years before dementia diagnosis, and weight decreases around 10 years before diagnosis.<sup>193</sup> An individual participant data meta-analysis identified that

high blood pressure might continue to be a risk in older age,<sup>194</sup> but some people who develop dementia have lower blood pressure than people without dementia, and therefore the evidence is mixed. These meta-analyses did not cover blood pressure variability, but a cohort study (n=2234; aged ≥65 years) measured blood pressure variability with assessments over 3, 6, 9, and 12 years and reported that each unit increase in systolic variability was associated with increased risk of dementia, with HRs ranging from 1.02 (95% CI 1.01–1.04) to 1.10 (1.05–1.16).<sup>195</sup>

Black Americans have higher recorded blood pressures than other US groups, which might be a contributor to a higher risk of dementia than in White Americans. This risk was considered in an individual participant data meta-analysis of five cohort studies of a total of 19 378 people with a mean age of 59.8 years (SD 10.4), in which Black Americans had significantly faster global cognitive decline than White Americans, but no significant difference was identified after adjustment for cumulative mean systolic blood pressure.<sup>196</sup>

There are three meta-analyses of RCTs for antihypertensive medication. Two meta-analyses identified that antihypertensive medication was protective against cognitive impairment and dementia,<sup>12,197</sup> and one with short (ie, range 1–5 years) follow-up did not identify a protective effect.<sup>198</sup> The meta-analysis of 12 RCTs (n=96 158), with a mean follow-up of 4.1 years (range 2.2–5.7), identified a lower risk of dementia or cognitive impairment in people taking antihypertensive medications than in controls, consisting of people taking placebo, taking alternative antihypertensive agents, or whose target blood pressure was higher than that of the intervention group (OR 0.93, 95% CI 0.88–0.98), and of cognitive impairment alone (0.93, 0.88–0.99).<sup>197</sup> The second meta-analysis used individual participant data from five RCTs (n=28 008) with placebo controls, three of which were included in the first meta-analysis,<sup>197</sup> and identified a lower risk of dementia in the treatment group than in the placebo control group (0.87, 0.75–0.99).<sup>12</sup> A Cochrane review, with three studies overlapping with the previous meta-analysis,<sup>12</sup> included 12 RCTs (eight placebo-controlled trials; n=30 412) with interventions lasting at least 12 months. The review concluded that there was a modest benefit of antihypertensive medication on cognitive change measured with the Mini Mental State Examination (MMSE; five studies; mean difference 0.20, 95% CI 0.10–0.29), but duration was too short to show a difference in dementia incidence (four studies; OR 0.89, 95% CI 0.72–1.09).<sup>198</sup> An individual participant data meta-analysis of 17 studies including people in LMICs and HICs (mean age 72.5 years [SD 7.5], follow-up 4.3 years) identified that people with untreated hypertension had a higher risk of dementia than healthy controls (HR 1.42, 95% CI 1.15–1.76), but this risk was attenuated or lost with treatment (1.13, 0.99–1.28).<sup>194</sup> One meta-analysis of individual participant data cohorts comprising

31090 adults without dementia at baseline, with a follow-up of at least 5 years, found that people with hypertension who were taking any antihypertensive drug were at lower risk of dementia than those who were not taking antihypertensive drugs (HR 0.88, 95% CI 0.79–0.98), but did not identify any differences between classes of drugs.<sup>199</sup> Although there is a scarcity of direct comparisons of the effect of different antihypertensives, a network analysis and systematic review identified that treatments with angiotensin 2 receptor blockers and calcium channel blockers (CCBs) were associated with lower dementia risk than other antihypertensives.<sup>200</sup> Mendelian randomisation studies suggesting high blood pressure is protective<sup>201–204</sup> are inconsistent with RCT findings, and mendelian randomisation study findings are likely to be influenced by survival bias.<sup>12,197,205</sup>

### Obesity and weight

We previously discussed that obesity in midlife is a risk factor for dementia.<sup>2</sup> A further systematic review and meta-analysis examining the association between obesity and dementia included 14 studies with 77 890 participants and identified that midlife obesity was associated with subsequent all-cause dementia (RR 1.31, 95% CI 1.02–1.68).<sup>206</sup> 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 larger versus smaller waist circumference was associated with a greater risk of cognitive impairment and dementia (HR 1.10, 95% CI 1.05–1.15), and this risk was greater in people older than 65 years than other ages.<sup>207</sup> Obesity is more common in people who exercise infrequently and is associated with diabetes and hypertension, which also cause cardiovascular disease,<sup>208</sup> so this association could possibly be mediated by other risk factors for dementia. Nonetheless, most studies in these meta-analyses adjusted for health conditions, such as hypertension, stroke, blood lipid concentrations, and diabetes, as well as demographic characteristics, which should have minimised the effect of these intermediaries.

A meta-analysis of interventional studies for weight loss identified 13 longitudinal studies (n=551) and seven RCTs (n=468) of participants with overweight (ie, BMI 25.0–29.9 kg/m<sup>2</sup>) or obesity (ie, BMI ≥30.0 kg/m<sup>2</sup>). Intentional modest weight loss of even 2 kg among trial participants was associated with improvements in cognition at median follow-up of 6 months (range 8–48),<sup>209</sup> 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 people who had bariatric surgery.<sup>210</sup>

Additionally, stigma in people with high BMI is associated with increased cortisol concentrations, inflammation, and negative health consequences, which might in turn contribute to the association with dementia.<sup>211</sup> Further work is needed to understand

mechanisms by which adiposity contributes to dementia risk.

A systematic review of 19 prospective studies, in which data were pooled, also identified an increased risk of dementia in people who were underweight (ie, BMI <18.5; HR 1.26, 95% CI 1.20–1.31).<sup>212</sup> A meta-analysis of individual participant data from 1.3 million people across 39 prospective cohort studies found that obesity was a risk factor for dementia in cohorts where the baseline measurement was taken more than 15 years before dementia onset but appeared to be protective if the baseline measurement was taken less than 10 years before dementia onset.<sup>14</sup> The authors suggested that this result was due to reverse causation, because people often lose weight before they develop dementia. Being underweight is also potentially linked with malnutrition, although being underweight can occur for many reasons.

### Excessive alcohol consumption

In the 2020 Commission, we reported that drinking more than 21 UK units (ie, 12 US units, 168 g) of ethanol per week in midlife compared with lighter drinking (ie, <14 UK units) was associated with an increased risk of dementia (RR 1.18, 95% CI 1.06–1.31).<sup>2</sup> Similarly, a subsequent individual participant meta-analysis of 131 415 participants from France, the UK, Sweden, and Finland found that, after adjusting for confounders, heavier drinking (ie, >21 units per week) in midlife was associated with an increased risk of dementia compared with lighter drinking (ie, 1–21 units per week; HR 1.22, 95% CI 1.01–1.48).<sup>213</sup> In line with this finding, a review of 28 systematic reviews concluded that heavy alcohol use (as defined by the individual studies) was associated with an increased risk of all-cause dementia and reduced grey matter volume in imaging studies.<sup>214</sup> Alcohol-induced loss of consciousness increased dementia risk in people with either moderate or heavy consumption.<sup>213</sup>

Some cross-sectional studies of older adults have reported a similar dementia risk in heavy alcohol drinkers and non-drinkers, but some people who are counted as non-drinkers were previously heavy drinkers.<sup>215</sup> A Japanese prospective study followed up 42 870 participants for 14.9 years and reported that not drinking (HR 1.29, 95% CI 1.12–1.47) and drinking more than 450 g of alcohol per week from midlife (1.34, 1.12–1.60) were associated with increased risk of dementia compared with light drinking (ie, <75 g/week).<sup>216</sup> A meta-analysis of individual participant data from 244 780 older adults (mean age 71.8 years [SD 7.5]) across 15 prospective cohort studies reported that, during 151 636 person-years of follow-up, dementia risk was lower in occasional (0.78, 0.68–0.89), light-to-moderate (1.3–24.9 g/day; 0.78, 0.70–0.87), and moderate-to-heavy drinkers (25.0–44.9 g/day; 0.62, 0.51–0.77) than in non-drinkers but was not lower in heavy drinkers (>45 g/day) than in non-drinkers (0.81, 0.61–1.08).<sup>217</sup> Mendelian



randomisation also indicated a causal link between alcohol consumption and an earlier age of onset of Alzheimer's disease and suggested that any link between not drinking and Alzheimer's disease is due to survivor bias.<sup>218</sup> Observational studies usually find a J-shaped dose-response, such that not drinking is associated with increasing dementia risk compared with light drinking. This result is probably because many non-drinkers have previously had high alcohol consumption or other illnesses that prevent them from drinking, and studies that correct for previous high alcohol consumption have reported that there is no excess mortality in the non-drinking group.<sup>215,219</sup>

A study of a nationwide, South Korean cohort of 3933382 participants that serially assessed alcohol consumption over 3 years reported that sustained heavy drinkers (ie,  $\geq 30$  g/day or 3 units per day) had an increased risk of all-cause dementia (HR 1.08, 95% CI 1.03–1.12), and reducing drinking from heavy to moderate levels (ie, 15.0–29.9 g/day) reduced the risk of all cause dementia (0.92, 0.86–0.99) compared with sustained heavy drinking.<sup>220</sup> Sustained mild (ie,  $< 15$  g/day; 0.79, 0.77–0.81) or moderate alcohol consumption (0.83, 0.79–0.88) or initiating mild alcohol consumption (0.93, 0.90–0.96) were also associated with lower risk of all-cause dementia than sustained non-drinking; however, some non-drinkers might have been former heavy drinkers. Overall, reduction of excessive alcohol or sustained light drinking is associated with a lower dementia risk than is excessive alcohol. A lack of clear evidence exists that not drinking alcohol increases the risk of dementia. The observational evidence of excess risk for non-drinkers might be due to people who have previously drunk large amounts, abstained at the time when data were gathered (and been classified as non-drinkers), and then might return to drinking.

### Social isolation

We have previously discussed social isolation or infrequent social contact as a risk factor for dementia.<sup>2</sup> Since then, two systematic reviews reported that less frequent social contact was associated with higher risk of dementia. The first review, which included eight studies with a total of 15762 participants, reported higher dementia risk (RR 1.57, 95% CI 1.32–1.85) for people with less frequent social contact than for people with more frequent social contact, with social contact dichotomised as less or more frequent within individual studies and the amount of contact varying between different studies.<sup>221</sup> The second review (which included one study that was included in the previous review) reported a smaller increased risk (1.18, 1.08–1.30).<sup>222</sup> Duration of follow-up might partly explain the inconsistent results from these studies; for example, seven of the eight studies in one of the reviews had less than 4 years of follow-up, making reverse causation likely.<sup>221</sup> However, two subsequent studies of participants

from the UK Biobank, with mean follow-up of 8.8 years<sup>223</sup> and 12 years (SD 1.7),<sup>224</sup> found that dementia risk was higher in people who were more socially isolated (ie, defined as meeting at least two of three criteria of: living alone, seeing family or friends less than once a month, and participating in no weekly group activities) at baseline than less socially isolated individuals (ie, people who did not meet these criteria).

Loneliness is linked to, but differs from, social isolation because it is about people's feelings that their social contact is inadequate.<sup>225</sup> Loneliness was also associated with increased dementia risk in three reviews comprising three to eight studies (RR 1.26, 1.14–1.40; 1.38, 0.98–1.94; and 1.58, 1.19–2.09).<sup>221</sup> An increased dementia risk of 34–91% was reported in subsequent studies, in the USA over 10 years, in the Netherlands and Sweden over 14 years, and in Japan over 5 years.<sup>226–230</sup> Some, but not all, of these studies found that the association persisted after adjustment for potential confounders, including infrequent social contact (figure 7).

Participation in social activities is also linked but is distinct from social isolation and has been associated with decreased dementia risk. Two studies with serial social activity measurement reported that declining participation in social activities was associated with higher dementia risk in the short term, but not with a long-term follow-up.<sup>235,236</sup> This finding suggests that the link with participation might be at least partly due to reverse causation, whereby decline occurs during the preclinical phase of dementia.<sup>224</sup>

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.<sup>225</sup> Risk was reported to be consistent across individuals with different polygenic risk scores for Alzheimer's disease,<sup>223</sup> and social isolation was linked to lower grey matter volume in the temporal, frontal, and other brain regions than for people who were not socially isolated.<sup>225</sup>

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 3-month intervention with a primary outcome of cognition recruited 235 people aged 75 years or older who were lonely and showed a small significant improvement in performance on the Alzheimer's Disease Assessment Scale-Cognitive Subscale (mean difference in change of  $-2.6$  points per 100 points),<sup>237</sup> but studies from the USA<sup>238</sup> and China<sup>239</sup> did not show that facilitator-led group activities were beneficial. Studies of multidomain interventions that included group components suggested small cognitive benefits (Cohen's  $d$  0.13;<sup>240</sup> mean MMSE difference of 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



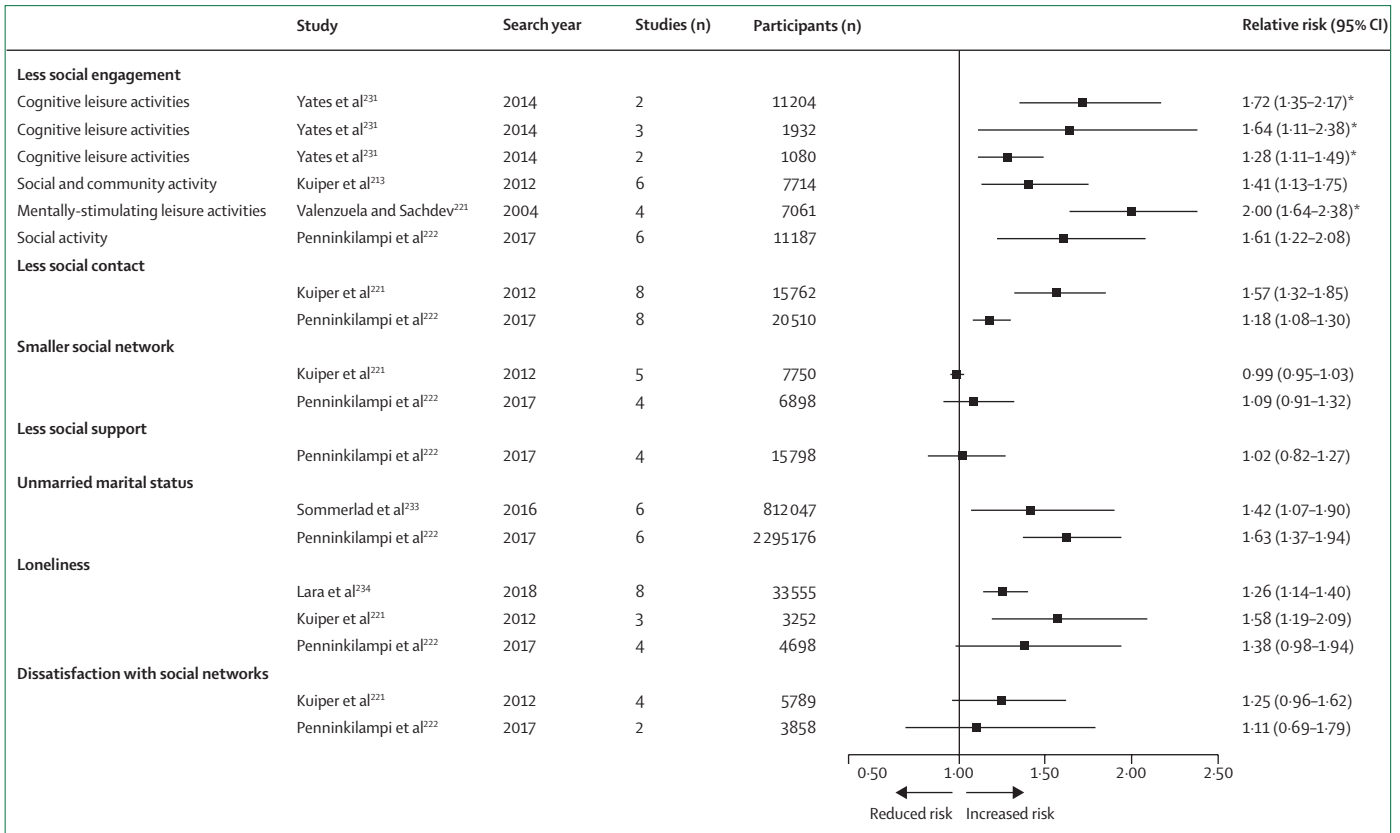


Figure 7: Different aspects of social participation and risk of dementia

Adapted from Sommerlad et al,<sup>235</sup> by permission of Springer Nature. \*Inverted from the published paper for consistency.

numbers (between-group difference of 6.2 points on the Repeatable Battery for the Assessment of Neuropsychological Status score;  $p=0.004$ ).<sup>241</sup> The contribution of the social component of multidomain intervention is unclear. Existing studies are too small and follow-up is too short to identify whether these social components of multidomain interventions 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 is a potential contributor to many long-term conditions across the life course. In the 2020 *Lancet* Commission, we reported agreement that particulate matter air pollution,  $PM_{2.5}$  (fine particles with a diameter  $\leq 2.5 \mu m$ ), and  $PM_{10}$  (particles with a diameter  $\leq 10 \mu m$ ) were risk factors for dementia and cognitive impairment, despite substantial heterogeneity across studies in durations of exposure, covariates in the analysis, outcomes, and risk of bias.<sup>2</sup> Continuing research interest 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 (eg, one review analysed only studies providing HRs, comprising 20 studies involving 91 391 296 people and reported an HR of 1.03 (95% CI 1.02–1.05) per  $1 \mu g/m^3$  increment in  $PM_{2.5}$ .<sup>242</sup> A conservative pooled estimate, obtained from a meta-analysis of five studies that used active case ascertainment of high-quality studies, reported an HR of 1.17 (0.96–1.43) per  $2 \mu g/m^3$  increment in  $PM_{2.5}$ , although CIs were wide and included the null.<sup>243</sup> Pooled HRs were reported from five studies each of nitrogen dioxide (1.02 [0.98–1.06] per  $10 \mu g/m^3$ ) and nitrogen oxides (1.05 [0.98–1.13] per  $10 \mu g/m^3$ ) and four studies of ozone (1.00 [0.98–1.05] per  $5 \mu g/m^3$ ), none of which were significant. Other pollutants have been assessed by too few studies for meta-analysis.<sup>243</sup>

In both HICs and LMICs, where air pollution is often high and increasing,  $PM_{2.5}$  and  $PM_{10}$  concentrations have been associated with dementia, MCI, and Alzheimer’s disease.<sup>244–247</sup> Ambient (ie, outdoor) and household (ie, indoor) air pollution might have distinct or synergistic risks. Studies in LMICs have shown that compared with clean fuel, solid fuel use, a proxy for household air pollution, is associated with higher dementia risk and accelerated cognitive decline among middle-aged and older adults (ie, aged  $>45$ –50 years).<sup>248,249</sup> Residential wood

and coal burning stoves are a source of indoor air pollution, and are reported to contribute 38% of the UK's PM<sub>2.5</sub> emissions and associated health risks.<sup>250</sup>

A US, 7-year, cohort study of more than 18 million participants reported that the PM<sub>2.5</sub> constituent with the strongest association with dementia risk was black carbon (HR 1.12 [95% CI 1.11–1.14] per 1 µg/m<sup>3</sup> increment).<sup>251</sup> The studies have mainly been in older adults at baseline, but this factor does not rule out an effect earlier in life.

