Dementia prevention, intervention, and care

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Executive summary

Acting now on dementia prevention, intervention, and care will vastly improve living and dying for individuals with dementia and their families, and in doing so, will transform the future for society.

Dementia is the greatest global challenge for health and social care in the 21st century. It occurs mainly in people older than 65 years, so increases in numbers and costs are driven, worldwide, by increased longevity resulting from the welcome reduction in people dying prematurely. The *Lancet* Commission on Dementia Prevention, Intervention, and Care met to consolidate the huge strides that have been made and the emerging knowledge as to what we should do to prevent and manage dementia.

Globally, about 47 million people were living with dementia in 2015, and this number is projected to triple by 2050. Dementia affects the individuals with the condition, who gradually lose their abilities, as well as their relatives and other supporters, who have to cope with seeing a family member or friend become ill and decline, while responding to their needs, such as increasing dependency and changes in behaviour. Additionally, it affects the wider society because people with dementia also require health and social care. The 2015 global cost of dementia was estimated to be US$818 billion, and this figure will continue to increase as the number of people with dementia rises. Nearly 85% of costs are related to family and social, rather than medical, care. It might be that new medical care in the future, including public health measures, could replace and possibly reduce some of this cost.

Dementia is by no means an inevitable consequence of reaching retirement age, or even of entering the ninth

Key messages

1 The number of people with dementia is increasing globally
Although incidence in some countries has decreased.

2 Be ambitious about prevention
We recommend active treatment of hypertension in middle aged (45–65 years) and older people (aged older than 65 years) without dementia to reduce dementia incidence. Interventions for other risk factors including more childhood education, exercise, maintaining social engagement, reducing smoking, and management of hearing loss, depression, diabetes, and obesity might have the potential to delay or prevent a third of dementia cases.

3 Treat cognitive symptoms
To maximise cognition, people with Alzheimer's disease or dementia with Lewy bodies should be offered cholinesterase inhibitors at all stages, or memantine for severe dementia. Cholinesterase inhibitors are not effective in mild cognitive impairment.

4 Individualise dementia care
Good dementia care spans medical, social, and supportive care; it should be tailored to unique individual and cultural needs, preferences, and priorities and should incorporate support for family carers.

5 Care for family carers
Family carers are at high risk of depression. Effective interventions, including STrAtegies for RelaTives (START) or Resources for Enhancing Alzheimer's Caregiver Health intervention (REACH), reduce the risk of depression, treat the symptoms, and should be made available.

6 Plan for the future
People with dementia and their families value discussions about the future and decisions about possible attorneys to make decisions. Clinicians should consider capacity to make different types of decisions at diagnosis.

7 Protect people with dementia
People with dementia and society require protection from possible risks of the condition, including self-neglect, vulnerability (including to exploitation), managing money, driving, or using weapons. Risk assessment and management at all stages of the disease is essential, but it should be balanced against the person's right to autonomy.

8 Manage neuropsychiatric symptoms
Management of the neuropsychiatric symptoms of dementia including agitation, low mood, or psychosis is usually psychological, social, and environmental, with pharmacological management reserved for individuals with more severe symptoms.

9 Consider end of life
A third of older people die with dementia, so it is essential that professionals working in end-of-life care consider whether a patient has dementia, because they might be unable to make decisions about their care and treatment or express their needs and wishes.

10 Technology
Technological interventions have the potential to improve care delivery but should not replace social contact.

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decade. Lifestyle factors might reduce, or increase, an individual's risk of developing dementia. In some populations dementia is already being delayed for years, while in others the number of people living with it has increased. In this Commission, we have extended available models of risk by including hearing loss, derived from a new review and meta-analysis that we did for this report, and social isolation. By incorporating potentially reversible risk factors from different phases of the life-span and not just old age, we are able to propose a novel life-course model of risk, from which population attributable fractions (PAF) have been derived to show the possible effect on future incidence of successful elimination of the most potent factors. We have brought together all this evidence and have calculated that more than a third of dementia cases might theoretically be preventable. An increase in childhood education and exercise, maintaining social engagements, reducing or stopping smoking, and management of hearing loss, depression, diabetes, hypertension, and obesity could all contribute to prevention or delay of dementia. There is also preliminary evidence about other potentially modifiable risk factors. We have outlined the mechanisms by which these risk factors affect the brain.

Of course, not everyone will be able to make changes; some changes will not make a difference and some risks of dementia are genetic and not currently modifiable. Nonetheless, delaying dementia for some years for even a small percentage of people would be an enormous achievement and would enable many more people to reach the end of life without developing dementia. Many people present to services with mild cognitive impairment, a risk state for dementia, which occurs in up to a fifth of people aged older than 65 years, and this state provides an opportunity for more targeted interventions.

Many of dementia's manifestations are now known to be manageable, and while the underlying illness is generally not curable, it might be modifiable with good dementia care. In this report, we have summarised what should be done now, and when the available evidence is not definitive, we have made this clear.

We have itemised interventions that can transform the lives of people with dementia and their families; maximising cognition, decreasing distressing associated symptoms, reducing crises, and improving quality of life. Timely diagnosis is a prerequisite to receiving these interventions. We are interested in what works and have included pharmacological, psychological, environmental, and social interventions. If these interventions are implemented, people with dementia will have their cognition optimised and they will be less likely to be agitated, depressed, or have troublesome psychotic symptoms, and family carers will have reduced levels of anxiety and depression. It is also important to discuss future decision making as soon as possible with people with dementia and allow them to nominate someone to enact prespecified wishes or make choices consistent with their values.

People with dementia are usually older than 65 years, often have comorbidities, and might need help in coping with these illnesses. A third of older people now die with dementia and all professionals working in end-of-life care need to make this knowledge a central part of their planning and communication.

In this Commission, we have detailed evidence-based approaches to dementia and its symptoms. Services should be available, scalable, and give value. Professionals and services need to use what works, not use what is ineffective, and be aware of the difference.

Overall, there is good potential for prevention and, once someone develops dementia, for care to be high-quality, accessible, and give value to an underserved, growing population. Effective dementia prevention, intervention, and care could transform the future for society and vastly improve living and dying for individuals with dementia and their families. Acting now on what we already know can make this difference happen.

Introduction

As the world's population increases in age, the number of people living with dementia grows, and this figure is projected to continue to rise, especially in low and middle-income countries (LMICs; figure 1).[1] Around 47 million people were living with dementia worldwide in 2015, affecting the individual living with it, their family, as they become more dependent, and the wider society, which provides and often pays for care and support. The annual global cost of dementia is estimated to be US$818 billion.[2] Nearly 85% of costs are related to family and social, rather than medical, care. Future medical care, including public health measures, could replace and reduce some of this cost.[3] The number of people with dementia is expected to increase to 66 million by 2030, and 131 million by 2050,[2] driven by rising numbers of older adults.[4,5] However, some recent population studies have found a lower incidence of dementia than predicted from previous projections, and therefore, while the increase and crisis related to providing care continues, this might not be quite as large as previously predicted.[6,7]

Dementia has long been considered to be neither preventable nor treatable, but encouraging progress has been made. This *Lancet* Commission on Dementia Prevention, Intervention, and Care met to consolidate emerging knowledge about what can work and what individuals should do to prevent and manage dementia, particularly with the health systems in high-income countries. Many of dementia's manifestations are now known to be manageable, and while the underlying illness is not curable, the course might be modifiable with good dementia care. Available interventions and care can improve the trajectory of symptoms and the family's ability to cope with them, and thus change the

experience of the course of dementia. Additionally, there is evidence that an important fraction of dementia is preventable.

Dementia and mild cognitive impairment are characterised by a decline from a previously attained cognitive level, but in dementia, in contrast with mild cognitive impairment, the decline affects activities of daily living or social functioning.[8] In mild cognitive impairment, although the patient can still engage in complex activities—eg, paying bills or taking medication—greater effort or new strategies might be required. Dementia is usually preceded by mild cognitive impairment and the boundary between the two is grey; many people present to dementia services with mild cognitive impairment.

There are many different types of dementia, and Alzheimer's disease is the most common. Vascular dementia is the next most common, followed by dementia with Lewy bodies. Mixed dementia with features of more than one cause is also common. Frontotemporal degeneration and dementias associated with brain injury, infections, and alcohol abuse are less common.[9] In this Commission, when we use the word dementia we are referring to all the different types of dementia.

The word dementia is derived from the Latin words de (out of) and mens (mind), and its use has been considered by some to have demeaning connotations. There are stigmatising cultural beliefs about dementia, such as it is a punishment or a curse.[10] This stigma can lead to people avoiding diagnosis because they might feel stigmatised by others or in their own mind. The Diagnostic and Statistical Manual of Mental Disorders (DSM) 5 has stopped using the word dementia and instead uses the phrase "major neurocognitive disorders".[11] These are illnesses with demonstrable neural substrate abnormalities together with cognitive symptoms, which occur in people who have had normal brain development.[12] Mild neurocognitive disorder has also been added to DSM 5, equating to the WHO International Classification of Diseases (ICD-10) classification of mild cognitive disorder.[8]

Assessment of the needs of a person with dementia has to consider other illnesses and medications that affect and interact with the dementia, and the individual's social and physical living environment. Dementia usually occurs in people aged over 65 years,[13] when comorbidity is common. Age-related physical-health problems and dementia co-occur more often than by chance alone. This co-occurrence is because some physical problems, such as diabetes and hypertension, increase the risk of Alzheimer's disease and vascular dementia, making a mixed dementia more likely to occur; and the more physical illnesses a person has, the more likely they are to develop dementia, possibly related to a lack of resilience and repair, contributing to all of these problems.[14] Impaired mental and physical function also interfere with exercise or social activities.[15] These health and social challenges affect diagnosis, prognosis, response to treatment, and need for health and social care. Yet people with complex needs are generally underrepresented in trials; individuals who are eligible for and participate in research tend to be fitter, younger, male, and more highly educated.[16]

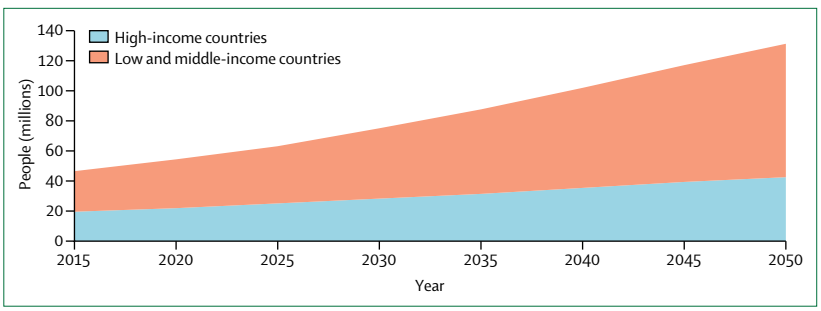

Figure 1: **Growth in numbers of people with dementia in high-income and low and middle-income countries**
Reproduced from Prince and colleagues,[2] by permission of Alzheimer's Disease International.

In this Commission, we have used the best available evidence to make recommendations. When evidence is incomplete we have summarised the balance of evidence and explained its strengths and limitations. An overall limitation is that this evidence is generally focused on, and from, high-income countries and we have less evidence from LMICs.

Prevention of dementia

Demographics and dementia

The number of people with dementia is rising rapidly (figure 1), primarily due to worldwide ageing populations, particularly in LMICs.[1,17] This association is expected and widely reported.[18,19]

Although no disease-modifying treatment for any common dementia is available, a delay in the onset of dementia would benefit even the oldest adults.[20] An unexpected decline in age-specific dementia incidence or prevalence has been reported in some countries, such as the USA, the UK, Sweden, the Netherlands, and Canada.[6,7,21–26] Conversely, an increase in the incidence of dementia in China[27] and prevalence in Japan[28,29] has been reported, while in Nigeria the incidence and prevalence are stable.[30] Results of two US studies[25,26] showed that the decrease in age-specific prevalence (despite an increase in the absolute number of people with dementia) was associated with an increase in education.

These data suggest reduced dementia risk in successive generations according to their lifetime exposure to health and lifestyle factors. In some countries, the current cohort of people aged over 65 years is cognitively healthier than their predecessors with greater resilience, as a result of reduced exposure to dementia risk factors or increased exposure to protective factors.[31] However, the increasing mid-life rates of obesity and associated ill-health are projected to lead to a 19% increase in dementia in China and a 9% increase in the USA.[32]

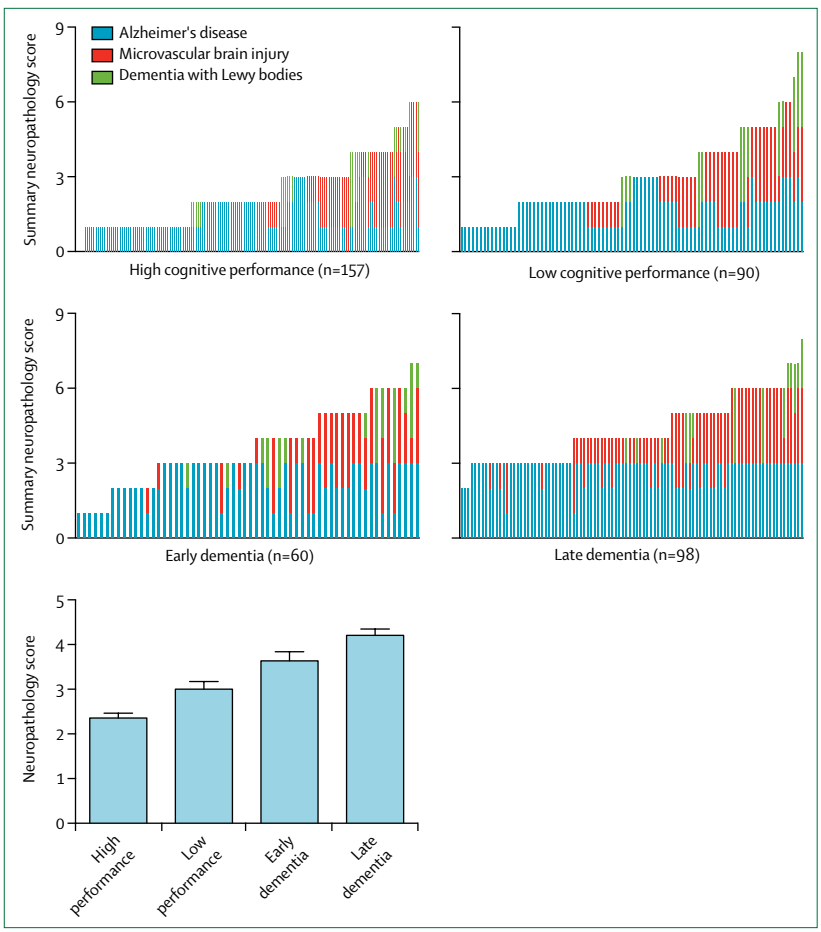

Figure 2: **Brain autopsy results from cognitively healthy individuals**
Reproduced from Cholerton and colleagues,[41] by permission of Elsevier. Data are expressed as summary neuropathology score (potential range from 0 to 9) ranked from lowest to highest, with each stacked bar showing an individual's burden, or neuropathology score, with data as mean (SE).

Complexity of dementia neuropathology complicates prevention

Some dementia risk factors, including cardiovascular disease, cerebrovascular disease, metabolic and psychiatric factors, diet, lifestyle, and education, are potentially modifiable.[33] Dementia is heterogeneous and risk factors vary, and also coexist, for different types of dementia. Vascular brain injury, including strokes and microvascular infarcts, not only leads to vascular dementia, but occurs more commonly in older people with Alzheimer's disease than those without Alzheimer's disease,[34–36] and is present in some people who do not have dementia. In individuals with both neuropathological Alzheimer's disease and lacunar infarcts, the cognitive impairment is more severe than those without such infarcts.[37] These patients are sometimes diagnosed as having mixed dementia,[38] Alzheimer's disease in which plaques and tangles are seen alongside microvascular infarcts, or, less commonly, Lewy bodies, all of which are likely to contribute to cognitive decline.[39–43]

It is possible, as we show in the section on modifiable risk factors for dementia, to model the effect of changing potentially modifiable risk factors. The available evidence for the effect of lifestyle changes on cognitive decline is mixed. The changes in incidence reported in diverse countries provide evidence that reducing or increasing rates of dementia are both possible. Lower rates indicate either that onset has been delayed for some people or that other competing causes of mortality occurred.[44] In 2014, the European Union Joint Programme on Neurodegenerative Disease Research[45] called for population-based and disease-based cohorts to be exploited to obtain the high-quality evidence that is necessary to capture the range of potential health effects and confounding factors that start in midlife, and to provide evidence on the direction of causality.

Although modification of risk factors is important in dementia prevention, age, the greatest risk factor for dementia overall, is unmodifiable. Dementia usually presents in older age, with exponential increases in incidence at the age of 65 years or older. Overall, about 80% of dementias are in people aged 75 years or older[13,46] and there might be an interaction between age, neuropathology, comorbidity, and the clinical presentation. Age on its own would probably be a less powerful risk factor once other risk factors and comorbidity are taken into account, but it still remains an important consideration, especially as life expectancy continues to increase.

A focus on resilience: cognitive reserve

Some people with neuropathological changes of Alzheimer's disease do not have dementia,[41] indicating resilience. Figure 2 illustrates how some individuals in community-based US studies[41] who are cognitively healthy tolerate a large and mixed burden of vascular, Lewy body, and Alzheimer's neuropathology. These findings have led to the concept of cognitive reserve, which is that people who have such brain reserve can tolerate more neuropathology without cognitive and functional decline, and therefore develop dementia more slowly than people without this type of brain reserve.[47] This reserve is related to either the brain anatomical substrate or adaptability of cognition, due to factors that we discuss in the next section.[48,49]

The theory suggests that less cognitive reserve leads to earlier development of dementia. Furthermore, it suggests that populations with, for example, increased rates of hypertension might develop dementia earlier, because the resultant neuropathology reduces the cognitive reserve buffer. As predicted, cumulative and dose-related exposure to reserve-enhancing factors, namely physical exercise, intellectual stimulation, or leisure activities, over the lifespan was associated with reduced risk of dementia in late life, even among individuals with genetic predisposition to dementia.[50] Furthermore, those with less cognitive reserve as a result

of intellectual disability develop dementia at a younger age.[51] Additionally, people of African origin residing in the UK and USA who have high rates of hypertension, have increased rates of dementia at a younger age.[52–54]

We believe that a broader approach to prevention of dementia, including promoting resilience, makes sense in our ageing societies. Strategies for promoting resilience to prevent or delay the onset of dementia are extrapolated from studies[23,24] on declining dementia incidence, which report that healthier lifestyles are associated with declining prevalence of cognitive impairment and dementia. Cognitive resilience in later life is likely to be enhanced by building brain reserve earlier in life through education and other intellectual stimulation.[55,56] Through neuronal branching and plasticity, such changes might subsequently be translated into brain reserve. Lower rates of late-life dementia are associated with higher education levels.[25] Improved socioeconomic status during gestation and early childhood has a protective association with late-life dementia risk.[57] These findings indicate that an improvement in brain reserve[55,56,58] combined with interventions known to prevent damage are ways to promote resilience.

Modifiable risk factors for dementia

Prevention is better than cure and underlies the growing interest in modifiable risk factors. Any future disease-modifying treatment for dementia will not remove the need for its effective prevention. In published work on dementia risk, midlife has been defined as 45–65 years and later life as older than 65 years. We have used these definitions throughout this Commission for consistency, but these risks are often relevant throughout the life course. Much of this work focuses on estimating the population attributable fraction (PAF), which is the percentage reduction in new cases over a given time if a particular risk factor were completely eliminated. The work to date focuses on well established cardiovascular risk factors for dementia, including diabetes, midlife hypertension, midlife obesity, physical inactivity, and smoking, as well as depression and low educational attainment.[33]

PAF for modifiable risk factors

We sought to calculate a combined PAF for known modifiable risk factors for dementia (table 1). We decided which risk factors to include by identifying those listed in the UK National Institute of Health and Care Excellence (NICE)[59] and US National Institutes of Health (NIH)[60] guidelines. For risk factors included in studies[33,61] reporting dementia PAF—vascular risk factors, not continuing in education beyond primary school, and depression—we used their data on relative risk (RR) and prevalence. For the additional risk factors included in our calculations, we sought systematic reviews of their RR and prevalence and, in the absence of one, we asked other authors of the *Lancet* Commission for suitable papers and did our own meta-analysis. We focused on all-cause rather than cause-specific dementia because there were most data for this outcome, except for smoking where we used the figures for Alzheimer's disease because these were more reliable. As far as possible, we used prevalence and RR data from international studies to make our figures relevant to global dementia risk.

NICE and NIH identify social isolation and peripheral hearing loss as potentially modifiable dementia risk factors. We used a systematic review and meta-analysis for social isolation and incident dementia to calculate its PAF.[62] This study[62] divided the exposure into social contact (telephone or face-to-face contact with family or friends), social participation (belonging to or taking part in community activities or organisations), and loneliness (a subjective feeling of dissatisfaction at one's level of social contact). We used the figures for social contact because we judged it as the most accurate measure of actual contact time. The weighted RR for incident dementia associated with less frequent social contact was 1·57 (95% CI 1·32–1·85). PAF calculations require knowledge of the prevalence of the risk factor, but this measure was not given in any of these papers. There was also heterogeneity in the definition of infrequent social contact in individual papers. We therefore used results from a representative sample of older people in the UK[63] to estimate prevalence and we incorporated the prevalence of reporting social contact less than monthly as social isolation, which is probably a conservative definition.

	Relative risk for dementia (95% CI)	Prevalence	Communality	PAF	Weighted PAF*
Early life (age <18 years)					
Less education (none or primary school only)	1·6 (1·26–2·01)	40·0%	64·6%	19·1%	7·5%
Midlife (age 45–65 years)					
Hypertension	1·6 (1·16–2·24)	8·9%	57·3%	5·1%	2·0%
Obesity	1·6 (1·34–1·92)	3·4%	60·4%	2·0%	0·8%
Hearing loss	1·9 (1·38–2·73)	31·7%	46·1%	23·0%	9·1%
Later life (age >65 years)					
Smoking	1·6 (1·15–2·20)	27·4%	51·1%	13·9%	5·5%
Depression	1·9 (1·55–2·33)	13·2%	58·6%	10·1%	4·0%
Physical inactivity	1·4 (1·16–1·67)	17·7%	26·6%	6·5%	2·6%
Social isolation	1·6 (1·32–1·85)	11·0%	45·9%	5·9%	2·3%
Diabetes	1·5 (1·33–1·79)	6·4%	70·3%	3·2%	1·2%

Data are relative risk (95% CI) or %. Total weighted PAF adjusted for communality=35·0%. PAF=population attributable fraction. *Weighted PAF is the relative contribution of each risk factor to the overall PAF when adjusted for communality.

Table 1: **Potentially modifiable risk factors for dementia**

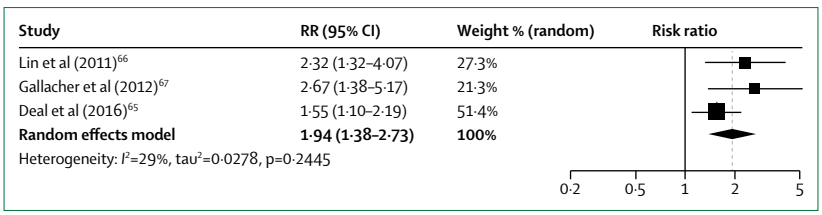

Figure 3: **Forest plot of the effect of hearing loss on incidence of dementia 9–17 years later in cognitively healthy people**
Hearing loss was measured by pure-tone audiometry. RR=risk ratio.

Panel 1: Method for calculation of population attributable fraction and communality

Formula for individual population attributable fraction (PAF):

$$PAF = \frac{Pe\,(RRe - 1)}{1 + Pe\,(RRe - 1)}$$

Calculation of communality:

- Input data on all nine risk factors in our model
- Calculate tetrachoric correlation to generate correlation coefficients and a correlation matrix
- Conduct a principal-component analysis on the correlation matrix to generate eigenvectors, which are directions mapped onto the datapoints and from which variance to the data is measured. These represent unobserved factors underlying all the variables that explain the variance observed
- Components with eigenvalues ≥1 were retained in the model
- Communality was calculated as the sum of the square of all factor loadings (ie, how much each unobserved component explained each measured variable)

Calculation of overall PAF:

$PAF = 1 - [(1 - PAF_1)(1 - PAF_2)(1 - PAF_3)...]$

Each individual risk factor's PAF was weighted according to its communality using the formula:

Weight (w) = 1 – communality

Weighting was included in the calculation of overall PAF using the formula:

$PAF=1 - [(1 - w*PAF_1)(1 - w*PAF_2)(1 - w*PAF_3)...]$

Pe=prevalence of the exposure. RRe=relative risk of disease due to that exposure.

To our knowledge, no systematic reviews have been done for hearing loss and incident dementia. We therefore consulted experts to generate a list of relevant studies and used the quality checklist for prognosis studies,[64] defining high-quality papers as those that had followed a cohort of cognitively healthy people for at least 5 years, had an objective measure of peripheral hearing (pure-tone audiometry), had incident dementia as an outcome, and had adjusted for age and cardiovascular risk factors as potential confounding factors. Three studies[65–67] met these criteria, with follow-up over 9 years, 12 years, and 17 years. Each found that peripheral hearing loss was a significant risk factor for dementia. We meta-analysed these data and calculated a pooled RR of 1·94 (95% CI 1·38–2·73; figure 3).

The attributable risk in a population depends on the prevalence of the risk factor and the strength of its association (RR) with the disease. In our calculations, we have used RRs from systematic reviews and, although these were adjusted for many confounders, they could not have been adjusted for all the risk factors in our total PAF calculation. Therefore, use of the formula for calculation of individual risk factor PAF for circumstances in which all confounding risk factors have been adjusted for would be inappropriate.[68] We therefore used a version of the formula from a previous study,[33] which is more appropriate when confounding has not been fully accounted for.[33,61]

Communality of risk factors

We used figures from the 2014 Health Survey for England (HSE), a representative sample of more than 10 000 UK community-dwelling adults, to calculate communality of risk factors—the variance in observed variables accounted for by common factors—to allow calculation of each factor's unique risk.[33,69,70] HSE data have all the relevant risk factors except social contact frequency, so we used cohabitation as a proxy measure for social contact, with the assumption that those participants who live with someone else have higher levels of social contact than those who live alone. Our principal component analysis, extracted using this method, found that three principal components explained 53% of the total variance between the nine risk factors, suggesting substantial overlap. Table 1 shows the prevalence, communality, and RR, with the PAF adjusted for communality of each included risk factor. We then calculated overall PAF (table 1) using the same formula as reported in other studies,[33] but incorporating the additional variables of hearing loss and social isolation (panel 1). Figure 4 presents the new model of life-course risk factors.

