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# Dementia prevention, intervention, and care: 2020 report of the Lancet Commission



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## Executive summary

The number of older people, including those living with dementia, is rising, as younger age mortality declines. However, the age-specific incidence of dementia has fallen in many countries, probably because of improvements in education, nutrition, health care, and lifestyle changes. Overall, a growing body of evidence supports the nine potentially modifiable risk factors for dementia modelled by the 2017 *Lancet* Commission on dementia prevention, intervention, and care: less education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, and low social contact. We now add three more risk factors for dementia with newer, convincing evidence. These factors are excessive alcohol consumption, traumatic brain injury (TBI), and air pollution. We have completed new reviews and meta-analyses and incorporated these into an updated 12 risk factor life-course model of dementia prevention. Together the 12 modifiable risk factors account for around 40% of worldwide dementias, which consequently could theoretically be prevented or delayed. The potential for prevention is high and might be higher in low-income and middle-income countries (LMIC) where more dementias occur.

Our new life-course model and evidence synthesis has paramount worldwide policy implications. It is never too early and never too late in the life course for dementia prevention. Early-life (younger than 45 years) risks, such as less education, affect cognitive reserve; midlife (45–65 years), and later-life (older than 65 years) risk factors influence reserve and triggering of neuropathological developments. Culture, poverty, and inequality are key drivers of the need for change. Individuals who are most deprived need these changes the most and will derive the highest benefit.

Policy should prioritise childhood education for all. Public health initiatives minimising head injury and decreasing harmful alcohol drinking could potentially reduce young-onset and later-life dementia. Midlife systolic blood pressure control should aim for 130 mm Hg or lower to delay or prevent dementia. Stopping smoking, even in later life, ameliorates this risk. Passive smoking is a less considered modifiable risk factor for dementia. Many countries have restricted this exposure. Policy makers should expedite improvements in air quality, particularly in areas with high air pollution.

We recommend keeping cognitively, physically, and socially active in midlife and later life although little evidence exists for any single specific activity protecting

against dementia. Using hearing aids appears to reduce the excess risk from hearing loss. Sustained exercise in midlife, and possibly later life, protects from dementia, perhaps through decreasing obesity, diabetes, and cardiovascular risk. Depression might be a risk for dementia, but in later life dementia might cause depression. Although behaviour change is difficult and some associations might not be purely causal, individuals have a huge potential to reduce their dementia risk.

In LMIC, not everyone has access to secondary education; high rates of hypertension, obesity, and hearing loss exist, and the prevalence of diabetes and smoking are growing, thus an even greater proportion of dementia is potentially preventable.

Amyloid- $\beta$  and tau biomarkers indicate risk of progression to Alzheimer's dementia but most people with normal cognition with only these biomarkers never develop the disease. Although accurate diagnosis is important for patients who have impairments and functional concerns and their families, no evidence exists to support pre-symptomatic diagnosis in everyday practice.

Our understanding of dementia aetiology is shifting, with latest description of new pathological causes. In the oldest adults (older than 90 years), in particular, mixed dementia is more common. Blood biomarkers might hold promise for future diagnostic approaches and are more scalable than CSF and brain imaging markers.

Wellbeing is the goal of much of dementia care. People with dementia have complex problems and symptoms in many domains. Interventions should be individualised and consider the person as a whole, as well as their family carers. Evidence is accumulating for the effectiveness, at least in the short term, of psychosocial interventions tailored to the patient's needs, to manage neuropsychiatric symptoms. Evidence-based interventions for carers can reduce depressive and anxiety symptoms over years and be cost-effective.

Keeping people with dementia physically healthy is important for their cognition. People with dementia have more physical health problems than others of the same age but often receive less community health care and find it particularly difficult to access and organise care. People with dementia have more hospital admissions than other older people, including for illnesses that are potentially manageable at home. They have died disproportionately in the COVID-19 epidemic. Hospitalisations are distressing and are associated with poor outcomes and high costs. Health-care professionals

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## Key messages

- Three new modifiable risk factors for dementia
- New evidence supports adding three modifiable risk factors—excessive alcohol consumption, head injury, and air pollution—to our 2017 *Lancet* Commission on dementia prevention, intervention, and care life-course model of nine factors (less education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, and infrequent social contact).
- Modifying 12 risk factors might prevent or delay up to 40% of dementias.
- Be ambitious about prevention
- Prevention is about policy and individuals. Contributions to the risk and mitigation of dementia begin early and continue throughout life, so it is never too early or too late. These actions require both public health programmes and individually tailored interventions. In addition to population strategies, policy should address high-risk groups to increase social, cognitive, and physical activity; and vascular health.
- Specific actions for risk factors across the life course
  - Aim to maintain systolic BP of 130 mm Hg or less in midlife from around age 40 years (antihypertensive treatment for hypertension is the only known effective preventive medication for dementia).
  - Encourage use of hearing aids for hearing loss and reduce hearing loss by protection of ears from excessive noise exposure.
  - Reduce exposure to air pollution and second-hand tobacco smoke.
  - Prevent head injury.
  - Limit alcohol use, as alcohol misuse and drinking more than 21 units weekly increase the risk of dementia.
  - Avoid smoking uptake and support smoking cessation to stop smoking, as this reduces the risk of dementia even in later life.
  - Provide all children with primary and secondary education.
- Reduce obesity and the linked condition of diabetes. Sustain midlife, and possibly later life physical activity.
- Addressing other putative risk factors for dementia, like sleep, through lifestyle interventions, will improve general health.
- Tackle inequality and protect people with dementia
- Many risk factors cluster around inequalities, which occur particularly in Black, Asian, and minority ethnic groups and in vulnerable populations. Tackling these factors will involve not only health promotion but also societal action to improve the circumstances in which people live their lives. Examples include creating environments that have physical activity as a norm, reducing the population profile of blood pressure rising with age through better patterns of nutrition, and reducing potential excessive noise exposure.
- Dementia is rising more in low-income and middle-income countries (LMIC) than in high-income countries, because of population ageing and higher frequency of potentially modifiable risk factors. Preventative interventions might yield the largest dementia reductions in LMIC.

## For those with dementia, recommendations are:

- Provide holistic post-diagnostic care
  - Post-diagnostic care for people with dementia should address physical and mental health, social care, and support. Most people with dementia have other illnesses and might struggle to look after their health and this might result in potentially preventable hospitalisations.
- Manage neuropsychiatric symptoms
  - Specific multicomponent interventions decrease neuropsychiatric symptoms in people with dementia and are the treatments of choice. Psychotropic drugs are often ineffective and might have severe adverse effects.
- Care for family carers
  - Specific interventions for family carers have long-lasting effects on depression and anxiety symptoms, increase quality of life, are cost-effective and might save money.

should consider dementia in older people without known dementia who have frequent admissions or who develop delirium. Delirium is common in people with dementia and contributes to cognitive decline. In hospital, care including appropriate sensory stimulation, ensuring fluid intake, and avoiding infections might reduce delirium incidence.

Acting now on dementia prevention, intervention, and care will vastly improve living and dying for individuals with dementia and their families, and thus society.

## Introduction

Worldwide around 50 million people live with dementia, and this number is projected to increase to 152 million

by 2050,<sup>1</sup> rising particularly in low-income and middle-income countries (LMIC) where around two-thirds of people with dementia live.<sup>1</sup> Dementia affects individuals, their families, and the economy, with global costs estimated at about US\$1 trillion annually.<sup>1</sup>

We reconvened the 2017 *Lancet* Commission on dementia prevention, intervention, and care<sup>2</sup> to identify the evidence for advances likely to have the greatest impact since our 2017 paper and build on its work. Our interdisciplinary, international group of experts presented, debated, and agreed on the best available evidence. We adopted a triangulation framework evaluating the consistency of evidence from different lines of research and used that as the basis to evaluate evidence. We have

summarised best evidence using, where possible, good-quality systematic reviews, meta-analyses, or individual studies, where these add important knowledge to the field. We performed systematic literature reviews and meta-analyses where needed to generate new evidence for our analysis of potentially modifiable risk factors for dementia. Within this framework, we present a narrative synthesis of evidence including systematic reviews and meta-analyses and explain its balance, strengths, and limitations. We evaluated new evidence on dementia risk in LMIC; risks and protective factors for dementia; detection of Alzheimer’s disease; multimorbidity in dementia; and interventions for people affected by dementia.

Nearly all the evidence is from studies in high-income countries (HIC), so risks might differ in other countries and interventions might require modification for different cultures and environments. This notion also underpins the critical need to understand the dementias related to life-course disadvantage—whether in HICs or LMICs.

Our understanding of dementia aetiology is shifting. A consensus group, for example, has described hippocampal sclerosis associated with TDP-43 proteinopathy, as limbic-predominant age-related TDP-43 encephalopathy (LATE) dementia, usually found in people older than 80 years, progressing more slowly than Alzheimer’s disease, detectable at post-mortem, often mimicking or comorbid with Alzheimer’s disease.<sup>3</sup> This situation reflects increasing attention as to how clinical syndromes are and are not related to particular underlying pathologies and how this might change across age. More work is needed, however, before LATE can be used as a valid clinical diagnosis.

The fastest growing demographic group in HIC is the oldest adults, those aged over 90 years. Thus a unique opportunity exists to focus on both human biology, in this previously rare population, as well as on meeting their needs and promoting their wellbeing.

### Prevention of dementia

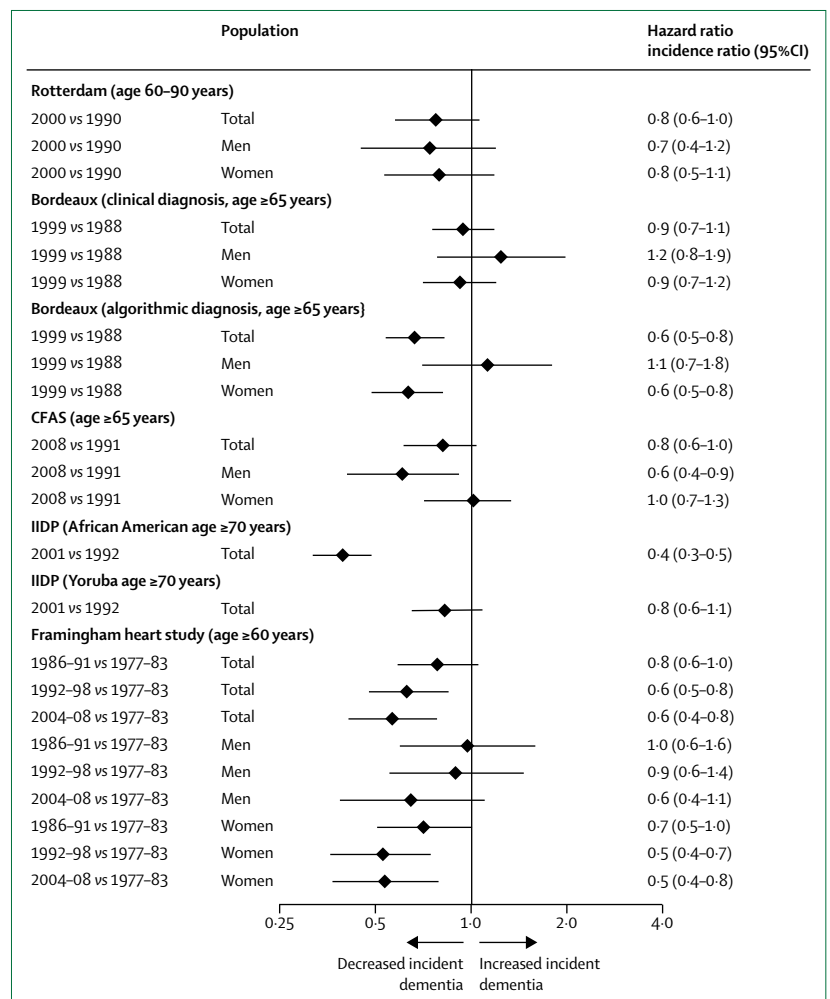
The number of people with dementia is rising. Predictions about future trends in dementia prevalence vary depending on the underlying assumptions and geographical region, but generally suggest substantial increases in overall prevalence related to an ageing population. For example, according to the Global Burden of Diseases, Injuries, and Risk Factors Study, the global age-standardised prevalence of dementia between 1990 and 2016 was relatively stable, but with an ageing and bigger population the number of people with dementia has more than doubled since 1990.<sup>4</sup>

However, in many HIC such as the USA, the UK, and France, age-specific incidence rates are lower in more recent cohorts compared with cohorts from previous decades collected using similar methods and target populations<sup>5</sup> (figure 1) and the age-specific incidence of dementia appears to decrease.<sup>6</sup> All-cause dementia

incidence is lower in people born more recently,<sup>7</sup> probably due to educational, socio-economic, health care, and lifestyle changes.<sup>2,5</sup> However, in these countries increasing obesity and diabetes and declining physical activity might reverse this trajectory.<sup>8,9</sup> In contrast, age-specific dementia prevalence in Japan, South Korea, Hong Kong, and Taiwan looks as if it is increasing, as is Alzheimer’s in LMIC, although whether diagnostic methods are always the same in comparison studies is unclear.<sup>2-7</sup>

Modelling of the UK change suggests a 57% increase in the number of people with dementia from 2016 to 2040, 70% of that expected if age-specific incidence rates remained steady,<sup>10</sup> such that by 2040 there will be 1.2 million UK people with dementia. Models also suggest that there will be future increases both in the number of individuals who are independent and those with complex care needs.<sup>6</sup>

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**Figure 1:** Incidence rate ratio comparing new cohorts to old cohorts from five studies of dementia incidence<sup>5</sup> IIDP Project in USA and Nigeria, Bordeaux study in France, and Rotterdam study in the Netherlands adjusted for age. Framingham Heart Study, USA, adjusted for age and sex. CFAS in the UK adjusted for age, sex, area, and deprivation. However, age-specific dementia prevalence is increasing in some other countries. IID=Indianapolis-Ibadan Dementia. CFAS=Cognitive Function and Ageing Study. Adapted from Wu et al,<sup>5</sup> by permission of Springer Nature.

In our first report, the 2017 Commission described a life-course model for potentially modifiable risks for dementia.<sup>2</sup> Life course is important when considering risk, for example, obesity and hypertension in midlife predict future dementia, but both weight and blood pressure usually fall in later life in those with or developing dementia,<sup>9</sup> so lower weight and blood pressure in later life might signify illness, not an absence of risk.<sup>11-14</sup> We consider evidence on other potential risk factors and incorporate those with good quality evidence in our model.

Figure 2 summarises possible mechanisms of protection from dementia, some of which involve increasing or maintaining cognitive reserve despite pathology and neuropathological damage. There are different terms describing the observed differential susceptibility to age-related and disease-related changes and these are not used consistently.<sup>15,16</sup> A consensus paper defines reserve as a concept accounting for the difference between an individual's clinical picture and their neuropathology. It, divides the concept further into neurobiological brain reserve (eg, numbers of neurones and synapses at a given timepoint), brain maintenance (as neurobiological capital at any timepoint, based on genetics or lifestyle reducing brain changes and pathology development over time) and cognitive reserve as adaptability enabling preservation of cognition or everyday functioning in spite of brain pathology.<sup>15</sup> Cognitive reserve is changeable and quantifying it uses proxy measures such as education, occupational complexity, leisure activity, residual approaches (the variance of cognition not explained by demographic variables and brain measures), or identification of functional networks that might underlie such reserve.<sup>15-20</sup>

Early-life factors, such as less education, affect the resulting cognitive reserve. Midlife and old-age risk factors influence age-related cognitive decline and triggering of neuropathological developments. Consistent with the hypothesis of cognitive reserve is that older women are more likely to develop dementia than men of the same

age, probably partly because on average older women have had less education than older men. Cognitive reserve mechanisms might include preserved metabolism or increased connectivity in temporal and frontal brain areas.<sup>17-21</sup> People in otherwise good physical health can sustain a higher burden of neuropathology without cognitive impairment.<sup>22</sup> Culture, poverty, and inequality are important obstacles to, and drivers of, the need for change to cognitive reserve. Those who are most deprived need these changes the most and will derive the highest benefit from them.