A longitudinal study with a mean follow-up of 6 years in 2927 Swedish residents (1845 [63%] women and 1082 [37%] men who did not have dementia at baseline; baseline mean age of 74 years [SD 10.7]) considered PM<sub>2.5</sub> and nitrogen oxide yearly from 1990 to examine whether cardiovascular disease (ie, atrial fibrillation, ischaemic heart disease, heart failure, and stroke) modified or mediated the association between pollution and dementia and reported that it did.<sup>252</sup> The effect of air pollution is worst among people with these pre-existing conditions.

There is emerging evidence on the potential effects of improved air quality on cognitive decline and dementia incidence. A French cohort study with a 12-year follow-up reported that a 12.2 µg/m<sup>3</sup> reduction in median PM<sub>2.5</sub> between 1990 and 2000 was associated with a decreased risk of dementia (HR 0.85, 95% CI 0.76–0.95).<sup>253</sup> Larger air quality improvement (reduction in PM<sub>2.5</sub> and NO<sub>2</sub> over 10 years) was associated with lower dementia risk in older US women.<sup>254</sup> In a quasi-experimental study, China's Air Pollution Prevention and Control Action Plan mitigated cognitive decline in older adults, indicating that strict clean air policies might reduce the risk of cognitive ageing (measured by the MMSE) associated with air pollution.<sup>255</sup> A difference in China's central heating policies between the north and the south led to differences in air pollution concentrations, and higher air pollution (ie, PM<sub>10</sub>, NO<sub>2</sub>, SO<sub>2</sub>, CO, and O<sub>3</sub>) in the northern sample was associated with a 42.4% higher dementia risk than for the southern sample.<sup>256</sup>

As the evidence base grows, it would be valuable to standardise study design, reporting, and analyses to allow comparisons and achieve a granular understanding of the association between air pollution and dementia.<sup>257</sup> 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 increasing support for the implementation of WHO global air quality guidelines that ultimately aim for mean annual PM<sub>2.5</sub> concentrations of less than 5 µg/m<sup>3</sup>.<sup>258</sup> It is unclear whether any safe concentration of air pollution exists, as every 1 µg/m<sup>3</sup> increase in PM<sub>2.5</sub> is associated with increased dementia risk.<sup>259</sup> The lowest annual PM<sub>2.5</sub> concentration in global megacities was 6.7 µg/m<sup>3</sup> in Miami, FL, USA, and the top five most polluted cities had annual mean concentrations of PM<sub>2.5</sub> between 89 µg/m<sup>3</sup> and

149 µg/m<sup>3</sup>.<sup>259</sup> Little is known about risk in relation to dementia subtypes and whether individual particulate matter constituents are important (eg, black carbon, sulphates, nitrates, and ammonium).

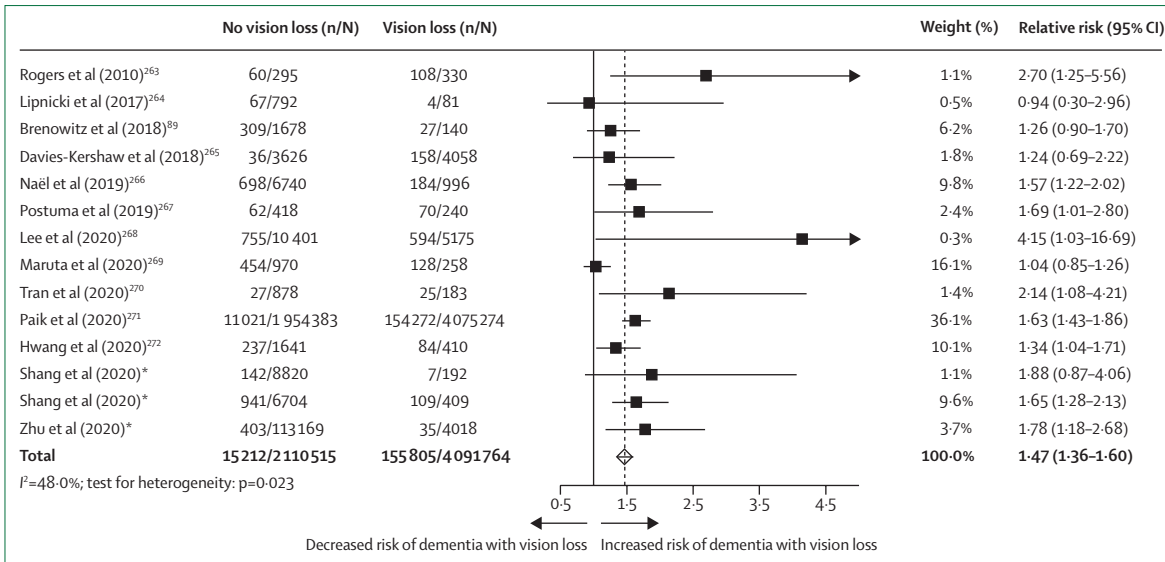
### Untreated visual loss

The global prevalence of avoidable vision loss and blindness, including common sight problems for which glasses are prescribed, in adults aged 50 years or older is estimated to be 12.6%, with prevalence being much higher in LMICs than in HICs.<sup>260</sup> This prevalence is distinct from cortical blindness seen in people with posterior cortical atrophy, which is usually due to Alzheimer's disease but often initially misdiagnosed as ocular disease.<sup>261</sup> Our Commission has not previously considered vision loss as a risk factor for dementia, but considerable new evidence has emerged. This evidence includes a meta-analysis of 14 prospective cohort studies, with follow-up of 3.7–14.5 years, including 6 204 827 older adults who were cognitively intact at baseline, of whom 171 888 developed dementia.<sup>262</sup> Vision loss was associated with a pooled RR for dementia of 1.47 (95% CI 1.36–1.60; figure 8). In an accompanying meta-analysis of 12 prospective cohort studies with 45 313 participants, 13 350 developed cognitive impairment, and the RR for vision loss and future cognitive impairment was 1.35 (1.28–1.41).

A second meta-analysis identified an increased risk of all-cause dementia (RR 1.38, 95% CI 1.19–1.59; n=37705) with visual loss.<sup>273</sup> When broken down into different eye conditions, an increased dementia risk was associated with cataracts (three studies; 6659 participants; 1312 cases; HR 1.17, 95% CI 1.00–1.38; I<sup>2</sup>=0.0%) and diabetic retinopathy (four studies; 43 658 participants; 7060 cases; 1.34, 1.11–1.61; I<sup>2</sup>=63.9%), but not with glaucoma (six studies; 175 357 participants; 44 144 cases; 0.97, 0.90–1.04; I<sup>2</sup>=51.5%) or age-related macular degeneration (three studies; 7 800 692 participants; >2559 cases, exact number could not be determined; 1.15, 0.88–1.50; I<sup>2</sup>=91.0%).

One US study of 16 690 participants investigated the inclusion of vision loss as an additional potentially modifiable risk factor in the life-course model based on the 2020 *Lancet* Commission and reported that the population attributable fraction (PAF) of vision impairment was 1.8% in that population.<sup>274</sup> As the prevalence of vision loss was higher in minority groups than in the White non-Hispanic group (9.9% of 3660 Black non-Hispanic people and 11.0% of 1880 Hispanic people vs 7.7% of 11 011 White non-Hispanic people), the risk and potential benefit might be greater in these populations.

A US study followed up 3038 older adults (ie, aged >65 years) with cataracts and healthy cognition at baseline for more than 20 years.<sup>275</sup> The analysis controlled for age, race, APOE genotype, education, smoking, and an extensive list of comorbidities and reported that people who had cataract extraction had significantly reduced dementia risk compared with those who did not have



**Figure 8: Meta-analysis of relative risk ratios of at least visual impairment compared with no visual impairment on incident all-cause dementia**  
 Adapted from Shang et al.<sup>262</sup> \*Unpublished studies; data published in Shang et al.<sup>262</sup>

cataract extraction (HR 0.71, 95% CI 0.62–0.83; 23 554 person-years of follow-up). Although a UK Biobank study of 300 823 people reported that people with cataracts had an increased risk of dementia (1.21, 1.01–1.46), there was no difference in dementia risk between those who had cataract surgery and healthy controls.<sup>276</sup>

The mechanisms behind these associations might be related to underlying illness, such as diabetes, which is a risk factor for dementia;<sup>2</sup> 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.<sup>277</sup> A Korean longitudinal health insurance database study of 6 029 657 people reported that dementia risk increased with severity of visual loss, supporting the hypothesis that vision loss in itself might be causal or that there is a dose–response effect to a shared causal factor.<sup>271</sup> A study of the links between diabetic retinopathy and dementia identified that the association between retinopathy and dementia remained after adjusting for diabetes severity measured by long-term glycaemia and renal function after more than 5 years of diabetic retinopathy.<sup>278</sup>

Increasing evidence supports an association between untreated vision loss and dementia risk and potential modification by treatment. We have therefore included visual loss as a risk factor in our analysis. Treatment for visual loss is effective and cost-effective for an estimated 90% of people; however, across the world, particularly in LMICs, visual loss is often not treated.<sup>260,274</sup> A clear opportunity for dementia prevention exists with treatment of visual loss.

### 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. These interventions vary in approach, from detailed individualised approaches supported by goal setting in person and those linked to digital platforms or mobile apps to approaches based on group activities. The existing evidence is preliminary because there are few completed studies but more than 40 trials are ongoing.<sup>279</sup> A 2021 Cochrane review identified nine RCTs of multidomain interventions for the prevention of dementia or cognitive decline, with 18 452 participants.<sup>280</sup> There was a high certainty of a small benefit of a multidomain intervention on overall cognition (composite Z score mean difference 0.03, 95% CI 0.01 to 0.06; three RCTs; n=4617; follow-up periods of 18–36 months),<sup>240,281,282</sup> particularly in people with the *APOE*  $\epsilon 4$  genotype (mean difference for carriers 0.14, 0.04 to 0.25; mean difference for non-carriers 0.04, –0.02 to 0.10; two RCTs; n=2043; follow-up 24–36 months), but the effect on dementia incidence had wide CIs (RR 0.94, 95% CI 0.76 to 1.18; two RCTs; n=7256; follow-up 6–13 years).<sup>283,284</sup> The pre-DIVA trial addressing cardiovascular risk factors (median follow-up of 10.3 years [IQR 7.0–11.0]; participants aged 70–78 years at baseline) showed similar results regarding dementia incidence.<sup>285</sup> More recently, the Age Well study recruited 1030 adults in Germany with higher than average scores on a dementia risk calculator incorporating age, sex, date of birth, height and weight, serum cholesterol, systolic and diastolic blood pressure, physical activity status, and years of education. Nurses instructed intervention participants to follow a multidomain intervention with two follow-up visits and five telephone calls over 2 years.<sup>286</sup> The intervention included nutrition and medication optimisation and physical, social, and cognitive activity with individual goals set with participants, but there was no effect on cognition over 24 months compared with controls who were given general health

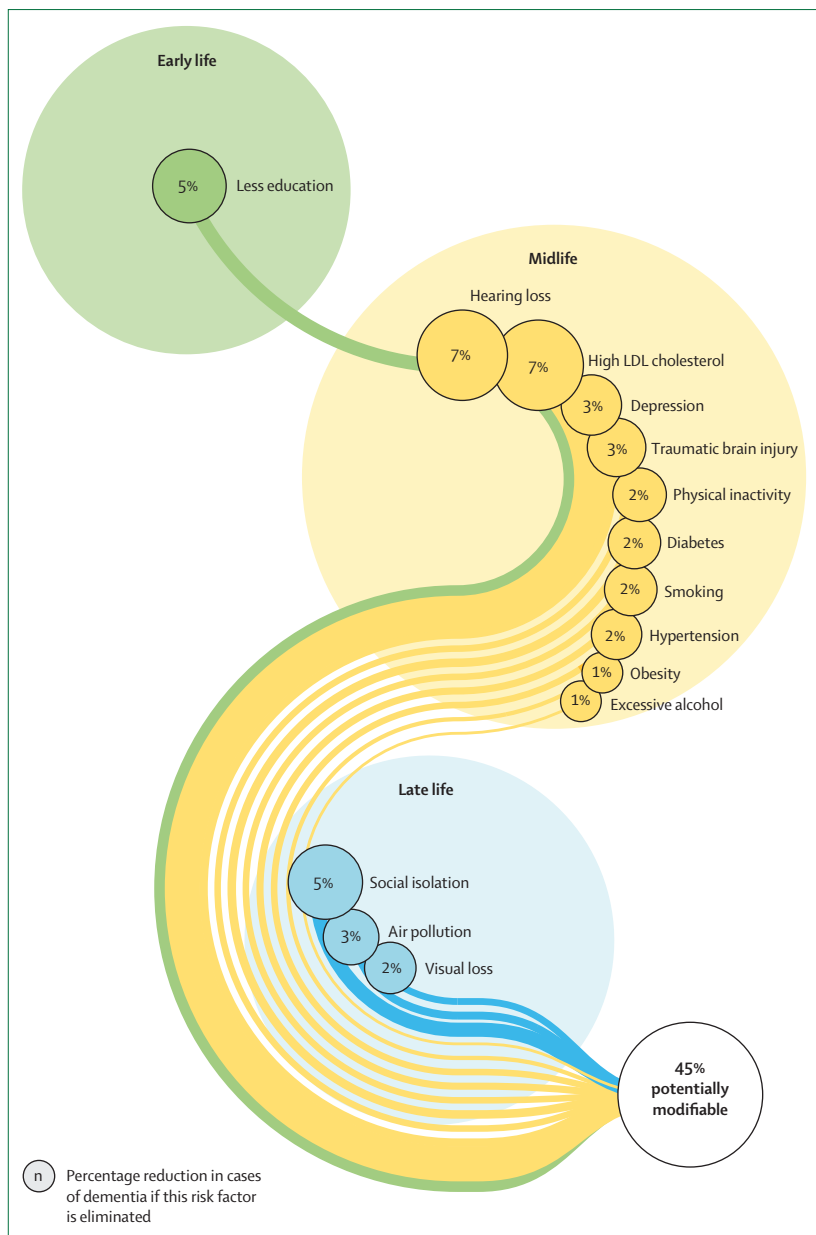


Figure 9: Population attributable fraction of potentially modifiable risk factors for dementia

advice. The investigators concluded that the intervention was not targeted enough or intense enough. The SMARRT trial assessed personalised risk reduction goals (172 adults aged 70–89 years) over 2 years via health coaching and nurse visitors. The intervention led to an improvement on the composite cognitive score (average treatment effect of standard deviation 0.14, 95% CI 0.03–0.25), a 74% improvement compared with the health education control, which included information on dementia risk reduction.<sup>287</sup>

A systematic review and meta-analysis of multidomain interventions for MCI found 28 RCTs of non-pharmacological multidomain interventions lasting up to

1 year in older adults with MCI (n=2711) and a moderate effect on global cognition (standardised mean difference 0.41, 95% CI 0.23–0.59;  $I^2=62%$ ), with improvements in executive function and memory compared with a single intervention active control.<sup>288</sup> The authors considered reasons for the heterogeneity, including that some studies were underpowered, but could not draw firm conclusions. One smaller systematic review of lifestyle RCTs in people with MCI found only three small RCTs (n=156) and reported a significant benefit for cognition with low heterogeneity.<sup>289</sup>

Studies have often recruited participants based on high cardiovascular risk.<sup>281</sup> A systematic review reported that the 10-year dementia risk for individuals eligible for four large-scale trials of multidomain (ie, two or more domains) interventions<sup>240,281,282,284,290</sup> was similar to that for those who were deemed ineligible; thus future trials might need to improve accuracy of identifying people at increased dementia risk.<sup>291</sup>

Some studies have used strategies to boost efficacy of and adherence to interventions, including intervention coaches to support behaviour change, digitally delivered personalised and scalable self-management interventions, and targeting people of lower socioeconomic status and people in LMICs.<sup>241,292–295</sup> These studies should clarify whether the cognitive benefits reported in existing trials can be replicated or increased and whether the multidomain interventions 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, whether they translate into a reduction in dementia incidence, or whether they can be implemented with similar adherence and effectiveness in low-income settings and populations at high risk.