Our results suggest that around 35% of dementia is attributable to a combination of the following nine risk factors: education to a maximum of age 11–12 years, midlife hypertension, midlife obesity, hearing loss, late-life depression, diabetes, physical inactivity, smoking, and social isolation. Conversely, completely eliminating the apolipoprotein E (ApoE) ε4 allele as the major genetic risk factor is calculated to produce a 7% reduction in incidence, with the PAF calculation methods.[71]

Effects of potentially modifiable risk factors on the brain

Figure 5 shows a summary of the suggested mechanisms linking potentially modifiable risk factors to dementia. Vascular damage to the brain not only increases risk of

microvascular and macrovascular lesions but also of atrophy and neurodegeneration. Oxidative stress and inflammation are associated with deposition of amyloid β.[72] Diabetes and metabolic syndrome are associated with atherosclerosis and brain infarction, and glucose-mediated toxicity causes microvascular abnormalities and neurodegeneration.[73] Evidence of impaired insulin receptor activation in Alzheimer's disease[74] has led to suggestions that it might represent an insulin-resistant brain state.[75] Exercising more in midlife is associated with a reduced risk of dementia.[76] Exercise is postulated to have a neuroprotective effect, potentially through promoting release of brain-derived neurotrophic factor (BDNF),[77,78] reducing cortisol, and reducing vascular risk. Exercise alone does not seem to improve cognition in healthy older adults.[79]

Specific risk factors and mechanisms

Here we discuss the specific risk factors and their effects.

Education

Less education is associated with an RR of dementia of 1·59 (95% CI 1·26–2·01) and the high PAF is because of the large worldwide estimated prevalence of 40%. Less time in education, which we defined as no secondary school education, has the second highest PAF in our model. Low educational level is thought to result in vulnerability to cognitive decline because it results in less cognitive reserve,[58] which enables people to maintain function despite brain pathology.[80] We do not yet know whether education after secondary school is additionally protective.

Hearing

Recognition of hearing loss as a risk factor for dementia is relatively new and has not been included in previous calculations of PAF, nor has it been a priority in the management of those at risk of cognitive impairment. Results of cohort studies[65–67,81–88] that have investigated hearing have usually shown that even mild levels of hearing loss increase the long-term risk of cognitive decline and dementia in individuals who are cognitively intact but hearing impaired at baseline. However, although there are 11 positive studies, two studies[89,90] found no increased risk in adjusted analyses.

The risk of hearing loss for dementia in the meta-analysis of three studies,[65–67] which we did for this Commission (pooled RR 1·94, 95% CI 1·38–2·73; figure 3), is not only higher than the risk from other individual risk factors, but it is also pertinent to many people because it is highly prevalent, occurring in 32% of individuals aged older than 55 years.[91] Its high RR and prevalence explains the high PAF. We have used the prevalence of hearing loss in individuals older than 55 years to calculate PAF because this age was the youngest mean age in which presence of hearing loss was shown to increase dementia risk.[67] Hearing loss is therefore grouped with the midlife risk

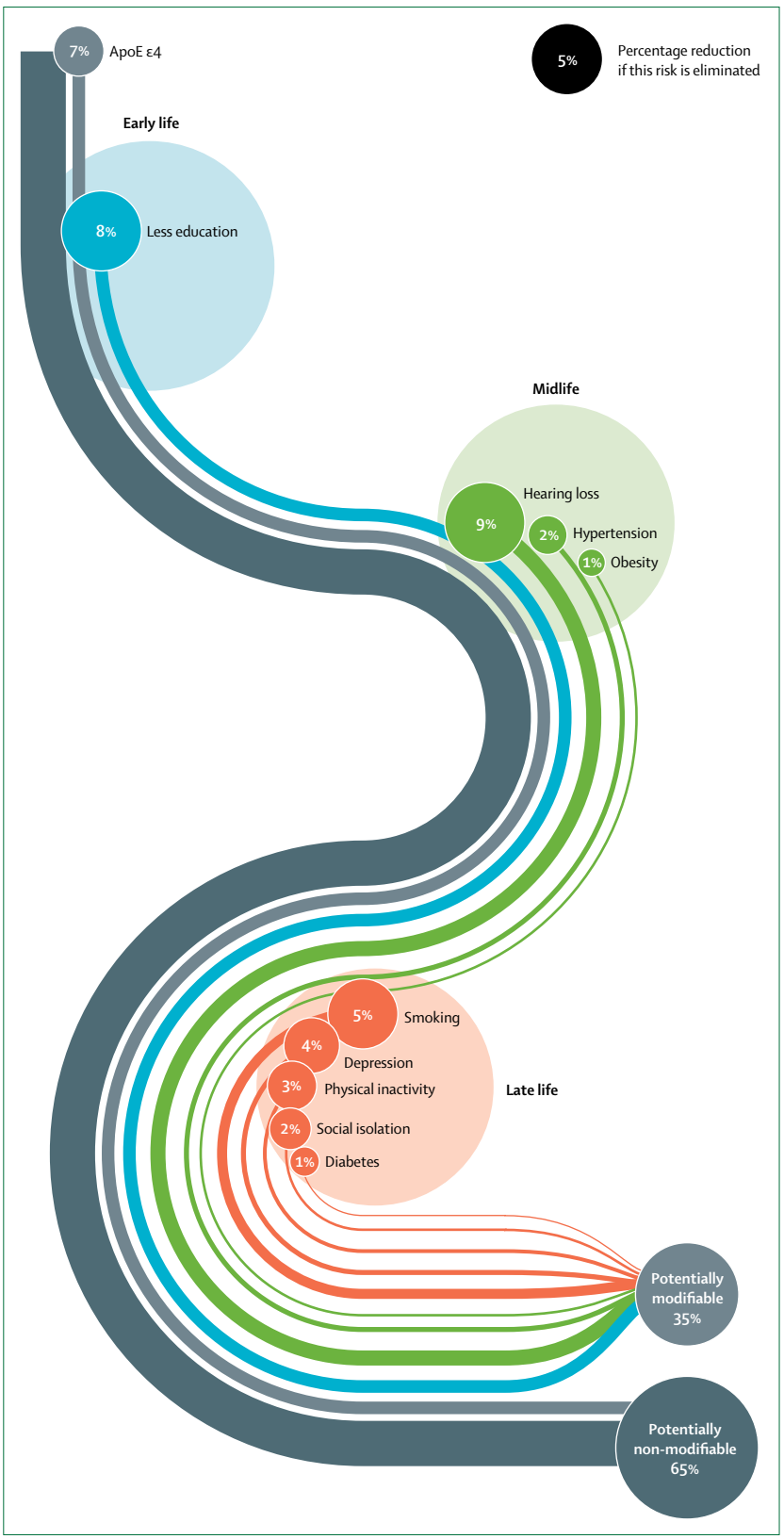

Figure 4: **Life-course model of contribution of modifiable risk factors to dementia**
Numbers are rounded to nearest integer. Figure shows potentially modifiable or non-modifiable risk factors.

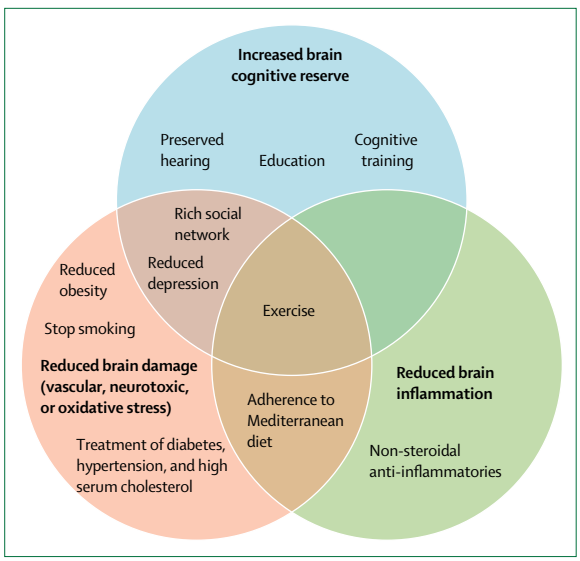

Figure 5: **Potential brain mechanisms for preventive strategies in dementia**

factors, but evidence suggests that it continues to increase dementia risk in later life.

The mechanism underlying cognitive decline associated with peripheral hearing loss is not yet clear; nor is it established whether correction, such as hearing aids, can prevent or delay the onset of dementia. Older age and microvascular pathology increase the risk of both dementia and peripheral hearing loss, and might therefore confound the association. Hearing loss might either add to the cognitive load of a vulnerable brain leading to changes in the brain,[92] or lead to social disengagement or depression[93,94] and accelerated atrophy,[95] all of which could contribute to accelerated cognitive decline.[96] Although impaired hearing might detrimentally affect performance on formal cognitive assessments, individuals with impaired baseline hearing had normal baseline cognition so this cannot account for the findings.

Experimental evidence on whether hearing aid use might alleviate some of these negative effects is not available. Any intervention would require greater complexity than merely suggesting to people that they use a hearing aid because only a minority of people with hearing loss are either diagnosed or treated,[97] and when hearing aids are prescribed many people do not use them.[98]

Central hearing loss is distinct from peripheral hearing loss. It is a difficulty in understanding speech in noise that is not explained by cochlear (peripheral) hearing impairment and does not improve with peripheral amplification (such as hearing aids).[99] It is unlikely to be a modifiable risk factor and could be a prodromal symptom of Alzheimer's disease causing impaired speech perception, especially in the presence of competing sounds.[100] This theory is consistent with the fact that central auditory areas are affected by Alzheimer's disease pathology.[101] It is very unlikely that central hearing impairment would account for the association between peripheral hearing loss and dementia identified in studies, because the central hearing loss that is followed by Alzheimer's disease is rare, at 2% of the older population,[100] while the prevalence of peripheral hearing loss in the studies included in our meta-analysis in a similar middle-aged and older population (mean ages in the three included studies were 55 years, 64 years, and 75·5 years) is much larger (28%, 43%, and 58%, depending on the specific study). Mild central hearing loss might be more prevalent than the estimate of 2%, but this has not been linked to increased risk of dementia.[102]

A small pilot intervention,[103] Hearing Equality through Accessible Research & Solutions (HEARS), used visual materials and training for the participant and a family member to increase usage of listening devices in cognitively healthy adults with a mean age of 70 years. The results of the pilot intervention showed that it might be possible to increase their use.

Exercise and physical activity

Older adults who exercise are more likely to maintain cognition than those who do not exercise. No randomised trials are available to show that exercise prevents cognitive decline or dementia, but observational studies have found an inverse relation between exercise and risk of dementia. Results of one meta-analysis[104] of 15 prospective cohort studies following up 33 816 individuals without dementia for 1–12 years reported that physical activity had a significant protective effect against cognitive decline, with high levels of exercise being the most protective (hazard ratio [HR] 0·62, 95% CI 0·54–0·70). Another meta-analysis[105] included 16 studies with 163 797 participants without dementia and found that the RR of dementia in the highest physical activity groups compared with the lowest was 0·72 (95% CI 0·60–0·86) and the RR of Alzheimer's disease was 0·55 (95% CI 0·36–0·84). Physical exercise leads to benefits in older people without dementia, such as improving balance and reducing falls,[106] improving mood,[107] reducing mortality, and improving function.[108]

Diabetes, hypertension, and obesity

Among the vascular risk factors, hypertension had the highest PAF, but all had PAFs below 5%.[109] Obesity is linked to pre-diabetes and metabolic syndrome, which is characterised by insulin resistance and high concentrations of peripheral insulin. Peripheral insulin anomalies are thought to cause a decrease in brain insulin production, which can impair amyloid clearance.[110] An increase in inflammation and high blood glucose concentrations could also be mechanisms by which diabetes impairs cognition.[111]

Smoking

Smoking had the third highest PAF, in keeping with previous analyses.[33] The association with cognitive

impairment might be due to the link between smoking and cardiovascular pathology, but cigarette smoke also contains neurotoxins, which heighten the risk.[112] Again, its high prevalence contributes to the high PAF. Interventions are being used to reduce cigarette smoking, and smoking has and is declining in most countries; although in 2015, smoking seemed to be increasing in the eastern Mediterranean and Africa.[113]

Depression

Depressive symptoms can be a part of the clinical presentation of dementia, which has led to debate as to the direction of causation: whether depression is a prodromal symptom or an independent risk factor for dementia. Cohort studies[114] with longer follow-up times show a link between number of depressive episodes and risk of dementia, which strengthens the assertion that depression is a risk factor for dementia. However, a cohort study[115] following people for up to 28 years before the development of dementia found that it was only in the 10 years before dementia incidence that depressive symptoms were higher in people with dementia than those without dementia. This suggests that midlife depression is not a risk factor for dementia. However, it remains unclear whether the high depressive symptoms seen in people who go on to develop dementia are a cause of dementia at a time of vulnerability or an early symptom of dementia. It is biologically plausible that depression increases dementia risk because it affects stress hormones, neuronal growth factors, and hippocampal volume.[116] Antidepressant prescriptions have increased in the past three decades and this increase is hypothesised to affect dementia incidence since animal data suggest that some antidepressants, including citalopram, decrease amyloid production.[117–119]

Social contact

The PAF for social contact was similar to that for hypertension and physical inactivity. As with depression, social isolation might be a prodrome or a part of the dementia syndrome. However, evidence is growing that social isolation is a risk factor for dementia and it increases the risk of hypertension,[120] coronary heart disease,[121] and depression.[122] Social isolation might also result in cognitive inactivity, which is linked to faster cognitive decline and low mood.[62] All these are risk factors for dementia themselves, which highlights the importance of considering the social engagement of older people and not only their physical and mental health.

Regarding lifestyle, individuals who adhere to a Mediterranean diet (low intake of meat and dairy, high intake of fruit, vegetables, and fish) have fewer vascular risk factors and reduced plasma glucose and serum insulin concentrations, insulin resistance, and markers of oxidative stress and inflammation.[123] Not smoking, exercising regularly, eating fruit and vegetables daily, and drinking only a moderate amount of alcohol increase life expectancy and health in ageing,[124] so the interest in the effect of these factors on cognition is increasing. We do not have data to include dietary factors and alcohol in our calculations, but we believe that they could be important.

Other factors

Concerning head injuries, most are mild and the commonest head injury is a non-repetitive traumatic brain injury. The largest study of traumatic brain injury found that 865 (12%) of 7130 participants in a 20-year longitudinal cohort study[125] had a history of traumatic brain injury (defined as >1 h loss of consciousness). This injury was neither associated with a greater risk of development of dementia nor Alzheimer's disease, nor increased plaques and tangles in the 1589 participants who had an autopsy. However, traumatic brain injury was associated with the development of Parkinson's disease and Lewy body pathology.[125]

Results of a meta-analysis[126] of seven studies, following up people at least 1 year after traumatic brain injury, found it was not associated with increased risk of all-cause dementia. However, traumatic brain injury increased the risk of Alzheimer's disease (odds ratio [OR] 1·40, 95% CI 1·02–1·90).[126] There is some evidence that this effect is modified by sex; the risk of dementia following traumatic brain injury is greater for men.[127,128] The meta-analysis also found no difference in risk between single and repetitive traumatic brain injury. It concluded that the studies had limitations and were heterogeneous.

The type of short-term brain pathology typically caused by a head injury related to a single blast in a military setting is unclear.[129] Repetitive mild head injury in athletes or from war is associated with chronic traumatic encephalopathy, a progressive tauopathy that can eventually manifest as dementia.[130] The US Institute of Medicine has concluded that moderate or severe traumatic brain injury, such as in war, is a risk factor for Alzheimer's disease,[131] but overall the evidence seems to be that non-repetitive traumatic brain injury does not predispose to all-cause dementia.

Visual impairment and sleep disorders have received some attention for their role in the development of cognitive impairment.[59] Sleep might promote repair of damage caused by other factors, but given the absence of systematic reviews or enough consistent, high-quality evidence, we have not been able to include sleep in our calculations of PAF. It has been suggested that bilingualism might specifically contribute to cognitive reserve, protect against cognitive decline, and delay the onset of dementia. However, a systematic review and meta-analysis[132] of prospective studies of the effects of bilingualism on future dementia gave a combined odds ratio of dementia of 0·96 (95% CI 0·74–1·23) in bilingual participants (n=5527) compared with monolinguals. Thus, when distinguishing prospective from retrospective studies there was no indication that

bilingualism protects from cognitive decline or dementia from prospective studies. One longitudinal study[133] found that living near major roads increases the chance of having a recorded diagnosis of dementia. Similarly, a prospective 11 year cohort study of women older than 65 years found increased risks of cognitive decline and all-cause dementia associated with exposure to particulate air pollutants to neurodegenerative changes.[134] This study and animal models suggest that airborne particulate pollutants accelerates neurodegenerative processes through multiple pathways, including increasing amyloid deposition, APP processing, and other pathways independent of amyloid deposits.

Limitations of the data

Causality in longitudinal studies

The PAF model assumes a causal association between a risk factor and dementia, and a causative link is required for interventions to lead to actual reductions in the incidence of dementia. With regard to causality, the most convincing evidence would be from randomised controlled trials (RCTs) in humans. These trials are not possible for many proposed dementia risk factors, such as education, but we know that falling age-specific incidence is associated with more education.[25] In the absence of this experimental human evidence, causality criteria have been proposed.[135]

The emergent risk factors we have included in the PAF calculation, including hearing loss and social engagement, meet these criteria, suggesting plausible causal relations. For example, with hearing loss: for strength of association, our meta-analysis showed an effect size of 1·94 (95% CI 1·38–2·73). For consistency, the three high-quality cohort studies identified in our meta-analysis reported a statistically significant association between peripheral hearing loss and dementia, with overlapping 95% CIs. Regarding temporality, the studies measured hearing loss, then followed up people without dementia for at least 9 years, identifying incident dementia cases during this follow-up. Concerning biological gradient, a dose response exists whereby the RR of dementia is increased by 1·89 for mild hearing loss, 3·00 for moderate, and 4·94 for severe.[66] For plausibility, in animal models, hearing loss precedes changes in brain structures,[136] volume,[137] and networks.[138] An improvement of hearing (and social and exercise interventions) might improve cognition by environmental enrichment, associated with reduced amyloid deposition in mouse models.[139] Additional human-specific mechanistic pathways are possible because of the importance of language relative to other species; language is a key element of the coevolution of larger brain size, social interaction, and larger-scale group cooperation in humans.[140] Hearing loss in humans might therefore result in uniquely interrelated and detrimental social, cognitive, and brain effects.

Modifiability of the risk factors

PAF reflects the proportional reduction of incident dementia cases that available evidence suggests would occur if risk factors were eliminated. This figure should be interpreted with caution because it is not feasible to completely eliminate any of these risk factors, and some risk factors can also be part of the dementia syndrome. However, our understanding of what we could and should target provides an opportunity to consider better management or preventive strategies to reduce the burden of risk.

Differences in PAF estimates

Our assessment of the combined effect of potentially modifiable risk factors is higher than previous estimates reported. However, we have incorporated two additional risk factors, one of which, hearing loss, is extremely common in middle and later life, so would be expected to have a high PAF. We have been conservative in our estimates by calculating communality from the HSE from 2014, whereas previous estimates used data from 2006. We have made our estimates as conservative as possible by calculating communalities for adults older than 65 years of age, because this age group is the most vulnerable to dementia, and correlation between risk factors is likely to be more relevant in this age group than in all adults.

When in the life course is a risk factor important?

Although we have presented the available evidence about specific times when a risk factor has been shown to be important during the life course, it might be relevant at other times. Ongoing education might continue to increase cognitive reserve, for example. Similarly, diabetes, hypertension, depression, being sedentary, and smoking are probably important risk factors in middle age and later life, and hearing loss may be a risk in late as well as mid-life.

Other risk factors not in our model

We have not incorporated other potential risk factors, such as diet, alcohol, living near major roads, or sleep, which could be relevant. Therefore, the potentially preventable fraction of dementia might be underestimated in our figures.

Reverse causality

The direction of causality is sometimes unclear and might sometimes be bidirectional. For example, reduced socialisation or increased depressive symptoms might be caused by, and cause, cognitive decline, and thus our figures could be an overestimate. When considering some risk factors that occur not long before the onset of impairment, it is difficult to be sure of direction of causation—eg, whether depression increases the risk of dementia or dementia increases the risk of depression or if the association is bidirectional.

Communality of risk factors

Our communality calculations take into account shared mechanisms of reversible risk factors, but it is also possible that genes might predispose to both dementia and hypertension, depression, or hearing loss.

Global estimates of prevalence

The prevalence of risks we have used are from the largest populations we could find, but these are not always global and will differ in different parts of the world, with varying cultures and incomes.

Data quality

Finally, the quantity of data differ so that the estimates for hearing loss are less stable than those for hypertension, smoking, or diabetes because we used fewer studies to contribute to the estimates presented.

Importance of PAF findings

The general principle is that dementia has an important proportion of modifiable risk factors, whether we assume the true PAF to be lower or higher than our estimate. Modifying risk factors could translate into a large effect on the global burden of dementia, which would then have huge implications for social and health-care costs.

While public health interventions will not delay, prevent, or cure all potentially modifiable dementia, the management of metabolic, mental health, hearing, and cerebrovascular risk factors might push back the onset of many cases for some years. Dementia prevalence would be halved if its onset were delayed by 5 years.[141] Estimates suggest that a 10% reduction in the prevalence of the seven principal health and lifestyle factors would reduce worldwide dementia prevalence by more than a million cases, or an intervention that delayed dementia by a year could decrease the number of people living with dementia globally by 9 million in 2050.[33,61] While we might not expect risk factor modification to have this magnitude of effect in reality, any reduction in dementia risk would be a great achievement.

Interventions to prevent dementia

The existence of potentially modifiable risk factors does not mean that all dementia is preventable or make it more treatable once established. Some intervention studies[142,143] have built on the evidence of modifiable dementia risk factors to reduce dementia incidence, testing the effects of physical activity, cognitive training, or medication, including antihypertensives. The low dementia incidence means that trial sample sizes have to be large and length of study long to show a reduction in dementia cases. The multiple risk factors contributing to dementia could explain why most prevention trials have been inconclusive,[144] leading to the development of multimodal preventive strategies.

Antihypertensive drugs

Although most intervention trials have been ineffective, the exception is antihypertensive drugs. A trial of the antihypertensive indapamide, with the option of perindopril, in people without dementia but who were hypertensive (defined as 160–200/<110 mm Hg) and older than 80 years, was stopped early because a reduction of stroke and mortality in the treatment group meant it was unethical to continue placebo.[145] Therefore, the trial did not fulfil the power calculation and the 95% CIs overlapped between treatment and placebo groups (HR 0·86, 95% CI 0·67–1·09). However, when these data were combined in a meta-analysis,[145] with other placebo-controlled trials of antihypertensive treatment, the combined risk ratio for dementia favoured treatment (HR 0·87, 95% CI 0·76–1·00). Similarly, another meta-analysis[146] showed a reduction in cognitive decline in the treatment groups (weighted mean difference 0·42, 95% CI 0·30–0·53). This outcome was consistent with an RCT[147] that aimed to reduce systolic blood pressure to less than 150 mm Hg in people aged older than 60 years without dementia using nitrendipine (10–40 mg per day), with the possible addition of enalapril (5–20 mg per day) or hydrochlorothiazide (12·5–25 mg per day), which reduced the incidence of dementia compared with the placebo. In the Prevention of Dementia by Intensive Vascular Care (preDIVA) trial,[148] treatment of hypertension also seemed to be important. The benefits of strictly managing hypertension must be balanced with risks, and target blood pressure for people aged older than 80 years should be less than 150/90 mm Hg.[149]

Other medications

By contrast, trials of non-steroidal anti-inflammatory drugs (NSAIDs),[150] a 24-week RCT of the oral hypoglycaemic drug rosiglitazone,[151] oestrogen hormone-replacement therapy, statins,[152] vitamins, and ginkgo biloba extract have all been negative.[3] There is good evidence from two negative trials[152] (with 26 340 participants aged 40–82 years, of whom 11 610 were aged 70 years or older with risk factors for vascular disease) that statins do not prevent (or increase) cognitive impairment or dementia.

While several meta-analyses[153,154] have shown hormone-replacement therapy to have a 29–44% protective effect against dementia, a more recent review[155] of both observational and intervention studies concludes that there are neither harmful nor beneficial effects of hormone-replacement therapy in relation to dementia, with negative effects being more likely in women in poor health, especially those with cardiovascular disease and diabetes. At present, hormone-replacement therapy cannot be recommended to prevent dementia; however, it is possible that there might be beneficial effects for a subgroup of healthy women receiving treatment in the perimenopausal period. Furthermore, most research was in women

taking orally administered conjugated equine oestrogens and progesterone, and the long-term effects of more recently developed molecules and transdermal administration are unknown.

Mediterranean diet

447 healthy participants, with a mean age of 67 years, at high cardiovascular risk but with no cardiovascular disease or substantial cognitive impairment were randomly assigned to one of three dietary groups.[156] These were a Mediterranean diet supplemented with extra virgin olive oil (1 L per week), a Mediterranean diet supplemented with mixed nuts (30 g per day), or a control diet (advice to reduce dietary fat); adherence to the dietary supplementation was measured by urine testing. In the primary analysis of composite cognitive change over 4 years, individuals in the intervention groups had better cognitive outcomes than the control group. Secondary analysis of the numbers developing mild cognitive impairment was not significantly different between groups, and no participants developed dementia, suggesting that this intervention might have an effect on cognitive ageing, but not the dementia syndrome. Participants who withdrew had worse baseline cognition and more ApoE ε4 genotypes than completers, thus being more likely to be cognitively impaired at follow-up, and the control group had the most dropouts, which suggests that the intervention's benefits could have been underestimated.

Cognitive interventions

Initial evidence that engaging in cognitively stimulating activities might benefit cognition and reduce dementia risk came from epidemiological studies. One study[109] assessed the frequency of participation in seven common activities that are mentally stimulating at baseline and followed up 801 older adults without dementia for 4·5 years. A 1-point increase in the cognitive activity score was associated with a 33% reduction in the risk of Alzheimer's disease. A meta-analysis[58] of 29 279 individuals from 22 longitudinal cohort studies, with a median follow-up of 7·1 years, calculated a summary OR of incident dementia of 0·54 (95% CI 0·49–0·59) for high versus low brain reserve, including engagement in mentally stimulating activities, after controlling for other dementia predictors such as age, sex, general health, cerebrovascular disease, education, occupation, and baseline cognition. This outcome suggests that cognitive reserve is not a static property, but might be amenable to manipulation by cognitive interventions in later life.

There is some evidence of generalised cognitive improvements from either single domain or reasoning training in healthy older people, but not of prevention of cognitive decline or dementia. When 2802 healthy older people (65–94 years old) were randomised to receive ten group sessions focusing on attention, memory, or reasoning, improvements occurred within the trained domains,[157] with functional benefits at 10-year follow-up.[158] An online study compared reasoning training with general cognitive training and an active control in 6742 participants, of whom 2912 were older than 60 years. Although the dropout over the 6-month study was substantial, reasoning training showed generalised benefits in both trained and untrained measures of executive function (effect size [d]=0·42), on activities of daily living (d=0·15), and verbal learning (d=0·18).[159] The combination of cognitive training with other lifestyle interventions in the FINGER trial[160] and MAPT trial[161] is described in the section about studies using combination strategies. The commercial brain training tools that are widely promoted often have claims that they can prevent cognitive decline, but these are not yet substantiated by evidence.