Smoking increases air particulate matter, and has vascular and toxic effects.<sup>23</sup> Similarly air pollution might act via vascular mechanisms.<sup>24</sup> Exercise might reduce weight and diabetes risk, improve cardiovascular function, decrease glutamine, or enhance hippocampal neurogenesis.<sup>25</sup> Higher HDL cholesterol might protect against vascular risk and inflammation accompanying amyloid- $\beta$  (A $\beta$ ) pathology in mild cognitive impairment.<sup>26</sup>

### Dementia in LMIC

Numbers of people with dementia in LMIC are rising faster than in HIC because of increases in life expectancy and greater risk factor burden. We previously calculated that nine potentially modifiable risk factors together are associated with 35% of the population attributable fraction (PAFs) of dementia worldwide: less education, high blood pressure, obesity, hearing loss, depression, diabetes, physical inactivity, smoking, and social isolation, assuming causation.<sup>2</sup> Most research data for this calculation came from HIC and there is a relative absence of specific evidence of the impact of risk factors on dementia risk in LMIC, particularly from Africa and Latin America.<sup>27</sup>

Calculations considering country-specific prevalence of the nine potentially modifiable risk factors indicate PAF of 40% in China, 41% in India and 56% in Latin America with the potential for these numbers to be even higher depending on which estimates of risk factor frequency are used.<sup>28,29</sup> Therefore a higher potential for dementia prevention exists in these countries than in global estimates that use data predominantly from HIC. If not currently in place, national policies addressing access to education, causes and management of high blood pressure, causes and treatment of hearing loss, socio-economic and commercial drivers of obesity, could be implemented to reduce risk in many countries. The higher social contact observed in the three LMIC regions provides potential insights for HIC on how to influence this risk factor for dementia.<sup>30</sup> We could not consider other risk factors such as poor health in pregnancy of malnourished mothers, difficult births, early life malnutrition, survival with heavy infection burdens alongside malaria and HIV, all of which might add to the risks in LMIC.

Diabetes is very common and cigarette smoking is rising in China while falling in most HIC.<sup>31</sup> A

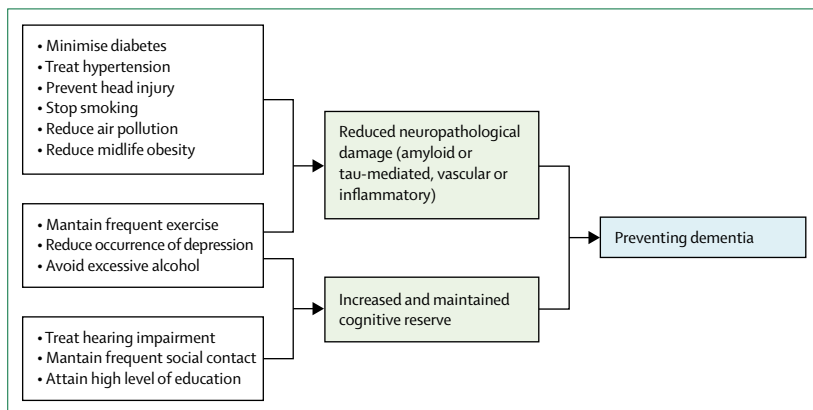


Figure 2: Possible brain mechanisms for enhancing or maintaining cognitive reserve and risk reduction of potentially modifiable risk factors in dementia



meta-analysis found variation of the rates of dementia within China, with a higher prevalence in the north and lower prevalence in central China, estimating 9.5 million people are living with dementia, whereas a slightly later synthesis estimated a higher prevalence of around 11 million.<sup>30,32</sup> These data highlight the need for more focused work in LMIC for more accurate estimates of risk and interventions tailored to each setting.

### Specific potentially modifiable risk factors for dementia

Risk factors in early life (education), midlife (hypertension, obesity, hearing loss, TBI, and alcohol misuse) and later life (smoking, depression, physical inactivity, social isolation, diabetes, and air pollution) can contribute to increased dementia risk (table 1). Good evidence exists for all these risk factors although some late-life factors, such as depression, possibly have a bidirectional impact and are also part of the dementia prodrome.<sup>33,34</sup>

In the next section, we briefly describe relevant newly published and illustrative research studies that add to the 2017 Commission’s evidence base, including risks and, for some, mitigation. We have chosen studies that are large and representative of the populations, or smaller studies in areas where very little evidence exists. We discuss them in life-course order and within the life course in the order of magnitude of population attributable factor.

#### Education and midlife and late-life cognitive stimulation Education level reached

Higher childhood education levels and lifelong higher educational attainment reduce dementia risk.<sup>2,35–37</sup> New work suggests overall cognitive ability increases, with education, before reaching a plateau in late adolescence, when brain reaches greatest plasticity; with relatively few further gains with education after age 20 years.<sup>38</sup> This suggests cognitive stimulation is more important in early life; much of the apparent later effect might be due to people of higher cognitive function seeking out cognitively stimulating activities and education.<sup>38</sup> It is difficult to separate out the specific impact of education from the effect of overall cognitive ability,<sup>38,39</sup> and the specific impact of later-life cognitive activity from lifelong cognitive function and activity.<sup>39,40</sup>

#### Cognitive maintenance

One large study in China tried to separate cognitive activity in adulthood from activities for those with more education, by considering activities judged to appeal to people of different levels of education.<sup>40</sup> It found people older than 65 years who read, played games, or bet more frequently had reduced risk of dementia (n=15 882, odds ratio [OR]=0.7, 95% CI 0.6–0.8). The study excluded people developing dementia less than 3 years after baseline to reduce reverse causation.

|                                      | Relative risk for dementia (95% CI) | Risk factor prevalence | Communality | Unweighted PAF | Weighted PAF* |
|--------------------------------------|-------------------------------------|------------------------|-------------|----------------|---------------|
| <b>Early life (&lt;45 years)</b>     |                                     |                        |             |                |               |
| Less education                       | 1.6 (1.3–2.0)                       | 40.0%                  | 61.2%       | 19.4%          | 7.1%          |
| <b>Midlife (age 45–65 years)</b>     |                                     |                        |             |                |               |
| Hearing loss                         | 1.9 (1.4–2.7)                       | 31.7%                  | 45.6%       | 22.2%          | 8.2%          |
| TBI                                  | 1.8 (1.5–2.2)                       | 12.1%                  | 55.2%       | 9.2%           | 3.4%          |
| Hypertension                         | 1.6 (1.2–2.2)                       | 8.9%                   | 68.3%       | 5.1%           | 1.9%          |
| Alcohol (>21 units/week)             | 1.2 (1.1–1.3)                       | 11.8%                  | 73.3%       | 2.1%           | 0.8%          |
| Obesity (body-mass index ≥30)        | 1.6 (1.3–1.9)                       | 3.4%                   | 58.5%       | 2.0%           | 0.7%          |
| <b>Later life (age &gt;65 years)</b> |                                     |                        |             |                |               |
| Smoking                              | 1.6 (1.2–2.2)                       | 27.4%                  | 62.3%       | 14.1%          | 5.2%          |
| Depression                           | 1.9 (1.6–2.3)                       | 13.2%                  | 69.8%       | 10.6%          | 3.9%          |
| Social isolation                     | 1.6 (1.3–1.9)                       | 11.0%                  | 28.1%       | 4.2%           | 3.5%          |
| Physical inactivity                  | 1.4 (1.2–1.7)                       | 17.7%                  | 55.2%       | 9.6%           | 1.6%          |
| Diabetes                             | 1.5 (1.3–1.8)                       | 6.4%                   | 71.4%       | 3.1%           | 1.1%          |
| Air pollution                        | 1.1 (1.1–1.1)                       | 75.0%                  | 13.3%       | 6.3%           | 2.3%          |

Data are relative risk (95% CI) or %. Overall weighted PAF=39.7%. PAF=population attributable fraction. TBI=traumatic brain injury. \*Weighted PAF is the relative contribution of each risk factor to the overall PAF when adjusted for communality.

**Table 1: PAF for 12 dementia risk factors**

This finding is consistent with small studies of midlife activities which find them associated with better late-life cognition; so for example, in 205 people aged 30–64 years, followed up until 66–88 years, travel, social outings, playing music, art, physical activity, reading, and speaking a second language, were associated with maintaining cognition, independent of education, occupation, late-life activities, and current structural brain health.<sup>41</sup> Similarly, engaging in intellectual activity as adults, particularly problem solving, for 498 people born in 1936, was associated with cognitive ability acquisition, although not the speed of decline.<sup>42</sup>

#### Cognitive decline

The use it or lose it hypothesis suggests that mental activity, in general, might improve cognitive function. People in more cognitively demanding jobs tend to show less cognitive deterioration before, and sometimes after retirement than those in less demanding jobs.<sup>43,44</sup> One systematic review of retirement and cognitive decline found conflicting evidence.<sup>45</sup> Subsequently, a 12-year study of 1658 people found older retirement age but not number of years working, was associated with lower dementia risk.<sup>46</sup> Those retiring because of ill health had lower verbal memory and fluency scores than those retiring for other reasons.<sup>47</sup> Another study found a two-fold increase in episodic memory loss attributable to retirement (n=18 575, mean age 66 years), compared to non-retirees, adjusting for health, age, sex, and wealth.<sup>48</sup> Similarly, in a cohort of 3433 people retiring at a mean age of 61 years, verbal memory declined 38% (95% CI 22–60) faster than before retirement.<sup>44</sup> In countries with

younger compared to higher retirement ages, average cognitive performance drops more.<sup>49</sup>

### Cognitive interventions in normal cognition and mild cognitive impairment

A cognitive intervention or cognition-orientated treatment comprises strategies or skills to improve general or specific areas of cognition.<sup>50</sup> Computerised cognitive training programmes have increasingly replaced tasks that were originally paper-and-pencil format with computer-based tasks for practice and training.<sup>51</sup>

Three systematic reviews in the general population found no evidence of generalised cognition improvement from specific cognitive interventions, including computerised cognitive training, although the domain trained might improve.<sup>52–54</sup>

A meta-analysis of 17 controlled trials of at least 4 hours of computerised cognitive training, (n=351, control n=335) for mild cognitive impairment, found a moderate effect on general cognition post-training (Hedges'  $g=0.4$ ,  $0.2-0.5$ );<sup>55</sup> however few high quality studies and no long-term high quality evidence about prevention of dementia currently exists. A meta-analysis of 30 trials of computerised, therapy-based and multimodal interventions for mild cognitive impairment found an effect on activities of daily living ( $d=0.23$ ) and metacognitive outcomes ( $d=0.30$ ) compared to control.<sup>56</sup> A third systematic review identified five high quality studies, four group-delivered and one by computer, and concluded the evidence for the effects of cognitive training in mild cognitive impairment was insufficient to draw conclusions.<sup>53</sup> A comprehensive, high quality, systematic overview of meta-analyses of cognitive training in healthy older people, those with mild cognitive impairment and those with dementia, found that most were of low standard, were positive and most reached statistical significance but it was unclear whether results were of clinical value because of the poor standard of the studies and heterogeneity of results (figure 3).<sup>51</sup>

In the only randomised controlled trial (RCT) of behavioural activation (221 people) for cognition in amnesic mild cognitive impairment, behavioural activation versus supportive therapy was associated with a decreased 2-year incidence of memory decline (relative risk [RR]  $0.12$ ,  $0.02-0.74$ ).<sup>57</sup>

### Hearing impairment

Hearing loss had the highest PAF for dementia in our first report, using a meta-analysis of studies of people with normal baseline cognition and hearing loss present at a threshold of 25 dB, which is the WHO threshold for hearing loss. In the 2017 Commission, we found an RR of 1.9 for dementia in populations followed up over 9–17 years, with the long follow-up times making reverse causation bias unlikely.<sup>2</sup> A subsequent meta-analysis using the same three prospective studies measuring hearing using audiometry at baseline, found an increased risk of dementia (OR 1.3, 95% CI 1.0–1.6) per 10 dB of

worsening of hearing loss.<sup>58</sup> A cross-sectional study of 6451 individuals designed to be representative of the US population, with a mean age of 59.4 years, found a decrease in cognition with every 10 dB reduction in hearing, which continued to below the clinical threshold so that subclinical levels of hearing impairment (below 25 dB) were significantly related to lower cognition.<sup>59</sup>

Although the aetiology still needs further clarification, a small US prospective cohort study of 194 adults without baseline cognitive impairment, (baseline mean age 54.5 years), and at least two brain MRIs, with a mean of 19 years follow-up, found that midlife hearing impairment measured by audiometry, is associated with steeper temporal lobe volume loss, including in the hippocampus and entorhinal cortex.<sup>60</sup>

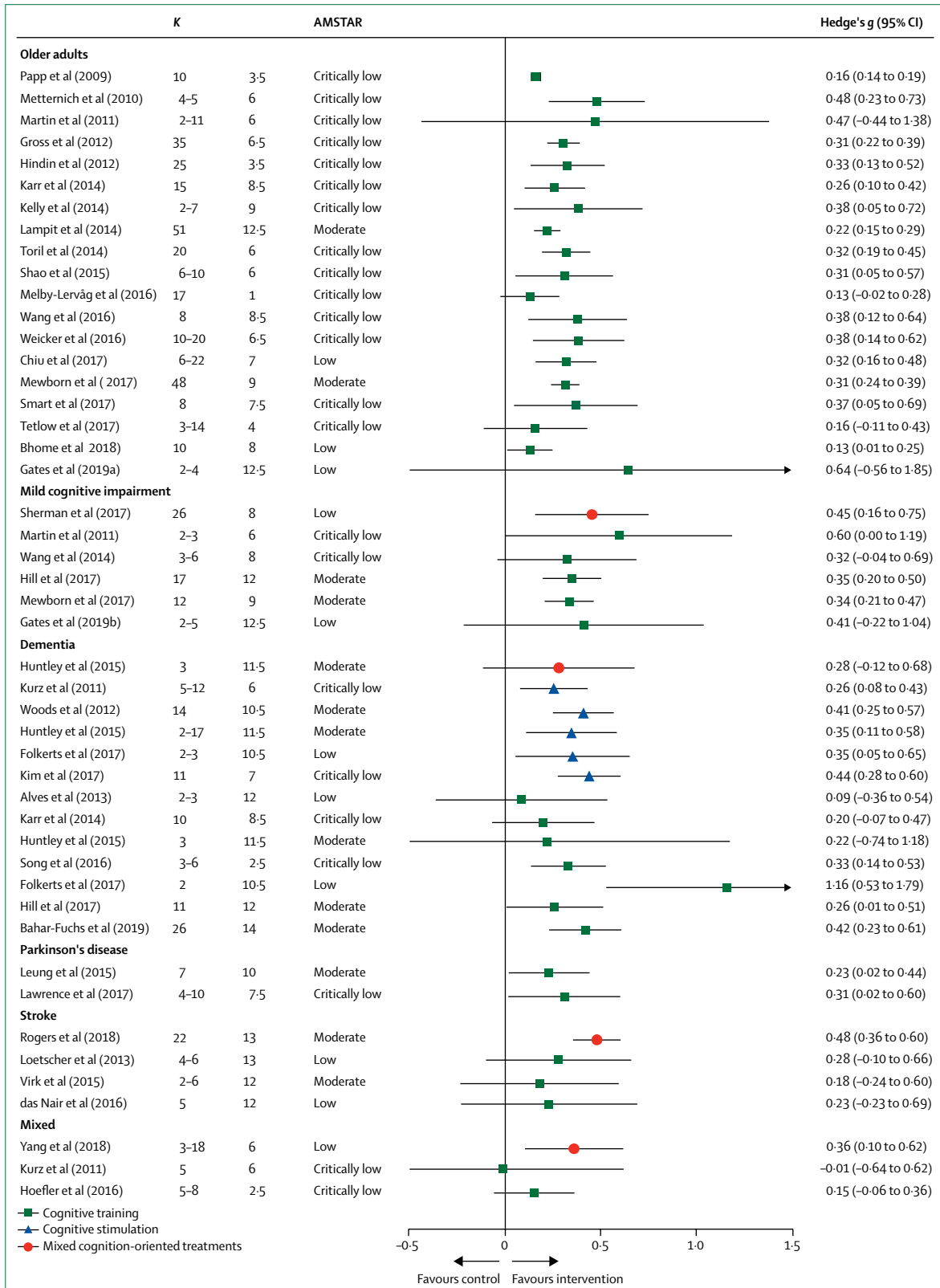
### Hearing aids

A 25-year prospective study of 3777 people aged 65 years or older found increased dementia incidence in those with self-reported hearing problems except in those using hearing aids.<sup>61</sup> Similarly, a cross-sectional study found hearing loss was only associated with worse cognition in those not using hearing aids.<sup>62</sup> A US nationally representative survey of 2040 people older than 50 years, tested every two years for 18 years, found immediate and delayed recall deteriorated less after initiation of hearing aid use, adjusting for other risk factors.<sup>63</sup> Hearing aid use was the largest factor protecting from decline (regression coefficient  $\beta$  for higher episodic memory 1.53;  $p<0.001$ ) adjusting for protective and harmful factors. The long follow-up times in these prospective studies suggest hearing aid use is protective, rather than the possibility that those developing dementia are less likely to use hearing aids. Hearing loss might result in cognitive decline through reduced cognitive stimulation.