A review of multidomain intervention trials for dementia prevention found that only 26 (62%) of 42 studies reported any ethnicity data and, in those, individuals from non-White, minority ethnic groups accounted for only a small proportion of participants.<sup>296</sup> White race was reported in 23 trials, Black or African American ethnicity was reported in 15 trials, Asian ethnicity was reported in six trials, American Indian or Alaska Native ethnicities were reported in three trials, and Hawaii Native or Pacific Islander ethnicities were reported in one trial. The FINGERS study<sup>240</sup> did not report ethnicity or dementia incidence but reported that the effects of the intervention on cognitive function were the same across socioeconomic categories (albeit within a fairly affluent cohort). All but 61 (2%) of 2700 participants in the HATICE study (ie, an internet-based, coach-supported, goal-setting approach) were White.<sup>282</sup> Results were not disaggregated by ethnicity, but the effect of the intervention was greatest in people with the lowest baseline educational attainment.

Overall, even interventions with modest effects could theoretically have substantial preventive effects at the population level, including for people who are less

affluent or in low-income settings. Interventions for individual and multiple risks would potentially be cost-effective but scalability is challenging,<sup>7,297–299</sup> and interventions might need to be repeated at intervals to achieve sustained benefits.

**Total PAF calculation**

**PAF calculation**

We incorporated the two new risk factors—ie, high LDL cholesterol and untreated vision loss—and the 12 factors in our previous model into our life-course model of dementia. We used the largest, most recent worldwide meta-analyses for the prevalence and RR of risk factors or, if not available, the best data. Sources and justifications are detailed in the appendix (pp 2–6). We performed new meta-analyses for the RRs for depression and hearing loss previously described in this paper.

We used data from all 37 000 participants aged 45 years or older 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,<sup>175,300,301</sup> to estimate communalities (ie, clustering of risk factors) of the 14 risk factors. The appendix (pp 5–10) shows the PAF formula, risk factor definitions, and steps, including Stata code, in calculating communality and PAF. Our analysis identified five principal components, explaining 54% of the total variance between the 14 risk factors, indicating a substantial overlap in risk factor prevalence, which we then accounted for 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, RR, and unweighted and weighted PAFs adjusted for communality for all 14 potentially modifiable dementia risk factors.

**Strengths and limitations**

This paper 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 RRs 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 evidence might have overestimated or underestimated the risk. 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 did new meta-analyses for only depression and hearing loss (as there were no recent reviews) and might therefore have missed some new evidence. We have detailed how we conducted these analyses but had not preregistered 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.

	RR for dementia (95% CI)	Risk factor prevalence, %	Communality, %	Unweighted PAF, %	Weighted PAF, %	Weighted PAF rounded to nearest whole number, %
<b>Early life</b>						
Less education	1·6 (1·3–2·0) <sup>302</sup>	23·2% <sup>303</sup>	0·608	12·2%	4·5%	5%
<b>Midlife</b>						
Hearing loss	1·4 (1·0–1·9)*	59·0% <sup>304</sup>	0·609	19·1%	7·0%	7%
High LDL cholesterol	1·3 (1·3–1·4) <sup>36</sup>	76·5%†	0·469	18·7%	6·9%	7%
Depression	2·2 (1·7–3·0)*	7·2% <sup>305</sup>	0·452	8·3%	3·0%	3%
Traumatic brain injury	1·7 (1·4–1·9) <sup>127</sup>	12·1% <sup>306</sup>	0·423	7·8%	2·9%	3%
Physical inactivity	1·2 (1·2–1·3) <sup>173</sup>	27·5% <sup>307</sup>	0·567	6·4%	2·4%	2%
Smoking	1·3 (1·2–1·4) <sup>148</sup>	22·3% <sup>308</sup>	0·650	6·3%	2·3%	2%
Diabetes	1·7 (1·6–1·8) <sup>309</sup>	9·3% <sup>310</sup>	0·493	6·4%	2·3%	2%
Hypertension	1·2 (1·1–1·4) <sup>311</sup>	31·1% <sup>312</sup>	0·595	5·9%	2·2%	2%
Obesity	1·3 (1·0–1·7) <sup>306</sup>	13·0% <sup>313</sup>	0·622	3·8%	1·4%	1%
Excessive alcohol consumption	1·2 (1·0–1·5) <sup>213</sup>	13·3% <sup>213</sup>	0·772	2·6%	1·0%	1%
<b>Late life</b>						
Social isolation	1·6 (1·3–1·8) <sup>221</sup>	24·0% <sup>314</sup>	0·408	12·6%	4·6%	5%
Air pollution	1·1 (1·1–1·1) <sup>315</sup>	75·0% <sup>315</sup>	0·341	7·0%	2·6%	3%
Untreated vision loss	1·5 (1·4–1·6) <sup>262</sup>	12·7% <sup>260</sup>	0·553	6·0%	2·2%	2%
Overall PAF for all risk factors	..	..	..	..	45·3%	45%

RR=relative risk. PAF=population attributable fraction. \*Calculated by the authors in this Commission. †Prevalence derived from 37 000 participants aged ≥45 years from the Norwegian HUNT study.<sup>316</sup>

**Table 1: RR, prevalence, and PAF for all 14 potentially modifiable dementia risk factors**



We used worldwide figures of prevalence where possible, which include disproportionate amounts of data from HICs, although we have included evidence that risk factor prevalence varies between countries.<sup>30,31</sup> Most global research is from HICs, so LMICs are under-represented due to a scarcity of data. We have assumed that risk factors cause dementia and have included additional evidence that altering these risk factors has the potential to change the prevalence of dementia. We did not include risks that had mixed evidence, and acknowledge that other risk factors exist. Evidence is scarce on how risk and protective factors might cluster or vary within and across different nations. Participants in the HUNT study had a lower prevalence of alcohol abuse than worldwide figures and lived in a HIC with little ethnic diversity. Additionally, we could not find a worldwide estimate of the 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 socioeconomic deprivation; for example, where people live is linked to exposure to air pollution and the possibility of finding reasonably priced healthy food within reasonable walking distance and having the resources and skills to prepare it is linked to obesity and diabetes. Socioeconomic deprivation is strongly linked to education and its incorporation into our communality calculations will reduce the individual effects of considering individual modifiable components. We were unable to meta-analyse data on air pollution, although the data consistently suggest that this factor is a risk for dementia.

We have additional evidence that longer exposure to a risk has a greater effect (eg, diabetes) and that risks act more strongly in people who are vulnerable than in the general population (eg, air pollution). Thus, it is important to redouble efforts to treat existing conditions in the best possible way for all at risk. However, although this risk modification affects the population, it will not guarantee that any individual will avoid dementia. Additionally, it is crucial to think about communities and people with multiple risks, in whom approaches beyond the individual treatment or exhortation of behaviour change have a potentially larger effect over the longer term. The length or intensity that is required of an intervention to make a difference is unknown, but it is hopeful that the risk associated with smoking can be reduced across time, and indeed a reduction in smoking prevalence might be one of the factors associated with the decreased dementia prevalence seen in some populations. Although association is not causation, the effect on cognition seen in RCTs assessing multi-component interventions, hearing aid provision, and hypertension treatment and the naturalistic changes with reduction in air pollution, cigarette smoking, social contact, hearing and vision treatments, and increases in cognitive stimulation through work continue to suggest a causal association with the clinical expression of

dementia. People with low socioeconomic status in both LMICs and HICs are at greater risk than the rest of the population and should be a priority for intervention. Considerable evidence exists that lifestyle and policy changes to reduce risk factors are important for people whether or not they are at increased genetic risk of dementia. We have summarised key points to emphasise our recommendations based on the literature we have presented. Although there are major gaps in our understanding of risk, action should not wait, because there are ways to reduce the chances of developing dementia, which benefit individuals, families, and society.

### Public health approach

Although dementia is a leading public health challenge, a public health view is quite a novel approach to dementia prevention. Risks can be conceptualised as something that the individual can change, but a public health approach recognises the life-course generation of ill health that is associated with socioeconomic deprivation. The socioeconomic patterning of conditions such as type 2 diabetes and obesity and behaviours such as smoking and excess alcohol consumption start in early life.<sup>317</sup> Understanding the cause of risk inequalities, such as unequal access to education, unequal access 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.<sup>318,319</sup> Since cardiovascular health and smoking partly mediate the association between socioeconomic deprivation and dementia,<sup>143,320–322</sup> life-course, population-level approaches to support physical activity, not smoking, and a non-obesogenic, healthy diet (which could also affect 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 presymptomatic build-up of pathology means that many years or decades of study might 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 clarify the effects of initiatives to reduce risk factors on dementia risk.<sup>64</sup> Several population-level interventions can be appropriately tailored to cultural and economic contexts, which theoretically could substantially reduce dementia prevalence, inequalities, and system-wide costs. These interventions include fiscal policies, such as subsidies to increase the affordability of healthy foods and taxation to reduce the affordability of alcohol, tobacco, and unhealthy food; levies to encourage product reformulation; and removing financial barriers to continuing education and cleaner fuels.<sup>179,297,323,324</sup> Marketing policies could also be

used; for example, reducing exposure to advertisements for unhealthy products and use of well designed mass media campaigns that shift sociocultural norms.<sup>179,297,323,325</sup> Legislative and availability policies include smoking bans in public places, reducing hours of alcohol sales, making healthy food more accessible than it currently is, reducing density of fast-food outlets, providing 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.<sup>179,297,323</sup> Physical adaptations to the environment could make exercising and socialising accessible and safe by optimising urban planning, accessibility, and infrastructure, as recommended in WHO's Global Age Friendly Cities Guide.<sup>326</sup> Finally, housing policies could be used as an intervention—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. Interventions that have been shown to have an effect on smoking, excessive alcohol use, obesity, hypertension, air pollution, and head injury were modelled for their effect on dementia, and all were cost saving and improved quality of life.<sup>327</sup>

### Potential risk factors considered with insufficient evidence to include in the model

We know that other potentially modifiable risk factors exist, and we considered several of these factors but, on balance, judged that not enough consistent evidence exists to meet our high bar for inclusion as modifiable risk factors. These risk factors include too little sleep, an unhealthy diet, infections, and mental health conditions.

#### Sleep

As we discussed in the 2020 *Lancet* Commission, it is unclear whether short (ie, usually defined as  $\leq 5$  h) and long (ie, usually defined as  $\geq 10$  h) sleep duration is associated with increased risk of cognitive decline and dementia or whether people who are developing dementia have disturbed sleep in the prodromal stage.<sup>2,328–330</sup> Two meta-analyses included studies using various definitions for length of sleep, with short duration often being less than or equal to 7 h and long duration being more than 8 h, and with a follow-up of less than 10 years until incident dementia, and their findings of an inverted U-shaped association between sleep duration and dementia risk are subject to potential reverse causation bias.<sup>329,331</sup> Some studies are noteworthy because of long-term follow-up, but no studies reported data for people who developed dementia soon after sleep duration ascertainment separately from data for those who developed dementia after 5–10 years from when sleep measures were recorded.<sup>300,332–337</sup> The reverse causation hypothesis is supported by a longitudinal brain MRI study

of 3893 healthy adults, which reported that brain atrophy rates were not associated with either longer (ie,  $>7$  h) or shorter (ie,  $\leq 7$  h) sleep duration nor quality of sleep when controlling for BMI, socioeconomic status, and mood.<sup>338</sup> However, cross-sectionally, sleep duration was associated with cortical thickness, and the authors suggested that healthy brains support healthy sleep duration.

In the Million Women study of 830716 women (mean age 60.0 years at baseline [SD 4.9]) with a 17-year follow-up, there was a slightly higher risk of dementia (RR 1.08, 95% CI 1.04–1.12) among those who reported shorter but not very short sleep duration (ie,  $<7$  h) than in people who reported 7–8 h of sleep.<sup>339</sup> In the Whitehall II study, persistent short sleep duration of 6 h or less at ages 50, 60, and 70 years compared with persistent normal sleep duration (ie, 7 h) was associated with a 30% increased dementia risk independently of sociodemographic, behavioural, cardiometabolic, and mental health factors.<sup>340</sup> In a Norwegian cohort of 7492 people with follow-up of 11 years, insomnia (which might differ from short sleep duration) was not associated with all-cause dementia, Alzheimer's disease, or cognitive score.<sup>300</sup>

Shift work, in which some work is outside the normal working day, might disrupt the circadian rhythm and in turn increase the risk of cardiovascular disease and some other illnesses. A systematic review found heterogeneous evidence of dementia risk and could not draw conclusions.<sup>341</sup> A subsequent UK Biobank study examined whether shift work might be related to dementia and followed up 170722 people for a median of 12.4 years, of whom 27450 (16.1%) did shift work (mean age at baseline of 52.8 years [SD 7.1] in shift workers and 51.8 years [7.0] in non-shift workers). Shift work was associated with an increased risk of dementia (HR 1.30, 95% CI 1.08–1.58), but risk was not higher in people who worked night shifts than in people who worked day shifts, although the power to detect differences was low.<sup>342</sup>

In a Swedish cohort of 28775 individuals aged 65 years and older, the association between long sleep duration (ie,  $>9$  h/night) 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, emphasising the role of reverse causation bias.<sup>336</sup> Similarly, in the US Million Women study, there was no association between long sleep duration (ie,  $>8$  h) or daytime napping and dementia after the first 5 years of follow-up.<sup>339</sup> A UK Biobank mendelian randomisation study reported a small association between habitual napping and increased brain volume (unstandardised  $\beta$  15.80 cm<sup>3</sup>, 95% CI 0.25–31.34) but no difference in hippocampal volume or cognitive tests.<sup>343</sup>

Along with duration of sleep, emerging evidence suggests that quality of sleep, specifically sleep apnoea, might be associated with dementia. A systematic review and meta-analysis of 11 studies including 1333424 participants who were followed up for up to 14.9 years identified that people with sleep apnoea had an

increased risk of developing dementia (HR 1.43, 95% CI 1.26–1.62).<sup>344</sup> Few of these studies adjusted for obesity. It might be worth considering implementation of screening questions about dementia in people with sleep apnoea.

Sleep disturbances are postulated to increase dementia risk through several processes.<sup>328</sup> They often co-occur with other conditions affecting dementia risk (eg, diabetes, depression, and alcohol consumption). Additionally, people with impaired sleep might be treated with benzodiazepines, which might be related to cognitive decline. One systematic review and meta-analysis identified very low-quality evidence of an increased risk of dementia in people taking benzodiazepines in 11 studies with follow-up lasting 72–264 months (OR 1.38, 95% CI 1.07–1.77;  $I^2=98\%$ ;  $n=980\,860$ ).<sup>345</sup> A prospective cohort study reported that the risk was higher in people taking a low benzodiazepine dose compared with those taking higher doses, suggesting that the association is not causal.<sup>346</sup> Experimental studies support a detrimental effect of acute sleep deprivation on immediate cognitive performance.<sup>347</sup>

Biological mechanisms include neuroinflammation,<sup>348</sup> atherosclerosis,<sup>349</sup>  $\alpha$ -synucleinopathies (ie, dementia with Lewy bodies and Parkinson's disease dementia),<sup>350</sup> and impaired clearance of amyloid  $\beta$  because sleep duration is reduced.<sup>351</sup> However, clearance of amyloid  $\beta$  usually occurs during deep sleep at the beginning of the night, which lasts 1–2 h, so is unlikely to be affected in those reporting sleep disturbances.<sup>352–354</sup> Amyloid plaque build-up contributes to poor sleep in older adults through its direct effects on sleep–wake-regulator brain regions.<sup>355,356</sup> Some evidence also exists for an association of amyloid  $\beta$  accumulation with disruption of the circadian rhythm and sleep pattern in cognitively healthy adults.<sup>357</sup>

Since the 2020 *Lancet* Commission, further evidence has indicated that prolonged sleep is not a risk factor for dementia, although dementia and its prodrome might cause prolonged sleep. People should not curtail their sleep to reduce dementia risk. Benzodiazepines do not appear to cause dementia.

