The Lancet standing commission on dementia prevention, intervention and care

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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 due to improvements in education, nutrition, health-care, and lifestyle changes**.** Overall, there is growing evidence for the nine potentially modifiable risk factors for dementia that the Lancet 2017 commission modelled previously; education, hypertension, hearing impairment, smoking, obesity, depression, exercise, diabetes and social contact. We now add three more risk factors for dementia with more recent, convincing evidence. These are higher alcohol consumption, traumatic brain injury 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 they account for around 40% of worldwide dementias, which theoretically could be prevented or delayed by eliminating these risk factors. The potential for prevention is high and may be higher in low and middle-income countries (LMIC) where more dementias currently occur.

Our new life course model and evidence synthesis has important worldwide policy implications. It is never too early and never too late in the life course for dementia prevention. Early-life risks, such as less education affect cognitive reserve; midlife and old age risk factors influence reserve and triggering of neuropathological developments. Culture, poverty and inequality are important obstacles to, or drivers of, the need for change. Those who are most deprived need the changes 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 late-life dementia. Mid-life systolic blood pressure control should aim for ≤130mmHg 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 mid- and late-life but there is little evidence for any single specific activity being protective against dementia. Using hearing aids appears to reduce the excess risk from hearing loss. Sustained mid-life, and possibly late-life, exercise protects from dementia, perhaps through decreasing obesity, diabetes and cardio-vascular risk. Depression may be a risk for dementia, but in later life dementia may cause depression. Although behaviour change is difficult and some associations may not be purely causal, there remains huge potential for individuals to reduce their dementia risk.

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

Amyloid beta and tau biomarkers indicate risk of progression to Alzheimer's dementia but most people with normal cognition and these biomarkers never develop AD. While accurate diagnosis is important for patients and families who have impairments and functional concerns, there is a lack of evidence to support pre-symptomatic diagnosis in everyday practice.

Our understanding of dementia aetiology is shifting, with recent description of new pathological causes. In the oldest old, in particular, mixed dementia is more common. Blood biomarkers may

hold promise for future diagnostic approaches and are more scalable than CSF and brain imaging markers.

Wellbeing is the goal of much 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, be cost-effective and may save money.

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. Such hospitalisations are distressing and are associated with poor outcomes and high costs. Health-care professionals 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 may 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.

Key messages

1. There is updated evidence for adding three modifiable risk factors – excessive alcohol consumption, head injury and air pollution - to our original Lancet Commission life course model of nine factors (less education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, and infrequent social contact).
2. These 12 risk factors may prevent or delay up to 40% of dementias if modified.
3. 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 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.
4. Specific actions for risk factors from across the lifecourse are:

    i. Aim to maintain systolic BP ≤130 mmHg in midlife from around age 40 years (antihypertensive treatment for hypertension is the only known effective preventive medication for dementia).
    ii. Encourage use of hearing aids for hearing loss and reduce hearing loss by protection of ears from high noise levels.
    iii. Reduce exposure to air pollution and second hand tobacco smoke.
    iv. Prevent head injury
    v. Limit alcohol use, as alcohol misuse and drinking >21 units (14 drinks) weekly increase the risk of dementia

vi. Avoid smoking uptake and support smoking cessation to stop smoking, as this reduces the risk of dementia even in late-life
vii. Provide all children with primary and secondary education.
viii. Reduce obesity and the linked condition of diabetes and thus decrease dementia.
ix. Sustained mid-life, and possibly late-life physical activity is associated with reduction in the risk of dementia
x. Addressing other putative risk factors for dementia, like sleep, through lifestyle interventions, will improve general health.

5. Clearly many risk factors cluster around inequalities and in vulnerable populations. Thus tackling them will not involve only health promotion but societal action to improve the circumstances in which people live their lives. Examples include creating environments that have physical activity as a norm, reduce the population profile of blood pressure rise with age through better patterns of nutrition, and in which there is reduced potential exposure to excessive alcohol. Dementia is rising more in LMIC than in high-income countries, because of population ageing and higher frequency of potentially modifiable risk factor**s**. Preventative interventions may yield the largest dementia reductions in LMIC.

For those with dementia recommendations are:

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

Introduction

Worldwide around 50 million people live with dementia, and this is projected to increase to 131 million by 2050,[1] rising particularly in low and middle-income countries (LMIC) where around two-thirds of people with dementia live.[1] Dementia affects individuals, their families and the economy, with global costs estimated to exceed US$800 billion annually.[1]

We re-convened the Lancet Commission [2] to identify the 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 this 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. There is updated evidence about dementia risk in LMIC; risks and protective factors for dementia; detection of Alzheimer's dementia (AD); multimorbidity in dementia and interventions for people affected by dementia.

Nearly all the evidence is from studies in high-income countries (HIC), so risks may differ for other countries and interventions may require modification for different cultures and environments. This 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 aged over 80, progressing more slowly than AD, detectable at post-mortem, often mimicking or comorbid with AD.[3] This reflects increasing attention 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 old, those aged over 90. This represents a unique scientific opportunity to focus on both human biology, in this previously rare population, as well as on meeting their unique needs and promoting their well-being.

Prevention of dementia

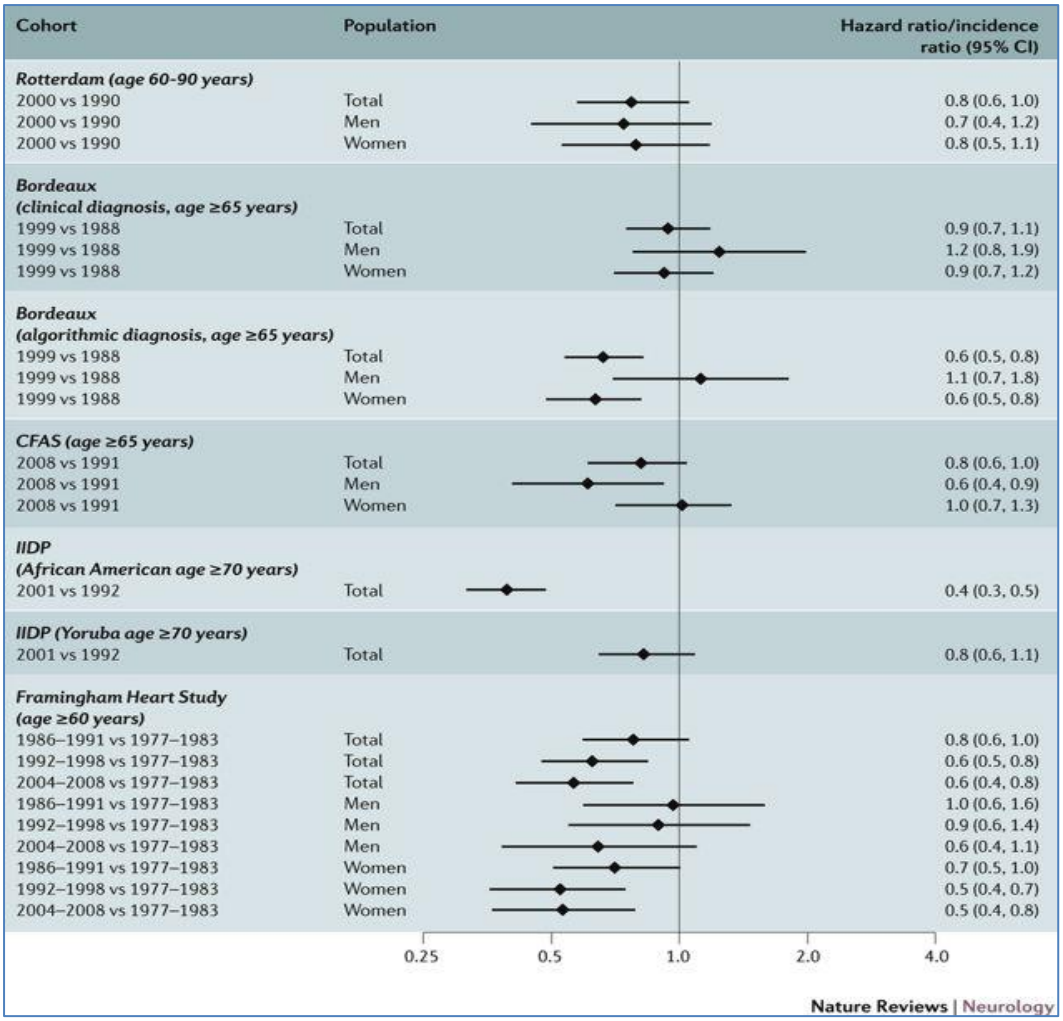
The number of people with dementia is rising. Predictions about future trends in dementia prevalence vary depending on the underlying assumptions and geographical region, but generally suggest substantial increases in overall prevalence related to population ageing. For example, according to the Global 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.[4]

However, in many countries such as the US, UK and France, age-specific incidence rates are lower in recent compared to earlier cohorts collected using similar methods and target populations [5] (Figure

1) and there appears to be a decrease in age specific incidence of dementia. In, for example, England, public health models from UK population based studies suggest a declining trend in age-specific dementia incidence. [6] All-cause dementia incidence is lower in people born more recently,[7] probably due to educational, socio-economic, health care and lifestyle changes. [2,5] However, in these countries increasing obesity, diabetes and declining physical activity may reverse this trajectory.[8,9] In contrast, age-specific dementia prevalence in Japan, South Korea, Hong Kong and Taiwan looks as if it is increasing, as is AD in non-Western countries, although it is unclear whether diagnostic methods are always the same in comparison studies. [5,7] [6]

Modelling the UK change, suggests a 57% increase in the numbers of people with dementia from 2016 to 2040, 70% of that expected if age-specific incidence rates remained steady, [10] 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.[6]

In our first report, this commission described a life-course model for potentially modifiable risks for dementia.[2] Life-course is important when considering risk, for example, obesity and hypertension in mid-life predict future dementia, but both body weight and blood pressure usually fall in late-life in those with or developing dementia,[9] so late-life lower weight and blood pressure may signify illness not an absence of risk.[11-14] We consider evidence about other potential risk factors and incorporate those with good quality evidence in our model.



with permission **Figure 1: Incidence rate ratio comparing new cohorts to old cohorts from five studies of dementia incidence** [5] Age-specific dementia prevalence is increasing in some other countries. IIDP (Indianapolis–Ibadan Dementia Project) in USA and Nigeria; Bordeaux study France; and Rotterdam, Netherlands study adjusted for age. Framingham Heart Study, USA adjusted for age and sex. CFAS = Cognitive Function and Ageing Study UK; adjusted for age, sex, area and deprivation.

Figure 2 summarises possible mechanisms of protection from dementia. These involve cognitive reserve, which allow for cognition maintenance despite pathology and neuropathological damage. There are different terms describing the observed differential susceptibility to age- and disease-related changes and these are not used consistently.[15,16] A recent consensus paper defines "reserve" as a concept accounting for the difference between an individual's clinical picture and their neuropathology. It divides it into neurobiological brain reserve (for example, numbers of neurones and synapses at a given time point), brain maintenance (as neurobiological capital at any time point, based on genetics or lifestyle reducing brain changes and pathology development over time) and cognitive reserve (CR) as adaptability enabling preservation of cognition or everyday functioning in spite of brain pathology.[15] CR 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 may underlie such reserve.[15]

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 they have on average had less education than have older men. Cognitive reserve mechanisms may include preserved metabolism or increased connectivity in temporal and frontal brain areas. [17-21] People otherwise in good physical health can sustain a higher burden of neuropathology without cognitive impairment. [22] Culture, poverty and inequality are important obstacles to and drivers of the need for change. Those who are most deprived need the changes most and will derive the highest benefit.