### TBI

The International Classification of Disease (ICD) defines mild TBI as concussion and severe TBI as skull fracture, oedema, brain injury or bleed. Single, severe TBI is associated in humans, and mouse models, with widespread hyperphosphorylated tau pathology, and mice with APOE  $\epsilon 4$  compared to APOE  $\epsilon 3$  allele have more hippocampal hyper-phosphorylated tau after TBI.<sup>64,65</sup> TBI is usually caused by car, motorcycle, and bicycle injuries; military exposures; boxing, horse riding, and other recreational sports; firearms; and falls.<sup>66</sup> A nationwide Danish cohort study of nearly 3 million people aged 50 years or older, followed for a mean of 10 years, found an increased dementia (HR 1.2, 95% CI 1.2–1.3) and Alzheimer's disease risk (1.2, 1.1–1.2).<sup>67</sup> Dementia risk was highest in the 6 months after TBI (4.1, 3.8–4.3) and increased with number of injuries in people with TBI (one TBI 1.2, 1.2–1.3;  $\geq 5$  TBIs 2.8, 2.1–3.8). Risk was higher for TBI than fractures in other body areas (1.3, 1.3–1.3) and remained elevated after excluding





**Figure 3: Pooled results of meta-analyses investigating objective cognitive outcomes of cognition-oriented treatment in older adults with and without cognitive impairment**  
 K represents the number of primary trials included in the analysis. If a review reported several effect sizes within each outcome domain, a composite was created and k denotes the range of the number of primary trials that contributed to the effect estimate.  
 AMSTAR=A MeaSurement Tool to Assess systematic Reviews (max score 16).  
 Adapted from Gavelin et al,<sup>53</sup> by permission of Springer Nature.

those who developed dementia within 2 years after TBI, to reduce reverse causation bias.<sup>67</sup>

Similarly, a Swedish cohort of over 3 million people aged 50 years or older, found TBI increased 1-year dementia risk (OR 3.5, 95% CI 3.2–3.8); and risk remained elevated, albeit attenuated over 30 years (1.3, 1.1–1.4).<sup>68</sup> ICD defined single mild TBI increased the risk of dementia less than severe TBI and multiple TBIs increased the risk further (OR 1.6, 95% CI 1.6–1.7 for single TBI; 2.1, 2.0–2.2 for more severe TBI; and 2.8, 2.5–3.2 for multiple TBI). A nested case control study of early onset clinically diagnosed Alzheimer's disease within an established cohort also found TBI was a risk factor, increasing with number and severity.<sup>69</sup> A stronger risk of dementia was found nearer the time of the TBI, leading to some people with early-onset Alzheimer's disease.

Military veterans have a high risk of occupational TBI, and formal record keeping allows long-term follow-up. A study of 178 779 veterans with TBI with propensity-matched veterans without TBI found dementia risk was associated with TBI severity (HR 2.4, 95% CI 2.1–2.7 for mild TBI without loss of consciousness; 2.5, 2.3–2.8 for mild TBI with loss of consciousness; and 3.8, 3.6–3.9 for moderate to severe TBI).<sup>70</sup> Similarly women veterans with TBI had increased risk of dementia compared to those without TBI (1.5, 1.0–2.2).<sup>71</sup>

A cohort study of 28 815 older adults with concussion, found the risk of dementia doubled, with 1 in 6 developing dementia over a mean follow-up of 3.9 years, although those taking statins had a 13% reduced risk of dementia compared to those who were statin-free. They suggest future RCTs as statins might mitigate injury-related brain oedema, oxidative stress, amyloid protein aggregation, and neuroinflammation.<sup>72</sup>

The term chronic traumatic encephalopathy describes sports head injury, which is not yet fully characterised and covers a broad range of neuropathologies and outcomes, with current views largely conjecture.<sup>73</sup> The evidence has subsequently been strengthened by a study on Scottish former soccer players reporting that they are more likely than controls to have Alzheimer's disease specified on their death certificates (HR 5.1, 95% CI 2.9–8.8) and to have been prescribed any dementia-related medications (OR 4.9, 95% CI 3.8–6.3) but not on medical records.<sup>74</sup> The study controlled for socioeconomic class based on residential address, which in footballers might be less linked to level of education.

### Hypertension

Persistent midlife hypertension is associated with increased risk of a late life dementia. In the Framingham Offspring cohort comprising 1440 people, elevated systolic blood pressure ( $\geq 140$  mm Hg in midlife; mean age 55 years) was associated with an increased risk of developing dementia (HR 1.6, 95% CI 1.1–2.4) over an 18 year follow-up period.<sup>12</sup> In this study risk increased further if hypertension persisted into later life (mean age

69 years; HR 2.0, 95% CI 1.3–3.1). In the same cohort, people in late midlife (mean age 62 years) with ideal cardiovascular parameters (current non-smoker, body mass index [BMI] 18.5–25 kg/m<sup>2</sup>, regular physical activity, healthy diet, optimum blood pressure <120/<80 mm Hg, cholesterol, and normal fasting blood glucose) were compared to people with at least one of these risks.<sup>75</sup> Those with ideal cardiovascular parameters had a lower 10-year risk of all-cause dementia (HR 0.8, 95% CI 0.1–1.0), vascular dementia (0.5, 0.3–0.8) and clinically diagnosed Alzheimer's disease (0.8, 0.6–1.0). In a UK cohort study of 8639 civil servants, a single measure of systolic blood pressure of 130 mm Hg or higher at age 50 years but not at age 60 or 70 years was associated with increased risk of dementia (1.4, 1.1–1.7).<sup>13</sup> In those with persistent systolic blood pressure of 130 mm Hg or higher, from mean age 45 to 61 years, dementia risk is increased even if free of cardiovascular disease relative to those without hypertension (1.3, 1.0–1.7).

A further cohort study has provided potential insights into mechanisms, reporting that midlife hypertension, defined as from age 40 years, was associated with reduced brain volumes and increased white matter hyperintensity volume but not amyloid deposition.<sup>76</sup> Of note, blood pressure declines in later life and this decline is associated with and, potentially caused by, dementia development (HR 2.4, 95% CI 1.4–4.2).<sup>12,13,77</sup>

### Antihypertensive drugs, aspirin, and statins

The US and Puerto Rico Systolic Blood Pressure Intervention Trial (SPRINT) in 9361 hypertensive adults aged 50 years and older, was stopped early because of significantly fewer cardiovascular events and deaths occurring in the intensive treatment arm (aiming for systolic <120 mm Hg, n=4678) in comparison with standard treatment (systolic <140 mm Hg, n=4683).<sup>78</sup> Cognitive assessment continued after stopping the trial intervention in SPRINT MIND.<sup>79</sup> In the intensive compared with the standard treatment group, there were 7.2 dementia cases as opposed to 8.6 cases per 1000 person-years (HR 0.8; 95% CI 0.7–1.0) within on average 2 years from the end of the intervention period and 5 years after baseline. Pre-specified secondary outcomes were also reduced in the intensive arm for mild cognitive impairment (14.6 vs 18.3 cases per 1000 person-years; HR 0.8, 95% CI 0.7–1.0), combined mild cognitive impairment or dementia (20.2 vs 24.1 cases per 1000 person-years; HR 0.9, 95% CI 0.7–1.0)<sup>79</sup> making this the first trial to suggest reduction of risk for mild cognitive impairment. Those who were lost to follow-up were at greater risk of dementia than those who continued but follow-up rates did not differ according to intervention group.<sup>80</sup>

Four meta-analyses of blood pressure medications to lower high blood pressure with six studies overlap have provided combined estimates of effects. All meta-analyses suggest reduced dementia in those in the

interventions arms for outcomes of any dementia as well as clinically diagnosed Alzheimer's disease. The first included randomised controlled trials (RCTs) of any drug to lower blood pressure and reported a reduction in risk of around 10% at marginal significance (RR 0.9, 95% CI 0.9–1.0).<sup>81</sup> Meta-regression showed risk lowered more if the achieved systolic pressure differential was larger between the intervention and control group. The second included 15 trials and observational studies of diuretics involving 52 599 people (median age 76 years) with 6.1 years median follow-up (dementia HR 0.8, 95% CI 0.8–0.9 and Alzheimer's disease 0.8, 0.7–0.9).<sup>82</sup> The third included used individual participant data from six observational studies; (dementia 0.9, 0.8–1.0 and Alzheimer's disease 0.8, 0.7–1.0; figure 4).<sup>83</sup> The fourth focused on people prescribed calcium channel blocker only, included 10 RCTs and observational studies comprising 75 239 hypertensive older adults (median age 72 years, median follow-up 8.2 years) found lowered dementia risk (RR 0.7, 95% CI 0.6–0.9).<sup>84</sup> A 2019 meta-analysis addressing which class of anti-hypertensive drug to use to lower risk of either incident dementia or

cognitive decline, found over 50 000 participants in 27 studies and reported no consistent difference in effect according to which class of drug was used.<sup>85</sup>

A Cochrane review reported good evidence that statins given to older people at risk of vascular disease do not prevent cognitive decline or dementia.<sup>86</sup> One RCT found 100 mg aspirin versus placebo in 19 114 healthy adults older than 65 years did not reduce dementia (HR 1.0, 95% CI 0.8–1.2), death, physical disability, or cardiovascular disease over a period of 4.7 years.<sup>87</sup>

**Physical inactivity, exercise, and fitness**

Studies of physical activity are complex. Patterns of physical activity change with age, generation, and morbidity and are different across sex, social class, and cultures. The studies suggest a complicated relationship with the potential for both risk reduction and reverse causation.

Meta-analyses of longitudinal observational studies of 1–21 years duration showed exercise to be associated with reduced risk of dementia.<sup>2</sup> A further overview of systematic reviews concluded that there is convincing

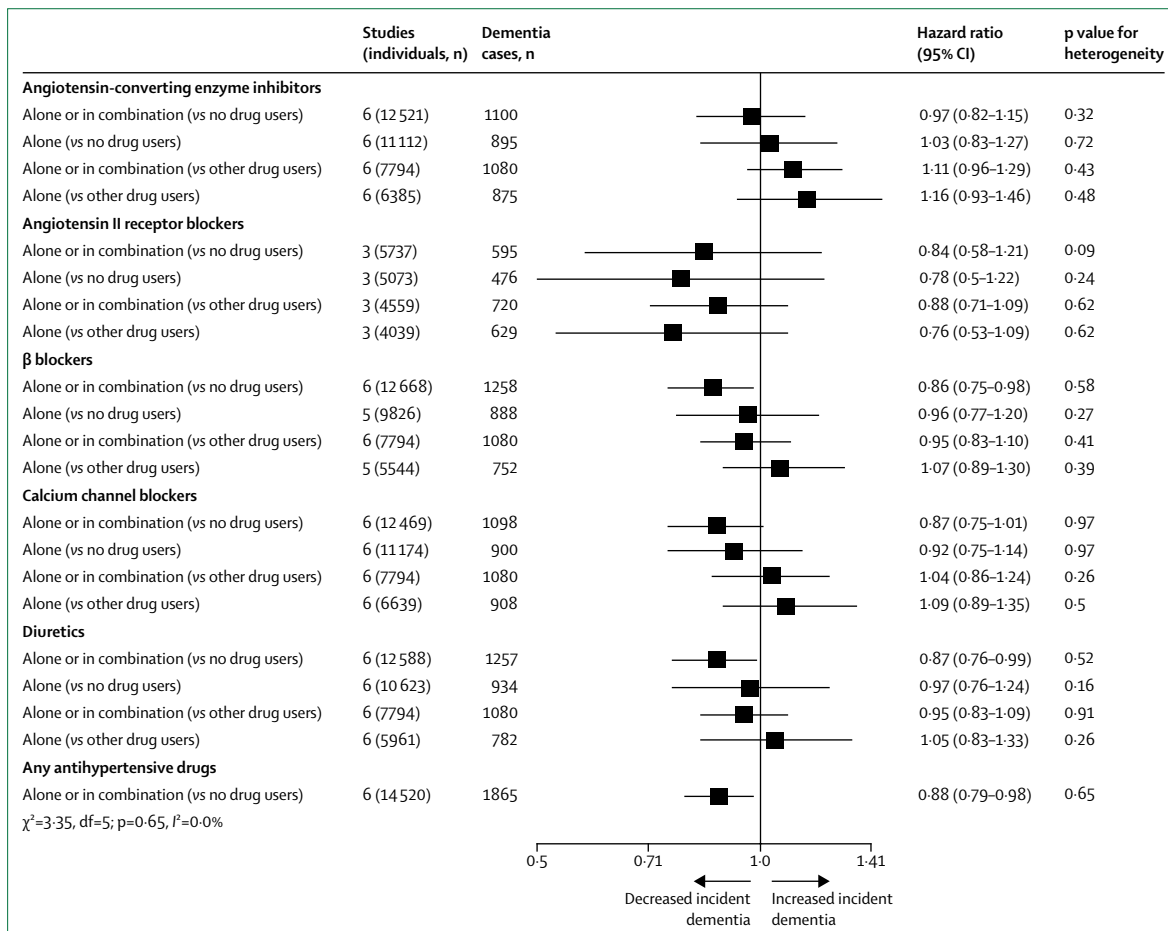


Figure 4: Associations of antihypertensive medication use with incident dementia in those with high blood pressure. Adapted from Ding et al,<sup>83</sup> by permission of Elsevier.

evidence for physical activity protecting against clinically diagnosed Alzheimer's disease.<sup>88</sup>

Since the 2017 Commission, the HUNT study of 28 916 participants aged 30–60 years has been published, reinforcing the previous literature in this area. At least weekly midlife moderate-to-vigorous physical activity (breaking into a sweat) was associated with reduced dementia risk over a 25-year period of follow-up (HR 0.8, 95% CI 0.6–1.1) but the confidence intervals were wide.<sup>89</sup> In contrast the Whitehall Study reporting on the 28-year follow-up of 10 308 people, found that more than 2.5 hours of self-reported moderate-to-vigorous physical activity per week, lowered dementia risk over 10, but not 28 years.<sup>33</sup> Very long-term studies are unusual; however, one 44-year study recruited 191 women (mean age 50) purposively to be representative of the Swedish population and reported that 32% of the participants with low baseline peak fitness, 25% with medium, and 5% with high fitness developed dementia (high vs medium HR 0.1, 95% CI 0.03–0.5, low vs medium 1.4, 0.7–2.8).<sup>90</sup>

An individual-level meta-analysis of 19 observational studies of relatively younger adults included 404 840 participants' data (mean baseline age 45.5 years; mean follow-up duration 14.9 years), reporting an increased incidence of all-cause dementia (HR 1.4, 95% CI 1.2–1.7) and clinically diagnosed Alzheimer's disease (1.4, 1.1–1.7) in those who were physically inactive in the 10-year period before diagnosis.<sup>91</sup> Notably, however, no difference in dementia risk measured 10–15 years before time of dementia incidence was found except in those with comorbid cardio-metabolic disease (RR 1.3, 95% CI 0.8–2.1).

People might stop exercising due to prodromal dementia so inactivity might be either a consequence or a cause or both in dementia and might be more of a risk in those with cardiovascular morbidity. As with other outcomes, exercise might be required to be sustained and continue nearer the time of risk.<sup>92</sup>

#### *Trials of exercise*

Since the 2017 Commission several meta-analyses and systematic reviews have been published with three high quality meta-analyses which we include. The first included 39 RCTs with an unclear total number of participants examining moderate or vigorous exercise of any frequency lasting 45–60 min per session in cognitively normal adults aged older than 50 years. This analysis reported global cognitive improvements (standard mean difference [SMD]=0.3, 95% CI 0.2–0.4) for moderate or vigorous resistance (13 studies) or aerobic exercise (18 studies) lasting 45–60 min per session with no difference between them but no effect found for yoga.<sup>93</sup> A second meta-analysis of RCTs in people with mild cognitive impairment found global cognition improved in the intervention group (0.3, 0.1–0.5) with aerobic exercise having a higher effect (0.6, 0.5–0.6).<sup>94</sup> This study did not have dementia as an outcome

measure. A third meta-analysis of RCTs of longer term exercise found five studies (four lasting 12 months and one 24 months) with 2878 participants with normal baseline cognition.<sup>95</sup> The incidence of dementia was 3.7% (n=949) for exercisers and 6.1% (n=1017) for controls (random effect RR 0.6, 95% CI 0.3–1.1; fixed effect as no evidence of heterogeneity 0.7, 0.4–1.0). The authors concluded that the study showed no significant effect of exercise for reducing dementia, mild cognitive impairment, or clinically significant cognitive decline but was underpowered. WHO guidelines have been published since the 2017 Commission, suggesting specific activity levels drawing on these, and one further systematic review which considered sex differences on the effect of exercise.<sup>96,97</sup> It concluded the evidence points towards physical activity having a small, beneficial effect on normal cognition, with a possible effect in mild cognitive impairment, mostly due to aerobic exercise.<sup>97</sup> Evidence about the effect of specific types of exercise, such as progressive muscle resistance training, on dementia risk is scarce.