Exercise and physical activity interventions

RCTs of exercise interventions for cognition in healthy older adults have been less successful than might have been expected from the longitudinal cohort studies. Some meta-analyses[79] have either reported no overall evidence that exercise improves cognition in healthy older adults, or that benefits are limited to specific cognitive domains. One meta-analysis[162] reviewed 25 RCTs of aerobic exercise, resistance training, or tai chi. 15 of these studies reported improvements for exercise versus controls on measures of executive function, memory, or composite measures of cognition. However, the only significant results from the meta-analysis were for an improvement in reasoning for resistance training versus stretching or toning controls (two studies with 135 participants; mean difference 3·16, 95% CI 1·07 to 5·24) and an improvement with tai chi versus no exercise control (two studies with a total of 156 participants) in processing speed (–11·05, –15·90 to –6·21) and attention (–1·19, –1·83 to –0·55). Conversely, a meta-analysis[163] of 29 studies of aerobic exercise in healthy adults, including three studies of participants with mild cognitive impairment, found overall exercise-related improvements in memory of people with mild cognitive impairment (Hedges' g 0·237; p=0·05). An RCT[164] of 100 adults with mild cognitive impairment, randomised to resistance training or cognitive training, reported that resistance training significantly improved the primary cognitive outcome, Alzheimer's Disease Assessment Scale-cognition (ADAS-cog; effect size –0·33), at 6 months and executive function at 18 months. The potential mechanisms for physical exercise to improve cognition or prevent dementia are indirect effects on other modifiable risk factors, such as obesity, insulin resistance, hypertension, hypercholesterolaemia, and general cardiovascular fitness, and via direct neurological effects, such as increased neurogenesis, cerebral blood flow, and BDNF concentrations.[78,165,166] Some inter-individual variability

in response, which contributes to the conflicting RCT findings, might be related to individual differences in exercise-related neuroplasticity.[167] Alternatively, protective effects in long-term studies accumulate over years rather than over a short time, and people who exercise might be different in several ways to people who do not. One RCT[168] of walking for 40 min three times a week for a year (*vs* stretching and conditioning) showed exercise training increased hippocampal size and improved memory in healthy adults aged 55–80 years. Overall, scientific evidence that physical activity reduces dementia risk is not sufficient.[169]

Social engagement

Longitudinal studies suggest that social interaction might prevent or delay dementia, but there is an absence of evidence from intervention studies that social activity prevents cognitive decline or dementia. People who live alone, have never married, are divorced, or widowed have an increased risk of all-cause dementia.[170] Results of a meta-analysis[62] of social activity found that incident dementia risk was elevated for people with little social activity participation (RR 1·41, 95% CI 1·13–1·75) and infrequent social contact (RR 1·57, 95% CI 1·32–1·85), but not for people who had low satisfaction with social contact (1·25, 0·96–1·62). The relatively short follow-up period in some studies precludes strong conclusions about the direction of causation.

Compared with people without dementia, people with dementia might be less motivated to engage socially or find more difficulties in organising activities, be embarrassed by their difficulties, or worried they might be unable to manage previous activities or might get lost. Social norms and low tolerance for cognitive decline of others can result in increasing isolation of many people with dementia. At early stages of cognitive decline, people report feeling lonelier than people with intact cognition.[171] While many family members might increase contact as the person with dementia requires more support, visits by family members tend to decrease as the dementia becomes more severe, because relatives might find it distressing or are unsure that their relative gains from their visits. People with more severe dementia might move homes for support at a further distance from their previous social support network.

Little is known about the effect of social activity interventions on cognition. One pilot RCT[172] for older adults, with social activity as an intervention component, found adults with impaired executive function showed significant improvements. Another pilot RCT[173] compared cognitive training, a health promotion course, and a book club as interventions for people with subjective memory problems but not dementia, and found no between-group difference.

Studies using combination strategies to prevent dementia

FINGER study

The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)[160,174] provided four intensive lifestyle-based strategies (diet, exercise, cognitive training, and vascular management) to more than 600 people who were older than 60 years and at high risk of dementia according to their age, sex, education, systolic blood pressure, total cholesterol, and physical activity.[175] The study compared cognition in the intervention group versus controls who received general health advice. This highly intensive intervention consisted of about 200 meetings (300 h) with health professionals and trainers over 2 years.

Participants in the intervention group showed a mean improvement versus the control group in a composite measure of cognition (d=0·13) on executive function and processing speed, but not memory. Despite the intervention's intensity, the effect was small, although this outcome shows potential for lifestyle modification to improve cognitive function in people at risk of dementia. Pragmatic multimodal models for dementia prevention should be tested in other populations and settings.[160] Earlier intervention and longer follow-up will determine whether these approaches reduce dementia risk.

PreDIVA study

The preDIVA study[176] in the Netherlands also aimed to reduce vascular risk factors to prevent dementia in a 6-year multi-domain, nurse-administered, open-label, cluster RCT with a total of 3526 participants aged 70–78 years from general practice. Smoking habits, diet, physical activity, weight, and blood pressure were monitored and individually tailored lifestyle advice according to protocol was provided, supported by motivational interviews. Blood glucose and lipid concentrations were assessed every 2 years in both groups, and when indicated otherwise. If indicated, medication was given for hypertension, diabetes, or dyslipidaemia. Dementia incidence did not differ significantly between the intervention and usual care group over 6·7 years (HR 0·92, 95% CI 0·71–1·19).[148] The authors thought the negative findings might have been related to the relative absence of cardiovascular risk factors in the study population, decreasing the possibility of risk reduction. An accompanying editorial noted that 10% more of the participants in the intervention group than in the control group who were not using antihypertensives at baseline were subsequently treated, and in those participants, the risk of dementia was reduced (22 [4%] of 512 intervention developed dementia *vs* 35 [7%] of 471 control; HR 0·54, 95% CI 0·32–0·92).[177] These outcomes illustrate the importance of targeted interventions and of a clear model linking risk factors to dementia.

MAPT trial

The MAPT RCT[161] with 1525 participants aged 70 years or older tested omega 3 polyunsaturated fatty acids and a multidomain intervention (43 group sessions integrating physical activity, cognitive training, and nutritional advice and three preventive sessions), either alone or in combination, compared with placebo medication. The primary outcome of combined cognitive scores did not differ between each intervention and the control group over 3 years. Most were highly educated and were thought to live a healthy lifestyle. Post-hoc exploratory analyses in which both groups receiving the multidomain intervention were pooled showed a beneficial effect on outcomes compared with control and particularly in participants with higher cardiovascular risk or imaging evidence of brain pathology. Other multidomain studies are ongoing, such as the HATICE trial, which uses a less costly e-health intervention, but the results are not yet available.

Dementia intervention: what, when, for how long, and for whom?

Such programmes are not yet ready for implementation as large-scale public health interventions because of the desire for conclusive RCTs to confirm efficacy, the cost and intensity of interventions needed to change behaviour, and doubts as to the underlying cause of dementia. However, numerous examples exist in which public health interventions have reduced disease incidence before the disease process has been understood—eg, hand-washing reducing puerperal fever, clean water eliminating cholera, and condoms reducing HIV transmission. Risk-reduction strategies implemented in many countries in cardiovascular and metabolic health, cigarette smoking, depression, social and physical activity, and hearing might account for the decreased incidence of dementia in more recent cohorts.

Although dementia is diagnosed in later life, pathology develops years earlier.[178] Increasing evidence from epidemiological, clinical, imaging, and biomarker studies[179,180] suggests that dementia, especially Alzheimer's disease, could be a clinically silent disorder starting in mid-life, whose terminal phase is characterised by dementia. A fundamental question is, therefore, when in the lifespan should dementia prevention programmes be implemented and for how long? Available evidence from studies[177] seems to show that providing modestly enhanced care to non-targeted patients already receiving medical care does not reduce dementia.

Key points and recommendations

Prevention or delay of dementia onset is a public health priority with potential to reduce not only the disability of individuals but also the associated societal and economic burden. In many countries dementia is already being delayed for years. Thus, while results of trials, which by their nature are relatively short and include a smaller number of people, have been disappointing, results from risk factor modification for whole populations or high-risk populations have been more promising.

Dementia might constitute the terminal stage of disease processes beginning decades earlier, and lifestyle changes targeting these processes might sometimes prevent or delay dementia onset. There is good evidence that treatment of hypertension reduces dementia incidence and preliminary evidence that modification of several risk factors has a beneficial effect on cognition. The interventions most likely to be beneficial (increasing education in early life, increasing physical activity and social engagement, reducing smoking, treating hypertension, diabetes, and hearing impairment) are safe and confer other health benefits.

Early detection of preclinical Alzheimer's disease

Preclinical Alzheimer's disease occurs when there are early Alzheimer's pathogenic changes but no memory impairment.[181] These pathogenic changes in Alzheimer's disease include extracellular deposition of amyloid β (Aβ protein) from cleaved amyloid precursor protein, which is the main component of plaques, and intracellular accumulation of tau protein, which is the main constituent of tangles.

The main purpose of preclinical detection of Alzheimer's disease is to identify individuals at high risk of progression to dementia due to Alzheimer's disease, so that they can have the opportunity to participate in treatment trials to delay or prevent cognitive decline. These individuals can also be informed and make changes in their lifestyle, which might delay onset of dementia. Some people might also find prognostic information to be useful, because it allows them to make plans and lifestyle changes for a possible future dementia.

Many or even most of those individuals found to be at risk of dementia will die in good cognitive health, at a merely theoretical risk of developing dementia, and thus it is important that risk information—eg, amyloid scan results—is presented cautiously because it has the potential to cause harm without compensatory benefit. The potential of early detection will be realised if effective Alzheimer's disease-modifying treatments for these stages are developed, in which case detection would be essential to determine to whom such treatments should be offered and services would have to change and expand to accommodate this. The ethical implications of pre-dementia biomarker testing are profound, but have not been determined in any detail.[182]

Preclinical Alzheimer's disease is also known as asymptomatic at-risk state for Alzheimer's disease, because the predictive value of this pathology is uncertain. Those with rare familial Alzheimer's disease are sometimes termed as having presymptomatic Alzheimer's disease and are expected to develop Alzheimer's disease.[183] Alzheimer's disease has an insidious onset and most people pass through a preclinical asymptomatic phase

when cerebral Aβ42 and other abnormal proteins are accumulating in the brain, followed by mild cognitive impairment, and ultimately progress to dementia.[184] Abnormal biomarkers are common, with 10–30% of cognitively healthy older people, depending on age, having substantial brain amyloid deposits on PET scanning; these increase with age and are more likely to be high in individuals with the ApoE ε4 allele.[185] Biomarker studies have been in highly selected populations and we do not know their predictive value in more general populations of older people. Most cognitively healthy older people, with substantial amyloid depositions detected in a scan, do not decline clinically over the following 18–36 months.[186] However, amyloid positivity on scan was the most accurate predictor of progression to dementia from mild cognitive impairment in one study,[187] with 59% progressing to dementia within 3 years. Similarly, 3-year conversion from mild cognitive impairment to Alzheimer's disease was predicted by low baseline cerebrospinal fluid amyloid-β concentrations (equivalent to high brain amyloid-β concentrations).[188] A small, 3-year, longitudinal study[189] of 32 cognitively healthy, amyloid-positive older adults and 73 amyloid-negative older adults found eight (25%) amyloid-positive individuals had developed mild cognitive impairment or dementia due to Alzheimer's disease over 3 years, while only one individual with a negative amyloid scan developed mild cognitive impairment. Overall, although amyloid deposition is a risk for the development of Alzheimer's disease,[190] its precise predictive value is still unknown.[185]

Numerous pharmacological compounds have been developed over the past few decades to combat dementia.[3,191] The results of trials have all been negative and consideration is now being given to drug development for earlier disease stages, so-called preclinical Alzheimer's disease, characterised by biomarkers or the pathology of Alzheimer's disease without signs or symptoms. For example, the European Prevention of Alzheimer's Disease programme, a Horizon 2020/Innovative Medicines Initiative in collaboration with the European Federation of Pharmaceutical Industries and Associations was designed to address this question by developing a platform able to deliver large preclinical proof-of-concept trials for both existing and newly developed compounds.[192] A central problem, however, for both prevention and disease-modifying interventions is outcome measures. If treatment is to be given to cognitively and functionally intact individuals in the decades before dementia onset, then the outcome measures could be biomarkers or time to dementia diagnosis. Time to diagnosis would need large populations and many years of follow-up. Any assessment should include side-effects because these might limit long-term treatment. Further information on cognitive function, imaging, and biomarkers is needed to establish what should be measured and to determine treatment effect size.

Cohorts of healthy older people and individuals at risk, such as the PREVENT study,[193] Alzheimer's Disease Neuroimaging Initiative (ADNI)[194] and Dominantly-Inherited Alzheimer's Network (DIAN),[195] are being assembled for these purposes. Several clinical trials are aimed at prevention in people who are cognitively well but at higher risk of Alzheimer's disease because of genetics or biomarkers.[196]

Key points and recommendations

Depending on their age, 10–30% of cognitively healthy older individuals have abnormal brain amyloid or Aβ and tau concentrations in cerebrospinal fluid. Only a few of these adults will progress to mild cognitive impairment or dementia due to Alzheimer's disease over 3 years. There are potential ethical concerns about identification of a population at risk of dementia, many of whom might not develop dementia in their lifetime. Therefore, at present the main purpose of biomarkers is to identify and characterise higher risk individuals to take part in trials.

Mild cognitive impairment

Mild cognitive impairment is also occasionally called cognitive impairment no dementia.[197,198] It has been defined as an objective cognitive impairment, reported by a patient or relative, in a person with essentially normal functional activities, who does not have dementia.[199] It can broadly be considered as an intermediate state between healthy ageing and early dementia, which sometimes reverts to healthy cognition. Mild cognitive impairment is probably best conceptualised as a probability state, which can be used to delineate a population at higher risk of dementia, with cognitive decline not meeting diagnostic criteria for dementia. People with mild cognitive impairment are clinically and neuropathologically heterogeneous.[197] It affects many more people than dementia does, and estimates of prevalence vary from 4% to 19% of people aged 65 years or older, depending on the definition used and how it is interpreted.[198,200,201] Functional decline secondary to cognitive impairment has previously been the entry point of people with neurodegenerative disorders into the health and social care system, but many people now present with mild cognitive impairment. Around 39% of those diagnosed with mild cognitive impairment in specialist settings and 22% in population studies develop dementia over the subsequent 3 to 10 years,[202] compared with 3% of the population without mild cognitive impairment at the same age.[203] Mild cognitive impairment can be divided into amnestic mild cognitive impairment, defined as individuals with a particular impairment of episodic memory[204] often thought to be likely to develop into Alzheimer's disease, and non-amnestic mild cognitive impairment.

Prodromal Alzheimer's disease

People with amnestic mild cognitive impairment and a positive cerebrospinal fluid Aβ and tau biomarker test, or

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positive Aβ PET scan, have been termed as having prodromal Alzheimer's disease[181,183] or mild cognitive impairment due to Alzheimer's disease,[205] an advance over the heterogeneous term mild cognitive impairment. This subgroup is more likely to progress to Alzheimer's disease.[199] In other subgroups, mild cognitive impairment might be caused by vascular pathology or herald other types of dementia.

Development of future mild cognitive impairment interventions should recognise this heterogeneity or direct specific interventions at homogeneous subgroups—eg, those likely to have prodromal Alzheimer's disease. However, if disorders such as Alzheimer's disease can be diagnosed in the preclinical or prodromal period then treatment would ideally be given then.

Risk factors for progression from mild cognitive impairment to dementia

As summarised in a systematic review,[206] evidence from prospective studies indicates that diabetes, prediabetes, metabolic syndrome, lower serum folate concentrations, and the presence of neuropsychiatric symptoms increase the risk of progression from mild cognitive impairment to dementia, but less education does not. A Mediterranean diet decreases the risk of conversion from amnestic mild cognitive impairment to Alzheimer's disease compared with other diets.[206] A slightly different view emerged from a large, but unreplicated, community cohort study in which people were retrospectively classified as having mild cognitive impairment.[207] It suggested that risk factors for progression to dementia differed between men and women; interventions should focus principally on risk of stroke in men, and depressive symptomatology and reducing anticholinergic medication in women.[208]

The concept of mild behavioural impairment[209] is proposed to describe people at an increased risk of dementia due to the presence of late-life acquired neuropsychiatric symptoms, such as apathy, affective symptoms, impulse control problems, or social inappropriateness, which are viewed in this context as being prodromal dementia symptoms. A third to three-quarters of people with mild cognitive impairment have neuropsychiatric symptoms, most commonly depression, anxiety, apathy, and irritability.[210] Some of the symptoms might be a reaction to the experience of declining abilities. Neuropsychiatric symptoms might be indicators of people who are at higher risk of dementia because they predict conversion to dementia.[206] However, neuropsychiatric symptoms might be implicated in the cause of dementia, through neuroendocrine axis activation, or interact synergistically with a biological factor, such as genetic predisposition. Either of these putative associations suggests treatment might have the potential to delay dementia, but whether they are truly potentially modifiable risk factors rather than identifying individuals who are further along the path to a dementia syndrome is unclear.

PAF for modifiable risk factors

To highlight the potential for slowing progression of mild cognitive impairment to dementia, we have calculated the PAF using the formula in panel 1, for those modifiable risk factors shown in systematic reviews to affect the rate of progression. These are having diabetes, the presence of neuropsychiatric symptoms, and not adhering to a Mediterranean-style diet. The individual risk factor PAFs represent the percentage of people who would theoretically not progress to dementia from mild cognitive impairment if that risk factor could be completely eliminated. The direction of causality of neuropsychiatric symptoms discussed previously, however, remains.

We calculated communality for these risk factors using data from the HSE on people older than 65 years using the methods described earlier. In the absence of data on Mediterranean diet, we used obesity as a proxy measure for not following a Mediterranean diet and we used depression for neuropsychiatric symptoms. We have also conservatively assumed that the prevalence of these factors in people aged 65 years or older is the same as in the population with mild cognitive impairment. The principal component extracted with this method explained 45% of the total variance between the three risk factors. Using these methods, we calculated that 21·7% of dementia progression from mild cognitive impairment is potentially preventable by eliminating poor diet, diabetes, and neuropsychiatric symptoms (assuming these are risk factors for, not symptoms of, or the result of, dementia). Table 2 shows data on RR, prevalence and communalities, and PAF for progression to dementia from mild cognitive impairment. These risks are ones for which we have data, but other factors, including hearing and social interaction, might be important in mild cognitive impairment; however, evidence is scarce at present.

Interventions to reduce or delay conversion

People with mild cognitive impairment have almost all been diagnosed after requesting a memory assessment and are seeking to reduce their risk of dementia, so have relatively high motivation to change. NICE recommends follow-up, so if dementia is diagnosed, planning can begin at an early stage, but with no specific treatments.[211] An NIH report[174] recommended trials of interventions for dementia prevention encompassing multiple risk factors and targeting high-risk individuals.

Multimodal interventions are likely to be needed to prevent progression to dementia in mild cognitive impairment. These interventions might involve approaches to decrease neuropathological damage (treating vascular risk factors, diabetes, diet, exercise), combined with those that maximise function (cognitive and social stimulation, treatment of neuropsychiatric symptoms). Understanding of which components are useful and how to streamline and make these interventions cost-effective will be challenging.

Cognitive interventions

One systematic review[212] identified six studies of cognitive training in participants with mild cognitive impairment. Four studies reported improvements on objective memory outcomes immediately following training; however, only one out of three studies that included general cognitive outcomes reported benefits. Similarly, global cognition did not improve with cognitive training in three small trials;[213] in one trial it was a primary outcome, and findings on other secondary outcomes were not consistently significant.

Exercise interventions

There is mixed evidence that exercise can improve cognitive outcomes in mild cognitive impairment. In a review[214] of 14 studies, 92% of cognitive outcomes reported were not significant, and only 42% of effect sizes were classified as potentially clinically relevant (effect size >0·20). A systematic review[213] found memory did not improve with exercise. In one very high-quality study,[215] a 1-year moderate aerobic exercise intervention had no effect on cognitive outcomes compared with relaxation, balance, and flexibility exercise active control, although post-hoc analysis showed some effect in individual domains in women and a different effect in men. The results of less high-quality studies[213] were mixed but did not suggest generalised cognitive improvement compared with control. Overall, no conclusive evidence for exercise in mild cognitive impairment exists.

Medication

One systematic review[213] found no evidence that any drug interventions delay conversion to dementia in a general population with mild cognitive impairment. However, phase 2 studies[216] of aducanumab, a monoclonal antibody that selectively targets aggregated amyloid β, found that it reduced amyloid protein in the brain of patients with prodromal or mild Alzheimer's disease in a dose-dependent manner and slowed clinical decline. Phase 3 studies are now taking place.

Cholinesterase inhibitors

The incidence of Alzheimer's disease did not reduce in four high-quality trials[213] in which this was the primary outcome—two assessed galantamine, one donepezil, and one rivastigmine. Donepezil improved global cognition in one high-quality trial in which it was a primary outcome measure, and a second in which it was a secondary outcome, but it did not improve in three other large, high-quality trials[213] of cholinesterase inhibitors. Post-hoc analyses of RCT data[217,218] indicate some benefit in specific populations characterised by the presence of biomarkers. Cerebral atrophy was less in people taking galantamine who had the ApoE ε4 allele than in those with other ApoE variants,[217] and cognitive response to donepezil was higher in butyrylcholinesterase-K carriers than those with other genotype profiles.[218] However, these post-hoc analyses should be treated with caution as no study has found a subtype difference when that was the primary hypothesis. Additionally, no studies have reported on functional effects or rate of progression to dementia.

	Relative risk for dementia (95% CI)	Prevalence	Communality	PAF	Weighted PAF*
Diabetes	1·65 (1·12–2·43)	6·4%	7·6%	4·0%	1·5%
Neuropsychiatric symptoms	2·52 (1·18–5·37)	29·0%	61·1%	30·6%	11·5%
Diet	1·92 (1·10–3·33)	32·5%	66·7%	23·0%	8·7%

Data are relative risk (95% CI) or %. Total weighted PAF adjusted for communality=21·7%. We used population prevalence of obesity as a proxy for diet and depression as a proxy for neuropsychiatric symptoms. PAF=population attributable fraction. *Weighted PAF is the relative contribution of each risk factor to the overall PAF when adjusted for communality.

Table 2: **Potentially modifiable risk factors for progression to dementia from mild cognitive impairment**

NSAIDs

Trials[213,219] have not shown NSAIDs to be effective in mild cognitive impairment. One high-quality study[220] found that rofecoxib, a selective COX-2 inhibitor increased incident cases of Alzheimer's disease. A smaller study[221] found triflusal (*vs* placebo) had no significant effect on cognition as a primary outcome measure, although it was associated with a reduced risk of the secondary outcome, conversion to Alzheimer's disease. Because any beneficial anti-inflammatory effect might be long-term, people with mild cognitive impairment might not be the appropriate treatment population.[219]

Statins

We could not find any interventional trials of statins. However, one longitudinal observational study[222] found statins did not affect cognitive decline in people with mild cognitive impairment.

Vitamin B and E and folic acid

Vitamin E did not reduce incident dementia or have any effect on a range of secondary outcomes in one high-quality study.[223] Two placebo-controlled trials[215,224] found that B vitamins (B12 and B6 plus folate) had no significant effect on immediate memory over 6 months[215] or global cognition.[224]

Ginkgo biloba

On primary outcomes, 240 mg per day ginkgo biloba did not reduce the incidence of dementia, Alzheimer's disease, or cognitive decline over 6 years in high-quality trials.[225–227]

Key points and recommendations

Up to a fifth of people aged older than 65 years have mild cognitive impairment and diagnosis in developed countries is rising. Nearly half of people with amnestic mild cognitive impairment, also known as mild cognitive impairment due to Alzheimer's disease, or prodromal

Alzheimer's disease develop dementia in 3 years. This time is a potential intervention window to delay its onset and reduce incidence and prevalence, although no effective interventions are available. Results of longitudinal studies suggest that addressing diabetes might help reduce conversion from mild cognitive impairment to dementia. Multimodal and multicomponent interventions targeting heterogeneous causes of progression to dementia in people at risk of dementia (not necessarily with mild cognitive impairment) might reduce risk of cognitive decline, but have not been trialled in mild cognitive impairment specifically. Any intervention developed to reduce the progression to dementia from mild cognitive impairment will need to be practical and replicable so it can be scaled up. Cholinesterase inhibitors are not effective in mild cognitive impairment and should not be used.

Diagnosis of dementia

Increasing the diagnosis

Public health strategies and plans to increase the diagnosis of dementia are in place in many countries, including Bulgaria, Denmark, France, Israel, Malta, the Netherlands, Norway, Switzerland, and the UK. The English strategy was instituted after variations in diagnosis across regions of England were highlighted.[228] The strategy consists of three parts. First, a public and practitioner information campaign, including television and newspaper adverts to counter the argument that a diagnosis of dementia was not worthwhile, which was rooted in the mistaken beliefs that dementia is inevitable as we age and that no treatment or support is available. The second part was to provide practitioners with the confidence and tools to make a diagnosis and increase the number of diagnostic memory clinics.[229] Finally, diagnosis rates were monitored and targeted at the primary care level; a so-called quantified ambition to reach a two-thirds diagnosis rate. Since this strategy started, diagnosis rates in the UK have increased from an initial base of less than 40% in 2009 to 50% in March, 2014, and to 67% in November, 2015, with a concomitant increase in the prescription of anti-dementia drugs.[230]

Screening or case finding for dementia

Screening all older people for dementia is not recommended because benefits are unclear.[231] However, case finding, such as searching systematically for people at high risk, might be appropriate considering that a disproportionate number of people with dementia are admitted to hospital as an emergency for physical ill-health before dementia is diagnosed, so that possibly 40% of older people in hospital have dementia.[232] These hospital admissions typically lead to poorer outcomes and longer admissions than for people with similar physical problems but without dementia. This outcome is possibly because people might be treated without recognition that they lack capacity to consent to treatment or be discharged home without additional support for complex medication regimens and without participating in or understanding the discharge plan.[232,233] Clinicians should therefore consider case finding in older people admitted to hospital to improve their management and outcomes.