Exercise increases and smoking decreases HDL–cholesterol and docosahexaenoic acid blood levels (DHA) which in one study were associated with reduced dementia and AD risk independently of cardiovascular health and the allele APOEε4. [23] Smoking increases air particulate matter, and has vascular and toxic effects.[23] Similarly air pollution may act via vascular mechanisms.[24] Exercise may reduce weight and diabetes risk, improve cardiovascular function, decrease glutamine or enhance hippocampal neurogenesis. [25] Higher HDL-cholesterol may protect against vascular risk and inflammation accompanying amyloid-beta (Aβ) pathology in Mild Cognitive Impairment (MCI). [26]

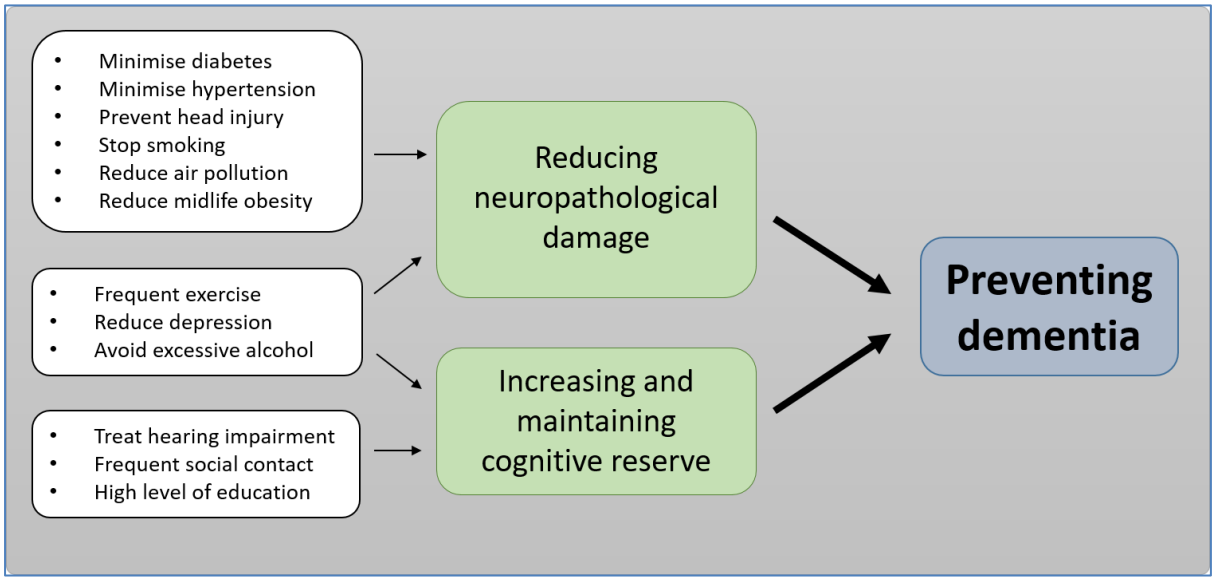


Figure 2. Possible brain mechanisms for enhancing or maintaining cognitive reserve and risk reduction of potentially modifiable risk factors in dementia

Dementia in Low and Middle Income Countries (LMIC)

Numbers of people with dementia in LMIC are rising faster than in higher income countries 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. [2] Most research data for this calculation came from high-income countries and review evidence shows there is a relative lack of specific evidence of the impact of risk factors on dementia risk in LMIC, particularly from Africa and Latin America[27].

Calculations taking into account country-specific prevalence of the nine potentially modifiable risk factors indicates population attributable fractions 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. [28 29] There is therefore higher potential for dementia prevention in these countries than in global estimates which use data which is predominantly from higher income countries. National policies on access to education, addressing causes and management of high blood pressure, causes and treatment of hearing loss, socioeconomic and commercial drivers of obesity including influences on physical inactivity may be risk reduction strategies in many countries if not currently in place. The higher social contact observed in these three LMIC regions provide potential insights for higher income countries to influence this risk factor for dementia.[30]. We have not been able to take into account 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 may add to the risks in LMIC.

Diabetes is also very common and cigarette smoking is rising in China while falling in most high-income countries. [31] A meta-analysis found variation of the rates of dementia within China, with a higher prevalence in the north and lower in central China, estimating there was 9.5 million people with dementia, whereas a slightly later synthesis estimated a higher prevalence of around 11 million. [30,32] 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, traumatic brain injury, alcohol misuse) and later life (smoking, depression, physical inactivity, social isolation, diabetes, air pollution) can contribute to increased dementia risk (table 1). There is good evidence for all these risk factors although there is the possibility that some late-life factors, such as depression, have bidirectional impact and are also part of the dementia prodrome [33 34]

In the following section, we briefly describe relevant newly published and illustrative research studies that add to the 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 there is very little evidence. We discussed them in lifecourse order and within the lifecourse in the order of strength of population attributable factor.

Education, midlife and late-life cognitive stimulation

Education level reached

Higher childhood education levels and lifelong higher educational attainment reduce dementia risk. [2,35,36 37] New work suggests overall cognitive ability increases, with education, before reaching a plateau in late adolescence, when there is greatest brain plasticity; with relatively few further gains with education after age 20.[38] This suggests cognitive stimulation is more important in early life; much of the apparent later effect may be due to people of higher cognitive function seeking out cognitively stimulating activities and education.[38] It is difficult to separate activities from earlier achievements, [38,39] and late-life cognitive activity associated with lifelong cognitive function. [39,40]

Cognitive maintenance

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

This is consistent with small studies of mid-life activities which find they are associated with better late-life cognition; so for example, in 205 people aged 30-64 years, followed 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. [41] 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. [42]

Cognitive decline

The 'use it or lose it' hypothesis suggests that mental activity, in general, may increase cognitive activity. People in more cognitively demanding jobs tend to show less cognitive deterioration before, and sometimes after retirement than those in less demanding jobs. [43,44] One systematic review of retirement and cognitive decline found conflicting evidence. [45] Subsequently, a 12-year study of 1658 people found older retirement age but not number of years working, was associated with lower dementia risk.[46] Those retiring because of ill health had lower verbal memory and fluency scores than those retiring for other reasons. [47] Another study found a two-fold increase in episodic memory loss attributable to retirement (n=18,575, mean age 66), compared to non-retirees, adjusting for health, age, sex and wealth.[48] Similarly, in a cohort of 3433 people retiring at mean age 61 years, verbal memory declined 38% (95% CI 22-60) faster than before retirement. [44] In countries with younger compared to higher retirement ages, average cognitive performance drops more. [49]

Cognitive interventions in normal cognition and Mild Cognitive Impairment

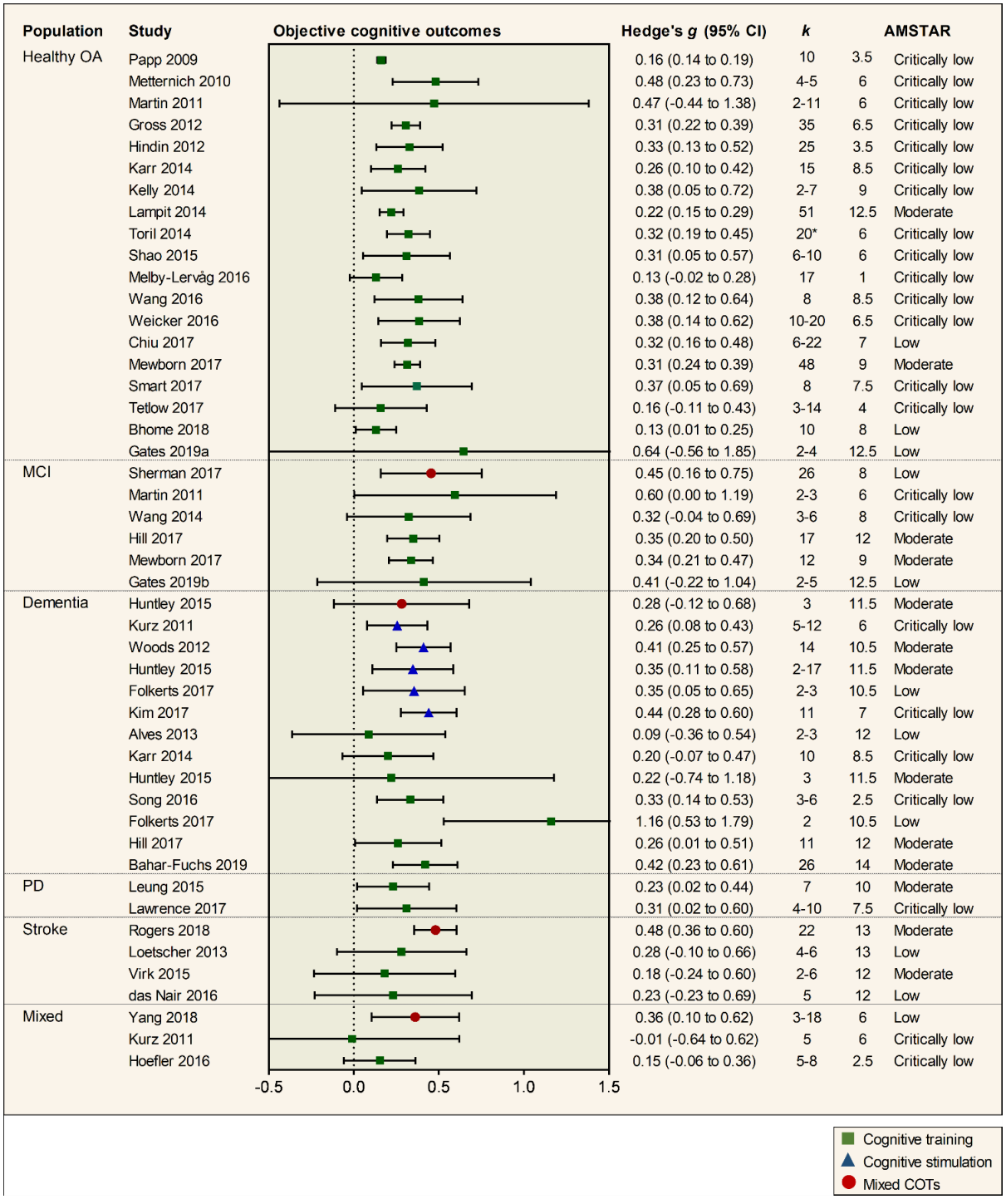
A cognitive intervention or cognition-orientated treatment comprises strategies or skills to improve general or specific areas of cognition.[50] Computerised cognitive training (CCT) programmes have increasingly replaced tasks that were originally paper-and-pencil format with computer-based tasks for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

Three systematic reviews in the general population found no evidence of generalised cognition improvement from specific cognitive interventions, including computerised cognitive training (CCT), although the domain trained may improve. [52-54]

A meta-analysis of 17 controlled trials of at least 4 hours of CCT (N=351; control N=335) for Mild Cognitive Impairment (MCI), found a moderate effect post-training on general cognition (Hedges' g=0.4; 0.2-0.5) [55] but there were few high quality studies and there is currently no long-term high quality evidence about prevention of dementia. A meta-analysis of 30 trials of computerised, therapy-based and multimodal interventions for MCI found an effect on activities of daily living (ADL) (d= 0.23) and metacognitive outcomes (d = 0.30) compared to control. [56] 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 MCI was insufficient to draw conclusions. [53] A

comprehensive, high quality, systematic overview of meta-analyses of cognitive training in healthy older people and those with MCI, found that most were of low standard, all were positive and 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 (see figure 3).[51]

In the only RCT of behavioural activation (221 people) for cognition in amnestic MCI (aMCI), behavioural activation vs supportive therapy was associated with a decreased 2-year incidence of memory decline (relative risk (RR) 0.12; 0.02-0.74). [57]



AMSTAR= A MeaSurement Tool to Assess systematic Reviews (max score 16) **Figure 3 Pooled results of meta-analyses investigating objective cognitive outcomes of cognition-oriented treatment in older adults. With permission** [51]

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 World Health Organisation threshold for hearing loss. In the previous Lancet commission, we found a RR of 1.9 for dementia in populations followed over 9-17 years, making reverse causation bias unlikely. [2] 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 10dB of worsening of hearing loss. [58] A cross-sectional study of 6451 individuals designed to be representative of the US population, with a mean age of 59.4, found a decrease in cognition with every 10dB reduction in hearing and that continued to below the clinical threshold so that subclinical levels of hearing impairment (below 25 dB) were significantly related to lower cognition.[59] While 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), at least two brain MRIs, with a mean of 19 years follow-up, found that audiometry measured midlife hearing impairment, is associated with steeper temporal lobe volume loss, including in the hippocampus and entorhinal cortex. [60]