#### **Diabetes**

In the 2017 Commission we reported on diabetes as a risk factor for dementia. Distinguishing between treated and untreated diabetes as a risk factor for dementia is challenging in observational studies. In a pooled meta-analysis from over 2.3 million individuals with type 2 diabetes across 14 cohort studies, including 102 174 with dementia, diabetes was associated with an increased risk of any dementia (RR 1.6, 95% CI 1.5–1.8 for women and 1.6, 1.4–1.8 for men).<sup>98</sup> The risk of dementia increased with the duration and severity of diabetes. The effect of different diabetic medications on cognition or dementia outcomes remains unclear as few studies have investigated this area.<sup>99</sup> However, one meta-analysis of cohort studies of diabetes reported that, cross sectionally, people with diabetes taking metformin had lower prevalence of cognitive impairment (three studies OR 0.6, 95% CI 0.4–0.8) and, longitudinally, reduced dementia incidence (six studies HR 0.8, 95% CI 0.4–0.9) compared with those taking other medications or no medication.<sup>100</sup> However another analysis did not find a protective effect of metformin for incident dementia (three studies, RR 1.1, 95% CI 0.5–2.4) with possible harm with insulin therapy (1.2, 1.1–1.4); but this did not account for severity of diabetes of those with type 2 diabetes on insulin.<sup>99</sup> A Cochrane review reported intensive compared to standard diabetes control trials with 5 year follow up (n=11 140), showing no impact on cognitive decline (1.0, 95% CI 0.9–1.1) or dementia (1.3, 0.9–1.9).<sup>101</sup>

Overall type 2 diabetes is a clear risk factor for development of future dementia; however, whether any particular medication ameliorates this risk is unclear. Intensive diabetic control does not decrease the risk of dementia.

### Combined cardiovascular risk factors

Studies of individual cardiovascular risk factors usually control for other cardiovascular risks, which cluster in individual people. This does not take into account the combinations and contexts in which risk occurs. A UK study of 7899 people aged 50 years followed up for 25 years, calculated a cardiovascular health score based on four behaviour-related (smoking, diet, physical activity, BMI) and three biological (fasting glucose, blood cholesterol, blood pressure) metrics each coded on a three-point scale (0, 1, 2).<sup>100</sup> A better score was associated with a lower risk of dementia (HR 0.9, 95% CI 0.9–1.0 per 1 point scale increment), for both behaviour-related (HR/1 point increment in subscales 0.9, 95% CI 0.8–0.9) and biological subscales (0.9, 0.8–1.0), maintained in people free of cardiovascular disease over the follow-up (0.9, 95% CI 0.8–1.0). These authors also reported an association of the score on the scale with hippocampal atrophy and total brain volume but not white matter hyperintensities. This finding underlines the importance of clustering of cardiovascular risk factors in midlife, as studies of individual risk factors in this sample had not shown a significant association, when controlling for other individual risks.<sup>33</sup>

### Excessive alcohol consumption

Heavy drinking is associated with brain changes, cognitive impairment, and dementia, a risk known for centuries.<sup>102</sup> An increasing body of evidence is emerging on alcohol's complex relationship with cognition and dementia outcomes from a variety of sources including detailed cohorts and large-scale record based studies. Alcohol is strongly associated with cultural patterns and other sociocultural and health-related factors, making it particularly challenging to understand the evidence base.

A French 5-year longitudinal study of over 31 million people admitted to hospital, found alcohol use disorders (harmful use or dependence as defined in ICD) were associated with increased dementia risk, calculated separately for men and women (women HR 3.3, 95% CI 3.3–3.4, men 3.4, 3.3–3.4).<sup>103</sup> The relationship of dementia with alcohol use disorders was particularly clear in the earlier onset dementias (age less than 65 years) in which 56.6% had an alcohol use disorder noted in their records (n=57 353; 5.2% all dementias).

A systematic review incorporating 45 studies of light to moderate drinking using a variety of definitions reported a reduced risk of dementia compared with not drinking (RR 0.7; 95% CI 0.6–0.91).<sup>104</sup> Risk was not reported separately for men and women. Drinking less than 21 units of alcohol per week (1 unit of alcohol=10 mL or 8 g pure alcohol) might be associated with a lower risk of dementia.<sup>105,106</sup> A 5-year follow-up study of 13 342 men and women volunteers from UK biobank aged 40–73 years who drank, included few heavy drinkers and did not analyse abstainers.<sup>106</sup> The study reported that those who drank more than 12 units per week declined slightly more in

reaction time in a perceptual matching task than those who drank less ( $\beta_2=-0.07$ , 95% CI  $-0.09$  to  $-0.04$ ).<sup>106</sup> The UK Whitehall study with 23 years follow-up, included 9087 participants aged 35–55 years at baseline.<sup>107</sup> Drinking more than 21 units per week and long-term abstinence were both associated with a 17% (95% CI 4–32 and 13–23 respectively) increase in dementia compared to drinking less than 14 units. Drinking more than 14 units was also associated with right sided hippocampal atrophy on MRI.<sup>108</sup>

### Weight control and obesity

Overweight is an emerging concern, given the changing BMI across the world's ageing population. New evidence supports the relationship between increased BMI and dementia from a review of 19 longitudinal studies including 589 649 people aged 35 to 65 years, followed up for up to 42 years. It reported obesity (BMI  $\geq 30$ ; RR 1.3, 95% CI 1.1–1.6) but not being overweight (BMI 25–30; 1.1, 1.0–1.2) was associated with late-life dementia.<sup>109</sup> In a further meta-analysis of individual level data from 1.3 million adults (aged  $\geq 18$  years), which included two studies from the meta-analysis cited above,<sup>109</sup> higher body mass measured before probable preclinical and prodromal dementia was associated with increased dementia risk (RR 1.3, 1.1–1.7/5-unit increase in BMI).<sup>11</sup>

### Weight loss in midlife and dementia risk

A meta-analysis of seven RCTs (468 participants) and 13 longitudinal studies (551 participants) of overweight and obese adults without dementia, mean age 50 years, found weight loss of 2 kg or more in people with BMI greater than 25 was associated with a significant improvement in attention and memory. All but one of the studies included participants aged younger than 65 years. The RCTs reported memory improvement over 8–48 weeks (SMD=0.4, 95% CI 0.2–0.6) and short-term longitudinal studies found improvement over a median of 24 weeks (SMD=0.7, 95% CI 0.5–0.8); however, data about the long-term effects or the effect of weight loss in preventing dementia are absent.<sup>110</sup>

### Smoking

Smokers are at higher risk of dementia than non-smokers,<sup>2</sup> and at a higher risk of premature death before the age at which they might have developed dementia, introducing some bias and uncertainty in the association between smoking and risk of dementia.<sup>111,112</sup> Stopping smoking, even when older, reduces this risk. Among 50 000 men aged older than 60 years, stopping smoking for more than 4 years, compared to continuing, substantially reduced dementia risk over the subsequent 8 years (HR 0.9; 95% CI 0.7–1.0).<sup>113</sup> Worldwide, 35% of non-smoking adults and 40% of children are estimated to be exposed to second-hand smoke,<sup>114</sup> although literature on the impact of this exposure and dementia risk is scarce. One study indicated that in women aged 55–64 years,



second-hand smoke exposure was associated with more memory deterioration and the risk increased with exposure duration even after controlling for other confounding factors.<sup>115</sup>

### Depression

Depression is associated with dementia incidence, with a variety of possible psychological or physiological mechanisms. It is also part of the prodrome and early stages of dementia. Reverse causation is possible whereby depressive symptoms result from dementia neuropathology that occurs years before clinical dementia onset. These explanations are not mutually exclusive. As in diabetes, few studies considering depression as a risk factor for dementia have distinguished between treated and untreated depression. In a meta-analysis of 32 studies, with 62 598 participants, with follow-up from 2 to 17 years, a depressive episode was a risk factor for dementia (pooled effect size 2.0, 95% CI 1.7–2.3).<sup>116</sup> Meta-regression analysis revealed a non-significant trend for the association between depression and incident dementia to be weaker when the length of follow-up was longer. The Norwegian HUNT study, suggested that symptoms of psychological distress predicted dementia 25 years later however with wide bounds of uncertainty (HR 1.3, 95% CI 1.0–1.7).<sup>89</sup> Two further studies differentiate between late-life and earlier life depressive symptoms. The UK Whitehall study, in a follow-up of 10 189 people, reports that in late life these symptoms increase dementia risk but not at younger ages (follow-up 11 years HR 1.7; 95% CI 1.2–2.4; follow-up 22 years 1.0, 0.7–1.4).<sup>34,117</sup> A 14-year longitudinal study of 4922 initially cognitively healthy men, aged 71–89 years, found depression was associated with 1.5 (95% CI 1.2–2.0) times the incidence of dementia but this association was accounted for by people developing dementia within 5 years of depression.<sup>118</sup> The use of antidepressants did not decrease this risk.

A study of 755 people with mild cognitive impairment and with a history of depression from the Australian longitudinal Alzheimer's Disease Neuroimaging Initiative, considered the effect of selective serotonin-reuptake inhibitor (SSRI) treatment, such as citalopram, known to reduce amyloid plaque generation and plaque formation in animal models.<sup>119</sup> The study found that more than 4 years of such treatment was associated with delayed progression to clinically diagnosed Alzheimer's disease. People treated with antidepressants seem likely to differ from those who are not treated. Thus, the question of whether antidepressant treatment mitigates dementia risk remains open.

### Social contact

Social contact, now an accepted protective factor, enhances cognitive reserve or encourages beneficial behaviours, although isolation might also occur as part of the dementia prodrome. Several studies suggest that less social contact

increases the risk of dementia. Although most people in mid and later life are married, by the time they reach older age, disproportionate numbers of women are widowed as they outlive their husbands, thus reducing their social contact. In these generations, marital status is therefore an important contributor to social engagement. Additionally, most marriages are in the relatively young, and married people usually have more interpersonal contact than do single people—this gives a long-term estimate of the effect of social contact. A systematic review and meta-analysis including 812 047 people worldwide found dementia risk to be elevated in lifelong single (RR 1.4, 95% CI 1.1–1.9) and widowed people (1.2, 1.0–1.4), compared with married people and the association was consistent in different sociocultural settings.<sup>120</sup> Studies adjusted for sex and we do not know if a differential risk between men and women exists. Differences persisted in studies that adjusted for education and physical health so might be attributable to married people having more social contact, rather than solely because they tend to have better physical health and more education, although residual confounding is possible. A systematic review and meta-analysis of 51 longitudinal cohort studies of social isolation and cognition included 102 035 participants aged 50 or more years at baseline, with follow-up of 2–21 years.<sup>121</sup> High social contact (measured through either or both of social activity and social network) was associated with better late-life cognitive function ( $r=0.05$ , 95% CI: 0.04–0.065) and no differences according to sex or length of time followed up.

A new meta-analysis found that in long-term studies ( $\geq 10$  years), good social engagement was modestly protective ( $n=8876$ , RR=0.9, 95% CI 0.8–1.0); but loneliness was not associated with dementia risk.<sup>122</sup> No long term ( $>10$  years) studies of loneliness and dementia outcomes have been done.

A UK 28-year follow-up study of 10 308 people found that more frequent social contact at age 60 years was associated with lower dementia risk over 15 years of follow-up (HR for one standard deviation social contact frequency 0.9, 95% CI 0.8–1.0). This finding suggests more frequent social contact during late middle age is associated with a modest reduction in dementia risk, independent of socio-economic and other lifestyle factors.<sup>123</sup> A Japanese longitudinal cohort study of 13 984 adults aged older than 65 years with a mean of 10 years follow-up calculated a five-point social contact scale based on: marital status; exchanging support with family members; having contact with friends; participating in community groups; and engaging in paid work. It found the score to be linearly associated with reduced dementia risk; those who scored highest on the five-point scale were 46% less likely to develop incident dementia compared with those in the lowest category.<sup>124</sup>

Despite clear cultural variation in the meaning and perception of social isolation, findings of protective effect of more social contact are largely consistent in different



settings and for either sex across the studies and meta-analyses.<sup>118,120,121</sup>

#### Social interventions

Little evidence of the effects of social interventions on dementia exists but a systematic review of low quality RCTs of 576 adults aged 60 or more years with normal cognition found facilitated meeting and discussion groups were associated with improved global cognition and increased brain volume at follow-up.<sup>118</sup>

#### Air pollutants

Air pollution and particulate pollutants are associated with poor health outcomes, including those related to non-communicable diseases. Attention has turned to their potential effect on the brain. Animal models suggest airborne particulate pollutants accelerate neurodegenerative processes through cerebrovascular and cardiovascular disease, A $\beta$  deposition, and amyloid precursor protein processing.<sup>125,126</sup> Although the higher levels of dementia from air pollutants are still subject to the potential for residual confounding, the effects on animal models are evidence of physiological effects over and above those driven by life-course deprivation.

High nitrogen dioxide (NO<sub>2</sub>) concentration (>41.5  $\mu\text{g}/\text{m}^3$ ; adjusted HR 1.2, 95% CI 1.0–1.3), fine ambient particulate matter (PM)<sub>2.5</sub> from traffic exhaust (1.1, 1.0–1.2)<sup>127–129</sup> and PM<sub>2.5</sub> from residential wood burning (HR=1.6, 95% CI 1.0–2.4 for a 1  $\mu\text{g}/\text{m}^3$  increase) are associated with increased dementia incidence. Traffic often produces NO<sub>2</sub> and PM<sub>2.5</sub> and it is hard to separate their effects, although evidence for additive effects of different pollutants exists.<sup>127–129</sup> A systematic review of studies until 2018 including 13 longitudinal studies with 1–15 years follow-up of air pollutants exposure and incident dementia, found exposure to PM<sub>2.5</sub>, NO<sub>2</sub>, and carbon monoxide were all associated with increased dementia risk.<sup>24</sup> The attributable burden of dementia and excess death from PM<sub>2.5</sub> in one large 10-year US study was particularly high in Black or African American individuals and socio-economically disadvantaged communities and related to particulate PM<sub>2.5</sub> concentrations above the US guidelines.<sup>130</sup>

#### Sleep

Mechanisms by which sleep might affect dementia remain unclear, but sleep disturbance has been linked with  $\beta$ -amyloid (A $\beta$ ) deposition,<sup>131,132</sup> reduced glymphatic clearance pathways activation,<sup>133</sup> low grade inflammation, increased Tau, hypoxia<sup>132,134</sup> and cardiovascular disease.<sup>135</sup> Sleep disturbance is hypothesised to increase inflammation which raises A $\beta$  burden, leading to Alzheimer's disease and further sleep disturbance.<sup>136</sup>

Two meta-analyses showed similar findings. The first was a synthesis of longitudinal studies with an average of 9.5 years follow-up and the second reported cross-sectional and prospective cohort studies of mixed quality with different methods of measuring sleep. Sleep

disturbances were defined broadly, often self-reported and including short and long sleep duration, poor sleep quality, circadian rhythm abnormality, insomnia, and obstructive sleep apnoea. All these disturbances were associated with a higher risk of all-cause dementia (RR 1.2; 95% CI 1.1–1.3)<sup>137</sup> and clinically diagnosed Alzheimer's disease (1.6, 1.3–1.9) compared with no sleep disturbance, although not all cohort studies excluded those with cognitive impairment or dementia at baseline from their analyses.<sup>138</sup> A U-shaped association has been reported between sleep duration and risk of mild cognitive impairment or dementia with higher risks of dementia with less than 5 hours (HR=2.6; 95% CI 1.4–5.1) compared with more than 5 and less than 7 and more than 10 hours sleep (2.2, 1.4–3.5) and risks for all-cause dementia and clinically diagnosed Alzheimer's disease being similar.<sup>135,139–141</sup>

The postulated mechanisms of reduced sleep leading to accumulation of Alzheimer's type pathology is inconsistent with the evidence that both more sleep and less sleep are associated with increased risk of dementia. New onset late-life sleep disturbance, a few years before clinical dementia, might be part of the natural history of the dementia syndrome, appearing to be a risk factor, or reflect other disorders, for example, mood disturbances or cardiovascular disease.<sup>135,142</sup> Hypnotic use might increase risks although this is unclear and a 2018 study<sup>139</sup> suggests that findings of a connection were related to reverse causality and confounders.<sup>143</sup> When benzodiazepine use was considered, in one study, sleep length was no longer significant<sup>139</sup> but not in all studies.<sup>135</sup> Those taking hypnotics were at greater risk of dementia than those who did not regardless of sleep duration.<sup>139</sup> Medication for sleep disturbance might be harmful and benzodiazepines are associated with falls, hospital admissions, and possibly dementia.<sup>139,144</sup>

#### Diet

Nutrition and dietary components are challenging to research with controversies still raging around the role of many micronutrients and health outcomes in dementia. Observational studies have focused on individual components ranging from folate and B vitamins, Vitamin C, D, E, and selenium amongst others as potential protective factors.<sup>88</sup> There has been a move towards considering the evidence base for whole diets in the last 5 years, particularly high plant intake such as in the Mediterranean diet (high intake of vegetables, legumes, fruits, nuts, cereals, and olive oil; low intake of saturated lipids and meat) or the similar Nordic diet, rather than individual nutrients, which might reduce cognitive decline and dementia.<sup>145</sup> One example is a longitudinal cohort study of 960 participants, ages 58–99 years, in which those reporting the highest intake of green leafy vegetables, equivalent to 1.3 servings per day, had less cognitive decline over 4.7 years than those reporting the lowest intake ( $\beta=0.05$  standardised units

95% CI 0.02–0.07).<sup>146</sup> The authors report this difference as being equivalent to being 11 years younger. A further prospective cohort study with three midlife dietary assessments in 8255 people, followed up for a mean of nearly 25 years, found neither healthy dietary pattern nor Mediterranean diet protected from dementia, except in those with cardiovascular disease, suggesting that diet might influence dementia risk by protecting from the excess risk of cardiovascular risk factors.<sup>147</sup>

#### Dietary interventions

As well as whole diets, there has been some interest in multi-nutrient interventions. A systematic review and a Cochrane review including RCTs of supplements (A, B, C, D, and E; calcium, zinc, copper, and multivitamins trials, n-3 fatty acids, antioxidant vitamins, and herbs) found a lack of evidence for supplement use to preserve cognitive function or prevent dementia in middle-aged (45–64 years) or older people (aged 65 years and older).<sup>148,149</sup> Cochrane reviews found no evidence for beneficial effects on cognition of those with mild cognitive impairment of supplementation with B vitamins for 6 to 24 months<sup>150</sup> or with vitamin E in preventing progression from mild cognitive impairment to dementia.<sup>151</sup> A 24-month RCT of 311 people of a multi-nutrient drink containing docosahexaenoic acid, vitamins B12, B6, folic acid, and other nutrients; found no significant effect on preventing cognitive deterioration in prodromal Alzheimer's disease.<sup>152</sup> The authors comment that the control group's cognitive decline was much lower than expected, leading to an inadequately powered trial.