Timely detection of dementia

A timely diagnosis, meaning communicating a diagnosis at a time when the person with dementia and their carers will benefit from interventions and support, is a prerequisite for good dementia care. Many people with dementia are never given the diagnosis,[234] only 20–50% of those with dementia have a diagnosis recorded in primary care notes, and this number is lower in lower-income countries than high-income countries.[235] Many receive a diagnosis when it is too late for them to make decisions about their own and their family's future or to benefit from interventions. Although some people do not wish to know the diagnosis, people with dementia and their families find diagnostic uncertainty anxiety-provoking and are often relieved by diagnostic certainty.[236–239] Yet diagnosis is often delayed for several years, resulting in increased anxiety and carer burden in the interim.[237] Timely diagnosis allows people to plan for the future, decide to have experiences they would otherwise delay, benefit from treatments, and access social support and voluntary care. These interventions can reduce or delay the progression of cognitive and neuropsychiatric symptoms[240] and decrease crises by, for example, supporting people to pay bills and take prescribed medication and delay care home entry. Additionally, knowing there is a diagnosis helps families to understand their relative's behaviour and allows them to access evidence-based therapies (discussed in more detail in the treatment section), which improve coping skills, reducing their high risk of developing affective disorders.[241–243] There are few adverse effects of diagnosis and most people say they would want to know if they had developed dementia.[244]

Timely diagnosis is often difficult for a variety of reasons,[237] such as people considering the symptoms are an inevitable part of ageing, people with memory problems being reluctant to consult their general practitioner about their memory or denying problems when seen,[238] possibly related to fear of the diagnosis and concerns about stigma,[10] and lack of insight. General practitioners might be reluctant or unsure how to make this diagnosis[245] and might not include cognitive evaluation for older adults as part of routine patient management. The short time reported in a cohort between initial recorded diagnosis and death suggests diagnosis is frequently made late and at a time of crisis.[246] Later diagnosis is a particular problem for those from minority ethnic groups, where stigma and a lack of understanding that dementia is an illness can be especially problematic[247] and where there might be poor access to or no acceptance of medical care.[248]

A systematic review[249] of trials to increase the diagnosis of dementia found no clearly successful intervention. Although educating general practitioners increased their ability to diagnose dementia, this approach did not increase diagnoses in practice, and local campaigns were ineffective on their own. A case-finding approach in primary care, in which patients and families are asked about concerns regarding their memory and intent to act on them, might delineate a group who are more likely to have dementia.[250] An intervention to increase timely diagnosis by empowering patients led to an increase in patients presenting to the general practitioner but no change in the rate of referral to dementia diagnostic services.[251]

Key points and recommendations

Diagnosis of dementia is a vehicle to improve care but is often delayed. While screening for dementia is not recommended, clinicians should consider case finding in high-risk groups. Successful strategies to increase diagnosis to date have been at the level of public health policy and include the public and health-care practitioners, because strategies aimed just at practitioners have not been effective.

Making the diagnosis

National guidelines in many countries recommend that people with suspected dementia are referred to a specialist memory clinic or individual specialist doctor.[234,252] Guidelines recommend a systematic approach, including history taking from the patient and informant, review of medication, structured cognitive assessment, blood tests, and (in some countries) structural imaging. The blood tests are to detect comorbid illness, whose treatment might improve cognition, and the very rare reversible dementias, such as those caused by hypothyroidism or infection—eg, syphilis or HIV.[253]

Imaging can be either CT or MRI and its purpose is to exclude rare treatable causes and to elucidate the cause, allowing pharmacological and psychosocial treatments to be tailored to the specific dementia subtype.

Cognitive testing

There are many short validated cognitive tests, with a systematic review[254] identifying 22 tests; professionals have to consider which to use and interpret the results, taking into account the setting and the individual patient's premorbid education, language and literacy skills, and any current motor, hearing and visual impairment. The most commonly used test is the Mini-Mental State Examination (MMSE),[255] but it lacks sensitivity in patients with high premorbid educational attainment and suspected early impairment, and intellectual property rights limit its broad use internationally.[256] The short form of the Addenbrooke's Cognitive Examination (ACE-R or its equivalent ACE-III), available in many languages, is more sensitive.[254,257] The shorter forms of the ACE and Montreal Cognitive Assessment are also effective in detecting dementia with Parkinson's disease or dementia with Lewy bodies.[258,259] The Rowland Universal Dementia Assessment Scale[260] is useful when literacy or education is low. Computerised assessments are likely to be used more often in the future.

Neuroimaging

Most national guidelines suggest that structural neuroimaging is part of routine clinical assessment of dementia, although in many areas access to neuroimaging is not feasible, and some countries—eg, Canada[261]—do not recommend its routine use. CT scans are cheaper, quicker (helpful if patients have trouble lying flat or remaining still), and can be used in those with pacemakers.[262] However, MRI is the preferred imaging method for early diagnosis because of its greater sensitivity and ability to differentiate dementia subtypes, especially for those with vascular lesions.

Structural imaging: regional and progressive brain atrophy

The pattern of regional brain atrophy helps to distinguish the common neurodegenerative causes of dementia—eg, frontotemporal dementia from Alzheimer's disease.[263] Disproportionate hippocampal atrophy suggests Alzheimer's disease rather than vascular dementia or dementia with Lewy bodies, but there is overlap.[264] Rates of brain atrophy on serial MRI are increased (3–4 times) in Alzheimer's disease relative to age-matched control individuals.[265,266] A repeat scan after a year might clarify the diagnosis, distinguishing changes from natural morphological variation.

Medial temporal lobe atrophy on MRI also differentiates Alzheimer's disease from healthy ageing; as a result, these findings have been incorporated into new research diagnostic criteria for Alzheimer's disease, prodromal Alzheimer's disease, and mild cognitive impairment due to Alzheimer's disease.[181] MRI also differentiates Alzheimer's disease from vascular dementia or dementia with Lewy bodies with more than 80% sensitivity and specificity and is predictive of progression from mild cognitive impairment to Alzheimer's disease with almost the same level of accuracy.[267,268]

Vascular abnormalities

Evidence of clinically significant vascular burden on imaging is a prerequisite for a diagnosis of vascular dementia. Clinically significant vascular burden is defined as either many lacunae, strategic infarcts, a substantial burden (>25%) of white matter lesions, or a combination of these.[269] The degree of vascular pathology has to credibly account for the clinical cognitive impairment[269] because some degree of vascular change is typical in older populations without dementia and therefore is also present in other forms of dementia.[270] Because Alzheimer's disease and cerebrovascular disease commonly coexist, it is often difficult to ascribe accurately the relative contributions of each to an individual's cognitive decline. However, clinicians should ensure that

substantial vascular changes are present if the dementia is to be attributed entirely to vascular pathology.

Functional and molecular imaging

PET imaging using fluorodeoxyglucose (^{18}F) as a radiotracer (FDG-PET) permits in-vivo assessment of brain metabolism and supports assessment of frontotemporal dementia, particularly when clinical assessment is uncertain and there is little change on structural imaging. It shows focal frontal or temporal hypometabolism, or both, which is characterised by temporoparietal and posterior cingulate hypometabolism.[181,271] Therefore, in the USA, the use of FDG-PET for differentiating frontotemporal dementia from Alzheimer's disease is reimbursable by Medicare to patients who meet diagnostic criteria for both Alzheimer's disease and frontotemporal dementia.[272] FDG-PET has greater accuracy than imaging of cerebral perfusion with hexamethylpropyleneamine oxime single photon emission CT.[273,274]

Functional imaging is helpful clinically in distinguishing dementia with Lewy bodies from other causes of dementia because dopamine depletion can be detected by dopamine transporter (DAT) scans.[275,276] In moderate dementia, when dementia with Lewy bodies is suspected, a normal DAT scan reliably excludes dementia with Lewy bodies, although at early stages there is a 20% false-negative rate.[273]

Molecular imaging of amyloid or tau is a major research advance and is a promising method for diagnosis of Alzheimer's disease with several amyloid PET tracers licensed for clinical use.[277] Published so-called appropriate use criteria suggest amyloid PET imaging is most appropriate when diagnostic uncertainty exists about possible Alzheimer's disease after expert evaluation[278] and is most helpful for young-onset or unexplained progressive dementias. Cerebral amyloid plaque accumulation in Alzheimer's disease is thought to precede clinical symptoms by more than a decade, which gives amyloid PET high sensitivity but relatively low specificity in older individuals. Although widely used in research, clinical use of amyloid imaging is limited by its cost in the absence of a disease-modifying treatment and uncertainties about the risk of false-positive Alzheimer's disease diagnoses. Tau imaging is currently only a research tool.[278,279] MRI incorporating diffusion imaging has great sensitivity and specificity for prion disease, which is a rare cause of dementia; typical changes are virtually pathognomonic.[263]

Cerebrospinal fluid and blood biomarkers

Routine testing of cerebrospinal fluid or blood for biomarkers is not currently recommended clinically by any national guidelines, although the American Academy of Neurology recommends cerebrospinal fluid testing for investigation of patients younger than 65 years with dementia[280] and the European Federation of Neurological Societies recommends its use in atypical clinical presentations of Alzheimer's disease.[281] However, there is interest in the future value of such tests as they have the potential to elucidate the dementia subtype at an earlier stage, because cerebrospinal fluid changes supportive of a diagnosis of Alzheimer's disease can be identified up to 15 years before the clinical presentation of dementia.[195,282] Current practice varies globally, from routine use in the Netherlands and Sweden, where 40% of people with newly diagnosed dementia had a lumbar puncture,[283] to infrequent use in North America, where biomarker analysis is reserved for research settings with strict protocols,[284] reflecting uncertainty about the added value of these investigations, because heightened diagnostic accuracy does not translate to tailored drug treatments.

However, there is little doubt that analysis of biomarkers improves diagnostic accuracy of Alzheimer's disease; such biomarkers might in future be markers of disease progression or outcome targets for clinical trials. Many potential biomarkers represent neurodegeneration, amyloid precursor protein metabolism, tangle pathology, function of blood–brain barrier, or glial activation due to inflammation.[285] However, results tend to be from highly selected populations, so that even a meta-analysis of many studies might produce overly optimistic performance results. There can also be reproducibility and accuracy difficulties in the measurement of amyloid (but not tau) biomarkers. A comprehensive meta-analysis,[286] of 15 potential biomarkers across 231 studies, found that elevated concentrations of cerebrospinal fluid T-tau (average ratio for Alzheimer's disease *vs* control was 2·54, 95% CI 2·44–2·64), P-tau (1·88, 1·79–1·97), and low cerebrospinal fluid Aβ42 (0·56, 0·55–0·58) differentiated between people with Alzheimer's disease and healthy controls. A similar pattern distinguished between people with mild cognitive impairment who go on to develop Alzheimer's disease and those who do not (average ratio 1·76 for T-tau, 1·72 for P-tau, and 0·67 for cerebrospinal fluid Aβ42). Other biomarkers studied had little value, except for cerebrospinal fluid neurofilament light protein (2·35, 95% CI 1·90–2·91) and plasma T-tau (1·95, 95% CI 1·12–3·38).[286]

No specific fluid biomarkers exist or are clinically recommended for dementia with Lewy bodies or the frontotemporal dementias in general, but the above approaches might differentiate these forms of dementia from Alzheimer's disease.[285,287] Specific genetic variants of frontotemporal dementia can be identified with plasma and cerebrospinal fluid biomarker testing, such as by reduced cerebrospinal fluid and plasma concentrations of the protein progranulin[287] in people with progranulin gene (*GRN*) mutations,[288] but accurate prognosis or differential treatment of these frontotemporal dementia subtypes has not yet been developed enough for clinical value. Dementia caused by rapidly progressive prion disease is rare but might be detected with high sensitivity and specificity with cerebrospinal fluid biomarkers.[285,289]

Cerebrospinal fluid biomarker analysis has the potential for adverse consequences. There are direct risks of pain, anxiety, and post-lumbar puncture headache,[284] and cost implications, although the only cost-effectiveness analysis judged it to be, at €205 (approximately £175 or US$230), a cost-effective investigation for diagnosis of possible Alzheimer's disease in mild cognitive impairment.[290] Diagnosis might also be delayed by additional investigations, a situation that would be exacerbated by more widespread use.

Further research into the predictive value of fluid biomarkers and the development of standardised analytic techniques and normal laboratory ranges is needed.[285,287,291] Previous guidelines suggested that cerebrospinal fluid analysis should be reserved for when rare reversible causes of cognitive decline are suspected[292] (eg, if a history of metastatic cancer, suspicion of CNS infection, reactive serum syphilis serology, hydrocephalus, age younger than 55 years, rapidly progressive or unusual dementia, immunosuppression, or suspicion of vasculitis) and updated diagnostic criteria for Alzheimer's disease suggest that cerebrospinal fluid analysis should not be routine.[291]

Genetic testing

Genetic contributions to dementia are complex and genetic testing is not recommended for all because of ethical concerns about uncertain benefit and potential harm. The *ApoE ε4* allele is the only genetic factor that greatly increases susceptibility to late-onset Alzheimer's disease (onset age older than 65 years).[293] Compared with *ApoE ε3* homozygotes, *ApoE ε4* heterozygotes have a three times higher risk of Alzheimer's disease and homozygotes a 15 times higher risk.[294] As *ApoE ε4* alone does not cause Alzheimer's disease, testing for the allele is not clinically recommended.[281]

Young-onset familial Alzheimer's disease is linked in 50% of cases to mutations in the amyloid-β precursor protein, presenilin 1 (*PS1*), or *PS2* genes.[295] Several contributory genes for the frontotemporal dementias have been identified, including *GRN*, microtubule-associated protein tau, and *C9ORF72*. Again, the clinical implications of these specific diagnoses are not sufficiently clear for routine testing.[296] Testing of patients and unaffected at-risk relatives for genetic causes of dementia is not routinely done and should only be done with fully informed consent, after genetic counselling.

Key points and recommendations

Diagnosis requires structured history taking, cognitive tests, and blood screening. Results of cognitive testing should be interpreted in the light of premorbid education, language, and literacy skills, and any current motor, hearing, and visual impairment. We recommend structural neuroimaging for suspected Alzheimer's disease and vascular dementia with MRI, if available. For individuals who cannot tolerate MRI, CT imaging should be used, and if possible hippocampal volume should be assessed. Vascular changes often coexist with Alzheimer's disease but a diagnosis of vascular dementia requires demonstration of major infarcts, a substantial burden (>25%) of white matter lesions, or many lacunae or strategic infarcts. Functional imaging of dopamine is helpful for distinguishing Lewy body disease from Alzheimer's disease. Cerebrospinal fluid testing for dementia-related biomarkers is not routinely used in most countries but is reserved for the exclusion of rare reversible causes of dementia or for possible young-onset dementia.

Treatment of dementia

Principles of assessment and treatment in people with dementia

People with dementia have complex problems because they have symptoms in many domains. These include cognition, neuropsychiatric symptoms, activities of daily living, and usually comorbid physical illnesses. Interventions have to consider the person as a whole and attend to their medical, cognitive, emotional, psychological, and social needs. Thus, individuals require different treatments and these will change with the course of the dementia. Assessment of an individual's problems in these areas is termed needs assessment.[297]

Everyone with dementia should have their physical health including medication reviewed, a risk assessment, management plan, and interventions to maximise cognition. We have taken the clinical approach of considering individual needs in cognition, psychosis, agitation, depression, sleep, and apathy and then we discuss possible approaches to management, including psychological, social, environmental, physical, and medication. We have drawn algorithms to help navigate these complex plans. All are consistent with the multi-disciplinary DICE approach for the assessment and management of neuropsychiatric symptoms of dementia,[298] which can be used as a general approach. After we discuss what treatments to use, we discuss their delivery.

Principles of psychological, social, and environmental management

Around 100 RCTs have been published in the past 10 years with intermediate (not high) level evidence about outcomes in dementia.[299] In this section, we address the evidence for management strategies for specific syndromes, such as depression or agitation. We discuss those strategies aimed at helping family carers. While interventions are diverse, many follow a consistent pattern. The most effective psychosocial treatments are usually multimodal, individualise care, and train carers in skills including optimising communication, coping, and environmental adaptations.[300] The treatment of dementia has no magic bullet—ie, treatments that target all symptoms with one type of intervention, either

pharmacological or non-pharmacological, do not work. All treatments require that target symptoms are defined and measured.

Such strategies and programmes involve more than professionals being nice or providing advice. Rather, those interventions that show the best results are structured and systematic. Some organisations have published manuals and materials available to professionals working with carers and people with dementia.[243,301–305] Many other approaches have been tried and not worked, so it is important to use evidence-based strategies.

Risk assessment and management

Part of the initial assessment of all people with dementia is to evaluate and manage risk, to enable people with dementia to live well at home for as long as possible. The risks change throughout the course of dementia and therefore require regular reassessment. Most societies place a high ethical value on autonomy.[306] Therefore, risk management must balance the rights of a person with dementia with those of society and families' usually beneficent wishes to reduce risks. The general principle is of risk enablement, to allow people to have an acceptable amount of risk, managed by using the least restrictive options.[307] This strategy requires an assessment of the decisional capacity of the person with dementia regarding risks. The risks that should be considered arise mainly because of decreased ability to maintain safety, through forgetting, apathy, decreased insight, or poor judgment. Such risks include, but are not limited to, nutritional deficiencies resulting from being unable to plan to eat and drink well; not being able to understand or remember to take medication as prescribed; lack of safety at home through falls, floods, fire, or gas escape, with subsequent risks to other people; poor road safety both in walking and in driving; and potential vulnerability to crime and abuse from others.[308–310]

Removing means of serious harm, including access to guns for people with dementia and carers who have thoughts of causing harm, would be a practical way of protecting from harm. Preventing people with dementia who cannot drive safely from doing so protects people with dementia, carers, and society; there are country-specific rules about driving.

Family, friends, or care professionals frequently manage other risks on an everyday basis. They use simple measures such as ensuring vulnerable people with dementia are not left alone in risky situations, prompting to eat, using automatic alarms for heat, smoke, gas, or movement, and wearing alert bracelets with contact details. There are also legal measures, such as a family member being nominated as an attorney, so that families can pay bills and manage money, and we discuss these further in the section on family carers. Medication should be simplified and can be packaged in easy-to-manage forms (blister packs, dosette boxes), and family, services, or technology can remind people to take them. The following sections address these in more detail, including how to offer support and assess capacity to make decisions, and potential technological approaches.

Cognition

Drugs for cognition

The only approved drug treatments in many countries for cognitive symptoms of dementia are for Alzheimer's disease, dementia with Lewy bodies, or Parkinson's disease dementia. They target biochemical abnormalities as a consequence of neuronal loss, but do not modify the underlying neuropathology or its progression. Cholinesterase inhibitors might partly restore the deficit in acetylcholine arising from loss of neurons in the nucleus basalis of Meynert and in the central septal area, projecting to cortical regions.[311] Memantine might attenuate the toxic effects of glutamate released from degenerating neurons, although its exact mechanism of action is uncertain.[312] No drug has shown neuroprotective potential in humans.[313] Few studies of anti-dementia drugs provide placebo-controlled data beyond 6 months. Anti-dementia drugs are not indicated in mild cognitive impairment because people with prodromal Alzheimer's disease did not show clinically meaningful improvement or slowing of progression in trials of cholinesterase inhibitors, and systematic reviews of mild cognitive impairment trials[213,314] suggest increased mortality risks.

Cholinesterase inhibitors

Three cholinesterase inhibitors, donepezil, rivastigmine, and galantamine, are in routine use. Donepezil is available as a tablet or orodispersible tablet, rivastigmine is available as a transdermal patch or capsule or liquid, and galantamine as a capsule. Most evidence about these three drugs for Alzheimer's disease is summarised in the 2006 review[315] from the Cochrane collaboration. All cholinesterase inhibitors at optimal doses, compared with placebo, show modest benefit on cognition (2·4 point difference on ADAS-cog).[316] They also show a mean difference of 1·37 points on MMSE (figure 6), which is equivalent to the minimum clinically important difference.[317] Since 2006, the studies published have confirmed the cognitive benefit of cholinesterase inhibitors.[318–320] There are also benefits in global change, assessed by clinician with carer's input (figure 7), and activities of daily living. An updated Cochrane review[321] of rivastigmine treatment in Alzheimer's disease found a similar but slightly smaller effect. The very small difference in behavioural symptoms on the neuropsychiatric inventory[322] (mean difference –2·44, 95% CI –4·12 to –0·76) is not a clinically significant difference. Although these studies[315] did not exclude people, they did not purposively recruit participants with neuropsychiatric symptoms, so this finding might be limited to people with relatively minor symptoms. We report the effect of cholinesterase inhibitors in managing syndromes in the mild cognitive impairment and agitation section.

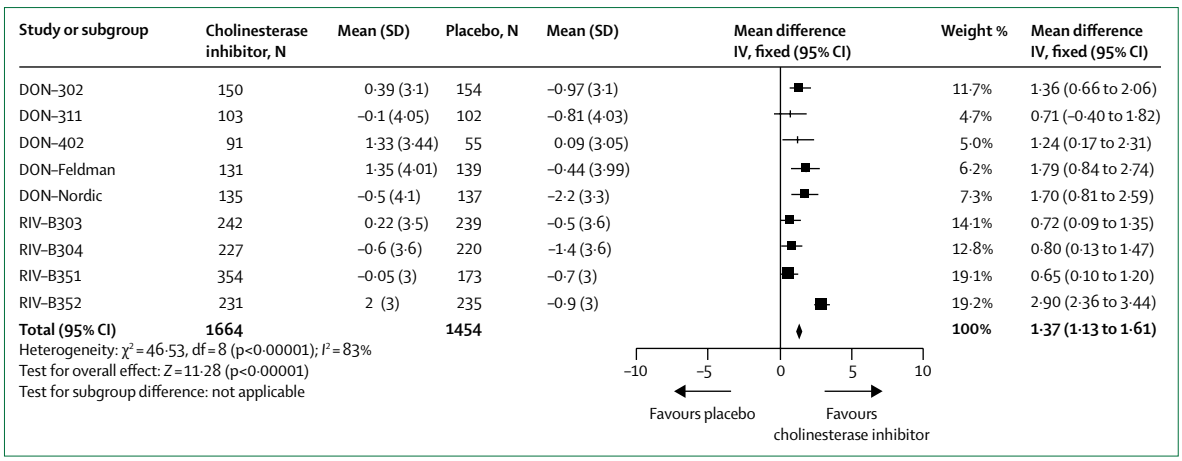

Figure 6: **Effect of cholinesterase inhibitors at optimum dose on cognition**
Reproduced from Birks,[315] by permission of the Cochrane Database of Systematic Reviews. Measured by MMSE in Alzheimer's disease; mean change in score from baseline at 6 months or later. ChEI=cholinesterase inhibitors. DON=donepezil trial. RIV=rivastigmine trial.

Cholinesterase inhibitors are sufficiently clinically effective and cost-effective for NICE to recommend any of them for managing mild-to-moderate Alzheimer's disease.[323] It is not possible to assess who are responders on the basis of their initial response to medication, so treatment should continue if the patient agrees to and tolerates the medication. The cholinesterase inhibitors are fairly well tolerated, but adverse events seen in patients taking such medications include nausea, vomiting, diarrhoea, vivid dreams (reported for donepezil only, and ameliorated by morning dosing) and leg cramps, and RCTs[315] report higher withdrawals due to adverse events in patients taking cholinesterase inhibitors than placebos.

Because trials of cholinesterase inhibitors have not usually continued over years, it was previously unclear if treatment benefits of cholinesterase inhibitors continued as Alzheimer's disease progressed. However, the results of the DOMINO trial,[324,325] a well done, double-blind, discontinuation study, found that donepezil cessation (replaced by a placebo) in patients with moderate-to-severe Alzheimer's disease (MMSE <12) was accompanied by a cognitive (MMSE mean difference 1·9) and functional decline, an increase in neuropsychiatric symptoms, and doubling of risk of care home admission in the year after discontinuation. These results suggest cholinesterase inhibitors should be continued for people whose dementia has become severe.

The potential for greater benefit from higher doses of cholinesterase inhibitors is theorised from imaging showing that 10 mg donepezil resulted in inhibition of only 19–27% of cerebral cortical acetylcholinesterase activity.[326,327] A double-blind RCT[328] of 1371 people with moderate-to-severe Alzheimer's disease found that, after 24 weeks, patients taking a 23 mg donepezil tablet every day scored 2·2 points higher on the 100-point Severe Impairment Battery than patients continuing to take 10 mg daily. Clinician assessment of overall severity and functioning did not differ between groups and more people in the high-dose group (18·6%) than the low-dose group (7·9%) withdrew from the study due to adverse events, most commonly gastrointestinal.[328] Post-hoc analyses suggested greater benefit of high-dose donepezil for severe dementia, but this suggestion was not replicated in a study[329] that found no significant difference between 10 mg and 23 mg donepezil tablets in severe dementia. While the US Food and Drug Administration (FDA) has licensed a 23 mg donepezil tablet, and it is used in the USA in later stages of Alzheimer's disease,[330] the clinical effectiveness remains uncertain. Rivastigmine 24 h patches come in doses of

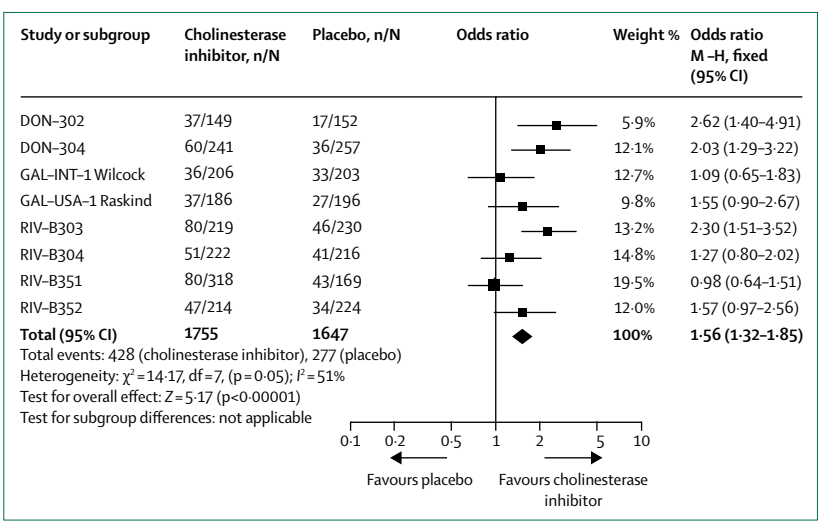

Figure 7: **Effect of cholinesterase inhibitors at optimum dose on global assessment**
Reproduced from Birks,[315] by permission of the Cochrane Database of Systematic Reviews. Measured by Clinician's Interview-Based Impression of Change plus caregiver input in Alzheimer's disease; mean change in score from baseline at 6 months or later. ChEI=cholinesterase inhibitors. DON=donepezil trial. GAL=galantamine trial. RIV=rivastigmine trial.