Hearing aids

A 25-year prospective study of 3,777 people aged ≥65 found increased dementia incidence in those with self-reported hearing problems except in those using hearing aids. [61] Similarly, a cross–sectional study found hearing loss was associated with worse cognition only in those not using hearing aids. [62] A US nationally representative survey of 2040 people aged >50, tested two-yearly for 18 years, found immediate and delayed recall deteriorated less after initiation of hearing aid use, adjusting for other risk factors.[63] Hearing aid use remained the largest factor protecting from decline (regression coefficient β for higher episodic memory = 1.53; p <.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. It may be that hearing loss is a mediating factor; for example, persons with hearing loss have reduced cognitive stimulation

Traumatic brain injury

ICD defines mild traumatic brain injury (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 ε4 compared to APOE ε3 allele have more hippocampal hyper-phosphorylated tau post-TBI. [64] [64,65] TBI is usually caused by car, motorcycle and bicycle injuries; military exposures; boxing, horse riding and other recreational sports; firearms; and falls[66]. A nationwide Danish cohort study of nearly three million people aged ≥ 50 years, for a mean of 10 years, found an increased dementia and AD risk in people with TBI (respectively HR 1·2; 95% CI 1·2- 1·3; HR 1·2; 95% CI 1·1- 1·2). [67] Dementia risk was highest in the 6 months after TBI (HR 4.1; 95% CI 3·8- 4·3) and increased with number of injuries (one TBI HR 1·2, 95% CI 1·2 - 1·3; ≥5 TBIs HR 2·8, 95% CI 2·1 - 3·8). Risk was higher for TBI than fractures in other body areas (HR 1·3, 95% CI 1·3–1·3). It remained elevated after excluding those who developed dementia <2 years after TBI, to reduce reverse causation bias. [67]

Similarly, a Swedish cohort of over 3 million people aged ≥50 years, found TBI increased one-year dementia risk (OR 3.5; 95% CI 3.2, 3.8); and risk remained elevated, albeit attenuated over 30 years (O.R 1.3; 1.1, 1.4). [68] ICD defined single mild TBI increased the risk of dementia less than severe and multiple TBIs increased the risk further (mild, moderate and severe respectively, OR 1.6; 95% CI 1.6-1.7; OR, 2.1; 2.0, 2.2; OR, 2.8; 2.5, 3.2 respectively). A nested case control study of early onset clinically diagnosed AD within an established cohort also found TBI was a risk factor, increasing with number and severity. [69] There was a stronger risk of dementia nearer the time of the TBI, leading to some people with early-onset AD.

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 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 (LOC); HR 2.5; 95% CI 2.3-2.8 for mild TBI with LOC; and HR 3.8; 95% CI 3.6-3.9 for moderate to severe TBI.[70] Similarly women veterans with TBI had increased risk of dementia compared to those without TBI; HR 1.5; 95% CI 1.0-2.2. [71]

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 not. They suggest further RCTs as statins may mitigate injury-related brain oedema, oxidative stress, amyloid protein aggregation, and neuroinflammation. [72]

The term chronic traumatic encephalopathy (CTE) describes sports head injury, which is not yet fully characterised and covers a broad range of neuropathologies and outcomes, with current views largely conjecture.[73] The evidence has subsequently been strengthened by a study on Scottish former soccer players reporting that they are more likely than controls to have AD 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- 6.3but not on medical records.[74] The study controlled for socio-economic class based on residential address, which in footballers may differ from level of education and there will be confounding factors that could not be investigated.

Hypertension

Persistent mid-life hypertension is associated with increased risk of a late life dementia. In the Framingham Offspring cohort comprising 1440 people, elevated systolic blood pressure (SBP ≥ 140mmHg in mid-life; 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)[12]. 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 mid-life (mean age 62 years) with ideal cardiovascular parameters (current non-smoker, body mass index 18.5 - 25 kg/m, regular physical activity, healthy diet, optimum BP <120/<80 mmHg, cholesterol, and normal fasting blood glucose) were compared to people with at least one of these risks.[75] They had a lower 10-year risk of all-cause dementia (HR 0.8; 95% CI 0.1-1.0), vascular dementia (HR 0.5; 95% CI 0.3-0.8) and clinically diagnosed AD (HR 0.8; 95% CI 0.6-1.0). In a UK cohort study of 8639 civil servants, a single measure of BP ≥130mmHg at age 50 but not at age 60 or 70 was associated with increased risk of dementia (HR 1.4; 95% CI 1.1, 1.7). [13] In those with persistent SBP ≥ 130 mmHg, from mean age 45 to 61 years, dementia risk is increased

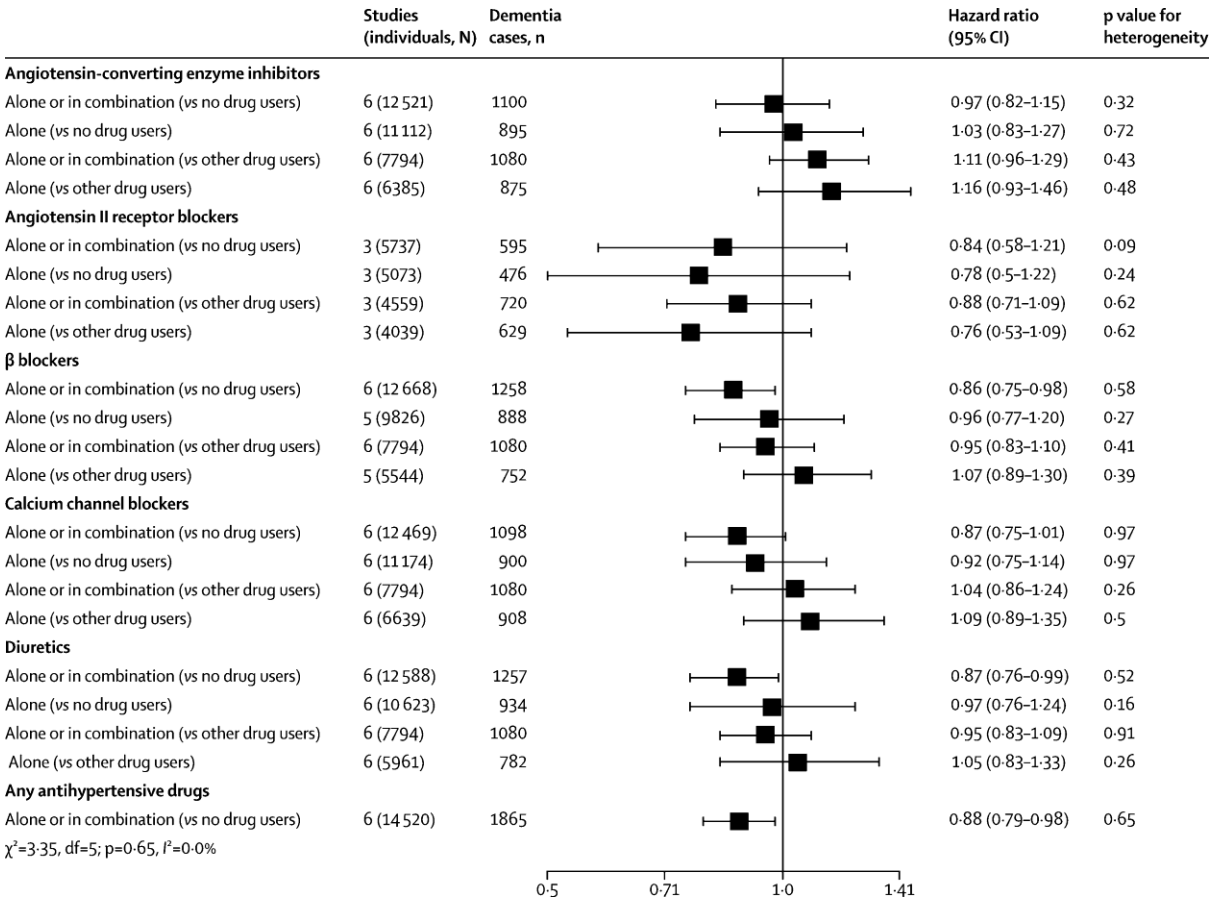
even if free of cardiovascular disease (CVD) relative to those without hypertension (HR 1.3; 95% CI 1.0-1.7).

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

Antihypertensive drugs, aspirin and statins

The US and Puerto Rico Systolic Blood Pressure Intervention Trial (SPRINT) trial in 9361 hypertensive adults aged ≥50, was stopped early as there were significantly fewer cardiovascular events and deaths in the intensive treatment arm (aiming for systolic <120mm Hg; n=4678) in comparison to standard treatment (systolic <140mmHg; n=4683). [78] Cognitive assessment continued after stopping the trial intervention in SPRINT MIND.[79] In the intensive compared to the standard treatment group, there were 7.2 dementia cases as opposed to 8.6 cases /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 MCI (14.6 vs 18.3 cases/1000 person-years; HR, 0.8; 95% CI 0.7-1.0), combined MCI or dementia (20.2 vs 24.1 cases/1000 person-years; HR, 0.9; 95% CI 0.7-1.0) [79] making this the first trial to suggest reduction of risk for MCI. Those who were lost to follow-up were at greater risk of dementia than those who continued but follow-up data rates did not differ according to intervention group.[80]

Four recent 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 AD. The first included RCTS of any drugs to lower blood pressure and reported a reduction in risk of around 10% at marginal significance (relative risk [RR] 0.9; 95% CI 0.9-1.0).[81] 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 AD HR 0.8; 95% CI 0.7- 0.9). [82] The third included used individual participant data from six observational studies; (dementia HR 0.9; 95% CI 0.8 -1.0) and (AD HR 0.8; 95% CI 0·7-1.0) (see Figure 4). [83] 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). [84] A recent 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 there was no consistent difference in effect according to which class of drug was used.[85]



[83]**Figure 4 Associations of antihypertensive medication use with incident dementia in those with high blood pressure** with permission

A Cochrane review reported good evidence that statins given to older people at risk of vascular disease do not prevent cognitive decline or dementia. [86] One RCT found 100mg aspirin versus placebo in 19,114 healthy adults aged >65 did not reduce dementia (HR 1.0; 0.8-1.2), death, physical disability or CVD over a period of 4.7 years. [87]

Physical inactivity, exercise and fitness

Studies of physical activity are complex. Patterns of physical activity change with age, generation and are different across sex, social class, cultures and with morbidity. 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. [2] A further overview of systematic reviews recently concluded there was convincing evidence of physical activity protecting against clinically diagnosed AD. [88]

Since the earlier Commission, the HUNT study of 28,916 participants aged 30-60 years has been published, reinforcing the previous literature in this area. It was reported that at least weekly mid-life 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 are wide. [89] In contrast the Whitehall Study reported on the 28-year follow-up of 10,308 people, found >2.5 hours self-reported moderate-to-vigorous physical activity/week, lowered

dementia risk over 10, but not 28 years.[33] Very long-term studies are unusual but there is one 44-year study of just 191 women (mean age 50) recruited purposively to be representative of the Swedish population. It reported that 32% of those with low measuring baseline peak fitness,, 25% with medium, and 5% with high fitness developed dementia (high versus medium HR 0.1; 95% CI 0.03-0.5, low vs medium HR 1.4; 95% CI 0.7-2.8). [90]

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 AD (HR 1.4; 95% CI 1.1- 1.7) in those who were physically inactive in the 10 year period before diagnosis.[91] Importantly, 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 may stop exercising due to prodromal dementia so inactivity may be either a consequence or a cause or both in dementia and may be more of a risk in those with cardiovascular morbidity. As with other outcomes, exercise may be required to be sustained and continue nearer the time of risk[92].

Trials of exercise

Since the original 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 minutes/session in cognitively normal adults aged >50 years. This 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 minutes per session with no difference between them but no effect found for yoga.[93] A second meta-analysis of RCTs in people with MCI found global cognition improved in the intervention group (SMD 0.3; 95% CI 0.1-0.5) with aerobic exercise having a higher effect (SMD: 0. 6; 95% CI 0.5-0.6). 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) with 2878 participants with normal baseline cognition.[94] The incidence of dementia was 3.7% (n = 949) for exercisers and 6.1% (n = 1,017) for controls (random effect RR = 0.6; 95% CI = 0.3-1.1; fixed effect as no evidence of heterogeneity RR = 0.7; 95% CI = 0.4-1.0). The authors concluded that there was no significant effect of exercise for reducing dementia, MCI or clinically significant cognitive decline but the study was underpowered. WHO guidelines have been published since the first Commission, suggesting specific activity levels drawing on these, and one further systematic review which considered sex differences on the effect of exercise. [93-96] It concluded the evidence points towards physical activity having a small, beneficial effect on normal cognition, with a possible effect in MCI, mostly due to aerobic exercise.[97] There is a lack of evidence about the effect of specific types of exercise, such as progressive muscle resistance training on dementia risk.