Meta-analysis of two RCTs with 471 participants with normal cognition found the Mediterranean diet improved global cognition compared to controls (SMD 0.2, 95% CI 0.0–0.4).<sup>153</sup> A further meta-analysis identified five RCTs (n=1888) with a weak effect on global cognition (SMD 0.2, 95% CI 0.0–0.5)<sup>154</sup> but no benefit of Mediterranean diet for incident cognitive impairment or dementia.

The WHO guidelines recommend a Mediterranean diet to reduce the risk of cognitive decline or dementia, as it might help and does not harm, but conclude Vitamins B and E, polyunsaturated fatty acid, and multicomplex supplementation should not be recommended.<sup>97</sup>

#### Trials of combination strategies to prevent dementia

The FINGER RCT was a 2-year multidomain intervention to prevent cognitive decline and dementia in 1260 people with cardiovascular risk factors aged 60–77 years, recruited from a Finnish national survey. Similar multidomain studies were discussed in the 2017 Commission.<sup>2</sup> FINGER found a small group reduction in cognitive decline in the intervention group compared with control (comprehensive neuropsychological test battery Z score 0.02, 95% CI 0.00–0.04) regardless of

baseline sociodemographic, socio-economic, cognitive, or cardiovascular status.<sup>155</sup> However, in a subgroup analysis, greater beneficial effects were observed on processing speed in individuals with higher baseline cortical thickness in Alzheimer's disease areas.<sup>156</sup>

The Healthy Ageing Through Internet Counselling in the Elderly (HATICE) study recruited 2724 older people (≥65 years) in the Netherlands, Finland, and France with two or more cardiovascular risk factors.<sup>157,158</sup> It compared an interactive internet platform plus remote support by a coach, aiming to improve self-management of vascular risk factors, with a non-interactive control platform with basic health information. A small improvement in the cardiovascular risk composite primary outcome was observed in the intervention group compared with the control group at 18 months, mainly through weight loss, and the dementia risk score was slightly lower in those who received the intervention (mean difference –0.15, 95% CI –0.3 to –0.0). A larger effect was observed in the younger age group (65–70 years) and those with the lowest level of education, who had a higher baseline risk, suggesting that targeting high-risk populations might be more effective. Several multidomain preventive trials are ongoing—for example, World Wide FINGERS.

#### Total PAF calculation

We incorporated excessive alcohol consumption, TBI, and air pollution into our life-course model of dementia, as well as the original nine risk factors, because of the updated evidence. To calculate new RRs for excessive alcohol consumption, TBI and air pollution, we systematically reviewed the literature and did new meta-analyses for excessive alcohol consumption and TBI. For the other nine factors, we used values for RR and risk factors prevalence from our previous analysis and calculated communality using the same method as in the 2017 Commission.<sup>2</sup>

#### PAF calculation

We used a representative sample of over 10 000 UK community-dwelling adults, to calculate communality (clustering of risk factors) of 11 risk factors for which data existed,<sup>159</sup> to allow calculation of each factor's unique risk. As we could find no datasets measuring TBI, with the other 11 risk factors of interest, we could not calculate its communality. We therefore used the mean of the other 11 communalities to calculate a weighted PAF, so we could include TBI. We used cohabitation as a proxy measure for social contact, and urbanicity for air pollution exposure. Our analysis found four principal components, explaining 55% of the total variance between the eleven risk factors, suggesting substantial overlap. The appendix (p 2) shows the PAF formula and the steps in calculating communality and we detail our new meta-analyses

For the World Wide FINGERS network see <http://www.fingers.com/>

See Online for appendix

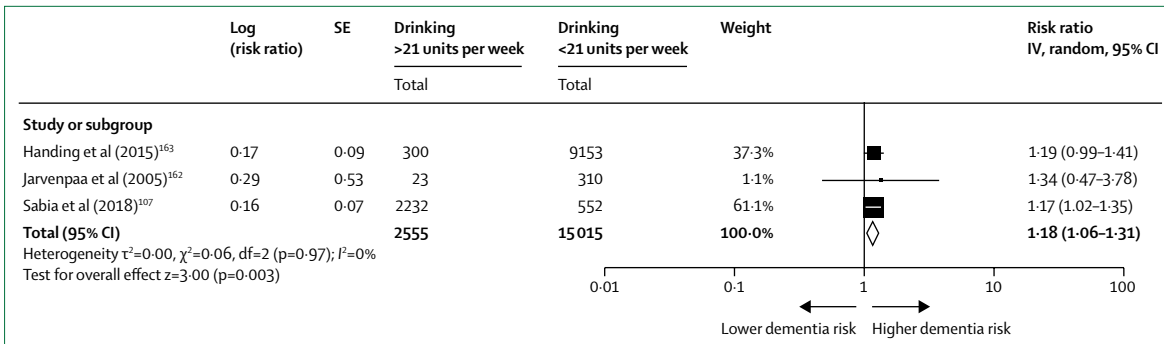


Figure 5: Meta-analysis of relative risk of dementia associated with drinking more than 21 units of alcohol per week in midlife compared to lighter consumption of alcohol

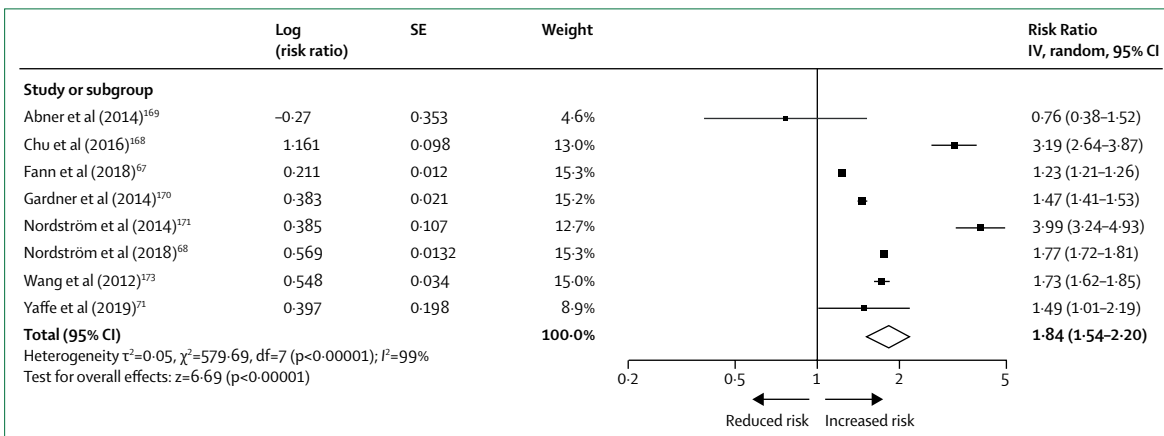


Figure 6: Meta-analysis of relative risk of all-cause dementia associated with all severity midlife traumatic brain injury

next, which we used to update the figure and perform our new calculations.

### Incorporation of the new chosen risks in new systematic reviews

#### Alcohol

We searched, from inception to Oct 29, 2019, Embase, Allied, and Complementary Medicine, MEDLINE, and PsycINFO terms “dementia” OR “dement\*” OR “AD” OR “VaD”, “Alzheimer\*” AND “alcohol” OR “ethanol” OR “alcohol\*” OR “drink\*” OR “drunk\*” to update an earlier review.<sup>160</sup> We used inclusion criteria: original population-based cohort studies measuring drinking during midlife, as alcohol intake tends to fall with age,<sup>161</sup> alcohol consumption quantified at baseline by units or number of drinks (one drink, 1.5 units) per week; and all-cause dementia ascertained at follow-up using validated clinical measures. We contacted authors for additional data.<sup>162</sup> Three studies met our inclusion criteria.<sup>107,162,163</sup> We converted HRs to RRs<sup>164</sup> and used raw data<sup>162</sup> to calculate RR,<sup>165</sup> for our random effects meta-analysis using Generic Inverse Variance Methods. The RR associated with drinking—more than 21 units (168 g) of alcohol weekly—compared with lighter drinking was 1.18 (95% CI 1.06–1.31; figure 5). We used Health Survey England

figures for heavier drinking prevalence to calculate PAF as we could not find a worldwide estimate. The weighted PAF was 0.8.

#### TBI

To estimate the RR of TBI of all severities for all cause dementia, we searched Embase, Medline, and PsycINFO from Jan 1, 2016, to Oct 21, 2019, updating an earlier search,<sup>166</sup> using terms (“traumatic brain injury” or “head injury” or “brain injury” or TBI) AND (neurodegeneration or “cognitive dysfunction” or dementia or “Alzheimer’s disease” or “Parkinson’s disease” or “frontotemporal dementia”). We converted HR figures to RR.<sup>164,167</sup> We used inclusion criteria: original population-based cohort studies, baseline TBI of all severities reported, and all-cause dementia ascertained at follow-up using validated clinical measures. We combined four new studies meeting inclusion criteria<sup>67,68,71,168</sup> with the four studies meeting criteria from the original review in a random effects meta-analysis.<sup>166</sup> The pooled RR was 1.84 (95% CI 1.54–2.20) for all cause dementia from all severities of TBI (figure 6) although there was heterogeneity in study-specific estimates, possibly because of different populations. We used the TBI adult population prevalence of 12.1% from a meta-analysis to calculate PAF.<sup>173</sup> The weighted PAF was 3.4.

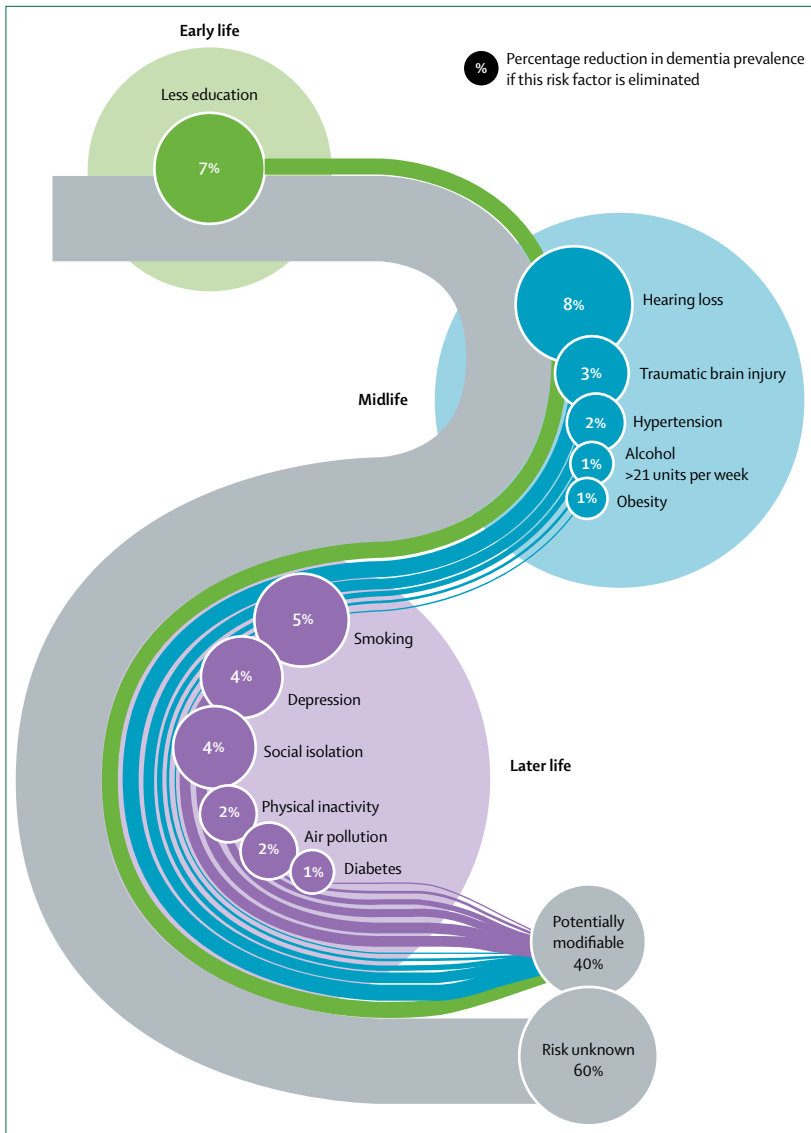


Figure 7: Population attributable fraction of potentially modifiable risk factors for dementia

**Pollution**

A 2019 systematic review synthesised observational studies, finding consistently increased risk of dementia from air pollution, but heterogeneous comparator groups precluded meta-analysis.<sup>24</sup> We updated the search, using the same search terms and searching MEDLINE, Embase, and PsycINFO from Sept 20, 2018, (the end date of the last search) to Oct 22, 2019. We included longitudinal studies with assessment of all cause air pollution exposure; use of formal assessment of cognitive function at baseline; report of incident all-cause dementia, data from adults (age ≥18 years); and a minimum follow-up of 6 months. As meta-analysis was not possible, we used data from the only study of all-cause air pollution with the outcome of all-cause dementia, with low-moderate risk of bias. This

population-based, observational cohort was from Canada, where pollutant concentrations are among the lowest in the world and examined 2066639 people, with a mean baseline age of 67 years.<sup>174</sup> We calculated the RR of dementia for those in the three highest quartiles compared to the lowest was 1.09 (1.07–1.11). The attributable fraction for exposure to the highest three quartiles versus the lowest quartile of PM<sub>2.5</sub> and NO<sub>2</sub> was 6.1% (4.8–7.5). The weighted PAF was 2.3.

Table 1 displays the prevalence, communality, relative risk, unweighted and weighted PAFs adjusted for communality. Figure 7 shows the updated life-course model of potentially modifiable risk factors for dementia, including the three new risk factors.

**Strengths and limitations**

This Commission is the most comprehensive analysis to date and updates the 2017 Commission with emerging risk factor evidence convincing enough to calculate PAF for potentially reversible risk factors. We reviewed the literature systematically for the chosen risk factors and provided illustrative new literature to update our synthesis and identify data to calculate communality. We find a hopeful picture with an estimate of around 40% of all cases of dementia being associated with 12 potentially modifiable risk factors.

We have made assumptions to calculate this new model. We used global figures for dementia risk although we know the risk factors prevalence varies between countries and most global research is from HIC, so LMIC are under-represented because of lack of data. We have assumed a causal relationship between risk factors and dementia, although we have been cautious and not included risk factors with less good evidence. No single database exists with all 12 risk factors together, but we found 11 of the factors in a UK database and used the mean figure for communality calculations for TBI. We calculated communality for the other 11. We do not know how far findings of communality in other geographical populations might differ, or in those with a differing distribution of age groups or sex. We found that social isolation was not explicitly measured and had to use proxies, such as cohabitation when considering prevalence, which are approximate.

Specifically, evidence for the association of alcohol misuse with dementia comes from HIC and future studies from LMIC are needed to complete the picture. Exposure to air pollution changes over a lifetime and is inextricably linked to poverty and deprivation. However, the effects on animal models suggests specific physiological effects over and above those driven by life-course deprivation. We also considered the overlap with education for this and other risk factors and the correction for education, strongly inversely linked to deprivation, will address at least some of the confounding. However, the results in one study which reported the effect of air pollution on incident dementia showed very little

difference in estimates before and after adjustment for education and other risk factors, suggesting little residual confounding exists.<sup>174</sup> We were also unable to meta-analyse data on pollution and thus unlike the other relative risks, the figure comes from only one study, from an area of low pollution so is likely to be an underestimate.