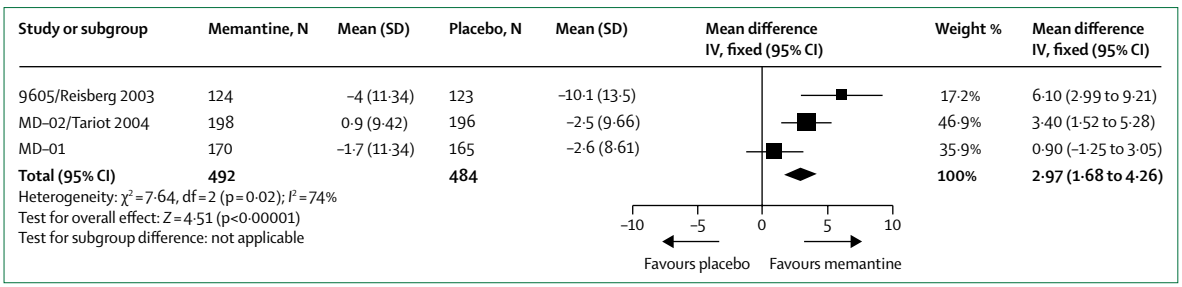

Figure 8: **Effect of memantine at optimum dose on cognition**
Reproduced from McShane and colleagues,[340] by permission of the Cochrane Database of Systematic Reviews. Measured by the Severe Impairment Battery in moderate to severe Alzheimer's disease; mean change in score from baseline at 6 months or later.

4·6 mg, 9·5 mg, and 13·3 mg. The OPTIMA trial[331,332] found that the 13·3 mg patch was better than the 9·5 mg patch for activities of daily living (at week 48) and cognition (at week 24) in people with mild-to-moderate Alzheimer's disease.

Cholinesterase inhibitors are also used for dementia with Lewy bodies, and both rivastigmine (6–12 mg) and donepezil (5 mg and 10 mg) have been found in double-blind, placebo-controlled trials[333,334] to be safe and well tolerated, with a cognitive effect and a reduction in visual hallucinations. Results of meta-analyses[335,336] have found that cholinesterase inhibitors improve cognition and global function in dementia with Lewy bodies and Parkinson's disease dementia. Only the largest of four trials[335] assessing behaviour showed a nominally significant, and very small, effect on behaviour. Cholinesterase inhibitors or memantine are not recommended for vascular[337] or frontotemporal dementias.[338]

Memantine

Memantine is a non-competitive modulator of the N-methyl-D-aspartate receptor and normalises glutamatergic neurotransmission. It prevents excitatory aminoacid neurotoxicity.[339] It is usually given up to a dose of 20 mg per day. A meta-analysis[340] summarised three trials of more than 1000 patients with moderate-to-severe Alzheimer's disease (MMSE 3–14) and three unpublished studies of around 1000 patients with mild-to-moderate Alzheimer's disease, all lasting 6 months. In the moderate-to-severe group, there was a small beneficial effect on cognition (figure 8), activities of daily living, mean levels of neuropsychiatric symptoms, and global assessment (mean difference on Clinician's Interview-Based Impression of Change Plus Caregiver Input 0·28, 95% CI 0·15–0·41). A marginal beneficial effect on cognition was shown in the mild-to-moderate groups, which was not accompanied by effects on behaviour or everyday functioning.

Two trials[341,342] of memantine in mild-to-moderate dementia with Lewy bodies found improvement in global impression; one of the trials found improvement in mean behavioural symptoms,[341] but no benefit was found in other clinical domains. A marginal benefit for cognition in mild-to-moderate vascular dementia did not equate to any global or functional improvement.

Two consensus panels[343,344] made tentative positive recommendations for the benefit of a combination of memantine and cholinesterase inhibitors in moderate-to-severe Alzheimer's disease on the basis of a meta-analysis showing small but significant benefit for global assessment, cognitive ability, and neuropsychiatric symptoms without major differences in the incidence of adverse events. The single study[345] considering the combination of high-dose rivastigmine patch (13·3 mg/24 h) and memantine for severe Alzheimer's disease found no additional therapeutic benefit, but that this combination was safe.

No controlled data are available on the efficacy of memantine beyond 6 months or on its ability to delay progression from mild cognitive impairment to dementia. Memantine is an option for managing moderate Alzheimer's disease for people who cannot take cholinesterase inhibitors, and for managing severe Alzheimer's disease.[323] An extended release formulation of memantine at a higher dose of 28 mg daily is licensed in the USA for moderate-to-severe Alzheimer's disease and has a more convenient dosing schedule. A placebo-controlled trial[346] found it was effective in people with moderate-to-severe Alzheimer's disease, but the observed effects were not larger than those of the standard formulation at lower doses and no direct comparison has taken place.

Souvenaid

Souvenaid is a medical food product for oral consumption formulated to meet nutritional requirements in Alzheimer's disease and comprises docosahexaenoic acid, eicosapentaenoic acid, uridine-monophosphate, choline, phospholipids, folic acid, vitamins B6, B12, C, and E, and selenium. These components are hypothesised to be useful as precursors and cofactors for the formation of neuronal membranes, and consumption of Souvenaid increases their concentrations.[347,348] However, a double-blind trial[349] of 527 participants with mild-to-moderate Alzheimer's disease showed no difference in the ADAS-cog outcomes. A

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systematic review and meta-analysis[350] found good-quality studies with a total of 1011 participants and global cognition, functional levels, or behaviour did not differ between placebo and treatment groups.

Key points and recommendations

Cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) have a small but clinically important effect on cognition and function at all Alzheimer's disease severities but have side-effects. Donepezil and rivastigmine have a positive effect on cognition, and in the Lewy body disorders, in reduction of hallucinations. Memantine has a smaller effect on cognition in moderate-to-severe Alzheimer's disease.

Other cognitive interventions

Cognitive interventions encompass a range of approaches to maintain or improve cognition through mentally stimulating activities. There are three main cognitive intervention approaches.

Cognitive stimulation therapy

Cognitive stimulation therapy[351] is the psychological approach with the strongest evidence for improving cognition. It stems from reality orientation and is usually group-based. It consists of group sessions led by a trained coordinator incorporating social activity, reminiscence, and simple cognitive exercises (panel 2). Results of meta-analyses[352,353] found that cognitive stimulation therapy benefits general cognition (Hedges' g effect size 0·51, 95% CI 0·35–0·66, equivalent to a mean difference of cognitive stimulation therapy *vs* control of 1·78 points; 95% CI 1·23–2·33 on the MMSE; figure 9),[352] which is similar to that of cholinesterase inhibitors; although, unlike in cholinesterase inhibitor trials, the control group in cognitive stimulation therapy trials[353] has no placebo therapy. A Cochrane review[353] found that cognitive stimulation therapy might improve self-reported quality of life (standardised mean difference [SMD] 0·38, 95% CI 0·11 to 0·65), but had no significant effect on activities of daily living (0·21, –0·05 to 0·47). Cognitive stimulation therapy is cost-effective for people with mild-to-moderate dementia and is recommended in the UK by NICE. Despite the evidence of effectiveness however, limitations include an absence of active-control interventions, few attempts to mask raters, and few follow-up studies to clarify how long effects last.[352] The group-based and multicomponent nature of cognitive stimulation therapy also means it is unclear which aspects of the intervention are the most useful and whether the social element is crucial, a distinct possibility because individualised cognitive stimulation therapy has not been found to be effective.[369] Overall, while clearly efficacious, the evidence that this therapy reaches the threshold for a minimum clinically important difference is debatable, and it might not be effective in all settings.

***Panel 2:* Cognitive stimulation therapy**

The aim of cognitive stimulation therapy is to actively mentally stimulate participants through cognitive activities and reminiscence, multisensory stimulation, and group social contact. Each session is led by a facilitator. The standard cognitive stimulation therapy model is a group intervention of 14 themed sessions, each lasting approximately 45 min and held twice per week. This standard programme has been manualised and can be potentially administered by anyone working with people with dementia and held in care homes, hospitals, or day centres.

The programme includes:

- A non-cognitive warm-up activity (eg, soft ball game and song)
- Elements of reality orientation including a board displaying personal and orientation information

Sessions then focus on different themes, including childhood, food, current affairs, use of money, faces, scenes, and quizzes or word games.

Cognitive training

Cognitive training involves theoretically driven strategies or exercises targeting specific cognitive domains, usually with an adaptive level of difficulty. It might have benefits in healthy adults older than 65 years, but not for those with mild cognitive impairment.

Relatively few RCTs exist on cognitive training in dementia, and their small sample sizes, variability in outcome measures, and multiple techniques used make it difficult to evaluate single strategies. A meta-analysis[352] to assess cognitive training for common clinical outcomes of general cognition (MMSE and ADAS-cog) found only four RCTs that reported these outcomes. The pooled effect sizes were small and not significant (eg, MMSE effect size of 0·22, 95% CI –0·75 to 1·18). Similarly, a Cochrane review[370] found no significant effects of cognitive training on global outcome measures or activities of daily living in patients with Alzheimer's disease and vascular dementia. However, an RCT[371] of 18 sessions of either adaptive chunking training or a control intervention for 30 min over 8 weeks for 30 patients with mild Alzheimer's disease led to improvements in verbal memory and general cognitive function, and further testing of adaptive training is required.

Cognitive rehabilitation

Cognitive rehabilitation aims to improve everyday function by helping the patient set individual goals and devising strategies to achieve these,[372] and might be useful for patients with mild-to-moderate Alzheimer's disease, for whom individualised goals to improve specific functions could improve function and quality of life. A large multicentre study[373] of goal-orientated cognitive rehabilitation in mild Alzheimer's disease is underway.

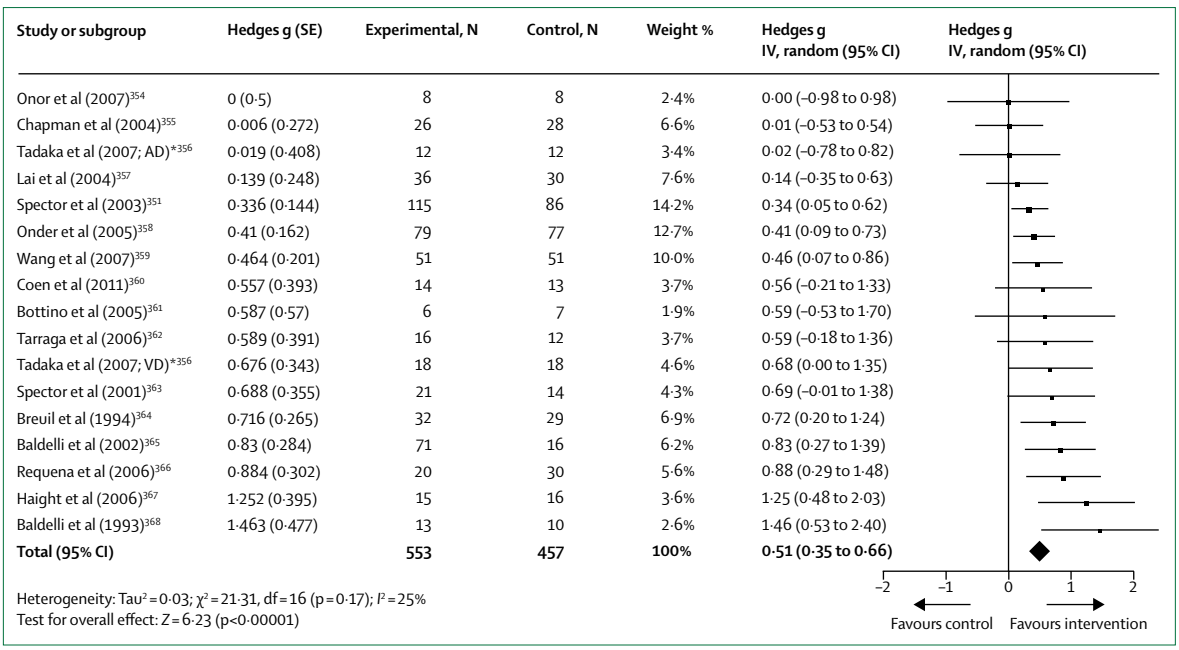

Figure 9: **Effect of cognitive stimulation therapy versus usual care on cognition**
Reproduced from Huntley and colleagues,[352] by permission of BMJ Publishing Group. Measured by MMSE.

Few trials exist of cognitive rehabilitation in people with dementia. In one RCT,[374] 653 patients with mild Alzheimer's disease (mean MMSE 21·6) were randomised to group cognitive training, group reminiscence therapy, or individualised cognitive rehabilitation weekly for 12 weeks, then every 6 weeks for 21 months. Cognitive decline for all interventions was not reduced compared with usual care, but the individual cognitive rehabilitation group showed significantly lower functional decline at 24 months compared with the control group. Neither intervention (*vs* controls) was superior on secondary cognitive, functional, or behavioural outcomes.

Key points and recommendations

Group cognitive stimulation therapy improves cognition in patients with mild-to-moderate dementia. It is unclear whether the active component is cognitive or social because individual cognitive stimulation therapy is ineffective or whether the effect size is clinically significant. Individual cognitive rehabilitation can be effective for patients with mild-to-moderate dementia with specific functional goals, but its cost-effectiveness requires more evidence.

Exercise interventions for cognition

The evidence from RCTs that exercise interventions improve cognitive and functional outcomes in patients with dementia is highly variable. A systematic review[375] of four RCTs of exercise interventions in Alzheimer's disease reported a significant overall SMD on cognitive outcomes compared with controls of 0·75 (95% CI 0·32–1·17). By contrast, a Cochrane review[376] of nine studies with 409 participants did not find a significant difference and rated the quality of evidence as very low. The Finnish Alzheimer Disease Exercise Trial[377] reported that a year-long programme improved executive function, measured with a clock drawing test (effect size in the home-based exercise group d=0·25, 95% CI 0·06 to 0·48 *vs* d=–0·10, –0·27 to 0·16 in the control group), but not verbal fluency, and there were no effects in other domains.

However, in the Cochrane review,[376] there was an overall significant benefit of exercise on activities of daily living (SMD=0·68, 95% CI 0·08 to 1·27) in six trials with 289 participants. The functional benefits are illustrated by the FINALEX trial,[378] in which 210 home-dwelling patients with Alzheimer's disease were randomly assigned to group or tailored exercise twice a week for 1 year or to usual treatment control. Although the study was unblinded, the tailored home-based exercise group declined less on the functional independence measure at 12 months (mean change –7·1, 95% CI –3·7 to –10·5) than controls (–14·4, –10·9 to –18·0).

Overall, RCTs examining exercise interventions in dementia are few and limited by small sample sizes, lack of masking, inadequate comparator groups, variable form, frequency, duration, and intensity of exercise, and the use of multicomponent interventions masking the effect of an exercise component. It is possible that a dose-response association between exercise and cognition exists, and that high-intensity exercise gives more beneficial cognitive effects.[379] It has been hypothesised that there is an intensity threshold beyond which cognitive benefits become more pronounced.[380] Supporting this

hypothesis, a subanalysis of the ADEX trial[381] found that high-intensity training is required for cognitive improvement in patients with mild Alzheimer's disease. Participants doing higher intensity exercise with more than 70% maximum heart rate (n=66) improved in the primary cognitive outcome versus control, whereas participants doing moderate intensity exercise had no significant improvement.[382]

Key points and recommendations

Engaging in exercise is helpful for a variety of reasons, including cardiovascular and cerebrovascular health, diabetes, obesity, strength, and protection against frailty. Exercise programmes for people with mild-to-moderate dementia are feasible and well tolerated, and exercise offers positive small effects on function for people with dementia, but whether it helps cognition is unclear. The most persuasive evidence to date on exercise is for high-intensity interventions to help cognition in mild Alzheimer's disease. Whether exercise programmes that reach the aerobic fitness thresholds that affect hippocampal volume or BDNF concentrations convey cognitive benefits in participants without Alzheimer's disease is unknown.

Neuropsychiatric symptoms

Neuropsychiatric symptoms in dementia are common, they generally increase with the severity of dementia and affect nearly everyone with dementia at some point during their illness.[383,384] Although many different symptoms exist, they often co-occur and there are several different models of how they cluster—eg, into affective, psychotic, and other symptoms.[385] They also vary with the underlying cause of dementia, with visual hallucinations being more common in Lewy body dementia.[386] Of those with any symptoms on the Neuropsychiatric Inventory at baseline, 81% still had some symptoms after 18 months, although this frequency varies according to the specific symptom—apathy and hyperactivity (agitation, disinhibition, irritability, aberrant motor behaviour, and euphoria) are particularly persistent.[387] Factor analysis of crosssectional data from the European Alzheimer's Disease Consortium has suggested four neuropsychiatric sub-syndromes with overlapping symptoms: psychosis (delusion, hallucination, and sleep disorder), affective (depression and anxiety), apathy (apathy and appetite disorder), and hyperactivity.[388] The overlap between these symptoms highlights the need for careful assessment of symptoms and potential causes, advocated by the DICE (Describe the problem, Investigate the cause, Create a plan, Evaluate the effectiveness of it) approach,[389] and in this section, we present the best evidence supporting the management of these syndromes. We discuss the evidence for providing pleasant events and maximising communication to prevent and manage agitation, although these strategies are inherent to providing good-quality care to all people with dementia.

Psychosis

Around 18% of people diagnosed with dementia experience psychosis at any one time, with prevalence greater in moderate and more severe dementia. Psychotic symptoms tend to persist in most people for several months.[390,391]

Types of psychotic symptoms in dementia

Delusions are the most common psychotic symptom in people with Alzheimer's disease. These are usually simple, rather than systematised and bizarre. They commonly involve theft, abandonment, infidelity, or poisoning. Misidentification symptoms—beliefs that the identity of a person, such as a spouse, has been changed or replaced, the phantom boarder, or misidentifications when looking in the mirror—also occur. Hallucinations are less common, and in contrast with other psychiatric disorders, are more commonly visual than auditory. Auditory hallucinations are usually sounds, individual words or phrases, and rarely commenting or commanding voices. Tactile or olfactory hallucinations are uncommon. A substantial proportion of people with dementia are not distressed by their psychotic symptoms. Others are distressed and these symptoms can be associated with family carer distress, risk of care home admission, worse general health, and increased mortality.[392] In Alzheimer's disease, psychotic symptoms are associated with more rapid cognitive decline, and this trajectory precedes psychotic symptoms onset.[392–395]

Psychotic symptoms are prominent in dementia with Lewy bodies, in which well formed visual hallucinations are a core diagnostic criterion, but seem to be less common in frontotemporal dementia,[396] except in some rare genetic forms.[397] No genetic contribution to psychotic symptoms has been identified, despite familial aggregation of symptoms. Imaging techniques find grey matter volume, blood flow, or glucose metabolism changes are more pronounced in neocortical regions than in temporal lobe structures in patients with Alzheimer's disease and psychosis.[398] Misinterpretations of reality by a person with dementia are often contributed to by sensory deprivation, vision loss, hearing loss, and inappropriate sensory stimulation, and might increase the risk of psychosis.[399]

Principles of assessing and managing psychotic symptoms in dementia

Assessment should start with investigating the nature and context of symptoms, primarily to determine whether psychotic symptoms (as opposed to mistaken beliefs due to memory loss) are truly present (figure 10).

People with dementia are vulnerable to delirium in which psychotic symptoms can be prominent, so this

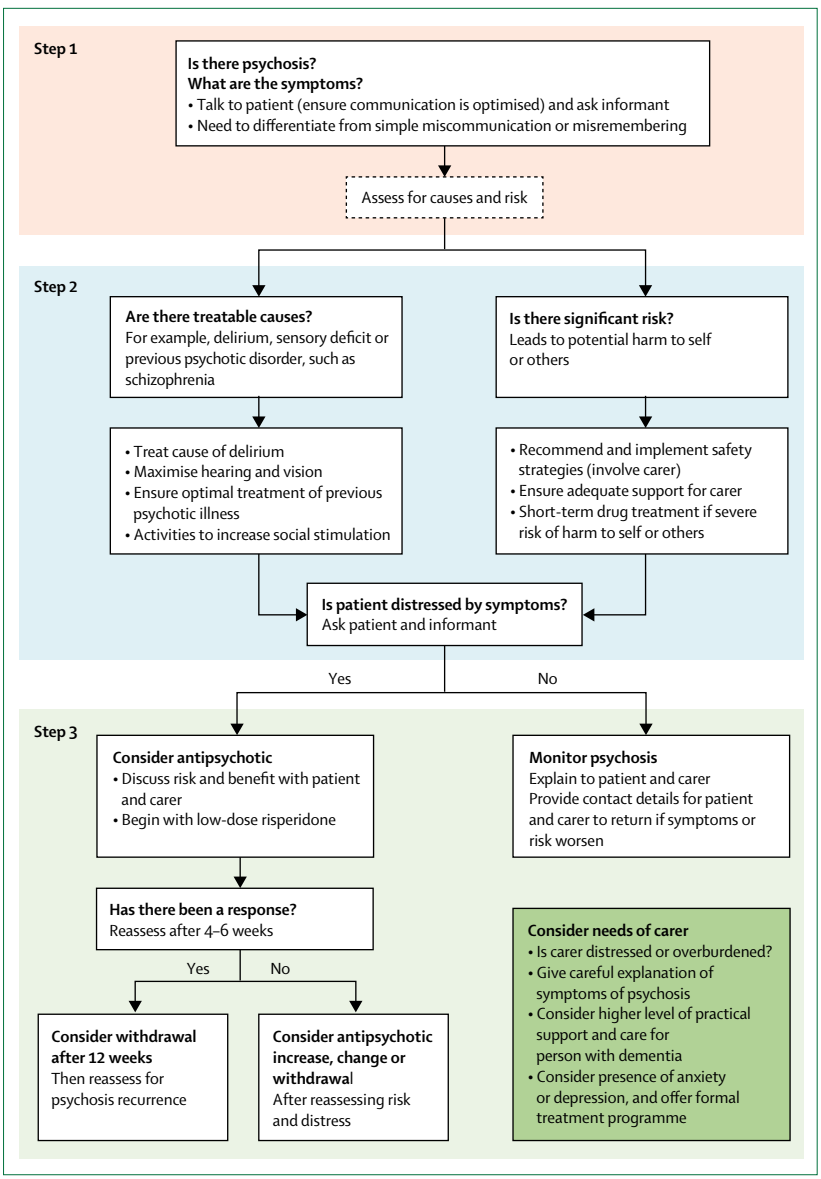

Figure 10: **Approaches to assessment and management of psychosis in dementia**

cause should also be considered. Treatment of the underlying causes of delirium will often relieve symptoms. In patients who are not distressed by their psychosis, management can be limited to an explanation of the symptoms to the patient and family. If the patient agrees, social stimulation such as participation in clubs and centres and treatment of visual or hearing problems by better lighting, ophthalmological treatments, removing ear wax, or using hearing aids sometimes help. Discussion of the risks and benefits of antipsychotic treatment will often lead to the conclusion that they are not indicated.[400] In dementia with Lewy bodies, when antipsychotics are more likely to cause side-effects, rivastigmine (or donepezil)[333,334] are helpful for visual hallucinations but antidepressants and other cholinesterase inhibitors do not seem to be effective.[333,401]

Antipsychotic use in dementia

Harmful effects of antipsychotics in dementia

Antipsychotics might cause particular harm in dementia; side-effects include sedation, extrapyramidal symptoms, and increased risk of cerebrovascular events and mortality.[402,403] People taking antipsychotics have higher mortality (22·6–29·1%) than those taking other psychotropic medications (14·6%), except for anticonvulsants.[404] Concerns about the use of antipsychotics began in 2002.[405] The US FDA issued a black-box warning about atypical antipsychotics in 2005, which expanded to include first generation or conventional antipsychotics in 2008. Mortality on typical antipsychotics, including haloperidol, seems to be up to twice that of risperidone, with greater risk at higher doses.[402,406–408] Patients who have been recently started on antipsychotics seem to be particularly at risk, especially in the first 30 days.[408,409]

In the USA, antipsychotic prescription began to reduce before the official warning and then decreased more sharply from 2005 to 2007.[405] In 2009, in the UK, it was calculated that two-thirds of the 180 000 people with dementia who were prescribed these drugs might not need them and their administration was associated with an estimated 1800 excess deaths (or 1%) and 1600 excess strokes annually.[410] The UK Call to Action campaign mandated the recording of the number of people with dementia on antipsychotics, discussions about their use with family and carers, consideration of alternatives, and review every 3 months. In 2012, an audit of practice showed a large reduction in prescribing, along with an increase in the dementia diagnosis rate.[411]

A meta-analysis[412] of RCTs of risperidone treatment for patients with dementia (1009 risperidone *vs* 712 placebo) found a lower RR of cerebrovascular events in patients treated with risperidone who had depression or delusions associated with dementia, compared with patients without, and a reduction in RR of death in patients with depression. Antipsychotics cause more cognitive impairment than placebo.[403,413] In most people with Alzheimer's disease, the adverse effects of conventional antipsychotics and the newer atypical antipsychotic medication offset their benefits.[414]

Indications for using antipsychotics in people with dementia

Antipsychotic medication should only be used when symptoms cause distress or increase risk—eg, beliefs that someone is trying to harm the patient or poisoning their food. A discussion with the patient, their family, and staff to decide whether possible benefits are likely to outweigh risks should be documented. Medications should be used to treat to target : if they do not improve the target symptom, they should be reassessed and

either uptitrated, changed, or stopped altogether. Evidence for the efficacy of antipsychotics in treating psychosis in dementia is scarce; this evidence is mainly for risperidone 0·5–1 mg, the only antipsychotic specifically licensed for use in dementia in the USA, Europe, and UK, with some evidence for aripiprazole.[389,403] For other antipsychotics, lack of evidence of efficacy is not necessarily evidence of no efficacy, but pooled study data[403,415–417] suggest that quetiapine and olanzapine are not effective.

Even when antipsychotics are effective, treatment discontinuation should be considered after up to 12 weeks. One double-blind RCT[418] of antipsychotic discontinuation found that for most people with Alzheimer's disease who have been on antipsychotics for prolonged periods, withdrawal had no detrimental effect on cognition or functional status, but individuals with the most severe neuropsychiatric symptoms might have benefited from continuing on antipsychotics. In patients with dementia and psychosis with agitation who had taken antipsychotics for 32 weeks, discontinuation caused more relapses (24 (60%] of 40 on placebo *vs* 23 [33%] of 70 remaining on risperidone),[419] and this result is supported by other studies.[420] Withdrawal of antipsychotics should be considered for all, but with caution for individuals who had associated agitation and distress.

Key points and recommendations

New onset psychosis might be due to treatable causes, such as delirium, or related to hearing loss and other sensory deprivation. These causes should be considered and, if present, treated. Many patients with psychosis in dementia are not distressed and do not need antipsychotics or other drug treatment. A few patients who are very distressed or are at risk to themselves or others might benefit from medication in addition to psychological, environmental, and social approaches.

Some evidence exists to support the use of antipsychotic drugs, particularly risperidone 0·5–1 mg, in severe psychosis in dementia, but these drugs lead to an increased risk of serious adverse outcomes, which should be discussed with the patient and family. These outcomes should be reviewed and withdrawal considered after 12 weeks. In addition, we believe that medications should treat to target and if they are not working at an adequate dose they should be reviewed and another treatment considered. Rivastigmine and donepezil might be helpful in hallucinations in dementia with Lewy bodies.