Overall, evidence appears to indicate that short sleep duration might be associated with a small, increased risk of dementia, but evidence about the characterisation of short sleep is scarce, and no information exists on sleep quality or circadian rhythm disturbance, which might 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 findings are contradictory regarding their link with cognition and dementia.<sup>2</sup> A diet encompasses multiple healthy and unhealthy types of food and drinks and is

often part of a way of life, so observed effects might be related to lifestyle or be independent of it.<sup>358</sup> The availability of foods and drinks comprising the Mediterranean and similar diets tends to be lower in LMICs than in HICs.

Diets similar to the Mediterranean diet include the 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. In 2019, WHO made a conditional recommendation of Mediterranean diet for reduction of dementia risk, meaning that they were unsure about the balance of evidence between desirable and undesirable effects.<sup>324</sup> Since then, there have been several new studies. One systematic review and meta-analysis identified 16 cohort studies with follow-up ranging from 2.2 years to 41 years.<sup>359</sup> High diet quality relative to low diet quality was associated with lower dementia risk (RR 0.82, 95% CI 0.70–0.95;  $n=66\,930$ ; 12 studies). This risk was similar when only studies that had follow-up for more than 10 years were included (0.78, 0.62–0.99; six studies) or when restricted to the outcome of Alzheimer's disease (0.61, 0.47–0.79; six studies). By contrast, studies using a continuous Mediterranean diet score identified no significant association between Mediterranean diet adherence and risk of dementia. A subsequent larger meta-analysis of three cohort studies with 224049 participants identified that increased adherence to the MIND diet score was associated with decreased risk of dementia (HR 0.83 [95% CI 0.72–0.95] for every 3-point increment;  $I^2=0\%$ ).<sup>360</sup> A third systematic review reported a protective effect of the Mediterranean diet against global cognitive decline in ten of 21 studies, against incident dementia in three of eight studies, and against Alzheimer's disease in two of four studies.<sup>361</sup>

Since these reviews, a Swedish prospective cohort study of 28025 people in midlife (ie, mean age at first assessment of 58.1 years [SD 7.6], median follow-up of 19.8 years [IQR 4.8]) reported that neither adherence to dietary recommendations nor to the modified Mediterranean diet (ie, a diet based on the traditional Mediterranean diet but adjusted, for example, to meet cultural variations) decreased the risk of dementia, Alzheimer's disease or vascular dementia, or Alzheimer's disease pathology.<sup>362</sup> These results were unchanged when people who developed dementia in the 5 years after baseline were excluded. By contrast, a UK Biobank study ( $n=60\,298$ ; mean age at baseline of 63.8 years [2.7], mean follow-up of 9.1 years [1.7]) reported that higher adherence to the Mediterranean diet was associated with decreased dementia risk compared with lower adherence, independent of *APOE* status.<sup>363</sup> A US cohort study of older people ( $n=581$ , mean age at first assessment of 84.2 years [5.8]) reported that MIND and Mediterranean dietary patterns, particularly consumption of green leafy vegetables, were inversely correlated with amyloid  $\beta$  load, phosphorylated tau tangles, and global Alzheimer's disease pathology at post mortem.<sup>364</sup>

Ultraprocessed foods are formulations of processed food substances (ie, oils, fats, sugars, starch, and protein isolates) containing little or no whole foods. Classifications of food vary because the definition is vague. A cross-sectional US study of 3632 participants aged 60 years or older reported that overall cognitive performance and memory were not associated with the percentage of daily dietary energy intake from ultraprocessed food after correction for confounders.<sup>365</sup> A longitudinal study from Brazil (n=10775; mean age at baseline of 51.6 years [SD 8.9]; median follow-up of 8 years [range 6–10]) reported a 28% faster rate of global cognitive decline ( $\beta$  -0.004, 95% CI -0.006 to -0.001) and a 25% faster rate of executive function decline ( $\beta$  -0.003, -0.005 to 0.000) in individuals whose ultraprocessed food consumption was in the highest three quartiles than in those in the lowest quartile after adjustment for relevant sociodemographic and clinical variables.<sup>366</sup> These studies are not long enough to rule out reverse causation bias.

A French study (n=1279; mean age at baseline of 74.3 years [SD 4.9]; follow-up of 17 years) reported that increased concentrations of omega-3 index in plasma were associated with a decreased risk of dementia (HR 0.87 [95% CI 0.76–0.98] for 1 SD) and less decline in medial temporal lobe volume.<sup>367</sup>

The gut microbiome encompasses all microbes in the gut. Changes in the gut microbiome occur as people age or as a result of obesity, diet, infection, cardiovascular disease, sleep issues, or little physical activity. Changes in the microbiome might mediate the effects of diet on the brain,<sup>358</sup> facilitate neuroinflammation and cell death, and be a risk factor for dementia.<sup>368</sup> Few studies have examined the associations of the gut microbiome with dementia, and we cannot draw any conclusions.

#### *Dietary interventions*

Designing dietary interventions is difficult because the correct doses, forms, timing in life, and duration are unclear.<sup>358</sup> The caveats in long-term RCTs outlined previously in this paper in terms of practicality, ethics, and bias are particularly salient here. The Commission previously identified convincing evidence that vitamins did not prevent cognitive deterioration in the general population, as did WHO.<sup>2,124</sup> Since then, further studies have not produced convincing benefit.

A 3-year RCT of a dietary educational intervention—ie, dietary counselling and either MIND diet or mild calorie-controlled diet—in 604 older people without cognitive impairment but with a positive family history of dementia, a BMI higher than 25, and a suboptimal diet, reported no between-group differences in global cognition and a secondary brain MRI outcome.<sup>369</sup> Both groups improved in cognitive score, had a similar weight loss of around 5 kg, and had similar MRI outcomes.

COSMOS-MIND was a 3-year RCT, nested in the cardiovascular COSMOS RCT in 2262 volunteer participants (mean age of 72.97 years [SD 5.63]). The trial tested

separately daily cocoa extract, which contained cocoa flavanols (ie, primary analysis), and multivitamin mineral.<sup>370</sup> Cocoa extract (plus or minus multivitamin mineral) had no effect on global cognition whereas multivitamin mineral supplementation alone led to a small, not clinically but statistically, significant global cognition benefit (mean Z score 0.07, 95% CI 0.02–0.12) in memory and executive function. The authors suggested that the observed cognitive benefits of multivitamin mineral supplementation might be more pronounced among older adults with cardiovascular disease than those without and that further studies should be conducted in a more diverse cohort.

COSMOS-WEB was a subset of COSMOS that substantially overlapped with COSMOS-MIND but examined only people who were randomly assigned to receive cocoa extract containing cocoa flavanols or placebo and reported that the cocoa extract intervention did not enhance memory over 1–3 years.<sup>371</sup> A 24-week RCT of anthocyanins (ie, a flavonoid found in berries and fruit that is thought to be anti-inflammatory, antioxidant, and to improve lipid profile) in 206 people aged 60–80 years without dementia showed no difference in cognitive outcomes.<sup>372</sup> The authors suggested that this absence of effect might be because of insufficient power and duration, because there was a difference between the groups in the slopes of cognitive decline.

#### *Decisions*

In conclusion, nutritional epidemiology studies often, but inconsistently, report an association between diet and biomarkers, cognitive decline, dementia, or Alzheimer's disease. Studies are of few diets and mostly focus on those in high-income countries, consisting of Mediterranean or similar diets, which are rich in vegetables, nuts, berries, beans, seafood, and whole grains. Clinical trials have generally reported that nutritional and dietary interventions do not reduce cognitive impairment. Intervention results are small, heterogenous, usually not significant, and could be considered hypothesis-generating at best but do not support the primary hypotheses. Positive results in some subgroups indicate that future investigation might be useful and that long-term interventions might be needed to show an effect.

Eating a diet high in fruit and vegetables and low in ultra-processed foods is good for many health conditions and affects the dementia risk factors of obesity, diabetes, and hypertension, but insufficient evidence exists to say that this diet is directly useful for dementia prevention. Data for the effect of malnutrition in early life are also scarce.

#### **Infections and systemic inflammation**

In one meta-analysis of individual participant data, severe peripheral systemic infections requiring admission to hospital were linked to increased dementia risk, and associations persisted after adjustment for age, sex,



socioeconomic status, health behaviours, BMI, hypertension, diabetes, and APOE genotype (HR 1.22, 95% CI 1.09–1.36).<sup>373</sup> This result might be partly explained by smaller brain volume and lower white matter integrity, indicating brain vulnerability, in people who are admitted to hospital with infection compared with age-matched controls who are not hospitalised.<sup>374,375</sup> A subsequent electronic register study of almost 1 million UK adults showed that people with infections resulting in admission to hospital, but not those treated in primary care, had a higher risk of dementia or Alzheimer's disease than those without infection.<sup>376</sup> Several viruses and bacteria were associated with dementia risk and risk was higher not only in people with CNS infections but also with extra-CNS infection compared with people without infection or other types of infection.<sup>373,377,378</sup> In the Baltimore Longitudinal Study of Aging (n=1009), accelerated white matter atrophy was observed among individuals with a history of symptomatic herpetic infections,<sup>379</sup> however, another study reported no association between herpes simplex infection and cognitive decline or brain atrophy.<sup>380</sup>

Sepsis, pneumonia, lower respiratory tract infections, skin and soft tissue infections, and urinary tract infections are all associated with increased rates of dementia in human and animal studies.<sup>376</sup> Similarly, increased concentrations of peripheral inflammatory markers are linked to increased dementia risk: one meta-analysis of ten studies, with follow-up ranging from 2 years to 25 years, reported that people with the highest quartile of CRP concentrations had a higher dementia risk than people with the lowest quartile (HR 1.34, 95% CI 1.05–1.71), with similar results for IL-6 in four studies (1.40, 1.13–1.74) and ACT in three studies (1.54, 1.14–2.08) but not PAF acetylhydrolase (1.06, 0.94–1.18).<sup>381</sup> Increased inflammatory marker concentrations are also associated with increased cognitive decline.<sup>382</sup>

Little longitudinal evidence exists on the long-term effects 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 might increase the risk of cognitive impairment, with one meta-analysis identifying slightly more impairment in global cognition 7 months after COVID-19 infection than in healthy adult controls with no known history of cognitive impairment (Montreal Cognitive Assessment score mean difference -0.94, 95% CI -1.59 to -0.29).<sup>383</sup> Additionally, decreases in grey matter thickness and total brain size have been reported 6 months after SARS-CoV-2 infection in 785 UK Biobank participants compared with people who had not had SARS-CoV-2.<sup>384</sup> COVID-19 might also have increased risks of dementia by changing population habits; for example, studies showed that COVID-19 infection and the late stages of the pandemic were associated with decreased exercise and higher risk of obesity than no infection or earlier stages of the pandemic.<sup>385</sup>

### *Mechanisms of the effects of infection and inflammation*

The mechanisms by which infections might contribute to increased dementia risk are 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 than people without dementia. Although the blood–brain barrier protects the brain, there are multiple mechanisms for peripheral and central immune communication, including direct pathways of peripheral immune cell infiltration across the blood–brain barrier and indirect pathways of systemic inflammation-driven modulation of CNS microglial function.<sup>386,387</sup> Animal and in-vitro studies show that inflammatory stimuli might initiate long-term priming of the microglia and peripheral CD4<sup>+</sup> and CD8<sup>+</sup> T cells to a proinflammatory state,<sup>388–390</sup> potentially increasing amyloid plaque deposition.<sup>391</sup> Long-term immune activation and systemic inflammation can also adversely affect brain capillaries, increasing the permeability of the blood–brain barrier and related entry of neurotoxic plasma components, blood cells, and pathogens into the brain.<sup>392,393</sup>

As hospital-treated infections are more strongly associated with vascular dementia than with Alzheimer's disease, mechanisms might involve vascular inflammatory pathways.<sup>373,376</sup> Dysfunction of the blood–brain barrier has been linked to microbleeds and perivascular oedema, compromising microcirculation and inducing ischaemic damage.<sup>394</sup> 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 decreased dementia risk, although this association might be partly due to confounding factors because people who receive vaccinations might have different health behaviours and better access to health care compared with those who do not receive vaccinations.<sup>395</sup> One population cohort study using UK general practice records of 13 383 431 adults older than 50 years reported no effect of vaccines on the risk of dementia when adjusted for potential confounders.<sup>396</sup>

One systematic review and meta-analysis concluded that there was no strong evidence from large RCTs that interventions using non-steroidal anti-inflammatory drugs to modify infection and inflammation result in a reduction in cognitive impairment or risk of dementia progression.<sup>397</sup> Non-steroidal anti-inflammatory drugs for Alzheimer's disease, such as naproxen and celecoxib for 1–3 years or aspirin 100 mg for 9.6 years in older adults (ie, aged ≥70 years) with a first-degree relative with Alzheimer's disease, did not decrease dementia risk,<sup>398</sup>



and these drugs also increased adverse events.<sup>399</sup> Minocycline, a tetracycline antibiotic that protects against the toxic effects of amyloid  $\beta$  in vitro and in animal models of Alzheimer's disease, did not delay the progression of cognitive impairment in people with mild Alzheimer's disease over a 2-year period in a multicentre clinical trial.<sup>400</sup>

Interventions that help to avoid infection, such as vaccinations, hand washing, and ventilation, and therefore reduce risk or severity of inflammation and vascular events are good for general health but their effects on dementia risk are unclear.

#### Dental disease

Dental disease, including gum inflammation (ie, periodontal) disease, is associated with chronic, inflammation-driven disorders and might be a risk factor for dementia.<sup>401</sup> People with better childhood cognitive function have better dental health and, throughout life, use more preventive dental care and lose fewer teeth than their counterparts, which precedes potential mechanisms of compromised nutrition, chronic periodontitis, and inflammation related to dental disease by many decades.<sup>402</sup>

A nationwide Swedish study controlling for demographic factors, socioeconomic factors, and other health conditions of people aged 40–80 years did not identify a higher incidence of dementia in 7992 individuals with caries and periodontal disease than in 29182 matched controls over 7.6 years.<sup>403</sup> A US study controlling for demographic factors, vascular health, and socioeconomic status reported that, in 3521 people aged 65 years or older, varying periodontal pathogens were associated with either all-cause dementia, Alzheimer's disease, or having Alzheimer's disease as the underlying cause of death on the death certificate over 26 years of follow-up.<sup>404</sup> The dental disease group had less education, lower disposable income, and more comorbidities than the group without dental disease. There is a scarcity of consistent, high-quality evidence that dental and periodontal disease are risk factors for dementia.

#### Decisions

The extent to which infections and inflammation are modifiable risk factors for dementia is unclear, because most studies were conducted in older people with short follow-up. Specific pathogens cross the blood–brain barrier, such as syphilis, HIV, and herpes, and directly cause dementia, which is not the same as infection being a risk itself. Inflammation might be a common pathway for many risk factors for dementia.

#### Bipolar disorder

A review of five longitudinal studies with follow-up durations of 4–11 years examined associations between bipolar disorder and dementia.<sup>110</sup> No meta-analysis was performed because several studies used the same database and all were based on one of two population-based cohorts (in Australia or Taiwan), but a consistent

association was identified between bipolar disorder and dementia risk (HRs between 2.31 and 4.55). One included study reported that greater severity of bipolar disorder (measured by the number of psychiatric admissions) was associated with higher dementia risk than was bipolar disorder that required no psychiatric admissions: the rate of dementia was higher in individuals who had one or two psychiatric admissions (RR 2.4, 95% CI 1.9–3.1) and more than two admissions (5.7, 4.8–6.8) per year. 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 identified an overall increased risk of all-cause dementia over a median of 11 years (RR 2.52, 95% CI 1.67–3.80), although heterogeneity was high ( $I^2=99.7\%$ ).<sup>405</sup> Most included studies were of individuals with schizophrenia, and only one study specifically reported findings for early-onset schizophrenia (ie, at age <40 years), which showed higher dementia risk than for individuals without schizophrenia but lower risk than late-onset schizophrenia (ie, at age >40 years).<sup>406</sup> Another lifespan study included in the review also reported lower dementia risk in younger (ie, aged 18–49 years) versus older (ie, aged 50–64 and  $\geq 60$  years) individuals with schizophrenia.<sup>407</sup> However, a third lifespan study reported higher dementia risk in people with onset of psychotic disorders at younger ages (ie, aged 18–60 years) than at older ages (ie, aged 41–80 or 51–90 years),<sup>408</sup> which was potentially attributable to more deaths in older cohorts than the younger cohort. 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 effects of specific comorbidities or antipsychotic medication on dementia risk or on risk for specific dementia types.