Diabetes mellitus

In the earlier Commission we reported on diabetes as a risk factor for dementia. It is challenging to distinguish between treated and untreated diabetes as a risk factor for dementia 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. In this diabetes was associated with an increased risk of any dementia (women: RR 1.6; 95% CI 1.5-1.8; men: RR 1.6; 95% CI 1.4,-1.8). [98] The risk of dementia increased with the length and severity of diabetes. The relationship with different diabetic medications on cognition or dementia outcomes remains unclear as few studies have investigated this area. [99] However, one meta-analysis of cohort studies of diabetes reported that, cross sectionally, people with diabetes taking metformin had lower prevalence of cognitive impairment (3 studies, OR 0.6; 95% CI 0.4-0.8) and, longitudinally, reduced dementia incidence (6 studies HR 0.8; 95% CI 0.4-0.9) compared with those taking other medications or no medication. [101] However another did not find a protective effect of metformin for incident dementia (3 studies, risk ratio (RR) 1.1; 95% CI 0.5 to 2.4) with possible harm with insulin therapy (RR 1.2; 95% CI 1.1 - 1.4); but this did not account for severity of diabetes of those with type 2 diabetes on insulin.[99] A Cochrane review reported intensive compared to standard diabetes control trials with 5 year follow up (n = 11,140) no impact on cognitive decline (RR 1.0; 95% CI 0.9-1.1) or dementia (RR 1.3; 95% CI 0.9- 1.9). [100]

Overall type 2 diabetes is a clear risk factor for development of future dementia but it is unclear that any particular medication ameliorates this risk. 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 followed for 25 years, calculated a cardiovascular health score based on seven items- behavioural (smoking, diet, physical activity, body mass index) and biological (fasting glucose, blood cholesterol, blood pressure) each coded as 0, 1 or 2.[101] 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 behavioural and biological subscales (HR/ 1 point increment in subscales 0.9; 95% CI 0.8-0.9) and 0.9 (95% CI 0.8-1.00), respectively), maintained in people free of cardiovascular disease over the follow-up (HR/ 1 point increment 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 underlines the importance of clustering of cardiovascular risk factors in midlife, as studies of individual risk factors in this sample had not shown this significant association, when controlling for other individual risks.[33]

Excessive alcohol

Heavy drinking is associated with brain changes, cognitive impairment and dementia, a risk known for centuries. [102] There is increasing evidence emerging on alcohol's complex relationship with cognition and dementia outcomes from a variety of sources including detailed cohorts and largescale 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 International Classification of Disease; 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; 95% CI 3·3- 3·4). [103] The relationship of dementia with alcohol use disorder 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 compared to not drinking (RR 0.7; 95%CI 0.6-0.91). [104] Risk was not reported separately for men and women. Drinking no more than 21 units/week (equivalent to 14 drinks) may be associated with a lower risk of dementia.[106] [105] There were few heavy drinkers in a 5-year follow-up study of 13342 men and women volunteers from UK biobank aged 40-73 years old who drank and the study did not analyse abstainers.[106] It reported that those who drank more than one drink every day (equivalent to > 12 units/week) declined slightly more in reaction time in a perceptual matching task than those who drank less (β2 = −0.07, 95% CI -0.09 − -0.04). [106] In the UK Whitehall study with 23 years follow-up, there were 9087 participants aged 35-55 years at baseline. [107] Drinking >21 units/week and long term abstinence were both associated with a 17% (95% CI 4-32 and 13-23 respectively) increase in dementia compared to <14 units. Drinking >14 units was also associated with associated MRI right sided hippocampal atrophy. [108]

Weight control and obesity

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

Weight loss in mid-life 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, found weight loss of ≥2kg in people with BMI>25 was associated with a significant improvement in attention and memory. In all but one of the studies participants were aged under 65 years old. The RCTs reported memory improvement over 8-48 weeks (SMD = 0.4; 95% CI 0.2–0.6) and longitudinal studies found SMD = 0.7; 95% CI 0.5–0.8 but there is no data about the long-term effects or the effect of weight loss in preventing dementia.[110]

Smoking

Smokers are at higher risk of dementia than non-smokers,[2] 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.[111,112] Stopping smoking, even when older, reduces this risk. Among 50,000 men age >60, stopping smoking for >4 years, compared to continuing, reduced dementia risk over the subsequent 8 years substantially (HR 0.9; 95% CI 0.7-1.0). Worldwide, it has been estimated that 35% of non-smoking adults and 40% of children are exposed to second-hand smoke (SHS).[113] There is scarce literature on the impact of this exposure and dementia risk. One study indicated that in middle-aged women aged 55-64, SHS exposure was associated with more memory deterioration and the risk increased with exposure duration even after controlling for other confounding factors.

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 also possible whereby depressive symptoms result from dementia neuropathology which occur 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).[114] 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 (pooled effect size 1.97, 95% CI 1.67-2.32). In the Norwegian HUNT study, there was suggestion 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).[89] Two further studies differentiate between late-life and earlier life depressive symptoms. The UK Whitehall study, in a follow up of 10189 people, report that in late life these 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 HR, 1.0; 95% CI, 0.7-1.4). [34,115] 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. [120] The use of antidepressants did not decrease this risk.

In a study of 755 people with MCI from the Australian longitudinal Alzheimer's Disease Neuroimaging Initiative (ADNI) with a history of depression, considered the effect of SSRI treatment as citalopram is known to reduce amyloid plaque generation and plaque formation in animal models. It found that >4 years SSRI treatment was associated with delayed progression to clinically diagnosed AD. It seems likely that people treated with antidepressants will differ from those who are not. Thus, the question of whether antidepressant treatment mitigates dementia risk remains open.

Social contact

Social contact, now an accepted protective factor, enhance cognitive reserve or encourage beneficial behaviours, although isolation may also occur as part of the dementia prodrome. Several recent studies suggest that lower 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 reducing their social contact. In these generations, marital status is therefore 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 (RR 1.2; 95% CI 1.0-1.4), compared with married, people and the association was consistent in different socio-cultural settings. Studies adjusted for sex and we do not know if there is a differential risk between men and women. Differences persisted in studies that adjusted for education and physical health so may be attributable to married people having more social contact, 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 years at baseline, with follow-up ranging from 2-21 years. [116] 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 there were no differences according to sex or length of time followed-up.

A new meta-analysis found that in long-term studies (≥10 years), good social engagement was modestly protective (n=8876, RR = 0.9; 95% CI 0.8-1.0); but in the loneliness meta-analysis, loneliness was not associated with dementia risk.[117] There have been no long term (>10 years) studies of loneliness and dementia outcomes.

A UK 28-year follow-up study of 10,308 people found that more frequent social contacts at age 60 years was associated with lower dementia risk over 15 years of follow-up (HR for one standard deviation social contact frequency 09; 95% CI 0.8-1.0). This 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. [118] A Japanese longitudinal cohort study of 13 984 adults aged >65 years old with mean 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. [119]

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.[116,120,121]

Social interventions

There is little evidence of the effects of social interventions but a systematic review of low quality RCTs of 576 adults aged ≥60 with normal cognition found facilitated meeting and discussion groups were associated with improved global cognition and increased brain volume at follow-up.[120]

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, Aβ deposition, and Amyloid Precursor Protein (APP) processing.[122,123] While the higher levels of dementia from air pollutants are still subject to the potential for residual confounding, the effects on animal models are also evidence of physiological effects over and above those driven by lifecourse deprivation.

High nitrogen dioxide (NO_2) concentration (>41.5 μg/m^3; adjusted HR 1.2; 95% CI 1.0-1.3), fine ambient particulate matter ($PM_{2.5}$) from traffic exhaust (adjusted HR 1.1; 95% CI 1.0-1.2) [124-126] and $PM_{2.5}$ from residential wood burning (HR=1.6, 95% CI 1.0–2.4 for a 1 μg/m3 increase) are associated with increased dementia incidence. Traffic often produces NO_2 and $PM_{2.5}$ and it is hard to separate their effects, although there is evidence for additive effects of different pollutants.[124-126] A systematic review of studies until 2018 found 13 longitudinal studies with 1-15 years follow-up of air pollutants exposure and incident dementia, exposure to $PM_{2.5}$, NO_2, and carbon monoxide were all associated with increased dementia risk. [24] The attributable burden of dementia and excess death from $PM_{2.5}$ in one large 10-year US study was particularly high in black or African American

individuals and socioeconomically disadvantaged communities and related to particulate levels above the US guidelines.[127]

Sleep

Mechanisms by which sleep may effect dementia remain unclear, but sleep disturbance has been linked with Aβ deposition,[128,129] reduced glymphatic clearance pathways activation,[130] low grade inflammation, increased Tau, hypoxia[129,131] and CVD. [132] Sleep disturbance is hypothesised to increase inflammation which raises β-amyloid burden leading to AD and further sleep disturbance.[133]

There are two recent meta-analyses with 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. They defined sleep disturbances broadly; often it was self-reported and included short and long sleep duration, poor sleep quality, circadian rhythm abnormality, insomnia and obstructive sleep apnoea (OSA). They were all associated with a higher risk of all-cause dementia (RR 1.2; 95% CI 1.1-1.3)[134] and clinically diagnosed AD (RR 1.6; 95% CI 1.3-1.9) compared to no sleep disturbance, though not all cohort studies excluded those with cognitive impairment or dementia at baseline from their analyses.[135] A U-shaped association has been reported between sleep duration and risk of MCI or dementia with higher risks of dementia with <5 hours or (HR=2.6; 95% CI 1.4-5.1) < 7 hours and >9 or 10 hours sleep (HR=2.2; 95% CI 1.4-3.5) and risks for all-cause dementia and clinically diagnosed AD being similar.[136] [132,137,138]

The postulated mechanisms of reduced sleep leading to accumulation of Alzheimer's Type pathology is inconsistent with the evidence that both more and less sleep are associated with increased risk of dementia. New onset late-life sleep disturbance, a few years before clinical dementia, may 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 CVD. [132,139] Hypnotic use may increase risks although this is unclear and a recent study suggest that findings of a connection were related to reverse causality and confounders .[136] [140] When benzodiazepine use was considered, in one sleep length was no longer significant [136] but not in all studies. [132] Those taking hypnotics were at greater risk of dementia than those who did not whatever the sleep duration. [136] Medication for sleep disturbance may be harmful and benzodiazepines are associated with falls, hospital admissions and possibly dementia. [141] [136]

Diet

Nutrition and dietary components are challenging to research with controversies still raging around the role of many micronutrients and health outcomes in dementia. There has been a focus on individual components ranging from folate and B vitamins, Vitamin C, D, E and selenium amongst others in observational studies as potential protective factors. [88] There has been a move towards considering the evidence base for whole diets in recent years, particularly high plant intake such as in the Mediterranean diet (MeDi) or the similar Nordic diet, rather than individual nutrients, which might reduce cognitive decline and dementia. [142] One example of this 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/day, declined less cognitively over 4.7 years than those reporting the lowest intake (β = 0.05 standardized units 95%CI 0.02 - 0.07). [143] The authors report this difference as being equivalent to being 11 years younger. A further prospective cohort study

with three midlife dietary assessments in 8,255 people, followed for a mean of nearly 25 years, found neither healthy dietary pattern nor Mediterranean diet protected from dementia, except in those with CVD, suggesting that diet may influence dementia risk by protecting from the excess risk of cardiovascular risk factors. [144]

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 or older people.[145, 146] Recent updated Cochrane reviews found no evidence for beneficial effects on cognition of those with MCI of supplementation with B vitamins for six to 24 months[147] or with vitamin E in preventing progression from MCI to dementia. [148] A 24-month RCT of 311 people of a multi-nutrient drink containing DHA, vitamins B12, B6, folic acid and other nutrients; found no significant effect on preventing cognitive deterioration in prodromal AD. [149] 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 MeDi diet (high intake of vegetables, legumes, fruits, nuts, cereals, and olive oil; low intake of saturated lipids and meat) improved global cognition compared to controls (SMD 0.2; 95% CI 0.0-0.4). 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) [150] but no benefit of MeDi for incident cognitive impairment or dementia.