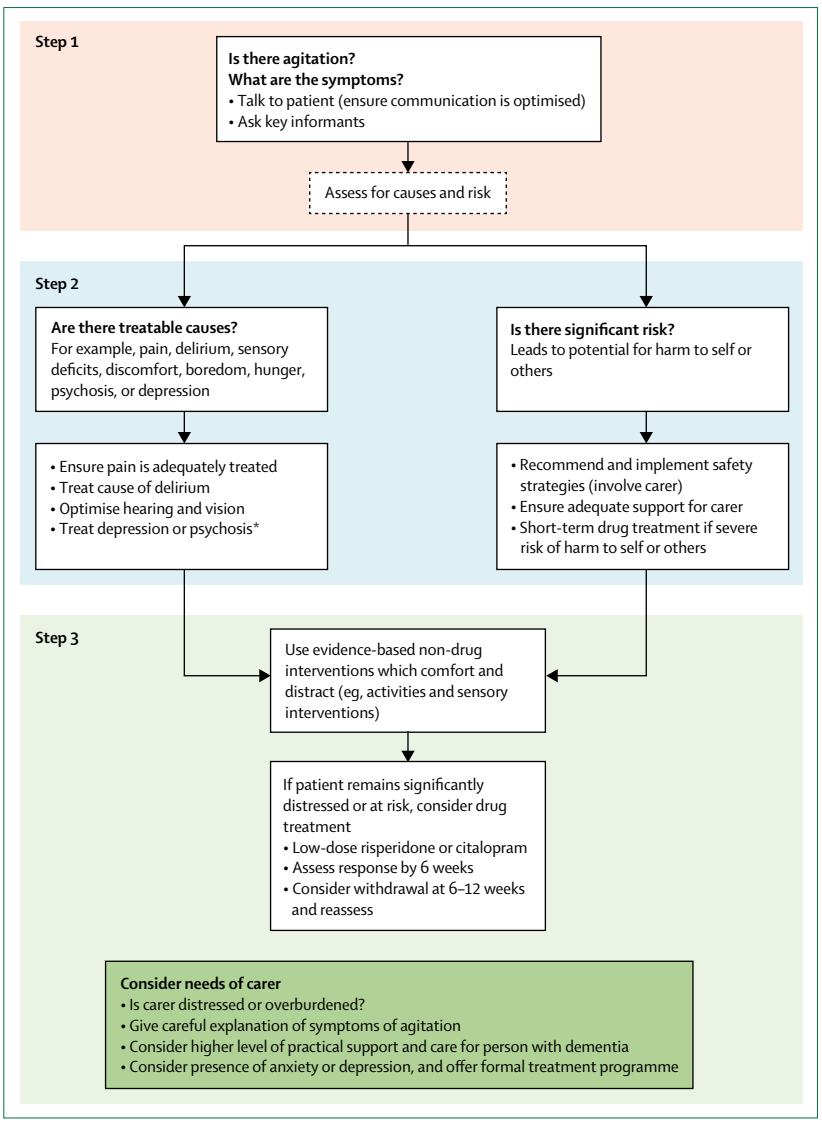

Figure 11: **Approaches to assessment and management of agitation in dementia**
*For more on treatment of depression or psychosis see figures 10 and 14.

Agitation

Many people with dementia show a range of behaviours, including restlessness, pacing, repetitive vocalisations, and verbally or physically aggressive behaviour that is usually described as agitation.[421,422] The behaviours are often accompanied by a feeling of inner tension, although this tension is more difficult to detect in people with more severe dementia. The cause of these symptoms varies. They might be a communication of physical or psychological distress, a misinterpretation of threat, or result from delusions or hallucinations in a person with dementia-related brain pathology, which reduces their ability to communicate, satisfy, or even know their needs and makes it more likely that they will repeat a behaviour.[422–424] Agitation is often most prominent or problematic during personal care. Aggressive behaviours are usually conceptualised as a subtype of agitation, as in the Cohen-Mansfield Agitation Inventory (CMAI), although not in the Neuropsychiatric Inventory.[422] In many studies and in the Neuropsychiatric Inventory agitation subscale, a person with agitation (or aggression) is described as being uncooperative or difficult to handle.[322]

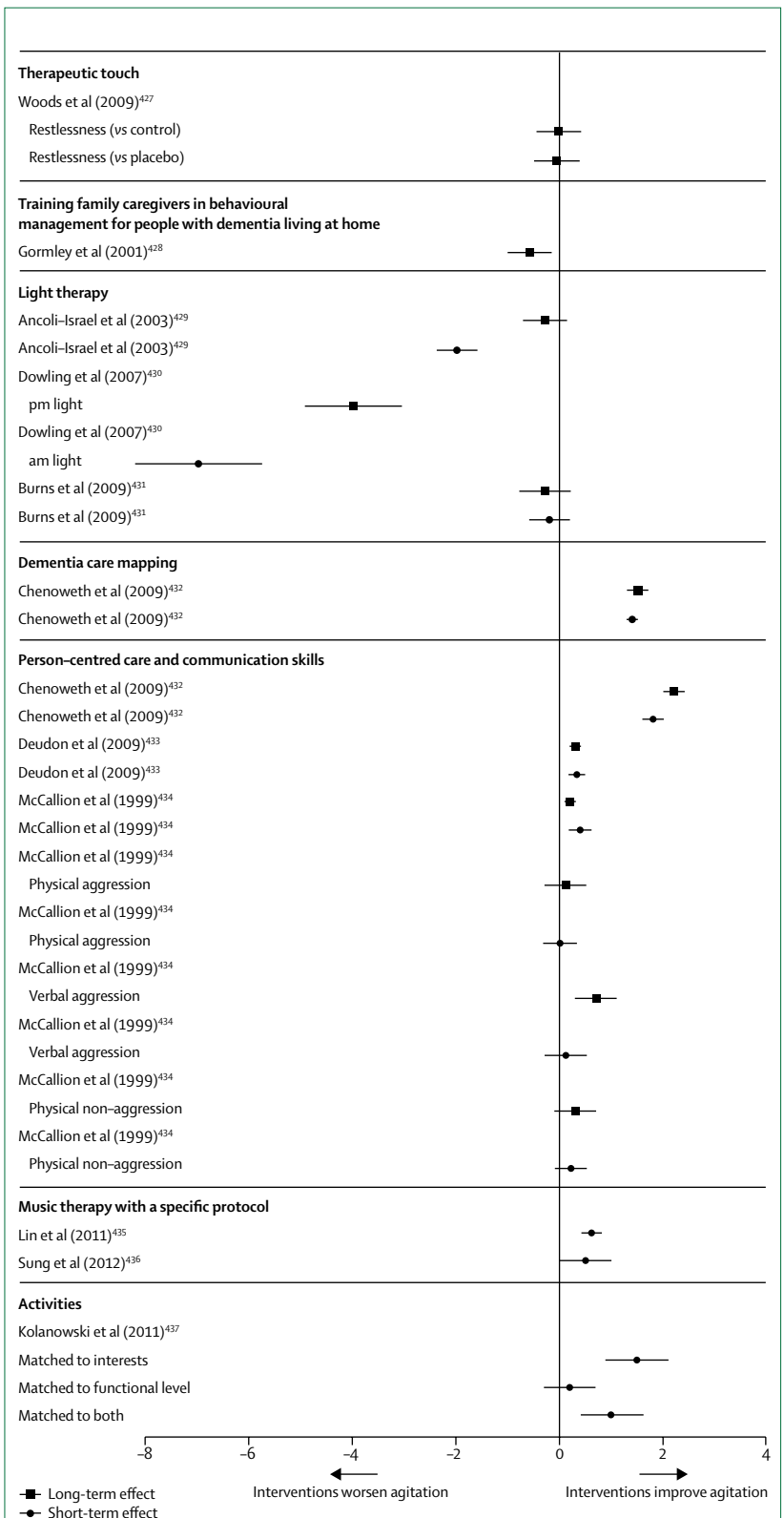

Figure 12: **RCTs of effect of psychosocial interventions versus controls for agitation in dementia**
Reproduced from Livingston and colleagues,[426] by permission of the Royal College of Psychiatrists. Standardised effect size and 95% CI, when calculable, for agitation immediately and in the longer term.

Agitated behaviours are common in dementia, more so in moderate or severe dementia, with around half of people with dementia exhibiting such behaviour occasionally every month, and over 20% having clinically significant symptoms.[391] The rates vary depending on the setting, but are more common in care homes, possibly, in part, because the symptoms are associated with the breakdown of care in domestic settings and care home admission. The symptoms are persistent,[387] so that nearly 15 (38%) of 40 individuals with clinically significant agitation still had symptoms 6 months later[391] and 15 (56%) of 27 individuals with aberrant motor behaviour on the neuropsychiatric inventory, such as pacing or doing things repetitively, remained symptomatic 18 months later.[390] Caring for an agitated person with dementia is more difficult and time consuming than caring for those without agitation; the additional costs of managing agitation account for around 12% of the costs of dementia.[425]

Assessment and management of agitation in dementia

Figure 11 outlines approaches to managing agitation in dementia. This approach should start with asking the person what is wrong. If they cannot say, important causes of agitation to be considered and addressed include the person feeling frightened, hungry, thirsty, hot, or cold. People who suddenly become agitated might be physically unwell, in pain, or delirious. Carers should be consulted about the probable causes of the behaviour, including triggers and unmet needs. Carers' reactions to agitation might relieve or increase it. Overstimulation or complex environments might also exacerbate agitation.

Treatment of agitation in dementia

Interventions to improve communication as treatments for agitation

A systematic review[426] of RCTs calculated standardised effect sizes (SES) of psychological and social interventions for agitation immediately and in the longer term (figure 12). Interventions focused on staff in care homes improving communication with residents with dementia and identifying and responding to their wishes (called person-centred care, communication skills training, or adapted dementia care mapping), which decreased symptomatic (SES=0·3–1·8) and severe agitation immediately (SES=1·4) and up to 6 months afterwards (SES for symptomatic=0·2–2·2; SES for severe=1·5). Panel 3 exemplifies use of communication skills to decrease agitation.

Pleasant activities and occupational interventions for agitation

Most people enjoy activities that interest them and become restless when bored. Engaging in meaningful and pleasurable activities is hypothesised to improve health and wellbeing by reconnecting individuals to their physical and social environment; supporting self-esteem; building neural connections through complex interactions; and

promoting a sense of role continuity, purpose, or personhood, self-identity, and meaning (figure 13).[171]

Activity can be a therapeutic agent to target agitation in individuals with dementia at home,[439] in hospitals,[440] or in residential settings,[426,441] while they are engaged in it. One systematic review[426] found that activities in care homes reduced participants' amount of agitation during the activity (SES=0·2–1·1), as did music therapy using a protocol (SES=0·5–0·6; figure 12). Whether individualising activities further reduced agitation was unclear, perhaps as the activity was effectively individualised because those able and interested engaged in it. There was no evidence that effects lasted beyond the intervention period, or for benefit in severe agitation.[375] As activity reduces supervision time, it might be cost-effective.[440]

As cognition deteriorates, the types of activities people like and can do, and the frequency and amount of participation they can manage, change[438] as the ability to initiate, plan, and organise activities deteriorates. Figure 13 summarises strategies for individualising activities and pleasant events for individuals with varying cognitive levels for therapeutic use.[171,172,442,443]

Social engagement and sensory interventions for agitation

Social engagement is a necessary condition for wellbeing throughout life, and its absence might cause agitation in people with dementia. It encompasses physical proximity to others, eye contact, conversation, and sensory stimulation including touch. Social activity has been suggested to improve quality of life among people with dementia, although no evidence from high-quality RCTs exists.[444] A systematic review[426] found that clinically significant agitation reduced during sensory interventions, including massage. For many successful group interventions, positive social engagement might be an important mechanism.

In care homes, personal care is an opportunity for positive one-to-one social interactions, but in practice communication is often minimal or comprised of commands or instructions.[445] Training staff how to communicate with people with dementia during personal care could be useful. In the UK, the ongoing Managing Agitation and Raising QUality of lifE in dementia study (MARQUE) is quantifying the frequency of agitation in care home settings and determining the efficacy of a manualised approach to training care home staff to improve everyday communication and interaction with people with dementia.

A before–after intervention study[446] in 111 nursing home residents with severe dementia found live social stimuli (eg, with people) decreased agitation more than did activities (eg, folding envelopes, reading, music). Similarly, one-on-one social interaction, music, and watching a videotape reduced agitation.[447] Live social stimuli (visit from a baby or a pet and one-to-one social interactions) also increased pleasure more than exposure to a life-like doll or robotic animal, and these dolls might be an activity rather than, as sometimes conceptualised, a simulated social presence.[448] Another open study[449] offering social interaction, environmental modification, or personalised music found that social interaction was most often effective. An open study[442] providing different social stimuli for people with dementia in care homes found that residents spent more time interacting with humans than animals and with animals as opposed to toys.

Reviews[240,423] of studies of simulated presence therapy with audiotapes of families found inconclusive evidence of efficacy in any domain. Unpleasant stimuli, which are experienced as an invasion of personal space or threat, might cause agitation.[450]

For more on **MARQUE** see http://www.ucl.ac.uk/psychiatry/marque

Other non-pharmacological interventions for agitation

Light therapy (figure 12) and aromatherapy have not been found to be effective for agitation.[426] There is no evidence from RCTs[426] that exercise reduces agitation in care home residents.

Panel 3: Example of communication skills and person-centred care for agitation during personal care

Communication skills and person-centred care involve considering what the person with dementia understands, is trying to say, and what they want, rather than being focused on completing a task, such as personal care, to help them. It involves verbal and non-verbal communication.

This example is about being aware that someone with dementia who requires personal care might not understand or remember this. When that happens, well intentioned, necessary care might be experienced as assault and the person could become agitated. The principles of communication are to:

- Identify yourself and others if the patient does not remember
- Explain what is happening, when it is happening, one step at a time (because the person with dementia might not remember)
- Use calm, reassuring tones
- Ensure you can be heard
- Avoid negative words and tone
- Ask one thing at a time
- Speak slowly
- Allow the person with dementia sufficient time to respond
- Offer simple choices (no more than two at a time)
- Help the patient find words for self-expression (and check if you have understood correctly)
- Lightly touch to reassure, calm, or redirect
- Use relaxing sensory stimuli, such as music or soft lighting, if they enjoy it

Drug treatment of agitation

Antipsychotics for agitation

Antipsychotics were the first-choice drugs for agitation in dementia, until evidence of their harmfulness

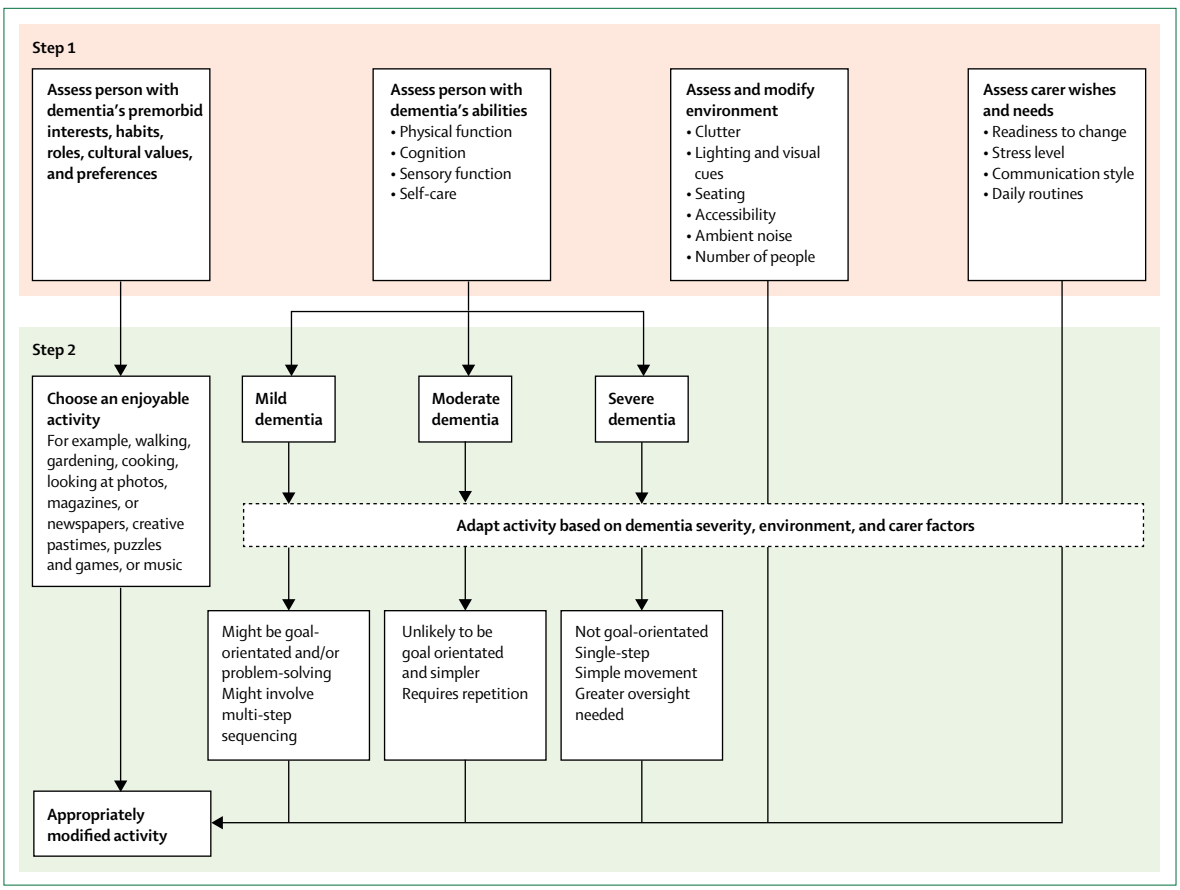

Figure 13: **Guidance for use of pleasant activity as a therapeutic intervention in dementia**
Figure inspired by Regier and colleagues.[438]

showed the need for cautious prescribing and monitoring. Risperidone at a modal daily dose of less than 1 mg improved agitation and psychotic symptoms, particularly when aggression was the target symptom; possibly more in severe aggression, with a difference of around 1–1·5 points on the CMAI subscale when compared with placebo.[451] Haloperidol also has effects on aggression, although not on other symptoms of agitation. Olanzapine and quetiapine did not improve psychosis, aggression, or agitation, but aripiprazole might improve agitation.[451] Overall, risperidone has the best evidence for benefit of any atypical antipsychotic, but only over 12 weeks.[451] Withdrawal trials[418,452] of antipsychotics have not found an effect on agitation or neuropsychiatric symptoms, except for those who have most severe symptoms.

Other drugs for agitation

Drugs for cognition, including donepezil and memantine, have not been shown to be useful for agitation in RCTs when agitation is the target symptom,[453,454] and agitation can be an adverse effect of cholinesterase inhibitors. A double-blind RCT[420] of memantine withdrawal suggested no advantage in the treatment of neuropsychiatric symptoms, including agitation.

An RCT of citalopram 30 mg showed efficacy for agitation with a 0·93 point difference on the Neurobehavioral Rating Scale agitation subscale and clinical global rating (the co-primary outcome) and a 2·4 point difference in the total CMAI compared with placebo,[455] although it causes QT prolongation[456] and worsening of cognition.[455] Notably, about half of patients responded later in the course of a 9-week clinical trial.[457] Pharmacokinetic studies suggested that the R-citalopram enantiomer, more than the S enantiomer, accounted for more of the adverse effects and deteriorating cognition, as well as less likely treatment response,[458] and using the S-enantiomer might be a future avenue. Like other selective serotonin reuptake inhibitors, citalopram can cause akathisia and other extrapyramidal symptoms,[459] although they do so less commonly than antipsychotics. Additionally, they can cause prolonged QT interval, cognitive impairment, falls, and hyponatraemia.[460] An analysis to assess heterogeneity of response showed that citalopram was not effective for individuals with more severe agitation, with more impaired cognition, and in

patients who resided in long-term care, but was more effective in those who were less agitated and less severely cognitively impaired.[461] Citalopram showed no efficacy on the agitation scale of the neuropsychiatric inventory.[462] The dose used was 30 mg and the maximum dose usually used for people older than 60 years for the UK labelling or 65 years for the FDA labelling is 20 mg.[463]

Citalopram was compared with antipsychotics in two earlier trials[464,465] for behavioural symptoms, including agitation and psychosis in hospitalised patients without depression but with dementia. It was no less efficacious than the antipsychotic, but both showed low tolerability with more than half of participants dropping out because of illnesses, side-effects, and absence of efficacy, including worsening. In one trial,[464] citalopram (mean dose 31·1 mg) was prescribed (at a higher dose than now recommended) and risperidone was given at a mean dose of 1·36 mg; dropouts were very high for both drugs at 56% for each (25 [47%] of 53 patients given citalopram and 20 [40%] of 50 patients given risperidone) over the 12-week trial, but the citalopram group had fewer adverse events. In the second trial,[465] citalopram 20 mg was more effective than placebo for agitation for up to 17 days; discontinuation rates for citalopram, perphenazine 6·5 mg, and placebo were all more than 50% for all three groups.

A pilot RCT[466] of dextromethorphan–quinidine suggested benefit in the treatment of agitation with good tolerability, and further RCTs are underway. A non-placebo-controlled trial of stepwise increase in analgesia over 8 weeks for nursing home residents with moderate-to-severe dementia and behavioural disturbances found a 7-point difference in the CMAI and a decrease in general neuropsychiatric symptoms 4 weeks after the end of the study;[467] however, the reduction of 13 points in the CMAI in the placebo group of another trial in care homes[453] suggests cautious interpretation. Preliminary evidence has suggested beneficial effects of treatment with carbamazepine and mirtazapine, which are currently being trialled in the UK (NCT03031184).

Key points and recommendations

Agitation might be due to discomfort, physical illness, delirium, or pain that require treatment. Carer response and an overstimulating environment can also worsen agitation. A human need for social contact exists, and this need includes people with dementia. Families and care staff often need help in the skills of maintaining communication and social contact. Interventions to improve communication, activities, and sensory interventions are first-line therapy after physical comfort is established. Activities can effectively engage people with dementia and be integrated within diverse settings. The activities can help agitation in care homes while they are happening. Psychotropic drugs for agitation should be used only when there is a high risk or other strategies are unsuccessful and patients are very distressed. Antipsychotics are of low efficacy in agitation in dementia, but risperidone 0·5–1 mg daily might be used for severe aggression, to prevent harm to the patient or others. Additionally, citalopram might benefit agitation—especially in individuals with milder Alzheimer's disease and milder agitation—but has important side-effects (which are different and often less than those of antipsychotics). Adverse events include prolonged QT interval, cognitive impairment, falls, hyponatraemia, akathisia, and other extrapyramidal symptoms.[460]

Depression

Depression is common in people with dementia. Estimates of its prevalence vary, but probably more than 20% of people with dementia have diagnosable depression at any one time, and many others have some depressive symptoms.[468] It is distressing, reduces quality of life, exacerbates cognitive and functional impairment, and is associated with increased mortality and carer stress and depression.[469,470] Many people with mild depression improve without specific treatment, although the services they use are likely to address, at least in part, situational factors predisposing to depression, such as loneliness, understimulation from lack of activity, or being cared for by a depressed carer.[471]

Evidence for treatment of depression in dementia is heterogeneous. Although somewhat speculative, depression in dementia probably differs from depression in people without dementia in biological, psychological, and social terms.[471,472] One suggested classification of depressive features in dementia includes: a group in which depression is situationally determined as a reaction to the effects of dementia; a homophenotypic group in which the syndrome looks like depression, but might differ biologically and be related to neurodegeneration; and a group with a past history of depression (which is a recurrent disorder) or who develop a true episode of major depressive disorder in dementia. Although we do not know from trial evidence, a previous good antidepressant response will probably predict future response.

Principles of assessment and management of depression in dementia

Figure 14 summarises the approach to assessing and managing people with dementia who have depressive symptoms. It is important to consider whether they are at a clinically significant risk, particularly of harming themselves intentionally or by self-neglect, and address these with strategies, possibly including hospital admission if at serious risk. Hypoactive-type delirium or pain might present with depressive features, so these should be considered and, if present, treated. Careful assessment is required to differentiate the features that can be part of dementia, such as apathy, poor concentration, or memory, from a depressive disorder

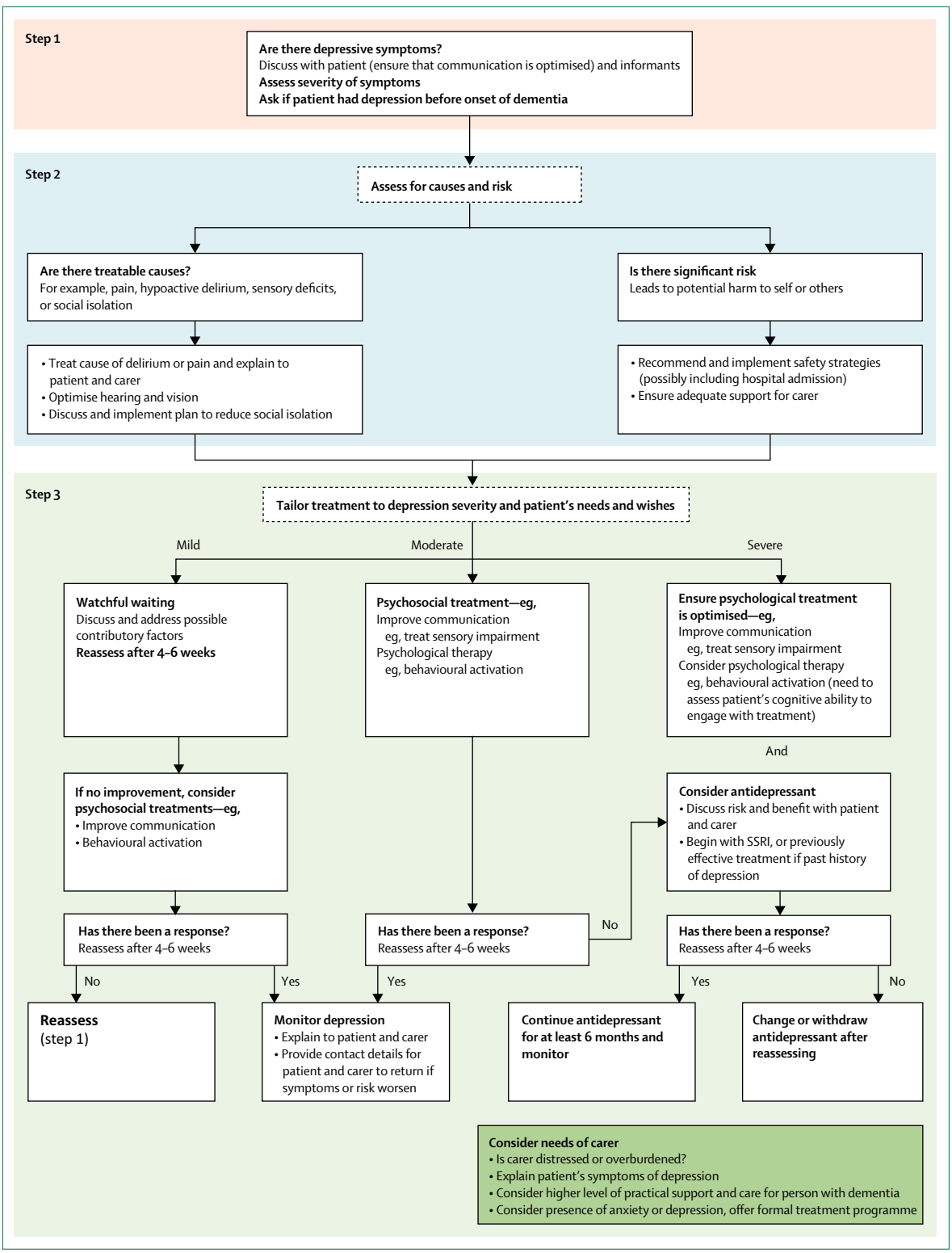

Figure 14: **Approaches to assessment and management of depression in dementia**
SSRI=selective serotonin reuptake inhibitors.