The longitudinal evidence linking potentially modifiable risk factors to dementia generally fulfils causality criteria in observational data (strength, consistency, biological plausibility, temporality, dose–response, coherence, and quasi-experimental studies, for example, more education or using hearing aids). When measuring a risk nearer to the age of dementia onset, then it is more likely that prodromal change affects, or even causes it. Alternatively, a risk factor might act on preclinical pathology or even cause dementia near the time of exposure. Thus, excessive alcohol, and TBI are particularly important in young-onset dementia, although many early onset dementias relate to genetic risks. Risk factors might also matter more at a time of higher biological vulnerability, which the studies we have drawn on cannot establish. The length of exposure required for risk or protection effect, and their inter-relationships as they change across life is unclear—it seems probable that longer or more intense exposure has stronger effects. Additionally, as our communality figures show, risk factors overlap. We cannot establish from these data if having multiple risk factors has an additive or synergistic effect. Association does not prove causation, however, as already noted, the reductions in prevalence and incidence in several HIC suggests that at least some of the risk factors estimated here do have a causal relationship with the clinical expression of dementia.

### Key points and recommendations

We judge that sufficient new evidence supports adding three additional modifiable risk factors for dementia to our 2017 Commission model (excessive alcohol, traumatic brain injury, and air pollution). We have been able to add updated evidence on the nine risk factors implicated in the 2017 Commission (education, hypertension, hearing impairment, smoking, obesity, depression, inactivity, diabetes, and social contact). Reduction of these risk factors might be protective for people with or without a genetic risk, although study findings have not been entirely consistent.<sup>175–178</sup> As we noted in the 2017 Commission, others have previously calculated an estimate of the risk associated with APOε4 at 7% taking into account some other risk factors and this estimate highlights how relatively important potentially modifiable risk factors are in dementia.<sup>2,179</sup>

For some risk factors, the pattern of risk and the individual's other health, both physical and mental, might be especially important. Currently, the evidence suggests a Mediterranean or Scandinavian diet might have value in preventing cognitive decline in people with intact cognition, particularly as one component of a healthy lifestyle, although how long the exposure has to

be or during which ages is unclear. We do not recommend taking additional vitamins, oils, or mixed dietary supplements as a means of preventing dementia as extensive testing in trials has not led to signals of beneficial effects.

Data from RCTs on interventions to prevent cognitive decline, all-cause dementia, or Alzheimer's disease are few. For some key life influences, only observational data, particularly related to natural experiments such as changing the statutory education age, are possible. These influences should be investigated systematically wherever possible. Others can theoretically be investigated but the long follow-up required for midlife risk and protective factors and non-random attrition in longer studies are challenging. Using intermediate endpoints, such as cognition, and dementia onset in research remains uncertain because no intermediate markers with such a close relationship to dementia outcomes exist that it would be possible to predict with certainty for any given individual, age, and sex. Overall, the evidence for treating hypertension is strongest and high blood pressure throughout midlife increases the risk of dementia even without stroke.

Although a need for more evidence is apparent, recommendations should not wait, as clear indications of ways to reduce the chances of developing dementia without causing harm will also lead to other health and wellbeing benefits.

Our recommended strategies for dementia risk reduction include both population-wide and targeted interventions (panel). It is important to remember that more socially disadvantaged groups, including Black, Asian, and minority ethnic groups, are particularly at risk.

Although we have more to learn about effectiveness, avoiding or delaying even a proportion of potentially modifiable dementias should be a national priority for all.

### Interventions and care in dementia

Not all dementia will be preventable and we present the latest evidence on intervention and care for dementia. To date the emphasis has been on specific subtypes of dementia, most notably on Alzheimer's disease, which has been conceptualised over the years in a variety of changing diagnostic criteria—eg, DSM IV and DSM V.<sup>180,181</sup> Intense efforts have been put into biomarkers for early preclinical detection of the disease process before it becomes dementia. Biomarkers need to show reliability and validity, and for dementias they also need to be very closely and clearly related to clinical syndrome outcomes in the way that, for example, human papillomavirus is for cervical cancer, and hypertension has been for stroke.

### Biomarkers and detection of Alzheimer's disease

Markers of neurodegeneration linked to clinical dementia include brain volume loss—ie, hippocampal volume loss and entorhinal cortex and medial temporal cortical thinning—seen in structural imaging. The most studied



**Panel: Recommended strategies for dementia risk reduction**

Risks are particularly high in more socially disadvantaged populations including in Black, Asian, and minority ethnic groups.

**Population-wide**

- Prioritise childhood education for all, worldwide
- Implement social public health policies that reduce hypertension risk in the entire population
- Develop policies that encourage social, cognitive, and physical activity across the life course for all (with no evidence for any specific activities being more protective)
- Scrutinise the risks for hearing loss throughout the life course, to reduce the risk of exposure to this risk factor
- Reduce the risk of serious brain trauma in relevant settings, including occupational and transport
- National and international policies to reduce population exposure to air pollution
- Continue to strengthen national and international efforts to reduce exposure to smoking, both for children and adults, and to reduce uptake and encourage cessation

**Targeted on individuals**

- Treat hypertension and aim for systolic blood pressure <130 mm Hg in midlife
- Use hearing aids for hearing loss; we need to help people wear hearing aids as many find them unacceptable, too difficult to use, or ineffective
- Avoid or discourage drinking 21 or more units of alcohol per week
- Prevent head trauma where an individual is at high risk
- Stopping smoking is beneficial regardless of age
- Reduce obesity and the linked condition of diabetes by healthy food availability and an environment to increase movement
- Sustain midlife, and possibly late-life physical activity

molecular markers are in Alzheimer's disease and are amyloid and tau, which PET and CSF detect clinically. The prevalence of particular pathologies at different ages is important in interpretation of such studies. So, for example, population derived studies show increases in plaques in the population from less than 3% at age 50–59 years to around 40% at age 80–89 years.<sup>182</sup>

*Amyloid imaging*

Amyloid imaging detects amyloid in the brain with high sensitivity and specificity in both cognitively normal and people with Alzheimer's disease when the gold-standard comparison is either neuropathology or clinical diagnosis, distinguishing Alzheimer's disease from other neurodegenerative conditions.<sup>183</sup> Amyloid imaging is not a diagnostic test for dementia. A US study of randomly selected older people from the community recruited 1671 people (mean age of 71 years).<sup>182</sup> The prevalence of PET detected amyloid positivity increased from 2.7% (95% CI 0.5–4.9) of people without cognitive impairment aged 50–59 years to 41.3% (95% CI 33.4–49.2%) aged 80–89 years.<sup>182</sup> In 10-year follow-up PET positivity was associated with a higher probability of developing Alzheimer's disease compared with those who were amyloid negative (HR 2.6, 95% CI 1.4–4.9). In participants with mild cognitive impairment who were amyloid positive the probability (HR 1.9, 95% CI 0.9–3.9) was

not very different to those who were amyloid negative (1.6, 0.8–3.4).

Similarly, an 8-year follow-up study of 599 volunteers (average age 70 years) in Australia found that cognitively normal PET amyloid-positive people had an elevated risk of developing Alzheimer's disease compared with amyloid negative (17.7% vs 8.1%; OR 2.4, 95% CI 1.5–4.0).<sup>184</sup> Over 80% of the 266 people who were PET amyloid-positive did not go on to develop a cognitive impairment within 8 years, showing positive status does not predict impairment for most people in a timeframe that might be a useful prognostic window. Follow-up at 5 years of amyloid-positive participants with normal cognition or mild cognitive impairment versus amyloid negative people found the same pattern of increased risk (2.6, 1.4–4.9). Risk also increases per 1 year of age (HR 1.05, 95% CI 0.55–2.0/year), and APOEε4 status (2.6, 1.4–5.0).<sup>184</sup>

Most people who are amyloid positive with no other markers have not developed Alzheimer's disease dementia during their lifetime. A model of lifetime risks of people who are amyloid positive without any other biomarkers finds it to be 8.4% for a 90-year-old woman who is cognitively normal at baseline, 23.5% for a 75-year-old woman and 29.3% for a 65-year-old woman.<sup>185</sup> The 10-year risk is considerably less, so a 65-year-old woman with only amyloid biomarkers but who is cognitively normal and has no neurodegeneration has a 10-year Alzheimer's disease risk of 2.5% and a man 2.3%, but the risk is higher with accompanying neurodegeneration (table 2).<sup>185</sup>

Overall, the knowledge of PET-measured amyloid and tau status and MRI-derived cortical thickness in a general population derived sample, only adds a small improvement, which might not be clinically important for predicting memory decline over a model with clinical and genetic variables.<sup>186</sup>

Using amyloid PET in patients with cognitive impairment of uncertain causes, results in changes to the clinical diagnosis of Alzheimer's disease<sup>187</sup> and sometimes to medication prescription. We do not know whether PET use improves patient care or decreases care costs. Many people have a mixed cause of dementia and a positive result does not indicate only Alzheimer's disease.

*Fluid biomarkers*

PET imaging is very costly (US\$3000 in the USA) and although used in some clinical settings remains the topic of research to understand its usefulness in broader populations. Fluid biomarkers—ie, blood and cerebrospinal fluid tests—have become a more practical focus of interest since it has become possible to measure specific proteins linked to the proteins associated with the neuropathologies of Alzheimer's disease.<sup>188</sup> A composite blood biomarker for amyloid tested in a discovery dataset and then a validation cohort of participants aged 60–90 years who were already taking part in studies in Japan or Australia had areas under the receiver operating



|          | Normal state 1 | Amyloidosis state 2 | Neurodegeneration state 3 | Amyloidosis and neurodegeneration state 4 | Mild cognitive impairment and amyloidosis and neurodegeneration state 5 | Mild cognitive impairment and neurodegeneration state 6 |
|----------|----------------|---------------------|---------------------------|---|---|---|
| 60 years | 0.2 (0.06–0.8) | 1.3 (0.6–2.5)       | 3.6 (1.1–14.2)            | 7.1 (4.5–10.9)                            | 93.5 (91.1–95.0)  | 57.2 (48.2–67.9)  |
| 65 years | 0.5 (0.14–1.8) | 2.5 (1.2–4.9)       | 4.3 (1.4–15.0)            | 10.7 (6.8–16.2)                           | 91.7 (89.2–93.5)  | 55.4 (46.6–65.8)  |
| 70 years | 1.1 (0.34–3.5) | 4.7 (2.4–8.7)       | 5.5 (2.0–16.6)            | 15.5 (10.0–22.8)                          | 88.6 (85.8–90.6)  | 52.2 (43.8–62.4)  |
| 75 years | 2.2 (0.74–6.5) | 7.8 (4.1–14.0)      | 7.3 (2.9–19.0)            | 20.8 (13.7–29.7)                          | 83.8 (80.7–86.2)  | 47.4 (39.6–57.0)  |
| 80 years | 3.7 (1.3–9.8)  | 11.1 (6.0–18.7)     | 9.3 (3.9–20.9)            | 24.4 (16.4–33.8)                          | 75.8 (72.2–78.7)  | 40.0 (33.1–48.6)  |
| 85 years | 4.7 (1.8–11.0) | 11.5 (6.5–18.5)     | 9.7 (4.3–19.3)            | 23.1 (15.8–31.2)                          | 63.7 (59.6–67.2)  | 30.0 (24.5–37.2)  |
| 90 years | 3.8 (1.5–8.2)  | 8.2 (4.7–12.9)      | 7.1 (3.3–13.3)            | 16.8 (11.5–22.6)                          | 46.7 (42.7–50.2)  | 19.1 (15.3–24.3)  |

Data are relative risk (95% CI) or %. Reproduced from Brookmeyer and Abdalla<sup>188</sup> by permission of Elsevier.

**Table 2: Ten-year risks by age of developing Alzheimer's disease for women based on amyloidosis alone and in the presence of neurodegeneration and mild cognitive impairment**

characteristic curves of 96.7% for discovery and 94.1% for validation. The blood biomarker had sensitivity and specificity above 80% against amyloid PET measurement<sup>188</sup> and correlated with CSF concentrations of A $\beta$ 1–42. These results are similar to other amyloid blood biomarkers<sup>189,190</sup> and harmonisation to a common reference standard is now vital. Although CSF A $\beta$ 1–42/1–40 ratio and amyloid PET are now considered interchangeable,<sup>191</sup> CSF tau biomarkers have only correlated weakly with brain tau as currently measured by radioligands.<sup>192</sup> Neurofilament light protein is measured in many cohorts; however, it is non-specific. People with Huntington's disease, multiple sclerosis, mild cognitive impairment, and Alzheimer's disease might have raised blood neurofilament light concentrations, which are a marker of neurodegeneration.<sup>193–195</sup>

#### Key points and conclusions

To be useful in clinical practice biomarkers must be well understood in the populations to which they are going to be applied, including the effects of age and sex on results. There is now reasonable evidence that amyloid and tau measured by PET or in fluid indicate increased risk for development of cognitive impairment in older adults but at the individual level prognostication is not possible as most cognitively normal people with these markers do not develop dementia within a clinically relevant timeframe. Negative amyloid results can be useful for ruling out current Alzheimer's pathology in people with cognitive impairment when the cause is uncertain and show an individual is unlikely to develop Alzheimer's disease during the next few years. High neurofilament light concentrations indicate a neurodegenerative process but not its cause. The value of biomarkers, in terms of diagnostic value, has not been addressed in different representative populations and particularly not in those from LMIC. The potential advantages of blood biomarkers are their low cost and their wider acceptability and applicability in many settings. In many areas of medicine more reliable diagnostic tests have improved research, including epidemiological and public health research and trials, to help distinguish cause from symptom

(tuberculosis from a fever) or assess risk factor and disease (hypercholesterolaemia and ischaemic heart disease). Those biomarkers developed for the underlying biology of the dementia syndrome are subject to the same assessment of value.

#### Principles of intervention in people with dementia

In the 2017 Commission, we discussed that when concerns are raised by patients or family, an accurate diagnosis is helpful. Such a diagnosis provides a gateway to intervention and services where available, for planning for possible futures, and support for family, as well as to research. Unfortunately, these services are not always available. National plans for dementia support timely diagnosis and offer help to individuals and their families.

We did not address screening of those not presenting with concerns but rigorous systematic reviews by the US Task Force on Prevention have found an absence of evidence of benefit and harm.<sup>196</sup> The first trial of population screening took place in the USA, screening 4005 primary care patients aged 65 years or older. No clear benefit or harm in terms of quality of life, mood, or increasing diagnostic rates was found.<sup>197</sup> Other strategies might become more valuable in time such as sensitive awareness of risk factors, when routine records suggest an individual might be deteriorating cognitively.<sup>198</sup>

People with dementia have complex problems with symptoms in many domains. Those providing support and any interventions must consider the person as a whole, as well as their context and their close carers, whether family or friends. Individuals' medical, cognitive, psychological, environmental, cultural, and social needs must be given consideration.<sup>2</sup> In the context of under provision of services, this notion is and will continue to be a challenge. Dementia, as an illness which affects cognition by definition, affects the ability to organise activities and people with dementia often need help to do what they enjoy—for example, listen to music, or go to gardens and parks. Wellbeing is one of the goals of dementia care.

### Interventions once a diagnosis has been made

#### Medication

Cholinesterase inhibitors have a useful, modest role in improving cognition and activities of daily living in patients with mild-to-moderate Alzheimer's disease and memantine can be prescribed in combination or each drug used separately for moderate and severe Alzheimer's disease.<sup>2199,200</sup> However, although available in most countries these drugs are no longer remunerated in France because it is felt that they offer only a small benefit while shifting clinician's attention from other interventions. Whether non-prescribing of this drug will help patients by removing an intervention with known benefit or be detrimental to them is unknown.<sup>201</sup> No advances have been reported in A $\beta$  therapeutics, with negative results from phase 3 trials of monoclonal antibodies (eg, solanezumab, crenezumab) and inhibitors of  $\beta$ -secretase, a protease involved in the production of A $\beta$  peptides.<sup>202</sup> Aducanumab previously abandoned as futile now has further unpublished results. Three 5HT6 antagonists and the calcium channel blocker nilvadipine<sup>203,204</sup> have also been ineffective. These drugs also show substantial impact during treatments at so-called therapeutic concentrations on the leakiness of blood vessels. The long-term impact of such side-effects is unknown. Anti-tau, anti-amyloid, and anti-inflammatory drugs continue to be in focus and some argue that pre-symptomatic interventions are necessary, especially if targeting A $\beta$  production, but no evidence of efficacy<sup>205</sup> and some evidence of worsening target symptoms currently exists.<sup>206</sup>

#### Cognitive training in people with dementia

A meta-analysis of 12 controlled trials of 389 people with mild dementia, completing 4 or more hours of group-based computerised cognitive training (mean age 66–81 years, 63.5% female participants), found a small, statistically significant beneficial effect on overall cognition, driven by two trials of virtual reality or Video games (SMD=0.3, 95% CI 0.0–0.5), one with a low and one with a high risk of bias.<sup>55</sup>

A Cochrane review<sup>207</sup> found 33 trials of cognitive training, only one of which overlapped with the study above, with around 2000 participants with mild-to-moderate dementia, most with a high or uncertain risk of bias.<sup>207</sup> People completing cognitive training, compared with usual treatment or non-specific activities, had small-to-moderate effects on overall cognition (SMD 0.4, 95% CI 0.2–0.6) and specific cognitive abilities such as verbal fluency and improvements lasted for a few months to 1 year. No direct evidence was observed to suggest that cognitive training was better than cognitive stimulation therapy.