The WHO guidelines recommend a Mediterranean diet to reduce the risk of cognitive decline or dementia, as it may help and does not harm, but conclude Vitamins B and E, PUFA and multi-complex supplementation should *not be recommended*. [97]

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 earlier commission.[2] FINGER found a small group reduction in cognitive decline in the intervention group compared to control (comprehensive neuropsychological test battery Z score 0·02; 95% CI 0·00, 0·04) regardless of baseline sociodemographic, socioeconomic, cognitive or cardio-vascular status. [151] However, in a subgroup analysis, there were greater beneficial effects on processing speed in individuals with higher baseline cortical thickness in Alzheimer's disease areas. [152]

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. [153,154] 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. There was a small improvement in the cardiovascular risk composite primary outcome in the intervention group compared to control group at 18 months, mainly through weight loss the cognition secondary outcomes, although the predicted dementia risk score was slightly

lower in those who received the intervention (mean difference −0·15, −0·3 to −0·0). There was a larger effect 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 may be more effective. There are currently several ongoing multidomain preventative trials e.g. Worldwide Fingers.

Table 1: Population Attributable Fraction (PAF) for 12 dementia risk factors

PAF is the relative contribution of each risk factor to the overall PAF when adjusted for communality

Risk factor	Relative Risk for dementia (95% CI)	Risk factor prevalence (%)	Communality (%)	Unweighted PAF (%)	Weighted PAF* (%)
Early life (<45)					
Less education	1·6 (1·3-2·0)	40.0	61.2	19.4	7.1
Mid-life (age 45-65)					
Hearing loss	1·9 (1·4-2·7)	31.7	45.6	22.2	8.2
Traumatic brain injury	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 >21units/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
Later life (age >65)					
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
Overall weighted PAF					**39.7%**

Total PAF calculation

We incorporated excessive alcohol consumption, TBI and air pollution into our life-course model of dementia because of the updated evidence. To calculate new RRs for excessive alcohol consumption, TBI and air pollution, we systematically reviewed the literature and performed 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. [2]

Incorporation of the new chosen risks new systematic reviews

Alcohol

We searched, from inception to 29th October 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.[155]

Inclusion criteria

- Original population-based cohort studies measuring drinking during midlife, as alcohol intake tends to fall with age, [156]
- Alcohol consumption quantified at baseline by units or number of drinks (one drink = 1.5 units) per week
- All-cause dementia ascertained at follow-up using validated clinical measures.

We contacted authors for additional data. [157] Three studies met our inclusion criteria. [107,157,158] We converted HRs to RRs [159] and used raw data [157] to calculate RR, [160] for our random effects meta-analysis using Generic Inverse Variance Methods. The RR associated with drinking > 21 units (14 drinks; 168g) of alcohol weekly, compared to lighter drinking was 1.18; 95% CI 1.06, 1.31 (Figure 5). We used Health Survey England (HSE) figures for heavier drinking prevalence to calculate PAF as we could not find a worldwide estimate. The weighted PAF was 0.8.

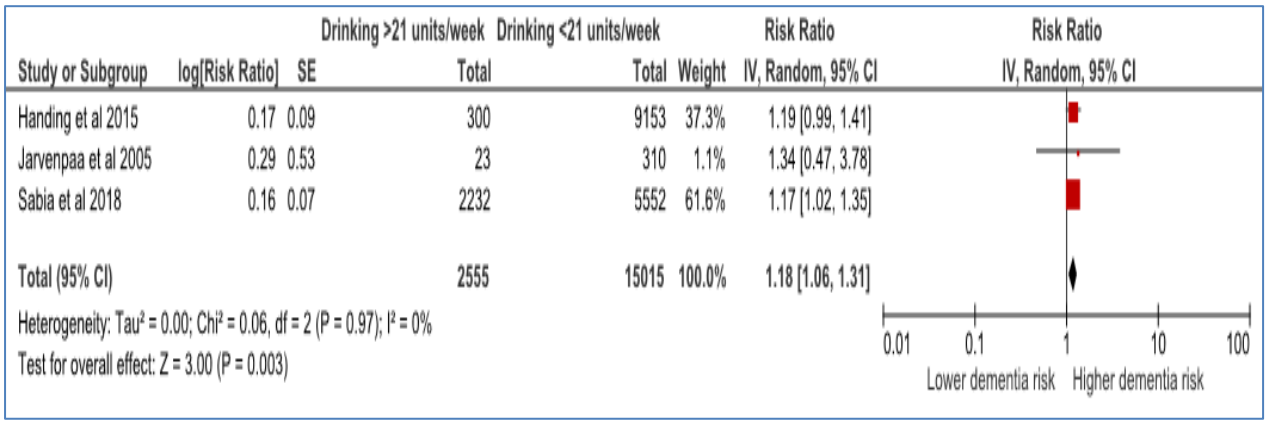


Figure 5: Meta-analysis of relative risk of dementia associated with drinking >21 units of alcohol/week in midlife compared to lighter consumption of alcohol

Traumatic brain injury

To estimate the RR of TBI of all severities for all cause dementia, we searched Embase, Medline and PsycINFO from 1st January 2016 to 21st October 2019, updating an earlier search, [161] 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. [159 162]

Inclusion criteria:

- Original population-based cohort studies
- Baseline TBI of all severities reported
- All-cause dementia ascertained at follow-up using validated clinical measures.

We combined four new studies meeting inclusion criteria [67 68 71 163] with the four studies meeting criteria from the original review in a random effects meta-analysis.[161] The pooled RR was 1.84; 95% CI 1.54 -2.20 for all cause dementia from all severities of TBI (Figure 6) though 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.[164] The weighted PAF was 3.4.

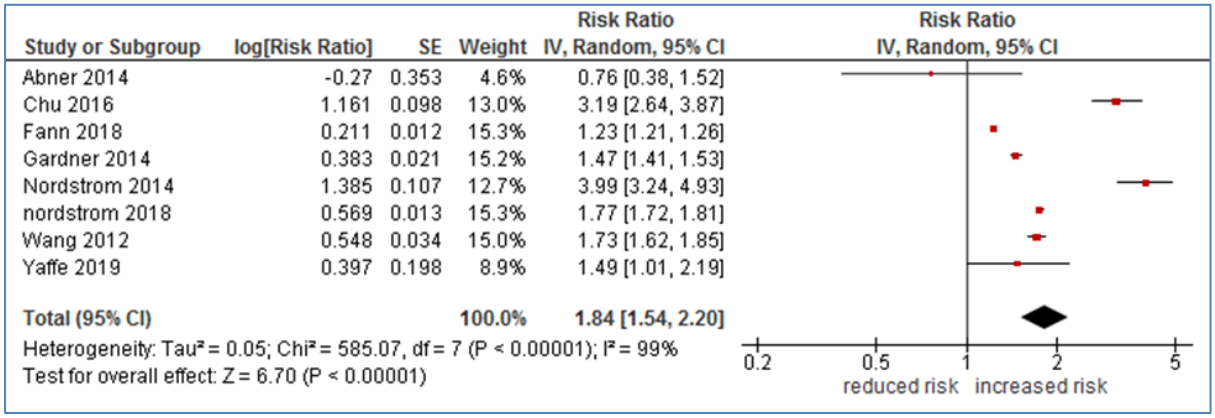


Figure 6: Meta-analysis of relative risk of all-cause dementia associated with all severity midlife Traumatic Brain Injury

Pollution

A 2019 systematic review synthesised observational studies, finding consistently increased risk of dementia from air pollution, but heterogeneous comparator groups precluded meta-analysis.[24] We updated the search, using the same search terms and searching MEDLINE, Embase, and PsychINFO from 20 September 2018 (the end date of the last search) to 22nd October 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); and a minimum follow up 6 months. We therefore 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 Ontario, Canada, where pollutant concentrations are among the lowest in the world and examined 2,066,639 people, with a mean baseline age of 67 [165]. 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 $PM_{2.5}$ and NO_2 was 6.1% (4.8-7.5). The weighted PAF was 2.3.

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,[166] to allow calculation of each factor's unique risk. As we could find no datasets measuring TBI, and 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,

884 suggesting substantial overlap. Appendix 1 shows the PAF formula and the steps in calculating
885 communality. Table 1 displays the prevalence, communality, relative risk, unweighted and weighted
886 PAFs adjusted for communality. We present in Figure 7 the new updated life course model of
887 potentially modifiable risks factors for dementia. F*igure 7* the updated life course model of

potentially modifiable risks factors for dementia.

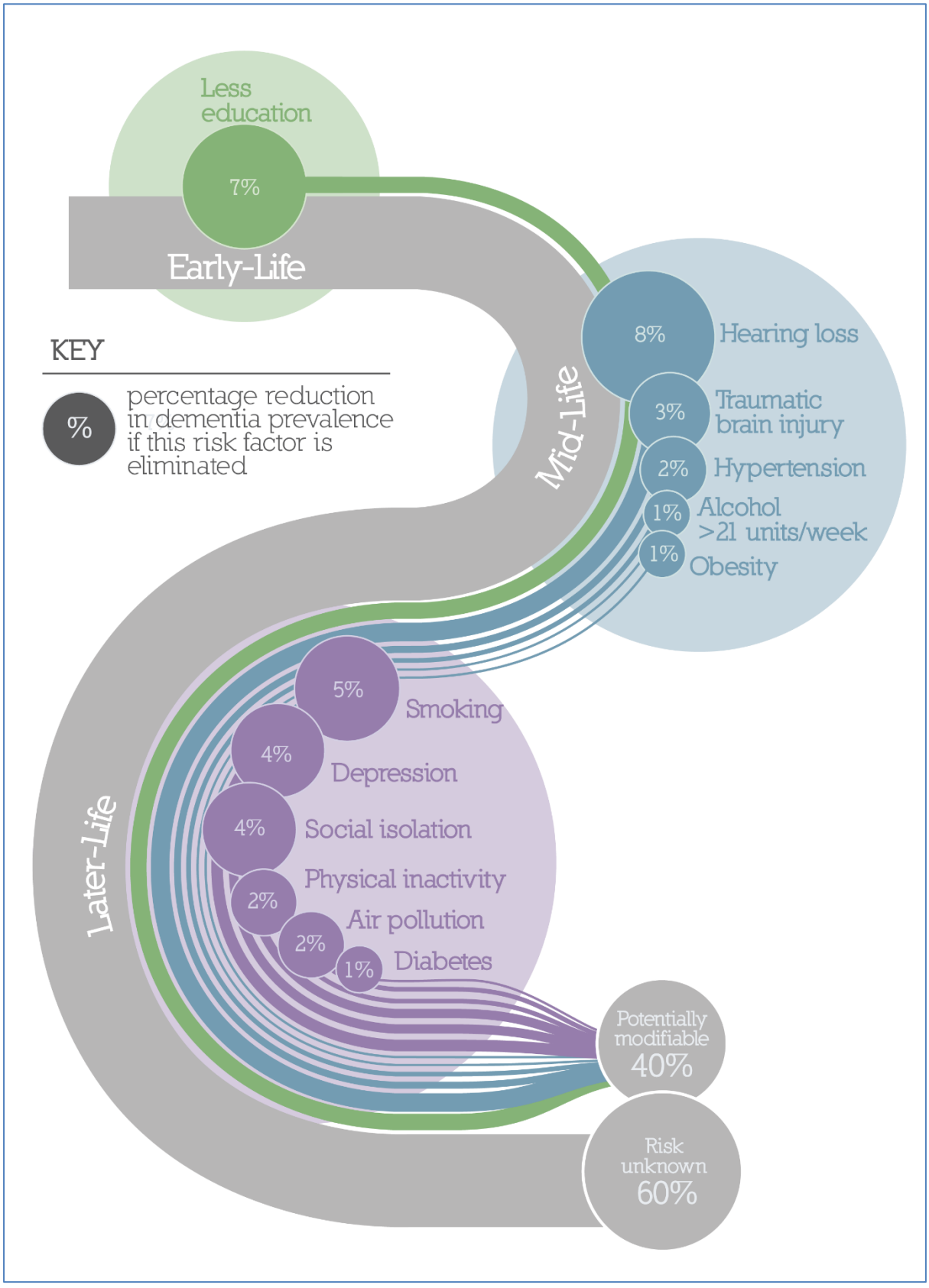


Figure 7: Population attributable fraction of potentially modifiable risk factors for dementia

Strengths and limitations

This is the most comprehensive analysis to date and updates the earlier Lancet 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 recent literature. Using this we have updated our synthesis and identified data to calculate communality. We find a hopeful picture with an updated 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 vary between countries and most global research is from high-income countries, 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. There is no single database with all 12 risk factors together, but we found 11 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 high-income countries and future studies from low- and middle-income countries are need 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 lifecourse 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 suggests there is little residual confounding. [165] 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 may act on preclinical pathology or even cause dementia near the time of exposure. Thus, alcohol and TBI are particularly important in young-onset dementia, although most early onset dementias relate to genetic risks. Risk factors may 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 likely 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 high income countries 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 there is sufficient new evidence to add three additional modifiable risk factors for dementia to our earlier Commission model (alcohol, traumatic brain injury, and air pollution). We have been able to add updated evidence on the nine risk factors implicated in the first commission (education, hypertension, hearing impairment, smoking, obesity, depression, inactivity, diabetes and social contact). Reduction of these risk factors may be protective for people with or without a genetic risk, although study findings have not been entirely consistent.[167,168] [169,170] As we noted in the previous Commission others have previously calculated an estimate of the risk associated with APOE4 is 7% taking into account some other risk factors and this highlights how relatively important potentially modifiable risk factors are in dementia. [2,171]

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

There are few data from RCTs on interventions to prevent cognitive decline, all-cause dementia or AD. For some key life influences, only observational data, particularly related to natural experiments such as changing the statutory education age, are possible. These 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 as there are no intermediate markers that have such a close relationship with dementia outcomes that it's 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 mid-life increases the risk of dementia even without stroke.