People with schizophrenia have lower brain volumes at onset than the age-matched population, suggesting a neurodevelopmental cause,<sup>409</sup> and cognitive impairment, which is a core feature of schizophrenia, is already present at onset.<sup>410</sup> There is no clear link between this cognitive impairment and specific neuropathology related to Alzheimer's disease,<sup>411</sup> and despite mainly having typical age-related trajectories of cognitive functioning during midlife, people with schizophrenia show accelerated brain ageing (on neuroimaging) compared with healthy controls and people with depression or bipolar disorder.<sup>412</sup> One systematic review found that people with schizophrenia with cardiovascular risk factors, including metabolic syndrome (13 studies;  $n=2800$ ; effect size 0.31, 95% CI 0.13–0.50), diabetes (eight studies;  $n=2976$ ; 0.32, 0.23–0.42), and hypertension (five studies;  $n=1899$ ; 0.21, 0.11–0.31), had significantly worse cognition than people with

schizophrenia without cardiovascular disease risk factors.<sup>413</sup> A higher prevalence of known dementia risk factors throughout midlife, such as cardiovascular disease, hyperlipidaemia, obesity, smoking, and social isolation, contributes to increased cognitive decline in older age.<sup>414</sup> People with very late-onset (ie, aged >60 years) schizophrenia-like psychosis have a particularly high risk of developing dementia, with an HR of 4.22 (95% CI 4.05–4.41).<sup>415</sup> Although some of this risk can be explained by potential misdiagnosis of psychosis symptoms in dementia as very late-onset schizophrenia-like psychosis, dementia diagnosis rates remain higher in people with very-late-onset schizophrenia-like psychosis than in individuals without the condition for 20 years following diagnosis, and very late-onset schizophrenia-like psychosis might represent a dementia prodrome.

Overall, there is consistent evidence that people with schizophrenia have higher rates and earlier onset of dementia than others, including people with depression or bipolar disorder.<sup>416</sup> People with schizophrenia have high cardiovascular morbidity, less education than their healthy counterparts, and cognitive impairment related to schizophrenia. We judge that it is unclear whether schizophrenia independently predisposes to dementia beyond the fact that people with schizophrenia more often have other risk factors. We do not know whether early intervention can modify pre-existing cognitive impairment specific to schizophrenia. Few studies have investigated dementia risk in people with bipolar disorder, but findings have been consistent regarding an increased risk. We recommend, in line with WHO guidelines,<sup>417</sup> to address the increased risk of physical health inequalities for people with schizophrenia and people with bipolar disorder and that enhanced attention is also paid to treating modifiable dementia risk factors.

### Anxiety

A review of seven longitudinal studies identified no increased risk of dementia in people with anxiety disorders (RR 1.18, 95% CI 0.96–1.45), although individual studies had mixed findings and results were not adjusted for depression.<sup>410</sup> A subsequent study of 2551 adults aged 60–64 years who were followed up for 12 years reported no association of anxiety disorders themselves with cognition (after adjusting for depression) or with cognitive decline.<sup>418</sup> People with anxiety for whom psychological treatment was effective had a lower incidence of all-cause dementia after a median of 3.12 years (IQR 1.72–4.70; HR 0.83, 95% CI 0.78–0.88) than those for whom psychological treatment was not effective.<sup>419</sup> This result might suggest that people who have anxiety as part of preclinical dementia are less likely to find psychological treatment effective. A meta-analysis identified no association between anxiety symptoms and amyloid  $\beta$  (n=5141; 13 studies) or tau (n=1126; four studies) pathology in cognitively healthy adults.<sup>420</sup>

### Post-traumatic stress disorder

A systematic review of the associations between post-traumatic stress disorder and dementia identified three studies on this topic in the USA, Denmark, and Taiwan, with sample sizes ranging from 8750 to 489 994, and all studies observed an increased risk of dementia in people with post-traumatic stress disorder versus those without post-traumatic stress disorder in their 11–17 years of follow-up, ranging from an HR of 1.70 to 4.37.<sup>110</sup> The risk was more marked in people with comorbid depression than in people without depression, but the risk remained after adjustment for depression. An earlier systematic review and meta-analysis that included these studies and another five studies suggested that post-traumatic stress disorder is a risk factor for dementia, although there was considerable heterogeneity between the included studies (HR 1.61, 95% CI 1.43–1.81;  $I^2=85.8\%$ ).<sup>421</sup> Despite the increased dementia risk, a follow-up study over 5 years identified no increase in Alzheimer's disease pathology in people with post-traumatic stress disorder and suggested that the increased dementia risk is from other causes.<sup>422</sup> There is only one meta-analysis, and evidence is too heterogenous to generalise and conclude at this stage that post-traumatic stress disorder is a modifiable risk factor for dementia.

### Menopause and hormone replacement therapy

The role of menopause and hormone replacement therapy (HRT) was not discussed in the 2020 *Lancet* Commission, but it is possible that menopause and HRT might partly explain the higher prevalence of dementia in women than men due to the association between HRT and increased dementia risk.<sup>423</sup> Meta-analytic data found that woman with menopause occurring at age 45 years or older had a lower risk of dementia than those younger than 45 years when menopause occurred (RR 0.87, 95% CI 0.78–0.97;  $I^2=56.0\%$ ).<sup>424</sup>

Two nested case-control studies that used routinely collected primary care data from 16 291 women with dementia and 68 726 age-matched controls without dementia reported increased risks of developing Alzheimer's disease in women who had used oestrogen-progestogen therapy for 5–9 years (RR 1.11, 95% CI 1.04–1.20) and for 10 years or more (1.19, 1.06–1.33) compared with women who did not use HRT.<sup>425</sup> In line with these findings, a study of 5589 Danish women who developed dementia and 55 890 age-matched controls aged 50–60 years found increased risk of all-cause dementia and Alzheimer's disease in women who had used oestrogen-progestogen therapy compared with those who had never used this therapy (HR 1.24, 95% CI 1.17–1.33). Risk increased with more years of use, ranging from an HR of 1.21 (1.09–1.35) for use for 1 year or less to 1.74 (1.45–2.10) for use for more than 12 years.<sup>426</sup> People taking HRT had increased risk whether they started therapy at younger (ie,  $\leq 55$  years) or older ages (ie, aged >55 years). The same risk was not identified for progesterone-only or oestrogen-only therapy, and

another study showed a lower risk of all-cause dementia among people younger than 80 years who had been taking oestrogen-only therapy for at least 10 years than among women not exposed to HRT (OR 0.85, 95% CI 0.76–0.94) but not for people who had taken the therapy for less time.<sup>425</sup>

A meta-analysis of 23 heterogeneous RCTs, nine of which combined oestrogen and progesterone use, reported that any HRT use had a small but significant negative effect on global cognition (standardised mean difference  $-0.04$ , 95% CI  $-0.08$  to  $-0.01$ ;  $I^2=0.0\%$ ).<sup>427</sup> Subgroup analysis showed no positive effect in short-term or long-term use of HRT in different age groups but a more negative effect if initiated after age 60 years. A further meta-analysis of RCTs identified high-quality evidence that women should not take oestrogen-only therapy after menopause to prevent dementia and some evidence that this therapy increased the risk of dementia.<sup>397</sup>

Overall, it is unclear whether menopause and HRT are causally related to dementia risk. There is some evidence that oestrogen-only therapy, long durations of treatment, and older age at initiation of HRT, might increase dementia risk.

### Multimorbidity and frailty

People with multimorbidity of chronic and severe illness are at increased risk of dementia, particularly if these illnesses begin in midlife.<sup>428,429</sup> Up to 24% of people aged 50 years and older are estimated to have frailty, and frailty is more common in women.<sup>430</sup> In a longitudinal study of 14490 Americans aged 50 years or older (mean age 72.2 years [SD 8.9]), more frailty was associated with lower neuropsychological test score<sup>431</sup> and a higher risk of developing MCI and dementia (HR for MCI of 1.66, 1.55–1.78 and HR for MCI to dementia of 1.14, 1.02–1.28 per 0.1 increase on frailty index).<sup>432</sup> A further study of 1.7 million adults in New Zealand over 30 years of follow-up reported that physical illness (defined as coronary heart disease, gout, chronic obstructive pulmonary disease, diabetes, cancer, traumatic brain injury, stroke, or myocardial infarction) was associated with dementia risk (RR 1.19, 95% CI 1.16–1.21).<sup>408</sup> In a UK Biobank study of 206 960 participants, multimorbidity was associated with an increased risk of incident dementia over 15 years of follow-up (mean 11.2 years [SD 2.2]) after adjusting for age, sex, ethnicity, education, socioeconomic status, and *APOE*  $\epsilon 4$  status (HR 1.63, 95% CI 1.55–1.71).<sup>429</sup> The risk was higher in individuals with cardiovascular and cardiometabolic clusters of disease and those without the *APOE*  $\epsilon 4$  gene. Outcome-wide studies, such as the Danish disease trajectory,<sup>433</sup> Finnish community-dwelling studies,<sup>434</sup> and the Health Improvement Network in French and UK general practice records,<sup>434</sup> linked dementia risk to a wide range of diseases, which might 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,<sup>435</sup> Alzheimer's disease biomarkers,<sup>436</sup> and polygenic risk score,<sup>437</sup> so dementia risk conveyed by each of these factors 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.<sup>438</sup> This diagnosis is distinct from screening and, as set out in the 2020 *Lancet* Commission, the only trial of dementia screening was in US primary care patients aged 65 years or older. This trial showed neither benefit nor harm in quality of life or depression and anxiety symptoms at 1 month and in health-care use, advance care planning, and dementia recognition by physicians at 1 year, and so we do not recommend screening.<sup>439</sup>

A review of people seeking diagnosis from 32 studies across 13 countries identified that people with suspected dementia and family carers reported multiple barriers and facilitators to diagnosis.<sup>440</sup> 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, previous 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, 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 dementia.<sup>441,442</sup> People in LMICs are more likely to present to services in late stages of dementia than people in HICs, perhaps due to several factors, including good support at home in LMICs and lack of public health education, awareness, resources, accessibility, stigma, and belief.<sup>441,443</sup> 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.<sup>444,445</sup>

Dementia incidence<sup>446–448</sup> and prevalence<sup>36</sup> is higher in some minority ethnic groups than in White individuals in countries such as the USA and the UK. Notably, incidence and prevalence are higher in these groups

when measured by population-based surveys rather than by use of electronic health records, indicating an under-recording or under use of services by some groups in routine data.<sup>449</sup> Cognitive screening tools that have primarily been developed in White, English-speaking populations might be unsuitable in more diverse populations because they are affected by education and cultural background.<sup>450</sup> It is therefore key that cognitive assessment includes awareness of cultural diversity within the populations that they are used in, ensuring that tools are not dependent on literacy and education level as appropriate.<sup>451</sup> One possible quality indicator for dementia care is the proportion of individuals with dementia who receive a diagnosis, but the recording of a dementia diagnosis on an individual's health-care record is lower for some ethnicities than others, so any assumption of a similar prevalence in minoritised populations is likely to be inaccurate. These measures are therefore likely to be 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,<sup>452</sup> resulting in a lack of clarity about what can be defined as good diagnostic services and care, and there is only indirect evidence that diagnosis of dementia is beneficial.<sup>453</sup>

The rationale for early or timely diagnosis is to sustain the wellbeing and health of people with dementia and their families by making care and treatment available. A diagnosis upholds an individual's right to know about their illnesses.<sup>438</sup> Across three small studies identified in one review, a total of 92 (89%) of 103 people with a diagnosis of dementia said they wanted to know their diagnosis.<sup>454</sup> Another study reported that 998 (91%) of 1091 people who were diagnosed reported benefits in getting the diagnosis and 655 (60%) people wished they had known their diagnosis earlier.<sup>455</sup> These studies reported the views of people who had a diagnosis, although did not necessarily seek the diagnosis at an early stage. The views of people without a diagnosis were not represented in these studies.

Diagnosis can provide psychological benefits and time to adjust. Diagnosis facilitates access to services, when they are available, that provide practical information, advice, guidance, and psychological and drug treatments. These services can support people's ability to manage their condition, plan for the future, and make decisions about care, support, and financial and legal affairs while they have capacity.<sup>456</sup> Potential economic benefits from reducing health and social care costs by preventing unnecessary admissions to hospitals and care homes have been modelled.<sup>457–459</sup>

There are theoretical harms of a diagnosis of dementia,<sup>456,460</sup> 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. Evidence from a US national cohort study showed a decreased risk of suicide in people with a diagnosis of dementia (n=63 255) or MCI (n=21 085) compared with propensity matched patients (HR 0.71, 95% CI 0.53–0.94) but an increase in short-term suicide attempts (ie, in those diagnosed any time in the 5 years before the study) after people were informed they had MCI (1.34, 1.09–1.65) or dementia (1.23, 1.05–1.44).<sup>461</sup> There was no long-term increase in suicide attempts.

Mobile and wearable devices hold promise for detection and diagnosis of neurodegenerative disease because their routine use in the general population is widespread and increasing and they can contain multiple sensors to study physical changes and cognitive abilities.<sup>462</sup> Nonetheless, a review of 20 mobile apps<sup>463</sup> reported that none met the criteria for use as a screening tool. Another review of 275 apps<sup>464</sup> 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 artificial intelligence, 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 Alzheimer's disease**

Research on biomarkers for Alzheimer's disease pathology has progressed since the 2020 *Lancet* Commission. Biomarkers that measure amyloid  $\beta$ , tau, and neurodegeneration are now incorporated into some definitions of Alzheimer's disease pathology (ie, the amyloid–tau–neurodegeneration or A–T–N approach).<sup>465,466</sup> The presence of these biomarkers does not mean that someone has dementia; however, the absence of these biomarkers indicates the likely absence of Alzheimer's disease pathology (but does not exclude other causes of dementia).<sup>467</sup>

#### *Neuroimaging*

CT can show vascular changes, atrophy, and other reasons for neurodegeneration and is cheaper and more accessible than MRI, although its precision is lower. Although several types of MRI exist, the simplest is structural MRI (for cerebral atrophy, primarily in the hippocampus, entorhinal cortex, and medial temporal lobe).

Advanced MRI sequences, including diffusion tensor imaging, arterial spin labelling, and susceptibility-weighted imaging, are needed to improve detection of brain microhaemorrhage and oedema that can occur with amyloid antibody treatment. Magnetic resonance spectroscopy, functional MRI, and PET (ie, in-vivo measurement of disease pathology by use of ligands) are

emerging and useful metabolic and functional biomarkers. The limitations of these advanced imaging techniques include cost, patient consent and suitability, and expertise required to perform the procedures and interpret the results, although automated assessment performs nearly as well.<sup>468</sup> Amyloid-PET and tau-PET correlate with post-mortem amyloid plaques and neurofibrillary tangles.

#### CSF biomarkers

A low CSF A $\beta$ 42-to-A $\beta$ 40 ratio alone or combined with high phosphorylated tau (p-tau) is correlated with amyloid plaques and Alzheimer's disease pathology. These CSF biomarkers can be used to evaluate underlying Alzheimer's disease pathology as a possible cause of dementia or cognitive impairment and, in asymptomatic populations, to identify people at high risk of developing clinical Alzheimer's disease for inclusion in clinical trial populations,<sup>469,470</sup> but there are important considerations in the interpretation of the biomarker changes. Interpretation depends on the clinical details and the age of the individual, because coincidental amyloid pathology is common at older ages. This interpretation issue applies to amyloid PET as well as CSF and plasma biomarkers. Overall biomarker interpretation depends on the clinical context.

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 (ie, total tau, phosphorylated tau, A $\beta$ 42 and A $\beta$ 40, NF-L, and neurogranin) that have been validated against imaging methods. The advantage of CSF biomarkers, including NF-L, plasma tau phosphorylated at Thr181 (p-tau181), and GFAP (an astrocytic marker that appears to change around the time of amyloid accumulation<sup>471</sup>), is their ability to detect early phases of disease. Biomarker changes 9–18 years earlier are associated with subsequent cognitive decline and diagnosis of dementia.<sup>472–474</sup> The disadvantages of these biomarkers are lack of infrastructure in many systems, the need for specialised health-care services, and concern around invasiveness.

CSF-based protein aggregation and amplification assays, such as real-time quaking-induced conversion, are well established in the clinical diagnosis of Creutzfeldt–Jakob disease.<sup>475</sup> A similar approach has been developed for Lewy body dementia, and assays to detect neuronal  $\alpha$ -synuclein in CSF show great promise.<sup>476,477</sup> A meta-analysis showed pooled sensitivities of 0.88 and specificities of 0.95 in distinguishing people with synucleinopathies from healthy controls and people with other types of dementia.<sup>478</sup> As with Alzheimer's disease, biomarker results for Lewy body pathology become positive before symptoms of clinical dementia or parkinsonism develop and so might not be the cause of cognitive symptoms, especially in older adults. Further work is needed to clarify the position of neuronal

$\alpha$ -synuclein assays in clinical practice, but they are likely to have a large role in the future. As with other assays, data from ethnically diverse cohorts are scarce.