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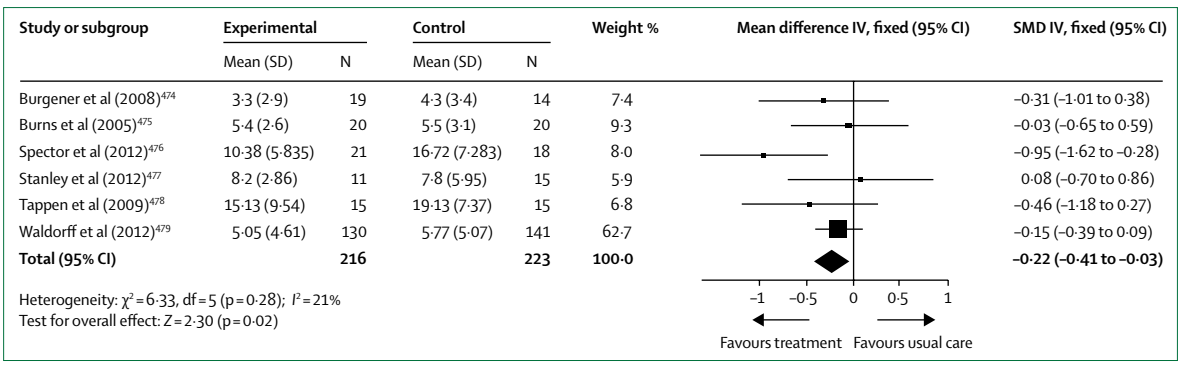

Figure 15: **Effect of psychological treatment versus treatment as usual on depression**
Reproduced from Orgeta and colleagues,[473] by permission of the Cochrane Database of Systematic Reviews. SMD=standardised mean difference.

and delineate the severity of depression. Treatment should be tailored to the patient's needs and wishes and depend on the depression's severity.

Treatment of depression in dementia

Psychological therapy

Evidence is inconclusive that psychological therapies might have an effect in treatment of symptoms of depression in people with dementia. A systematic review and meta-analysis[473] identified six RCTs of psychological therapies involving 439 participants with dementia and depression or depressive symptoms. Overall, psychological therapies, including cognitive behavioural therapies, interpersonal therapy, or counselling, compared with treatment as usual, were effective in slightly reducing depressive symptoms (SMD –0·22, 95% CI – 0·41 to –0·03), but the quality of the evidence was low. Only one of the individual studies showed positive results (figure 15).[480] Psychological treatment reduced clinician-rated anxiety, measured with the Rating Anxiety in Dementia scale (mean difference –4·57, 95% CI –7·81 to –1·32), but not self-rated or carer-rated anxiety,[480] although this evidence was also of low quality. Additionally, preliminary pilot study evidence indicates that behavioural activation, including pleasant events and engaging in activities, might reduce depression.[173]

Exercise

A Cochrane review[376] found no significant benefit of exercise on depression (SMD 0·14, 95% CI –0·07 to 0·36). However, the Reducing Disabilities in Alzheimer's Disease programme, based on the Seattle protocols,[439] included exercise training, carer education, and problem solving to enable and encourage participation in enjoyable exercise and found that the combination improved physical disability in 153 people with Alzheimer's disease and there was a small (possibly not clinically significant) difference in depressive symptoms, but exercise might not have been the active component.[303]

Drug treatments

Antidepressants are often the first-line therapeutic option for depression in dementia, but have no definitive evidence for their effectiveness.[481] Individuals with depression in dementia are likely to have a different neurochemistry than individuals who have depression without dementia, and this difference might partly explain the poorer response to antidepressant treatment.[482,483] Despite this lack of evidence, people with Alzheimer's disease are three times as likely to be prescribed antidepressants as those of the same age without dementia.[484]

The Cochrane review[485] of antidepressants for treatment of depression in dementia concluded that the evidence for clinical effectiveness was equivocal and weak and that the small possibility of positive effect was driven by the preliminary DIADS study[486] of sertraline, which was highly positive. Since that review, the much larger DIADS-II (n=131)[487,488] and HTA-SADD (n=326)[471] studies did not find that sertraline was superior to placebo in the treatment of depression in dementia. Although most people included did not have severe depression, there was no difference according to the severity of depression. Few trials have investigated the effects of newer, non-selective serotonin reuptake inhibitor antidepressants on depression in dementia, but the HTA-SADD trial[471] found that mirtazapine, a noradrenergic and specific serotonergic antidepressant, was also no better than placebo treatment over 13 and 39 weeks. A few older and generally smaller trials[485] have investigated tricyclic antidepressants and monoamine oxidase inhibitors. Although an earlier study[489] recruited 694 patients to compare moclobemide 400 mg to placebo, only 511 participants had dementia (all types), the outcome measures were not validated in dementia, and it is not possible to separate the data of individuals with dementia from the rest of the participants who had cognitive decline. Like this study, others often do not meet the quality thresholds for inclusion in systematic reviews and the outcome measures used are not optimised for dementia.[483] The absence of efficacy in treating mild-to-moderate depression with antidepressants or psychological

interventions is perhaps understandable as we are trying to treat a complex, heterogeneous, multifactorial phenomenon with a simple intervention. Most studies that have evaluated the effectiveness of antidepressants in people with dementia exclude people with severe depression.

Very few data are available on the response to antidepressants in people with dementia who have had depressive episodes in earlier life. Their response to antidepressants might be similar to that of people with depression without dementia. As we have discussed, depression might be a prodromal symptom of dementia but can also occur in people who have a long history of depressive disorder. However, possible attenuation in the treatment response due to the neurodegeneration and neurochemical changes that are part of dementia is also plausible. Although we do not have trials in this specific group, it seems unlikely that dementia would make them entirely resistant to previously effective psychological or drug therapy. In the absence of trial data, clinical practice for individuals who have a past history of treatment response to antidepressants before development of dementia would be to use this treatment as a first-line treatment for depressive episodes following the diagnosis of dementia.

Overall, despite being very commonly used, the evidence for antidepressants having a positive role in depression in people with dementia is weak. Additionally, there is no good evidence that antidepressants are effective in improving other outcomes, such as activities of daily living, cognition, clinical severity, or carer burden. However, antidepressants have some adverse effects, which are common and sometimes serious.[455,456,471,487] In view of these adverse effects and the absence of evidence for positive effects, they should not be used in people without a history of depression in younger ages, unless psychosocial treatments are unsuccessful. Some individuals might benefit from antidepressants, but we do not have trial data with which to identify this group. Clinical decision making will always rely on an individualised assessment of risks, harms, and potential benefits. The dilemma of treatment with antidepressants for dementia is highlighted by the apparent paradox that once started, they might be difficult to stop, and it is unclear how long they should be continued. The one RCT[490] of antidepressant discontinuation was in nursing home residents with dementia and found that discontinuation led to increased depressive symptoms. While this result suggests efficacy in this group, it might also be that the increase in depressive symptoms is a transient withdrawal syndrome. No similar studies have been done in community settings or in people with a less severe dementia.

Key points and recommendations

Many people with dementia and depression will improve with time. Management of possible contributory factors to depression should be encouraged. Evidence is inconclusive that increasing activity, decreasing isolation, and talking therapies might help depressive symptoms, and we await definitive trials. In the meantime, these therapies should be the first-line management in mild-to-moderate depression in dementia. Antidepressants have not been shown to be effective in dementia and have side-effects, so are not first-line treatments for depression in dementia. We recommend not starting antidepressants in people with dementia, unless there is a history of depressive episodes before the dementia or the patient has not responded to social or psychological treatment and is moderately or severely depressed. Stopping antidepressant treatment in people with severe dementia can lead to increased depressive symptoms.

Sleep

Causes of sleep disturbances in older people with dementia are heterogeneous and complex, occurring in 25–55% of individuals with neurodegenerative dementias.[491–493] Sleep disturbances might be caused by one or more of pain and physical health conditions, anxiety, lack of activity, and neurodegenerative changes. Impaired melatonin production occurs in Alzheimer's disease and other dementias because of neuronal loss in the suprachiasmatic nucleus,[494,495] leading to a decreased regularity of sleep, impaired sleep initiation and continuity, and difficulty maintaining wakefulness during daylight. Sleep disturbance predicts family carer depressive symptoms, increases care burden, and leads to care home admission, substantially elevating care costs.[496] A Cochrane review[497] found no definitive evidence from trials of pharmacological treatments for sleep in older people with dementia (cholinesterase inhibitors, donepezil and galantamine; antidepressants, trazodone and mirtazapine; or melatonin and ramelteon) and there were no RCTs of benzodiazepines or non-benzodiazepine hypnotics. There was some suggestion that trazodone 50 mg might be useful, but no large trials have been done.

Bright light therapy used in this group of older people with dementia and sleep disturbances, without measuring patients' individual disturbed circadian rhythm, has also been ineffective (figure 16).[503] Most evidence about sleep hygiene and light comes from small, often pilot, studies with low methodological rigour, leading to insufficient and conflicting evidence.[504] Nevertheless, preliminary evidence from a pilot RCT[505] of 36 participants suggests that light therapy and activity could help sleep, as can education and behavioural techniques. Light therapy can come from natural light, a dawn simulation alarm, or light boxes, and does not necessarily require the patient to remain still. Actigraphs, which are worn like watches, and measure the patient's activity, light exposure, and circadian rhythm, allow for an attempt to anchor circadian rhythms to day and night with light therapy.

No treatments are available that have definitive evidence of effectiveness, so health teams use a mixture of sleep hygiene measures and psychotropic medication,

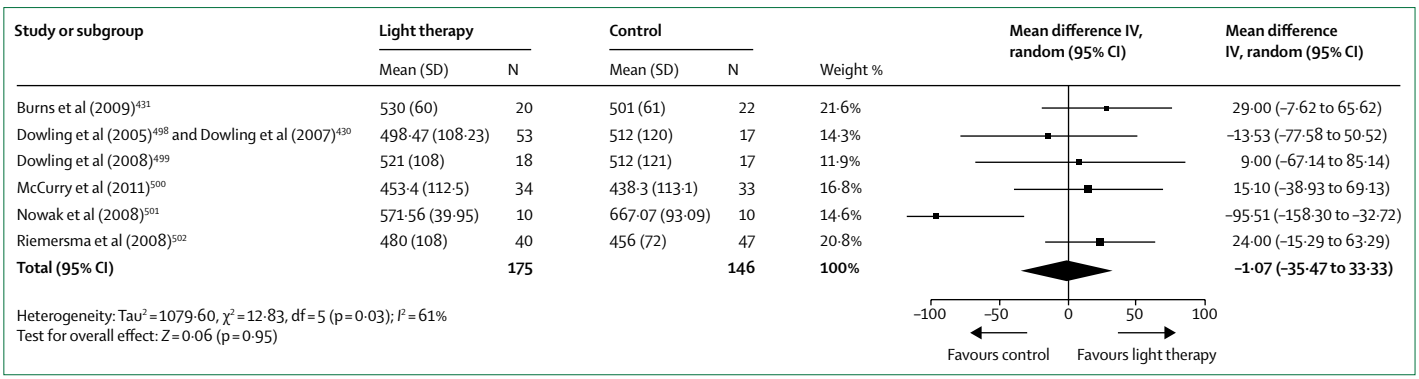

Figure 16: **Effect of 10 days to 10 weeks of bright light treatment on total sleep duration**
Reproduced from Forbes and colleagues,[503] by permission of the Cochrane Database of Systematic Reviews.

extrapolated from other conditions. Patients in nursing homes taking benzodiazepines or Z drugs (the non-benzodiazepine sedatives—eg, zopiclone, eszopiclone, zaleplon, zolpidem, or zimeldine) had worse sleep at baseline than patients not taking the drugs, but over a year both groups deteriorated and patients taking hypnotics did not have better outcomes than those not taking hypnotics.[506] Benzodiazepines also immediately increase the risk of falls.[507] Thus, without definite benefits, and with strong evidence of harm, including increased mortality in general populations of older people,[508] Z drugs and benzodiazepines should be avoided, if possible.[497]

Rapid eye movement sleep behaviour disorder

Rapid eye movement (REM) sleep behaviour disorder occurs in around 20% of patients with dementia with Lewy bodies and in Parkinson's disease dementia.[493] REM sleep disorder causes vivid, frequently frightening, dreams and loss of sleep paralysis during REM sleep, allowing motor activity or dream enactment, including aggression and fleeing, thus risking injury to the patient or person sharing the same bed.[509,510] Practical measures to prevent injury from falling out of bed—eg, a bed rail—can be used, and low-dose oral clonazepam (0·25–2 mg) can suppress REM sleep. Cohort studies[386,510] have found that clonazepam works well in most people; studies of melatonin in non-responders are very small.

Key points and recommendations

Sleep disorders are heterogeneous and the cause of sleep problems can be pain or discomfort in addition to dementia. Very preliminary data suggest that sleep might respond to a combination of tailored light therapy and sleep hygiene. No definitive evidence is available that any drug is effective for sleep disorders in most dementias and they can harm. REM sleep behaviour disorder in the Lewy body dementias can respond to low-dose clonazepam.

Apathy

Apathy is one the commonest and most persistent neuropsychiatric symptoms.[387] In a review[511] of the largest non-pharmacological intervention studies, 15 of 17 studies of tailored activity and eight of the nine studies using non-tailored activity reported a positive or partly positive outcome. However, the commonly used scales have items related to time spent doing activity so the evaluation might be somewhat circular: provide tailored activity and people spend time doing things that interest them. In the Improving Well-being and Health for People with Dementia (WHELD) study,[512] antipsychotic review combined with social activity or exercise led to a reduction in apathy as a secondary outcome. The Alzheimer's Disease Methylphenidate Trial (ADMET)[513] of 60 people given 20 mg methylphenidate or placebo found no difference in the apathy evaluation scale, but more people in the intervention group were rated as mildly to markedly improved. Therefore, although no definitive trials have been done on management of apathy, interventions that increase activity or methylphenidate might be helpful. Figure 13 summarises strategies for using activity with people with dementia.

Care and support

Family carers as decision makers

Family carers are the most important resource available for people with dementia.[234] Caring can bring emotional rewards but also difficulties for a family member. When dementia is mild, decisions about everyday life, social care, and medical treatment can usually be made by the person with dementia, usually with support from family or friends. As dementia progresses, the person with dementia loses the mental capacity to make more complex decisions and the carer becomes the substitute decision maker, changing the relationship of partners and reversing the role of parents with children.[237,238,514,515] The best interest decision of a substitute decision maker includes consideration of what the person would have wanted rather than the decision maker's judgment of beneficence. Figure 17 sets out, as an example, the process of assessing mental capacity within the UK legal framework. Substantial variability exists regarding legal issues between countries, and between states in the USA.

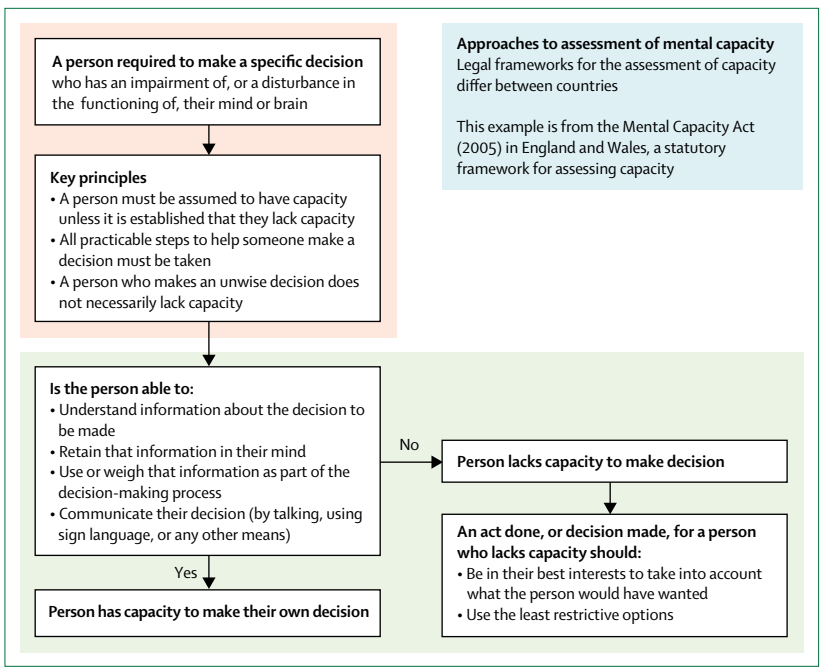

Figure 17: **Approaches to assessment of mental capacity**

Families supporting people with dementia have reported that the most difficult decisions to make or decide as a proxy are how and when to use health and social services for dementia; whether to agree to potentially distressing medical interventions; whether someone should live at home or in a care home; taking over legal matters, including power of attorney and driving; and making plans for the person with dementia if their carer was too ill to continue their caring role.[516–518] Driving is frequently contentious and some places—eg, the UK and California—require notification of a dementia diagnosis, while others have guidelines about driving and dementia. Notification does not automatically lead to a driving ban.

Lasting, Enduring, or Durable Power of Attorney, as it is labelled in different countries, allows a person who understands the decision to nominate a trusted person to be an authorised attorney for future decisions should they be unable to make them themselves. A similar legal mechanism for protecting personal and financial welfare for people with dementia includes guardianship or court of protection orders, which are put in place when someone has lost capacity, and cannot appoint an Attorney.

In England, the Mental Capacity Act sets out a framework to decide whether someone has the capacity to make a specific decision and, if not, who the designated decision maker is (figure 17). This power of attorney is most commonly enacted for financial decisions but can be used for decisions on health or social care matters. Most carers welcome the legal authority but still often find it distressing and difficult to make decisions; this decisional conflict is exacerbated by insufficient information, lack of emotional support, including family disagreement, being unsure what the person with dementia would have chosen, and adhering to a solution conceived before the situation changed.[237,238,516,519] Proxy decision making is facilitated by discussions while a person with dementia retains some ability to consider what could happen in the future.[516,520] Families might require support, immediately after diagnosis and subsequently, and this support might usefully be delivered as a professionally supported decision aid. These provide structured information relevant to the decision, which can then be discussed with a knowledgable facilitator.[518,520] Carers who received the DECIDE intervention, a facilitated decision aid to support the decision of whether a person with dementia should move to a care home, had reduced carer decisional conflict in one small non-blinded RCT.[521] Decisional conflict is associated with people not making and regretting decisions.

Key points and recommendations

Many decisions about health, care, and finances are made by the family carer because people with dementia frequently lose mental capacity to make complex decisions. People might be able to contribute to decisions but not make them independently. Capacity is situation specific. Early and ongoing capacity assessment is helpful. Health-care professionals should discuss how decisions will be made about future care with patients, when dementia is in its early stage, and at any stage with carers. Use of structured decision aids might reduce decisional conflict. Jurisdiction-specific legal frameworks and guidelines outline processes for assessing decisional capacity, safety to continue driving, and appointing a lasting, enduring, or durable attorney.

Caring for family carers

Families usually provide most of the care to people living at home. This care can be psychologically and physically demanding. About 40% of family carers of people with dementia have clinically significant depression or anxiety; others have important but less severe psychological symptoms.[242,522] Family carers have worse physical health, more absences from work, and report lower life quality than non-carers.[523] Spouses of people with dementia are at increased risk of dementia.[524] Female co-resident carers and people looking after someone with neuropsychiatric symptoms are most at risk; although perhaps counterintuitively, caring for someone with more severe cognitive impairment does not predict psychological distress.[300,525] Carer depressive and anxiety symptoms affect not only the individual but also their relative with dementia and wider society, because carer psychological morbidity, particularly depression, predicts care breakdown and therefore care home admission[526] and elder abuse.[527] Most people like family members with dementia to continue living at home as long as possible and people with dementia have

a better quality of life when they do so.[528] Therefore, knowing how to effectively prevent or manage such symptoms is important.

Specialist, individually tailored, multicomponent psychological support to family carers, in which carers make active choices—eg the Resources for Enhancing Alzheimer's Caregiver Health (REACH) intervention—reduce the frequency of, although not necessarily the time to, care home admission.[241,529,530] Some programmes, including those of the Seattle Protocols, have also reported that training family members to understand the interpersonal and environmental aspects of behaviour of relatives with dementia can decrease those problems and relatedly, decrease their own distress.[439] Specialist individual (as opposed to group) behavioural or coping strategy interventions have been efficacious, with six being the minimum number of sessions of individual behaviour management that were needed.[300,531] Cognitive behavioural therapy and other therapies developed primarily to target depression do not effectively treat carer anxiety.[525] Some approaches train carers to identify precipitating events and their role in behavioural difficulties and situation, and encourage changing the response or the environmental factors linked to these problems rather than expecting the person with dementia to change.[299] The mechanism of these effects could relate to carers changing their coping strategies and using more acceptance-based or emotion-focused strategies.[532,533]

Education to increase knowledge about dementia is always part of a successful multicomponent intervention, but by itself does not seem to improve carers' mental health.[534,535] Similarly, group behavioural therapy, support by trained experienced family carers, support for patient and carer together, and 2 years of education, group reminiscence therapy, counselling, and social support were not effective carer interventions.[479,536–538]

One continuing mixed individual intervention for carers was effective by 8 months (but not at 4 months) in reducing depression, continued working 3 years after the intervention started.[539] It consisted of two individual and four extended family sessions (excluding the patient), which encompassed education and strategies around the particular problems, followed by an ongoing support group and the provision of ad-hoc counsellors as needed. The intervention was also successful in reducing care home admission.[302] However, six family meetings (two individual and four with the wider family) did not prevent (as opposed to treat) anxiety and depression in the carer.[540]

The STrAtegies for RelaTives (START) intervention, which was developed from REACH, is a manual-based eight-session therapy targeted at coping with individual problems, but also includes planning for the future and relaxation, and leaves the carer with their own manual with a plan to continue strategies they had found effective.[541] It successfully reduced anxiety and depressive symptoms and both prevented and treated depression in carers and is cost-effective.[243,542,543] Its effect continued for 2 years, at which point many carers were still using the manual and choosing which of the strategies, including relaxation techniques, they continued to use.[544] The intervention is being implemented in some centres in the UK and, because it is delivered by supervised psychology graduates rather than highly trained clinical psychologists, it is practical. There is evidence that the REACH intervention programme could generate savings in carer time and therefore in cost, but it is expensive because it is delivered by clinical psychologists.[545]

Key points and recommendations

Family carers of people with dementia are at high risk of depression and anxiety disorders. Effective interventions are individually tailored, multicomponent, and focus on individual carers (sometimes with their extended family) making active choices. They might work for an extended period and might prolong the time that people with dementia can live at home. Many interventions help carers to understand that they are able to change the situation, but the person with dementia usually cannot change themselves. Information by itself is not enough. Many such passive interventions are ineffective so services should use interventions for which evidence is available.

Protection for people with dementia

Definitions of abuse

Abuse is defined as "a violation of an individual's human and civil rights by another person(s)"[546] and can take different forms. These include verbal or psychological abuse, encompassing screaming and shouting, name-calling, threatening, or humiliating and physical abuse, including hitting, shoving, or handling roughly, inappropriate medication use, restraint, or confinement. Proportionate self-defence is not abuse. Neglect (including allowing self-neglect) is defined as ignoring medical or physical care needs, failure to provide access to appropriate health or social care, or withholding the necessities of life, such as adequate nutrition, medication, and heating. Financial and sexual abuse involves persuading someone to enter into a financial or sexual transaction to which they have not consented or cannot consent. Institutional abuse encompasses harms arising from institutional policies or routines—eg, only allowing access to food and drink at certain times.

In research, cases of abuse are identified by setting thresholds for the severity or frequency of an abusive behaviour that constitute significant abuse.[547] In clinical settings, the terms abuse and neglect are often reserved for serious violations that meet thresholds for formal intervention. Less serious violations, frequently including acts of omission, that meet criteria for abuse are often conceptualised as poor care in clinical practice rather than named as abuse.

Some researchers use the term potentially harmful behaviour in preference to abuse. This term might avoid

Panel 4: **Case vignette of abuse in dementia and management strategy**

Unintentional abuse

Problem

Mr Smith moved to a care home when his son, with whom he had lived, moved abroad. Mr Smith continually asked when he would go home and see his son and could not remember his son had moved. Staff avoided Mr Smith because they did not know how to reply. He became increasingly agitated, refused personal care, and was sometimes physically aggressive. His skin began to break down through neglect.

Assessment

He was referred to mental health services and a nurse met with staff and talked to his son. Staff discovered that team members had each been responding in different ways—some saying his son was on holiday and he would go home soon, others saying that this was his home now, and others not answering him. His son told the nurse that he felt guilty and had avoided calling his father because he thought his calls would disrupt him from settling in the home.

Management

The care staff and nurse worked out that saying his son loved him and encouraging him to talk about his son helped Mr Smith, and they agreed to give that consistent message. They reassured his son that regular contact would help and he started regular video calls. Staff worked with family to add personal possessions and photographs to his room making it more home-like.

Staff also talked to him during personal care, gently explaining what they were doing, and played music that he liked. They planned that staff members he trusted would, when possible, give personal care. He began to accept personal care again.

The staff maintained these strategies when things were better.

the implication of intent that is often thought to be present in the term abuse, which is pejorative, but fails to distinguish harm that violates human rights from accidental harm. Abuse is sometimes perpetrated consciously but is often behaviour in response to practical management difficulties, without sufficient thought or regard to the violation of human rights it creates (see panel 4 for case example).