While there is a need for more evidence, recommendations should not await this, as there are clear indications of ways to reduce the chances of developing dementia without causing harm that will also lead to other health and wellbeing benefits.

Our recommended strategies for dementia risk reduction include both population-wide and targeted interventions

Population wide:

- Prioritise childhood education for all, worldwide.
- Implement social public health policies that reduce hypertension risk in the whole population.
- Develop policies that encourage social, cognitive and physical activity across the lifecourse for all but there is no evidence for specific activities being protective.
- Scrutinise the risks for hearing loss throughout the lifecourse, in order to reduce the risk of exposure to this risk factor in later life.

- 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 to reduce uptake and encourage cessation.

Targeted on individuals

- Treat hypertension and aim for SBP <130mmHg in mid-life.
- Use hearing aids for hearing loss. We need to help people wear them as many find them unacceptable, too difficult to use or ineffective.
- Drinking 21 units (14 drinks) /week or more is a risk factor for dementia.
- 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.
- Sustained mid-life, and possibly late-life physical activity protects from dementia.

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 below we present the latest evidence about intervention and care for dementia. To date there has been an emphasis on specific subtypes of dementia. Most notably over the last decades into Alzheimer's Disease, which has been conceptualised in a variety of changing diagnostic criteria over the years, for example, DSM 1V and DSM V. [172,173].This implies early pre-clinical detection of the disease process before it becomes dementia, and to this end there has been an intense effort to detect biomarkers that predict clinical outcomes. Biomarkers need to show reliability and validity, and in the area of this Lancet Commission they also need to be very closely and clearly related to clinical syndrome outcomes in the way that, for example, HPV now is for cervical cancer, and hypertension has been for stroke.

Biomarkers and detection of AD

Markers of neurodegeneration linked to clinical dementia include brain volume loss, including hippocampal volume loss and entorhinal cortex and medial temporal cortical thinning seen in structural imaging. The most studied molecular markers are in AD and are amyloid and tau, which Positron Emission Tomography (PET) and cerebrospinal fluid (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 there are increases in plaques in the population from less than 3% at age 50 to 59 to around 40% at age 80 to 89. [174]

Amyloid imaging

Amyloid imaging detects amyloid in the brain with high sensitivity and specificity in both cognitively normal and people with AD when compared to either neuropathology or clinical diagnosis distinguishing AD from other neurodegenerative conditions. [175] It is not a diagnostic test for dementia but for whether there is amyloid in the brain. A US study of randomly selected older people from the community recruited 1671 people (mean age of 71 years).[174] The prevalence of

PET detected amyloid positivity increased from 2.7% (95% CI 0.5-4.9) of people without cognitive impairment aged 50 to 59 years to 41.3% (95% CI 33.4-49.2%) aged 80 to 89 years. [174] In 10-year follow up PET positivity was associated with a higher probability of developing AD dementia compared to those who were amyloid negative; HR 2.6 (95% CI1.4 -4.9). It was not very different for participants with aMCI who were amyloid positive vs amyloid negative, HR 1.9 (95% CI 0.9- 3.9) for and 1.6 (95% CI 0.8 -3.4) respectively.

Similarly, an 8 year follow-up study of 599 volunteers (average age 70) in Australia found that cognitively normal (CN) PET amyloid positive people had an elevated risk of developing AD compared to amyloid negative (17.7% vs 8.1%, OR: 2.4; 95% CI 1.5- 4.0). [176] Over 80% of the 266 who were PET amyloid positive did not go onto develop within eight years, showing positive status does not predict impairment for most people in which might be a useful prognostic window. Follow-up at 5-years of CN or aMCI amyloid positive participants vs amyloid negative found the same pattern of increased risk (OR 2.6; 95% CI 1.4- 4.9). Risk also increases with older age (HR=1.05, 95% CI 0.55-2.0/year), and APOEε4 status (HR=2.6, 95%CI 1.4-5.0).[176]

Most people who are amyloid positive with no other markers have not developed AD 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 and 29.3% for a 65 year old.[177] 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 AD risk of 2.5% and a man 2.3%, but the risk is somewhat higher with accompanying neurodegeneration (Table 2).[177]

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 for predicting memory decline over a model with clinical and genetic variables, which may not be clinically important.[178]

Age	Normal state 1	A state 2	N state 3	A & N state 4	MCI & A & N state 5	MCI & N state 6
60	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	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	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	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	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	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	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)

Table 2: Ten-year risks %; (95% Confidence intervals) by age of developing Alzheimer's disease dementia for females based on amyloidosis (A) by itself and in the presence of neurodegeneration (N), and mild cognitive impairment (MCI) *with permission*

Using amyloid PET with patients with cognitive impairment of uncertain causes, results in changes to the clinical diagnosis of AD[179] 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 AD.

Fluid biomarkers

PET imaging is very costly ($3000 in US) and although used in some clinical settings remains the topic of research to understand its usefulness in broader populations. Fluid biomarkers, i.e. 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.[180] A composite blood biomarker for amyloid tested in a discovery dataset and then a validation cohort of participants aged 60 to 90 for amyloid burden (areas under the receiver operating characteristic curves (AUCs) 96.7% for discovery and 94.1% for validation who were already taking part in studies in Japan or Australia. It had sensitivity and specificity above 80% against amyloid PET measurement [180] and correlated with CSF levels of Aβ1–42. These results are similar to other amyloid blood biomarkers [181,182] and harmonization to a common reference standard is now vital. Whilst CSF Aβ1-42/1-40 ratio and amyloid PET are now considered interchangeable, [183] CSF tau biomarkers have only correlated weakly with brain tau as currently measured by radioligands. [184] Neurofilament light (NfL) protein is being measured in many cohorts. It is, however, non-specific and people with Huntington's disease, multiple sclerosis, MCI and AD may have raised blood NfL, as it is a marker of neurodegeneration.[185-187]

Key points and conclusions

To be useful in clinical practice biomarkers must be very 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 PET or fluid measured amyloid and tau 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 AD during the next few years. High NfL levels indicate a neurodegenerative process but not its cause. The value of biomarkers, in terms of diagnostic value, has not been properly addressed in different representative populations and particularly not in LMICs. 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 syndrome (TB from a fever) or assess risk factor and disease (hypercholesterolaemia and ischaemic heart disease). Those developed for the underlying biology of the dementia syndrome must be subject to the same assessment of value.

Principles of intervention in people with dementia

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

We did not address screening of those not presenting concerns but rigorous systematic reviews by the US Task Force on Prevention have found an absence of evidence of benefit and harm. [188] The first trial globally of screening took place in the US, screening 4005 primary care patients aged 65 years or older. It found no clear benefit or harm in terms of quality of life, mood or increasing diagnostic rates. [189] Other strategies may become more valuable in time such as sensitive awareness of risk factors, when routine records suggest an individual may be in decline. [190]

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. This needs to balance their medical, cognitive, psychological, environmental, cultural and social needs.[2] In the context of underprovision of services, this 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 ADL in mild-to-moderate AD and memantine can be prescribed in combination or each drug used separately for moderate and severe AD. [2,191,192] However while available in most countries these are no longer remunerated in France because as they feel that their benefit is small and they shift clinician's attention from other interventions; it is unknown whether this will help patients or be detrimental to them.[193] There have been no advances in Aβ therapeutics, with negative results from phase 3 trials of monoclonal antibodies (e.g., solanezumab, crenezumab) and inhibitors of β-secretase 1 (BACE1), a protease involved in the production of Aβ peptides. [194] Aducanumab previously abandoned as futile now has further unpublished results. Three $5HT_6$ antagonists and the calcium channel blocker nilvadipine [195,196] have also been ineffective. These medications also show substantial impact during treatments at 'therapeutic' levels on the leakiness of blood vessels. The long-term impact of such side effects is unknown. There is a continuing focus on anti-tau, anti-amyloid and anti-inflammatory drugs and some argue that pre-symptomatic interventions are necessary, especially if targeting Aβ production, but there is no current evidence of efficacy [197] and of worsening target symptoms.[198]

Cognitive training in people with dementia (CT)

A meta-analysis of 12 controlled trials of 389 people with mild dementia, completing ≥4 hours of group based computerized cognitive training (CCT), (mean age from 66 to 81 years old, 63.5% female participants) found a small, statistically significant beneficial effect on overall cognition, driven by two trials of virtual reality or Nintendo Wii (SMD=0.3; 95% CI 0.0-0.5), one with a low and one with a high risk of bias.[55]

A second systematic review, a Cochrane review found 33 trials of CT, only one of which overlapped with the study above, with around 2,000 participants with mild-to-moderate dementia, most with a high or uncertain risk of bias. People completing CT, 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 one year. There was no direct evidence suggesting it was better than cognitive stimulation therapy.

Exercise and physical activity

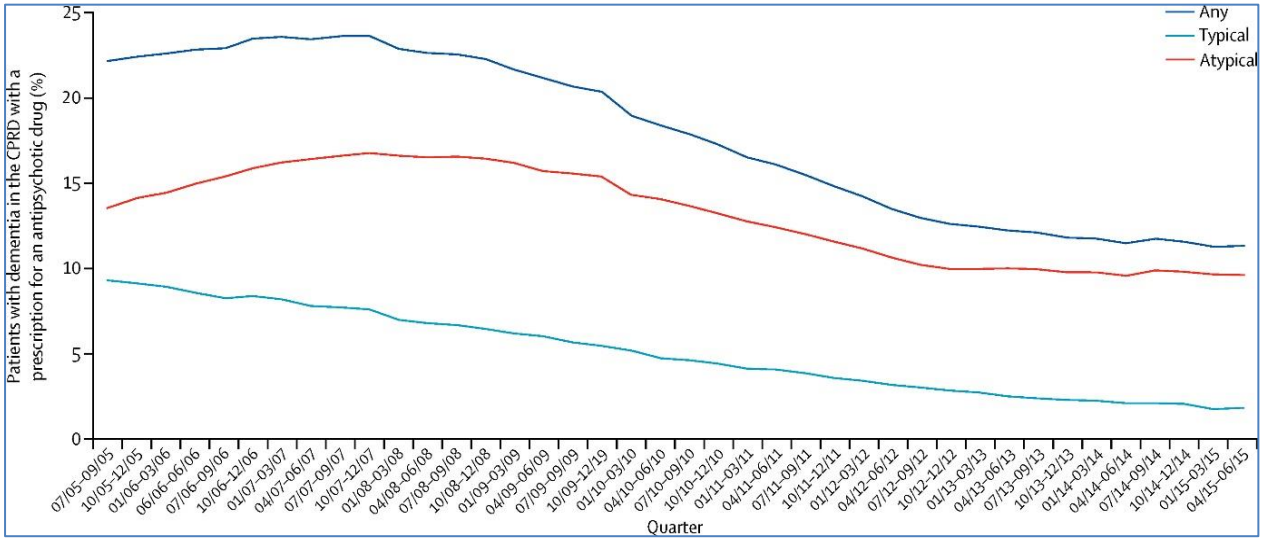
The Dementia and Physical Activity (DAPA) RCT found moderate-to-high intensity aerobic and strength exercise training did not slow cognitive impairment in people with mild-to-moderate dementia but improved physical fitness. [199] The US Reducing Disability in Dementia (RDAD) study implemented an at-home multicomponent intervention including exercise education, training to increase pleasant events, and activator-behaviour-consequence problem-solving approach over six weeks by case managers in 255 community dwelling people with dementia aged over 60 and their family carer and were able to follow-up 140 (54.9%). They found increased physical activity; days of taking ≥ 30 minutes of exercise; (effect size 0.6; 95% CI 0.4- 0.8; post-treatment and at 13 months 0.3; 95% CI 0.1-0.5) in a pre/post intervention comparison.