#### Blood-based biomarkers

Since the 2020 *Lancet* Commission, research has progressed into the validity of blood-based biomarkers for the specific diagnosis of Alzheimer's disease in individuals with dementia. CSF or PET markers might be replaced by blood-based biomarkers in determining eligibility for clinical trials and cohort studies in the future and for staging the extent of pathology related to Alzheimer's disease, although further evidence of validity in each specific population of people with dementia is needed. Blood biomarkers might 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 Alzheimer's disease.<sup>479</sup> The A $\beta$ 42-to-A $\beta$ 40 ratio in plasma detected with a high-precision assay has a strong correlation with amyloid-PET positivity.<sup>480,481</sup> Plasma p-tau181, tau phosphorylated at Thr217 (p-tau217), and tau phosphorylated at Thr231 (p-tau231) might have as good or better accuracy than CSF amyloid  $\beta$ , p-tau, and total tau at predicting a positive amyloid PET and hence Alzheimer pathology.<sup>482–484</sup> Blood-based biomarkers offer low cost, scalability, and acceptability, overcoming several limitations of PET biomarkers and CSF biomarkers with lower patient and clinician burden through local sample collection and potential central quality-controlled processing, increasing access to a pathology-specific diagnosis of Alzheimer's disease.

#### Meaning of predictive markers

Multiple neuropathologies are common in older populations and more common than Alzheimer's disease pathology alone (figure 1).<sup>20</sup> Amyloid  $\beta$  plaque prevalence is age-related (ie, >20% over age 70 years; >30% by age 80 years),<sup>485</sup> meaning that a positive amyloid  $\beta$  biomarker result should be interpreted cautiously in older individuals: it reflects amyloid  $\beta$  plaque pathology but might not be the cause of impairment. Nonetheless, if an individual is negative for amyloid  $\beta$  biomarkers (ie, negative for plaques on PET or has a high CSF A $\beta$ 42-to-A $\beta$ 40 ratio), a diagnosis of Alzheimer's disease is unlikely, irrespective of age. Because amyloid  $\beta$  plaque accumulation occurs many years before the onset of neurodegeneration or cognitive symptoms, a positive amyloid  $\beta$  biomarker result alone was shown to be only a modest predictor of future cognitive impairment compared with a negative amyloid PET scan over 6 years of follow-up (HR for developing dementia in participants with a positive amyloid  $\beta$  but negative tau biomarker result vs those with both negative amyloid  $\beta$  and tau biomarker results was 1.6, 95% CI 0.5–5.4).<sup>486</sup>

As discussed in the 2020 *Lancet* Commission, most cognitively healthy people who are amyloid  $\beta$  positive



either on brain imaging or CSF do not develop Alzheimer's disease over the next 10 years, or during their lifetime. In a US volunteer sample of 1524 participants (698 women), the prevalence of amyloid  $\beta$  positivity was 10% (95% CI 6–14) among women at age 70 years whereas the prevalence of clinically defined probable Alzheimer's disease was 1% (1–1).<sup>487</sup> By age 85 years, the prevalence of amyloid  $\beta$  positivity was 33% (24–41) whereas the prevalence of clinically defined probable Alzheimer's disease was 9% (9–12), with similar figures for men. One community-based autopsy cohort study of amyloid  $\beta$ , tauopathy, and neurodegeneration markers reported that only 8% of 398 participants with amyloid  $\beta$  and tauopathy (but no neurodegeneration) markers compared with 68% participants with amyloid  $\beta$ , tauopathy, and neurodegeneration markers had incident dementia in the last 5 years of life.<sup>488</sup>

Tau-PET uptake occurs at a later stage and age than amyloid-PET uptake and is more closely associated with cognitive dysfunction than is amyloid-PET.<sup>489,490</sup> Biomarkers of neurodegeneration, such as hippocampal atrophy, medial cortex thinning, low glucose uptake on fluorodeoxyglucose (FDG)-PET, or increased CSF NF-L (ie, a non-specific marker of neurodegeneration), are more closely associated temporally with cognitive decline than amyloid  $\beta$  and tau CSF biomarkers.<sup>491</sup> People without cognitive impairment who have amyloid  $\beta$  and tau in the medial temporal lobe or temporal neocortex are more likely to decline cognitively compared with people who have neither, and over 6 years, the risk in individuals that are tau positive in the temporal neocortex might approach 50%, but samples are small and estimates imprecise.<sup>486</sup> Other biomarkers and progress in proteomics and metabolomics might uncover new pharmacological targets.<sup>492–494</sup>

Clinically, blood-based biomarkers might not add value to prediction of whether people will develop Alzheimer's dementia (ie, Alzheimer's disease plus substantial cognitive impairment). A combination of multiple blood-based biomarkers and demographic information, such as age and sex, might allow for calculation of individualised risk of developing Alzheimer's disease, as has been done in a population with MCI.<sup>495</sup>

Additionally, most research has been in almost exclusively White populations, and a systematic review identified five studies, of which none were done in Black African participants but some were in African American participants.<sup>496</sup> Study participants are often younger than most people with dementia. Small studies in African Americans report lower concentrations of p-tau in both cognitively healthy individuals and people with dementia than in White Americans and so the generalisability of biomarkers from White populations is unclear. A subsequent review identified seven studies and again reported lower tau concentrations in Black individuals with dementia than in White individuals with dementia, but none of the studies identified greater vascular burden

as an explanation.<sup>497</sup> The authors of the review suggested that differences in social determinants of health between the White and Black samples might be an explanation. This difference being due to social determinants is consistent with a study of an African American and non-Hispanic White, community-based sample of adults that identified no independent association of plasma biomarkers for Alzheimer's disease based on self-reported race, with age, sex, chronic kidney disease, and vascular risk factors contributing to observed variation.<sup>498</sup>

### Patient selection in Alzheimer's disease trials: biomarker and genetic testing

Another development since the 2020 *Lancet* Commission has been the use of amyloid-PET as an eligibility criterion and as a surrogate clinical outcome for clinical trials of anti-amyloid  $\beta$  antibody therapies for participants with early Alzheimer's disease. Phase 2 and phase 3 trials of monoclonal antibodies—ie, aducanumab, lecanemab, donanemab, and gantenerumab—that target amyloid  $\beta$  plaques, fibrils, soluble protofibrils, and oligomeric amyloid  $\beta$  species all required evidence of amyloid plaque pathology for trial enrolment, mainly from amyloid PET.<sup>499–502</sup> Phase 3 trials of lecanemab and donanemab showed modest efficacy in slowing cognitive decline in early Alzheimer's disease (for both MCI and dementia). The phase 3 trial of donanemab required people with early Alzheimer's disease to have both positive amyloid-PET and tau-PET, allowing participants to be divided into low and intermediate or high positive tau burden groups.<sup>503</sup> Both the lecanemab and donanemab trials used amyloid-PET to assess amyloid  $\beta$  lowering and showed marked removal of amyloid within 18 months.<sup>499,501</sup> Additionally, achieving a low level of amyloid PET binding was a stopping criterion in the donanemab trial. In the future, blood biomarkers could be used to assess whether to perform a PET scan and thus lower the cost of such trials.<sup>504,505</sup>

Knowledge about genetic testing in dementia has advanced rapidly, but genetic testing is not widely used because 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 Alzheimer's disease increases the precision of the diagnosis, helps family members to establish personal risk, might 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 an autosomal dominant genetic mutation, and testing in the appropriate clinical setting might be important.<sup>506</sup>

Although it is well established that APOE genotype substantially affects Alzheimer's disease risk,<sup>507</sup> genetic testing for the APOE  $\epsilon 4$  allele is not used diagnostically, and many people with Alzheimer's disease do not carry the  $\epsilon 4$  allele. APOE alleles contribute to the heterogeneity of the Alzheimer's disease course. A post-mortem study (n=1109) reported 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 ε2 carriers (−2.43 vs −3.03 MMSE points per year) compared with *APOE*ε3/ε3 carriers.<sup>508</sup>

**Summary of biomarkers now and in the future**

Biomarkers identify a particular pathology, not a clinical syndrome, and a biomarker is not a diagnostic test for dementia. Amyloid-PET and CSF amyloid and tau assays are approved by the US Food and Drug Administration (FDA) for marketing and reimbursement as Alzheimer’s disease diagnostic aids to help to establish the presence of amyloid plaques and Alzheimer’s disease pathology.

There are clear ethical implications if biomarker testing is used in people without cognitive impairment as markers of people with (asymptomatic) Alzheimer’s disease, as testing has the potential to increase the measured rates of Alzheimer’s disease without there being any increase in the numbers of people with cognitive impairment or dementia, and could misidentify people who will not develop dementia potentially causing harm. Currently, biomarkers alone should not be used for diagnosis and to determine treatment as most people with a positive amyloid β biomarker alone will never develop dementia. The stated hope is that if effective and safe pre-symptomatic therapies are developed and then become accessible, cost-effective biomarkers for Alzheimer’s disease or other dementias may become important to predict which individuals are likely to progress to illness and when, or as surrogate endpoints for efficacy and to increase equity (figure 10).<sup>505</sup>

**Interventions once a diagnosis has been made**

*Principles of intervention in people with dementia*

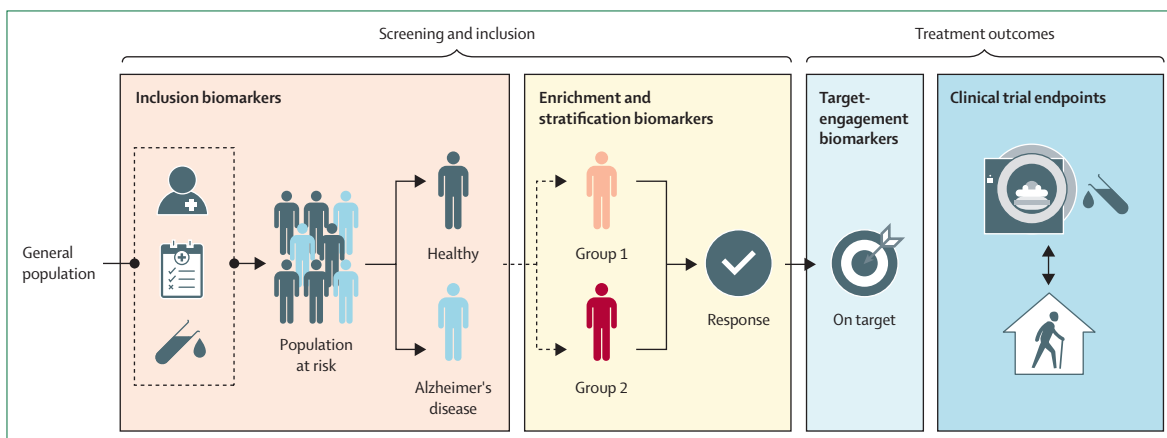
Dementia is progressive and people living with dementia require reassessment and use of tailored approaches to

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 symptoms.

People with dementia are individuals whose support and intervention needs are influenced by their own life course, family, friendship, culture, and environment as well as changing cognitive, neuropsychiatric, functional, and physical symptoms, as we discussed in the 2020 *Lancet* Commission.<sup>2</sup> Despite the availability of evidence-based practices, dementia continues to be underdetected and many individuals’ and family carers’ needs are unevaluated and unmet.<sup>3</sup>

Published best practices for dementia care globally include managing medical conditions, such as high blood pressure, diabetes, and chronic obstructive pulmonary disease; 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 antihypertensive treatments if blood pressure is decreasing; 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.<sup>2,3,10</sup>

Most interventions for dementia are developed in HICs. Interventions should be co-designed with local communities to ensure appropriateness for the context, culture, beliefs, and practices, which vary within and between countries.<sup>509</sup> In LMICs, dementia is often not recognised and diagnosed and, when it is, people living with dementia are often faced with insufficient resources for treatment and care, including treatment of other illnesses and support for families.<sup>510</sup> The appropriateness of the use of evidence-based interventions in LMICs can



**Figure 10: Vision of the future use of biomarkers for dementia in clinical trials**

Future uses include screening and inclusion (eg, identifying people with increased risk or a condition of interest and identifying who might respond) and as surrogate outcome measures (eg, using biomarkers as a target or as a surrogate endpoint in clinical trials). Reproduced from Hansson et al.<sup>466</sup>

be uncertain, not only because of the scarcity of health-care infrastructure and resources to deliver them, but also because of cultural differences that might make them inappropriate or less effective than in HICs.

The effectiveness of interventions developed in one setting will vary with acceptability and feasibility in different populations and thus, although the core principles should stay the same in different countries, interventions should be tailored in language and culture.<sup>511,512</sup> 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.<sup>513–515</sup>

A systematic review considering culturally tailored interventions for people living with dementia and family carers identified that culturally adapted interventions were as acceptable, feasible, and effective when used in LMICs as in their original context as long as the core components were not compromised in the adaptation process.<sup>511</sup> Adaptation involves considering local cultures, needs, and resources and identifying barriers and facilitators to the implementation of the intervention. Opinions differ as to whether it is necessary to conduct a full RCT in a new setting when an intervention has already been reported to be effective because biological, ethnic, cultural, and socioeconomic heterogeneity might influence treatment response and safety.<sup>511,516</sup> Following cultural adaptation, interventions need to be tested and their components evaluated in the local context to establish their acceptability and feasibility and to help to 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.<sup>511</sup> Other important considerations are cultural appropriateness of outcome measures, many of which are developed in HICs, and scalability of the intervention.

Multicomponent dementia care models with person-centred care coordination aim to target assessment of risk and need for the person living with dementia and the family carer using evidence-based approaches. A meta-analysis found that co-ordinating interventions improved neuropsychiatric symptoms (mean difference  $-9.5$ , 95% CI  $-18.1$  to  $-1.0$ ; four studies) and carer burden (standardised mean difference  $-0.54$ , 95% CI  $-1.01$  to  $-0.07$ ;  $p=0.02$ ; five studies) with heterogeneity in outcome.<sup>517</sup> Individual studies of care coordination have shown reduced care-home admission and cost-effectiveness from a societal and individual perspective,<sup>518</sup> but the meta-analysis of care coordination RCTs did not show a significant reduction in care-home admission or hospitalisation.<sup>517</sup> Models that include a partnership between primary and specialised care might lead to reduced health-care costs.<sup>519</sup>

Although there are often positive aspects of being a family carer, caring for a family member with a deteriorating

illness, such as dementia, is usually increasingly difficult. The difficulty can vary across the course of dementia, with greater anxiety and depression for some near the onset of disease than later in the disease course. A meta-analysis (43 studies; 19 911 participants) reported a pooled prevalence of depression in family carers of 31.2% (95% CI 27.7–35.2).<sup>520</sup> Evidence exists that some multicomponent carer interventions are effective in the short and long term, and these interventions usually include information about medical and community-based resources, skills training, stress reduction and coping techniques, emotional support, and future planning.<sup>2,521–525</sup> These interventions reduce the prevalence of family carer depression, burden, and stress and are cost-effective and cost saving. Evidence suggests that the interventions are effective in HICs, but little evidence exists in LMICs.<sup>526</sup> Interventions can be culturally adapted and delivered by trained facilitators without clinical qualifications. The Strategies for Relatives intervention, which was developed in and was 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 voluntary settings.<sup>527,528</sup> In another study in the USA, an intervention delivered by daycare staff reduced carer depression at 1 year.<sup>529</sup> A Cochrane review of RCTs on remote delivery of interventions including information and support for family carers identified 26 studies and reported that these interventions were no more effective than usual care.<sup>530</sup> A meta-analysis of internet-based psychoeducation for carers showed a small effect on depressive symptoms (standardised mean  $-0.19$ , 95% CI  $-0.03$  to  $0.35$ ) but not on anxiety, burden, and quality of life.<sup>531</sup>

## Interventions for cognitive symptoms

### *Symptomatic treatment:*

#### *cholinesterase inhibitors and memantine*

In the previous *Lancet* Commissions, we discussed cholinesterase inhibitors and memantine, which are the available drugs for the treatment of cognitive symptoms in people with Alzheimer's disease and Lewy body dementia. Although the drugs were initially evaluated for people with mild-to-moderate Alzheimer's disease, meta-analyses of RCTs indicate that these drugs are also associated with a reduction in symptom severity (standardised mean difference  $0.37$ , 95% CI  $0.26$ – $0.48$ ; four studies), improvement in cognition (mean difference  $0.78$ , 95% CI  $0.33$ – $1.23$ ; three studies), improvement in activities of daily living (standardised mean difference  $0.15$ , 95% CI  $0.04$ – $0.26$ ; five studies), and decrease in mortality (RR  $0.60$ , 95% CI  $0.40$ – $0.89$ ; six studies) in people with severe dementia compared with placebo.<sup>532</sup>

Since the previous Commissions, longer-term, real-world studies have been published. One study of a register of all incident Alzheimer's dementia diagnoses in Sweden showed that 11 652 individuals who took cholinesterase inhibitors performed slightly and

persistently better on the MMSE, with an average of 5 years of follow-up, than did 5826 propensity-matched individuals who did not take cholinesterase inhibitors (0.13-point [95% CI 0.06–0.20] higher score per year), with a dose–response effect.<sup>533</sup> A similar, propensity-matched, longer-term study reported larger differences between people who did and did not take cholinesterase inhibitors: in 1572 individuals with dementia, the average decrease in MMSE score in people taking cholinesterase inhibitors was 5.4 points compared with 10.8 points in those not taking cholinesterase inhibitors at the end of 13.6 years of follow-up ( $p < 0.001$ ).<sup>534</sup> There was a strong association between cholinesterase inhibitors and lower all-cause mortality (HR 0.59, 95% CI 0.53–0.66). Additionally, in a study of 592 patients with dementia with Lewy bodies, the 100 participants who took cholinesterase inhibitors (0.67, 0.48–0.93) and 273 participants who took cholinesterase inhibitors and memantine (0.64, 0.50–0.83) had significantly lower risk of death than 219 participants who did not take cholinesterase inhibitors or memantine, after controlling for sociodemographic factors, physical and cognitive health, and medication use. People taking cholinesterase inhibitors or both cholinesterase inhibitors and memantine also spent significantly less unplanned time in hospital for physical disorders than people who took neither drug.