Surveys recording abusive behaviours without implication of intent, which is generally a legally determined construct, or blame, which is socially determined, find that abuse is more likely to happen to people with dementia. 6% of older people in the general population reported that they have been subject to substantial abuse during the past month; among frail older people, nearly a quarter reported substantial psychological abuse. A third of family carers report acting abusively towards people with a diagnosis of dementia living in the community (most with mild or moderate dementia).[547] 16% of staff in care homes, where most people have moderate or severe dementia, had witnessed substantial psychological abuse.[548]

Factors increasing the risk of abuse for people with dementia

Most people with dementia are not abused, but many older people who are abused have dementia. People might be vulnerable to abuse through isolation, reduced autonomy due to care dependency, controlling relationships with carers or partners, and difficulties remembering or communicating their experiences. In the older population, dementia is probably the most common cause of this vulnerability. More than a third of family carers report behaving abusively towards the person for whom they care.[549] Abuse can be reciprocal because people with dementia who are verbally or physically abusive towards carers are especially likely to be abused.[527,549]

People with dementia who have neuropsychiatric symptoms, including acting aggressively towards their family carers, and whose family carers feel more burdened, spend more hours caring, and have more psychological morbidity, are more likely to be abused than individuals without these symptoms.[527,550] That is, unsurprisingly, distressed carers who have more to cope with are more likely to act abusively than carers who are less distressed. Cross-cultural differences reported in the prevalence of abuse in the community probably reflect differences in where people with more severe dementia are cared for, with higher community rates of abuse in countries where people with severe dementia are more commonly cared for in their own homes,[551] and high occurrence of abuse in care homes in countries where most people with severe dementia live in this setting.[551]

Prevalence of abuse for people with dementia

Abuse of older individuals is inherently difficult to study. It is hidden, often perpetrated against vulnerable people, by those on whom they depend. Prevalence estimates are affected, and possibly underestimated, by the inability, fear, or embarrassment of older people to report the abuse. Some studies[547] have asked paid or family carers to self-report these behaviours and they seem willing to but might not see it as abusive behaviour, often arising due to stress and burden. We must measure abuse to develop interventions to reduce it, but care workers reporting abuse face potential adverse legal, employment, and social consequences, so anonymous reporting is probably necessary for research,[552,553] making intervention difficult.

Approaches to prevent and reduce abuse in people with dementia

Abuse might go unacknowledged if families or professional staff feel there are no better management options and is therefore underdetected and under-reported.[554] Staff who detect abuse might not report it because they do not know how to, or because they empathise with the perpetrator, fear recrimination, or expect responses to be inappropriate and punitive.[555] Encouragement of naming and reporting of abusive behaviour is an important first step to reducing it. Good evidence exists that interventions can effectively increase professionals' knowledge about abuse and their ability to detect and manage it.[556,557]

Management of the most serious cases of abuse, including financial abuse, physical violence, and

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occasionally murder, involves criminal justice systems. National legal frameworks for managing abuse vary; in California, medical professionals have been criminally charged and sentenced under elder abuse laws for the illegal chemical restraint (medication for the sole purpose of sedation) of patients.

Most clinical studies[558] seeking to reduce abusive behaviour target physical restraints in care home or hospital settings and often show this reduction is possible using person-centred approaches. Restraints are defined as anything restricting movement, such as bilateral bed rails, belts, and fixed tables in a chair. These restraints can cause distress, violate human rights, impair future mobility and skin integrity, and usually do not prevent falls. Restraints can sometimes be because of society's unwillingness to provide adequate dementia care resources. Care workers delivering care with inadequate training and resources might use restraints to try to prevent harm. The judgment of what is restraint can be granular. Bed rails might be used only to prevent someone with excessive movement during sleep falling out of bed, and therefore, not using them might be neglectful abuse. One carer briefly and gently holding a person's hand during personal care so they do not hit another carer is proportionate and might be comforting. Reduction in physical restraint is an observable outcome and, in countries where physical restraint is permissible in some circumstances, less likely to be hidden.

Any disproportionate restraint is unacceptable; ethical and legal opinions vary about the relative harms of using sedative drugs or physical restraint to manage symptoms that might cause harm. Psychotropic medication to manage agitation and aggression would generally be considered more acceptable. By contrast, the Netherlands has traditionally preferred seclusion and physical restraint in preference to medication, although this situation is changing.[559] In the UK and the USA, cases of relatives placing cameras in care homes and witnessing abuse have been well publicised. Use of monitoring technology to detect harm to people with more severe dementia is one way of detecting abuse to stop it. However, such technology might compromise a person's privacy and like other interventions, risk and benefits need to be balanced, ideally undertaken with the individual's permission or, if not possible, in their best interest.

Few examples are available of intervention studies including elder abuse as an outcome aside from restraint. This outcome might reflect concerns about the validity of asking perpetrators or vulnerable people to self-report abuse, but elder abuse can be measured reliably and with validity.[548] In the only intervention study[542,560] to measure abusive behaviour by family carers as an outcome, no evidence was found that the START intervention reduced abusive behaviour. For ethical reasons, researchers intervened to manage abuse in both groups, which might have masked any intervention effect. Interventions that aim to reduce burden of care, carer distress, and neuropsychiatric symptoms in people with dementia might prevent abuse in community settings, but no evidence is available to show this. More work to develop definitive interventions to reduce other forms of abuse is needed, including trials with abusive behaviour as an outcome. These should adequately measure and address neglect, which is common. Abuse of older, vulnerable people in society, like child abuse, cannot be allowed to continue.

Key points and recommendations

One in four vulnerable older people might experience abuse, and only a small proportion is reported. Many older people who experience abuse have dementia. Most abusive behaviour happens when quality of care is poor and carers, family, or professionals do not have other strategies to manage difficult situations. Abuse is sometimes, but rarely, sadistic. Good evidence is available that person-centred care reduces use of restraint in care homes and hospitals and should be implemented. Accurate identification of abusive behaviour is a prerequisite of testing interventions to reduce it; for paid carers this behaviour probably needs anonymous reporting. We can measure abuse in a reliable and valid way. Interventions to increase professionals' knowledge about the ability to detect and manage abuse are needed.

Dying with dementia

Dementia shortens life, even after controlling for age and multi-morbidity. This outcome varies between populations and progression might be faster in women and individuals with younger-onset dementia.[561] A UK population study[562] found a median survival time from diagnosis of dementia to death of 4·1 years. In a primary-care study,[246] where diagnosis sometimes occurs at a late stage, median survival times from diagnosis were 6·7 years in individuals diagnosed at ages 60–69 years, decreasing to 1·9 years for individuals diagnosed when aged 90 years or older. Dementia was the sixth leading cause of death in the USA in 2011, and 600 000 Americans with Alzheimer's disease died in 2014.[563] Given its increasing prevalence, one in three people older than 60 years are predicted to die with dementia.[18]

Definition of optimal end-of-life care

Despite dementia being associated with a shortened life, it is often not perceived to be life-limiting or terminal and there is sometimes a failure to adopt a palliative approach to care.[564–566] This failure might result in poor management of symptoms towards the end of life, causing considerable distress to the person with dementia and their family.

Caring for someone with dementia at the end of life has specific difficulties: a person with dementia can lose cognitive abilities, function, and capacity, in contrast with cancer and other advanced chronic diseases. They might be unable to make decisions about their care and

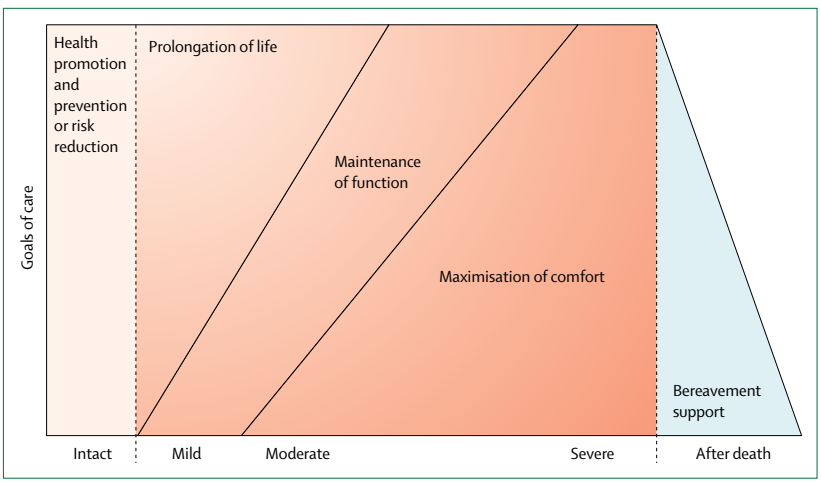

Figure 18: **Model of palliative care in dementia**
Reproduced from van der Steen and colleagues,[571] by creative commons licence (CC BY-NC 3.0).

treatment or express their needs and wishes as death approaches. Considerable prognostic uncertainty exists; the course of dementia is unpredictable and varies greatly between individuals. Prognostic tools have been developed but little evidence is available to suggest that knowing the prognosis changes management, improves outcomes such as comfort, or is helpful to the person with dementia and their families and carers.[567]

It has been argued that we should acknowledge and hold the uncertainty, and focus on maximising comfort and quality of life, rather than estimating prognosis[568] or developing strict criteria for when the person with dementia should be able to access hospice care.[569] This focus is in keeping with the goals of palliative care: the active, total care of patients whose disease is not responsive to curative treatment. Control of pain, of other symptoms, and of psychological, social and spiritual problems is paramount. The goal of palliative care is achievement of the best quality of life for patients and their families.[570]

The European Association of Palliative Care has defined optimal palliative care for people with dementia.[571] In this consensus process, recommendations were made about person-centred care; communication and shared decision making; optimal treatment of symptoms and providing comfort; setting care goals and advance planning; continuity of care; psychosocial and spiritual support; education of the health-care team; and societal and ethical issues. Their model of care stresses the importance of changing care goals throughout the course of dementia (figure 18).

The European Association of Palliative Care acknowledges the vital role of carers and family members who might experience distress and anticipatory grief.[572] Family carers are often decision makers and might make difficult and emotionally demanding choices at the end of life—eg, regarding feeding and resuscitation—as we discussed in the caring and supporting sections.

Key challenges in end-of-life care

Research on end-of-life care has focused on people with advanced dementia rather than people with less severe dementia dying from other conditions. Specifically, it is unknown how people in the earlier dementia stages with a terminal illness navigate services and make complex treatment decisions, and if they have equitable access to good end-of-life care.

Most symptoms that people with advanced dementia experience can be managed by those with generalist knowledge of palliative care and good-quality nursing. However, it is essential that staff have the skills and knowledge to consider the needs of people with dementia.[573,574]

People with advanced dementia experience a range of symptoms, which might be poorly detected and undertreated.[575] Pressure sores, agitation, and swallowing difficulties are common, and the total symptom burden is similar to individuals dying with cancer.[566,576] People with advanced dementia are often immobile, bed bound, at risk of aspiration, and have impaired immunological function increasing their risk of pneumonia, urinary infections, and other infections.[577] Assessment and management of pain is essential because, untreated, it leads to reduced quality of life, depression, and might worsen agitation and other neuropsychiatric symptoms.[578] Many tools are available to assess pain in dementia;[579] however, they also measure distress and discomfort, which can be caused by factors such as cold, poor positioning, boredom, or no social contact.[580,581]

Using artificial nutrition and hydration (including intravenous fluids and parenteral feeding) in advanced dementia is particularly difficult and emotive. Little evidence exists that artificial nutrition and hydration reduce the risk of aspiration pneumonia, prolong life, or improve nutritional status or quality of life.[582] Difficulty swallowing and decreased appetite, sometimes secondary to lower calorie requirements, are common features of advanced dementia.[583] Families are concerned that their relative will feel hungry or thirsty, and the provision of food and helping with eating is often a way to enact their care for their relative. Practices about using percutaneous endoscopic gastrostomy and nasogastric tubes varies between countries[584,585] and across different US states,[586] possibly because of legal differences.

Directly transferring interventions and models from the cancer field might not work. In contrast with the cancer workforce, most end-of-life care for people with dementia is provided by care assistants in care homes, the most common setting in which people with dementia die.[580] Good person-centred care requires a whole-person approach and several multicomponent complex interventions and pathways have been developed. Training and educational programmes on end-of-life care

for nursing home staff improve knowledge and increase bereaved family members' satisfaction with end-of-life care.[587,588] Research has focused on specific interventions, such as pain management, or when not to treat—eg, with antibiotics—rather than active palliative interventions.[589] Complex interventions taking into account variation between care homes and the need for coordinated multidisciplinary care have been developed but need further testing.[4,587] Most people with dementia prefer to die in their usual place of residence, unless they have pain or distress and cannot be treated there. Improving continuity of care could decrease costs by reducing emergency department visits and hospital admissions, which usually do not prolong life and can be very distressing.

While advance care planning has been suggested as a way to improve choice, autonomy, and ultimately end-of-life care, a person, even in the earliest stages of dementia, might struggle to imagine their future self and make a definitive plan.[590] Whether advance care plans, made soon after the diagnosis of dementia, change outcomes or improve the quality of death is unknown. People with dementia, and their family and friends, find advance care planning discussions helpful, but value these plans as an ongoing process rather than committing an advance care plan to paper.[591,592] Assisted dying for people with dementia is controversial and emotive, raising complex legal and ethical issues. Legality varies by country. The main reason that carers of people with advanced dementia consider assisted dying is the distress of the person with dementia.[593] This provides a strong rationale for providing maximal comfort and quality of life as death approaches.

Key points and recommendations

People with dementia might be unable to communicate their needs, so assessment and management of pain and discomfort are key to providing good end-of-life care. Prognostic uncertainty exists, so the priority is adopting a needs-based care approach focusing on the person with dementia and their carers. Optimum palliative care for people with dementia recognises the role of family members and that they might experience distress and anticipatory grief. Training and educating nursing home staff on end-of-life care improves knowledge and increases satisfaction with such care in bereaved family members and should be routinely implemented.

Delivery of care

Case management models for people with dementia

Case management is delivered by a specific individual or a team through an individualised, collaborative, evidence-based plan of care with and for patients and family needs. It integrates the complex network of health and social care professionals needed in dementia and responds to patient needs.[211] Case management usually includes standardised assessment, carer education, and implementation of an individualised plan. Social workers, nurses, or specialist dementia workers can be coordinators to achieve patient-centred care by providing access to resources, planning care, assessing environmental needs, educating and supporting carers, implementing plans, monitoring, and reassessing.[594–596] Content and implementation vary among and within countries.[596] Case management is based on chronic disease management models; improvement in care incorporates patient, provider, and system level interventions.[597] It uses an inter-professional team, including physicians, nurses, psychologists, physical and occupational therapists, and social workers to address patients' and families' complex medical, psychological, and social needs.[598–600] Additional support includes assisting with decisions about finances and health care and referral to key services such as transportation, home assistance, meal delivery, and adult day programmes.[600] Care management refers to general coordination of care, but the terms are often used synonymously.[601]

Family carers often do not know about available services,[602] so do not request or use them. The organisation of care provision differs between countries, and services might be free at the point of delivery or require individual purchase, sometimes with reimbursement. However, people with dementia use less health care even when freely available than others with similar health needs; instead these individuals use social care, and typically family carers provide more care rather than increase care access.[603,604] An increase in frequency of service use by family carers would require professionals to make the system of dementia care visible throughout the course of dementia, so that the right support can be identified and accessed.[605]

Studies of case management models for people with dementia

Panel 5 shows case management approaches. Systematic reviews[596,606–608] and meta-analyses[529,609] of case management in dementia included 23 trials from nine countries. 70% of the studies were of poor or fair quality, and assessed interventions that varied in content; duration (most were 12–18 months); setting (eg, primary care, social services); integration with health systems; care team composition; intensity and method of contact; whether they interfaced with patients, carers, or both; and which outcomes were targeted. Case management approaches also differ in the extent to which they are adapted to meet individual needs targeting specific outcomes[610] or use specific guidelines whereby the same intervention is offered to all individuals.[611]

These reviews show that case management has a low to moderate effect on patients' quality of life and on adherence to practice recommendations, and did not lead to decreased costs. The results of the reviews found case management reduced carer burden and depression (moderate effect size), but little evidence was available that these approaches benefit patients on outcomes such as neuropsychiatric symptoms, cognition, function, or mortality.[606–608]

Panel 5: **Approaches to case management in dementia**

Individual needs

- Begin with multidimensional assessment, communication, and arranging or signposting services
- Use evidence-based recommendations as foundations of the intervention for medical, social, and supportive care
- Involve family carers
- Tailor care plan to unique individual and cultural needs, preferences, and priorities

Service planning

- Promote scalability and sustainability
- Produce effective programme packages, which include organisational readiness and fully manualised protocols
- Expand workforce capable and competent to provide this dementia care and support

Long-term care placement was the primary outcome in about half of the RCTs. Case management was associated with a low reduction in risk of nursing home admission up to 18 months (when intervention duration was <2 years),[607,608] but did not affect resource use or health-care costs over the duration of 1 year.[606] However, continuity of care (patients seeing fewer different clinicians, despite their comorbidities) is associated with fewer hospital admissions and lower costs of care than no continuity of care.[612] Few studies[606,608] have specifically assessed cost-effectiveness.

Case management provided by social workers as part of collaborative care in the USA reduced care inequalities.[613] The US Care of Persons with dementia in their home Environment study (COPE),[614] a multidisciplinary study with patients receiving health care and carers receiving advice, found that at 4 months there was less functional dependence than usual care; although this difference had disappeared at 9 months. Alternative models of case management for dementia, such as the Maximizing Independence at Home model (MIND at Home), are emerging, which use well trained, non-clinical staff as the front-line coordinators, supported by nurses, physicians, and social workers. Preliminary evidence suggests these models, which might be scalable with a larger potential workforce, are able to care for people with dementia and have the potential to improve care.[297,610]

Key points and recommendations

Case management connects and facilitates access to different types of needed services for people with dementia. There is an absence of high-quality effectiveness and cost-effectiveness data, however. There is also heterogeneity between case management approaches, no manualised practice and standardisation, and little information on how and what to implement. It should incorporate evidence-based interventions as best practice in dementia care. Case management might improve patients' quality of life and reduce nursing home or hospital admissions for people with dementia. Making case management available, scalable, and sustainable will require expanding and training the workforce.

Care homes and assisted living

Although most people with dementia are cared for by family members, many people with dementia eventually move into care homes when family carers are unable to manage their increasing care needs. Care homes might not offer specialist dementia services,[615] despite around 80% of residents having dementia.[616–622]

Care homes are highly complex and differ in terms of organisational characteristics (eg, proprietary status, size of unit), processes (access to specialised dementia care, case management, or palliative care), and structures of care (hours of care provided per resident, level of expertise, or diversity of workforce).[623] They differ in terms of practices such as antipsychotic prescribing, indicating that provision of care is driven both by clinical need and the organisational culture of the care home.[624,625]

People living in care homes usually have a lesser quality of life than those at home, possibly because they had more physical or neuropsychiatric symptoms or less support at home, which led to their move to a care home.[528,626] Some residents have more social support, reduced isolation, and improved care when they move to a care home than if they lived at home and their quality of life improves.[627,628] A systematic review[623] found that interventions that incorporate person-centred care, activity, and sensory stimulation might decrease agitation. However, a meta-analysis[629] of care home interventions found there was not enough evidence to recommend any particular programme or compare effectiveness.

Person-centred care can be taught to staff and increases job satisfaction.[630] The Staff Training in Assisted-living Residences (STAR) study[301] was a pilot intervention with only little evidence but initial positive results. The programme trained clinicians, family members, and other health-care professionals to engage with the person through four manual-guided workshops, augmented by on-site sessions and leadership sessions. Residents had fewer affective symptoms and staff a less adverse reaction to residents' behavioural difficulties than those not in the non-intervention group. It has now been translated into practice.[631,632] Increasing international concern about high levels of psychotropic medication use, particularly antipsychotics,[633] has led to decreased use for people with dementia. Interventions such as education and support of care home staff or multicomponent interventions have reduced short-term inappropriate prescribing of antipsychotic drugs in care homes, but evidence of long-term effectiveness and sustainability is still needed.[634] However, a study[635] in care homes that already had low frequency of antipsychotic use found that reducing antipsychotics, without adding other interventions for neuropsychiatric symptoms is not helpful because

neuropsychiatric symptoms generally increase. Implementation of effective interventions requires substantial training and longer term supervision or working alongside care home staff for a prolonged period.[636]

Care transitions from acute care to care homes require communication barriers to be addressed between hospitals and nursing homes and between families and care home staff in order to improve outcomes for patients by lowering incidence of both transfer and transfer-related harm, such as mistakes in medication.[587,637–639]

Leadership in care homes

Leadership can play an important part in implementing evidence-based practice and is a key tool in facilitating care home changes.[640] It can ensure consistent implementation and sustainability, instil values consistent with high-quality care, such as cooperation between care home staff and health-care professionals,[641] ensure quality standards and procedures are in place,[642] and foster a climate that recognises skills and advances employees' careers.[643,644] Other successful elements of facilitating and sustaining interventions include interactive training, post-training support, aiming to train most staff, retaining written materials afterwards, and building interventions into routine care.[636]

Assisted living

Assisted living (extra-care sheltered housing, intermediate care housing, housing with care, or assisted living residences) is an increasingly common option for people with dementia, who are unable to live in their own home.[645] Estimates indicate that 45–67% of residents of such facilities have dementia, of whom more than half have moderate-to-severe dementia and at least one neuropsychiatric symptom.[646,647] People with dementia living in these settings often do not access treatment.[646,648] Integration of dementia services in these settings, staff education and training, and monitoring of psychotropic medication might improve treatment and care for people with dementia.[649]

Interest in home-like residential care models and development of fit for the future residential settings is increasing.[650] Examples include the Eden Alternative and other small-scale facilities, which are sometimes specifically designed for people with dementia.[651] No defined key characteristics of these models or information about outcomes are available.[652] Some studies[653–655] indicate that people with dementia might benefit from these models in their physical functioning; however, comparative-effectiveness and cost-effectiveness research is incomplete.[652]

Key points and recommendations

Interventions in care homes require longer-term working with professionals after the initial education to sustain the intervention and address and change organisational culture. A combination of communication strategies and clear procedures to increase physical and social activity might reduce or prevent agitation in care homes.

Technological innovations in dementia care

Panel 6 gives an overview of available and possible future uses of dementia-related devices. The huge advances in the development of health-care devices, including electronic health records, portal technologies, and wireless communications,[656] are likely to have a key role in future dementia care. Given the progressive nature of dementia, certain devices might have a window of usefulness to people with dementia and their carers.[657] Although somewhat overlapping, dementia health-care technologies can be divided into five general categories. (1) Technologies for diagnosis and assessment, such as computerised neuropsychological assessments and telemedicine to facilitate examinations, testing, and therapy in remote areas.[658] (2) Monitoring, including sensors (motion, infrared, video, pressure, moisture, and vital sign measurement) to detect changes in the environment or health status of the person with dementia.[656,658,659] (3) Assistive, including cognitive aids (eg, reminder systems for medication management), assistance for activities of daily living, and safety devices (eg, electrical outlet shutoff devices).[656,658,659] (4) Therapeutic, including those that address communication, companionship, and activity.[656,658] Despite interest in the animal-assisted interventions in long-term care settings, often using social assistive robots, very few well controlled studies have been done.[660,661] (5) Carer supportive,[658,659] including technology either to help carers with the care of the person with dementia or support their own wellbeing.[658,662,663]

Challenges and priority areas for the future

Technological innovations for people with dementia and their carers is an area of substantial growth, but few rigorous RCTs[664] have been done for most devices for people with dementia, with most research exploring feasibility and acceptability rather than clinical-effectiveness. The available published work concentrates on technical aspects of delivery or physical disability.[659] Many of these devices are not implemented or evaluated. Despite the potential applicability of technological innovations, important challenges need to be addressed. The aim of technological innovations should be to improve care without unacceptably increasing risks for people with dementia and their families. Preserving privacy and autonomy for the person with dementia is also important. While some devices have the potential to enhance safety, they also raise concerns in relation to replacing or reducing human contact.[665] The development and use of devices used to restrict or restrain people with dementia raise additional concerns.

Panel 6: **Possible use for technological innovations in dementia care**

Diagnosis and assessment
- Computerised diagnostic assessment: neuropsychological assessments and video-conferenced examinations
- Detecting progression: wearable sensors to detect changes in gait or activities of daily living
- Virtual reality: assessment of activities of daily living, such as meal preparation

Monitoring
- Environmental sensors: detection of changes in movement, such as falls; sensors to detect and intervene in the environment—eg, heat or gas, satellite tracking devices, or remote viewing camera
- Physiological sensors: devices measuring pulse, blood pressure, oxygen saturation, blood glucose, or sleep; or so-called smart garments with sensors that send biometric data

Assistive technology
- Cognitive aids: reminder systems—eg, medication management; activities of daily living prompting—eg, a tool that prompts user through handwashing; cognitive training
- Activities of daily living assistance: robots to help with eating, washing, and mobility
- Safety: electrical outlet shut-off devices, hands-free taps, and water temperature sensors
- Combination: robot to assist with care and monitor physiological or environmental changes and send information to carers

Therapeutic technology
- Communication: support reminiscence-based communication between people with dementia and their carers or chat groups
- Companionship: robotic animals
- Activity: technology to deliver music, messages, images, and video tailored to an individual's interests

Carer-supportive technology
- Telemedicine: video-conferencing with professionals
- Online information: virtual assistance for managing challenges or web-based tools to support carer decision making
- Peer support: carer online or phone support groups

Key points and recommendations

Advances in the use and application of technological innovations might help people with dementia to live in safe, stimulating, and functionally enabling environments, and support and assist carers and professionals in improving quality of care. However, evidence on the effectiveness for most devices is not available. Caution is therefore needed to protect people with dementia from overselling of ineffective and potentially unsafe devices. Technology is not a replacement for human contact.

Conclusions

Continued progress will build on what has long informed dementia care: to prevent the preventable, treat the treatable, and care for both the person living with dementia and the carer. In this Commission, we have brought these strands together, informed by our understanding of the best evidence, and explained the reasons for our conclusions. Evidence is always incomplete but we present the available evidence and the conclusions we have reached transparently. From this evidence and by recognising that in each area more must be done, we have suggested what can and should be done now.

Our recommendations are informed by the knowledge that dementia impairs cognition and therefore challenges the ability of people to make decisions for themselves, understand, and communicate what they want and need. Therefore, we must take the utmost care and the necessary time to elicit the views of people with dementia and of their family carers.

Additionally, giving people information about how to prevent or treat dementia is an essential first step, but is not enough. There is a responsibility, not just as professionals but as a society, to implement this evidence into interventions that are widely and effectively used for people with dementia and their families. Interventions have to be accessible, sustainable, and, if possible, enjoyable or they will be unused. Delivery of interventions will vary according to the health system, with some countries having free health care at the point of delivery for all and other countries having to implement this care as part of a programme. Interventions that provide both the evidence and manuals with the necessary materials are easier to implement and to alter according to the country in which they are used. It is important to consider who will deliver programmes and practicalities so that they are widely available to people with dementia and their families.

People live with dementia in our societies, which should encounter, accept, contain, and support them. This entails community design to foster safe, affordable social activity and transportation, in addition to creation of societies in which people with dementia can be integrated. Thus, while we recommend specific interventions to prevent dementia, diagnose it early, manage the cognitive and neuropsychiatric symptoms, support carers, and improve living and dying with dementia, it is important that this health and social care occurs within, rather than separate from, society, so we can become truly dementia friendly.

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Contributors

GL, AS, NM, VO, and JH drafted and redrafted the whole report. NM, AS, and GL conceived the new PAF calculation and NM led the statistical analysis. SGC led the new meta-analysis for hearing impairment and dementia risk. All authors contributed to sections of the reports and all revised the paper for important intellectual content.

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