Interventions for neuropsychiatric symptoms (NPS) of dementia

NPS are common and often clustered in people with dementia. They may precede dementia and are associated with tau and amyloid neuropathology.[200] This suggests that underlying neurobiological mechanisms may underpin neuropsychiatric symptoms. However, there are also likely to be other drivers which relate to the person with dementia's environment, and personal history . Neurodegeneration could lead to increased vulnerability to stressors or triggers. Genetics, cognitive reserve, resilience, medical comorbidities and environment may 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 NPS should focus on basic health: describe and diagnose symptoms, look for causes such as pain (using validated pain assessments may help), illness, discomfort, hunger, loneliness, boredom, lack of intimacy and worry that could cause the behaviours and alleviate these while considering risks of harm.[2]

Figure 8a: Proportion of patients with a diagnosis for dementia living at home or in a care home prescribed an antipsychotic drug *with permission* **[201]**

There is no new evidence of medication effectiveness for these symptoms; risperidone in low doses (0.5mg daily oral usually recommended) and some other antipsychotics are often ineffective and have adverse effects.[2] Specific initiatives have led to a decrease in antipsychotic prescriptions for



people with dementia, although they are often replaced by another psychotropics (figure 8 a, b), such as benzodiazepines, antidepressants and mood stabilizers. [201] These lack evidence of efficacy for neuropsychiatric symptoms but show clear evidence of possible harm; for example, trazodone and benzodiazepines increase fall related injuries.[141] It is important to carefully assess major policy changes carefully, within and across countries for unintended consequences (and perhaps unexpected benefits) and their costs.

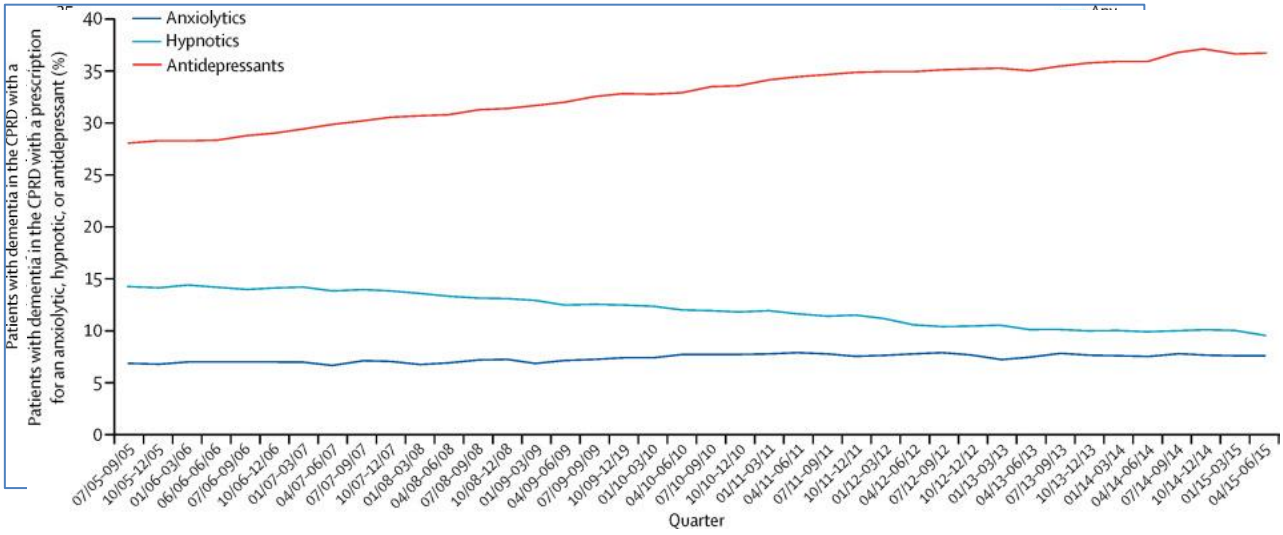


Figure 8b: Proportion of patients with a diagnosis of dementia prescribed an anxiolytic, hypnotic, or antidepressant *with permission*

Evidence is slowly accumulating for the effectiveness, at least in the short-term, of person-centred psychosocial interventions tailored to individual needs. In Germany, a six-month 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 GP for 634 people (mean age 80) living with dementia at home with a primary carer or alone. [202] The mean MMSE was 23, only 38% had a formal diagnosis of dementia; the majority of participants had mild dementia but some had moderate and some severe. The intervention consisted of psychosocial management of treatment and care, medication management and carer support and education and discussion with a psychiatrist or neurologist. It was associated with better outcomes for neuropsychiatric symptoms compared to care as usual (CAU), but because of deterioration in CAU (Neuropsychiatric Inventory, NPI -7.5; 95% CI -11.1- -3.8; CAU NPI; increased from 7.2 to 15.2; 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 Program (TAP-VA) RCT, tailored to the person with dementia living at home and a family member versus eight telephone-based education sessions, recruited 160 participants with 64% follow-up, imputing values for the rest. [203] Non-completers having more severe neuropsychiatric symptoms. It reported a large reduction in overall neuropsychiatric symptoms immediately after the intervention, which were better in the TAP-VA

group on the neuropsychiatric inventory (mean difference in score = 24.3; 95%CI 3.1- 45.6); and in dependence and pain but this was not sustained four months later.

Depression

Since the last Commission two new systematic reviews of antidepressants to treat depression in dementia reported moderate quality evidencethat antidepressant treatment for people with dementia does not lead to better control of symptomatology compared with placebo. [204,205]

Agitation

Agitation is distressing for people with dementia and those around the patient, and contributes significantly to the overall costs increasing as the level of agitation increases. [206] There is an increasing body of evidence on this important behaviour, mostly focused on care homes settings. These findings are important as these represent the most affected populations but as many people with dementia reside at home this still leaves a major gap in knowledge.

Care home residents with agitation often find sitting still difficult and therefore may not be included in activities. [207,208] Two new cluster RCTs of professionals delivering multicomponent, interdisciplinary, interventions in care homes successfully reduced agitation. The WHELD study included participants with or without NPS 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 -4.3points; 95% CI −7.3, −1.2). [209] The TIME study 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 led to reduced agitation at 8 and 12 weeks; NPI (-1.1 points; 95% CI -0.1- -2.1; and -1.6; 95% CI -0.6- - 2.7) and CMAI (-4.7 points; 95% CI -0.6- -8.8; and- 5.9; 95% CI -1.7- -10.1). [210] These effects sizes are similar to those seen for medications, but without harmful side effects.[211] [2] A further RCT of a six-session intervention with staff in groups, teaching staff to understand agitation as related to medical, psychological or social unmet needs and implement strategies to meet these needs, using the DICE approach[212] (Describe, Investigate, Create, Evaluate) to recognise and respond to resident's unmet needs of; pleasant events and communication strategies. The intervention did not reduce agitation symptoms, although it was cost-effective, improving quality of life. [213] Overall, the current evidence for agitation in care homes favours multi-component interventions by staff and not drug interventions. This still leaves a major gap in knowledge about those living at home who comprise the majority of those with dementia.

Psychotic symptoms in dementia

People with dementia may be wrongly thought to have delusions when they misremember, and new psychotic symptoms are often due to delirium, so thorough assessment of symptoms is essential.[2] Management of psychosis in dementia should start with non-pharmacological interventions; however, evidence for their effectiveness for psychosis in dementia is weaker than for agitation. [214] Antipsychotics for psychosis in dementia should be prescribed in as low a dose and for the shortest duration possible.[2] However, a Cochrane review of antipsychotics withdrawal found two trials with participants who had responded to antipsychotic treatment. These reported that stopping antipsychotics was associated with symptomatic relapse[215] suggesting the need for caution in any medication withdrawal in this group. There was low-quality evidence that, in general,

discontinuation may make little or no difference to overall NPS, adverse events, quality of life or cognitive function.[216]

Apathy

Apathy may 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. [217] Another study in care homes observed engagement increased during activities in those who attended the groups. [218] 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 - -0.4, n = 145, 3 studies, low-quality evidence) but not on the NPI apathy subscale, MD -0.1; 95% CI -3.9- 3.7, n = 85, 2 studies). [219]

Sleep

There is no evidence that medication for sleep in dementia is effective [220] and considerable evidence for harm, for example, earlier death, increased hospitalisation and falls. [136,141] Testing of non-pharmacological interventions is ongoing. [221]

Carers

Carer distress related to neuropsychiatric symptoms beyond dementia symptoms themselves was associated in one study with increased use and costs of health services, [222] highlighting the need for effectively identifying, educating, and supporting distressed carers. An RCT reporting six-year follow-up after the 8 session START intervention found continuing effectiveness for carer depressive symptoms (adjusted mean difference (MD) -2.00; 95% CI -3.3, -0.6, n=243) and risk of case-level depression, with patient-related cost being approximately three times lower than those who did not receive the intervention (median £5,759 versus £16,964 in the final year; p =0.07). Another US study followed 663 people 51% with mild, 31% moderate and 18% severe dementia (any type), mean age 73, 55% with female family carer. Depression rather than symptoms of people with dementia predicted emergency department use for people with dementia, with a 73% (95%CI 17.3-23.0) increase when carers were depressed.

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 ≥18 for inclusion; mean 24) and a family carer. Individuals had two-to-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 to usual treatment (effect size 0.8; 95% CI 0.6 -1at both 3 and 9 months).[223] The treatment did not improve participants' quality of life, mood, self-efficacy, cognition, carer stress, health status and was not cost-effective. A systematic review 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 bene individual rather than group interventions, in-home physiotherapist delivered tailored exercise (2 studies, larger one positive, 140 people with AD, smaller study negative, 35 people), individualised cognitive rehabilitation (mild or moderate dementia; 2 studies; 257 CR intervention groups and 255 controls), and in-home activities-focused occupational therapy (people with mild to moderate

dementia, 3 studies, 201 intervention,191 controls) reduced functional decline compared to controls but group-exercise and reminiscence therapies were ineffective.[224]

People with dementia have other illnesses

Multimorbidity is a huge challenge in dementia, not only because people with dementia have increased rates of other diseases, but also because they often find it particularly difficult to organise care. People with dementia may 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. [225] People with dementia consult primary care less often than those without dementia, [226] dental visits decline, [227] and family members, if involved, often feel they lack knowledge to assist. [228] Healthcare professionals need education to be more comfortable, understanding and positive in communicating with people with dementia.[229]

Around 70-80% of people diagnosed with dementia in primary care have at least two other chronic illnesses.[230,231] 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 may be from other mechanisms.[22] Compared to the general older population, people with dementia have increased rates of cerebrovascular disease, [231-234] stroke, [235] Parkinson's disease, [231,233] diabetes, [233] [235]skin ulcers, anxiety and depression, [231,233] pneumonia, incontinence and electrolyte disturbance.[233] Multi-morbidity in people with dementia is associated with faster functional decline [236] and worse quality of life for people with dementia and their family carers. [237]

Hospital admissions

Hospitalisation in people with dementia is associated with adverse, unintended consequences, including distress, functional and cognitive decline, and high economic costs. [238-240] People with dementia have 1.4 to 4 times more hospital admissions than others with similar illnesses. [239,241-243]