These studies are observational, not RCTs, and might reflect residual confounding based on willingness to initiate treatment, so people taking cholinesterase inhibitors might have unmeasured factors that would lead to better outcomes than for people who are unable or unwilling to initiate treatment. Trials show that cholinesterase inhibitors do not cure or stop cognitive decline but have short-term, modest positive effects and that stopping this treatment is associated with worse outcomes in the long term. Clinicians can offer these relatively affordable (compared with other drugs for dementia, and compared with requiring more care), readily available medications (in HICs but not LMICs) with few side-effects for people with Alzheimer's disease and Lewy body dementia.

#### *Amyloid- $\beta$ -targeting antibodies for Alzheimer's disease*

Since the 2020 *Lancet* Commission, there have been positive trials of three anti-amyloid- $\beta$  monoclonal antibodies for treatment of MCI due to Alzheimer's disease and mild Alzheimer's disease dementia in people with positive amyloid  $\beta$  biomarkers as well as three negative trials. In two conflicting, identically designed, phase 3 trials (ENGAGE and EMERGE), aducanumab was associated with a decline of 0.39 points (95% CI 0.09–0.69) compared with placebo on the Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB; out of a total possible score of 18) at 18 months in one study, and a non-significant outcome favouring placebo in the other trial.<sup>500</sup> The CLARITY-AD trial of lecanemab was

associated with a difference in CDR-SB points of 0.45 (0.23–0.67) compared with placebo after 18 months of treatment and less decline in secondary cognitive, activities of daily living, and composite outcomes.<sup>499</sup> Presence of *APOE*  $\epsilon 4$  is an important predictor of amyloid-related imaging abnormalities (ARIA), seen as MRI signal abnormalities. Effusion or oedema (also known as vasogenic odema) ARIA (ARIA-E) and cerebral microhaemorrhage ARIA (ARIA-H) are often present with treatment with anti-amyloid  $\beta$  antibodies. Participants who were treated with lecanemab and were *APOE*  $\epsilon 4$  homozygous had a 33% (46 of 141 participants) incidence of ARIA-E compared with an 12% (58 of 479 participants) incidence in participants who were *APOE*  $\epsilon 4$  heterozygous and 5% (15 of 274 participants) incidence in participants who were not *APOE*  $\epsilon 4$  carriers.<sup>499</sup> Thus, the boxed warning for lecanemab recommends *APOE* genotyping and patient counselling before treatment.<sup>535</sup> Figures were similar with donanemab: 41% (58 of 143 participants) incidence of ARIA-E in participants who were *APOE*  $\epsilon 4$  homozygous, 23% (103 of 452 participants) incidence for people who were heterozygous, and 16% (40 of 255 participants) incidence for people who were not carriers.<sup>501</sup>

People in the TRAILBLAZER-ALZ 2 trial who were taking donanemab had a smaller decline than the placebo group on the integrated Alzheimer Disease Rating Scale (cognition and functioning). The decline was  $-10.19$  (95% CI  $-11.22$  to  $-9.16$ ) in the drug group and  $-13.11$  ( $-14.10$  to  $-12.13$ ) in the placebo group after 18 months of treatment, and the intervention group had less decline in secondary cognitive, activities of daily living, and composite outcomes.<sup>501</sup> Since these studies were published, two new studies of the subcutaneously administered antibody gantenerumab with 2-year follow-up have shown similar biomarker clearance, with reduction in amyloid plaques but no significant effect on CDR-SB points ( $-0.31$  and  $-0.19$ ).<sup>502,536</sup> The difference between the drug group and placebo group was of similar size in some domains to the more positive trials but did not reach statistical significance.<sup>536</sup> Similarly, a trial of solanezumab,<sup>537</sup> did not slow cognitive decline in people with preclinical Alzheimer's disease or affect amyloid plaque concentration but did influence CDR-SB, in line with the other studies ( $-0.34$ ).<sup>536</sup>

Biogen, the manufacturer of aducanumab, has subsequently announced that they are withdrawing the drug from the market and that the phase 4 trial will be stopped. The FDA approved lecanemab in July, 2023.<sup>499</sup> The approvals were based partly on the reasonable expectation that a reduction in amyloid-PET load, or plaques, was likely to predict clinical benefit, although correlations between reduction in plaques and change on clinical ratings scales are positive but weak. These antibodies have not been tested in people with moderate or severe dementia, with the lowest participant MMSE score at 22 for lecanemab and 20 for donanemab.

**Panel: Summary of controversies surrounding amyloid- $\beta$ -targeting antibodies****Efficacy**

The cognitive benefit is modest. It is unclear whether the benefit is clinically meaningful or what the duration of effect is.

**Difficulties in implementation**

Monthly or fortnightly infusions are needed, requiring many visits to an infusion centre over a typical 18-month treatment period. Frequent MRIs are needed for safety surveillance. Substantial restructuring of existing health-care infrastructure might be needed for the required physician visits, infusions, laboratory tests, MRIs and PET scans, and management of adverse effects. Infrastructure that could support this level of intervention is insufficient in many health-care systems.

**Costs**

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

**Monitoring and side-effects**

Regular clinical and radiological monitoring are required for oedema and haemorrhage, which might occur in 20% of patients on lecanemab and nearly twice that in patients on donanemab.

**Exclusions**

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

The clinical importance of these differences in cognitive outcomes at the end of trials is controversial.<sup>538–541</sup> There is excitement about positive results, which have been hoped for over the years, but no consensus exists about whether these treatments are a huge advance or not or whether the observed benefits need to be balanced with the known burden, risks, and costs.<sup>542</sup>

**Clinical implications and generalisability of amyloid- $\beta$ -targeting drugs for cognitive symptoms**

The modest effectiveness of these drugs is an important advance. In those that are effective, whether clinical benefits with treatment beyond 18 months will increase, remain steady, or reduce is unknown. Future results from open-label extensions of trials might help to answer these questions, but there will be many dropouts and morbidity and mortality from other diseases. The small effect of antibody treatment makes it difficult to discount the potential of unmasking due to adverse effects, such

as ARIA-E and ARIA-H and decreased brain volume on MRI.<sup>499,500,543</sup>

The stringent eligibility criteria for clinical trials of drugs for Alzheimer's disease often makes the study population's health better than that of the general Alzheimer's disease population,<sup>544</sup> and historically excluded racial and ethnic backgrounds are under-represented, although there were higher numbers of people from minoritised groups in the lecanemab trial than in other published immunotherapy trials. Only 237 (27%) of 869 participants in a community-recruited study using data from the Mayo Clinic Study of Aging had a positive amyloid-PET scan and met the criteria for MCI or mild dementia.<sup>546</sup> Of these people, only 19 (8%) would have met the lecanemab trial eligibility criteria, although drug trials by their nature have very constrained inclusion criteria.

A meta-analysis of 101 drug trials for Alzheimer's disease reported that a median of 94.7% (IQR 81.0–96.7) of participants in 46 trials with data were White and most trials excluded people with psychiatric illness (79 [78%] of 101 trials), cerebrovascular disease (68 [67%] trials), and cardiovascular disease (72 [71%] trials) and required a family carer to attend infusions (81 [80%] trials).<sup>546</sup> It is difficult to generalise findings to most people with Alzheimer's disease who have high levels of multimorbidity and mixed neuropathology and to those who live in countries where health-care systems could not support this level of intervention.

So far, the only marketing authorisation outside the USA has been for lecanemab in Japan and China, although other authorities are making decisions. Lecanemab is nominally priced at US\$26 500 per patient per year.<sup>547</sup> The price that Medicare, the US Veterans Administration, and private insurers will pay is unknown. Additionally, costs are associated with the many physician visits, biweekly infusions, laboratory tests, MRIs, PET scans, and management of side-effects. Medicare patients are typically required to co-pay up to 20% of these costs. The US Institute for Clinical and Economic Review reported that the cost-effective annual pricing was lower than that charged for lecanemab, falling between \$8900 and \$21 500.<sup>548</sup> Donanemab infusions are less time consuming, given less frequently (ie, monthly), and less costly overall than lecanemab infusions because donanemab infusions are discontinued when amyloid is removed and so around 60% of people require treatment for only 1 year.<sup>501</sup>

Based on the US pricing, if lecanemab was available in the 27 EU countries for people qualifying for the drug, then treatment costs are estimated at €133 billion per year, equivalent to over half of the total pharmaceutical expenditures in the EU<sup>549</sup> before treatment-related costs are considered. However, historically the EU and the UK have paid less than the US list price for new and expensive medications.

Finding amyloid- $\beta$ -targeting treatments that influence cognition is an important milestone and might be the



	Intervention	Target population	Study design	Key outcomes
Ballard et al <sup>558</sup>	Wellbeing and health for people with dementia intervention: care staff trained to promote tailored person-centred activities and social interactions and a system for changing inappropriate medications	Staff trained by the trial team provided the intervention for nursing home residents	9-month cluster RCT using an intention-to-treat analysis within 69 UK care homes (n=847)	Improved quality of life, agitation, and neuropsychiatric symptoms and cost savings
Gitlin et al <sup>559</sup>	TAP in which carers were trained to use activities and given disease education and stress reduction techniques	Trained occupational therapists provided activities tailored to interests and abilities at home	Single-blind, parallel RCT in 160 pairs of veterans with dementia and their family carers	Decreased behavioural symptoms and pain for the person with dementia and maintenance of daily function at 4 months, but no effect by month 8
Gitlin et al <sup>560</sup>	TAP	Occupational therapists provided eight sessions in a TAP at home to individuals with agitation with moderate dementia	Single-blind RCT in 250 pairs of people with a dementia diagnosis and clinically significant agitation or aggression and their carers	TAPs did not help agitation; carers reported that the TAP made life easier, increased their ability to provide care, and improved the person with dementia's life somewhat or very much; the TAP group had fewer deaths and hospitalisations than the attention control group
Gitlin et al <sup>561</sup>	TAP with subsample of 153 White and 90 Black pairs of carers and people with dementia	Occupational therapist provided tailored activities and instructions at home to carers of people with dementia	Single-blind, two-arm RCT in 193 White and Black pairs	Behavioural benefits for people with dementia at 3 months, which were stronger for Black pairs than White pairs
Lamb et al <sup>557</sup>	Aerobic and strength exercises tailored to fitness and health status	Physiotherapists and exercise assistants prescribed and supervised interventions for people with dementia	Multicentre, pragmatic, investigator-masked RCT (n=494)	No effect on quality of life or neuropsychiatric symptoms but greater cognitive impairment was reported in exercise group than the control group
Sanders et al <sup>556</sup>	Research staff trained participants in combined walking and strength exercise for an aerobic and strength training intervention	Health-care staff selected participants with mild-to-moderate dementia in day or residential care	RCT (n=91)	No effects on cognition, endurance, mobility, balance, and leg strength but gait speed improved after high-intensity exercise
Harwood et al <sup>552</sup>	Tailored and progressive dementia-specific programme focusing on strength, balance, physical activity, and performance of activities of daily living	Intervention delivered by health-care staff to people with mild dementia or mild cognitive impairment	RCT (n=365)	Did not improve activities of daily living, physical activity, or quality of life or reduce falls

RCT=randomised controlled trial. TAP=tailored activity programme.

**Table 2: RCTs of activity programmes for people with dementia**

beginning of the development of impactful drugs for cognition (panel).<sup>550</sup> Currently, the effects of all drugs are small.<sup>536</sup> The resources required to support early biomarker-based diagnosis, supervision of administration and safety, and buying the drugs will mean that roll-outs into many health systems will be slow or non-existent in some. If amyloid- $\beta$ -targeting treatments are approved for a less restrictive group than used for the original trials, such as people with early disease or multimorbidity, then we recommend that they are used in research centres to investigate both the adverse effects for typical patients and whether the long-term effects support disease modification or not. Subcutaneous therapies, as discussed earlier, continue to be trialled and would substantially reduce burden and increase access.

#### 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 from a few months to 1 year.<sup>2</sup> A 2023 Cochrane review of 25 studies using the MMSE, with 1893 participants in total, found that there was moderate-quality evidence of a clinically important difference of 1.99 points

(95% CI 1.24–2.74) between cognitive stimulation and control groups and clinically relevant improvements in communication and social interaction.<sup>551</sup> Improvements were larger when sessions were twice, rather than once, weekly and in people with mild compared with moderate dementia.

#### Interventions for neuropsychiatric symptoms of dementia

##### Activity interventions

A systematic review and meta-analysis of seven studies (n=160) of tailored activity programme interventions identified a moderate effect on improving quality of life (standardised effect size Cohen's *d* 0.79, 95% CI 0.39–1.18), decreasing neuropsychiatric symptoms (0.62, 0.40–0.83), and decreasing carer burden (0.68, 0.29–1.07).<sup>552</sup> This review included small pilot trials in LMICs, which showed similar effects and validated the transferability between settings.<sup>553,554</sup> These interventions might also be cost saving because of decreased use of routine health-care systems by people receiving the intervention.<sup>555</sup> Good-quality RCTs of exercise interventions for people with dementia reported that these interventions did not improve neuropsychiatric symptoms, cognition, or functioning.<sup>556,557</sup>

Studies vary in the quality of evidence and design strategies, from feasibility studies and small RCTs to large multisite, cluster randomised trials (table 2).

Overall, the evidence supports earlier trials showing that co-ordinated care and different types of activities and being actively engaged reduced depression and neuropsychiatric symptoms and improved overall wellbeing 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 individuals' interests, preferences, and abilities and involve the family carer. The scalability and implementation of tailored activity interventions, and the potential cost-effectiveness of these interventions, require further research, with only two studies evaluating cost-effectiveness. By contrast, RCTs of exercise as an activity did not report any improvement in mental health domains in either community or care homes.<sup>556–557</sup>

#### *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, insufficient activity and light, pain, anxiety, and the environment.<sup>563</sup> A meta-analysis reported the pooled prevalence of clinically significant sleep disturbance in community-dwelling people with dementia to be 19% (95% CI 13–25; n=2753), and prevalence has not changed over time, suggesting that treatment has not improved sleep.<sup>564</sup> Sleep disturbance was less common among people with Alzheimer's disease (24%, 16–33, n=310) than people with dementia with Lewy bodies (49%, 37–61; n=65). The prevalence was similar in a meta-analysis of care-home residents (55 studies; n=22780; 20%, 16–24).<sup>565</sup>

Little evidence exists that medication is effective. One review including nine RCTs,<sup>566</sup> each rated to be low-quality, identified low-certainty evidence in a small trial (n=30) that trazadone 50 mg for 2 weeks might increase the total time spent asleep (mean difference 42.5 min, 95% CI 0.9 to 84.0) but there was no clear effect on other sleep parameters. Use of an orexin antagonist for 4 weeks in 274 people with mild-to-moderate Alzheimer's disease increased time spent asleep (28.2 min, 11.1 to 45.3) and decreased time spent awake after sleep onset (–15.7 min, –28.1 to –3.3) without increasing adverse effects but did not affect the number of awakenings. There was no evidence of melatonin efficacy. There are no RCTs of benzodiazepines, zopiclone, zaleplon, or zolpidem for sleep in people with dementia, but these drugs might cause notable harms. In longitudinal primary care studies, higher doses of so-called Z-drugs, such as zopiclone, zaleplon, zolpidem (equivalent to  $\geq 7.5$  mg zopiclone or  $> 5$  mg diazepam), in people with dementia were associated with increased fracture and stroke risks and so should be avoided for this purpose.<sup>567</sup> No conclusive evidence exists that non-pharmacological interventions

improve sleep in dementia, although trials are underway.<sup>568</sup>

#### *Depression*

We previously described the evidence that antidepressants are no more effective than placebo for depression in people with dementia.<sup>2</sup> People in both groups show improvement, and it could 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. Depression in people with dementia is likely to differ from depression in those without dementia, and the brain changes in different subtypes of dementia might reduce the effectiveness of antidepressants.<sup>569</sup>

A Cochrane review of RCTs of psychological treatments for depression and anxiety in people with MCI or dementia (ie, four studies with cognitive behavioural therapy, eight with behavioural activation, and three with problem solving therapy) identified that cognitive behavioural therapy-based treatments added to usual care for people with dementia or MCI and depressive symptoms or depressive diagnosis had a large effect (standardised mean difference –0.84, 95% CI –1.14 to –0.54;  $I^2=24%$ ; four studies, of which three were problem solving therapies; 194 participants), but there was little or no effect in those without depressive symptoms or diagnosis at baseline.<sup>570</sup> Supportive and counselling treatments were not effective.