#### Exercise and physical activity

The Dementia and Physical Activity RCT<sup>208</sup> found moderate-to-high intensity aerobic and strength exercise

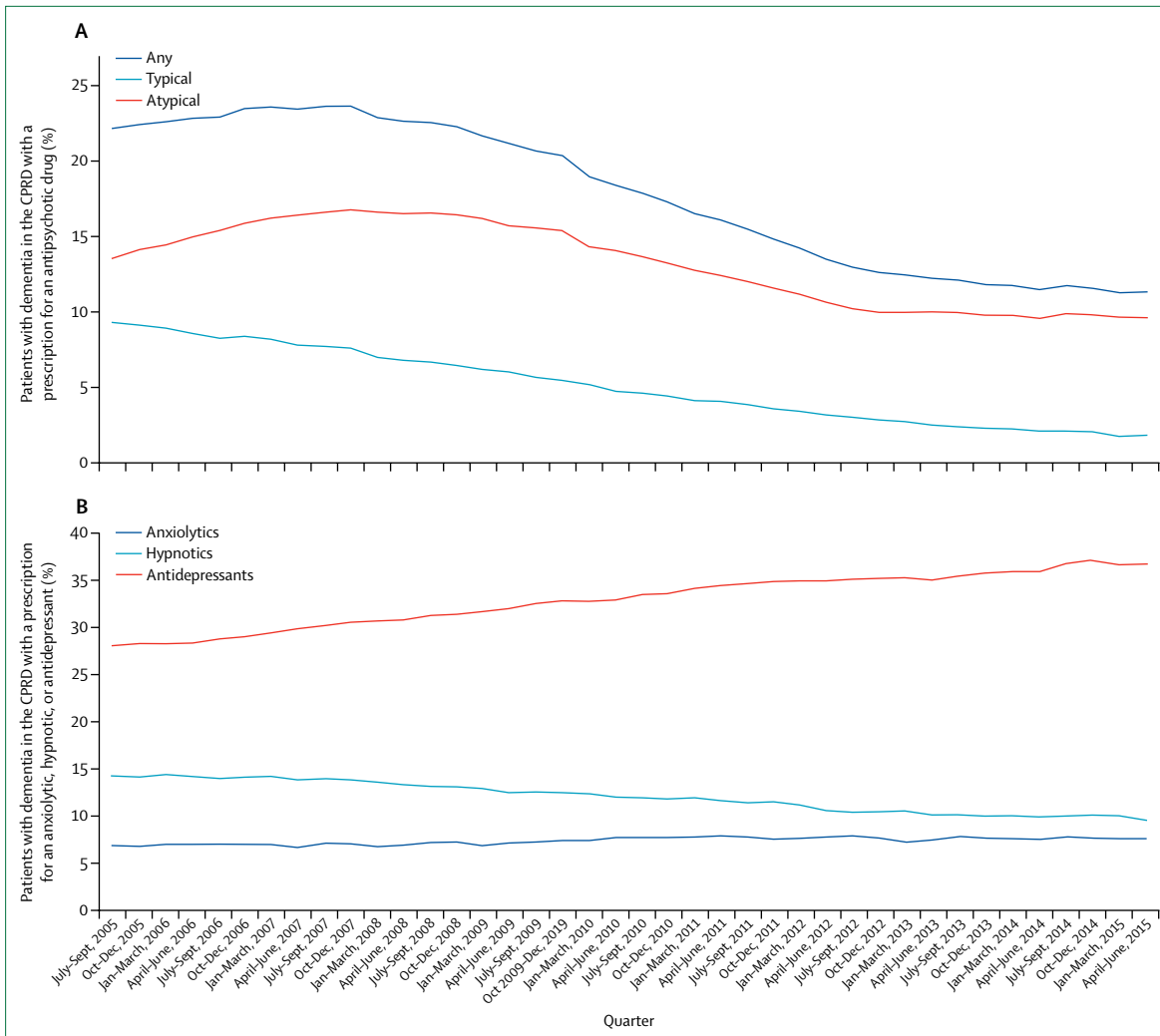
training did not slow cognitive impairment in people with mild-to-moderate dementia but improved physical fitness. The US Reducing Disability in Dementia study<sup>209</sup> implemented an at-home multicomponent intervention including exercise education, training to increase pleasant events, and activator-behaviour-consequence problem-solving approach over 6 weeks by case managers in 255 community dwelling people with dementia older than 60 years and their family carer and were able to follow up 140 (54.9%). The study found increased physical activity; days of taking 30 or more minutes of exercise (effect size 0.6, 95% CI 0.4–0.8 after the treatment and 0.3, 0.1–0.5 at 13 months) in a before and after intervention comparison.

### Interventions for neuropsychiatric symptoms of dementia

Neuropsychiatric symptoms are common and often clustered in people with dementia. These symptoms might precede dementia and are associated with tau and amyloid neuropathology.<sup>210</sup> This suggests that underlying neurobiological mechanisms might underpin neuropsychiatric symptoms. However, other drivers relating to the personal history and the environment of the person with dementia are also likely to exist. Neurodegeneration could lead to increased vulnerability to stressors or triggers. Genetics, cognitive reserve, resilience, medical comorbidities, and environment including responses of carers might modify these relationships. Needs and responses will also be individual and relate to a person's own social, cultural, and historical context. First-line assessment and management of neuropsychiatric symptoms should focus on basic health: describe and diagnose symptoms; look for causes such as pain (using validated pain assessments might help), illness, discomfort, hunger, loneliness, boredom, lack of intimacy and worry that could cause the behaviours and alleviate these while considering risks of harm.<sup>2</sup>

No new evidence of medication effectiveness for these symptoms exists; risperidone in low doses (0.5 mg daily) and some other antipsychotics are sometimes effective but often ineffective and have adverse effects.<sup>2</sup> Specific initiatives have led to a decrease in antipsychotic prescriptions for people with dementia, although often replaced with other psychotropics (figure 8), such as benzodiazepines, antidepressants, and mood stabilisers.<sup>211</sup> These psychotropics lack evidence of efficacy for neuropsychiatric symptoms but show clear evidence of possible harm; for example, trazodone and benzodiazepines increase fall-related injuries.<sup>144</sup> Major policy changes should be assessed carefully, within and across countries for unintended consequences (and perhaps unexpected benefits) and their costs.

Evidence is slowly accumulating for the effectiveness, at least in the short term, of person-centred evidence-based psychosocial interventions. In Germany, a 6-month



**Figure 8: Proportion of patients with a diagnosis of dementia prescribed an antipsychotic drug (A) and those prescribed an anxiolytic, hypnotic, or antidepressant (B)**

CPRD=Clinical Practice Research Datalink. Reproduced from Donegan et al,<sup>211</sup> by permission of Elsevier.

cluster RCT of nurse-delivered, supervised dementia care management used a computer-assisted nurse assessment to determine personalised intervention modules, then a multi-disciplinary team discussion and agreement with the physician for 634 people (mean age 80 years) with dementia living at home with a primary carer or alone.<sup>212</sup> The mean mini mental state examination (MMSE) was 23, only 38% had a formal diagnosis of dementia; the majority of participants (51%) had mild dementia but some had moderate and some severe dementia. The intervention consisted of psychosocial management of treatment and care, medication management and carer support, and education and discussion with a psychiatrist or neurologist. The intervention, compared with care as usual, was associated with better outcomes for neuropsychiatric symptoms (Neuropsychiatric Inventory [NPI] score  $-7.5$ , 95% CI  $-11.1$  to  $-3.8$ ), however this effect could be because

of deterioration in care as usual (in the care as usual group NPI increased from 7.2 to 15.2; in the intervention group NPI increased from 7.6 to 8.2). This between-group reduction in neuropsychiatric symptoms was greater than that expected, extrapolating from other study results, with antipsychotic medication. Effects on quality of life were only apparent for those people living with a carer.

An eight-session home-based tailored activity programme RCT, tailored both to the person with dementia living at home and to a family member compared with eight telephone-based education sessions, recruited 160 participants with 64% follow-up, imputing values for the rest.<sup>213</sup> The study reported a large reduction in overall neuropsychiatric symptoms immediately after the intervention, which were better in the group receiving home-based tailored activity programme on the neuropsychiatric inventory (mean difference in score 24.3,

95% CI 3.1–45.6), and on functional dependence and pain but this was not sustained 4 months later. Non-completers had more severe neuropsychiatric symptoms.

#### Depression

Since the 2017 Commission two new systematic reviews of antidepressants to treat depression in dementia reported moderate quality evidence that antidepressant treatment for people with dementia does not lead to better control of symptomatology compared with placebo.<sup>214,215</sup>

#### Agitation

Agitation is distressing for people with dementia and those around them, and contributes substantially to the overall costs as the level of agitation increases.<sup>216</sup> The body of evidence on this key behaviour is growing, mostly focused on care-home settings. These findings are valuable as these populations are most affected; however, because many people with dementia reside at home a major gap in knowledge remains.

Care home residents with agitation often find sitting still difficult and therefore might not be included in activities.<sup>217,218</sup> Two new cluster RCTs of professionals delivering multicomponent, interdisciplinary, interventions in care homes successfully reduced agitation. The WHELD study<sup>219</sup> included participants with or without neuropsychiatric symptoms and provided person-centred care, aiming to improve communication with people with dementia. It implemented social, sensory experiences or other activities; educated about antipsychotic review; and addressed physical problems, finding lower Cohen Mansfield Agitation Inventory (CMAI) at 9 months (MD -4.3 points, 95% CI -7.3 to -1.2).<sup>219</sup> The TIME study<sup>220</sup> for people with moderate-to-high levels of agitation consisted of a manual-based comprehensive assessment of the resident and structured case conference for the staff and doctor, to create a tailored plan, and then implement it. This intervention led to reduced agitation at 8 weeks (NPI -1.1 points, 95% CI -0.1 to -2.1; CMAI -4.7 points, -0.6 to -8.8) and 12 weeks (NPI -1.6, -0.6 to -2.7; CMAI -5.9, -1.7 to -10.1).<sup>220</sup> These effect sizes are similar to those seen for medications, but without harmful side-effects.<sup>2,221</sup> A further RCT studied a six-session intervention with staff in groups, teaching staff to understand agitation as related to medical, psychological, or social unmet needs and to implement strategies to meet these needs, using the describe, investigate, create, and evaluate approach.<sup>222</sup> The intervention did not reduce agitation symptoms, although it was cost-effective, improving quality of life.<sup>223</sup> Overall, the current evidence for agitation in care homes favours multi-component interventions by clinical staff, including considering if drugs might harm, and not drug interventions. Thus a major gap remains in knowledge about people living at home who comprise the majority of those with dementia.

#### Psychotic symptoms in dementia

People with dementia might be wrongly thought to have delusions when they misremember, and new psychotic symptoms are often due to delirium, thus thorough assessment of symptoms is essential.<sup>2</sup> Management of psychosis in dementia should start with non-pharmacological interventions; however, evidence for effectiveness of these interventions for psychosis in dementia is weaker than for agitation.<sup>224</sup> Antipsychotics for psychosis in dementia should be prescribed in as low a dose and for the shortest duration possible.<sup>2</sup> However, a Cochrane review of antipsychotics withdrawal found two trials with participants with dementia who had responded to antipsychotic treatment. These reported that stopping antipsychotics was associated with symptomatic relapse<sup>225</sup> suggesting the need for caution in any medication withdrawal in this group. There was low-quality evidence that, in general, discontinuation might make little or no difference to overall neuropsychiatric symptoms, adverse events, quality of life or cognitive function.<sup>226</sup>

#### Apathy

Apathy might be conceptualised as the opposite of engagement, comprising reduced interest, initiative, and activity. Like people without dementia, those with dementia engage more in preferred activities, but require additional support to do so.<sup>227</sup> A study in care homes observed engagement increased during activities in those who attended the groups.<sup>228</sup> A Cochrane review of the few people who had been in drug RCTs of methylphenidate versus placebo for apathy in dementia found small improvements on the apathy evaluation scale (MD -5.0, 95% CI -9.6 to -0.4, n=145, three studies, low-quality evidence) but not on the NPI apathy subscale (MD -0.1, 95% CI -3.9 to 3.7, n=85, two studies).<sup>229</sup>

#### Sleep

There is no evidence that medication for sleep in dementia is effective<sup>230</sup> and considerable evidence for harm—ie, earlier death, increased hospitalisation, and falls—exists.<sup>139,144</sup> Testing of non-pharmacological interventions is ongoing.<sup>231</sup>

#### Carers

Carer distress related to neuropsychiatric symptoms rather than the dementia symptoms was associated in one study with increased use and costs of health services,<sup>232</sup> highlighting the need for effectively identifying, educating, and supporting distressed carers. An RCT<sup>233</sup> reporting 6-year follow-up after the eight session STrAtegies for RelaTives intervention—manual-based coping intervention delivered by supervised psychology graduates—found continuing effectiveness for depressive symptoms in carers (adjusted MD -2.00; 95% CI -3.4 to -0.6) and risk of case-level depression, with

patient-related cost being approximately 3 times lower than those who did not receive the intervention (median £5759 vs £16964 in the final year;  $p=0.07$ ).<sup>233</sup> Another US study<sup>234</sup> followed up 663 people, mean age 77 years, 55% women. Caregiver depression rather than symptoms of people with dementia predicted emergency department use for people with dementia, with a 73% (RR 1.73, 95% CI 1.3–2.3) increase.<sup>234</sup>

### Functioning

A UK RCT of 14 sessions of cognitive rehabilitation focused on individual goal attainment with therapy delivered at home by an occupational therapist or nurse to 475 participants with mild-to-moderate dementia (MMSE  $\geq 18$  for inclusion; mean 24) and a family carer.<sup>235</sup> Individuals had two or three goals; the most common was engaging in activities (21% of goals). The intervention group reported increased goal attainment over 3 and 9 months compared with usual treatment (effect size 0.8, 95% CI 0.6–1.0 at both 3 and 9 months).<sup>235</sup> The treatment did not improve participants' quality of life, mood, self-efficacy, cognition, carer stress, or health status and was not cost-effective. A systematic review<sup>236</sup> of RCTs without meta-analysis for overall effect size, concluded that all interventions which had improved functioning in people living with dementia in the community have been individual rather than group interventions. These were: in-home physiotherapist delivered aerobic exercise (two studies, larger one positive, 140 people with Alzheimer's disease; smaller study negative, 30 people with Alzheimer's disease), individualised cognitive rehabilitation (mild or moderate dementia; two studies; 257 cognitive reserve intervention groups and 255 controls), and in-home activities-focused occupational therapy (people with mild to moderate dementia, three studies, 201 intervention, 191 controls) reduced functional decline compared to controls but group-exercise and reminiscence therapies were ineffective.<sup>236</sup>

### People with dementia have other illnesses

Multimorbidity is a huge challenge in dementia, not only because people with dementia have increased rates of other illnesses, but also because they often find it particularly difficult to organise care. People with dementia might forget to tell their family or health professionals of symptoms, struggle to understand or follow agreed plans, and are more likely to forget to drink and eat, increasing falling and infection rates.<sup>237</sup> People with dementia consult primary care less often<sup>238</sup> and have fewer dental visits<sup>239</sup> than those without dementia and their family members, if involved, often feel they lack knowledge to assist.<sup>240</sup> Health-care professionals need education to be more comfortable, understanding, and positive in communicating with people with dementia.<sup>241</sup>

Around 70–80% of people diagnosed with dementia in primary care have at least two other chronic illnesses.<sup>242,243</sup>

People who are physically more frail are more likely to have dementia, but the relationship between pathology and symptoms in these people is comparatively weak suggesting that dementia might be from other causes.<sup>22</sup> Compared to the general older population, people with dementia have increased rates of cerebrovascular disease,<sup>243–246</sup> stroke,<sup>247</sup> Parkinson's disease,<sup>243,245</sup> diabetes,<sup>245,247</sup> skin ulcers, anxiety and depression,<sup>243,245</sup> pneumonia, incontinence, and electrolyte disturbance.<sup>245</sup> Multimorbidity in people with dementia is associated with faster functional decline<sup>248</sup> and worse quality of life for people with dementia and their family carers.<sup>249</sup>

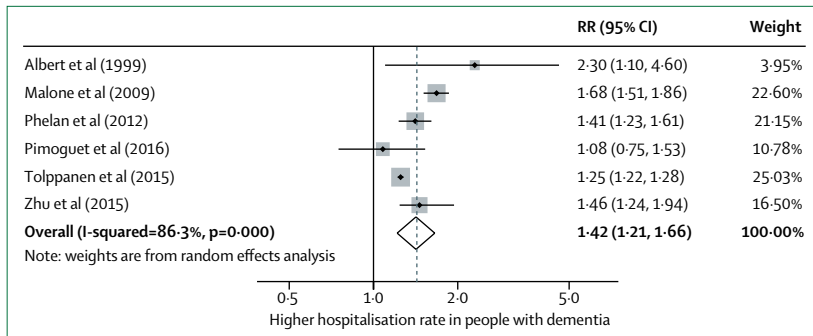
### Dementia and COVID-19

Severe acute respiratory syndrome coronavirus 2, was first identified in patients with viral pneumonia in Hubei province, China.<sup>250</sup> Severity and mortality of the associated disease (COVID-19) worsen with increasing age<sup>251</sup> and with pre-existing illnesses such as hypertension and diabetes,<sup>252</sup> and thus many people with dementia are at particular risk. Death certificates from the UK indicate that dementia and Alzheimer's disease were the most common underlying conditions, specified in 11 950 deaths (25.6% of all deaths involving COVID-19) in March to May, 2020.<sup>253</sup> Many charities, practitioners, and academics supporting people with dementia have issued guidance based on current evidence and best practice, including advance consideration of whether people would wish to be hospitalised if they develop severe COVID-19. Concern has been expressed that the illness and consequent distancing might increase family carer stress, loneliness, neuropsychiatric symptoms and use of psychotropic medication, and lead to complications, including future dementia. Interventions delivered remotely through technology have also been implemented in some places.<sup>254–257</sup>

People with dementia might struggle to adhere to measures to reduce virus transmission, as they might not understand or remember about required changes to behaviour, such as physical distancing and hygiene, leading to increased risk to themselves and their carers.<sup>258</sup> They might additionally be vulnerable if they depend on others for daily activities or personal care, as this necessitates close personal contact.