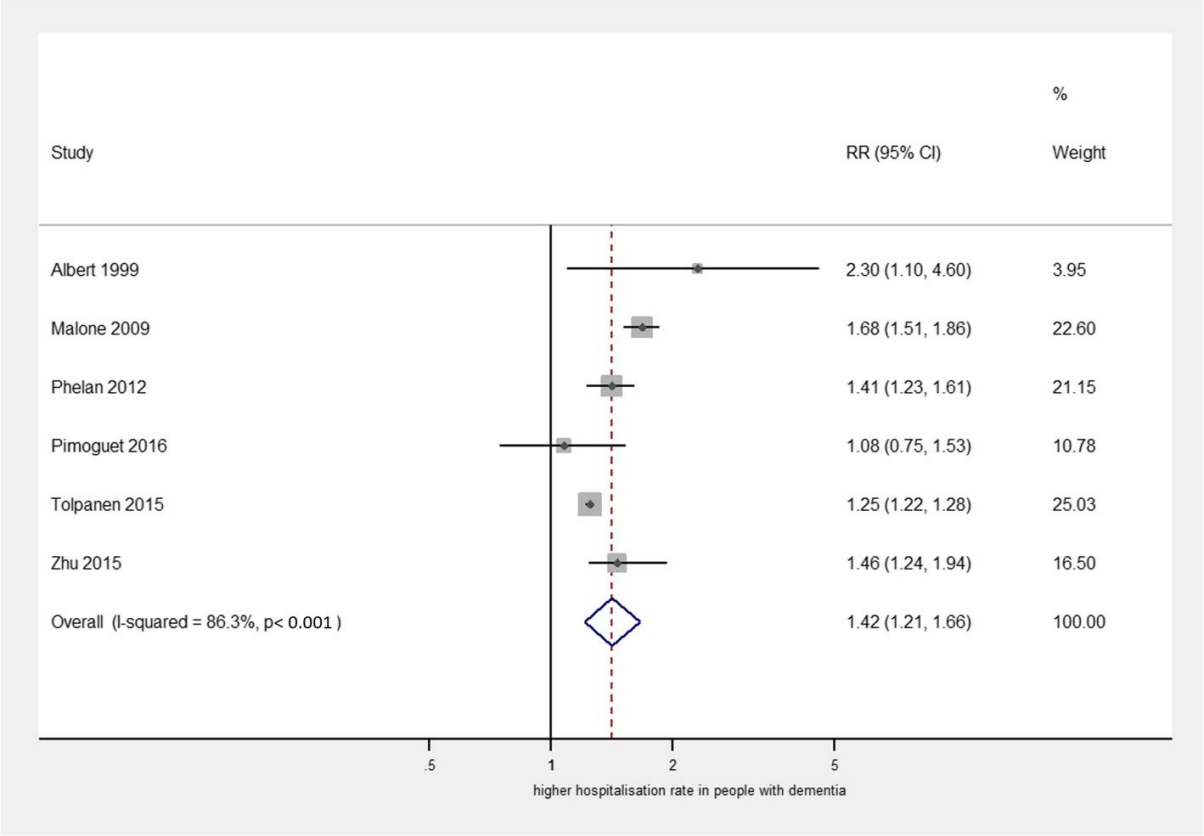


Figure 9 Systematic review and meta-analysis of hospitalisation rates of people with dementia compared to those without dementia controlled for age and sex (with permission)[244]

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 hospitalisation compared to those without, after adjusting for age, sex, and physical comorbidity (RR 1.4; 95% CI 1.2 -1.7; see figure 9). [244] Hospitalisation rates in people with dementia ranged from 0.37 to 1.26/person-year in high-quality studies. Admissions are often for conditions that might be manageable in the community (potentially preventable hospitalisations). [241] People with dementia experience longer and more frequent admissions and readmissions; healthcare expenditure for people with moderate-severe dementia is around double that of people without dementia. [242,245,246] Early detection and management of physical ill health in people with dementia, particularly of pain, falls, diabetes, incontinence and sensory impairment, is important. [191,247,248] However, no intervention has successfully reduced hospital admissions of community-dwelling people with dementia, [249] although education, exercise, rehabilitation and telemedicine have reduced admissions for older people without dementia. [250]

High quality care for people with dementia takes longer than caring for others with the same condition. [251] Recognition of dementia in hospital inpatients is necessary for optimum care, [252] but dementia is often undetected or unrecorded. [253] In the UK however, detection rates have increased over the past 10 years. [254]

Physical illness, delirium and dementia

Dementia and delirium frequently occur together. In one hospital inpatients' survey nearly 35% of those aged >80 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).[255] People with delirium are 12 times more likely to be diagnosed with dementia in the future than others, either because of pre-existing undiagnosed dementia, or because delirium has neurotoxic effects and so precipitates dementia.[256] People with similar neuropathology show faster cognitive decline if they develop delirium than if they do not.[257] Additionally, older people without dementia declined cognitively more than twice as fast after an emergency hospital admission for any cause, compared to those not admitted, suggesting any severe illness is associated with cognitive decline.[258] 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.[259] 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, there is no evidence for medication efficacy, including cholinesterase inhibitors, antipsychotic medication or melatonin.[260-262] The Hospital Elder Life Program (HELP) intervention to prevent delirium in those admitted to hospital reduced delirium incidence and includes people who are cognitively impaired. It is a multidisciplinary treatment consisting 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.[263]

A network meta-analysis of drugs for prevention and treatment of delirium did not include studies of people with dementia, so we cannot recommend drugs for people with dementia and delirium as this research may be inapplicable to people with dementia.[264]

There is little high quality research on managing delirium in dementia. One RCT compared a specialist medical and mental health unit to usual care for 600 “confused” people aged >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.[265] A further RCT of cognitively stimulating activities for people with delirium in dementia did not improve the delirium. [266]There is currently no definitive evidence that any medication improves delirium in people with dementia: cholinesterase inhibitors, antipsychotics, and sedating benzodiazepines are ineffective and antipsychotics and benzodiazepines are associated with mortality and morbidity.[238,261,267-270] Given the risk of dementia in people who develop delirium, its prevention, and possibly advances in its management, may offer a means for dementia prevention. [271]

Link between very old age, frailty and dementia

The fastest growing demographic group in most advanced countries are people 90 and over. In one well characterized post-mortem cohort of the oldest old (n=1079; mean age 90) dying with dementia, found that neuropathological features of Alzheimer disease account for about half of the cognitive decline seen and people diagnosed with AD had mixed causes of dementia. [272] Although AD neuropathology was the commonest cause of dementia, Alzheimer changes rarely occurred on their own, so only 9% of people with dementia had pure AD pathology [273] People who have Alzheimer pathology without developing dementia tend to have fewer age-related health deficits than those who develop it with even low levels of plaques and tangles. [274] 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 AD pathology and dementia (figure 10). [22] As with delirium, some of this additional health risk may be modifiable. This approach suggests a new type of therapy focus on specific age-related processes that underpin many diseases of late life.

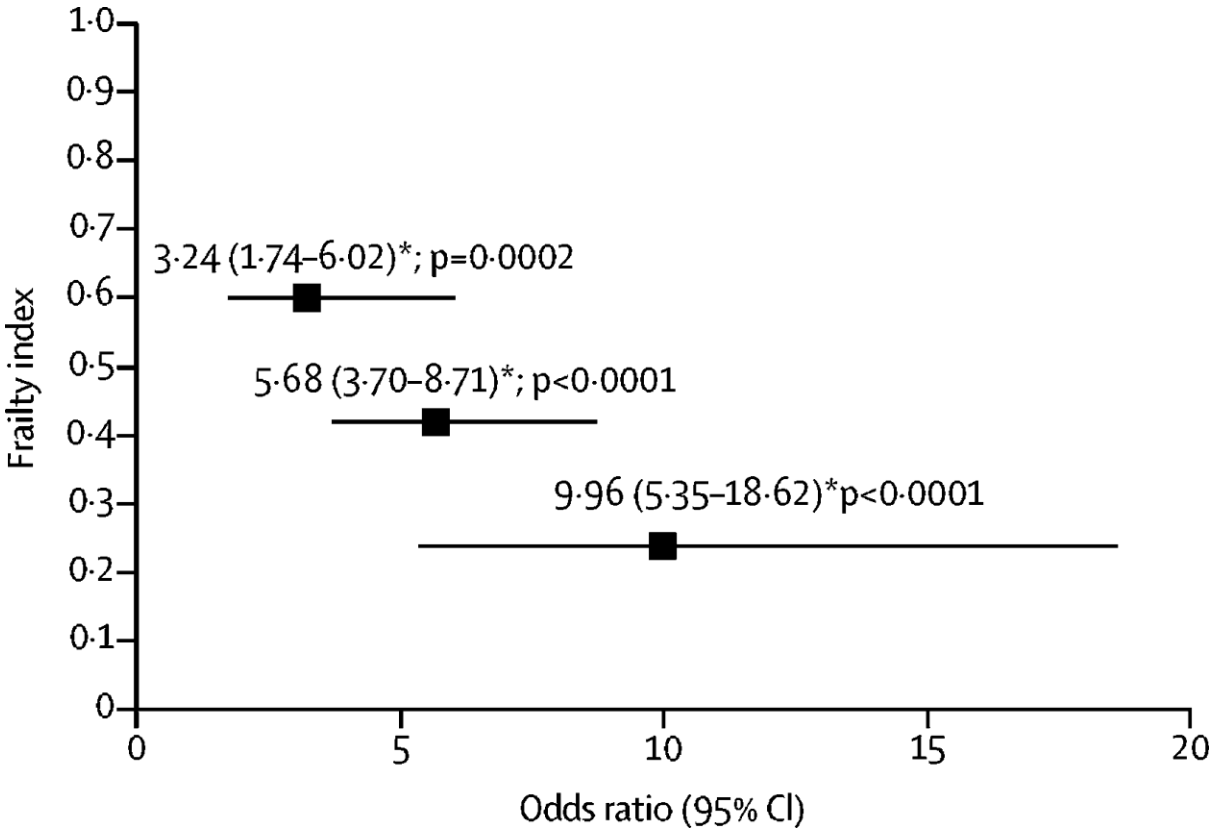


Figure 10 (with permission) **Moderation analyses of the relationship between Alzheimer's disease pathology and clinical diagnosis of Alzheimer's dementia (adjusted for age, sex, and education). As frailty increased, the odds of a neuropathological diagnosis of Alzheimer disease corresponding to a clinical diagnosis decreased.** [22]

End-of-life care in dementia

There are increasing numbers of people dying with dementia but we lack evidence of the best end-of-life care. As well as more people with dementia, trends in age-standardised death rates (3.6%) for dementia increased slightly between 1990-2016, with pronounced increases in the US and Japan and decreases in Western-Europe and Central Latin America.[4] There is more willingness to include dementia on the death certificate, which accounts for some of the rise. The increase may be related to dementia becoming manifest at later ages and increasing physical frailty [22] and be related to a faster decline.

Most people with dementia may die while still in the mild-to-moderate stages while only about a quarter of those dying with dementia have severe dementia.[275,276] The trajectory of dementia is often unpredictable[277] 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.[277] 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. [278,279] In a 9-month UK prospective study, of 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).[277]

Capacity to make abstract decisions, including about the future, may be lost early in dementia[280]. 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.[281] However, people may not be able to predict their future wishes, this may explain why family carer proxies show only low-to-moderate agreement with stated end-of-life treatment preferences of people with dementia.[282] Advance care planning may, however, reduce carers' uncertainty in decision-making and improve perceptions of quality of care.[283]

Partners of people dying with dementia experience poorer mental health than those facing bereavement from other causes. [284] possibly because of long and difficult caring responsibilities. This may be ameliorated through sensitive and timely information, particularly regarding the progression of dementia, [285] individually or through family and staff case-conferencing. [286,287]

Conclusions

Knowledge about risk factors and potential prevention, detection, and diagnosis of dementia is improving although significant gaps remain.[288] In this 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 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 persons 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, AS, JH and NM contributed to literature searches and quality assessments for systematic reviews; JH and NM performed meta-analyses; GL, NM, JH and AS conceived the new PAF calculation and NM led the statistical analysis. GL, JH, AS, NM. DA, CB, SB. AB, JCM, CC, SC, NF, RH, HK, EL, VO, KR, KR, ES, QS, LS and GS attended the conference to discuss the content.

ELS, EL, AS, DA, JH, GL wrote first draft of sections of the paper. GL wrote the first draft of the whole paper and revisions of drafts. CB 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.

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