#### *Psychosis, agitation, and delirium*

Psychosis can precede dementia and, as discussed in the risk section, very-late-onset schizophrenia might be a dementia prodrome.<sup>571</sup> Psychotic symptoms in dementia are associated with a particular tauopathy and neocortical synaptic disruption, but whether this pathology causes psychotic symptoms is unknown.<sup>571</sup> A modest association also exists between psychosis in Alzheimer's disease and APOE  $\epsilon 4$ , which does not account for all of the risk.<sup>572</sup>

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 might be due to delirium.<sup>1</sup>

If a person with dementia is not distressed by psychosis, then they might 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.

Cholinesterase inhibitors have a very small effect on improving psychosis in people with Alzheimer's disease, as shown by a meta-analysis of individual participant data from 12 RCTs of cholinesterase inhibitors for psychotic symptoms as secondary outcomes in Alzheimer's disease (effect size for delusions –0.08, 95% CI –0.14 to –0.03,  $I^2=0%$ ; hallucinations 0.09, –0.14 to –0.04;  $I^2=0%$ ; n=5580).<sup>573</sup> Caveats remain about

any antipsychotic use, which include increased dementia-specific mortality; therefore, antipsychotics might be appropriate for people whose psychosis creates distress or functional impairment and should be prescribed at as low a dose as possible and for the shortest time possible. Meta-analyses suggest that risperidone and aripiprazole are the antipsychotics with the best evidence for treatment of psychosis in people with dementia, with evidence that there is less risk of stroke with risperidone for delusions than for other indications.<sup>2,571</sup>

An RCT of pimavanserin (an atypical antipsychotic with selective 5-HT<sub>2A</sub> inverse agonist effect) withdrawal in dementia-related psychosis was stopped early due to lower rates of relapse in the treatment group versus the placebo group, which appeared to be driven by effects in people with Parkinson's disease.<sup>574</sup> A US retrospective cohort study comparing pimavanserin (n=3227) with atypical antipsychotics (n=18442) in people with Parkinson's disease with or without dementia reported a lower mortality rate in those treated with pimavanserin (HR 0.65, 95% CI 0.53–0.79).<sup>575</sup> An earlier RCT of efficacy in Alzheimer's disease psychosis showed differences favouring pimavanserin at week 6 but not at weeks 2, 4, 9, or 12.<sup>576</sup> Pimavanserin is approved as a treatment for psychosis in Parkinson's disease, but the FDA rejected the drug for treatment of dementia-related psychosis and Alzheimer's disease psychosis.

We previously recommended, 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.<sup>1</sup> Immediate action requires assessment of the underlying reasons for agitation, such as pain and distress, and management of these before use of medication.

Certain antipsychotics, such as risperidone, are licensed in the UK, Australia, Canada, and the EU for treating agitation in people with dementia. In May, 2023, brexpiprazole became the first antipsychotic to obtain FDA marketing approval in the USA for treating agitation in people with Alzheimer's disease, but it does not afford better efficacy or safety than other atypical antipsychotic drugs for this indication.<sup>577–579</sup> A phase 3 study (n=433) showed that treatment with brexpiprazole 2 mg per day for agitation in people with Alzheimer's disease was associated with an improvement on the Cohen-Mansfield Agitation Inventory by 3.77 points versus placebo at 12 weeks.<sup>578</sup> The most recent large, 12-week, phase 3 RCT of brexpiprazole 2–3 mg per day for agitation in Alzheimer's disease (n=345) reported an improvement on the Cohen-Mansfield Agitation Inventory by –5.3 points compared with placebo.<sup>580</sup> In comparison, a pooled analysis of three RCTs of risperidone that used the Cohen-Mansfield Agitation Inventory (n=1150) showed that a mean dose of 1 mg/day was associated with an improvement of –5.4 points on

the Cohen-Mansfield Agitation Inventory at 12 weeks.<sup>581</sup>

The main concern with antipsychotic drugs in people with dementia is increased risk for cardiovascular adverse events and mortality.<sup>582</sup> Brexpiprazole treatment was associated with more deaths than placebo (six deaths vs one death), although significance was not reported.<sup>580</sup> Risperidone is the atypical antipsychotic with the largest RCT evidence base in the treatment of agitation. Antipsychotics should be used only after a thorough assessment and management of the underlying causes of agitation, consideration of a trial of non-pharmacological strategies, and a discussion of any potential risks with the person with dementia and their family carers, depending on capacity.

Delirium is common, under-recognised, and undertreated in older people. One cohort study reported that baseline cognition was lower in older people (ie, aged ≥70 years) who developed delirium than in the whole cohort including those who did not develop delirium.<sup>583</sup> In the 2020 *Lancet* Commission, we discussed how delirium and dementia frequently occur together but no definitive evidence exists that any medication improves delirium. Sedating benzodiazepines are ineffective and, like antipsychotics, are associated with increased mortality and morbidity.<sup>2</sup>

Delirium superimposed on dementia is associated with longer time spent in hospital, worse cognitive and functional outcomes, and a higher risk of care home admission and mortality.<sup>584</sup> A recent meta-analysis identified that delirium was significantly associated with future cognitive decline (effect size Hedges g 0.45, 95% CI 0.34–0.57).<sup>585</sup> In a UK study, 209 (13.8%) of 1510 participants in a prospective cohort with median age of 77 years (IQR 73–82) were admitted to hospital at least once over a follow-up of 30 months or more, of whom 115 (55.0%) had at least one episode of delirium.<sup>586</sup> People who were more cognitively impaired were more likely to be admitted to hospital and more likely to develop delirium; furthermore, the delirium was more severe and longer than for people with better cognition. Similarly, in a UK prospective cohort of people older than 65 years, 82 (40%) of 205 people who were admitted to hospital developed delirium. This result was associated with a cognitive decline at 1 year of –1.8 points (95% CI –3.5 to –0.2) on the MMSE.<sup>587</sup> Overall cognitive impairment is a risk factor for delirium, which in turn is a risk factor for further cognitive deterioration and functional decline.<sup>588</sup>

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 are also crucial. Additionally, it is essential to monitor the health of people who are discharged from hospital with delirium. These people 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 people without dementia might decrease dementia risk, but currently we cannot be sure.<sup>589</sup>

### Lessons learnt from COVID-19 and dementia

COVID-19 by itself and the associated social isolation and lockdown has had a substantial, disproportionate, negative impact on symptoms and mortality of people with dementia and on their families and carers.<sup>590</sup> People with dementia had higher mortality from COVID-19 (meta-analysis of ten studies; OR 5.17, 95% CI 2.31–11.59; n=119 218) than people without dementia.<sup>591</sup> A systematic review of the effects of social isolation during the COVID-19 pandemic identified that nine (60%) of 15 studies with a total of 6442 participants reported worse than expected deterioration in cognition and 14 (93%) of 15 studies reported worsening or new onset of non-cognitive symptoms.<sup>592</sup>

Care-home residents usually need personal care, and thus cannot be isolated from staff. Families were frequently restricted or forbidden to visit during the pandemic to contain risk, thus leaving people isolated.<sup>590,593</sup> Larger care homes and homes that used more agency staff, transferred staff between settings, tested less often for COVID-19, and had less access to personal protective equipment had higher levels of infection and mortality.<sup>594</sup>

Long-term lessons for other pandemics include a policy ensuring that people are not admitted to a care home when their infection status is positive or unknown to avoid exposing existing residents. We now know the positive effects of restricting the movement of care-home staff between homes and ensuring that staff have priority access to and wear personal protective equipment to reduce infection. People with dementia require access to care that is appropriate for them, and it is impossible to completely isolate people who need 24 h 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 2020 *Lancet* Commission, people with dementia often have other illnesses and die earlier than people without dementia.<sup>2</sup> People with dementia or another decision maker, such as 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.<sup>595</sup> 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 scarce.

Technologies to assess dementia symptoms have little evidence about effectiveness. A review of 14 studies of sensing technologies for dementia symptoms showed that, in seven studies, actigraphy correlated with agitation and aggression in people with dementia, but there was an absence of evidence for other technologies.<sup>596</sup> A review of 55 studies of assessments of sleep quality in dementia identified five studies with actigraphy, but these studies showed no benefit of actigraphy compared with questionnaire-based instruments.<sup>565</sup>

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 no clear evidence of efficacy.<sup>597</sup> An RCT in 495 people with dementia reported that 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 terms of 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.<sup>598</sup> In a systematic review of 66 studies, use of socially assistive robots was generally feasible and acceptable to people with dementia and their carers and to health-care professionals, but there was no evidence of effect on cognition, neuropsychiatric symptoms, or quality of life.<sup>599</sup>

Generally, there is an absence of evidence to recommend specific technologies for dementia management. Technologies should, where possible, supplement rather than replace existing face-to-face care to avoid leading to harmful social isolation. There is concern that future technology might reduce equity by creating accessibility issues for people with little financial resources.

### Conclusions

The number of people living with dementia is set to increase in all countries, and policy makers should prioritise resources to enable risk reduction to prevent or delay dementia and interventions to improve symptoms and life for people with dementia and their families. The prevention approach should be directed at addressing risk factor levels at an early stage and continuing throughout the life course. 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 (ie, cholesterol, diabetes, obesity, and blood pressure), reducing head injury, and maintaining and encouraging physical activity. Policy changes can improve education (in quality as well as years of education) and reduce smoking, alcohol use, the risk of TBI, air pollution, and salt and sugar in food, thus targeting



obesity, hypertension, and diabetes. Structural changes can help to increase exercise and reduce social isolation. Notably, interventions or lifestyle changes at any stage of life can alter the risk of dementia.

There is much more evidence now than existed when the 2020 *Lancet* Commission was published that interventions can help to retain cognition and prevent dementia. These interventions should be targeted at people who need them most. In many countries, interventions known to benefit people with dementia are not available or a priority. Good-quality diagnosis, care planning, and tailored post-diagnostic support enable the prevention of harm, treatment of neuropsychiatric symptoms, and protection of quality of life for people with dementia and their family carers. Effective interventions exist, but they are not delivered at scale to everyone that would benefit from them.

The advent of disease-modifying drugs for dementia is a long-awaited scientific breakthrough, but results vary from modestly positive to neutral, and the clinical implications are still unclear. There is exciting progress in the field of biomarkers, but biomarkers are not enough by themselves to justify diagnosis. Clinically, biomarkers should be used only to help to classify the neuropathology in people with dementia, particularly that of Alzheimer's disease. Drug and psychosocial treatments are progressing, and there are more people living with dementia than ever before. It is even more important now, therefore, that care for people with dementia and their families is improved.

#### 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. SGC, AS, and GL conceptualised and performed new meta-analyses. GL, NM, GS, and AS conceived the new population attributable fraction calculation and defined the variables. GL and NM updated prevalences and relative risks for the population attributable fraction. NM carried out the analysis for weighted population attributable fraction. GL, SGC, AS, JH, NM, KYL, SA, DA, SB, NCF, CPF, LNG, RH, HCK, MK, EBL, NN, KR, QS, KS, AS-M, LSS, YY, and SW attended the meeting to discuss the content of this Commission. GL and SGC accessed verified the meta-analysis for hearing aids. AS and GL accessed and verified the new data for the regression meta-analysis. NM and GL accessed and verified the new data to calculate communality and PAFs. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

#### Declaration of interests

SA declares grants from the Indian Council for Medical Research (2022–25), the Government of Karnataka (2022–23), Rotary Bangalore Midtown (2022–23), Lowes Services India (2022–25), and Wellcome Trust (2023–26); payment for expert testimony received by Indian Council of Medical Research and Ashoka University; and a travel grant paid by University College London for being part of the *Lancet* Commission. SB declares grants from National Institute for Health and Care Research (NIHR), Economic and Social Research Council, Engineering and Physical Science Research Council, Canadian Institute for Health Research, the Alzheimer's Association, the Alzheimer's Society, Health Education England, Alzheimer's Association, Alzheimer's Society, and Health Education England. He has held the following positions: Non-Executive Director Somerset NHS Foundation Trust, Trustee of the Alzheimer's Society, Executive Dean of the University of Plymouth, and Pro-Vice Chancellor of the University of

Nottingham. AB acts as a consultant for Lilly, TauRx Pharmaceuticals, and Eisai and carries out medico-legal work for solicitors. NCF declares consulting fees from F Hoffmann-La Roche, Eli Lilly, Ionis, Biogen, and Siemens; participation in data safety monitoring or advisory board for Biogen; and being a member of the Research Strategy Council for the Alzheimer's Society. LNG declares owning tailored activity programme licences. MK declares grants from Wellcome Trust (221854/Z/20/Z), the Medical Research Council (R024227), the National Institute on Aging (R01AG062553, R01AG056477), and the Academy of Finland (350426). KYL declared fellowship from Medical Research Council. EBL receives grants from the National Institutes of Health (NIH) and royalties from UpToDate. GL declares support for the manuscript from the Alzheimer's Society, the Alzheimer's Society UK, and UK Research and Innovation, who gave grants to pay for travel and accommodation. She is supported by the University College London Hospitals' NIHR Biomedical Research Centre, by North Thames NIHR Applied Research Collaboration, and as an NIHR Senior Investigator and has grants from NIHR Health Technology Assessment, NIHR Programme Grants for Applied Research, the Alzheimer's Association, the Norwegian Research Council, and Wellcome, outside of the submitted work. She works with the Alzheimer's Society as a member of the Research Strategy Council and is a trustee of Nightingale Hammerson care homes. KR declares grants from Canadian Institutes of Health Research, the Canadian Frailty Network, and Research Nova Scotia; royalties from Biotech, Qu Biologics, AstraZeneca UK, BioAge Labs, Congenica, Icosavax, KCR, Faraday Pharmaceuticals, Synairgen Research, Enanta Pharmaceuticals, Pfizer, Boehringer Ingelheim International, Fresenius Kabi Deutschland, Baycrest Geriatric Care, and Shanghai Ark Biopharmaceutical; payment or honoraria from University of British Columbia, Fraser Health Authority, McMaster University, Chinese Medical Association, Wake Forest University Medical School Centre, University of Omaha, and Atria Institute; participation on data safety or advisory board for EpiPharma; and leadership of the Canadian Consortium on Neurodegeneration in Dementia, Cap Breton University, and Nova Scotia Health. KS declares support from the Japan Society for the Promotion of Science fund (22H03352, 21KK0168, 16KK0059). LSS declares support from Della Martin Foundation, the NIH (P30 AG066530, R01 AG051346, R01 AG062687, R01 AG051346, R01 AG055444, P01 AG052350, R01 AG053267, R01 AG074983, R01 AG063826), Abbott, Biohaven, Biogen, Eisai, and Eli Lilly and consulting fees from AC Immune, Cortexyme, Alpha-cognition, BioVie, Athira, Eli Lilly/Avid, Corium, Lundbeck, Merck, Muna Therapeutics, Novo-Nordisk, Neurim, NeuroDiagnostics, Ono, Otsuka, Roche/Genentech, Cognition, Lighthouse, GW Research, ImmunoBrain, and Bristol Myers Squibb. AS declares grants from Wellcome Trust, the Alzheimer's Association, Brain Canada, and the NIHR. YY declares support from the National Natural Science Foundation of China (72374013) and the National Key R&D Program of China (2023YFB4603200, 2023YFC3606400). SW declares an NIHR doctoral training fellowship. GS has participated on advisory boards for the following pharmaceutical companies manufacturing drugs against Alzheimer's disease: Biogen, Roche, and Eisai. LG is an inventor of a training program for health and human service professionals in an evidence-based tailored activity intervention, the Tailored Activity Program; she and her respective universities are entitled to fees. All other authors declare no competing interests.

#### Acknowledgments

We are partnered with University College London, who provided rooms and logistic support, and the Alzheimer's Society, the Economic and Social Research Council, and Alzheimer's Research UK and we thank them for financial help. These organisations funded the fares, accommodation, and food for the Commission meeting. The funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. We thank Seema Duggal (University College London, London, UK) for her administrative help, including managing finances and booking rooms and food. We thank the HUNT Research Centre (Norwegian University of Science and Technology, Levanger, Norway), with Arnulf Langhammer, Jørn Sjøberg Fenstad, and Håvard Horndalen Tveit, for their work in defining risk factors and extracting and processing their data to provide us with



figures on communality. We thank Ruan-Ching Yu (University College London, London, UK) for their contribution to the hearing systematic review and meta-analysis, Cecilia S Lee for their contribution to reading and commenting on the initial draft text on vision, and Lindsay Wallace for their contribution to reading and commenting on the initial text and first draft paper on public health.

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