This situation is particularly concerning in those care homes, where many residents have dementia and where many COVID-19 deaths have occurred in many countries<sup>259–261</sup> with reports of more than half of residents being admitted to hospital. In US nursing homes, among 10 576 people with confirmed COVID-19, residents living with dementia made up 52% of COVID-19 cases; yet, accounted for 72% of all deaths (an increased risk of 1.7).<sup>262</sup> The number of people living together in care homes means that the infection of an individual, either staff or resident, could endanger more people than in traditional or family households. Although evidence exists that if staff are sufficiently and rigorously protected





**Figure 9: Systematic review and meta-analysis of hospitalisation rates of people with dementia compared to those without dementia controlled for age and sex**  
 Reproduced from Shepherd et al,<sup>271</sup> by permission of Springer Nature.

they are unlikely to develop COVID-19, many staff have become unwell and some have died.<sup>263,264</sup> Illness means that there are fewer people to care for residents at a time when they need particularly high levels of care. This situation is particularly relevant in the care of residents with dementia, if they are expected to remain in their own rooms, rather than eating and participating in activities with others. Staff or residents might also be moved between care homes and increase risk in other homes.<sup>261</sup> Restrictions on visitors to private homes, care homes, and hospitals might cause greater distress for people with dementia and they might not understand why people are wearing masks, recognise who is behind it, or understand speech when lips are covered. Lack of restrictions means that the visitors might also be at elevated risk.<sup>261</sup>

The impacts of COVID-19 on people with dementia might be particularly severe in LMICs, due to smaller health budgets for testing and protective equipment, capacity of health-care systems, quality of care home provision and patterns of workforce mobility.<sup>264</sup>

Thus, people with dementia are particularly vulnerable to COVID-19 because of their age, multimorbidity, and difficulties in maintaining physical distancing.<sup>250–252</sup>

We recommend rigorous public health measures of protective equipment and hygiene, including not moving staff or residents between care homes or admitting new residents when their COVID-19 status is unknown, should mitigate impacts on people with dementia. It is also imperative that there is frequent and regular testing of staff in care homes for infection, ensuring staff have sick pay so that they do not come in when symptomatic and interim care is being set up for people discharged from hospital so that only those who are COVID-19 free come to live in care homes. Resident testing should encompass asymptomatic as well as symptomatic people, when there is exposure within the home to COVID-19. In the future, many homes might be able to start to provide oxygen therapy so that those who do not want to be admitted to hospital are still able to access oxygen therapy. In addition, it is also important to reduce isolation by providing the necessary equipment

and a brief training to relatives on how to protect themselves and others from COVID-19; so that they can visit their relatives with dementia in nursing homes safely when it is allowed. Further evidence is needed to inform responses to this and future public health emergencies.

### Hospital admissions

Hospitalisation in people with dementia is associated with adverse, unintended consequences, including distress, functional and cognitive decline, and high economic costs.<sup>265–267</sup> People with dementia have 1.4 to 4 times more hospital admissions than others with similar illnesses.<sup>266,268–270</sup>

A systematic review and meta-analysis including 34 studies of 277 432 people with dementia found that in the six studies which compared the two groups, people with dementia had increased hospital admissions compared with those without dementia, after adjusting for age, sex, and physical comorbidity (RR 1.4, 95% CI 1.2–1.7; figure 9).<sup>271</sup> Hospitalisation rates in people with dementia ranged from 0.37 to 1.26 per person-year in high-quality studies. Admissions are often for conditions that might be manageable in the community (potentially preventable hospitalisations).<sup>268</sup> People with dementia experience longer and more frequent admissions and readmissions; health-care expenditure for people with moderate-severe dementia is around double that of people without dementia.<sup>269,272,273</sup> Early detection and management of physical ill-health in people with dementia, particularly of pain, falls, diabetes, incontinence, and sensory impairment, is important.<sup>199,274,275</sup> However, no intervention has successfully reduced number of hospital admissions of community-dwelling people with dementia,<sup>276</sup> although education, exercise, rehabilitation, and telemedicine have reduced admissions for older people without dementia.<sup>277</sup>

High-quality care for people with dementia takes longer than caring for others with the same condition.<sup>278</sup> Recognition of dementia in hospital inpatients is necessary for optimum care,<sup>279</sup> but dementia is often undetected or unrecorded.<sup>280</sup> In the UK however, detection rates have increased over the past 10 years.<sup>281</sup>

### Physical illness, delirium, and dementia

Dementia and delirium frequently occur together. In one hospital inpatients' survey nearly 35% of those older than 80 years experienced delirium; those with prior cognitive impairment had 15 times the risk of developing delirium than those without (OR 15.3, 95% CI 5.2–45.4).<sup>282</sup> People with delirium without known dementia are more likely to be diagnosed with dementia in the future than others, either because of pre-existing undiagnosed dementia or cognitive impairment, present in 20.7% (95% CI 11.9–29.5) and 37.8% (27.3–88.3) respectively of one cohort, or because delirium has neurotoxic effects and so precipitates dementia.<sup>283</sup> People with similar



neuropathology show faster cognitive decline if they develop delirium than if they do not.<sup>284</sup> Additionally, older people without dementia declined cognitively more than twice as fast after an emergency hospital admission for any cause, compared with those not admitted, suggesting any severe illness is associated with cognitive decline.<sup>285</sup> Risk factors for delirium in dementia include sensory impairment, pain, polypharmacy, dehydration, intercurrent illnesses, such as urinary tract infections or faecal impaction, and an unfamiliar or changing environment.<sup>286</sup> Delirium in older people should prompt consideration of underlying dementia.

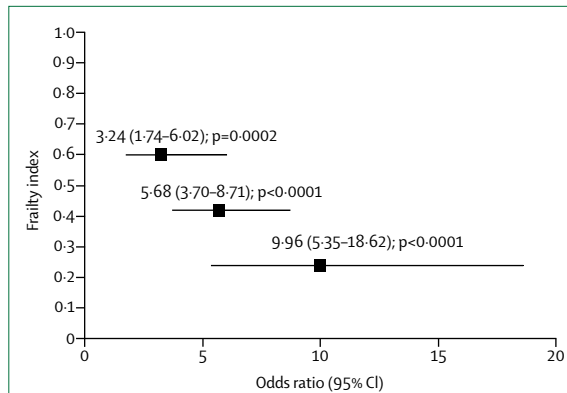
Most research on delirium prevention has been in people without dementia. It suggests targeting hydration, stopping medication predisposing to delirium, monitoring the depth of anaesthesia, and sleep promotion. However, no evidence for medication efficacy, including cholinesterase inhibitors, antipsychotic medication, or melatonin exists.<sup>287–289</sup> The Hospital Elder Life Program<sup>290</sup>—an intervention to prevent delirium in those admitted to hospital—reduces delirium incidence and includes people who are cognitively impaired. This multidisciplinary treatment consists of daily visits, orientation, therapeutic activities, sleep enhancement, early mobilisation, vision and hearing adaptation, fluid repletion, infection prevention and management of constipation, pain, and hypoxia, and feeding assistance.<sup>290</sup>

A network meta-analysis of drugs for prevention and treatment of delirium did not include studies of people with dementia, thus we cannot use this to recommend drugs for people with dementia and delirium as this research might be inapplicable to them.<sup>291</sup>

Little high-quality research exists on managing delirium in dementia. One RCT compared care at a specialist medical and mental health unit to usual care for 600 confused people older than 65 years, acutely admitted to hospital and found no difference in the primary outcome of days spent at home or in hospital, but increased family satisfaction.<sup>292</sup> A further RCT of cognitively stimulating activities for people with delirium in dementia did not improve the delirium.<sup>293</sup> No definitive evidence that any medication improves delirium in people with dementia exists: cholinesterase inhibitors, antipsychotics, and sedating benzodiazepines are ineffective and antipsychotics and benzodiazepines are associated with mortality and morbidity.<sup>265,288,294–297</sup> Given the risk of dementia in people who develop delirium, its prevention, and possibly advances in its management, might offer a means for dementia prevention.<sup>298</sup>

### Link between very old age, frailty, and dementia

The fastest growing demographic group in most advanced countries are people aged 90 years and older. One well characterised post-mortem cohort of the oldest old (n=1079; mean age 90 years) dying with dementia, found that neuropathological features of Alzheimer's disease account for about half of the cognitive decline seen as



**Figure 10: Moderation analyses of the relationship between Alzheimer's disease pathology and clinical diagnosis of Alzheimer's dementia (adjusted for age, sex, and education)**

As frailty increased, the odds of a neuropathological diagnosis of Alzheimer disease corresponding to a clinical diagnosis decreased. Reproduced from Wallece et al,<sup>22</sup> by permission of Elsevier.

people diagnosed with Alzheimer's disease had mixed causes of dementia.<sup>299</sup> Although Alzheimer's disease neuropathology was the commonest cause of dementia, Alzheimer's disease changes rarely occurred on their own, so only 9% of people with dementia had pure Alzheimer's disease pathology.<sup>300</sup> People who have Alzheimer's disease pathology without developing dementia tend to have fewer age-related health deficits than those who develop it with even low concentrations of plaques and tangles.<sup>301</sup> A moderation analysis showed that the relationship between Alzheimer's disease pathology and dementia status differed according to level of frailty (adjusted for age, sex, and education) with increasing frailty weakening the relationship between Alzheimer's disease pathology and dementia (figure 10).<sup>22</sup> As with delirium, some of this additional health risk might be modifiable. This approach suggests a new type of therapy focus on specific age-related processes that underpin many diseases of late life might reduce the incidence or severity of dementia.

### End-of-life care in dementia

The numbers of people dying with dementia are increasing but the evidence for the best end-of-life care is scarce. Trends in age-standardised death rates (3–6%) for dementia increased slightly between 1990–2016, with pronounced increases in the USA and Japan and decreases in western Europe and central Latin America.<sup>4</sup> Dementia is more readily being included on death certificates, which accounts for some of the rise. The increase might be related to dementia manifesting at later ages, with higher physical frailty<sup>22</sup> leading to a faster decline.

Most people with dementia might die while still in the mild-to-moderate stages whereas only about a quarter of those dying with dementia have severe dementia.<sup>302,303</sup> The trajectory of dementia is often unpredictable<sup>304</sup> and palliative care initiation should reflect need not prognosis.

Decision making about end of life is complex and simple rules of thumb, co-designed with staff and carers, provided clarity in some small studies.<sup>304</sup> One RCT testing decision-aids about families' and doctors' goals of care for people with advanced dementia led to increased palliative care content in care plans.<sup>305,306</sup> In a 9-month UK prospective study, 85 care home residents with advanced dementia from 14 homes were likely to be living with distressing symptoms, specifically agitation (54%) or pain (61% on movement).<sup>304</sup>

Capacity to make abstract decisions, including about the future, might be lost early in dementia.<sup>307</sup> Therefore, advance care planning, designed to empower people with dementia and improve quality of dying, might theoretically be something everyone should do before developing dementia.<sup>308</sup> However, people might not be able to predict their future wishes. This might explain why family carer proxies show only low-to-moderate agreement with stated end-of-life treatment preferences of people with dementia.<sup>309</sup> Advance care planning might, however, reduce carers' uncertainty in decision making and improve perceptions of quality of care.<sup>310</sup>

Partners of people dying with dementia experience poorer mental health than those facing bereavement from other causes<sup>311</sup> possibly because of long and difficult caring responsibilities. This might be ameliorated through sensitive and timely information, particularly regarding the progression of dementia,<sup>312</sup> individually or through family and staff case-conferencing.<sup>313,314</sup>

## Conclusions

Knowledge about risk factors and potential prevention, detection, and diagnosis of dementia is improving although significant gaps remain.<sup>315</sup> In this Commission report, we have specified policy and individual changes to delay the onset of cognitive impairment and dementia and better ways to support and treat people with dementia and their families and to improve their quality of life.

Interventions, including organisation of the complex physical illness and social needs, to support people affected by dementia can have a huge effect when taken as a whole. Our ambition is for worldwide provision of resources for an adequate level of wellbeing to people with dementia and their carers with a better evidence base to guide individual care and policy making alike. With good quality care, people can live well with dementia and families can feel supported.

### Contributors

GL, JH, AS, and NM contributed to literature searches and quality assessments for systematic reviews. JH and NM performed meta-analyses. GL, JH, AS, and NM conceived the new PAF calculation and NM led the statistical analysis. GL, JH, AS, NM, DA, CLB, SB, AB, JC-M, CC, SGC, NF, RH, HCK, EBL, VO, KRi, KRo, ELS, QS, LSS, and GS attended the conference to discuss the content. GL, JH, EBL, AS, DA, and ELS wrote first drafts of sections of the paper. GL wrote the first draft of the whole paper and revisions of drafts. CBa reviewed and contributed to revision of the final drafts. All authors contributed to sections of the reports and all revised the paper for important intellectual content.

### Declaration of interests

AS reports grants from Wellcome Trust (200163/Z/15/Z), outside the submitted work. DA reports grants from Eli Lilly, during the conduct of the study. CBa reports grants and personal fees from Aca-dia and Lundbeck; and personal fees from Roche, Otsuka, Biogen, Eli Lilly, and Pfizer, outside the sub-mitted work. SB reports grants and personal fees from AbbVie, personal fees and non-financial sup-port from Eli Lilly, and personal fees from Eleusis, Daval International, Boehringer Ingelheim, Axovant Sciences, Lundbeck, and Nutricia, outside the submitted work; and he has been employed by the Department of Health for England. NF reports non-financial support from Eli Lilly, outside the submitted work. LNG and her institutions (Johns Hopkins University, Baltimore, MD, USA, Drexel University, Philadelphia, PA, USA, and Thomas Jefferson University, Philadelphia, PA, USA) are entitled to receive royalties from fees associated with online training for the tailored activity program, which is an evidence-based program referenced in the Review. RH reports grants from Department of Health, NIHR HTA Programme, outside the submitted work; and he is a Scientific Trustee of the charity Alzheimer's Research UK. MK reports grants from the UK Medical Research Council (S011676, R024227), NordForsk (the Nordic Programme on Health and Welfare, 75021) and the Academy of Finland (311492), outside the submitted work. EBL reports other (royalties) from UpToDate, outside the submitted work. KRo reports personal fees from Clinical Cardio Day-Cape Breton University, Sydney, NS, Canada, CRUIGM-Montreal, Jackson Laboratory, Bar Harbor, MA, USA (speaker fees), MouseAge, Rome, Italy (speaker fees), Lundbeck, Frontotemporal Dementia Study-Group, SunLife Insurance, Japan, outside the submitted work. He is a President and Chief Science Officer of DGI Clinical, which in the last 5 years has contracts with pharma and device manufacturers (Baxter, Baxalta, Shire, Hollister, Nutricia, Roche, Otsuka) on individualised outcome measurement. In 2017, he attended an advisory board meeting with Lundbeck. He is also Associate Director of the Canadian Consortium on Neurodegeneration in Aging, which is funded by the Canadian Institutes of Health Research, and with additional funding from the Alzheimer Society of Canada and several other charities, as well as, in its first phase (2013-2018), from Pfizer Canada and Sanofi Canada. He receives career support from the Dalhousie Medical Research Founda-tion as the Kathryn Allen Weldon Professor of Alzheimer Research, and research support from the Canadian Institutes of Health Research, the QEII Health Science Centre Foundation, the Capital Health Research Fund and the Fountain Family Innovation Fund of the QEII Health Science Centre Foundation. LSS reports grants and personal fees from Eli Lilly, Merck, and Roche/ Genentech; personal fees from Avraham, Boehringer Ingelheim, Neurim, Neuronix, Cognition, Eisai, Takeda, vTv, and Abbott; and grants from Biogen, Novartis, Biohaven, and Washington University DIAN-TU, outside the submitted work. The remaining authors declare no conflict of interests.

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